Skills in Rheumatology

Hani Almoallim
Mohamed Cheikh
Editors

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Hani Almoallim
Department of Medicine
College of Medicine, Umm Al-Qura University (UQU)
Makkah
Saudi Arabia

Mohamed Cheikh
Department of Medicine
Doctor Soliman Fakeeh Hospital
Jeddah
Saudi Arabia

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To my father, who left the world after a lifetime of leaving smiles on the faces of those around him. His kindness knew no bounds, and whose presence sparked joy into those dealing with him. His love for life only equaled by his love for giving that was only limited by our ability to receive. I have no doubt that without him would not be who I am today.

Hani Almoallim

To my biggest fan, the greatest mother I could have asked for, and to all my family, who have been providing their support whenever I need it most.

Mohamed Cheikh

Introduction

How to Use This Book?

This is a book that deals with the daily practice of rheumatology! We did not write it just to make another book! It is not a book to be added to the list that already exists on the shelf! It is a small practical one, in which we rather focus on the skills that the physician, the patient, or caregiver might need to take care of rheumatologic complaints and diseases!

Many junior staff start working in Rheumatology or see patients with arthritis may find themselves incompetent in basic skills while evaluating such patients. This book provides a comprehensive yet simple guide for junior or senior staff to deal with rheumatology patients.

You do not need to read the whole book to get its benefits nor do you need to read it linearly. You just need to read the relevant section you are interested in. For example, if you just need to know how to examine the small joints of the hands, you can go directly to musculoskeletal (MSK) examination chapter: hands examination or if you need to know details about a biological drugs used in Rheumatology, you can go directly to the pharmacology chapter: biological drugs. In other words, you may determine in advance what you need to master each time you hold the book!

The book consists of three parts. The first part is about basic skills in rheumatology. There is a comprehensive approach to history taking of patients with arthritis. We suggest this approach on the basis of differential diagnosis. Any patient with arthritis needs a comprehensive MSK examination, laboratory evaluation, pharmacological drugs analysis and radiological assessment. (You may just need to know what drugs are the patient taking especially if he/she has an established diagnosis of arthritis?). We put special emphasis on low back pain, as there is a distinctive approach to this complaint. There is a significant delay that may reach 7–10 years before one can diagnose a patient with diseases characterized by inflammatory back pain like ankylosing spondylitis (AS).

The second part of the book is designed to address common medical problems affecting patients with arthritis. It is truly said that to be good in rheumatology you need to be good in internal medicine! Rheumatologic diseases are systemic diseases affecting nearly all body systems. This comprehensive approach to common medical problems should emphasize the reader's skills not only in Rheumatology but also in general internal medicine. A reader can approach this part at any point. If a systemic lupus erythematosus (SLE) patient

has anemia, there is a hematology chapter one can go to directly to; or if another SLE patient has headaches, stroke, and/or other neurological complaints, just read the chapter that deals with how to approach neurological complaints that contain elegant flow chart, tables, and diagnostic algorithms. There is also a chapter about pediatric Rheumatology highlighting the essential issues in dealing with rheumatic diseases in this young age group.

The last part of the book is a compilation of recent recommendations for management guidelines and current classification criteria in Rheumatology. Lately, there has been a tremendous progress in the practice of Rheumatology worldwide. This has resulted in the introduction of new recommendations for the management and classification criteria. We tried to bring in this part all efforts that have been produced to enhance the practice of Rheumatology. However, if you need to read further details about the management of a particular disease beyond the guidelines, you would need to read from recent medical literature.

To sum up: this book is a practical guide designed for building your skills in dealing with Rheumatology patients. We focus on diagnostic approaches to medical problems. You may find more than one style in the different chapters you are going to read. This is because each contributor thought about the best approach to deliver the contents. This may explain partly the variations in writing styles in some chapters. Dealing with a patient with a skin condition in rheumatology may not have the same approach as when dealing with a patient with shortness of breath. We offer variety of approaches to entertain the reader.

We hope that medical students, interns, residents, fellows, general practitioners, and rheumatologists appreciate the efforts put into making this book a useful aid to deliver a better care for patients with arthritis.

The objectives of this book are as follows:

1. To compose a comprehensive approach to managing patients with arthritis.
2. To perform MSK examinations for the most commonly involved joints in inflammatory arthritis.
3. To interpret autoantibodies in the appropriate clinical settings.
4. To discuss indications and contraindications of the most common drugs used in rheumatology practice.
5. To order appropriate imaging modality for assessing patients with rheumatic complaints.
6. To construct a diagnostic approach to common medical problems affecting patients with rheumatic diseases.
7. To review recent classification criteria and treatment recommendation guidelines in rheumatology.

We hope you will enjoy reading this book. We welcome your comments and feedback.

Makkah, Saudi Arabia — Hani Almoallim
Jeddah, Saudi Arabia — Mohammad Cheikh

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About the Editors

Hani Almoallim has been a practicing rheumatologist for more than 17 years. He is a qualified educationalist and has been teaching rheumatology to undergraduate and postgraduate students since 2004. He has published over 80 papers on rheumatology, internal medicine, and medical education in peer-reviewed, international journals and on MedEdPORTAL (the official publication site for the American Association of Medical Colleges (AAMC)). He is the Chair Professor of Alzaidi Chair of Research in Rheumatic Diseases at Umm Alqura University and established the first data registry for rheumatoid arthritis in Saudi Arabia. He has conducted many educational workshops on early arthritis for trainees and general practitioners. He has observed and studied the reasons behind gaps in knowledge and skills among trainees in the practice of rheumatology.

Mohamed Cheikh is a consultant in internal medicine and a rheumatology fellow and has participated in several educational activities as well as research projects with Prof. Almoallim. He is actively involved in training young physicians to perform musculoskeletal system examinations.

Part I

Basics in Rheumatology

History-Taking Skills in Rheumatology

1

Laila Alharbi and Hani Almoallim

1.1 Introduction

History taking in rheumatology is the most important skill needed for proper handling of a patient with a rheumatological complaint. Obtaining a good history will help you to reach almost 90% of your diagnosis. However, history taking is mostly depending on experience and practice rather than theoretical recall. Here in this section, we provide you with the most important points in history taking you should use while dealing with rheumatological patients. There is an approach to history taking in rheumatology started as with the classical approach in history taking like any other disease. There is much focus on rheumatological aspects related to the onset of joints pains, patterns, symmetry of joints involvement, number of joints involved, and ultimately rheumatology review of systems. We summarized the classic symptomatic correlations with certain rheumatological diseases. We present briefly a suggested approach to your presentation of the entire case.

1.1.1 Objectives

1. To compose a comprehensive and organize history for patients with rheumatological problems.
2. To recall the most important points in eliciting history for certain rheumatological diseases.
3. To construct a differential diagnosis in rheumatology.
4. To develop an approach for monitoring patients with arthritis.

1.2 Approach to History Taking in Rheumatology

This approach is based on the assumption that majority of patients with rheumatological diseases present at the beginning with joint(s) pain. Rheumatological diseases are systemic diseases affecting almost all body systems with no system that is preserved. You may have patients with neurological complaints (like hemiplegia because of ischemic stroke) end up with the diagnosis of a rheumatological disease like systemic lupus erythematosus (SLE) and secondary antiphospholipid syndrome (APS). Here the initial presentation was not joints pain, but yet the final diagnosis was rheumatological. This concept emphasizes the point that good foundations in general internal medicine is essential to the rheumatology practice.

L. Alharbi
Medical College, Umm Al Qura university, Makkah, Saudi Arabia

Department of Internal Medicine, Skåne University Hospital, Malmoe, Sweden

H. Almoallim (✉)
Medical College, Umm Al-Qura University (UQU), Makkah, Saudi Arabia
e-mail: hmmoallim@uqu.edu.sa

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The approach to joints pain for any new patient should establish two basic issues: the personal data and then full analysis of the presenting illness. The latter includes the followings (Fig. 1.1).

1. Onset.
2. Duration.
3. Patterns of joints affected.
4. Symmetry.
5. Number of joints affected.
6. Associated symptoms.
7. Constitutional symptoms.
8. Functional impairment.
9. Relieving and aggravating factors.
10. Rheumatology review of systems.

This should be followed by the classical components in any history taking in internal medicine (past medical and surgical history, family history, drug and allergy, and social history).

Here is a brief description about each one of the above.

1. Onset: The patient should determine whether joint(s) pain have started suddenly or gradually. This is essential as the top differential diagnoses that should be ruled out for sudden

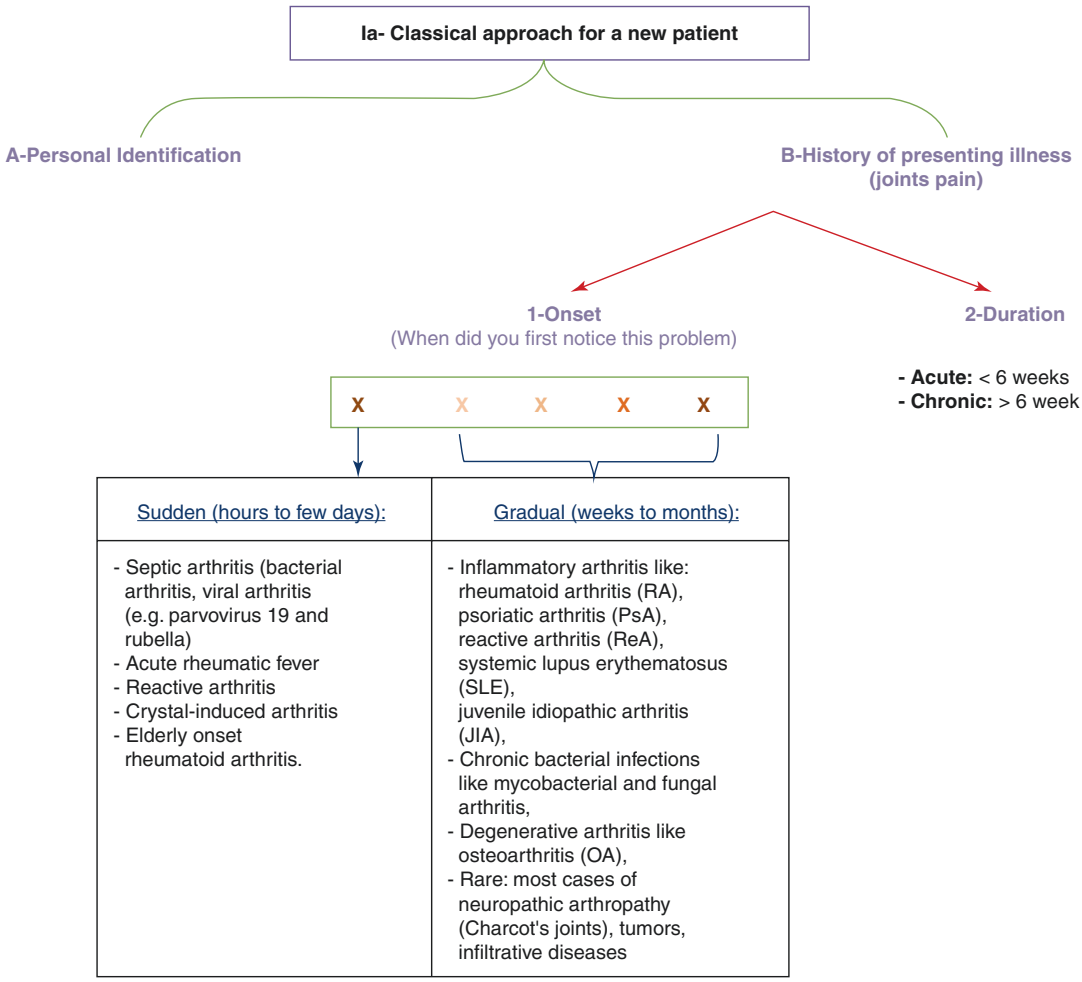

Fig. 1.1 Approach to history taking in rheumatology

onset of joints pains are septic arthritis and crystal-induced arthritis (after excluding trauma as a possible cause for joints pains) (Fig. 1.2). Gradual onset joint pains have long list of differential diagnoses including the classic rheumatological diseases like rheumatoid arthritis (RA) and SLE (see Fig. 1.2).

2. Duration: It is essential to determine whether the joint pains have been present for less or more than 6 weeks. Classically, arthritis caused by acute viral illnesses like parvovirus B19 infection can cause RA-like arthritis in distribution but with less than 6 weeks duration. Duration more than 6 weeks is an essential criteria to diagnose RA based on 2010 classification criteria of RA (see Chap. 25).
3. Patterns of joints affected: Each rheumatological disease has a pattern of presentation that should be recognized from this early stage. Each pattern has a differential diagnosis (Figs. 1.3 and 1.4).

Predominant small joints involvement (like in pattern A) particularly the wrists, metacarpophalangeal (MCP), proximal interphalangeal (PIP), and metatarsophalangeal (MTP) joints is a classical presentation for RA. Other disorders like SLE, psoriatic arthritis (PsA), polyarticular gout, and reactive arthritis (ReA) can present in a similar way. The commonest joints involved in RA, for example, are wrists and MCP (2nd and 3rd). It has to be noted that distal interphalangeal (DIP) joints involvement is rarely ever involved in RA. These joints (DIP) are

Make sure the origin of the pain is from the joint itself, NOT from the periarticular sructures. One tip is to ask the patient to point the site of the pain by his/her finger!

Fig. 1.2 Identifying the site of the pain

Fig. 1.3 Patterns of joints affected

Joints	Differential Diagnosis
Symmetrical polyarticular MCP PIP and MTP joints	RA, SLE, PsA, Polyarticular gout and ReA.
DIP joint(s)	PsA, OA
Bony swellings of DIPs or PIPs or 1st CMC joint (base of thumb)	OA
Proximal girdle joints	Polymyalgia rheumatica and RA
Asymmetrical large joint oligoarticular disease	ReA, PsA, ankylosing spondylitis {AS)
Acute monoarticular disease	Infection, gout, pseudogout
Chronic monoarticular	PsA, RA, AS, OA and chronic infection (e.g. tuberculosis (TB))
Axial, sacroiliac and girdle joints	AS
Axial joints	Lumbar & cervical spondylosis/OA
Dactylitis (sausage digit)	PsA, ReA, AS, TB, sarcoidosis, sickle cell disease.

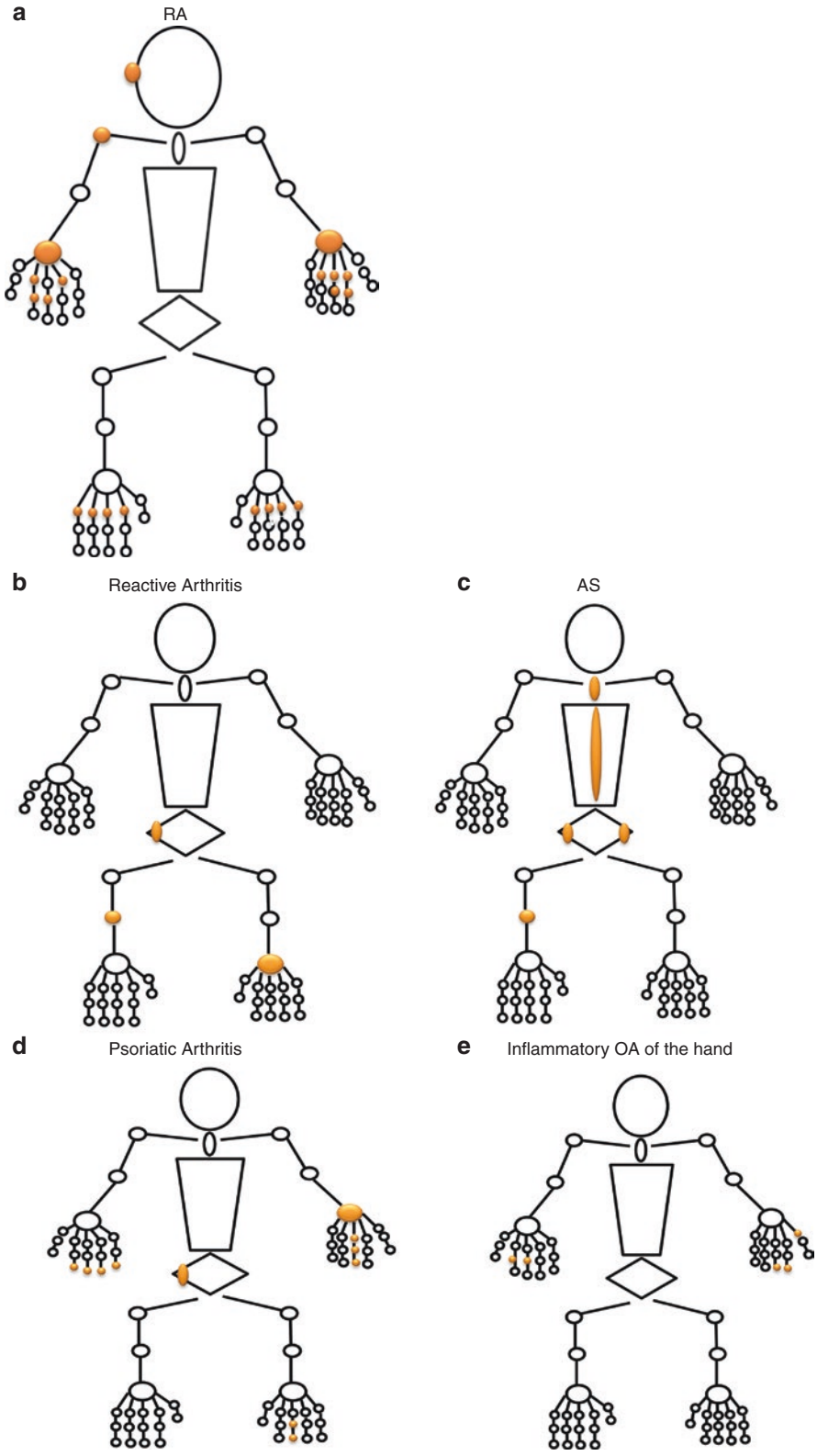

Fig. 1.4 Each rheumatological disease has a pattern. (**a**) Rheumatoid arthritis. (**b**) Reactive arthritis. (**c**) Ankylosing spondylitis. (**d**) Psoriatic arthritis. (**e**) Inflammatory osteoarthritis of the hand

predominantly involved in patients with PsA and inflammatory osteoarthritis (OA) of the hands. Classical presentation of inflammatory OA of the hands (pattern E) involves DIPs, PIPs, and first carpometacarpal joint just at the base of the anatomical snuff. It has to be noted as a physical examination caveat that the swellings of the joints in inflammatory OA of the hands are bony! It represents the degenerative changes happening in the cartilage with osteophyte formation. Predominant large joints involvement in the lower limbs (pattern B) is a classical presentation for ReA. A group of disorders called spondyloarthritis (SpA) (include ankylosing spondylitis (AS), PsA, ReA, and arthritis associated with inflammatory bowel diseases (IBD-related arthritis) and undifferentiated spondyloarthritis) (see Chap. 23 for detailed classification criteria) has particular predilection of large joints of the lower limb. Sacroiliac joints can be involved in an asymmetrical fashion (pattern B) in ReA or can be symmetrically involved (pattern C) with inflammation of all the insertions of tendons and ligaments to the bones of the back (this is called enthesitis, and such inflammatory process in the back is called spondylitis). Therefore, (pattern C) is a classical presentation for AS. Spondylitis per say can be a manifestation of any disease of the SpA group of disorders. Large joints like proximal girdle joints (shoulders and hips) can be involved predominantly in diseases like polymyalgia rheumatica and RA. There is one feature that is quite classical for PsA and crystal induced arthritis. It is the inflammation of all articular and periarticular structures in one digit (dactylitis). This is not a feature for RA. It has to be noted then, involvement of small joints like in (pattern D) with predominance of DIPs, dactylitis, and asymmetrical sacroiliac joint involvement is classical for PsA.

For acute sudden monoarticular joint involvement, a septic process and/or crystal-induced arthritis should be ruled out. The knee joint is the commonest joint involved in septic arthritis, while the first metatarsophalangeal joints are the commonest joint involved in gout. For chronic monoarticular joint involvement, a chronic infectious process should be ruled out like tuberculosis or brucellosis. However, systemic rheumatic diseases like RA can rarely present with a monoarticular joint only.

4. Symmetry: This might have been covered partly in the above section. It has been included here to help the evaluator remember it all the time and consider it while composing the differential diagnosis. There are diseases like PsA that can present in several different ways including symmetrical arthritis like RA and asymmetrical arthritis involving only few joints like the DIPs. Symmetrical arthritis does not include in the differential diagnosis only known rheumatological diseases like RA and SLE. There are less common diseases like sarcoidosis, and paraneoplastic syndromes can present with arthritis (Fig. 1.5).
5. Number of joints involvement (How many joints affected?): Again, this feature has been covered partially above (Figs. 1.6 and 1.7). The emphasis is on a monoarticular single joint involvement when it should be considered a medical emergency. If a septic monoarticular joint was not diagnosed and treated properly, it will lead unfortunately to irreversible damage and lifelong disability if not death from disseminated infection [1]. It is hard clinically to separate between oligoarticular and polyarticular in the initial workup as will be shown in Chap. 3. A list of possible differential diagnosis is provided for you just to give a knowledge background base to proceed further in the history from patients with joints pains.
6. Associated symptoms: Obtaining history of redness, swelling, and morning stiffness is essential in any patient with joints pains. Any severely inflamed joint will cause obvious swelling observed by the patient. Keep in mind that sometimes, swellings of the small joints can be detected by physical examination only as the patient did not notice any

Symmetry of the joints

Symmetrical arthritis

Inflammatory:	- RA, PsA, SLE, JIA (systemic and polyarticular types), adult onset Still's disease, Sjögren's syndrome - Other systemic rheumatic diseases: SLE, mixed connective tissue disease (MCTD), adult onset rheumatic fever, polymyalgia rheumatica, erosive inflammatory osteoarthritis, calcium pyrophosphate deposition disease (CPPD) (pseudo-RA type)
Infectious:	- Viral arthritis especially parvovirus arthritis - Lyme disease
Infiltrative:	- Sarcoid arthritis (acute type) - Amyloid arthropathy - Hemochromatosis arthropathy
Neoplastic:	- Primary infiltrative/paraneoplastic: Leukemia - Chemotherapy induced (classically post breast cancer therapy)
Endocrinal:	- Myxedematous arthropathy

Asymmetrical arthritis:

Inflammatory:	- ReA - PsA - Pauciarticular JIA - Oligoaricular or polyarticular gout - CPPD disease (pseudogout type)
Infectious:	- Bacterial arthritis - Bacterial endocarditis.

Fig. 1.5 Symmetry of the joints

Fig. 1.6 Number of joints involvement (How many joints affected)

MONOARTICULAR (Single joint)	OLIOONUICULAR (2-4 joints)	POLYARTICULAR (More than 4 joints)
DD	**DD**	**DD**
- Traumatic - Inflammatory: Pauciarticular JIA, crystal-induced - Infectious: bacterial, fungal, TB, viral (AIDS). - Neoplastic - Infiltrative: one type of chronic sarcoidosis - Miscellaneous: Acute coagulopathy, Hemoglobinopathy	- Oligoarticular JIA - Reactive Arthritis - Psoriatic arthropathy	- Inflammatory: RA, JIA (polyarticular and Still), adult Still, Sjögren's - SLE and other connective tissue diseases - Seronegative spondyloarthropathies - CPPD disease - Vasculitides - Neoplastic: Paraneoplastic syndromes, metastasis, leukemia, lymphoma - Infiltrative: Sarcoidosis

Single red hot joint in RA: It should be remembered that the uncommon occurrence of a red hot joint in the context of RA may be due to superimposed septic arthritis and not to the disease process itself.

Monoarthritis in SLE: The occurrence of monoarthritis in a patient with SLE suggests infection or osteonecrosis.

Fig. 1.7 Alarming presentation of arthritis in RA and SLE

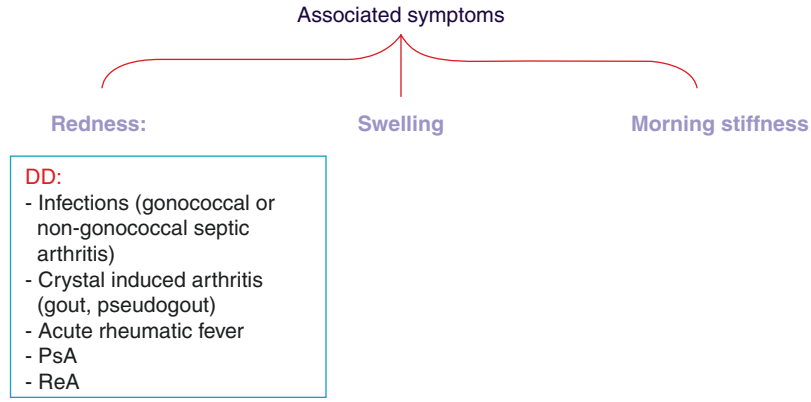

Fig. 1.8 Associated symptoms

because of its small size. Redness is one of the cardinal signs of inflammation. Active RA does not cause redness usually unless there is a superimposed infection in that joint that it is red. Therefore red and swollen joints are caused classically by septic arthritis and/or crystal induced arthritis (Fig. 1.8).

7. Constitutional symptoms: Obtaining these symptoms in any history obtained from patients for whatever symptoms presented is essential. Fever and arthritis are common clinical association. Again, septic arthritis whether in a monoarticular or polyarticular presentation should be ruled out. There is a full outline for this combination: fever and arthritis in Chap. 11. Apart from fever, the following symptoms should be obtained: weight loss, loss of appetite, night sweat, and fatigue. It has to be noted that patients with inflammatory arthritis often feel a general malaise. Fibromyalgia patients often report feeling ill (if I go shopping I am wiped out for the next 3 days). On the other hand, OA patients may be a bit tired but not really unwell.
8. Functional impairment: any inflamed joint will affect the functionality of the patient. The followings should be obtained:
   - How has the arthritis affected your daily ability to self-care?
   - How has the arthritis affected your ability to sleep well and to do things at home, work, and leisure?
9. Relieving and aggravating factors: Here the focus should be mainly on the effect of activity on the symptoms. Activity tends to aggravate joint pains caused by a degenerative process of the interarticular cartilage, i.e., OA, to be a reliving factor for inflammatory back pain as going to be shown in Chap. 6 about low-back pain. Use of nonsteroidal anti-inflammatory drugs (NSAIDs) tends to relive symptoms in a remarkable way in patients with inflammatory arthritis in comparison with patients with degenerative arthritis (OA) (Fig. 1.9).
10. Rheumatology review of systems: After your full analysis of the joints pain(s), now it is time to think which rheumatological diseases might be the top in your differential

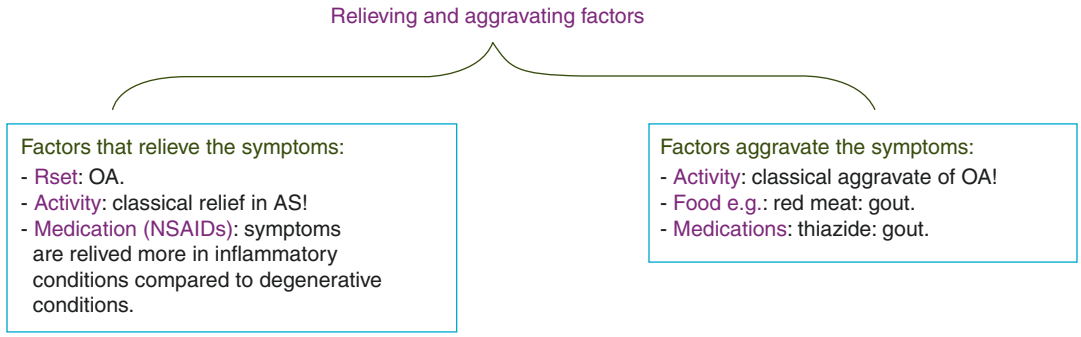

Fig. 1.9 Relieving and aggravating factors

diagnosis. All rheumatological diseases are systemic diseases with significant involvements of other body parts (Fig. 1.10). Some patients may not correlate the relationship between numbness, tingling sensations, and joints pain(s) (some patients may present with arthritis and mononeuritis multiplex like in vasculitis or RA). Others may not remember to mention history of skin disease like psoriasis. Obtaining obstetric history is extremely important for any childbearing female patient as there are many complications in pregnancy related to SLE and/or APS (see Chap. 17). For all of these reasons, it is your rule to review all possible symptoms that might be present and help you in composing your differential diagnosis. All possible symptoms are complied in an approach from head to toe just to help you mastering this part of the history.

- **Past medical history:**
  - History of any rheumatic disease (RA, SLE, gout, psoriasis, etc.).
  - History of recent infections (think of ReA!).
  - History of chronic diseases. There are some rheumatological associations with diabetes mellitus (see Chap. 21).
- **Family history:**
  - Ask if similar condition happened in the family.
  - Any family history of RA, SLE, psoriasis, etc.
- **Medications and allergy:**
  - Detailed medication history.
  - Any allergy from food and/or drugs?
- **Past surgical history:**
  - History of any previous operations.
  - History of blood transfusion.
- **Social history:**
  - Marital status and occupation (tendinitis in typist!). How many children? Where do they live?
  - History of contact with TB or jaundiced patients: essential prior to start of disease modifying anti-rheumatic drugs (DMARDs) and biological therapy.

1.3 Historical Correlation

Some patients may present initially with symptoms suspected for a certain disease. Then you need to check other symptoms related to this disease that might help you to make your diagnosis from historical grounds only! This is different than rheumatology review of systems mentioned above. Actually, as your skills in obtaining history from patients with joints pain grow, you will notice yourself combing this step with rheumatology review. For example, you are evaluating a young female patient with joint pains. You have a suspicion for SLE as you are proceeding in your history; then during your history taking, you should cover all common presentation of SLE!

SYSTEMS	SYMPTOMS SHOULD BE ASKED
1- Hair	Hair loss, alopecia, psoriatic rashes (in the hair line)
2- CNS:	History of stroke, weakness, seizure, psychosis: SLE. Mononeuritis multiplex, peripheral neuropathy: vasculitis, SLE Lymph node enlargement in the neck: SLE, lymphoma with sjögren syndrome
3- Eyes:	Dryness: sjögren syndrome. Redness (uveitis): AS Pallor: anemia from many causes in RA or SLE.
4- Face:	Cheek: Photosensitivity: SLE Red cheeks (butterfly rash): SLE Scaring hyperpigmentation: SLE Parotid gland enlargement: sjögren Telangectasia: scleroderma Mouth: Dryness: sjögren syndrome Ulcer: SLE (painless), inflammatory bowel disease (IBD), Behcet's, RA (from methotrexate use)
4- Chest (Respiratory & Cardiovascular systems):	SOB, chest pain, palpitation: SLE, RA History of PE/DVT: SLE, antiphospholipid antibody syndrome (APS) History of bronchial asthma: Eosinophilic granulomatosis with polyangitis (EGPA) (Churg- Straus)
5- Gastrointestinal tract (GIT):	Ask about all symptoms of GIT! History of jaundice: viral hepatitis. History of recent gastroenteritis or bloody diarrhea: ReA History of IBD: enteropathic arthritis. History of dysphagia: scleroderma History of HBV: vasculitis. History of HCV: chronic HCV can present as RA! Ask about risk factors of HBV, HCV and HIV prior to start any disease modifying antirheumatic drug (DMARDs).
6- Urinary system:	Frothy urine: lupus nephritis. Hematuria: lupus nephritis, anti-glomerular basement membrane disease (Goodpasture).
7- Sexual and obstetric history:	History of recent STD's: ReA. History of oral/genital ulcers: Behcet's disease. History of still birth at any age and/or history of three recurrent abortion: APS
8- Lower Limb:	History of non-palpable purpura, lower limb edema, nodules: vasculitis
9- Ask about Smoking and alcohol intake.	Smoking predisposes to RA, decrease response to DMARDs and biological therapy Adjust alcohol intake in patients recieveing methotrexate Alcohol is a risk factor for gout

Fig. 1.10 Rheumatological review of systems

The common symptoms for some diseases have been complied for you (Figure 1.11**a**, **b**, **c** historic correlation). Some of the questions may not be related to symptomatology! It might just address risk factors. If you are assessing a patient with pain in the first MTP and/or with a red swollen knee joint and you are suspecting gout as a possible diagnosis, then you need to check for risk factors for gout: prior history of uric acid renal stones, alcohol intake and use of diuretics, etc.

Diseases	Certain historical points
1- Patient with suspected SLE	Ask about the following symptoms: - Alopecia (hair loss) - Malar rash - Mouth ulcer - Photosensitivity - Discoid lupus - Raynauds phenomenon - Pleuritic chest pain - Headache - Hematuria - Psychosis, seizures - Vascuilitic rash - Urinary symptoms - Detailed obstetric history
2- Patient with suspected vasculitis	Ask about the following symptoms: - Claudication: Takayasu's arteritis - Fatigue, fever, myalgias, headache, diplopia, jaw claudication: giant cell arteritis - Wight loss, myalgias, peripheral neuropathy (numbness), abdominal pain, livedo retieularis: Polyarteritis nodosa (PAN) - Sinusitis, saddle nose deformity, hemoptysis, chest pain, hematuria, uveitis, history of DVT or PE, granulomatosis with polyangiitis (GPA) (Wegener's) or microscopic polyangiitis (MPA). - History of Asthma, granulomatous vasculitis, eosinophilia: EGPA. - Abdominal pain, palpable purpura, polyarthralgias, microscopic hematuria: IgA vasculitis (IgA V) (Henoch-Schonlein). - Oral/genital ulcer, uveitis, erythema nodosum: Behcet's syndrome. - Weakness: gradual, progressive, painless, symmetrical and proximal. It may involve shoulder, pelvic girdle and neck flexors, but no involvement of facial or ocular muscles! - Dermatologic: erythematous rash on sun exposed skin, heliotrope rash over upper eyelid, Gottron's papules over the dorsum of PIP and MCP joints.
3- Patient with suspected myositis	Ask about: - Myalgia and arthralgia. - Dysphagia and dysphonia. - Raynoud's phenomena. - Symptoms suspected of malignant conditions: weight loss, fatigue, bleeding per rectum, smoking and chronic cough .. etc. - Drugs.
4- Patient with suspected gout	- Pain in 1st MTP (sudden onset), may involve ankles, feet and knees, bursitis (olecranon, patellar). - History of previous attack of gout, chronic tophaciuos gout (deforming arthritis). - Risk factors: uric acid renal stones, history of hyperuricemia, chronic renal disease, myelo & lymphoproliferative diseases, increase meat, seafood and alcohol intake, use of diuretics and pyrazinamide. - Alcohol. - Family history of gout.
5- Patient with suspected Sjögren's syndrome	Ocular: dry eyes Mouth: dry mouth, decrease salivation, drinking fluid while swallowing, difficulties with speech, change in taste and parotid enlargement Ask about the following risk factors: - Head and neck radiation. - AIDS. - HCV. - Lymphoma. - Sarcoidosis. - Anticholenergic drugs. - GVHD (graft versus host disease)
6- Patient with suspected Spondyloarthritis	Ask about the following symptoms: - Red eye (uveitis) - Psoriasis - Recurrent/previous infections: gastroenteritis, STDs, tonsillitis - Dysphagia - IBD - Inflammatory back pain - Lower limb joints pain - Plantar fasciitis/Achilles tendinitis
7- Patient with suspected Septic Arthritis.	Ask about the following symptoms: - Joint pain, - Joint swelling or history of joint edema, - Fever, - Sweating and Rigors (I) - Role out any source of local or disseminated infections by asking about: - Headache - Sore throat - Productive cough - Urinary symptoms, GI symptoms. - History of wound infection or abscess.

Fig. 1.11 Historical correlation

1.4 Physical Examination

This is just to remind you about the particular approach of physical exam techniques that should be performed and then presented (Fig. 1.12). A comprehensive approach to joints examination is presented in Chap. 2.

1.5 How to Present your Case

You are ready now to present your case! You have built an organized approach to history taking from patients with joints pain(s). You have performed a comprehensive physical examination focusing on evaluation of these joints and whether there is true articular process like arthritis or periarticular process like tendinitis (see Chap. 22). Simply you need to present your history and physical examination in the same manner mentioned above with focusing on positive findings and important negatives. After your history and physical examination presentation, it is required from you to sum up all your information together. It is better to start with your impression (summary of the case) and then your problem list and differential diagnosis.

1.5.1 Impression

This (age) who is (known to have (chronic diseases)) presents with:

- History (usually presenting complain).
- Physical exam(mention obvious findings).
- Lab results (mention the important results related to the case) (if it is known to you).

1.5.2 Problem List

In this section you have to make a list with all your patient's problems or complains starting with the most serious and important one. This should guide you to reach the diagnosis easily.

This is a suggested approach on how to write a problem list:

Regarding the first problem:

1. Write your differential diagnosis for this issue and mention which diagnosis is more relevant with your case and why.
2. Write your management plan, if further investigations and/or referral are needed.

Fig. 1.12 Physical examination

Physical Examination	Details
1- General Appearance and Vitals sign	As usual.
2- General Exam	Eyes Scalp Mouth Parotid Neck lymph nodes Skin (redness, thickness) Nails (pitting, periangular erythema)
3- Specific exam for any joint	I- General appearance: Deformity , swelling II- Inspection: Skin: redness, sacrs and rash Ligaments and tendons Muscles Bones III- Screening Exam: Check for range of motion (ROM) IV- Palpation: Effusion, tenderness, warm and crepitus. V- Range of motion: Active and passive. VI- Special tests.
4- Examination of the other systems	CNS, CVS, Chest and Abdominal exam.

See the diagram below for more details (Fig. 1.13).

1.6 Follow-Up Patient

Established patients with rheumatological diseases have frequent visits to outpatient clinics. They come for routine visits for assessing the progress of their disease and review the management plan of their chronic disease. Here are suggested tips for you to help you deal with these patients.

You should ask about:

1. Pain (how he/she is doing since last visit).
2. Which joints are particularly affecting you today?
3. Associated symptoms (morning stiffens (mins), swelling).
4. How well controlled do you feel the arthritis is?
5. What drugs are you taking? Your adherence? Do you get any benefit?
6. Any functional impairment?

You should not forget to:

7. Do not forget to examine his/her all joints.
8. Do not forget to review all his/her medications.
9. Do not forget to review his/her previous investigations (Fig. 1.14).

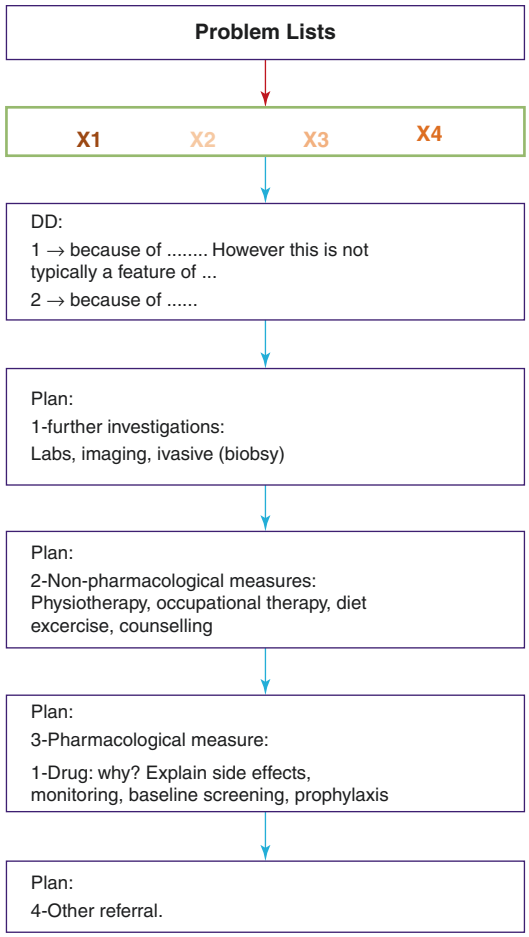

Fig. 1.13 Problem lists

1.7 The 2011 ACR/EULAR Definitions of Remission in Rheumatoid Arthritis Clinical Trials

1.7.1 Boolean-Based Definition [2]

At any time point, patient must satisfy all of the following:

- Tender joint count ≤1+
- Swollen joint count ≤1+
- C-reactive protein ≤1 mg/dl
- Patient global assessment ≤1 (on a 0-10 scale)+.

1.7.2 Index-Based Definition

Simplified Disease Activity Index score of ≤3 [3].

Definitions for some of the outcome measures in rheumatology are compiled in Fig. 1.15. Further

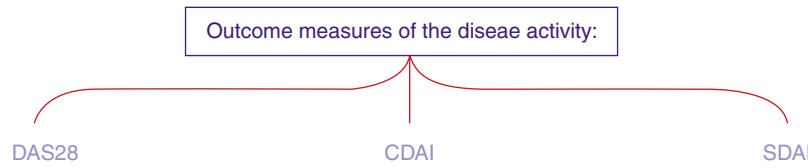

Fig. 1.14 Outcome measures of the disease activity

Outcome measures of the disease activity	Parameters	Interpretation
1-DAS28	a. How many Tender joints? b. How many Swollen joints? c. ESR or CRP level.	1- DAS28 <= 2.6: Remission 2- DAS28 > 2.6 and <= 3.2: Low disease Activity 3- DAS28 > 3.2 and <= 5.1: Moderate Disease Activity 4- DAS28 > 5.1: High Disease Activity
2-CDAI	a. How many Tender joints? b. How many Swollen joints? c. The PGA represents the patient's self-assessment of disease activity (0 to 10 scale) d. The EGA represents the evaluator's assessment of disease activity(0 to 10 scale)	1- CDAI <= 2.8: Remission 2- CDAI > 2.8 and <= 10: Low disease Activity 3- CDAI> 10 and <= 22: Moderate Disease Activity 4- CDAI > 22: High Disease Activity
3-SDAI	a. Tender joint count (using 28 joints) b. Swollen joint count (using 28 joints) c. PGA (0 to 10 scale) d. The EGA (0 to 10 scale) e. CRP level	1- SDAI <= 3.3: 2- SDAI > 3.3 and <= 11: Low Disease Activity 3- SDAI > 11 and <= 26: Moderate Disease Activity 4- SDAI > 26: High Disease Activity

Fig. 1.15 Outcome measures of disease activity in RA and their interpretation

reading is required from you to know more about the implications of its use in the management of patients with RA (Fig. 1.15 outcome measures of disease activity in RA and their interpretations).

Abbreviations

AIDS	Acquired immunodeficiency syndrome
AS	Ankylosing spondylitis
CDAI	Clinical Disease Activity Index
CMC	Carpometacarpal joints
CNS	Central nervous system
CPPD disease	Calcium pyrophosphate dihydrate *disease*
CVS	Cardiovascular system
DAS-28	Disease activity score
DIP	Distal interphalangeal
DVT	Deep venous thrombosis
EGA	Evaluator Global disease Activity
GVHD	Graft vs. host disease
HBV	Hepatitis B virus
HCV	Hepatitis C virus
IBD	Inflammatory bowel disease
JIA	Juvenile idiopathic arthritis
MCP	Metacarpophalangeal joints
MCTD	Mixed connective tissue disease
MTP	Metatarsophalangeal
NSAIDs	Nonsteroidal anti-inflammatory drugs
OA	Osteoarthritis
PAN	Polyarteritis nodosa
PE	Pulmonary embolism
PGA	Patient Global disease Activity
PIP	Proximal interphalangeal
RA	Rheumatoid arthritis
SDAI	Simplified Disease Activity Index
SLE	Systemic lupus erythematosus
STDs	Sexually transmitted diseases

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2 Approach to Musculoskeletal Examination

Hani Almoallim, Doaa Kalantan, Laila Alharbi, and Khaled Albazli

2.1 Introduction

Musculoskeletal (MSK) symptoms are one of the most common reasons for patients to seek medical attention. Despite the high prevalence of musculoskeletal disorders in all fields of clinical practice, doctors continue to describe poor confidence in their musculoskeletal clinical skills. Here in this chapter an overview of the epidemiology of MSK disorders and the current status of MSK competency skills among clinicians will be discussed. Then a general approach to MSK examination will be introduced. The rest of the chapter will address detailed approach to upper limb and lower and back joints examination. Each section will start with a brief approach to pains originating from each site. Good history is part of the MSK examination.

2.1.1 Objectives

1. To discuss the current status of musculoskeletal (MSK) examination competency skills among clinicians.
2. To construct a diagnostic approach to single joint pain.
3. To demonstrate a comprehensive approach to MSK examination of all body joints.

2.2 Epidemiology of Rheumatic Diseases

MSK symptoms are the most common health complications requiring medical attention and accounting to 20% of both primary care and emergency room visits. MSK conditions affect one in five adults [1]. In a health survey, MSK disorders were ranked first in prevalence as the cause of chronic health problems, long-term disabilities, and consultations with a health professional [2]. In Saudi Arabia, MSK disorders are the second major cause of outpatients visit in primary care centers and private clinics. This is corresponding to findings in several other reports from different parts of the

H. Almoallim (✉)
Professor of Medicine, College of Medicine, Umm Al-Qura University (UQU), Makkah, Saudi Arabia
e-mail: hmmoallim@uqu.edu.sa

D. Kalantan
Al-Noor Specialist Hospital, Makkah, Saudi Arabia

L. Alharbi
College of Medicine, Umm Al Qura University, Makkah, Saudi Arabia

College of Medicine, Skåne University Hospital, Malmoe, Sweden

K. Albazli
Department of Medicine, Faculty of Medicine in Al- Qunfudhah, AlUmm Al-Qura University, Makkah, Saudi Arabia

The George Washington University School of Medicine and Health Sciences, Washington, D.C., USA

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world. Low back pain is the most prevalent of musculoskeletal conditions; it affects nearly everyone at some point in time and about 4–33% of the population at any given point [2].

MSK disorders are a very common cause of health problems. They result in limiting work in developed countries. Besides, up to 60% of people on early retirement or long-term sick leave claim a MSK problem as the reason [1].

2.3 Current Status of MSK Examination

A continuous neglect is observed in musculoskeletal examination skills in clinical practice. Thus problems of patients with complaints about bones and joints are often ignored and underestimated by doctors. Many studies suggest that training in MSK disorders is inadequate in both medical schools and most residency training programs. In Saudi Arabia and in many parts of the world, undergraduate and postgraduate medical teaching of MSK disorders is currently brief and not directly relevant to the knowledge and skills commonly required for management of these conditions in an outpatient setting [1, 3]. Educational deficiencies in MSK disorders have been reported extensively in undergraduate curricula and postgraduate training programs (Box 2.1) [3].

Box 2.1 Educational deficiencies in MSK examination skills

Causes of musculoskeletal (MSK) examination skills deficiencies [2]	Solution of MSK examination deficiency [2]
1. Vague training of MSK disorders in undergraduate programs. 2. Examination of the MSK system is often regarded to be complex in comparison with other organ systems. 3. Underestimation of the prevalence of MSK conditions and their impact on individuals and society. 4. MSK disorders are not considered to be main competencies of medical graduates because they are not life threatening conditions. 5. The lack of standardized approach to the clinical assessment of MSK problems, whether pertaining to primary care, rheumatology, or orthopedics. 6. Lack of proper standard teaching in MSK disorders results in the low competence in MSK examination skills. 7. Lack of summative evaluation of MSK examination skills contributes to low level of competency among medical graduates. 8. The disparity in the approach to examination between rheumatologists and orthopaedic surgeons mostly lead to poor performances in MSK examinations. 9. The lack of appropriate teaching and evaluation in MSK disorders; clinical teachers are not usually skilled in MSK examinations and thus bone and joint diseases are not screened.	1. To define competencies that should be mastered while dealing with MSK disorders. 2. To agree on what MSK skills should be mastered by medical students. 3. Standardized approach to the clinical assessment of MSK problems (Figs. 2.1 and 2.2). 4. Experts in various specialities work more closely together and look for the commonality of approach when treating a patient as they often treat the same patients but from separate angles. 5. Another solution would be an integrated MSK disease course for medical students, bringing together orthopedics, rheumatology, and physical medicine and rehabilitation. This approach has been found to be effective. 6. The method of teaching MSK examination skills should follow interactive approaches and hands-on teaching sessions where learners are involved in the teaching process.

As there is no standardized approach to the clinical assessment of MSK problems, one of the direct solutions for this is to have unified approach to MSK disorders. The approach should consist of screening examination (this is basically active range of motion testing (ROM)), inspection, palpation, ROM, and special tests (see below). The other direct solution is to have a clear objective from each MSK examination encounter based on historical facts obtained from patients. Each clinician should have then an objective for the MSK examination, whether signs of arthritis to be sought or signs of periarthritis with soft tissue inflammation (ligaments, tendons, bursae, cartilage, etc.). For example, a young female patient with small joints pain for 6 weeks should have a different objective for the MSK examination than a young male with knee joint pain following a football match. The objective for the MSK examination for the female patient with small joints pain should be to look for signs of arthritis, while the objective for the MSK examination of the male patient is to look for signs of periarthritis mainly ligamentous or meniscus injuries in his knee. This is not to underestimate the comprehensive approach to any joint with performing all steps (screening, inspection, palpation, ROM, special tests) but rather to get more focus on the techniques that should yield the signs suggestive of the preliminary diagnosis that was made initially based on the history obtained from the patient.

A number of different medical specialties are usually involved in treating patients with musculoskeletal complaints. This comprises general practitioners, family physicians, internists, orthopedic, and surgeons. However, the various practitioners may work in teams with other health professionals, but they often lack a multispecialty focus which results in treating the same patients in a segmented manner and from different inconsistent angles.

Based on a literature review published with details in reference [2], Box 2.1 shows some summarized causes of MSK examination skills deficiencies. Some suggested solutions were mentioned as well. One of these solutions is to have a standardized approach to MSK examination (see examination of the hand and wrist joints) (see Table 2.1.)

2.4 General Approach to MSK Examination

Clinicians have perceived the MSK examination across the world as complex and difficult to perform. This can be solved if the approach to MSK examination across different disciplines were unified. This approach starts by initiating the MSK examination using the following steps:

- Inspection: The basic anatomical structures overlying joints should be inspected for any changes. This includes inspection of the skin, tendons, muscles, and bones (joints). Skin changes like redness, rashes, and color changes should be noted. Loss of skin wrinkling may indicate swelling in underneath structures. Synovial sheaths covering tendons might be swollen. Muscles might be wasted. Bone and/or deformities might be obvious to observe.
- Screening exam: this is basically an active range of motion (ROM) testing to assess for gross pathology. The patient performs the full range of movement of the examined joint by own effort. If the active ROM was entirely normal without any limitation and/or pain, the joint examined can be considered normal. This step is introduced early on in this approach in order to focus the detailed MSK exam in joints with significant abnormal active ROM testing. The screening exam might be normal for arthritis affecting small joints of the hand and/or feet particularly in early stages of arthritis.
- Palpation: this is basically palpating for tenderness over different anatomical structures (bone, joint, tendons, bursae, fascia). Tenderness over the joint line (where two bones forming the joint are meeting) might indicate arthritis. There are special approaches to palpate small and large joints that will be explained in this chapter. Palpation for one of

the cardinal signs of inflammation, hotness (warmth), should be considered as well.

- Range of motion testing: there is active and passive ROM testing. If you have done the active ROM during the screening exam, you may now just perform the passive form or repeat it again. In cases of true intra-articular disease process (true inflammation of synovial membrane as in case of inflammatory arthritic disorders, for example, rheumatoid arthritis or psoriatic arthritis), the active and the passive ROM will be both restricted. While in cases of periarticular disease processes (affecting tendons, ligaments, bursae, fascia) the active ROM will be restricted and/or limited with tenderness, the passive ROM should be entirely normal. It is normal because you exclude the contribution of the affected tendon or ligament in the movement by doing it passively. However, there are exceptions to this general rule. Handling of the joints during MSK examination is essential. You should avoid assessing ROM while you are holding the joint itself. You should hold the assessed joint from distal and proximal areas trying also to hold other joints. You should mainly assess the ROM by holding bony structures forming the joint rather than the joint itself. This is not to cause pain over the joints from your holding. An issue might interfere with your ability to evaluate the origin of the pain; whether from the ROM or from your holding that causes stress over the joint results in pain.
- Special tests: these tests are conducted to examine for possible causes of the joint pain particularly soft tissue structures around the joint. As a general rule to examine for tendon- and/or ligament-related problems, you need to "stretch" the tendon to assess if this stretch can aggravate the symptoms and/or to "stress" it. If the function of tendon that you are assessing is extension, for example, to stress it you need to exert your force as an examiner in flexion while the patient is maintaining his joint in extension and resisting your flexion. If there is tenderness while performing this test, it might be due to tendinitis.
- Complete your exam: the MSK exam for any particular joint is not complete without evaluating other joints (above and below the joint being examined). In addition, a neurovascular evaluation is essential to exclude any possibility of neurological and/or vascular origins of the joint pain. Assessing peripheral pulses, examining the motor system, and evaluating for sensory loss are essential for comprehensive evaluation.

There are two important steps that should be addressed for any patient with joints pain. The first is determining in your history the location of the pain whether it is anterior, posterior, lateral, or medial pain. This could be achieved by simply asking the patient to point by his/her finger to the site that is causing pain at the joint. Each one of these sites has its differential diagnosis as a cause for pain. This should lead to the next step that is considering the anatomical structures at the site of the pain determined by the patient. You should continue taking your comprehensive history addressing the risk factors and trying to rule in or rule out the possible differential diagnosis you created by now from these steps.

After completing your history, you should determine now the objective of your MSK examination. Examining a young female who presents with small joints pains should have different objective than examining a young college student who presents with knee joint pain after a soccer game! For the young female patient, your objective should be looking for signs of arthritis: small joints pain swelling and/or tenderness. You may base on your history to look for signs of systemic lupus erythematosus, for example. While the objective of MSK examination for the college student should be to look primarily for signs of soft tissue injuries in his affected knee. This is not to underestimate the value of performing comprehensive MSK examination for the affected joint. It is rather a process to construct an approach to diagnosis utilizing historical findings and combining it with an objective-oriented MSK examination.

The following section is divided into three: the upper limb, the lower limb, and the back examination. Each section starts with a brief review of

the anatomy and then a description on the approach to pain origination from that particular joint. This is followed by a stepwise approach to examination of that joint using the inspection, screening exam, palpation, ROM, and special tests approach. The reader should realize the importance of applying the knowledge learned from this chapter into practice. This continued practice is the assuring way to the mastery level in competency skills in MSK examination.

2.5 Musculoskeletal Examination of Upper Limb Joints (Fig. 2.1)

The joints included in upper limb are hand and wrist, elbow, and shoulder. There is a brief review of the important anatomical landmarks that should be mastered because it has clinical correlations. This will be referred to as the first step. Then an approach to pain originating from this joint will be discussed focusing on anatomical differential diagnosis. The second step will be to follow the stated approach in MSK examination with descriptions whenever it is necessary. Illustrations have been used sometimes as a self-explanatory toll.

2.5.1 The Hand and Wrist Joints

2.5.1.1 First Step: The Anatomy

Anatomy of the Hand Joints (Fig. 2.1)
Each hand consists of 27 bones: 8 carpals, 5 *metacarpals*, and each finger having three phalanges except the thumb which has only two phalanges (Fig. 2.1). The joint is the articulation between two bones, so between the two phalanges there is interphalangeal joints, proximal (PIP) and distal (DIP); between the phalanges and metacarpal bones, metacarpophalangeal joint (MCP); between the metacarpals and carpal bones, carpometacarpal joint (CMC); and between the carpals bones, the intercarpal joints.

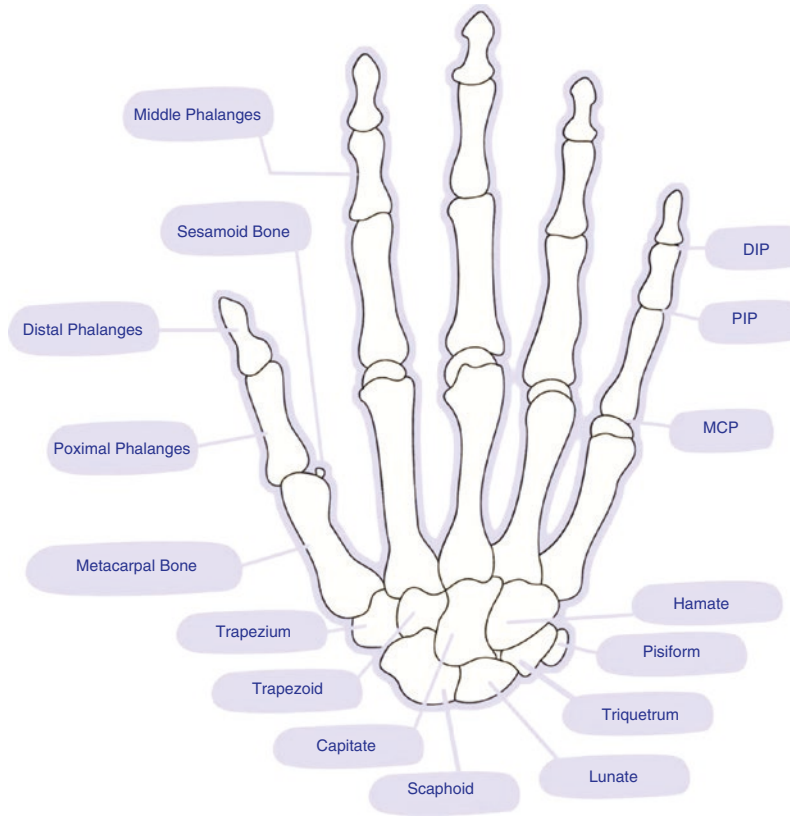


Fig. 2.1 Anatomy of the hand

There are around 62 muscles in the hand divided as intrinsic and extrinsic muscles. The intrinsic muscles are thenar, hypothenar, and interosseous muscles. The extrinsic muscles are flexors in the volar of the hand and extensors in the dorsum of the hand. There is also the synovial sheath, which is always involved in inflammatory arthritis.

The hand is innervated by three important nerves, which are radial nerve providing sensory supply to the dorsum of the hand, median nerve providing sensory supplies to three, and half finger and ulnar nerve sensory supplying the little finger and half of ring finger. All the small muscles of the hands are supplied by ulnar nerve except (LOAF) the lateral two lumbricals, opponens pollicis, the abductor pollicis brevis, and the flexor pollicis brevis. Be aware that the extensors of the thumb are supplied by radial nerve.

Approach to Hand Pain

The approach of any patient presenting with hand pain should include:

- History.
- Physical examination.
- Differential diagnosis.

In the history, you should ask about the location of the pain whether it is located in the dorsal, volar, radial, or ulnar sides of the hand (Table 2.1). Then you should think about the anatomical structures in each one of these sites and what possible diseases might cause the pain.

If the patient presents with dorsal pains, the anatomical structures that might be included are MCPs, PIPs, DIP joints, or wrist joint. The diseases that affect these joints are mainly arthritic disorders. Detailed approach to history taking should be undertaken as it was explained in Chap. 1. Tendons can be involved which result in tendinitis or, if the entire finger is swollen, dactylitis.

The anatomical structures included in patients presenting with volar pains are flexor tendons causing flexor tenosynovitis or what is known as trigger finger. Palmar fascia involvement results in Dupuytren's contracture. Median nerve compression as it passes below the flexor retinaculum causes a condition called carpal tunnel syndrome.

If the patient presents with radial pain (the thumb), the anatomical structure are snuffbox area. This is surrounded laterally by tendons of extensor pollicis brevis and abductor pollicis longus muscles, medially by tendon of extensor pollicis longus muscle and in the roof the scaphoid bone. The classical diseases affecting this area are de Quervain's tenosynovitis and first carpometacarpal osteoarthritis. Other diseases like thumb fracture and extensor carpi radials tendinitis are less commonly observed.

Ulnar pain is rare. Possible diseases affecting this site of the hand could be originated from ulnar nerve compression, tenosynovitis of flexor carpi ulnaris, and/or traumatic injuries.

2.5.1.2 Second Step: The Approach

It is always:
- Inspection.
- Screening exam.
- Palpation.
- Range of motion.
- Special tests.

Table 2.1 The differential diagnosis of wrist and hand pain according to the location of the pain

Dorsal	Volar	Ulnar	Radial
Arthritis • Wrist • MCP • PIP • DIP • Tendinitis – Dactylitis Trauma: – Scaphoid fracture	• Carpal tunnel syndrome • Dupuytren's disease • Trigger finger • Arthritis	• Trauma • Ulnar nerve entrapment • Tenosynovitis: Flexor carpi ulnaris	• Anatomical snuff box: – De Quervain's tenosynovitis – First carpometacarpal osteoarthritis • Tenosynovitis of extensor carpi radialis • Trauma: Thumb fracture

Inspection

Nails: evidence of psoriasis, vasculitis.
Skin: redness, scars, rashes.
Muscles: wasting, atrophy.
Bones and joints: swelling, deformities.

Remember:
- Always inspect dorsal and palmar aspects.
- Start distally to proximally.

Screening Exam

The aim is to screen for gross pathology.

- It is basically active ROM testing.
- First, extend fingers and wrist (palmar aspect upward). Make a fist, and then extend again. Make a tuck position, and then extend again. Make a prayer sign and then wrist flexion with all fingers facing the ground opposite of the prayer sign. Lastly, assess grip strength (Fig. 2.2).

Palpation

The major aim is to look for evidence of arthritis in the form of warmth, effusion, and joint line tenderness.

Palpate: joints, bone, and soft tissue.

Start with dorsum of the hand for nodules; palpate MCPs with a scissor technique and PIPs and DIPs with four fingers technique, follow the third metacarpal bone to feel capitate and the joint line of the wrist; and then feel scaphoid in the anatomical snuff box and other bones for tenderness.

Make a scissor-like shape with your fingers, joining the index and middle fingers together and joining the ring and little finger together. Hold the patients hand from the sides at MCPs level. Flex the MCPs to 90° and with your two free thumbs from both hands, feel the joint line for every MCP joint to assess for effusion, swelling, and/or tenderness (Fig. 2.3) [3].

This technique is called four fingers because you should use your four fingers which are the thumb and index finger of each hand (Fig. 2.4). With your thumb and index fingers of one hand, hold each PIP from the side and press firmly. With your other hand's thumb and index fingers, hold the same PIP joint from an anteroposterior direction and push intermittently in and out, looking for effusion, swelling, and/or tenderness [3].

With your thumb, follow the third metacarpal bone on the dorsal aspect of the hand until reaching a dimple at the capitate level (Fig. 2.5). Your thumb should exert a firm, continuous pressure on this point with your other thumb pushing intermittently in and out, just half an inch away from the other thumb on the wrist joint line, looking for effusion, swelling, and/or tenderness [3].

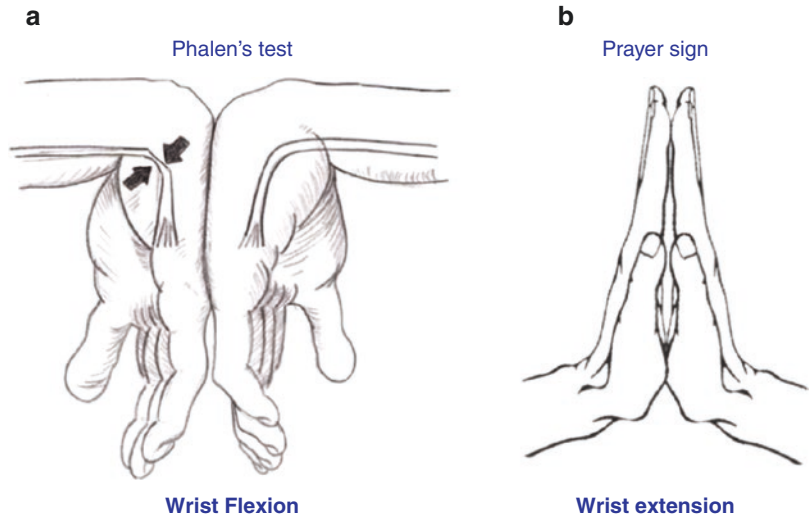


Fig. 2.2 (**a**) Wrist flexion and (**b**) wrist extension

Fig. 2.3 Scissor technique

Fig. 2.4 Four fingers technique

Fig. 2.5 Two thumbs technique

Range of motion

- You have done active ROM in your screening exam.
- Do it again for the wrist joint: extension, flexion, ulnar deviation, and radial deviation.
- For passive ROM of the wrist: hold the distal forearm with one hand, and grasp the palmar aspect with the other hand. Avoid holding the hand from the MCP site as this might be painful if there is arthritis.
- Now move the wrist passively to extension, flexion, ulnar deviation, and radial deviation.

You should observe and comment on tenderness, stiffness, and/or limitation of movement and end-range stiffness. All these are expected signs of arthritis.

Special tests

- This is to assess stability of the wrist joint. This is important particularly in pain in wrist joint following traumatic injuries.
- For de Quervain's tenosynovitis: do Finkelstein's test (Fig. 2.6). This is simply a trial to overstretch the tendon and examine for tenderness if it is elicited with this technique to suggest the diagnosis. To stress the tendon, push the extended thumb to flexion and ask the patient to resist your flexion. If there is pain, this would confirm the diagnosis.
- Carpal tunnel syndrome is reviewed thoroughly in "Diabetes and Rheumatology" Chap. 21.

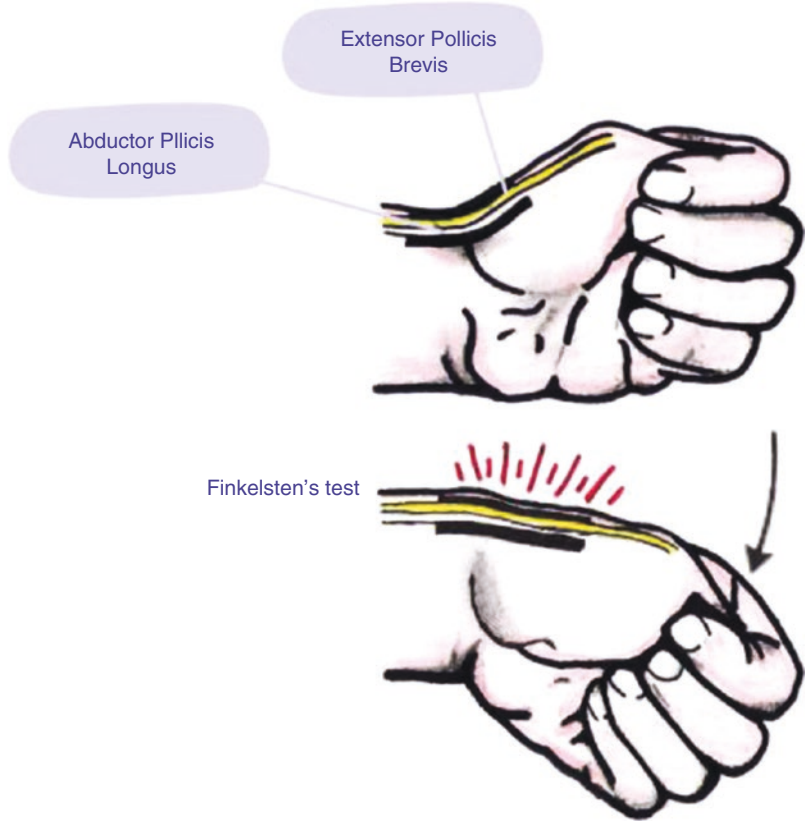


Fig. 2.6 Finkelstein's test

2.5.2 The Elbow Joint

2.5.2.1 First Step: The Anatomy (Figs. 2.7 and 2.8)

The elbow joint is composed of three bones, which articulate together to form three joints, three ligaments, and muscles. The bones that form the joints are the distal part of the humerus, the proximal part of the radius, and the ulna laterally and medially. They articulate together to form three joints, the humeroulnar joint, the radiohumeral joint, and the proximal radioulnar joint. These joints are held together through a network of ligaments; the major three ligaments are the medial collateral ligament, the lateral collateral ligament, and the annular ligament. What makes the elbow flex, extend, supinate, and pronate are the muscles of the elbow joint, such as the biceps muscles and its tendon, the triceps muscles, the brachioradialis, the flexor forearm muscles attached to medial epicondyle, and the extensor forearm muscles attached to lateral epicondyle. Branches from median, ulnar, musculocutaneous, and radial nerves supply this joint.

Approach to Elbow Pain

The approach to any patient presents with elbow pain should include:

- History.
- Physical examination.
- Differential diagnosis.

In the history you should determine the location of the pain by simply asking the patient to point to the tender spot in his elbow. Lateral elbow pain is the most common site for clinical presentation. Other sites are medical and posterior elbow pains. After determining the site, then a simple standard approach should be followed including the onset of the pain, its duration, severity, radiation, aggravating and reliving factors, and history of trauma. The occupation of the patient as well as detailed history of sports activities is essential to obtain.

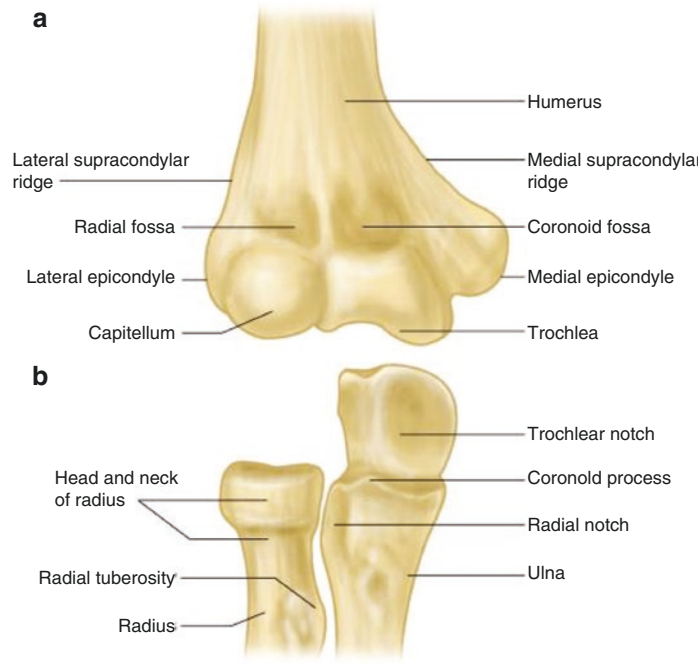


Fig. 2.7 Elbow Joint anatomy: bones

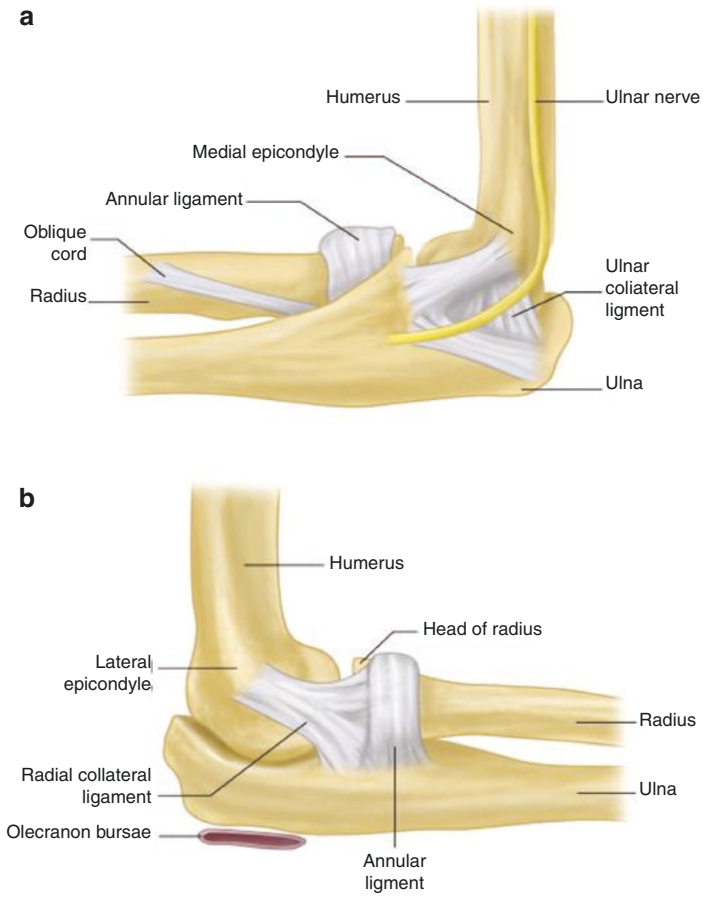


Fig. 2.8 Elbow Joint anatomy: nerves and ligaments

Box 2.2 Differential Diagnosis of Elbow Pain

Lateral elbow pain
Common: 1. Lateral epicondylitis 2. Referred pain (cervical, upper thoracic spine)
Less common: 1. Synovitis 2. Radiohumeral bursitis 3. Radial tunnel syndrome (posterior interosseous nerve entrapment)
Not to be missed: 1. Osteochondritis dissecans.
Medial elbow pain
Common: 1. Medial epicondylitis 2. Medial collateral ligament sprain
Less common: 1. Ulnar neuritis 2. In children: Avulsion fracture of the medial epicondyle
Not to be missed: 1. Referred pain
Posterior elbow pain
1. Olecranon bursitis 2. Triceps tendinopathy 3. Posterior impingement

Repetitive minor trauma from overuse might precipitate epicondylitis with micro tears affecting the common tendon insertion. You may ask also about functional limitation, swelling, and/or instability of the joint. A swollen elbow should lose its ability to be fully extended. History of shoulder and/or neck pain should be obtained as pain in the elbow may be simply a referred one from these sites.

Differential Diagnosis

Depends on the location of pain (Box 2.2).

2.5.2.2 Second Step: The Approach

It is always:

- Inspection.
- Screening exam.
- Palpation.
- Range of motion.
- Special tests.

Inspection

Examine both elbows for asymmetry

Expose the upper arm completely and examine:

- Skin: rashes, abrasions, erythema, redness, scars, subcutaneous nodule, subcutaneous psoriasis.
- Muscle: wasting, atrophy.
- Bones and joints:
  - Swelling: localize over olecranon bursae, e.g., olecranon bursitis or diffuse particularly in area between olecranon process and lateral or medial epicondyle, e.g., elbow arthritis.
  - Deformity: assess the carrying angle (Fig. 2.9):

Ask patient to extend arm in anatomical position (palm facing anteriorly), the longitudinal axes of upper arm and forearm from a lateral (valgus) angle at elbow joint known as the carrying angle (5°in male, 10°–15° in female).

Screening Exam

- The aim is to screen for gross pathology.
- It is basically active ROM testing (Fig. 2.10).
- A quick way to evaluate this is to ask patient to comb the hair and watch any abnormal moment.
- Ask patient to do:
  - Extension.
  - Flexion.
  - Supination.
  - Pronation.

Palpation

Should include palpation of:

- Skin and soft tissue: muscles, ligaments, tendons, and epitrochlear lymph nodes. This lymph node is located just 1 cm above medical epicondyle in the antecubital fossa and then 1 cm distally on the shaft of the ulna. It is hard to feel in obese patients.
- Bony landmarks that should be palpated:
  - Medial epicondyle: any tenderness suggestive of medical epicondylitis.
  - Medial epicondylar ridge: any tenderness suggestive of elbow joint arthritis?

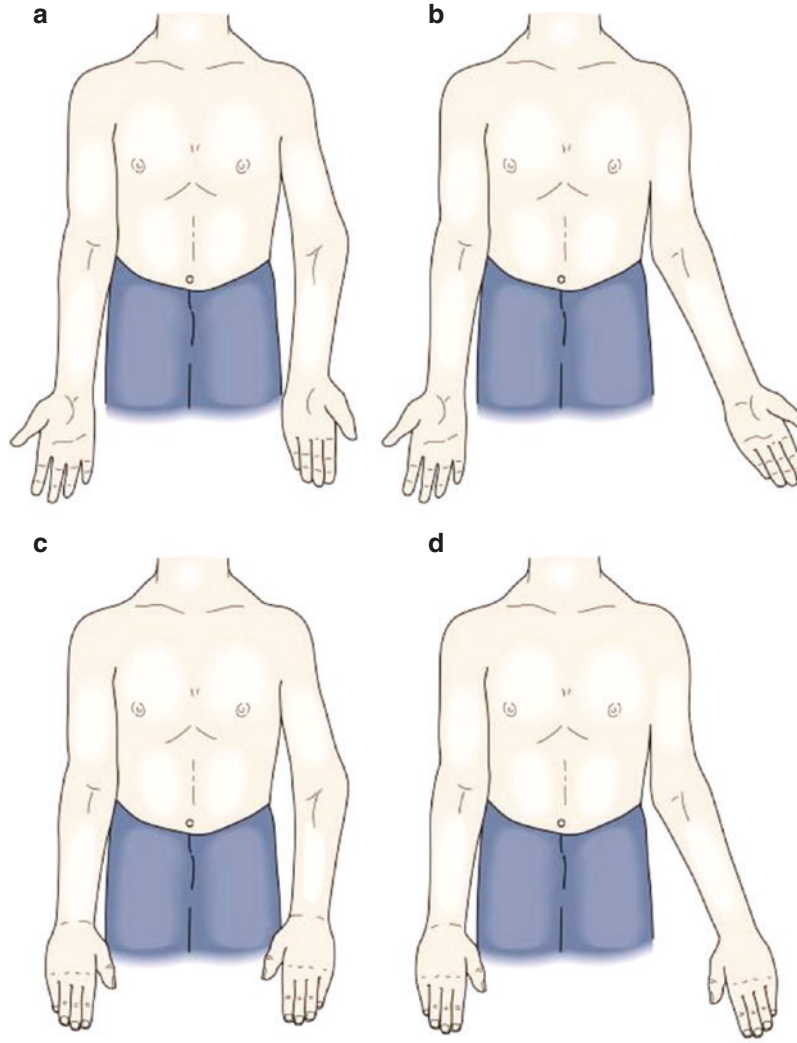


Fig. 2.9 Abnormality in carrying angle: (**b**, **d**) Cubitus valgus. (**a**, **c**) Cubitus varus (gunstock deformity). Effect of swelling: it holds the joint in partial flexion [4]

  - Lateral epicondyle: any tenderness suggestive of lateral epicondylitis?
  - Lateral epicondylar ridge: any tenderness.
  - Olecranon process: any tenderness suggestive of olecranon bursitis?
  - Superficial surface of the ulna (as far distal as the wrist).
  - Radial head.
- Elbow joint line: palpate for tenderness, effusion, and/or nodules.

Ulnar nerve: runs in capital groove behind the medial epicondyle.

Start by palpating the posterior aspect: the three palpation landmarks (the medial epicondyle, the lateral epicondyle, and the apex of the olecranon) form an equilateral triangle when the elbow is flexed 90° and a straight line when the elbow is in extension. The points between the olecranon process while the elbow is in 90° of flexion and the medical or lateral epicondyle represent the joint line of the elbow joint (Fig. 2.11). If there is tenderness elicited while palpating these points, it indicates elbow joint arthritis. Otherwise, effusion may be elicited by palpation.

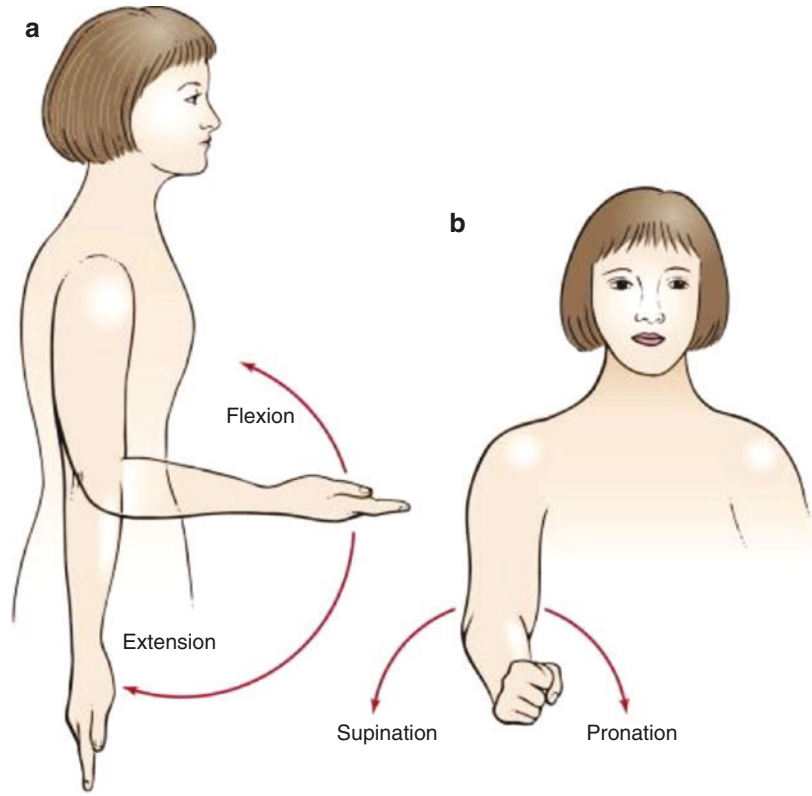


Fig. 2.10 Active range of motion of the elbow joint

Range of Motion

- You have done active ROM in your screening exam.
- Place one of your examining hands just above the elbow joint holding the distal end of the arm. The other hand should be holding the distal end of the forearm just few centimeters above the wrist joint. Examine passive range of motion for the following actions:
  - Flexion: bend the patient's elbow slowly by bringing both of your hands together.
  - Extension: move your hands away from each other to extend the patients elbow. Note that some patients particularly females may have hyperextensible joints that may cause few extra-degrees of elbow hyperextension.
  - Supination: with the hand holding the distal forearm, bring the palm of the patient to let it face upward.
  - Pronation: now let the palm face downward.

Presence of tenderness, limitation, stiffness, and/or end of range stiffness may indicate presence of arthritis.

Special Tests

Golfer's Elbow Test

This is to test for medial epicondylitis.

Ask the patient to have their elbow and fingers flexed. Palpate the medial epicondyle with one hand, and grasp the patient's wrist with the other hand, and then ask the patient to flex the elbow and wrist against resistance (Fig. 2.12). A positive test would be a complaint of pain or discomfort along the medial aspect of the elbow in the region of the medial epicondyle.

Tennis Elbow Test

This is to test for lateral epicondylitis.

Ask the patient to have their elbow and fingers extended. Palpate the lateral epicondyle with one hand, and grasp the patient's wrist with the other hand, and then ask the patient to

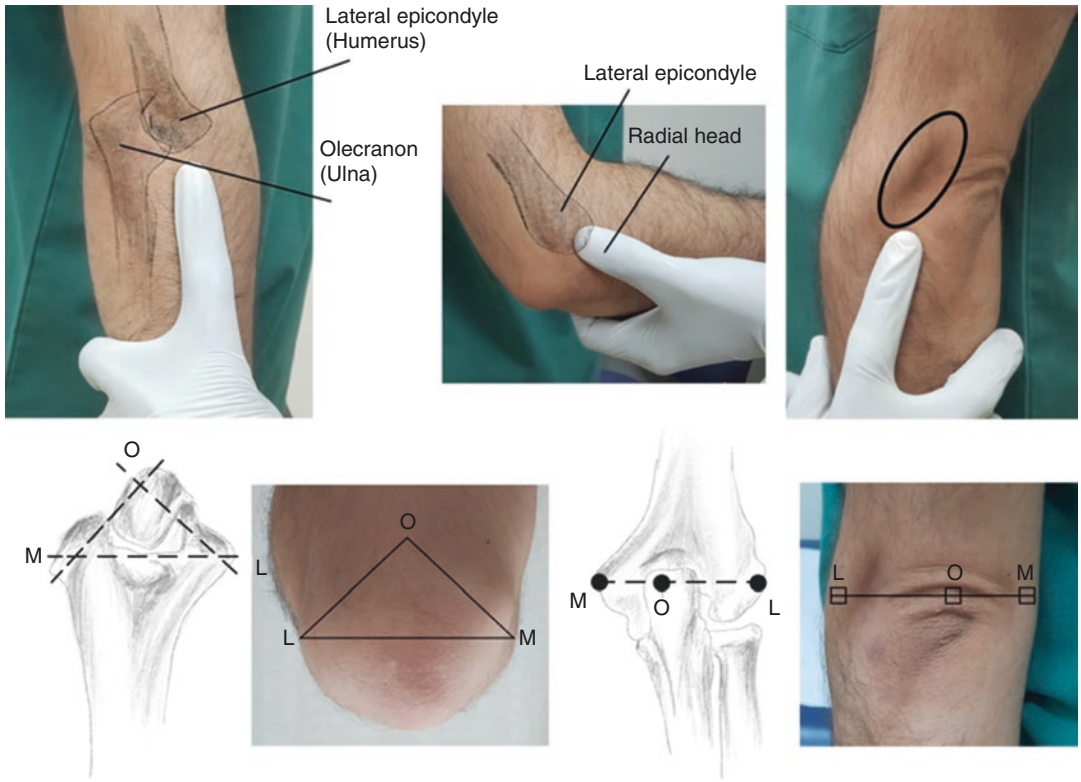


Fig. 2.11 Some anatomical landmarks in the elbow joint. O: olecranon process, M: medial epicondyle, L: lateral epicondyle

extend the elbow and wrist against resistance (Fig. 2.13). A positive test would be a complaint of pain or discomfort along the lateral aspect of the elbow in the region of the lateral epicondyle.

Elbow Flexion Test (Ulnar Nerve)

This test is to evaluate for cubital tunnel syndrome (Fig. 2.14).

Ask the patient to hold their elbows fully flexed for 3 min with their wrists in neutral position and their shoulders adducted at their sides. The test is considered to be positive if paresthesias were elicited within the ulnar nerve distribution of the hand.

2.5.3 The Shoulder Joint

2.5.3.1 First Step: The Anatomy (Fig. 2.15)

The shoulder consists of three bones, four articular surfaces, muscles, and ligaments. The bones include clavicle, proximal humerus, and scapula. The articular surfaces include sternoclavicular joint, acromioclavicular joint, gleno-

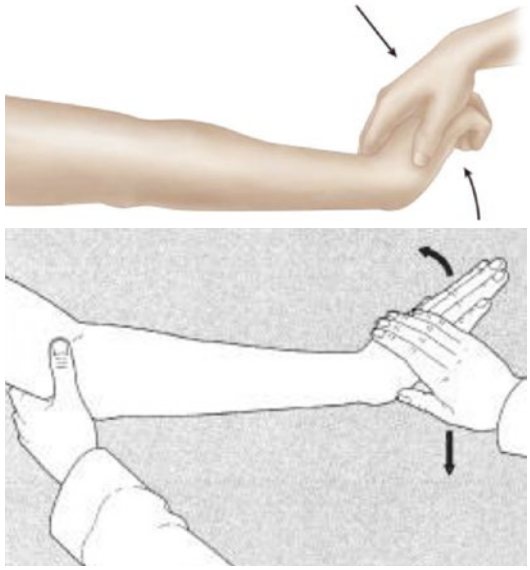


Fig. 2.12 A special test for medial epicondylitis

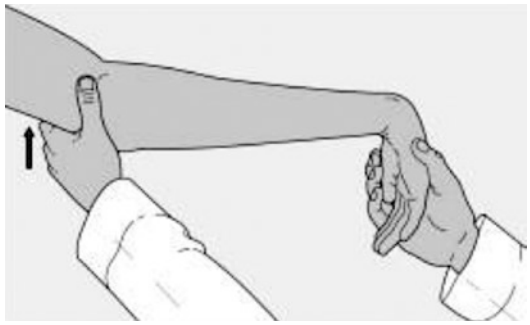


Fig. 2.13 A special test for lateral epicondylitis: see text

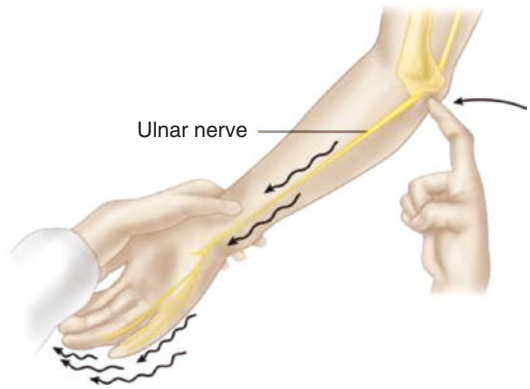


Fig. 2.14 Elbow flexion test

humeral joint, and scapulothoracic articulation. The muscles of shoulder are rotator cuff which includes supraspinatus, infraspinatus, subscapularis, and teres minor. The subscapularis muscle rotates the humerus internally, while the infraspinatus and teres minor rotate the humerus externally. Abduction of the humerus is accomplished by supraspinatus along with deltoid muscle.

For the ligaments of the shoulder, they are the glenohumeral ligaments which are superior, middle, and inferior glenohumeral ligaments.

Approach to Shoulder Pain

Shoulder pain represents either intrinsic or extrinsic pathologies. Intrinsic pathologies account for 85% of the cases and include traumatic, acute, and chronic causes. While extrinsic pathologies account only for 15% of the cases which represent referred pain that can be of cardiac, respiratory, gastric, or diaphragmatic in origin. The approach to patients present with shoulder pain should always start with:

- History.
- Physical examination.
- Differential diagnosis.

Start analysis of the shoulder pain by first determining the site of the pain. To assure accurate workup you may ask the patient to point one finger to the site of the pain by one finger. Shoulder pain can be classified into three categories according to the site: anterior, lateral, or posterior (Table 2.2).

Lateral shoulder pain is the most common, and it is classical for rotator cuff tendinitis. Anterior shoulder pain is classical for glenohumeral arthritis. Posterior shoulder pain, which is the least common, usually represents referred pain.

Following this step you need to cover other aspects of pain history to help you narrow the differential diagnosis according to the anatomical location and other important pieces of information you are going to collect from the patient. This should include the duration, nature, aggravating factors (with lifting, reaching or pushing) and

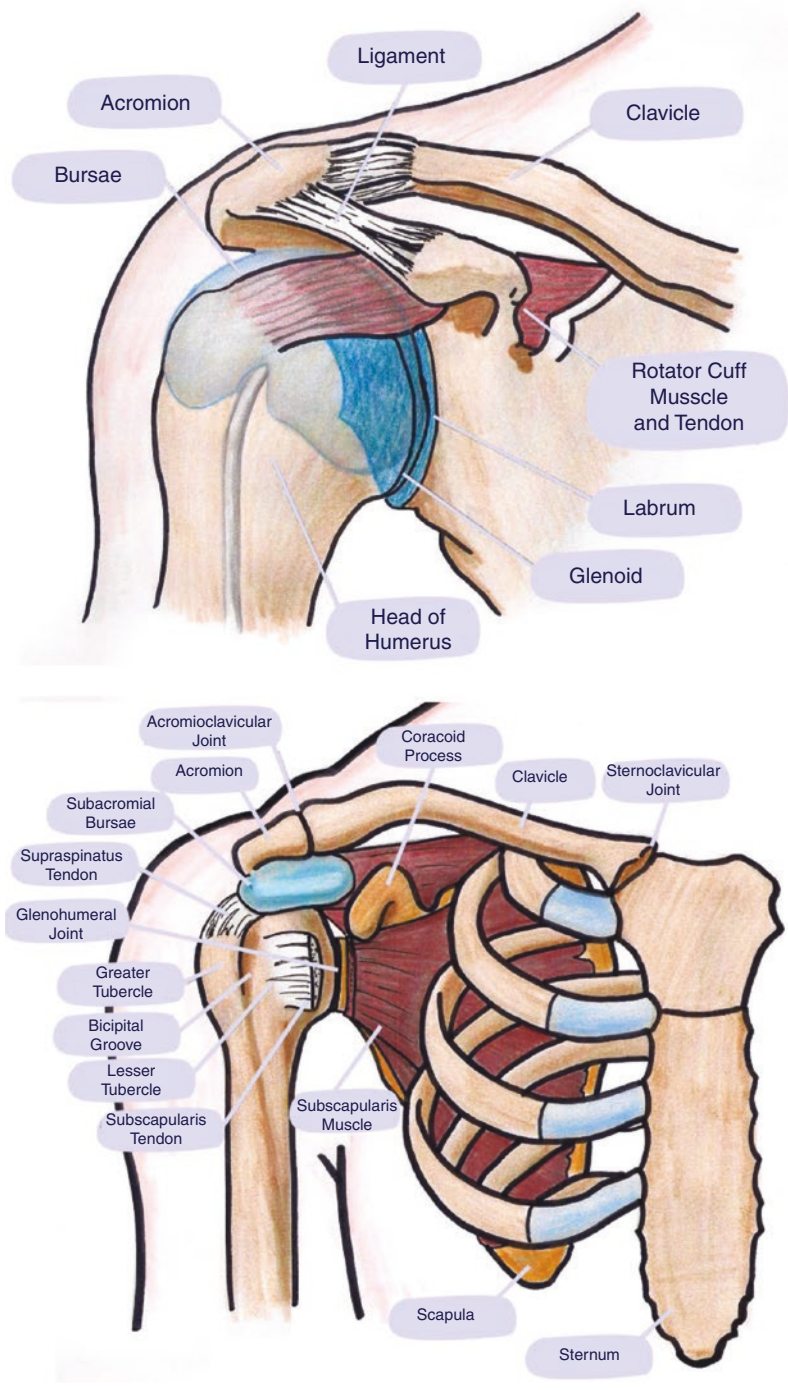


Fig. 2.15 Anatomy of the shoulder joint

relieving factors, radiation (shoulder pain that radiates past elbow can be due to cervical pathology), history of trauma, and sports activities. Past medical history: diabetic and patients with thyroid diseases are at risk of developing adhesive capsulitis.

Table 2.2 Differential diagnosis of shoulder pain

Lateral shoulder pain	Anterior shoulder pain	Posterior shoulder pain
Rotator cuff tendinitis. Adhesive capsulitis	Adhesive capsulitis Acromioclavicular pathologies Glenohumeral joint arthritis Biceps tendinitis Sternoclavicular injuries	– Rotator cuff tendinitis involving the external rotators – Referred pain • Diaphragm • Gall bladder • Perforated duodenal ulcer • Heart • Spleen • Apex of lungs

2.5.3.2 Second Step: The Approach

It is always:
- Inspection
- Screening exam
- Palpation
- Range of motion
- Special tests

Remember:
- Always inspect anteriorly, laterally, and posteriorly

Inspection
- Skin: redness, scars, rashes.
- Muscles: wasting, atrophy of deltoid (squaring sign).
- Bones and joints: swelling particularly anteriorly obscuring the coracoid process area; this is in case of glenohumeral joint effusion, deformities (acromioclavicular (AC) joint, clavicle), scapula elevation (back), and asymmetry posteriorly (look at back exam for asymmetry).

Screening Exam
The aim is to screen for gross pathology.

- It is basically the active ROM testing (Fig. 2.16).
- Ask the patient to abduct (ABD) shoulders to 90°, then supinate forearms (externally rotating (ER) the shoulders), continue abduction to 180°, do painful arc by bringing both shoulders to zero position again (if the patient develops pain, it indicates positive painful arc test suggestive rotator cuff tendinitis (RCT)), then ask patient to bring his hands behind the neck (ER + ABD), and then move hands backward over the back internal rotation (IR) and adduction (ADD) (IR + ADD). Then try bringing your thumbs on your back as high as possible (Apley's scratch; Fig. 2.17), and finish with forward flexion and extension.
- Shoulder elevation, protraction, retraction, and circumduction.

Palpation
- Remember: shoulder (or glenohumeral joint) effusion is usually detected anteriorly (this is not a common finding).
- Palpate for bony and soft tissue structures: start with sternoclavicular joint (SC joint), then move to feel clavicle, AC joint, acromion, subacromial bursae (a lateral structure just below the acromion) (tenderness indicates RCT, greater trochanter (GT) (rotator cuff inserts here, you are feeling the capsular attachment of glenohumeral joint (GH joint) medially feel bicipital groove (long head of biceps), coracoid process where the short head of biceps inserts (it is painful!)
- Palpate for crepitus by simply feeling over the joints while moving the shoulder.

Range of Motion
- The aim is to differentiate between intra-articular and extra-articular pathology.
- In intra-articular pathology (arthritis), active and passive ROM are limited due to inflammation of the synovial membrane that moves during both active and passive ranges. There is usually effusion that might limit the ROM whether it was passive or active. Even if here was no effusion, the inflammation of the synovial membrane itself would limit the ROM passively and actively because of the pain.

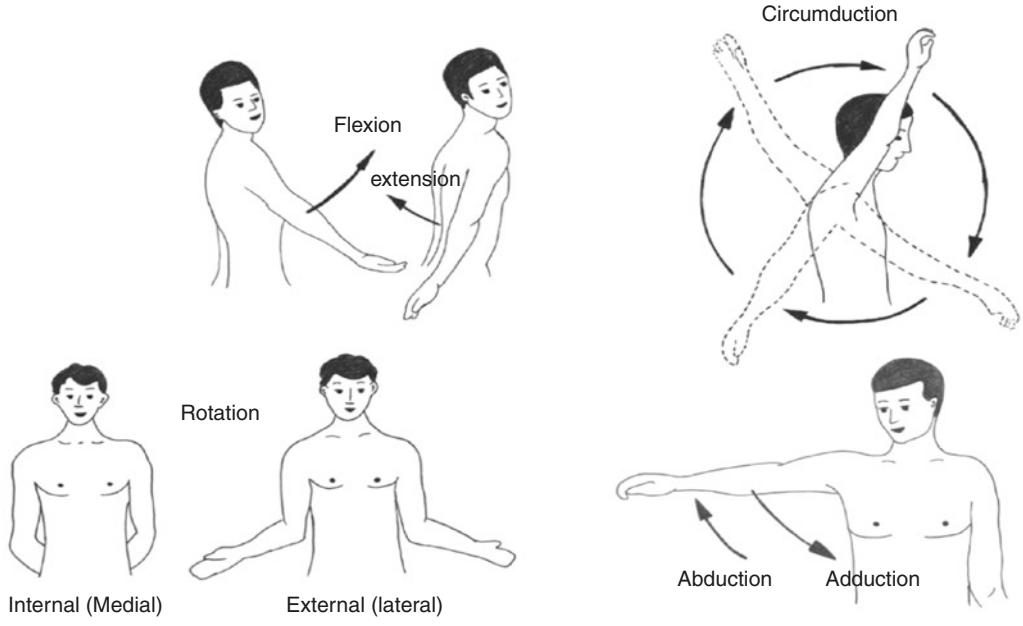


Fig. 2.16 Range of motion testing for shoulder joint

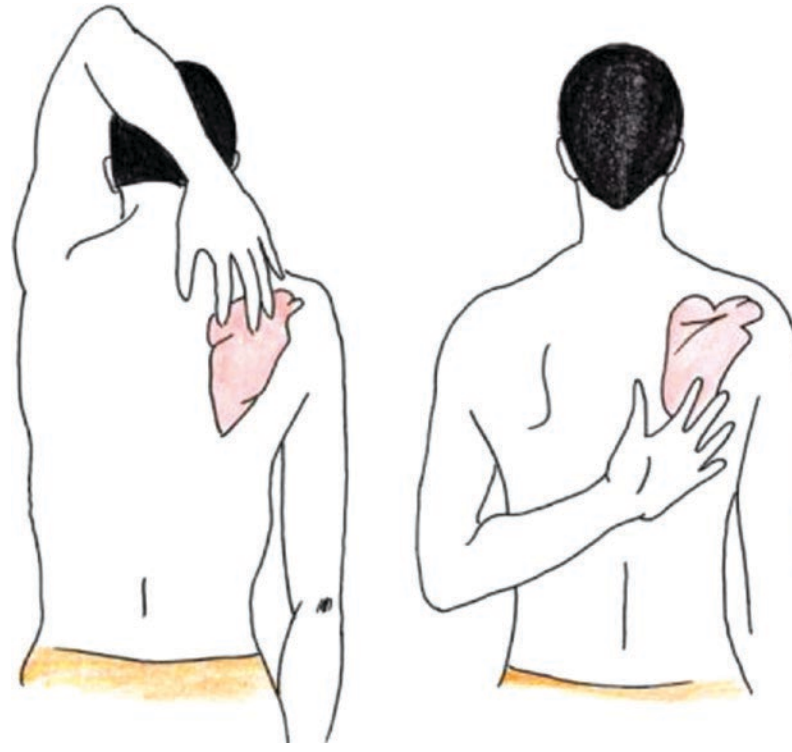


Fig. 2.17 Apley's scratch test

- In extra-articular pathology (periarthritis), the active range is limited only. Here, there is synovial membrane inflammation to limit any kind of movement in the joint. Instead, there is pathology in structures around the joint like in RCT or subacromial (subdeltoid) bursitis. Here the active ROM will be limited but the passive is not.
- You need to test two components to determine with accuracy the cause of the pain.
- Active ROM was assessed during the screening exam.
- For passive ROM: watch the location of your hands!
- Place your right hand on the right shoulder over AC joint firmly. This is to stabilize the scapula in order to do isolated GH joint movement without scapular elevation. The other hand should hold the proximal forearm.
- Do shoulder abduction up to 90°. This is a pure GH joint movement. Normally, there should be zero scapular elevation. Then do ER and IR, while the shoulder is abducted at 90°. Then adduct the shoulder back to zero position where the forearm and the elbow are just beside the body. Then do extension. Then remove your right hand on the right shoulder and do forward flexion.
- You can assess ER + IR while at zero abduction with arms on the sides.
- Repeat the same approach for the left shoulder with your left hand stabilizes the scapula over the left AC joint.

Principle
To assess tendons you need to stretch the tendon (impingement) and/or stress it!

Special Tests

Several MSK examination techniques will be described to assess for specific diseases affecting the shoulder joint. The emphasis should be as stated earlier on the combined evaluation for any patient with MSK complaints of the history and MSK examination findings in order to reach to a correct diagnosis. The diagnostic accuracy for majority of these tests is limited [5]. However, combining careful history taking skills with competent MSK examination findings should help improve the diagnostic accuracy at least to narrow your differential diagnosis rather than reaching an accurate diagnosis.

For RCT

- Painful arc (as described above): from 120° to 60°.
- Isometric resisted abduction while the arm is in zero degree. If there is pain developing, this could be due supraspinatus tendinitis.
- *Empty can sign:*
  (Shoulder abducted 90° + forward flexion 30° away from the body on horizontal line + thumb down (IR)—supraspinatus) (Fig. 2.18).

Infraspinatus and Teres Minor

- Isometric resisted ER (elbow flexed 90° with the arm at the side).
- In the same position, you can assess isometric resisted IR for subscapularis tendinitis (Fig. 2.19).

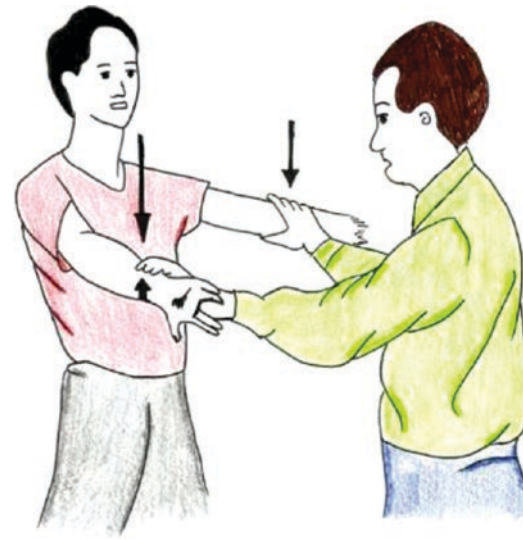


Fig. 2.18 Supraspinatus examination ("Empty can" test)

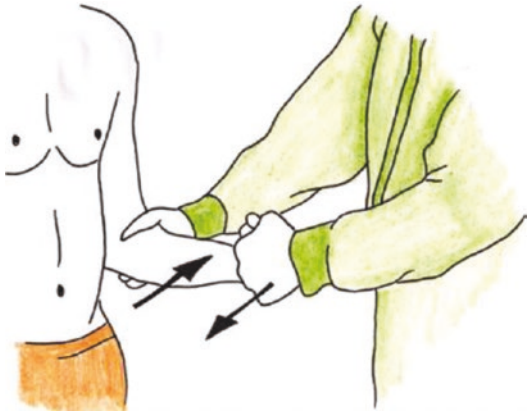


Fig. 2.19 Infraspinatus and teres minor examination

Left off Test

This test is performed with isometric resisted IR while the patient adducting his shoulder and internally rotating it. Presence of pain while resistance may indicate subscapularis tendinitis (Fig. 2.20).

Hawkins Impingement Sign

Shoulder horizontal adduction in 90° of flexion then adduct shoulder more with passive IR; this should reproduce symptoms (Fig. 2.21).

Drop Arm Test (Fig. 2.22)

This is to test for complete supraspinatus tear. Sudden push to an abducted shoulder may result in arm drop if there is complete supraspinatus tear.

For AC joint:

- Painful arc (as described above): when it produces pain from 180 to 120. It is usually due to AC joint pathology rather than RCT.
- There is another test called cross-body adduction test (Fig. 2.23). The patient simply performs horizontal adduction with the shoulder in flexion. This might reproduce pain due AC joint pathology.
- For bicipital tendinitis:
  - Speed's test: resisted shoulder flexion at 90° with elbow extended and forearm supinated.
  - Yergason's sign (Fig. 2.24): resisted supination of the forearm with elbow 90° flexion. It

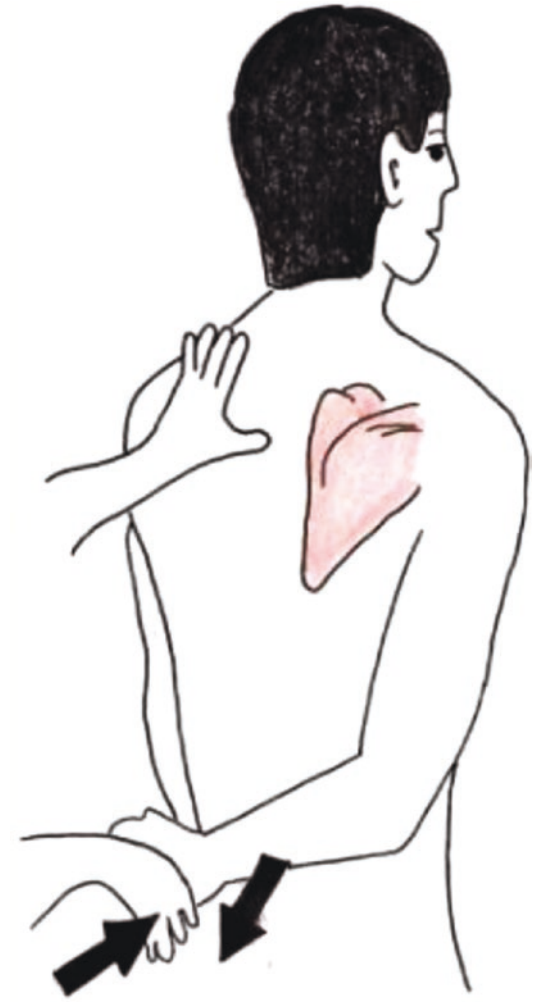


Fig. 2.20 Left off test

Fig. 2.21 Hawkins' test for subacromial impingement or rotator cuff tendinitis

has to be noted that rupture of the long head of biceps is rarely associated with significant weakness in elbow flexion. This is probably due to the fact that 85% of elbow flexion is from brachioradialis and short head of biceps rather than from long head of biceps.

- For glenohumeral joint instability:
- Anterior apprehension test (Fig. 2.25) (supine, 90 ABD and 90 ER, apply gentle forward pressure to posterior aspect of humeral head).

Fig. 2.22 Arm drop test

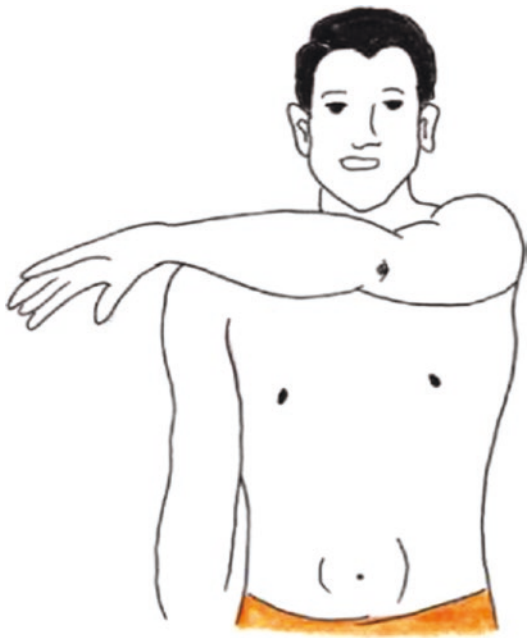


Fig. 2.23 Cross-arm test for acromioclavicular joint disorder

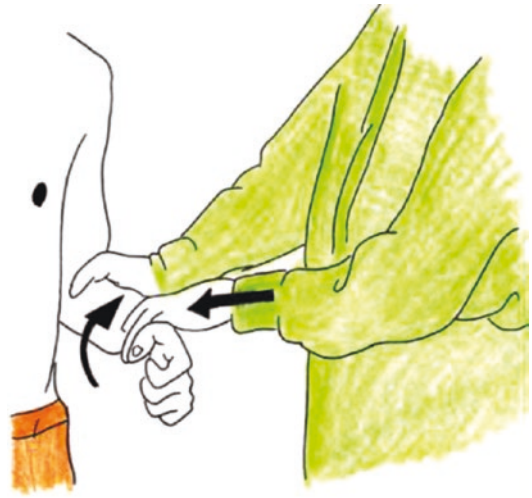


Fig. 2.24 Yergason test for biceps tendon instability or tendinitis

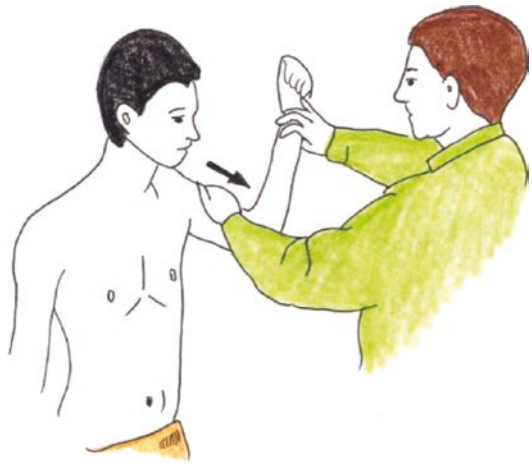


Fig. 2.25 Apprehension test for anterior instability

2.6 Musculoskeletal Examination of the Lower Limb Joints

The joints included in lower limb are ankle, knee, and hip. As in the upper limb section, there is a brief review of the important anatomical landmarks that should be mastered because it has clinical correlations. This will be referred to as the first step. Then an approach to pain originating from this joint will be discussed focusing on anatomical differential diagnosis. The second

step will be to follow the stated approach in MSK examination with descriptions whenever it is necessary. Illustrations have been used sometimes as a self-explanatory toll.

2.6.1 Ankle Joint

2.6.1.1 First Step: The Anatomy

- Bones of the Foot (Fig. 2.26)
- Ankle and foot consist of 26 bones, 33 ligaments, and more than 100 muscles and tendons. The main structures are:
- **Bones:** tibia and fibula and tarsal bones, which are calcaneus, talus, navicular, and cuboid, and three cuneiforms bones, five metatarsals, 14 Phalanges (proximal, intermediate and distal), and two sesamoid bones.
- **Joints:** ankle joint, subtalar joint, metatarsophalangeal joints (MTP), and interphalangeal joints.
- **Ligaments**: anterior and posterior tibiofibular ligament, anterior and posterior, talofibular ligament (ATFL and PTFL) and deltoid ligament (Figs. 2.27 and 2.28).
- **Muscles and tendons:** anterior tibialis, peroneal, extensors, and flexors muscles and tendons (Fig. 2.29).

Approach to Ankle Pain

The approach of any patient presents with ankle pain should include:

- History.
- Physical examination.
- Differential diagnosis.

The first step in any history of a joint pain is determining the site of the pain. This simply can be achieved by asking the patient to point out by one finger the site of the pain. The following steps should focus on comprehensive approach to pain analysis including duration, progression, aggravating and relieving factors, and history of trauma. Here, it is important to ask about and examine the patient's shoes. RA classically affects MTPs and ankles. The first MTP joint can be affected classically by gouty arthritis. History of acute first MTP joint pain with swell-

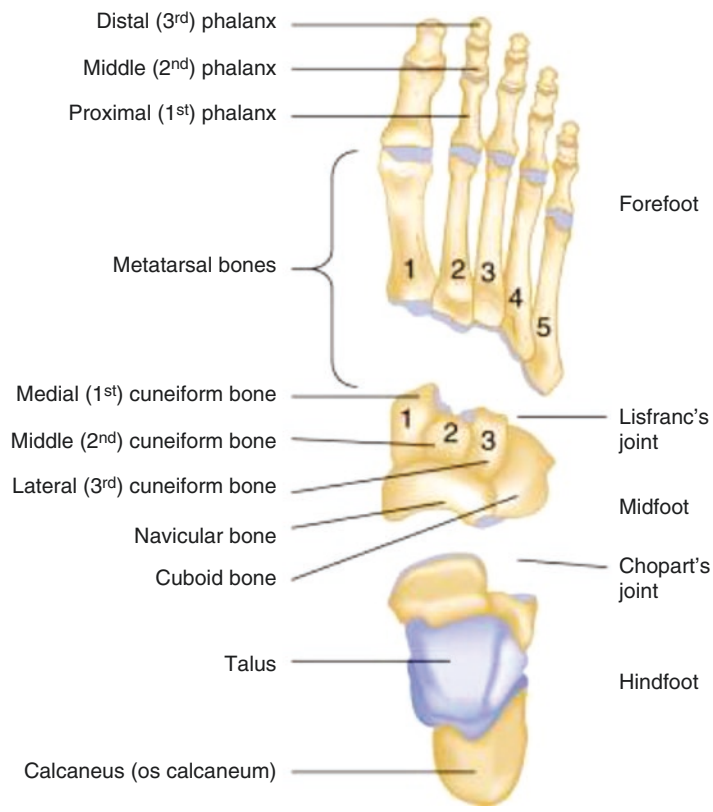


Fig. 2.26 Bones of the foot

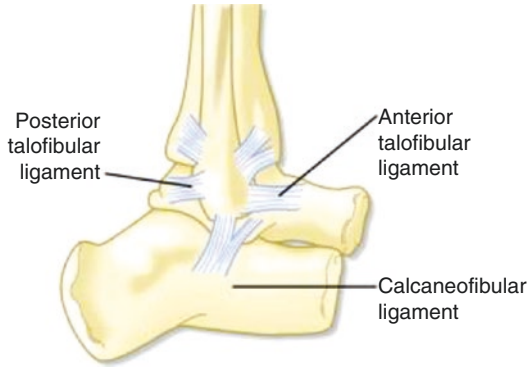


Fig. 2.27 Bones and ligaments of the ankle

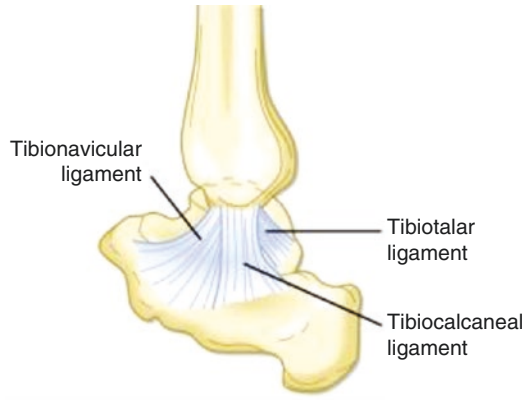


Fig. 2.28 Bones and ligaments of the ankle

ing and redness is diagnostic for gout. Acute gout might mimic cellulitis as it may cause soft tissue swelling and redness as well. The first MTP joint can be involved chronically in osteoarthritis. The interphalangeal joints can be involved in psoriatic arthritis (PsA) that might give identical presentation to RA. In addition, PsA might cause diffuse swellings in one or more than one toe called dactylitis. It may cause Achilles tendinitis and/or plantar fasciitis. Subtalar joint is classically affected in osteoarthritis. History of trauma-related pain should direct the attention immediately to soft tissue problems (periarthritis rather than arthritis). Table 2.3 lists the possible differential diagnosis according to the site of the ankle and foot joints pain.

2.6.1.2 Second Step: The Approach

It is always:
- Inspection
- Screening exam
- Palpation
- Range of motion
- Special tests

Inspection

Expose both ankles and feet and examine for asymmetry. Then follow the standard approach in inspection as it was explained at the introduction of this chapter.

Remember: Always examine anteriorly, medially, laterally, and posteriorly.

- Nail: evidence of psoriasis.
- Skin: scar, redness, rashes, wart, ulcers, blister, calluses, corn, erythema, ecchymosis, change in color.
- Muscle and tendons: wasting, atrophy, and swelling posteriorly for Achilles tendinitis.
- Bone and joint: swelling, deformity (hammer toe, clawing or crowding of the toes, hallux valgus of forefoot), arch of the foot.

Screening Exam

- The aim is to screen for gross pathology.
- It is basically the gait and active ROM testing. For any lower limb joint examined, gait examination is a mandatory step.
- Ask the patient to walk in a straight line and then on toes and on heels.
- Ask the patient to run a short distance (if it possible, this is of great value in assessing periarthritis).
- Ask the patient to hop five times on each foot (if it possible) and then squat and stand from squatting position.
- This quick screening tool actually has assessed the neuromuscular integrity for the lower limb. Walking on the toes, for example, assessed hyperextension of MTPs. If there is

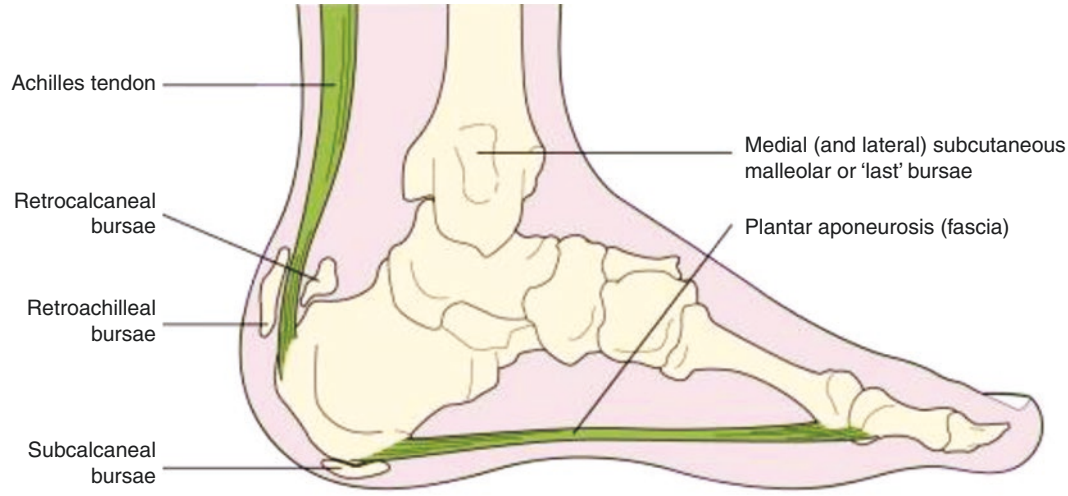


Fig. 2.29 Achilles tendon and plantar fascia

Table 2.3 Differential diagnosis according to the site of the ankle and foot joints pain

Anterior	– Rheumatoid arthritis – Gout arthritis – Osteoarthritis – Tendinitis
Lateral	– Peroneal tendinitis, rupture, or subluxation caused usually by rheumatoid arthritis
Medial	– Tarsal tunnel syndrome – Posterior tibial tendinitis
Posterior	– Achilles tendinitis/rupture – Retrocalcaneal bursitis
Planter	Plantar fasciitis

arthritis in these joints, the patient will not be able to perform this. In addition, walking on toes assessed plantar flexion in ankle joints and extension of knees and hips. Squatting and standing from squatting position have assessed, in addition of joints, the strength of proximal muscles. Walking on heels is an excellent screening for plantar fasciitis. The different steps applied in this screening exam assessed as well almost all the nerve roots for the lower limbs.

Palpation

The major aim is to look for evidence of arthritis in the form of warmth, effusion, and joint line tenderness. Tenderness might be felt laterally and/or medially if there is ligamentous pathology:

- Palpate skin and soft tissue (muscles, ligaments, and tendons).
- Determine joint lines and palpate for tenderness:
  - Ankle joint: (tibia, fibula, and talus joint) perform plantar flexion/dorsiflexion to locate joint line or just medial to the strong tendon of tibialis anterior as it passes over the ankle joint to be inserted at the base of first metatarsal bone.
  - Subtalar joint (talocalcaneal joint): perform inversion/eversion or adduction/abduction of the midfoot to locate this joint. Usually, it can be palpated below and anterior to lateral malleolus.
  - MTPs: Press firmly and intermittently with your thumb and index finger over these joints to illicit tenderness. It is much more reached from plantar aspect than the dorsal aspect of the feet.
  - Medially: Palpate the big toe at the site of the first MTP, and move along the first metatarsal to feel the metatarso-cuneiform joint. Palpate the navicular tubercle, the head of the talus, and the medial malleolus.
  - Laterally: Start palpating the fifth metatarsal bone to feel the styloid process, and then reach the cuboid bone to the calcaneus. Palpate for the peroneal tubercle to the lateral malleolus.

- Posteriorly: Feel the Achilles tendon and follow its insertion at the calcaneus for any tenderness. Just lateral and medial to the insertion of the Achilles tendon, feel for retrocalcaneal bursitis on both sides (lateral and medial) of the tendon.
- Inferiorly (plantar aspect): Feel for tenderness at the insertion of plantar fascia under the medial side of the heel.

In assessing dorsiflexion: the knee must be flexed for proper evaluation

Range of Motion (Fig. 2.30)

- You have done active ROM in your screening exam, but you may repeat active ROM now for detailed examination.
- Examination includes passive and active ROM for the following actions: plantarflexion, dorsiflexion, inversion, and eversion of the foot and flexion and extension of the toes, particularly the big toe.
- Hold the distal leg with one hand while the knee in a flexed position. Then hold the feet from central position just between the ankle and the MTP joints. Now, perform slowly full dorsiflexion (20° from neutral position) by bringing the ankle to the leg, and then push the ankle away from the leg for plantarflexion (50° from neutral position). Now, grasp the feet and perform inversion and eversion. In the same position, you may perform midfoot ad duction and abduction as well. Note any limitation of movement, tenderness, stiffness, and/or end range stiffness.

Special Tests

- Squeeze test (Fig. 2.31): This test aims to stress the MTPs looking for tenderness due to arthritis. Simply squeeze the sides of MTP joints at the level of the heads of phalanges.
- Peroneal subluxation test:
- This is to assess the peroneus longus tendon rupture or instability. Ask the patient to sit down and actively dorsiflexes and everts the foot against resistance; and simultaneously palpate the peroneal tendon posterior to the distal fibula. Pain, clicking, or sensation of instability may indicate subluxation of the peroneal tendon. This test is abnormal when 3–5 mm translocation is present compared with the opposite side.
- The anterior drawer test (Fig. 2.32):

  Evaluate stability of the anterior talofibular ligament (ATFL): stabilize the anterior portion of the distal tibia and fibula with your hand, and use your other hand to cup the heel of the patient foot and pull it toward yourself.
- The inversion stress test (Fig. 2.33):
- Evaluate the stability of the lateral ligament complex (the ATFL and the calcaneofibular ligament (CFL)).
  - Stabilize the anterior portion of the distal tibia and fibula with your hand, and use your other hand to cup the heel of the patient foot.
  - The ATFL is evaluated by maximally plantarflexing the ankle and then inverting the rear foot.
  - The CFL is evaluated by maximally dorsiflexing the foot and then inverting the rear foot.
  - The test is considered abnormal when 10°–15° more inversion is present, compared with the opposite side.
- Test for Morton's neuroma:
- Grasp consecutive metatarsal heads and compress them together. If a click, as well as reproduction of the patient's pain, occurs, a Morton's neuroma should be suspected.
- Thompson test (Fig. 2.34):

  Ask the patient to lie in prone position with the foot hanging off the table, and then squeeze the gastrocnemius muscle. If the foot does not plantarflex, rupture of the Achilles tendon must be considered.

2.6.2 Musculoskeletal Examination of the Knee Joint

2.6.2.1 First Step: The Anatomy (Fig. 2.35)

The bones and articulation of knee joints consists of four bones, which are femur, tibia, fibula, and patella. There are three articulations: medial tib-

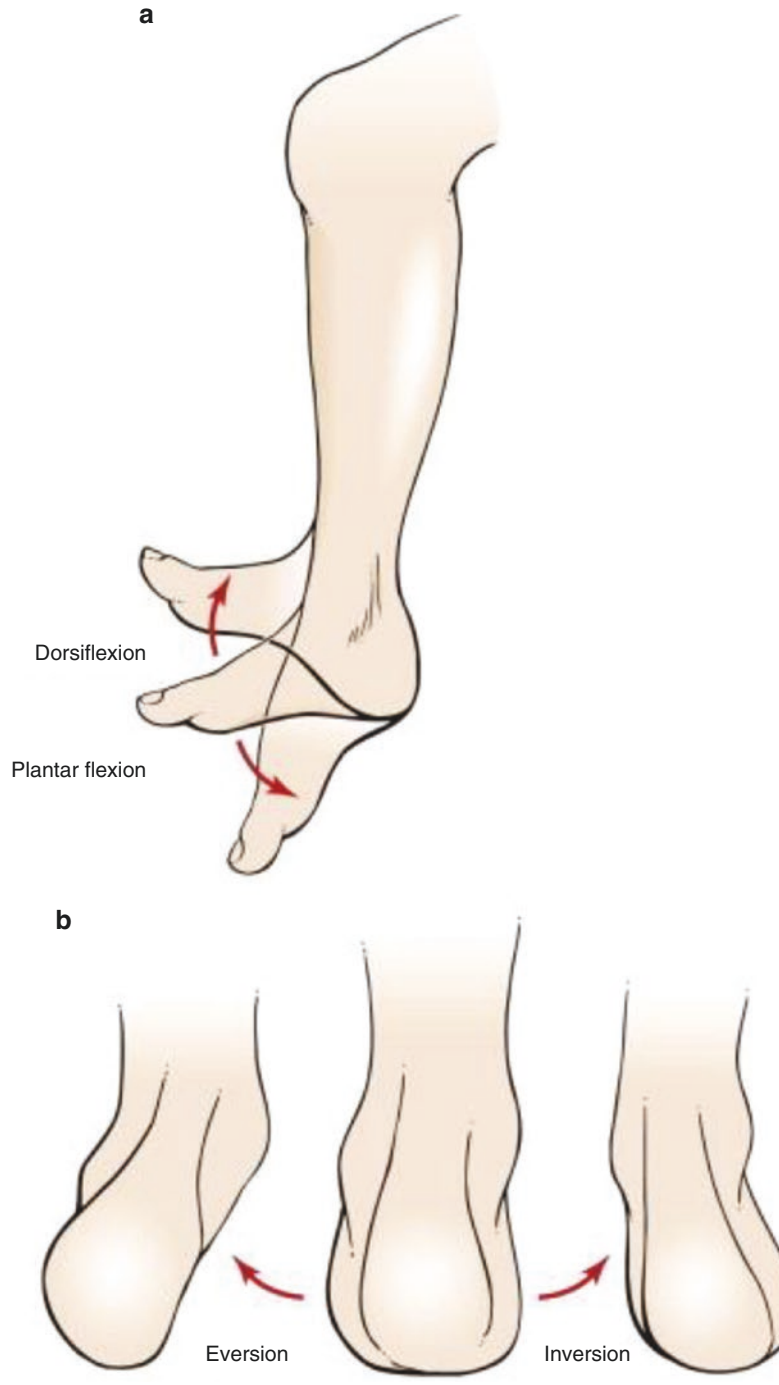


Fig. 2.30 Range of motion of the ankle joint

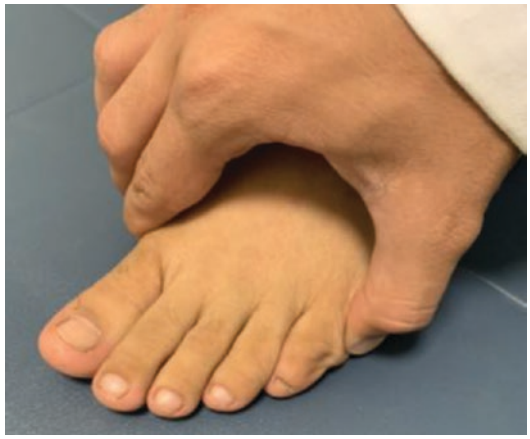


Fig. 2.31 Squeeze test

iofemoral, lateral tibiofemoral, and patellofemoral articulation. The knee joint has many bursae: in the anterior aspect suprapatellar bursae, prepatellar bursae, and superficial and deep patellar bursae and in the medial aspect pes anserine. Cartilage and ligaments of the knee are anterior and posterior cruciate ligaments, medial and lateral collateral and medial and lateral menisci.

Approach to Knee Pain

The approach of any patient presents with knee pain should include:

- History.
- Physical examination.
- Differential diagnosis.

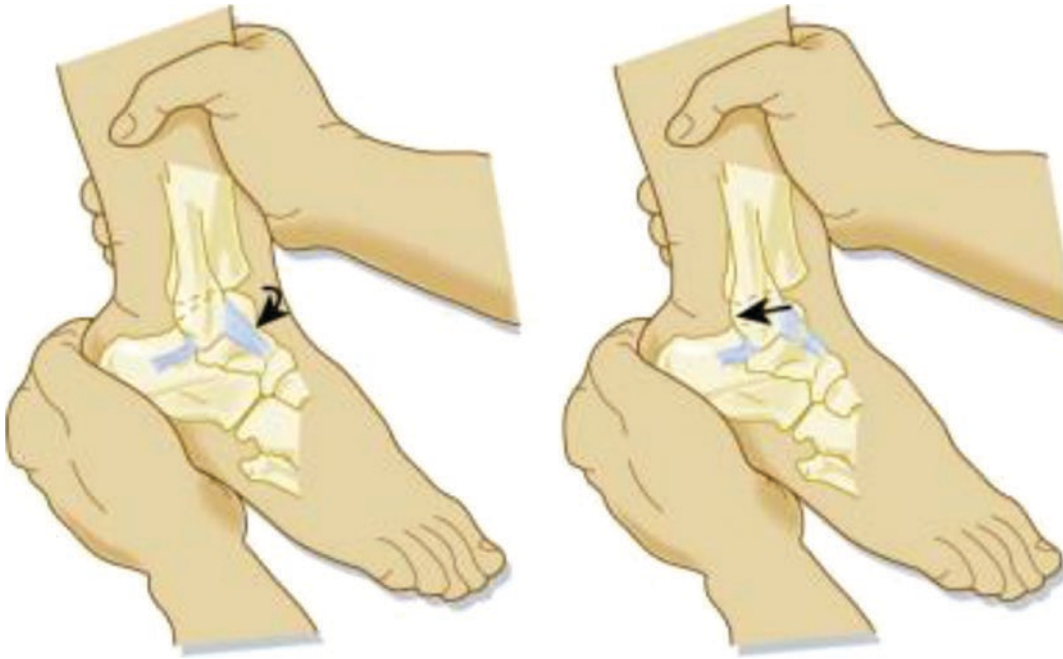


Fig. 2.32 Anterior drawer test

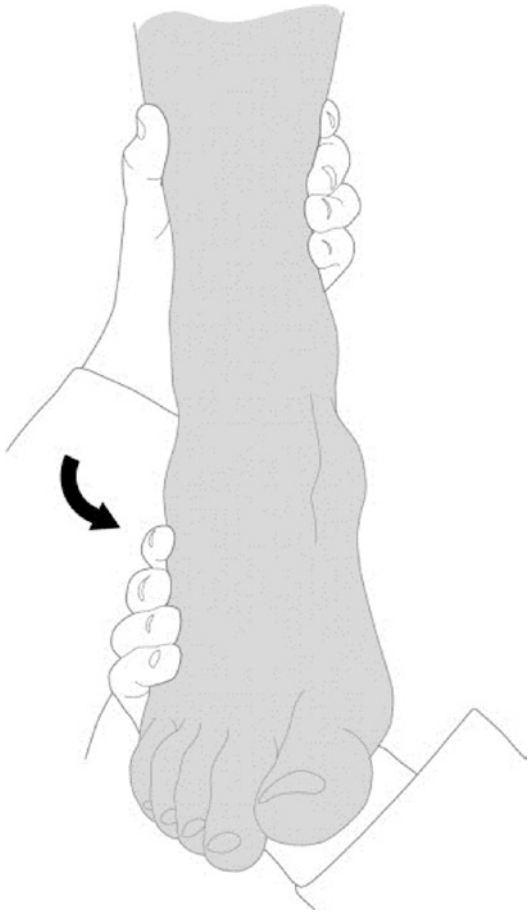


Fig. 2.33 The inversion stress test

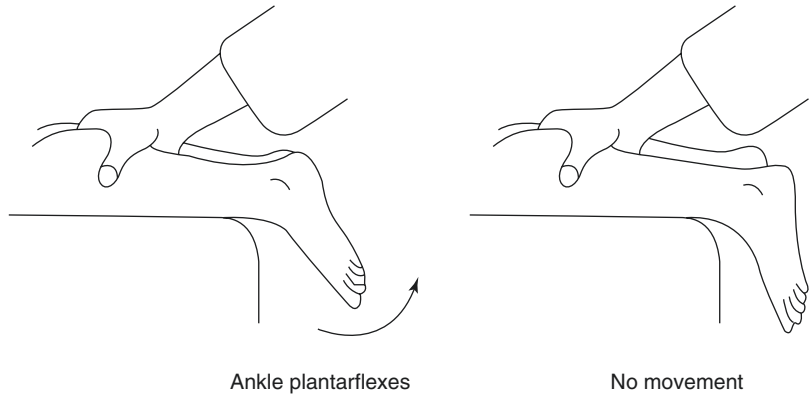
The first step is to determine the site of the pain. This is achieved by asking the patient to point by one finger to the site of the pain. In some condition like anserine bursitis, the location of the pain is totally away from joint line. Determining the site of the pain is extremely an important step for reaching accurate diagnosis. Detailed history including duration, progression, and aggravating and relieving factors should follow. History of trauma should be clearly outlined particularly if it was sports related. There are many soft tissue structures that can be affected with traumatic injuries. The knee is the most common joint involved in septic arthritis. Symptoms suggestive of an infectious process like fever should be obtained as well. The knee as well is a common joint in osteoarthritis and crystal deposition diseases (like pseudogout).

Table 2.4 provides a classification of the knee pain according to the site of the pain and its differential diagnosis.

2.6.2.2 Second Step: The Approach

It is always:
- Inspection
- Screening exam
- Palpation
- Range of motion
- Special tests

Fig. 2.34 Calf squeeze test



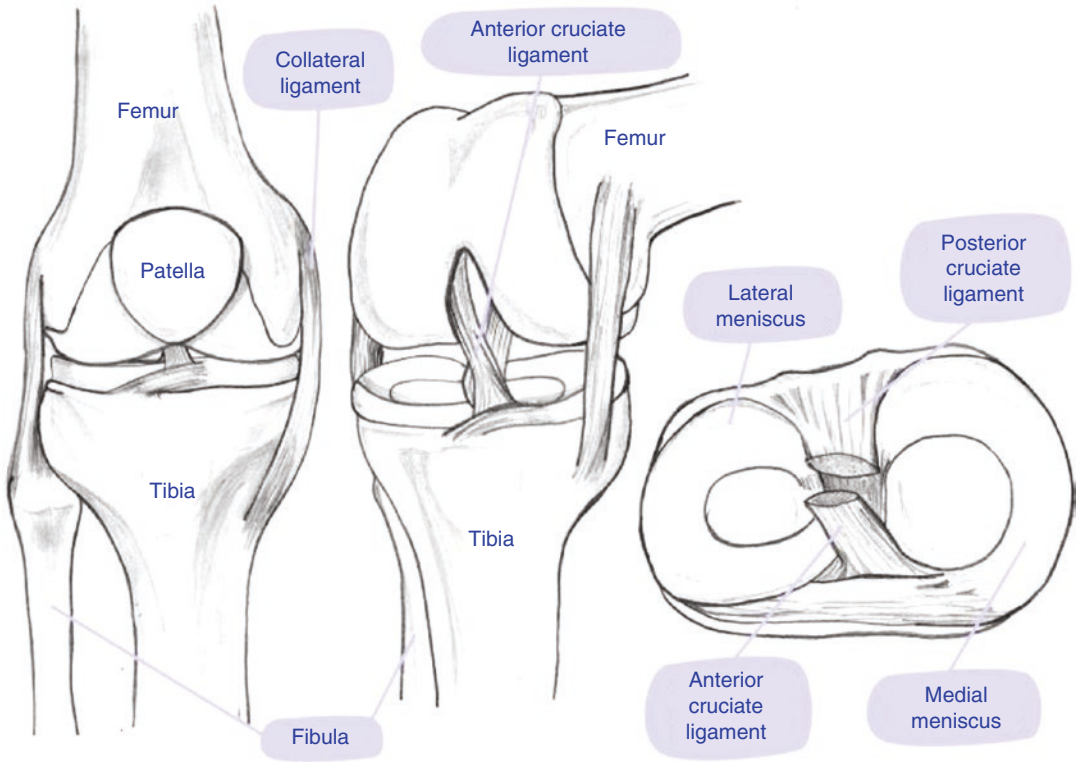


Fig. 2.35 Anatomy of the knee

Table 2.4 A classification of the knee pain according to the site of the pain and its differential diagnosis

	Common	Not to be missed
Anterior	– Arthritis – Osteoarthritis – Prepatellar bursitis – Jumper's knee (patellar tendinitis)	– Ligamentous injury – Tibial apophysitis (Osgood-Schlatter lesion) – Patellofemoral pain syndrome (chondromalacia patellae)
Lateral	– Iliotibial band tendinitis	– Lateral collateral ligament sprain – Lateral meniscal tear
Posterior	– Popliteal cyst (baker's cyst)	– Posterior cruciate ligament injury
Medial	– Pes anserine bursitis	– Medial collateral ligament sprain – Medial meniscal tear

Inspection

- Skin: redness, scars, rashes.
- Muscles: wasting (note medial fibers of quadriceps), atrophy.
- Bones and joints: swelling, deformities – genu varus (common in osteoarthritis of the knee joint) and genu valgus deformities.

Screening Exam

- The aim is to screen for gross pathology.
- It is basically the gait and active ROM testing.
- Ask the patient to walk and comment if the gait is normal or abnormal.
- Ask the patient to walk on toes, heels, and squat and stand up from the squatting position (see details in ankle joint exam above).

Palpation

- The major aim is to look for evidence of arthritis in the form of warmth, effusion, and joint line tenderness.
- Palpate for tenderness over the patella, patellar tendon, suprapatellar bursae, prepatellar bursae (housemaid knees), anserine bursae (medially below joint line, just 2 cm from tibial tuberosity), and tibial tuberosity (where the

patellar tendon inserts, it can be tender in patellar tendinitis).
- Palpate for crepitus, osteophytes, and popliteal cyst.
- The maneuvers used to detect effusion:
  1. Bulge sign:
     - Milk the knee with the palmar or dorsal aspect of your fingers 1–3 times from the tibial side to medial side of the femur. Wait for a few seconds.
     - Now with your fingers, milk the fluid down from the femur side to the tibia laterally. Note the bulge of fluid on the medial side. This method detects mild effusion.
  2. Patellar tap test:
     - Compress the suprapatellar pouch with one hand. With the tips of the fingers of the other hand, give a sharp downward push on the patella. Feel the patella's clunk against the femoral condyles. This method detects moderate effusion.
  3. Balloon sign:
     - Compress the suprapatellar pouch with one hand. Place the thumb and index (or long) finger of the other hand on either side of the patella at the level of the joint line. Now if you press with these fingers, you should feel the fluid pushing away the other hand. This test is positive for large effusion.

Range of Motion

The aim is to differentiate between intra-articular and extra-articular pathology.

- In intra-articular pathology (arthritis), active and passive ranges of motion are limited (see explanation in shoulder joint exam).
- In extra-articular pathology (periarthritis), the active range is limited only.
- You need to test two components: active and passive ROM.
- Ask the patient to bring both heels toward the pelvis as much as possible (flexion), and then ask the patient to put his knees flat on the bed (extension).
- For passive ROM testing, ask the patient to relax. With one hand covering the entire knee anteriorly and the other holding the heel, flex the knee and then extend it. You should comment on tenderness, stiffness, end of range stiffness, and/or limitation of movement.

Special Tests

- The aim is to look for the integrity of menisci and ligaments around the knee.
- For menisci integrity, you can use the McMurray test (Fig. 2.36): hold the knee with one hand, while the patient is in supine position. Bring the knee to full flexion. Now, extend the knee slowly with applying valgus stress from the lateral aspect of the knee you

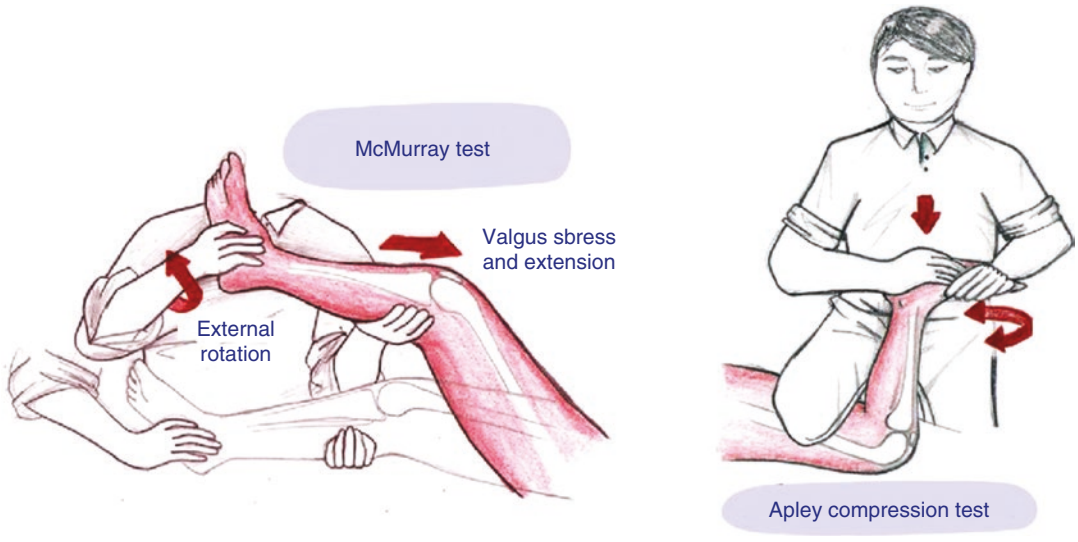


Fig. 2.36 McMurray test and Apley compression test

are holding with your hand, while the other hand is externally rotating the knee from the ankle. The test is considered positive if there is pain and/or popping sound.

- Apley's compression test: here the patient lies in prone position with the knee being examined flexed at 90°. You should stabilize the knee by placing your leg pressing over posterior aspect of the patient's thigh. Apply now compressing pressure over the knee from the ankle with external rotation force. The test is considered positive if it produces pain.
- For cruciate ligaments (CL), you can use the anterior drawer test (Fig. 2.37): you should sit on the patient's feet for stabilization the flexed knees to around 90°. Place your hands on the tibial plateau from medical and lateral aspects, and then try to push tibia anteriorly over the femur toward your side (anterior drawer test) or posteriorly (posterior drawer test). Any displacement particularly when compared with the other knee is considered positive for cruciate ligament instability. The Lachman test: the patient here is in supine position. You should place one of your hands above the knee joint line with a good grasp, while the other is just below the knee joint line. In around 20–30° of passive knee flexion, try to apply contradicting forces by two hands; one pushes anteriorly while the other pushes posteriorly. Any excessive displacement is considered positive (Fig. 2.38). The validity of these tests has been questioned [5]. In general, this test is more sensitive than the anterior drawer test [4].
- For collateral ligaments, you can apply valgus and varus stresses, while the knee is held in 40–70° of flexion to assess for medial and lateral collateral ligaments, respectively. With positive result, there will be laxity and wide openings of the joint.

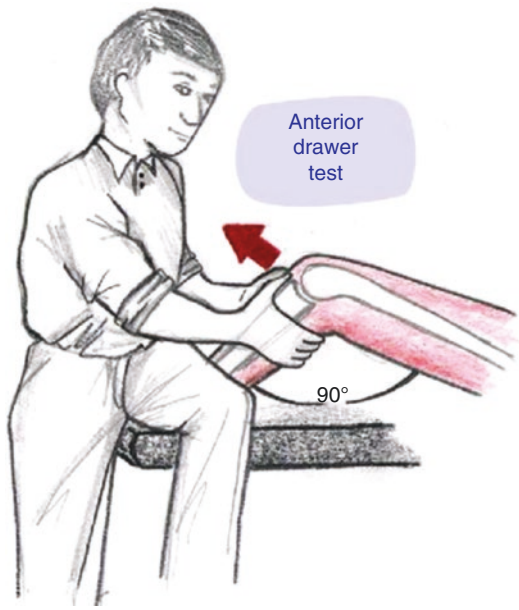


Fig. 2.37 Anterior drawer test

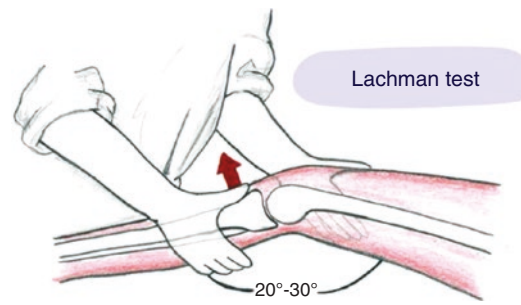


Fig. 2.38 Lachman test

2.6.3 Musculoskeletal Examination of the Hip Joint

2.6.3.1 First Step: The Anatomy (Fig. 2.39)

The hip joint is formed by the articulation between the round head of the femur and the acetabulum. It is a ball and socket joint with one part, the acetabulum, which is fixed in the body. Three bones compose the acetabulum: Ilium, ischium, and pubis. Femoral neck, Greater Trochanter (GT), and lesser trochanter are bony structures of anatomical significance. Femoral neck is vulnerable site for osteoporotic fractures. This site is used to measure bone mineral density to diagnose osteoporosis. The insertion of hip abductors and extensors are at the GT. While the hip flexor (iliopsoas) inserts at the lesser trochanter. An important bursae covers the GT which can be inflamed and cause symptoms. Symphysis pubis is a fibrocartilage that can cause symptoms.

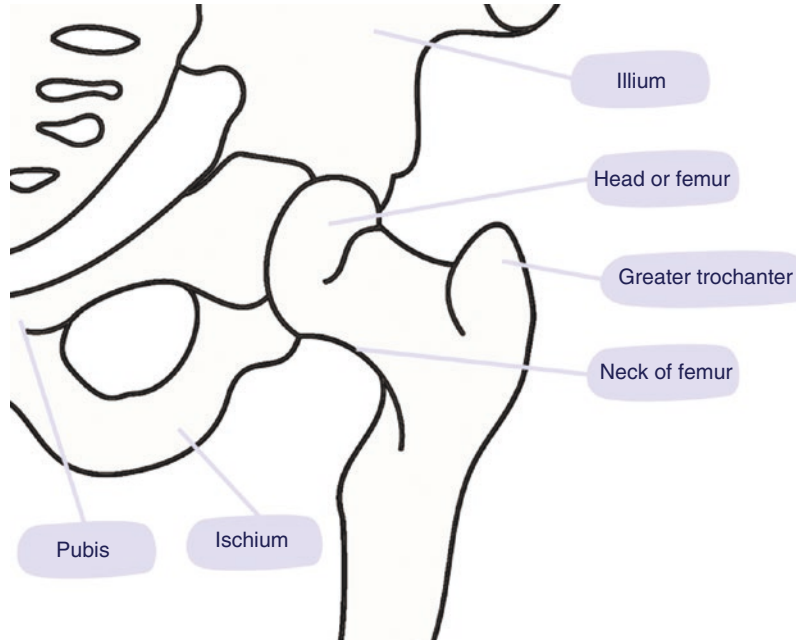


Fig. 2.39 Anatomy of the hip joint

Approach to Hip Pain

It is important to determine the site of pain. This is an essential step in the history of any joint pain. True hip joint pain (due to arthritis of head of femur articulating with the acetabulum) can be felt only anteriorly in the groin region. In the case of hip arthritis, you can expect to find, in addition to groin pain, severe limitation in the ROM actively and passively. Hip joint is a deeply seated joint; for this reason aspiration is always performed under fluoroscopic or US guidance. Pains that felt elsewhere in the hip region could be due other structures around the hip joint and still called by patients as "hip pain." Trochanteric bursitis is a classical example of a lateral hip pain in moderately obese female. Here there is tenderness by palpation in the lateral hip, and the active adduction and/or abduction may be painful, but usually the passive ROM is intact. In meralgia paresthesia (lateral cutaneous nerve entrapment), there is usually pain in the anterolateral hip region with entirely normal ROM. There are many structures posteriorly that can cause pain. Sacroiliac joint gives rise to posterior hip pain and usually referred to by some patients as buttock pain. Lumbar radiculopathy is another differential diagnosis. The patient should be asked then to point to the site of hip pain by one finger to exactly determine it. Table 2.5 summarizes the most important differential diagnosis of hip pain according to its site.

2.6.3.2 Second Step: The Approach

It is always:
- Inspection
- Screening exam
- Palpation
- Range of motion
- Special tests

Inspection

- You should start inspection from standing position and inspect anteriorly, laterally, and posteriorly. Then you can continue your examination after screening exam and palpation, while the patient is in supine position.
- Standing:
  - Back:
    Skin: redness, scars, rashes.
    Muscles: wasting, atrophy.

Table 2.5 Classification of the hip pain according to the site of the pain and its differential diagnosis

Site of the pain	Common	Less likely	Not to be missed
Anterior	Arthritis Synovitis Osteoarthritis Chondropathy Osteitis pubis	Stress fracture Hip joint instability	Synovial chondromatosis Avascular necrosis (AVN) of the head femur Slipped capital femoral epiphysis (SCFE) Tumor Legg-Calve-Perthes disease
Lateral	Trochanteric bursitis Greater trochanter pain syndrome	Referred pain from lumbar spine	Fracture of neck of femur Nerve root compression Tumor
Posterior	Sacroiliac joint disease, Lumbar radiculopathy Inferior hip joint osteophytes associated with hip arthritis		

Bones and joints: assess symmetry and pelvic obliquity – inspect posterior superior iliac spine (PSIS) (dimples of Venous) as they should be align to one level. Asymmetry may give clues to cases with chronic low back pain without apparent etiology. Inspecting gluteal folds, tip of scapula can assess symmetry.

– Lateral: inspect for lumbar lordosis and possible swelling or redness over greater trochanter.
– Anterior: symmetry can be assessed by inspecting anterior superior iliac spine (ASIS). Rarely, fullness in the groin region may indicate hip arthritis. However, significant hip joint pathology can occur without apparent swelling. Inspect also for rashes, redness, and scars.

Screening Exam

- Apparent leg length: from xiphoid cartilage or umbilicus to medial malleolus
- True leg length: from ASIS to medial malleolus

- The aim is to screen for gross pathology.
- It is basically the gait and active ROM testing.
- Note position: external rotation (ER) indicates hip joint pathology as internal rotation (IR) is lost first in arthritis.
- See ankle joint exam above for details of gait assessment. Simply you should ask the patient to walk/turn/walk on toes/on heels/squat (if possible) and stand from squatting position. This is a comprehensive evaluation of the neuromuscular integrity of the lower limb. Walking by itself is a good screening for hip flexion and extension. Squatting position is a good screening again for hip flexion and extension.
- Assess Trendelenburg sign: ask the patient to stand on the affected side that has classically hip joint arthritis (diseases like osteoarthritis) with week hip abductors and extensors. Then ask the patient to raise the normal side. Normally, the pelvis in the unsupported side will be raise due to the tone of strong muscles from the other supported side. In this sign and because of weakness of hip muscles from arthritis, the muscle tone here cannot support the pelvis in the other unsupported side, and this will result in pelvis drop in the unsupported side with positive sign. Trendelenburg gait is basically the same explanation, but when the patient needs to walk, bending laterally toward the supported side will raise the dropping unsupported pelvis producing the classical waddling gait with bilateral involvement of both hips.
- Note the type of gait (Fig. 2.40).

Palpation

- You can start palpation, while patient is still in standing position.
- Back: palpate paraspinal muscles, sacroiliac joint (SI joint) (1 inch medical + inferior to PSIS), iliac crest, and ischial tuberosity (IT)

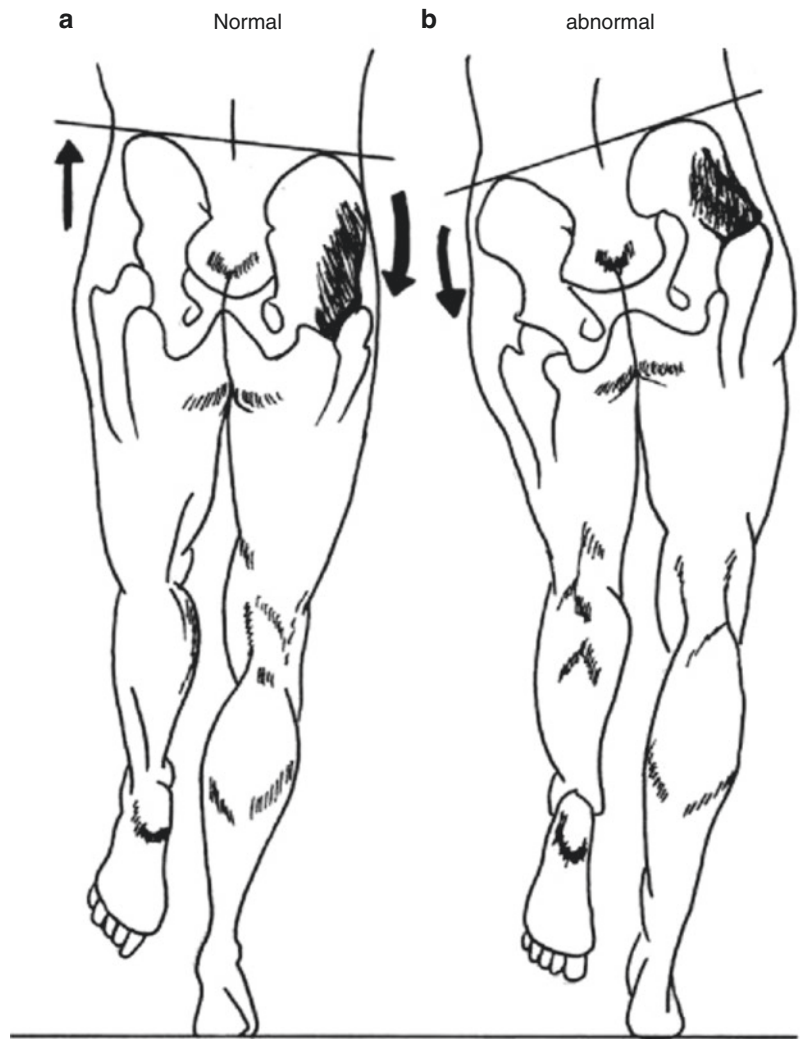


Fig. 2.40 Types of gait: normal (**a**) and abnormal (**b**)

(you may ask the patient to step on a stool using the limb under examination), feel GT, and feel sciatic nerve between the IT and GT.

- Lateral: palpate trochanteric bursae (Fig. 2.41).
- Anterior: palpate groin region – lymph nodes, pulses, hernia, ASIS, hernial orifice, pubic tubercle (where adductor longus originates), symphysis pupis – note any discrepancies in leg length.
- You may continue your palpation now, while the patient is in supine position.
- Quick screening: "frog" leg position—external rotation (ER) + abduction (ABD) + knee flexion—then compare both sides. In this position you may feel adductor longus tendon by asking the patient to adduct the hip against resistance and then just follow the adductor longus tendon until its origin from the pubic tubercle. Eliciting pain here may give you the diagnosis of adductor longus tendinitis.
- Flex hips and knees then extend them and look for leg length discrepancy.

Range of Motion

- You have done active ROM in your screening exam for two important hip movement flexion and extension. Now, you need to do comprehensive assessment of ROM (Fig. 2.42).
- In supine position: ask the patient to flex hip as much as possible; you may combined hip

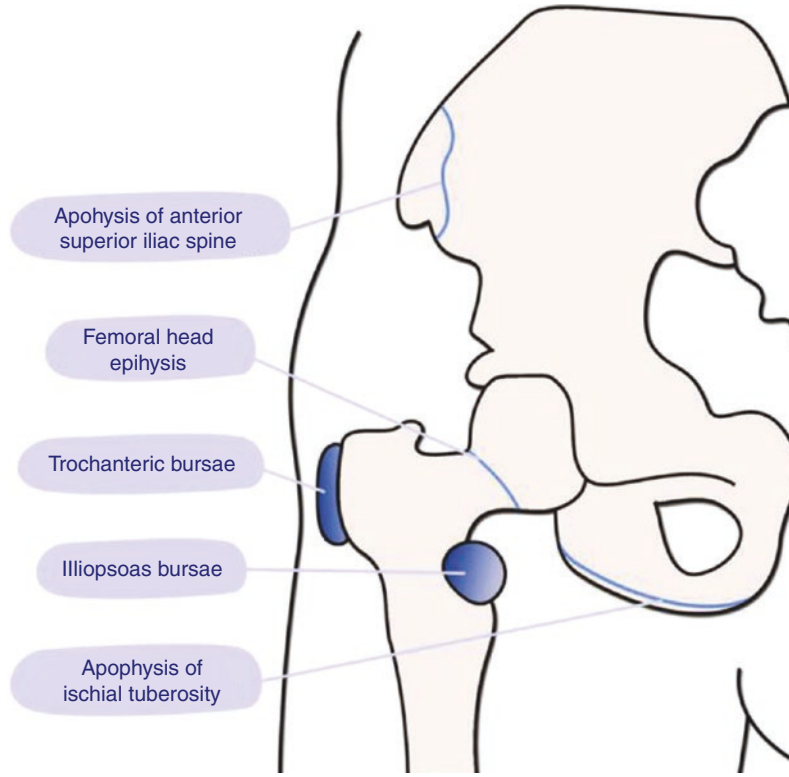


Fig. 2.41 Trochanteric and iliopsoas bursae

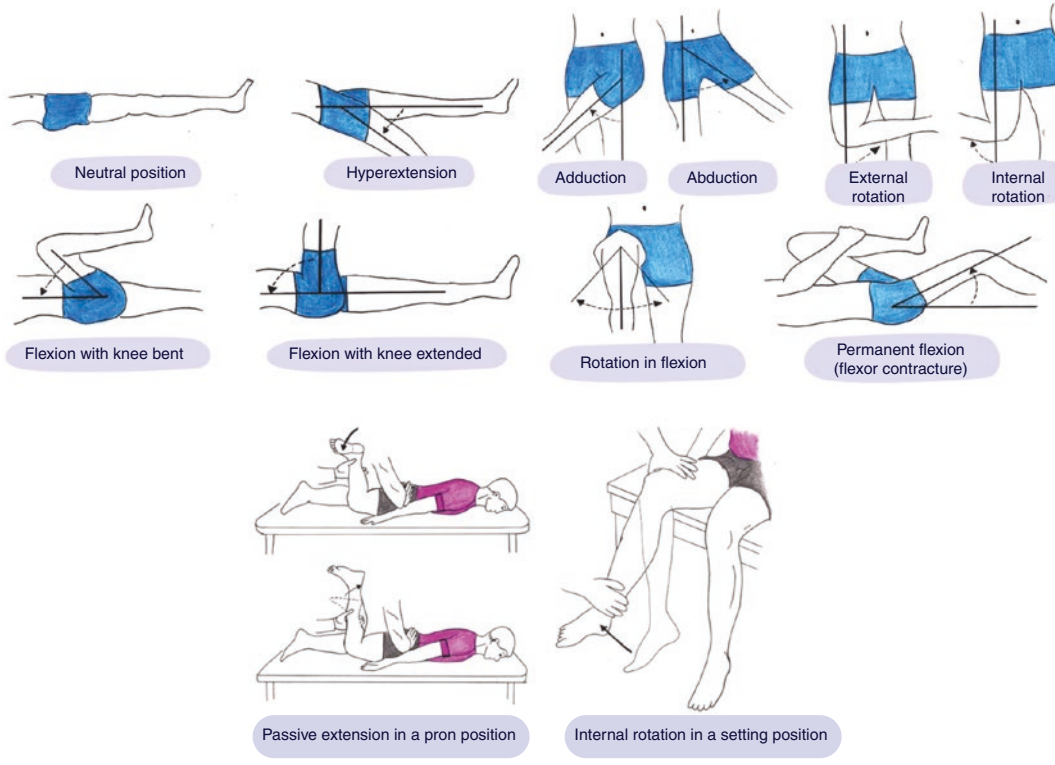


Fig. 2.42 Range of motion testing for hip joint

and knee active flexion by asking the patient to bring the knee to abdomen. Back to supine position and ask patient to abduct the hip laterally to as much possible and return to each hip one at time and ask the patient to cross midline. This is adduction. Back to supine position, and ask the patient to bring both plantar surfaces of both feet together facing each other with both knee flexed. This is external rotation (ER), and it is called "frog" leg position. The opposite of this position is the assessment of internal rotation (IR). The other position for active ER and IR is while patient is sitting at the edge of the bed with the knees and hips flexed. Bringing the leg away is IR and toward the midline is ER. The same technique can be done while the patient is supine. Extension can be assessed while the patient is in lateral decubitus position with the hip moved posteriorly.

- Active: Flexion 120°
  - Abduction 50°
  - Adduction 30°
  - Frog leg (for ER) 45°
  - Opposite of frog leg (for IR) 35°
  - Or in prone position: do active ER + IR
  - Assess ER + IR through leg rolling while hips are extended.
- In lateral decubitus position: you may palpate trochanteric bursae and perform active extension 30°.
- The passive ROM can be assessed, while the patient is in supine position. Flex the hip and try to bring it to patient's abdomen. Back to neutral position, and while putting one hand on the pelvis, take the hip to abduction, and use the same technique for the other hip. Perform passive adduction by crossing midline. For ER, flex hip and knee to 90°, then hold knee with one hand and the heel with the other hand, and then bring heel medially. For IR: bring heel laterally. Assess passive extension in lateral decubitus position or in prone position.

Special Tests

- Hip fixed flexion deformity:
- Thomas test: bring both knees to patient's abdomen and then extend one hip. If it failed to extend fully, there is fixed flexion hip deformity.
- Trochanteric bursitis:
- Tenderness over GT with pain elicited by resisted abduction.
- Radiculopathy:
- Straight leg raising test and slump test (see back exam).
- Piriformis syndrome:
- Resisted abduction while hip is flexed at 90° and adducted (Fig. 2.43).
- Tightness in iliotibial band (Ober's test):

  In lateral decubitus, neutralize hip and knee at 90°, and then abduct hip: a tight iliotibial band prevents the hip from adducting passively (Fig. 2.44).

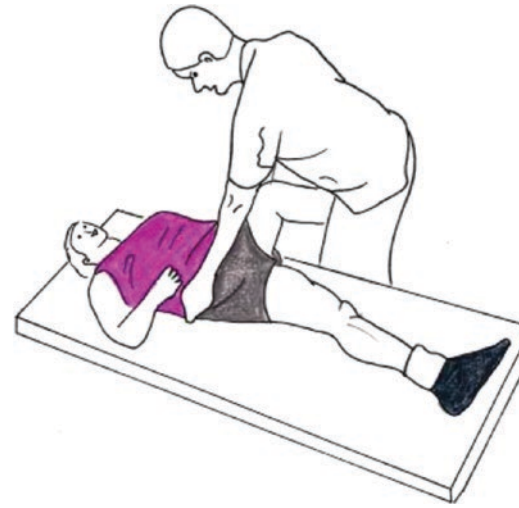


Fig. 2.43 Testing for piriformis syndrome

2.7 Back Examination

2.7.1 First Step: The Anatomy

- The spine represents the axial skeleton of the back, and it is composed of 32–33 small bones, called vertebrae (7 cervical, 12 thoracic, 5 lumbar, 5 fused sacral, and 3 or 4 coccygeal) (Figs. 2.45 and 2.46). The vertebrae bear the majority of the body weight and transfer it to lower limbs and also provide protection and support to spinal cord. A typical

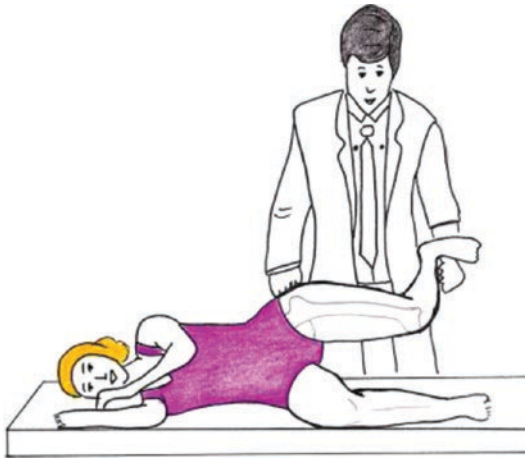


Fig. 2.44 Ober's test

vertebra is consisted of anterior body and posterior arch enclosing the vertebral canal where the spinal cord extends from the brain to the area between the end of first lumbar vertebra and top of second lumbar vertebra (L1 or L2 vertebral levels). Between each vertebra is a cartilaginous joint, called intervertebral disc. The discs limit the movements between the individual vertebrae and also act as a shock absorber (Fig. 2.47). The vertebral bodies are strictly attached to the intervertebral discs by two main ligaments: anterior and posterior longitudinal ligaments. Each pair of vertebrae is also connected by a synovial joint called facet joints. This is formed by the inferior articular process of one vertebra joining the superior articular process for the vertebra just below it. The facet joints give the spine its flexibility as there are two facet joints between each pair of vertebrae, one on each side. While the joints allow flexibility, the mobility of the spine is provided by the surrounded paraspinal muscles extended laterally along the spine.

- In the vertebral foramen posteriorly, the spinal cord extends down to the end of the second lumbar vertebra. Below this level, the spinal canal forms a group of nerve fibers, called the cauda equina. This group of nerves goes to the pelvis and lower limbs. Attached to each segments of the spinal cord, there is a pair of 31 spinal nerves exiting the vertebral foramina through vertebral notches of the adjacent pedicles. The spinal nerves exit the intervertebral foramina in relation to vertebral levels as the following: nerves of C1-C7 exit superior to the pedicles of the same-numbered level, C8 nerve inferior to C7 pedicles, and then T1 and below exit inferior to the pedicles of the same-numbered level.
- Different injuries and diseases may affect the components of spine and its surrounded paraspinal muscles resulting in back pain (Figs. 2.48 and 2.49) (See Chap. 6).

2.7.2 Second Step: The Approach

It is always:
- Inspection.
- Screening exam.
- Palpation.
- Range of motion.
- Special tests.

2.7.2.1 Inspection

You may start your examination by explaining to your patient the steps of your exam. After proper exposure, start your inspection, while the patient is standing. You may ask one of the family members to be around.

Always inspect the patient posteriorly, laterally, and anteriorly.

- **Alignment:** you should be familiar with the normal alignment of the spine. This is to help inspect for abnormal alignment that may give rise to chronic back pains: kyphosis, scoliosis, and exaggerated or lost lumbar lordosis. In patients with ankylosing spondylitis (AS), lumbar lordosis is usually lost from spondylitis. This also can be lost due to severe muscle spasm over the lower back.
- **Skin:** Inspect for erythema, hair patch, café au lait spots, nodules, and/or scars.
- **Muscles**: wasting, atrophy.

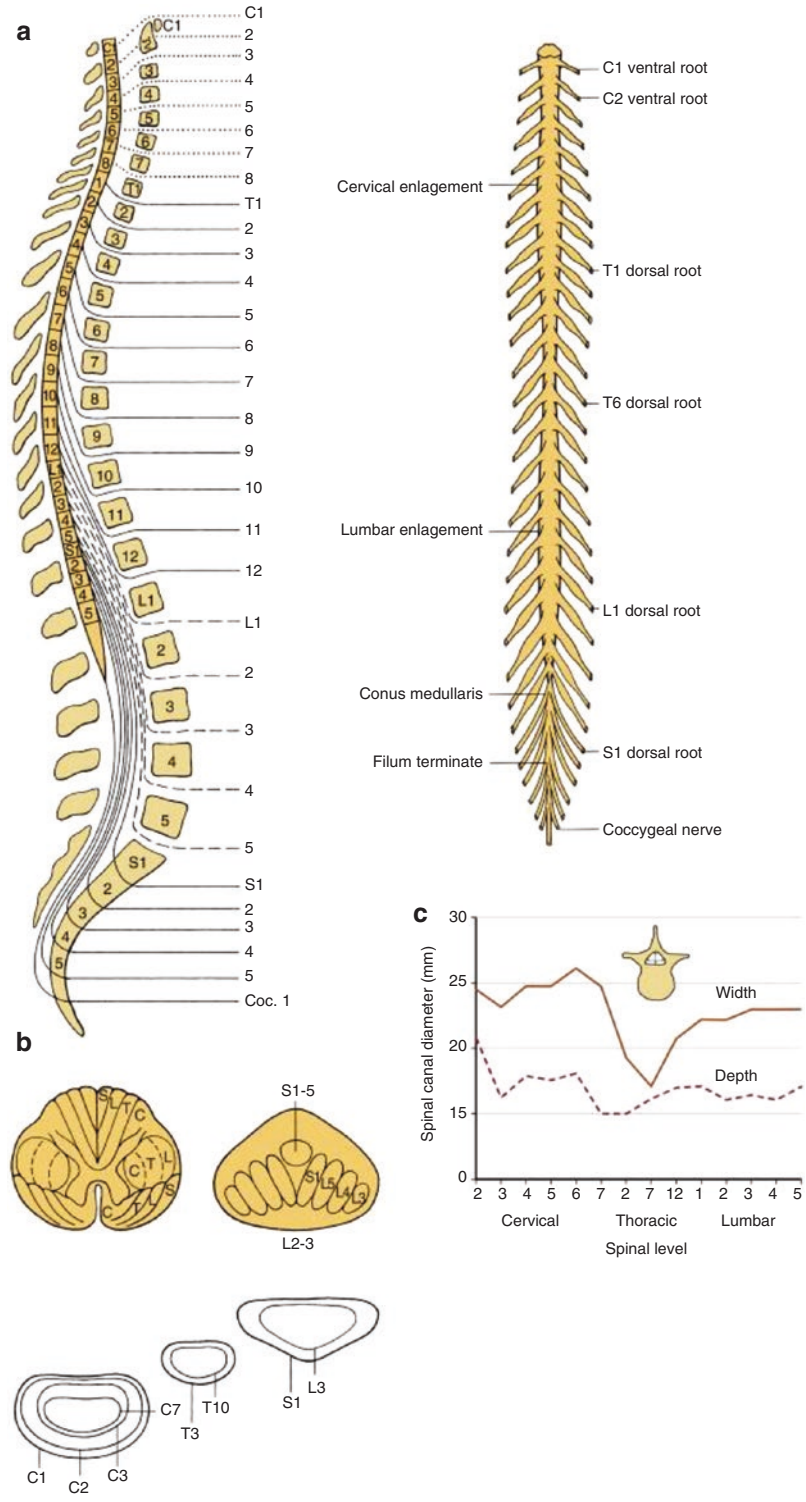


Fig. 2.45 Bones of the spine [6]

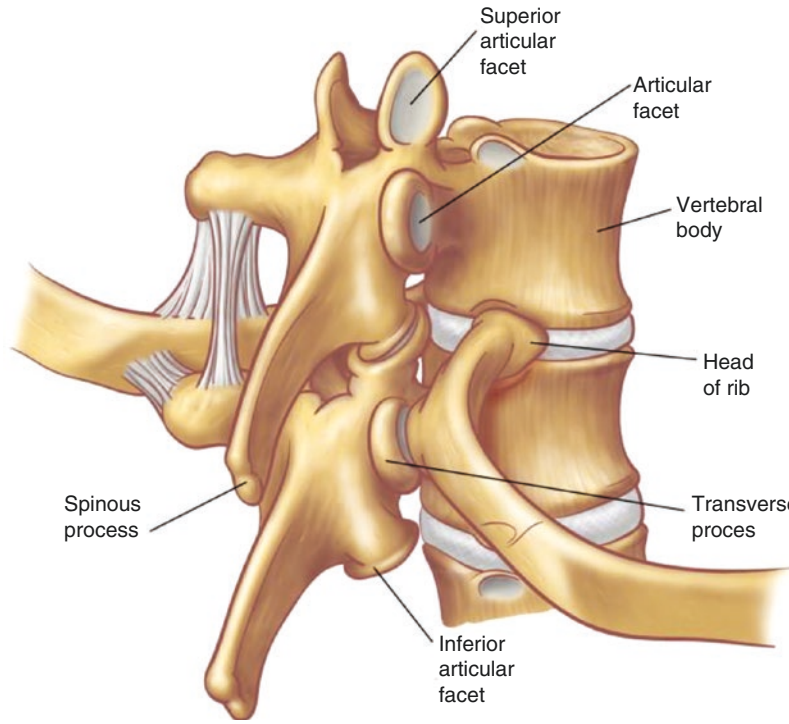


Fig. 2.46 Structures of lateral spine

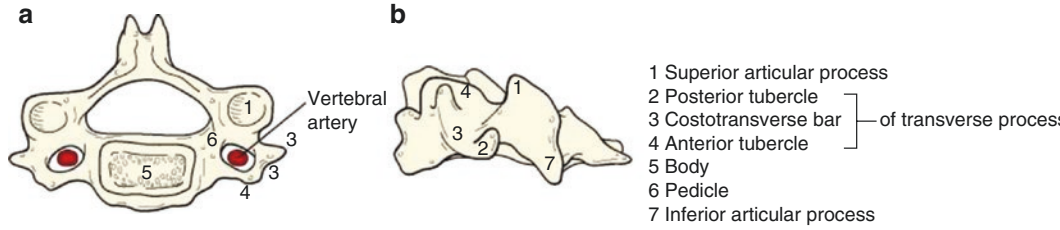


Fig. 2.47 Structure of a vertebra

- **Symmetry**: check symmetry of the back by assessing whether tips of scapulae are at one level or not. Also for the iliac crests and gluteal folds. Inspect PSIS (dimples of Venous) as they should be align to one level. You may ask the patient to flex the hip and observe while you are standing behind the patient the symmetry and whether the asymmetry is corrected or not.

2.7.2.2 Screening/Gait Assessment

- **Gait:** straight walking while watching for abnormal flexion (suggestive of spinal stenosis or facet joint pathology), abnormal extension (suggestive of disc pathology), or Trendelenburg gait (Fig. 2.50).
- **Screening for neurological integrity:** walking on toes (L5, S1) and then on heels (L4, L5), knee extension (L3, L4); then ask patient

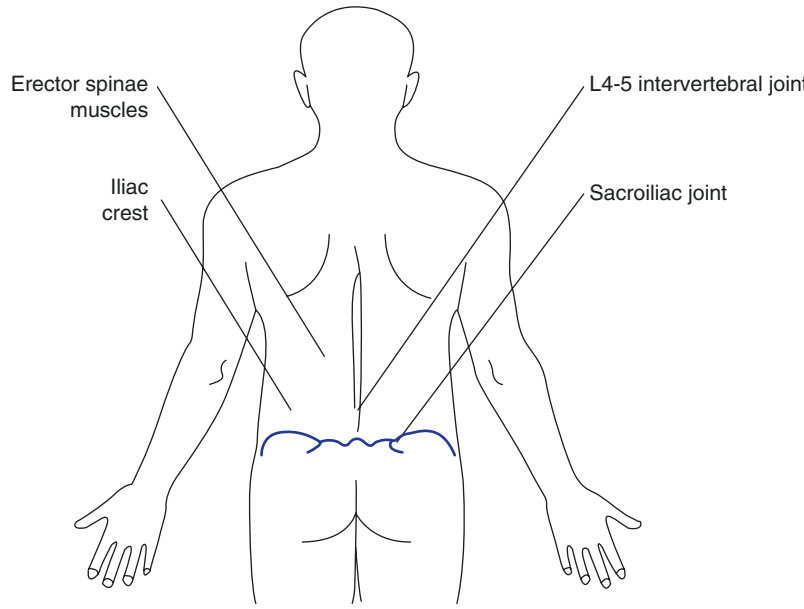


Fig. 2.48 Some surface anatomy landmarks

to squat and stand from squatting position, hip flexion (L2, L3), and hip extension (L5, S1).

- **Position:** watch as patient changing position.
- **Asses Trendelenburg sign (see hip joint exam):** the patient stands on affected side and then raises the normal side, and in a positive test, the unsupported side will drop.
- **Note the type of gait:** normal gait passes through two phases stance and swing phases. The stance phase consists of heel strike, mid-stance, and toe off. The swing phase has an acceleration and deceleration components. A common gait abnormality in rheumatology is antalgic gait which is simply short stance phase gait due to pain in one of the lower limb joints.

2.7.2.3 Palpation

Start palpation while patient is in prone position. Palpate spinous processes over the midline from cervical down to sacral regions (Fig. 2.51). You may percuss to illicit severe tenderness that might indicate discitis. You may palpate now the paramedian spinal structures including muscles (for tenderness and/or spasms as majority of low back pain is caused by muscle strain and/or spasm), interspinous or supraspinous ligaments, and facet joints. Keep in mind the low specificity of these techniques. You may palpate now iliac crests for tenderness suggestive of enthesitis a hall mark feature of spondyloarthritis, while palpation observe any skin and/or soft tissue fluid collection suggestive of an abscess. Palpate the dimples of Venus at the level of S2 as the sacroiliac joints lie beneath them. It can be severely tender in sacroiliitis. You may ask the patient to stand and put his feet on a chair or a stool and you can posteriorly identify by palpation two bony prominences: the ischial tuberosity medially and the GT laterally. The sciatic nerve can be palpated in the area between these two. Severe tenderness can be illicit in patients with sciatica and/or piriformis syndrome.

2.7.2.4 Range of Motion

This can be assessed by asking the patient to perform the following:

- **Flexion:** ask patient to bend forward with extended knees and bring fingers to floor. The distance between the long finger and the floor can be documented and used to follow up response of treatment in cases of spondylitis.
- **Extension:** stabilize the pelvis and ask the patient to extend the back as much as possible. Figure 2.52 demonstrates ROM of cervical spine.

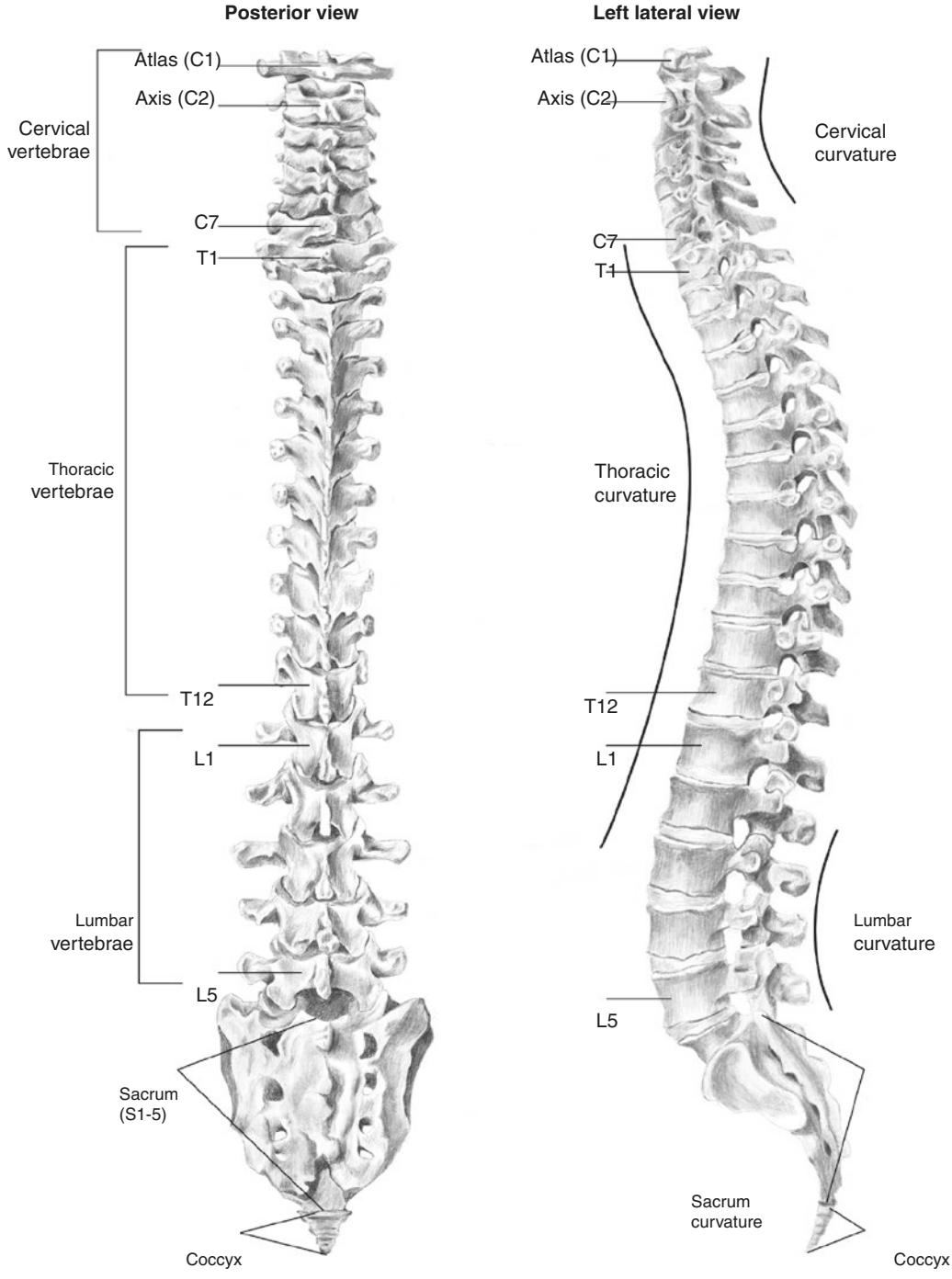


Fig. 2.49 Vertebral column [7]

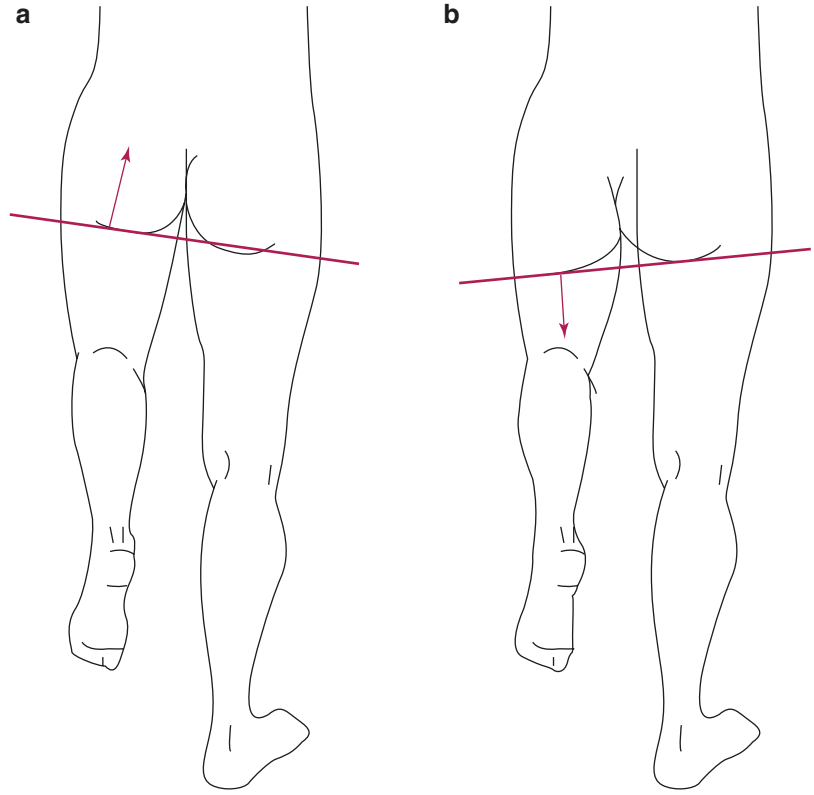


Fig. 2.50 Trendelenburg sign: (**a**) normal response. (**b**) Abnormal response with drop of the pelvis in the unsupported leg due to weakness in the opposite (supported leg) muscles. This will result in Trendelenburg gate

Fig. 2.51 Areas for palpitation

- **Lateral flexion:** The patient may stand against the wall and bend laterally and trying to slide the fingers to fibula. The distance between the long finger and the fibula or the floor can be documented and used in monitoring response to therapy in spondylitis (Fig. 2.53).
- **Thoraco-lumbar rotation:** This is best examined while the patient is sitting at the edge of the bed. Ask the patient to turn to the side without moving the pelvis as much as possible; up to 70° can be achieved normally. This movement can be checked passively to examine for any tenderness, stiffness, limitation, and/or end of range stiffness (Fig. 2.53).

2.7.2.5 Special Tests

Straight Leg Raising Test (SLRT) (Fig. 2.54)
This is to test for radiculopathy of L5-S1. Keep the patient in supine position with extended hip and knee. Then flex the hip slowly until a complaint of shooting radicular pain or tightness is

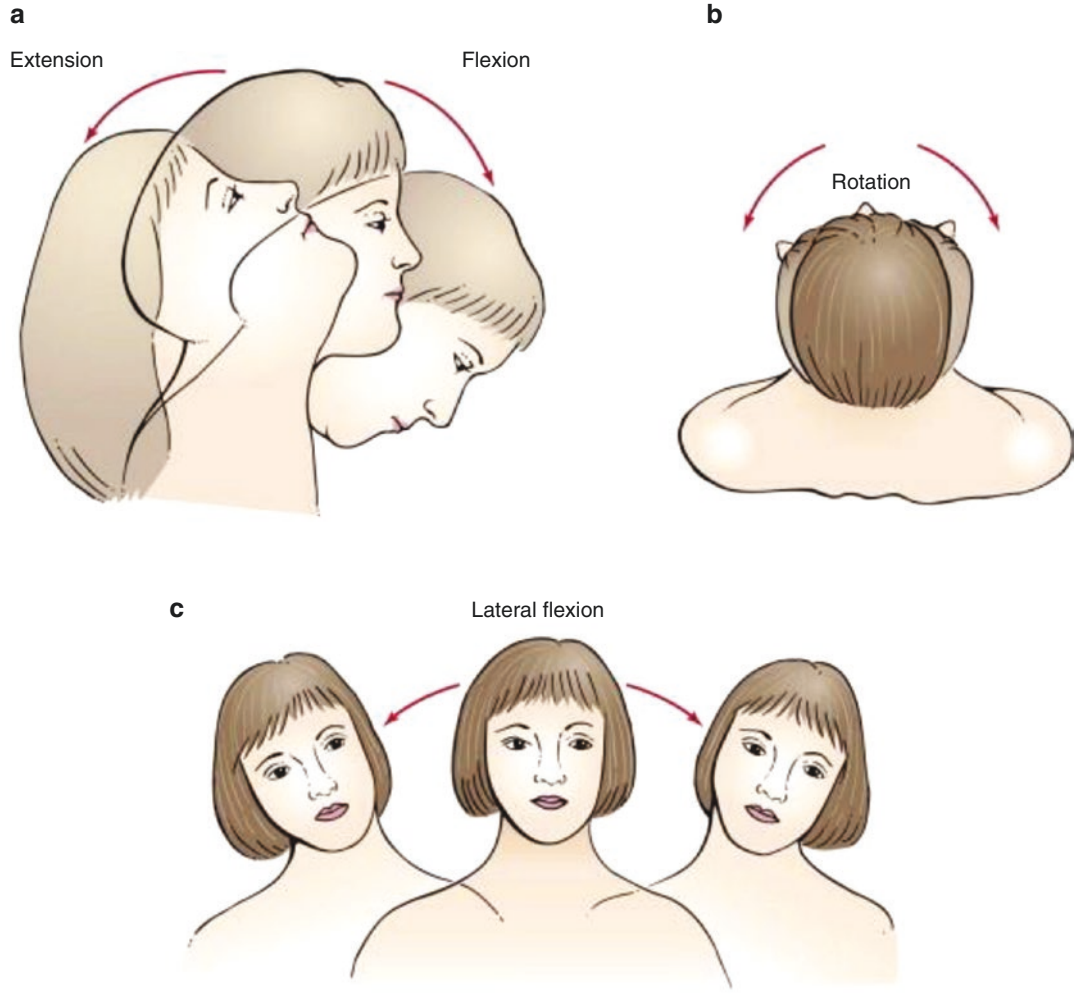


Fig. 2.52 Range of motion of cervical spine

reached. The test can be considered positive with classical radiation of the pain at 30–70° of leg elevation. Just lowering the examined leg few degrees before the pain appeared and then passive dorsiflexion of the ankle is performed as a confirmatory technique. Symptoms should recur in strongly positive test (Fig. 2.55).

Slump Test (Fig. 2.56)

This test is performed again to look for radiculopathy at L5-S1. The patient should be sitting at the edge of the bed with both arms stabilized over the back. You should flex the outstretched extended leg to be examined by holding the toes or the ankle, and at the same time, ask the patient to flex the neck and bring the chin to the chest wall. A shooting radicular pain might result from this stretch indicating a positive test.

Sacroilliac Joints Exam

Patrick test and compression test: perform (FABER test (flexion abduction external rotation test)) Fig. 2.57. Flex the hip, abduct, and externally rotate it while the other leg in extended. Then compress over the iliac crest of the extended leg and over the knee of the flexed leg. A positive test produces pain in the sacroiliac joint of the leg being tested.

Modified Schober's Test

This test is to assess for limited lumbar spinal flexion. Mark the PSIS (dimple of venous) by

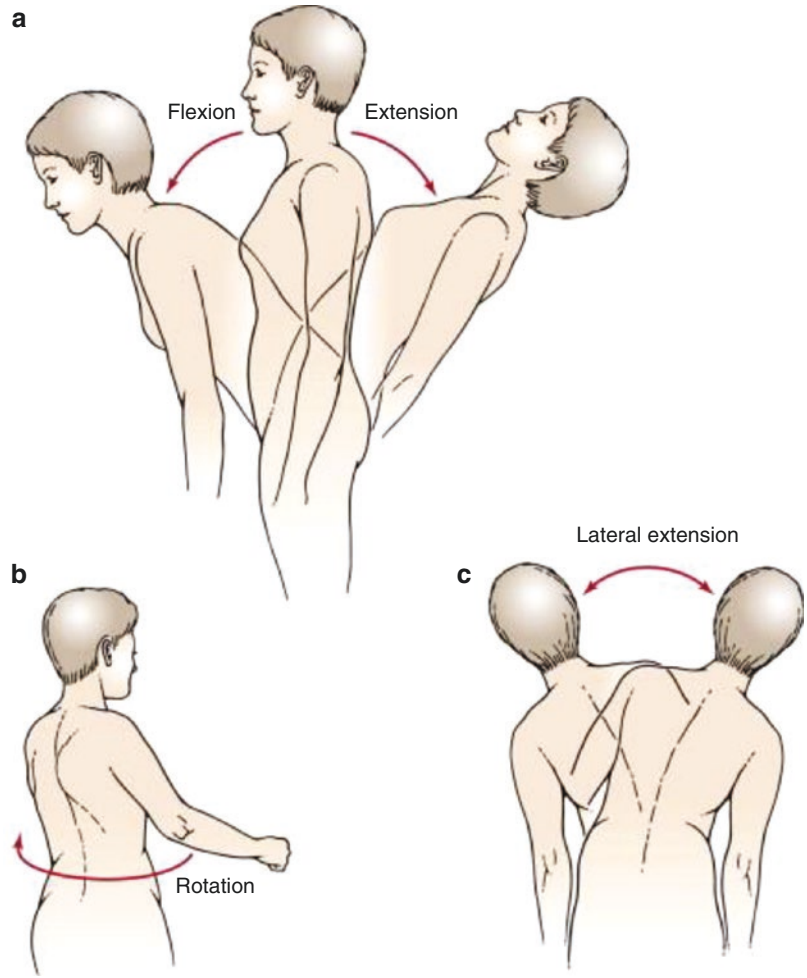


Fig. 2.53 Range of motion of thoracolumbar spine. (**a**) Flexion and extension. (**b**) Rotation. (**c**) Lateral extension

drawing a line connecting both points. At the center of this line, mark a point. Using a tape measure placed at the center point, mark 5 CM below this line and 10 CM above this line. Then ask the patient to bend forward without bending the knees. Now, measure the distance between the points. The distance between the two points should be more than 15 by 5 additional CM (≥ 20 CM). Any movement that results in less than this is considered abnormal.

Neurological Exam

Detailed neurological exam should be conducted. The motor findings are reliable and should direct further intervention with the patient. One of the simple tests to perform is muscle bulk by a tape measure from a fixed bony prominence. More than 1 CM difference is considered abnormal for patients presenting with radicular symptoms. Rectal tone (S3,4,5) should be also performed in the right clinical settings. Fig. 2.58 represents a quick tool to examine in brief the roots of the lower limb. This quick approach includes examining the power of the following movement (note that it goes for simplicity from 2 to 5): hip flexion (L2), knee extension (L3), ankle dorsiflexion (L4), big toe extension (L5), and ankle plantar flexion (S1). This is in addition to sensory exam as shown in Fig. 2.59. Sensory level is an important clinical finding to be determined in the right clinical setting in order to decide on further intervention and follow-up. Figure 2.60 summarizes the steps of back examination.

Acknowledgments The authors are grateful for the help provided by Mohamed Cheikh, Mawaddah Al hadeedi, Abdulrahman Kabli, Rehab Simsim, and Waleed Hafiz in composing this chapter.

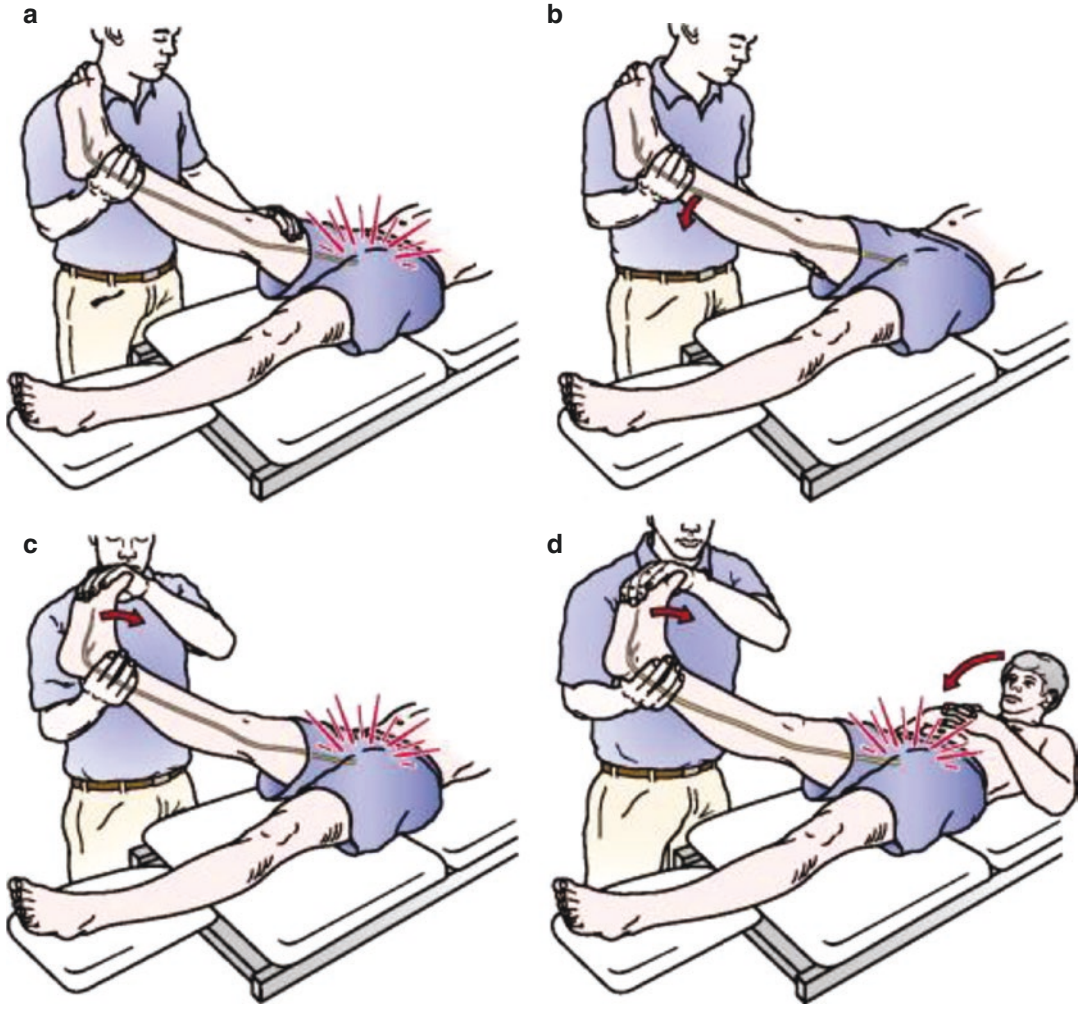


Fig. 2.54 Straight leg raising test

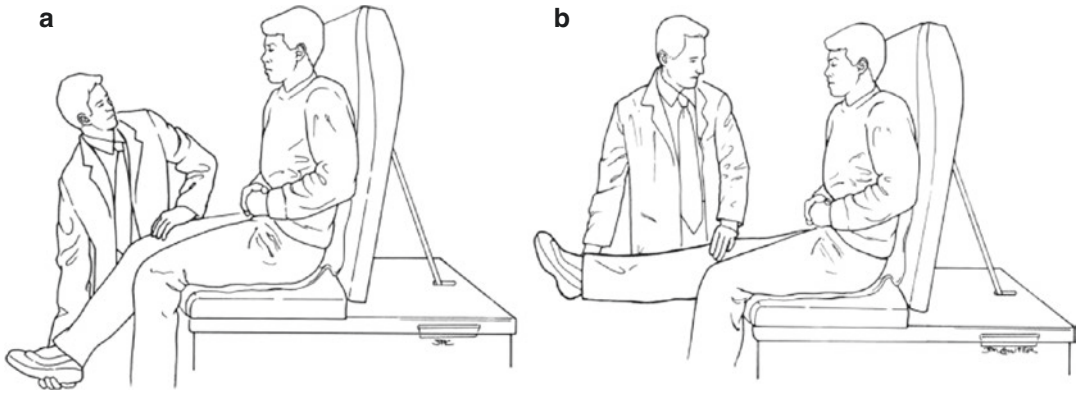


Fig. 2.55 Another approach to test for radiculopathy at L5-S1

Fig. 2.56 Slump test

Fig. 2.57 FABER test (flexion abduction external rotation test)

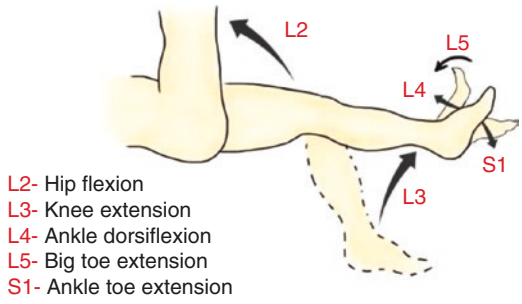
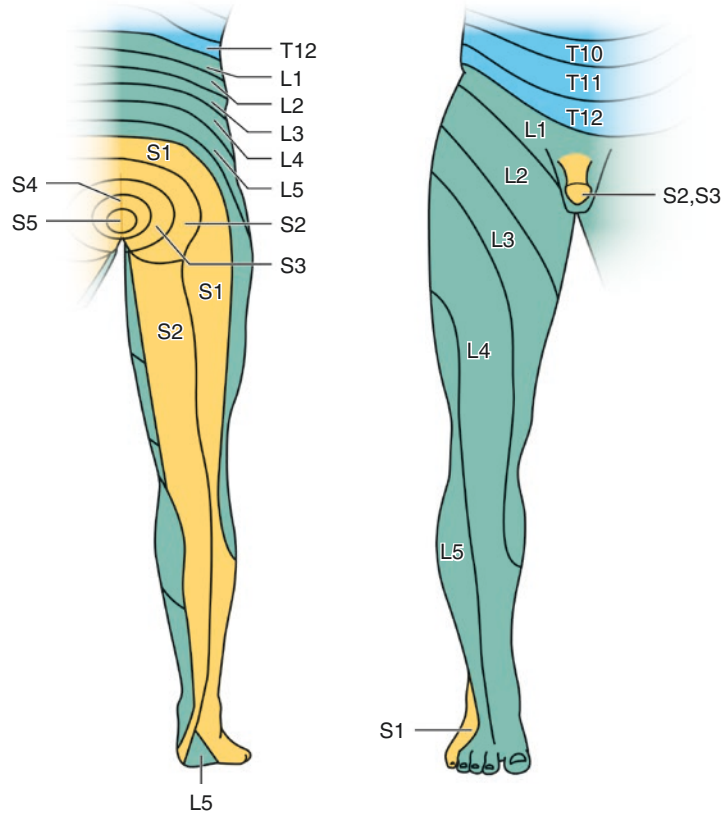


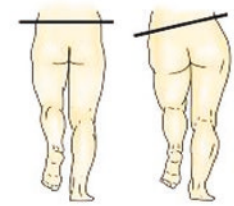
Fig. 2.58 Quick tool to examine in brief the roots of the lower limb

Fig. 2.59 Levels of principle dermatomes of the lower limb



Gait

- **Gait:** straight walking while watching for abnormal flexion (stenosis or facet joint), extension (disc), or Trendelenburg gait.
- **Screening:** walking on toes then on heels.
- **Position:** watch as patient changing position.



Inspection

- **Alignment:** Kyphosis, scoliosis, or loss or exaggerated lordosis.
- **Skin:** Erythema, hair patch, Café au lait spots, nodules, and or scars.
- **Inequality**: watch for iliac crest and pelvic inequality => at the level of L4-5: ask patient to flex his/her hip.
- **N.B:** Always inspect the patient posteriorly and laterally.

Palpation

- Examine the patient in the prone position.
- **Spinous processes**: tenderness or defects.
- **Inter-spinous ligament.**
- **Supraspinous ligament.**
- **Paraspinal muscles.**
- **Iliac crest:** tenderness (Spondyloarthritis) or nodules. PSIS –Sacroilliac joint -S2
- Ischial tuberosity -Sciatic nerve -Greater trochanter.

Range of Motion

- **Flexion:** finger-floor
- **Extension:** stabilize the pelvis and measure the distance
- **Lateral flexion:** Finger-fibula (against the wall).
- **Tohoraco-lumbar rotation:** 70° normally.

Special Test

- Straight leg raising test (SLRT)
- Slump test
- Sacro-illiac joints exam: Patrick test and compression test
- Modified Schober's test
- Neurological exam: Muscle bulk by tape (Radiculopathy) and rectal tone (S3,4,5)

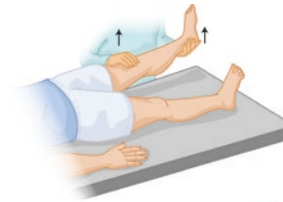


Fig. 2.60 Summary of back examination

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3 Laboratory Interpretation of Rheumatic Diseases

Altaf Abdulkhaliq and Manal Alotaibi

3.1 Introduction

Generally the diagnosis of rheumatic diseases is based on a set of clinical, serological, and radiological measures. The discovery of a novel test that appears to be considerably more disease-specific and preferably sensitive would be of value for the early diagnosis and immediate, effective therapy to prevent joint deterioration, functional disability, and unfavorable disease outcome [1].

However, components of acute phase reaction proteins such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) or rheumatoid factor (RF) lack specificity and sensitivity and could not reach the expectation of earlier diagnosis of specific rheumatic diseases. Therefore, the discovery of immunologic laboratory tests has occupied a valued position in the practice of rheumatology and has helped define the pathophysiology of various rheumatic conditions such as the immunologic basis of rheumatoid arthritis (RA) [2, 3] and explain the contribution of genetic basis to autoimmune disease via the association of ankylosing spondylitis (AS) with HLA-B27 and RA with certain HLA-DR alleles [4, 5].

Hence the salient existence of such immunologic laboratory tests has assisted the more precise diagnosis of diverse rheumatologic conditions that may share some clinical characteristics. In addition, these tests can provide valuable evidence concerning disease manifestation, activity and prognosis, and therapeutic monitoring.

Essential terms concerning the laboratory tests are needed to be defined such as sensitivity, specificity, and positive and negative predictive values. *Sensitivity* refers to the ability of the test to detect the proportion of patients with a disease which usually have a positive test result. However, *specificity* refers to the ability of the test to detect the proportion of patients without the disease which usually have a negative test result. *Predictive value* refers to the likelihood of disease or non-disease based on a positive or negative test result. A high positive predictive value test indicates that the patient with a positive test result most probably has the disease in question. Similarly, a high negative predictive value test indicates that the patient with a negative test result most likely does not have the disease in question.

Unlike with sensitivity and specificity of the test, the predictive value is markedly affected by disease prevalence. For instance, the predictive value of a positive rheumatologic test in patients with polyarthralgia is likely to be higher in a rheumatology clinic than in a family physician's clinic [6].

A. Abdulkhaliq (✉)
College of Medicine, Umm Al-Qura University, Makkah, Saudi Arabia
e-mail: aaabdulkhaliq@uqu.edu.sa

M. Alotaibi
Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Internal Medicine Department, College of Medicine, Umm Al-Qura University, Makkah, Saudi Arabia

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The subsequent sections will discuss the stepwise approach to the diagnostic workup of rheumatic diseases and are presented as follows:

- Inflammatory markers (ESR and CRP)
- Rheumatoid factor (RF)
- Antinuclear antibody (ANA) profile, for instance, anti-double-stranded DNA antibodies (anti-dsDNA) and anti-ribonucleic protein (RNP) antibodies
- Other disease-specific antinuclear antibodies and cytoplasmic antibodies
- Complement deficiencies and decreased complement activity in certain medical conditions
- Components and classification of synovial fluid analysis
- Other biochemical tests: renal function tests and urine analysis (this section is not in the scope of the current chapter but it will be discussed in details in the chapter of "Renal System and Rheumatology")

3.1.1 Objectives

By the end of the current chapter, the candidates should be able to:

- Identify the rule of acute phase reaction proteins in rheumatic diseases.
- Interpret the auto-antibodies' results based on clinical findings.
- Classify various types of joint effusions based on clinical and laboratory analysis of synovial fluid.

3.2 Acute Phase Reactants

Acute phase reactants (APRs) or proteins are defined as those proteins whose serum concentrations increase or decrease by at least 25% during inflammatory states. Changes in levels of APR largely result from the effects of cytokines, including interleukin (IL)-6, IL-1 beta, tumor necrosis factor-alpha (TNF-alpha), and interferon gamma.

Serum APR level measurements are useful because they frequently reflect the presence and intensity of an inflammatory process. The assessment of APR may be most helpful in patients with RA, polymyalgia rheumatica, and giant cell arteritis.

However, APR measurements in clinical use are not specific to any particular disease.

The most widely used indicators of the acute phase response are the ESR and CRP [7].

ESR and CRP definitions, measurements, uses, and other important aspects are addressed in Table 3.1.

3.3 Rheumatoid Factor (RF) and Anti-citrullinated Protein Antibody (ACPA)

3.3.1 Definition

RF is an antibody directed against the Fc fragment of immunoglobulin G (IgG). It may be of any isotype: IgG, IgA, IgE, and IgM. RF-IgM is the only one measured in clinical practice. The origin of RF is incompletely understood [7]. ACPAs are antibodies that are targeted against citrulline which is situated on proteins. Important clinical features of RF including measurement and common issues while dealing with it in clinical practice are all addressed in Table 3.2.

3.4 Antinuclear Antibodies (ANAs)

3.4.1 Definition

ANAs are serologic hallmarks of patients with systemic autoimmune disease. These antibodies should be ordered when the clinical assessment of the patient suggests the presence of an autoimmune or connective tissue diseases [7]. Clinical aspects of ANAs are discussed in Table 3.3.

Table 3.1 ESR versus CRP

Definition	**ESR**		**CRP**
	ESR is an indirect measurement of serum acute phase protein concentrations, defined as the rate (mm/hour) at which erythrocytes suspended in plasma settle when placed in a vertical tube, reflects a variety of factors, most notably the plasma concentration of fibrinogen [7]		CRP is defined as a pentameric protein comprised of five identical, non-covalently linked 23-KD subunits arranged in cyclic symmetry in a single plane. It is a component of the innate immune response and has both pro-inflammatory and anti-inflammatory actions. CRP can activate the complement system and enhance the apoptotic cell clearance [7]
Methods of measurement	Cont. **ESR**		Cont. **CRP**
	The Westergren method	**The Wintrobe method**	It is measured by immunoassay technique or nephelometry [7]
	Uses a 200-mm tube and has a dilution step that correct for the effect of anemia. It is the preferred method and can detect an ESR more than 50–60 mm/h [7, 8]	Uses a 100-mm tube and has no dilution step [7, 8]	
Sensitivity and specificity	An advanced rate does not diagnose a specific disease, but it does indicate that an underlying disease may exist [7, 8]		Although CRP is a sensitive reflector of inflammation, it is not specific for inflammation [9]
	An elevated ESR observed together with a normal CRP is often a false-positive value for the ESR; this may reflect the effects of blood constituents, such as monoclonal immunoglobulins, that are not related to inflammation but that can influence the ESR. However, this conclusion is not always valid. As an example, the ESR may be markedly elevated in patients with active systemic lupus erythematosus (SLE), while the CRP response is muted. These variations may be explained by differences in the production of specific cytokines or their modulators in different diseases [10]		
Normal result	– Normal values for the Westergren method are: **Men** = 0–15 mm/h **Women** = 0–20 mm/h **Children** = 0–10 mm/h – A normal value does not rule out the disease – Non-inflammatory conditions that can elevate ESR include aging, female sex, obesity, pregnancy, and race [7, 8] – The age-adjusted upper limit of normal for ESR is: **Male** = age/2 **Female** = (age+10)/2	– Normal value is less than 0.08 mg/dl – CRP levels vary with age, sex, and race [7] – The age-adjusted upper limit of normal for CRP is: **Male** = age in years/50 **Female** = (age in years/50) + 0.6 [9]	

(continued)

Table 3.1 (continued)

Abnormal results	1-**Causes of marked ESR elevation (more than 100 mm/hr):** 1. Infection (bacterial 33%) 2. Connective tissue diseases (gain cell arteritis, polymyalgia rheumatica, SLE, vasculitides 25%) 3. Malignant neoplasms and renal disease 17% 4. Inflammatory disorders 14% [7, 11] **Causes of marked decreased in ESR (0 mm/h):** 1. Afibrinogenemia/ dysfibrinogenemia 2. Agammaglobulinemia 3. Increased plasma viscosity 4. Extreme polycythemia [7, 11]	**Values between 0.3 and 1 mg/dL may indicate:** 1. Minor degrees of inflammation, e.g., periodontitis 2. Minor degrees of metabolic malfunction (non-inflammatory states), e.g., obesity and insulin resistance [7, 9] **Values greater than 1 mg/dL can indicate:** Clinically significant inflammation [9] **Values greater than 8–10 mg/dL may indicate:** 1. Bacterial infection 2. Systemic vasculitis 3. Metastatic cancer 4. Trauma, burns, and surgery [7, 9]
Advantages and disadvantages	1. Inexpensive, familiar, and easy to perform 2. As a patient's condition worsens or improves, the ESR changes are relatively slow [12] 3. A literature review was conducted for all clinical trials and observational studies of disease-modifying medications and corticosteroids in RA to elaborate on the laboratory results of both ESR and CRP before treatment and 4 weeks to 24 weeks after treatment in the same patients, and it has been concluded that the ESR was more sensitive to change than the CRP at 12 weeks and 24 weeks of treatment [13]	1. It rises more quickly and falls more quickly than ESR [11] 2. Measurements of CRP concentrations are of prognostic value in rheumatoid arthritis and can help guide management [11, 13–15] 3. CRP alone may have been in favor as a simple, validated, reproducible, non-age-dependent test for disease activity assessment [12] 4. CRP had been found to be more sensitive and specific marker for diagnosing bacterial infections in SLE compared to procalcitonin (PCT) [14, 15]. However, further meta-analysis report of studies describing the role of PCT or CRP as a biomarker of infection in autoimmune diseases has determined that PCT test is more specific than sensitive [16]. In addition, a later study has confirmed that PCT test is superior to CRP test in detecting superimposed bacterial infections in active SLE patients, where the PCT levels are correlated with the progression of bacterial infection and used to monitor the response to antibiotic treatment [17]
	The serum protein electrophoresis is the most sensitive test for detecting inflammatory changes. It is the most expensive, directly quantifies the acute phase response [7]. However, there is no single best laboratory test to reflect inflammation The optimal use of acute phase protein measurements may be to obtain several measurements, most commonly ESR and CRP, rather than a single test [9, 14, 18] **Additional tests** suggest systemic inflammation: Low albumin and mild elevation of hepatic alkaline phosphatase [7]	

3.4.2 Methods of Measurement

- Indirect immunofluorescence method using "fluorescence microscope" is the gold standard method to detect ANAs. Currently most laboratories use human epithelial cell tumor line (HEp2 cells) as a substrate to detect antibodies that bind to various nuclear antigens (ANAs) instead of frozen section of rodent organ cells.
- Other methods that can be used for detection of specific ANA include ELISA, immuno-blotting, and Western-blotting methods.

Table 3.2 Characteristics of RF

<table>
<tr><td>Measurement</td><td colspan="3">It is measured by nephelometry, radioimmunoassay, enzyme-linked immunosorbent assay (ELISA), and latex agglutination techniques, although there is no single technique that has clear advantage over others. Automated methods, such as nephelometry and ELISA, tend to be more reproducible than manual methods [7]. The most commonly used technique to measure ACPA is the ELISA for antibodies against cyclic citrullinated peptides (CCP).</td></tr>
<tr><td>Sensitivity and specificity</td><td colspan="3">• The sensitivity of RF in RA has ranged from 26% to 90%
• The reported sensitivity of the RF test in RA has been as high as 90%. However, population-based studies, which include patients with mild disease, have found much lower rates of RF-positive RA (26 to 60%) [19]
• The sensitivity of ACPA testing is similar to RF at around 75%. However it provides much higher specificity rates at around 95%.
• The specificity is 85% [19]
• The specificity to a young healthy population is about 96% [19, 23]</td></tr>
<tr><td>Positive results
Cont. Positive results</td><td colspan="3">The common denominator for the production of RF (positive result) is chronic immune stimulation</td></tr>
<tr><td></td><td>Healthy individuals</td><td>Non-rheumatic disorders</td><td>Rheumatic disorders</td></tr>
<tr><td></td><td>• RF is present in some healthy individuals, especially the elderly (3–25%), male and female are affected equally, and only 20% of cases is the RF level significantly positive
• RF has been found in 2–4% of young, healthy individuals [7, 20]</td><td>1. Chronic infection, e.g., AIDS, mononucleosis, parasitic infections, chronic viral infection (hepatitis B or hepatitis C (HCV) 54–76%), chronic bacterial infections (tuberculosis, subacute bacterial endocarditis (SBE))
2. Cryoglobulinemia 40–100% especially with HCV
3. Pulmonary disorders, such as sarcoidosis
4. Malignancy, especially after radiation or chemotherapy and B-cell neoplasms
5. Primary biliary cirrhosis [7, 21]

Positive ACPA can be found in the following non rheumatological diseases:
1. Active tuberculosis (varying rates)
2. Chronic obstructive pulmonary disease (5%)
3. It is important to note that unlike RF, ACPAs are rarely found in patient with hepatitis C virus</td><td>1. Rheumatoid arthritis 26–90%
2. Sjögren's syndrome 75–95%
3. Mixed connective tissue disease 50–60%
4. Mixed cryoglobulinemia (types II and III) 40–100%
5. Systemic lupus erythematosus 15–35%
6. Polymyositis or dermatomyositis 5–10%
7. Sarcoidosis 15% [7, 21]

ACPAs were found to be positive in the following autoimmune diseases:
1. SLE and primary Sjogrens Syndrome (17%)
2. Psoriatic arthritis (8-16%)</td></tr>
<tr><td>Can RF be used as a screening test?</td><td colspan="3">• Measurement of RF is a poor screening test to diagnose or exclude rheumatic disease in either healthy populations or in those with arthralgias but have no other symptoms or signs of rheumatic disease [20]
• In a population study, it has been found that the presence of both RF and anti-citrullinated protein antibody (ACPA) in apparently healthy people substantially increases the probability of having RA. So the presence of the two autoantibodies (RF and ACPA) is associated with a relative risk of approximately 70% [20]
• The RF has a higher positive predictive value (PPV) if ordered more selectively in patients with a modest or higher chance of having an RF-associated rheumatic disease such as RA, Sjögren's syndrome, or the mixed cryoglobulinemia syndrome. Included in this group are patients with prominent morning stiffness, with sicca symptoms, or with arthralgia or arthritis in a rheumatoid distribution (i.e., symmetric polyarthritis involving small joints) [19]
• Higher titers of RF have a higher positive predictive value for RA [19].</td></tr>
</table>

(continued)

Table 3.2 (continued)

Significance of measuring RF and ACPA in known RA cases	• RF-positive patients with RA may experience more aggressive and erosive joint disease and extra-articular manifestations than those who are RF-negative. Similar findings have been observed in juvenile idiopathic arthritis [19] • RF status may be useful in combination with other indicators, including HLA-DRB1, CRP, the ESR, and severity of synovitis on physical exam, to predict progression of radiographic changes in RA patients and to guide treatment [19] • ACPA positivity was found to be associated with more erosive joint disease, especially apparent on radiographs. It was also found to be better at predicting these changes than RF
RF and monitoring of rheumatic diseases	• The change in RF level does not reflect changes in RA disease activity • RF should not be used routinely to monitor RA disease activity in clinical practice • RF titer may fall with effective treatment of RA in patients who are originally RF-positive [19, 22] • In Sjögren's syndrome, the disappearance of a previously positive RF may herald the onset of lymphoma. That is why some clinicians check RF repeatedly in patients with Sjögren's syndrome. The clinical utility of this practice, however, has not been critically assessed [19, 22]
Antibody status (ACPA/RF)	• RF and ACPA have the potential to revert and convert during the early course of disease. Fluctuations in RF and ACPA were not associated with clinical outcomes [23] • Repeated measurement of ACPA or RF during the first year after onset of arthritis does not offer major additional information [24]
RF and the mortality	Patients with RA with positive RF, especially IgA and IgM isotypes, carry a risk of dying earlier than patients without these serological findings [25]

Table 3.3 ANA characteristics

Positive result	• It is defined as the level of ANA that exceeds the level seen in 95% of the normal population • In most laboratories, this level is a titer of 1:40 to 1:80 that are reported positive • Clinically significant titers in laboratories that use HEp-2 cells as substrate are usually more than or equal to 1:160 [7, 26]			
	Systemic autoimmune diseases	**Organ-specific autoimmune diseases**	**Infections**	**Others**
	1. SLE 93% 2. Scleroderma 85% 3. Mixed connective tissue disease 93% 4. Polymyositis/ dermatomyositis 61% 5. Rheumatoid arthritis 41% 6. Rheumatoid vasculitis 33% 7. Sjögren's syndrome 48% 8. Drug-induced lupus 95–100%; (e.g., procainamide, hydralazine, isoniazid, and quinidine) 9. Discoid lupus 15% 10. Pauci-articular juvenile chronic arthritis 71% [7, 26]	1. Hashimoto's thyroiditis 46% 2. Graves' disease 50% 3. Autoimmune hepatitis 63–91% 4. Primary biliary cirrhosis 10–40% 5. Primary autoimmune cholangitis 100% 6. Idiopathic pulmonary arterial hypertension 40% 7. Multiple sclerosis 25% [7, 26]	– Chronic infectious diseases (mononucleosis, hepatitis C infection, SBE, tuberculosis, and HIV) and some lympho-proliferative diseases – Malignancy (rare) with the exception of dermatomyositis [7, 26]	1. Highly relatives of patient 15–25% 2. Normal elderly 20% 3. Patients with silicone breast implant 15–25% [7]
Is ANA used as a screening test?	– No, it cannot be used as a screening test for autoimmune disorders in the general healthy population in the absence of clinical findings as it may be present in very low specificity titer in normal population 5% – It should be used primarily as a confirmatory test when the clinicians strongly suspect SLE or autoimmune disorders – A patient with a negative ANA and strong clinical evidence of SLE or another SS-A-associated disease, antibodies to SS-A should be ordered [7]			

(continued)

Table 3.2 (continued)

Is ANA used for monitoring diseases?	– No, there is no evidence about use of ANA titer as a monitor to follow disease activity in patients with SLE and autoimmune diseases [7]				
ANA patterns	The pattern type has been found to have relatively low sensitivity and specificity for different autoimmune disorders, and thus tests for specific antibodies have largely replaced the use of patterns				
	The homogeneous or diffuse pattern Represents antibodies to the DNA-histone complex (anti-DNP (LE cell) and anti-histone)	**The peripheral or rim pattern** It is produced by antibodies to DNA (anti-dsDNA) and antibodies to nuclear envelope antigens (anti-laminin)	**The speckled pattern** It is produced by antibodies to SM, RNP, Ro/SSA, La/SSB, Scl-70, centromere, proliferating cell nuclear antigen (PCNA), and other antigens	**The nucleolar pattern** It is produced by antibodies to RNA polymerase I, proteins of the small nucleolar RNP complex (fibrillarin, Mpp10, and hU3–55 K), Th/to, B23, PM-Scl, and NOR-90, and other antigens	**The centromeric pattern** It is produced by antibodies to proteins that are associated with the site of chromosomal constriction. Proteins designated, CENP-A, CENP-B, CENP-C, etc., are only present on active centromeres (i.e., during meiosis and mitosis) [7, 26]
ANA titer	– The presence of very high concentrations of antibody (titer >1:640) should arouse suspicion of an autoimmune disorder. However, its presence alone is not diagnostic of disease – If no initial diagnosis can be made, it is our practice to watch the patient carefully over time and to exclude ANA-associated diseases – An accurate ANA with titer, in combination with a full history and physical examination, can be extremely useful in the diagnosis and exclusion of connective tissue disease [26]				
	– 1–2% of patients who have active and untreated SLE will have a negative ANA, and this is because the substrate used in ANA test did not contain a sufficient antigen to detect SS-A antibodies – 10–15% of SLE patients will become ANA-negative with treatment or inactive disease – 40–50% of SLE patients with end-stage renal disease on dialysis will become an ANA-negative [7]				

3.5 ANA Profile

3.5.1 Definition

An ANA profile consists of many antibodies to measure specific ANAs for certain nuclear antigens. It should be performed when the screening test for ANA is positive and when further information is needed regarding the type of autoimmune disorder [7].

ANA profile antibodies and their specific uses are elaborated on Table 3.4.

3.6 Other Disease-Specific Antinuclear Antibodies and Cytoplasmic Antibodies

These antibodies have to be ordered individually according to the set-up diagnosis based on patient's symptoms and clinical presentations, and they include:

1. **Anti-histone antibodies**: sensitive (70%) for drug-induced lupus but nonspecific and have limited diagnostic utility because they may also be present in patients with SLE. The best test to conduct in patient with suspected drug-induced lupus is antichromatin antibody test, not anti-histone antibody test [7]. However, anti-histone antibody test might be of value in patients having a positive ANA test with history of exposure to medications-induced lupus, such as procainamide (Pronestyl) and isoniazid (INH) [27].
2. **Anti-Th/To antibodies**: crest syndrome 20% [7].
3. **Anti-SCL-70 antibodies** (topoisomerase1): diffuse **systemic** sclerosis (scleroderma) 22–40% [7]. They are highly specific but not sensitive for scleroderma [29].
4. **Anti-tRNA synthetase antibodies (anti-Jo-1, other)**: polymyositis 20–30% [7].
5. **Anti-neutrophil cytoplasmic antibodies (ANCAs)**:

Table 3.4 The standard ANA profile

Measured antibodies	Associated diseases	Characteristics
Anti-dsDNA antibodies (directed against double-stranded DNA)	SLE 60%	– It is very specific for SLE – It is the one that used to follow SLE disease activity; high titers are associated with lupus nephritis or a flare of lupus activity [27]
Anti-U1 RNP antibodies (ribonuclear protein)	SLE 30%, progressive systemic sclerosis (low titer), and mixed connective tissue disease (MCTD)	– A very high level of this antibody is highly suggestive of MCTD [28]
Anti-SM (smith) antibodies	SLE 30%	– It is very specific for SLE – The sensitivity of anti-dsDNA and anti-Sm for the diagnosis of SLE is relatively low – Anti-Sm antibodies generally remain positive, even when a patient has entered remission; therefore it may be especially useful diagnostically when a SLE patient's disease is relatively inactive [28]
Anti-SS-A (RO) antibodies	SLE 30%, primary Sjögren's syndrome 70%, neonatal lupus, sub-acute cutaneous lupus (SCLE), secondary Sjögren's syndrome (rare) [28]	
Anti-SS-B (LA) antibodies	SLE 15%, Sjögren's syndrome 60% [28]	
Anti-centromere antibodies	Crest syndrome 98%, diffuse scleroderma 22–36% [28]	

- **Cytoplasmic anti-neutrophil cytoplasmic antibodies (C-ANCA)**, the most common c-ANCA target is serine proteinase-3: granulomatous polyangiitis (GPA) (Wegener granulomatosis) 90%, microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA) (rare). Its titer can correlate with GPA disease activity [30].
- **Perinuclear anti-neutrophil cytoplasmic antibodies (P-ANCA)**, the most common p-ANCA target is myeloperoxidase: MPA 70%, pauci-immune glomerulonephritis, and EGPA, or myeloperoxidase (−)—ulcerative colitis, chronic infection, and neoplasm (rare) [30].

6. **Anti-mitochondrial antibodies (AMAs)**: primary biliary cirrhosis 80% [7].
7. **Antibodies to the gp210 and p62 proteins of the nuclear pore complex**: primary biliary cirrhosis 10–40% [7].

3.7 Circulatory Complement Components

Complement is an important effector pathway of innate immunity and has a role in the pathogenesis of some of rheumatic conditions, namely, SLE.

Causes of Decreased Circulatory Complement Components

- Hereditary complement deficiencies (decreased production)
- Secondary complement deficiencies (acquired) [31]

3.7.1 Mechanism of Acquired Complement Deficiencies

1. Increased level of circulatory immune complexes (increased consumption of complements) due to:
   - Infectious causes
   - Glomerulonephritis
   - Rheumatic diseases:
     (a) **SLE**: Low C4 and C3 levels occur in about 50% of patients with SLE. Levels of C3 and C4 are decreased with increased severity of SLE, especially renal disease. A return to normal levels with treatment is a good prognostic sign. Serial observations reveal decreased levels preceding clinical exacerbation.
     (b) **Cryoglobulinemia**: The complement profile shows decreased levels of C4 and C2 with normal or slightly lowered C3.
     (c) **Systemic vasculitis** especially polyarteritis nodosa, urticarial vasculitis: 50% of patients with polyarteritis may have decreased serum complement levels. Its values can be helpful in assessing the clinical course, especially the response to therapy.
     (d) **RA** with extra-articular manifestation (rare) [7, 32].
2. Reduced hepatic synthesis (uncommon)
3. Loss of complement components in the urine (rare) [30]

3.8 Synovial Fluid Analysis

The presentation of one or more hot, swollen joints is a common medical emergency, and synovial fluid aspiration, the so-called arthrocentesis, is the single most important test helping in the diagnosis of different types of arthropathies [33].

Therefore, specialized laboratories analyze synovial fluid to either confirm the diagnosis of crystal-associated arthropathies, support the diagnosis of septic arthritis, or establish other rheumatologic diagnoses such as mono-arthritis or joint effusion [34].

The complete analysis of synovial fluid includes macroscopic (gross appearance), microscopic, and specific stain tests to provide detailed information about the joint's condition and helps in establishing the diagnosis and treatment [35]. Description of macroscopic analysis of synovial fluid includes color, clearance, volume, and viscosity. However, the microscopic analysis can differentiate between inflammatory and infectious processes by measuring a complete leukocyte count. In addition, a differential of the synovial WBC count should be ordered, so that if the results came positive for infectious process, the performance of Gram-stain and culture tests will provide guidance to diagnosis and/or antibiotic therapy [36].

Microscopic examination specifically can also allow the detection and identification of various types of crystal by using polarized light microscope. Refer to Table 3.5 for an overview on important issues as regards arthrocentesis and synovial fluid analysis. However, Table 3.6 shows the classification of joint effusions into normal, inflammatory, non-inflammatory, and septic effusion based on clinical and laboratory analysis of synovial fluid with the causes of each type [37, 38]. Indications, contraindications, complications, and specimen analysis of synovial fluid are presented in Table 3.5. Classification and causes of joint effusions based on laboratory analysis of synovial fluid are presented in Table 3.6. Fig. 3.1 is the clinical diagnostic approach for painful peripheral joint.

3.9 Key Notes

- The likelihood diagnosis of septic arthritis is markedly increased with higher synovial WBC counts. It has been illustrated that for synovial WBC count the likelihood ratio (LR) of having septic arthritis is as follows [34]:
  – WBC count <25,000/μL, the LR is 0.32 at 95% CI.
  – WBC count ≥25,000/μL the LR is 2.9 at 95% CI.
  – WBC count >50,000/μL, the LR is 7.7 at 95% CI.

Table 3.5 Overview on arthrocentesis and synovial fluid analysis

Indications	Contraindications	Complications	Specimen handling	Synovial fluid analysis
1. According to the American College of Rheumatology (ACR), synovial fluid analysis should be performed in the febrile patient with an acute flare of established arthritis to rule out superimposed septic arthritis 2. Unexplained joint, bursa, or tendon sheath swelling 3. Suspected crystal-induced arthritis 4. Repeated aspiration and analysis may be indicated to follow up the response of septic arthritis to treatment and may also be valuable for diagnosis of some cases of gout in which the initial aspirate does not have detectable crystals [34]	1. There is no absolute contraindication 2. Bleeding diatheses and cellulites are considered as relative contraindication; it could make the approach to the joint space difficult due to the overlying swelling [37]	1. Infection 2. Hemarthrosis 3. Pain 4. Cartilage injury 5. Vasovagal syncope [37]	1. Aspiration is performed under aseptic technique with quick transfer of specimen for culture to the sterile tubes and plated as soon as possible 2. If the transfer is delayed more than 6 hours, many changes would occur, for example, decrease in leukocyte count or decrease in crystal numbers [36]	The WBC count and the percentage of PMN cells can help to differentiate between non-inflammatory, inflammatory, and septic joint conditions. These tests are the best diagnostic tool available for detecting bacterial arthritis [36] 1. Gram stain and cultures should be ordered even with relatively low suspicion of infection 2. Crystal search using polarized light microscopy 3. Chemistry analysis should not be routinely ordered [37]

Table 3.6 Classification and causes of joint effusions based on laboratory analysis of synovial fluid

Fluid features	Normal	Non-inflammatory	Inflammatory	Pyarthrosis or septic arthrosis
Appearance	Clear, highly viscous, colorless	Clear to slightly turbid	Slightly turbid, yellow or yellow-green	Turbid to very turbid, yellow or yellow-green
Total WBC count/MM3	0–200	200–2000	2000–50,000	50,000–150,000
Polymorphonuclear cell (PMN)%	<10%	<20%	20–70%	≥75%
Causes		– Osteoarthritis – Joint trauma – Hypertrophic osteoarthropathy – Neuropathic arthropathy – Avascular necrosis [37, 38]	– RA – Gout – Pseudogout – Psoriatic arthritis – AS – SLE – Reiter syndrome – Sarcoidosis – Rheumatic fever – Wegener granulomatosis – Infectious arthritis – SBE [37, 38]	1. It is a septic arthritis until proven otherwise by the fluid culture 2. Pseudosepsis include reactions to intra-articular injections, gout, Reiter's syndrome, leukemic infiltration, and RA [37, 38]

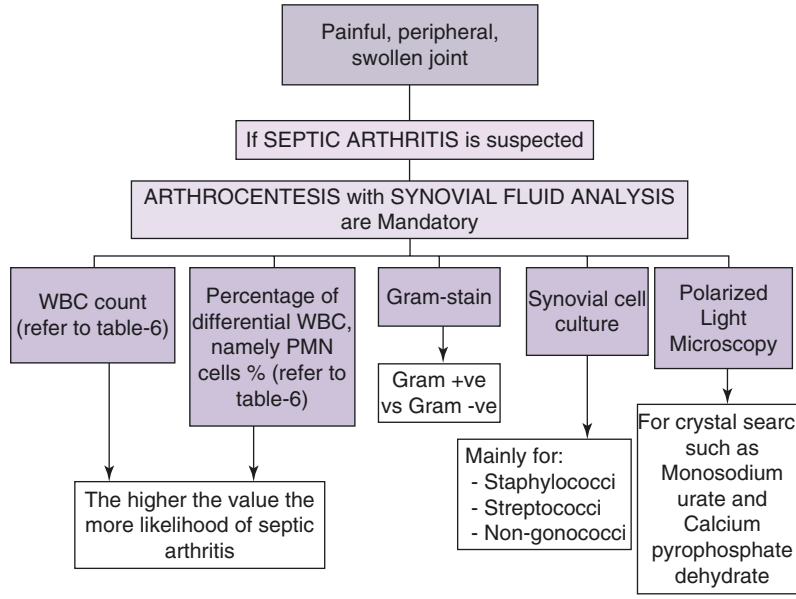

Fig. 3.1 Clinical approach for painful peripheral joint

  - WBC count >100,000/μL, the LR is 28.0 at 95% CI.
- Polymorphonuclear (PMN) cells of 90% are associated with increasing likelihood of septic arthritis of 3.4, while if the percentage of PMN cells is less than 90%, the likelihood decreases down to 0.34 (95% CI) that supports the clinician's suspicion of bacterial arthritis [38, 39].
- Eosinophilic cells in the synovial fluid suggest parasitic infection, allergy, Lyme disease, or neoplasm [40].
- If there is a suspicion of joint involvement by a neoplasm or hematologic malignancy, formal cytological examination should be ordered [38].
- Hemorrhagic effusions may be caused by hemophilia, anticoagulation or other bleeding diathesis, scurvy, trauma, neuropathic arthropathy, and tumors [38].

3.9.1 Gram Stain

- It is used to identify common bacterial organisms (Gram-positive versus Gram-negative coverage) for the diagnosis and treatment of septic arthritis.
- It may be the only evidence of infection with fastidious organisms that are not able to grow in culture [41].
- The *sensitivity* is not known precisely.
  - In non-gonococcal bacterial arthritis, it is in range from 50% to 70%.
  - In gonococcal arthritis, it is <10% [41].
- The *specificity* is high when performed and interpreted by an experienced clinician or technician [41].

3.9.2 Synovial Fluid Culture

- The synovial fluid samples should be routinely sent for culture for staphylococci followed by streptococci and Gram-negative bacteria (non-gonococcal causes).
- Antibiotics should generally not be given prior to joint aspiration [42, 43].
- **The specificity**: Positive synovial culture should be indicative of septic arthritis in 100% of cases with exclusive of contamination and laboratory error [42, 43].
- **The sensitivity**: It is not known precisely because of the lack of an alternative gold standard. The joint aspirate should be cultured for

Table 3.7 Gout versus pseudo-gout

	Crystal	Shape	Birefringence	Color of crystals parallel to axis of red-plate compensator
Gout	Monosodium urate (MSU)	Needle	Negative	Yellow
Pseudogout	Calcium pyrophosphate dehydrate (CPPD)	Rhomboid or rectangular	Positive	Blue [48]

N. gonorrhoeae or unusual organisms (TB, Lyme disease, or fungal infections) when the history is suggestive [42, 43].

3.9.3 Diagnostic Approach

- It should be noted that the absence of organisms on Gram stain or a negative subsequent synovial fluid culture does not rule out the diagnosis of septic arthritis especially if clinical suspicion is high. In such condition, an empirical treatment of the case as septic arthritis should be implemented [44–46].
- Moreover, it has been suggested that the "gold standard" for the diagnosis of septic arthritis is the level of clinical suspicion by an expert physician in the management of patients with musculoskeletal disease [35, 45].
- Similarly, another study had concluded that combining Gram stain and culture of synovial fluid with clinical follow-up is the best approach used to detect patients missed by Gram stain and culture alone [36].

3.9.4 Crystal Search Using Polarized Light Microscopy

Polarized light microscope (PLM) is a fundamental tool for detection and identification of various types of crystals present in synovial fluid depending on their shape (needle, rhomboid, cigar-shaped, etc.) birefringence, location (intracellular or extracellular), and quantity (scarce or plentiful). The obtained results of PLM help the clinicians in diagnosing and managing a case of monoarthritis. However, the presence of artifacts in microscopic analysis can confuse the inexperienced observer; therefore, a suitable interpretation of the synovial fluid analysis using PLM requires at least two experienced observers [47]. The microscopic features of common types of crystals that can differentiate between clinical cases of gout and pseudogout are illustrated in Table 3.7.

3.10 Summary

Due to the fact that musculoskeletal symptoms are exceedingly common compared with the prevalence of systemic rheumatic disease, the pretest probability of systemic rheumatic disease in the population is rather low compared with musculoskeletal symptoms that are nearly ubiquitous. Therefore, establishing the diagnosis of a rheumatic disease may require exclusion of other differential diagnoses that present in a similar fashion. Even the disease established-guidelines, which are often used by clinicians, perform poorly during the assessment of a patient presenting with new polyarthritis [49]. As a consequence, widely used laboratory tests can be very specific and permit rapid diagnosis and appropriate management. However, clinicians should be aware of the false-positive tests that may result in inappropriate management and unnecessary concern.

Generally, serum rheumatologic tests are most helpful for confirming a clinically suspected diagnosis. For instance, testing for RF is appropriate when suspecting RA, Sjögren's syndrome, or cryoglobulinemia, whereas ANA testing is highly sensitive for SLE and drug-induced lupus. Although an elevated ESR is a sensitive test for polymyalgia rheumatica and temporal arteritis, its specificity is quite low. In addition, ESR levels are frequently linked to the disease activity in rheumatoid arthritis and may found to be of value for monitoring therapeutic response. However, anti-double-stranded

DNA antibodies are usually associated with lupus nephritis, and their titer often correlates with disease activity in SLE. On the other hand, cytoplasmic anti-neutrophil cytoplasmic antibody test is highly sensitive and specific for GPA.

In order to increase the utility and decrease the cost-effectiveness of the laboratory testing of rheumatic disease, these tests should be used more selectively and avoid absolute overreliance on lab results. However, a logic combination of the clinical background and the testing results would provide the appropriate diagnosis of the rheumatic conditions. Finally, as Shmerling RH has stated, "the passage of time is one of most useful diagnostic tests as many patients with musculoskeletal symptoms improve over time without a clear diagnosis" [50].

Acknowledgments The authors would like to thank Dr. Waleed Hafiz for his assistance in the development of this chapter.

Abbreviations

(IL)-6	Interleukin-6
AMAs	Anti-mitochondrial antibodies
ANA	Antinuclear antibody profile
ANCAs	Anti-neutrophil cytoplasmic antibodies
anti-dsDNA	Anti-double-stranded DNA antibodies
anti-gp210	Anti-glycoprotein-210 antibodies
anti-p62	Anti-protien-62 antibodies
anti-SCL-70	Anti-topoisomerase1 antibodies
anti-Th/To	Antibodies to Th/To ribonucleoprotein
APRs	Acute phase reactants or proteins
AS	Ankylosing spondylitis
C4 and C3	Complements
C-ANCA	Cytoplasmic anti-neutrophil cytoplasmic antibodies
CI	Confidence interval
CRP	C-reactive protein
EGPA	Eosinophilic granulomatosis with polyangiitis
ELISA	Enzyme-linked immunosorbent assay
ESR	Erythrocyte sedimentation rate
GPA	Granulomatous polyangiitis
HEp2 cells	Human epithelial cell tumor line
HLA-B27	Human leukocyte antigen B27
HLA-DR	Human leukocyte antigen MHC class II
IgG	Immunoglobulin G
IL-1	Interleukin-1
INH	Isoniazid
LR	Likelihood ratio
MPA	Microscopic polyangiitis
MPA	Myeloperoxidase
P-ANCA	Perinuclear anti-neutrophil cytoplasmic antibodies
PLM	Polarized light microscope
PMN	Polymorphonuclear cells
Pronestyl	Procainamide
RF	Rheumatoid factor
RNP	Anti-ribonucleic protein antibodies
SLE	Systemic lupus erythematosus
TNF-alpha	Tumor necrosis factor-alpha
WBC	White blood cell count

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4 Pharmacotherapy in Systemic Rheumatic Diseases

Layla Borham and Waleed Hafiz

4.1 Introduction

Over the past two decades, better understanding of the immunopathophysiologic basis of various rheumatic diseases led to the discovery of variety of drugs that are now approved and widely used in clinical practice. These drugs are categorized into the following categories: nonsteroidal anti-inflammatory drugs (NSAIDs), synthetic disease-modifying anti-rheumatic drugs (sDMARDs), biological disease-modifying anti-rheumatic drugs (bDMARDs), corticosteroids and drugs used in crystal-induced arthritis. Few other drugs are also used by rheumatologists. These include anti-resorptive drugs and symptom-specific drugs.

4.2 Learning Objectives

By the end of this chapter, you should be able to:

- Recall the main drug categories used in the treatment of systemic rheumatic diseases
- Explain the mechanism of action, dosages, indications, adverse effects, cautions, contra-indications and pregnancy category of each drug

4.3 Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Nonsteroidal anti-inflammatory drugs (NSAIDs) are effective anti-inflammatory, antipyretic and analgesic drugs. Although they differ widely in their chemical class, they share the property of blocking the production of prostaglandins (PGs). This is achieved by inhibiting the activity of the enzyme prostaglandin G/H synthase (PGHS), also called *cyclooxygenase* (COX).

There are two different COX isoforms, COX-1 and COX-2. Inhibition of COX-2 by NSAIDs blocks PG production at sites of inflammation, while inhibition of COX-1 in certain other tissues, most importantly platelets and the gastroduodenal mucosa, can lead to common adverse effects of NSAIDs such as bleeding, bruising and gastrointestinal ulceration [1].

In addition to their use in rheumatoid arthritis and osteoarthritis, NSAIDs are widely used in the symptomatic management of other rheumatic diseases characterized by chronic musculoskeletal pain and diverse forms of acute pain.

L. Borham
Clinical Pharmacology Department
Faculty of Medicine, Umm Al-Qura and Cairo University, Makkah, Saudi Arabia
e-mail: borhaml@hotmail.com

W. Hafiz (✉)
Faculty of Medicine, Umm Al-Qura University, Makkah, Saudi Arabia
e-mail: wahafiz@uqu.edu.sa

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NSAIDs are associated with elevated cardiovascular disease risk and risk for gastrointestinal bleeding and ulceration [2, 3]. For that, it is important to identify patients with these risks, and if present, avoiding NSAIDs or using intermittent, low-dose and short half-life drugs is advisable. It is also important to know that use of NSAIDs together with aspirin, which is an NSAID too, can increase gastrointestinal toxicity and lead to aspirin resistance [4].

Patients who take regular doses of NSAIDs should undergo periodic assessment of blood pressure, haemoglobin level, electrolytes and renal and liver function tests.

Complete details about different NSAIDs are shown in Table 4.1

4.4 Synthetic Disease-Modifying Anti-Rheumatic Drugs (sDMARDs)

This category consists of drugs that have been used as first-line therapies in the majority of systemic rheumatic diseases. Although their precise mechanism of action is still incompletely understood, they have both anti-inflammatory and immunomodulatory effects.

Generally, the choice of a sDMARD therapy should be decided for each patient individually. This should also give attention to patient's age, fertility plans, comorbid conditions and other concomitant drugs. Adverse effects from sDMARDs may cause significant morbidity and mortality. So, appropriate dosing and monitoring for toxicity are required.

4.4.1 Methotrexate

Over the past 25 years, methotrexate has become the sDMARD of choice in the treatment of rheumatoid arthritis and is used in many other rheumatic diseases as well (psoriasis, psoriatic arthritis, polymyositis, dermatomyositis, granulomatosis with polyangiitis, giant cell arteritis, subacute lupus erythematosus, scleroderma and vasculitis).

Methotrexate increases the concentration of adenosine, which is a potent inhibitor of inflammation. It also inhibits the enzyme dihydrofolic acid reductase [5].

The effects of methotrexate can be enhanced by using the subcutaneous form instead of the oral form or by splitting the oral dose (within 12-h window) when doses greater than 15 mg weekly are given [6]. Doses should be adjusted based on renal and hepatic function.

A weekly oral dose of folic acid 5–10 mg given 48–72 h post methotrexate dose protects against mucosal ulceration and keeps folic acid levels optimum [7].

4.4.2 Leflunomide

Leflunomide is approved for the treatment of rheumatoid arthritis. It has both anti-inflammatory and immunomodulatory effects. It inhibits the enzyme dihydroorotate dehydrogenase and pyrimidine synthesis [8].

Loading doses are not used in clinical practice due to gastrointestinal toxicity. Leflunomide is found to have a very long half-life because of its enterohepatic recirculation [9]. It is absolutely contraindicated in pregnancy.

4.4.3 Azathioprine

It is an imidazolyl derivative of mercaptopurine. It antagonizes purine metabolism and may inhibit the synthesis of DNA, RNA and proteins. It also inhibits cellular metabolism [10].

Azathioprine can be effective as a glucocorticoid-sparing agent in remission maintenance therapy, particularly in systemic lupus erythematosus and necrotizing vasculitis.

Table 4.1 Nonsteroidal anti-inflammatory drugs (NSAIDs)

Mechanism of action	Indication and doses	Adverse effects and caution	Pregnancy and lactation
	Ibuprofen		**Ibuprofen**
Inhibit COX-1 and COX-2 isoenzymes, thus inhibiting prostaglandin synthesis and release of inflammatory mediators	**Pain:** 300–800 mg PO q6hrs **Fever:** 100–200 mg PO q4–6hrs PRN **Inflammatory diseases:** 400–800 mg PO q6–8hrs **Osteoarthritis:** 300 mg, 400 mg, 600 mg or 800 mg PO q6–8hrs; not to exceed 3.2 g/day **Rheumatoid arthritis:** 300–800 mg PO q6–8hrs; not to exceed 3.2 g/day	May cause elevated creatinine or liver enzymes in patients with active SLE. Gastrointestinal complaints like erosion, ulceration or bleeding Hepatotoxicity, asthma, rashes, itchiness, tinnitus, dizziness, headache and aseptic meningitis (particularly in patients with systemic lupus erythematosus) Fluid retention and renal toxicity occur less frequently **Drug interactions:** 1. Concomitant administration with aspirin will antagonize the irreversible platelet inhibition induced by aspirin 2. Reduce the natriuretic effect of furosemide and thiazides in some patients 3. May also increase lithium plasma levels due to decreased renal clearance 4. Use of NSAIDs with ACE inhibitors may potentiate renal disease states 5. Concomitant administration with prednisone may increase the risk of GIT ulceration	Pregnancy category: C or D at 30 weeks of gestation or more May cause premature closure of ductus arteriosus Lactation: Excreted into breast milk, use not recommended
	Naproxen		**Naproxen**
	Pain: 500 mg PO initially followed by 250 mg PO q6–8hrs PRN; alternatively, 500 mg q12hr. Not to exceed 1250 mg/day PO **Rheumatoid arthritis, ankylosing spondylitis or osteoarthritis:**500–1000 mg PO divided q12hrs. Not to exceed 1500 mg/day PO		Pregnancy category: B or D if used for prolonged periods or near term Lactation: Excreted into breast milk, use should be carefully evaluated
	Meloxicam		**Meloxicam**
	Rheumatoid arthritis, osteoarthritis or ankylosing spondylitis: 7.5–15 mg PO daily; not to exceed 15 mg/day		Pregnancy category: C or D at 30 weeks of gestation or more May cause premature closure of ductus arteriosus Lactation: Excretion into breast milk is unknown, use not recommended
	Celecoxib		**Celecoxib**
Inhibits COX-2 isoenzymes (does not affect COX-1), thus inhibiting synthesis of prostaglandin and release of the inflammatory mediators	**Rheumatoid arthritis, osteoarthritis or ankylosing spondylitis:** 200 mg PO once daily or divided Q12hr	Headache, hypertension, abdominal pain, nausea and vomiting Fluid retention and renal toxicity occur less frequently Increased risk of cardiovascular events and gastrointestinal toxicity	Pregnancy category: C or D at 30 weeks of gestation or more May cause premature closure of ductus arteriosus Lactation: Excreted into breast milk, use should be carefully evaluated

It can induce severe myelosuppression in patients with low or absent thiopurine methyltransferase (TPMT) activity that is affected by a polymorphism that can be identified by genetic screening [11]. Severe myelosuppression can also occur in patients with normal TPMT activity, and regular monitoring of white blood cell counts is recommended.

Azathioprine interacts with allopurinol and this can lead to fatal myelosuppression. Concomitant use of these two drugs should be avoided.

4.4.4 Hydroxychloroquine

It is an anti-malarial drug and a well-tolerated sDMARD that is now used as a cornerstone therapy in patients with systemic lupus erythematosus and in combination therapy regimens for rheumatoid arthritis [12].

Hydroxychloroquine is more commonly used than chloroquine. It has a very long half-life, attributed to its affinity for melanin-containing cells in the skin. Doses of hydroxychloroquine should not exceed 6.5 mg/kg/day in chronic therapy to minimize the risk of retinal toxicity [13]. Although routine laboratory monitoring is not required, ophthalmologic screening is an essential component of toxicity monitoring.

Diabetic patients initiating hydroxychloroquine should be instructed to follow blood sugars closely because of the hypoglycaemic effects of the drug.

Hydroxychloroquine is considered safe in pregnancy; it is recommended that most pregnant patients with SLE remain on the drug to improve pregnancy outcomes.

4.4.5 Sulfasalazine

It is a sDMARD that has both antimicrobial and anti-inflammatory properties. The exact mechanism of action is unknown. However, it is a 5-aminocyclic acid derivative that inhibits leukotriene synthesis [14].

Sulfasalazine is commonly used as part of combination therapy for rheumatoid arthritis. Its dose should be increased gradually with regular laboratory monitoring to minimize the risk of adverse effects and drug intolerance.

Gastrointestinal intolerance and rash are common side effects. Monitoring complete blood counts, liver transaminases and creatinine levels should be done periodically during therapy [15].

4.4.6 Mycophenolate Mofetil

It is a powerful inhibitor of lymphocyte proliferation that has a potential glucocorticoid-sparing effect. It is used for the treatment of patients with various rheumatic diseases. It inhibits inosine monophosphate dehydrogenase enzyme which decreases T- and B-cell proliferation and antibody production [16].

Mycophenolate mofetil can be used as a remission induction agent in lupus nephritis and is now increasingly used for remission maintenance treatment of systemic lupus erythematosus and necrotizing vasculitis [17].

It is generally well tolerated, although diarrhoea and leucopenia may necessitate its discontinuation. Complete blood counts should be performed within the first 2 weeks of therapy and then once every 6–8 weeks thereafter if no cytopenia is noted [18].

4.4.7 Cyclophosphamide

It is an alkylating agent and one of the most potent immunosuppressive therapies available. It is a prodrug which prevents and inhibits cell division [19].

The indications for its use include induction of remission in lupus nephritis. It is also used to treat rheumatoid vasculitis, interstitial lung disease associated with connective tissue diseases and many types of systemic vasculitides.

Although very effective, it has the potential for devastating toxicity both in the short and long term. Its toxicities include myelosuppression, infection, ovarian failure, haemorrhagic cystitis and malignancy including bladder cancer, especially with high cumulative doses.

The intermittent intravenous doses given every 3–4 weeks are associated with less bladder toxicity compared to oral daily doses [20]. To further minimize bladder toxicity, intravenous fluids, anti-emetics and MESNA (2-mercatpoethanesulfonic acid) may be used.

4.4.8 Tofacitinib

Tofacitinib is a targeted sDMARD that is now approved for the treatment of rheumatoid arthritis. It inhibits the enzymes janus kinase 1 (JAK1) and janus kinase 3 (JAK 3) and thus prevents the phosphorylation and activation of signal transducers and activators of transcription (STATs), which transmit extracellular information into the cell nucleus, influencing DNA transcription [21].

The most commonly reported adverse effects which occur in less than 5% of patients treated with tofacitinib are upper respiratory tract infections, headache, diarrhoea and nasopharyngitis. Neutropenia and lymphopenia are also reported in less than 1% of patients and laboratory monitoring is recommended.

4.4.9 Apremilast

This sDMARD is now approved for the treatment of psoriatic arthritis and psoriasis. It is a small molecule inhibitor of phosphodiesterase-4 (PDE4), which breaks down cyclic adenosine monophosphate (cAMP) in inflammatory cells. This results in down-regulation of the expression of a number of the pro-inflammatory factors like tumour necrosis factor alpha (TNFα), interleukin-17, interleukin-23 and many others and up-regulation of the anti-inflammatory interleukin-10.

Headache, back pain, nausea, diarrhoea, fatigue, nasopharyngitis, upper respiratory tract infections and weight loss are common adverse effects and are reported in up to 10% of patients taking apremilast [22].

Complete details about different sDMARDs are shown in Table 4.2.

4.5 Biological Disease-Modifying Anti-Rheumatic Drugs (bDMARDs)

The bDMARDs target specific components of the immune response that are dysregulated and are thought to be the cause of the disease process. These components are called pro-inflammatory cytokines. Tumour necrosis factor (TNF), interleukin-1 (IL-1), interleukin-6 (IL-6) and others

Table 4.2 Synthetic disease-modifying anti-rheumatic drugs (sDMARDs)

Drug name	Mechanism of action	Indication and doses	Adverse effects and caution	Pregnancy and lactation
Methotrexate (Trexall)	Inhibits the enzyme dihydrofolic acid reductase	**Rheumatoid arthritis:** 10–25 mg weekly in single PO dose, not to exceed 30 mg 15–25 mg SC weekly if tablets are not tolerable **Juvenile rheumatoid arthritis:** 10 mg/m^2 PO/IM weekly, then 5–15 mg/m^2 weekly in single dose or in 3 divided doses given q12hrs **Dosing modifications:** Renal impairment 1. CrCl 61–80 mL/min: Give 75% of dose 2. CrCl 51–60 mL/min: Give 70% of dose 3. CrCl 10–50 mL/min: Give 30–50% of dose at normal dosing interval 4. CrCl<10 mL/min: Avoid use Hepatic impairment 1. Bilirubin 3.1–5.0 mg/dL or AST >180 international units/L: Give 75% of dose 2. Bilirubin >5.0 mg/dL: Avoid use	Most commonly ulcerative stomatitis, leucopenia, nausea and abdominal distress A weekly dose of folic acid 5–10 mg given 48–72 h post methotrexate dose protects against mucosal ulceration and keeps folic acid levels optimum High doses can cause severe haematologic and gastrointestinal toxicity Progressive dose-related hepatotoxicity in the form of enzyme elevation occurs frequently, but cirrhosis is rare (< 1%) A rare "hypersensitivity" lung reaction with acute shortness of breath *Drug interactions*: NSAIDs and salicylate administered concomitantly with lower doses of methotrexate, reduce the tubular secretion of methotrexate and may enhance its toxicity Trimethoprim antibiotic may increase the toxicity of methotrexate	Pregnancy category: X Lactation: Excreted into breast milk, do not nurse **Methotrexate toxicity** Leucovorin is an antidote that restores folate and displaces intracellular methotrexate Oral, IV, or IM 15 mg (approximately 10 mg/m^2) every 6 h until methotrexate concentration declines to <0.005 mcg/mL (0.01 μM) If 24-h S_{cr} increases 50% over baseline, 24-h methotrexate concentration is >2.27 mcg/mL (5 μM, or 48-h methotrexate concentration is >0.409 mcg/mL (0.9 μM); increase leucovorin dosage immediately to 150 mg (approximately 100 mg/m^2) IV every 3 h until methotrexate concentration declines to <0.005 mcg/mL (0.01 μM)
Leflunomide (Arava)	Reversibly inhibits pyrimidine synthesis	**Rheumatoid arthritis:** 10–20 mg PO daily Dosing modifications: Can be used safely in renal impairment Cholestyramine 8 g PO TID for 11 days to wash out drug's active metabolite prior to conceive	Diarrhoea, respiratory infections, alopecia, hypertension, skin rash, gastrointestinal symptoms and liver injury are common **Contraindicated in:** 1. Active liver disease (ALT is double) 2. Active infections 3. Myelosuppressive diseases	Pregnancy category: X Lactation: Excretion into breast milk is unknown; do not nurse

Azathioprine (Imuran)	A 6-mercaptopurine derivative, inhibits the synthesis of both DNA and RNA Also inhibits cellular metabolism	**Rheumatoid arthritis:** Initial: 1 mg/kg IV/PO daily or divided BID, may increase as follows: 1. By 0.5 mg/kg/day after 6–8 weeks 2. By 0.5 mg/kg/day q4Weeks, no more than 2.5 mg/kg/day 3. Maintenance: Reduce dose by 0.5 mg/kg q4Weeks until lowest effective dose reached **Lupus nephritis:** Induction and maintenance therapy: 2 mg/kg/day PO with or without low-dose corticosteroids	Bone marrow suppression, anaemia, skin rashes, fever, nausea, diarrhoea and some increase in infection risk Rarely, fever, rash and hepatotoxicity signal acute allergic reactions **Drug interactions:** Allopurinol will decrease the metabolism of azathioprine	Pregnancy category: D Lactation: Excreted into breast milk at low levels, use not recommended
Hydroxychloroquine (Plaquenil)	Suppresses response of T lymphocyte mitogens Decreases WBC chemotaxis Stabilizes lysosomal enzymes Inhibits DNA and RNA synthesis. Traps free radicals	**Rheumatoid arthritis and systemic lupus erythematosus:** 200–400 mg daily. Not to exceed 6.5 mg/kg/day	Dizziness, nightmares, rash, itching, aplastic anaemia, leucopenia, alopecia, thrombocytopenia, nausea, vomiting, diarrhoea and abdominal cramps Corneal changes or deposits and retinal damage with long-term use Skin and musculoskeletal pigmentation	Pregnancy category: C Lactation: Compatible with nursing
Cyclosporine (Neoral)	Calcineurin inhibitor that suppresses both cellular and humoral immunities	**Rheumatoid arthritis:** 3–5 mg/kg/day divided into two doses	Nephrotoxicity. Drugs that inhibit CYP3A like diltiazem and potassium-sparing diuretics increase nephrotoxicity. So, serum creatinine should be closely monitored Other toxicities include hypertension, hyperglycaemia, gum hyperplasia, gingival hyperplasia, hyperkalaemia, hepatotoxicity and hirsutism	Pregnancy category: C Lactation: Excreted into breast milk, use not recommended
Sulfasalazine (Azulfidine)	5-Aminocyclic acid derivative inhibits leukotriene synthesis	**Rheumatoid arthritis:** Enteric coated: 2–3 g/day divided into 3 doses. Dose should be increased gradually	Tinnitus, hearing loss, hepatotoxicity and gastrointestinal complaints like erosion, ulceration or bleeding and drug rash	Pregnancy category: B or D if used for prolonged periods or near term. Increases kernicterus risk Lactation: Excreted into breast milk, used with care

(continued)

Table 4.2 (continued)

Drug name	Mechanism of action	Indication and doses	Adverse effects and caution	Pregnancy and lactation
Mycophenolate (Cellcept)	Inhibits inosine monophosphate dehydrogenase Inhibits T and B-cell proliferation and antibody production	**Class III/IV lupus nephritis:** Induction: 1 g PO q12hrs for 6 months Maintenance: 0.5–3 g/day or 1 g PO BID Administer with initial IV corticosteroid pulse for 3 days and then prednisone 0.5–1 mg/kg/day PO; after a few weeks, taper prednisone to lowest effect dose	Hyperglycaemia, hyperkalaemia, increased urea, hypertension, various infections, hypocalcaemia, hypercholesterolaemia and hypomagnesaemia Vomiting and diarrhoea are common Hepatic toxicities are infrequent but must be monitored	Pregnancy category: D Lactation: Excretion into breast milk is unknown, use not recommended
Cyclophosphamide (Cytoxan)	Immunosuppressive, a pro-drug which prevents and inhibits cell division	**Juvenile idiopathic arthritis/ vasculitis:** 10 mg/kg IV every 2 weeks **Lupus nephritis:** Induction therapy is by one of the following: 1. Low dose: 500 mg IV every 2 weeks for 6 doses plus corticosteroids, then maintenance with mycophenolate mofetil or azathioprine 2. High dose: 500–1000 mg/m^2 IV monthly for 6 doses plus corticosteroids **Dosing modifications:** Hepatic impairment: Give 75% of normal dose if transaminase levels are >3 times upper limit of normal or bilirubin is 3.1–5 mg/dL Renal impairment: CrCl<10 mL/min, give 75% of normal dose; CrCl>10 mL/min, give full dose	Can cause significant dose-related infertility in both men and women Nausea and vomiting, bone marrow suppression, alopecia, haemorrhagic cystitis and, rarely, bladder carcinoma	Pregnancy category: D Lactation: Excreted into breast milk, use not recommended

Tofacitinib (Xeljanz)	Inhibits the JAK-STAT signalling pathway	**Rheumatoid arthritis:** 5 mg PO Q12hrs or 11 mg of the extended-release tablet daily **Dosing modifications:** Co-administration with cytochrome P450 3A4 inhibitors: Not to exceed 5 mg daily Moderate renal or hepatic impairment: Reduce dose to less than 5 mg daily It has not been studied in patients with severe haptic impairment or in patients with CrCl <40 mL/min	Upper respiratory tract infections, headache, diarrhoea, nasopharyngitis, neutropenia and lymphopenia No contraindications have been listed	Pregnancy category: C Lactation: Excretion into breast milk is unknown, use not recommended
Apremilast (Otezla)	Small molecule inhibitor of PDE-4	**Active psoriatic arthritis or plaque psoriasis (moderate to severe):** Day 1: 10 mg PO in AM Day 2: 10 mg AM and PM Day 3: 10 mg AM and 20 mg PM Day 4: 20 mg AM and PM Day 5: 20 mg AM and 30 mg PM Day 6 and thereafter: 30 mg BID **Dosing modifications:** Mild to moderate renal or hepatic impairment, no adjustment required CrCl <30 mL/min: Reduce dose to 30 mg daily	Headache, back pain, nausea, diarrhoea, fatigue, nasopharyngitis, upper respiratory tract infections and weight loss Worsening depression, suicidal thoughts and other mood changes may also occur Concurrent use of strong cytochrome P450 enzyme inducers can result in loss of apremilast efficacy	Pregnancy category: C Lactation: Excretion into breast milk is unknown, use not recommended

are the pro-inflammatory cytokines found in the rheumatoid synovium. Few other bDMARDs target B and T cells. These agents have considerable efficacy in the treatment of patients with rheumatoid arthritis and other systemic inflammatory disorders.

4.5.1 TNF-α Blockers

Five TNF-α inhibitors are approved for the treatment of selected rheumatic disease by the United States Food and Drug Administration. These are adalimumab, etanercept, infliximab, golimumab and certolizumab.

A 2008 systematic review of synthetic and biologic DMARD therapy for rheumatoid arthritis concluded that anti-TNF monotherapy was similar in efficacy to treatment with methotrexate alone, while the combination of an anti-TNF agent with methotrexate reduced disease activity more and slowed radiographic progression to a greater extent than did anti-TNF monotherapy or methotrexate alone [23].

Most patients with rheumatoid arthritis respond to treatment with TNF inhibitors, with significant improvements in signs and symptoms of disease, significant decrease in radiographic damage and significant improvement in quality of life and functional status.

They have also proved to be highly effective in treating patients with ankylosing spondylitis, psoriatic arthritis, psoriasis, Crohn's disease and juvenile idiopathic arthritis. However, they were ineffective in patients with scleroderma or vasculitis.

4.5.2 Rituximab

Rituximab is a chimeric monoclonal antibody that binds to CD20 antigen and leads to B-cell inhibition [24]. It is an effective biologic therapy for rheumatoid arthritis with a greatest benefit in seropositive patients. If given as two infusions of 1 gram each, it slows the radiographic progression in rheumatoid arthritis.

Rituximab is considered as a safe drug in rheumatoid arthritis, but infusion reactions can occur; most are mild to moderate. Pre-medication with methylprednisolone, diphenhydramine and acetaminophen can reduce these reactions.

Rituximab therapy carries a risk of hepatitis B reactivation amongst patients who have positive hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (anti-HBc). All patients should be screened for HBsAg and anti-HBc prior to starting treatment [25].

4.5.3 Abatacept

It is a fully human fusion protein that inhibits costimulation (an essential step in the induction of adaptive immune responses) and inhibits T-cell activity [26].

Abatacept can be used when sDMARDs and/or other biologic drugs have failed to control inflammatory arthritis. Infection risk with abatacept is higher compared to other biologics [26].

It is administered as a 30-min intravenous infusion that is usually achieved without complications. Subcutaneous administration is equally effective and is now approved.

Abatacept is used to treat rheumatoid arthritis and polyarticular juvenile idiopathic arthritis. Clinical trials on abatacept in psoriatic arthritis and scleroderma have shown promising results [27].

4.5.4 Tocilizumab

It is a humanized monoclonal antibody that antagonizes the cytokinetic effect of IL-6. It has been approved for treatment of rheumatoid arthri-

tis [28] and systemic onset juvenile idiopathic arthritis. It was recently granted a breakthrough designation status by the United States Food and Drug Association for giant cell arteritis based on positive results from a phase 3 clinical trial [29].

A dose of 4 mg/kg is started initially and then increased to 8 mg/kg based on clinical response. It is administered intravenously every 4 weeks. Administration through the subcutaneous route is also available. It may cause dyslipidemia but is generally well tolerated. Periodic monitoring of lipid profile along with other routine investigation is required.

4.5.5 Ustekinumab

Ustekinumab is a humanized monoclonal antibody that binds to and interferes with the biological effects of IL-12 and IL-23. It is approved for the treatment of psoriatic arthritis and moderate to severe plaque psoriasis [30].

It is administered at a dose of 45 mg subcutaneously at week zero, followed by a second dose at week 4 and then every 12 weeks. Nasopharyngitis, upper respiratory tract infections and nausea are common side effects.

4.5.6 Secukinumab

Secukinumab is a humanized IgG1 monoclonal antibody that selectively binds to IL-17A and inhibits its pro-inflammatory action. It is approved for the treatment of active ankylosing spondylitis, psoriatic arthritis and moderate to severe plaque psoriasis [31].

Nasopharyngitis, upper respiratory tract infections and diarrhoea are common side effects. If administered with a loading dose, 150 mg subcutaneously is given at weeks 0, 1, 2, 3 and 4 followed by 150 mg every 4 weeks. Without a loading dose, 150 mg subcutaneously is administered every 4 weeks.

Complete details about different bDMARDs are shown in Table 4.3.

4.6 Glucocorticoids

Glucocorticoids exert both anti-inflammatory and immunosuppressive effects. They inhibit prostaglandin and leukotriene synthesis, reduce macrophage phagocytosis and inhibit the release of collagenase and lysosomal enzymes [32].

Generally, five types of glucocorticoids are used in rheumatology daily practice. These are hydrocortisone, prednisolone, methylprednisolone, triamcinolone and dexamethasone. They differ considerably in potency and biologic half-life as shown in Table 4.4. They are used in the majority of systemic rheumatic diseases.

The chronic use of low-dose glucocorticoids can cause multiple adverse events [33]. For that, the dose of glucocorticoids should be tapered as quickly as possible to the lowest effective dose when chronic use is anticipated. Serum glucose, lipid profile and bone mineral density to prevent glucocorticoid-induced osteoporosis should be performed to monitor toxicity. Patients should also be screened frequently for polydipsia, oedema and shortness of breath, visual changes, weight gain and changes in blood pressure during therapy.

Complete details about different glucocorticoids are shown in Table 4.4.

Table 4.3 Biological disease-modifying anti-rheumatic drugs (bDMARDs)

Drug name	Mechanism of action	Indication and doses	Adverse effects and caution	Pregnancy and lactation
Infliximab (Remicade)	Chimeric monoclonal antibody against TNF-α	**Rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis: Initially:** IV infusion at a dose of 5 mg/kg at weeks 0, 2 and 6 **Maintenance:** 5 mg/kg IV infusions every 8 weeks. Dose may be increased to 10 mg/kg	**Common:** Infusion reactions (itching, hives, rash, nausea, headache) and upper respiratory infections (colds, sinusitis, bronchitis, etc.) Rare and serious: Serious bacterial infections, unusual infections (tuberculosis and fungal), worsening of CHF, hepatitis B reactivation, hepatotoxicity, possible malignancies, haematologic and neurologic events, lupus-like syndrome	Pregnancy category: B Lactation: Excretion into breast milk is unknown, use not recommended
Adalimumab (Humira)	Humanized monoclonal antibody against TNF-α	**Rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis:** 40 mg SC once every other week		Pregnancy category: B Lactation: Excretion into breast milk is unknown, use not recommended
Etanercept (Enbrel)	TNF receptor fusion protein	**Rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis:** 50 mg SC once weekly or 25 mg SC twice weekly		Pregnancy category: B Lactation: Excretion into breast milk is unknown, use not recommended
Certolizumab (Cimzia)	Humanized monoclonal antibody against TNF-α	**Rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis: Initially:** 400 mg SC at weeks 0, 2 and 4 **Maintenance:** 200 mg SC every other week		Pregnancy category: B Lactation: Excretion into breast milk is unknown, use not recommended
Golimumab (Simponi)	Humanized monoclonal antibody against TNF-α	**Rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis:** 50 mg SC once monthly		Pregnancy category: B Lactation: Excretion into breast milk is unknown, use not recommended
Rituximab (MabThera)	Monoclonal antibody, binds to CD20 antigen B-cell inhibitor	**Rheumatoid arthritis:** 1000 mg IV infusion for 2 doses 2 weeks apart (one cycle) Repeat cycle every 24 weeks or based on clinical evaluation **Systemic lupus erythematosus, granulomatosis with polyangitis and Microscopic polyangitis:** 375 mg/m^2 IV every week for 4 weeks	**Common toxicity:** Infusion reactions, nausea, upper respiratory tract infections, hypertension, arthralgias, pruritus and pyrexia **Rare and serious:** Fatal infusion reactions Severe mucocutaneous reactions Progressive multifocal leucoencephalopathy Hepatitis B reactivation with fulminant hepatitis Neurologic events Lupus-like syndrome	Pregnancy category: C Lactation: Excretion into breast milk is unknown, use not recommended

Table 4.3 (continued)

Drug name	Mechanism of action	Indication and doses	Adverse effects and caution	Pregnancy and lactation
Abatacept (Orencia)	Human fusion protein, inhibits co-stimulation T-cell inhibitor	**Rheumatoid arthritis:** According to body weight: < 60 kg = 500 mg IV 60–100 kg = 750 mg IV > 100 kg = 1000 mg IV At weeks 0, 2 and 4 Then repeated every 4 weeks thereafter or may be given as weight-based IV loading dose, then 125 mg SC once weekly	**Common:** Infusion reactions, headaches, upper respiratory tract infections, nausea and nasopharyngitis **Rare and serious:** Serious bacterial infections Possible malignancies COPD exacerbation	Pregnancy category: C Lactation: Excretion into breast milk is unknown, use not recommended
Tocilizumab (Actemra)	Interleukin-6 (IL-6) antagonist	**Rheumatoid arthritis:** 4 mg/kg IV every 4 weeks initially, may be increased to 8 mg/kg IV every 4 weeks based on clinical response SC: 162 mg every week	**Common:** Infusion reactions, dyslipidemia, headaches, upper respiratory tract infections, nausea and nasopharyngitis **Rare and serious:** Serious bacterial infections	Pregnancy category: C Lactation: Excretion into breast milk is unknown, use not recommended
Ustekinumab (Stelara)	Interleukin-12 and 23 (IL-12, IL-23) antagonist	**Psoriatic arthritis:** 45 mg SC at weeks 0 and 4, then every 12 weeks	**Common:** Infusion reactions, upper respiratory tract infections, nausea and nasopharyngitis **Rare and serious:** Serious infections and malignancies	Pregnancy category: B Lactation: Excretion into breast milk is unknown, use not recommended
Secukinumab (Cosentyx)	Interleukin-17A (IL-17A) antagonist	**Psoriatic arthritis and ankylosing spondylitis:** With a loading dose: 150 mg SC at weeks 0, 1, 2, 3 and 4 followed by 150 mg every 4 weeks Without a loading dose: 150 mg SC every 4 weeks	Nasopharyngitis, upper respiratory tract infections and diarrhoea	Pregnancy category: B Lactation: Excretion into breast milk is unknown, use not recommended

Table 4.4 Glucocorticoids

Mechanism of action	Indication and doses	Adverse effects and caution	Pregnancy and lactation
Anti-inflammatory and immunosuppressive drugs	**Methylprednisolone:** Used as a pulse dose in various severe systemic rheumatic diseases: Severe lupus nephritis, severe vasculitis: 1 g IV over 1 h ×3 days **Prednisolone:** Used as a high dose (1 mg/kg/day) for some active severe forms of vasculitis and then tapered slowly. Or initial dose can be started and then increased or decreased based on clinical response. Dose must be tapered slowly **Hydrocortisone:** Used as pre-medication or during the perioperative period	Fat redistribution on the face (moon face), oedema, fluid retention, hypokalaemia, hypertension, aggravation of diabetes, muscular atrophies and weakness, fatigability, menstrual cycle disturbances, peptic ulcer and increase in the risk of infections Adrenal insufficiency at rapid withdrawal of the treatment Bone disorders: Glucocorticoid-induced osteoporosis Neuropsychiatric disorders, nervousness, insomnia, depression, aggravation of epilepsy, increase in intracranial pressure in children Ocular disorders: Glaucoma, cataract Haematological effects: Leucocytosis and thrombocytosis, decrease of T-cell lymphocytes	Pregnancy category: C Lactation: Compatible with nursing but use with caution
Drug name	**Duration of action**	**Anti-inflammatory potency**	**Equivalent dose**
Hydrocortisone	Short acting	Potency is 1 for a 20 mg dose	20 mg oral dose
Prednisolone	Intermediate acting	4 times more potent than hydrocortisone	5 mg oral dose is equivalent to 20 mg hydrocortisone
Methylprednisolone	Intermediate acting	5 times more potent than hydrocortisone	4 mg oral dose is equivalent to 20 mg hydrocortisone
Triamcinolone	Intermediate acting	5 times more potent than hydrocortisone	4 mg oral dose is equivalent to 20 mg hydrocortisone
Dexamethasone	Long acting	30 times more potent than hydrocortisone	1 mg oral dose is equivalent to 20 mg hydrocortisone

4.7 Anti-Resorptive Drugs

4.7.1 Bisphosphonates

Alendronate, risedronate, ibandronate and zoledronic acid are effective for the treatment of osteoporosis. These drugs inhibit bone resorption, increase bone mass and reduce the incidence of fractures. They are considered as first-line therapy for osteoporosis in post-menopausal women and men because of their efficacy, favourable cost and the availability of

safety data. For those who cannot tolerate oral bisphosphonates; who have difficulty with dosing requirements, including the inability to sit upright for 30–60 min; or who have relative contraindications to bisphosphonates (achalasia, scleroderma oesophagus, oesophageal strictures), intravenous zoledronic acid is the choice of therapy. Bisphosphonates should be avoided in renal impairment. They are also avoided in women of childbearing age due to foetal risk. Bisphosphonates cross the placenta and accumulate in the foetal bones [34].

4.7.2 Raloxifene

It is a selective oestrogen receptor modulator that inhibits bone resorption and reduces the risk of vertebral fracture. It is suggested for those who cannot tolerate or are not candidates for bisphosphonate therapy [35]. It is also usually chosen for osteoporosis when there is an independent need for breast cancer prophylaxis.

4.7.3 Teriparatide

It is a recombinant formulation of endogenous parathyroid hormone. It stimulates osteoblast function, increases gastrointestinal calcium absorption and increases renal tubular reabsorption of calcium. In postmenopausal women, teriparatide has been shown to decrease osteoporosis-related fractures. This drug is also suggested for those who cannot tolerate or are not candidates for bisphosphonates therapy [36].

4.7.4 Denosumab

It is a fully human monoclonal antibody that specifically binds to receptor activator of nuclear factor kappa B ligand (RANKL). It reduces the formation, function and survival of osteoclasts, which results in decreased bone resorption and increased bone density. It is suggested for those who cannot tolerate or are not candidates for bisphosphonate therapy [37].

Complete details about different anti-resorptive drugs are shown in Table 4.5.

Table 4.5 Anti-resorptive drugs

Drug name	Mechanism of action	Indication and doses	Adverse effects and caution	Pregnancy and lactation
Alendronate (Fosamax)	Bisphosphonate, inhibits resorption of bones Increases density of bones	**Osteoporosis (treatment and prevention), osteoporosis in men, glucocorticoid-induced osteoporosis:** 70 mg PO once weekly If CrCl is <35, not recommended Reduces hip and spinal fracture risk by 50%	Hypocalcaemia, hypophosphataemia, abdominal pain, nausea, diarrhoea, acid regurgitation, esophagitis and bony pain Must be taken at early morning with plain water on empty stomach. Then must stay in upright position for 30 min. Ensure adequate use of calcium and vitamin D	Pregnancy category: C Lactation: Excretion into breast milk is unknown; use caution

(continued)

Table 4.5 (continued)

Drug name	Mechanism of action	Indication and doses	Adverse effects and caution	Pregnancy and lactation
Ibandronate (Boniva)	Bisphosphonate, inhibits resorption of bones Increases density of bones	**Osteoporosis in postmenopausal women (treatment and prevention):** 150 mg PO every month. Or 3 mg IV every 3 months If CrCl is <30, not recommended No efficacy in non-vertebral fractures	Upper respiratory infections, back pain, dyspepsia, esophagitis and bony pain Must be taken at early morning with plain water on empty stomach. Then must stay in upright position for 30 min. Ensure adequate use of calcium and vitamin D	Pregnancy category: C Lactation: Excretion into breast milk is unknown; use caution
Risedronate (Actonel)	Bisphosphonate, inhibits resorption of bones Increases density of bones	**Osteoporosis (treatment and prevention), osteoporosis in men, glucocorticoid-induced osteoporosis:** 5 mg PO once daily, or 35 mg PO once weekly, or 150 mg PO once monthly If CrCl is <30, not recommended Reduces vertebral fracture risk by 41% and non-vertebral fracture risk by 39% over 3 years	Bony pain, diarrhoea, headache, abdominal pain, esophagitis and dysphagia Must be taken at early morning with plain water on empty stomach. Then must stay in upright position for 30 min Ensure adequate use of calcium and vitamin D	Pregnancy category: C Lactation: Excretion into breast milk is unknown; avoid using
Zoledronic acid (Aclasta)	Bisphosphonate, inhibits resorption of bones Increases density of bones	**Osteoporosis (treatment and prevention), osteoporosis in men, glucocorticoid-induced osteoporosis:** 5 mg IV every year for treatment and every 2 years for prevention If CrCl is <30, not recommended Reduces hip fracture risk by 41%, spinal fracture risk by 71% and non-vertebral fracture risk by 25% over 3 years	Bony pain, diarrhoea, headache, abdominal pain, nausea, fever, fatigue and anaemia Ensure adequate use of calcium and vitamin D	Pregnancy category: D Lactation: Excretion into breast milk is unknown; avoid using

Table 4.5 (continued)

Drug name	Mechanism of action	Indication and doses	Adverse effects and caution	Pregnancy and lactation
Teriparatide (Forteo)	Recombinant parathyroid hormone stimulates osteoblasts Increases density of bones	**Osteoporosis (treatment and prevention), osteoporosis in men, glucocorticoid-induced osteoporosis:** 20 mg SC once daily into thigh or abdominal wall Reduces spinal fracture risk by 65% and non-spinal fracture risk by 54%	Hypercalcaemia, bony pain, flulike illness, nausea and orthostatic hypotension Ensure adequate use of calcium and vitamin D	Pregnancy category: C Lactation: Safe
Raloxifene (Evista)	Selective oestrogen receptor modulator Increases density of bones	**Osteoporosis in postmenopausal women:** 60 mg PO once daily Reduces spinal fracture risk by 30–55%	Hot flashes, headache, flu syndrome, sinusitis, arthralgias and infection Increased risk of thrombosis and embolism. Thus, contraindicated in patients with history of thrombosis	Pregnancy category: X Lactation: Contraindicated
Denosumab (Prolia)	Monoclonal antibody, inhibits resorption of bones Increases density of bones	**Osteoporosis (treatment and prevention), osteoporosis in men:** 60 mg SC every 6 months	Bony pain, hypercholesterolaemia, cystitis, upper respiratory infections, sciatica and hypocalcaemia Ensure adequate use of calcium and vitamin D	Pregnancy category: X Lactation: Excretion into breast milk is unknown; avoid using
Strontium ranelate	Musculoskeletal agent Increases density of bones	**Osteoporosis (treatment and prevention), osteoporosis in men:** 2 g/day dissolved in water, prior to bedtime, 2 h after eating (preferably) If CrCl is <30, not recommended	Diarrhoea, nausea, headache, dermatitis and eczema	Pregnancy category: NA Lactation: Excretion into breast milk is unknown; avoid using

4.8 Drugs Used in Crystal Arthropathy

4.8.1 Colchicine

It is a uricosuric agent that prevents activation, degranulation and migration of neutrophils associated with mediating some gout symptoms. It can be used for both acute flare and prophylaxis against recurrent attacks of gouty arthritis [38].

Common adverse effects of colchicine may include diarrhoea and abdominal cramping. It is contraindicated in severe renal or hepatic impairment. Colchicine treatment may also benefit patients with acute episodes of pseudogout and arthritis due to other crystals.

4.8.2 Allopurinol

It is a xanthine oxidase inhibitor that inhibits its conversion to uric acid. It is considered as the first-line urate-lowering agent for the treatment of chronic gout. The dose of allopurinol should

Table 4.6 Drugs used in crystal arthropathy

Drug name	Mechanism of action	Indication and doses	Adverse effects and caution	Pregnancy and lactation
Colchicine	Uricosuric agent, prevents activation and migration of neutrophils	**Acute gout flare:** 1.2 mg PO at first sign of flare, then 0.6 mg PO 1 h later. Do not exceed 1.8 mg in 1-h period **Gout prophylaxis:** 0.6 mg PO once or twice daily. Do not exceed 1.2 mg/day	Gastrointestinal symptoms, fatigue and headache	Pregnancy category: C Lactation: Excreted into breast milk, use caution
Allopurinol	Xanthine oxidase inhibitor, inhibits its conversion to uric acid	**Chronic gout:** 100 mg/day initially, increase weekly to reach 200–300 mg/day. Do not exceed 600 mg/day in severe cases If CrCl is <40, 150 mg/day If CrCl is <20, 100 mg/day If CrCl is <10, 100 mg/2 days	Nausea, rash, vomiting, arthralgias and rarely Steven-Johnson syndrome	Pregnancy category: C Lactation: Excreted into breast milk, use caution
Febuxostat	Xanthine oxidase inhibitor, inhibits its conversion to uric acid	Chronic gout: Initial: 40 mg PO once daily. Maintenance: 40–80 mg PO once daily	Nausea, rash, vomiting, arthralgias and liver function abnormalities	Pregnancy category: C Lactation: Excretion into breast milk is unknown

be adjusted based on the stage of renal disease. Febuxostat is another urate-lowering agent that can be used if allopurinol is to be avoided [39]. Allopurinol decreases the metabolism of azathioprine.

Complete details about different drugs used in crystal arthropathy are shown in Table 4.6.

4.9 Symptom-Specific Drugs

Systemic rheumatic diseases are multi-system diseases that can affect different body organs. These disease cause symptoms that can be either due to the immunopathologic changes or adverse effects from the DMARD therapy. Most of these rheumatic symptoms are effectively treated with different DMARDs. However, few other symptoms require additional specific drugs. For example, Raynaud's phenomenon, fatigue, generalized aches and pains and acid reflux are common symptoms that patients describe to their rheumatologists. Table 4.7 provides a list of common symptom-specific medications that rheumatologists prescribe during their daily clinical practice. Table 4.8 defines the pregnancy categories for pharmacological agents.

Table 4.7 Common symptom-specific drugs

Drug name	Mechanism of action	Indication and doses	Adverse effects and caution	Pregnancy and lactation
Dihydropyridine calcium channel blockers	Inhibit influx of extracellular calcium ions across myocardial and vascular smooth muscle cell membranes, resulting in vasodilation of main coronary and systemic arteries	**Raynaud's phenomenon:** **Nifedipine:** 30–120 mg (extended release) PO daily **Amlodipine:** 5–10 mg PO daily	Peripheral oedema, dizziness, flushing and headache	Pregnancy category: C Lactation: Excreted into breast milk, discontinue drug or refrain from nursing
Sildenafil	Inhibits phosphodiesterase-5, thus increasing cyclic guanosine monophosphate to allow smooth muscle relaxation and vasodilation	**Raynaud's phenomenon:** 5 or 20 mg PO 3 times daily	Dizziness, flushing, headache and epistaxis	Pregnancy category: B Lactation: Excretion into breast milk is unknown
Pilocarpine	Cholinergic parasympathomimetic with muscarinic action, increases secretion of exocrine glands	**Xerostomia associated with Sjogren's syndrome:** 5 mg PO up to 4 times daily	Sweating, headache, flushing, dizziness, nausea, urinary frequency and diaphoresis	Pregnancy category: C. Lactation: Excretion into breast milk is unknown.
Amitriptyline	Anticholinergic, serotonin and norepinephrine reuptake inhibitor.	**Fibromyalgia:** 10–50 mg PO at bedtime, dose can be escalated up to 200 mg daily.	Dizziness, headache and dry mouth	Pregnancy category: C Lactation: Excreted into breast milk, discontinue drug or refrain from nursing
Duloxetine	Serotonin and norepinephrine reuptake inhibitor	**Fibromyalgia:** 30 mg PO daily initially for 1 week, then increase to 60 mg daily	Dizziness, headache, dry mouth and somnolence	Pregnancy category: C Lactation: Excreted into breast milk, discontinue drug or refrain from nursing
Proton pump inhibitors	Bind to hydrogen-potassium-exchanging adenosine triphosphatase in gastric parietal cells, resulting in suppression of acid secretion	**Heart burn or gastritis:** **Omeprazole:** 20–40 mg PO daily **Esomeprazole:** 20–40 mg PO daily	Headache, flatulence, indigestion, nausea and abdominal pain	Pregnancy category: C Lactation: Excretion into breast milk is unknown, discontinue drug or refrain from nursing

Table 4.8 Pregnancy category definitions

Category	Definition
A	Generally acceptable. Controlled studies in pregnant women show no evidence of foetal risk
B	May be acceptable. Either animal studies show no risk but human studies not available or animal studies showed minor risks and human done and showed no risk
C	Use with caution if benefits outweigh risks. Animal studies show risk and human studies not available or neither animal nor human studies done
D	Use in life-threatening emergencies when no safer drug is available. Positive evidence of human foetal risk
X	Do not use in pregnancy. Risks involved outweigh potential benefits. Safer alternative exists
NA	Information not available

Abbreviations

ACEIs	Angiotensin-converting enzyme inhibitors
ALT	Alanine amino transferase
Anti-HBc	Hepatitis B core antibody
AST	Aspartate aminotransferase
BID	Two times a day
cAMP	Cyclic adenosine monophosphate
COX	Cyclooxygenase
CrCl	Creatinine clearance
DMARDs	Disease-modifying anti-rheumatic drugs
HBsAg	Hepatitis B surface antigen
IL	Interleukin
IM	Intramuscular
IV	Intravenous
MESNA	2-Mercatpoethanesulfonic acid
NSAIDs	Nonsteroidal anti-inflammatory drugs
PDE-4	Phosphodiesterase-4
PGHS	Prostaglandin G/H synthase
PGs	Prostaglandins
PO	Orally (by mouth)
PRN	As needed (pro re nata)
q6hrs	Every 6 hours
QID	Four times a day
RANKL	Receptor activator of nuclear factor kappa B ligand
SC	Subcutaneous
SLE	Systemic lupus erythematosus
STATs	Signal transducers and activators of transcription
TID	Three times a day
TNF	Tumour necrosis factor
TPMT	Thiopurine methyltransferase

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Radiology in Rheumatology

5

Nizar Al Nakshabandi, Ehab Joharji, and Hadeel El-Haddad

5.1 Introduction

This chapter addresses different modalities of imaging in approaching the common musculoskeletal diseases (explaining the radiological part of diagnosis), we included: infectious arthritis (septic, tuberculous, and brucellosis), metabolic arthritis (gout and CPPD), rheumatoid arthritis, spondyloarthropathies (ankylosing spondylitis, psoriasis, and reactive arthritis), and degenerative bone diseases like osteoarthritis; it also addresses the role of the musculoskeletal interventional radiologist in the management of rheumatological diseases.

5.2 Learning Objectives

By the end of this chapter, you should be able to:

- Identify the radiological modalities used to diagnose different rheumatological disorders and their appropriate utilization.
- Emphasize on the importance of early radiological detection of infectious arthritis.
- Address the role of the radiologist in the prevention of the long-term rheumatological disabilities.
- Define the proper interpretation of the different musculoskeletal radiological modalities.

5.3 Infectious Arthritis

5.3.1 Septic Arthritis

Septic arthritis is an emergency and a type of destructive infectious arthropathy; it can cause significant mortality and morbidity, if unrecognized and left untreated. Irreversible joint destruction to a joint can be prevented by early diagnosis and prompt and effective treatment [1]. It is well-known that the definite diagnostic method is arthrocentesis by identification of an organism in the synovial fluid. The presence of painful, swollen joint and fever should raise clinical suspicion. Radiological studies play a significant role especially in cases where synovial fluid cannot be retrieved. In these cases, ultrasound- or fluoroscopic-guided joint aspiration demonstrates their importance in reaching the diagnosis. In general, imaging has an adjunct role to arthrocentesis in diagnosing septic arthritis. Effusion and inflammation in some joints like the hip and sacroiliac

N. Al Nakshabandi (✉)
Professor of Radiology, King Saud Medical City, College of Medicine, King Saud University, Riyadh, Saudi Arabia
e-mail: nizar.nakshabandi@ksu.edu.sa

E. Joharji
Umm Al-Qura University, Mecca, Saudi Arabia

H. El-Haddad
Department of Medicine, Dr. Soliman Fakeeh Hospital, Jeddah, Saudi Arabia

Hematology Fellow, King Abdulaziz Medical City, Jeddah, Saudi Arabia

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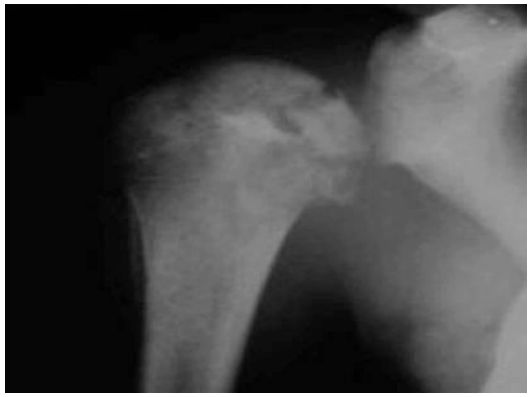

Fig. 5.1 AP view of the right shoulder demonstrates widening of the glenohumeral joint indicative of an effusion with sclerotic changes present on both sides of the sacroiliac joint

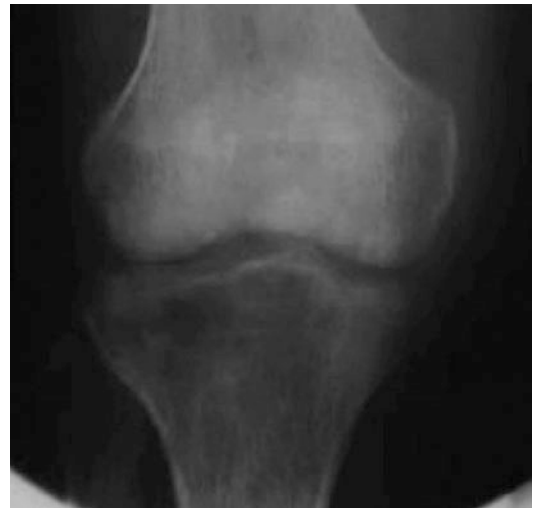

Fig. 5.2 AP view of the right knee demonstrates sclerotic changes present in the distal femur with periarticular osteopenia present in the tibia indicative of hyperemia

joints are difficult to examine clinically but can be detected by scintigraphy, CT scan, or MRI for defining extent of infection. MRI is a useful modality, while CT-guided bone biopsy or aspiration is the test of choice for defining the extent of bone involvement [2]. In rare cases, associated osteomyelitis or concurrent joint disease may be present, so radiographs should be obtained for an infected joint. In addition, it is useful to have a baseline radiograph to follow the response to therapy. In cases of failure to respond to intravenous antibiotics therapy, imaging should not be underestimated as it may change the line of management and guide intervention.

The following demonstrates the imaging modalities used to diagnose septic arthritis and characteristic findings in each one.

5.3.1.1 Radiographs

Conventional radiography should always be the first imaging technique used, although results are usually normal at presentation and generally lack sensitivity and specificity. The radiological findings vary according to the stage of the disease, for example, in the very early stage of the disease, X-ray may be normal, joint effusion may be seen Fig. 5.1, hyperemia may cause juxta-articular osteoporosis (Fig. 5.2), joint space may narrow due cartilage destruction in the acute phase, subchondral bone destruction may be evident on both sides of a joint, reactive juxta-articular sclerosis may develop if left untreated, and, in severe cases, ankylosis may develop (Fig. 5.3). In acute osteomyelitis, the early finding is osteopenia and then cortical destruction and periosteal new bone formation. Subacute and chronic osteomyelitis have different imaging features than marginal sclerosis and osteopenia, which indicate areas of healing. In chronic osteomyelitis, the most specific finding is a sequestrum (a fragment of dead bone surrounded by inflammatory tissue), which radiographically appears as a focal area of sclerotic bone within an area of lucency [1].

5.3.1.2 Ultrasonography

A noninvasive and inexpensive technique, it is considered an improved method for the early diagnosis of septic arthritis, with joint effusion and echoes inside being the characteristic finding of a septic joint. Clearly, it is superior to radiographs in detecting joint effusions as it can detect minor effusions, as small as 1–2 ml, and this allows ultrasound-guided arthrocentesis to be performed in patients with suspected septic arthritis. Furthermore, it is useful for examining inaccessible joints such as the hip. It can also show increased perisynovial vascularity using color Doppler. Echogenic debris may be present; it is very helpful in differentiating between tran-

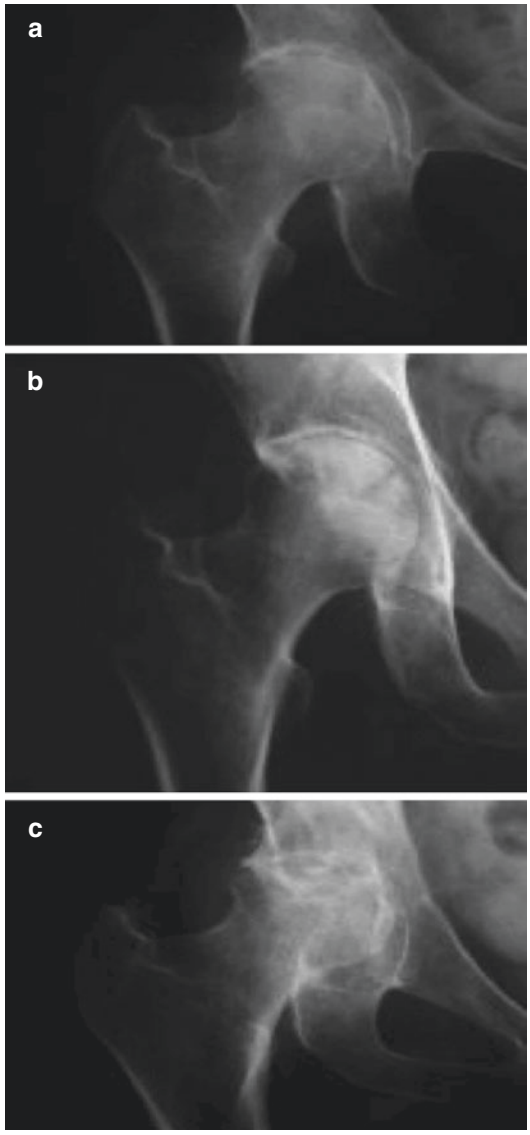

Fig. 5.3 Septic arthritis of the hip, (**a**) moderate osteoarthritic changes with concentric joint space narrowing early, (**b**) demonstrates sclerotic changes in the femoral head indicative of avascular necrosis after 4 months, (**c**) end stage after 8 months demonstrates flattening of the femoral head with osteolysis

sient synovitis and fresh hemorrhagic effusions. Echo-free image is seen in transient synovitis and fresh hemorrhagic effusions, while clotted hemorrhagic collections and septic arthritis do not have an echo-free image. This means that a negative sonogram will exclude fluid collection and the presence of echo-free effusion will virtually rule out septic arthritis [3]. However, for joints with non-distensible capsules (e.g., sacroiliac, sternoclavicular, and acromioclavicular joints), septic arthritis cannot be excluded in the absence of a visible joint effusion, and, if suspected, MR (or CT) imaging together with guided joint aspiration should be undertaken [4]. As mentioned earlier, on ultrasound, the hallmark of septic arthritis is the presence of a joint effusion in a patient with clinical signs and symptoms of joint infection. Ultrasound allows early diagnosis and treatment of septic arthritis, by enabling recognition and guiding the aspiration of joint fluid at an early stage [4]. Joint fluid in septic arthritis may be hypoechoic and clearly demarcated from joint synovium and capsule or hyperechoic and less clearly demarcated from joint synovium or capsule [4].

There are numerous advantages of clinical application of ultrasonography for the diagnosis of septic arthritis. Ultrasound is very sensitive in detecting the joint effusion of septic arthritis. The pathological extent of septic arthritis, in addition to the joint effusion and the joint surrounding subperiosteal abscess and cortical erosion, can be clearly defined and may indicate a concurrent osteomyelitis, which will help clinicians to treat by appropriate surgical debridement. Ultrasound can also help the clinicians avoid unnecessary needle joint aspiration by differentiating soft tissue abscess or tenosynovitis from septic arthritis [5].

5.3.1.3 CT Scan

CT features of septic arthritis are similar to the radiograph features; a fat-fluid level can be a specific sign in the absence of trauma. CT is better for visualizing local edema, bone erosions, osteitis foci, and sclerosis.

CT scan is also an imaging modality which may contribute to the decision of treatment, whether medical or surgical, not in septic arthritis itself but in concurrent osteomyelitis, and is able to detect some radiological features that indicate the need for surgical intervention and cannot be detectable by conventional imaging, for example, sequestra, medullary involvement, and the extent of sinus tracts; from this point, the value of CT

scan in planning medical and surgical treatment of chronic osteomyelitis is appreciated [6].

5.3.1.4 MRI

In general, MRI is the most powerful modality used for the evaluation of musculoskeletal joint infections and provides better resolution than radiography or CT scan for detecting joint effusion and for differentiating between bone and soft tissue infection. When IV gadolinium contrast is used with MRI showing the synovial enhancement, the sensitivity and specificity increase to 100% and 77%, respectively [7].

Joint effusion, cartilage and bone destruction, soft tissue abscesses, bone edema, and cortical interruption all are MRI findings of septic arthritis with or without osteomyelitis; MRI also can differentiate acute from chronic osteomyelitis. In acute infections, there is no sharp zone of transition between normal and abnormal bone marrow, and there is no cortical thickening or sequestrum (Figs. 5.4–5.6).

The presence of bone erosions is a good indicator for an infected joint, but it can also be a finding of non-septic inflamed joint. The same findings can be present in both infected and inflamed joint, so no single sign can be considered as pathognomonic for a septic joint or help

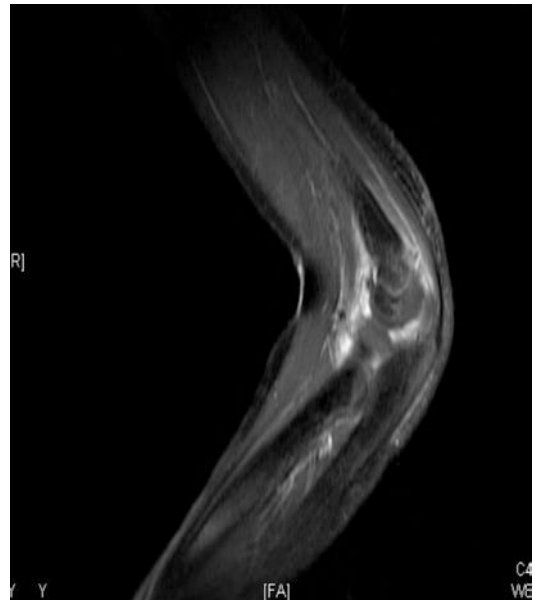

Fig. 5.5 T1-weighted images on your right demonstrate no effusion

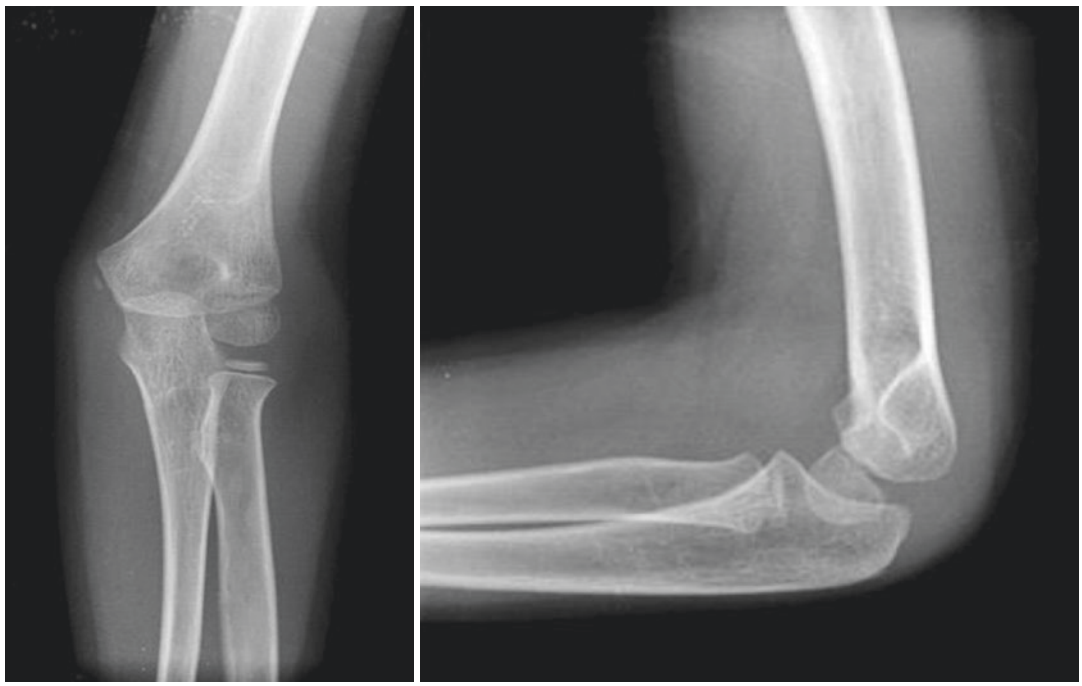

Fig. 5.4 AP and lateral radiographs of the left elbow demonstrate no specific abnormality

exclude its presence. Therefore, MRI is unable to differentiate between infective and other inflammatory arthritis [8].

5.3.1.5 Scintigraphy

This imaging modality can be helpful when evaluating suspected septic arthritis, particularly in the setting of prosthetic joint. Leukocyte-labeled 111-In combined with 99-Tc sulfur colloid studies provides accuracy of 90% in this clinical situation. Uptake of the 111-In in an area that does not show marrow activity with sulfur colloid is considered positive for infection [7].

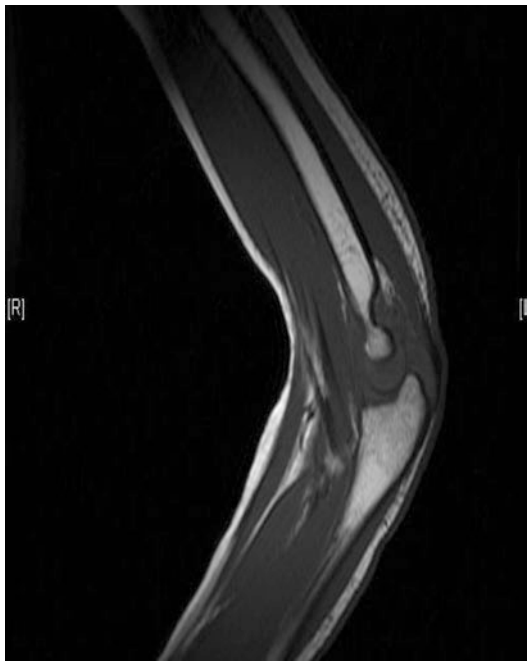

Fig. 5.6 T1 fat-suppressed images with IV gadolinium on your left demonstrate enhancement of the synovial lining of the elbow joint with some fluid present

5.3.2 Tuberculous Arthritis

Tuberculous arthritis is usually monoarticular, like other infectious joint diseases; the large joints, such as the hip and the knee, are most commonly involved, but in general, any other joint can be affected, with lower extremity joints being more affected than upper extremity joints [9]. Tuberculous arthritis is still considered a major concern for clinicians and healthcare workers, especially in developing countries. Advanced stage of the disease may be the first presentation, because of the delay in diagnosis.

In contrast to the old time when the diagnosis was made based on the clinical and basic radiological presentation alone (Table 5.1) [10], nowadays, the radiological investigations improved with more new modalities and new interventional methods, making the diagnosis of an infected joint more easy at any stage. In early stages of the disease, when plain X-rays are negative, it is considered a diagnostic dilemma, so, to avoid missing the diagnosis, the new diagnostic modalities like ultrasonography, CT, MRI, and image-guided aspiration of synovial fluid for PCR and tissue diagnosis should be used [10].

Usually, tuberculous arthritis is secondary to tuberculous osteomyelitis, in which a primarily tuberculous metaphyseal focus crosses the epiphyseal plate. One of the hallmarks of tuberculous skeletal infection is this transphyseal spread, which is not found in pyogenic arthritis,

Table 5.1 Clinico-radiological classification of tuberculosis of the hip [10]

Stages	Clinical findings	Radiologic features
Synovitis	Flexion, abduction, external rotation, apparent lengthening	Haziness of articular margins and rarefaction
Early arthritis	Flexion, adduction, internal rotation, apparent shortening.	Rarefaction, osteopenia bony erosions in femoral head, acetabulum or both No reduction in joint space
Advanced arthritis	Flexion, adduction, internal rotation, shortening	All of the above and destruction of articular surface, reduction in joint space
Advanced arthritis with subluxation/dislocation	Flexion, adduction, internal rotation with gross shortening	Gross destruction and reduction of joint space, wandering acetabulum

Source: Tuli, Tuberculosis of Skeletal system, fourth ed., 2010. p. 72.

so, without pre-existing osteomyelitis, arthritis less frequently occurs, owing to hematogenous spread of the tubercle bacillus to the synovial membrane [9].

Like any inflammatory joint, reactive hyperemia causing juxta-articular hyperemic osteoporosis, osseous erosions, and cortical and subcortical destruction on both sides of the joint space may be seen. Granulomatous inflammation can cause synovial thickening, and joint effusion may result in expansion of the joint; granulomatous synovial lesions expand inwards from the joint periphery, eroding the articular surface, with patchy cartilage destruction, erosions, and lytic bone lesions [9]. In a tuberculous joint, further extension to adjacent para-articular soft tissue with collection of cold abscess and sinus tracts may occur if not treated and discovered early, so early diagnosis is essential [9]. Radiological investigations play an important role in the diagnosis of tuberculous arthritis.

The following demonstrate the imaging modalities used to diagnose tuberculous arthritis and characteristic findings in each one:

5.3.2.1 Radiograph

Plain X-rays are reliable for detecting and for follow-up of treatment of tubercular joint.

Features are summarized in the Phemister's triad, which consists of juxta-articular osteoporosis, peripheral osseous erosions, and gradual narrowing of the joint space.

In tight or weight-bearing joints like the hip, knee, and ankle, marginal erosions are characteristic features of tuberculous arthritis.

In the early stage of tuberculous arthritis, lack of sclerosis or periostitis is another typical feature. In the end stage of tuberculous arthritis, severe joint destruction and eventually sclerosis and fibrous ankylosis may occur. Bony ankylosis may also occur, but it is less common than in pyogenic arthritis and, when present, is more likely to be secondary to previous surgical intervention [9].

5.3.2.2 Ultrasonography

The only finding is joint effusion, which is nonspecific and can occur in any joint inflammation.

5.3.2.3 CT Scan

CT scan is able to demonstrate bone destruction, sequestration, as well as extension of infection to the surrounding soft tissue or any sinus tract formation (Fig. 5.7) [9].

5.3.2.4 MRI

To detect early changes, MRI is the study of choice. On T2-weighted images, joint effusion appears hyperintense, loose bodies, calcifications and hemosiderin deposits due to bleeding may be hypointense; therefore, tuberculous arthritis should be considered in the differential; when an articular lesion with low- or intermediate-signal intensity on T2-weighted images is seen, marrow changes are of low-signal intensity on T1-weighted images and of high-signal intensity on T2-weighted images.

MRI is better than CT to detect associated soft tissue abnormalities, such as cellulitis, myositis, sinus tract formation, and para-articular collections. With IV gadolinium contrast, sinus

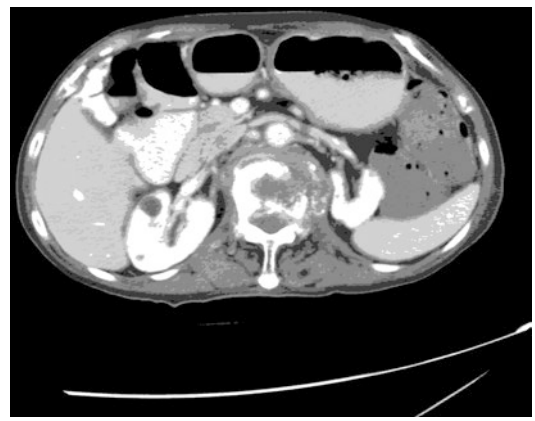

Fig. 5.7 CT scan of the abdomen and the level of the T12 demonstrate a destructive lesion of the body of T12 on the left side extending into the left parapelvic region with some calcification and enhancement peripherally

tracts display a linear high-signal intensity on T2-weighted images with marginal "tram track enhancement" on T1-weighted images. Tuberculous collections may be slightly hyperintense on T1-weighted images, in contrast to collections originating from many other infections (Fig. 5.8).

Precontrast T1-weighted images show a hyperintense rim around these collections, which enhances after administration of gadolinium contrast [9].

For differentiation of tuberculous arthritis and pyogenic arthritis, MR imaging of bone abnormalities, extra-articular lesions, and associated abscesses provides useful information [11].

5.3.3 *Brucella* Arthritis

Brucellosis is still considered a major health and economic issue in many parts of the world, and it can affect different parts of the body. Radiological investigations play an important role in the diagnosis and management of brucellosis [12]. Any joint in the body can be affected by *Brucella*, including sternoclavicular joints and sacroiliac joints, with large joints having more affinity to be involved. In long standing and neglected cases of *Brucella*, avascular necrosis of the femoral head can occur [12]. A favorite location for *Brucella* septic arthritis and osteomyelitis is the sacroiliac joint, and its involvement can extend to bone and muscle involvement in the region [8]. It also affects both joint spaces in the sacroiliac joint and causes erosive and bony destruction of the sacroiliac joint, with enhancement, which is one of the hallmarks of *Brucella* septic arthritis [12]. The radiologic features of the affected joints are indistinguishable from those of tuberculous or pyogenic arthritis; thus, differentiation depends on laboratory findings [13].

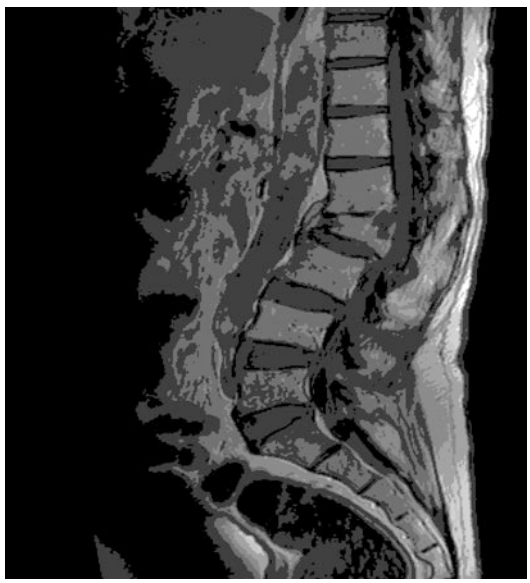

Fig. 5.8 Sagittal MRI T1-weighted of the lumbar spine demonstrates kyphotic deformity of L2 with destructive lytic lesions of the body of L2 and L5 from tuberculous involvement

5.3.3.1 Radiograph

The radiographic findings in a *Brucella* arthritis are not specific and range from poorly defined joints, joint space narrowing or widening, ankylosis, sclerosis, subchondral erosions, to no visible abnormalities [14].

5.3.3.2 Ultrasonography

Like any joint inflammation or infection, ultrasound can detect joint effusion, which is a nonspecific finding, and guide aspiration of synovial fluid to help in the diagnosis.

5.3.3.3 CT Scan

One of the hallmarks of *Brucella* septic arthritis is that it affects both joint spaces in the sacroiliac joint and causes erosive and bony destruction of the sacroiliac joint, with enhancement [12].

5.3.3.4 MRI

In *Brucella* sacroiliitis, bone marrow edema and intra-articular synovial fluids are important clues for early diagnosis. Sclerosis and ankylosis are observed in late phase of the disease.

Peripheral joint involvement can be diagnosed by the presence of bone marrow edema, joint derangement, enhancement of synovium, and periarticular soft tissues after intravenous injection of gadolinium (Figs. 5.9 and 5.10) [15].

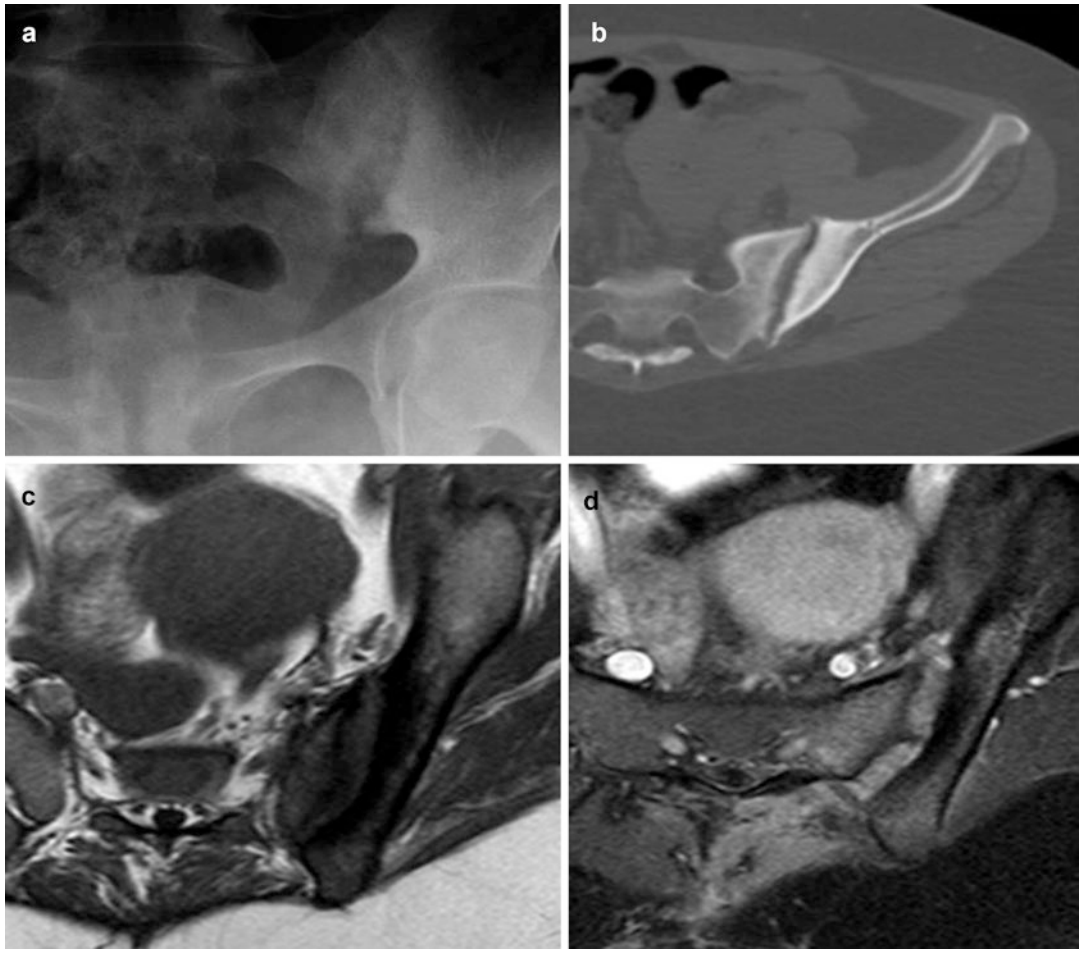

Fig. 5.9 (**a**) Plain radiograph of the left sacroiliac joint demonstrates sclerotic changes on the iliac side of the sacroiliac joint and widening of the sacroiliac joint on the left side. (**b**) demonstrates sclerotic changes of the left sacroiliac joint on the iliac side with widening of the sacroiliac joint. (**c**) Axial T1-weighted image demonstrates sclerotic changes of the sacroiliac joints with some widening. (**d**) demonstrates widening of the left sacroiliac joint with marked enhancement following gadolinium administration that extends into the left paraspinal muscles and subcutaneous tissue

5.3.3.5 Scintigraphy

Joints involved in a vast majority of patients show an increased uptake on bone scans.

5.4 Metabolic Arthritis

5.4.1 Gouty Arthritis

Gout is a common cause of arthritis; it can be diagnosed by expert clinician based on clinical picture and laboratory findings, with little or even no benefit from imaging, but still imaging is needed in cases where deep structures like the spine or sacroiliac joints are affected or when the gouty joint mimics mass lesion or infection. However, many patients with gout visit non-specialized physician, and in such cases, imaging may have an adjunctive role in gout diagnosis and management. Different radiological findings can be found in gout, for example, erosions, synovial proliferation, tophus, bone marrow edema, cartilage involvement, and joint effusion, all these findings need different imaging modalities, with

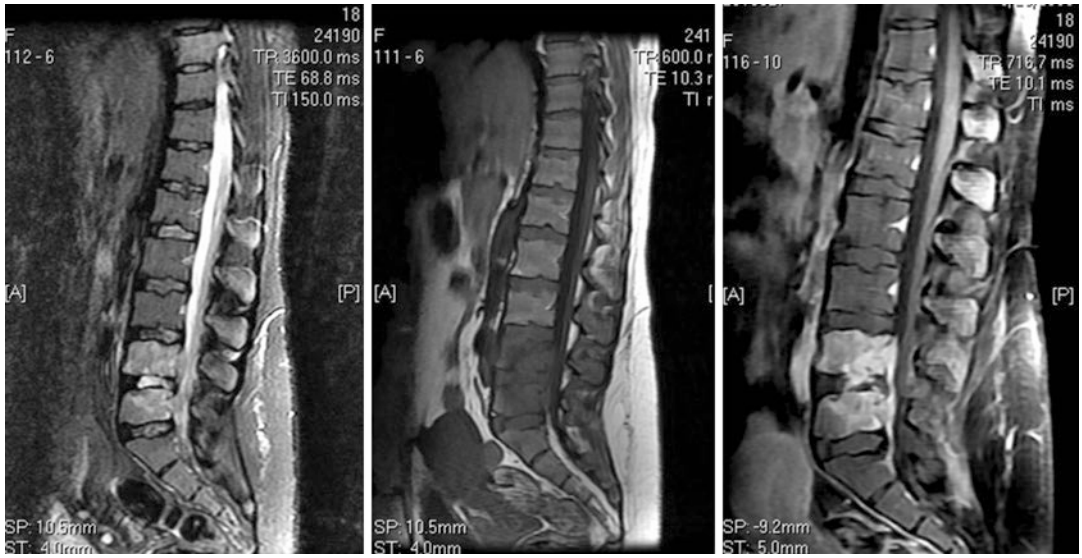

Fig. 5.10 First image on your left demonstrates high signal changes in the L4 and L5 vertebral bodies on this T2-weighted sagittal MRI of the lumbar spine. Middle image is a sagittal T1-weighted image of the lumbar spine with extensive low-signal changes of L4 and L5 with involvement of the disc space. The third image on the right is a sagittal MRI T1-weighted image with gadolinium enhancement and demonstrates marked enhancement of the L4 and L5 vertebral body with enhancement of the L4-L5 disc space

Table 5.2 Comparative utility of X-ray, US, CT, and MRI in the diagnosis of gout [16]

	X-ray	US	CT	MRI
Erosion	+	++	+++	++
Effusion	+	+++	++	+++
Synovial proliferation	–	+++	+	+++
Tophus	+	+++	++	+++
Joint space narrowing	+++	–	+++	+++
Tendon pathology	–	+++	++	+++
Bone marrow edema	–	–	+	+++
Tophus or synovial vascularity	–	+++	–	+++

Source: Review Article, Imaging Appearances in Gout, Volume 2013 (2013), Article ID 673401, 10 pages.

different utilities for each, based on sensitivity (Table 5.2) [16].

5.4.1.1 Radiographs

It is usually a late finding, underestimating the degree of involvement; first MTP involvement is a characteristic finding of gout, juxta-articular erosions with sclerotic margins and overhanging edges, and preservation of joint spaces and periarticular bony density until the disease process is late. The gouty deposits around the joint can be juxta-articular, intra-articular, and subchondral and usually not symmetric (Fig. 5.11). The hallmark of chronic gout is the formation of tophus, which is a soft tissue nodule that represents the granulomatous immune reaction of the body to monosodium urate (MSU) crystals. Tophus calcification is a late finding and may be associated with calcium metabolism disturbance. Erosions are often located next to a tophus (Figs. 5.12 and 5.13) [16].

5.4.1.2 Ultrasonography

Without contrast agent, sonography can detect tophaceous deposits in the soft tissues, joints, cartilage, as well as synovitis, erosions, and

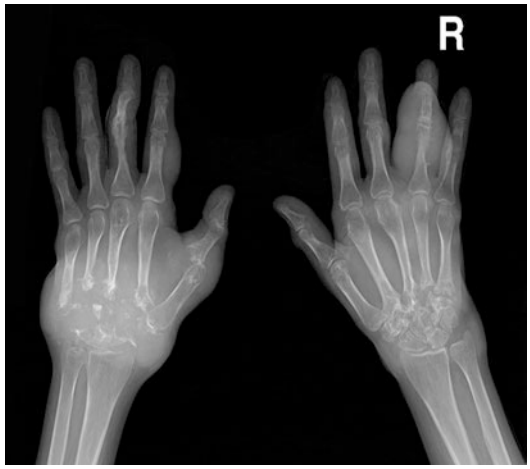

Fig. 5.11 AP view of both hands demonstrates punched out erosions of the left carpal bones along with marked soft tissue swelling at the wrist joint indicative of tophus formation

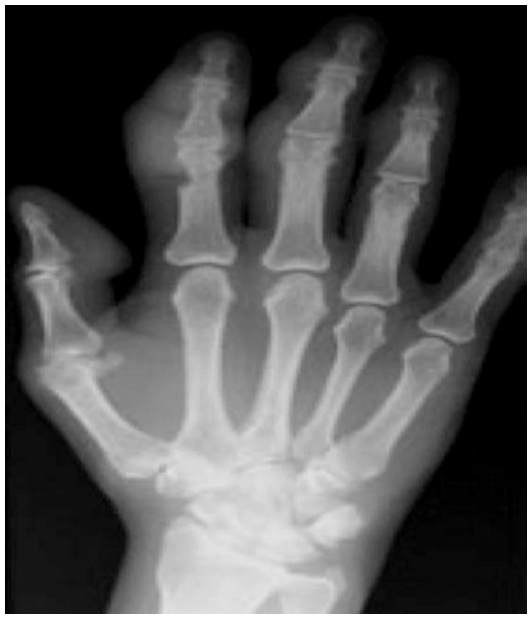

Fig. 5.12 AP view of the right hand demonstrates marked soft tissue swelling at the first metacarpophalangeal joint, second PIP along with punched out erosion of the proximal second phalanx

increased vascularity. It has a good role in the early diagnosis and monitoring the response of the treatment of gouty arthritis. In patients with an acute gout flare, or patients with history of prior gout attacks, or even patients with asymptomatic hyperuricemia, the "double contour sign" is a sign that can be seen by ultrasound, an irregular echogenic line, caused by urate deposition over the most superficial layer of hyaline cartilage, with a sensitivity ranging from 25% to 95% in patients with gout [16].

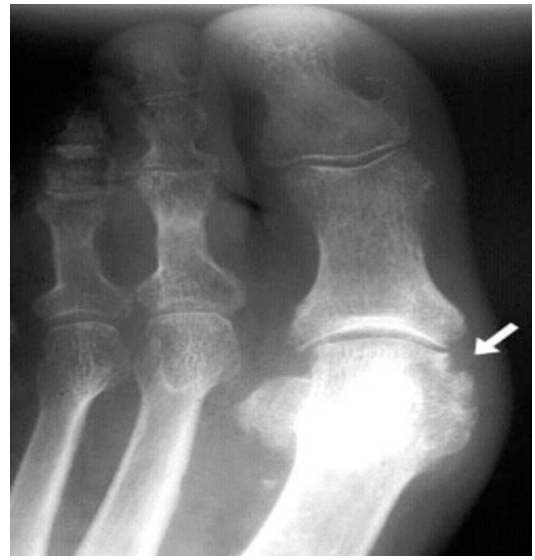

Fig. 5.13 AP radiograph of the left first toe demonstrates punched out erosion of the first metatarsophalangeal joint and first metatarsal head. Notice that the joint space is preserved

The tophus on ultrasonography appears as an anechoic halo and hyperechoic heterogeneous center. Tophi by ultrasound appearance could be either soft or hard tophi, based on sonolucency (soft tophi), and difficulty to image the structure below them (hard tophi), which are usually long-standing tophi [16]. Synovitis in gout by ultrasound shows mixed echogenicity, predominantly hyperechoic with associated increased vascularity. Some cases show hyperechoic foci which represent microtophi, resulting in "snow storm appearance."

Ultrasonography is excellent for identifying bursitis, intratendinous deposition, enthesitis, and subcutaneous nodules seen with gout [16].

5.4.1.3 CT Scan

Dual-energy computed tomography (DECT) has a promising role in diagnosing gout. Based on the spectral dual-energy properties, unique

color-coded aggregates of urate crystal can be seen. This distinguishes gout from other crystal deposition disease, such as hydroxyapatite crystal deposition disease. Characteristic gout erosions and tophi are very sensitive to be detected by conventional CT, but its use is limited by cost. Gouty tophus can be intra-articular or extra-articular, or located in tendons and subcutaneous tissues, with pressure points preponderance. CT and MRI are very accurate in following up response to treatment, as tophi are known to decrease in size, but ultrasonography is more practical for follow-up studies as it is more available at lower cost with less ionizing radiation [16].

5.4.1.4 MRI

When gout affects deep tissues like the spine or locations not amenable to clinical examination like interosseous deposits in the midfoot, MRI is very helpful. It is also accurate in diagnosing the extent of gout involvement of the bursae and tendons and any associated tendon tears. On MRI, tophi appear as low signal on T1-weighted MRI and mostly intermediate signal on T2-weighted MRI [16].

5.4.2 Calcium Pyrophosphate Dehydrate (CPPD) Deposition Disease or Pseudogout

CPPD or pseudogout is a syndrome that manifests as arthritis clinically and as chondrocalcinosis radiographically or as an arthropathy that resembles that of degenerative joint disease. Most likely joints to be involved are the knee, symphysis pubis, and triangular cartilage of the wrist, and they should be examined in suspected patients. CPPD crystals can be found in any cartilage and in the soft tissues where it may mimic calcific tendinitis [17].

5.4.2.1 Radiograph

Arthropathy of CPPD crystal deposition is characterized by sclerosis, joint space narrowing, and osteophyte formation which is difficult to distinguish from degenerative joint disease except by the affected sites which are different than the sites of true degenerative joint disease. For example, pseudogout should be considered if radiocarpal joint, the elbow, or only the patellofemoral compartment of the knee joint is showing degenerative joint disease (Figs. 5.14 and 5.15) [17].

5.4.2.2 Ultrasonography

Based on studies, ultrasonography is more useful in cases of chondrocalcinosis than radiograph which is not sensitive nor specific [18], and it is better than radiograph and CT scan in diagnosing chondrocalcinosis in CPPD cases [19].

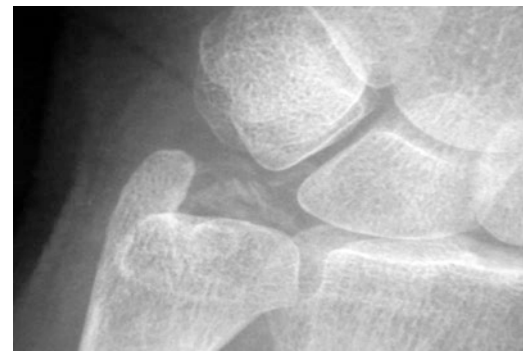

Fig. 5.14 AP oblique view of the right wrist demonstrates chondrocalcinosis of the triangular fibrocartilage complex

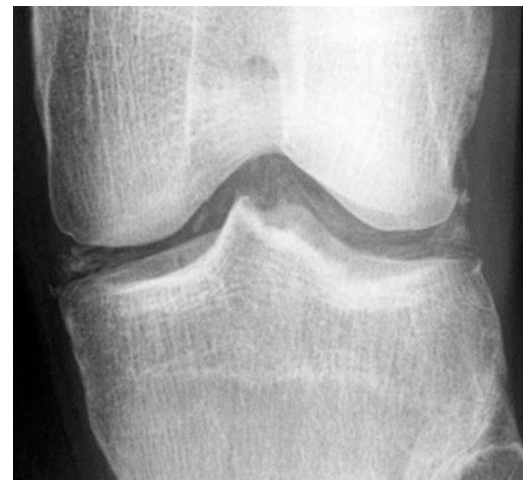

Fig. 5.15 AP view of the right knee demonstrates calcification of the articular lining of the knee. Consistent with chondrocalcinosis and related to calcium pyrophosphate dehydrate deposition disease

5.4.2.3 CT Scan

CT scan and conventional radiography are almost equal in the detection of chondrocalcinosis [19]. The pattern of CPPD on CT scans may show a calcific mass with a lobulated configuration, typically in the ligamentum flavum or within the joint capsule, and within the mass are septum like low-density areas. In addition, pressure erosions may be noted with disruption of adjacent bony cortex. Fine granular calcifications may also be noted. Subchondral cysts or erosions, as well as fractures, may be observed [20].

5.4.2.4 MRI

In detecting the CPPD deposits presence, MRI is not as sensitive as radiography, but 4 T MRI holds better promise in detecting CPPD crystals [21]. Calcifications of chondrocalcinosis are present on MRI as a signal void or decreased signal intensity. High-field MRI is especially effective for visualization of CPPD deposits. Because MRI does not visualize calcific structures well, CT scanning or radiographic confirmation is required; it has low sensitivity for visualization of CPPD deposits but can display massive deposition [20].

Rheumatoid arthritis (RA): It is the most common chronic inflammatory joint disease [22]. It is characterized by joint swelling, joint tenderness, and destruction of the synovial joints, leading to severe disability and premature mortality [23]. The hallmark of RA is bilateral symmetric arthritis of more than three joints (polyarthritis) [3]. Over 60% of patients initially present with symmetric arthritis of multiple small hand joints [3]. Typically, the second and third metacarpophalangeal (MCP) and the third proximal interphalangeal (PIP) joints are involved early in the course of the disease; the ulnar and radial aspects of the radiocarpal joint and the intercarpal, carpometacarpal, metacarpophalangeal, and proximal interphalangeal joints are other common sites [3]. Simultaneous synovitis of tendon sheaths of the wrists and hands is another distinct finding [3]. Bilateral and symmetric involvement of foot joints is another typical manifestation of RA [3]. The metatarsophalangeal and the interphalangeal (great toe) joints are favored sites [3]. All midfoot joints may be involved [3]. The talonavicular, subtalar, and tarsometatarsal joints are specific target areas [24].

Later in the course of the disease, large extremity joints and cervical spine joints could be insulted.

The role of radiology in RA is to either diagnose the disease or assess the disease status and progression.

5.4.2.5 Radiographs

Conventional radiography (CR) has been considered the gold standard for imaging in RA, its sensitivity for structural damage in RA diagnosis is low, and disease activity cannot be assessed [25]. When there is diagnostic doubt, CR, ultrasound, or MRI can be used to improve the certainty of a diagnosis of RA above clinical criteria alone [25]. CR of the hands and feet should be used as the initial imaging technique to detect damage. However, ultrasound and/or MRI should be considered if CR do not show damage and may be used to detect damage at an earlier time point (especially in early RA) [25]. The periodic evaluation of joint damage, usually by radiographs of the hands and feet, should be considered [25]. Monitoring of functional instability of the cervical spine by lateral radiograph obtained in flexion and neutral should be performed in patients with clinical suspicion of cervical involvement. When the radiograph is positive or specific neurological symptoms and signs are present, MRI should be performed [25].

Erosion: It is discontinuity of the white cortical line (marginal erosions) and subsequently become projection-like (Figs. 5.16 and 5.17).

Subcortical cysts: These are cystic changes in the subcortical bone which are easily identified as translucent lesions [24].

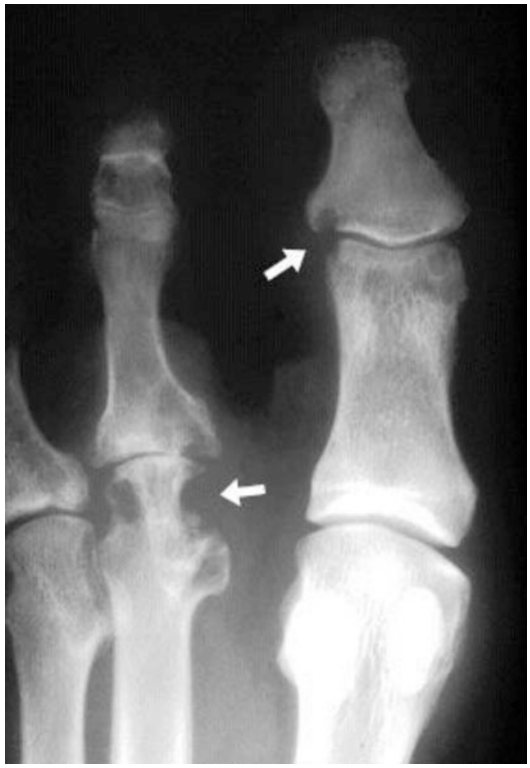

Fig. 5.16 PA view of the forefoot shows erosive changes (arrow)

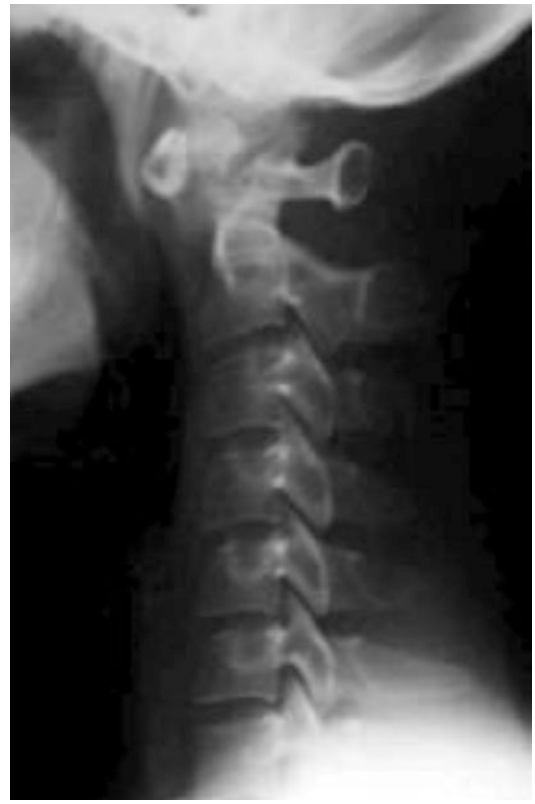

Fig. 5.17 Flexed lateral view of the cervical spine shows straightening of the cervical spine with atlantoaxial subluxation

Joint space narrowing: It is a late finding of RA and can be detected by CR (Fig. 5.18).

Periarticular osteopenia: This refers to non-sharp cortical end plates [3]. This finding is important especially radiographs are used as the first-line imaging tool.

Effusion: Plain radiographs demonstrate indirect signs of effusion such as joint space widening and soft tissue swelling as well as shifting of fat pads [24].

5.4.2.6 Ultrasonography/Magnetic Resonance Imaging (MRI)

Over the past decade, there have been significant advances in the field of musculoskeletal imaging, especially in the application of ultrasound (US) and magnetic resonance imaging (MRI) to the management of rheumatoid arthritis (RA). Both modalities offer significant advantages over the previous standards of clinical examination and radiography and allow direct visualization of both joint inflammation and structural damage. Although measuring similar pathology, each of these imaging tools has its own benefits and limitations, understanding of which can help researchers and clinicians to determine the appropriate role for these tools in RA joint assessment [22].

Ultrasound and/or MRI should be considered if CR do not show damage and may be used to detect damage at an earlier time point (especially in early RA) [25].

Synovitis: Cytokines mediate capillary leakage and edema in the acute phase. This facilitates syno-

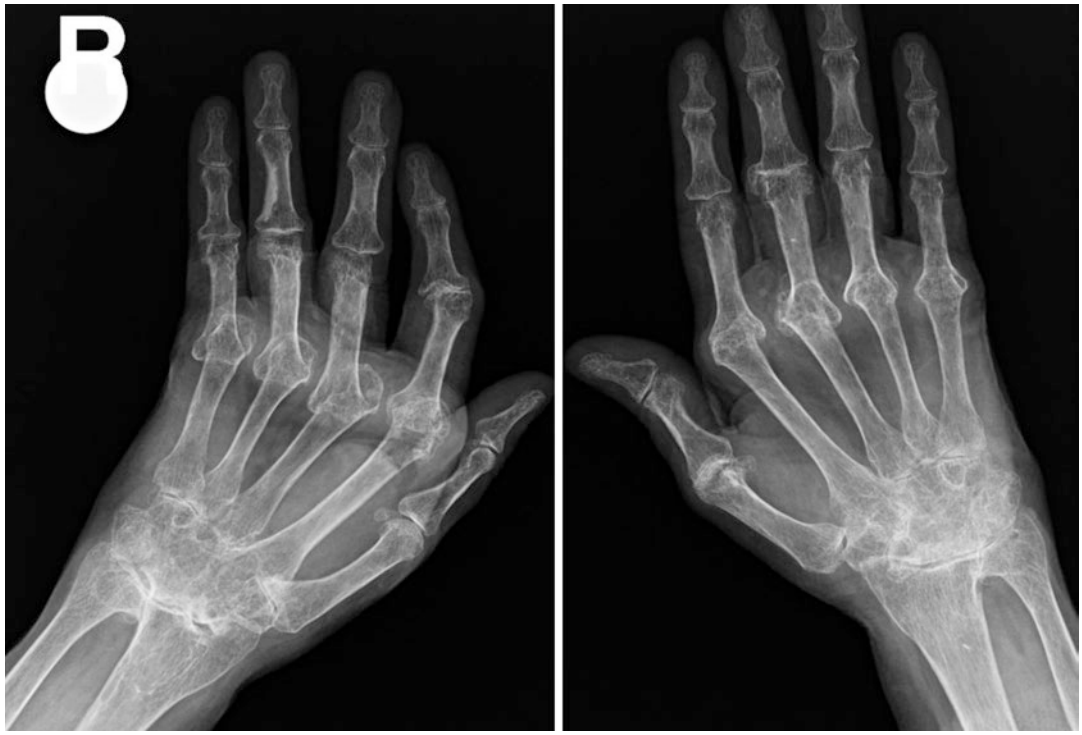

Fig. 5.18 PA view of the hands shows joint space narrowing, erosions, and diffused osteoporosis

vial swelling and leads to widening of the joint space, which may well be exaggerated by effusion [24]. Synovitis initially starts at bare areas.

Subcortical cysts: A number of more than three, in an eccentric location, and non-sharp margins increase the likelihood that the subcortical cyst is the result of an inflammatory joint process [3]. On MRI, arthritic cysts usually do not contain fat or trabecular bone [3]. When subcortical cysts are detected by MRI or US, they are considered pre-erosive changes.

Effusion: Both US and MRI can detect small effusion in small joints.

Periarticular osteopenia: This finding is a secondary indirect sign of synovitis.

Bone marrow edema (BME): MRI is the only modality of choice which can detect this finding. BME is a very useful prognostic indicator in RA. Affected marrow will readily show significant uptake of contrast material [24]. It is associated with disease activity.

Erosions: Naturally, erosions arise at the bare areas first due to the lack of the protecting cartilage layer. The diagnosis of erosions is very important as it may well influence therapy. MR imaging demonstrates erosions clearly [24]. US can detect them too.

Computed tomography (CT): It detects all bony changes and pathology; however, its use is limited due to high radiation.

Scintigraphy: Baseline inflammatory disease measured by scintigraphy appears to be associated with radiographic progression. In addition, multiple regression analysis has demonstrated that progression of radiographic joint destruction was primarily predicted by 99mTc-IgG scintigraphy, while joint swelling and erythrocyte sedimentation rate (ESR, IgM rheumatoid factor (RF)) are not predictive. This suggests that scintigraphy may be superior to conventional clinical and laboratory measurements in the prediction of joint destruction [25].

5.5 Summary

The diagnosis of RA is based on history, clinical examination, and laboratory results. If there is a doubt about RA diagnosis, the radiologic modalities take place to improve the diagnosis. CR is the gold standard modality for imaging in RA. MRI and/or US should be considered if the CR does not show any abnormality.

Assessment and follow-up periodic radiographs should be obtained for follow-up. MRI and/or US assesses the disease progression.

Spondyloarthropathies (SpA): They are a group of diseases that have a strong association with human leukocyte antigen B27 (HLA-B27), are characterized by inflammation of sacroiliac joints (sacroiliitis), and affect axial and appendicular skeleton. They include ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis known as Reiter's syndrome, and other uncommon arthritic diseases.

Ankylosing Spondylitis (AS): It is a disease that affects young age group, is rarely seen after the age of 40, and is more predominant in male gender. The inflammation affects the axial skeleton in symmetrical way and starts at sacroiliac joint in almost all cases. Spondylitis occurs in 50% of patient with AS and starts at the thoracolumbar and lumbosacral spines. Cervical spine joints are rarely seen affected alone. AS is easy to diagnose as it has a unique pattern of distribution and clear clinical picture.

Radiography: CR is still the first imaging modality and should be obtained for the diagnosis of AS. Anteroposterior (AP) pelvic, AP, and lateral spine X-ray should be ordered when AS is suspected. Other radiologic modalities are used to detect the disease in earlier stage or to determine the prognosis. CR can detect many changes in AS but not at early stage as compared to MRI and CT scan.

Erosions: Small erosions resembling the serrated edges of the postage stamp typically start at iliac side of the joint early in the disease course [26]. In the spine, the earliest change is enthesitis at the insertion of annulus fibrosis fibers. This process is a result of erosions and reactive sclerosis which occur at vertebral corner (Romanus lesions) (shiny corners) and cause vertebral squaring. AS is the least erosive spondyloarthropathy.

Ossification: The ossification of the ligaments at sacroiliac joints may appear as star shape, and complete joint fusion may be seen in advanced stage. As the disease progresses in the spines, the ossification starts developing at annulus fibrosis (s**yndesmophytes**). When the ossification continues through the apophyseal joint, complete spinal fusion occurs (**bamboo spine**). In advance disease, **dagger sign** (Fig. 5.19) appears which is the ossification of supra- and interspinous ligaments and can be detected by radiograph as slim ossified streak. When the ligamentous ossification occurs together with ossification of apophyseal joint capsules, there are three vertical

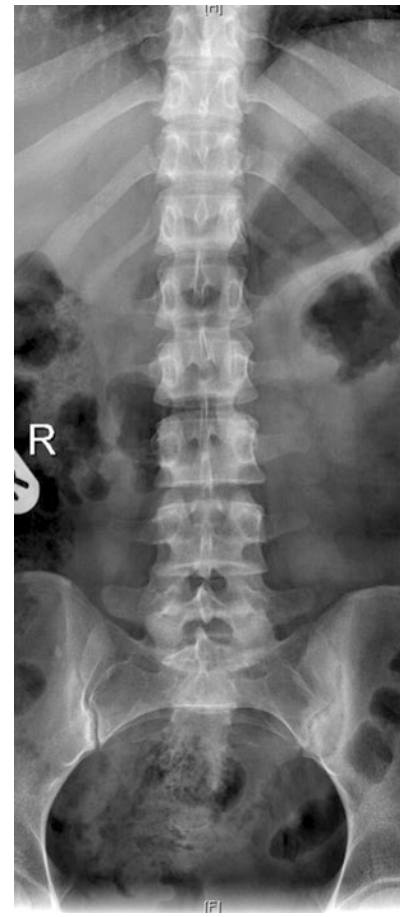

Fig. 5.19 PA view of the pelvis and spines shows bone fusion at sacroiliac joint (ankylosed) and spine fusion (dagger sign)

radiodense lines on frontal radiography (**trolley-track sign**) [27].

Ultrasonography: It has some utility for the evaluation of sacroiliitis when it is very active by using Doppler ultrasonography to assess blood flow and synovitis [26]. It may be useful in some cases in young children as an initial study but is limited to the evaluation of soft tissues surrounding the joint and not the joint itself [26]. Ultrasound may be used for diagnostic and therapeutic injections into the sacroiliac joints as an alternative to fluoroscopy in some cases [26].

Magnetic Resonance Imaging (MRI): MRI has become the gold standard imaging modality for the diagnosis of SpA of sacroiliac joints and spine [26]. It is very sensitive and specific to detect inflammatory changes in and around the sacroiliac joints and spine. Therefore, MRI findings are divided into active and chronic inflammatory findings.

5.5.1 Active Inflammatory Findings

Bone Marrow Edema (BME): It can appear in the sacroiliac joints and spine. It is strongly associated with disease activity and reflects the response to the treatment (Fig. 5.20).

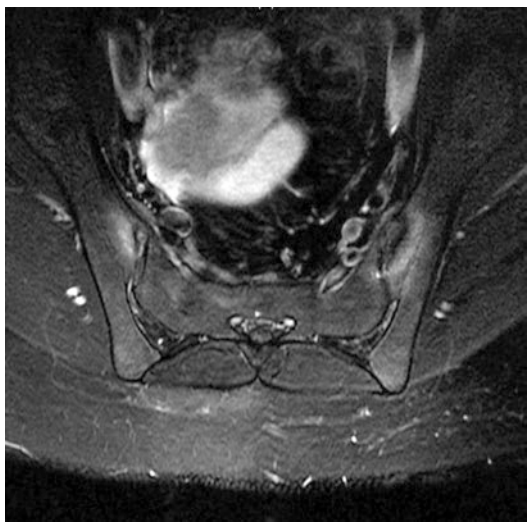

Fig. 5.20 MRI of the sacroiliac joints shows reduced bilateral sacroiliac joint space with symmetrical focal bone marrow edema along the iliac side of both joints

Synovitis/Capsulitis: These findings rarely occur without the occurrence of other findings in AS.

Enthesitis: This finding almost always occurs at muscle insertion and is considered a transient feature.

5.5.2 Chronic Inflammatory Findings

Sclerosis: This appears as low intensity on MRI and mainly develops at joint margins.

Fat deposition: This occurs at bone marrow area in the sacroiliac joint and at vertebral corners in the spine.

Bone bridging: This results from the ossification of ligaments which further lead to the formation of bone bridging and ankylosis as a final result.

Erosions: They are bony defects that can be seen as irregular shapes at joint margins.

Computed tomography (CT): CT is superior to MRI in detecting erosions. It is also used in case of trauma and emergency if fracture is suspected.

Psoriatic arthritis (PsA): PsA is a chronic systemic disease characterized by inflammatory joint changes and is accompanied with skin psoriasis. PsA affects joints asymmetrically. It involves the hands (no sparing joint), feet, and axial skeleton and rarely affects large joints. PsA develops in 7% of patients with skin psoriasis [26]. Axial psoriatic arthritis occurs in approximately 40% of patients with peripheral PsA [26].

Radiography: Radiographs are the first radiologic modality that should be obtained. The radiographic hallmark of PsA is the combination of destructive changes and bone proliferation.

Erosion: It is discontinuity of the white cortical line. Marginal erosion is an early PsA sign which then becomes irregular and ill-defined because of bone formation adjacent to erosions. This sign is also called "pencil in cup" (Fig. 5.21).

Joint space narrowing: Dramatic joint space narrowing may lead to serious disability.

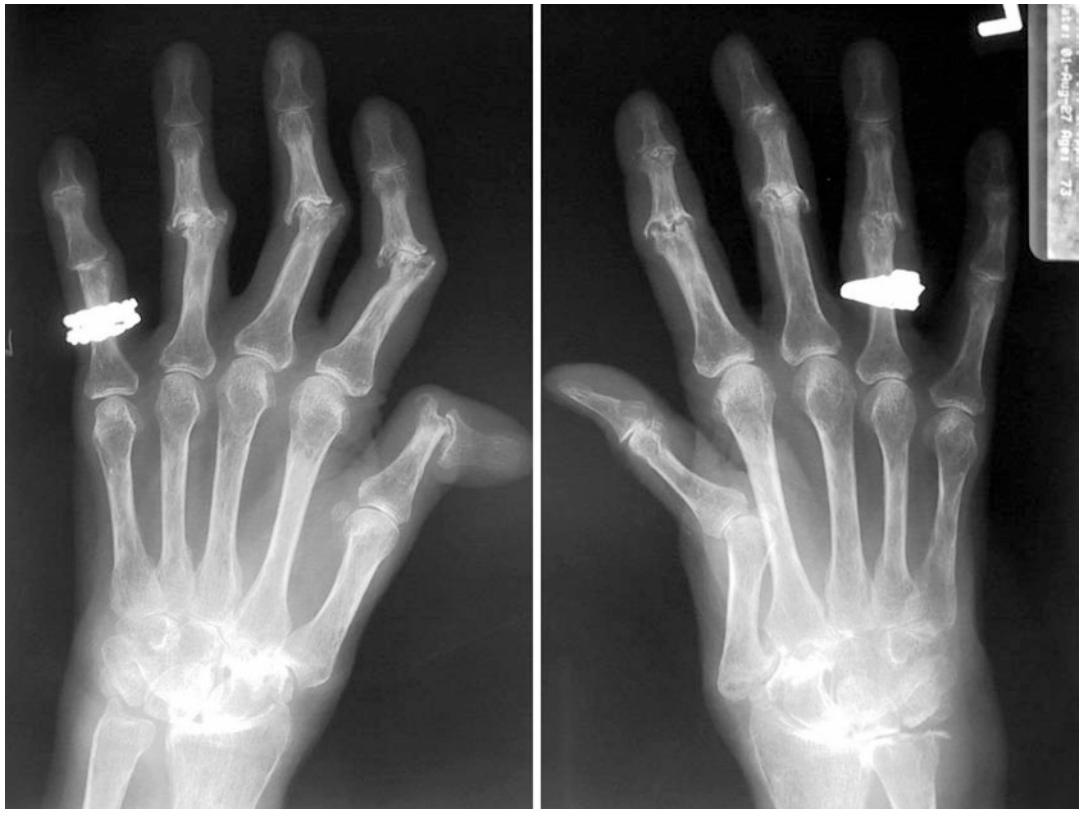

Fig. 5.21 AP view of the hand shows aggressive erosions (pencil in cup) which appear in all PIP joint of both hands; bone proliferation appears at distal part of metacarpal bones. Pan-carpal bone involvement. MCP joints are spared

Bone proliferation: This is a feature of PsA involving particularly metaphysis and diaphysis of the hands and feet.

Ultrasonography: Ultrasound (US) in conjunction with power Doppler (PD) indicative of degree of inflammatory activity has an increasing important role in the evaluation of PsA. In fact, US is useful mainly for its ability to assess musculoskeletal (joints, tendons, entheses) and cutaneous (skin and nails) involvement, to monitor efficacy of therapy and to guide steroid injections at the level of inflamed joints, tendon sheaths, and entheses [28].

Synovitis: Asymptomatic US synovitis and enthesopathy may indicate subclinical musculoskeletal involvement [28].

Erosions: These can also be detected by US.

Tenosynovitis: US findings indicative of tendon involvement include fusiform swelling and focal derangement of tendon echotexture [28]. Achilles tendon, plantar fascia, patellar tendon, and tenosynovial sheaths of the hand and ankle are frequently affected in patients with PsA [28].

Enthesitis: US signs of enthesitis include hypoechoic swelling of the tendon insertion, enthesophytes, and possible bursal enlargement [28].

Magnetic resonance imaging (MRI): This modality is mainly used when the axial skeleton is affected. MRI is the most sensitive imaging for the detection of subtle bilateral changes, which can be important in distinguishing PsA from septic sacroiliitis. The spondylitic changes in PsA and reactive arthritis appear more randomly than those in AS. Large chunky-appearing paravertebral ossification is commonly seen in the thoracolumbar junction. These ossifications do not bridge the intervertebral discs as seen in AS. Ankylosis, squaring of vertebral bodies, and spinal fusion are very rare in PsA.

Computed tomography (CT): CT has little role in the assessment of peripheral joints but may be useful in assessing elements of spine disease [28]. The accuracy of CT is similar to MRI in the assessment of erosions in sacroiliac joints; however, CT has radiation and is not effective in detecting synovial inflammation [28].

Reactive Arthritis (ReA): It is previously known as Reiter's syndrome. It is usually accompanied by conjunctivitis and urethritis. It affects males between the ages of 15 and 35 years. Arthritis might be the only clinical manifestation of ReA. The radiographic features are identical to those in PsA, but the difference is in the pattern of distribution which begins in the feet and then hand. History and clinical examination are helpful in differentiating ReA from PsA.

Osteoarthritis (OA): OA is the most common arthropathy in elderly. It impacts the quality of life, and it has a major implication on public healthcare. OA asymmetrically affects joints of the hands (sparing MCP joints), shoulders, feet, knees, hip, and spine.

Radiography: CR is the gold standard radiologic modality in detecting OA. It detects many OA features. Radiographic progression appears specific (91%) but not sensitive (23%) for cartilage loss [29].

Joint space narrowing: Non-uniform narrowing of the joint spaces occurs in OA.

Osteophytes: These are joint spurs that occur along joint margins. Osteophytes can also be observed on the joint line (Fig. 5.22). The definition of OA relies on the presence of osteophytes on anteroposterior weight-bearing radiographs [29].

Sclerosis: It is seen as an increased density on radiograph [30].

Cyst formation: This is seen as a loss of trabecular structure [30].

Ultrasonography: US is widely used in RA and has been accepted to be used in OA too. US has the advantage of assessing and visualizing many OA features without exposing the patient to radiation. One limitation of US is that it cannot penetrate the bony parts to visualize the structures beyond them. The use of US is more common for hand and knee OA and has very limited usage in the assessment of other joints.

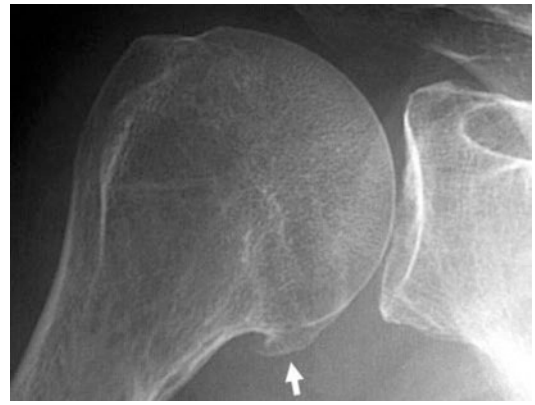

Fig. 5.22 AP view of the shoulder joint shows osteophyte formation (arrow)

Osteophyte: They can be seen as a disturbed acoustic window.

Synovitis: This appears as thickening of synovial membrane.

Erosions: They can be detected in erosive OA.

Magnetic resonance imaging (MRI): MRI is widely used in knee OA and spondylolisthesis as it has the ability of providing a multiplanar image of all compartments. MRI can assess all features of OA, osteophytes, synovitis, effusion, joint spaces, bone marrow lesions, ligaments, cartilage, and vertebral height, as it decreases with degenerative diseases.

Computed tomography (CT): This test is of limited use as it exposes the patient to radiation. It still has its main role emergencies and in cases of suspected fracture.

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Part II

Diagnostic Approach to Common Medical Problems in Patients with Rheumatic Diseases

Low-Back Pain

6

Khaled Albazli, Manal Alotaibi, and Hani Almoallim

6.1 Introduction

Low-back pain (LBP) is mainly managed in primary health care. It is a symptom that is commonly belittled and misdiagnosed. This chapter aims to present a simple approach for the diagnosis and assessment of LBP according to the latest clinical recommendations. This content will discuss in details the definition and prevalence of LBP and the important stepwise approach to reach a diagnosis and start treatment. This approach starts from history-taking, physical examination, and radiological studies and, finally, concludes with the management and referral guidelines. Also, inflammatory back pain will be explained thoroughly in an easy to digest way.

A major advantage of this chapter is that carefully designed tables, diagrammatic presentations, and illustrations were used to help practicing clinicians perform proper and adequate work up for patients with LBP.

6.2 Learning Objectives

By the end of this chapter, you should be able to:

1. Present a comprehensive approach for the diagnosis and assessment of low-back pain in accordance with updated clinical guidelines.
2. Recognize the red flags of LBP and the proper time for referral.
3. Prevent the delay of the diagnosis and management of inflammatory back pain (IBP) to avoid the long-term disabilities.

6.3 Definition

LBP is defined as pain or stiffness in the area between the costal margin and the inferior gluteal folds; this pain could also extend to the lower limbs [1]. LBP can also be classified as acute or chronic; this would be helpful for prognostic and management purposes. Acute

K. Albazli
Department of Medicine, Faculty of Medicine in Al-Qunfudhah, Umm Al-Qura University, Makkah, Saudi Arabia

The George Washington University School of Medicine and Health Sciences, Washington, D.C., USA

M. Alotaibi
Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Internal Medicine Department, College of Medicine, Umm Al-Qura University, Makkah, Saudi Arabia

H. Almoallim (✉)
Medical College, Umm Al-Qura University (UQU), Makkah, Saudi Arabia
e-mail: hmmoallim@uqu.edu.sa

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LBP is considered if the symptom was present for less than 6 weeks, while sub-acute and chronic would be considered if the pain lasts from 6 to 12 weeks and more than 12 weeks, respectively [2]. Table 6.1 shows some important definitions for some terminologies used while dealing with patients complaining of LBP.

6.4 Prevalence

LBP is a worldwide problem that is more commonly found in females and those aged between 40 and 80 years [3–5]. Lifetime prevalence of LBP has increased significantly to become as high as 84%, while chronic LBP has reached 23%. Of this population, 11–12% will develop some form of impairment or disability.

6.5 Differential Diagnosis

Back pain is a frequently encountered symptom that could be caused by many specific and non-specific underlying causes, as shown in Table 6.2. However, mechanical low-back pain represents 97% of the causes [6].

6.6 Approach to Diagnosis

When assessing a patient presenting with LBP, it is important to rule out neurologic deficits or other serious inflammatory or medical conditions with a focused history and physical examination. Thorough assessments are also important to aid physicians in screening the patients who need further diagnostic investigations to rule out serious pathologies (see Fig. 6.1) [7, 8].

Table 6.1 Important terminologies in low-back pain

Spondylosis	A degenerative osteoarthritis of the spine. It can be seen radiographically as a narrowed disc with arthritic changes
Spondyloarthritis	Also called spondyloarthropathy is a group of inflammatory rheumatic diseases that cause arthritis. The most common is ankylosing spondylitis, which affects mainly the spine. Others include reactive arthritis, psoriatic arthritis, and enteropathic arthritis/spondylitis associated with inflammatory bowel diseases
Spondylolisthesis	Anterior or posterior displacement of a vertebra or the vertebral column in relation to the vertebrae below. The slippage is determined by spinal X-ray and graded from grade 1 to 4 Grade 1: Less the 25% slippage Grade 2: 25%–50% slippage Grade 3: 50%–75% Grade 4: More than 75%
Spondylitis	Inflammation of vertebrae manifested by back pain and progressive stiffness of the spine. The inflamed spine can be visible in MRI
Discitis	An inflammation of the intervertebral disc space often related to infection
Radiculopathy	Impairment of a nerve root, usually causing radiating pain, numbness, tingling, or muscle weakness that corresponds to a specific nerve root

The history-taking elements for LBP include the following:

- Type of onset and character may hint at the underlying pathology:
  - Bones: dull and nagging.
  - Muscles: dull aching.
  - Nerves: sharp and lightning like.

Table 6.2 Lower-back pain causes and risk factors

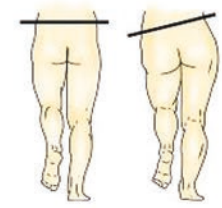
Specific causes of LBP	**Musculoskeletal:** • **Musculoligamentous strain**: Experienced by up to 80% of population at some time • **Fibromyalgia:** Widespread pain in all 4 quadrants of the body, at least 3 months, 11 out of 18 positive tender points on physical exam • **Osteoarthritis:** Affects mainly the hips, knees, spine, first CMC, DIP, and PIP • **Rheumatoid arthritis:** May affect facet joints. It presents with pain, swelling, and impaired function of joints with morning stiffness for ≥1 hour and has extra-articular manifestations, positive RF, and ACPA • **Spondylolisthesis:** Dull, aching pain in the lower lumbar or upper sacral region. Pain also extends into the buttocks or posterior thigh • **Vertebral compression fracture:** Symptoms could mean compression of the nerves at the fracture site: Numbness, tingling, weakness, and incontinence • **Inflammatory:** Spondyloarthritis (ankylosing spondylitis, reactive arthritis, psoriatic arthritis) **Spinal cord**: Myelopathy **Nerve root**: Radiculopathy **Degenerative or traumatic:** Disc herniation, spondylosis, fracture **Metabolic:** Paget's disease, osteomalacia **Neoplastic:** Lung, breast, prostate, multiple myeloma, lymphoma **Infectious**: TB discitis, osteomyelitis, epidural abscess, zoster, Lyme, CMV, HIV **Referred pain:** • **Gastroenterology:** PUD, cholelithiasis, pancreatitis, pancreatic cancer • **Genitourinary:** Pyelonephritis, nephrolithiasis, uterine or ovarian cancer, salpingitis • **Vascular:** Aortic dissection, leaking aortic aneurysm
Nonspecific causes	Poor posture, sitting and standing, lifting ergonomics, unknown causes
Risk factors	Overweight, smoking, pregnancy, long-term use of medication (e.g., corticosteroids), stress, depression, occupation

CMC carpometacarpal *joint*, *DIP* distal interphalangeal joint, *PIP* proximal interphalangeal *joint*, *RF* rheumatoid factor, *ACPA* anti-citrullinated protein antibodies, *CMV* cytomegalovirus, *HIV* human immunodeficiency virus, *PUD* peptic ulcer disease

  - Nerve root: sharp and shooting.
  - Sympathetic nerve: burning, pressure like, stinging, and aching.
  - Vascular: throbbing and diffuse.
- Duration: this would help guide imaging and treatment decisions.
- The site of pain and any radiation: this would help to rule out radiculopathy.
- Intensity of the pain.
- Continuous versus on and off.
- Progressive or not.
- Factors that improve or worsen the pain: daytime vs nighttime, certain positions, activity vs rest, and response to treatments.
- Severity of pain.
- Associated symptoms: extra-axial joint pain, sciatica, paresthesias, pseudoclaudication, and bowel/bladder dysfunction.
- Assess for symptoms specific for certain diseases like spondyloarthropathies, i.e., enthesitis, dactylitis, history of psoriasis, and bowel symptoms.
- Assess for red flags (see "radiological studies"):
  - History of trauma [9].
  - Symptoms suggestive of an infection or malignancy, i.e., fever and unexplained weight loss.
  - Neurological deficits or other symptoms that may give a clue to serious underlying pathologies like cauda equine syndrome, compression fractures, spinal stenosis, herniated disc, or radiculopathy.
- Review of systems:
  - Referred pain due to underlying visceral pathologies.

Gait

- **Gait:** straight walking while watching for abnormal flexion (stenosis or facet joint), extension (disc), or Trendelenburg gait.
- **Screening:** walking on toes then on heels.
- **Position:** watch as patient changing position.



Inspect for Trendelenburg gait

Inspection

- **Alignment:** Kyphosis, scoliosis, or loss of exaggerated lordosis.
- **Skin:** Erythema, hair patch, Café au lait spots, nodules, and or scars.
- **Inequality**: watch for iliac crest and pelvic inequality => at the level of L4-5: ask patient to flex his/her hip.
- **N.B:** Always inspect the patient posteriorly and laterally.

Inspect for Symmetry

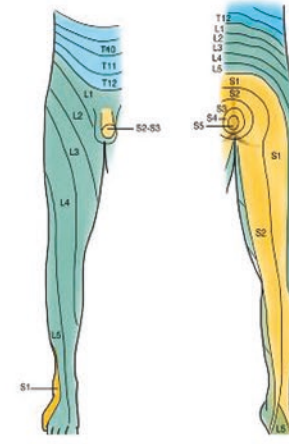
Palpation

- Examine the patient in the prone position.
- **Spinous processes**: tenderness or defects.
- **Inter-spinous ligament.**
- **Supraspinous ligament.**
- **Paraspinal muscles.**
- **Iliac crest:** tenderness (Spondyloarthritis) or nodules. PSIS –Sacroilliac joint -S2
- Ischial tuberosity -Sciatic nerve -Greater trochanter.

Palpation

Range of Motion

- **Flexion:** finger-floor
- **Extension:** stabilize the pelvis and measure the distance
- **Lateral flexion:** Finger-fibula (against the wall).
- **Tohoraco-lumbar rotation:** 70 degree normally.



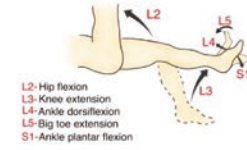
Testing of Dermatomes

Special Test

- Straight leg raising test (SLRT)
- Slump test
- Sacro-illiac joints exam: Patrick test and compression test
- Modified-modified schober's test
- Neurological exam: Muscle bulk by tape (Radiculopathy) and rectal tone (S3,4,5)

SLRT

Slump test



Testing of Myotomes

Fig. 6.1 Approach to back MSK examination

- Past medical and surgical history:
  - Previous history of cancer.
  - Medications.
  - History of osteoporosis and/or pathologic fractures.
  - Anxiety or depression.
- Social history: history of smoking, illicit drug use, and type of work.
- The physical examination steps for the assessment of LBP include the following (see Fig. 6.2):

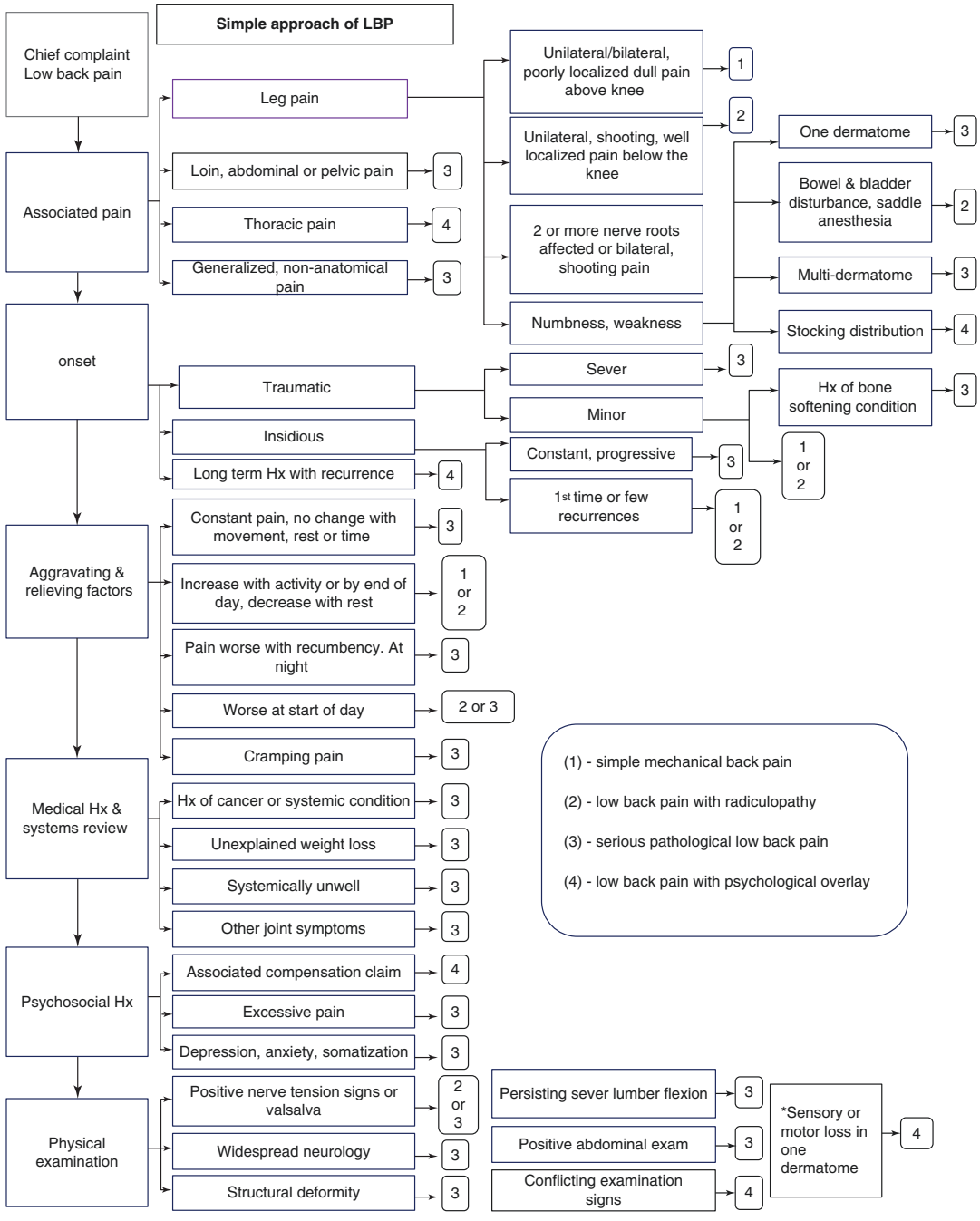


Fig. 6.2 Simple approach of LBP

– Inspection for skin changes and gait abnormalities.
– Palpation for tenderness.
– Range of motion.
– Special tests (Table 6.3).

Table 6.3 Special tests for LBP

Special test	Technique and significance
Straight leg raise test (SLRT)	• To test for the presence of a disc herniation • In supine position, flex the patient's hip while maintaining the knee in full extension • Watch for the degree of hip flexion where the patient reports pain • **Positive SLRT:** Radicular pain down the posterior portion of the tested leg at 40 degrees of hip flexion or less • Sensitivity 33%, specificity 87%
Slump test	• Ask the patient to hold hands behind his/her back while seated upright • Instruct to the patient to (slump) flex his/her spine, followed by neck flexion • With examiner's hand on top of head, the patient performs knee extension and dorsiflexion of foot • Ask the patient to return the neck to neutral (no flexion) • **Positive slump test:** The patient's symptoms are increased in the slumped position and released as the patient actively extends • Sensitivity 84%, specificity 83%
Patrick's test (FABER)	• To assess for the sacroiliac joint dysfunction or hip joint pathology • In supine position, bring the tested leg to hip flexion, abduction, and external rotation • Against the medial knee, try to bring the bent leg passively towards the table • **Positive test**: Reproduction of groin pain or buttock pain • Sensitivity 82%
Compression test	• To assess for the sacroiliac joint dysfunction • While standing behind the patient, bring him/her to sideline position • Ask the patient to flex hip at 60 degrees and knees at 90 degrees • Apply an inward/downward force on iliac crest • **Positive test:** Pain on sacroiliac joint • Sensitivity 69% and specificity 93%
Modified-modified Schober test	• Identify the PSISs by marking the inferior margins of the patient's PSISs with his or her thumbs • Mark along the midline of the lumbar spines horizontal to the PSISs • Make another mark 15 cm above the original mark • With a tape pressed firmly on the line between the two marked points, instruct the patient to bend forward into full lumbar flexion • Measure the new distance between the superior and inferior skin markings • Distance increases less than 5 cm indicates limited lower back flexion
Neurological assessment	• Measure the muscle bulk by tape • Assess for muscle power: Hip flexion (L2), knee extension (L3), ankle dorsiflexion (L4), big toe extension (L5), and ankle plantar flexion (S1) • Check knee reflex (L3 and L4) and ankle reflex (L5 and S1) • Check for skin sensory loss • Assess anal sphincter tone by digital examination (S3, 4, 5)

PSIS posterior superior iliac spine, *L* Lumbar vertebrae, *S* Sacral vertebrae

6.7 Radiological Studies for LBP

Acute LBP that is free of any red flags is generally a benign and self-limiting condition that does not warrant any further imaging evaluation. If there are any signs of complications, an MRI should be requested as it has replaced CTs and myelographies as the first-line imaging modality. MRIs are useful for detecting infections and neoplasia and for postoperative assessments. However, CTs are more useful in patients with abnormalities in bone structure and for evaluation of surgical fusion or instrumentation procedures. CTs are also useful when MRIs are contraindicated. Other imaging modalities like myelography/CT, discography/CT, and radioisotope bone scans can be used in selected patients [10, 11].

Red flags that warrant further imaging [9]:

- Onset above age 70 years old.
- Pain that has persisted for more than 6 weeks.
- History of trauma, even mild trauma in patients aged >50.
- History of surgery in the same site of pain.
- History of malignancy.
- History of IV drug abuse.
- History of osteoporosis or long-term use of steroids.
- Weight loss that is unexplained.
- Fever without an obvious source of infection.
- The presence of focal neurological deficits.
- The use of immunosuppressive medication.

Imaging studies that may be considered include:

1. **X-ray**
   - It is useful in delineating degenerative bone disease, disc prolapse, spondylolisthesis, fractures, and neoplasia and to assess prior surgical interventions.
   - Erythrocyte sedimentation rate (ESR) is a useful tool that can suggest the presence or absence of an infection or neoplasia. In patients with no more than 1 risk factor for systemic disease and an ESR less than 20, infections and malignancy would be considered less likely.
2. **CT**
   - It can help in detecting degenerative bone disease, spondylolisthesis, fractures, and malunion. It can also delineate inflammation in the sacroiliac joints.
   - It can show false-positive findings following trauma.
3. **MRI**
   - This is the optimal imaging modality for detection of soft tissue abnormalities. It should be offered to patients presenting with neurological deficits. It is a valuable tool for detecting conditions like disk herniation, spinal stenosis, osteomyelitis, discitis, spinal epidural abscess, bone metastasis, arachnoiditis, and neural tube defects.
   - It can reveal inflammatory changes in the sacroiliac joints before they start showing on plain X-rays.
4. **Electromyography (EMG)**
   - It is useful in patients complaining of radiculopathic pain with inconclusive findings on imaging modalities who may be considered for surgery.
   - It can be helpful in patients who were found to have multilevel affection on imaging.
5. **Radionuclide bone scans**
   - It is a more sensitive tool than plain X-rays, especially for the detection of hidden infections or malignancy.
   - In patient who have normal ESR values and plain radiographs, however, these will be of limited utility.

6.8 Detection of Inflammatory Back Pain

Inflammatory back pain (IBP) is usually diagnosed late especially in primary care settings. Causes for this delay may include difficulties in differentiating between mechanical and inflammatory back pain. IBP can lead to significant functional disability. The longer the diagnosis is delayed, the worse the functional outcome [11, 12].

Seronegative spondyloarthropathies are an important cause of IBP. They are a group of inflammatory diseases that are characterized by seronegative arthritis (rheumatoid factor negative) which is linked with the presence of the human leukocyte antigen HLA-B27.

The seronegative spondyloarthropathies include the following disorders:

- Undifferentiated spondyloarthritis.
- Ankylosing spondylitis: involves the spine, peripheral joints, and entheses. This disorder is a frequently underdiagnosed cause of low-back pain.
- Reactive arthritis or Reiter's syndrome: presents with conjunctivitis, urethritis, and arthritis.

- Spondyloarthritis associated with psoriasis: arthritis that is associated with psoriasis.
- Spondyloarthritis with inflammatory bowel disease: Crohn's disease and ulcerative colitis are often associated with ankylosing spondylitis or peripheral arthritis.
- Juvenile onset ankylosing spondylitis: affects children under the age of 16 years.

IBP definition criteria includes the following items [13, 14]:

- The pain has an insidious character.
- Pain increases at night.
- Pain that improves with activity and does not improve with rest.
- Onset of pain occurs in patients <40 years of age.

Four criteria out of five are required to make a diagnosis of IBP. The sensitivity and specificity of these criteria are at 77% and 91.7%, respectively. Referral to a rheumatologist should be considered if these criteria are fulfilled (Fig. 6.3) [15, 16].

6.9 Treatment of Low-Back Pain (Acute or Sub-Acute Pain) [17, 18]

- In patients with favorable prognosis, reassurance is imperative.
- Physical activity and supervised exercise regimens.
- Bed rest should not be recommended.
- Nonpharmacological therapy that can be used in an acute setting with moderate-quality evidence includes superficial heat, massage, and acupuncture. Low-quality evidence therapies include spinal manipulation.
- Second-line agents include nonsteroidal anti-inflammatory drugs, muscle relaxants, and duloxetine (as co-medications for pain control). Newer guidelines no longer support the use of acetaminophen and tricyclic antidepressants.
- Modalities such as electrotherapy should not be used.
- Medications and other therapies should only be used short term.
- There should be a multidisciplinary approach to treatment.

6.10 Treatment of Inflammatory Back Pain (IBP)

The main target for therapy is to decrease the severity of symptoms and inflammation and to halt the progression to impairment and functional disability. Nonpharmacological therapy includes exercise and patient counselling. Group exercises are favored over home exercises. Treatment of patients suffering from IBP should be tailored to each patient's individual manifestations and general condition. Factors that should be kept in mind include the patient's age, sex, presence of comorbidities, medication interactions, socioeconomic status, severity of symptoms and signs, and his overall prognosis. Certain clinical findings should be considered while formulating a therapeutic plan, such as axial or peripheral symptom predominance and entheseal and extra-articular affection.

If the patient complains of persistent symptoms, NSAIDs are used as first-line pharmacological therapy. In cases where NSAIDs are contraindicated or not tolerated, paracetamol and/or opioids can be used. Disease-modifying anti-rheumatic drugs (DMARDs) such as systemic steroids, sulfasalazine, and methotrexate were not found to be useful in axial predominant disease. However, intra-articular injections in affected sites can be beneficial.

If patients exhibit significantly active disease, anti-TNF agents can be considered. Surgery should be offered to patients suffering from pain that is refractory to all previously mentioned treatment lines. It can also be offered to patients with functional impairment and anatomical damage found on imaging [19]. Spinal corrective osteotomy can be considered in patients suffering from severe deformities and significant functional impairment. Referral to surgery should also be done in AS and acute vertebral fracture cases (Fig. 6.4).

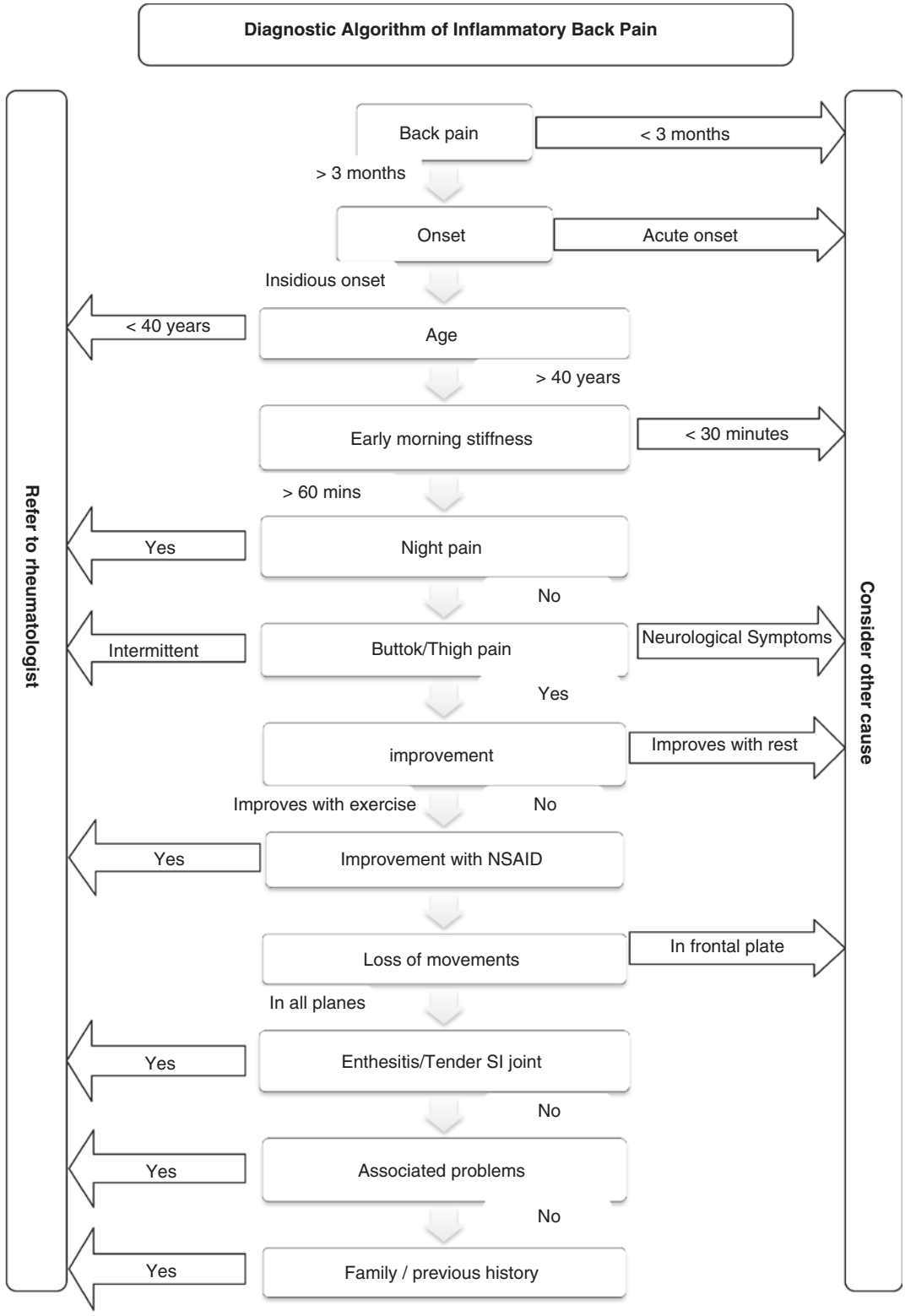


Fig. 6.3 Diagnostic algorithm of low back pain

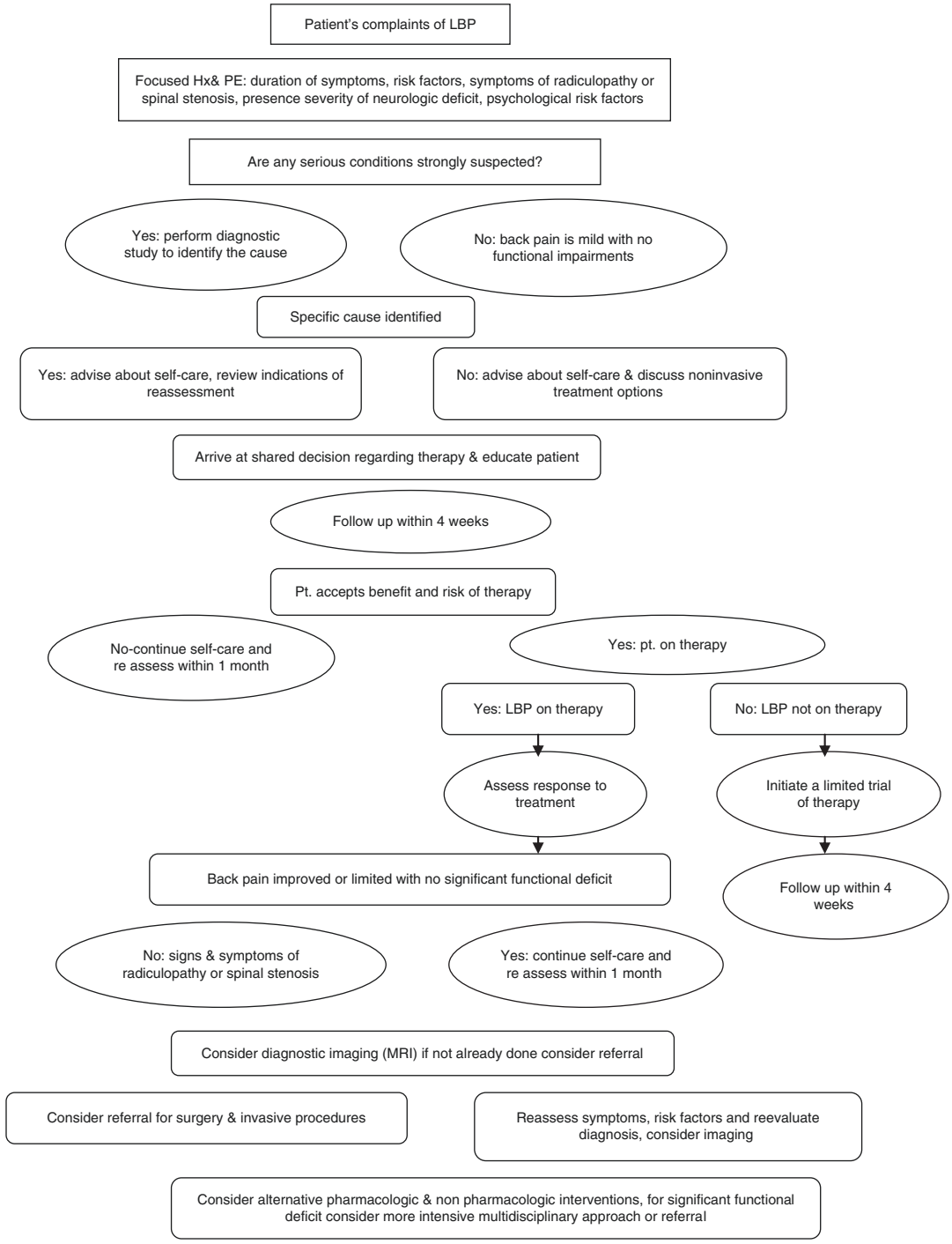


Fig. 6.4 How to approach a LBP patient in the clinic

6.11 Referral

Consultations to neurosurgery or orthopedics are needed if any of the following symptoms and/or signs occur:

1. Cauda equina syndrome: this should be suspected if the patient complains of typical features like bowel and bladder dysfunction (urinary retention), saddle anesthesia, and bilateral leg weakness and numbness.
2. Spinal cord compression: this should be suspected in cancer patients who have a risk of spinal metastasis. They may present with acute neurologic deficits and need emergent evaluation for surgical decompression or radiation therapy.
3. Progressive or severe neurologic deficits or if any neuromotor deficits that persist after 4 to 6 weeks of conservative therapy: these patients should be referred to a neurologist.
4. Sciatica, sensory deficit, or reflex loss persistent for 4–6 weeks in a patient with positive straight leg raise test, consistent clinical findings, and favorable psychosocial circumstances such as realistic expectations and absence of depression, substance abuse, or excessive somatization.

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Abbreviations

ACPA	Anti-citrullinated protein antibodies
AS	Ankylosing spondylitis
CMC	Carpometacarpal *joint*
CMV	Cytomegalovirus
DIP	Distal interphalangeal joint
DMARDs	Disease-modifying anti-rheumatic drugs
GI	Gastrointestinal
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
IBP	Inflammatory back pain
L	Lumbar vertebrae
LBP	Low-back pain
NSAIDs	Nonsteroidal anti-inflammatory drugs
PIP	Proximal interphalangeal *joint*
PSIS	Posterior superior iliac spine
PUD	Peptic ulcer disease
RF	Rheumatoid factor
S	Sacral vertebrae

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7 Pulmonary Manifestations of Connective Tissue Diseases

Rabab Taha and Maun Feteih

7.1 Introduction

Pulmonary manifestations cause a huge burden for patients with connective tissue diseases (CTD). It has been associated with higher rates of mortality and morbidity.

There are six CTDs which have significant pulmonary manifestations:

- Systemic sclerosis (SSc) or scleroderma.
- Rheumatoid arthritis (RA).
- Systemic lupus erythematosus (SLE).
- Sjogren syndrome (SS).
- Mixed connective tissue disease (MCTD).
- Polymyositis/dermatomyositis (PM/DM).

7.2 Chapter Objectives

- To develop a practical approach to chronic and acute dyspnea and cough for the previously mentioned CTDs' patients.
- To know when and how to screen for the pulmonary diseases related to the CTDs.
- To develop knowledge about most of the pulmonary manifestations of CTDs and how to diagnose them and treat them sufficiently.

7.3 About the Chapter

In the chapter, for every CTD, the pulmonary manifestations will be discussed according to the anatomical structure of the respiratory system as follows:

- Airways:
  - Upper airway.
  - Lower airway.
- Parenchyma:
  - Alveolar space.
  - Interstitium.
- Vasculature:
  - Pulmonary artery.
- Pleura:
  - Pleural space.
  - Pleura.
- Respiratory muscles:
  - Diaphragm.
  - Chest wall muscles.

7.4 To Get the Most of the Chapter

- In general, interstitial lung diseases (ILD) and pulmonary arterial hypertension (PAH) are the most common pulmonary manifestations of CTDs.

R. Taha (✉)
Infectious Diseases Unit, Internal Medicine Department, Doctor Soliman Fakeeh Hospital, Jeddah, Saudi Arabia

King Abdulaziz University, Jeddah, Saudi Arabia

M. Feteih
Pulmonary Medicine, King Faisal Specialist Hospital & Research Center, Jeddah, Saudi Arabia

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- The most common subtypes of ILD are nonspecific interstitial pneumonia (NSIP) and usual interstitial pneumonia (UIP). Furthermore, for all CTDs except SSc, NSIP, which presents with ground glass opacities (GGO) on high resolution computed tomography (HRCT), has better prognosis than UIP, which presents as reticular opacities with or without honeycombing on HRCT. That's because GGO represents an ongoing inflammatory process, while reticular opacities and honeycombing represent fibrosis.

Due to the rarity of some CTDs or some of the pulmonary manifestations, there are few or lack of large randomized control trials (RCTs) to relay on in decision making, which makes the management not standardized.

7.5 Important Information about Pulmonary Manifestations of CTDs before Going through the Chapter

Most of the pulmonary manifestations could occur before, co-exist, or after the CTD itself being clinically manifested.

- The prevalence of each entity of pulmonary manifestations related to each CTD is presented in Table 7.1.
- Screening for pulmonary complications in CTD patients is not well established. However, the following model seems to be acceptable to be applied to all CTDs, while physicians should tailor it according to their patients and the clinical context (Fig. 7.1).
- CTD-related interstitial lung disease (CTD-ILD) subtypes are similar to those in idiopathic interstitial pneumonia (IIP). Each subtype has been named according to its histological and/or radiological pattern (Table 7.2).
- Classification of pulmonary hypertension (Fig. 7.2; Table 7.3).
- The decision of when to start treatment in CTD-ILD is considered a dilemma because some patients present with respiratory symptoms and others are asymptomatic but have physiological (i.e., pulmonary function test [PFT]) or radiological (i.e. HRCT) abnormalities related to ILD. Thus, a useful stepwise approach developed by the authors of the Scleroderma lung study could be used depending on the severity of the disease on HRCT. See text below (SSc-ILD treatment) and combine it with (Fig. 7.3). We think it's appropriate to apply it to the rest of the CTD-ILD.
- The approach to screening for CTD-related pulmonary hypertension (CTD-PAH) is illustrated in Fig. 7.4 [1].
- The approach to acute dyspnea in CTDs is presented in Fig. 7.5.
- The approach to chronic dyspnea in CTDs is presented in Fig. 7.6.

Table 7.1 Connective tissue diseases and pulmonary manifestations

CTDs and common pulmonary manifestations					
	ILD	Airways	Pleura	Vascular	DAH
Systemic sclerosis	+++	–	–	+++	–
Systemic sclerosis	++	++	++	+	–
Primary Sjogren's syndrome	++	++	+	+	–
Mixed CTD	++	+	+	++	–
Polymyositis/dermatomyositis	+++	–	–	+	–
Systemic lupus erythematosus	+	+	+++	+	++

Adopted from Aryeh Fischer, Prof Roland du Bois. Interstitial lung disease in connective tissue disorders The Lancet, Volume 380, Issue 9842, Pages 689–698, 18 August 2012. The signs show prevalence of each manifestation (–, no prevalence; +, low prevalence; ++, medium prevalence; +++, high prevalence)
ILD interstitial lung disease, *DAH* diffuse alveolar hemorrhage, *CTD* connective tissue disease

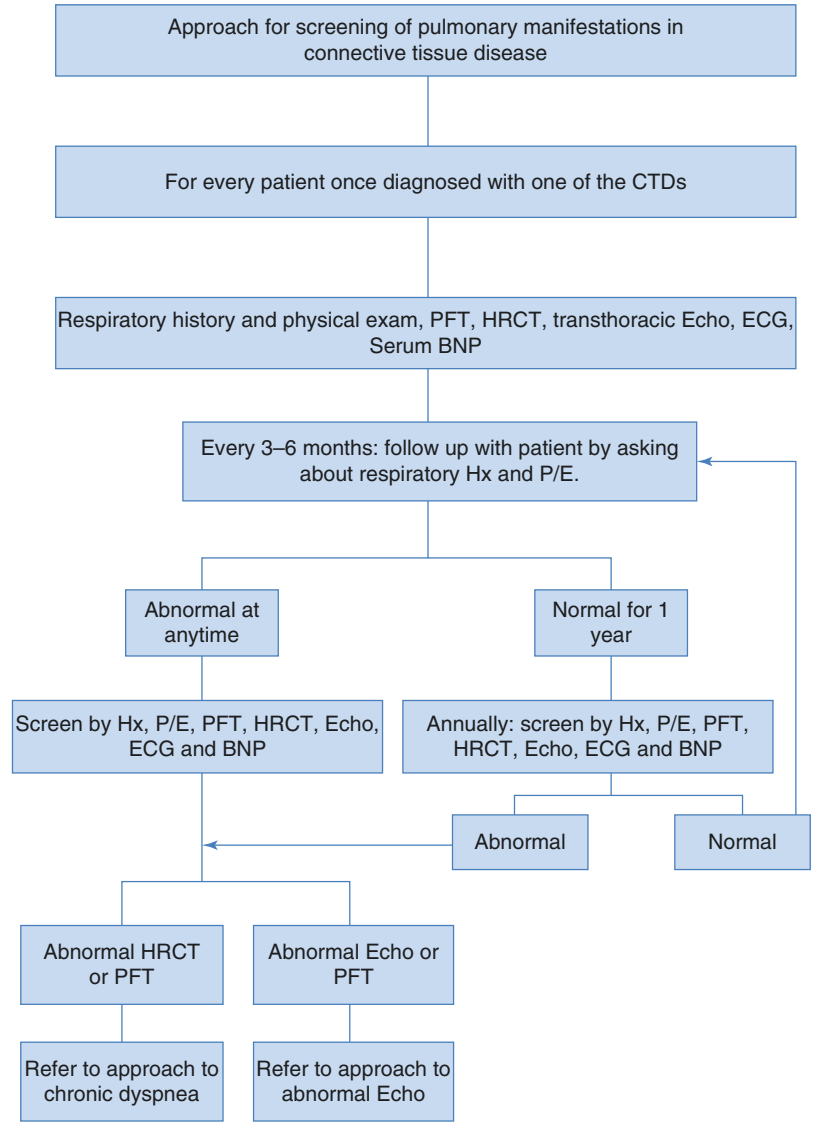

Fig. 7.1 Screening of pulmonary complications of CTDs. *BNP* B-type natriuretic peptide, *CTD* Connective tissue disease, *ECG* Electrocardiogram, *Echo* Echocardiogram, *HRCT* High-resolution computed tomography, *Hx* History, *P/E* Physical examination, *PFT* Pulmonary function test

- Pleural fluid analysis for CTDs (except for PM/DM and MCTD, due to the lack of sufficient information about them) (Table 7.4).
- Although drug-induced lung injury is an uncommon complication (mostly reported in observational studies), treating physicians should consider it as one of the differential diagnoses of lung injuries. Furthermore, it's important to know the common and serious adverse events of the medications used in CTD-ILD, so it would be easier to monitor them and follow them up with patients. Once drug-induced lung injury is suspected, one should take into consideration the duration between starting the drug and the development of pulmonary manifestation in addition to the dose of the drug. Eventually, there is no single test that could help in confirming this diagnosis. However, withdrawal of the offending drug appears to be best step to diagnose it besides other findings, which are presented in Table 7.5. Moreover, a useful website established by French pulmonologists from Dijon University has been launched to provide information about drugs causing lung toxicity (www.pneumotox.com). Of

Table 7.2 Radiological and histological patterns of idiopathic interstitial pneumonias

Radiological pattern	Histological pattern
IPF	UIP
NSIP	NSIP
OP	OP
LIP	LIP
RB-ILD	RB
AIP	DAD

Adopted from American Thoracic Society/European Respiratory Society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. Am J Resp Crit Care Med 2002; 165:277
IPF Idiopathic pulmonary fibrosis, *UIP* Usual interstitial pneumonia, *NSIP* Non-specific interstitial pneumonia, *OP* Organizing pneumonia, *LIP* Lymphocytic interstitial pneumonia, *RB-ILD* Respiratory Bronchiolitis interstitial lung disease, *RB* Respiratory Bronchiolitis, *AIP* Acute interstitial pneumonia, *DAD* Diffuse alveolar damage

note, doing bronchoalveolar lavage (BAL) is a must to rule out infections (bacterial, viral, fungal, mycobacterial).

7.6 Pulmonary Manifestations According to each CTD

7.6.1 Systemic Sclerosis or Scleroderma (SSc)

Systemic sclerosis (SSc) is a rare multisystem disease that involves skin and other body organs causing fibrosis and vascular complications. It is divided into local cutaneous systemic sclerosis (lcSSc), which is more commonly associated

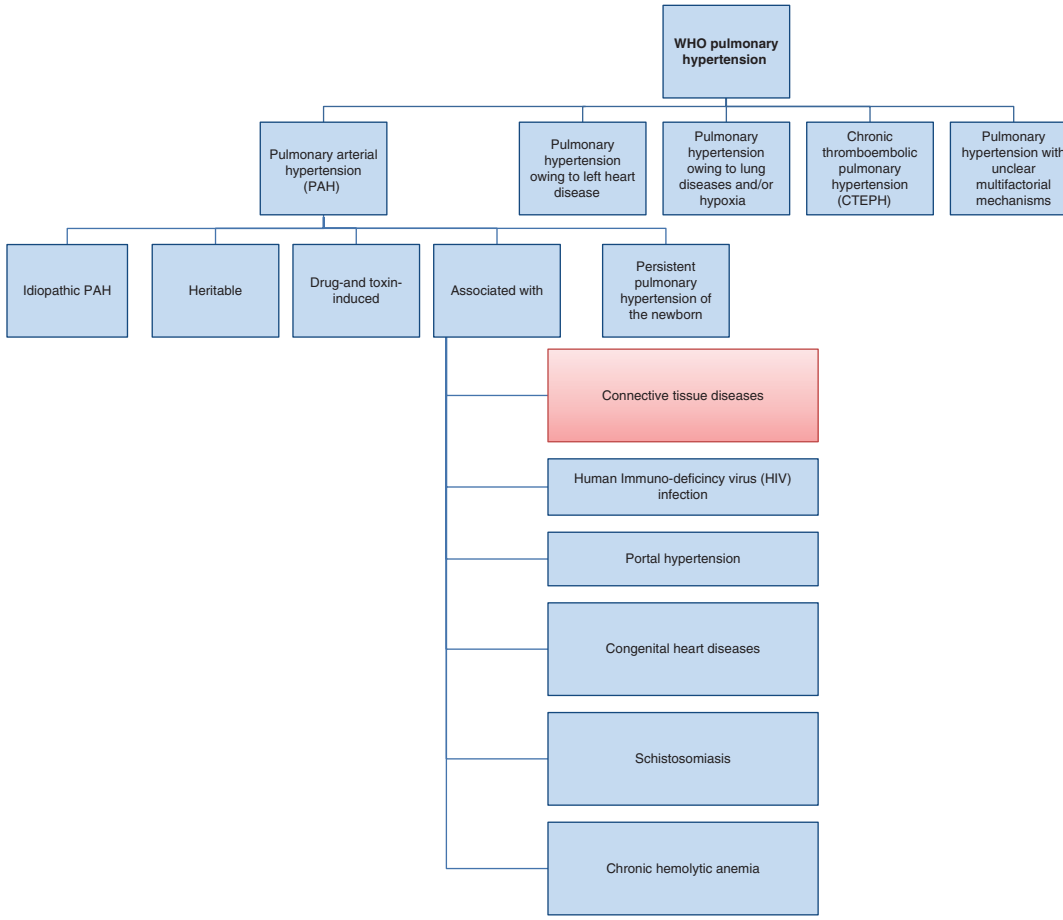

Fig. 7.2 World health organization (WHO) classification of pulmonary hypertension. (Adopted from Simonneau G, Galie N, Rubin L, et al. Clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2004;43 Suppl 1:S5–12)

Table 7.3 World health organization functional classification of pulmonary hypertension

	WHO functional classification
I	Patients with pulmonary hypertension but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue or dyspnea, chest pain, or heart syncope
II	Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in undue fatigue or dyspnea, chest pain, or heart syncope
III	Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes undue fatigue or dyspnea, chest pain, or heart syncope
IV	Patients with pulmonary hypertension resulting in inability to carry on any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may be present even at rest. Discomfort is increased by physical activity

Adopted from: Rich, S. Primary hypertension: executive summary. Evian, France. World Health Organization, 1998

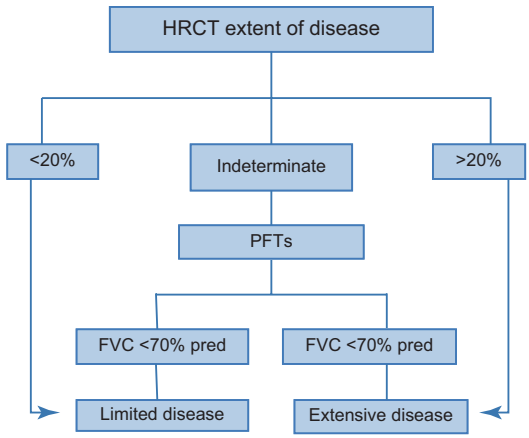

Fig. 7.3 A simple system to determine the extension of interstitial lung disease. *FVC* Forced vital capacity, *PFT* Pulmonary function test. (Adopted from Goh NS, Desai SR, Veeraraghavan S, et al. Interstitial lung disease in systemic sclerosis: a simple staging system. Am J Respir Crit Care Med 2008; 177: 1248–1254)

with the CREST syndrome, and diffuses systemic sclerosis (dcSSc) depending on skin involvement and distribution. Furthermore, lung involvement occurs in about 70% of SSc cases. Also, it is considered to be the leading cause of death in SSc patients [2]. Moreover, the most common pulmonary manifestations in SSc are ILD and PAH. While less common pulmonary involvements are pleural effusion, aspiration pneumonitis, spontaneous pneumothorax, bronchiectasis, drug-associated pneumonitis, and lung cancer.

7.6.1.1 Parenchymal Lung Diseases

SSc-associated interstitial lung disease (SSc-ILD), it occurs in about 40–52% of all SSc patients. However, the dcSSc type appears to be associated with higher risk to develop it compared with lcSSc. Risk factors are African American, gastroesophageal reflux disease (GERD), higher skin score, high level of C-reactive protein (CRP), hypothyroidism, cardiac involvement, Th/To ribonucleoprotein antibodies (anti-Th/To), and anti-topoisomerase I (Scl-70). On the other hand, anti-centromere antibody is considered protective against ILD in SSc. Of note, SSc-ILD is classified into limited versus extensive depending on HRCT finding and FVC (Fig. 7.3).

Presentation

Usually patients present with dry cough, shortness of breath, decreased exercise intolerance, fine bibasilar crackles, and, infrequently, finger clubbing.

Diagnosis

The diagnosis is made collectively by symptoms, signs, PFT (which mostly shows restrictive pattern with low diffusion lung capacity of carbon monoxide [DLCO]) and imaging (chest radiograph may appear normal at the beginning but then progresses to irregular linear opacities and marked interstitial marking). However, in HRCT, it may show GGO without honeycombing in NSIP or reticular pattern with basilar honeycombing in UIP with/without traction bronchiectasis. Furthermore, the most common subtypes of SSc-ILD are NSIP followed by UIP. Although usually the subtypes of ILD may affect the outcome of CTD-ILD, in SSc it is not the case. For that, it is enough to diagnose it as SSc-ILD without specifying the subtype. While BAL is helpful

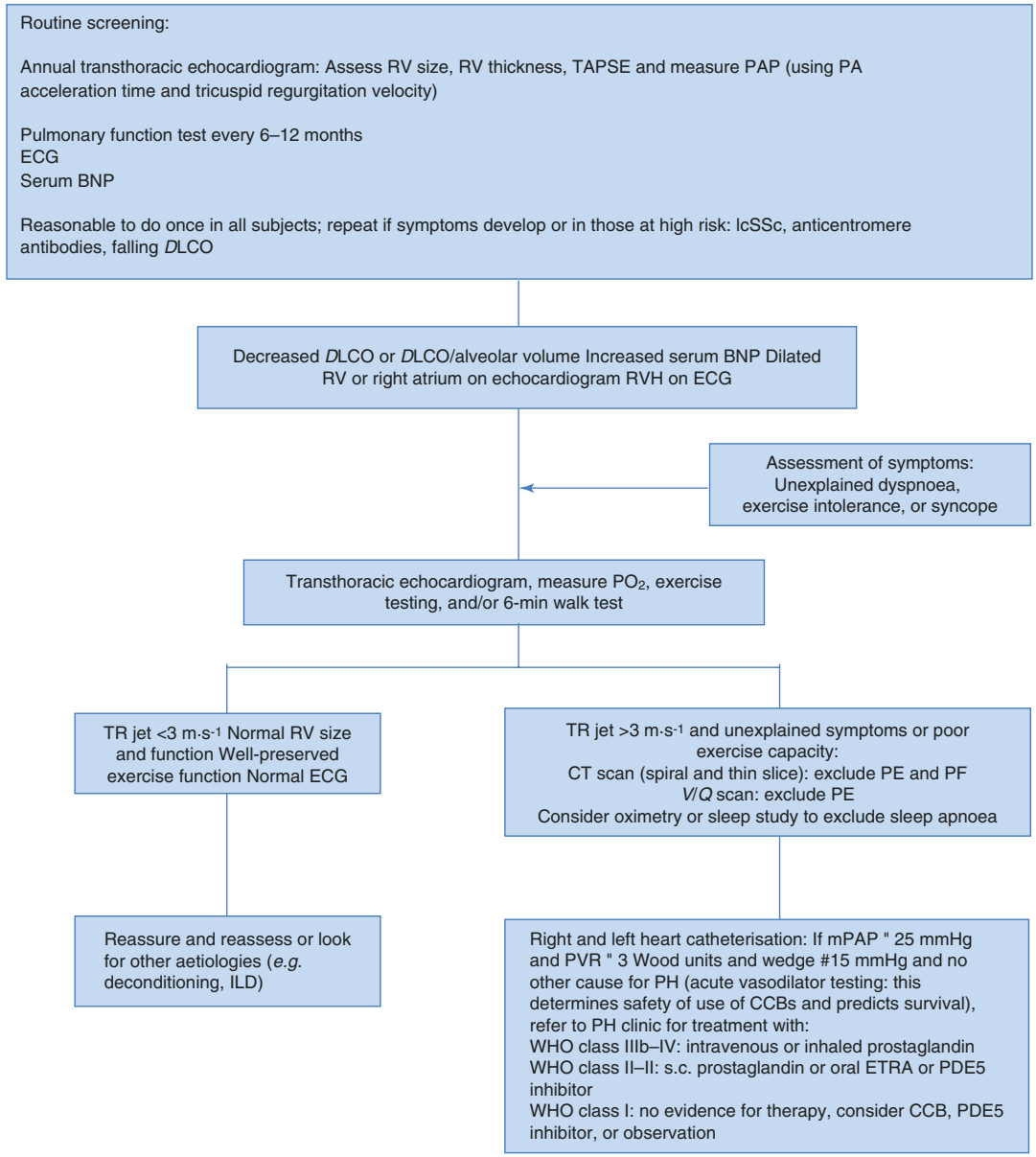

Fig. 7.4 The approach to screening for CTD-related pulmonary hypertension (CTD-PAH). *BNP* B-type natriuretic peptide, *CCBs* Calcium channel blockers, *DCLO* Diffusing capacity carbon monoxide, *ECG* Electrocardiogram, *ETRA* Endothelin receptor antagonist, *FVC* Forced expiratory vital capacity, *LcSSc* Limited cutaneous systemic sclerosis, *mPAP* mean pulmonary artery, *PDE-5 inhibitor* phosphodiesterase type 5 inhibitor, *PE* pulmonary embolism, *PF* pulmonary fibrosis, *RV* right ventricular, *RVH* right ventricular hypertrophy, *TAPSE* Tricuspid annular plane systolic excursion, *TR* Tricuspid regurgitation, *V/Q* Ventilation/perfusion, *WHO* World health organization, *WU* Wood Units. (Adopted from Sweiss NJ, Hushaw L, Thenappan T, et al. Diagnosis and management of pulmonary hypertension in systemic sclerosis. Curr Rheumatolo Rep)

in ruling out infection in the appropriate clinical context, lung biopsy is not usually required, unless such diagnosis is doubtful. Worth mentioning, the most serious complications of SSc-ILD are respiratory failure and pulmonary hypertension.

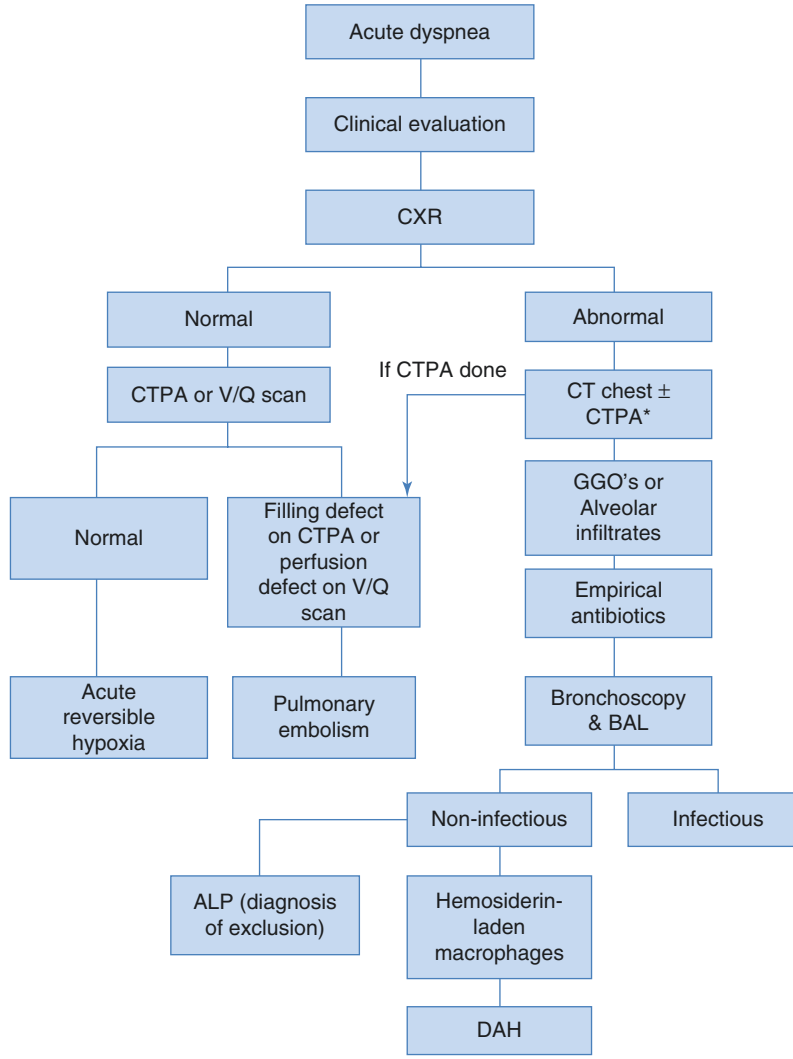

Fig. 7.5 Approach for acute dyspnea in systemic lupus erythematosus. Adopted from "Pulmonary manifestations of Systemic Lupus Erythematosus" (Chapter), Abdul Ghafoor Gari, Amr Telmesani, Raad Alwithenani, Systemic Lupus Erythematosus (Book), published by opentech. *ALP* Acute lupus pneumonitis, *BAL* bronchoalveolar lavage, *CXR* chest x-ray, *CT* computed tomography, *CTPA* computed tomography pulmonary angiogram, *DAH* diffuse alveolar hemorrhage, *GGO's* ground-glass opacities, *V/Q Scan* ventilation/perfusion lung scan

Prognosis

ILD in SSc has poor outcome despite treatment. It's associated with higher mortality. The median survival for patients is 5–8 years.

Treatment

Many issues are involved in treating SSc-ILD, which are the decision of initiation of treatment, treatment modalities, the follow-up of treatment, duration of treatment, and assessment of success of treatment and promising drugs.

It is difficult to decide whether to initiate treatment or not since treatment has a minor effect on the outcome of SSc-ILD. Physicians should balance between the benefit of treatment and the adverse drug reactions. Factos that favor starting treatment are the presence of respiratory symptoms, abnormal or declining lung functions (specially DLCO and forced vital capacity [FVC]), progressive disease, early intervention (within 12–24 months of the diagnosis of SSc-ILD), young age, GGO on HRCT, and no contraindications (such as active or suspected infection, neutropenia, history of cyclophosphamide hemorrhagic cystitis, pregnancy, and lactation) [3, 4].

When physician and patient agree to start treatment, there are three modalities available, which are drug therapy, lung transplantation, and hematopoietic stem cell transplantation. To start

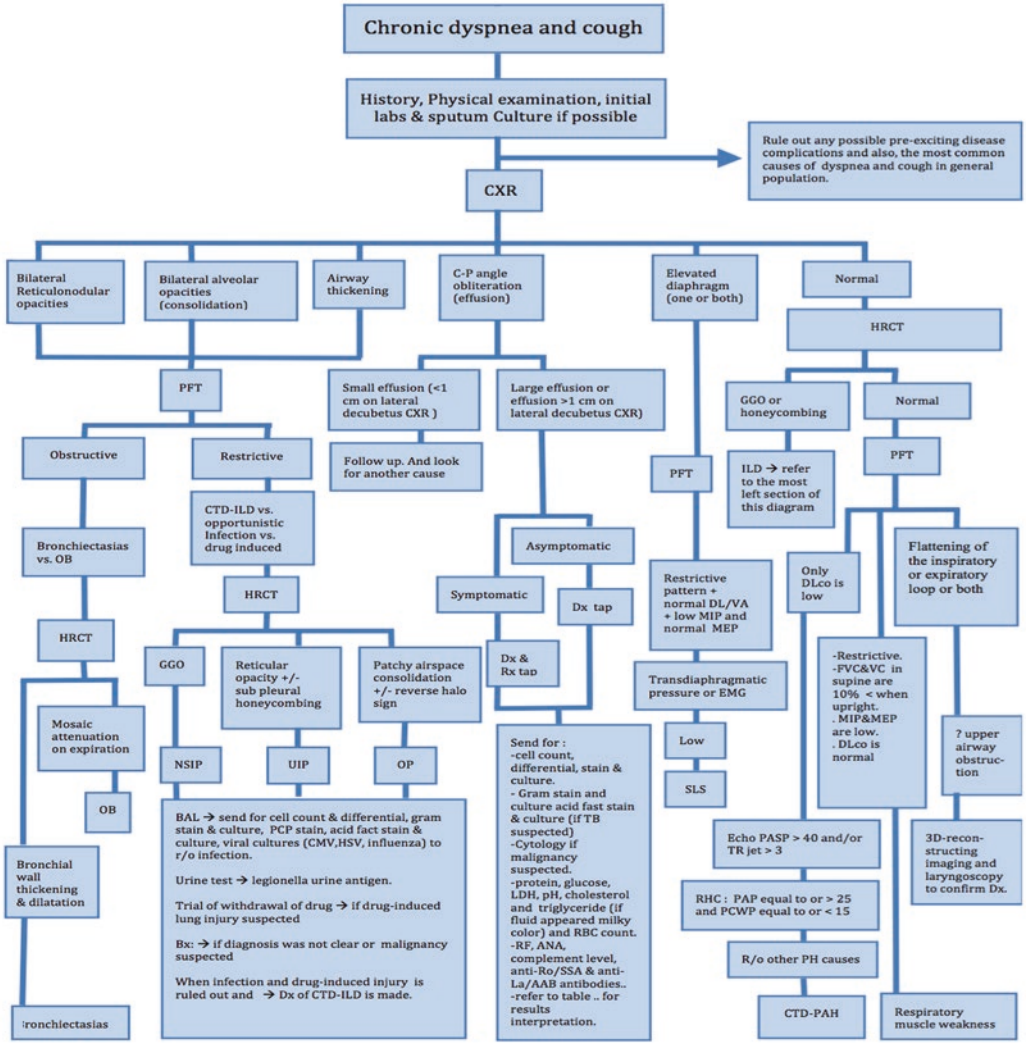

Fig. 7.6 The approach to chronic dyspnea in CTDs. *CXR* Chest X-ray, *CTD* Connective tissue disease, *C-P* Costophrenic angle, *Dx* Diagnostic, *Rx* Therapeutic, *Bx* Biopsy, *GGO* Ground glass opacity, *HRCT* High resolution computed tomography, *PFT* Pulmonary function test, *ILD* Interstitial lung disease, *NSIP* Non-specific interstitial pneumonia, *OP* Organizing pneumonia, *UIP* Usual interstitial pneumonia, *OB* Obliterative bronchiolitis, *DLco* Diffusion Lung capacity for carbon monoxide, *DL/VA* Diffusion per unit area of alveolar volume, *MIP* Maximum inspiratory pressure, *MEP* Maximum expiratory pressure, *VC* Vital capacity, *FVC* Forced vital capacity, *EMG* Electromyogram, *SLS* Shrinking lung syndrome, *PASP* Pulmonary artery systolic pressure, *TR* Tricuspid regurge, *RHC* Right heart catheterization, *PAP* Pulmonary artery pressure, *PCWP* Pulmonary capillary wedge pressure, *R/o* Role out, *PH* Pulmonary hypertension, *PCP* Pneumocystis pneumonia, *CMV* Cytomegalovirus, *HSV* Herpes simplex virus, *TB* Tuberculosis, *LDH* Lactate dehydrogenase, *RF* Rheumatoid factor, *RBC* Red blood cell, Anti-nuclear antibody

Table 7.4 Pleural fluid analysis for rheumatic diseases

	RA	SLE	Sjogren
Appearance	Variable	Clear	N/A
WBC	<5000 cells/mm^3	<5000	High lymphocytes
Glucose	Low (<1.6 mmol/L)	Normal/low	Normal
Protein	High (>30 g/L)	Low	High
Cholesterol	>5.18 mmol/L	N/A	N/A
RBC	0	0	N/A
pH	Low (< 7.3)	N/A	Normal
Cytology	Positive tadpole cells	N/A	N/A
Complement	Low	Low	Low
RF	>240 IU/mL (titer >1:320)	None	N/A
ANA	+/−	Positive (titer >1:160 is more sensitive than specific)	N/A
LDH	High (> 700 IU/L)	High	N/A
Anti-Ro/anti-La antibodies	N/A	N/A	Positive
Immune complex	High	High	N/A

ANA Anti-nuclear anti-body, *LDH* Lactate dehydrogenase, *RBC* red blood cell, *RF* rheumatoid factor, *N/A* not applicable

with, there is no drug, up to date, considered as the gold standard treatment for SSc-ILD because of lacking of strong evidence to relay on. However, commonly used regimen is cyclophosphamide (CYC) (oral or intravenous) combined with low dose glucocorticoids (equal to or less than 10 mg/day equivalent to prednisone) for 12 months duration [5–10].Then, physicians could stop the CYC and the steroids and start a maintenance therapy with azathioprine (AZA) for18 months [11]. Although oral cyclophosphamide is superior to IV route, some clinicians prefer the IV route due to possible less side effects as a result of lower cumulative dose. An alternative regimen to CYC and steroids is AZA plus low-dose prednisone [12, 13]. This regimen is inferior to CYC and steroids but could be used if patient could not tolerate CYC. Steroids are used mostly as an adjuvant therapy to cyclophosphamide with low doses (equal to or less than 10 mg/day equivalent to prednisone). That's because moderate to high doses (>15 mg/day equivalent to prednisone) could expose patients to the risk of developing scleroderma renal crisis (SRC), which presents with acute kidney injury (AKI), hypertension (including hypertensive crisis), and mild proteinuria. Of note, there are some other promising drugs such as mycophenolate mofetil [14–20], rituximab [21, 22], and imatinib [23, 24], but more trials are needed to compare their efficacy to cyclophosphamide.

Monitoring usually consists of monthly follow-up to make sure there are no drug adverse events and, then, a visit every 6 months to check for respiratory symptoms, PFT, and HRCT. Clinicians should monitor patients for CYC drug toxicity by monitoring white blood cell (WBC) count, renal function, and urine analysis (specially for red blood cells [RBCs]) in urine to predict hemorrhagic cystitis and/or proteinuria [25].

Afterward, the treatment is considered successful if stabilization (no improvement nor deterioration) of respiratory symptoms and PFT is achieved. However, mild to moderate improvement could occur.

Cyclophosphamide is associated with high toxicity profile, which is a concern for both patients and physicians. The new preferred regimen is mycophenolate mofetil (MMF) (oral or intravenous) along with glucocorticoids. Both regimens showed significant reduction in loss of pulmonary function, but mycophenolate mofetil has safer profile with less side effects, better toleration, and the improvement last longer with (MMF) than (CYC).

Table 7.5 Drug-induced lung injury in CTD

	Type of lung disease occur	Duration of drug use until symptoms occur	Dose of the drug and other risk factors	Hx and P/E	Blood work	PFT	Imaging	BAL and Biopsy	Treatment	Notice
Gold	Interstitial pneumonia (NSIP, OP or eosinophilia pneumonia.)	1 week–84 months (typically >6 months)	– 30–3000 mg total accumulative dose (specially >500 mg) – Female	Hx: Acute or chronic cough, dyspnea and fever within P/E: Crackles but no clubbing	Non-specific): Leukocytes and eosinophilia. (rarely: Leucopenia, thrombocytopenia and hypogammaglobulinemia)	– Restrictive pattern with low DLCO	CXR: Upper zone opacity (unlike in CTD_ILD which occur in the lower zone) HRCT: Non-specific: GGO or diffuse or patchy opacities	– BAL: High lymphocyte no, CD4+/CD8+ <1, also, use it to r/o infection – Biopsy: NSIP, OP or eosinophilia pneumonia	Stop the drug and start systemic corticosteroid	BO, pulmonary-renal syndrome and DAH
D-Penicillamine	OB	3–14 months	375–1250 mg/day	Subacute dyspnea on exertion and cough	N/A	Obstructive pattern with no response to bronchodilator	CXR: Normal or hyperinflation. HRCT: Mosaic attenuation	Biopsy: Typical for OB	Stop the offending drug and start prednisolone 1–1.5 mg/kg/day Using other immunosuppressive therapy (e.g., CYC or AZA) may help	N/A

NSAIDs	Eosinophilia pneumonia	N/A	N/A	Hx: Fever, cough dyspnea. P/E: Wheeze and crackles	Eosinophilia	N/A	Non-specific: Diffuse or patchy consolidations	Poorly defined granuloma + eosinophils infiltration	Stop the drug and in severe cases add systemic corticosteroid	N/A
MTX	ILD, acute lung injury (ALI) with DAD, pleurisy, pleural effusion, nodulosis, bronchitis, airway hyper-sensitivity and cough	12 weeks-18 years	– Minimum of <20 mg/week. – Age > 60 - rheumatoid pleuro-pulmonary involvement – Previous use of DMARD – Hypoal-buminemia – DM	Dyspnea, dry cough, fever +/− chest pain	Eosinophilia	– Restrictive – Low DLCO – High A-a gradient	Non-specific: Interstitial infiltrate	Cellular interstitial infiltrates, eosinophils, granuloma, DAD	Stop the drug and in severe cases add corticosteroid or other immuno-suppressive therapy like CYC or AZA. Folinic acid may be used (not fully studied)	Reusing the medication after the treatment of its adverse event is not recommen-ded
Leflуno-mide	Fatal exacerbation of previously diseased lung, diffuse nodulosis, pulmonary alveolar proteinosis and DAD	12 weeks	Previous lung disease or MTX pneumonitis	– Hx: Dyspnea, cough fever P/E: Crackles.	High C-reactive protein and KL-6	N/A	HRCT: GGO, reticular opacities and honey-combing or airspace disease	Bx: Pneumonitis with eosinophils, OP or DAD	Systemic steroids + Cholestyramine (8 g/day for 3 days)	Avoid using it when patients already have ILD. If new patients with no known ILD, screen by PFT and HRCT before starting the drug

(continued)

Table 7.5 (continued)

	Type of lung disease occur	Duration of drug use until symptoms occur	Dose of the drug and other risk factors	Hx and P/E	Blood work	PFT	Imaging	BAL and Biopsy	Treatment	Notice
TNF-a (etanercept, infliximab and adali-mumab)	Exacer-bation of ILD, UIP and OP	8 weeks	N/A	Dyspnea, cough and fever	N/A	N/A	Reticular opacities or airspace disease	Bx: Reticular opacities or airspace disease	Stop the drug and any DMARD added with it + systemic steroid (e.g., 40 mg/day)	N/A
CYC	NISP or fibrosis.	– Early onset: 1–6 months. – Late onset: >6 months	– 150 mg–81 g – Risk factors: If used with other drugs cause lung toxicity, e.g., bleomycin, busulfan and amiodarone	Dyspnea, cough +/– fever	N/A	– Restrictive pattern with low DLCO	– Early onset: GGO on HRCT. – Late onset: Reticular opacities with honey-combing (in the mid to upper zone, unlike in CTD-ILD)	Bx: Non-specific. But granuloma and hemosiderin could be present	– Early onset: Atop medication + systemic corticosteroids (prednisone 60 mg/day) – Late onset: Stop medication only. Steroid showed no effectiveness	N/A
AZA	OP and UIP	1 week–1 month	Total dose of 2300–28,600 mg	Dyspnea, cough and fever	N/A	N/A	N/A	To r/o infections	Stop medication and start systemic steroid	It's very rare for AZA to cause lung toxicity especially in CTD population

MMF	Acute respiratory failure, fibrosis and DAH	After 6 days	2 g/day	Dyspnea and cough	N/A	N/A	Diffuse airway opacity (could be in unilateral)	To r/o infections.	Stop the drug and start systemic corticosteroids (methyl-prednisolone 125 mg 4 time/day)	It's a rare compli-cation of MMF

AZA Azathioperine, *CYC* Cyclophosphamide, *MTX* Methotrexate, *MMF* Mycophenolate Mofetil, *DM* Diabetes mellitus, *NSAIDs* Non-steroidal anti-inflammatory drugs, *ILD* Interstitial pneumonia, *DAH* Diffuse alveolar hemorrhage, *DAD* Diffuse alveolar damage, *NSIP* Non-specific interstitial pneumonia, *TNF-a* Tumor necrosis factor –alpha, *Hx* History, *P/E* Physical examination, *KL-6* Human Kerbs Von Den Lungem 6, *DLCO* diffusion lung capacity for carbon monoxide, *A-a gradient* Alveolar-arterial gradient, *CXR* chest radiography, *GGO* graound glass opacity, *R/o* Rule out, *BAL* Bronchoalveolar lavage, *PFT* Pulmonary function test, *Bx* Biopsy, *DMARD* disease-modifying anti-rheumatic drugs, *N/A* Not applicable

Although the MMF duration in the last study was for 2 years, most of expertise recommend to continue the treatment for several years [26].

The second modality of treatment is lung transplantation. It is considered when drug therapy fails. The 1-year survival is 68–93% [27, 28]. Absence of GERD may play a great role in improving survival [27].

Last treatment modality is hematopoietic stem cell transplantation. It is still an experimental therapy. However, great improvement in FVC within 2 years occurred when using this method. Furthermore, it shows superiority to IV cyclophosphamide [29].

Aspiration Pneumonitis

A strong association between the degree of gastroesophageal reflux (GER) and the severity of ILD, which may raise the flag of microaspirations. However, it is still not clear whether the treatment of GER will improve or even prevent ILD [30, 31].

7.6.1.2 Vascular Diseases

SSc-associated pulmonary arterial hypertension (SSc-PAH).

Introduction

Pulmonary hypertension (PH) defined as mean pulmonary artery pressure (PAP) equals to or > 25 mmHg at rest. It can occur as a complication of SSc itself, which is SSc-PAH, or as a complication of ILD caused by SSc. Here, SSc-PAH is discussed.

It presents in 12–38% of SSc patients. Risk factors are increased number of telangiectases, lcSSc with anti-centromere antibody, dcSSc with ANA (dcSSc alone is less commonly associated with PAH), progressive decline in DLCO, and exercise-induced PAH on right heart catheterization.

Presentation

Patients usually present with exertional dyspnea, lethargy, and fatigue, which are the most common symptoms, and, less frequently, could be exertional angina, exertional syncope, symptoms of right ventricular failure (RVF) (due to Cor pulmonale), cough, hemoptysis, and Ortner's syndrome (horsiness due left recurrent laryngeal nerve palsy caused by pulmonary artery compression or other cardiac cause). On physical examination, if there is no right ventricular hypertrophy (RVH), loud pulmonary component of second heart sound is heard. However, If right ventricular hypertrophy present, then, parasternal heave, forth heart sound, prominent A wave in jugular venous pressure (JVP) could be noticed. Moreover, ascites and lower limb edema may be present. Recent studies showed that combination therapy with phosphodiesterase type 5 inhibitors or combination between (ERA/PDE5I) is superior than endothelin receptor antagonist alone by decreasing deterioration time, recent European guidelines recommend combination initial therapy, But it still has not established yet in American guidelines [32].

Screening

In regard to screening for SSc-PAH, physicians could use the same screening method as any patient newly diagnosed with SSc (Fig. 7.1). Also, other indications for earlier echocardiography screening are when symptoms, signs, and PFT findings are suggestive of PAH are present, such as DLCO <70% predicted or FVC/DLCO >1.6 and echocardiography with Doppler study findings are suggestive of PAH such as RVH, right ventricular enlargement (the chamber itself), right atrial enlargement, tricuspid regurge (TR), mid-systolic notch on the pulmonary artery Doppler flow tracing and shifting of the interventricular septum toward the left ventricle, pulmonary artery systolic pressure (PASP) >50 and the maximum tricuspid regurgitant jet velocity (TVR) >3.4.

Diagnosis

The SSc-PAH diagnosis is confirmed by right heart catheterization when mean pulmonary arterial pressure equals to or > 25 mmHg at rest and mean pulmonary capillary wedge pressure (PCWP) <15 mmHg after excluding other causes of PH such as having normal ventilation/perfusion scan (V/Q scan) (to rule out chronic thromboembolic disease), negative HIV and hepatitis serology, normal or mild ILD findings on

HRCT (to rule out significant ILD), and normal sleep study in the appropriate clinical context.

Prognosis

Although the advancement of treatment during the past decade has improved the survival, it's still worse than that in idiopathic PAH (IPAH) [33]. The 3-year survival is estimated to be 64% [33]. Moreover, early detection has a good impact in survival [34]. On the other hand, SSc-PAH associated with ILD has worse prognosis than that of SSc-PAH alone. The 3-year survival for SSc-PAH with ILD is 47% [35].

Treatment

In general, therapy is usually directed to the underlying cause of PAH and to the PAH itself if it persisted. However, since there is no specific treatment for SSc, the therapy will be directed to PAH itself. Nevertheless, many issues are involved in the treatment of SSc-PAH such as the decision of initiation of treatment, treatment modalities, duration of treatment, and follow-up of therapy.

The decision of initiation of treatment is all symptomatic patients defined by the World Health Organization (WHO) functional classes of II or more (i.e., at minimum to have dyspnea when doing ordinary activity). This category should receive treatment.

Treatment modalities are PAH specific drug therapy, supportive therapy, and lung transplantation. To start with, for the PAH specific drug therapy, there is no single drug that has shown superiority for treatment in SSc or other CTDs in general.

However, the drug classes that have shown effect in CTD-PAH are endothelin-1 receptor antagonists (ERA), phosphodiesterase type 5 (PDE5) inhibitors, and prostanoids (PGI-2). All of them improved the 6-min walk test (6MWT) [36]. Clinicians should, most of the time, start with monotherapy then step up for a combination if no improvement is observed. Furthermore, the choice for PAH-specific drug therapy depends on physician expertise, patient preference, and cost-effectiveness.

Also, supportive therapy should be considered for most patients. It consists of supplemental oxygen for patients with hypoxemia, to keep oxygen saturation > 90%. In addition, diuretics could be given for patients with fluid overload. Moreover, anticoagulation might be considered for all patients based on non-randomized trials, especially those who receive IV prostaglandins (due to the risk of catheter related thrombosis) but also one should weigh risk of bleeding against benefits [37]. Furthermore, warfarin is the drug of choice to reach a therapeutic INR of 1.5–2.5 [37]. On top of that, exercise, with a special training program (bicycle ergometer at lower and higher workload for 15–30 min/day, dumbbell training [0.5–1 kg], and respiratory training) could be advised. However, heart rate should be monitored not to reach above 120 beat/min and the oxygen saturation not to fall <90% (if a supplemental oxygen is given). These exercises has been tested and showed improvement in 6-min walk test (6MWT) [38, 39]. Lastly, digoxin is not usually used in PAH because there are no enough data to support its effectiveness [37]. Nevertheless, it is usually used in patients with COPD and biventricular failure [40].

As a last resort, when drug therapy fails, lung transplantation should be considered, specially, in patients with severe symptoms. The 2-year survival reaches 71% [27].

7.6.1.3 Airway Disease

Bronchiectasis

It is a common finding on HRCT, but usually not clinically manifested, reaching 59% of SSc patients, and this may be attributed to the high number of GERD and aspirations [41]. Clinicians should pay attention to bronchiectasis when intended to start immunosuppressive therapy due to the risk of sever lower respiratory tract infections [42].

Pleural Involvement

Pleural Effusion

Occurs in about 7% of SSc patients. Usually asymptomatic and occasionally associated with pericardial effusion. It resolves spontaneously.

Spontaneous Pneumothorax

It's a rare complication of SSc. Patients present with shortness of breath and/or pleuritic chest pain. The management depends on cardiopulmonary status and pneumothorax size on CXR. Supplemental oxygen and air drainage by needle aspiration or chest tube insertion should be considered depending on the clinical context.

Respiratory Muscle Weakness

This could lead to respiratory failure with or without hypercapnia [43, 44].

7.6.1.4 Systemic Lupus Erythematosus (SLE)

Background

SLE is a multisystem autoimmune disease and affects mostly women in childbearing age. Pulmonary involvement, manifested clinically or radiologically, occurs in around 25% of all SLE patients. They usually happen later in the course of the disease. Furthermore, most common pulmonary diseases are pleuritis (78%) followed by bacterial infections (58%), alveolar hemorrhage (26%), distal airway alterations (21%), opportunistic infections (14%), and, lastly, acute or chronic pulmonary thromboembolism (8%).

Pulmonary Manifestations

Pleural Diseases

Pleuritis

- Presents as pleuritic chest pain, shortness of breath, and fever. On physical examination, pleuritic friction rub may be heard. It is a clinical diagnosis. However, pleural biopsy could be done but rarely needed. If so, it shows peculiar immunofluorescent pattern characterized by staining of nuclei with anti-IgG, anti-IgM, and anti-C3 [45]. Treatment usually consists of NSAIDS for mild cases and steroid for severe cases.

Pleural Effusion

Presentation

It tends to be bilateral and small to moderate in size; however, large effusion may occur. It usually presents with shortness of breath, cough, and/or chest pain. Nevertheless, sometimes, it could be asymptomatic. Physical examination may show dullness on percussion, decrease tactile fremitus, decrease intensity of breath sound, and decrease vocal resonance.

Diagnosis

Although the following investigations could lead to the diagnosis of pleural effusion to be secondary to SLE, physicians should always rule out other common/serious causes of pleural effusion such as heart failure, parapneumonic effusion, and pulmonary embolism if suspected.

Chest radiograph shows blunting of costophrenic angle. Furthermore, pleural fluid analysis is shown in Table 7.4.

Treatment

Small asymptomatic pleural effusion needs no treatment. It resolves spontaneously. On the other hand, mild symptomatic effusion usually responds to NSAIDs [46], while severe symptomatic effusion is treated with steroids. Also, if patient is currently on steroids, increasing the dose may be required [46]. In refractory cases, tetracycline or talc pleurodesis might be an alternative option [47–49].

7.6.1.5 Parenchymal Lung Disease

Acute Lupus Pneumonitis (ALP)

Introduction

It's an uncommon but serious complication of SLE, which occurs in 2–8% of patients. It affects younger and newly diagnosed SLE patients and also could manifest as a fulminant pattern in pregnant women.

Presentation

Acute-onset fever, cough, shortness of breath, pleuritic chest pain, and, occasionally, hemoptysis. Physical examination shows signs of hypoxia and bibasilar crackles.

Diagnosis

It's a diagnosis of exclusion (Fig. 7.5). However, BAL, with or without transbron-

chial biopsy, must be done to rule out infection. Blood tests may show high levels of anti-Ro (anti-SS-A), which are associated with more likelihood of ALP. Chest radiograph may show bilateral alveolar infiltrates with predominance in lower lung fields. Also, pleural effusion may occur in half of the cases. Rarely, chest radiograph could be normal or showing nodules. Chest CT may show diffuse ground glass opacities. BAL, when done, the sample should be sent for cell count and differential, bacterial, fungal, and viral cultures, cytology, pneumocystis pneumonia (PCP) stain, and acid-fast bacilli (AFB) smear, and culture in the appropriate clinical context. Transbronchial biopsy, when done, shows non-specific diffuse alveolar damage (DAD) with or without alveolar hemorrhage and capillaritis. Less common pathologic features are alveolar edema, hyaline membrane formation, and immunoglobulin and complement deposition.

Treatment

Usually starts with empiric broad-spectrum antibiotics for 3 days. If no response, then, pulse steroids (1 g methylprednisolone daily for 3 days) should be started. Furthermore, adding another immunosuppressive agents like cyclophosphamide (CYC) could be considered [50]. In refractory cases, intravenous immunoglobulin (IVIG), plasma exchange, or rituximab may help [51–53].

Prognosis

It has poor prognosis with mortality reaching 50% [54]. BAL showing eosinophilia and neutrophilia have worse prognosis than lymphocytosis.

7.6.1.6 Diffuse Alveolar Hemorrhage (DAH)

Introduction

The prevalence ranges from <2% to 5.4% and it tends to recur. Furthermore, it occurs more frequently in lupus nephritis patients and with high levels of serum anti-DNA antibody.

Presentation

Usually presents with acute shortness of breath, cough, fever, and hemoptysis, although absence of hemoptysis dose not rule out DAH. The mean duration from onset of DAH to resolution of radiographic finding is 7.8 days. Physical examination reveals signs of respiratory distress and hypoxia.

Diagnosis

Blood tests may show acute drop in hemoglobin and low complement level. Chest radiograph may show bilateral alveolar infiltrates. But also could happen unilaterally in 18% of patients. Chest CT scan could show new bilateral ground glass opacities and consolidation. Moreover, magnetic resonance imaging (MRI) can suggest presence of blood. PFT show elevated DLCO (>130% predicted) due to excess hemoglobin in alveolar space. BAL is essential to rule out infection. Furthermore, bloody sample under microscope suggests DAH if hemosiderin-laden macrophages are present. Transbronchial biopsy could be done in stable patients. This may reveal bland hemorrhage (72%) or capillaritis (14%). Both of them are associated with intra-alveolar hemorrhage and hemosiderin-laden macrophages. Also, immunoglobulin G (IgG), complement 3 (C3), or immune complex deposition occurs in 50% of the cases. Thoracoscopic lung biopsy is rarely needed.

Treatment

Supportive therapy (i.e., mechanical ventilation) plays a major rule since most patients are admitted to the intensive care unit (ICU) [55, 56]. However, if infection is ruled out or BAL suggest hemorrhage, physician should start pulse intravenous steroids (methylprednisolone 1 g/day for 3 days) followed by 60 mg/day of oral prednisone plus intravenous CYC every 4 weeks (the CYC could be started after discharge from hospital) [55, 56]. In refractory cases, plasmapheresis is an effective alternative, which improves survival. Also, rituximab has shown promising results [56–58].

Prognosis

DAH has a very poor outcome with mortality ranges between 50% and 90% [55, 58].

7.6.1.7 Chronic ILD

Introduction

Occurs in around 9% of SLE patients [59, 60]. Moreover, the most common ILD patterns are NSIP, UIP, and lymphocytic interstitial pneumonia (LIP).

Presentation

The initial presentation could be a dry cough. Other symptoms are shortness of breath and decreased exercise intolerance. Physical examination could reveal fine bibasilar crackles; however finger clubbing is rare.

Diagnosis

It is made by symptoms, signs, PFT, and HRCT collectively. Lung biopsy is not usually required unless such diagnosis is doubted. Chest radiograph may be normal at the beginning but then progresses to irregular linear opacities and marked interstitial markings. HRCT may show GGO without honeycombing in NSIP. On the other hand, reticular pattern with basilar honeycombing occurs in UIP with/without traction bronchiectasis. Moreover, 30% of asymptomatic patients could have abnormal HRCT findings. PFT may show restrictive pattern with low DLCO. Also, it does not correlate with the severity of ILD in HRCT. BAL is helpful in rolling out infection. While biopsy needed to confirm the subtype of ILD when HRCT is controversial.

Treatment

In mild cases, systemic corticosteroid (prednisone 60 mg/day for at least 4 weeks) could be used [56]. However, for moderate to severe cases, a combination therapy of oral glucocorticoids and AZA is a choice [60]. Furthermore, in severe cases, a combination of oral glucocorticoids and CYC could be considered [60].

Prognosis

ILD associated with SLE has better prognosis compared to the idiopathic forms [61].

7.6.1.8 Pulmonary Vascular Diseases

Thromboembolic Disease

Introduction

Venous thromboembolic (VTE) events are well-known manifestations of SLE specially when antiphospholipid (aPL) antibodies are present. This, in turn, will establish the diagnosis of antiphospholipid syndrome. Patients diagnosed with antiphospholipid syndrome are at risk of recurrent DVT, PE, chronic thromboembolic pulmonary hypertension (CTEPH), abortions, DAH, and acute respiratory distress syndrome (ARDS). Furthermore, when small vessel occlusion occurs in three or more organs, the condition is known as catastrophic antiphospholipid syndrome (CAPS). SLE patients are at risk of VTE events with a prevalence of 9%. This percent would become as high as 42% if SLE patients had aPL. Moreover, aPL present in up to two thirds of SLE patients [62].

Presentation

Patients could present with deep vein thrombosis (DVT) or pulmonary embolism (PE). DVT presents with calf pain (usually unilateral), swelling, and redness. On the other hand, pulmonary embolism (PE) presents with shortness of breath, pleuritic chest pain, cough, and/or hemoptysis. Furthermore, CTEPH manifested as progressive shortness of breath and exercise intolerance.

Diagnosis

DVT is diagnosed by Doppler ultrasound (US). PE is confirmed by chest CT angiogram. Moreover, CTEPH needs all diagnostic procedures needed to diagnose PAH.

Treatment

Long-term anticoagulation with warfarin is highly recommended with targeting INR of 2.0–3.0. High-intensity warfarin (targeting INR 3.0–

4.0) showed no superiority to moderate intensity [63]. Some clinicians use long-term low-dose aspirin as a primary prevention [64].

CAPS is usually treated by systemic glucocorticoids, immunosuppressants, plasmapheresis, and/or IVIg in addition to anticoagulation [56].

Prognosis

For CAPS, the mortality reaches 50% [65].

7.6.1.9 SLE-Associated Pulmonary Arterial Hypertension (SLE-PAH)

Background

For definition of PAH, please see SSc-PAH.

The duration of SLE, since diagnosis, does not correlate with the risk of development SLE-PAH. Its prevalence varies between 0.5% and 15% in SLE patients. Risk factors are Raynaud's phenomenon, which occurs in 75% of SLE-PAH [54]; antiphospholipid antibodies (aPL), which present in 83% of SLE-PAH; and anti-U1 ribonuclear protein (RNP), which presents in >25% of SLE-PAH.

Presentation

Please see SSc-PAH.

Screening

Due to the rarity of PAH in SLE, annual echocardiogram screening should be directed to women in childbearing age, pregnant ladies, patients with Reynaud's phenomenon, anticardiolipin antibody, and anti-U1 RNP antibody [66].

Treatment

All patients should receive supportive therapy as needed (See SSc-PAH). On the other hand, mild PAH patients should receive immunosuppressive therapy alone, while moderate to severe PAH patients should receive PAH-specific therapy with or without immunosuppressive therapy [56].

PAH-specific therapies are effective in SLE-associated PAH specially epoprostenol, bosentan, sildenafil, ambrisentan, and tadalafil. They improved the 6MWT and functional class [67–70]. Adding immunosuppressive therapy (e.g., IV CYC with or without oral glucocorticoids) showed improvement in 6MWT and lowered PAP [71–74].

Acute Reversible Hypoxia

It's a rare complication of lupus, and patients usually present with acute and unexplained hypoxia and hypercapnia. Blood investigation may show high C3 levels. Chest radiograph could be normal. V/Q scan should show no evidence of PE. Lastly, arterial blood gases (ABG) shows increase alveolar-arterial (A-a) PO2 gradient. Furthermore, it responds quickly to high-dose systemic corticosteroids [75, 76].

7.6.1.10 Airway Disease

Upper Airway Involvement

Introduction

It occurs in around 30% of SLE patients. Also, it involves laryngeal mucosal inflammation or ulceration, cricoarytenoiditis, vocal cord paralysis, necrotizing vasculitis, and angioedema.

Presentation

Patients usually present with hoarseness and/or dyspnea. Moreover, they could develop angioedema symptoms such as lip and mouth swelling, dysphagia, odynophagia, and breathing difficulty.

Diagnosis

Chest radiograph and CT scan are usually normal. PFT may show flattening of the inspiratory or expiratory loop or both depending on the location of the obstruction. Furthermore, 3-D reconstructive images are needed to locate the site of obstruction. Fibro-optic laryngoscopy or bronchoscopy is needed for direct visualization of the vocal cord.

Treatment

Corticosteroids are of benefit in laryngeal mucosal inflammation or ulceration and vocal cord paralysis [77, 78]. However, in refractory cases, infectious causes should be considered (e.g., *Haemophilus influenzae* and *Streptococcus*.

Other rare pathogens are *Histoplasma*, *Coccidioides*, *Cryptococcus*, *Blastomycosis*, and *Candida*).

Lower Airway Involvement

Bronchiectasis

HRCT findings suggestive of bronchiectasis occur in around 21% of SLE patients. However, patients usually are asymptomatic [79].

Bronchiolitis Obliterans (BO)/Obliterative Bronchiolitis (OB)

It's a rare complication of SLE, which is characterized by severe airflow obstruction which is mostly irreversible. Patients usually present with progressive shortness of breath. Moreover, chest HRCT Shows mosaic attenuation pattern that gets accentuated in the expiratory images. PFT shows obstructive pattern. Biopsy is rarely required. Furthermore, anticholinergics were reported to have favorable outcome when compared to systemic steroids and immunosuppressive therapy [80, 81].

7.6.1.11 Muscle Involvement

Shrinking Lung Syndrome (SLS)

Introduction

It's an uncommon disorder, with a prevalence of 0.6–0.9% of SLE patients [80–82], characterized by unexplained dyspnea, decreased lung volumes, elevated diaphragm, and restrictive PFT pattern in the absence of parenchymal lung disease.

Presentation

Patients usually present with shortness of breath aggravated by being in supine position. Pleuritic chest pain is also reported. Physical examination reveals diminished breath sounds at the lung bases with or without crackles.

Diagnosis

Chest radiograph and HRCT show elevation of both diaphragms and basal atelectasis without evidence of parenchymal lung disease. PFT shows restrictive pattern with preservation of DLCO when corrected for alveolar volume (DL/VA). Also, respiratory muscle assessment could show reduced maximal inspiratory pressure (MIP) and stable maximal expiratory pressure (MEP).

Treatment

Oral glucocorticoids with or without other immunosuppressive therapy showed to be effective [83, 84]. Other options are AZA, methotrexate (MTX), CYC, and rituximab [82–87].

Prognosis

SLS has good prognosis when treated. Moreover, respiratory failure rarely occurs [64, 88].

7.6.1.12 Associated Lung Disorders

Adult Respiratory Distress Syndrome (ARDS)

It occurs in 4–15% of SLE patients. The most common cause of ARDS in SLE is sepsis. Other causes are ALP, DAH, and CAPS. Furthermore, it occurs more frequently in younger age group and is more progressive than in non-SLE patients. ARDS-related mortality contributes to 30% off all lupus deaths. Furthermore, mortality could reach up to 70%. The treatment is mainly supportive care.

Infectious Complications

Most of the SLE infectious complications happen in patients who are on immunosuppressive therapy. It accounts for 30–50% of all SLE deaths. Furthermore, bacterial infections are the most common (75%) followed by mycobacterial (12%) then fungal infections (7%) and lastly viruses (5%). It could mimic ALP or DAH, so, careful diagnostic approach is recommended. The diagnosis is usually conducted by chest radiograph and HRCT and also BAL to differentiate infectious from non-infectious causes (Fig. 7.5).

Pneumocystis Pneumonia (PCP) Prophylaxis

Since the incidence of PCP in SLE patients is very low (0.6%), it is not clear if all SLE patients

on immunosuppressants should receive prophylaxis. But, at least patients at highest-risk of PCP infection (e.g., who receive biologic agents or immunosuppressants in addition to high dose daily steroid) should do so. The prophylactic drug of choice is trimethoprim-sulfamethoxazole (TMP-SMX) [89].

Lung Cancer

SLE patients are at increased risk of developing lung cancer. Furthermore, histologically, adenocarcinoma is the most common type (similar to the general population). However, there is a tendency for uncommon thoracic malignancies like carcinoids and bronchoalveolar carcinoma.

Drug Reactions

Please refer to Table 7.5.

7.7 Rheumatoid Arthritis (RA)

7.7.1 Introduction

RA is an autoimmune disorder characterized by joint involvement in a chronic and symmetrical fashion. Pulmonary involvement considered one of the most frequent extraarticular manifestations together with the cutaneous involvement. Furthermore, around 10–20% of RA deaths are attributed to pulmonary causes. The most common pulmonary involvements are ILD, airway disease, rheumatoid nodule, and pleural effusion.

1. Pulmonary manifestations.
2. Parenchymal involvement.
3. Interstitial lung disease (ILD).

7.7.1.1 Introduction

It's the most common pulmonary manifestation of RA with a prevalence of 20–63% radiographically by HRCT. And up to 9.4% of the patients have clinically significant symptoms. Usually happens in a well-established RA disease. However, in around 20%, it could precede it. The most common patterns are UIP followed by NSIP then desquamative interstitial pneumonia (DIP) and organizing pneumonia (OP). Also, risk factors for that are older age group, male gender, history of cigarette smoking, high titer of rheumatoid factor (RF), and anti-cyclic citrullinated peptides (anti-CCP) [90].

7.7.1.2 Presentation

Symptoms start to appear when lung function is greatly impaired. Moreover, pleuritic chest pain occasionally accompanied ILD symptoms. Please see SSc-ILD for more information.

7.7.1.3 Diagnosis

Chest radiograph might be normal in affected patients especially in early disease [91]. However, chest HRCT is the most important tool to diagnose early RA-ILD. UIP manifests as reticulation and honeycombing, while NSIP presents with GGO with/without bronchiectasis. The correlation between the radiographic and the histopathologic pattern is poor in NSIP [86]. Also, OP appears as diffuses patchy alveolar opacity and GGO. It's common to see different patterns simultaneously [90]. PFT may show restrictive pattern with declining of DLCO to be the earliest PFT sign [92, 93]. BAL might be utilized to rule out opportunistic infections, DAH, and/or drug reactions [86, 94, 95]. Biopsy is not recommended as a regular investigation unless the radiologic pattern is unclear and another treatment could make a difference [90].

7.7.1.4 Treatment

Patients with mildly progressive disease should receive high dose prednisone [96]. However, there are anecdotal reports of using daily oral CYC and corticosteroids in rapidly progressive extensive disease [97]. There is also another regimen of monthly IV CYC combined with corticosteroids. In refractory cases, physician could use rituximab, infliximab, or tocilizumab. The routine use of these agents has not been established yet due to the lack of strong evidence and the questionable safety, which is under investigation [98]. Of note, PCP prophylaxis should be given.

7.7.1.5 Prognosis

In general, RA-ILD has mild and slowly progressive nature. However, spontaneous resolution could happen [99].

When DLCO is <54%, it is suggestive of worse prognosis [99]. On the other hand, NSIP has better prognosis than UIP [100, 101].

7.7.2 Pleural Diseases

7.7.2.1 Pleural Effusion

Introduction

It's the second most common pulmonary involvement in RA (after ILD) with a prevalence ranges between 5% and 22%. It usually occurs unilaterally and small to moderate in size; however, large effusions may occur. Moreover, it is associated with RA flares. Risk factors are smoking, previous pleurisy, rupture of subpleural nodule, and high effusion protein levels (prevents resorption).

Presentation

Mostly asymptomatic, but if not, dyspnea, fever, and chest pain (if pleurisy) are the main manifestations [102].

Diagnosis

Chest radiograph shows blunting of costophrenic angles. Chest CT scan is more sensitive than chest radiograph. Furthermore, thoracentesis, if done, pleural fluid analysis could be diagnostic as following (Table 7.4). Pleural biopsy may be considered when TB or malignancy is suspected or when thoracentesis is not diagnostic. Also, the parietal pleura are the mainly involved part rather than the visceral one. When biopsy is done, it shows absence of the normal mesothelial cells covering the pleura, and they are replaced by pseudostratified layer of epithelioid cells with giant cells [103].

Treatment

If asymptomatic, mostly it will resolve spontaneously in up to 36 months. However, if symptomatic, for acute relief, a therapeutic thoracentesis could be done. If no need for acute treatment, then start with NSAIDs. After that, if failed, moderate dose of oral glucocorticoids (10–20 mg prednisolone daily), intrapleural corticosteroids, fibrinolytics, or immunosuppressive could be given. In refractory cases, pleurodesis (mechanical or chemical) is an option.

Complications

The following complications may develop if pleural effusion is not treated. First of all, pleural fibrosis and lung entrapment, which could be treated by decortications. Moreover, bronchopleural fistula could develop, which intervention with video-assisted thoracoscopy (VATS) did not show effectiveness in RA. An open approach with thoracotomy and direct closure may be helpful. Lastly, empyema which can be treated with antibiotics (Usually it's polymicrobial infection) and drainage through chest tube. Worth mentioning, that bronchopleural fistula has been reported in the vast majority of the empyema cases in RA.

7.7.3 Pulmonary Vascular Diseases

7.7.3.1 PAH

It has lower prevalence than in other CTDs [104]. For presentation, diagnosis and treatment (see PAH in SSc).

7.7.3.2 DAH

It's a very rare complication of RA [105]. "Risk factors are treatment with infliximab, leflunomide, and rituximab [106–108]. For presentation, diagnosis, and treatment, please see DAH in SLE.

7.7.4 Airway Diseases: Upper Airway Diseases

7.7.4.1 Cricoarytenoid Arthritis

Introduction

The cricoarytenoid joint function is to abduct and adduct the vocal cord when a person speaks. Good history taking could reveal upper airway

symptoms in around two thirds of RA patients. The prevalence ranges between 26% and 55% with female predominance. Furthermore, joint abnormalities such as prominence, erosions, abnormal positioning of the vocal cord, and subluxation may occur [109].

Presentation

Patients usually presents with hoarseness of the voice (reaching 30%), dyspnea, sore throat, fullness sensation in the throat, shocking, stridor, dysphagia, and odynophagia.

Diagnosis

PFT shows fixed or variable upper airway obstruction. CT scan shows the abnormalities such as prominence, erosions, abnormal positioning of the vocal cord, and subluxation. Laryngoscopy may show vocal cord dysfunction.

Treatment

When patients presented with chronic symptoms, clinicians should start with medical treatment such as systemic or intra-articular steroid, which both have shown benefit. However, surgical options (e.g., tracheostomy, arytenoidectomy, arytenoidopexy) should be considered only if medical treatment failed [110].

On the other hand, patients may present with acute manifestations such as severe stridor and should get emergent tracheostomy [111].

Prognosis

Excellent results occur with aggressive therapy [112].

7.7.4.2 Vocal Cord Rheumatoid Nodule

Could mimic squamous cell carcinoma [111].

7.7.5 Airway Diseases: Lower Airway Diseases

7.7.5.1 Bronchiectasis

Prevalence ranges between 30% and 58% when elected by HRCT. However, only 1–5% of RA patients are symptomatic. Bronchiectasis usually is a late manifestation of RA, but it can precede the articular involvement. Furthermore, presentation and management is like any other bronchiectasis without rheumatoid arthritis.

7.7.6 Airway Obstruction and Bronchial Hyperreactivity

It occurs in about 60% of RA patients when documented by spirometry. Recurrent airway infections and smoking could precipitate airway disease in RA. Patients usually present with wheeze and productive cough. Furthermore, PFT may shows obstructive pattern. However, HRCT is more sensitive than PFT in detecting the obstruction. It shows air trapping, attenuation in lung heterogeneity, and bronchiectasis. The treatments are mainly inhaled corticosteroids and bronchodilators.

7.7.6.1 Bronchiolitis Obliterans (BO)

Introduction

It's a clinically progressive small airway disease, which is characterized by narrowing, ulceration, and scarring of the respiratory and terminal bronchioles. The prevalence varies between 8% and 65%. Also, risk factors are female gender, long-standing RA, D-penicillamine, gold salt, and methotrexate use [113, 114].

Presentation

Progressive dyspnea and dry cough are the most common presentations, while physical examination reveals inspiratory crackles and squeaks.

Diagnosis

PFT shows progressive irreversible airflow obstruction. However, HRCT is more sensitive than PFT in detecting the disease. It may show air trapping (mosaic pattern of regions of low attenuation which get accentuated on expiratory images). BAL is done to rule out infections if suspected, while biopsy shows airway narrowing, ulceration, scarring, and lymphoplasmacytic infiltrate.

Treatment

Physicians should stop offending agent and may start oral prednisone, some studies suggested the use of IV CYC as well [115, 116] or stop offending agent and start low dose oral macrolide (erythromycin 400–600 mg/day, clarithromycin 200–400 mg/day or azithromycin) for 6 months may be used as improvement was shown in the treatment of diffuse panbronchiolitis [117, 118].

Prognosis

Usually carries poor prognosis specially when using corticosteroids only. Thus, adding CYC or trying macrolides may be beneficial.

7.7.6.2 Follicular Bronchiolitis

Introduction

The bronchioles are invaded by lymphocytic, plasmacytic, and hyperplasic lymphoid follicles, and reactive germinal cells infiltrates. It has some overlap with COP and BO [114].

Presentation

Patients usually present with dyspnea and also may present with fever and cough.

Diagnosis

Chest radiograph may show reticular or reticulonodular opacities. Furthermore, HRCT shows bilateral centrilobular and peribronchial nodules associated with areas of GGO.

Also, PFT may show obstructive, restrictive, or both patterns. DLCO is usually decreased. BAL is done to rule out infections. Biopsy shows bronchioles, which are invaded by lymphocytic, plasmacytic, hyperplasic lymphoid follicles, and reactive germinal cells infiltrates.

Treatment

May start with corticosteroid then after tapering starts oral macrolides (erythromycin, clarithromycin, or azithromycin) for up to 1 year [119].

Prognosis

Follicular bronchiolitis has relatively good prognosis when treated.

7.7.7 Rheumatoid Nodule and its Complications: (Necrobiotic Nodule)

7.7.7.1 Rheumatoid Nodule

Introduction

Up to 32% of rheumatoid nodule occurs in the lungs. Also, because the most common site in the respiratory system is subpleural or interlobular, it could present by many different ways such as pneumothorax, cavities, pleural effusion, empyema, and bronchopleural fistula. Furthermore, it could be solitary or multiple nodules. On the other hand, radiologically, it could mimic non-small cell lung cancer. So, physicians should be meticulous when approaching such patients specially when there is history of smoking. Also, histologically, it has a great overlap with granulomatous diseases. For that, biopsy should be interpreted very carefully [120]. Risk factors for rheumatoid nodule are with male gender, positive rheumatoid factor (RF), long-standing disease (but may precede the diagnosis of RA), and smoking.

Presentation

Mostly asymptomatic. However, if symptomatic, it depends on the complication, e.g., cavities present with hemoptysis, pneumothorax presents with dyspnea and chest pain, pleural effusion presents with dyspnea, empyema presents with dyspnea and fever, and bronchopleural fistula presents with productive cough, dyspnea, and fever occasionally.

Diagnosis

Chest radiograph may show nodule but always should compare with previous chest radiographs to notice any changes in size or shape. Also, HRCT will give better details and physician should look for size, shape, lymph nodes, and effusions. It could be solid or as a cavity.

Treatment

If no complications, spontaneous resolution is the usual natural history. Moreover, rituximab has shown effectiveness in its resolution.

However, if complicated, treat accordingly (e.g., if secondary pneumothorax happened, it's better to perform surgical intervention to prevent recurrence).

Rheumatoid Nodulosis

It is multiple rheumatoid nodules in different places. Risk factors are methotrexate, etanercept, and leflunomide use. Actually, it could lead to the same presentations the rheumatoid nodule does. Furthermore, the treatment is usually to stop the offending drug and start hydroxychloroquine, D-penicillamine, colchicine, or sulfasalazine.

7.7.7.2 Caplan Syndrome (Rheumatoid Pneumoconiosis)

Introduction

It occurs in RA patients who get exposed to coal, silica, asbestos, and ceramics industry and roof tiles products. Furthermore, it characterized by rapid-onset lung nodules and could mimic TB or neoplasm. It occurs more commonly in Europe than in the United States. Also, it's more common in positive RF patients and in male.

Presentation

Most of the time patients are asymptomatic unless complicated by pneumothorax, pleural effusion, or progressive massive fibrosis, which is uncommon; they would present with dyspnea and/or chest pain. Also, rarely, patients may present with hemoptysis or *Aspergillus* colonization.

Diagnosis

Chest radiograph shows well-defined nodules starting from 0.5 cm in diameter and larger. Also, it could cavitate or calcify. Usually present in lung periphery [121]. HRCT may have a role in following up and detection of changes. Biopsy, since it could mimic TB or neoplasm, it is often done specially when there is high index of suspicion.

Treatment

There is no specific treatment, although some studies showed improvement when using corticosteroids when the lesions are compressive or rapidly progressive [122]. However, if complicated, treat accordingly.

Prognosis

It takes few weeks or months until nodules reach the final size. Usually, they remain at the final size for many years or may heal but leave behind an asteroid scar. Only 10% of the cavitations and the calcifications emerge.

7.7.8 Infections

7.7.8.1 Background

It's clear that lung infections is increased in RA patients since pneumonia is twice more common than in general population. However, it's very difficult to make sure if the risk of infection is due to RA itself or the immunosuppressive agents used to treat RA.

Immunosuppressive agents and risk of infection:

- **Corticosteroids**: It increases the risk of pneumonia by dose-depending mechanism. For most of patients, a dose of more than 10 mg/day is sufficient to cause it [123–126].
- **MTX**: With or without corticosteroids, it makes patients at risk of developing opportunistic infections, e.g., PCP and disseminated histoplasmosis [124, 127]. Usually occurs in the first 2 years of initiation the MTX [124].
- **Anti-tumor necrosis factor-alpha (TNF-a)**: Exposes patients to risk of many opportunistic infections, most importantly *Mycobacterium tuberculosis* (TB). Others like coccidioidomycosis, histoplasmosis, listeria, aspergillus, and norcodia have been reported [128].

7.7.8.2 Latent Tuberculosis Infection (LTBI) Screening [129]

Before initiating the treatment with any of the following biologic agents (adalimumab, certolizumab pegol, etanercept, infliximab, golimumab, abatacept, rituximab, or tocilizumab) a TB skin testing or interferon gamma release assay (IGRA) should be done to screen for latent TB infection (LTBI) regardless of the presence or absence of

TB risk factors. If negative results without presence of risk factors, then starting the treatment with the biologic agent is permissible. If negative results with the presence of TB risk factors, the physician should repeat the test in 1–3 weeks. If results are positive, CXR should be done. If negative CXR for TB signs, this is latent TB infection (LTBI), and referral to an infectious disease (ID) specialist should be undertaken. In this situation, the physician can initiate the treatment with the biologic agent after 1 month of starting the treatment of the LTBI. If positive CXR, then do sputum stain and culture for TB. If negative, it is LTBI. But if the sputum tested positive for TB, refer the patient to an ID specialist to start the treatment for active TB infection [129]. Of note, if patient is already on glucocorticoids, induration of 5 mm is considered positive [90].

For further reading, please see Infectious Disease Chap. 11.

7.7.8.3 Cancer

RA patients are at increased risk for developing lung cancer and lymphoma. The reason is not clear. But, a proposed theory could be due to RA itself, smoking, immunosuppressive therapy, or because RA is a middle age disease, which equals to the age at which cancers usually detected. Once mediastinal lymph node is detected, biopsy has to be undertaken as soon as possible.

7.7.8.4 Myopathy and Muscle Weakness

Introduction

Usually happens due to medication toxicity, rheumatoid vasculitis, and rheumatoid myositis. Physicians should suspect it when patients have progressive dyspnea with unclear cause and no improvement with treatment. Risk factors are the use of D-penicillamine and hydroxychloroquine.

Diagnosis

Blood tests show creatine-kinase (CK) within the normal limits. PFT show restrictive pattern. Also, FVC and VC in supine position is reduced by more than 10% than in upright. Furthermore, maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) are reduced. DLCO is normal unless another pathology present. Biopsy may be needed to confirm the diagnosis.

7.7.8.5 Fibrobullous Disease

It's a rare complication of rheumatoid arthritis and usually occurs in the apical part of the lung. It could be a complication of a rheumatoid nodule even in the absence of a radiological evidence.

7.7.8.6 Amyloidosis

Secondary amyloidosis, which involves lungs, has been reported. It could present as nodules, ILD, or tracheobronchomalacia.

7.8 Sjogren Syndrome (SS)

7.8.1 Background

It's an autoimmune disease characterized by involvement of exocrine glands through infiltration of lymphocytes. A clinically significant pulmonary manifestation occurs in around 9–24% of SS patients. Also, pulmonary involvements in asymptomatic SS patients who were detected by PFT, CT scan, or BAL reach 75% of patients. Also, pulmonary manifestations usually occur late in the disease course. Furthermore, if they were clinically significant, it could increase the risk of mortality by fourfold [130]. Risk factors for pulmonary involvement are positive rheumatoid factor, hypergammaglobulinemia, positive anti-Ro and anti-La, and decreased FVC and FVC1, smoking, elderly patients, and male sex. Overall, rituximab is a promising drug to treat SS and its extra-glandular manifestations (because it targets B lymphocytes), unlike anti-TNF drugs.

- Pulmonary manifestations.
- *Airway involvement.*
- Upper airway.
- Nasal crusting.

  Around 18.5% of SS patients complain of nasal crusting. It is found in 50% during physical exam. The treatment usually consists of the use of room humidifiers and saline nasal spray as needed.

7.8.2 Epistaxis

It occurs in around 31.8% of patients with SS. The treatment is the same as for any patient with epistaxis.

7.8.3 Hoarseness of the Voice

This occurs in about 1/3 of SS patients. The diagnosis is done by laryngoscopy, which shows most commonly dryness or thick mucus covering the vocal cords. However, rarely, the presence of Bamboo node, which is a transverse yellow or white submucosal lesion, occurs in the vocal folds. Also, granulomatous and non-granulomatous nodules have been reported.

7.8.4 Xerotrachea and Xerobronchitis

Usually developed due to structural of functional disability of the mucociliary cells to clear the thickened secretions. It occurs in around 17% of SS patients. Those usually presents almost always with dry cough. Chest radiograph, HRCT, and PFT are normal. On the other hand, recurrent bronchitis, bronchopneumonia, atelectasis, and peribronchial and peribronchiolar scarring and narrowing might occur as complications.

7.8.5 Lower Airway Disease

7.8.5.1 Follicular Bronchiolitis (FB)

Introduction

It's a benign lymphoproliferative disorder, characterized by hyperplasic lymphoid follicles distributed along the bronchioles and the peribronchiolar interstituim unlike the LIP, which involves the whole parenchyma. It is a histopathological diagnosis; however, it could be suspected by history, CT scan, and PFT results. It's a common manifestation of SS. Usually, patients present with cough, dyspnea, and sometimes fever.

Investigation

CT scan shows bilateral peribronchial and centrilobular nodules with size range between 1 and 3 mm but could reach up to 12 mm. Other findings are reticular opacities, GGO, and intrathoracic lymphadenopathy. Furthermore, PFT usually shows restrictive pattern but also could be obstructive pattern or both. Biopsy shows hyperplasic lymphoid follicles distributed along the bronchioles and the peribronchiolar interstitium.

Treatment

Primary treatment of SS could be enough. However, systemic corticosteroid is shown to be effective [131].

Prognosis

Has good prognosis when treated with corticosteroid.

7.8.6 Chronic Obstructive Pulmonary Disease (COPD)

It is found to be more prevalent in SS patients through their disease course, especially smokers, who have 5 times higher chance compared to non-smokers to develop COPD [132].

7.8.7 Lung Parenchyma

7.8.7.1 ILD

Introduction

It's the most common pulmonary manifestations of SS. Furthermore, the most common subtype are NSIP followed by lymphcytic interstitial pneumonia (LIP) then UIP and lastly OP. It is more common when patients have anti-Ro antibodies.

Subtypes

NSIP

It occurs in about 28–61%. Presentation is usually chronic dyspnea. Chest radiograph may show bilateral interstitial infiltrates. PFT shows restrictive pattern with decreased DLCO. HRCT

shows GGO (with subpleural and basilar predominance). Furthermore, reticular abnormalities with or without traction bronchiectasis could be found. Honeycombing happened with advanced disease. BAL is done to rule out infection when suspected. Biopsy shows uniform or homogenous pattern of cellular inflammation and/or fibrosis of the alveolar walls. Moreover, no need for treatment if patients are asymptomatic. However, if symptomatic with worsening symptoms, physician could give steroids (prednisone 1 mg/kg/day) [133]. Also, if refractory, immunosuppressive therapy (commonly AZA. Rarely CYC or cyclosporines) could be used [134–137]. The prognosis depends on the extent of fibrosis. The less fibrosis, the better prognosis [132].

Lymphocytic interstitial pneumonia (LIP)

It's one of the most common pulmonary manifestations of SS. It has potentials to progress into lymphoma. Thus, biopsy should always be considered if there is no response to standard therapy. The prevalence is 17% among SS patients who develop ILD [133] with female predominance [138]. Patients usually present with dyspnea and cough and, also, less commonly fever, weight loss and night sweat. Blood tests show polyclonal hypergammaglobulinemia (80% of cases). Chest radiograph may show bilateral reticular or reticulonodular opacities, more commonly in the lower zones. HRCT shows diffuse GGO and walled cysts (in 50% of cases). Also, interlobular septal thickening, centrilobular nodules, and bronchovascular bundle could be seen. PFT show restrictive pattern with low DLCO. BAL is done to rule out infection if suspected. Again, since it could progress to lymphoma, biopsy should always be considered if there is no response to standard therapy. Histopathology reveals infiltration of the interstitial septa and, sometimes, filling of the alveolar space by lymphocyte (B&T cells), plasma cells, and histiocytes. Patients usually treated with corticosteroids (start with prednisone 0.75–1.0 mg/kg/day then taper slowly for the following 3–6 months) [139–141]. Furthermore, initially, it responds well to corticosteroids. However, up to 1/3 of patients die due to progression of disease or due to the infectious complications resulted from the intensive immunosuppression therapy [142]. Rarely it could resolve spontaneously.

7.8.8 Pleural Involvement

7.8.8.1 Pleural Effusion

It's a very rare manifestation of SS. Therefore, when present, one should think of a secondary cause (i.e., in the setting of secondary SS), e.g., RA or SLE. Usually occurs bilaterally, but a unilateral presentation could happen. Pleural fluid analysis should be done for diagnosis (Table 7.4).

7.8.9 Pulmonary Vascular Disease

7.8.9.1 PAH

Introduction

It's a rare complication and usually occurs due to pulmonary artery vasculitis. Also, occasionally, it co-exists with Raynaud's phenomenon. Risk factors are Raynaud's phenomenon, ILD, skin vasculitis, hypergammaglobulinemia, positive anti-Ro, positive RF, and positive antiribonucleoprotein (anti-RNP) antibodies. Moreover, for presentation and diagnosis (see PAH in SSc). The mainstay of treatment is the use of PAH specific treatment (endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, or prostanoids) with/without immunosuppressive therapy [143].

7.8.10 Cancer

7.8.10.1 Lymphoma

Introduction

The risk of SS patients to develop lymphoma in general, not only pulmonary lymphoma, is 44 times compared with healthy population [144], while pulmonary lymphoma prevalence is 1–2% among SS patients [145]. Furthermore, SS patients could develop benign lymphocytic infiltration, like in LIP, and this in turn could progress

to lymphoma [145]. This benign lymphocytic infiltration is characterized by polyclonal B and T lymphocytes proliferation. Moreover, the most common type of lymphoma in SS patients is non-Hodgkin's lymphoma with a subtype of mucosa-associated lymphoid tissue (MALT) [145], while the most common pulmonary lymphoma is the low-grade extranodal marginal B-cell lymphoma of MALT type [145]. Risk factors are hypocomplementemia, cryoglobulinemia, vasculitis (palpable purpura), and severe exocrine involvement at time of diagnosis of SS [145].

Presentation

80% are asymptomatic at time of lymphoma diagnosis due to the incidental finding in radiological studies. If symptomatic: dyspnea, cough, weight loss, fatigue and sweat.

Diagnosis

Chest CT scan manifests as nodules (solitary or multiple), bilateral diffuse infiltrate, interstitial infiltration with slight lower zone predominance, mediastinal lymphadenopathy, and pleural effusion (usually do not occur alone rather happen with the parenchymal involvement). Furthermore, biopsy shows most commonly a non-Hodgkin's low-grade extranodal marginal B-cell lymphoma of MALT type [145]. Also, it has good prognosis with 5-year survival of more than 80% [146]. Of note, progression to high-grade lymphoma occasionally happens [145].

Pseudolymphoma

It's a rare and benign entity, also called pulmonary nodular lymphoid hyperplasia or bronchus-associated lymphoid tissue (BALT). It is characterized by infiltration of polyclonal lymphocyte and plasma cells. Usually it's asymptomatic but could present with dyspnea and cough. CT scan typically shows solitary nodule. However, less frequently, multiple nodules, which involve blood vessels, consolidation, mediastinal lymph node and/or pleural effusion, could be seen. Biopsy usually reveals bronchus-associated lymphoid tissue (BALT). Furthermore, corticosteroids or immunosuppressive therapy could be given [147]. It has good prognosis when treated [147]. However, rarely transforms into lymphoma.

Amyloidosis

Its prevalence is around 0.6%, and patients' presentation depends on the location such as larynx, trachea, bronchi, interstitium, and/or mediastinum. CT scan shows micronodular lesions (could be calcified or cavitary) predominantly in the subpleural area and in the lower lobes, while biopsy shows positive amyloid staining. The prognosis is usually good [148, 149].

7.9 Mixed Connective Tissue Disease (MCTD)

7.9.1 Introduction

It was first described in 1972 and defined as a combination of SSc, SLE, and polymyositis/dermatomyositis (PM/DM) with positive anti-ribonucleoprotein (Anti-RNP). Yet, it's not clear if it's a separate entity of disease or not. Furthermore, pulmonary manifestations occur in up to 65% of MCTD patients. Worth mentioning, that patients with MCTD could present with any pulmonary manifestations related to SLE, SSc, or PM/DM [150].

7.9.2 Pulmonary Manifestations

7.9.2.1 Lung Parenchyma

Interstitial Lung Disease (ILD)

Introduction

It occurs in around 50–65% of MCTD patients [150]. Also, esophageal dilatation is a risk factor for developing ILD [151].

Presentations

Please see ILD in SSc.

Diagnosis

In early stages, PFT shows reduction in DLCO only. Then, in late stages, it shows restrictive pat-

tern with low DLCO. HRCT shows septal thickening, GGO, and non-septal linear opacities with predominance in the periphery or within the lower lobe. Also, in fact, no study encountered pathological findings, but thought to be NSIP and UIP.

Treatment
Physician should start corticosteroid (methylprednisolone 2 mg/kg/day) for 4–6 weeks then assess, if no improvement add CYC oral or IV to complete 6 months [152].

Prognosis
Good prognosis (in terms of preventing further progression of the disease) if treated during the acute inflammatory phase (GGO). Once signs of fibrosis on HRCT present, the response will be poor.

Alveolar Hemorrhage
It's an uncommon manifestation. Also, for presentation, diagnosis, and treatment refer to SLE-associated DAH.

Pulmonary Vascular Disease
PAH
Prevalence ranges between 3.4% and 27%. Furthermore, for presentation, diagnosis, screening and treatment, see SSc-PAH.

Pleural Diseases
Pleural Effusion
It's a common manifestation of MCTD with prevalence about 50% [153]. Pleural fluid analysis is usually exudative and with lymphocytic predominance. Moreover, it usually resolves spontaneously. However, if it persists, then a trial of corticosteroid could be effective.

7.10 Polymyositis (PM)/ Dermatomyositis (DM)

7.10.1 Introduction

Pulmonary manifestations play big role in the mortality and morbidity of PM/DM patients. Moreover, the main pulmonary complications are ILD, aspiration pneumonia, and hypoventilation due to muscle weakness.

7.10.2 Pulmonary Manifestations

7.10.2.1 Parenchymal Lung Disease

Interstitial Lung Disease (ILD)

Introduction
It's the most common pulmonary complication, which reaches up to 65% when screened by CXR, HRCT, or PFT. Furthermore, it can present as an acute, chronic, or asymptomatic with radiological findings only. When it is symptomatic, more than 60% of patients present with cough and dyspnea and normal radiograph, HRCT, or PFT. Also, it is more common in DM than in PM. However, recently, a new subtype of DM has been reported, the clinically amyopathic dermatomyositis (CADM), which is DM without muscle involvement. This subset, when associated with anti-CADM-140 antibodies, associated with higher prevalence of rapidly progressive ILD. Risk factors are positive antihistidyl tRNA synthetase antibody (anti-Jo-1), Krebs Von den Lungen-6 (KL-6), serum surfactant protein D, serum cytokeratin 19 fragment (CK-19), and anti-CADM-140 antibody (which associated with rapidly progressive ILD). All of them aren't present in every center as a routine test.

Presentations
Patients usually present with dyspnea and cough.

Diagnosis
PFT shows restrictive pattern with low DLCO. While HRCT could shows NSIP, UIP, OP, or DAD pattern. BAL to rule out infection or drug-induced pneumonitis. Biopsy is rarely needed because the HRCT findings correlate well with histopathology. Although transbronchial lung biopsy is inferior to open lung biopsy, it is a good choice if opportunistic infection or neoplasms are suspected because open lung biopsy associated with high mortality rate.

Treatment

Most commonly, corticosteroids with (CYC, AZA, cyclosporines) are given [154–161]. However, IVIG alone or with corticosteroids has shown good results in progressive disease [162, 163]. Also, tacrolimus and rituximab, individually, are promising drugs [164–166]. Anti-tumor necrosis factor-alpha (Anti-TNF-a) and MTX are less likely to be effective. In fact, they may induce irreversible lung fibrosis [167].

Prognosis

ILD in PM/DM increases mortality. A 5-year survival ranges between 60% and 86% [168, 169]. Also, worse prognosis is expected with DM compared to PM. Furthermore, when corticosteroids combined with other immunosuppressive therapy, approximately 1/3 of the patients will improve, 1/3 will remain the same, and 1/3 will deteriorate [154]. Moreover, rapidly progressive ILD has fatal outcome with 3-year survival of around 24% [170].

7.10.2.2 Aspiration Pneumonia

It occurs in around 17% [171] of PM/DM patients and is related to the dysfunction happens to the pharynx and esophagus muscles which lead to abnormal swallowing and frequent regurgitation. Risk factors are severe muscle disease [172]. Furthermore, investigations and treatment are like any other case of aspiration pneumonia.

7.10.2.3 Pulmonary Vascular Disease

PAH

Occasionally happens. For, presentation, diagnosis, and treatment, see SSc-PAH.

7.10.3 Pneumothorax (PNX) and Pneumomediastinum and Subcutaneous Emphysema

7.10.3.1 Introduction

They occur in two different clinical scenarios. The first one is vasculopathy with or without mild ILD (vasculopathy such as skin ulcers or bronchial wall necrosis). The second one is severe ILD with or without vasculopathy. Whenever one of these complications (PNX, pneumomediastinum, or subcutaneous emphysema) happens, one should suspect pulmonary vasculitis. Diagnosis is made by chest radiograph and chest CT scan. Moreover, physicians should start corticosteroid and immunosuppressive therapy together at the beginning then taper the steroid gradually [173].

7.10.4 Respiratory Failure and Hypoventilation

7.10.4.1 Introduction

This happens due to severe respiratory muscle weakness with prevalence around 21.8% [171].

7.10.4.2 Diagnosis

PFT shows restrictive pattern. Furthermore, FVC and VC in supine position are reduced by more than 10% than in upright. Also, maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) are reduced. DLCO is normal unless another pathology is present. Chest radiograph may show decreased lung volumes, elevated diaphragms, and basal atelectasis.

7.10.4.3 Complications

Atelectasis and recurrent pneumonia may develop due to mucus plugging because of reduced cough reflex secondary to respiratory muscle weakness.

7.10.4.4 Treatment

Physicians should start immunosuppressive therapy. However, if failed, home mechanical ventilation could be used which could saves life and improves the quality of life.

7.10.4.5 Lung Cancer

There may be an association between lung cancer and myositis, especially DM.

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8 Nervous System and Rheumatology

Emad Alkohtani and Amal Alkhotani

8.1 Introduction

The nervous system can be affected by many rheumatologic disorders. The involvements are different in various diseases. Some rheumatologic diseases have prominent nervous system features, e.g. SLE, while in others these are minor (Table 8.1).

Patients with rheumatologic disorders can have nervous system involvement secondary to medications including immunosuppressive therapy or related to associated comorbidities. It also can be related or a sequel of the disease process itself.

The objective of this chapter is to provide a systemic approach to patients with various rheumatic conditions presenting with neurological syndromes.

8.1.1 Specific Objectives

By the end of the chapter, the reader should be able to:

1. Recognize different neurological manifestations associated with SLE.
2. Compose a diagnostic approach to SLE patients presenting with acute headache.
3. Compose a diagnostic approach to SLE patients presenting with chronic headache.
4. Manage SLE patients presenting with acute stroke.
5. Recall the different causes of stroke in SLE patients.
6. Recall the differential diagnosis of generalized seizure in SLE patients.
7. Recall the differential diagnosis of focal seizure in SLE patients.
8. Use appropriate investigation for SLE patients presenting with seizure.
9. Recognize SLE patients with seizure who will require long-term antiepileptic medications.
10. Compose a diagnostic approach and manage SLE patients presenting with spinal cord dysfunction.
11. Recognize neurological manifestations of rheumatoid arthritis (RA).
12. Recognize RA patients at high risk of cervical spine disease.
13. Manage RA patients with suspected cervical spine disease.
14. Recognize causes of neuropathy in RA patients.
15. Compose a diagnostic approach to RA patients presenting with neuropathy.
16. Compose a diagnostic approach to patients with neuropathy and skin rash.

E. Alkohtani
King Abdullah Medical City, Makkah, Saudi Arabia
e-mail: Emad.alkhotani@gmail.com

A. Alkhotani (✉)
Umm Al-Qura University, Makkah, Saudi Arabia
e-mail: amkhotani@uqu.edu.sa

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Table 8.1 Neurological involvement in rheumatic diseases

Condition	Neurological syndromes
Antiphospholipid syndrome	Transverse myelopathy, stroke, migraine, memory loss, demyelination, movement disorders
Temporal arteritis/ giant cell arteritis and Takayasu's arteritis	Headache, visual loss, papilloedema, amaurosis fugax, stroke
Systemic vasculitis	Peripheral neuropathy, mononeuritis multiplex, stroke, polymyositis, meningoencephalitis
Eosinophilic granulomatosis with polyangiitis	Peripheral or cranial neuropathy, mononeuritis multiplex, encephalopathy
Dermatomyositis—Polymyositis	Proximal myopathy
Mixed connective tissue disease	Proximal myopathy
Rheumatoid arthritis	Rheumatoid vasculitis causing stroke and/or neuropathy, atlantoaxial subluxation, polymyositis; mononeuritis multiplex, peripheral neuropathy
Systemic lupus erythematosus	Aseptic meningitis, demyelinating syndrome, chorea, myelopathy, seizures, anxiety/mood disorders; psychosis, Guillain-Barre´ syndrome, plexopathy; cranial and/or peripheral neuropathy, myasthenia gravis, autonomic disorder, stroke, migraine, headache
Behçet's disease	Meningitis, encephalitis, seizure, stroke, headache
Scleroderma	Proximal myopathy, plexopathy, intracerebral inflammation
Ankylosing spondylitis	Spinal stenosis
Granulomatosis with polyangiitis and polyarteritis nodosa	Peripheral or cranial neuropathy, mononeuritis multiplex, ocular disorders
Sjogren's syndrome	Myelopathy, polyneuropathy, motor neurone syndromes, cognitive Dysfunction

Table 8.2 Neuropsychiatric syndromes associated with systemic lupus erythematosus

NPSLE associated with the central nervous system	NPSLE associated with the peripheral nervous system
– Aseptic meningitis – Cerebrovascular disease – Demyelinating syndromes – Headaches – Movement disorders (chorea) – Myelopathy – Seizure disorders – Acute confusional state – Anxiety disorders – Cognitive dysfunction – Mood disorders – Psychosis	– Acute inflammatory demyelinating syndromes (Guillain-Barre´ syndrome) – Autonomic neuropathy – Mononeuropathy, single or multiplex – Myasthenia gravis – Cranial neuropathy – Plexopathy – polyneuropathy

8.2 Systemic Lupus Erythematosus (SLE)

In 1999, the American College of Rheumatology (ACR) established 19 different neuropsychiatric SLE syndromes (NPSLE) (Table 8.2).

In this chapter, the diagnostic approach to patients with SLE presenting with different neurological complaints will be presented. In general, obtaining good and detailed history and examination will assist to narrow the differential diagnosis and help with obtaining specific diagnostic tests (Table 8.3).

8.2.1 Headache

The prevalence of headache in patients with SLE is reported around 47.1–57% [1–3]. The differential diagnosis and approach to headache in SLE patients is different for acute versus chronic headache (Figs. 8.1 and 8.2). Patients with SLE can present with headache as primary disorders or can be secondary to other causes. The objective is to rule out serious causes before attributing it to primary headache disorder.

Table 8.3 Summary of NPSLE syndromes and differential diagnosis

NPSLE manifestations	Diseases to exclude	Notes
Headache	Aseptic meningitis, CNS infections, venous sinus thrombosis	1. Diagnosis of NPSLE is by exclusion of other important causes by ordering routine tests: **a. Laboratory:** CBC, electrolyte, renal, and liver function tests **b. CSF:** WBC, protein, glucose, gram stain and culture, viral PCR **c. Imaging:** Either CT brain or MRI brain and spinal cord according to the case **d. EEG, EMG, NCV** 2. Treatment is by glucocorticoids and immunosuppressive drugs and anticoagulant in certain conditions – In refractory cases, you can add one or all of the following: a. Plasmapharesis b. Intravenous immunoglobulin c. rituximab
Cognitive dysfunction	Drug side effects, depression, endocrine disorders like adrenal disease, stroke	
Stroke	Thromboembolic causes, cerebral vasculitis	
Seizure	Infection, electrolyte abnormalities, uraemia, hypertension, medication side effects, hypoxia or rarely brain tumour	
Acute confusional state	Metabolic causes like renal or liver failure, CNS infections, medication side effects, seizure, structural lesion, e.g. tumour	
Myelopathy	Infectious myelitis, neuromyelitis optica	
Movement disorders	Hereditary causes like Huntington's, Wilson, metabolic causes, structural like brain tumour	
Peripheral neuropathy	Metabolic causes like diabetes, infectious causes, vitamin deficiency, etc.	

8.2.1.1 Approach

Obtain a careful history of the headache: onset, duration, types, and precipitating, aggravating, and relieving factors. Headache that increases with coughing or sneezing and also that is worse with lying down raises the possibility of raised intracranial pressure. The presence of history of visual obscuration is also suggestive of increased intracranial pressure. Ask about any associated neurological symptoms that will make primary headache unlikely and necessitate neuroimaging. In female patients, ask about the relation of headache to the menstrual cycle. Headaches that worsen in relation to menstrual cycle likely will be migraine related.

In addition, a comprehensive evaluation of SLE itself (current active symptoms like joint pains, skin rashes, and urinary symptoms, duration, organ involvements, and prior NPSLE attacks).

Detailed drug history should be obtained as some may precipitate or worsen headaches, e.g. some nonsteroidal anti-inflammatory drugs (NSAIDs) like ibuprofen can cause aseptic meningitis.

On examination, look carefully for signs of meningitis and focal neurological deficits, and *do not forget* to look for papilledema.

Workup depends on your initial findings (Figs. 8.1 and 8.2).

Indications for neuroimaging:

1. New-onset headache or worsening of pre-existing headache.
2. Features suggestive of increased intracranial pressure from history or examination, e.g. papilledema.
3. Altered level of consciousness.
4. Focal neurological signs and symptoms.
5. Associated seizure.

Treatment depends on the cause of the headache. Patients with venous sinus thrombosis will require treatment with anticoagulants. Meningitis should be treated with antibiotic therapy. If the headache is attributed to primary headache disorders, use abortive therapy as indicated. If primary headache is frequent, preventive therapy should be considered according to the headache type.

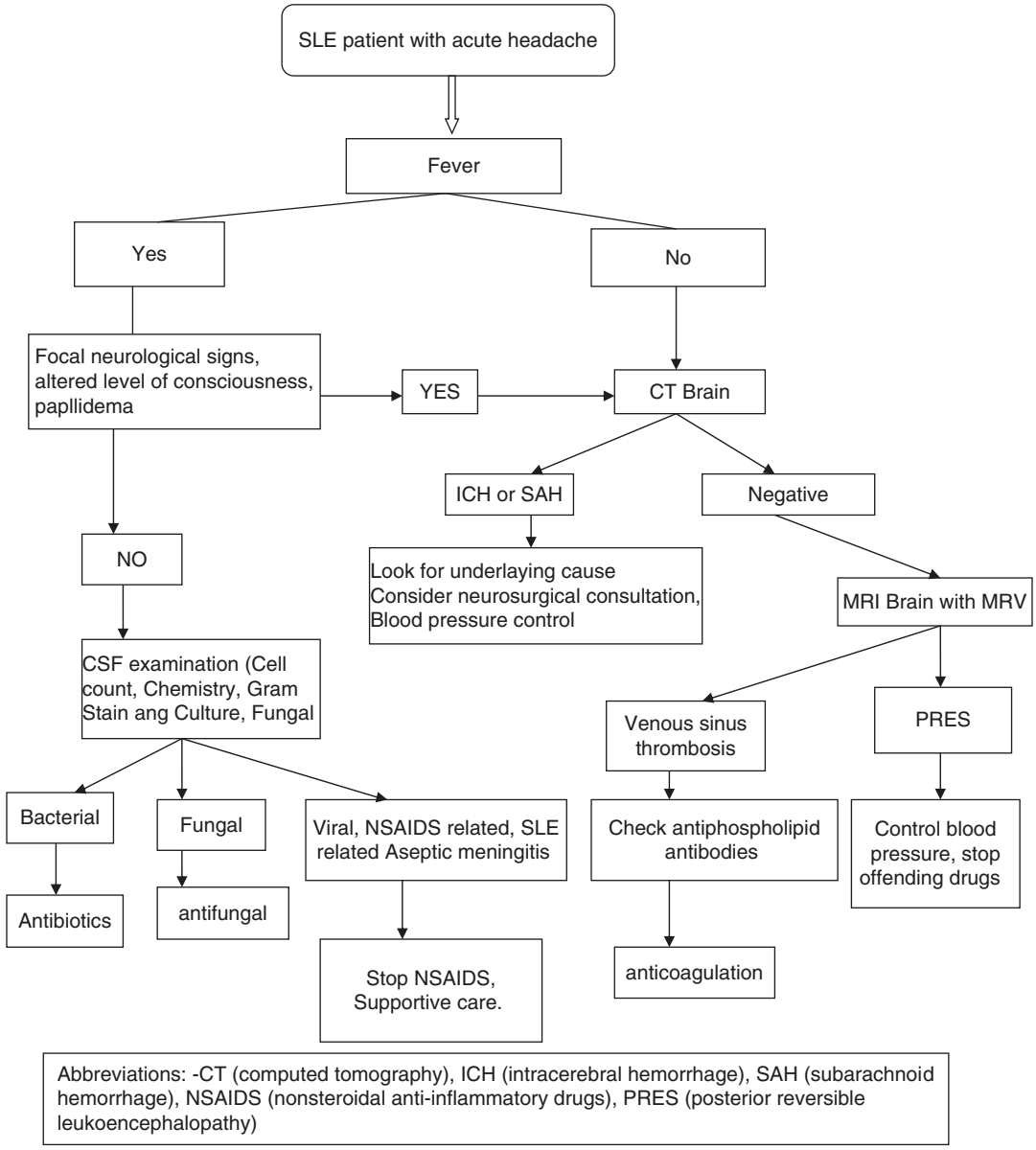

Fig. 8.1 Diagnostic approach to SLE patients with acute headache

8.2.2 Stroke

Cerebrovascular diseases account for around 2–17% [2–4] of all NPSLE events.

Approach to SLE patients with acute stroke is the same as in non-SLE patients (Fig. 8.3).

Keep in mind that in SLE patients, further consideration of the aetiology of the events should be considered. When patients with SLE present with acute neurological deficit within a 4.5-h window, immediate evaluation with brain CT scan is warranted to rule out presence of intracerebral haemorrhage. In absence of contraindication, thrombolytic therapy should be administered. Patient who arrived outside the thrombolytic window should have CT brain before starting antiplatelet therapy. The

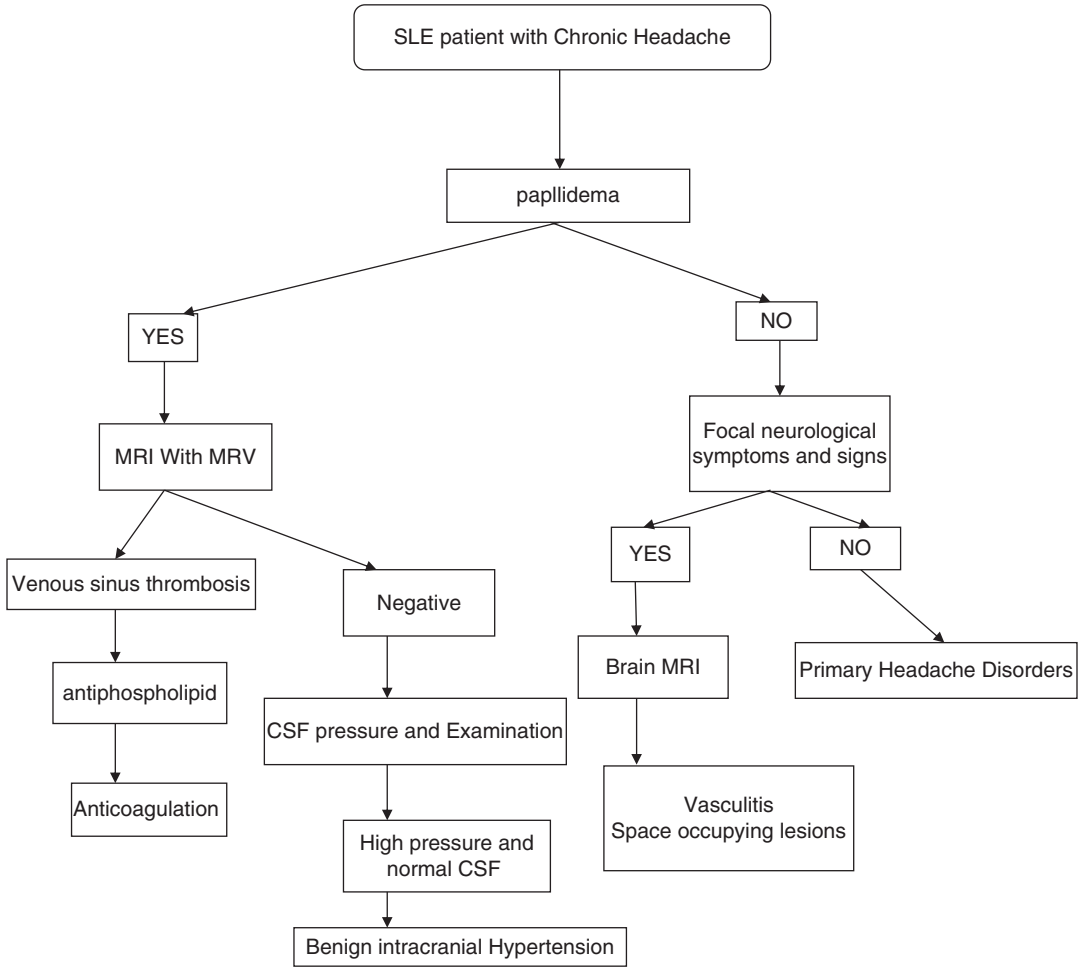

Fig. 8.2 Approach to SLE patient with chronic headache

initial workup for any SLE patient with stroke should include:

1. Fasting blood glucose.
2. Fasting lipid profile.
3. Carotid Doppler.
4. Holter monitoring.
5. Echocardiogram.
6. Antiphospholipid antibodies.

Disease activity should be determined (anti-dsDNA level, urinalysis, complement level (C3 and C4), creatinine). Specific treatment for active disease with immunosuppressive therapy should be considered. All patients should get cardiovascular risk factor modifications. In patients with negative antiphospholipid antibodies and with no indication for anticoagulation such as atrial fibrillation, antiplatelet therapy is the cornerstone for the prevention of further events. Patient with antiphospholipid antibodies should be anticoagulated with warfarin at an INR >3.0 or combined antiplatelet-anticoagulant (INR 2.0–3.0). There is no consensus agreement on this [5].

8.2.3 Seizure

Seizure is a transient neurological dysfunction that results from excessive abnormal discharges of cortical neurons. Seizure can be generalized or focal in onset. The differential diagnosis of generalized-onset seizure is different than focal-onset seizure (Table 8.4).

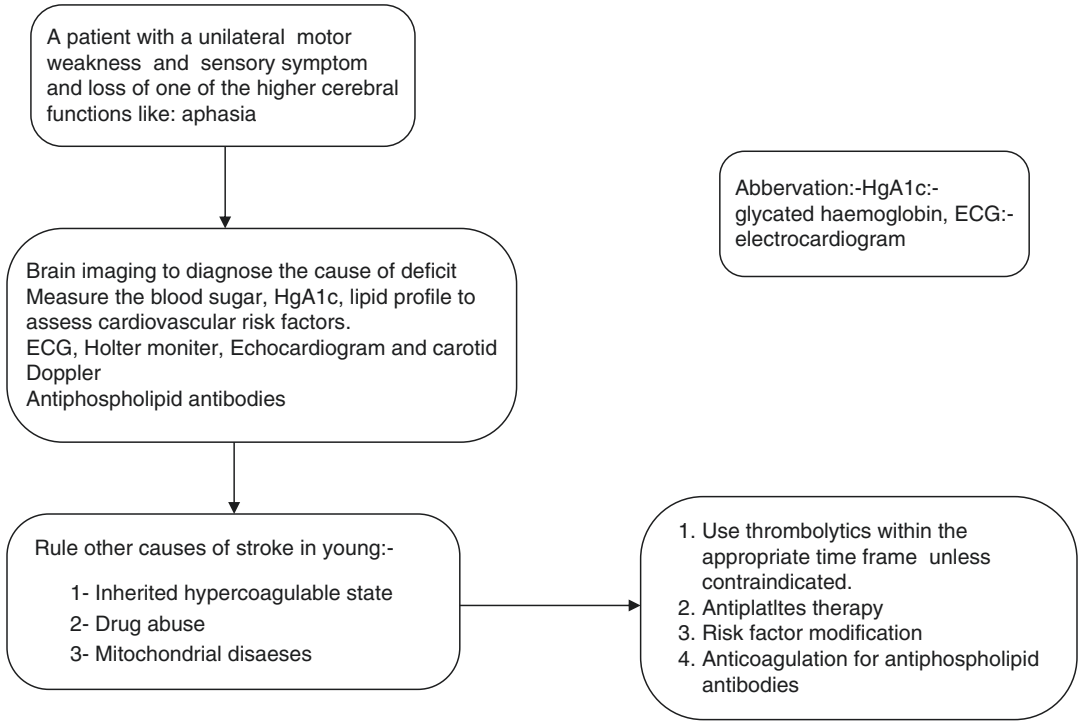

Fig. 8.3 Approach to SLE patients with acute stroke

Table 8.4 Cause of generalized versus partial onset seizure

Generalized seizure	Partial-onset seizure
Electrolyte imbalance	Venous sinus thrombosis
Medication side effect	Posterior reversible encephalopathy
Uraemia	Limbic encephalitis
Infection	Infection
NPSLE	Stroke

Table 8.5 Causes of seizure in SLE patients

Electrolyte imbalance
Uraemia
Medication side effect
Posterior reversible encephalopathy
Infection (meningitis, encephalitis, cryptococcal meningitis)
Limbic encephalitis
Venous sinus thrombosis
NPSLE (single unprovoked seizure)

Table 8.6 workup of SLE patients present with single seizure

Electrolytes
Renal profile
Liver profile
CBC
Brain MRI and MRV
EEG

Different aetiological factors can cause seizure in SLE patients (Tables 8.5 and 8.6). The prognosis and the need for further treatment of seizure are dependent on the cause of seizure [6, 7].

8.2.3.1 Tips in History

1. Disease activities.
2. Seizure onset, duration, and postictal events.
3. Determine the seizure type by asking if there was a preceding aura and by taking exact description of seizure from a witness.
4. History of fever.
5. Any associated other neurological symptoms or signs.
6. Medication history.
7. History of comorbidities, e.g. hypertension or renal failure.

8. Similar events in the past.
9. History of prior CNS insults, e.g. stroke.
10. Family history of epilepsy.

Treatment with an antiepileptic is not indicated for a single unprovoked seizure and for seizure secondary to metabolic causes. Use an antiepileptic in the presence of recurrent events, abnormal EEG, and abnormal neuroimaging which carry a higher risk of recurrence without treatment.

If seizure happens in a setting of high disease activities, treatment with immunosuppressive therapy is indicated.

8.2.4 Myelopathy

It is a condition that results from inflammation of the spinal cord. Although it is considered rarer than other NPSLE syndromes, its development carries poor functional outcome. The classical presentation is with symptoms of spinal cord dysfunction including motor weakness, sensory loss with sensory level, and loss of sphincter control. The presentation differs according to the specific localization of the cord inflammation (Table 8.7).

Patients with SLE can present with transverse myelitis and rarely can also present with longitudinal myelitis where more four segments of the cord are involved. The development of longitudinal myelitis carries a worse prognosis and mandates aggressive immunosuppressive therapy. In the presence of longitudinal myelitis, brain MRI should be done to rule out brain demyelination. Anti-NMO antibodies (neuromyelitis optica) should be sent for those patients.

When dealing with patients with symptoms of acute cord dysfunction, one should rule out surgical causes first as an early intervention will affect the outcome (Fig. 8.4). When surgical causes are excluded, patients should have CSF examination to rule out infectious causes of myelitis. Treatment with immunosuppressive therapy should be delayed. Combine it with antiviral therapy until negative culture is obtained.

Different immunosuppressive regimens have been used in patients with myelopathy including pulse steroid therapy with or without intravenous cyclophosphamide or plasmapheresis. Aggressive therapy with combined three modalities can be used for patients with more severe disease especially with longitudinal myelitis, although one case series did not show superior outcome with the combined three modalities [8]. That observation may be explained by the fact that patients who had combined therapy had severe disease at their presentation. In a subgroup of patients with antiphospholipid antibodies, the use of anticoagulation is recommended.

Table 8.7 Symptoms and signs of myelopathy according to the spinal level

Cervical cord	Motor weakness affecting four limbs (lower motor neuron signs at the level with upper motor neuron signs below the level of the lesion in chronic stage) Sensory loss below the level with cervical sensory level Loss of sphincter control Respiratory compromise in high cervical lesion
Thoracic cord	Motor weakness below the lesion (usually upper limb preserved unless T1 involved) Sensory loss below the lesion with truncal sensory level Loss of sphincter control

8.3 Rheumatoid Arthritis

Rheumatoid arthritis (RA) is the most common inflammatory destructive joint disease. Besides its articular manifestations, patients with RA exhibit multiple extra-articular manifestations. The nervous system can be involved at varying degrees in patients with RA [9]. Both central and peripheral nervous system can be involved (Fig. 8.5). Central nervous system involvements can happen in the form of necrotizing vasculitis or as a result from cervical spine involvements and the development of atlantoaxial subluxation. Peripheral nervous system involvement can be primary due vasculitis or secondary to the joint deformities or compression from rheumatoid nodules. Also the nervous system can be involved secondary to drug side effect.

The approach to patients with rheumatoid arthritis and atlantoaxial subluxation as well to patients presenting with neuropathy will be discussed (Fig. 8.6).

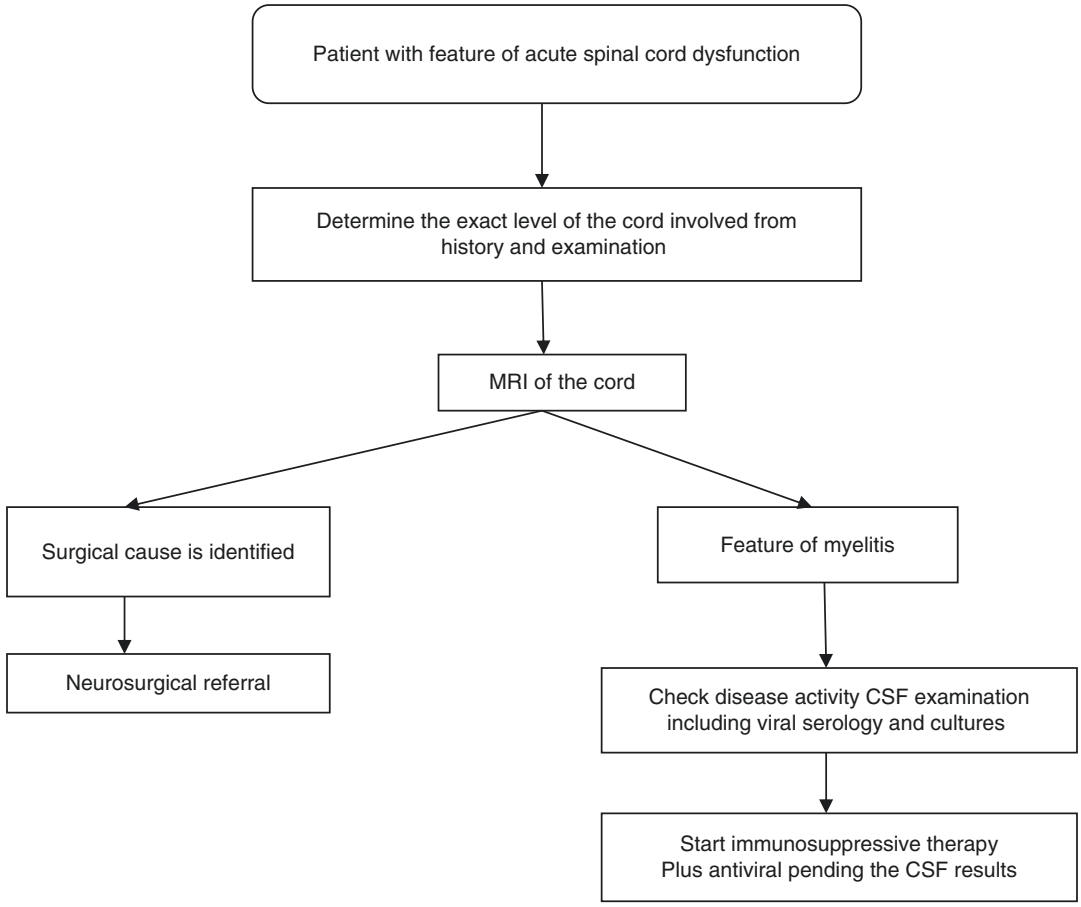

Fig. 8.4 Approach to patient with suspected myelopathy

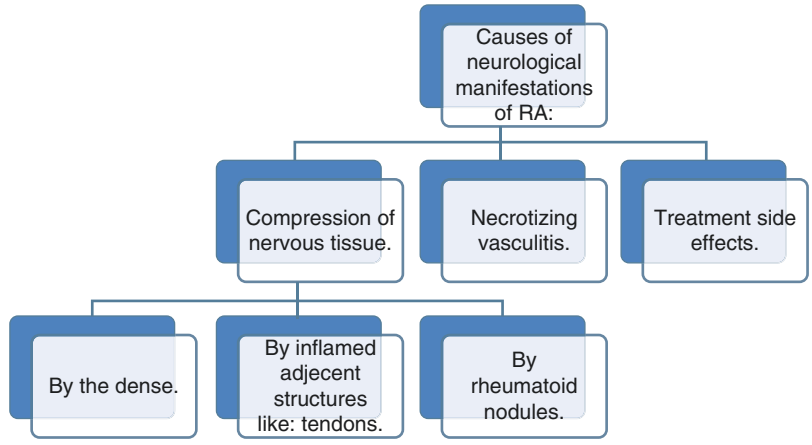

Fig. 8.5 Causes of neurological manifestations of RA

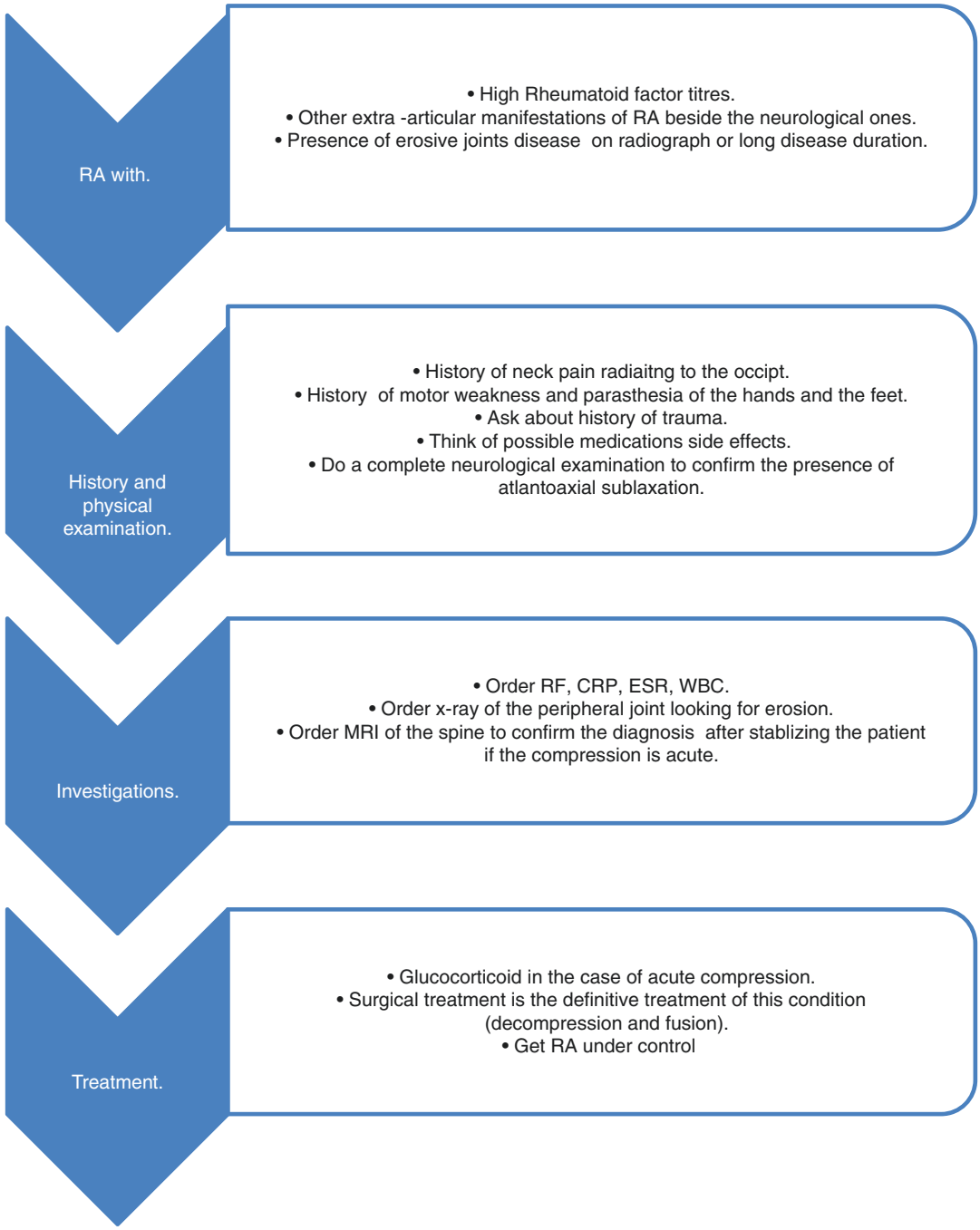

Fig. 8.6 Approach to RA patient with suspected atlantoaxial subluxation

8.3.1 Atlantoaxial Subluxation

1. RA is the most common inflammatory disorder affecting the cervical spine. The involvement of cervical spine is related to active erosive RA and early age of onset [10].
2. Craniocervical complications arise in 30–50% of patients with RA more than 7 years; however, the atlantoaxial subluxation with myelopathy develops in 2.5% of RA more than 14 years [11].
3. Cervical spine involvements by RA include atlantoaxial subluxation, cranial settling, subaxial subluxation, or combinations of the above.
4. Atlantoaxial subluxation is the most common type of cervical spine affection.
5. The subluxation can be anterior, posterior, or lateral, and the anterior subluxation is the most common type that results from laxity of the primary and secondary ligamentous structures.
6. It is very important to recognize this particular complication especially in neurologically normal patients, as early recognition and treatment will improve outcome.
7. Patients with atlantoaxial subluxation can be asymptomatic, or more commonly involve complaints of neck pain. Patients may present with occipital neuralgia, facial pain, ear pain, or pain in the suboccipital region.
8. In cases where cord compression already developed, patients would present with weakness, sensory symptoms related to the cord compression, as well as loss of sphincter control. *(When you deal with any RA patients presenting with any of the above symptoms, consider atlantoaxial subluxation).*
9. Detailed neurological examination is mandatory with careful evaluation for signs of myelopathy.
10. In order to prevent the development of neurological sequels, an evaluation for possible atlantoaxial subluxation radiologically is mandatory for any patient with RA at presentation and periodically thereafter and prior to any surgical procedures.
11. If atlantoaxial subluxation is suspected, besides assessing the disease activity with DAS-28 score, for example (see Chap. 1), and peripheral joint X-ray, the status of the cervical spine should be assessed. Plain X-ray that includes lateral, anteroposterior, open mouth odontoid views and lateral flexion-extension dynamics is necessary to assess joint stability.

More advanced imaging is required for patients with neurological symptoms to assess multilevel disease. MRI is better than CT scan to evaluate the neurological structures as well as to provide better look at the ligamentous structures.

The mainstay of treatment is early surgical intervention before the onset of severe neurological dysfunction, appropriate and aggressive disease-modifying therapy to control the disease activity, and adequate rehabilitation services to optimize neurological outcome.

8.3.2 Neuropathy

Neuropathy in patients with RA can result from nerve compression or secondary to vasculitis. When RA patients present with symptoms of mononeuropathy, it is essential to differentiate between neuropathy related to nerve compression and vasculitis as the treatment will be different.

Take appropriate history related to neurological complaints. The onset of symptoms, progression, and whether there is sensory and/or motor deficits should be checked. Check if the symptoms are all related to one nerve or multiple nerves (mononeuritis multiplex). Assess RA activity, severity with the presence of erosions on X-rays, functional decline, duration, and medications used for RA. On examination, try to identify the deficit and if you can which nerve is involved (Table 8.8). Examine all other peripheral nerves to assess whether it is a single or multiple processes. Examine the activity of RA and

Table 8.8 Things to look for in common nerve involvements

Nerve	Motor symptoms	Sensory symptoms	Notes
Radial nerve	Wrist drop due to weakness of extensors of the wrist and the fingers. Loss of elbow extension if the upper third of the nerve is affected	Loss of sensation over the anatomical snuff box	Flex the elbow, pronate the forearm, and extend the wrist and the fingers to demonstrate wrist drop if it is not clear
Median nerve	Loss or weakness of the thumb abduction mainly Loss of wrist flexors	Loss of sensation over the palmer aspect of the thumb, index, middle, and lateral half of the little finger and the corresponding part of the palm if it is affected above the wrist	Pen touching test for lesion at the wrist. Ochsner clasping for lesion in the cubital fossa
Ulnar nerve	Weakness of most of the small muscles of the hand which will lead clawing of the hand	Loss of sensation over the little finger the medial half of the ring finger	Froment's test can be used to demonstrate loss of thumb adduction in ulnar nerve affection
Femoral nerve	Weakness in knee extension	Loss of sensation over the medial aspect of the thigh and the leg	
Sciatic nerve	Weakness of all the muscles below the knee that results mainly in foot drop and weakness of the hip flexion	Loss of sensation over the posterior aspect of the thigh, all the aspects of the lower limb below the knee except for the medial aspect of the leg	It divides into the common peroneal nerve and the posterior tibial nerve at the level of the knee
Common peroneal nerve	Foot drop	Usually minimal sensory loss over the lateral aspect of the dorsum of the foot	Loss of eversion is another feature

assess deformity. Look for rheumatoid nodules. Nerve conduction studies (NCS) and electromyogram (EMG) will help to establish the diagnosis of nerve involvements. If it develops in a site of entrapment, e.g. carpal tunnel for median nerve and tarsal tunnel for posterior tibial nerve, the condition is most likely to be related to nerve compression rather than vasculitis and requires supportive care and may require surgical intervention. Neuropathy that develops in a non-compression site is related to vasculitis. Those patients may exhibit mononeuropathy or features of multiple nerve involvement (mononeuritis multiplex). Usually it happens in the setting of active erosive disease and with seropositive disease. Treatment with steroid should be initiated together with the use of disease-modifying therapy to achieve disease control. Patients with RA can also present with features of peripheral neuropathy that can be sensory, sensory-motor, or motor neuropathy. The approach to such patients will be discussed in the next part.

8.4 Neuropathy with Skin Rash

When neuropathy either mononeuropathy, mononeuritis multiplex, or peripheral neuropathy occurs in a setting of skin rash, vasculitis should be considered as an etiological factor. Vasculitis is a condition that results from inflammation of the blood vessels. It can be primary or secondary to other conditions, e.g. connective tissue disease, infection (hepatitis C), hypersensitivity reaction, and paraneoplastic condition. (See Chap. 19 for full details about vasculitis.)

Figure 8.7 shows the diagnostic approach to patient with neuropathy and rash.

8.4.1 Tips in History and Physical Examinations

1. Identify the nature of neuropathy (sensory, sensory-motor, motor, mono, multiple versus peripheral).

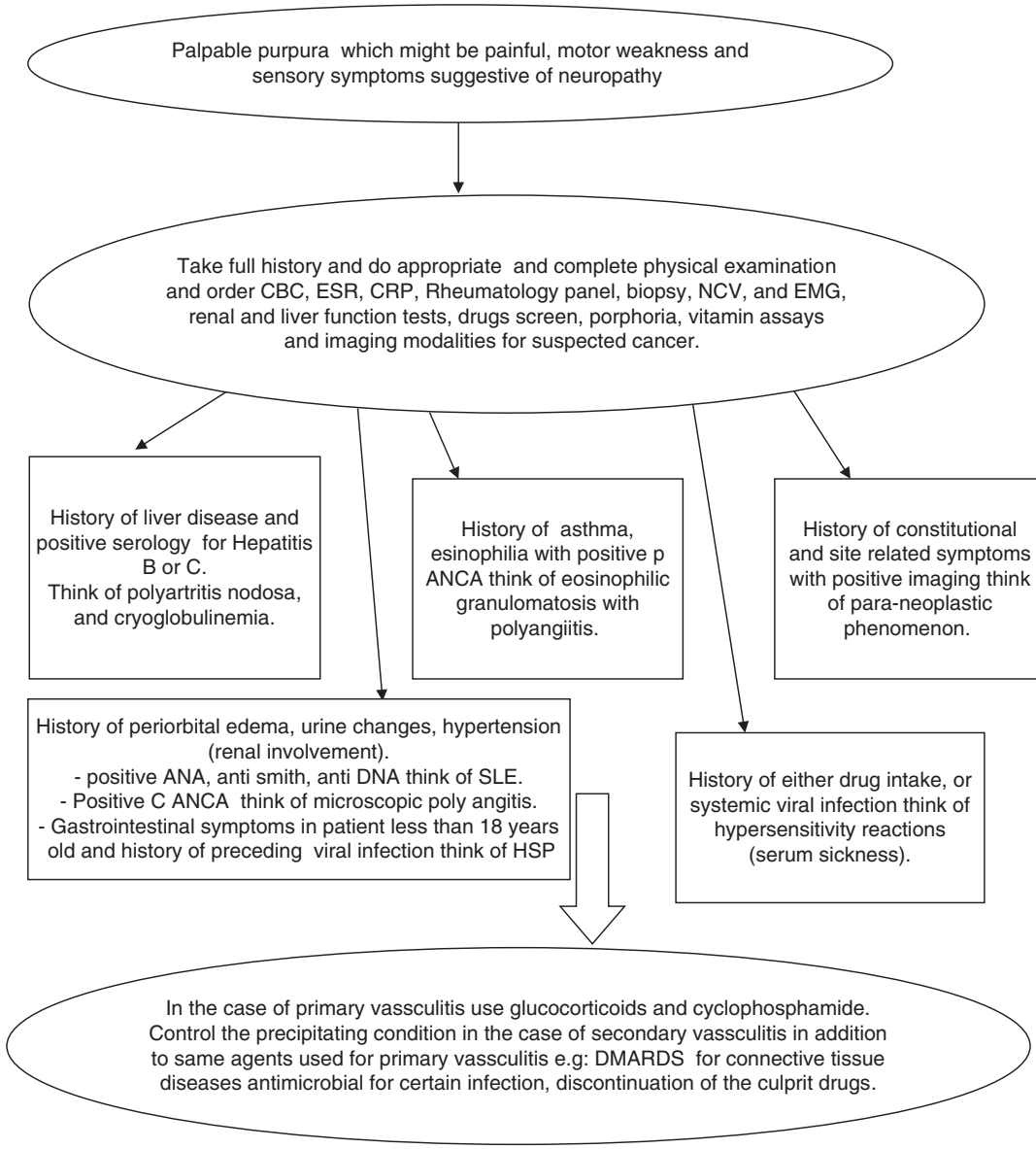

Fig. 8.7 Approach to patient with rash and neuropathy

2. Symptoms of asthma like shortness of breath may suggest Churg-Strauss syndrome, *eosinophilic granulomatosis with polyangiitis [EGPA]*, or *allergic granulomatosis*.
3. Symptoms of renal involvement like periorbital oedema and hypertension may suggest ANCA-associated vasculitis including microscopic polyangiitis and Henoch-Schonlein purpura (HSP).
4. The age of the patient may give a clue since HSP is rare in a patient who is older than 18.
5. Associated gastrointestinal symptoms are important findings in HSP.
6. Symptoms of liver involvement are essential to be established as hepatitis C is associated with cryoglobulinaemic vasculitis and hepatitis B is strong risk factor for polyarteritis nodosa.

7. History of recent use of drugs or recent systemic viral infection that can be associated with hypersensitivity reactions.
8. Symptoms of connective tissue diseases like SLE, RA, and Sjogren disease are suggestive for a secondary cause of vasculitis.
9. Constitutional symptoms can be associated with rheumatologic diseases or solid tumours like lung cancer or lymphoma in what is known as paraneoplastic phenomenon.
10. Family history of similar presentation as some genetically determined disease, e.g. porphyria can present with skin rash and neuropathy.
11. High risk factors, e.g. multiple sexual partner and IV drug abusers, may suggest infections like HIV and/or syphilis.
12. The patient's job is important to exclude exposure to certain toxins.
13. Pay attention to the patient's nutritional status as vitamin deficiencies can lead to neuropathy and rash that might be mistaken for vasculitis.
14. Thorough systemic examination is mandatory to help narrow your differential diagnosis.

8.4.2 Laboratory Investigations and Imaging Modalities

1. CBC, C-reactive protein, and ESR to assess the presence of inflammatory condition in the body like vasculitis and connective tissue disease.
2. NCS and EMG help to categorize the type of neuropathy [12].
3. Nerve biopsy is the ultimate gold standard to diagnose vasculitis as a cause of neuropathy [12].
4. Rheumatologic autoantibody profile like ANA, ANCA, RF, anti-DNA, anti-RO, anti-Jo, and anti-CCP will help identify if vasculitis were secondary to connective tissue disease (see for details in Chap. 4).
5. Assess the patient's liver, renal, thyroid, as well as glucose levels to help narrow the differential diagnosis.
6. Serology for hepatitis B and C, HIV, and cryoglobulin level and VDRL to exclude secondary syphilis.
7. Vitamin assays like B12, folate, and E to exclude vitamin deficiency as the cause of patient presentation.
8. Toxicology screen looking for drug toxicities.
9. Look for porphyrins according to which subtype you suspect in the patient.
10. Use the different imaging modalities to look for solid tumour or lymphoma if you think they are the culprit.

8.4.3 Treatment

1. Immunosuppressive therapy with glucocorticoids is the mainstay of treatment. Depending on disease severity, the addition of cyclophosphamide should be considered to minimize the risk of relapse, morbidity, and mortality [13].
2. Control the precipitating condition in the case of secondary vasculitis in addition to same agents used for primary vasculitis, e.g. DMARDs for connective tissue diseases, antimicrobial for certain infection, discontinuation of the culprit drugs, etc.

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9 Diagnostic Approach to Proximal Myopathy

Hani Almoallim, Hadiel Albar, and Fahtima Mehdawi

9.1 Introduction

Patients with muscle disorders are a diagnostic challenge to physicians, because of the various ways of presentation. A comprehensive approach should be followed systematically in order to reach the correct diagnosis. Weakness is a common symptom among patients including those with central or peripheral nervous systems diseases and those with muscular and/or neuromuscular diseases. Muscle weakness is not only a regular finding in rheumatologic diseases, but in inflammatory myopathies as well. This chapter focuses on skills needed to approach any patient that presents with weakness, specifically proximal myopathy.

In addition to IIM and CTD, proximal myopathy has a wide range of differential diagnosis including drugs, alcohol, thyroid disease, hereditary myopathies, malignancy, and infections. Clinical assessment should aim to distinguish proximal myopathy from other conditions that present with weakness. Patients with proximal myopathy who need prompt attention, like those with cardiac, respiratory, or pharyngeal muscle involvement, should be identified early and quickly.

In this chapter, the aim is to provide a systematic diagnostic approach to adult patients presenting with proximal myopathy. This is an essential step to establish the correct diagnosis in order to conduct the appropriate management.

9.1.1 Objectives

By the end of this chapter, you will be able to:

1. Identify true muscular weakness by history and physical examination.
2. Construct diagnostic approach to proximal myopathy.
3. Manage a case of inflammatory myopathy.

9.2 Clinical Presentation of Proximal Myopathy

Myopathies are diseases that primarily affect the muscles and are usually characterized clinically by weakness, fatigue, or stiffness. Symmetrical proximal muscle weakness, wasting, normal sensation, and normal stretch reflexes are classical findings in patients with myopathies particularly in IIM and myopathies associated with

H. Almoallim
Medical College, Umm Al-Qura University (UQU), Makkah, Saudi Arabia

H. Albar
King Faisal Specialist Hospital & Research Center, Jeddah, Saudi Arabia

F. Mehdawi (✉)
Doctor Soliman Fakeeh Hospital, Jeddah, Saudi Arabia

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CTD. Aching muscle cramps can also occur. Clinical presentations sometimes can be complex, hence the need to follow a comprehensive approach to weakness.

9.2.1 History

Weakness is a common complaint with different interpretations by patients. The aim of history taking is to try to define what the patient means by "weakness." The generalized feeling of tiredness and/or fatigability is usually associated with systemic diseases like congestive heart failure, cirrhosis, and anemia. In these patients there is usually a long-standing history of a chronic disease like ischemic heart disease and/or chronic liver disease. The activity in these patients is usually limited by dyspnea, chest pain, joint pain, fever, and/or depressed mood. Long-standing chronic diseases can lead to cachexia with severe muscle atrophy, wasting, and consequent generalized weakness. The sense of generalized tiredness and/or fatigability should be differentiated from the complaints of generalized body aches and pains in patients with fibromyalgia. The generalized body aches and pains have their own approach that is beyond the scope of this chapter.

Once it is established that the weakness is not a consequence of a non-muscular, generalized, systemic disease and there are no generalized body aches and pains, then it is essential to find out whether this weakness is localized to certain areas. Hemiparesis (weakness affecting upper and lower limbs on the same side of the body) should direct the history towards central nervous system diseases like stroke. Paraparesis (weakness of both lower limbs) and/or quadriparesis (weakness of the four body limbs) should limit the differential diagnosis to spinal cord and/or cerebral cortex and/or brain stem diseases. Monoparesis (weakness of one limb) is usually a disease of a peripheral nervous system including disc prolapse causing radiculopathy by compressing on a spinal nerve to peripheral nerve involvement in vasculitis. Figure 9.1 is a schematic that should be fol-

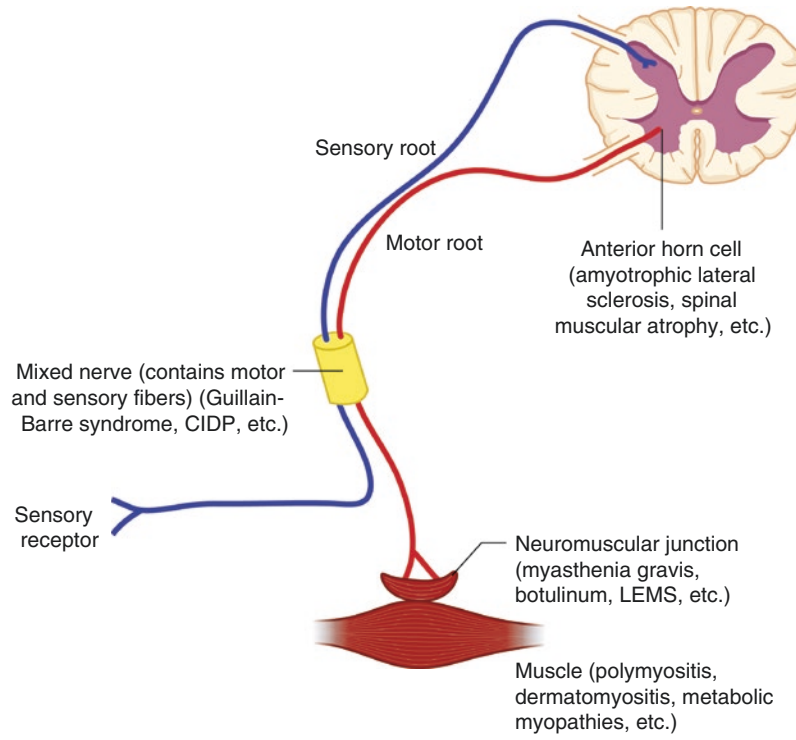

Fig. 9.1 The four anatomic stations underlying lower motor neuron weakness

lowed while obtaining history and examining patients with weakness.

Symmetrical weakness occurs in large number of diseases including inflammatory myositis, inherited muscle dystrophy, endocrine disorders, and neuromuscular junction diseases. In symmetrical and diffuse weakness, it is important to know if the weakness is proximal or distal. There are several clues in the history that point towards proximal myopathy (muscles of the trunk, shoulders, and thighs). The patient will have difficulty combing hair, difficulty climbing up the stairs, difficulty standing from a sitting position, and/or difficulty in getting up from bed. In distal myopathy, the patient will complain about difficulties while performing fine work like handling the objects by hands and driving. These patients may also present with wrist drop or foot drop. It must be noted that there are diseases affecting proximal muscles in an asymmetrical fashion like diabetic amyotrophy as well as diseases with both proximal and distal muscle weakness in symmetrical and/or asymmetrical fashion like in systemic lupus erythematosus (SLE) with myopathy and vasculitis, respectively. Inclusion body myositis, a rare IIM in elderly patients, presents with both proximal and distal myopathies simultaneously. The focus should be simply to identify the localization of the weakness, and then with comprehensive approach to history taking like what is described in Chap. 1, the differential diagnosis should be easier to obtain.

There are special characters for weakness that signify certain alerts to specific diagnoses. Ascending pattern of weakness should direct the attention towards demyelinating diseases like acute inflammatory demyelinating polyneuropathy (Guillain-Barre syndrome). Descending patterns that start centrally and proceed progressively to distal areas should direct the attention to infections like botulism. The weakness that is worsened by repetitive movement at the end of the day with double vision and drooping eyelids should direct the attention towards neuromuscular disorders like myasthenia gravis.

An extensive review of rheumatologic symptoms should follow; this was outlined thoroughly in Chap. 1. Detailed history of joint pain, skin rashes, fever, recent infections, bleeding tendencies, history suggestive of malignancies, and/or drug history (particularly statins and glucocorticoids) should all be obtained. Endocrine disorders should also be ruled out by reviewing common symptoms like neck swelling, diarrhea/constipation, and heat/cold intolerance. Further details are found below. Detailed family history should be obtained as there are several rare hereditary myopathies that run in families (see below). A family history may also be present in other causes of weakness including dermatomyositis, polymyositis, and potassium-related paralyses. A thorough neurological history is important. Sensory deficits, impaired level of consciousness, speech or visual defect, seizure, and sphincter control should be obtained from patients with weakness. In addition, social history will further help narrow the diagnosis; thus, history of smoking, alcohol, illicit drug use, and exposure to toxins like organic phosphorus should be obtained.

There are life-threatening symptoms associated with IIM like dysphagia and nasal regurgitation resulting from skeletal muscle involvement of the pharynx and upper third of the esophagus and/or chest pain and heart failure from cardiac muscle involvement. These should be identified promptly as they need urgent medical intervention. Breathlessness might suggest respiratory muscle involvement. Respiratory failure can occur in some diseases like Guillain-Barre syndrome, myasthenia gravis, and amyotrophic lateral sclerosis. Table 9.1 summarizes some of the common symptoms of diseases presenting with weakness.

9.2.2 Physical Examination

The physical examination is an objective confirmation of the distribution and the severity of the muscle weakness. The first step is to observe the patient doing certain activities like raising arms, standing up from a chair, or writing. This will determine if the weakness is proximal, distal, or combined. A comprehensive neurological examination should follow with higher function examination and examination of cranial nerves. You may find ptosis, ophthalmoplegia, and/or poor gag reflex in myasthenia gravis patients. The next

Table 9.1 Associated symptoms presented with muscle weakness

Disease	Symptoms
Dermatomyositis	Skin rash, e.g., upper eyelids (*heliotrope rash*), erythema of the knuckles (*Gottron rash*), anterior chest (*v sign*), or back (*shawl sign*) Weight loss, anorexia, bleeding tendency, abnormal vaginal bleeding, chronic cough (malignancy).
Inclusion body myositis	Frequent falls, dysphagia
Myasthenia gravis	Squint, dysphagia Compression symptoms of thymoma (cough, SOB)
Lambert-Eaton syndrome	Autonomic symptoms, e.g., dry mouth, impotence History of lung cancer
Mixed connective tissue disease and overlap syndrome	Other connective tissue disease's symptoms; arthritis, skin rash
Rhabdomyolysis	History of trauma, seizure, dark urine

step is performing detailed motor examination. This starts with inspection of the muscle bulk and determining whether if it is normal, atrophied, or hypertrophied. In addition to observation for any fasciculation that might suggest LMND, tone, power, reflexes, and gait should also be examined. Clear distinctions between signs of upper motor neuron disease (UMND) (hypertonia, hyperreflexia, and upgoing plantar response) and signs of LMND (for lesions from the anterior horn cell until muscles) (hypotonia, normal or low or absent reflexes, and equivocal or downgoing plantar response) should be made. Usually with signs of UMND, patients may present with hemiparesis, paraparesis, and quadriparesis or with variable locations in the central nervous system as in multiple sclerosis. Since weakness is a prominent sign present in both UMND and LMND, it is essential to assess the power and document the degree of weakness, as well as for proper future monitoring of this disease while on

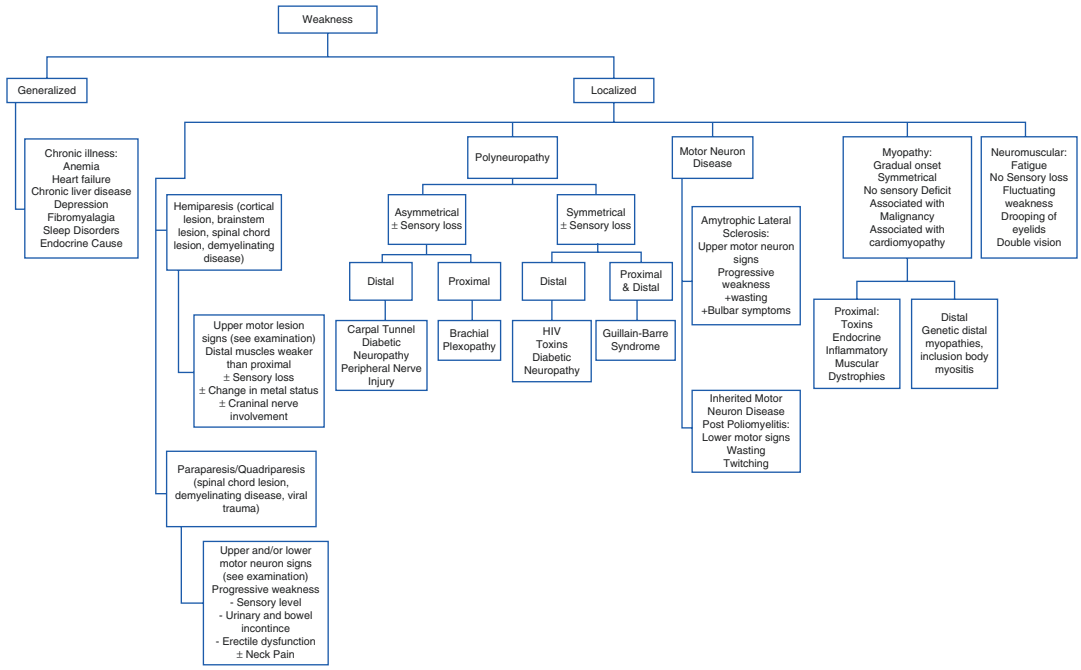

Fig. 9.2 Clinical approach to weakness

treatment. Clinical approach to weakness is illustrated in Fig. 9.2. Grades of power are shown in Table 9.2.

Reflexes are usually intact in proximal myopathy, and any signs of abnormal reflexes suggest neurological cause. The last step in the neurological examination is examining sensory level. For example, in peripheral neuropathy loss of sensation is parallel to the weakness. After comprehensive neurological examination, a search for extra-muscular signs should follow. The examination of the face, hands, lower limbs, chest, and abdomen is important, since any abnormality can help in the differential diagnosis. Few signs of common diseases presenting with myopathy are shown in Table 9.3.

There are certain associations essential to be recognized while performing the physical examination. These associations may easily reveal the diagnosis without spending efforts on unnecessary investigations. Changes in the mental status, for example, with muscle weakness may indicate electrolyte imbalance. Cardiovascular assessment may reveal signs of cardiomyopathy, which is associated with some inflammatory and hereditary myopathies. Pulmonary assessment may reveal crackles of interstitial lung disease associated with some inflammatory myopathies. Lymph node examination is essential as malignancies are associated with a significant number of IID including lymphoma. Small joint examination is essential as well to detect any tenderness and/or swelling suggestive of rheumatoid arthritis (RA) and/or systemic lupus erythematosus (SLE)-associated myopathies. Skin examination is helpful: signs like Gottron's papules in dermatomyositis, erythema nodosum in sarcoidosis, and skin bronzing in adrenal insufficiency (see Dermatology chapter). Also a search for any signs possibly related to underlying malignancy like finger clubbing, fecal occult blood, and hepatosplenomegaly should be made. Table 9.4 lists findings with their most likely definitive diagnosis. The vital signs should be measured to exclude any life-threatening problems. Postural hypotension can be seen in autonomic neuropathy, e.g., in diabetes mellitus and Lambert-Eaton syndrome. Also, body mass index (BMI) should be measured to assess if the patient is underweight suggestive of a malignant disease process.

Table 9.2 Grades of power

5	Normal muscle strength, full resistance
4	Reduced, but still against resistance
3	Further reduced, only against gravity
2	Only moves with gravity
1	Flicker of movement
0	No movement

9.3 Differential Diagnosis of Proximal Myopathy

Several conditions cause proximal myopathy. Myopathies can be classified into idiopathic or acquired. The clinical history and physical exam-

Table 9.3 Common signs with specific myopathies

	Head and neck	Hands	Chest and abdomen
Dermatomyositis	– Upper eyelids (heliotrope ash) – Lymphadenopathy or any mass (malignancy)	– Erythema of the knuckles (Gottron rash) – Clubbing (lung cancer)	– Erythema of anterior chest (v sign), or back (shawl sign) – Axillary lymphadenopathy, breast lump or abdominal mass
Overlap syndrome and MCTD	– Fish mouth, pinched nose (in scleroderma) – Malar rash, discoid lupus (in SLE)	Sclerodactyly, Raynaud's (in scleroderma). Arthritis (in SLE)	Signs of lung fibrosis and serositis
Lambert-Eaton syndrome	– Dry mouth and skin (autonomic neuropathy)	– Clubbing (lung cancer)	– Chest finding if there are complications for lung cancer e.g. pleural effusion, lymphadenopathy
Myasthenia gravis	SVC syndrome (thymoma)	–	–

Table 9.4 Correlation between findings and suggestive diagnoses of weakness

Findings	Suggestive diagnosis
Acute focal weakness decreased muscle power, hyperreflexia, hypertonia, positive Babinski sign, ± sensory deficit, ± loss of bladder/bowel control	Stroke, or spinal cord injury
Diffuse or localized peripheral weakness, muscle atrophy, fasciculations, hypotonia, loss of reflexes	Lower motor neuron disease
Asymmetrical distal weakness, muscle atrophy, hypotonia, loss of reflexes, sensory deficit "Glove and stocking" distribution	Peripheral neuropathy Diabetic neuropathy
Acute onset of combined weakness (ascending), fasciculations, loss of deep tendon reflexes, sensory deficit	Guillain-Barre syndrome
Facial weakness, fatigability, ptosis	Myasthenia gravis
Symmetrical weakness of proximal muscles, muscle wasting, with some types, muscle tenderness, normal reflexes, no sensory level	Proximal myopathies
Symmetrical distal weakness, with myotonic contractions	Myotonic dystrophy
Cardiomyopathy, and proximal muscle weakness	Inflammatory myopathies, hereditary myopathies
Mental status changes with proximal weakness	Myopathy-inducing electrolyte disorder (calcium or magnesium)

ination are essential in identifying the presence of a myopathy and narrowing down the differential diagnosis. In adults a major cause of myopathy is medication like statins [1]. Myopathy due to endocrine causes, for example, thyroid disease, Cushing disease, and adrenal diseases, should be diagnosed promptly because treating the primary condition will result in resolution of the myopathy [2]. Inflammatory diseases typically affect older adults including both proximal and steroid responsive disorders like polymyositis and dermatomyositis and distal and proximal myopathies with less response to steroid like inclusion body myositis. Rheumatologic disorders causing weakness, such as SLE and RA, can occur in young and elderly persons. Figure 9.3 summarizes the differential diagnosis of proximal myopathy. Further details about these disorders will be mentioned briefly in this section.

9.3.1 Toxins- and Drug-Induced Myopathy

Considering toxin and drug exposure in the differential diagnosis of every single patient presenting with proximal myopathy is essential. The timely diagnosis allows for optimum recovery. There are many drugs that cause proximal myopathy, such as lipid-lowering drugs, glucocorticoids, antimalarial drugs, antiretroviral drugs, alcohol, and cocaine [1]. There is an acute presentation in drug-induced myopathy. Statin therapy associated with muscle problems is seen in approximately 10–25% of patients treated in clinical practice. Statin-induced myopathy can present as myalgia and myositis or sometimes is severe enough to cause rhabdomyolysis. The average onset of statin-induced myopathy is weeks to months. The only treatment is discontinuation of statin which results in resolution of muscle symptoms [3]. Glucocorticoids are a common cause of muscle weakness. Long-term use of glucocorticoids results in an insidious onset of proximal myopathy. Muscle enzymes are usually normal. Relief of the weakness occurs with lowering the dose of glucocorticoids [4]. Alcohol-induced myopathy generally follows a history of long-standing alcohol intake and/or consumption of large amount of alcohol. Table 9.5 summarizes pertinent features of the common causes of toxin- and drugs-induced myopathy.

9.3.2 Endocrine Myopathy

Hormones play an essential role in body metabolism. Deficiency or excess in most hormones will affect muscle metabolism. In endocrine-related muscle diseases, the presentation is more likely to be fatigue than true muscle weakness. The

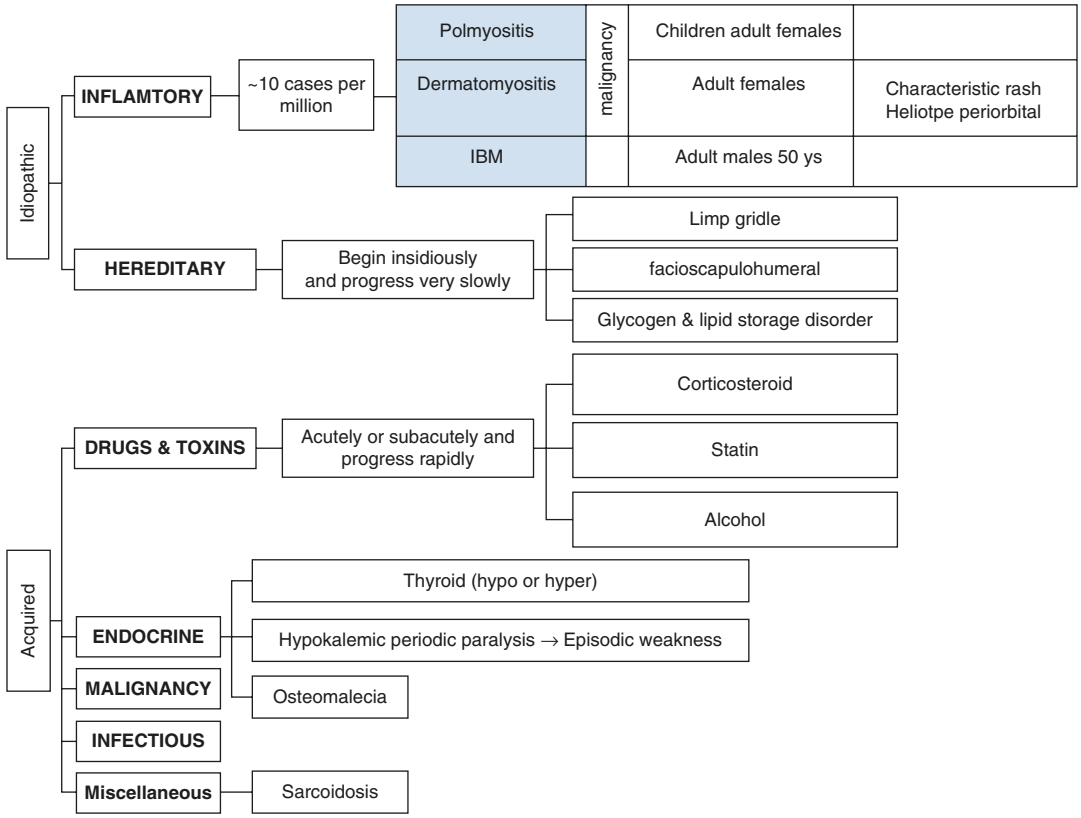

Fig. 9.3 Differential diagnosis of proximal myopathy

Table 9.5 Features of toxin- and drug-induced myopathy

Toxin/drug	Effect on muscle	Characteristics	Management
Alcohol	Large consumption of alcohol will cause direct muscle necrosis	Acute and chronic presentation Calf muscles Tenderness Swelling Generalized muscle cramps	Resolution with cessation of alcohol
Glucocorticoid	Direct catabolic effect Chronic use of prednisone at a daily dose of ≥30 mg/day Risk increases in elderly and malignancy	Proximal lower muscles Progressive Accompanied with atrophy No tenderness	Improved muscle strength within 3–4 weeks after lowering the dose
Statin	Varying degrees of muscle necrosis Severe complications such as rhabdomyolysis and myglobinuria Dose and duration dependent	Myalgia Malaise Muscle tenderness Muscle pain may be related to exercise	Muscle weakness will resolve with decreasing the dose or cessation of the statin

serum CK level is often normal (except in hypothyroidism). Nearly all endocrine myopathies respond to treatment [5].

Abnormalities in thyroid hormone can lead to a wide range of muscle diseases. For example, hypothyroid patients have frequent muscle complaints such as cramps, pain, and weakness. Almost one third of hypothyroid patients present with proximal myopathy. They present mainly with shoulder and hip muscle weakness. Treatment by thyroid replacement usually leads to resolution of symptoms and laboratory abnormalities [6]. Proximal myopathy is a very common presentation in hyperthyroid patients and may be the only symptom of the disease. Bulbar, respiratory, and even esophageal muscles may be affected, causing dysphagia and aspiration. Other neuromuscular disorders may occur in association with hyperthyroidism including hypokalemic periodic paralysis, myasthenia gravis, and a progressive ocular myopathy. Because proximal weakness is a presenting sign of hyperthyroidism and hypothyroidism, checking thyroid-stimulating hormone (TSH) is essential. Adrenal insufficiency causes muscle fatigue rather than true muscle weakness. Conn's syndrome can lead to proximal myopathy which is related to hypokalemia [7]. Pituitary disorders like acromegaly if long-standing can cause myopathy [8]. Neuromuscular complications of diabetes mellitus (DM) are mainly due to neuropathy which can be presented as asymmetrical proximal weakness. Ischemic infarction of the thigh muscles can present with severely uncontrolled diabetes [9] (see Chap. 21 (Diabetes and Rheumatology)). Table 9.6 summarizes pertinent findings of myopathies caused by endocrine disorders.

9.3.3 Dystrophic Myopathies

Dystrophic myopathies are a distinct group of inherited muscle disorders that generally present chronically. They are slowly progressive in nature resulting in muscle atrophy with exception of metabolic myopathies, where symptoms on occasion can be precipitated acutely. Each type of dystrophic myopathy has some characteristic structural abnormalities on muscle immunohistochemistry. Congenital myopathies present predominantly in the perinatal period. Some can present later in childhood, and these children may have a milder course of the disease. Multiple gene defects can give rise to similar clinical and ultrastructural phenotypes; thus, muscle immunohistochemistry should be tested to reach a final diagnosis. Table 9.7 shows the features of dystrophic myopathy [10].

9.3.4 Inflammatory Myopathies

Inflammatory myopathies are a group of complex diseases of unknown etiology. The most common types are dermatomyositis, polymyositis, and inclusion body myositis. Table 9.8 represents the current classification for IIM. The incidence of inflammatory myopathies is 5–10/million cases per year [11]. These diseases are characterized by progressive muscle weakness with extramuscular organ involvement and high serum muscle enzymes. Generally there is a female predominance 2:1, but in inclusion body myositis, the opposite is seen as it is three times more common in males [12]. The main pathophysiology is related to autoimmunity, though recent studies show that the mechanism of muscle damage is multiple and complex [13].

The clinical features of inflammatory myopathy in general are muscle weakness occurring within weeks to months. The distribution of weakness is mainly proximal in dermatomyositis and polymyositis, but as the disease progresses, distal muscles may become affected. On the other hand, distal muscle weakness is the initial presentation of inclusion body myositis. The onset of polymyositis is usually after the second decade of life. Dermatomyositis has two peaks, the first peak at around 10–15 years of age and the second peak between 40 and 70 years. Inclusion body myositis occurs after the age of 50. Table 9.9 summarizes the pathological and clinical features of the most common IID.

Dermatomyositis is known for its cutaneous manifestations. The rashes can precede, follow, or occur simultaneously with the myopathy.

Table 9.6 Pathophysiology and characteristics of endocrine myopathies

Endocrine disease	Pathophysiology	Characteristics
Hypothyroidism	Exact mechanism is unknown T4 is essential for metabolism Decrease in T4 leads to decrease in glycogenolysis which leads to impaired muscle function	Proximal myopathy occurs in one third (shoulder and hip girdle muscles) Muscle cramps, stiffness, pain are common complaints More common in women Muscle hypertrophy is a rare sign (Hoffman's sign) Delayed deep tendon reflexes
Hyperthyroidism	Exact mechanism is unknown Impaired muscle function may be due to increased cellular metabolism and energy utilization, increased catabolism and protein degradation, and inefficient energy utilization	Muscle weakness ± tenderness and atrophy in 60–80% of patients Presentation may be acute or chronic Two-thirds of patients with hyperthyroid myopathy report proximal weakness, mainly hip flexors and quadriceps Cramps are less common Atrophy is usually absent Bulbar symptoms may be present Associated with other neuromuscular diseases: Myasthenia gravis Periodic paralysis Progressive ocular myopathy
Hyperparathyroidism		25% of patients will have insidious onset of proximal myopathy, legs more than arms Atrophy is a common feature Fatigue, muscle pain, and hyperreflexia are common
Adrenal insufficiency		100% of patients present with weakness, but usually there is no objective proximal myopathy
Primary hyperaldosteronism		Weakness is a common complaint Weakness and paralysis are usually due to the hypokalemia
Cushing syndrome (see Glucocorticoid myopathy)		

Gottron's papules and heliotrope rash are pathognomonic features of dermatomyositis [14]. Dermatomyositis and polymyositis are also known to cause manifestations related to the cardiovascular system, respiratory system, and gastrointestinal system.

Patients diagnosed with IID tend to have a higher risk of developing malignancies. Patients with dermatomyositis or polymyositis have an increased risk of developing malignancy. Those with dermatomyositis are three to six times more likely and those with polymyositis are two to four times more likely than the normal population to develop ovarian, gastric, pancreatic, and lung cancer and non-Hodgkin lymphoma. Thus screening for malignancies is highly recommended in this population [15].

9.3.5 Myopathy Due to Infectious Disease

Infectious diseases may cause an acute presentation of weakness with muscle cramps, myoglobinuria, and rhabdomyolysis. Among the infectious causes, viral infections are the most

Table 9.7 Features of dystrophic myopathy

Type of myopathy	Distribution	Characteristic	Mode of inheritance
Duchenne	Proximal	Age of onset 3–5 years Weakness starts in the trunk Spreads to arms and legs Gower's sign Calf hypertrophy Wheelchair by ages 9–10 Cardiomyopathy Scoliosis/respiratory problems Cognitive impairment	X-linked
Becker's	Proximal	Age of onset 3–20 years Less severe than Duchenne	X-linked
Limb-girdle	Proximal	Age of onset 3–20 years Shoulder and hip muscles Low back pain Sparing of the face Cardiac involvement Contractures No cognitive impairment	AR/AD
Facioscapulohumeral muscular dystrophy (FSHD)	Proximal	Age of onset is variable (average 10–20 years) Infant form wheelchair by 9 years Severe facial weakness Inability to close eyes Inability to smile Weakness can involve shoulder and hips Early onset: Hearing loss, seizures, cognitive impairment	AD
Myotonic dystrophy	Distal	Age of onset is variable Most common adult-onset muscular dystrophy Type 1, type 2 Affects facial muscle, arms, legs Multisystem: Cardiac, cataract, sexual organs, cognitive impairment Excessive daytime sleepiness	AD

Table 9.8 Classification of idiopathic inflammatory myopathies

1. Primary idiopathic dermatomyositis
2. Polymyositis or dermatomyositis with malignancy
3. Juvenile dermatomyositis (or polymyositis)
4. Inclusion body myositis
5. Rare forms of idiopathic myositis
   - Granulomatous myositis
   - Eosinophilic myositis
   - Focal myositis
   - Orbital myositis

common. Myalgia is the most common symptoms, but can last up to 2–3 weeks. Usually myopathy due to viral infections is self-limiting, but severe cases may cause myoglobinuria and renal impairment.

Human immunodeficiency virus (HIV) is an important differential when approaching myopathy; the condition is often referred to as HIV polymyositis. HIV polymyositis can be a presenting manifestation of HIV infection or can occur in later stages. Patients with HIV polymyositis may present with asymptomatic elevation of CK levels, or as severe muscle tenderness and muscle weakness. HIV-related myopathy appears to have a better prognosis than idiopathic inflammatory myopathies. See the treatment section for how to manage HIV polymyositis.

Table 9.9 The pathogenetic mechanisms and clinical features of the most common IID

Condition	Pathogenesis	Age/sex	Clinical features	
Dermatomyositis	Humeral mediated process CD4 cells and B lymphocytes attack the vascular endothelium; result in necrosis of capillary and ultimately muscle atrophy	10–15 years 40–70 years F: M—2:1	Symmetrical proximal muscle weakness Pathognomonic: Heliotrope (purple) Periorbital edema; violaceous papules (Gottron's papules) or macules (Gottron's sign)	Both dermatomyositis and polymyositis: • 10% have interstitial lung disease (may lead to respiratory failure and death) • Increase rate of malignancy • Dysphagia, nasal regurgitation, and/or aspiration with increased age • Cardiac involvement in the form of myocarditis, conduction defects, and arrhythmias • Constitutional symptoms
Polymyositis	Cellular mediated process CD8 cytotoxic cells recognize MHC-1 on the muscle fiber, and this is the initiation of the necrotic process	Second decade of life F: M—2:1	Diagnosis by exclusion No skin manifestation Associated with HIV Histopathology is considered the most effective way to establish the diagnosis of PM	
Inclusion body myositis	The mechanism is poorly understood, but histopathology shows inflammatory cells surrounding myofibers and rimmed vacuoles, and some myofibers are attacked by CD8 cytotoxic cells	>50 years 3 times more in men	Insidious onset and progressive asymmetric distal weakness with wrist and index finger flexors weaker than extensors. Associated with early atrophy and poor response to steroid	

9.4 Diagnostic Approach

A thorough history and physical examination is the cornerstone to reach the diagnosis. Investigations should be tailored to screen for reversible causes of a myopathy (Fig. 9.4).

When the cause of muscle weakness is unclear, appropriate testing should be performed, and it is recommended to start with blood tests including electrolytes (potassium, calcium, phosphate, and magnesium), thyroid-stimulating hormone (TSH) level, alkaline phosphatase and 25 (OH) vitamin D level, and HIV [16].

9.4.1 Muscle Enzyme

The measurement of serum levels of muscle enzymes is of critical value for the evaluation and monitoring of muscular disorders. Creatine kinase (CK), lactate dehydrogenase (LD), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and aldolase are the serum muscle enzymes that are measured in clinical practice. In patients with suspected myopathy who do not demonstrate CK elevation, testing for aldolase can be helpful, but it is less sensitive and less specific [17].

Approach to high level of CK is demonstrated thoroughly in Table 9.10. It must be noted that CK elevation is, however, not specific to myopathy and further testing should be performed in a comprehensive approach. Table 9.11 shows the differential diagnosis to high CK level.

While diagnosing myocardial infarction, besides symptoms and abnormal ECG findings, there will be rise in CK-MB, the isoenzyme of CK, electrophoretically distinguished and high in concentration in the cardiac tissue. However, it is neither specific nor sensitive as troponins [18].

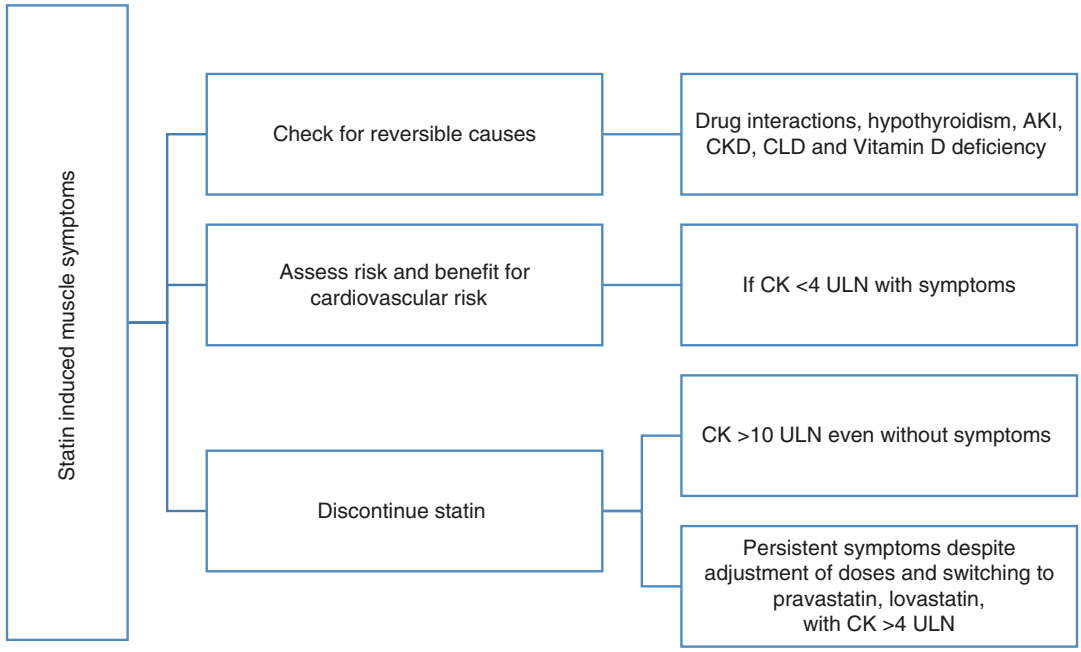

Fig. 9.4 Approach to statin-induced myopathy

CK might be falsely elevated secondary to ethnicity (can be high in Afro-Caribbean men), exercise (can remain elevated for up to 72 h), intramuscular injections, needle electromyography (EMG), medications, hypothyroidism, and motor neuron disease [16].

9.4.2 Rhabdomyolysis

Muscle injury due to vigorous exercise, medication, infection, and metabolic derangements can cause rhabdomyolysis. Severe myalgia, weakness, and red to brown urine due to myoglobinuria are classical initial presenting features. Rise of CK levels is typically seen after 2–12 h of injury and reaches its maximum within 24–72 h. A decline is usually seen within 3–5 days of cessation of muscle injury. Myoglobinuria is present in 50–75% of patients at the time of initial evaluation. Thus it is recommended to perform routine dipstick urine analysis in any patient with extremely elevated CK level and myopathy. There are serious metabolic derangements that complicate this massive muscle destruction in the body. Electrolyte imbalance and acute renal failure are serious examples.

9.4.3 Other Tests

In addition to CK, to diagnose rheumatologic myopathy, erythrocyte sedimentation rate (ESR) C-reactive protein (CRP), antinuclear antibody assay (ANA), rheumatoid factor, anti-double-stranded DNA, antiphospholipid antibodies, and anti-centromere antibodies should be ordered. In case of inflammatory myopathy, check for anti-Jo1 antibody, directed against histidyl-tRNA synthetase. Recognition of anti-Jo1 syndrome is important because such patients can develop extra-muscular features, such as interstitial lung disease, Raynaud's phenomenon, and arthritis [19].

Table 9.10 Approach to high CK level

Episodic Range from normal to rhabdomyolysis	Mild 3–four-fold ULN	High 100 fold ULN
Endocrine Hypothyroidism Hyperthyroidism Cushing's syndrome Acromegaly Electrolyte imbalance	*Drugs* Antimalarial, cholesterol-lowering drugs (statins), cocaine, alcohol, colchicine → 10- to 20-fold	*Rhabdomyolysis* Acute, massive muscle injury due to: Trauma, seizures, electrolyte imbalances, infections The degree of myoglobinuria might Correlate with the risk of acute renal failure CK levels decrease rapidly to normal after managing the cause
Metabolic myopathies Glycogen and lipid storage disease Carnitine palmitoyl transferase (CPT) Muscle phosphorylase deficiency	*Systemic vasculitis* Polyarteritis nodosa Wegener's Behçet's disease Sarcoidosis	
	Connective diseases Rheumatoid arthritis Systemic lupus erythematosus Sjögren's syndrome Scleroderma Specific autoantibodies anti-U1 RNP and anti-PM/Scl	*Infectious myopathies* Viral (EBV, HIV), bacterial, mycobacterium, fungal, parasitic
Periodic paralysis Primary hypokalemic periodic paralysis	*Inclusion body myositis* 80 percent of patients	*Polymyositis & dermatomyositis* Abnormal EMG and muscle biopsy findings correlation between the height of CK elevation at diagnosis and the severity of disease
	Dystrophic myopathies Limb-girdle dystrophies Facioscapulohumeral dystrophy, myotonic dystrophy CK levels peak by age 2 and then progressively fall, often to the normal range, as more and more muscle is replaced by fat and fibrosis	
	Motor neuron disease (amyotrophic lateral sclerosis)	

Table 9.11 Differential diagnosis to high CK level

• Differential diagnosis of CK with weakness – Inflammatory – Metabolic – Endocrine – Drug induced – Infectious (viral)	• Differential diagnosis of CK without weakness – Strenuous exercise – After EMG studies – Trauma – Post-surgery – Intramuscular injections – Metabolic and congenital myopathy – Medications – Race (African Americans)

9.4.4 Electromyography (EMG)

Electromyography (EMG) is a test that is used to record muscle electrical activity and assess the nerves that control the muscles. An abnormal electromyogram can indicate a neuropathy or neuromuscular disease. Characteristic EMG findings of myopathy include short duration and decreased amplitude of action potential unlike neuropathies that are characterized by increased duration and amplitude of action potential.

Although there are no pathognomonic features that distinguish different forms of myopathy, EMG can help distinguish inflammatory from non-inflammatory forms of myopathy. Normal EMG examination, however, would not exclude myopathy [18]. In case of polymyositis, the site of muscle biopsy should be opposite to where the EMG was conducted [16].

9.4.5 Muscle Magnetic Resonance Imaging (MRI)

MRI evaluates deep muscles not readily accessible by EMG and plays a role in the diagnostic process by identifying subclinical signs of muscle involvement. Fat-suppressed and short tau inversion recovery techniques differentiate between active myositis, pictured as edema, and chronic inactive myositis in patients with inflammatory myopathy, presented as fat [20]. A secondary role for muscle MRI is to provide information about the best site for muscle biopsy by showing which muscles are involved in the myopathic process.

9.4.6 Muscle Biopsy

Establishing the diagnosis of IID is essentially based on histopathological grounds. There are currently advanced therapies that can be used effectively in these patients. The justification of using these drugs or even steroids should be based on muscle biopsy. Open surgical biopsy is preferable to closed needle biopsy because of the patchy nature of inflammation in PM and so that adequate tissue could be obtained. However, in some circumstances, the biopsy is performed by expert radiologists. Muscle biopsy is a reliable instrument in the diagnosis of PM in 85% of the patients [18]. It is an outpatient procedure that may cause pain, bleeding, infection, or sensory loss. No special preparation is required other than that patients should discontinue using anticoagulants before the procedure [21].

The best muscles to biopsy are those moderately affected by the disease process but not atrophied. Previous sites of injections, EMG examination, or trauma should be avoided. The most common biopsy sites are the deltoid, quadriceps for proximal myopathy, and gastrocnemius for distal myopathies.

Technology using genetic markers is advancing rapidly. In inflammatory myopathies, immune staining for major histocompatibility classes I and II (MHC-I/II) is upregulated in myofibrils, whereas MHC-I immune staining alone is nonspecific [22].

9.4.7 Screening for Malignancy

Idiopathic inflammatory myopathies PM and DM have positive relation to malignancy; retrospective studies' results justify CT of the chest, abdomen, and pelvis in addition to age-appropriate screening tests such as colonoscopy and mammography for any patient newly diagnosed. This is shown in Southeast Asia where input of otolaryngologists is invaluable due to the higher incidence of nasopharyngeal carcinoma for DM patients. Recent advances in understanding of pathogenesis of idiopathic inflammatory myopathies have led to discovery of biomarkers like type 1 interferon and myeloid cell signatures to distinguish active disease from chronic injury [17].

9.4.8 Genetic Testing

Genetic testing is becoming increasingly useful in confirmation of patient with muscular dystrophies and heritable myopathies. These mutations can be identified through peripheral blood DNA analysis. Molecular testing often eliminates the need for muscle biopsy.

9.5 The Management of Myopathy

9.5.1 Inherited Myopathy

For most patients with congenital myopathy or muscular dystrophy, the treatment is mainly supportive. Physical therapy, occupational therapy,

management of contractures, nutrition, and genetic counseling together play a role in managing congenital myopathies. In patients with Duchenne muscular dystrophy, treatment with prednisone has been shown to improve strength and muscle bulk and slow the rate of natural progression of the disease. Patients should also be monitored over time for complications related to kyphoscoliosis or involvement of cardiac, respiratory, or bulbar muscles. Finally, genetic counseling should be offered to all patients with inherited myopathy and their family members.

9.5.2 Acquired Myopathy

Management of proximal myopathy depends on underlying etiology. Treatable causes should be sought and treated accordingly. Discontinuation of offending drug is likely to improve symptoms in patients with drug-induced myopathy, e.g., statins [5]. Dose reduction should be considered for those patients in whom abrupt discontinuation of drug may not be possible, e.g., steroid myopathy [6]. In HIV-related myositis, treatment with the combination of highly active antiretroviral therapy (HAART) and steroids may be beneficial.

Treatment of IIM is largely empirical because of paucity of well-controlled trials. Current evidence is mostly based on retrospective or open prospective trials involving small numbers of patients. Corticosteroids are the cornerstone in the treatment of PM and DM [19, 20]. In the absence of placebo-controlled trials, the optimal initial dose and duration of therapy are uncertain, but patients are generally started on 0.75–1 mg/kg body weight/day of prednisolone. Intravenous pulse methylprednisolone is initially considered for those with cardiac, respiratory, or pharyngeal muscle involvement to obtain quicker response. Because maximal improvement may not be seen for several weeks, the usual practice is to start tapering the dose of prednisolone only after about 4–12 weeks, guided by clinical improvement. Many patients relapse when corticosteroids are discontinued, and therefore, a maintenance dose of 5–10 mg/day is often required for several years. About a third of patients with PM or DM, and those with IIM, might fail to show any response to prednisolone. Second-line immunosuppressive drugs are tried in patients who do not respond to corticosteroids alone and in those with progressive disease and internal organ involvement. Choice of drug is largely empirical and depends on disease severity, extra- muscular manifestations, and personal experience of treating physician, again because of paucity of well-conducted trials.

Azathioprine [23] or methotrexate is usually preferred. Intravenous immunoglobulin (Ig), the only agent for which there is positive evidence from randomized placebo-controlled trial [21, 24], is especially useful for patients with dysphagia and treatment-resistant DM. Intravenous Ig is, however, expensive and limited in availability. Cyclophosphamide, given as monthly intravenous pulses for 3–6 months, is also an option for patients with respiratory muscle weakness, interstitial lung disease, or cardiac involvement [25]. Plasmapheresis has also been studied, but was not found to be helpful in a double-blind placebo-controlled trial [26]. Rituximab, a CD20 monoclonal antibody that depletes B cells, has been reported to have a favorable effect in small open-label uncontrolled trials [27, 28]. A new double-blind, placebo-phase trial in refractory adult and pediatric myositis using rituximab revealed good results [29]. Tumor necrosis factor inhibitors such as infliximab, adalimumab, and etanercept are ineffective in treating IID and may cause deterioration or trigger the disease [30]. Other biological agents that may be considered as experimental treatments include alemtuzumab, which is reportedly effective in polymyositis [31], and anti-complement C3 (eculizumab), which may be effective for the treatment of dermatomyositis. Overall, the long-term outcome of inflammatory myopathies has substantially improved, with a 10-year survival rate of more than 90% . Table 9.12 shows a step-by-step approach in the management of IID [32].

Input of physiotherapist is also valuable because randomized controlled trials among patients with IIM have demonstrated that exercise therapy, adapted to the patient's condition, is

Table 9.12 Approach to treatment of inflammatory myopathies

Clinical situation	Treatment for IID
New-onset disease	Prednisone (0.75–1 mg / kg) for 4–12 weeks
Weakness is severe + cardiac, respiratory, pharyngeal involvement	Intravenous glucocorticoids (1000 mg/day) for 3–5 days and then switch to oral
If patient responds to glucocorticoids	Start a glucocorticoid-sparing agent • Azathioprine • Methotrexate
If response to glucocorticoids is insufficient	Intravenous immune globulin (2 g/kg in divided doses over 2–5 days)
If response to glucocorticoids and intravenous immunoglobulin is insufficient	Consider initiating treatment with rituximab

Dalakas, Marinos C. "Inflammatory muscle diseases." *New England Journal of Medicine* 372.18 (2015): 1734–1747

beneficial and safe [33]. Benefits of exercise not only include improved muscle endurance, strength, and functional abilities but also prevent muscle wasting and fibrotic contractures.

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Bones and Rheumatology

10

Altaf Abdulkhaliq

10.1 Introduction

Bone is a target tissue in many inflammatory diseases including rheumatic diseases such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), systemic lupus erythematosus (SLE), and psoriatic arthritis.

A relationship between inflammation and bone disease has been established in a variety of clinical settings and animal models of inflammatory disease [1–4]. It has been established that the nature of the inflammatory disease can influence on the extent and type of bone disease and that even a small rise in the level of systemic inflammation can impact on bone remodeling and increase fracture risk [5].

The inflammatory joint disorders, namely, rheumatic diseases, are usually accompanied with extra-articular side effects, mainly bone loss, or osteoporosis that would result in an increased risk of fractures and deformities, which are in turn associated with increased morbidity and mortality [6]. Therefore, such types of musculoskeletal diseases are considered as one of the major causes of disability around the world and can explain the enormous cost of the musculoskeletal conditions to the community.

In order to easily understand the underlying pathology and mediators that affect bones in rheumatic conditions, a brief overview on bone structure, biology, physiology, and essential molecular mechanism and signaling pathways needs to be explained clearly.

10.2 Objectives

1. To explain the underlying bones pathology among patients with rheumatic diseases.
2. To identify the common bone lesions occur with rheumatic diseases.
3. To recognize the serious impact of developing secondary osteoporosis among patients with rheumatic diseases.
4. To provide an updated approach for prevention and treatment of glucocorticoid-induced osteoporosis (GIOP) and bone fractures among patients with rheumatic diseases receiving glucocorticoids.

10.3 Bone Structures

Bone is a dynamic and highly specialized form of connective tissue, in which the extracellular components are mineralized, thus giving the property of marked rigidity and strength while retaining some degree of elasticity. Bone represents a store of calcium and other inorganic ions

A. Abdulkhaliq (✉)
College of Medicine, Umm Al-Qura University, Makkah, Saudi Arabia
e-mail: aaabdulkhaliq@uqu.edu.sa

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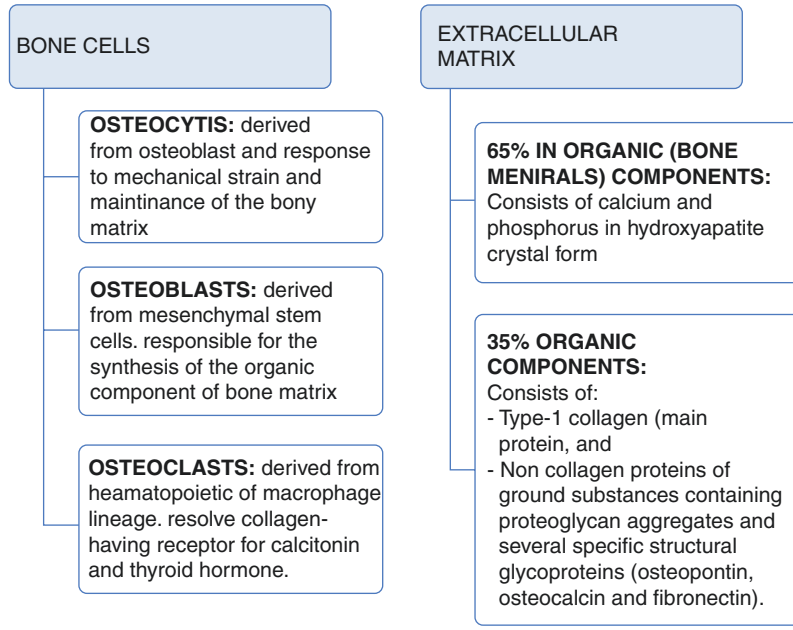

Fig. 10.1 Components of bone structure

and actively contributes to the maintenance of calcium homeostasis.

Two types of bone can be identified macroscopically: compact or cortical bone and cancellous or trabecular bone. Microscopically both types of bone have the same histological structure. Like other supporting connective tissues, bone is composed of cells and extracellular matrix that is made up of 35% of organic component and 65% inorganic component [7]. The inorganic part consists of calcium and phosphorus in hydroxyapatite crystal form, while the organic component consists of type 1 collagen and ground substance containing proteoglycan aggregates and several specific structural glycoproteins [8] (Fig. 10.1).

10.4 Bone Remodeling and Bone Cells

Bone remodeling is the lifelong process whereby old bone is removed by bone resorbing cells and subsequently replaced by new bone via the action of bone-forming cells to maintain the bone structure. Bone remodeling occurs normally in all individuals, and in adults about 25% of trabecular and 3% of cortical bone is replaced by such process each year [9]. Bone remodeling also helps to maintain mineral homeostasis via the liberation of calcium and phosphorus into the circulation. The remodeling process occurs at discrete sites on cortical and cancellous bone surfaces and involves the integrated and sequential actions of osteoclasts (bone resorbing cells) and osteoblasts (bone-forming cells), comprising anatomic structures known as basic multicellular units (BMUs).

10.4.1 Bone Cells

Mesenchymal stem cells have the potential to differentiate into various cell types including osteoblasts, chondrocytes, adipocytes, myoblasts, and fibroblasts. Determination of the final fate of the differentiation process is determined by and depending on the signaling transcription pathways that are activated during the initial phase of differentiation of mesenchymal progenitor cells [10, 11].

Among the important signaling pathways that are responsible to direct the differentiation into osteoblast lineage are the mitogen-activated protein kinase (MAPK) and protein kinase A (PKA)-dependent pathway [12] and Wnt-signaling pathway with its related β-catenin protein [13, 14]. Moreover, of the transcriptional factors, at least two are shown to be absolutely

essential for osteoblast differentiation from mesenchymal precursors including Runx2 [15–17].

The plasma membrane of activated osteoblast is rich in alkaline phosphatase and exhibits receptors for parathyroid hormone (PTH) [18], whereas the nuclei have receptors for estrogens [19], vitamin D3 [20], and glucocorticoids [21], which all are involved in the regulation of osteoblast differentiation and activity.

Osteoblasts contribute in the synthesis and secretion of new organic part of bone matrix (but not yet mineralized), called osteoid, between the secreting osteoblast layer and in contact with older bone matrix of previously formed bone. This process is referred to as *bone apposition* and is completed by further mineralization of the newly formed bone matrix (*deposition of calcium* salts into matrix), a process regulated by osteoblast too. At the end of the secreting period of osteoblasts, those osteoblasts are embedded within the bone and differentiated into osteocytes.

Osteoclasts originate from hematopoietic stem cells (HSCs), precisely from cells of the colony-forming unit of macrophage (CFU-M) that differentiate to multinucleated, giant, motile cells on stimulation with macrophage colony-stimulating factor (M-CSF) and receptor activator of nuclear factor-kappa B "NF_kB" ligand (RANKL) (Fig. 10.2).

Firstly, the osteoclast progenitors proliferate and differentiate into mononuclear preosteoclasts and then fuse with each other to form multinucleated cells. The terminal differentiation in this lineage is characterized by acquisition of mature phenotypic markers, such as the calcitonin receptor, tartrate resistant acid phosphatase (TRAP), and integrin αvβ3 [22]. The mature and active osteoclasts are characterized by a moderate

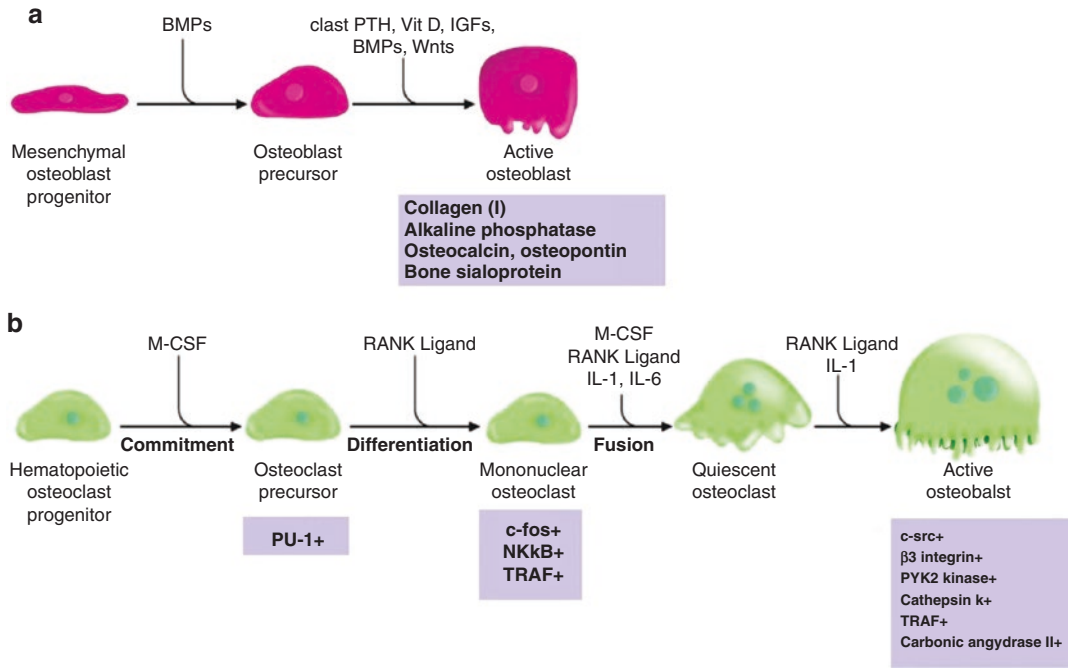

Fig. 10.2 Pathways regulating the development of (**a**) osteoblasts and (**b**) osteoclasts**.** Hormones, cytokines, and growth factors that control cell proliferation and differentiation are shown above the arrows. Transcription factors and other markers specific for various stages of development are depicted below the arrows. BMPs, bone morphogenetic proteins; Wnts, wingless-type mouse mammary tumor virus integration site; PTH, parathyroid hormone; Vit D, vitamin D; IGFs, insulin-like growth factors; Runx2, Runt-related transcription factor 2; M-CSF, macrophage colony-stimulating factor; PU-1, a monocyte- and B lymphocyte-specific ets family transcription factor; NFB, nuclear factor B; TRAF, tumor necrosis factor receptor-associated factors; RANK ligand, receptor activator of NFB ligand; IL-1, interleukin-1; IL-6, interleukin-6 [24]

rough endoplasmic reticulum, a well-developed Golgi apparatus, and abundant mitochondria, while the surface of their plasma membrane facing bone matrix is having ruffled border (clear or sealing zone), which is devoid of organelles but rich in actin microfilaments that form a ring of contractile protein serving to attach the cell to the bone surface via integrin receptors during the resorptive process [8]. *The clear zone* is a site of adhesion of the osteoclast to the bone matrix and creates a microenvironment where bone resorption takes place. From the ruffled border, osteoclasts secrete collagenase (and other proteolytic enzymes) and pump protons (low pH) into microenvironment and thus promoting the localized digestion of matrix and the dissolving of bone mineral (calcium salt crystal), respectively.

Several systemic and local factors have influenced osteoclasts and their bone resorption ability. In normal physiological conditions, the osteoclast activity is highly balanced by those factors. However, in pathological conditions, this balance becomes disturbed such as during excessive activation of the immune system, due to the secretion of additional pro-inflammatory cytokines, produced mainly by activated T cells [23].

10.4.2 The Remodeling Cycle

The remodeling cycle is comprised of four distinct phases including activation, resorption, reversal, and formation phase (Fig. 10.3). Bone remodeling starts with activation of the lining cells via increasing the surface expression of RANKL.

In the activation phase, RANKL interacts with its receptor RANK, thus triggering the recruitment of osteoclast progenitors to bone where they proliferate and differentiate into osteoclasts and attach tightly to the bone matrix.

Next is *the resorption phase*, when the activated osteoclasts possess ruffled borders under which the proteolytic enzymes are secreted and the *hydrogen ions are pumped* resulting in digestion of collagens and dissolving the mineralized

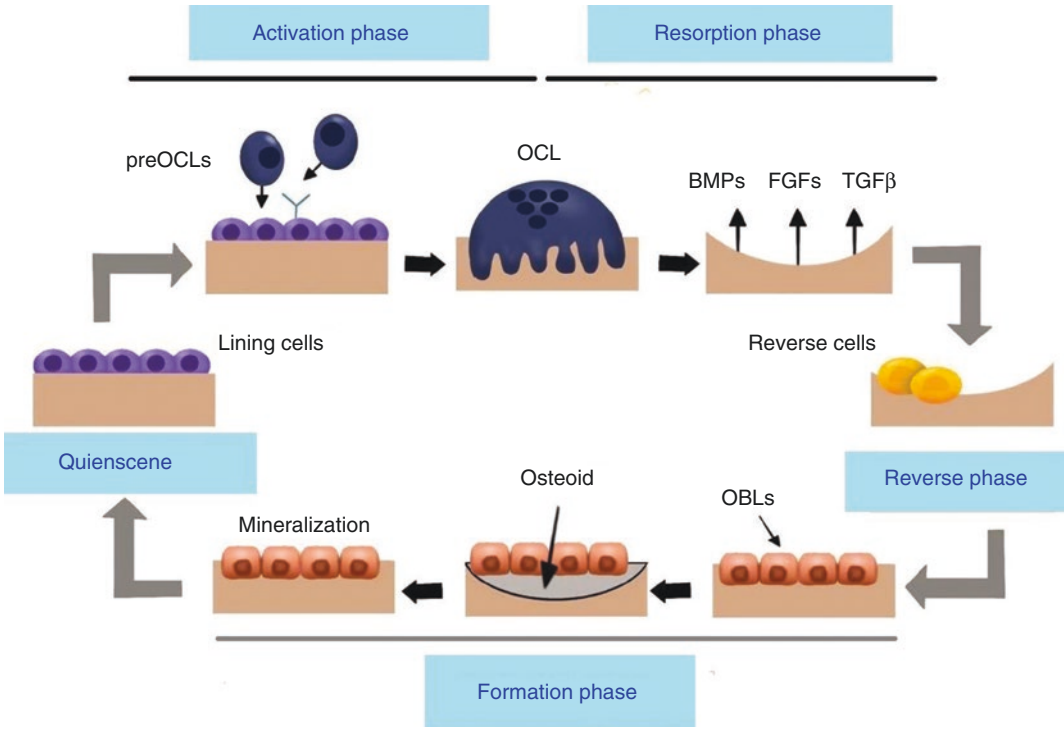

Fig. 10.3 Process and phases of normal bone remodeling [26]

matrix with the formation of a resorption cavity and allowing the release of several growth factors usually stored in the bone matrix. In addition, there is an accumulation of high concentration of calcium that directly controls osteoclasts activity resulting in cell retraction [25] and movement of osteoclasts across the bone surface to resorb a new area. At the end of this stage, osteoclasts undergo apoptosis after a life span of about 3 weeks, and thus the process of remodeling requires the continual production of osteoclast precursors.

In *the reversal phase*, the remnant debris of matrix degradation will be removed, while the released growth factors including bone morphogenetic proteins (BMPs), fibroblast growth factors (FGFs), and transforming growth factor-β (TGFβ) are likely to be responsible for recruitment of osteoblasts to cover the bottom of the resorption cavity, forming osteoid tissue until the cavity is filled.

In the final *formation phase* of bone remodeling, osteoblasts initially synthesize the organic matrix and then preside over its mineralization, thus completing the bone remodeling process. Toward the end of this process, some osteoblasts start to flatten and become quiescent lining cells; others become embedded in the matrix and differentiate into osteocytes, while the remaining of osteoblasts will undergo programmed cell death.

10.4.3 Factors Influencing Remodeling

The rate at which new osteoblasts and osteoclasts are supplied and the timing of apoptosis of these cells are crucial determinants of bone remodeling. The development of osteoclasts and osteoblasts is controlled by growth factors and cytokines produced in the bone marrow microenvironment and is modulated by systemic hormones and immunological mechanisms [27–30]. Certain signaling pathways, systemic hormones, pro-inflammatory cytokines, and growth factors are considered as fundamental regulators of bone remodeling.

Taken together, positive stimulator of osteoblast activity includes PTH, vitamin D3, IGFs, BMPs, and Wnt signaling, while those that promote osteoclast activation are monocyte-macrophage colony-stimulating factor M-CSF, RANKL, IL-1, and IL-6.

Eventually, the recent discovery of osteoprotegerin (OPG) and the subsequent identification of its cognate ligand, OPG ligand (OPGL or RANKL), have illuminated our understanding of the molecular basis that links between osteoblastogenesis and osteoclastogenesis and thereby the rate of bone remodeling upon which other inputs (hormonal, biomechanical, etc.) operate.

10.4.4 RANK/RANKL/OPG System

Despite that the principal function of the osteoblasts is to synthesize bone matrix proteins and to enhance bone mineralization, osteoblasts also play a crucial role in osteoclast biology that has been clearly demonstrated by the release of key molecules, which regulate osteoclastogenesis and bone resorption. Of these regulators are RANKL which is expressed on the surface of the osteoblast and interact with its receptor RANK [22] to mediate signals for osteoclast proliferation, differentiation, activation, and function [31] (Fig. 10.4), while OPG is acting as a decoy receptor for RANKL [32], noting that the OPG/RANK/RANKL system accounts only for signaling of osteoblasts to osteoclasts.

The human *RANK* is a polypeptide of 616 amino acids, related to the type 1 transmembrane protein class [33], and is expressed in various tissues such as the skeletal muscle, liver, and small and large intestines. Among bone cells RANK-mRNA is exclusively expressed in osteoclast precursor cells [22, 32]. On the other hand, *RANKL* is a TNF-related cytokine that exists in both transmembrane, the predominant form, and soluble (cleaved) forms [22]. The gene expression of RANKL can be found abundantly in the skeleton and lymphoid tissues and is produced by osteoblasts, bone marrow stromal cells, and other cells under the control of various pro-resorptive growth factors, hormones, and cytokines. Moreover, osteoblasts and stromal cells produce OPG, which binds to and thereby inactivates RANKL.

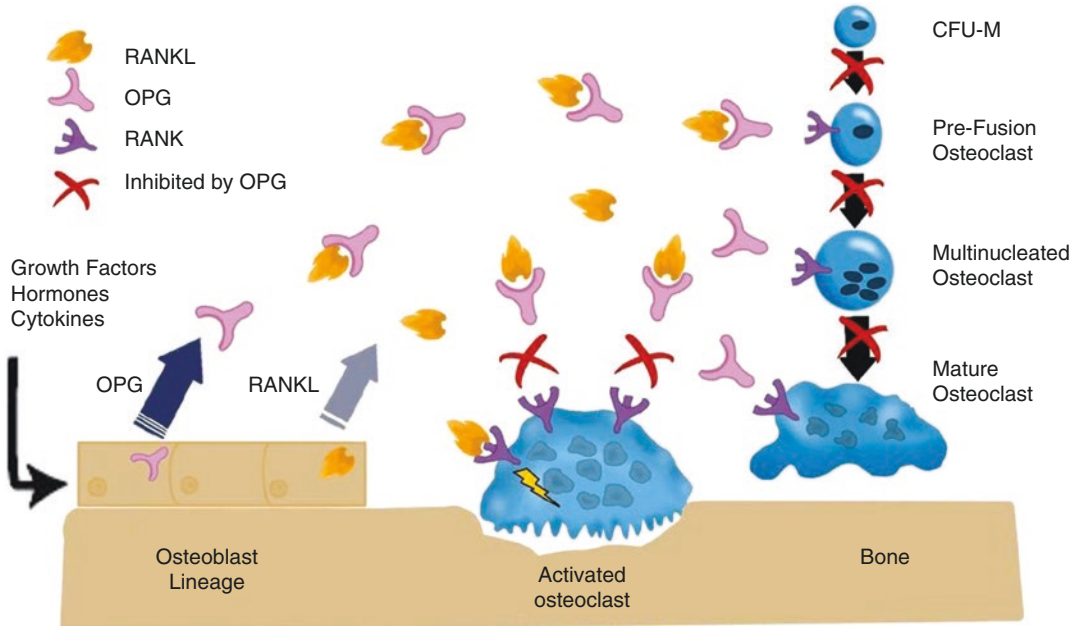

Fig. 10.4 Mechanisms of action for OPG, RANKL, and RANK [34]

Collectively, RANKL is of great importance for the development and function of osteoclasts through binding to its transmembrane-signaling receptor RANK [35]. RANK-RANKL interactions lead to pre-osteoclast recruitment, fusion into multinucleated osteoclasts, osteoclast activation, and osteoclast survival. These effects are very selective to bone and can be inhibited by the natural, soluble, decoy receptor OPG [32].

OPG is considered as a humoral regulator of bone resorption. It blocks osteoclast maturation and differentiation, and subsequently it can protect the bone from both normal osteoclast remodeling and ovariectomy-associated bone loss [36].

Certain human adult tissues showed a high level of OPG mRNA expression, namely, the heart, the bone, the placenta, and the thyroid gland [37]. It has been demonstrated that OPG expression is upregulated in various human osteoblastic cell systems by 1,25-dihydroxyvitamin D3, bone morphogenetic protein-2 (BMP-2), pro-inflammatory cytokines such as interleukin-1 (IL-1) [38], estrogen [39], as well as transforming growth factor-β (TGF-β) [40]. However, some discrepancies were noticed in the effect of these modulators on the expression of the OPG mRNA and OPG protein levels depending on the species of the cells used and on the stage of osteoblastic differentiation. In contrast, it has been established that glucocorticoids downregulate the OPG transcript in human osteoblast and in human marrow stromal cells [41, 42], and they can suppress OPG production resulting in acceleration of osteoclastic bone resorption [43].

10.5 Mediators of Bone Loss in Rheumatic Diseases

Systemic bone loss in rheumatic diseases occurs as a result of several factors including direct effects of inflammation, poor nutrition, reduced lean body mass, immobility, and the effects of therapeutic agents, specifically glucocorticoids. These mechanisms are complex and interrelated but are eventually mediated through influencing on the bone remodeling cycle and may result in increasing bone resorption, decreasing bone formation, but most commonly affecting both of these processes.

Adding to the referred mechanisms that cause bone loss, there are background predispos-

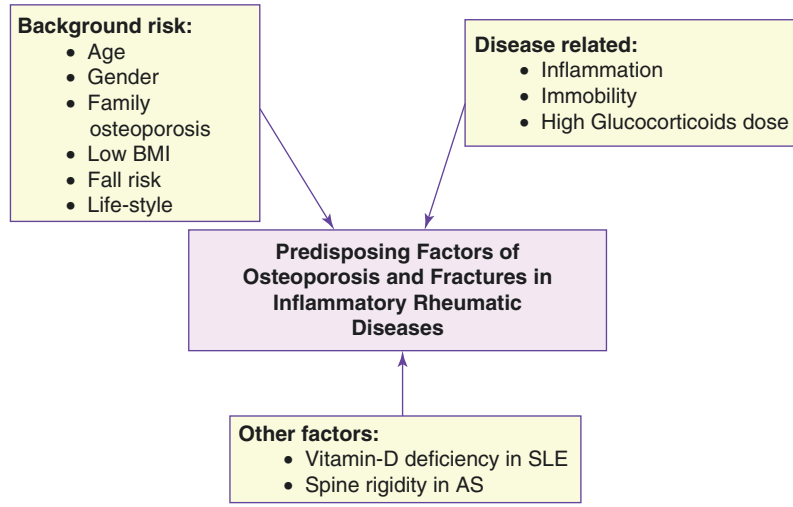

Fig. 10.5 Risk factors for osteoporosis and fractures in inflammatory rheumatic diseases [44]

ing factors, which increase the risk of fractures due to bone loss, and they include age, gender, family history of osteoporosis, low body mass index (BMI), falling risk, and sedentary lifestyle (Fig. 10.5) [44].

The following sections will discuss the main underlying mechanisms that cause bone destruction in different rheumatic conditions, namely, the disease activity (inflammation), immobility, and treatment with glucocorticoids are considered. Noting that each rheumatic disease has a unique effect on articular bone or on other site on skeleton whether local or generalized bone loss, however, they remarkably share common pathways of skeletal remodeling (the RANKL/OPG pathway), which is involved in the regulation of bone resorption. In addition, most human and animal studies in the field of rheumatic arthritis have referred to the osteoclast as the principal cell type mediating bone loss in arthritis [45].

10.5.1 Effects of Systemic Inflammation

Inflammatory process in rheumatic diseases is usually associated with skeletal destruction. The effects of inflammation in induction bone loss involve two mechanisms, the role of pro-inflammatory cytokines and/or the role of inflammatory cells.

10.5.1.1 Role of pro-Inflammatory Cytokines

- Many of the pro-inflammatory cytokines and growth factors (Fig. 10.6) [46] involved in the inflammatory processes in rheumatic diseases have been found to have a great impact on osteoclast differentiation and activation either directly, by acting on cells of the osteoclast lineage, or indirectly, by modulating the expression of the key osteoclastogenic factor (RANKL) and/or its inhibitor, OPG [47].
- Because a wide range of cytokines have positive and negative impact on OPG/RANKL system or directly on osteoclastogenesis, they are usually kept in balance in healthy subjects. However, imbalance of these cytokines occurs during inflammation but varies between disease states, and this variation would account for differences in predisposition to bone loss.
- The cytokines that have positive (stimulatory) effects on osteoclastogenesis include TNF-α, IL-1b, IL-6, IL-11, and IL-17, whereas those that have negative (inhibitory) effects include interferon (IFN)-γ, IL-4, and transforming growth factor-β (TGF-β) [48].
- For instance, tumor necrosis factor-alpha (TNF-α) can increase the expression of RANKL by osteoblasts and hence induce osteoclastogenesis and the bone-resorbing activity. However, TNF-α and interleukin-1 (IL-1) can synergize with RANKL to directly enhance bone resorption by osteoclasts.

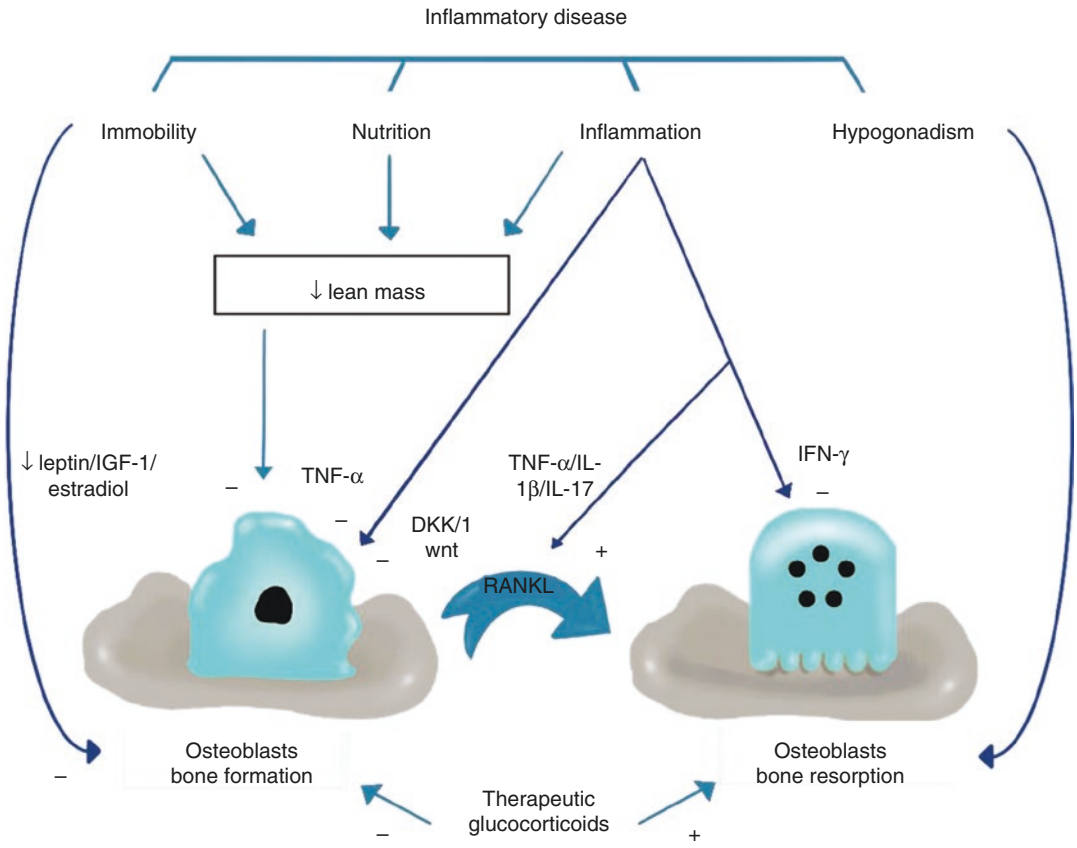

Fig. 10.6 Illustration of the impacts of chronic inflammatory disease on bone formation and resorption. A stimulatory effect is indicated by C and an inhibitory effect by K [46]

10.5.1.2 Role of Inflammatory Cells

- Under normal conditions, RANKL is derived from osteoblasts; however, during inflammation, a variety of inflammatory cells can also produce RANKL including lymphocytes and fibroblasts, which have been found in the inflamed synovium in various studies [49–51]. The expression or production of RANKL on/from non-osteoblastic cells causes a direct osteoclastogenic effect independent of osteoblasts.
- An example of these cells is T lymphocytes that are derived from Th17 subset, which has been called so after the ability of these lymphocytes to secrete IL-17, and hence they are considered to have an osteoclastogenic cytokine profile [52]. The presence of this lymphocyte subset prominently in inflammatory arthritis could explain the tendency to local osteoclastogenesis and thus bone destruction in this condition [53].
- A subsequent to the increased bone resorption, there should be also a stimulation of bone formation because the processes of bone resorption and formation are normally tightly coupled. However, during chronic inflammation, "uncoupling" of bone formation from resorption occurs with a suppressed or decreased bone formation relative to the high degree of resorption.

10.5.1.3 Causes of Uncoupling Process

The Wnt Signaling and its Antagonist, DKK1

Studying animal models of inflammatory arthritis could explain the uncoupling process via the implication of the Wnt-signaling pathway and precisely the Wnt antagonist dickkopf-1 (DKK1), in this process [54].

The canonical Wnt-signaling pathway is essential for bone development, directing differentiation of mesenchymal precursor cells into mature osteoblasts, as well as having a major role in the normal development of the skeleton in the embryo [55, 56]. The naturally occurring soluble Wnt antagonists such as DKK1, which suppress this process, are important during normal bone remodeling. This finding has been supported by that the DKK1 knockout mice develop an increased bone mass [57] and conversely myeloma cells with aberrant DKK1 expression are associated with purely lytic lesions with little evidence of bone formation [58].

The synovial fibroblast can secrete DKK1; however, in rheumatoid arthritis, the secretion is enhanced by TNF-α, and thus the circulating levels of DKK1 have been found much elevated in those patients [54]. Thus, the secreted DKK1 from the synovium would have a suppressive effect on osteoblast maturation and on OPG function leading to inhibition of local bone formation and increased bone resorption, respectively. Understanding the mechanism of Wnt signaling and its antagonist, DKK1 (Fig. 10.7), is very important, since administration of DKK1

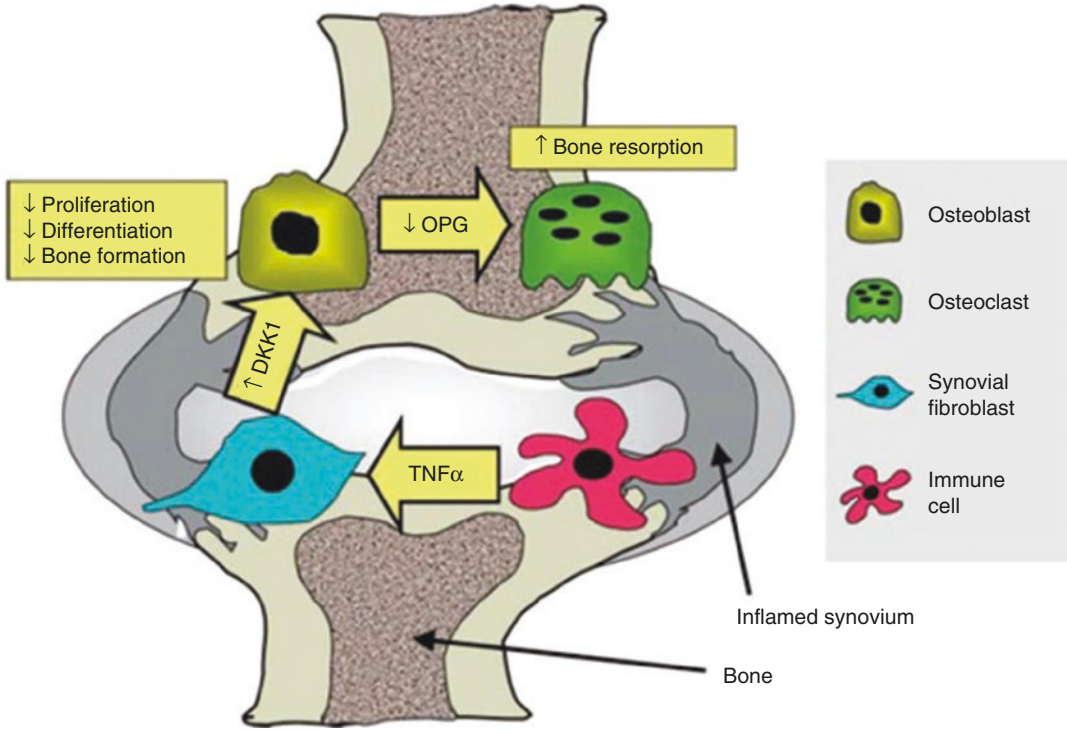

Fig. 10.7 Schematic illustration of the possible role of DKK1 in the bone remodeling imbalance in inflammatory joint disease. Production of DKK1 in response to TNF-α production by inflammatory cells is proposed to inhibit bone formation but increase bone resorption by osteoclasts through a suppression of OPG production by osteoblasts [46]

antibody would be able to prevent bone erosions and reverse this block on osteoblast formation which resulted in a paradoxical excess of bone formation during inflammation as proved by the development of new osteophytes [54].

Alteration of Glucocorticoid Signaling

The effects of glucocorticoids will be explained later in the following sections, but the current paragraph will discuss the influence of inflammation on glucocorticoid action in bone cells. Because of the intracellular metabolism of glucocorticoids by 11b-hydroxysteroid dehydrogenases (11β-HSDs) [59], it has become known that the levels of active glucocorticoids present within the circulation differ from that in the tissues. Specifically, 11β-HSD1 enzyme is expressed on osteoblast and can increase local glucocorticoid action in these cells by converting the inactive glucocorticoids such as cortisone and prednisone to their active counterparts' cortisol and prednisolone, respectively.

Overexpression of the enzyme in osteoblasts reduces proliferation and the synthesis of bone-specific proteins such as osteocalcin when cells are exposed to inactive glucocorticoids [60, 61]. It was reported previously by [62] that pro-inflammatory cytokines such as TNF-α or IL-1b can effectively induce the expression and activity of this enzyme in osteoblasts. Thus, during inflammation, osteoblasts at the site of bone exposed to pro-inflammatory cytokines are likely to also be exposed to high doses of locally active glucocorticoid [62, 63]. This is potentially a major mechanism by which the uncoupling process of osteoblasts and osteoclasts occurs. Overall, a high glucocorticoid level in osteoblasts will decrease bone formation through direct effects on osteoblasts [64], but it can also induce osteoclastogenesis due to upregulation of RANKL and downregulation of OPG in osteoblast precursors [42].

Studying the correlation of locally generated glucocorticoids with other proposed mechanisms of uncoupling such as DKK1 induction is essentially needed for therapeutic purposes of rheumatic diseases.

10.5.2 Effects of Immobility

Immobility has consequences on all inflammatory diseases specifically neuromuscular and joint disease. The major impact on bone occurs due to uncoupling process that results in reduced bone formation and increased bone resorption [65] with overall bone loss. It has been found that osteocytes mediates mechanosensing, which means they can response to mechanical strain and maintain bony matrix via modulation of the major pathways such as the Wnt pathway that couple bone formation and resorption [66]. This effect may partly be dependent on estrogen receptor signaling, and thus hypogonadism would reduce the mechanosensing [67].

Regular exercises can maintain force on bone and thus control bone loss through mechanical stimulation. However, a more advanced approach is the administration of a vibration signal that could stimulate mechanosensing effects, which in turn will induce an anabolic response to bone [46].

10.5.3 Effects of Glucocorticoids

Glucocorticoids (GCs) are frequently prescribed for patients with variety of chronic inflammatory diseases such as rheumatic diseases. An excess of circulating GCs has a major negative effects on bone [64, 68, 69]. These adverse effects on bone are owing to reduced bone formation, characterized by a low mineral apposition rate that is explained by decreased numbers of osteoblasts, while bone resorption is unchanged or even elevated [70], leading to the development of glucocorticoid-induced osteoporosis (GIOP).

Overall negative effects of GCs on bone are either directly on bone cells or indirectly by affecting the bone metabolism. The underlying molecular mechanisms of GIOP include the increased apoptosis of osteoblasts and osteocytes and increased half-life time of osteoclasts, i.e., the direct effects on bone cells (Fig. 10.8) [71]. It has been reported that the increased osteoblast apoptosis results in a significant reduction in bone formation, while decreased osteocyte num-

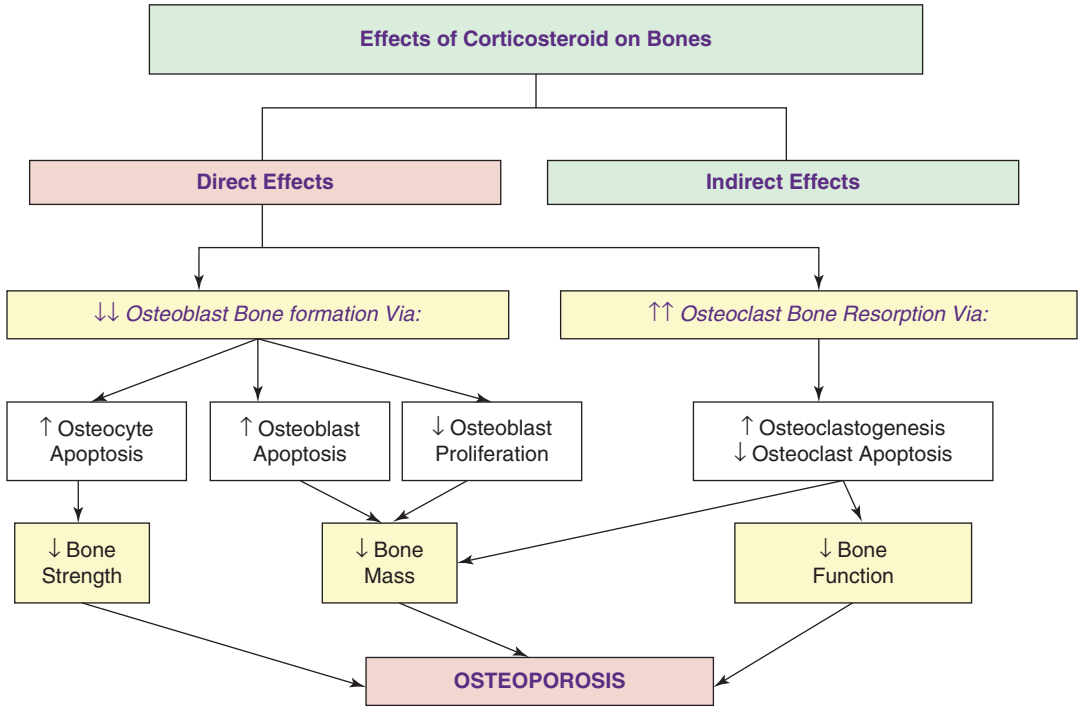

Fig. 10.8 The direct effects of glucocorticoids on bone [71]

bers result in a disturbed osteocyte-canalicular network and thus failure to respond to bone damage [72].

The process of apoptosis is induced by activating caspase-3 [73] and glycogen synthases kinase 3β (GSK3β), which suppresses the Wnt-signaling pathway by increasing the production of DKK-1, the Wnt pathway inhibitor [74, 75].

In addition to the increased apoptosis of osteoblasts, GCs impair osteoblast function by suppressing osteoblast differentiation [76] via interfering with both the bone morphogenetic protein (BMP) pathway and the Wnt-signaling pathway.

Moreover, recent studies proposed that high doses of GCs cause a shift of bone marrow stromal cells, the precursor cells of osteoblasts, to differentiate toward adipocytes instead of osteoblasts. This is mainly achieved either through an increased expression of the peroxisome proliferator-activated receptor-γ2 (PPR- γ2) and repression of the osteogenic transcription factor Runt-related protein 2 [77] or via suppression of AP-1, a process that not only mediates anti-inflammatory actions but also reduces bone strength [78].

In contrast to increased apoptosis of osteoblasts and osteocytes, GCs therapy would reduce the apoptosis of osteoclasts by extending their life span through upregulation of RANKL and suppression of OPG [42].

Likewise direct effects on osteoblasts, osteocytes, and osteoclasts, GCs have indirect effects on bone (Fig. 10.9). Previous studies asserted that GCs impair bone metabolism by inhibiting both the gastrointestinal absorption and the renal tubular reabsorption of calcium, leading to hypocalcaemia and the subsequent hyperparathyroidism [71]. Recent reports referred that GCs have influenced the bone mineralization by decreasing the production of important proteins for matrix formation, namely, osteocalcin and type 1 collagen [69]. Furthermore, GCs can cause steroid myopathy [79] [4] that may increase the risk of falling and thus indirectly increase the fracture risk.

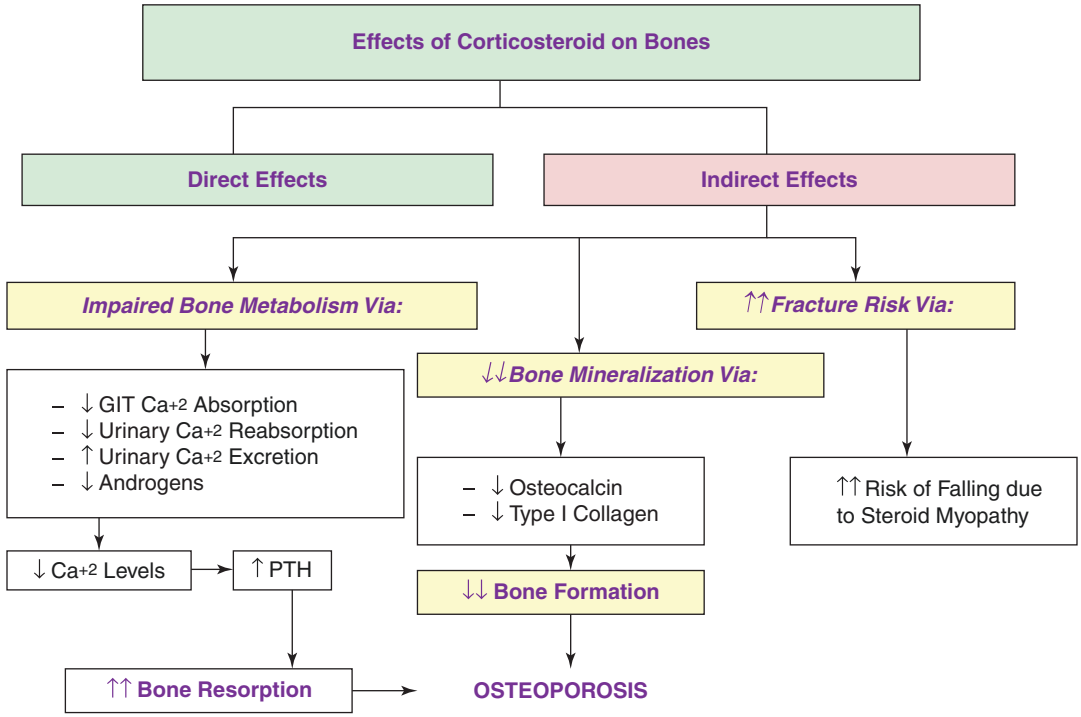

Fig. 10.9 The indirect effects of glucocorticoids on bone [71]

10.6 Common Bone Diseases Associated with Rheumatic Disease

Osteoporosis-related fragility fractures represent one of the most important complications that may occur in patients with rheumatic diseases; obviously, these fractures may contribute to an important decrease in quality of life, and hence osteoporosis becomes increasingly recognized as an eminent public health problem.

Osteoporosis is a metabolic bone disease characterized by both low bone density (mass) and low bone quality, which includes not only microarchitecture deterioration of bone tissue but also alterations in bone remodeling, damage accumulation (e.g., microfractures), and mineralization. These changes in bone density and quality enhance bone fragility with a consequent increase in fracture risk after minimal trauma. Osteoporosis is caused by an imbalance between bone formation and resorption with in favor of bone resorption over bone formation, leading to altered bone remodeling.

The reduction in bone mass can be quantified by measurement of bone mineral density (BMD) using dual-energy x-ray absorptiometry (DXA), which is the diagnostic method of osteoporosis [80]. Therefore, osteoporosis can be defined by DXA result when T score is ≤2.5 (i.e., bone density is 2.5 standard deviation below estimated peak BMD for the population), whereas osteopenia is defined when a T score is between −1 and −2.5.

10.6.1 Rheumatoid Arthritis and Bone Loss

Rheumatoid arthritis (RA) is characterized by three types of bone lesions: periarticular osteopenia, bone erosions, and osteoporosis:

- *Periarticular osteopenia* is one of the first radiographic signs of RA. It appears markedly in early disease and is mainly associated with disease activity.
- *Bone erosions* develop within the first months of the disease onset and account as the radiographic sign of RA and reflect undesirable prognosis of RA. Hence, the extent and severity of the erosions reflect the increasing disease activity and indicate the disability of the disease.

Within 6 months of disease onset, less than 50% of patients showed radiographic erosions, while almost 70% of the patients have erosions detected by MRI [81–83] and may be accompanied by bone edema, where CD34+ cells and potential osteoclast precursors [84] can be found during joint aspiration.

- *Osteoporosis* in RA is mainly characterized by marked loss of bone in the hip and the radius, while the axial bone is scarce, a pattern not similar to that of postmenopausal osteoporosis. In addition, several cross-sectional studies reported a lower bone mineral density (BMD) in patients with RA, with a twofold increase in osteoporosis compared to age- and sex-matched controls.

10.6.1.1 Predisposing Factor of Osteoporosis in RA

In addition to the risk factors of osteoporosis (Fig. 10.5), other factors may also contribute in RA, such as muscle wasting, glucocorticoids therapy, and disease duration. Interaction between several factors should be considered, for example, additional muscle wasting contributes to increased immobilization [85].

10.6.1.2 Pathological Process

- Several evidences suggested the presence of osteoclasts at the site of bone erosions, indicating the increased of bone resorption [86, 87].
- In RA, the local and generalized bone loss share common pathways: the RANKL/OPG pathway. The main inflammatory cytokines that have been found in RA and involve in upregulating RANKL, with subsequent activation of osteoclastogenesis, include TNF-α, IL-1, IL-6, and IL-17 [88, 89].
- The Wnt-signaling pathway is another pathway that regulates osteoblast activity, and thus the activation of the Wnt/β-catenin pathway is crucial for osteoblastic differentiation [90, 91]. There are two blockers of the Wnt-signaling pathway, dickkopf-1 (Dkk-1) and sclerostin, both of which play an important role in the pathogenesis of RA. TNF-α can induce both sclerostin and Dkk-1 [89], leading to inhibition of osteoblastic differentiation.
- Further studies in RA patients confirmed these pathological processes and revealed that OPG/RANKL ratio was lower than in healthy controls, while Dkk-1 and sclerostin were higher. After treatment with anti-IL-6, OPG/RANKL increased, Dkk-1 decreased, and sclerostin increased [92].

10.6.1.3 Management of Bone Loss in RA

- Recent treatments with biological agents were introduced in patients with rheumatoid arthritis. All available TNF-alpha blocking agents are quite successful in the prevention of erosion formation.
- However, progression of structural damage in RA patients treated with methotrexate can be avoided by denosumab, a fully human monoclonal IgG2 antibody that binds RANKL [93].
- It has also been found that in patients with RA treated with infliximab, the bone loss was abolished in the spine and hip, but not in the metacarpal cortical hand [94].
- Moreover, preventing the loss of vertebral strength in patients with RA can be principally achieved by treatment with alendronate [95].
- After this extensive review, here comes the value of early diagnosis of RA and early and aggressive intervention with disease-modifying anti-rheumatic drugs (DMARDs) to prevent bone destruction, osteoporosis, and erosions.

10.6.2 Systemic Lupus Erythematosus and Bone Loss

10.6.2.1 Predisposing Factors of Bone Loss in SLE

- In addition to the traditional background factors, there are also disease-related factors (Fig. 10.5) such as inflammation, metabolic factors, hormonal factors, serologic factors, and medication-induced adverse effects [96].
- Another factor that may contribute in decreased BMD in SLE is the associated high frequency of vitamin D deficiency [97–99], a metabolic condition that induces bone loss. Vitamin D deficiency might induce bone loss in SLE via several factors including (a) photosensitivity (so patients avoid exposure to the sun and use sunscreens), (b) dark skin pigment, (c) renal failure, and (d) treatment with GC (has a dual action, it can induce bone loss, but also it has a beneficial effect on bone mass by suppressing inflammation) and possibly hydroxychloroquine (HCQ) (via inhibiting hydroxylase α1 that form active vitamin D), which showed a controversial results [98, 100]. Due to these inconsistent results of HCQ, further studies in large groups of SLE patients and patients with other diseases treated with HCQ are needed to clarify the relationship between HCQ uses and bone metabolism.
- Changes in hormonal pattern may also negatively influence the BMD in patients with SLE, where a relatively high estrogenic and low androgenic state and a decrease in dehydroepiandrosterone (DHEA) have been demonstrated and associated with low BMD [101].
- Collectively, the factors that may adversely affect bone mass, resulting in osteoporosis and possible fracture risk in SLE, have been summarized in Table 10.1.

Table 10.1 Summary of risk factors for osteoporosis in patients with SLE [101]

Risk factors for osteoporosis in patients with SLE
Non-modifiable risk factors
• Caucasian or Asian ethnicity. • Female sex. • Advanced age. • Personal or family history of osteoporotic fractures. • High risk of falls. • Premature menopause.
Modifiable risk factors
• Weight < 127 lb. (58 kg). • Inadequate calcium and vitamin D intake. • Lifestyle habits: Smoking, alcohol use, high number of sedentary hours daily.
Risk factors specific for systemic lupus erythematosus
• **Medication use** [glucocorticoids, gonadotropin-releasing hormone agonists, cytotoxic drugs, antimalarial agent (HCQ)]. • Metabolic causes. – High frequency of vitamin D deficiency. – High homocysteine level. – Hormonal changes in SLE, a relatively high estrogen and low dehydroepiandrosterone (DHEA) [100] • Prolonged active SLE. • Systemic and localized inflammation.

10.6.2.2 Pathological Process

- Chronic systemic inflammation is a cause of bone loss in SLE, where the activated inflammatory cells at sites of inflammation produce a wide spectrum of cytokines that stimulate local and generalized bone resorption.
- Researchers have revealed increased serum levels of tumor necrosis factor (TNF) [103] and oxidized low-density lipoprotein (LDL) [104] in patients with active lupus. Oxidized LDL stimulates the activation of T cells, which in turn can increase the production of RANKL and TNF. Consequently, TNF and RANKL will induce the maturation and activation of osteoclasts [103]. In addition, oxidized LDL has the ability to inhibit osteoblast maturation, and hence it can negatively influence bone formation [105].
- Moreover, high levels of homocysteine (caused by inflammation) have been reported in patients with SLE, and this might be attributed to the accelerated bone loss [106, 107] via enhancing the bone resorption and reduction of bone formation.
- Until recently, the previous clinical studies have not been able to demonstrate the association between bone loss in SLE and the disease activity score [108–110]. However, several

studies showed an association between organ damage and reduced BMD [111], and because prolonged active SLE usually causes organ damage in the patients, this finding suggests that disease activity contributes to reduced BMD in SLE. Moreover, the Hopkins Lupus Cohort study [112] has established that low complement C4 levels (a measure of active disease) were a predictor of low spine BMD among patients with SLE.

10.6.2.3 Management of Bone Loss in SLE

- To approach bone health in SLE patients, the underlying risk factors for bone loss should be evaluated. For instance, evaluation of calcium and vitamin D levels and homocysteine status is recommended. Although there is not enough data relating the low levels of vitamin D and SLE activity, the possible association would suggest that replacement of vitamin D may have benefits beyond bone health for those patients [113].
- Supplementation with vitamin D should aim to keep the serum 25-hydroxyvitamin D [25(OH)D] level above 25 ng/mL, and calcium supplementation should be at the recommended daily allowance for the age of the patient (Table 10.2).
- Bear in mind that it takes approximately 3 months to achieve a steady state of 25(OH)D level once vitamin D supplementation is started, so rechecking a 25(OH)D should not be done earlier than 3 months [114, 115].
- Moreover, if homocysteine levels are elevated, folic acid should be initiated at 1 mg daily [116].
- Patients with SLE are at increased risk of bone loss due to the synergistic effect of the inflammatory process and its treatment with corticosteroids; therefore adequate management is essential to prevent osteoporotic fractures and maintain BMD. However, all preventative measures and pharmacological therapy will be mentioned later on under the section of "Glucocorticoid-Induced Osteoporosis" according to ACR 2010 recommendations.

Table 10.2 ACR 2010 Recommendations on counseling for lifestyle modification and assessment of patients starting glucocorticoids at any dose of >3 months duration

ACR 2010 recommendations on counseling for lifestyle modification
• Weight-bearing activities
• Smoking cessation
• Avoidance of excessive alcohol intake (>2 drinks per day).
• Nutritional counseling on calcium and vitamin D intake.
• Fall risk assessment .
• Baseline dual x-ray absorptiometry .
• Serum 25-hydroxyvitamin D level .
• Baseline height .
• Assessment of prevalent fragility fractures .
• Consider radiographic imaging of the spine or vertebral fracture assessment for those initiating or currently receiving prednisone 5 mg/day or its equivalent.
• Calcium intake (supplement plus oral intake) 1200–1500 mg/day[a].
• Vitamin D supplementation[a].

[a]Recommendations for calcium and vitamin D supplementation are for any dose or duration of glucocorticoids, rather than a duration of 3 months

10.6.3 Ankylosing Spondylitis and Bone Loss

Inflammation in ankylosing spondylitis (AS) is characterized by **subchondral bone marrow edema with subchondral bone** *erosive lesions* and eventually to **subchondral new** *bone formation* through the articular cartilage and ossification of the periarticular ligaments [85].

Bone edema is accounted as a sign of inflammatory activity and may affect limited or extensive parts of vertebrae (Fig. 10.10). Recent studies suggested a possible sequence of events of new bone formation in AS, as follows: first erosions at the site of inflammation, followed by repair reaction, and subsequently ended by new bone formation (10).

- *For instance*, at the corners of the vertebral bodies, there might be *marginal erosive lesions* with adjacent subchondral edema and sclerosis (Romanus lesion). Also, a new periosteal intraosseous *bone formation* was found and provided the typical picture of squaring of the vertebrae [85].

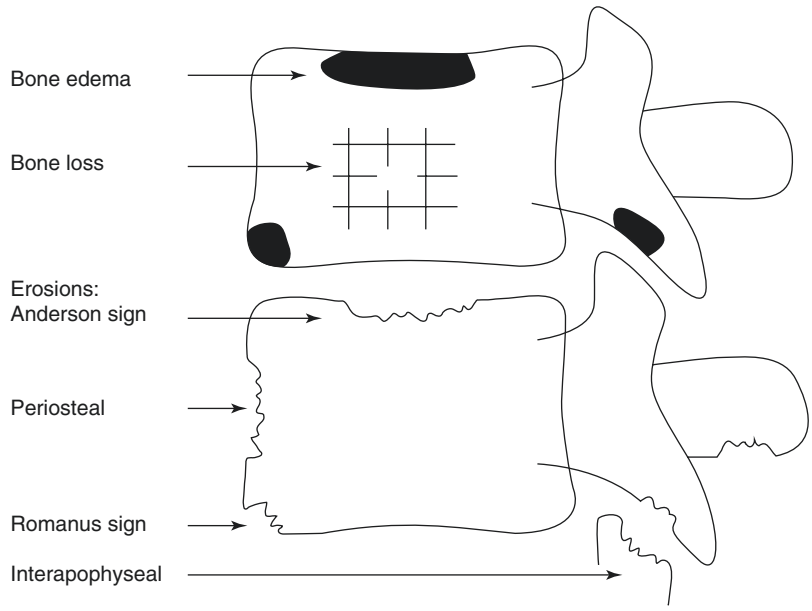

Fig. 10.10 Sites of bone edema, bone loss, and bone erosion in AS [85]

10.6.3.1 Fracture Risk in AS

Subsequent results to bone changes in AS lead to an increase in bone loss (osteoporosis) and bone fragility and therefore increased the risk of bone fractures.

- AS is associated with an elevated risk of vertebral fractures, which are six to seven times higher than in healthy population [117, 118], and these fractures are often accompanied by neurological signs and symptoms [119]. However, the increased in morphometric and clinical vertebral fractures [120] but not in peripheral (forearm or hip) fractures indicates a more local effect of AS on bone, unlike RA, where the inflammatory effects are more systemic. Furthermore, despite sharing similar pathogenesis of osteoporosis but with different clinical phenotypes, bone loss in AS is accompanied by new bone formation contrasting to RA and postmenopausal conditions,
- Of most important types of spinal fractures in AS includes wedging fracture, which contributes to spine rigidity and hyperkyphosis of upper part of the spine and impaired physical function [119, 121, 122]. In addition to wedging fracture, structural damage of the spine and the disease activity are other significant contributors to hyperkyphosis [123].

10.6.3.2 Management of Bone Loss in AS

- Because of the concomitant bone loss and the new abnormal bone formation and the presence of syndesmophytes, the reliability of BMD measurement is affected, and there would be a large variation in the prevalence of osteoporosis in patients with AS [124, 125].
- Taken together, AS is characterized by bone and cartilage degradation. The bone destruction reflects the systemic inflammatory effects on bone density and can be inhibited by TNF-α blocking agent. However, the cartilage damage might be related to syndesmophyte formation, which is not influenced by anti-inflammatory therapy [120]. This highlights the suggestion that bone degradation and new bone formation are uncoupled mechanisms in AS, the reason that might make their therapeutic intervention basically different.
- A remarkable but yet not confirmed finding has shown that the risk of clinical fracture

decreased in AS patients taking NSAIDs, which could relieve the inflammatory back pain and stiffness and thus improving the physical activity that helped in maintaining bone mass and reducing the risk of falling and subsequent fracture [126, 127]. In addition, it has recently been suggested that NSAIDs may also inhibit the formation and growth of syndesmophytes of AS in the spine via interfering with the prostaglandin metabolism. Therefore, if the divergent inhibitory effects of NSAIDs on osteoporotic fractures (bone loss) and progression of syndesmophytes (bone formation) can be confirmed, this would be an important clue in further explaining pathophysiological mechanisms in AS.

- In contrast to the treatment of osteoporosis in patients with RA, treatment of osteoporosis in patients with AS is not yet common. Data supporting the efficacy of this treatment in AS are rare. Of all bisphosphonates, alendronate and risedronate are found to be effective in increasing BMD in men. Alendronate and risedronate significantly increase BMD in both vertebrae and femur, with a significant reduction of vertebral fractures [128, 129]. More recently teriparatide was tested with the same aims, but only a positive effect on BMD could be shown [130]. It is clear that there is a need for evidence-based knowledge in these fields in the near future. Our studies highlight the need to develop strategies to identify high-risk patients with AS. Research on the treatment of osteoporosis to prevent vertebral fractures in these patients is urgently needed.

10.6.4 Glucocorticoid-Induced Osteoporosis (GIOP)

Steroids are widely used in the medical practice to treat various diseases such as asthma, systemic connective tissue diseases, and other autoimmune diseases and in addition to rheumatic diseases. Treatment with GCs results in bone loss within 1 month after initiation of the therapy but primarily occurs in the trabecular bone, so that it mainly increases the risk of vertebral fracture rather than non-vertebral fractures [79]. Fractures are considered the most clinically relevant risk of prolonged steroid therapy.

GIOP is a common type of secondary osteoporosis which occurs at any age and in both men and women. It has been known that one loss in GIOP is biphasic, with a rapid reduction in BMD of 6–12%* which occurs followed by a slower annual loss of about 3%* for as long as the glucocorticoids are administered [131, 132].

10.6.4.1 Impact of GIOP

- As a consequent to the bone loss during GCs therapy, it has been reported that the relative fracture risk within the first 3 months after initiation of the therapy increases by 75% even before any BMD changes occur [133].
- Although the increase of fracture risk has appeared to be dose dependent [134], it was found to be partially reversible so that the fracture risk would gradually return to baseline [135].

10.6.4.2 Approaching Managements of Patients with GIOP

- American College of Rheumatology (ACR) have developed and updated recommendations to provide guidance for prevention and treatment of GIOP in order to be applied by the physicians in light of each patient's circumstances.
- ACR recommendation 2001 [136] has been updated and replaced by ACR recommendation 2010 [137], which had expanded the recommendations for counseling (Table 10.2) and monitoring updated pharmacological guidelines and used patient's overall clinical risk instead of T score alone.
  - Afterward, ACR 2017 recommendations have been released for GIOP prevention and treatment, based on the balance of relative benefits and harms of the treatment options and highly considering the quality

of the evidence and patients' values and preferences [138]. Therefore, due to limited evidence on the benefits and harms of interventions in GC users, most recommendations in ACR 2017 guidelines are conditional or of good clinical practice. The strength of the recommendations is based on the fracture risk categories in GC-treated patients [138].

– The ACR 2017 recommendations for GIOP prevention and treatment have addressed, in addition to all adults' categories (< 40 years and > 40 years of age), special populations categories, namely children, people with organ transplants, women of childbearing potential, and people receiving very high-dose GC treatment.
– The initial approach of patients with GIOP begins with clinical assessment of fracture risk by interpreting detailed clinical and biochemical data, together with identifying the diagnostic criteria for assessment of bone mineral density (BMD) results, as follows:

1. **Clinical Assessment**: This is concerned with having detailed medical history to identify the cumulative risk factors for bone loss (Fig. 10.11) and performing proper physical examination to detect any underlying medical conditions or evidence of osteoporosis such as fracture, kyphosis, and loss of height or determine muscle strength and size.
2. **Biochemical Assessment:** The baseline levels of the following parameters are needed to be obtained in order to rule out any underlying medical diseases that may affect the outcome of GIOP such as low levels of calcium or vitamin D; those would affect the bone formation and metabolism [137, 138]. These parameters include:
   - Complete blood cell count.
   - Serum calcium and phosphorus.
   - Serum 25-hydroxyvitamin D.
   - Serum-free testosterone in males.
   - Estradiol in premenopausal women.
   - Renal Function Tests specifically 24-hour urinary calcium and sodium.
   - Liver function test, because healthy liver is important for synthesis of sex hormones.
3. **Assessment of Bone Mineral Density (BMD):** Measuring the BMD is one of the salient determinants of bone strength. It can be measured at different sites in the body by distinct methods. For instance, dual-energy x-ray absorptiometry (DXA) measures BMD mainly at lumbar spine and proximal femur, while quantitative computed tomography (QCT) is used mostly to estimate bone density at the forearm, tibia, or lumbar spine. The World Health Organization (WHO) has defined the diagnostic criteria for assessment of BMD results (Table 10.3) [139].
4. **Assessment and Classification of Fracture Risk:** Identifying patients with increased fracture risk solely using BMD assessment has some limitations due to its age dependency and its inaccuracy in measuring bone quality. Therefore, it has been recommended that fracture risk should be assessed using tools that calculate the absolute fracture risk for a given patient. One of the available tools proposed by the World Health Organization (WHO) is called Fracture Risk Assessment (FRAX) tool [140].

   FRAX is a unique model that is considered in calculating the risk of the following factors, **age, sex, race,** family history, the BMD, and the usage of BMD, but excludes the dosage and the evaluation of the risk factors of falls and the presence or absence of prevalent vertebral deformities, although they are known as risk factors for fractures. The output of FRAX calculation is a 10-year probability of hip fracture and the 10-year probability of a major osteoporotic fracture (clinical spine, forearm, hip, or shoulder fracture) [140].
   - Based on the risk factors shown in Fig. 10.11 as well as the FRAX results, adult patients receiving GC can be classified into low-, moderate-, and high-risk categories accordingly (Fig. 10.12). The ACR 2017 recommendations for GIOP prevention and treatment have addressed, in addition to all adults' categories (< 40 years and > 40 years of age), special populations, namely children, people with organ transplants, women of childbearing potential, and people receiving very high-dose GC treatment.

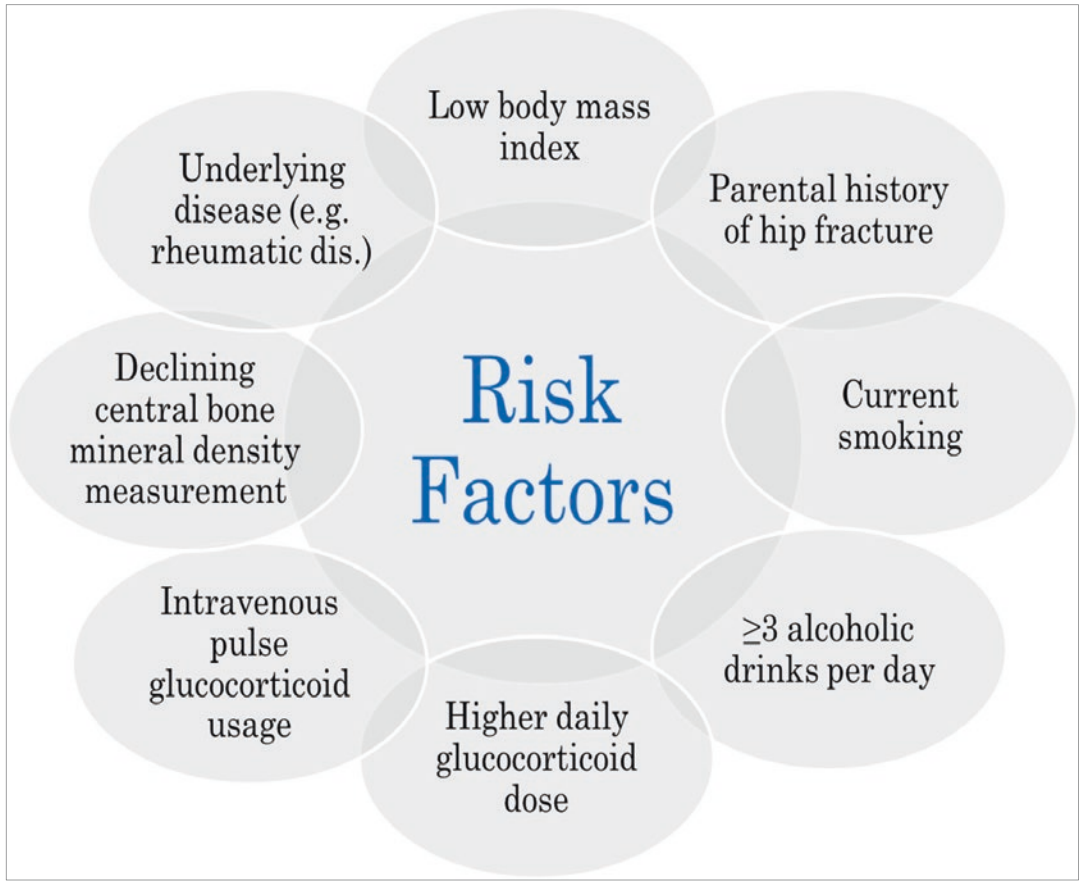

Fig. 10.11 Risk factors that may shift an individual to a greater risk category for GIOP (ACR 2010) [137]

Table 10.3 WHO criteria for assessment of BMD [139]

Diagnostic Criteria	Classification
T*= 0 to -1 SD	Normal
T = -1 to -2 SD	Osteopenia
T ≤ -2.5 SD	Osteoporosis
T ≤ -2.5 SD + fragility fractures	Severe osteoporosis

*T scores is the number of standard deviations(SD) below or above the peak bone mass in a young adult reference population of the same sex.

- Therefore, the primary implication of ACR 2017 recommendation is to clarify that all clinicians treating patients with GCs have to be aware of the GIOP risk, identify patients at high fracture risk (Fig. 10.12), and be able to provide the appropriate treatment [138].
- Moreover, the assessment of fracture risk may not only be useful in treatment decisions, but also in improving patients' treat-

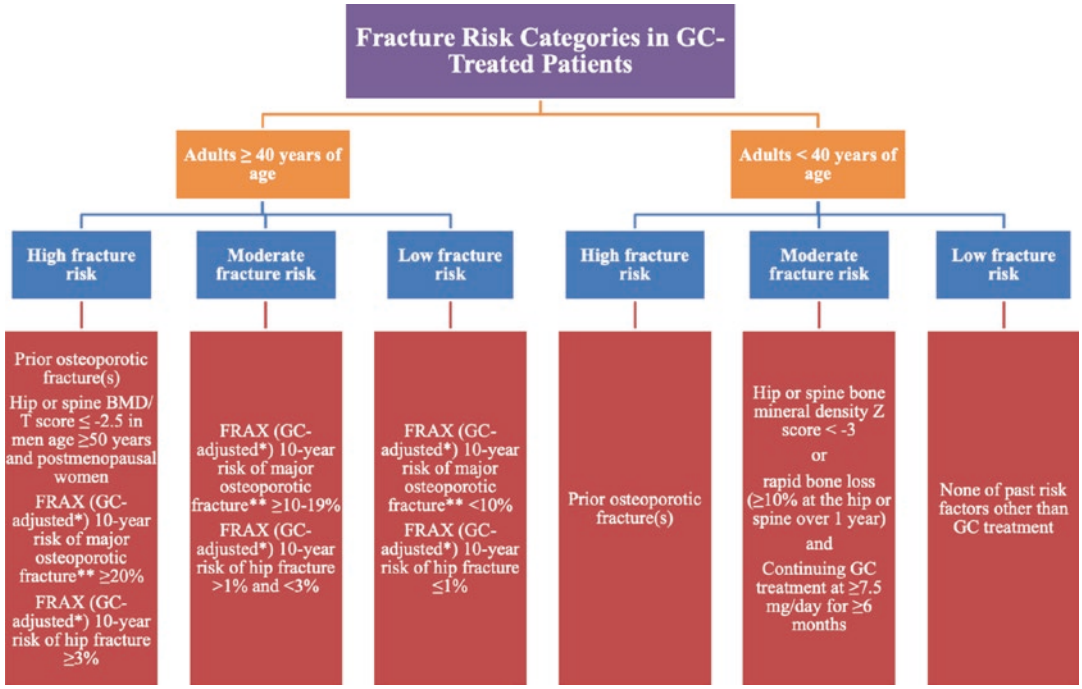

Fig. 10.12 Fracture risk categories in GC-treated patients [138]

ment compliance that would provide the patients a better insight into their future fracture risk.

10.6.4.3 Recommendations for Fracture Risk Assessment and Reassessment of Patient with GIOP

These recommendations are considered as good practice recommendations.

- Initial fracture risk assessment:

  For all adults and children, an initial clinical fracture assessment should be performed as soon within six months of the initiation of long-term GC treatment. This clinical assessment should include the following:
  - A detailed clinical history of GC use (dose, duration, mode, and pattern of use),
  - An evaluation of underlying risk factors for fracture including history of falls, fractures, frailty, others such as (malnutrition, significant weight loss or low body weight, hypogonadism, secondary hyperparathyroidism, thyroid disease, family history of hip fracture, history of alcohol use [at > 3 units/day] or smoking), and other clinical comorbidities.
  - A physical examination including measurement of weight and height, detailed examination of musculoskeletal system, and other clinical findings of undiagnosed fracture (e.g., spinal tenderness, deformity, and reduced space between lower ribs and upper pelvis).

  For adults >40 years old, the initial absolute fracture risk should be evaluated using FRAX with correction of GC dose and BMD (if available) as prompt as possible but within at least six months of starting the GC therapy (Fig. 10.13) [138].

  For adults <40 years old, BMD testing should be done as promptly as possible but at least within 6 months of starting the GC treatment if the patient has a history of previous OP fracture(s) (high risk) or if the patient has

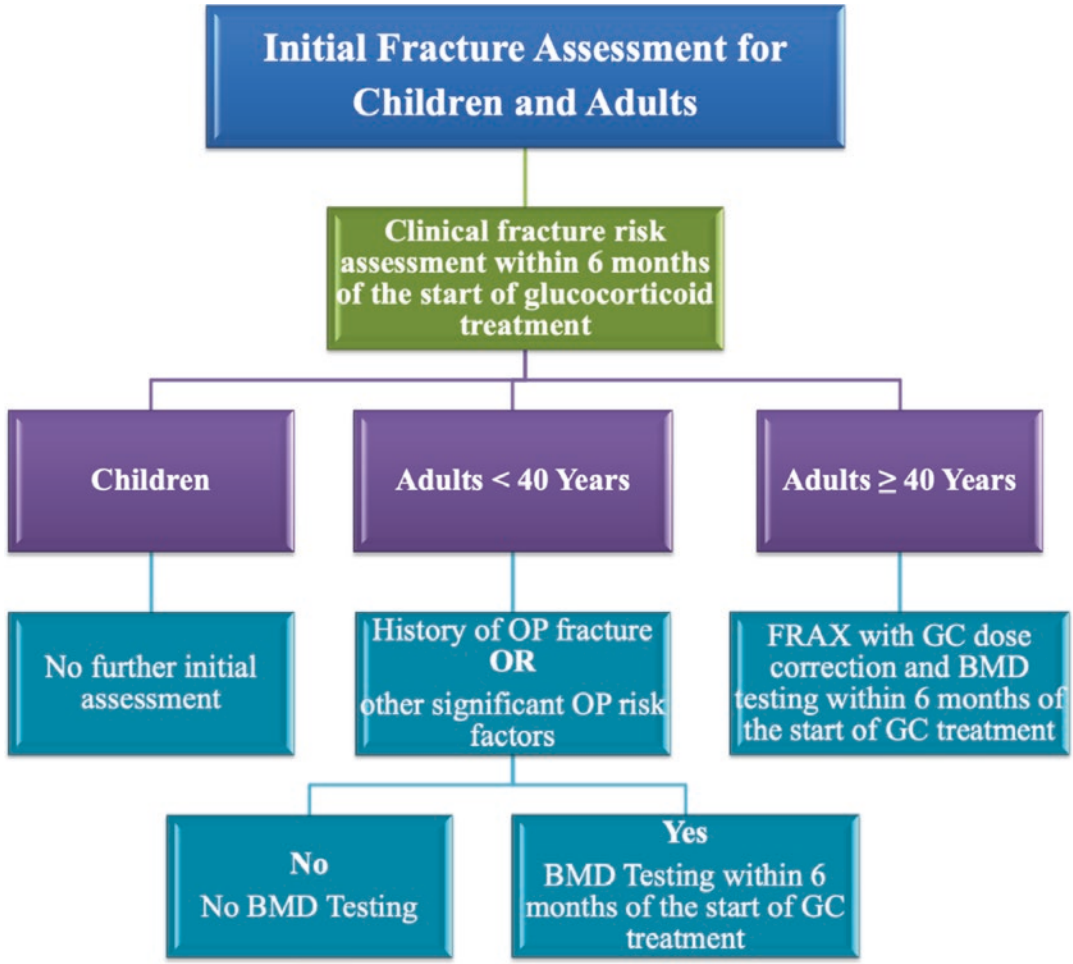

Fig. 10.13 Initial fracture risk assessment [138]

other significant OP risk factors (Fig. 10.13) [138].

- Reassessment of fracture risk:

  For all adults and children, if GC therapy is used continuously, a clinical fracture risk reassessment (as referred earlier) should be performed every 12 months. For detailed pathways of reassessment of clinical fracture risk in adults <40 and ≥40 years of age, refer to Fig. 10.14 [138].

10.6.4.4 Recommendations for Initial Treatment and Prevention of GIOP

- In addition to adjusting the pharmacologic treatment of GIOP, optimizing the dose of calcium and vitamin D uptake and counseling lifestyle modification are included within both the ACR 2010 and the ACR 2017 recommendations for treating patients with GIOP.
- A conditional recommendation is reported, generally for all adults on GC at a dose of ≥2.5 mg/day for ≥3 months, to optimize calcium intake (1000–1200 mg/day) and vitamin D intake (600–800 IU/day; serum level ≥20 ng/mL) [138, 141] alongside lifestyle modification with regard to weight, nutrition, smoking, and alcohol intake (Table 10.2).
- For children 4–17 years of age receiving GC therapy, a calcium intake of 1000 mg/day and vitamin D of 600 IU/day is recommended.

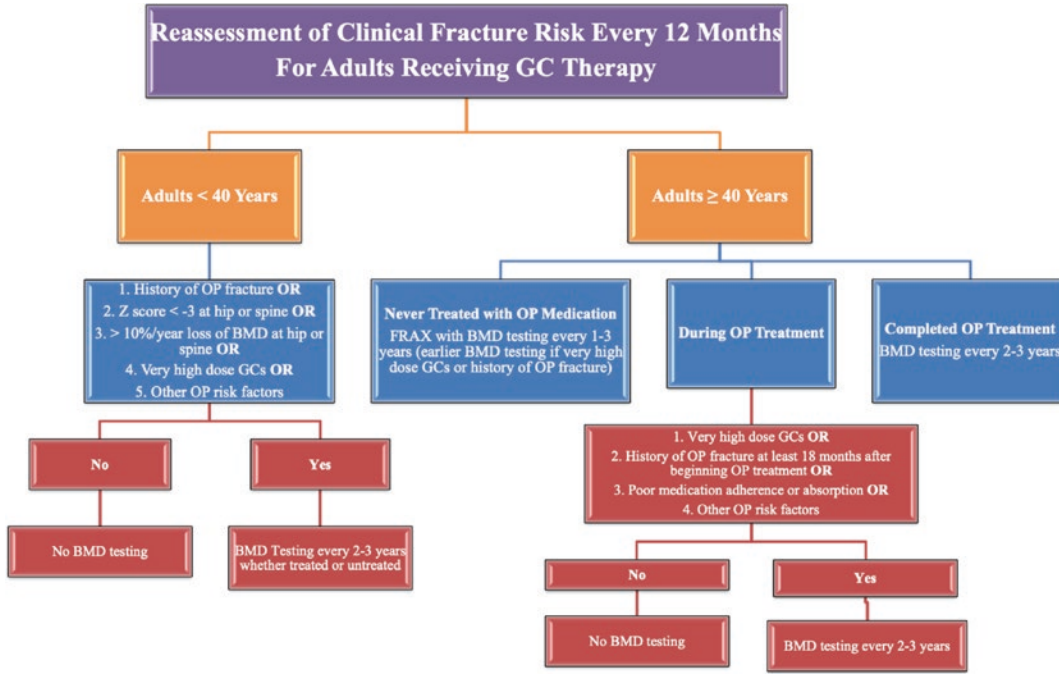

Fig. 10.14 Reassessment of fracture risk [138]

- The ACR 2017 recommendations of initial pharmacologic treatment are categorized according to the following groups and are highlighted in Fig. 10.15 and Table 10.4.
  - All adults >40 years of age, they are divided into women >40 years old but not of childbearing potential, and men >40 years old, who are at moderate to high risk of fracture (Fig. 10.15).
  - Adults <40 years of age, includes (women not of childbearing potential and men) with a history of OP fracture, or those continuing GC treatment (>6 months at a dose of >7.5 mg/day), who have either a hip or spine BMD with Z score <−3 or DXA result reveals bone loss of >10%/year at the hip or spine (Fig. 10.15).
  - Special populations that have further subgroups including (Table 10.4):

    Women who meet criteria for moderate-to-high risk of fracture and are of childbearing potential but do not plan to become pregnant within the period of OP treatment and are using effective birth control or are not sexually active.

    Adults >30 years of age who are receiving very high-dose GC treatment (initial prednisone dose of >30 mg/day [or equivalent GC exposure] and a cumulative annual dose of >5 gm) (Table 3 of main reference).

    Adults who have received an organ transplant and who are continuing treatment with GCs.

    GC-treated children at 4–17 years of age are further subdivided into two groups (Table 10.4).

10.6.4.5 Rationale of Pharmacotherapy of GIOP

- GIOP can be partially prevented by using bisphosphonates (alendronate and zoledronic acid) [142]. However, oral bisphosphonates are limited by low adherence rates, and therefore zoledronic acid provides the intravenous form of this medication and can be prescribed rather than the patient receiving no additional therapy beyond calcium and vitamin D.
- On the other hand, PTH 1-34 (teriparatide) therapy seems to be superior to oral bisphos-

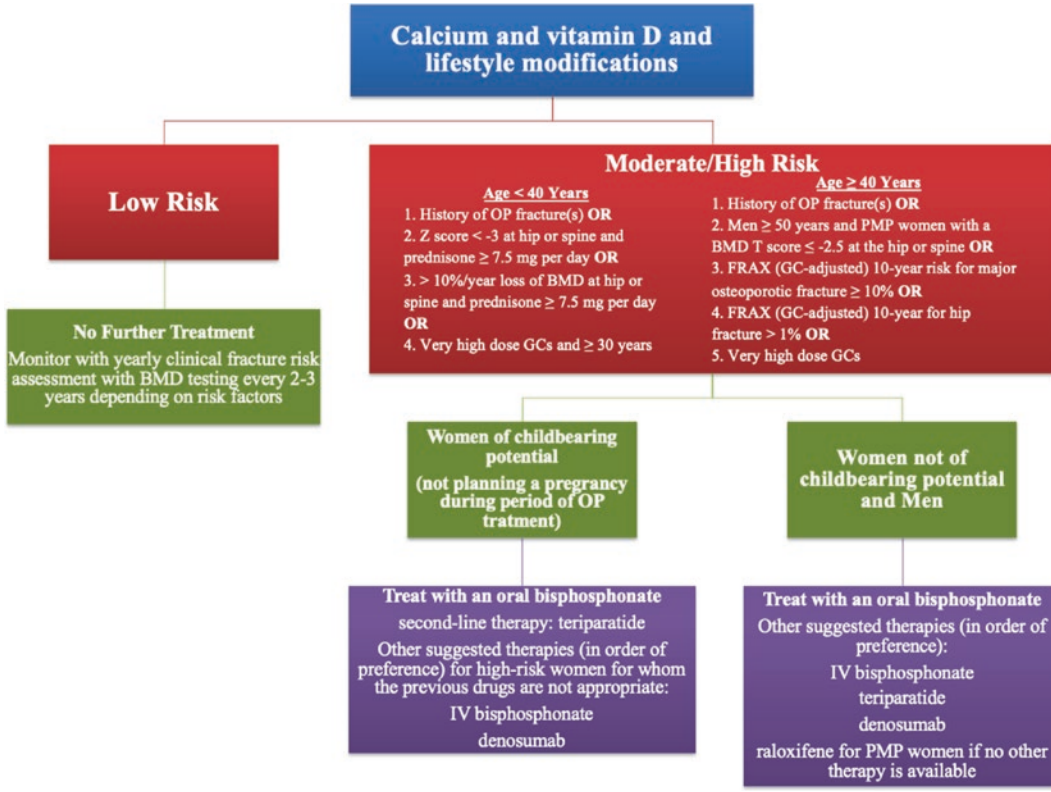

Fig. 10.15 Initial pharmacologic treatment for adults [138]. Recommended doses of calcium and vitamin D are 1000–1200 mg/day and 600–800 IU/day (serum level ≥20 ng/mL), respectively. Lifestyle modifications include a balanced diet, maintaining weight in the recommended range, smoking cessation, regular weight-bearing and resistance training exercise, and limiting alcohol intake to 1–2 alcoholic beverages/day. Very high-dose glucocorticoid (GC) treatment was defined as treatment with prednisone ≥30 mg/day and a cumulative dose of >5 gm in the past year. The risk of major osteoporotic (OP) fracture calculated with the FRAX tool should be increased by 1.15, and the risk of hip fracture by 1.2, if the prednisone dose is .7.5 mg/day (e.g., if the calculated hip fracture risk is 2.0%, increase to 2.4%)

phonates but is more expensive [143] and can be used if bisphosphonate is not appropriate.

- If neither oral nor IV bisphosphonates nor teriparatide treatment is appropriate, denosumab should be used rather than the patient receiving no additional treatment beyond calcium and vitamin D. Denosumab is a humanized monoclonal antibody to RANKL and is useful for GC-treated patients with renal insult but with stable serum Ca^{+2} levels and are not candidates for bisphosphonates or teriparatide. Denosumab has been approved for the prevention of vertebral and non-vertebral fractures, in women with postmenopausal osteoporosis [144]. Moreover, it was revealed that denosumab therapy increased spine and hip BMD and reduced bone turnover markers for 12 months in patients received GC [145]. A recent randomized, doubleblind, comparative study of denosumab and risedronate in patients ≥19 years of age taking prednisolone ≥7.5 mg/day for ≥3 months reported that denosumab significantly increased spine and femoral BMD compared to risedronate [146].
- If none of these medications is appropriate for postmenopausal women, raloxifene [selective estrogen receptor modulator (SERM)] should be used rather than the patient receiving no additional treatment beyond calcium and vitamin D. The order of the preferred treatments

Table 10.4 Recommendations for initial treatment for prevention of GIOP in special populations of patients beginning long-term GC therapy [138]

Recommendations for initial treatment for prevention of GIOP in special populations
Women of childbearing potential at moderate-to-high risk of fracture who do not plan to become pregnant within the period of OP treatment and are using effective birth control or are not sexually active Treat with an oral bisphosphonate over calcium and vitamin D alone, teriparatide, IV bisphosphonates, or denosumab. Oral bisphosphonates preferred for safety, cost, and because of lack of evidence of superior antifracture benefits from other OP medications. Other therapies if oral bisphosphonates are not appropriate, in order of preference: Teriparatide Safety, cost, and burden of therapy with daily injections Consider the following therapies only for high-risk patients due to lack of safety data on use of these agents during pregnancy: IV bisphosphonates Potential fetal risks of IV infusion during pregnancy Denosumab Potential fetal risks during pregnancy Conditional recommendations because of indirect and very low-quality evidence on benefits and harms of these treatments to the fetus during pregnancy
Adults age ≥30 years receiving very high-dose GCs (initial dose of prednisone ≥30 mg/day and cumulative dose >5 gm in 1 year) Treat with an oral bisphosphonate over calcium and vitamin D alone. Treat with an oral bisphosphonate over IV bisphosphonates, teriparatide, or denosumab. Oral bisphosphonates preferred for safety, cost, and because of lack of evidence of additional anti-fracture benefits from other OP medications. If bisphosphonate treatment is not appropriate, alternative treatments are listed by age (≥40 years and <40 years) in Fig. 10.15 Conditional recommendations because of low-quality evidence on absolute fracture risk and harms in this population
Adults with organ transplant, glomerular filtration rate ≥30 mL/min, and no evidence of metabolic bone disease who continue treatment with GCs Treat according to the age-related guidelines for adults without transplants with these additional recommendations: An evaluation by an expert in metabolic bone disease is recommended for all patients with a renal transplant. Recommendation against treatment with denosumab due to lack of adequate safety data on infections in adults treated with multiple immunosuppressive agents. Conditional recommendations because of low-quality evidence on antifracture efficacy in transplant recipients and on relative benefits and harms of the alternative treatments in this population
Children ages 4–17 years treated with GCs for ≥3 months Optimize calcium intake (1000 mg/day) and vitamin D intake (600 IU/day) and lifestyle modifications over not optimizing calcium and vitamin D intake and lifestyle modifications. Conditional recommendation because of lack of antifracture efficacy of calcium and vitamin D in children but limited harms
Children ages 4–17 years with an osteoporotic fracture who are continuing treatment with GCs at a dose of ≥0.1 mg/kg/day for ≥3 months Treat with an oral bisphosphonate (IV bisphosphonate if oral treatment contraindicated) plus calcium and vitamin D over treatment with calcium and vitamin D alone. Conditional recommendation because of very low-quality antifracture data in children but moderate-quality evidence of low harms of oral bisphosphonates in children and less potential harm of oral over IV bisphosphonates

GIOP glucocorticoid (GC)-induced osteoporosis, *IV* intravenous

was established according to a comparison of efficacy (fracture reduction), toxicity, and cost.

10.6.4.6 Follow-up Treatment Recommendations

Initial treatment failure is defined if the osteoporotic fracture occurs after 18 months of treatment initiation with oral bisphosphonate or if there is significant BMD reduction (≥10%/year) at follow-up. Various categories of treatment failure of GIOP are explained in Table 10.5 with appropriate recommendations according to the reassessment of fracture risk status.

10.7 Summary

Chronic inflammatory diseases, namely, rheumatic diseases such as rheumatoid arthritis, systemic lupus erythematosus, and ankylosing spondylitis, are commonly associated with extra-articular side effects, including bone loss and fractures. Osteoporosis-related fragility fractures represent one of the most important adverse outcomes that may occur in patients with rheumatic diseases. These fractures may contribute to a significant decrease in quality of life and thus would have a great impact on the economic status of the society.

Table 10.5 Recommendations for follow up treatment for prevention of GIOP [138]

Recommendations for follow-up treatment for prevention of GIOP according to reassessment of fracture risk
Adults age ≥40 years continuing GC treatment who have had a fracture that occurred after ≥18 months of treatment with an oral bisphosphonate or who have had a significant loss of bone mineral density (≥10%/year) [Definition of Treatment Failure] Treat with another class of OP medication (teriparatide or denosumab; or, consider IV bisphosphonate if treatment failure is judged to be due to poor absorption or poor medication adherence) with calcium and vitamin D over calcium and vitamin D alone or over calcium and vitamin D and continued oral bisphosphonate. Conditional recommendation because of very low-quality evidence comparing benefits and harms of the compared treatment options in this clinical situation.
Adults age ≥40 years who have completed 5 years of oral bisphosphonate treatment and who continue GC treatment and are assessed to be at moderate-to-high risk of fracture: Continue active treatment, without drug holiday, (with an oral bisphosphonate beyond 5 years or switch to IV bisphosphonate [if concern with regard to adherence or absorption] or switch to an OP treatment in another class) over calcium and vitamin D alone. Conditional recommendation because of very low-quality data on benefits and harms in GC-treated patients, but moderate-quality data in the general OP literature on benefits and harms of continuing treatment with oral bisphosphonates past 5 years for people at high risk of fracture.
Adults age ≥40 years taking an OP medication in addition to calcium and vitamin D who discontinue GC treatment and are assessed to be at low risk of fracture: Discontinue the OP medication but continue calcium and vitamin D over continuing the OP medication. Conditional recommendation made by expert consensus; evidence informing it too indirect for the population and very low-quality.
Adults age ≥40 years taking an OP medication in addition to calcium and vitamin D who discontinue GC treatment and are assessed to be at moderate-to-high risk of fracture: Complete the treatment with the OP medication over discontinuing the OP medication. Strong recommendation for high-risk patients based on expert consensus that patients who are at high risk should continue an OP treatment in addition to calcium and vitamin D. Conditional recommendation for moderate-risk patients because of lower fracture risk compared to potential harms.

The concept of osteoimmunology elucidates in depth the links between the immune system and bone physiology. The predisposing factors that cause the underlying pathology of bone loss in rheumatic patients are multifactorial. In addition to the traditional background fracture risks, such as age, BMI, and gender, there are potential bone loss mediators that substantially increase fracture risk in these patients. Of these common mediators are inflammation (high disease activity), immobility, and treatment with glucocorticoids. Other mediators would contribute in bone loss in rheumatic patients and may include poor nutrition, the increase of catabolic state, and the decrease in reproductive hormones (hypogonadism) in both men and women.

These effector mediators appear to interact in a complex and synergistic way to reinforce each other through various mechanisms that act on a shared common pathway, the bone remodeling cycle. The net result of these mediators is the production of a wide spectrum of cytokines that stimulate local and/or generalized bone resorption and that inhibit (as in RA) or stimulate (as in AS) bone formation. For instance, during the inflammatory process, the Wnt-signaling antagonist (DKK-1) is secreted from the synovial fibroblast and inhibits osteoblast maturation and OPG function leading to suppression of local bone formation. Therefore, administration of anti DKK-1 would be useful to prevent bone erosions and reverse the inhibition on bone formation. However, immobility will suppress the mechanosensing process of osteocytes leading to uncoupling of bone formation and bone resorption through the Wnt-signaling pathway.

Although GCs are frequently prescribed for the rheumatic patients, they have a great adverse impact on bone quality leading to GIOP. The overall effects of GCs on bone are either directly on bone cells or indirectly by affecting the bone metabolism, both of which result in enhancing bone resorption and decreasing bone formation. Inhibition of bone formation by GCs occurs by increasing the osteoblast and osteocyte apoptosis and/or impairing osteoblast function via suppressing the BMP pathway and the Wnt-signaling pathway. On the other hand, GCs can stimulate bone resorption by reducing osteoclast apoptosis via upregulation of RANKL and inhibition of OPG.

GIOP is a significant clinical complication that occurs as a result of adverse effects of the prescribed GCs for patients with rheumatic disease. ACR 2010 had set several recommendations updated that of ACR 2001 for evaluating and monitoring patients, who has just initiated or received GCs for/or more than 3 months duration. However later, ACR 2017 recommendations have been released and aimed to standardize the classification of patients at risk of GC induced fracture (Fig. 10.12). So that the appropriate recommendations can be applied on each category, while reducing the risk and burden of radiological testing and the anti-fracture therapy. Therefore, all clinicians treating patients with GCs should be aware of these fracture risks and identify the patient's level of fracture risk according to the ACR 2017 guidelines for assessment and reassessment of fracture risks. The recommendations of anti-fracture pharmacotherapy in order of preference, for prevention and treatment of GIOP, were based on their efficacy, potential harms, and cost. Hence, oral bisphosphonates were recommended as preferred first-line therapy over other recommended anti-fracture therapies.

Taking together, the salient approach for early diagnosis of rheumatic diseases would be very crucial and of great help in diminishing the magnitude of bone destruction that occur during the pathogenesis of these diseases and therefore preventing further bone erosion and osteoporosis. Finally, GIOP is a medical problem that patients should be aware of its fracture risk and clinicians should consider evaluating the fracture risks for all GC-treated patients and actively prevent reduction of bone mass.

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Fever and Rheumatology

11

Mohamed Cheikh and Nezar Bahabri

11.1 Introduction

In all the patients with rheumatic diseases, fever should prompt an immediate and thorough evaluation. There are different disorders that can cause fever and arthritis. Fever that is thought to be due to active rheumatic disease is seen in over 50% of patients with SLE30. However, it can be also related to or a sequel of an infectious process. There are many infectious diseases with rheumatological manifestations. The aim of this chapter therefore is to address variable relationships of fever with patients with arthritis. Fever of unknown origin will be addressed as some systemic rheumatic disease may present with fever. It is always a dilemma when an established patient with arthritis presents with fever. What should you do? This issue is addressed with a suggested diagnostic approach that guides you in a stepwise manner until you reach to the definitive diagnosis.

A quick review of rheumatological manifestations of some infections is presented. This is to widen your knowledge about this area in medicine and not to ignore common viruses, for example, in your differential diagnosis of fever and arthritis. Vaccination is quite an ignored aspect of clinical practice among patients with arthritis.

The objective of this chapter is to provide a systemic approach to patient with fever and arthritis.

Specific objectives:

By the end of the chapter the reader should be able to:

- Approach a patient with fever of unknown origin.
- Approach a patient with known rheumatological disease presenting with fever and recognize the common infections that affect immunocompromised patients.
- Recognize the rheumatological manifestations of common infectious diseases.
- Provide a safe and proper method of vaccinations to patients with rheumatological disease.

M. Cheikh (✉) · N. Bahabri
Doctor Soliman Fakeeh Hospital,
Jeddah, Saudi Arabia
e-mail: Mohamed.m.cheikh@gmail.com

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11.2 Fever of Unknown Origin (FUO)

11.2.1 Definition [28]

- Temp >38.3 on several occasions.
- Duration ≥3 weeks.
- No clear diagnosis after 1 week of in-hospital investigation.

11.2.2 Epidemiology

The epidemiology of FUO has changed over time due to scientific and technologic advances (better imaging, more advanced organism isolation, and more understanding of connective tissue disease). A prospective multicenter study on fever of unknown origin showed the following distribution: connective tissue diseases 22%, infection 16%, malignancy 7%, miscellaneous 4%, no diagnosis 51%.

Box 11.1 Initial evaluation for FUO

- Comprehensive History (Table 11.2)
- Detailed Physical examination (Table 11.2)
- CBC with differential & Blood film
- U&E–LFTs–LDH–ESR - CRP
- hepatitis A, B, and C serologies if LFTs are abnormal
- Blood cultures (X3 - different sites - several hours between each set - off antibiotics)
- HIV antibody assay and HIV viral load for patients at high risk
- Urinalysis + microscopic examination + urine culture
- CXR

Epidemiology: Table 11.1 shows the etiologies of FUO.

11.2.3 General Principles in the Treatment of FUO (Table 11.2)

Physician should explain to the patient that FUO is a well-known entity, and it needs time for investigation to decrease anxiety of the patient. Empiric therapy with antimicrobial or glucocorticoids *should not* be given to stable patients with FUO because it often obscure or delay the diagnosis [29]:

- The diagnostic yield of some investigation like cultures will be reduced after starting antimicrobial.
- Empiric treatment of a certain infection can affect other infection (e.g., therapeutic trial for tuberculosis with rifampicin may suppress staphylococcal osteomyelitis or diminish the ability to detect difficult to isolate organisms causing endocarditis.
- The duration of a therapeutic trial is also unclear.
- Initiation of glucocorticoid without rolling out infection can lead to severe life-threatening infections.

There are some exceptions where patient with FUO should be treated empirically. The exceptions are:

1. Septic or hemodynamically unstable patient → empirical treatment.
2. Immunocompromised or neutropenic patient→ empirical treatment.
3. Query giant cell arteritis → treat with corticosteroids until biopsy result → risk of visual loss.

Figure 11.1 shows a suggested algorithm to approach a patient with FUO.

Table 11.1 Etiologies of FUO [1–27]

Infection	• **Tuberculosis**: *require high clinical suspicion as patient can have normal PPD or interferon gamma release assay and may require biopsy to yield diagnosis.* • **Abscesses**: *Intra-abdominal, pelvic, dental, or paraspinal.* • **Osteomyelitis**: *some sites can have no localized symptoms like vertebral and mandibular osteomyelitis.* • **Endocarditis**: *consider culture negative organism→ HACK, Coxiella*, *Bartonella*, *T. whipplei*, *Brucella*, *Mycoplasma*, *Chlamydia*, *Histoplasma*, *and Legionella.* • Other causes: **Brucellosis**, **HIV**, *sinusitis, CMV, EBV, secondary syphilis, Lyme disease, prostatitis, visceral leishmaniasis*, *Q fever*, *leptospirosis*, *psittacosis*, *tularemia*, *melioidosis*, *disseminated gonococcemia*, *chronic meningococcemia*, *Whipple's disease*, *and yersiniosis.*
Connective tissue disease	• **Adult Still's disease**: *evanescent rash*, *arthritis*, *lymphadenopathy*, *and high ferritin.* • **Giant cell arteritis:** >50y, *headache*, *scalp pain*, *visual disturbances*, *myalgias*, *arthralgias*, *high ESR.* • Other: *polyarteritis nodosa*, *granulomatosis with polyangiitis*, *RA*, *SLE*, *psoriatic or reactive arthritis*, *PMR*, *Takayasu's arteritis*, *mixed cryoglobulinemia.*
Malignancy	• Lymphoma (especially non-Hodgkin's). • Leukemia. • Myelodysplasia. • Renal cell carcinoma (*increase HCT*, *microscopic hematuria*). • Hepatocellular carcinoma or other tumors metastatic to the liver. • Multiple myeloma. • Pancreatic and colon cancers, sarcomas, mastocytosis. • Atrial myxomas (*arthralgias*, *emboli*, *and hypergammaglobulinemia*).
Miscellaneous	• Drug-induced fever. • DVT/PE. • Hematoma. • Thyroid storm, thyroiditis, adrenal insufficiency, pheochromocytoma. • Sarcoidosis. • Alcohol or granulomatous hepatitis. • Hereditary periodic fever syndromes: FMF, TRAPS, hyper-IgD syndrome, muckle-Wells syndrome, and familial cold autoinflammatory syndrome.

Table 11.2 Initial evaluation for FUO

History	Physical examination
Carefl and through history including: • Any localizing symptoms. • Travel Hx (TB, malaria, hepatitis, typhoid fever, parasitic infections, Rocky Mountain spotted fever, or Lyme disease). • Exposure to TB patient. • Unpasteurized milk and cheese, • Animal and insect exposure. • Immunosuppression (medication or diseases). • Sexual contacts. • New unusual activity. • Drug and toxin history including alcohol, illicit drug use, over-the-counter medications and recent antimicrobial. • Ethnic background.	Complete physical examination including: • Skin, mucous membranes, and lymphatic system. • Abdominal palpation for masses or organomegaly. • Joint examination and the back → Pott's disease. • Heart auscultation → new murmur (infective endocarditis). • Sinuses. • Prostate examination.

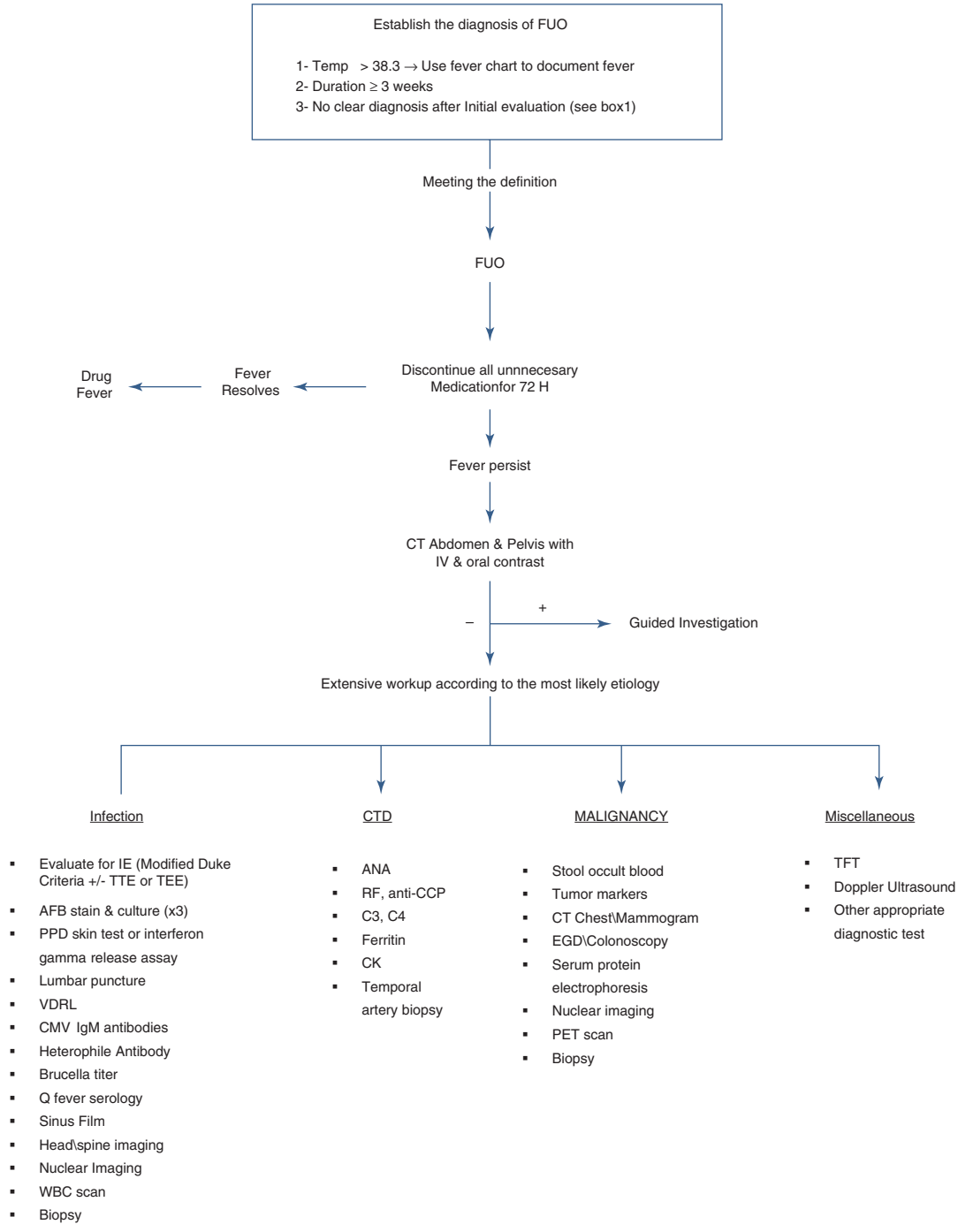

Fig. 11.1 Suggested algorithm to approach patient with FUO

11.2.4 Tips in FUO

- Think of uncommon presentations of common diseases rather than thinking of uncommon diseases.
- <40 Y → infection > rheumatological > malignancy.
- >40 Y → Infection > Malignancy > Rheumatological.
- Rheumatological disease usually present in stable condition.
- Empirical treatment not recommended unless there is an indication.
- If empiric treatment is a must avoid quinolone (TB resistance).
- Chills, rigors, night sweat (infection > rheumatological).
- Most of undiagnosed cases of FUO are related to viruses that we don't usually investigate.
- Viral infections can give a temperature up to 40–41 °C and can persist up to 3 weeks (average 9 days).

11.3 Fever and Rheumatology

11.3.1 Introduction

Approach to fever is a very challenging in a patient with rheumatic disease as it could be an infection, disease activity, or medication side effect. Fever that is thought to be due to active disease is seen in over 50% of patients with SLE [30]. On the other hand, fever is a rare presentation of RA disease activity. Infections are often difficult to diagnose and treat in this group of patient because of the following reasons:

1. Clinical manifestations of infections are often indistinguishable from the underlying disease and vice versa [52–55].
2. The typical signs and symptoms of infection may be absent because of concomitant immunosuppressive therapies [56–58].
3. The anti-inflammatory and antipyretic effects of glucocorticoids may diminish the usual systemic and localizing signs of infection.
4. With the immunosuppressive impact of the medication and the disease itself, the spectrum of potential pathogens is large, making empiric treatment difficult.

In patient with rheumatoid arthritis, bone and joints, skin, soft tissues, and the respiratory tract are the most frequently involved sites in infectious processes [33]. In patients with chronic inflammatory rheumatic or autoimmune diseases without arthritis, infections of the respiratory tract are the most common site. **Finally, ascribing fever to the underlying rheumatological disease itself in an immunosuppressed patient should be done only after reasonable and good efforts have been made to exclude infection.** Figure 11.2 shows suggested algorithm to approach a patient with rheumatic disorder presenting with fever.

Risk factors for infection in a patient with rheumatic disease include:

- Active disease.
- Long-term disease damage.
- Neutropenia.
- Lymphopenia.
- Hypocomplementemia.
- Renal involvement.
- Neuropsychiatric manifestations.
- Use of glucocorticoids and other immunosuppressive drugs.
- Arthrocentesis [23].

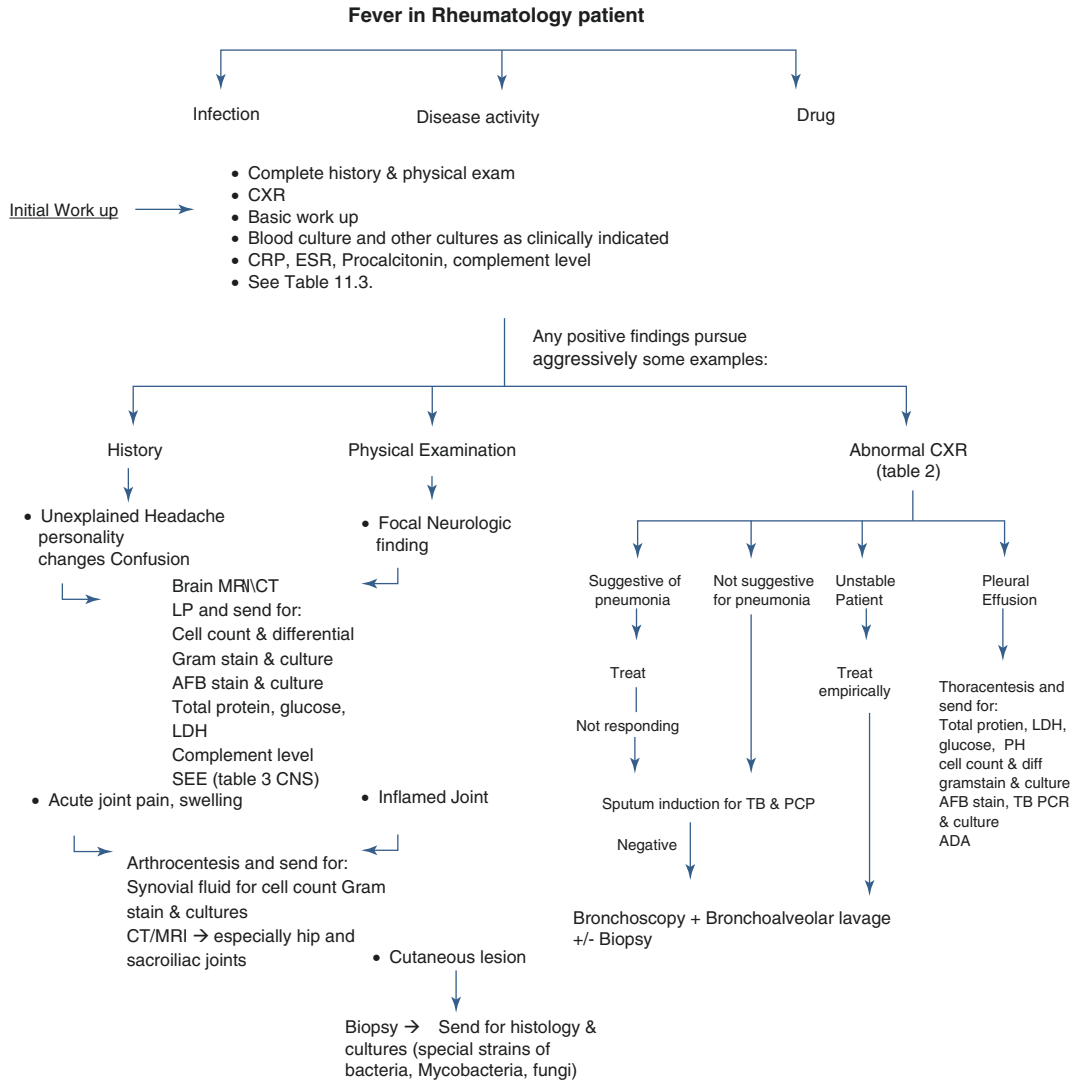

Fig. 11.2 Suggested algorithm to approach a patient with rheumatic disorder presenting with fever

Points to consider in the approach to this group of patients:

- Respiratory viral infections are the most common cause of fever in rheumatological patient as non-rheumatological patient.
- There is no single clinical or laboratory finding that can differentiate between infection, disease activity, or drug-induced insult as a cause of fever. It is rather a collective clinical and laboratory finding with good clinical judgment.
- One of the crucial points in determining the cause of fever is to know the patient's disease activity statues prior to presentation and if he is on immunosuppressive therapy or no.
- Both the patient's underlying rheumatic disease and its therapy need to be taken into con-

sideration when evaluating the white blood cell count in a febrile immunosuppressed patient because:
  - Glucocorticoids therapy can cause a neutrophilic leukocytosis.
  - Cytotoxic drug therapy can impair a patient's ability to mount a neutrophilic leukocytosis in response to infection.
  - Neutrophilic leukocytosis may be a manifestation of certain rheumatic diseases, such as active granulomatosis with polyangiitis [101].
- Recent systemic review and meta-analysis for the utility of procalcitonin as a diagnostic marker for bacterial infection in patients with autoimmune disease showed that:
  - Procalcitonin has higher diagnostic value than CRP for the detection of bacterial sepsis in patients with autoimmune disease, and the test for procalcitonin is more specific than sensitive 32.
  - Procalcitonin test is not recommended to be used in isolation as a rule-out tool 32.

11.4 Fever in Rheumatology Patient

11.4.1 History

Careful and through history including:

- Medication history → immunosuppressed (type and for how long)→ suspect new infection, particular if other signs of active disease have begun to remit.
- Onset of symptoms → few days → infection.
- Days to weeks → disease activity/opportunistic infection
- Fever pattern → episodic → disease activity/infection.
- Sustained → drug/CNS involvement
- Shaking chills occurred in significantly more patients with proven infections (68% versus 27% non-infectious).
- Contact with children (viral infection).
- Recent travel and exposure to TB.
- Vaccination history.

11.4.2 Physical Examination (Table 11.3)

Complete physical examination includes:

- Oral mucosal candidiasis →significant immunodeficiency → increased risk of opportunistic infections, such as PCP [36].
- Erythematous necrotic cutaneous lesions→? Gram-negative sepsis, in particular *P. aeruginosa*.
- Cutaneous vesicular rash → varicella.
- Pulmonary infiltrates + cutaneous lesions→? Disseminated histoplasmosis, *Cryptococcus*, and nocardiosis (Table 11.4).
- Pulmonary infiltrates + focal neurologic deficits→? Disseminated infection with mycobacteria, fungi (C. *neoformans*, *Aspergillus* spp.), or *Nocardia* spp. (Table 11.5).
- A detailed neurologic examination should be performed and repeated frequently to monitor the patient's progress.
- Each patient should undergo a careful ophthalmologic examination looking for papilledema, signs of retinal and choroid infection (e.g., cryptococcosis, toxoplasmosis), and proptosis (suggestive of orbital infection or cavernous sinus involvement).
- Parotid gland enlargement → mumps.

[39–57, 59–99].

Table 11.3 Possible pathogens by the predominant immune system defect caused by pharmacological agent used in the treatment of rheumatic disease [37–38]

Abnormality	Agent	Infection	
Qualitative defect of phagocytic function Or neutropenia	Corticosteroids Cyclophosphamide and other alkylating agents Azathioprine	Bacterial	**Gram positive** Coag (−) staph, *Staphylococcus aureus*, *Streptococcal* spp., *Corynebacterium* spp., *Bacillus* spp., *Nocardia* spp.
			Gram negative *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*
		Viral	VZV, HSV1&2, CMV
		Fungal	*Candida* spp., *Aspergillus* spp.
Defective cell-mediated immunity	Corticosteroids Cyclophosphamide Other alkylating agents Azathioprine Methotrexate Cyclosporine A	Bacterial	*Salmonella* spp., *Campylobacter*, *Listeria*, *Yersinia*, *Legionella*, *Rhodococcus*, *Nocardia*, TB, non-TB *Mycobacterium* spp.
		Viral	CMV, EPV, VZV, HSV, JC virus, BK virus
		Fungal	*Candida*, Histo, crypto, Coccidio, *Aspergillus*, pneumocystis, *Zygomycetes* spp., and other mold
		Parasites	*Toxoplasma*, *Cryptosporidium*, *Isospora*, *Microsporidia*, *Babesia*, *Strongyloides*
Defective humoral immunity and asplenia	Cyclophosphamide Corticosteroids (high dose) Azathioprine	Bacterial	**Encapsulated bacteria:** *Streptococcus pneumoniae* *Haemophilus influenzae* *Neisseria meningitidis* **Other bacteria:** *E. coli* And GNRs
		Viral	VZV, *Echovirus*, *Enterovirus*
		Parasites	*Babesia*, *Giardia*

11.5 Rheumatologic Manifestation of Infectious Diseases

11.5.1 Introduction

Rheumatologic manifestations of infectious diseases are well-recognized and relatively common. This topic will review the most common infectious diseases associated with rheumatologic manifestations. *An overview of each infectious agent is presented separately*.

11.5.1.1 Hepatitis B Virus Arthritis [104]

Evidences have shown that four rheumatologic syndromes are linked with hepatitis B virus infection.

Clinical and laboratory features of each syndrome will be described below.

11.5.1.2 Acute Hepatitis B and Arthritis

The symptoms are abrupt in onset, and they are composed of low-grade fever, a symmetrical polyarthritis which might be additive or migratory in pattern, morning stiffness, and other constitutional symptoms. The most common joints involved are the knees and small joints of the hands, but any peripheral joint might be involved with either arthralgia or frank arthritis. It may last from several days to several months**.**

11.5.1.3 Chronic Active Hepatitis B

Chronic active hepatitis is linked with joint discomfort and occasional rash. The joints

Table 11.4 Causes of CXR abnormalities in patient with rheumatic disease[a]

Radiographic pattern	Infectious causes	Noninfectious causes
Localized infiltrates	Bacterial pneumonia (including *Legionella* spp.) *Mycobacteria* spp. Opportunistic fungi: *Aspergillus* spp. *Histoplasma capsulatum* *Coccidioides immitis* *Cryptococcus neoformans* *Pneumocystis jiroveci* (*uncommon*)	Granulomatosis with polyangiitis Eosinophilic granulomatosis with polyangiitis Pulmonary embolus
Diffuse infiltrates	*Pneumocystis jiroveci* Bacterial pneumonia (haematogenous spread) *Mycoplasma pneumoniae* *Chlamydia* spp. *Mycobacteria* spp. (miliary pattern) Opportunistic fungi Viral Influenzae Cytomegalovirus Varicella-zoster virus (rare)	Systemic lupus erythematosus Rheumatoid arthritis Microscopic polyangiitis Granulomatosis with polyangiitis Eosinophilic granulomatosis with polyangiitis Scleroderma Sjogren's syndrome Dermatomyositis/polymyositis Pulmonary edema **Drug induced** Methotrexate Cyclophosphamide (rare) Azathioprine (rare)
Nodules or nodular infiltrates	Septic emboli *Staphylococcus aureus* *Pseudomonas aeruginosa* *Mycobacteria* spp. *Nocardia* spp. Opportunistic fungi	Granulomatosis with polyangiitis Eosinophilic granulomatosis with polyangiitis Rheumatoid arthritis Lymphoma

[a]The appearance or progression of pulmonary disease following the initiation or intensification of immunosuppressive therapy should always prompt a thorough evaluation for a possible infectious cause

Table 11.5 Infections in rheumatological patient and most common causes [34, 35, 100, 102, 103, 133–136]

Disease	Causes	Comments
Pneumonia	• Immunocompromised patient are prone to the same pathogens acquired in the community by immunocompetent hosts. • (*S. pneumoniae, S. aureus*, and enteric GNRs) are the most common isolated pathogens • Less common organism. Fungi (*Pneumocystis jirovecii*→most common OI, *Aspergillus* spp., *C. neoformans*, *C. immitis*, and *H. capsulatum*) TB & non-TB mycobacteria *Nocardia* spp. CMV HSV	• Pneumonia is one of the most frequent life-threatening infections in patients with rheumatic diseases. • Pneumonia in immunosuppressed rheumatic patient is a challenging diagnosis because of: 1. Pulmonary manifestations of certain rheumatic diseases and medications used to treat rheumatic diseases may produce many of the same clinical and radiographic abnormalities as pneumonia. 2. The usual radiographic appearance of pulmonary infections can be dramatically altered by immunosuppressive therapy.

(continued)

Table 11.5 (continued)

Disease	Causes			Comments
CNS Involvement	Clinical syndrome	Infectious causes	Non-infectious causes	• CNS involvement occurs in many rheumatic diseases, including granulomatosis with polyangiitis, polyarteritis nodosa, Behcet's disease, and most frequently SLE. • Immunosuppressive therapy increases the risk of CNS infections which may be indistinguishable from CNS manifestation of underlying rheumatic disease. • The usual signs and symptoms of life-threatening CNS infection may be greatly diminished or absent because of the effect of immunosuppressive therapy. • In lupus cerebritis, clinical and LP findings are almost similar to bacterial meningitis with the exception of: – Less nick stiffness in lupus cerebritis. – Normal lactic acid level (↑ bacterial). – Decreased C4 level in the CSF.
	Acute meningitis	***Bacterial*** *Listeria monocytogenes* *Streptococcus pneumoniae* *Haemophilus influenzae* *Neisseria meningitides* ***Viral:*** *Enterovirus*, *HIV*, *HSV*, *VZV*, *CMV*, *EBV*, *and others*	NSAIDS Azathioprine IVIG Sarcoid SLE Behcet's disease	
	Sub-acute meningitis	*Cryptococcus neoformans* *Listeria monocytogenes* *Mycobacterium tuberculosis* *Coccidioides immitis* *Strongyloides stercoralis*		
	Focal brain lesion	*Toxoplasma gondii* *Aspergillus* spp. *Nocardia* spp. *Cryptococcus neoformans* *Mycobacterium TB* JC virus (PML)	Lymphoma	
UTI	• Usually caused by gram negative organisms and may be accompanied by septicemia. • *Candida albicans*→ immunosuppressed .			• The incidence of UTI in immunosuppressed patients other than diabetics or renal transplant recipients is not higher than the incidence in immunocompetent individuals. • Neutropenia blunts the clinical manifestations of UTI and predisposes to bacteremia.

Table 11.5 (continued)

Disease	Causes			Comments
Skin infection	• Staphylococcus aureus, group A streptococci, and GNR.			
	Neutropenic	**Initial infection:** Gram negative and gram positive		
		Subsequent infection: Antibiotic-resistant bacteria, fungi		
	Cellular immune deficiency	Bacterial	*Nocardia* spp., atypical mycobacteria	
		Viral	VZV, HSV, CMV	
		Fungal	*Cryptococcus* species *Histoplasma* species	
Septic arthritis	• Staphylococcus aureus (most common), other species *Streptococcus pneumoniae*, groups B, C, and G *Strep*, *Haemophilus*, and gram-negative bacilli. • Consider →OI such as atypical mycobacteria and Pneumocystis *jirovec*i immunocompromised host.			• The risk of septic arthritis in RA patient, irrespective of therapy, is increased by 4–15-fold. • Diagnosis of septic arthritis in the rheumatoid patient is often delayed. • Use of anti-TNF therapy in RA is associated with a doubling in the risk of septic arthritis. • DMARDS can predispose some patients with rheumatoid arthritis to septic arthritis.
Osteomyelitis	Haematogenous	Usually monomicrobial → S. aureus (most common), *Mycobacteria*		
	Contiguous	Polymicrobial or monomicrobial → *Staphylococcus aureus*, coagulase-negative staphylococci, and (aerobic gram + anaerobic GPC and GNR)		
	In immunocompromised patients consider →*Aspergillus* spp., *Candida albicans*, *Mycobacteria* spp., *Salmonella* spp., or *Streptococcus pneumonia*			

(continued)

Table 11.5 (continued)

Disease	Causes	Comments
Bacteremia or fungemia	• The presentation and etiology of **bacteremia or fungemia** is similar to that in other patients. • Disseminated Neisseria and non-typhoid *Salmonella* infections are more common in SLE patients.	**Salmonella:** • Can cause serious infections in SLE patients. • Most cases occur during periods of active SLE and may be the presenting illness of SLE. • Although fever at presentation is the rule but 15% to 20% of patients may be afebrile. And most patients are not toxic or septic on admission. • Clinical syndromes include gastroenteritis, arthritis, and pneumonia. Less commonly diagnoses included cellulitis, osteomyelitis, urinary tract infection, or meningitis. **Neisseria:** • Patients are often young sexually active women with renal disease and low C3 and C4 levels. • Arthritis is a common presentation of disseminated *Neisseria* infection and less commonly meningitis and endocarditis.
Viral infection	• Viruses can cause both systemic and organ-specific disease. • The most common viral infections in patients with SLE are parvovirus B19 and CMV. Other herpesviruses are common in immunosuppressed SLE patients. • Viral infection can be easily confused with a lupus flare due to significant overlap in the features induced by acute viral infections (fever, arthralgia, malaise, cutaneous rash, lymphadenopathy, and cytopenia) and those observed in active SLE. • Acute viral infections are not adequately investigated in SLE patients and are only suspected after rolling out other causes of fever. • The differential diagnosis of SLE patients presenting with fever suspected to be of infectious origin should consider not only common bacterial infections but also opportunistic viral infections, especially in patients with severe SLE involvement or those who are on immunosuppressive therapy. This group of patient should have a detailed physical examination, serologic studies, and invasive organ-specific diagnostic procedures to rule out an underlying viral infection.	

Table 11.6 Rheumatic manifestations of hepatitis B virus

	Acute hepatitis B	Chronic active hepatitis B	Polyarteritis nodosa	Mixed cryoglobulinemia
Rheumatic manifestation	Transient symmetrical polyarthritis	Transient asymmetrical arthritis or arthralgia	Symmetrical polyarthritis in 50%	Chronic polyarthralgia, rarely arthritis
Systemic involvement	Evanescent erythematous urticarial or petechial rash	Erythematous rash rarely reported	Peripheral neuropathy, CNS, muscle, liver, skin, intestines, kidneys, and heart	(skin: Purpura, ulceration), kidney, liver and neuropathy
Serum HBs antigen	Present during rheumatic prodrome	Variable	Up to 40%	Rarely present
Serum free antibody to HBs antigen	Present in convalescent phase	Not present	Rarely present	Present in 48%

abnormality usually manifest as arthralgias which have a fleeting nature which have a fleeting nature (Table 11.6).

11.5.1.4 Polyarteritis Nodosa

- The incidence of HBs antigenemia in polyarteritis nodosa is varied based on the criteria used for diagnosis and the sensitivity of the technique used for detection of the HBs antigen.
- Clinically, these patients might present with multisystem involvement of the skin, muscles, nervous system, lungs, and polyarthritis as well as liver disease.

11.5.1.5 Essential Mixed Cryoglobulinemia

It has the following clinical features: non-thrombocytopenic purpura upon exposure to cold, diffuse arthralgia, and generalized weakness and hepatosplenomegaly; rarely it is associated with neuropathy and gangrene.

11.5.2 Hepatitis C Virus Arthritis

Hepatitis C virus (HCV) is associated with many rheumatologic manifestations including those related to joints, muscles, and connective tissue resulting from the body's immune system interaction with the infectious agent antigens with the subsequent immune complex formation that will be deposited in various parts of the body eliciting an inflammatory reaction that damage the involved organs. Patients who are infected with HCV often have no symptoms. Anyone newly diagnosed with arthritis or cryoglobulinemia should be tested for HCV infection. Also, there are certain drugs used in the treatment of HCV infection, e.g., interferon can worsen a related rheumatologic disease.

Arthritis is noted in 2 to 20% of HCV patients [107, 108]. The arthritis takes the form of evanescent rheumatoid-like picture in two-thirds of the cases and an oligoarthritis pattern in the rest. Rheumatologic manifestations include painful joints and muscle and fatigue, "the first and most common complain," and less commonly patients might have joint swelling and vasculitis.

Cryoglobulinemia happens when cryoglobulins (which are abnormal immunoglobulin) precipitate in cold temperature. It may affect the blood vessels specially during cold weather leading to "'Raynaud's phenomenon." [105, 106] The diagnosis of HCV can be made by finding HCV Immunoglobulins or by detecting the virus RNA.

Table 11.7 Rheumatic manifestations of Parvovirus B19 infection

Rheumatologic manifestations	Parvovirus B19 arthropathy	
	Male	Female
	30%	59%
	Children [113]	Adults [112]
	• Occur in about 8%. • Pattern: Asymmetrical or pauciarticular • Joint involved.It affects the knee most often • At times children may meet criteria of juvenile idiopathic arthritis.	• Occur in about 60%. • Many adult have arthritis alone without other symptoms. • Typical pattern. Acute onset symmetrical polyarticular arthritis • Joints involved. Proximal interphalangeal with metacarpophalangeal most commonly

11.5.3 Parvovirus B19 Arthropathy

Parvovirus B19 is the cause of fifth disease "slapped cheeks" or erythema infectiosum. The disease manifests by rash, arthritis/arthralgia, laboratory abnormalities, and other connective tissue diseases like syndrome. It may mimic systemic lupus (SLE) both in children and adults (Table 11.7) [109, 110].

Arthritis/arthralgia may accompany or follow the skin eruption. The rheumatologic symptoms may persist for weeks to rarely months with resolution, but recurrences are reported [111, 112].

The diagnosis of acute parvovirus infection is made by finding IgM antibody, while IgG antibody is evidence of preexisting exposure. Acute phase reactant, i.e., erythrocyte sedimentation rate and C-reactive protein are occasionally elevated. The leukocyte remains normal, but in some cases, rheumatoid factor and antinuclear antibody may be present in the acute period.

11.5.4 Dengue Virus

- The classical features of dengue virus (DV) are acute febrile illness, headache, and muscle and **joint pain**. It is also referred to as "breakbone fever." [114] **Arthralgia occurs in 60 to 80% of the patients infected with DV.**

Investigations may reveal leucopenia, thrombocytopenia, and elevated liver enzymes. A small percentage of patients may have potentially lethal forms known as hemorrhagic fever and dengue shock syndrome [115].

11.5.5 Septic Arthritis

It is a bacterial infection of the joint that is usually curable with treatment, but morbidity and mortality are still significant specially in patients who have underlying rheumatoid arthritis, patients who have prosthetic joints, elderly patients, and patients who have severe and multiple comorbidities. Incidence of septic arthritis 10 cases per 100,000 patient-years in general population in Europe [116]. Incidence of septic arthritis in patients with rheumatoid arthritis.

(Based on prospective British Society for Rheumatology Biologics Register)

1.8 cases per 1,000 patient-years in 3,673 patients taking non-biologic disease-modifying antirheumatic drugs, where 4.2 cases per 1,000 patient-years in 11,881 patients taking anti-tumor necrosis factor therapy.

Usually it is monoarthritis, but up to 20% of patients have infection in >1 joint "polyarticular." [116] The joints mostly affected are knee (which is the most common affected joint approximately 50%) followed by the hip, shoulder, and then elbow [120]. In IV drug users, axial skeletal joints are mainly involved often with *Staphylococcus aureus*.

The most common causes of septic arthritis in adults are: [116]

- *Staphylococcus aureus* most frequent causative agent, followed by *Streptococcus*.
- *Neisseria gonorrhoeae*, but it is considered *separately* as disseminated gonococcal infection.
- Gram negatives, *Haemophilus*, are usually seen in older patients.

In IV drug users, septic arthritis is frequently duo to methicillin-resistant Staphylococcus (MRSA), mixed infections, fungal infections, or unusual organisms [116]. Patients may have *1–2 weeks* history of joint pain, tenderness, warmth, redness, restricted motion, loss of function, and fever. Joint-related risk factors for infection are joint prosthesis, intra-articular injection, and joint trauma [119]. **Fever** occurs in about one-third of patients [116]. "**Large joints in legs (hips and knees) are the typical sites of infection.**" [116–118] Septic arthritis is diagnosed by clinical signs (hot, red, tender, swollen, restricted) with any of the following:

- Pathogenic organism in synovial fluid detected by culture and gram stain.
- Pathogenic organism isolated in blood or other site.
- Turbid synovial fluid in patient with recent antibiotic treatment.
- Synovial WBC count **more than 30,000**.
- Leukocytosis.

11.5.6 Poncet's Disease (Reactive Arthritis Associated with Tuberculosis) [121]

There is a new pattern of reactive arthritis associated with tuberculosis (TB), identified as Poncet's disease (PD) or tuberculous rheumatism, which is a sterile reactive arthritis that can emerge during any stage of acute TB infection. In a retrospective case series study, seven cases of Poncet's disease were identified:

- The most common presentation was extrapulmonary with involvement.
  - of multiple sites.
- Six out of seven patients developed arthritis after initiation of anti-TB drugs.
- One patient developed polyarthritis after completion of anti-TB medication.
- Asymmetrical polyarthritis was the most common pattern of joints involvement.

The resolution of the arthritis was with symptomatic treatment and continuation of anti-TB drugs. PD may manifest in a variable pattern during the course of active tuberculous infection. Physicians should be aware of this rare complication associated with a common disease to prevent delay in diagnosis and initiation of appropriate treatment.

11.6 Vaccination in Adult Patient with Autoimmune Inflammatory Rheumatic Diseases (AIIRD)

11.6.1 Introduction

It is well known that vaccination is one of the most effective measures to prevent infections and as discussed earlier in this chapter patient with autoimmune inflammatory rheumatic diseases is at increased risk of infection compared to the normal population with the respiratory tract being the most affected organ [122, 123]. However, vaccination of immunocompromised patients is challenging both regarding efficacy and safety. The efficacy of vaccinations in patients with AIIRD may be reduced, and there is a potential risk of flares of the underlying AIIRD following vaccination. The two major issues to consider in vaccine administration of this group of patients are what is the expected immune response following vaccination and what are the potential for worsening the underlying disease.

Table 11.8 Vaccinations by type

Inactivated vaccines	Live vaccines
Tetanus	Adenovirus
Haemophilus influenzae type b	Herpes zoster (shingles)
Hepatitis A and B	Measles, mumps, rubella
Human papillomavirus (HPV)	Varicella
Japanese encephalitis	Rotavirus
Pneumococcal	Yellow fever
Meningococcal	BCG
Typhoid (IM)	Typhoid (oral)
Inactivated polio	Live polio (oral)
Inactivated influenza	Live influenza (nasal spray)
Diphtheria	
Rabies	
Cholera	

11.6.2 General Rules

All inactivated vaccines can be administered safely to persons with AIIRD whether the vaccine is a killed whole organism or a recombinant, subunit, toxoid, polysaccharide, or polysaccharide protein-conjugate vaccine. Live viral and bacterial vaccines should be avoided whenever possible in immunosuppressed patients with AIIRD because it might lead to severe infection in immunocompromised patients (Table 11.8). Table 11.9 shows vaccinations recommendations in adult patient with autoimmune inflammatory rheumatic diseases (AIIRD).

Table 11.9 Vaccination recommendation in AIIRD * [124–127]

Inactivated influenza vaccine	Give annually	Special consideration
Pneumococcal polysaccharide (PPV23)	• Age 19 to 64 y. (one dose + revaccination dose) • All adults ≥65 y of age.	Minimum interval of 5 y between PPSV23 doses should be maintained
Pneumococcal 13 valent conjugate (PCV13)	• Age 19 to 64 y. • No revaccination.	
Tetanus toxoid vaccine	Like general population	In case of major and/or contaminated wounds in patients who received rituximab within the last 24 W ⇨ tetanus immunoglobulin's should be administered
Human papilloma virus vaccine (HPV)	Like general population	
Hepatitis A vaccine	Only recommended in patient at increased risk	Protective antibodies against hepatitis A should be absent
Hepatitis B vaccine	EULAR/ACIP ⇨ only for patient at increased risk ACR: • Should be given before starting DMARD or biologic drug. • If not ⇨ give to patients already on DMARD or biologic drug.	Protective antibodies against hepatitis B should be absent

Table 11.9 (continued)

Inactivated influenza vaccine	Give annually	Special consideration
Herpes zoster vaccine (HZV)	Special circumstances	• Before starting DMARDS or biologic agent. • At least 14 days before initiation of immunosuppressive therapy or 3 months after immunosuppression has stopped. • The following conditions not consider sufficiently immunosuppressive to be a contraindication for HZV: – MTX (<0.4 mg/kg/week), AZA (<3.0 mg/kg/day) or 6-mercaptopurine (<1.5 mg/kg/day) [4]. – Short-term corticosteroid (<14 days). – Low to moderate doses of corticosteroids (<20 mg/day of prednisone or equivalent). – Long-term alternate-day treatment with short acting preparation. – Maintenance physiologic doses (replacement therapy). – Topical, inhaled, intra-articular, bursal, or tendon corticosteroids injections.
Asplenic/hyposplenic	Give: • Influenza vaccine. • Pneumococcal vaccine. • Meningococcal C vaccine. • Haemophilus influenzae B .	AIIRD⇨ live in or travel to areas where other meningococcal strains are endemic (A, Y, W135), vaccination for these meningococcal subtypes is also indicated
Travelers with AIIRD	Vaccinations according to the general rules with some exception	Exceptions are: • BCG vaccine. • Oral poliomyelitis vaccine. • Oral typhoid fever. • Yellow fever .
PCP prophylaxis	Special circumstance	• Patients on a glucocorticoid dose ≥20 mg of prednisone daily for month or longer who also have another cause of immunocompromised .

[a]Vaccination in patients with AIIRD should ideally be administered during stable disease. *AIIRD* autoimmune inflammatory rheumatic disease, *MTX* methotrexate, *AZA* azathioprine [31, 128, 129, 130, 131, 132]

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12 Thrombosis in Rheumatological Diseases

Fozya Bashal

12.1 Introduction

Venous thromboembolism (VTE) is a disease of blood coagulation that occurs in the veins, most often in the calf veins first, from where it may extend and cause deep vein thrombosis (DVT) or pulmonary embolism (PE). The first described case of venous thrombosis that we know of dates back to the thirteenth century, when deep vein thrombosis was reported in the right leg of a 20-year-old man [1].

The risk of thrombosis is influenced by both genetic and environmental factors. The risk factors for venous thrombosis are immobility, major surgery, underlying medical conditions like malignancies, medication use such as hormonal therapies, obesity, and genetic predisposition. In contrast to that, the major risk factor for arterial thrombosis is atherosclerosis [2].

In 1859, a German scientist, Rudolf Virchow, elucidated the mechanism of pulmonary embolism and hence deduced the major pathogenic determinants for DVT and PE, named as Virchow's triad that comprised (1) blood stasis, (2) changes in the vessel wall, and (3) hypercoagulability. This triad still applies, with essentially all prothrombotic factors, whether systemic or molecular, influencing one of these three mechanisms [3] (Fig. 12.1).

DVT and PE are extremely common medical problems, and they are among the major cause of morbidity and death worldwide [3].

About 1–2 per 1000 individuals are affected by VTE per year with PE being the lethal complication and is associated with a high mortality rate that exceeds 15% in the first 3 months after diagnosis [4].

Although disturbance of the coagulation and anticoagulation mechanisms is a very important risk factor for VTE, several studies suggest the role of innate immunity in the development of VTE [4].

Venous thrombosis results from multiple interactions between acquired and inherited risk factors [4].

In this chapter, we discuss the association of thrombosis with autoimmune rheumatologic disorders. The pathophysiology of thrombosis, effects of inflammation, endothelial dysfunction, some novel factors on promoting thrombosis in different rheumatic disorders, diagnostic strategies for thromboembolic disease, and its treatment, management, as well as preventive measures will be addressed in detail. This chapter is useful for students, residents, fellows, and physicians interested in learning about rheumatic disease and thrombosis. The main objective of this chapter is to make the readers able to achieve the following goals:

F. Bashal (✉)
College of Medicine, Umm Al-Qura University, Makkah, Saudi Arabia
e-mail: fbbashal@uqu.edu.sa

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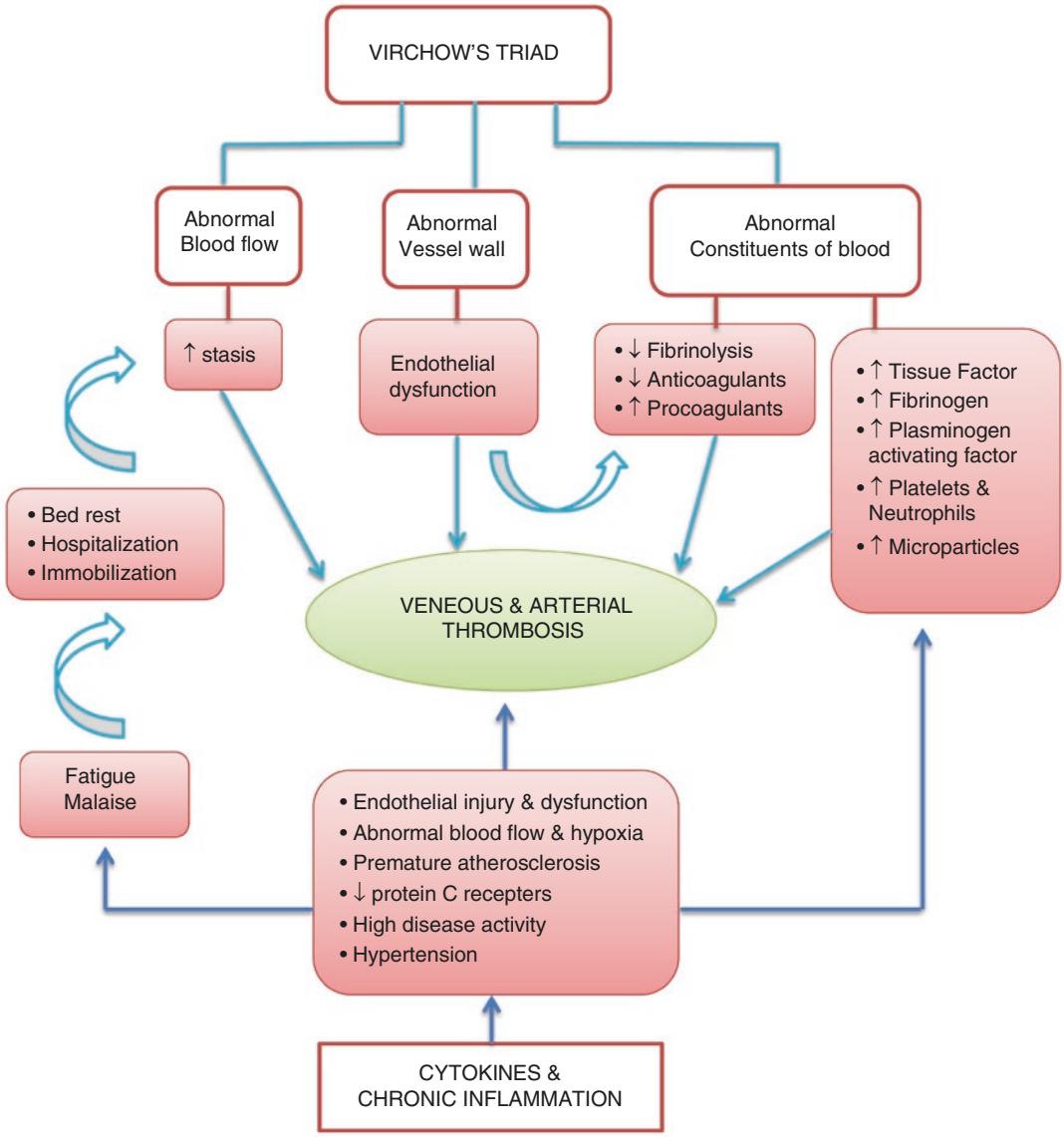

Fig. 12.1 Virchow's triad and some inflammatory changes and their association with venous and arterial thrombosis

1. Explain and discuss the pathophysiology of thrombosis in rheumatic diseases.
2. Recognize the multifactorial role of inflammation in inducing the hypercoagulable state which promote thrombosis in autoimmune rheumatic disorders.
3. Classify thrombosis in patients with rheumatologic diseases (arterial or venous) according to the presence of different risk factors and type of the disorders.
4. Identify the role of different autoantibodies in specific rheumatic diseases such as systemic lupus erythematosus and antiphospholipid syndrome that contribute to the high risk of thrombosis in these conditions.
5. Describe the effects of different therapies commonly used in patients with rheumatic disorders and their role in thrombosis promotion or prevention.

6. Recognize the clinical features of thromboembolic diseases, as well as formulate a comprehensive history of thrombosis from patients with rheumatic diseases.
7. Judge when to select specific assays for thrombophilia screening, clotting factors, autoantibodies, and other tests for thrombotic episodes in rheumatic diseases and choose the appropriate investigations necessary for the diagnosis of thrombosis in these patients.
8. Construct an approach to the diagnosis of thrombosis in rheumatic diseases based on patient's clinical presentation, pretest probability scores, and investigations.
9. Describe therapeutic regimens for thrombosis in rheumatic diseases.
10. Discuss the role of adjunctive and preventive therapy in thrombosis in rheumatic disease.
11. Identify conditions that mandate prophylaxis with antithrombotic medications in patients with rheumatic diseases.

To achieve these purposes, this chapter is written in three sections.

In Sect. 2 of this chapter, we will discuss the mechanism and pathophysiology of thrombosis in individual rheumatic disorders, i.e., systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), rheumatoid arthritis (RA), vasculitis, and Behçet's disease; this includes the effects and role of different medications used specifically in rheumatic disorders in promoting or preventing thrombosis.

In Sect. 3, we discussed in general the approach and the strategies for diagnosing VTE (DVT and PE) and arterial thrombi in different autoimmune rheumatic disorders.

In Sect. 4, we will discuss updates about the management of thrombosis in rheumatic diseases and recommendations for prophylaxis and secondary thrombosis prevention in rheumatic disorders.

12.2 Pathophysiology of Thrombosis in Rheumatic Disorders

Arterial and venous thrombosis and systemic inflammatory diseases are highly linked, and the systemic inflammation promotes an extensive cross-link to exist between inflammation and hemostasis [5]. Systemic inflammation disturbs the natural tight balance between the procoagulants and the anticoagulants in the blood by release of certain inflammatory markers and cytokines like tumor necrosis factor alpha (TNF-α) and interleukin-1 (IL-1) and interleukin-6 (IL-6) that finally promote a prothrombotic state [5] (Fig. 12.2).

Inflammation is a common feature of many rheumatic and immune-mediated disorders; systemic inflammation modulates thrombotic responses by suppressing fibrinolysis, upregulating procoagulants, and downregulating anticoagulants. Several studies indicate the role of innate immunity in promoting thrombosis as it was shown that coagulation and innate immunity have a common evolutionary origin; this leads to the concept that the immune system and coagulations system are linked [4]. These findings conclude that autoimmune disorders such as SLE, APS, Behçet's disease, RA, and vasculitis syndromes like Wegener's granulomatosis have been linked to an increased risk of venous thrombosis [4].

RA, as well as other types of arthritides and connective tissue diseases, are associated with accelerated atherosclerosis and increased cardiovascular morbidity and mortality [6].

Chronic systemic inflammation predisposes to accelerated atherosclerosis, a risk that is well-known in systemic lupus erythematosus (SLE) and in rheumatoid arthritis (RA) patients [7].

The mechanisms for an enhanced and premature atherosclerosis in autoimmune rheumatic disorders such as RA, SLE, and systemic sclerosis (SS) include chronic inflammatory process, immune dysregulation, and the classical risk fac-

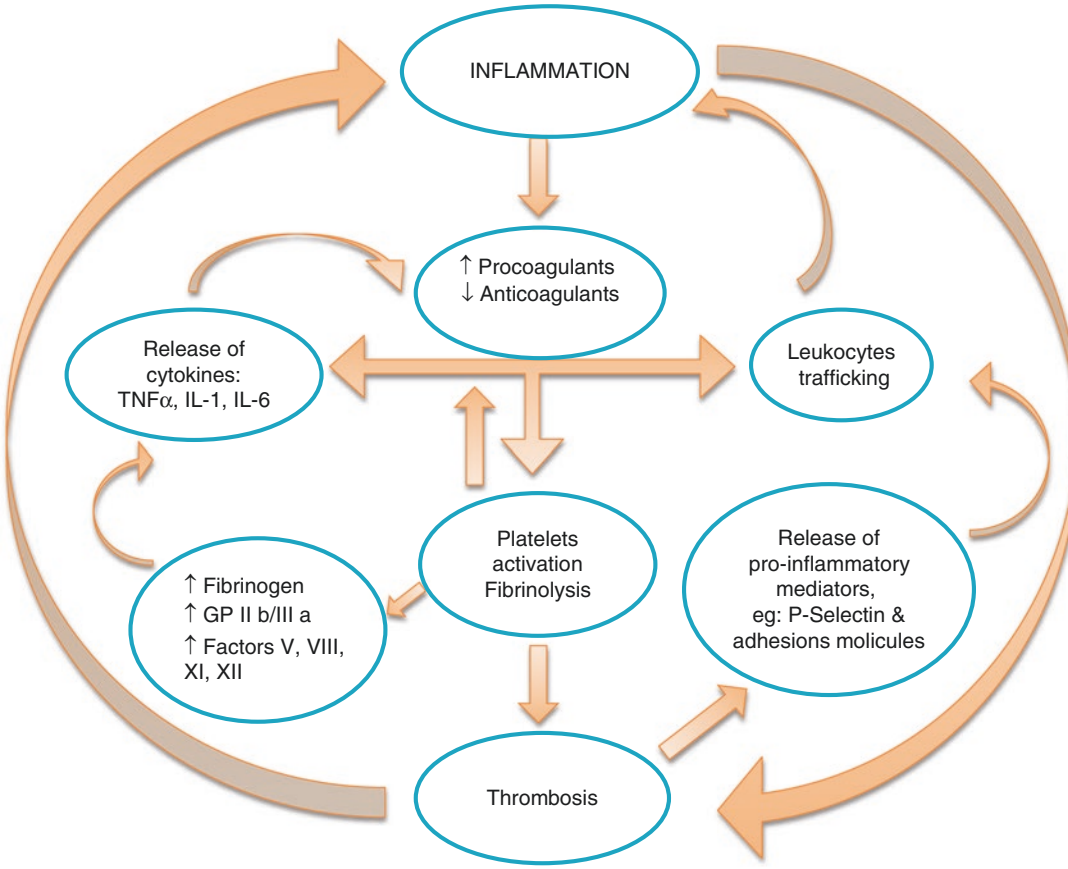

Fig. 12.2 Close relationship between mechanisms of inflammation and thrombosis in Rheumatic diseases

tors; this explains the very high risk of cardiovascular disease in patients with SLE and RA and some other autoimmune diseases [8].

The coagulation factor XII (FXII, Hageman factor) activity correlates with fibrinolysis [9]. Some studies had found the association between pulmonary embolism and decreased levels of FXII; one study was done on large cohort of patients in Japan with different rheumatic disorder reports that FXII reduction coexisted with the presence of antiphospholipid antibodies (a PL) in most thrombotic patients with rheumatic disorders; they conclude the presence of anti-FXII autoantibodies as a cause of FXII deficiency in the presence of aPL antibodies [9].

12.2.1 SLE and Thrombosis

Thrombosis in SLE is multifactorial, and hence SLE patients are at significantly increased risk of thrombosis and atherosclerosis. Arterial and/or venous thrombosis is a well-known clinical entity in SLE, with a prevalence >10%. This prevalence may even exceed 50% in high-risk patients [10]. The incidence of thrombosis in SLE patients according to two studies was 26.8 and up to 51.9 per 1000 patient-years, according to the disease duration [10]. Other study reported that the incidence of thrombosis was 36.3 per 1000 patient years [10]. In a 10-year prospective cohort study of patients with SLE, the most fre-

quent causes of death were active SLE (26.5%), thrombosis (26.5%), and infection (25%), with thrombosis dominating the second 5-year period of follow-up [11]. Patients with SLE have thrombosis at an early age than the age of thrombosis occurrence in the general population, with the incidence being increased in the first year, which may be explained by high disease activity, circulating immune complexes, cytotoxic antibodies, or a higher inflammatory state at first year of SLE diagnosis [10].

Thrombosis is the most frequent cause of death in SLE. With its frequent manifestation in patients with SLE, thrombosis contributes significantly to high morbidity and mortality [11].

Several studies showed that atherosclerotic cardiovascular and cerebrovascular diseases are more common causes of late deaths than active SLE itself. Some studies revealed that subclinical coronary heart disease and carotid plaque were present in a significantly higher proportion of SLE patients than in control subjects of similar age and sex with similar risk factors. Compared with individuals without SLE, the risk of myocardial infarction in SLE patients is 2–50 times higher, and the risk of stroke is 2–10 times higher. The prevalence of symptomatic coronary heart disease in SLE patients has been reported to be 6–20%, depending on the characteristics of the cohort, disease duration, study design, prevalence of antiphospholipid antibodies (aPL), and ethnic composition. 3–15% of SLE patients have a nonfatal stroke [12].

12.2.1.1 Risk Factor and Etiology of Thrombosis in SLE

Inflammation and Disease Activity

Inflammation promotes thrombosis through its several effects on blood coagulation [10, 13].

Inflammation induces the expression of tissue factor (TF), which is an important factor in coagulation initiation [10, 13]. The production of plasminogen activator inhibitor (PAI) is upregulated in inflammation which leads to decreased fibrinolysis activity and increases the risk of thrombosis [10]; high levels of C-reactive protein (CRP) released in inflammatory conditions facilitate the interaction between the monocyte and the endothelial and promote plasminogen activator inhibitor-1 (PAI-1) and TF [13]. In inflammation, fibrinogen, an acute phase reactant, is secreted in higher concentrations which further increase the risk of thrombosis in patients with SLE [13]. Inflammation impairs protein C pathway and decreases protein S level, thus worsening the risk of thrombosis in SLE patients who might have thrombotic events early in the disease as compared to patients without SLE [10, 13]. It was found that SLE patients with lupus nephritis have a high disease activity and inflammation, and this is associated with increase risk of DVT and renal vein thrombosis; they also frequently have systemic hypertension and hyperlipidemia which further worsen thrombotic risk [10].

Antiphospholipid (aPL) Antibodies

aPL antibodies are type of autoantibodies that directed towards phospholipid binding proteins, anionic phospholipids, or a combination of the two [9]; they include anticardiolipin antibodies (ACA), lupus anticoagulant (LA), and anti ß2-glycoprotein I (anti-ß2-GPI) [14]. aPL antibodies induce platelet activation, interfere with coagulation inhibitors such as protein C, inhibit antithrombin and fibrinolysis, and then initiate the formation of a thrombus [10]; they are associated with an increased risk of arterial and venous thrombosis in addition to recurrent pregnancy loss in which they comprise an antiphospholipid syndrome (APS) which could occur as a primary disease (primary APS) or associated with several autoimmune disorders, most frequently in SLE patients, where it is named as secondary APS [15]. Lupus anticoagulant is considered as significant risk factor for stroke and myocardial infarction [10] as well as a strongest predictor of thrombosis [15].

There is a significant occurrence of aPL antibodies among SLE patients [16]; about one-third

of patients with SLE show aPL positivity, but not all of them have the clinical presentation of thrombosis or APS [14].

In one retrospective study of 42 SLE patients, 60% were positive for one or two aPL antibodies, but only 27% of them (10 patients) had a history of APS. The most common clinical presentation was DVT/PE in eight patients. Less common was arterial thrombosis and pregnancy loss. One patient with a history of PE developed autoimmune hemolytic anemia. Another patient without history of DVT/PE presented with thrombocytopenia [16].

The risk of thrombosis in LA and ACA positive patients has been addressed by many researchers. In patients with SLE, 42% of LA-positive and 40% of ACA-positive individuals had a history of thrombosis; in contrast, the prevalence of thrombosis in LA-negative or ACA-negative SLE patients was only10–18% [10].

APS is the main cause of thrombosis and a major predictor of irreversible organ damage and death in SLE patients [15].

ACA might be transiently positive, or persistently positive, and considered significant when it tests positive on at least two occasions, 12 weeks apart. The risk of thrombosis was significantly higher in persistently positive ACA antibodies (33% risk) versus 3% risk in those with transiently positive ACA as shown in the prospective, observational cohort study by A Martinez-Berriotxoa et al. (2007) [15].

- Persistently positive ACA: patients are positive for IgG and/or IgM ACA at medium-high levels (titers ≥20 GPL and/or MPL) in whom more than two-thirds of the ACA determinations were positive; ACA were measured four or more times in all patients [15].
- Transiently positive ACA: patients are positive for IgG and/or IgM aCL in which less than two-thirds of the ACA determinations were positive; ACA were measured four or more times in all patients [15].

In all patients with SLE, even if there are no clinical manifestations, aPL antibodies should be done as they are considered part of American College of Rheumatology (ACR) classification criteria for SLE, and they have been associated with increased risk of thrombosis [10], as the first presentation can be fatal presenting with a CVA. Diagnosis allows prophylactic measures to be instituted in high-risk situations, e.g., prolonged immobility and postoperative states; increased awareness of APS should lead to earlier recognition of associated episodes and laboratory screening for all SLE patients to allow for prophylactic anticoagulation in high-risk situations [16].

Protein C and S and Antithrombin Deficiencies

They are rare but carry a higher risk for venous thrombosis [10].

Factor V Leiden

Activation of factor V leads to the formation of a cross-linked fibrin clot. Factor V Leiden (FVL) is the most common inherited risk factor for venous thrombosis in the general population and is an important factor for thrombosis in patients with SLE. FVL polymorphism is considered to be risk variant for thrombosis and confers resistance to activated protein C, thus shifting the balance towards thrombosis in the clotting cascade. FVL variant is found in 20–60% of patients with idiopathic DVT but without SLE. Patients with SLE and/or aPL positivity who have the FVL polymorphism have at least two times the odds of thrombosis compared to patients without this polymorphism. This observation places FVL to be an independent risk factor for thrombosis in SLE [11].

Hyperhomocysteinemia

Hyperhomocysteinemia is a strong and independent factor for increased risk of atherosclerosis, mainly of the carotid and coronary arteries, as well as venous thrombosis to some extent [10, 17]. 27.3% of SLE patients with thrombosis have hyperhomocysteinemia, which is significantly higher than those without thrombosis in whom it is detected at 16.9% [10]. Patients with shortened

APTT have a hypercoagulable state and were found to have high levels of homocysteine that place them at a higher risk of thrombotic events, as shown in a study done by T. M. K. Refai et al. (2002) [17]. In this study, the researchers found that 21% of SLE patients had elevated levels of homocysteine; interestingly, the level was higher in male patients more than in female ones and also those on prednisolone; they observed that lupus patients with hyperhomocysteinemia had a threefold increase in odds ratio of thrombotic episodes. This is partly because of the direct toxic effect of homocysteine on endothelium and partly indirect effects, such as induction of a vascular-endothelial-cell activator, promotion of vascular smooth muscle proliferation, and an inhibitory effect on endothelial cell growth; these findings support the hypothesis that hyperhomocysteinemia is an independent risk factor for thrombosis in young patients with SLE [17].

Traditional Risk Factors

Smoking is associated with worse outcome and mainly venous thrombosis by inducing endothelial damage; patients with SLE may have hypertension (HTN), diabetes mellitus (DM), and dyslipidemia which predispose them to thrombotic events. Older patients have more endothelial damage and vascular morbidity, and hence age is considered to be a risk factor for thrombosis in SLE [10].

12.2.1.2 Medication and Thrombosis in SLE

- Glucocorticoids have been used frequently in SLE; they mediate endothelial damage and hence lead to accelerated atherosclerosis; high doses of glucocorticoids are associated with abnormalities of the coagulation system [10]. Chronic glucocorticoid consumption has been reported to increase plasma von Willebrand factor (VWF) levels, endothelial dysfunction, increased oxidative stress, and insulin resistance. Glucocorticoids use also increases (PAI-1); it was found that secretion of t-PA levels is limited in patients receiving glucocorticoids, which further worsen the coagulation system and cause hypercoagulable state which further enhances thrombosis risk in SLE patients [18].
- Hydroxychloroquine (HCQ) is an antimalarial agent used in patients with SLE; it has antithrombotic effect by inhibiting platelet aggregation and adhesion and arachidonic acid release from stimulated platelets; it also decreases the thrombus size and the time of thrombus development which is dose dependent. HCQ inhibits GPIIb/IIIa receptor expression that is induced by aPL antibodies. Its role is more extended in the protection from thrombosis by lowering cholesterol level and lowering LDL; it also reduces interleukin-6 levels and decreases SLE flare episodes [10, 19].
- Aspirin (ASA) inhibits platelet aggregation through inhibition of cyclooxygenase enzyme and hence the synthesis of thromboxane A2 [10].

Table 12.1 summarizes the risk factors of thrombosis and accelerated atherosclerosis in SLE patients.

12.2.2 RA and Thrombosis

RA is a common chronic systemic inflammatory disease with worldwide distribution. There is

Table 12.1 Risk factors of thrombosis and accelerated atherosclerosis in SLE patients

1	Increased prevalence of traditional risk factors	HTN, DM, hyperlipidemia, smoking, obesity, old age.
2	Inflammation and high disease activity	↑ expression of TF, ↑ PAI, ↓ fibrinolysis, ↑CRP, lupus nephritis
3	Presence of antiphospholipid antibodies and/or APS	ACA, anti-ß2-GPI, LA in moderate to high titers
4	Hyperhomocysteinemia	
5	Genetic hypercoagulable states	Deficiency of proteins C and S, antithrombin and FVL
6	Drugs	Glucocorticoids (chronic use)

increased incidence of premature cardiovascular disease (CVD) and venous thrombosis in patients with rheumatoid arthritis and hence increased premature mortality and death on average 2.5 years earlier in community-based studies and approximately 18 years earlier in hospital-based studies than non-RA patients [20, 21]. The risk of VTE in patients with RA is increased to more than threefold than non-RA, as shown by Bacani A et al. (2012); they found that RA patients had a higher VTE cumulative incidence at 10 years than non-RA patients (6.7 in RA versus 2.8 in non-RA), and the risk of VTE was significantly higher within 90 days following hospitalization [20]. RA patients showed a higher age- and sex-adjusted increased risk of mortality (60%) and thromboembolic events (30%–50%) during a 5-year follow-up compared to non-RA patients. Similarly significant elevated risks (70% for death and 30%–40% for thromboembolic events) were seen when compared to OA patients. Several studies have shown that RA patients are 30%–60% more likely to suffer a cardiovascular event [19].

12.2.2.1 Risk Factor and Etiology of Thrombosis in RA

Lifestyle in RA

Patients with RA are physically less active due to their disease, and they may suffer from obesity, diabetes mellitus (DM), and hypertension that may result from medication use like steroids; some of RA patients are smokers as well; all these factors contribute to the accelerated atherosclerosis in RA subjects. Obesity is a time-dependent risk factor for development of VTE in RA patients, as shown by Bacani et al. in their study [20].

Inflammation

RA is characterized by a chronic inflammation that results in impaired immune system as well as persistent endothelial dysfunction, which predisposes to vascular wall damage and accelerated atherosclerosis. Such damage can be detectable by ultrasound measurement of carotid intima-media thickness (IMT) in a preclinical stage of the disease. Carotid IMT in RA patients is associated with markers of systemic inflammation and disease duration [22]. CD4+ are subsets of T cells that lack surface CD28 molecule (CD4 + CD28-) and expand when stimulated by endothelial autoantigens, in a subgroup of RA patients. Moreover, they infiltrate the atherosclerotic plaques and pose high pro-inflammatory and tissue-damaging properties which promote vascular injury. The role of these cells in contributing to early development of atherosclerosis in RA has been confirmed by recent studies which showed that RA patients with CD4 + CD28- cell expansion have a higher degree of endothelial dysfunction and a higher carotid IMT than patients without expansion of these cells [22].

High Disease Activity and High Levels of Inflammatory Markers

RA patients with high ESR and/or high CRP were found to have increased carotid artery IMT as well as increased probability of vessel plaque, which supports hypotheses of the relationship between systemic inflammation and atherosclerosis. ESR primarily reflects increased fibrinogen levels in response to systemic inflammation. The association between fibrinogen, as measured by the ESR, and increased carotid IMT suggests that inflammation-coagulation interactions may also have a role in atherogenesis. CRP is produced by the liver in response to interleukin-6, an earlier inflammation mediator, and can be found in the atheromatous lesions, suggesting its pathogenic role in atherothrombosis [23]; CRP is an independent risk factor for atherothrombotic disease [19].

Hospitalization

The relative risk factor for VTE is increased within 90 days post-hospitalization in RA patients. Orthopedic surgeries are reported to be a time-dependent cofactor risks for VTE development in RA patients that may develop within 90 days following lower extremity arthroplasty [20].

aPL Antibodies

RA patients may develop APL antibodies in 5%–75%, which increases the risk of VTE in these patients [20].

TNF-α

It causes endothelium damage and promotes blood coagulation through monocyte activation by increasing the TF levels [19].

Fibrinogen, VWF, Tissue Plasminogen Activator (t-PA) Antigen, and D-Dimer

Levels of these thrombotic variables are significantly higher in patients with RA [21].

Leukocytosis, Thrombocytosis, Increasing Platelet Activity, and Low Serum Albumin

These inflammatory markers are associated with increased cardiovascular risk and accelerated atherosclerosis in RA patients [19, 21].

High Systolic Blood Pressure (SBP) and Low Levels of High Density Lipoprotein (HDL)

High SBP in RA patients is mostly a result of a widespread use of NSAIDs and rarely can be caused by renal vasculitis and amyloidosis; HDL has a cardioprotective role against ischemia; low levels of HDL are found in RA. So, it is considered that both high SBP and low HDL are cardiovascular risk factors in patients with RA [21].

Rheumatoid Factor (RF)

RF positivity is associated with vascular injury and vasculitis, which increases plasma levels of VWF and t-PA that further enhance the thrombotic risks in RA patients [21].

Prothrombotic Condition in RA

Homocysteine (Hcy), in patients with RA the degree of inflammation is found to be correlated with Hcy levels. A positive relationship was found between the Hcy concentration and some parameters of inflammation, such as adhesion molecules and CPR [19].

Microparticles (MP) are membrane-bound vesicles that circulate in the blood and mediate inflammation and thrombosis. The most abundant MP in the blood come from platelets, and high levels of platelets MP were found in RA patients and correlated to high disease activity as measured by disease activity score (DAS 28). MP derived from granulocytes and monocytes have been found in the synovial fluid of RA patients as well; they stimulate TF and factor VII-dependent thrombin generation and lead to intra-articular inflammation and formation of fibrin clots, known as rice bodies [19].

12.2.2.2 Medications and Thrombosis in RA

- Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for pain management in RA, associated with enhance cardiovascular events risk through rising the blood pressure, especially indomethacin and piroxicam, which rise the mean arterial BP by approximately 5 mm Hg [21].
- Glucocorticoids, through their effects on blood pressure, insulin resistance, lipid profile, body weight, coagulation, and endothelial dysfunction, might significantly increase the risk of CVD in RA patients [19].
- Disease-modifying anti-rheumatic drugs (DMARDs), methotrexate (MTX), the most common DMARDs used in RA, inhibit the homocysteine-methionine pathway which leads to hyperhomocysteinemia, but the concomitant use of folic acid reduces homocysteine level, thus decreasing the risk of CVD in AR patients; a long-term follow-up of RA patients has shown that the use of MTX is related to reduced cardiovascular mortality, probably related to a reduction of disease activity. Leflunomide and cyclosporine can cause hypertension which increases the risk of cardiovascular disease in RA patients; the suboptimal control of inflammation by both these drugs also increases the risk of thrombosis. Antimalarials, such as HCQ, have a beneficial effect in decreasing the serum cholesterol and low-density proteins [19].
- Biologic Therapy with TNF-α Blockers.

  A recent study suggested that the risk of developing any CV event in RA is lower in patients who receive TNF-α blockers. One study reported that TNF-α blockade using infliximab improves endothelial function after 12 weeks of therapy. This improvement depends on the clinical improvement of the joint manifestations and on a decrease in the

CRP and ESR levels. Other studies have shown the potential effect of short-term adalimumab therapy on endothelial function in RA patients with long-standing disease [19].

12.2.3 Vasculitis and Thrombosis

Vasculitides are a heterogeneous group of diseases characterized by the presence of vascular inflammation, which can lead to either a vessel wall destruction (leading to aneurysm or rupture) or a vessel stenosis (leads to tissue ischemia and necrosis) [24].

12.2.3.1 Large Vessel Vasculitis

They include Takayasu's (TAK) and giant cell arteritis (GCA). Chronic vascular inflammation leads to endothelial dysfunction that results in a premature atherosclerosis. The risk of arterial thrombosis is increased; strokes and transient ischemic attacks (TIA) have a similar rate of occurrence in this form of vasculitis, but there has been no clear increased risk of venous thrombosis [5].

12.2.3.2 Medium Vessel Vasculitis

Polyarteritis nodosa (PAN) is associated with increased risk of both arterial thrombi and VTE. This risk is high during active disease (3.27 events/person/year versus 0.58 in patients with inactive disease) and independent of hepatitis B status. The coronary arteries are affected mainly by arterial thrombosis, but there is no clear association between ischemic strokes and PAN [5].

12.2.3.3 Small Vessel Vasculitis

They include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and Churg-Strauss syndrome. This type of vasculitis is associated with high risk of arterial as well as venous thrombosis. The risk of a first-time symptomatic VTE has been considered by some researcher to be as seven times first symptomatic VTE risk in SLE [5]. The prevalence of cardiovascular disease is high and biphasic; the highest risk of cardiac ischemia appears either within 4 years of diagnosis or after 10 years of diagnosis. Prospective data from four European Vasculitis Study Group trials found that 14% of patients with GPA and MPA will have a cardiovascular event within 5 years of diagnosis [5]. The age-standardized annual cardiovascular mortality rate was found to be 3.7 times higher than expected in the general population. The presence of proteinase 3 (PR3) antineutrophil cytoplasmic antibodies (ANCA) was found to be protective, whereas a positive myeloperoxidase ANCA test was associated with an increased risk of cardiovascular events. There is no evidence of increased risk of ischemic stroke in small vessel vasculitis [5].

12.2.3.4 Risk Factors for Thrombosis in Vasculitis

Changes in Endothelial Function and Hypercoagulability

The endothelium loses its anti-thrombogenic activity which results from its damage and activation during inflammation. During inflammation, several cytokines are released; these cytokines along with vessel ischemia cause endothelial damage. Circulating ANCAs also cause endothelial damage, and circulating endothelial cells as a marker for endothelial damage have been detected in ANCA-associated vasculitis (AAV) patients, especially when AAV is active [25].

Hypercoagulability

Hypercoagulable state is present in patients with active AAV, and it is triggered by pro-inflammatory cytokines, such as TNF-α and IL-1. It is manifested by the presence of high levels of D-dimers and thrombin-antithrombin III complexes which reflects activated clotting system, increased expression of tissue factor, which activates factor VIII factor which in turn increases VTE risk in these patients. Increased platelet aggregation and reduced fibrinolytic capacity during active disease are among the other hypercoagulable causes of thrombosis in AAV patients [25].

Hypereosinophilia in Churg-Strauss

Eosinophils contain preformed protein-containing granules which are released when activated. Some of these proteins have prothrombotic effects through releasing tissue factor and several other proteins and enzymes which result in decrease fibrinolysis and block the anticoagulant effects of endothelial bound and exogenous heparin, stimulate the production of platelet factor 4 from platelets, and inhibit protein C activation [5].

aPL Autoantibodies

They are well-known cause of VTE, and they are detectable in some patients with vasculitis (especially AAV); aPL antibodies were detected in 19% in patients with GPA (formerly known as Wegener's granulomatosis) according to one study [25].

12.2.3.5 Medications and Thrombosis in Vasculitis

- Cyclophosphamide, the most commonly drug used in the treatment of vasculitis, is associated with an increased risk of VTE in patients with AAV, through induction of vascular endothelial damage, endothelial cells apoptosis, platelet activation, and cytokines release [5].
- Corticosteroids, particularly in high doses, can be thrombogenic through induction of high levels of factor VIII and lower fibrinolytic activity [25].
- Low-dose ASA is proven to be beneficial in the prevention of cerebrovascular insults and visual loss in GCA and thus is recommended to use for same purpose in TAK [5].

12.2.4 Behçet's Disease (BD)

BD is a chronic inflammatory disorder of unknown cause; its manifestations are considered to be caused by an underlying vasculitis [26], characterized by recurrent oral aphthous ulcers, genital ulcers, and uveitis, followed by involvement of other systems causing thrombophlebitis, arthritis, pulmonary and neurological involvement, erythema nodosum, and gastrointestinal disease [27]. Vascular involvement is common in BD; it affects up to 40% of patients resulting in arterial and venous thrombosis and aneurysms particularly of pulmonary arteries [5, 27]; vessels of all sizes are involved, both in the arterial and venous systems [28]. Venous thrombi are more common with involvement of DVT and superficial thrombophlebitis [27]. Asymptomatic DVT of the extremities in patients with BD with no history of vascular thrombosis is reported to be 6% which is higher than that seen in a healthy population [5]. BD is associated with low rate of pulmonary thrombosis (between 4 and 10%); this is because of tight adhesions of the peripheral thrombosis to the venous walls [5]. Other sites of venous thrombi in BD are vena cava thrombosis, Budd-Chiari syndrome (which coexists with inferior vena cava and portal vein thrombosis), and cerebral venous sinus thrombosis. BD complicated with Budd-Chiari syndrome is associated with poor and mean survival of 10 months compared with 16 months in patients affected with Budd-Chiari syndrome without BD. Cerebral venous sinus thrombosis (CVT) is estimated to occur in 8% of BD patients and in about 13% of BD with neurologic involvement. CVT most commonly manifests as intracranial hypertension. CVT in BD more likely affects male gender, presents at a younger age, and less likely develops venous infarcts [5]. The mortality rate is higher in patients with BD who had venous thrombosis, especially if large vessel is involved (mortality rate reached 12.1%) than in those without VTE [28].

12.2.4.1 Risk Factors for Thrombosis in BD

Endothelial Cell Dysfunction

Inflammation and resultant endothelial dysfunction suppresses nitric oxide (NO) secretion in patients with active BD, thereby impairing its normal function of vasodilation and inhibition of platelet aggregation, which in turn increases the risk of thrombosis in BD [5].

Low Protein C

BD is associated with a significant reduction in activated protein C, lower endothelial protein C receptor levels, and increased resistance to activated protein C, leading to significant impairment of anticoagulation as well as anti-inflammatory properties of protein C. Lower levels of activated protein C is found in patients with a history of VTE as compared to those without VTE history, which increase the risk of recurrent thrombi further [5].

Activated Platelets and Microparticles (MP)

MP are small membrane particles derived from platelets, monocytes, and leukocytes; they are secreted in higher levels during active inflammation and lead to the expression of TF tissue factor and anionic phospholipids which trigger the coagulation cascade and increase the risk of thrombosis in patients with BD [5].

Vascular Endothelial Growth Factor (VEGF)

VEGF levels in BD patients with acute thrombosis were higher than those of BD patients in chronic stage. Also, higher levels of MCP-1 were found in BD patients with acute thrombosis as compared with healthy controls. The positive correlation of the elevated levels of various factors with venous thrombosis can be a useful marker to predict the likelihood of thrombosis in BD [29].

HLA-B51 and HLA-B35 Positivity

BD patient positive for HLA-B51 are at increased risk of VTE, while those with HLA-B35 are protective from VTE [55].

12.2.4.2 Medications and Thrombosis in BD

- Azathioprine, immunosuppression with azathioprine 2.5 mg/kg per day, decreased the rate of DVT according to one control trial [5].
- Glucocorticoids, cyclophosphamide, one large study had found that immunosuppressives and glucocorticoids significantly decreased the risk of recurrent DVT in 807 patients with BD [5]. The European League Against Rheumatism (EULAR) in 2008 recommended the use of immunosuppressants (glucocorticoids, azathioprine, cyclophosphamide, and cyclosporine A) in the management of acute DVT in patients with BD disease [5]. Immunosuppressive agents improve prognosis in patients with BD by decreasing the odds of venous thrombosis relapse in BD by fourfold; immunosuppression in Budd-Chiari syndrome is associated with a significant improvement in prognosis as shown in a study done by Desbois et al. [28]. A retrospective study of 37 patients with venous thrombosis in BD compared immunosuppressive agents, anticoagulation treatment, and the combination of immunosuppressive agents and anticoagulation treatment; 3 of the 4 patients in the anticoagulant-treated group (75%) developed new thromboses, compared to 2 of 16 patients in the immunosuppressive agent-treated group (12.5%) and 1 of 17 patients in the combination-treated group (5.9%) [28].

12.2.5 Antiphospholipid Syndrome (APS) and Thrombosis

APS is characterized by recurrent venous and arterial thrombosis and/or fetal loss in combination with the persistent presence of circulating aPL antibodies, which comprise LA, ACA, and/or anti β2GPI antibodies [30].

DVT is the most frequent clinical manifestation of APS. Larger veins like subclavian, iliofemoral, upper abdomen, portal, and axillary veins may be affected as well. Thrombosis of almost every organ has been described in APS, which result in different clinical conditions and syndromes, such as superficial thrombophlebitis; superior vena cava syndrome; renal vein thrombosis; adrenal infarction; Addison's syndrome; Budd-Chiari syndrome; pulmonary hypertension, due to recurrent pulmonary embolism; and diffuse pulmonary hemorrhage, due to microthromboses [31].

Arterial thrombosis consists a main clinical feature of APS, but appears less frequently than Venous, the most common site of arterial thrombosis is the cerebral circulation, leading to

stroke or transient ischemic attack (TIA), CVT, coronary, renal and mesenteric arteries thrombosis has been observed also. In women under 50 years, LA is considered to be a major risk factor for arterial thrombosis as shown in RATIO study (Risk of Arterial Thrombosis In Relation to Oral Contraceptives). CNS involvement in APS mainly strokes and TIAs is associated with high morbidity and mortality [31].

Other manifestations of hypercoagulopathy and thrombosis in APS include thrombocytopenia, hemolytic anemia, pregnancy loss, eclampsia, livedo reticularis, purpura, Libman-Sacks valvulopathy, amaurosis fugax, retinal vessels thrombosis, and avascular necrosis of the bones [32].

Table 12.2 Determinants of high- and low-risk factors for thrombosis in patients with APS

Patient's characteristics		Thrombosis risk level
1	Isolated (LA) positivity	High
2	Triple positivity (LA + aCL + anti-β2GPI)	High
3	Isolated persistent positivity of aCL (medium-high titers)	High
4	Isolated, intermittent positivity of aCL or anti-β2GPI (low and medium titers)	Low
5	Concomitant SLE	High
6	Presence of hypertension, hypercholesterolemia	High
7	Smoking, use of oral contraceptive pills	High

12.2.5.1 Risk Factors for Thrombosis in APS

aPL Autoantibodies

aPL antibodies are a heterogeneous group of different autoantibodies with distinct specificity for cardiolipin or for plasma proteins with affinity for anionic phospholipids such as β2 GPI, prothrombin, or annexin A5 [33]. Oxidized β2 GPI is able to bind to and activate dendritic cells which results in autoantibodies production [32]. aPL antibodies are highly thrombotic. The ACA are directed against cardiolipin and b2GPI, the anti-β2GPI antibody is directed against β2GPI, while the LA measures functional anti-β2GPI antibodies and antiprothrombin antibodies. β2GPI antibodies are responsible for the increased risk of thromboembolic complications; patients positive for all three aPL antibodies have a significant increased risk of recurrence of thromboembolic disease, while patients positive for only one of the three aPL antibodies hardly have a significant increase in recurrence compared to patients with thrombosis but without aPL antibodies as shown by Pengo et al. (2011) [34].

The presence of LA, triple positivity (combination of LA, aCL and β2GPI antibodies), isolated, but, persistently positive aCL at medium–high levels are conditions considered as a high risk serological aPL profile for thrombosis. Patients with triple positivity have aPL levels much higher than others, thus making thrombosis highest risk of thrombosis in this group. Patients with isolated aCL or β2GPI at low-medium titers, particularly if intermittently positive, are considered to have a low-risk profile for thrombosis [30] (Table 12.2).

LA positivity increased the risk of stroke 48-fold and the risk of myocardial infarction 11-fold, while β2GPI antibodies are associated with double risk for stroke as shown by Urbanus RT et al. in the RATIO study [30].

The Effects of aPL Antibodies on Endothelial Cells

Anti-β2GPI antibodies result in increased expression of adhesion molecules (ICAM-1, VCAM-1, E-selectin); aPL autoantibodies increase the synthesis and secretion of pro-inflammatory cytokines IL-1, IL-6, and IL-8 and increase TF expression and upregulation of tissue factor messenger RNA (mRNA) as well as enhancement of endothelin-1 levels [32]. aPL antibodies cause defective apoptosis of endothelial cells, which exposes membrane phospholipids to the binding of various plasma proteins [31, 32].

Hypercoagulable Effect of aPL Antibodies

Production of antibodies against coagulation factors, including prothrombin, protein C, protein S, and annexins, platelets activation to enhance endothelial adherence, activation of vascular endothelium, which, facilitates the binding of platelets and monocytes that result in a hypercoagulable state. aPL antibodies react with oxi-

dized LDL and predispose to atherosclerosis. Moreover, complement activation by aPL has been recognized as a possible significant cause in APS pathogenesis. Emerging evidence from murine models suggests that APL-mediated complement activation may be a primary event in pregnancy loss [32].

Platelet Activation and Aggregation by aPL

β2GPI antibodies activate platelets aggregation and release of platelets factor 4 (PF4) and thromboxane B2; aPL cannot bind to the surface of "intact" platelets, while they have the ability to bind to platelets with exposed negatively charged phospholipids in their membranes [31]. Bleeding time is prolonged in about 40% of patients with APS, without accompanying bleeding tendency, which indicates impaired platelet function in APS as a result of platelet activation by aPL. The expression of platelet membrane glycoproteins, particularly GPIIb-IIIa (fibrinogen receptor, critical in platelet aggregation) and GPIIIa, is also increased that enhance platelets aggregation further [31]. Another mechanism of platelets activation is the production of high plasma levels of active VWF in patients with β2GPI antibodies. In the normal conditions, binding of β2GPI to VWF results in inhibiting its ability to promote adhesion and platelet aggregation, but in the presence of anti-β2GPI antibodies, this anticoagulant effect is blocked [31]. β2GPI antibodies and LA induce the formation of stable thrombi and large aggregates, as shown by Jankowski et al. in animal model [31].

β2GPI Binding with Platelet Factor 4 (PF4)

PF4 is recognized recently as the dominant β2GPI-binding protein. PF4 binds in vitro, with high-affinity, recombinant β2GPI; PF4 tetramers can bind two β2GPI molecules simultaneously. Anti-β2GPI antibodies selectively interact with complexes composed of (β2GPI)2-(PF4)4. This reaction is higher against PF4-β2GPI complex than against β2GPI alone. Anti-β2GPI-β2GPI-PF4 complex significantly induced platelet p38 MAPK phosphorylation and thromboxane A_2 production [37]. p38 MAPK is mitogen-activated protein (MAP) kinase that controls many cellular responses, such as proliferation, migration, differentiation, and apoptosis. In platelets, p38 MAPK regulates platelet adhesion to collagen and aggregation [37]. β2GPI antibodies form stable complexes with PF4, leading to the stabilization of β2GPI, which facilitates antibody recognition. This interaction is found to be involved in the procoagulant tendency of APS [36].

Activation of Monocytes by aPL Antibodies

This will result in increased TF expression and activity as well as increased production of pro-inflammatory cytokines, which increases the risk of thrombosis in APS patients; many researchers had found high levels of soluble TF (sTF) in the peripheral blood of patients with a history of thrombosis and aPL [31, 35].

Other Risk Factors for Thrombosis in APS

Hypertension, smoking, hypercholestrolemia or estrogen use: the coexistent presence of these factors is associated with thrombosis. The interaction between aPL, smoking, and oral contraceptive pills (OCP) has been identified and clarified in the case-control study; the risk for suffering a stroke doubled among smoking LA-positive women, as compared with non-smokers; the risk of stroke among OCP users is increased to sevenfold. One study showed that all smoker women who had LA suffered a myocardial infarction [29]. Concomitant SLE in APS (SAPS) increases the risk of thrombosis further in these patients (see SLE and thrombosis in this chapter) [29].

12.3 Approach and Diagnosis of Thrombosis in Rheumatic Diseases

The clinical features of thrombosis in patients with rheumatic diseases are similar to that in patients with other diseases and the general population; therefore it is very important for the physician who attends such patients to take a careful detailed history, perform a thorough physical

examination, and do an appropriate workup (laboratory and imaging).

Unprovoked (idiopathic) venous thrombotic events are defined as venous thrombosis that occurs in the absence of any of the known risk factors; about 50% of patients presenting with a first idiopathic venous thrombosis have an underlying thrombophilia [38]; therefore special attention is needed to consider thrombophilia in the history and the workup of thrombosis.

12.3.1 History Taking

Symptoms of PE and DVT are not specific, so it is important to ask about the risk factors such as the age, previous history of VTE, recent long-distance travelling for active malignancy, coagulation disorders, hormone replacement therapy (HRT) in postmenopausal women, use of an oral contraceptive pills (OCP) in a female of childbearing age, abdominal/pelvic surgery/knee joint replacement, and diseases or conditions that lead to limited mobility [39–42], as well as a comprehensive history of rheumatic disorders that associated with increased risk of thrombosis, especially if VTE is recurrent, or unusual presentation in the absence of the known risk factors, or if the patient is a young one with no known predisposing factors for thrombosis, or if the patient presents with multiple thrombi at different sites or had both arterial and venous thrombosis.

Detailed history of medications must be taken in patients with rheumatic disorders, as some of them have thrombotic risks, while others have a protective role (see details of thrombosis and medications in individual disorder in Sect. 1).

Inquire about the constitutional symptoms in rheumatic disorders, this includes fever, sweats, loss of appetite and weight.

History of skin rashes, such as malar rash, photosensitivity, raynaud's phenomenon if SLE is considered in the differential diagnosis of VTE. Mouth and genital ulcers and visual complaints may provide a clue to the presence of BD or other rheumatic diseases.

A careful obstetrical history is mandatory if APS (either primary or secondary) is suspected to be the cause of thrombosis in a young female in the absence of the traditional risk factors.

Inquiries about the renal complications must be included in the history in patients with SLE who presents with thrombotic episodes.

Patients with PE present to the emergency room (ER) and may complain of sudden dyspnea, pleuritic and non-pleuritic chest pain, cough or hemoptysis, fever, and diaphoresis; they may have cyanosis or syncope especially if massive PE [41, 43, 44]. Patients may have DVT at the same time which can be asymptomatic, since less than 25% of PE patients presented with symptoms and signs of DVT [41].

Patients suffering from DVT may complain of sudden ipsilateral leg swelling, redness, intermittent cramps, and pain in the calf or leg [45–47]. Presence of risk factors will increase suspicious of DVT which include prior history of DVT or PE, recent surgery, active cancer, trauma, hospitalization, immobility, co morbidities, family history of VTE, advanced age, current pregnancy, hormonal contraceptives and hormonal replacement therapy, and obesity [42, 45, 47, 48].

DVT and PE are considered combined emergency problem; 70% of patients diagnosed with PE have DVT in their leg and 50% of DVT patients established asymptomatic PE [47]. For that, we must diagnose DVT to prevent PE by history, physical examination, and investigations [48].

12.3.2 Physical Examination

The physical examination of patients with PE reveals some signs, of which tachypnea is the most common [43, 49]; other signs such as hypotension and cardiogenic shock may present in massive PE. Signs of right ventricular failure (RVF) such as tachycardia, distended neck veins, and tricuspid regurgitation may be there; wheezes, loud pulmonary component of second heart sound (loud P_2), and pleural rub may also be heard sometimes [44]. Signs of DVT must be looked for [43]; they include leg redness, edema, warmth, tenderness, superficial dilation of veins,

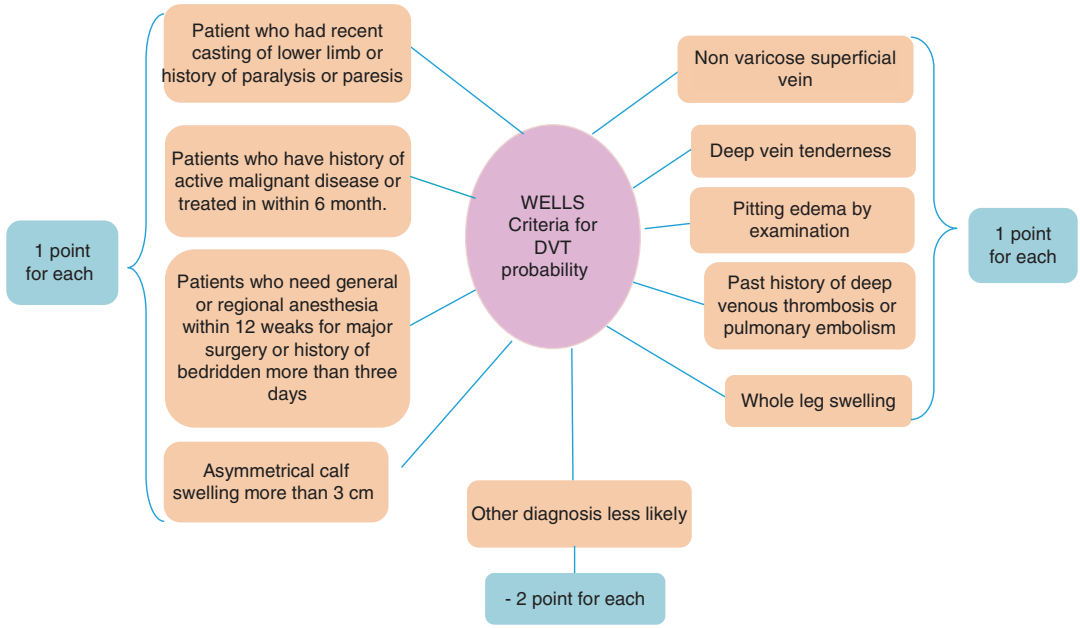

Fig. 12.3 Wells Criteria for DVT Probability

and fever; tachycardia and sign of pulmonary embolism should be looked for as well even in the absence of symptoms [47, 50].

Rheumatic disorders should be considered as the top most differential diagnosis in unusual presentation of different forms of thromboembolic diseases such as young patients with no known risk factors, or thrombosis in unusual sites, or in case of multiple or mixed arterial and venous thrombi; thus, a careful examination should be done.

Many diseases mimic the sign and symptoms of DVT and PE, rendering the physical examination to be not enough for diagnosis, although very essential to perform [47, 50]. Therefore, another methods need to be used before going further to work up these patients.

12.3.3 Clinical Pretest Probability (CPTP) for VTE

CPTP includes Wells and modified Wells criteria [44, 51]; it is a useful and important method to determine the probability of DVT and PE, respectively, and to classify the risk as low, medium, and high and is helpful in selecting the proper test for workup [41].

Wells criteria is based on history and physical examination and classifies the patient as high risk if score is between 3 and 8 points, moderate risk if 1–2 points, and low risk if 0 to −2 points [44, 45, 48, 50, 52]. For details see Fig. 12.3 and Table 12.3.

In modified Wells criteria, the total point is 12, based on symptoms and signs and risk to get the disease. Patients are considered low risk if less than 2 points, intermediate risk if 2 to 6 points, and high risk if more than 6 points [8, 16]; the probability of PE is also categorized as likely and less likely; if it was more than 4 points, the patients are likely to have PE [44]. Clinical sign and symptoms of DVT (3points), other diagnosis less likely than pulmonary embolism (3 points), heart rate (HR) > 100/min (1.5 points), immobilization >3 days or surgery in previous 4 weeks (1.5 points), previous PE or DVT (1.5 point), hemoptysis (1 point) and malignancy (1 point) [44, 51]. Figure 12.4 and Table 12.4.

12.3.4 Laboratory and Radiology Workup

Duplex ultrasound (DUS) is recommended as an initial imaging test for patients with high and moderate clinical probability of DVT, if DUS is positive then DVT is established, but if negative then D-dimer should be obtained, positive D-dimer and negative DUS after that follow up the patient and repeat the ultrasound, but if both DUS and D dimer are negative, DVT is ruled out, while a low clinical probability of DVT require D-dimer as initial test, if negative, DVT is ruled out, but if positive, DUS should be done [44]. Venography is indicated in patients with high clinical probability and negative DUS or if DUS cannot be done [48] (Fig. 12.5).

D-dimer is recommended for patients with low or intermediate risk for PE, and, if negative, PE is ruled out, but if positive, then CT pulmo-

Table 12.3 Wells criteria for DVT probability

1	Active cancer or cancer treated within 6 month	1 point
2	Calf swelling 3 cm greater than the other leg (measured 10 cm below the tibial tuberosity)	1 point
3	Prominent superficial veins (non-varicose)	1 point
4	Pitting edema in symptomatic leg	1 point
5	Paralysis, paresis, or recent orthopedic casting of a lower extremity	1 point
6	Localized tenderness in the deep vein system	1 point
7	Recent bed rest for >3 days or major surgery requiring regional or general anesthetic within past 12 weeks	1 point
8	Previous history of DVT or PE	1 point
9	Swelling of entire leg	1 point
10	Alternative diagnosis at least as probable	-2 point

Table 12.4 Modified Wells criteria for PE probability

1	Clinical sign and symptoms of DVT	3 points
2	Alternative diagnosis less likely than PE	3 points
3	Heart rate > 100/min.	1.5 points
4	Immobilization >3 days or surgery in previous 4 weeks	1.5 points
5	Previous PE or DVT	1.5 points
6	Hemoptysis	1 points
7	Malignancy	1 points

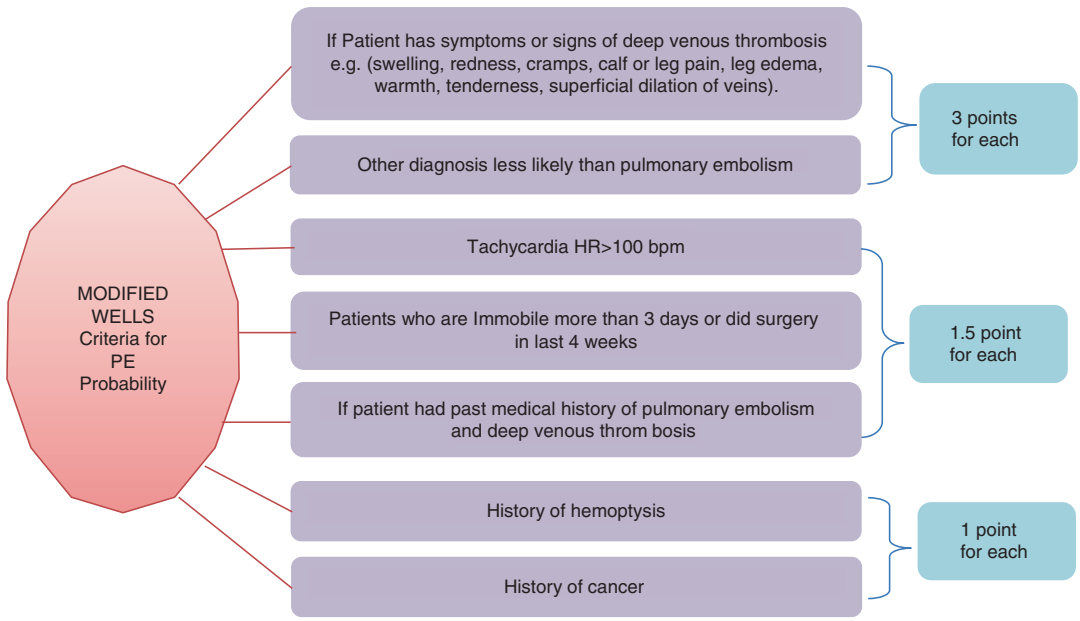

Fig. 12.4 Modified Wells Criteria for PE Probability

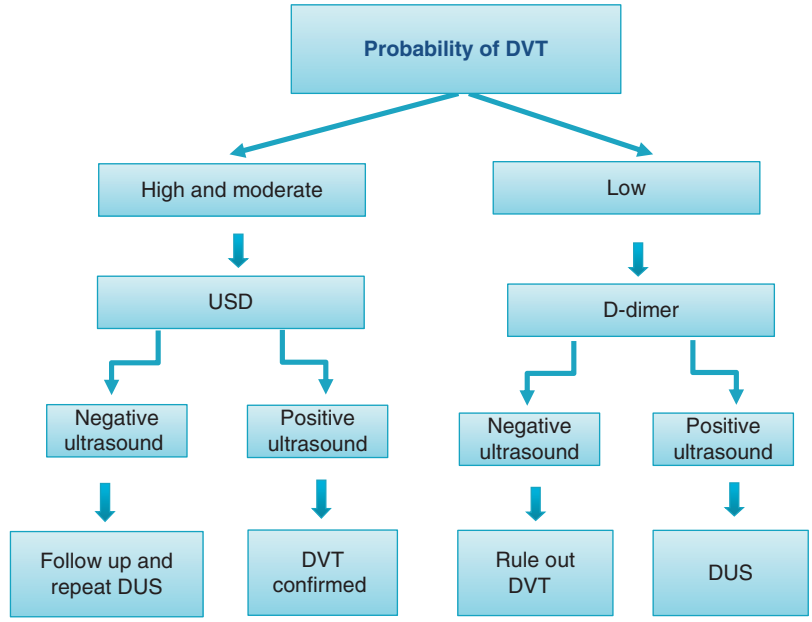

Fig. 12.5 Probability of DVT algorithm

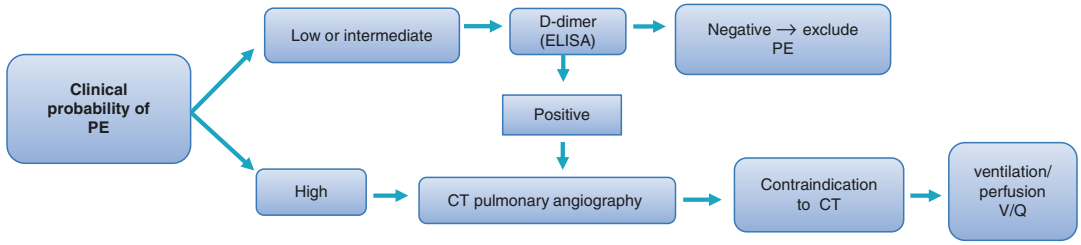

Fig. 12.6 Clinical probability of PE

nary angiography (the gold standard) [39] is required. If patient's risk for PE is high, CT pulmonary angiography should be done, but in situation where contraindication for contrast is used in CT angiogram such as in patients with renal failure, ventilation/perfusion (V/Q) scan can be done [43, 51, 53] (Fig. 12.6).

Pulmonary embolism rule out criteria (PERC) is used in patients who are less likely to have PE (4 points or less); factors of PERC are age < 50 years, HR < 100/min, oxygen saturation >94%, no unilateral leg swelling, no hemoptysis, no surgery or trauma within 4 weeks, no prior DVT or PE, and no estrogens or progestin use. If patients met these criteria, they are regarded as negative for PE, and no further investigations are needed, but if PERC is not met, they are considered positive for PE, and D-dimer should be tested; if it is negative, PE is ruled out [44, 54] (Fig. 12.7).

Other imaging such as chest X-ray may be required to confirm the diagnosis; chest X-ray is usually normal in PE, but it is important to exclude other diseases. Signs of PE on chest radiograph are atelectasis, pleural-based infiltrates, or effusions, there may be a wedge shaped opacity and oligemia - cut off - of arteries, and right descending enlargement of the pulmonary artery) [39, 43, 44].

In PE, ECG may show supraventricular arrhythmia, signs of right ventricular (RV) strains, right axis derivation, T-wave inversion in

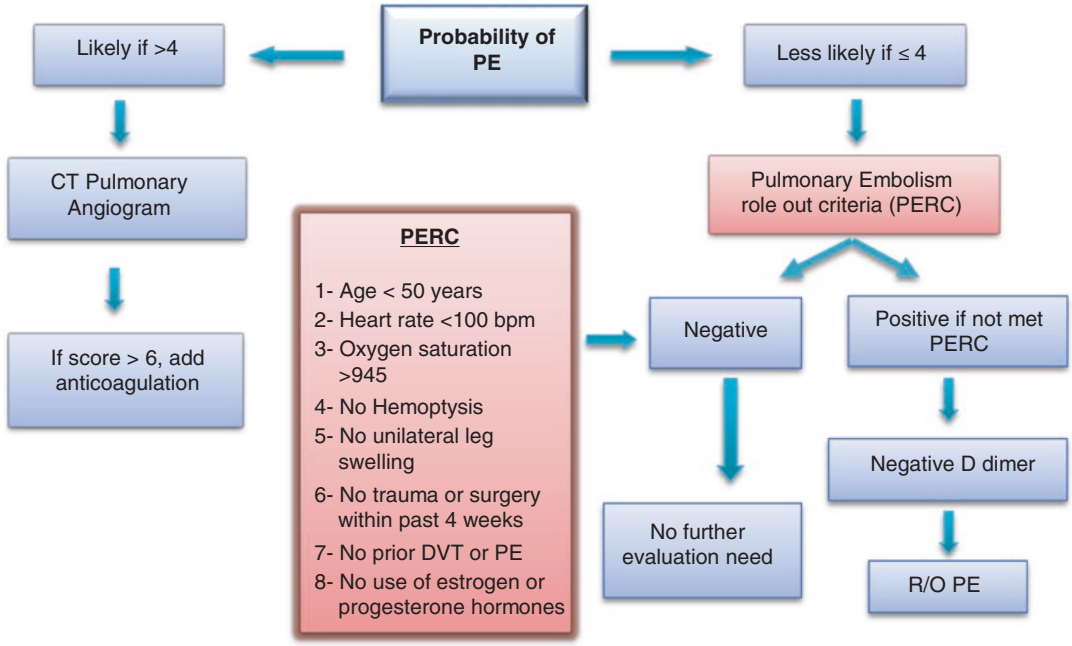

Fig. 12.7 Probability of Pulmonary Embolism algorithm

V_1–V_4, right bundle branch block, $S_1Q_3T_3$, and QR in V_1 or P pulmonale [39, 43, 44].

Arterial blood gases can show hypoxemia, hypocapnia, and widened (A-a) O2 gradient [44].

In patients with PE, check troponin and brain natriuretic peptide (BNP) levels, since their high levels are associated with RV strain and linked to increased mortality in PE [44].

Laboratory investigations include general and specific workup. Generally, for all patients with thrombosis, full blood count, renal and liver function, and coagulation profile need to be done. Specific workup for thrombophilia and hereditary hypercoagulable disorders, this includes: Factor V Leiden, Prothrombin 20210A, Protein C and S, Antithrombin III [38], as they also can present in autoimmune rheumatic disorders such as SLE. Acquired hypercoagulable states includes anti- aPL antibodies (LA, ACA, β2GP1) should be done in idiopathic thrombosis or if there multiple thrombi, HLA-B51 test for BD if thrombosis is at an usual site (Bud Chairi syndrome) or both arterial and venous thrombi or idiopathic CVT should be considered [55].

Other blood workup includes acute phase reactants that measure disease activity (CRP, ESR), since their high levels correlate with high risk of thrombosis and atherosclerosis in certain diseases such as RA [19].

12.4 Management of Thrombosis in Rheumatic Diseases, Prophylaxis, and Secondary Prevention of Thrombosis

12.4.1 Management of Thrombosis in Rheumatic Diseases

There are no specific recommendations for the management of thrombosis in patients with rheumatic disorders, the same plan of treatment as of patients with other diseases and general population. Anticoagulation with intravenous unfractionated heparin (UFH) or subcutaneous low molecular weight heparin (LMWH), followed by warfarin, is the initial treatment strategy for cases with acute thrombosis [57].

Treatment of patients with PE depends on clinical probability of pulmonary embolism and hemodynamic stability of patients, initial treatment with anticoagulant if clinical probability is high or intermediate and cannot get the investigation within 4 h and in case of low probability and investigation deferred for 24 hours, anticoagulant therapy include LMWH, or fondaparinux, both are administered subcutaneously, do not require monitoring of PT and APTT, and not to be used in renal failure, UFH is administered intravenously and it is preferred in massive PE. If there is contraindication to anticoagulant, then inferior vena cava filter should be considered. Thrombolytic therapy is used in patients who have hemodynamic instability [40, 41] (Fig. 12.8).

In patients with DVT, LMWH is recommended, as it is superior to UFH especially in pregnant and patient with cancer, but it should not be used in patient with renal failure; they should be treated with unfractionated heparin (Fig. 12.9); warfarin should be started together with LMWH until targeted INR is reached; inferior vena cava filter is indicated in patient with contraindication to anticoagulation therapy [45, 48, 56] (Fig. 12.10).

Compression stocking is used within 1 month of DVT diagnosis to prevent post-thrombotic syndrome and for at least 1 year after diagnosis [45, 56].

Anticoagulation with warfarin had been associated with several disadvantages related to the drug itself such as slow onset of action, variable pharmacologic effects, food-drug interactions, prolonged half-life, and the need for close monitoring of INR [65]. However, several large studies have been done in this field, and researchers had found that the NOACs are now emerging as the alternative anticoagulation therapy to conventional therapy for patients with acute VTE; the advantages of these novel anticoagulant therapy are many and overcome the troubles of warfarin therapy, such as the fixed therapeutic dose, without the need of dose adjustment; they do not require routine laboratory monitoring of PT and INR. They reach their peak efficacy within 1 to 4 h after ingestion; thus a prolonged period of bridging therapy is not required when switching from initial treatment with UFH or LMWH to

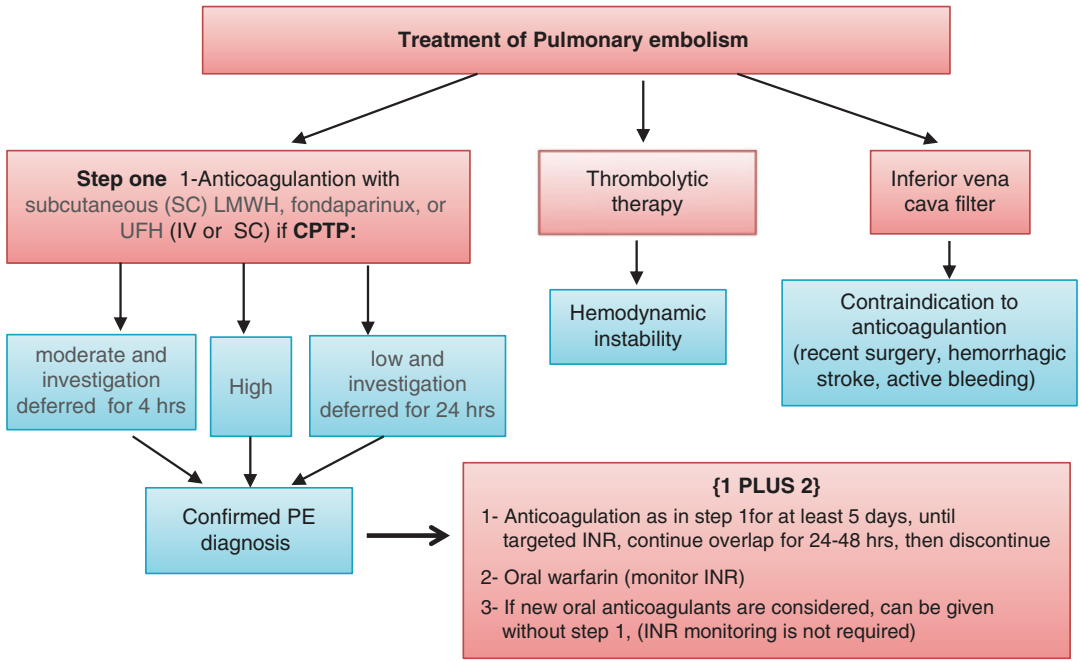

Fig. 12.8 Treatment of PE

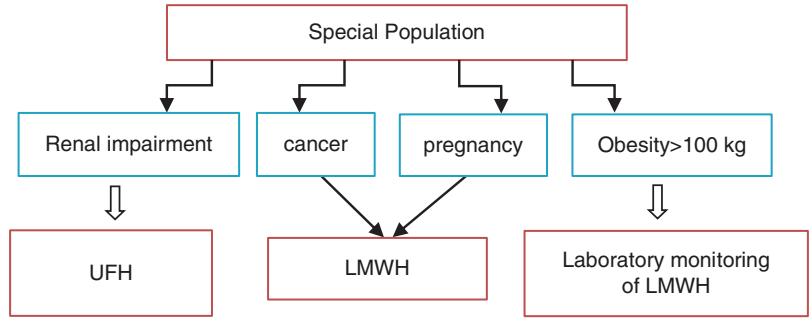

Fig. 12.9 Characteristics of special population and types of heparin

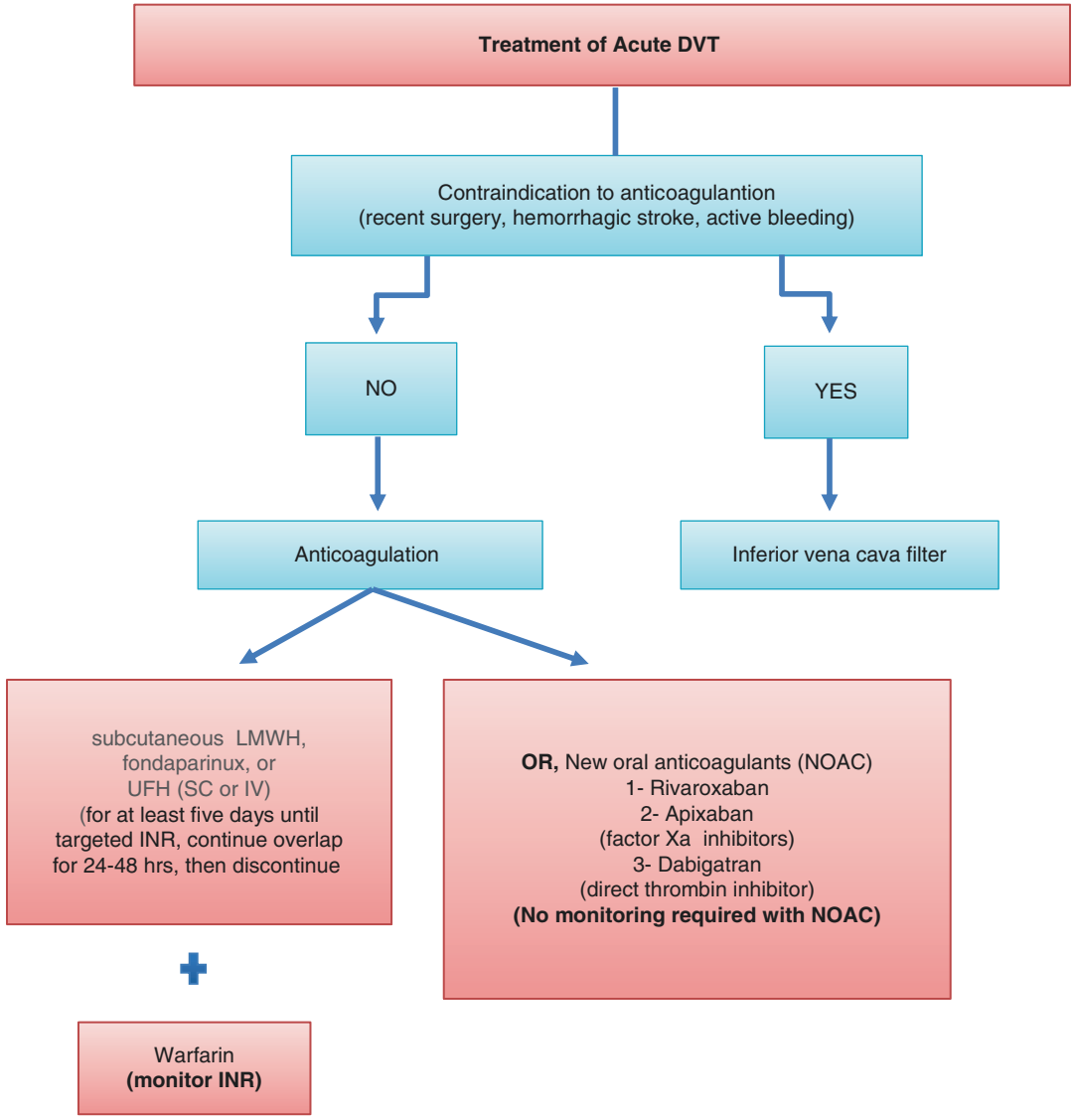

Fig. 12.10 Management of DVT algorithm.

these novel agents and less risks of major bleeding. Unfortunately, the antidote for bleeding events is not available yet [64,65,66]. No data is available regarding the safety of NOACs in pregnancy, for which it should be avoided in a pregnant patient and also in some other conditions such as patients with mechanical heart valves and in severe renal insufficiency [65].

Two groups of NOACs are available, factor Xa inhibitors (rivaroxaban, apixaban) and direct thrombin inhibitors (dabigatran). The safety and efficacy of these agents for the treatment and prevention of recurrent VTE have been studied by large randomized prospective trials [64].

Apixaban has a rapid onset of action and is approved for use in the prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (AF) and in the primary prevention of VTE in adult patients who have undergone elective total hip or total knee arthroplasty [65].

Apixaban is effective for the prevention of recurrent VTE if patients complete 6 to 12 months of anticoagulant therapy for acute VTE, with major bleeding risk similar to those for placebo.

Therapy with apixaban was compared with conventional anticoagulant therapy in patients with acute symptomatic VTE in the AMPLIFY trial (Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy) [66]. The AMPLIFY study has very impressive results and concluded that a fixed-dose oral apixaban alone was as effective as conventional treatment which consists of enoxaparin followed by warfarin and was associated with a clinically relevant reduction of 69% in major bleeding, and its efficacy in patients with PE was similar to that in the patients with DVT. Moreover, the efficacy and the reduction in major bleeding with apixaban were consistent with that of warfarin, but clinically relevant non-major bleeding were less. Interestingly, The efficacy and safety of apixaban were consistent in all patients participated in the trial including patients older than 75 years, obese patients of more than 100 kg, use of parenteral anticoagulant treatment before randomization, and treatment duration. AMPLIFY trial results are very promising and encouraging to consider apixaban a safe and effective regimen for the initial and long-term VTE treatment [66].

12.4.1.1 Special Consideration for Thrombosis in Rheumatic Disorders

- Patients with rheumatic diseases and thrombosis need a long-term management (indefinite) for thrombosis especially those with aPL autoantibodies to prevent recurrent thrombosis, that is, secondary thrombosis prevention; they require the optimal intensity of anticoagulation with warfarin [30, 57].
- Several studies had proven that high-intensity treatment with warfarin to maintain INR = 3.0 with or without low-dose aspirin was more effective than moderate-intensity warfarin or low-dose aspirin for the prevention of recurrent thrombosis in aPL-positive patients, but, recently, some trials demonstrated that high-intensity anticoagulation (INR 3.1–4.0) was no better than moderate intensity (INR 2.0–3.0). So, moderate-intensity anticoagulation is the current standard of treatment of first venous thrombosis [57–60] (Fig. 12.9).
- For the management of acute DVT in BD immunosuppressive agents such as corticosteroids, azathioprine, cyclophosphamide, and cyclosporine A are recommended, but there is no evidence of benefit from, and uncontrolled experience with anticoagulation, use of antiplatelet or antifibrinolytic agents in the management of DVT or for the use of anticoagulation in arterial thrombosis in patients with BD, in patients with CVT (dural sinus thrombosis) treatment with is corticosteroids is recommended (modified EULAR 2008 recommendation) [59]. Anticoagulant therapy must be used cautiously and only after systemic immunosuppressant, and if thrombi are not extensive, antiplatelet treatment with low-dose aspirin is probably sufficient [61].
- • In patients with a low-risk aPL profile, who had first venous thrombosis in the presence of a known transient risk factor, anticoagulation could be limited to 3–6 months [30].

12.4.2 Prophylaxis and Secondary Thrombosis Prevention in Rheumatic Disorders

- Daily ASA in doses of 75–325 mg are suitable for inhibition of platelet aggregation for prophylaxis against cardiovascular events in RA patients [19].
- Prophylaxis use of LMWH to prevent venous thrombosis during periods of immobilization, as immobilization in RA patients is related to disease activity and inflammation [19].
- ASA (75–150 mg/day) is recommended for the prevention of cerebrovascular events and vision loss in GCA, and it should be also considered for the primary prevention of cardiovascular events in TAK [5].

12.4.2.1 Primary Prophylaxis in SLE Patients

- HCQ reduces thrombotic risk and disease-related morbidity and mortality in SLE and is recommended for all patients unless it is contraindicated [10].
- HCQ plus low-dose ASA is recommended for SLE patients with positive LA or ACA (medium-high titers) [30].

12.4.2.2 Primary Prophylaxis in APS Patients

- In asymptomatic individuals, aPL antibodies positivity is an incidental finding; thus, primary prophylaxis can be considered with ASA 81 mg per day [59, 60].
- Healthy individuals, with positive aPL antibodies in high titers and with no thrombotic manifestations, should be advised for a primary prophylaxis with ASA 325 mg orally daily [60].
- HCQ 400 mg orally daily decreases aPL antibody titers and thus protects from further thrombotic episode; that is based on trials in animal models and an indirect evidence from human studies, so more studies are needed to prove this effect of HCQ for standard recommendation in healthy aPL-positive patients [60] (Fig. 12.11).

12.4.2.3 Primary Prophylaxis in High-Risk Situations

All patients with aPL positivity should receive usual doses of LMWH in high-risk situations, such as surgery, prolonged immobilization, and puerperium [30]; the same is applied for all patients with other rheumatic disorders.

12.4.2.4 Secondary Prophylaxis in Patients with Positive aPL Antibodies

- Patient who suffered from either arterial or venous thrombosis and aPL who do not fulfill criteria for APS should be managed in the same manner as aPL-negative patients with similar thrombotic events [30].
- Recurrent venous thrombosis has been reported in patients with APS at 3% to 24%. Secondary prophylaxis with high-intensity warfarin (INR = 3–4), or moderate-intensity warfarin (INR = 2–3) plus ASA is recommended [60].
- Treatment of APS patients with arterial thrombosis is controversial, and only ASA 325 mg/day can be given or moderate-intensity warfarin (INR = 2–3) alone or combined low-dose ASA or high-intensity warfarin (INR > 3) [30, 60].
- In pregnant women, with recurrent fetal loss, a combination of ASA and heparin is recommended. ASA 81 mg/day should be started when attempting conception, and when the pregnancy is confirmed, heparin subcutaneously should be started as LMW (enoxaparin 1 mg/kg/day, dalteparin 5000 units/day, or nadroparin 3800 units/day) or as unfractionated (5000–10,000 units 12 hourly) [60].
- In catastrophic APS, a combination therapy is required with (1) anticoagulation with intravenous (IV) heparin for 7–10 days, (2) steroids in high doses with (IV) methylprednisolone 1 g daily for 3 or more days, (3) IV immune globulin (IVIG) 0.4 mg/kg/body weight/day for 4–5 days, and/or (4) plasmapheresis for 3–5 days at least with fresh frozen plasma replacement [60].

(See Fig. 12.11 for treatment and secondary prophylaxis of thrombosis in APS)

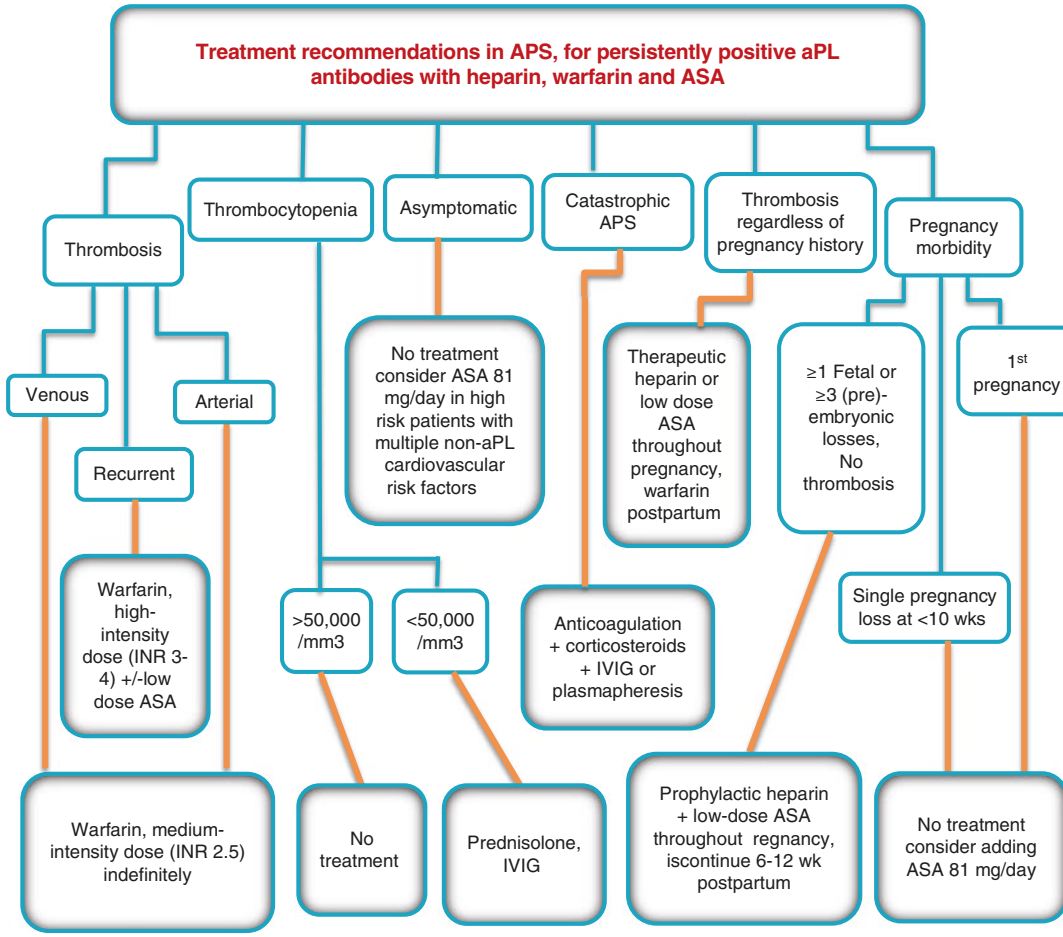

Fig. 12.11 Recommendation for treatment and prevention of thrombosis in patients with APS

- In patients with a low-risk aPL profile without SLE, who have first non-cardioembolic cerebral arterial event due to one of the reversible risk factors, antiplatelet agents are considered for the secondary prophylaxis [30].

12.4.2.5 Refractory and Difficult Situations in aPL-Positive Patients

In patients with difficult management due to recurrent thrombosis, fluctuating INR levels, major bleeding, or a high risk for major alternative therapies with a long-term low LMWH, HCQ or statins are needed for the management of acute thrombosis as well as the secondary prophylaxis [30].

12.4.2.6 Statin Role for the Prophylaxis against Thrombosis in Rheumatic Diseases

Statins have pleiotropic effect (anti-inflammatory, antioxidant, and potent antithrombotic) in addition to a lipid-lowering effect. Thus, by inhibition of atherosclerosis progression, statin decreases the cardiovascular risk for arterial thrombosis in rheumatic and other diseases [62]. Several studies revealed that the use of statins is associated with decrease levels of inflammatory markers such as IL-6, IL-8, MCP-1, and CRP which cause endothelial dysfunction. In addition to that, statins were found to exert an antioxidant function by increasing nitric oxide synthase level. In

the JUPITER trial, use of rosuvastatin in patients with elevated CRP levels results in a significant reduction of DVT [63]. Knowing these advantageous effects of statin, it is advised to consider it for prophylaxis of venous thrombosis in rheumatic diseases, but further trials are needed in this field [63].

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The Blood in Rheumatology

13

Nahid Janoudi and Ammar AlDabbagh

13.1 Introduction

Hematologic disorders including anemia, white blood cells abnormalities, platelet abnormalities, coagulopathy, and hematologic malignancies can be manifested in many autoimmune rheumatic diseases [1].

This chapter discusses the most common hematological abnormalities in rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). It also provides a simple approach to evaluate hematological abnormalities in patients with RA or SLE. This approach includes the most common causes, differential diagnosis, treatment, and prevention, with a special emphasis on ruling out life-threatening and urgent conditions.

13.2 Objectives

- Describe hematological manifestations of rheumatic diseases including different types of anemia, white blood cells, and platelets abnormalities, with brief about malignancies in rheumatoid arthritis.
- Construct a diagnostic approach to anemia in rheumatoid arthritis.
- Describe hematological manifestations of systemic lupus erythematosus including different types of anemia, white blood cells, and platelets abnormalities, with brief about lymphadenopathy, splenomegaly, and antibodies to clotting factors and antiphospholipids.
- Construct a diagnostic approach to anemia in systemic lupus erythematosus.
- Describe macrophage activation syndrome (MAS), and construct a diagnostic approach to it.

13.3 Hematological Manifestations of Rheumatoid Arthritis (RA)

13.3.1 Introduction

A review of hematologic involvement in RA is presented here, with an algorithm constructing a simple approach to RA patients with hematological manifestations (causes, diagnosis, and treatment) which is shown in Fig. 13.1.

13.3.1.1 Anemia

Anemia of chronic disease (ACD) and iron deficiency anemia (IDA) are considered the most common hematologic manifestations in patients with rheumatic diseases [2], with an estimated

N. Janoudi
Doctor Soliman Fakeeh Hospital,
Jeddah, Saudi Arabia

A. AlDabbagh (✉)
Internal Medicine, Gastroenterology and Hepatology Consultant, Jeddah, Saudi Arabia
e-mail: aaldabbagh@fakeeh.care

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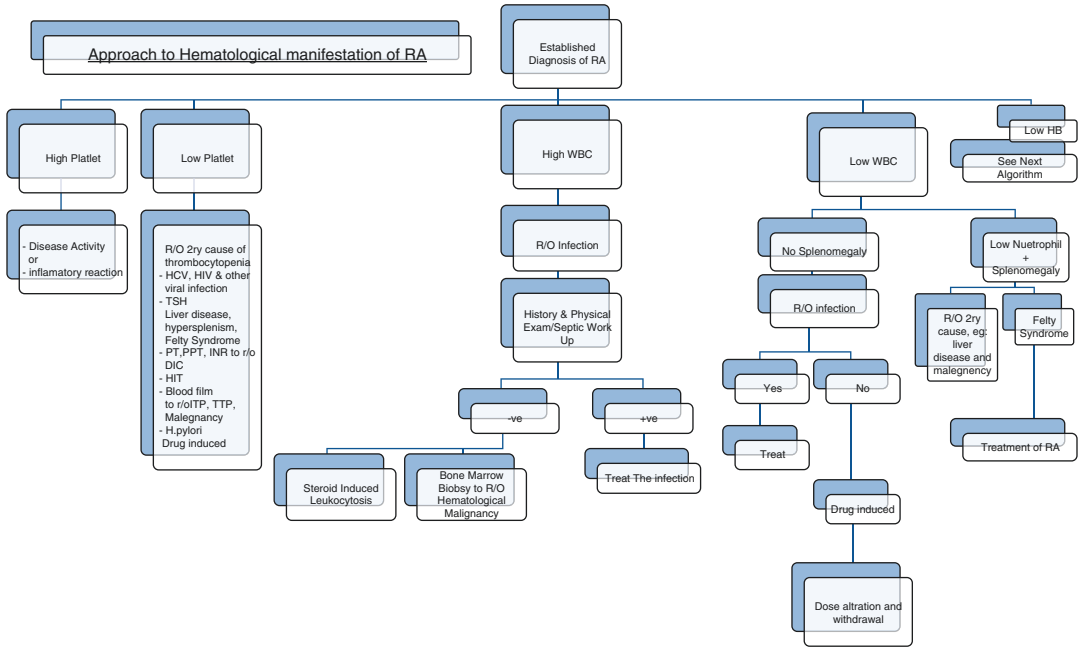

Fig. 13.1 Algorithmic approach for hematological manifestations of rheumatoid arthritis (RA). Classified by the affected component of the blood (platelets, HB, or WBC), in this approach; the authors suggest to broaden the differential diagnosis and to rule out non-rheumatological causes of mentioned abnormalities, including systemic diseases, infections, and drug-induced and primary hematological diseases. The evidence to support this approach is based on cumulative literature, current guidelines, and the author's experience (Abbreviations: *RA* rheumatoid arthritis, *R/O* rule out, *HCV* hepatitis C virus, *HIV* human immunodeficiency virus, *TSH* thyroid stimulating hormone, *PT* prothrombin time, *PTT* partial thromboplastin time, *INR* international normalization ratio, *DIC* disseminated intravascular coagulation, *HIT* heparin-induced thrombocytopenia, *ITP* immune thrombocytopenic purpura, *TTP* thrombotic thrombocytopenic purpura, *H. pylori Helicobacter pylori*, *WBC* white blood cell, *HB* hemoglobin, *2ry* secondary, *-ve* negative, *+ve* positive)

prevalence in RA (30%–70%) in different studies [3, 4].

Anemia of Chronic Disease (ACD)

The ACD is associated with the following laboratory abnormalities:

- Mean corpuscular volume (MCV) and mean corpuscular hemoglobin concentration (MCHC) are usually normal (normocytic and normochromic) but may decrease due to concurrent iron deficiency, often to values characteristic of microcytic hypochromic anemia.
- The ferritin level is usually high with low serum levels of transferrin and iron [5].
- Bone marrow biopsy usually shows the presence of hemosiderin and normal cellularity, with increased numbers (in most cases) of plasma cells that are associated with lymphoid aggregates. However, these findings are unpredictable and usually represent the various etiologies of cytopenias in RA patients.

The pathogenesis of the ACD is not entirely known. There are two major reasons seem to be of significant: defect in hemoglobin synthesis due to the diminished available iron secondary to iron trapping in macrophages and difficulty in bone marrow to produce more red blood cells in response to the anemia [6]. Immune mediators, such as tumor necrosis factor-alpha (TNF-alpha), interleukin-1, interleukin-6, interleukin-10, and interferon gamma, have great impact on these changes [6, 7]. Hepcidin, that is produced by the liver in response to inflammation, may have a great role in ACD, as it decreases iron absorption in the intestines and iron release from macrophages.

Low levels of erythropoietin and decreased response to erythropoietin may lead to the anemia in RA; these findings led to using erythropoietin in such patients which resulted in some increase in hemoglobin levels in few patients with improvement in arthritis symptoms [2, 8, 9].

Since the anemia may correlate with RA activity, patients may need higher doses of erythropoietin, which a medication with a high cost [10]. Hence, it should be considered only for patients with severe symptomatic anemia [11].

In the algorithm provided, if RA patient presents with normocytic normochromic anemia without hemolytic manifestations (normal levels of LDH and reticulocyte and negative Coombs' test) and no other obvious inflammatory causes, patient should be treated with iron supplement and disease modifying anti-rheumatic drugs (DMARDs), and consider erythropoietin for symptomatic anemia (Fig. 13.2).

Iron Deficiency Anemia (IDA)

Iron deficiency anemia can be seen in up to 50% to 75% of RA patients who have chronic active disease [12].

It is mostly caused by chronic blood loss from gastritis (induced by prednisone [13] and/or non-steroidal anti-inflammatory drugs), peptic ulcer, or gastro esophageal reflux.

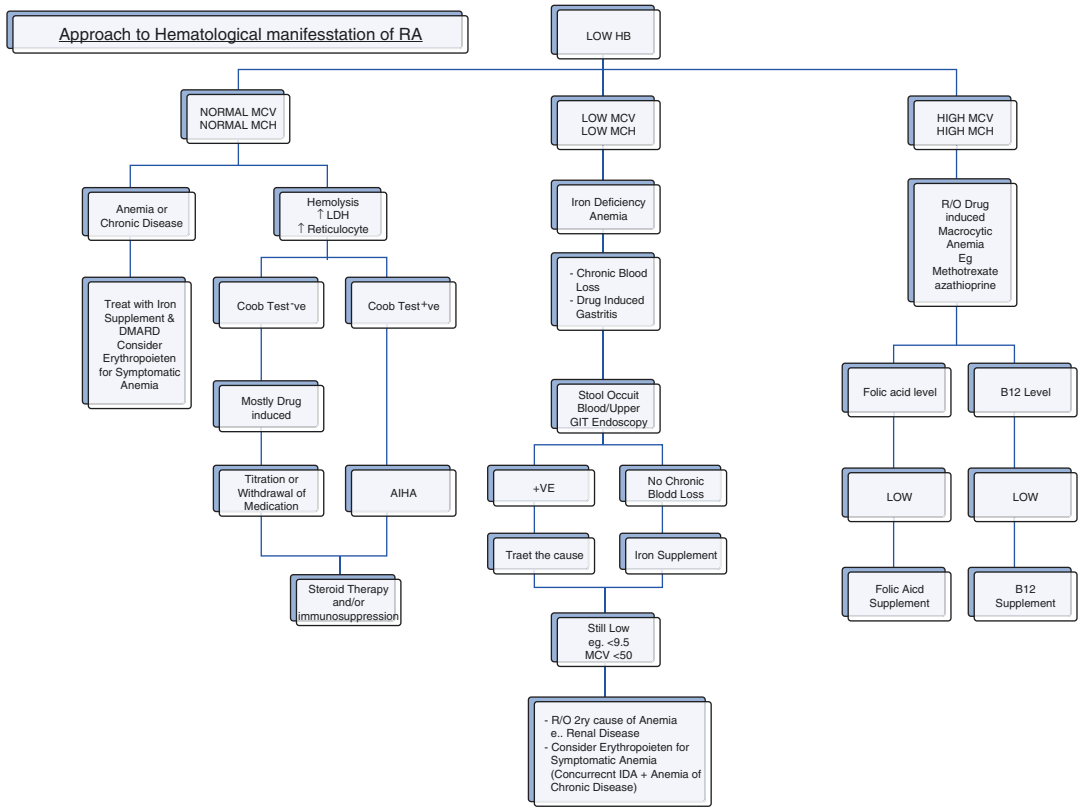

Fig. 13.2 Algorithmic approach for anemia in RA patients. In this approach the authors classified the anemia according to MCV and MCH, aiming to widen the differential diagnosis and to include non-rheumatological causes and co-factors. The evidence to support this approach is based on cumulative literature, current guidelines, and the author's experience (Abbreviations: *HB* hemoglobin, *MCV* mean corpuscular volume, *MCH* mean corpuscular hemoglobin, *LDH* lactate dehydrogenate, *−ve* negative, *+ve* positive, *DMARD* disease-modifying anti-rheumatic drugs, *AIHA* autoimmune hemolytic anemia, *2ry* secondary)

As with all patients, occult blood in stool should not be neglected. All RA patients with IDA, epigastric pain, and/or occult blood in the stool should undergo upper gastrointestinal endoscopic examination.

Making the diagnosis of IDA among RA patients could be challenging, since the routine laboratory indices with mild to moderate iron deficiency may overlap with the ACD [14.15]. Thus, if iron deficiency is suspected, it may be most reliably verified by the absence of iron stores on bone marrow examination [14]. However, pursuing for bone marrow biopsy may be unnecessary if clear signs of iron deficiency such as a mean cell volume below 85, serum ferritin concentration below 40 mcg/L, and transferrin saturation $\leq 7\%$ are present [15].

RA patients frequently may have both IDA and ACD. In such case, the hemoglobin level usually decreases to below 9.5 g/dL, and the mean corpuscular volume is usually less than 80.

Measurement of serum soluble transferrin receptor (TfR) may be useful in differentiating IDA from anemia of chronic disease. [16].

Macrocytic Anemia

Less frequently, a megaloblastic anemia secondary to deficiency of folic acid or vitamin B12, methotrexate, or azathioprine is found in RA patients [2].

One study of 25 patients with RA noted vitamin B12 and folic acid deficiency in 29% and 21% of patients, respectively [2]. It was found that more than one type of anemia can present simultaneously in RA patients with anemia. Identifying each type could be masked by another.

Folic acid deficiency anemia in RA is usually due to the combination of increased requirements and reduced intake (e.g., pregnancy in a patient on a restricted diet) or to concurrent iron deficiency. On the other hand, there may be a genetic predisposition to develop macrocytosis and bone marrow toxicity with azathioprine. Approximately 0.3% of normal subjects have very low levels of thiopurine methyltransferase, one of the enzymes responsible for azathioprine metabolism. This abnormality is genetically determined and is linked to a higher risk of myelosuppression and macrocytic anemia [5].

The diagnosis is established by demonstrating a reduced folate level or vitamin B12 level, ; however, blood film is recommended to suggest the diagnosis and to rule out malignancies.

Hemolytic Anemia

Hemolytic anemia is not a typical feature of RA, although antibody-mediated, Coombs' positive hemolytic anemia has been described, primarily in Felty's syndrome [17].

Drug-induced hemolysis may also occur and is usually reversible when the offending drug is withdrawn, but most patients require corticosteroid therapy.

Bone Marrow Hypoplasia with Anemia

One of the serious hematologic complication of RA is bone marrow hypoplasia, ; luckily it is not frequently seen in RA patients. When present, it is mostly observed in association with Felty's syndrome, renal failure, and the administration of gold, penicillamine, azathioprine, cyclophosphamide, or other immunosuppressive agents.

Pure Red Cell Aplasia

This uncommon hematologic abnormality among RA patient should be suspected if the patient has severe normocytic normochromic anemia with very low absolute reticulocyte count without evidences of blood loss or hemolysis. Autoimmune suppression of erythroid stem cells, DMARDs, and parvovirus infection have been implicated in this complication [18], although single case report suggests that pure red cell aplasia could be an extraarticular manifestation of RA [19]. Isolated case reports have noted improvement in patients treated with corticosteroids, cyclophosphamide, azathioprine, or cyclosporine [20].

Treatment of Anemia in RA

Effective therapy of patient with RA and anemia is based upon an accurate determination of the cause of the anemia. As a result:

- Vitamin deficiencies leading to anemia should be corrected by the administration of folic acid or vitamin B12.
- Iron should not be given unless iron deficiency has been documented. It is recommended to

start with a combination of oral ferrous sulfate, which is usually given with 250 to 325 mg of ascorbic acid and on an empty stomach to enhance iron absorption. Alternatively, ferrous gluconate 300 mg three times daily may be used.
- Patients with persistent gastric intolerance to iron tablets may tolerate elixir of ferosol.
- If oral therapy fails, it is switched to intramuscular iron, and only very rarely parenteral iron as a slow IV infusion can be used.
- **Hemolysis** can be managed with corticosteroids (prednisone 60 mg/day).
- If no response is observed after 1 to 2 weeks, an immunosuppressive agent may be administered, such as azathioprine (50 to 150 mg/day).
- **DMARD-induced bone marrow suppression** should be treated by dose alteration or complete withdrawal of the suspected drug.
- **The ACD** often responds to therapy directed against RA, including DMARDs, and/or corticosteroids (prednisone at a dose of 0.5 to 1.0 mg/kg per day) [2].
- Several interventional studies have demonstrated the efficacy of erythropoietin in treating the anemia of RA [11]; however, only a limited number of patients with RA and ACD may require this treatment. High doses (300 to 800 units/kg/week given subcutaneously once or twice a week) are required, making this an expensive form of therapy. One specific role for erythropoietin among patients with RA is in the peri-operative management of anemia. Treating anemia in this setting may prevent the need for transfusion [2].

13.3.1.2 White Blood Cell (WBC) Count Abnormalities

Neutropenia and Felty's Syndrome

The principal leukopenic disorder among patients with RA is Felty's syndrome, which is defined as a triad of RA, splenomegaly, and neutropenia.
- Splenomegaly is not necessarily present [21].
- This disorder occurs in about 1% of patients with RA. Patients with this syndrome often has an advanced form of nodular RA, with high levels of rheumatoid factor.
- This disorder may be accompanied by severe infections, vasculitis, ulcers, neuropathic symptoms, interstitial lung disease, secondary Sjögren's syndrome, hepatomegaly, and lower extremity hyperpigmentation. These manifestations are rare in the current era of early aggressive therapy with DMARDs.

Although leukopenia is a common consequence of many rheumatic diseases, it is most frequently caused by the administration of DMARDs, including azathioprine, methotrexate, gold salts, sulfasalazine, and penicillamine [22, 23]. In addition, viral infections are another important differential diagnosis and should be excluded before considering the diagnosis of Felty's syndrome.

Management of Felty's syndrome is aimed at suppressing the inflammatory rheumatoid disease. There are several reports on the good outcome with use of gold salts, methotrexate, and biological therapy in these patients. In one retrospective review of all Felty's syndrome cases (1979 to 2003), it was concluded that Felty's syndrome is considered a mild disease and is not commonly linked to infectious complications. Gold is an effective treatment of Felty's syndrome [21].

Leukocytosis

Leukocytosis can occur during an inflammatory flare of RA. However, an associated bacterial infection must be considered and should excluded in such patients.

Eosinophilia

Significant eosinophilia occurs in some patients with RA. It usually correlates with the presence of vasculitis, pleuropericarditis, pulmonary fibrosis, subcutaneous nodules, or gold-induced skin rashes [23].

13.3.1.3 Platelet Abnormalities

Thrombocytosis is common in RA, and a positive correlation has been found between the platelet count and disease activity. Extreme thrombocytosis has been noticed with extraarticular manifestations of the disease, particularly pulmonary involvement, peripheral neuropathy, and vasculitis [24]. The mechanism of thrombocytosis is unclear yet.

Thrombocytopenia is rare in RA, mostly induced by drug treatment such as gold, penicillamine, methotrexate, azathioprine, and TNF antagonists [25, 26]. Felty's syndrome, is another cause of thrombocytopenia in RA patients.

13.3.1.4 Hematological Malignancies in RA

Several studies have noted a higher risk of hematologic malignancy among RA patients contributing significantly to a higher morbidity and mortality of the disease [27–30]. Most large registries noted a higher risk for the development of lymphoproliferative diseases, particularly non-Hodgkin lymphoma (NHL). A study of nearly 18, 000 RA patients noted a higher risk of lymphoma in patients with RA in comparison to the general population (the standardized incidence ratio or SIR) (SIR of1.9) [31]. Although the risk in those treated with anti-tumor necrosis factor-alpha agents was greater than that for patients treated with methotrexate (SIRs of 2.9 and 1.7, respectively), the authors of the study noted that this difference could result if patients with active RA, who have a higher increased risk of developing lymphoma, were more often managed with anti-TNF therapy than those with less active RA.

The results of studies that have addressed the question of whether TNF inhibitor use is associated with increased cancer risk are mixed, and large observational studies were unable to demonstrate a significant increase in either hematologic malignancies or solid tumors for patients taking biologic DMARDs compared with those taking methotrexate [32, 33].

13.4 Hematological Manifestations of Systemic Lupus Erythematosus (SLE)

13.4.1 Introduction

Hematological involvement is commonly seen in (SLE) and could be the presenting manifestations of SLE in many patients. Also, it could mimic many primary hematological disorders.

The most common forms of hematologic manifestations in patients with SLE are anemia, leukopenia, thrombocytopenia, and the antiphospholipid syndrome (APS). Further details about APS and thrombosis are found in Chap. 12 (Thrombosis in Rheumatological diseases).

In this chapter; an overview of the hematologic manifestations of SLE will be discussed, with an algorithm at the end constructing a simple approach to hematological manifestations in SLE patients (Fig. 13.3).

13.4.1.1 Anemia

Many patients with SLE may have anemia at some point of time; the most common types of anemia in such patients are anemia of chronic disease, IDA, autoimmune hemolytic anemia (AIHA), drug-induced myelosuppression, and anemia associated with chronic renal failure which is uncommon [34]. There are different mechanisms which may explain the development of anemia in patients with SLE; at the end of this chapter, you will find a simple approach regarding common differential diagnosis, causes, and investigations. Figure 13.4 shows an algorithmic approach for Anemia in SLE patients.

Anemia of Chronic Disease

In a single-center prospective study of 132 SLE patients with anemia, ACD found as the most common type, representing 37% of all patients [34]. ACD is classified as normocytic and normochromic anemia and may be associated with a low reticulocyte count and a low serum iron, ; however bone marrow iron stores are adequate, and ferritin concentration is usually high.

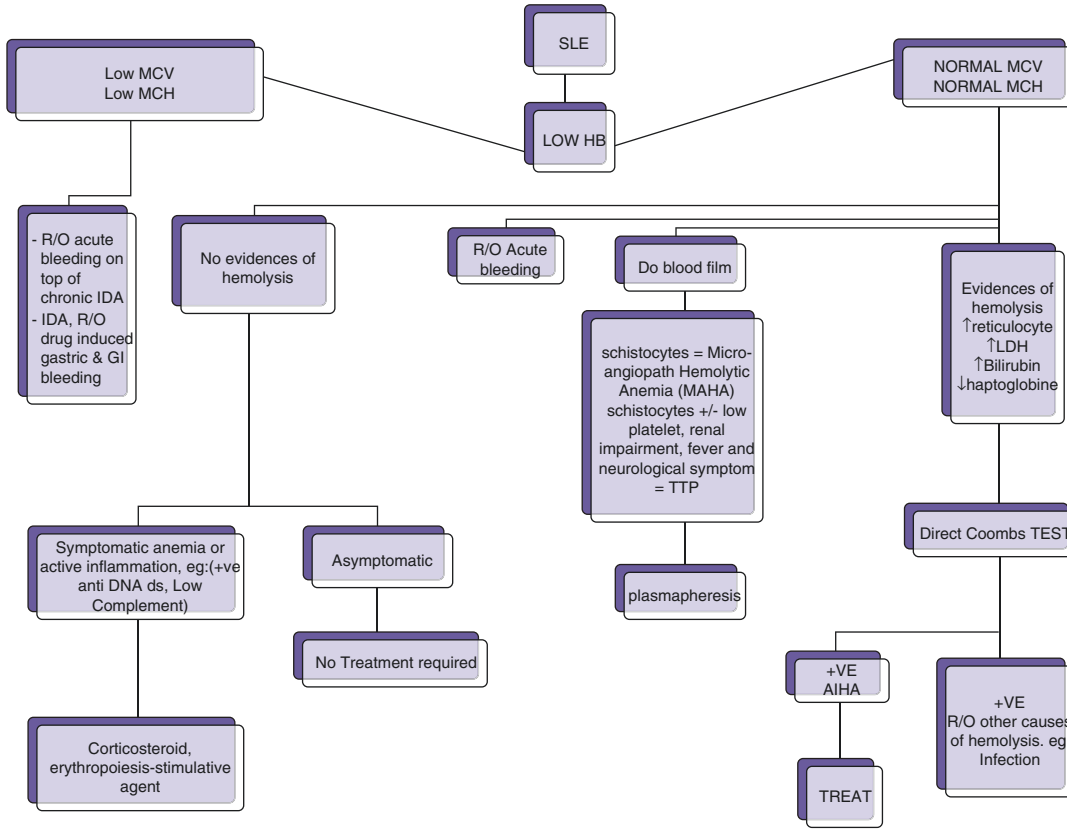

Fig. 13.3 Algorithmic approach for anemia in SLE patients. In this approach the authors classified the anemia according to MCV and MCH, aiming to widen the differential diagnosis and to include non-rheumatological causes, life-threatening causes, and co-factors. The evidence to support this approach is based on cumulative literature, current guidelines, and the author's experience (Abbreviations: *HB* hemoglobin, *MCV* mean corpuscular volume, *MCH* mean corpuscular hemoglobin, *LDH* lactate dehydrogenate, *−ve* negative, *+ve* positive, *IDA* iron deficiency anemia, *AIHA* autoimmune hemolytic anemia, *TTP* thrombotic thrombocytopenic purpura, *2ry* secondary)

13.4.2 Treatment

Usually the treatment is not indicated unless the patient has symptomatic anemia or renal impairment.

Patients with symptomatic anemia secondary to ACD and with no indication for corticosteroid or other immunosuppressant agents may be offered a therapy to enhance erythropoiesis, e.g., epoetin alfa (recombinant human erythropoietin). It should be started at 80 to 120 units/kg per week (usually as 2 to 3 injections per week). The patient should be reassessed after one month, and the dose should be increased monthly until the hemoglobin level is maintained at ≥11 g/dL.

Darbepoetin alfa; a unique molecule that stimulates erythropoiesis with a longer half-life than recombinant human erythropoietin. A typical dose of darbepoetin alfa for adults is 0.45 mcg/kg once a week.

Erythropoietin was evaluated in patients with SLE and ACD; it was found that 58% of patients in one study had an adequate response to erythropoietin supplementation [35].

Patients with symptomatic anemia secondary to ACD who had insufficient response to erythro-

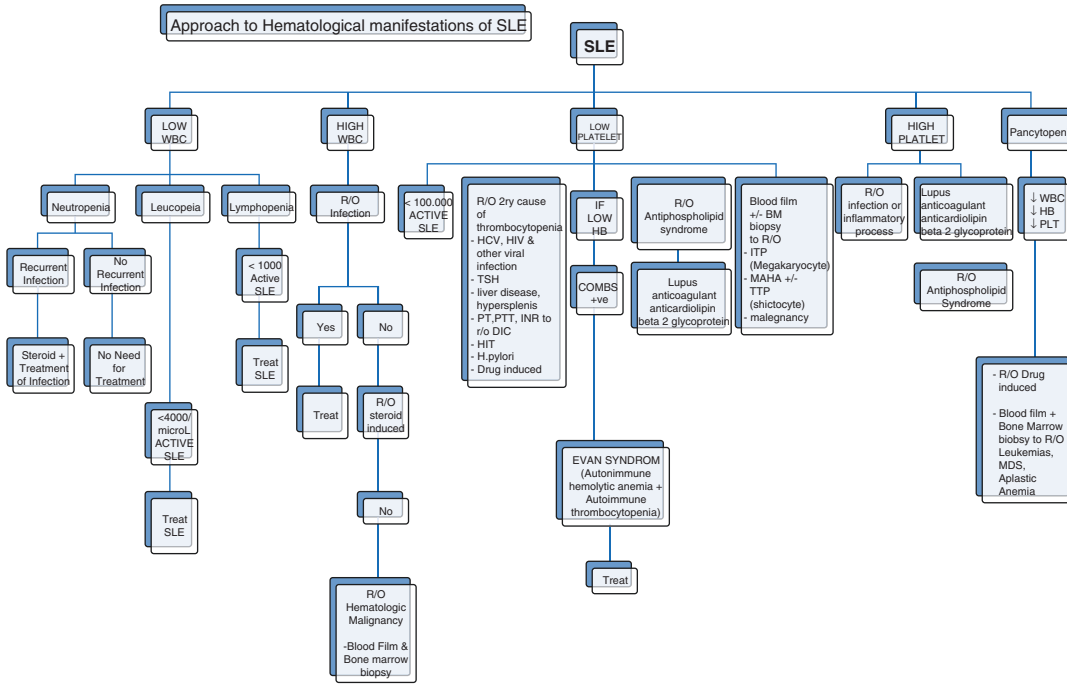

Fig. 13.4 Algorithmic approach for hematological manifestations of systemic lupus erythematosus (SLE). Classified by the affected component of the blood (platelets, HB, or WBC), in this approach, the authors suggest to broaden the differential diagnosis and to rule out non-rheumatological causes of mentioned abnormalities, including systemic diseases, infections, and drug-induced and primary hematological diseases. The evidence to support this approach is based on cumulative literature, current guidelines, and the author's experience (Abbreviations: *RA* rheumatoid arthritis, *R/O* rule out, *HCV* hepatitis C virus, *HIV* human immunodeficiency virus, *TSH* thyroid stimulating hormone, *PT* prothrombin time, *PTT* partial thromboplastin time, *INR* international normalization ratio, *DIC* disseminated intravascular coagulation, *HIT* heparin-induced thrombocytopenia, *ITP* immune thrombocytopenic purpura, *TTP* thrombotic thrombocytopenic purpura, *MAHA* microangiopathic hemolytic anemia, *H. pylori Helicobacter pylor*i, *WBC* white blood cell, *HB* hemoglobin, *Plt* platelets, *2ry* secondary, *-ve* negative, *+ve* positive, *BM* bone marrow, *MDS* myelodysplastic syndrome)

poietin supplementation, often improve on glucocorticoids at high doses (1 mg/kg/day) which is usually the next step in their management.

After 1 month of being on steroid, if the response is insufficient (e.g., hemoglobin still <11 g/dL), glucocorticoids dose should be tapered down rapidly and stopped.

If there is a response, the dose should be tapered as rapidly as to possible to the lowest dose that maintains the improvement.

13.4.2.1 Iron Deficiency Anemia (IDA)

IDA is the second most prevalent type of anemia in patients with SLE [36]; in female, it could be secondary to menorrhagia, or it may represent an acute or chronic blood loss from gastrointestinal tract usually as a result of chronic administration of NSAIDs and corticosteroids. It can exacerbate and/or coexist with ACD.

Long-standing anemia of chronic inflammation can also result in to IDA.

Diffused pulmonary hemorrhage is an uncommon cause of anemia in patients with SLE.

13.4.2.2 Autoimmune Hemolytic Anemia (AIHA)

AIHA is an antibody-mediated erythrocyte destruction, and it may found in 5% to 14% of SLE patients [35].

(AIHA) is characterized by:

- High reticulocyte count,
- Reduced haptoglobin levels,
- High indirect bilirubin concentration,
- Positive direct Coombs' test,
- Found in up to 10% of SLE patients [37, 38].

Approximately 2/3 of patients with SLE-associated AIHA have symptoms at the onset of SLE [26]. The presence of hemolytic anemia could be associated with other sever SLE features including lupus nephritis, neuropsychiatric manifestations, and serositis. Some patients may have a positive Coombs' test without evidence of hemolysis. [36, 37]. The antibodies are divided into IgG-mediated "warm, ", and IgM-mediated "cold" agglutinin.

Treatment: AIHA usually improves on corticosteroids (1 mg/kg/day of prednisone) in 75 to 96% of patients [39].

Once the hematocrit starts to increase and the reticulocyte count decreases, prednisone can be quickly tapered down.

If the patient didn't achieve response, pulse steroid can be considered (e.g., 1 g methylprednisolone intravenously daily for 3 days) [39], azathioprine (up to 2 mg/kg per day) [40], cyclophosphamide (up to 2 mg/kg) [40], or splenectomy [41, 42].

Response rates for splenectomy in AIHA can reach up to 60% [41], ; however, other study has contradictory result [30]. In case of refractory AIHA, one can consider intravenous immune globulin [30], danazol (in doses of 600 to 800 mg/day) [42], mycophenolate mofetil [44], and rituximab [45].

Anemia due to chronic kidney disease:

An inappropriately low level of erythropoietin is the major feature of anemia due to chronic kidney disease. In this setting, typically decreased production of erythropoietin by the impaired kidneys plays a major role in the pathogenesis of this type of anemia. In such patients, specially patients with no other evidence of inflammation, prescribing erythropoiesis-stimulating agents could be indicated in symptomatic anemia or if the hemoglobin is less than 11 g/dL.

13.4.2.3 Red Cell Aplasia

In SLE, red cell aplasia may occur secondary to antibody-mediated injury to erythropoietin or erythroblast in the bone marrow, although it is uncommon, but it has been reported [46, 47]. This type of anemia usually improves on corticosteroid, ; in refractory cases cyclophosphamide and cyclosporine have been successfully used.

13.4.2.4 Microangiopathic Hemolytic Anemia (MAHA)

SLE is one of many causes of thrombotic microangiopathic hemolytic anemia [48]. It usually presents with schistocytes in peripheral blood smear and high serum lactate dehydrogenase (LDH) levels as well as high indirect bilirubin concentration.

As you will see in the algorithm at the end of this chapter, it is essential to consider MAHA in any SLE patient who present with normocytic normochromic anemia, MAHA is manifested by schistocytes in peripheral film which necessitate urgent treatment with plasmapheresis and corticosteroid .

Thrombotic thrombocytopenic purpura (TTP), which is life-threatening condition, is typically manifested by a pentad of thrombocytopenia, fever, microangiopathic hemolytic anemia (MAHA), neurologic manifestations, and renal impairment.

Other patients with MAHA may not manifest with fever or neurologic abnormalities, presenting a condition called hemolytic-uremic syndrome (HUS). The pathogenesis of this syndrome isn't entirely known [49].

Treatment: In MAHA and TTP, plasmapheresis is considered the most important acute intervention. Because of the adverse outcome which associated with delay in its initiation, it should be started immediately in all patients with suspected TTP [50, 51].

In a review study, 28 patients with TTP managed with plasmapheresis, glucocorticoids alone,

or no therapy. The mortality rate was 25% in those treated with plasmapheresis, 50% in glucocorticoids alone group, and 100% in those who received no therapy [53].

The current recommendations suggest that plasma exchange should be immediately in the patients diagnosed to have TTP; it should be carried on at least for 5 days, along with pulse steroid (methylprednisolone 1 g intravenously daily for 3 days) with the first dose usually given immediately after the first plasmapheresis session [50]. Recently, in some cases of TTP anti-CD20 antibody, rituximab has been used, however more data are needed [52].

TTP-HUS is often associated with reduced activity of ADAMTS13 (<10%), usually due to an inhibitor of ADAMTS13 activity. However, results of ADAMTS13 activity measurement should not influence the decision to initiate plasma exchange, and plasmapheresis shouldn't be delayed while awaiting its result [50, 53].

13.4.3 WBC Abnormalities

At the end of this chapter, the reader will find an algorithm which constructing an approach to SLE patients who present with WBC abnormalities; including leukocytosis, leucopenia, neutropenia, lymphocytopenia, and other abnormalities. This approach emphasizes rolling out serious conditions as well as considering SLE related WBC disorders.

13.4.3.1 Leucopenia and Neutropenia

Leucopenia is a characteristic feature of SLE and can include lymphopenia, neutropenia, or both. It defined as less than 4000 cells/mL of white blood cell (WBC) count, and it usually represents an active disease. According to the American College of Rheumatology (ACR, leucopenia is considered as one of the criteria to diagnose SLE [54]. It can be seen in up to 50% to 60% of SLE patients [55, 56].

Other comparative retrospective study which was done in Saudi Arabia showed that the most common hematologic presentation among SLE patients was leukopenia which was found in 58.7% of the patients [57].

In some cases, leukopenia becomes challenging specially if the patients require a medication that can cause bone marrow suppression, e.g., cyclophosphamide, azathioprine, methotrexate, and, rarely, cyclosporine, mycophenolate mofetil, or HCQ. If a patient developed a rapid leucopenia, hemophagocytic syndrome should be considered, and proper workup should be perused [55].

Neutropenia may reflect primary hematological disease, infection, or treatment side effects (e.g., cyclophosphamide or azathioprine); however, all those causes should be considered in correlation with history and clinical finding. In SLE, neutropenia which attributed to an active disease usually respond to steroids.

13.4.3.2 Lymphocytopenia

Lymphopenia is considered one of the most prevalent hematological features of SLE, and although it was noted to be contributory to leucopenia, yet it can be independent to total white blood cell count. Reduced absolute lymphocytic count can correlate with SLE activity, and those with absolute lymphocytic count less than 1500/μL at diagnosis may have a higher frequency of fever, musculoskeletal manifestations, and neuropsychiatric manifestations [55].

13.4.3.3 Decreased Eosinophils and Basophils

Generally, corticosteroids may contribute to a low absolute eosinophil and monocyte counts.

Basophil count can be reduced as well in SLE, especially during lupus flare, basophil degranulation usually occurs which result in the release of platelet activating factor and as well as other mediators which can play a role in vascular permeability and immune complex deposition [31].

13.4.3.4 Treatment of Leukopenia

Not all SLE patients with leucopenia need to be treated, unless the patient has neutropenia with recurrent infections. On other hand, side effects of the treatment may complicate the situations, ; prednisone (10 to 60 mg/day) may increase the leucocyte count but may result in high risk of

infections as well; immunosuppressive therapies like azathioprine or cyclophosphamide may contribute toward the worsening of the leukopenia through their effect on bone marrow suppression [31]. In such cases, these medications should be used with caution and frequent monitoring of white blood cell count and for signs of infections.

Treating leukopenia in SLE in other settings may result in unfavorable outcomes. As an example, recombinant granulocyte colony-stimulating factor (G-CSF) studied in the treatment of sever neutropenia associated with refractory infections, although it was effective in increasing neutrophilic count, yet it was associated SLE flare in three out of the nine patients in this study [32].

13.4.3.5 Leukocytosis

Leukocytosis can be found in patients with SLE. Two contributing factors include underlying infectious process or leukocytosis associated with high dose of steroids [31]. It also can be found during SLE flare. In case of leukocytosis secondary to infections, shifting of granulocytes to more immature forms (a left shift) is usually seen.

13.4.4 Platelet Abnormalities

Both qualitative and quantitative disorders of platelets are not uncommon in SLE patients; at the end of this chapter, you will find a simple approach to platelets disorders, considering the life-threatening conditions, disease activity, and other associated diseases. It has been found that almost in 25% to 50% of SLE patients may have a mild thrombocytopenia with platelet counts ranging between 100, 000 and 150, 000/microL, and 10% of SLE patients may have more severe form in which the counts become less than 50, 000/microL [1].

In a cohort study of 632 patients with SLE, the percentage of patients with platelet counts ranging between 50, 000 to 100, 000/μL was 54%, while those with counts between 20, 000 and 50, 000/μL represent 18%, and patients with counts less than 20, 000/μL represent 28% of the cohort [58].

There are many potential causes of thrombocytopenia in SLE patients. Among them, immune-mediated platelet destruction is considered the most common cause, but platelet consumption is another factor specially in association with MAHA or may be due to reduced platelet production secondary to cytotoxic medications.

Pathogenesis—the main mechanism is binding of immunoglobulin to the surface of the platelets which later get involved in the phagocytosis inside the spleen, similar to idiopathic thrombocytopenic purpura (ITP) [51]. Another mechanism in some patients involves bone marrow suppression by cytotoxic medications, increased consumption due to a thrombotic microangiopathy (e.g., TTP), the antiphospholipid syndrome, or antibodies against the thrombopoietin receptor on megakaryocytes or their precursors.

Patients with SLE can present initially with ITP followed by other manifestations later on.

In patients with isolated ITP, it has been found that 3–15% may develop SLE [59]. Evans syndrome, which is defined as the presence of both autoimmune thrombocytopenia and autoimmune hemolytic anemia, can also precede the onset of SLE.

Thrombocytopenia is uncommonly severe, and complications related to bleeding are generally low as a minority of patients only experiences severe bleeding. However, it is well-known that thrombocytopenia in patients with SLE considered poor prognostic factor and put the patient at risk of other organ involvement such as cardiac involvement, nephritis, or neuropsychiatric manifestation [38, 48].

Our algorithm at the end of this chapter simplified the approach to thrombocytopenia in SLE patients;, we suggest to do peripheral blood smear to rule out serious conditions such as MAHA, TTP, and malignancies; to order lupus anticouagulant and anticardiolipin to rule out APS; to do hemolysis workup and direct Coombs' test to rule out AIHA and Evans syndrome;, and to consider disease activity as well as secondary thrombocytopenia causes in your differential diagnosis.

Treatment: In patients with thrombocytopenia with counts ranging between 20, 000/microL and 50, 000/microL, usually they have prolonged

bleeding time; however bleeding is rarely seen with this range, while counts of less than 20, 000/microL can be associated with petechiae, purpura, ecchymoses, epistaxis, gingival, and other clinical bleeding. Treatment is usually indicated for patients with symptoms and counts of less than 50, 000/microL and for those with counts of less than 20, 000/microL. Glucocorticoid therapy is the main treatment, prednisone (1 mg/kg per day in divided doses) [47]. Dexamethasone also can be used as 40 mg/day dose for 4 days, with repeating the doses every 2–4 weeks, an intervals of 2–4 weeks may have similar remission rates and better long-term responses than those treated with daily prednisone [39]. The majority of patients improve on glucocorticoid within 1–8 weeks; in case of no response within 1–3 weeks or intolerance to steroids, other lines of therapy should be considered. The choice of second medication depends on the severity of the thrombocytopenia and the presence of other SLE manifestations.

- **Azathioprine** (0.5 to 2 mg/kg per day) [60].
- **Cyclophosphamide**, given as daily oral doses or intravenous pulse therapy. Intravenous pulse cyclophosphamide is usually preferred in patients with concurrent active lupus nephritis [40].
- **Intravenous immune globulin**, which is an effective and usually considered a first choice in conditions when a quick increase in platelets is needed, e.g., active bleeding or in case of emergency surgery [43].
- **Mycophenolate mofetil**, usually considered in patients who failed other medications [41].
- **Rituximab**—It is a chimeric monoclonal antibody which has been used as well to treat primary ITP (without SLE) refractory to previously mentioned therapies. It is given as once weekly dose for 4 consecutive weeks at doses of 375 mg/m^2 [42].
- **Splenectomy**—Splenectomy may increase the platelet count, but it does not reliably make a consistent remission of thrombocytopenia. After splenectomy, relapse may happen and has been reported at varying times from 1 to 54 months following surgery.
- **Thrombocytopenia following splenectomy—**Some patients may have persistent thrombocytopenia following splenectomy;, those patients may respond to azathioprine, cyclophosphamide, rituximab, intravenous immunoglobulin, or danazol [44]. Patient who underwent splenectomy is at high risk of pneumococcal infections;, that's why it is highly recommended for patients to receive immunization with pneumococcal vaccine before splenectomy if possible.
- **Danazol** (400 to 800 mg/day) [45]—May be considered for patients who failed other therapies. In a series of 34 patients, excellent long-term results were achieved with danazol [46].
- **Vincristine—**Successful use of vincristine has been reported [46].

13.4.4.1 Thrombocytosis

Thrombocytosis is unfrequently seen in patients with SLE.

We suggest to ruling out secondary causes such as infection or other inflammatory process, or APS.

As an example, among 465 patients with SLE, 17 (3.7%) were found to have thrombocytosis (platelet ≥400, 000/mm3). Three of these patients had one or more of the following features on peripheral blood film: Howell-Jolly bodies, spherocytes, and target cells.

Ultrasound, CT, and liver-spleen scintigraphy failed to demonstrate a spleen. All three patients had aPL [69]. These observations suggest that autosplenectomy may occur in patients with SLE, perhaps mediated by aPL.

13.4.5 Pancytopenia

Destruction of all three cell line (red blood cells, white blood cells, and platelets) may occur peripherally;, it also may suggest bone marrow failure, as in the case in aplastic anemia. Hence, bone marrow biopsy is the most significant diagnostic test to do. In a study published in 2012, concluded that among SLE patients with peripheral cytopenia, the incidence of bone marrow

abnormalities is high. Bone marrow may be one of the common affected organs by immune dysregulation in active SLE. Peripheral cytopenia can be consequently improved after treatment of disease activity; hence, bone marrow biopsy should be recommended in patients with refractory cytopenia to conventional treatment [61].

There are many causes of bone marrow failure which include drugs and coexisting diseases such as acute leukemias, myelodysplastic syndromes, severe megaloblastic anemia, paroxysmal nocturnal hemoglobinuria (PNH), and infections. Furthermore, unexplained cytopenia can be associated with bone marrow necrosis, dysplasia, and distortion of the bone marrow architecture [62, 63].

13.4.6 Lymphadenopathy and Splenomegaly

Patients with SLE may present with lymphadenopathy, which could be regional or peripheral lymphadenopathy. The common sites involved in SLE lymphadenopathy are cervical and axillary nodes. In a cohort of 698 patients with SLE, lymphadenopathy was found in 59% of the study group. Patients who presented with lymphadenopathy as initial presentation represented 1% of the cohort. Furthermore, the lymph nodes' size ranged from 3 to 4 centimeter in diameter, most of them were not tender and soft. [64].

The typical histological finding in SLE lymphadenopathy includes reactive lymphoid follicular hyperplasia with variable levels of coagulative necrosis. A usual finding, yet highly associated with SLE, is the presence of hematoxylin bodies [1].

SLE lymphadenopathy is present usually initially at the diagnosis and during SLE flares in most of the cases. When SLE patient presents with an enlarged lymph node, other etiologies should be considered such as infection and lymphoproliferative disorders (e.g., angioimmunoblastic T-cell lymphoma); both of these diseases are relatively common in SLE compared to normal population. In case of infectious lymphadenopathy, lymph nodes are usually tender.

Splenomegaly may present in 10–46% of SLE patients, especially during SLE flares, and it should not necessarily be linked to cytopenia.

Based on the fact that splenomegaly and lymphadenopathy are common among SLE patients, physicians should consider lymphoproliferative disorders in those patients, especially because patients with SLE have up to fivefold higher risk of non-Hodgkin lymphoma [65].

Kikuchi-Fujimoto disease (KFD), also known as histiocytic necrotizing lymphadenitis, is a disease characterized by the presence of fever, lymphadenopathy commonly in cervical nodes, and constitutional symptoms [67].

KFD is usually self-limited, and sometimes confused with SLE or lymphoma. Typically, it is present in young women, and preceded by flu-like illness. The etiology of KFD remains unknown. No specific laboratory tests are associated with this disease, ; however, 50% of the patients may develop mild leucopenia. Histological finding of hematoxylin bodies and plasma cells and the DNA deposition in the blood vessels are highly associated with SLE lymphadenitis and help differentiating between the two diseases. It is always recommended to exclude SLE with proper serological testing before making the diagnosis of KFD. There have been few reports of SLE with coexisting KFD [55, 64, 66].

Castleman disease, also known as angiofollicular lymph node hyperplasia, is one of the rare lymphoproliferative diseases which manifested as enlarged lymph node that may or may not be associated with constitutional symptoms and could be confused with SLE or lymphoma. Its etiology remains unknown.

13.4.7 Antibodies to Clotting Factor and Phospholipids

Hematologic manifestations of SLE may involve coagulation system in some patients. SLE patients may have antibodies directed against the following factors VIII, IX, XI, XII, and XIII [1].

These antibodies can cause a biochemical abnormality (in vitro), but it also can cause

some clinical abnormalities manifested as overt bleeding.

Antiphospholipid antibodies (aPL) are commonly seen in SLE patients. They can cause a prolonged partial thromboplastin time through lupus anticoagulant activity. Clinically, these antibodies have well-recognized risks of arterial as well as venous thrombosis and thrombocytopenia. Additionally, female in childbearing age with aPL is at high risk fetal loss [68].

Moderate to high titers of aPL and other antibodies to binding proteins such anticardiolipin antibodies can be associated with certain clinical features. If aPL is present with certain clinical features, it may suggest the presence of antiphospholipid syndrome (APS) (see Chap. 12, , Thrombosis in Rheumatological diseases).

High prevalence of aPL in SLE patients following treatment with cyclophosphamide was noted in a single retrospective study that compared 177 cyclophosphamide-treated SLE patients to 203 patients with SLE never treated with this alkylating agent [52]. Sero-conversion occurred at a higher rate in the cyclophosphamide-treated patients (19 versus 1%, respectively).

13.5 Macrophage Activation Syndrome (MAS)

13.5.1 Introduction

The macrophage activation syndrome (MAS), also known as hemophagocytic lymphohistiocytosis (HLH), is a condition that requires urgent attention and treatment. It is classically associated with systemic juvenile idiopathic arthritis in children and adult onset Still's disease [69], but can occur in any rheumatic disease including SLE, RA, vasculitis, Sjögren's syndrome, mixed connective tissue disease, systemic sclerosis, and inflammatory myopathies [70]. MAS can develop anytime during rheumatologic disease. It can be the first manifestation of the rheumatologic disease or may occur while patient is on treatment. It may also be associated with infection.

Hematological manifestation of MAS includes pancytopenia, hepatosplenomegaly, hyperferritinemia, and coagulopathy.

An overview of MAS is presented here, with an algorithm at the end constructing a simple approach to diagnose MAS/HLH in a patient with rheumatologic disorder.

13.5.1.1 Pancytopenia

Together, anemia and thrombocytopenia are present in more than 80% of patients [71–73]. The median hemoglobin level is 7.2 g/dl, and platelet count is 69, 000/microL [71]. Neutropenia with absolute counts below 1000/microL is not uncommon.

Patients with juvenile idiopathic arthritis and adult onset Still's disease may develop cytopenia later in the course of disease as they tend to have elevated blood counts prior developing MAS.

13.5.1.2 Hepatosplenomegaly

Reticuloendothelial system is commonly affected in MAS/HLH. In retrospective study including 249 patients of HLH, hepatomegaly was observed in 95% and lymphadenopathy in 33% of the patients. Another European registry includes 122 patients, 97% of them were found to have splenomegaly [74].

13.5.1.3 Hyperferritinemia

Severe hyperferritinemia is associated with MAS/HLH;, a level above 10, 000 ng/mL is 90% sensitive and 96% specific for MAS/HLH [75].

In HLH-94 study, it was found that ferritin greater than 10,000, 5000, and 500 ng/mL were seen in 25, 42, and 93%, respectively [72]. It is very rare to have MAS/HLH with ferritin levels below 500, ; however, low ferritin does not totally exclude MAS.

13.5.1.4 Coagulopathy

High partial thrombin time and high prothrombin time due to liver involvement and impaired liver synthetic function in association with disseminated intravascular coagulopathy are seen in MAS/HLH [70].

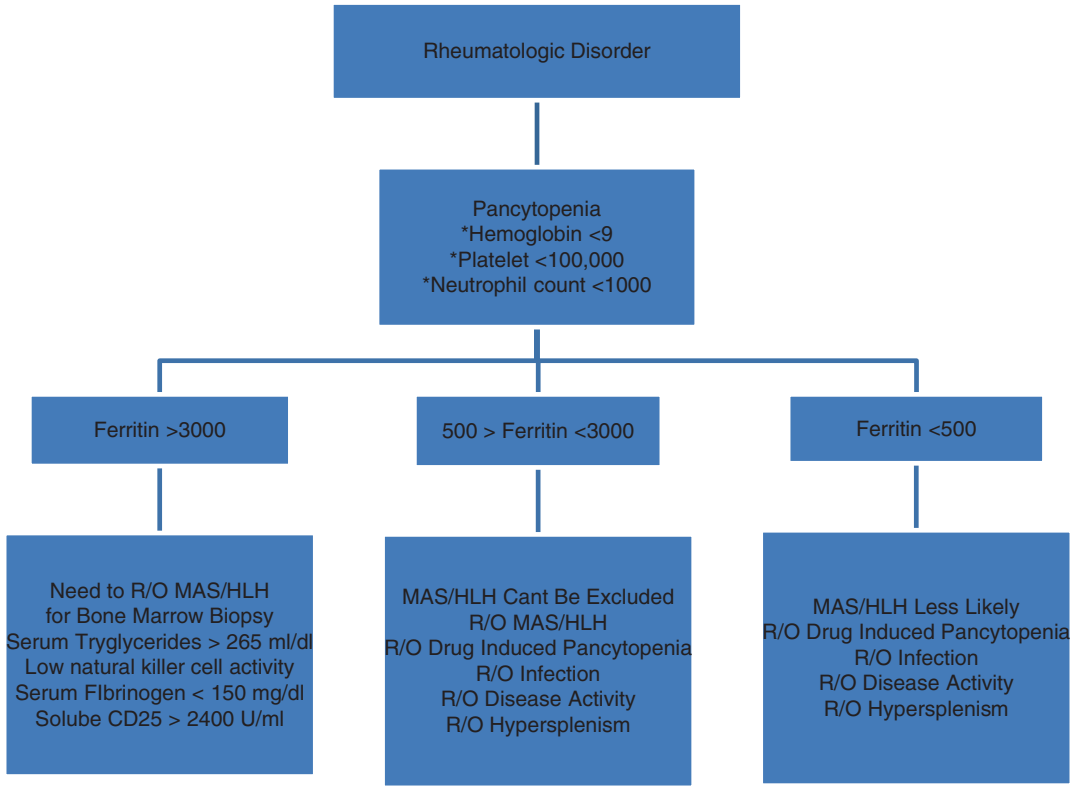

Fig. 13.5 Algorithmic approach for hyperferritinemia with pancytopenia in rheumatological diseases patients. This approach is based on ferritin level; the authors suggest to broaden the differential diagnosis and to rule out disease activity and non-rheumatological causes, including systemic diseases, infections, and drug-induced and primary hematological diseases. The evidence to support this approach is based on cumulative literature, current guidelines, and the author's experience. (Abbreviations: *R/O* rule out, *MAS* macrophage activation syndrome, *HLH* hemophagocyticlymphohistiocytosis)

The HLH-2004 revised diagnostic criteria are used to diagnose MAS/HLH. Five out of the eight criteria as shown in Fig. 13.5 are required for the diagnosis.

13.5.2 Treatment

Salvage treatment for adults with refractory/relapsing HLH usually requires intensification using combined chemotherapy and consolidation with allogenic stem cell transplantation. Novel agents are providing promising therapeutic alternatives including those incorporating ruxolitinib (JAK1/2 inhibitor), anakinra (IL-1 blockade), alemtuzumab, and emapalumab [76].

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Renal System and Rheumatology

14

Sami Alobaidi, Manal Alotaibi, Noura Al-Zahrani, and Fahmi Al-Dhaheri

14.1 Introduction

Many rheumatic diseases can be associated with different complications in kidneys and urinary tract. The goal of this chapter is to provide a summary of renal manifestations in rheumatic diseases that is easily accessible by students, residents, and practitioners.

The material presented provides a simple approach to patients presenting with renal and rheumatic manifestations. It is not meant to be an exhaustive review.

It presents a stepwise approach to the evaluation of proteinuria and hematuria in patients with rheumatic diseases. It also provides a summary on the renal complications of rheumatic diseases. The chapter also discusses lupus nephritis (LN) in more detail as it is common and severe manifestation of systemic lupus erythematosus with increased risk of death and end-stage renal disease.

14.2 Objectives

By the end of this chapter, you should be able to:

1. Construct a diagnostic approach to patients with proteinuria or hematuria.
2. Diagnose and manage lupus nephritis (LN).
3. Discuss renal involvement in different rheumatic diseases.
4. Review the common side effects of antirheumatic medications on kidney function.

14.3 Proteinuria

Proteinuria screening among populations is based on measurement of albumin in random urine dipstick test. Most adolescents who have proteinuria through dipstick test do not have renal disease, and this proteinuria usually resolves on repeat testing. However, prolonged proteinuria is suggestive of kidney disease in patients with diabetes mellitus, hypertension, primary renal disease, SLE, or other systemic illnesses [1].

Proteinuria greater than 200 mg/24 h is considered abnormal. Urine protein excretion ranging between 200 and 3000 mg/24 h is termed

S. Alobaidi (✉)
Department of Medicine, College of Medicine, University of Jeddah, Jeddah, Saudi Arabia
e-mail: salobaidi@uj.edu.sa

M. Alotaibi
Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Internal Medicine Department, College of Medicine, Umm Al-Qura University, Mecca, Saudi Arabia

N. Al-Zahrani
Bahra Primary Health Care Center, Ministry of Health, Makkah, Saudi Arabia

F. Al-Dhaheri
Doctor Soliman Fakeeh Hospital, Jeddah, Saudi Arabia

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sub-nephrotic range proteinuria. Nephrotic range proteinuria is typically more than 3000 mg/24 h.

Proteinuria is an important indicator of renal disease activity and progression. It reflects an underlying pathology causing a change in the permeability properties of the glomerular filtration barrier [1].

A stepwise approach that may help physicians detect and evaluate benign and pathological causes of proteinuria is illustrated in Fig. 14.1.

14.4 Hematuria

Microscopic hematuria refers to the presence of erythrocytes in urine that can be exclusively detected by microscopic exam or dipstick analysis. It is a frequent reason for referral to urology or nephrology. It is often asymptomatic and found incidentally on routine urine examination.

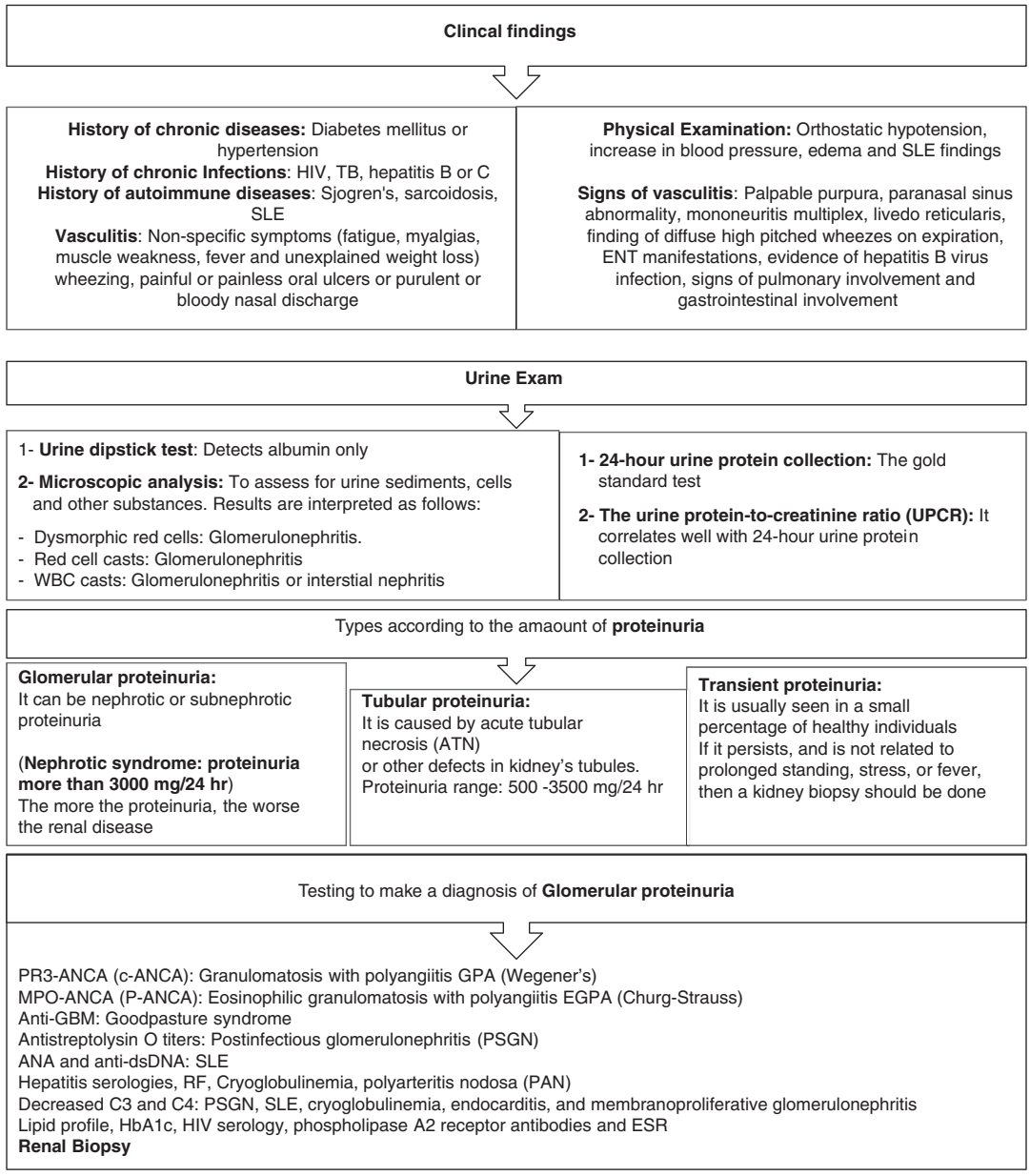

Fig. 14.1 Approach to a patient with proteinuria [1]

Macroscopic (grossly visible) hematuria is more commonly associated with malignancy than microscopic hematuria. For this reason, a full investigation, including upper tract imaging and cystoscopy for the lower tract, for all patients with macroscopic hematuria is usually required.

Opinions regarding which patients with microscopic hematuria should be evaluated and need to be investigated remain controversial [2, 3].

Figures 14.2 and 14.3 provide simplified approaches to detect and evaluate significant microscopic hematuria according the recent guidelines [2, 3].

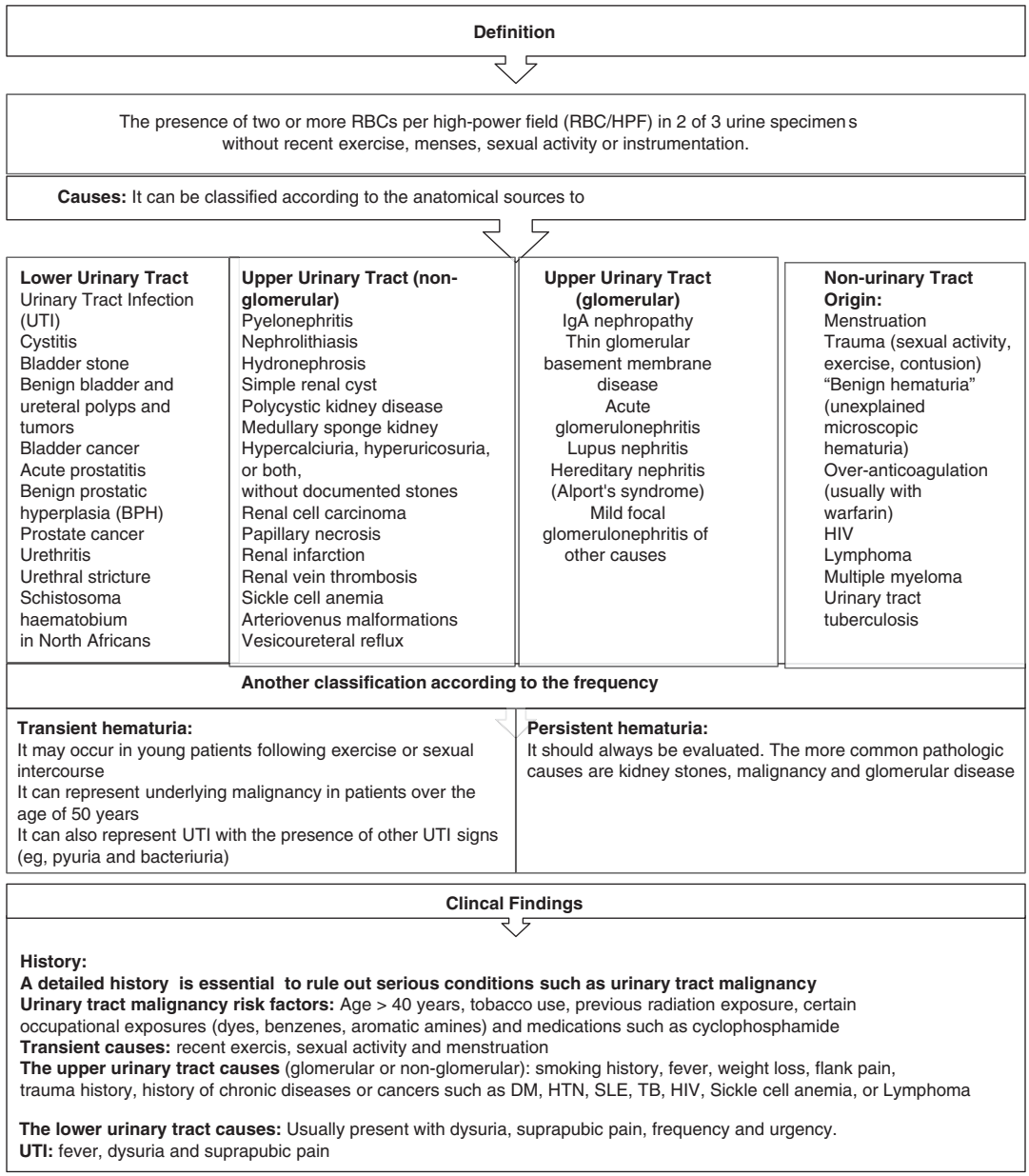

Fig. 14.2 approach to a patient with hematuria.

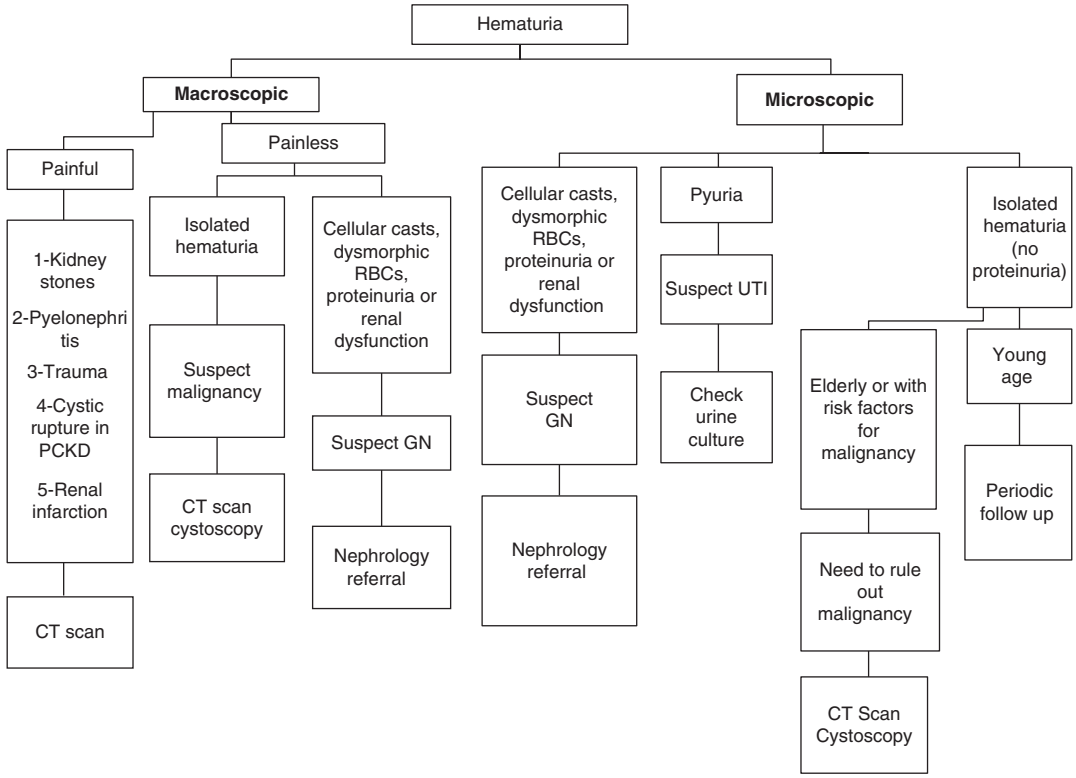

Fig. 14.3 Classification of hematuria

14.5 Renal Involvement in Different Rheumatic Diseases

Rheumatic diseases are frequently associated with renal complications. These complications include vascular, glomerular, and tubulointerstitial changes.

Drug-induced renal impairment should be included in the differential diagnosis of renal complications in a rheumatic patient.

Renal involvement clinically manifests in many different ways. The spectrum ranges from slight functional disorders such as slight erythrocyturia/proteinuria with normal renal function to rapidly progressive renal failure. Table 14.3 provides a summary of renal involvement in different rheumatic diseases.

14.6 Lupus Nephritis (LN)

Renal involvement is common in SLE. It is the leading cause of morbidity and mortality in patients with lupus, characterized by the loss of self-tolerance, production of autoantibody, and development of immune complexes that deposit in the kidney to induce nephritis. Proteinuria is one of the most commonly observed abnormalities in patients with lupus nephritis [6].

Figure 14.4 provides an overview of pathogenesis, clinical manifestations, and complications of lupus nephritis.

14.6.1 Diagnostic Criteria

Criteria for lupus nephritis in patients with SLE include any of the following conditions (Table 14.1):

1. **Persistent proteinuria.**
   - 500 mg/24 h protein
   - 3+ protein on urine dipstick
   - Spot urine protein/creatinine ratio > 0.5 mg/mg.
2. **Cellular casts.**
3. **Active urinary sediment** (> 5 red blood cells/high power field [RBC/hpf], > 5 white blood cells[WBC]/hpf in the absence of infection, or cellular casts limited to RBC or WBC casts).
4. **Renal biopsy**: Immune complex-mediated glomerulonephritis compatible with lupus nephritis.
5. **Opinion of rheumatologist or nephrologist** [11]**.**

14.6.2 Treatment

The American College of Rheumatology (ACR) recommends treatment according to the International Society of Nephrology/Renal Pathology Society (ISN/ RPS) classification of lupus nephritis. (Check sect. 3 for full presentation of the recommendation for management guidelines). Response to treatment is based on several factors including age, gender, location, and race/ethnicity (Table 14.2) [14].

14.6.3 Adjunctive Treatments

1. Hydroxychloroquine for all patients with SLE unless contraindicated.
2. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers if proteinuria ≥500 mg/24 h [15]
3. Statin therapy if LDL cholesterol >100 mg/dL (2.6 mmol/L).
4. Control hypertension at a target of ≤130/80 mm Hg [11]

Note: Patients with lupus should remain on antimalarial therapy even during disease quiescence as it was shown to be associated with associated with reduced risk of renal damage, improved survival, and decreased incidence of lupus flares [16].

14.7 Sjögren's Syndrome

Sjögren's syndrome is a chronic inflammatory disorder characterized by lymphocytic infiltration of the lacrimal and salivary glands which result in dryness of the eyes and mouth [17]. Systemic features may include arthritis, renal, hematopoietic, pulmonary involvement, and vasculitis (Fig. 14.5). These manifestations are secondary to vasculitis, autoantibody-mediated mechanisms, or lymphocytic infiltration of the target organs. The prevalence of renal involvement ranges from 2 to 67% [22].

14.8 Cryoglobulinemic Syndrome (CG)

Cryoglobulinemic vasculitis is an immune-complex-mediated disease caused by the deposition of cryoglobulins in the small- and medium-sized arteries and veins. Renal involvement is noted in around 20% of patients with mixed cryoglobulinemic vasculitis and usually diagnosed 2.5 years after the disease onset. Membranoproliferative glomerulonephritis is reported in around 80% of patients [23]. Figure 14.6 provides an overview of renal involvements in CG.

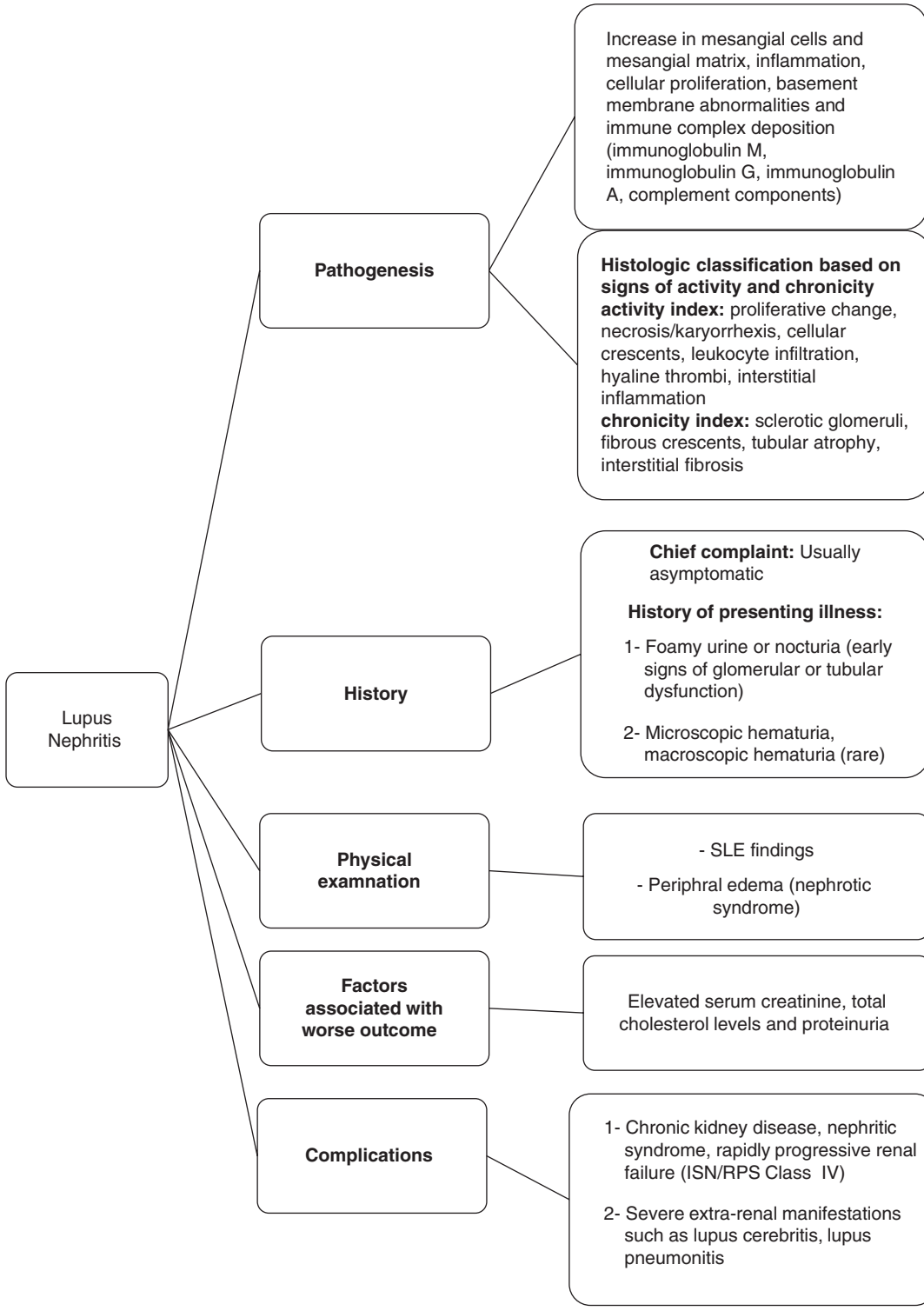

Fig. 14.4 Overview of pathogenesis, clinical manifestations, and complications of lupus nephritis [7–9]

Table 14.1 Recommended workup for suspected lupus nephritis

Tests	Findings	Analysis
	Serum creatinine	To evaluate renal functions [6]
	Antinuclear antibodies (ANA)	Frequently positive in patient with connective tissue disease and high sensitive for SLE and drug-induced lupus [6]
	Anti-double-strand DNA antibodies (anti ds-DNA)	High in patient with LN, it plays an important role in induction of tissue damage, and it correlates with disease activity [6]
	Antiphospholipid antibodies (APLA)	To evaluate autoimmune disease especially SLE**,** its presence means increase risk of thrombosis [6]
	Anti-C1q antibodies	It is sensitive and specific to diagnosis of lupus nephritis and evaluating the disease activity [10]
	Complement 3 (C3) and complement 4 (C4)	Lack of C3 and C4 may indicate lupus nephritis because the presences of these complement components exert a protective effect against disease onset, although it may be normal [6]
Urine studies	**Persistent proteinuria**	- Increases incrementally within severity classes - >500 mg/24 h protein - >3+ protein on urine dipstick - Spot urine protein/creatinine ratio > 0.5 [6, 11]
	Dysmorphic erythrocytes	- Indicate inflammatory glomerular disease [6, 11]
	RBC or WBC cells	- (> 5 red blood cells/high power field [RBC/hpf], > 5 white blood cells[WBC]/hpf in the absence of infection - Indicate glomerulonephritis or tubulointerstitial disease [6, 11]
	Cellular casts	- RBC or WBC casts which indicate inflammatory glomerular disease [6, 11]
	Lipiduria	- May result from abnormal glomerular permeability [6, 11]
Renal biopsy	**Indications**	**American College of Rheumatology (ACR) recommendations**
	1 to confirm suspected nephritis 2 to evaluate disease activity and damage 3 to determine appropriate therapy 4 to make sure that the type, duration, and intensity of treatment matches the severity of disease 5 to predict outcome and identify the alternative causes of renal disease	- Biopsy is highly recommended in patients with systemic lupus erythematosus with the following: Increasing serum creatinine without alternative cause (such as sepsis, hypovolemia, or medication induced). Confirmed proteinuria ≥1000 mg/24 h (either 24-hr urine specimens or spot protein/creatinine ratios). Combinations of following (confirmed in ≥2 tests done within short period and in the absence of alternative causes). Proteinuria ≥500 mg/24 h plus hematuria (≥ 5 red blood cells per high power field). Proteinuria ≥500 mg/24 h plus cellular casts. All patients with clinical evidence of active lupus nephritis, previously untreated, should have renal biopsy to classify glomerular disease by current International Society of Nephrology/Renal Pathology Society (ISN/ RPS) classification (unless biopsy is strongly contraindicated) [11] **Second biopsy:** To detect disease progression **Indications:** 1. When the patient does not respond to therapy 2. In case of worsening of renal function [12]

Table 14.2 Summary of the classification and treatment of lupus nephritis [11, 13]

Classifications of lupus nephritis	Treatment
Class I (minimal mesangial LN) and class II (mesangial proliferative LN)	Treated as dictated by the extra-renal clinical manifestations of lupus
Class III LN (focal LN) and class IV LN (diffuse LN)	**Initial therapy**: Corticosteroids (1 mg/kg, to be tapered according to clinical response) combined with either cyclophosphamide (500 mg IV every 2 weeks for 6 doses) or mycophenolate mofetil (up to 3 g per day as tolerated) **Maintenance therapy**: Mycophenolate mofetil (1–2 g/d in divided doses) or azathioprine (1.5–2.5 mg/kg/d) and low-dose oral corticosteroids (≤10 mg/d prednisone equivalent)
Class V LN (membranous LN)	**Non-nephrotic-range proteinuria**: Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Corticosteroids and immunosuppressive therapy use is dictated by the presence of extrarenal manifestations of lupus **Persistent nephrotic-range proteinuria:** Corticosteroids plus an additional immunosuppressive agent—(Cyclophosphamide, tacrolimus, cyclosporine), mycophenolate mofetil or azathioprine
Class VI LN (advanced sclerosis LN)	Treated with corticosteroids and immunosuppressive therapy only as dictated by the extra-renal manifestations of lupus. Discussion of renal replacement therapy (dialysis vs kidney transplant)

14.9 Scleroderma

Scleroderma is manifested by widespread progressive fibrosis of the skin and internal organs due to accumulation of collagen. Renal involvement occurs in around half of the patients and is manifested as mild proteinuria, worsening kidney function, and/or hypertension (Fig. 14.7) [26]. Scleroderma renal crisis is the most serious renal manifestation which occurs in 5 to 10% of patients with systemic sclerosis, more commonly in diffuse cutaneous systemic sclerosis [27].

14.9.1 Rheumatoid Arthritis (RA)

Rheumatoid arthritis is a systemic inflammatory disorder of unknown etiology that primarily involves the joints. It has been reported that the annual incidence of rheumatoid arthritis is around 40 per 100,000. Females are affected two to three times more often than males, and the peak onset is between 50 and 75 years of age [28]. An observational study has shown that the incidence of impaired kidney function is higher in patients with rheumatoid arthritis; these changes were anticipated by many factors like cardiovascular disease, dyslipidemia, elevated sedimentation rate in the first year of rheumatoid arthritis, and NSAIDs use [29]. Figure 14.8 provides an overview of renal involvement in RA.

14.9.2 Renal Involvement in Vasculitis

14.9.2.1 Polyarteritis Nodosa (PAN)

It is a systemic necrotizing vasculitis of medium-sized and occasionally small vessels [34]. It is a rare disease and characterized by the absence of antineutrophil cytoplasmic antibodies (ANCA) [34]. Any organ can be affected including the kidneys (renal artery involvement is common and leads to stenosis, hypertension, and eventually chronic kidney disease) (Fig. 14.9). This disease spares the lungs [34]. Most cases are idiopathic; however, 33% of cases are associated with chronic HBV infection [34]. Renal disease is the most common cause of death. It is fatal if left untreated, but has favorable response to treatment [34].

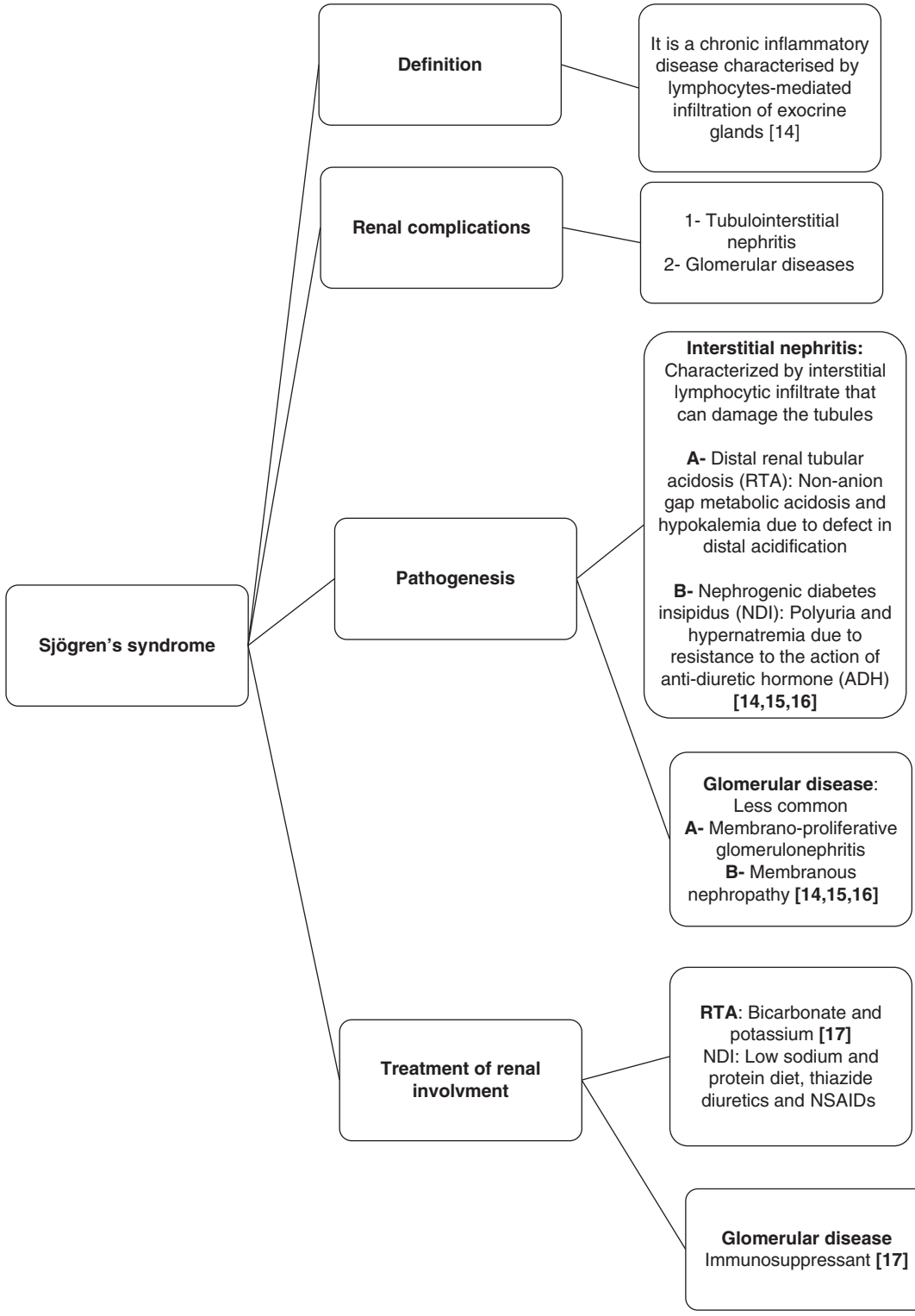

Fig. 14.5 Renal involvement in Sjögren's syndrome: [18–21]

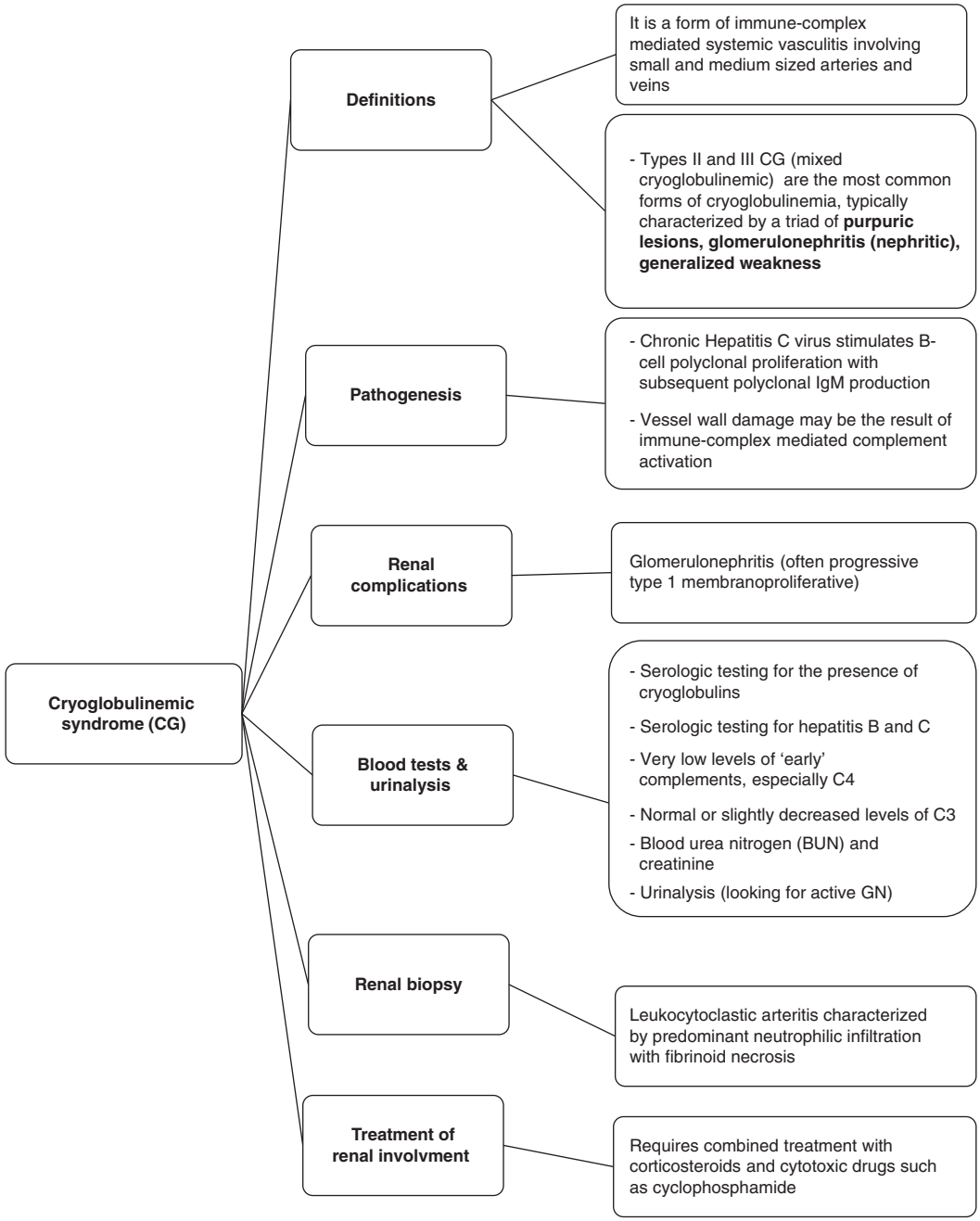

Fig. 14.6 Overview of renal involvements in CG [23]

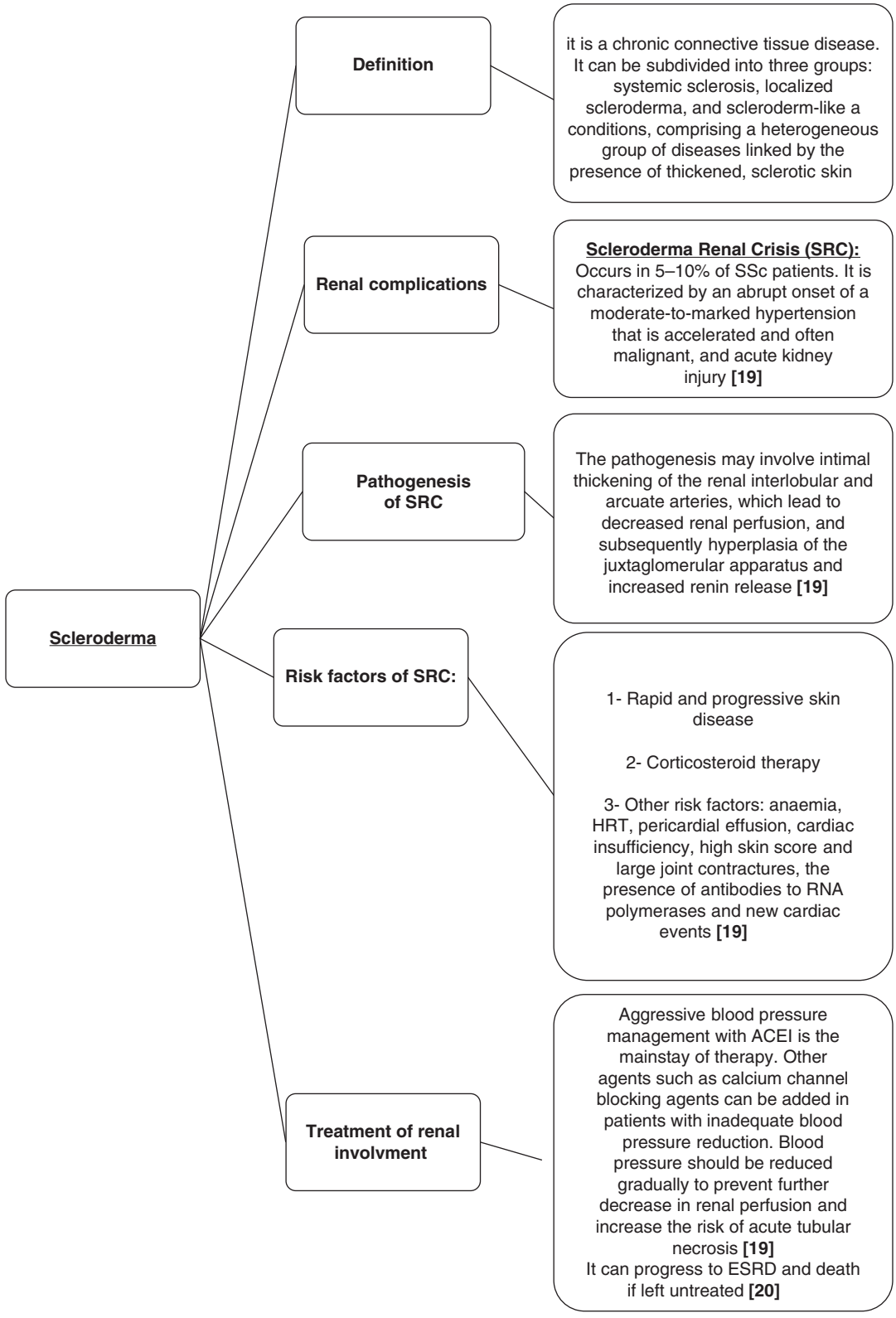

Fig. 14.7 Renal involvement in scleroderma [24, 25]

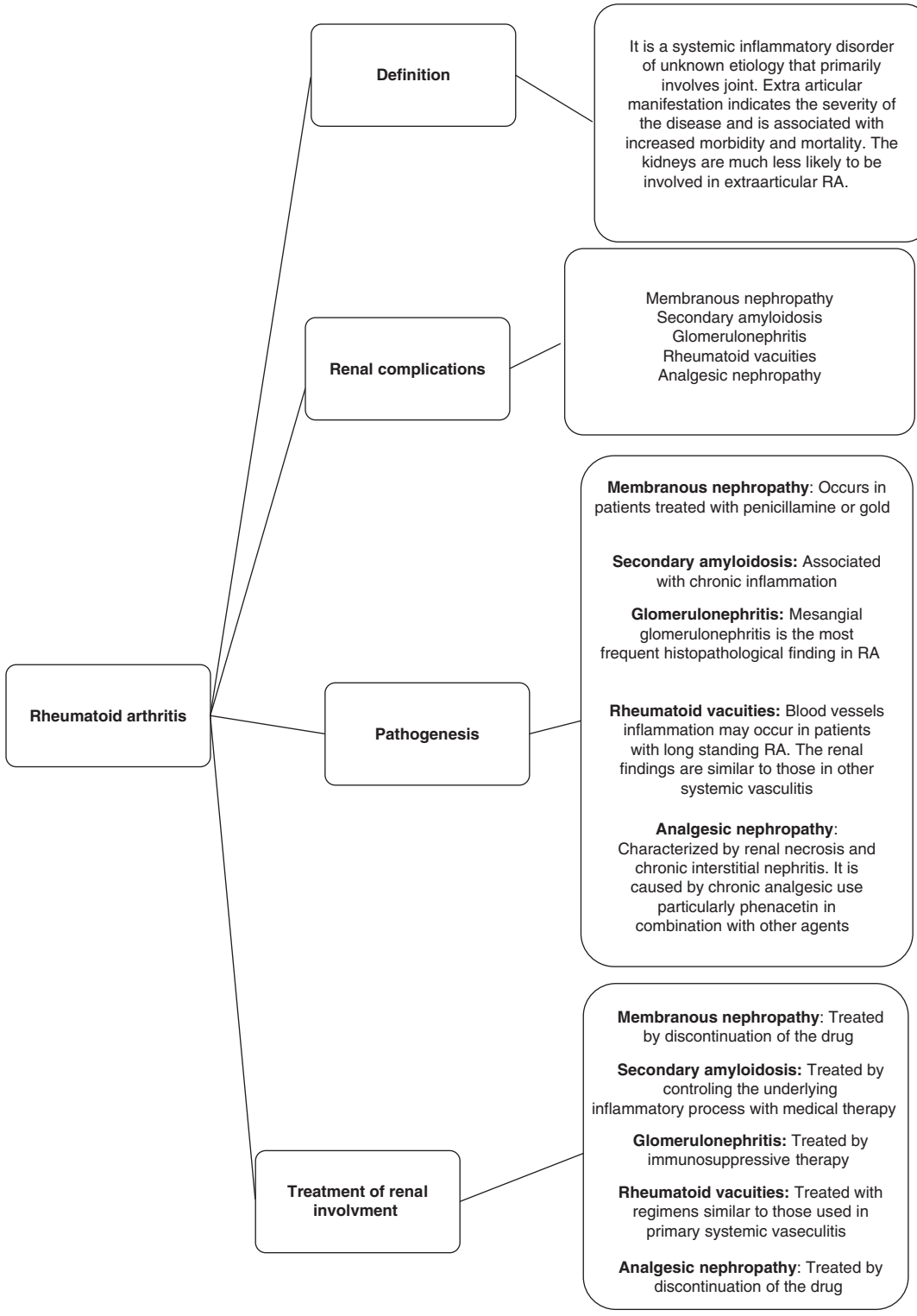

Fig. 14.8 Overview of renal involvement in RA [30–33]

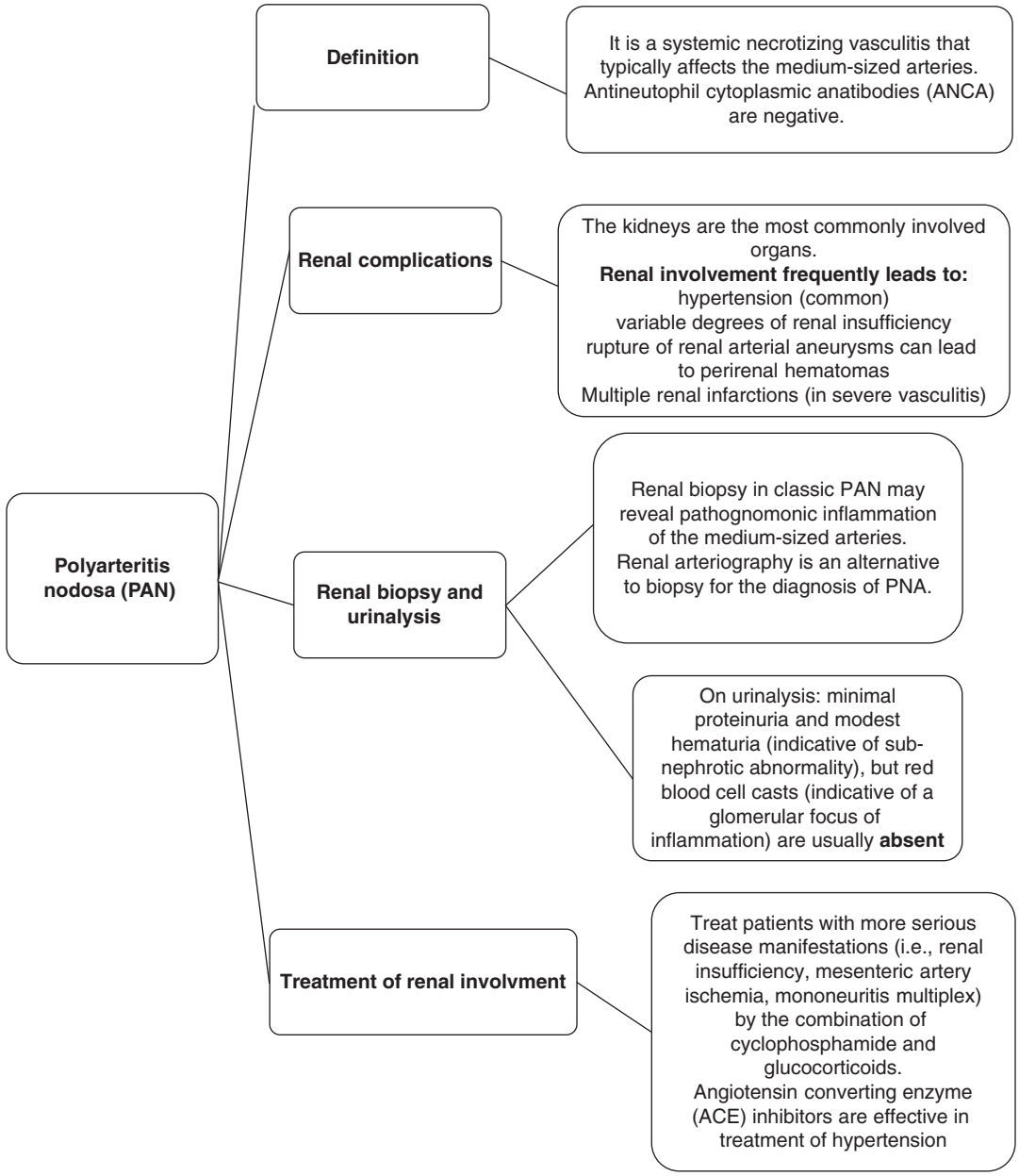

Fig. 14.9 Medium vessel vasculitis: polyarteritis nodosa (PAN) [34]

14.9.3 Eosinophilic Granulomatosis with Polyangiitis EGPA (Churg-Strauss)

It is a systemic necrotizing vasculitis that affects small-sized muscular arteries [35]. It is a rare disease and characterized by the presence of antineutrophil cytoplasmic antibodies (ANCA) [35]. Asthma, peripheral eosinophilia, and granulomas on histology are common associations with this disease [35]. Renal involvement can lead to pauci-immune rapidly progressive glomerulonephritis (Fig. 14.10) [35].

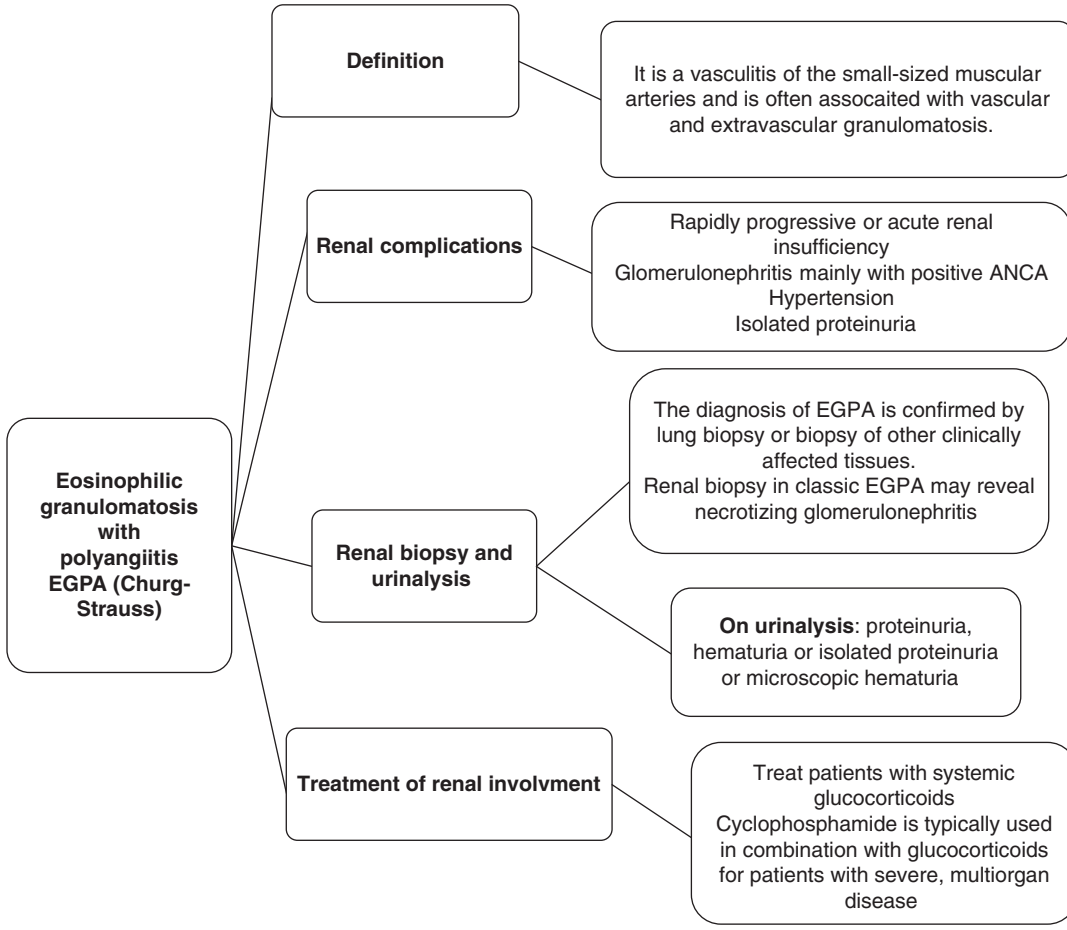

Fig. 14.10 Eosinophilic granulomatosis with polyangiitis EGPA (Churg-Strauss) [35]

14.9.4 Granulomatosis with Polyangiitis GPA (Wegener's) and Microscopic Polyangiitis (MPA)

These are systemic vasculitides of the medium- and small-sized arteries, as well as the venules and arterioles [29]. They are known to cause many renal complications, e.g., glomerulonephritis, acute kidney injury, and proteinuria (Fig. 14.11) [29, 30].

Rapidly progressive glomerulonephritis is a common and severe feature with Wegener's granulomatosis or proteinase-3 (PR3)-ANCA vasculitis, and it might lead to end-stage renal diseases [29, 30]. In addition, necrotizing granulomatous inflammation is the histopathologic hallmark of GPA [29, 30]. Microscopic polyangiitis or myeloperoxidase (MPO)-ANCA vasculitis are associated with chronic renal injury more than glomerulonephritis [29, 30].

14.9.5 Henoch-Schönlein Purpura (HSP) (IgA Vasculitis)

It is a systemic vasculitis of the small-sized blood vessels (the post-capillary venules), characterized by the deposition of IgA-containing immune complexes [40].

IgA vasculitis is considered the most common systemic vasculitis in children [40]. Renal involvement occurs in 20% to 100% of patients. HSP nephritis is common and generally mild in children (particularly young children) (Fig. 14.12). It is mainly presented with microscopic hematuria or proteinuria [40] (Table 14.3).

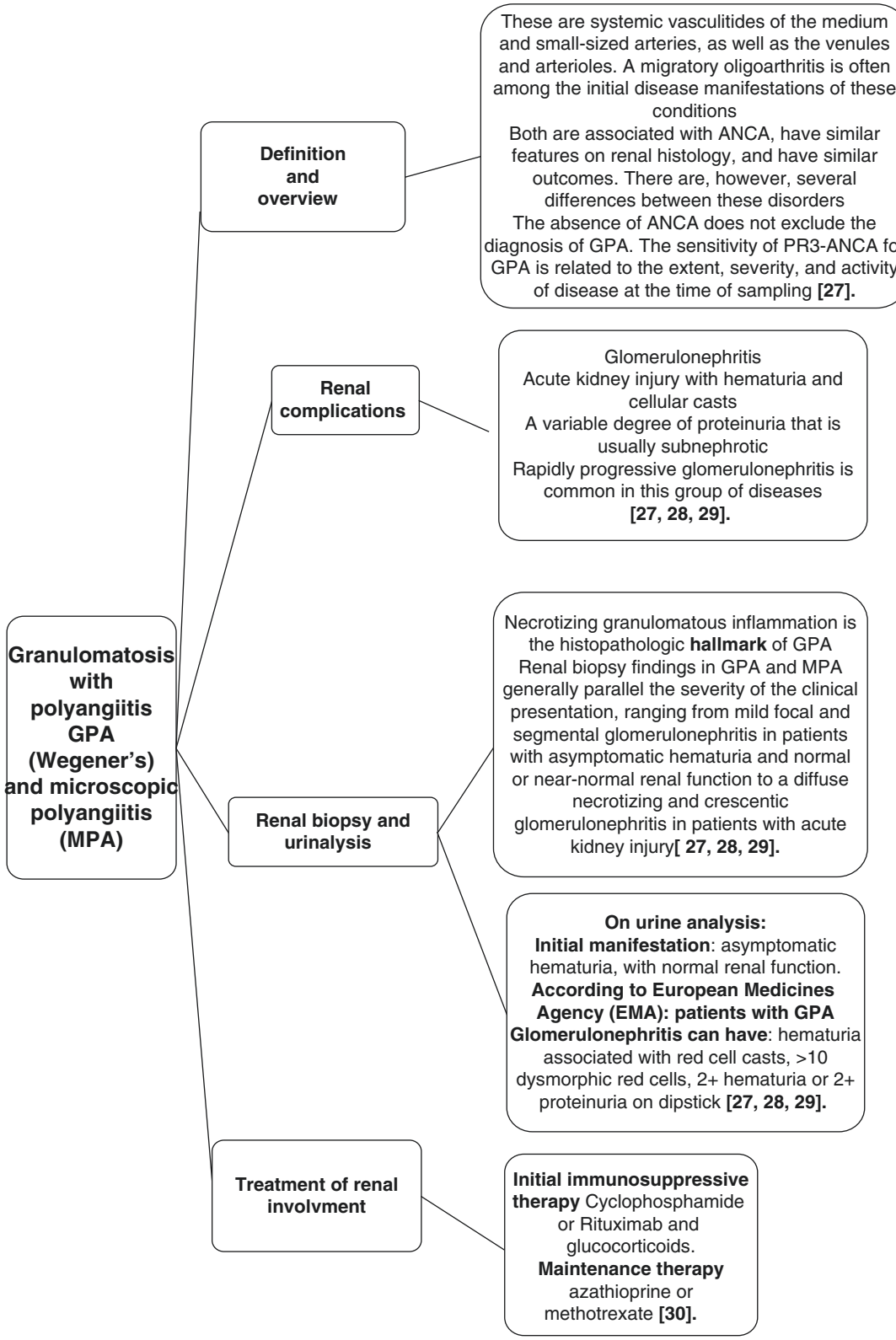

Fig. 14.11 Granulomatosis with polyangiitis GPA (Wegener's) and Microscopic Polyangiitis (MPA) [36–39]

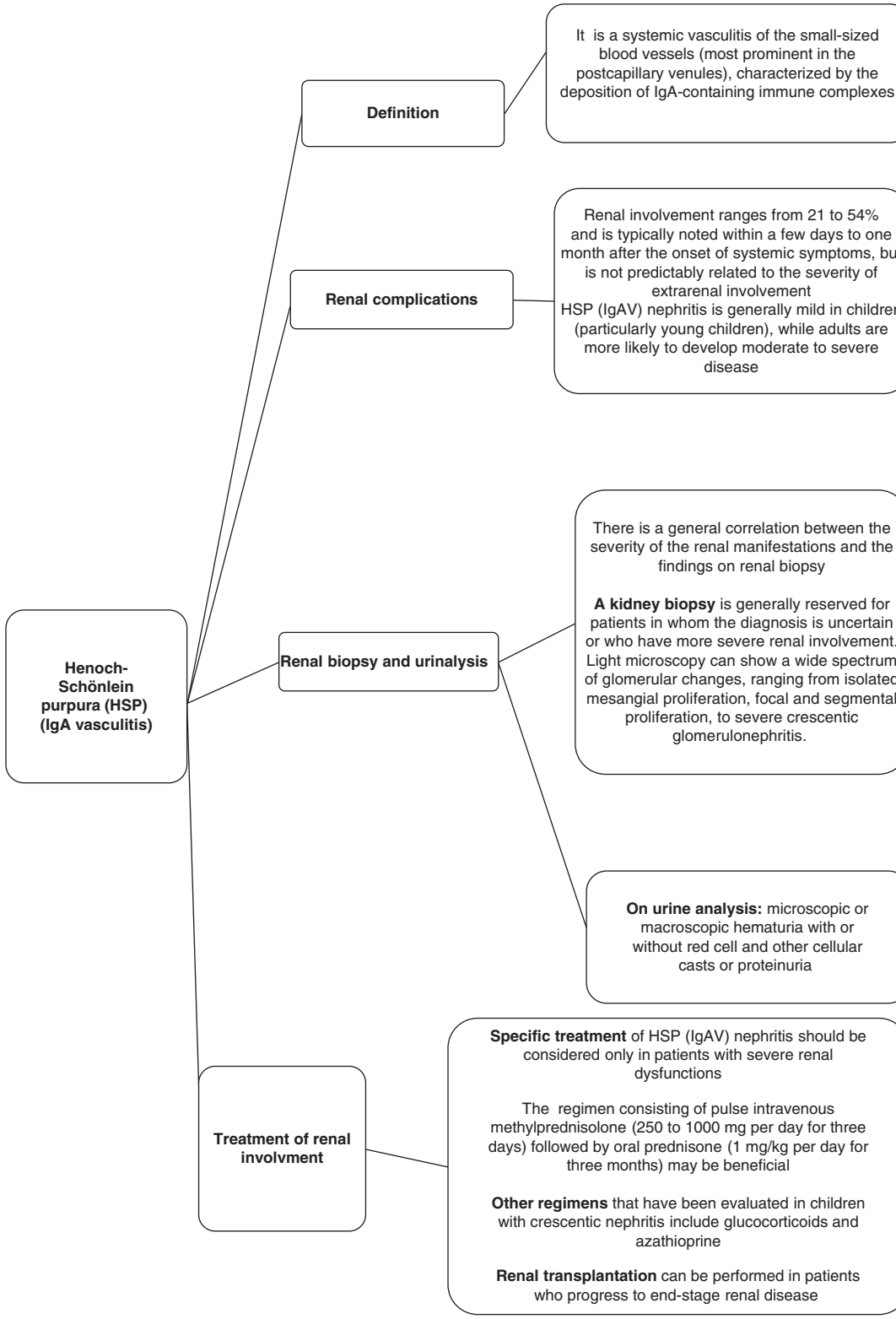

Fig. 14.12 Henoch-Schönlein purpura (HSP) (IgA vasculitis) [40]

Table 14.3 Summary of renal involvement in different rheumatic diseases

Rheumatic disease	Renal complications
Systemic lupus erythematosus	• Interstitial nephritis. • Necrotizing vasculitis. • Glomerulosclerosis. • Chronic kidney disease. • Nephritic syndrome. • Rapidly progressive renal failure .
Sjögren's syndrome	• Interstitial nephritis (may precede onset of sicca symptoms). • Renal tubular acidosis (types I and II) (in 11%). • Interstitial cystitis (rare). • Glomerulonephritis (rare). • Nephrolithiasis (rare).
Cryoglobulinemia	• Membranoproliferative glomerulonephritis (60 to 80%).
Henoch-Schönlein purpura (HSP) (IgA vasculitis)	• Hematuria with or without proteinuria. • Isolated hematuria. • Nephritic syndrome. • Renal insufficiency. • Hypertension. • End-stage renal failure.
Polyarteritis Nodosa	• Hypertension (common). • Variable degrees of renal insufficiency. • Rupture of renal arterial aneurysms can lead to perirenal hematomas. • Multiple renal infarctions (in severe vasculitis) .
Granulomatosis with polyangiitis GPA (Wegener's) and microscopic polyangiitis (MPA)	• Glomerulonephritis. • Acute kidney injury with hematuria and cellular casts. • Subnephrotic proteinuria. • Rapidly progressive glomerulonephritis.
Eosinophilic granulomatosis with polyangiitis EGPA (Churg-Strauss)	• Focal segmental glomerulonephritis common but renal failure rare. • Rapidly progressive or acute renal insufficiency. • Glomerulonephritis mainly with positive ANCA. • Hypertension. • Isolated proteinuria .
Rheumatoid arthritis (RA)	• Acute tubular necrosis related to nonsteroidal anti-inflammatory drug (NSAID) use. • Secondary amyloidosis due to the chronic inflammation; it is now relatively rare in RA. • Nephrotic syndrome secondary to membranous nephropathy. • Necrotizing glomerulonephritis. • Destructive inflammation within the walls of renal arteries.
Mixed connective tissue disease (MCTD)	• Glomerulonephritis. • Renal vasculopathy. • Malignant hypertension. • Immune complex-mediated nephritis. • Interstitial nephropathy. • Severe renal disease (rare) [4]
Scleroderma	• Renal impairment usually mild. • Scleroderma renal crisis rare (occurs in 1%–10%).
Ankylosing spondylitis	• Secondary renal amyloidosis. • Immunoglobulin A (IgA) nephropathy. • Membranoproliferative glomerulonephritis. • Treatment-associated nephrotoxicity. • Membranous glomerulonephritis (rare). • Focal glomerulosclerosis (rare). • Proliferative glomerulonephritis (rare) [5]

Table 14.4 Renal side effects of commonly used drugs in rheumatic diseases

Drugs	Renal side effect
NSAIDs	- Acute tubular necrosis (ATN) - Acute interstitial nephritis (AIN) - Analgesic nephropathy: papillary necrosis and chronic interstitial nephritis - Minimal change disease - Membranous glomerulonephritis - Hyperkalemia - Hyponatremia - Salt and water retention - Renal tubular acidosis
Cyclooxygenase-2 (COX-2) selective inhibitors	Acute kidney injury Salt and water retention
Calcineurin inhibitors (cyclosporine and tacrolimus)	Acute kidney injury Hyperkalemia Chronic interstitial fibrosis and tubular atrophy Hypophosphatemia Hypomagnesaemia Global glomerular sclerosis Focal segmental glomerulosclerosis
Methotrexate	Crystal-induced AKI (mainly with high dose IV)
Sulfasalazine	Interstitial nephritis (rare) Nephrotic syndrome (rare)
Leflunomide	Interstitial nephritis (rare)
Gold	Membranous glomerulonephritis
Bisphosphonates	Acute tubular necrosis Focal segmental glomerulosclerosis Minimal change disease
Penicillamine	Membranous glomerulonephritis Minimal change disease
Azathioprine	Interstitial nephritis (rare)

14.9.6 Renal Side Effects of DMARDs and NSAIDs

Renal toxicity of disease-modifying antirheumatic drugs (DMARDs) and nonsteroidal anti-inflammatory drugs (NSAIDs) varies depending on the age and the kidney function of the patient. Side effects are commonly observed in elderly patients with compromised kidney function. Therefore, the use of NSAID should be avoided in patients with chronic kidney disease. Cyclosporine, gold, and penicillamine are associated with more serious renal side effects. Fortunately, gold and penicillamine are now very rarely used for the treatment of rheumatic diseases. Others like methotrexate, azathioprine, antimalarials, sulfasalazine, and leflunomide are safer with relatively less renal toxicity [35, 36]. Table14.4 summarized the renal side effects of commonly used drugs in rheumatic diseases.

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Skin Manifestations of Rheumatological Diseases

15

Taha Habibullah, Ammar Habibullah, and Rehab Simsim

15.1 Introduction

There are many rheumatic diseases presenting with skin manifestations. This could be the first presenting feature of a systemic rheumatic disease. In addition, some of these skin manifestations could be an indication of an active disease or a sign of a serious medical emergency. In this chapter the skin manifestations of common rheumatic diseases will be described. Particular focus will be placed on rheumatic diseases with polyarthritis. The differential diagnosis of erythema nodosum will be discussed as this condition is observed in several disorders with arthritis. There are many drugs used in rheumatology, some of them like allopurinol can lead to life-threatening dermatological conditions. A quick review on some of these conditions will be outlined. At the end of this chapter, the reader should be able to recognize different dermatological signs associated with patients with arthritis, discuss the differential diagnosis of erythema nodosum, and recognize life-threatening dermatological conditions.

15.2 Objectives

- To identify the dermatological signs in patients presenting with polyarthritis.
- To construct a diagnostic approach to patients presenting with erythema nodosum.
- To recognize life-threatening dermatological conditions.

15.3 Polyarthritis with Skin: (Diagram 15.1)

15.3.1 Rheumatoid Arthritis (RA)

RA is a chronic inflammatory disorder that affects the joints and causes symmetrical arthritis. It usually involves extra-articular structures like the skin, eye, lung, heart, kidney, blood vessels, and bone marrow. The skin manifestations of RA will be discussed here.

15.3.2 Pyoderma Gangrenosum

It presents as an inflammatory and ulcerative disorder of the skin. It's an uncommon neutrophilic dermatosis. It presents commonly as an inflammatory papule or pustule that progresses to a painful ulcer; it may also present with bullous, vegetative, peristomal, and extracutaneous lesions.

T. Habibullah (✉)
Al-Noor Specialist Hospital, Makkah, Saudi Arabia
e-mail: thabibullah@moh.gov.sa

A. Habibullah · R. Simsim
King Abdullah Medical City, Makkah, Saudi Arabia

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15.3.3 Rheumatoid Vasculitis

Inflammation of blood vessel is a central feature of RA, and it is considered as one of the primary events in the formation of rheumatoid nodule. Histologically it is characterized by mononuclear cell cuffing of postcapillary venule. It occurs in patients with long-standing joint-destructive RA. It affects vessels from medium vessel to small arterioles; it leads to ischemia and necrosis to blood vessel "occlusion."

15.3.4 Rheumatoid Nodule

It is one of the most common cutaneous manifestations in RA. The nodule is seen on pressure area such as olecranon process and many other areas in the body. It is firm, with size varies between 2 mm and 5 cm; non-tender and moveable in subcutaneous tissue; it could be painful, interfere with function, and may cause neuropathy [1]. Around 75% of patients with Felty's syndrome have a nodule [1], and a vast majority of patient with nodule have positive RF [2]. Patients with nodule are more likely to have vasculitis [3] (Figs. 15.1 and 15.2).

15.3.5 Skin Ulceration

It may result from venous stasis, vasculitis, arterial insufficiency, and neutrophilic infiltration [4].

There are many cutaneous changes that occur in patients with RA such as granulomatous dermatitis and medication-induced skin changes, and also there are rare manifestations as linear bands or annular lesions, urticarial eruption, erythema elevatum diutinum, and dermal papule.

15.3.6 Systemic Lupus Erythematosus (SLE)

The dermatological manifestations are the most common presentation of SLE in general. They involve the skin, mucous membranes, and hair.

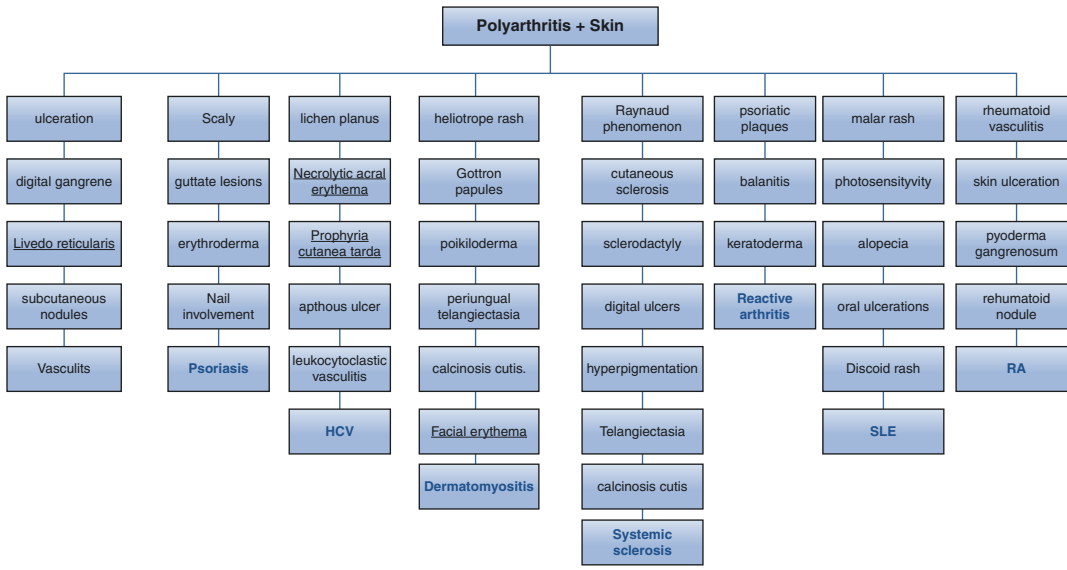


Fig. 15.1 The dermatological signs of patient presenting with polyarthritis. Source: Kelley's textbook of rheumatology . available on:- www.medscape.com

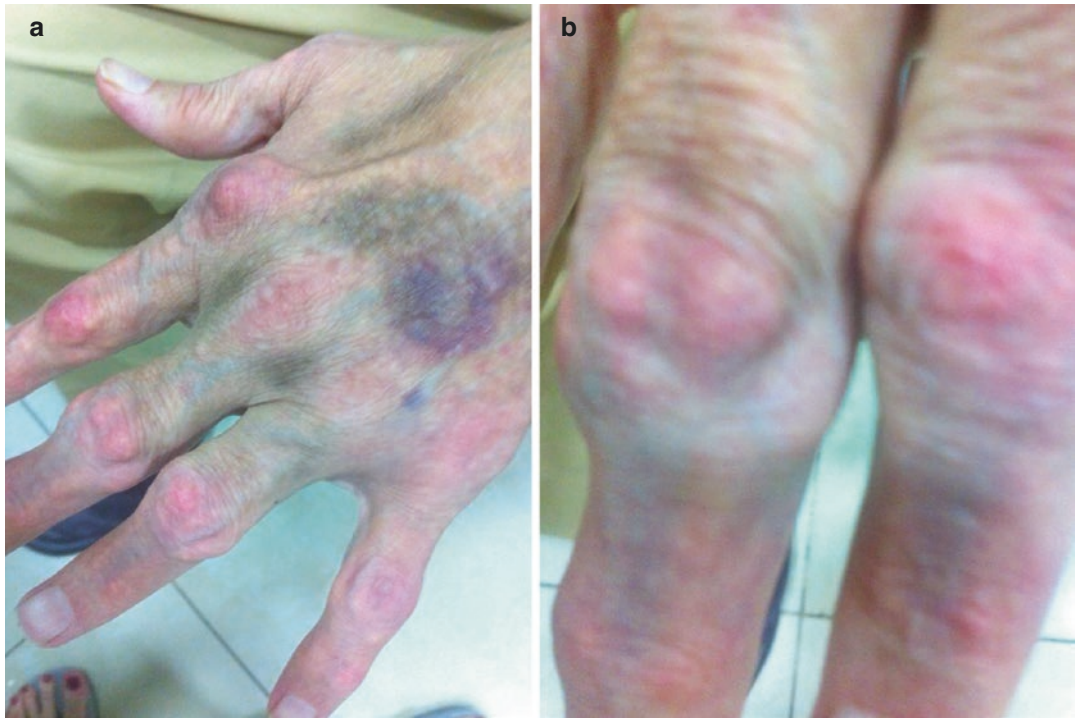


Fig. 15.2 Periarticular skin-colored rheumatoid nodule

The new classification criteria of SLE contains acute cutaneous lupus erythematosus (ACLE) lesions, subacute cutaneous lupus erythematosus (SCLE), and chronic cutaneous lupus erythematosus as follows.

15.3.7 ACLE (Localized)

15.3.7.1 Malar Rash

Characterized by erythematous butterfly-shaped rash over the cheeks and nasal bridge sparing the nasolabial folds, it can be flat or raised, painful, and lasting for days to weeks [5].

15.3.7.2 Disseminated (Generalized) ACLE

This lesion is characterized by erythematous to violaceous, scaly maculo-papular widespread exanthum symmetrically involves trunk and extremities. Other nonspecific lesions can be seen, for example; subungual erythema, ulcers, pitting scars stubby hair cheilitis, periorbital edema, and diffuse telogen effluvium [5].

15.3.7.3 SCLE

The clinical fissures of this type are characterized by circulating anti-Ro and anti-La antibodies and the HLA-B8 and HLA-DR3 haplotype. There are two variants that have been identified: annular variant and papulosquamous variant. The annular variant contains slightly raised erythemas with central clearing, while the papulosquamous variant consists of psoriasis-like or eczematous-like lesions. These two variants usually involve UV-exposed skin, including the lateral aspects of the face, the "V" of the neck, the upper ventral and dorsal part of the trunk, and the dorsolateral aspects of the forearms [5]. SCLE lesions commonly lead to hypopigmentation or depigmenta-

tion and never lead to scarring. The systemic symptoms are mild like arthralgias and musculoskeletal complaints [5].

15.3.7.4 CCLE

This is also called discoid CLE characterized by erythematous discoid plaque that becomes hyperkeratotic and finally leads to atrophy and scarring and can lead to dyspigmentation; it mainly involves the face, ears, and neck but may be widespread, and there are no relation of sun exposure. This lesion can affect the mucosal membranes including the lips, mucosal surfaces of the mouth, nasal membranes, conjunctivae, and genital mucosa. CCLE has several types like hypertrophic/verrucous lupus erythematosus, lupus erythematosus tumidus, lupus panniculitis/profundus, chilblain lupus erythematosus, and DLE–lichen planus overlap [5].

15.3.8 Others

15.3.8.1 Photosensitivity

Macular rash present only after sun exposure may appear on the face, arms, or hands and persist for more than 1 day [6].

15.3.8.2 Discoid Rash

Erythematous patches with keratotic scaling over sun-exposed areas, plaque-like in character with follicular plugging and scarring [6] (Fig. 15.3).

15.3.8.3 Alopecia

Mainly affects the temporal regions or creates a patchy pattern of hair loss [7] (Fig. 15.4).

15.3.8.4 Oral Ulcer

It is an important manifestation of SLE; it occurs more than three times per year and is usually painless [7].

Fig. 15.3 Discoid lesions of lupus erythematosus. Show dyspigmentation, atrophy, and scarring

15.3.8.5 Systemic Sclerosis "Scleroderma"

Scleroderma is a term used to describe a thickened skin. It may affect the skin and subjacent tissues, or it may be associated with systemic involvement [8].

15.3.8.6 Raynaud Phenomenon

Changes of the color of the digits due to abnormal vasoconstriction of digital arteries and cutaneous arterioles due to a local defect in normal vascular responses, (pallor , cyanosis and then redness). It is exaggerated by cold temperatures or emotional stress [9] (Fig. 15.5)

15.3.9 Telangiectasia

It may develop anywhere within the body but mostly seen in perioral area, hands, and anterior chest. It's small dilated blood vessels that locate beneath the dermis on skin (venule) (Fig. 15.6).

Fig. 15.4 Diffuse non-scarring alopecia

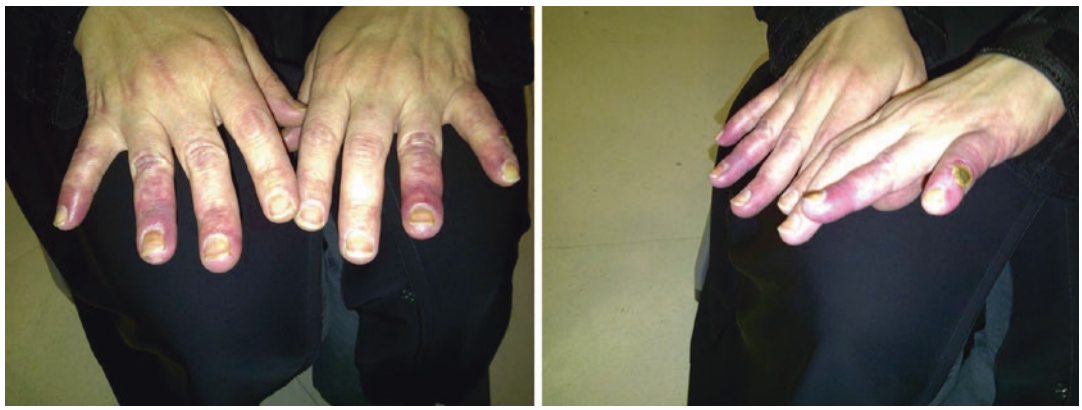


Fig. 15.5 Raynaud's phenomenon. Note the demarcation of color difference (pallor and cyanosis)

15.3.10 Sclerodactyly

It is a localized thickening and tightness of the skin of the fingers or toes. Sclerodactyly is commonly associated with atrophy of the underlying soft tissues. It is considered as a characteristic feature of scleroderma (Fig. 15.7).

15.3.11 Cutaneous Sclerosis

It is the formation of scar tissue in the skin or in tissues around joints (Fig. 15.8).

Note the tight and shiny appearance of skin.

15.3.12 Digital Ulcers

With scleroderma, repeated episodes of spasm of the fingers (Raynaud's) can cause pitted fingertip scars, and in some people this results in fingertip ulcers [10].

15.3.13 Calcinosis Cutis

It is mostly asymptomatic and developed gradually, in which amorphous, insoluble calcium salt deposits in the skin and subcutaneous tissue [11]. It's usually firm, multiple, whitish dermal papules, plaques, nodules, or subcutaneous nodules. The lesion spontaneously ulcerated, and it may be tender and may restrict joint mobility. In severe cases it may cause cutaneous gangrene due to vascular calcification which diminishes the pulse.

Hyperpigmentation and finger swelling are also considered as skin manifestations which occur in systemic sclerosis.

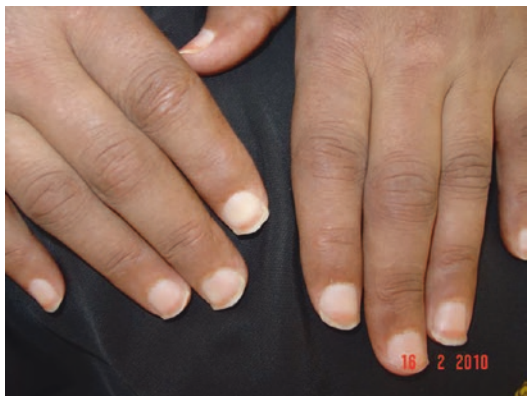
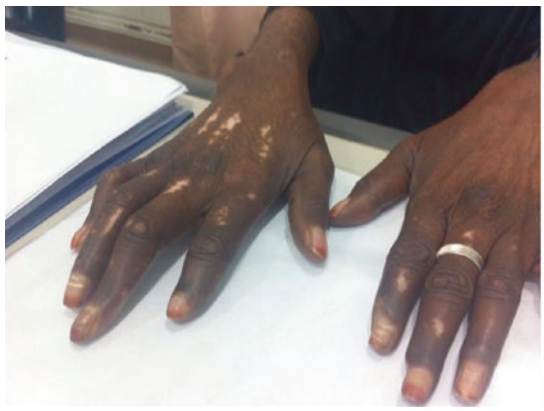


Fig. 15.6 Telangiectasia

Fig. 15.8 Cutaneous sclerosis



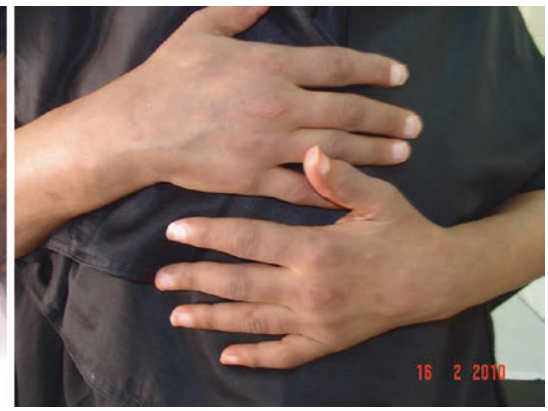


Fig. 15.7 Sclerodactyly

15.4 Psoriasis

15.4.1 Scales (Fig. 15.9)

15.4.1.1 Nail Involvement

Nail disease is more common in patients with psoriatic arthritis [12]. There is usually involvement of the nail matrix or nail bed. Nail abnormalities may include: beau lines, leukonychia, onycholysis, oil spots, subungual hyperkeratosis, splinter hemorrhages, spotted lunulae, transverse ridging, cracking of the free edge of the nail, and uniform nail pitting.

15.4.1.2 Erythroderma

Patients commonly present with generalized erythema, then after the onset of erythema 2–6 weeks, scaling appears usually from flexural area. Pruritus commonly results in excoriations. If it persist for weeks, hair may shed, nails may become ridged, thickened and it may shed. Inflammation and edema in periorbital skin may occur resulting in ectropion (Fig. 15.10).

15.4.1.3 Guttate Lesion

It is a clinical presentation that is characterized by a distinctive, acute eruption of small, droplike, 1–10 mm in diameter, salmon-pink papules, usually with a fine scale. It occurs primarily on the trunk and the proximal extremities; also it may have general distribution on the body [13] (Fig. 15.11).

15.4.1.4 Psoriatic Arthritis

Psoriatic arthritis is one of the seronegative spondyloarthropathies which include ankylosing spondylitis and reactive arthritis. The prevalence of psoriatic arthritis among individuals with psoriasis is ranging from 7 to 48% [14–18]. There are several patterns of joint involvement in psoriatic arthritis patients [19]:

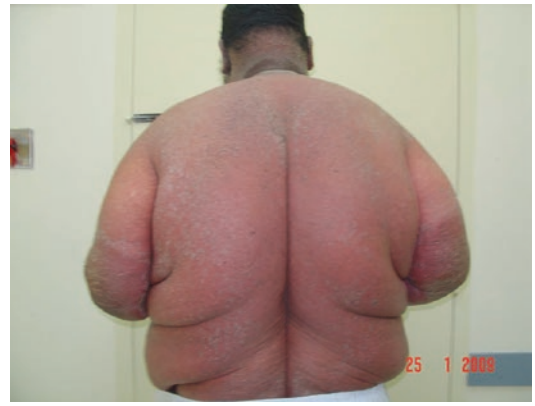


Fig. 15.10 Generalized erythroderma with scaly skin appearance

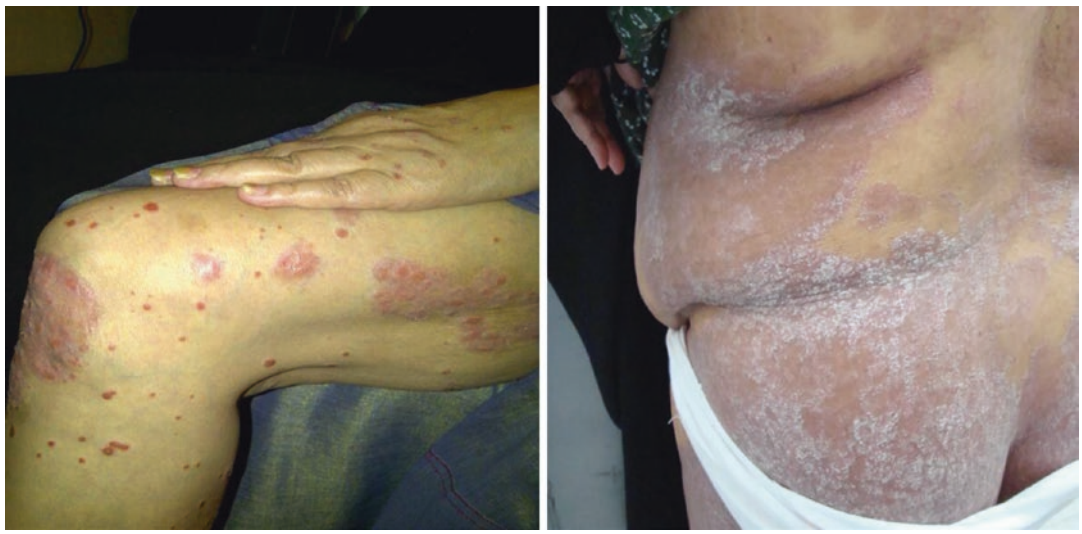


Fig. 15.9 Psoriatic plaques. Note the white to silvery scales over an erythematous base

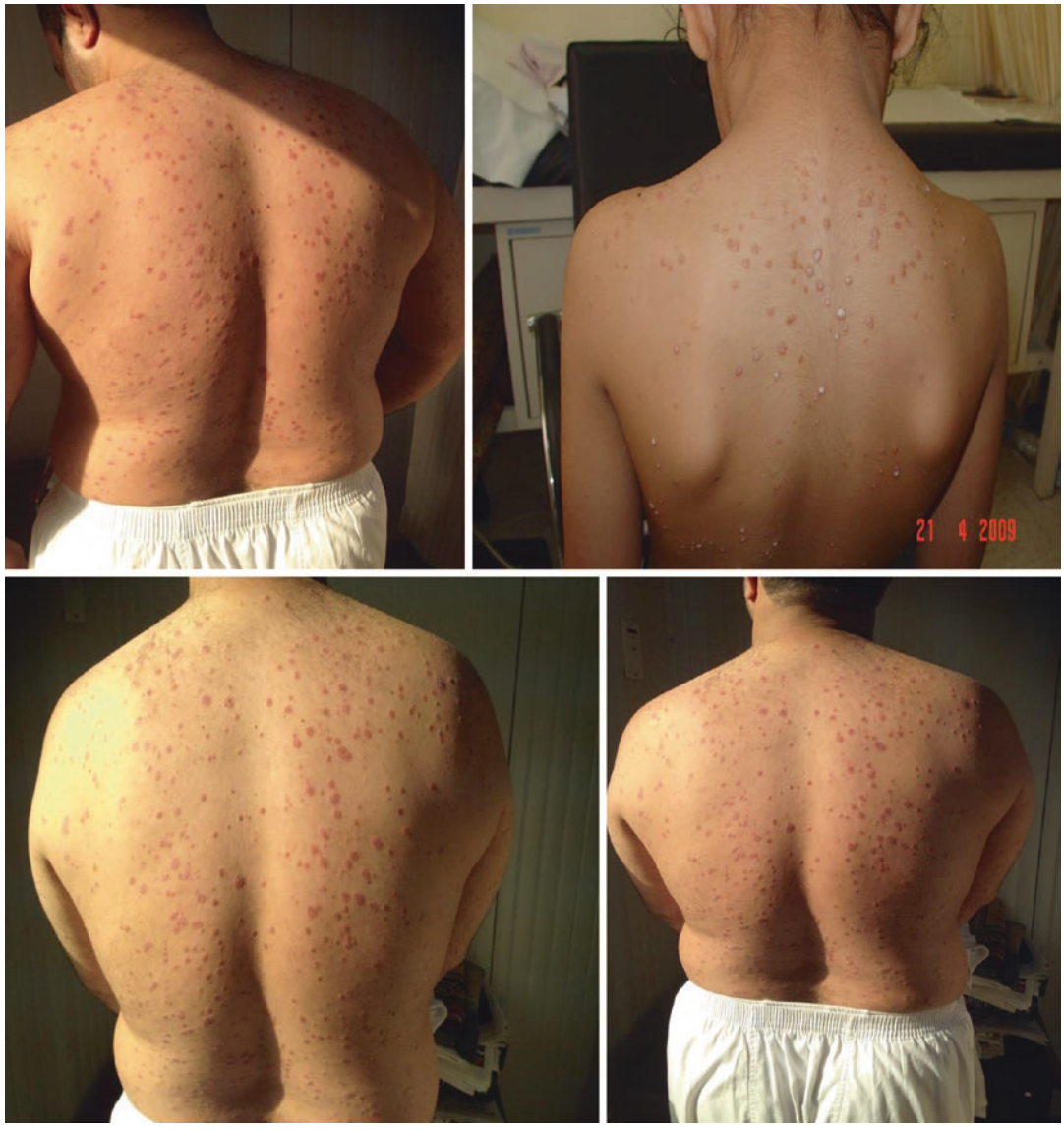


Fig. 15.11 Guttate psoriasis. Small discrete papules and plaques with fine scales

- Distal arthritis which involves distal interphalangeal (DIP) joints.
- Asymmetric oligoarthritis.
- Symmetric polyarthritis.

- Arthritis mutilans, characterized by deforming and destructive arthritis.
- Spondyloarthropathy which includes sacroiliitis and spondylitis.

15.4.2 Dermatomyositis (DM)

15.4.2.1 Gottron's Papules

They are symmetrical erythematous eruptions which involve the extensor aspects of the metacarpophalangeal (MCP) and interphalangeal (IP) joints and may involve the skin between them; they may be associated with scale and ulcer if the eruption was prominent [20] (Fig. 15.12).

15.4.2.2 Heliotrope Eruption

Erythematous lesion occurs on the upper eyelids and may be associated with eyelid edema (Fig. 15.13).

15.4.3 Facial Erythema

This lesion can mimic the malar rash seen in SLE. To easily differentiate between both of them, look at the nasolabial fold; if it is involved, then the rash is mainly due to DM; however, if it is not involved, then the rash is mainly due to SLE (Fig. 15.14).

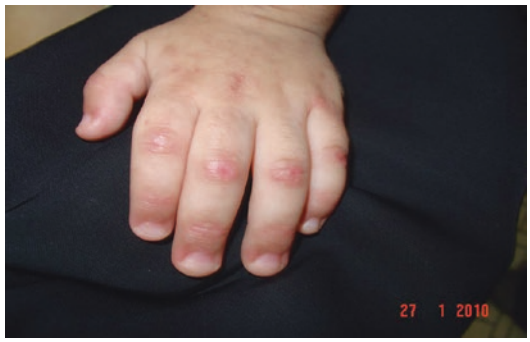


Fig. 15.12 Gottron's papules. Flat-topped papules over the proximal interphalangeal and metacarpophalangeal joints

Fig. 15.13 Heliotrope sign. Note the pink to violaceous discoloration over eyelids and forehead

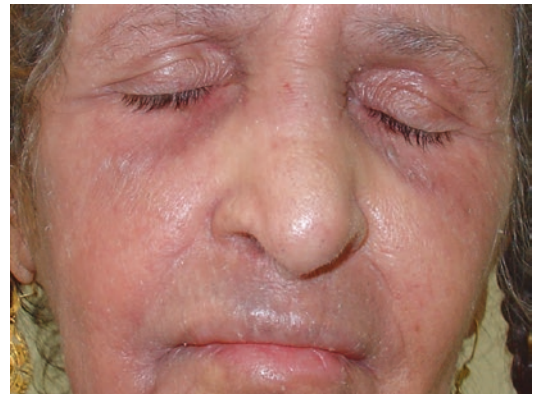


Fig. 15.14 Facial erythema

15.4.4 Photodistributed Poikiloderma

Poikiloderma consists of both hyperpigmentation and hypopigmentation; it always occurs in upper chest, the V of the neck, and upper back (shawl sign); it may come as macular (nonpalpable) or papular erythema if it happens in early stages of cutaneous disease. It is usually associated with pruritus, and this is the difference between DM and photo-exacerbated eruption of lupus erythematosus. If the patient presents with poikiloderma on the lateral aspects of the thighs, this is now called Holster sign (Fig. 15.15).

15.4.5 Periungual Abnormalities

These are characterized by erythematous lesion with vascular changes in the capillary nail beds which also may be associated with areas of dilatation and dropout and with periungual erythema [21].

15.4.6 Psoriasiform Changes in Scalp

The scalp lesion in DM is diffuse, associated with prominent scaling and poikilodermatous changes.

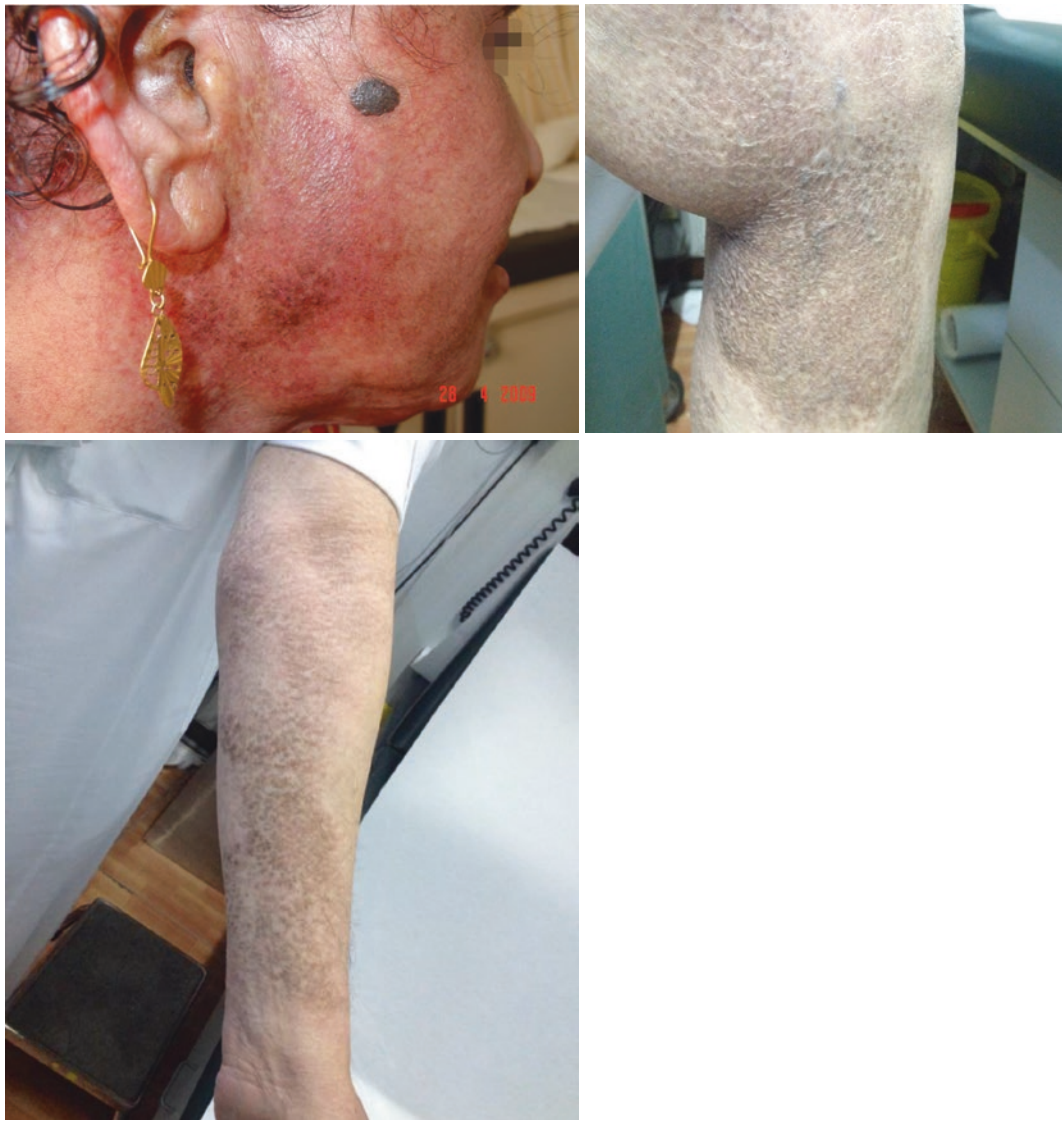


Fig. 15.15 Photodistributed poikiloderma. Note the hyperpigmentation, hypopigmentation, telangiectasia, and atrophy

It may be difficult to distinguish from seborrheic dermatitis and psoriasis. It happens usually as a result of severe burning, pruritus, or sleep disturbance.

15.4.7 Calcinosis Cutis

It is more common in juvenile DM than adult DM. It means deposition of calcium within the skin. It is associated with a delay in treatment with glucocorticoids and immunosuppressive therapy; this lesion can be seen in other diseases like systemic sclerosis and SLE but more common with DM [22, 23].

15.4.8 Reactive Arthritis

15.4.8.1 Circinate Balanitis

It is an asymptomatic genital lesion characterized by shallow ulcers in the penis [24].

15.4.8.2 Keratoderma

Hyperkeratotic skin rashes involve soles and palms [24] (Fig. 15.16).

15.4.9 Hepatitis C Virus (HCV)

15.4.9.1 Porphyria Cutanea Tarda

It is a skin lesion strongly associated with HCV and characterized by photosensitivity, bruising skin, fragility, facial hirsutism, and vesicles or bullae that can become hemorrhagic. It is a skin disease caused by a reduction of hepatic uroporphyrinogen decarboxylase activity [25].

15.4.9.2 Leukocytoclastic Vasculitis

This lesion is usually associated with palpable purpura and petechiae that usually involve the lower extremities and may happen in conjunction with essential mixed cryoglobulinemia; in skin biopsy, there is dermal blood vessel destruction associated with a neutrophilic infiltration in and around the vessel wall (Fig. 15.17) [26].

15.4.10 Lichen Planus

It involves mucus membranes, hair, and nails characterized by flat-topped, violaceous, pruritic papules with a generalized distribution. In skin biopsy, there is a dense lymphocytic infiltration in the upper dermis [27, 28] (Fig. 15.18).

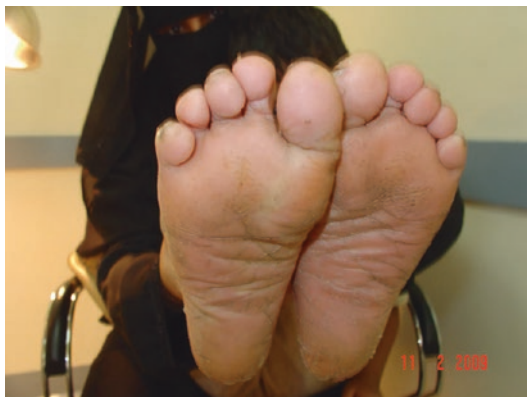


Fig. 15.16 Keratoderma blennorrhagicum. Note the thick yellow scales on the soles

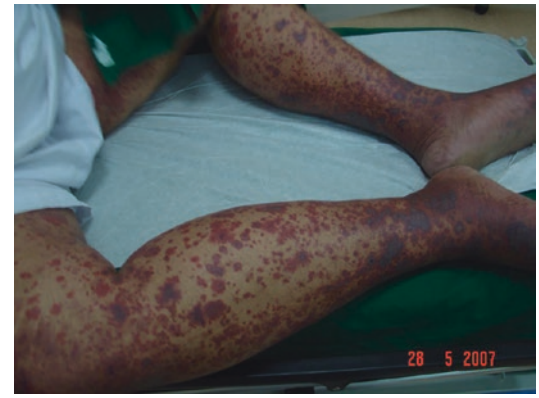


Fig. 15.17 Leukocytoclastic vasculitis. Note the scattered palpable purpura and hemorrhagic macules

15.4.11 Necrolytic Acral Erythema

This lesion is pruritic and characterized by sharply marginated, erythematous to hyperpigmented plaques with variable scale and erosion which involves the lower extremities (Fig. 15.19) [29].

15.4.12 Polyarteritis Nodosa

15.4.12.1 Livedo Reticularis

It is characterized by tenderness and it does not blanch with active pressure [30–32].

15.4.12.2 Ulcerations

It usually involves the lower extremities [30–32].

15.4.13 Digital Ischemia

It may be associated with splinter hemorrhages and gangrene [30–32].

15.5 Sarcoidosis

It is a granulomatous disease and defined as presence of non-caseating granulomas in different tissues and organs such as lymph nodes, eyes, joints, brain, kidneys, lung, and skin. The signs that appear with sarcoidosis are as follows.

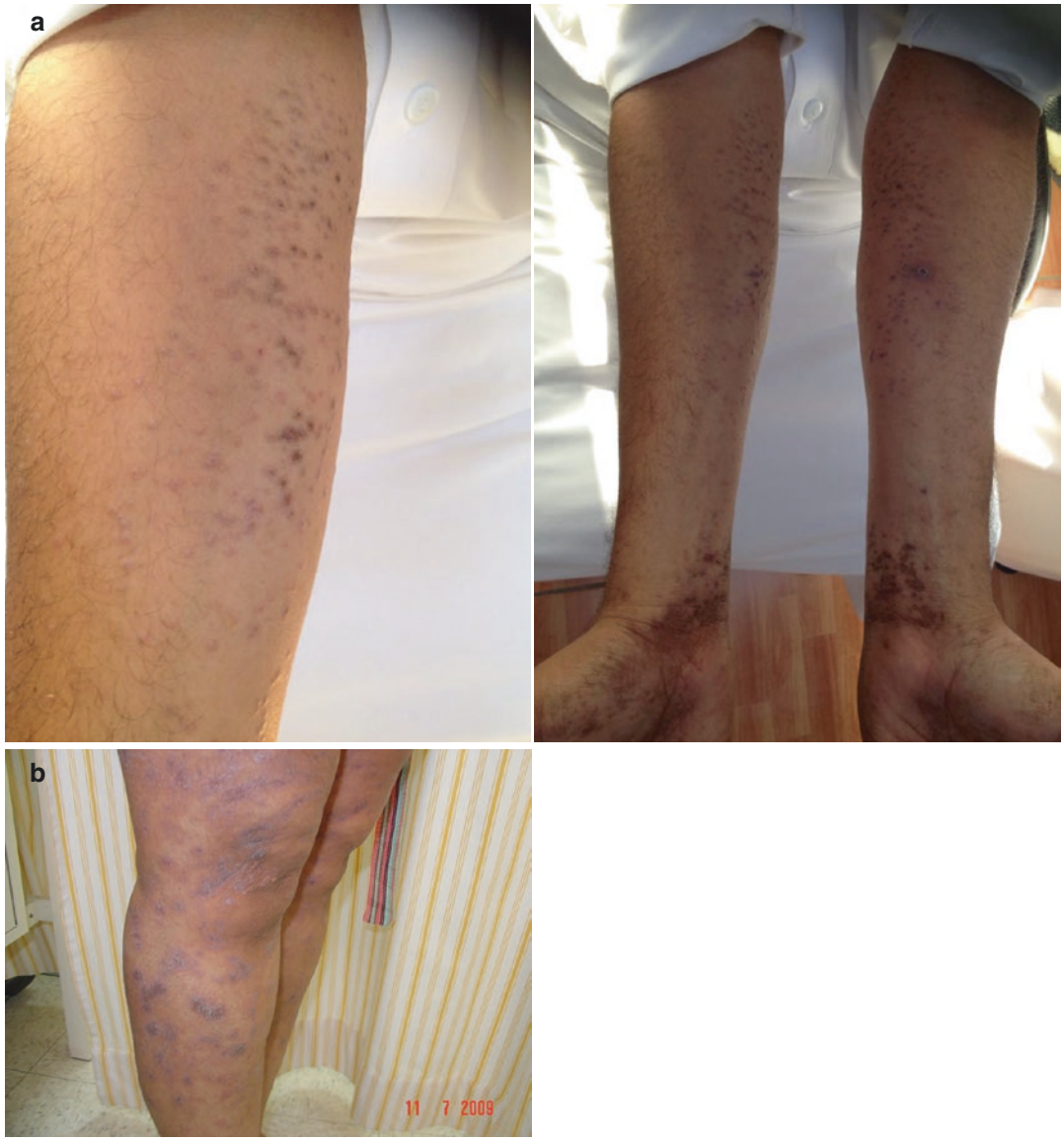


Fig. 15.18 Flat-topped, polygonal, and violaceous papules of lichen planus

15.5.1 Erythema Nodosum

It is the most common nonspecific lesion of sarcoidosis and characterized by inflammatory, tender, erythematous, subcutaneous plaques and nodules in the anterior tibial areas. The patient can present with low-grade fever, arthritis, and lower extremity edema (Fig. 15.20) [32].

15.5.2 Papular Sarcoidosis

It is the most common specific lesion characterized by numerous non-scaly, skin-colored, yellow-brown, red-brown, violaceous, or hypopigmented 1 to 10 mm papules, and the papules can demonstrate a slight central depression. The most common site is the face,

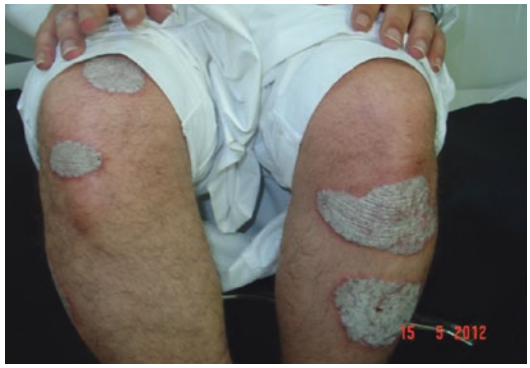


Fig. 15.19 Necrolytic acral erythema

with a predilection for the eyelids and nasolabial folds [33].

15.5.3 Nodular Sarcoidosis

Subcutaneous sarcoidosis or nodular sarcoidosis, all these terms describe the nodule arising from subcutaneous tissue [32]; it is one of the most common lesions in sarcoidosis, and it results from large collections of sarcoidal granulomas in the dermis or subcutaneous tissue characterized

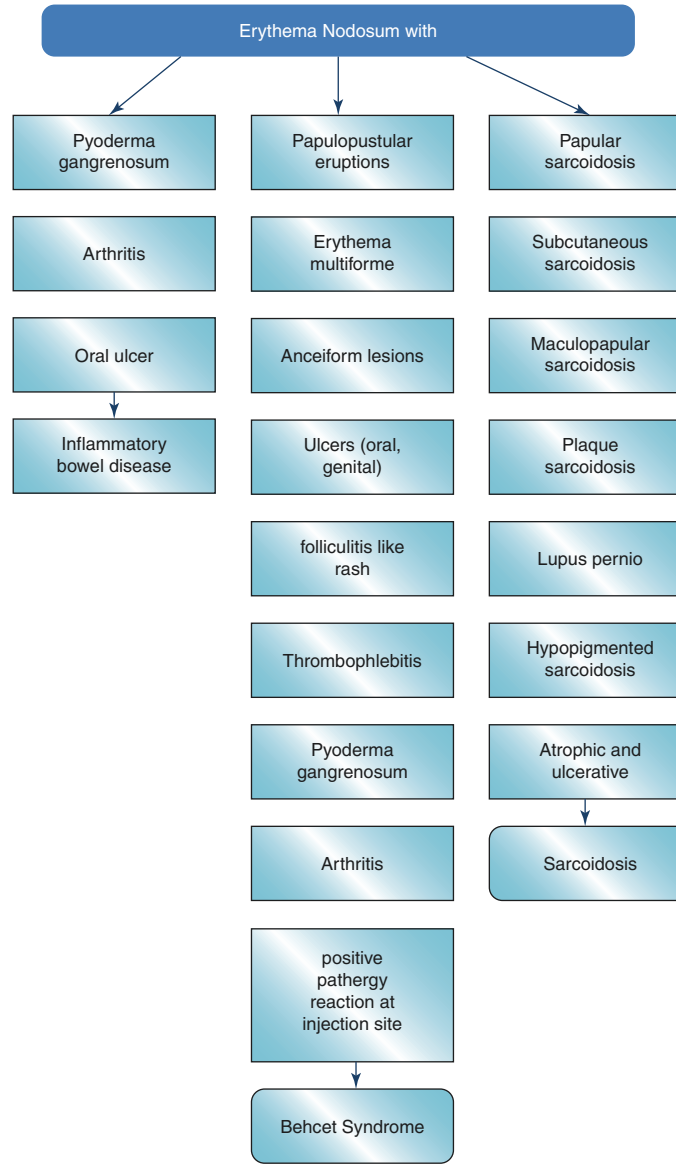


Fig. 15.20 Erythema nodosum

as asymptomatic or mildly tender, flesh-colored, erythematous, violaceous, and hyperpigmented. The upper extremities are the most common site of nodular sarcoidosis [34]. It can be single or multiple, and its size could be about 1 and 2 cm in diameter. The differential diagnosis of subcutaneous sarcoidosis includes lipomas, cysts, cutaneous manifestations of lymphoproliferative malignancies, subcutaneous granuloma annulare, foreign body, or granulomas [35, 36].

15.5.4 Maculopapular Sarcoidosis

This lesion is characterized by raised papules that are often around 1 mm in diameter, slightly tender, pruritic, slightly hyperpigmented patches, red, brown, or violaceous in color [37]; the most common sites are facial and eyelid areas, and it may involve mucous membranes, neck, trunk, or extremities [32].

15.5.5 Plaque Sarcoidosis

This lesion is characterized by oval or annular shaped, indurated, different color such as flesh-colored, erythematous or brown rash that may have scale at the end stage. The most common sites involved are the arms, shoulders, back, and buttocks; it has common features with psoriasis, lichen planus, discoid lupus, granuloma annulare, cutaneous T cell lymphoma, secondary syphilis, and Kaposi's sarcoma [36].

15.5.6 Lupus Pernio

This lesion is characterized by erythematous, indurated papules, plaques, or nodules [38]; the most common sites involved are the face, nasal tip, alar rim, and cheeks, and it may involve ears and lips [39]. If this lesion is not treated, it will progress rapidly and increase in thickness, size, and induration. After the lesion is resolved, it will leave scar [37]. This lesion is associated more with extracutaneous manifestations such as respiratory tract involvement and lytic and cystic bone lesions [40].

15.5.7 Hypopigmented Sarcoidosis

It affects mostly dark-skinned persons of African descent, and the lesion is characterized by round to oval, hypopigmented, well-demarcated patches and may have raised plaques [33, 41].

15.5.8 Atrophic and Ulcerative Sarcoidosis

This lesion is a combined lesion meaning it is involved with atrophic and ulcerated lesions, which are characterized by depressed plaques not elevated [42]; this lesion is associated with other mucocutaneous manifestations of sarcoidosis. The ulcerative lesion is more common in women and black patients [43].

15.6 Rheumatic Fever

Acute rheumatic fever is a non-suppurative sequela that occurs after 2–3 weeks of group A streptococcus and pharyngitis. It mostly affects children aged 5 to 15 years. This disease is characterized by arthritis, carditis, chorea, erythema marginatum, and subcutaneous nodules. The damage to the cardiac valve is chronic and it may progress [44].

To make a diagnosis of rheumatic fever, there is a special criterion called Jones Criteria, which involves major and minor manifestations which are as follows.

The major manifestations:

- Arthritis.
- Carditis.
- Chorea.
- Erythema marginatum.
- Subcutaneous nodules.

The minor manifestations:

- Arthralgia.
- Fever.
- Elevated acute phase reactants (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP]).
- Prolonged PR interval.

In this chapter we will talk only about the rheumatological and dermatological manifestations, which are as follows.

15.6.1 Arthritis

It is the early symptom of rheumatic fever. The classical history of arthritis involves migratory polyarthritis within days to a week. The meaning of migratory is "it affects the joint then migrates to the other joint"; the most common joints involved are knees, elbows, and wrists [36]; the patient will complain of limitation in his movement because of the severity of the joint pain. The inflammation of each joint lasts no more than 1 week and the signs of inflammation are usually present [45].

15.6.2 Erythema Marginatum

This lesion appears early in the course of the rheumatic fever characterized by an evanescent, pink or faintly red, non-pruritic rash; the outer edge is sharp and the inner is diffuse; it has continuous margins and sometimes has a ring shape. It usually affects the trunk and may affect the limbs, but it is unlikely to affect the face [46]. The course of this lesion is intermittent meaning that it appears, disappears, and then reappears in a matter of hours [47].

15.6.3 Subcutaneous Nodules

This lesion is characterized by symmetrical, firm, painless lesions ranging from a few millimeters to 2 cm in size, and the average number of nodules is about three to four, and it has non-inflamed skin above it. The nodules present over the bony surface or prominence or near tendons. This lesion appears 1 week after the disease and is associated with sever carditis lasting no more than 1 month. We can distinguish rheumatic fever nodules from rheumatic arthritis nodules as the rheumatic fever nodules are smaller and more short-lived than the nodules of rheumatoid arthritis and almost involve the olecranon, while rheumatoid nodules are usually found 3 to 4 cm distally; finally all of them involve the elbows [48].

15.7 Behçet's Disease

Behçet's disease is a complex, multi-systemic disease that involves the mucocutaneous, ocular, cardiovascular, renal, gastrointestinal, pulmonary, urologic, and central nervous systems, the joints, blood vessels, and lungs. Men are more commonly affected by this disease than women, and it is more common in the third decade of life, but it can occur at any age. Signs and symptoms of this disease may precede the onset of the mucosal membrane ulcerations by 6 months to 5 years, and prior to the onset of the disease, the patient experiences generalized and various symptoms.

In patients with Behçet's disease, a variety of cutaneous changes appear on them [49].

15.7.1 Erythema Nodosum-like Lesion

It is red to violet and painful subcutaneous nodule. It occurs on the extremities especially the lower extremities; also it can present on the face, neck, and buttocks. It resolves spontaneously or it may ulcerate leaving a scar and hyperpigmentation area.

15.7.2 Acneiform Lesion

It may be more common in those with associated arthritis [50]. It consists of papules and pustules that are difficult to distinguish from ordinary acne [51].

15.7.3 Folliculitis-like Rash

It distributes on the back, face, neck, chest, and hairline of patients. It resembles acne vulgaris.

15.7.4 Papulopustular Eruptions

Pustular skin lesions are often not sterile and may contain *Staphylococcus aureus* and *Prevotella* spp. [52].

15.7.5 Erythema Multiforme-like Lesions

15.7.6 Superficial Thrombophlebitis

It is a migratory superficial thrombophlebitis of the skin. It may be associated with deep vein thrombosis that causes lower extremities edema.

15.7.7 Ulcers (Oral, Genital)

During physical exam:

- **Oral ulcer:** difficult to distinguish from common aphthae (Table 15.1).
- **The most common sites** are the tongue, lips, buccal mucosa, and gingiva; the tonsils, palate, and pharynx are less common sites. The interval between recurrences ranges from weeks to months.
- **Genital ulcers:** recurrent and painful, and it may cause scarring.

Table 15.1 Oral ulcer description on physical examination

Oral ulcer description on physical exam			
More extensive	More painful	More frequent	Appear singly or in crops
Lesions can be shallow or deep (2–30 mm in diameter)	Have a central, yellowish, necrotic base and a punched-out, clean margin	Evolve quickly from a pinpoint flat ulcer to a large sore	Located anywhere in the oral cavity
Subside without leaving scars		Persist for 1–2 weeks	

15.7.8 Pyoderma Gangrenosum

It is an ulcerative cutaneous condition starting from a small, red papule or pustule and then changing into an ulcerative lesion.

15.7.9 Positive Pathergy Reaction at Injection Site

Nonspecific inflammatory reaction to scratches and intradermal saline injection is a common and specific manifestation to these lesions.

15.7.10 Arthritis

During an exacerbation of disease, a non-erosive, asymmetrical arthritis occurs in about 50% of patients with this disease. It involves large and medium joints (wrist, knee, and ankle). Also for the patient with Behçet's disease, experiencing myalgias and migratory **arthralgias** without overt arthritis is common. On the other hand, **arthritis** occurs in about 50% of patients with Behçet's disease [53].

There are also genital, ocular, gastrointestinal, joint, and neurologic manifestations.

15.8 Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) includes two major disorders, which are ulcerative colitis and Crohn's disease. This group of diseases cause many extraintestinal manifestations including eye, skin, joint, renal, and urologic conditions. In this chapter we will talk about skin and the **musculoskeletal** manifestations of IBD. The most common skin lesions presenting with IBD are erythema nodosum and pyoderma gangrenosum and other less common lesions such as Sweet syndrome, necrotizing cutaneous vasculitis, and psoriasis.

15.8.1 Erythema Nodosum (EN)

This lesion is equally present in ulcerative colitis and Crohn's disease, and it is characterized by raised, tender, red or violet subcutaneous nodules, which are around 1 to 5 cm in diameter. The most common sites involved are the extensor surfaces of the extremities, specifically over the anterior tibial area. The presence of erythema nodosum reflects the activity of the intestinal disease and usually disappears by management of intestinal manifestations. Also this lesion is diagnosed clinically, and if we take a biopsy, it will show focal panniculitis, which is rarely done [54].

15.8.2 Pyoderma Gangrenosum

This lesion is less common than EN, and it has a severe course because of its persistence, and it is an uncomfortable lesion preceded by trauma to the skin and initially appears as single or multiple erythematous papules or pustules [55]. The most common site involved is the legs, but it can appear at any site including abdomen and at the site of surgical scars or at the stoma after colectomy. It may form deep ulceration that contains purulent material by subsequent necrosis of the dermis, and usually the culture of the purulent material is sterile. Pyoderma gangrenosum reflects the activity of IBD disease, and it needs a course of high-dose glucocorticoids over several weeks of treatment [56].

15.8.3 Oral Ulcer

It is a common manifestation in patients with IBD, especially patients with Crohn's disease.

15.8.4 Musculoskeletal Manifestations

The musculoskeletal manifestations of IBD are considered the most common extra-intestinal manifestation, and they include; non-destructive peripheral arthritis and axial arthritis, other less common **musculoskeletal manifestations are** osteoporosis, osteopenia, and osteonecrosis.

15.8.5 Arthritis

The joints that are involved are the spine, sacroiliac joints, and appendicular joints; there are two types of peripheral arthritis: type 1 is acute and remitting and type 2 is a chronic problem and causes frequent relapses; other joint pain can result from complications of IBD such as bacterial infection of the sacroiliac or peripheral joints or as adverse effects from chronic use of glucocorticoid such as osteonecrosis, and those complications must be distinguished from sterile inflammation [57].

15.9 Severe and Life-Threatening Conditions (Fig. 15.21)

15.10 Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

They are rare, acute immune complex medited hypersensitive and life that are nearly always drug-related. Allopurinol is the most common cause [58]. They are a consequence of extensive keratinocyte cell death that results in the separation of significant areas of skin at the dermal-epidermal junction, producing the appearance of scalded skin [59]. We can classify this disease simply into as follows:

- **Stevens-Johnson syndrome (a minor form of toxic epidermal necrolysis)**: less than 10% body surface area (BSA) detachment.
- **Overlapping Stevens-Johnson syndrome/ toxic epidermal necrolysis**: detachment of 10–30% of the BSA.

Toxic epidermal necrolysis: detachment of more than 30% of the BSA.

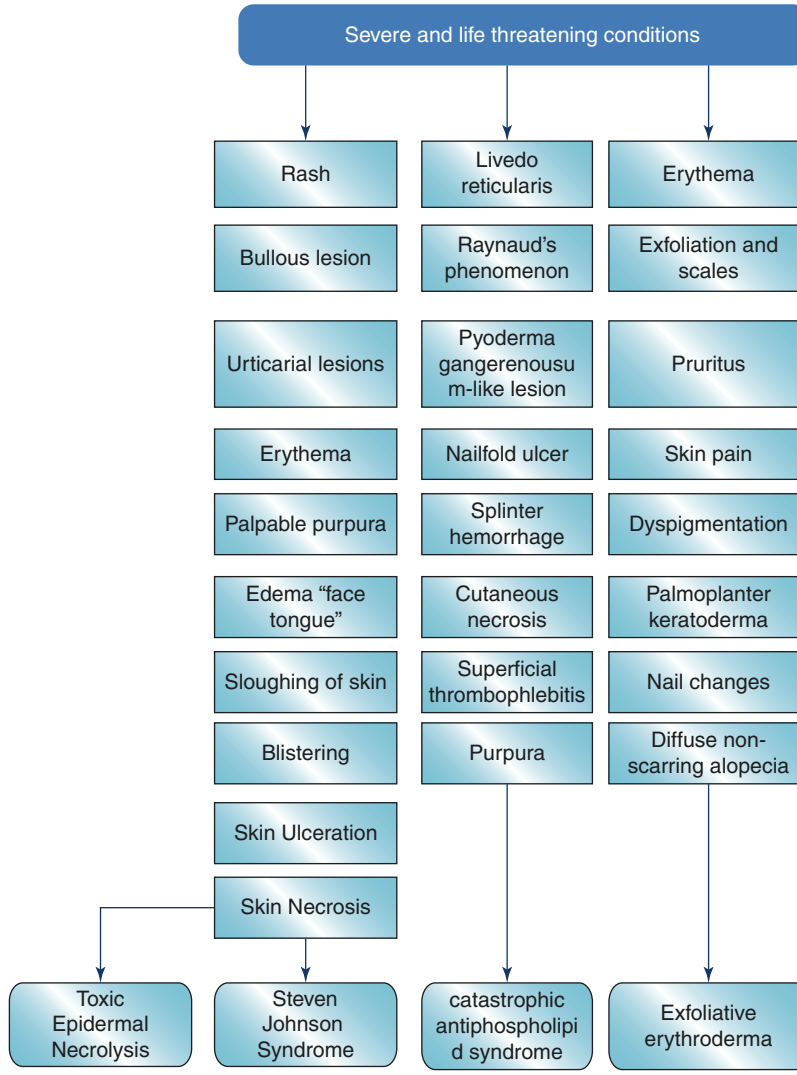


Fig. 15.21 Severe and life-threatening conditions

The initial symptoms of Stevens-Johnson syndrome and toxic epidermal necrolysis that precede cutaneous manifestations by 1 to 3 days are fever, productive cough with thick purulent sputum, pain on swallowing, headache, arthralgia, and malaise.

A patient with SJS and TEN may complain of a rash, which appears first on the trunk, spreading to the neck, face, and proximal upper extremities. The following points are characteristic of cutaneous lesions:

15.10.1 Rash

It first appears as macules and then develops into papules, vesicles, bullae, urticarial plaques, or confluent erythema (erythroderma) (Fig. 15.22).

15.10.2 Bullous Lesions

It appears as flaccid blisters and may rupture leaving denuded skin (Fig. 15.23).

15.10.3 Urticarial Lesions (Not Pruritic)

It may be edematous, erythematous to pale area involving the dermis and epidermis (Fig. 15.24).

Fig. 15.22 Dusky to violaceous rash of toxic epidermal necrolysis

15.10.4 Erythema

Erythema and erosions of the buccal, ocular, and genital mucosae are present in more than 90% of patients.

15.10.5 Palpable Purpura

15.10.6 Edema (Face, Tongue)

15.10.6.1 Sloughing of Skin

- Skin looks like wet cigarette paper.
- Skin ulceration.
- Skin necrosis.
- Nikolsky sign: it should be sought by exerting tangential mechanical pressure with a finger on several erythematous zones and considered positive if dermal-epidermal cleavage is induced (Fig. 15.25).

15.11 Erythroderma Exfoliation

More than 90% of body surface areas are involved by generalized redness and scaling of the skin due to generalization of pre-existing dermatoses (such as psoriasis or atopic dermatitis), drug reactions, or cutaneous T-cell lymphoma (CTCL) [60]. The clinical features are as follows:

15.11.1 Erythema

15.11.1.1 Exfoliation and Scales (2–6 Days after Erythema)

There is variation in the size and the color of the scales. In acute phases, scales are usually large and crusted while in chronic states are smaller and drier. Occasionally, the cause of the erythroderma is suggested by the character of the scale:

- Fine scale in atopic dermatitis or dermatophytosis.
- Bran-like in seborrheic dermatitis.
- Crusted in pemphigus foliaceus.
- Exfoliative in drug reactions.

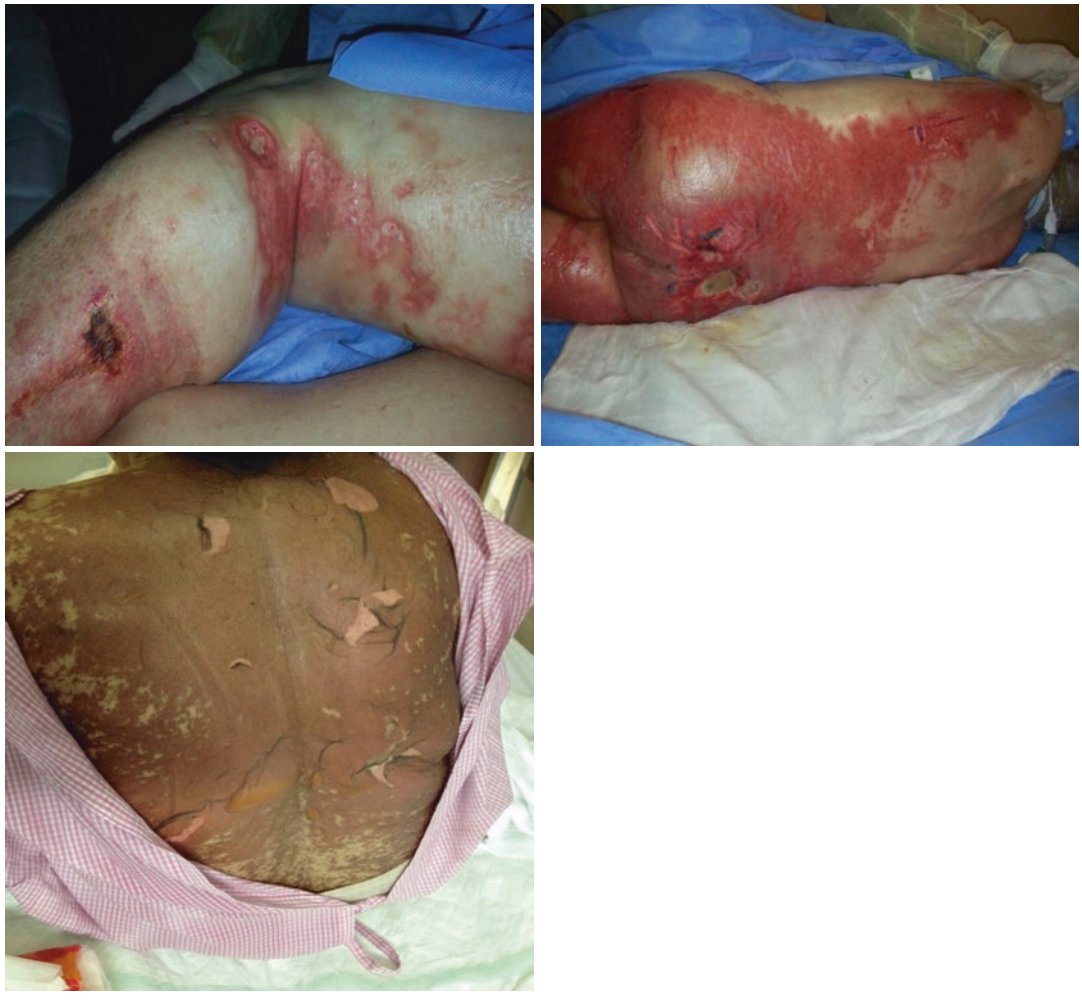


Fig. 15.23 Flaccid bullae with detachment of necrolytic epidermis

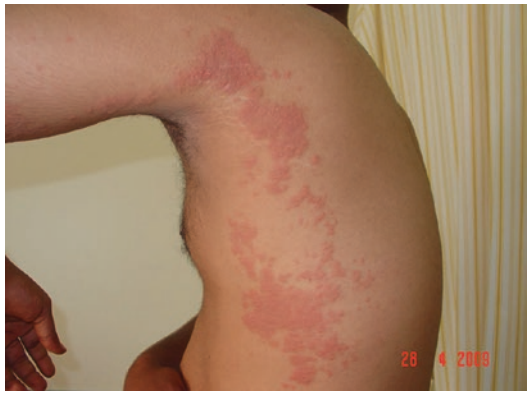


Fig. 15.24 Urticarial plaques (wheals)

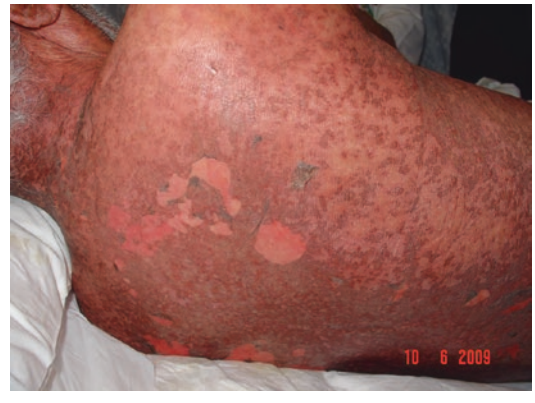


Fig. 15.25 Nikolsky sign

15.11.2 Pruritus

Approximately 90% of patients complain from it, so it is the most frequent complaint. Thickness of the skin and areas of lichenification are seen in one-third of cases due to itching.

15.11.3 Pain

Most patients complain of severe skin pain.

15.11.4 Dyspigmentation

Hyperpigmentation area (45%) observed more frequently than hypo- or depigmentation (20%).

15.11.5 Palmoplantar Keratoderma

Hyperkeratosis of the palms and soles. Approximately 30% of erythrodermic patients present with it.

15.11.6 Nail Changes

They are related to the underlying cause of erythroderma, for example, pit in psoriasis or horizontal ridging in dermatitis. Most often "shiny" nails are observed, but discoloration, brittleness, dullness, subungual hyperkeratosis, Beau's lines, paronychia, and splinter hemorrhages can be seen.

15.11.7 Diffuse Non-scarring Alopecia

It appears in 20% of patients with chronic erythroderma.

15.11.8 Systemic Manifestation

- Generalized peripheral lymphadenopathy.
- Pedal or pretibial edema.
- Facial edema.
- Tachycardia.
- Splenomegaly is rarely seen and occurs most often in association with lymphoma.

15.11.9 Complications

- Multiple seborrheic keratosis.
- Cutaneous infection with *Staphylococcus aureus*.
- Bilateral ectropion.
- Purulent conjunctivitis.
- Risk of cardiac failure.
- Anemia.

15.12 Gonococcal Arthritis

Considered as the most common form of septic arthritis in the United States and caused by gram-negative diplococcus *Neisseria gonorrhoeae*. It is composed of two forms:

– Bacteremic form (arthritis-dermatitis syndrome).
– Septic arthritis form (localized to the joint) [58]

Bacteremic form (arthritis-dermatitis syndrome)

- Migratory arthralgias and arthritis:
  It presents as:
  – Polyarticular.
  – Asymmetric.
  – Upper extremities involvement more than lower extremities.
  – The most commonly affected joints are wrists, elbows, knees, and ankles.
  – It may evolve into a septic arthritis.
- Tenosynovitis:
  An inflammation that involves the tendon and its sheath; it is almost always asymmetrical and commonly over the dorsum of the wrist and hands. Also, it can affect the ankle, knee, and metacarpophalangeal joints [60].
- Dermatitis:
  Around 40–70% of patients with bacteremic form are affected.

It presents as:
- Tiny maculopapular, pustular, or vesicular lesions on an erythematous base.
- Painless and non-pruritic lesions.
- The lesion's center may become necrotic or hemorrhagic.
- The lesions may rarely resemble erythema nodosum or erythema multiforme [60].

Other presentations may include:

- Fever, rarely higher than 39 °C.
- Fitz-Hugh-Curtis syndrome (gonococcal perihepatitis).
- Sepsis with Waterhouse-Friderichsen syndrome.
- Gonococcal endocarditis (rare in the antibiotic era).
- Gonococcal meningitis (very rare in the antibiotic era).

Septic arthritis form:

It presents as an acute inflammation to the joints with signs of:

- Joint effusion.
- Warmth.
- Tenderness.
- Reduced range of motion.
- Marked erythema.

One form of complication is permanent joint damage. Other complications are pericarditis, perihepatitis, pyomyositis, glomerulonephritis, meningitis, endocarditis, and osteomyelitis [58].

Abbreviations

RA	Rheumatoid arthritis
PND	Paraneoplastic neurological disorders
HCV	Hepatitis C virus
SLE	Systemic lupus erythematosus
ACLE	Acute cutaneous lupus erythematosus
SCLE	Subacute cutaneous lupus erythematosus
CCLE	Chronic cutaneous lupus erythematosus
DLE	Discoid lupus erythematosus
DIP	Distal interphalangeal joint
DM	Dermatomyositis
CTCL	Cutaneous T-cell lymphoma
ESR	Erythrocyte sedimentation rate
CRP	C-reactive protein
IBD	Inflammatory bowel disease
EN	Erythema nodosum
SJS	Stevens-Johnson syndrome
TEN	Toxic epidermal necrolysis
BSA	Body surface area

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Cardiovascular Diseases and Rheumatology

16

Rania Alhaj Ali, Hussein Halabi, and Hani Almoallim

16.1 Introduction

The prevalence of various cardiovascular diseases (CVD) in the different rheumatologic disorders is a very important topic. Each disease has a number of unique manifestations despite the fact that an overlap is present due to shared common risk factors, which may be related to the longer life expectancy of the recent therapeutic advances. A growing understanding of the role of inflammation and immune system in the initiation and progression of atherosclerosis as well as the early detection of cardiovascular manifestations is due to the availability and use of sophisticated noninvasive cardiac and vascular diagnostic technology. Such discipline results in the detection of cardiac manifestation unique to each rheumatologic disorder. This was not possible previously due to short life expectancy, limited therapeutic interventions, vague understanding of pathological process for each disease, and the limited diagnostic resources.

Cardiovascular diseases (CVD), including coronary artery diseases (CAD), can be present at the time of or after the diagnosis of rheumatologic disease. Cardiovascular association can be the principal introduction of the rheumatologic diseases in case of late diagnosis. The manifestations of CVD in rheumatologic diseases vary from subclinical to severe manifestations [4, 5], and they involve different structures of the heart. They can lead to significant morbidity and mortality. Therefore, we need to draw attention to their symptoms, to the risk factors that contribute to CVD development, as well as adaption of preventive measures that may control them. We will also consider the coronary artery disease (CAD), which maybe a crucial contributor to morbidity and mortality in numerous rheumatological diseases [6–9].

The prevalence of atherosclerotic CAD is increased in patients with chronic inflammatory rheumatic diseases, particularly in those with systemic lupus erythematous (SLE) and rheumatoid arthritis (RA) [10, 11]. The increased risk of CAD results from both traditional risk factors and factors unique to these rheumatic diseases [12, 13]. For example, accelerated atherosclerosis is one of the important risk factors for the development of CAD, and it can be attributed to the prolonged inflammatory process in these diseases, vascular endothelial dysfunction, and a specific form of

R. A. Ali (✉)
King Faisal Specialist Hospital and Research Center, Jeddah, Saudi Arabia
e-mail: n3527378@kfshrc.edu.sa

H. Halabi
Department of Internal Medicine, King Faisal Specialist Hospital and Research Center, Jeddah, Saudi Arabia

H. Almoallim
Medical College, Umm Al-Qura University (UQU), Makkah, Saudi Arabia

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low-density lipoprotein (LDL). The importance of metabolic syndrome in various rheumatic diseases and its implications on morbidity and mortality will be discussed as metabolic syndrome, which is commonly diagnosed among those patients and also plays an important role in the CVD development [14–16].

Several medications are now used in the management of various rheumatologic diseases, which can affect the development of CAD—either by decreasing or increasing the CAD severity or by decreasing or increasing its risk factors. In fact, many discussions are held nowadays with focus on how and when to use them. For example, the use of aspirin and statins in rheumatology and their effect on CAD. We will discuss the latest guidelines for their use here.

In this chapter, we address the various cardiovascular events that patients are exposed to, with CAD as one of the major factors that increase their mortality [10]. We will also discuss the important areas in regard to the identification of high-risk groups that need interventions, how to decrease the risk of CAD in these groups, and the way to better understand the effects of common medications on the risk of CAD in these patients.

16.2 Cardiovascular Manifestations in the Rheumatic Diseases

In this section, we look at CVD involvements in the different rheumatologic diseases and address the important issues in regard to their development (Tables 16.1 and 16.2 give a summary of the points given below).

The coronary artery disease (CAD) contributes significantly to the morbidity and mortality in various rheumatic diseases, whereas the occurrence of atherosclerotic CAD is increased in patients with chronic inflammatory rheumatic

Table 16.1 Type of CVD diseases

Disease	CVD	
RA	Atherosclerotic	• Myocardial infarction. • Congestive heart failure. • Peripheral arterial disease.
	Non-atherosclerotic	• Pericarditis. It is possible to occur as an inflammatory manifestation of RA. • Myocarditis and endocarditis. They are also possible to occur as a complication in RA. • Vasculitis. (e.g., aortitis, coronary arteritis) It can cause neurovascular disease (e.g., mononeuritis multiplex), cutaneous ulceration, or organ infarction based on the affected artery. • Other less common complications. Conduction abnormalities • Amyloidosis. • Pulmonary hypertension.
SLE	Pericardium	• Pericarditis. • Pericardial effusion.
	Myocardium	• ECG findings: Prolonged PR intervals. • MRI to help in diagnosis.
	Endocardium and valves	• Systolic murmur: Possibly from hyperdynamic state because of anemia. • Libman-sacks endocarditis .
Systemic sclerosis	Histology of CVD in SSc	• Hemosiderin deposits. • Involvement of subendocardial layers.
	Myocardium	• Fibrosis affects the myocardium in both ventricles and the conducting system. • Tricuspid regurgitation.
	Pulmonary arteries	• Pulmonary hypertension with irreversible fibrosis at the arterial walls, which will cause resistance against right ventricular contraction.

Table 16.1 (continued)

Disease	CVD	
Antiphos--pholipid syndrome	CAD	• MI and cardiac death with APL positive. • Unstable angina.
	Valvular disease	• Mitral, aortic, and less common in tricuspid valves. • It can progress to heart failure.
	Pseudo-endocarditis	• Vegetation commonly at the mitral and aortic valves. • High APL. • Blood culture is negative for infection.
	Peripheral artery disease	• At lower extremities.
	DVT	• Most common venous manifestation. • Pulmonary embolism is a common eventual complication.
	Intracardiac thrombus	• Not common and usually misdiagnosed.
Ankylosing spondylitis	Conduction defects	Inflammation and fibrosis of interventricular septum will cause damage of atrioventricular node, which can lead to first, second, and third-degree heart block and bundle branch block
	Aortic incompetence	Aortic wall inflammation (aortitis) above and behind sinuses of valsalva, and may extend below to the aortic roots and the wall of the mitral valve
	Left ventricular dysfunction	A possible increased connective tissue involvement in the myocardium
	Less common	• Pericarditis. • Cardiomyopathy. • Mitral valve disease. • Endocarditis .
Psoriatic arthritis	• CAD • Cerebral vascular disease. • Peripheral vascular disease.	
Inflammatory myopathies	• Myocarditis. • CAD. • Affected myocardial small vessels .	
Systemic vasculitis	• CAD • Myocardium, pericardium, endocardium, and conduction system involvements. • Peripheral vascular disease.	

Table 16.2 Summarized types of CVD in rheumatologic diseases

Disease	RA	SLE	APS	SSc	AS	PsA
MI	✓	✓	✓	✓	✓	✓
CHF	✓	✓		✓	✓	
PAD	✓	✓	✓			✓
PH				✓		
Myocardial diseases	✓	✓		✓	✓	✓
Endocardial diseases	✓	✓	✓		✓	
Valvular disease	±	✓	✓		✓	
Pericarditis	✓	✓		✓	✓	
Arteritis (coronary, aorta)						
Conduction defects	±			✓	✓	✓

Symbol definitions, MI: Myocardial infarction, CHF: Congestive heart failure, PAD: Peripheral arterial disease, PH: Pulmonary hypertension, SSc: Systemic sclerosis, AS: Ankylosing spondylitis, PsA: Psoriatic arthritis. ±: in case of rheumatoid nodule

diseases, particularly those with SLE and RA. This again is emphasizing the importance of those conditions to the development of CAD. This increased risk is mediated by the presence of both traditional risk factors and factors unique to those with systemic inflammatory disorders. It is a matter of higher risk as well as the presentation.

A larger proportion of patients with RA has a clinical silent CAD in comparison to demographically similar individuals in the general population. Patients with RA are also less likely to report chest pain during an acute coronary event than those without RA. It is still uncertain why this is happening, but acceptable explanations include the following: many patients with active disease and joint damage are less physically active; therefore, they are less likely to place suf-

ficient demand on the heart to elicit angina, which may attribute to RA pain. Patients with CAD tend to use nonsteroidal anti-inflammatory drugs (NSAID), glucocorticoids, or disease-modifying antirheumatic drugs (DMARDs), which can change their pain perception. Patients with rheumatoid arthritis (RA) have a reduced life expectancy when compared with the general population. Cardiovascular death is considered the leading cause of mortality in patients with RA; it is responsible for approximately half the deaths observed in RA [8]. Epidemiologic studies have shown that this increased mortality is largely attributed to cardiovascular diseases, primarily CAD. Considerable evidence suggests that inflammation plays a role in the pathogenesis of atherosclerosis [10]. The prevalence of cardiovascular comorbidity is difficult to assess accurately since CAD has a tendency to remain silent in the rheumatoid patients, but deaths from CVD occur earlier than in the general population. It has also been suggested that the increased risk of CAD in RA precedes the onset of clinical rheumatoid disease [17].

The lowering of CAD morbidity and mortality by recognizing patients at risk, and revealing their nontraditional[1] risk factors as well as their contribution in developing cardiovascular complications are important. Many rheumatic diseases have their share of these complications, e.g., RA, SLE, and vasculitis. The studies showed the importance of prevention strategies. Furthermore, many studies have been discussing various reasons of the increased in cardiac manifestations and the risk of mortality due to CAD. One could be the increase of traditional risk factors and its explanation. The second could be the special nontraditional risk factors, which are related to the pathophysiology of rheumatic diseases (See Tables 16.1 and 16.2).

Traditional risk factors include smoking,[2] hypertension, diabetes mellitus (DM), hyperlipidemia, and obesity [12].

The **nontraditional risk factors** are associated with elevation of CAD occurrences, which include severity of the disease, more extra-articular manifestation at presentation, corticosteroids, NSAIDs, and the low socioeconomic status. The presence of the accelerated atherosclerosis in those patients is associated with CAD development and subsequently the increased mortality from CAD in them (Tables 16.3 and 16.4).

16.2.1 Rheumatoid Arthritis (RA)

Rheumatoid arthritis is a chronic systemic inflammatory disease, which affects approximately 1% of the adult general population [18]. It has many extra-articular manifestations (e.g., heart and lung) in about 40% of patients with RA over their life time [19]. The mortality gap in comparison to the general population widened with the dramatic improvement in the overall mortality rate in the latter group [20]. For example, if we compare the general population to the patients with RA, there is an increased incidence of cardiovascular events, including myocardial infarction, stroke, and cardiac death among the patients with RA.

Cardiovascular disease is recognized as the leading cause of death in RA patients, accounting for nearly 40% of mortality [18]. Patients with RA are at twofold increased risk for myocardial infarction and stroke, with risk increasing to nearly threefold in patients who have had the disease for 10 years or more [18]. Congestive heart failure appears to be a greater contributor to excess mortality than ischemia. This increased cardiovascular disease risk in RA patients seems to be independent of traditional cardiovascular risk factors. Pathogenic mechanisms include prooxidative dyslipidemia, insulin resistance, prothrombotic state, hyperhomocysteinemia, and immune mechanisms, such as T-cell activation

[1]Patients are exposed to both the traditional risk factors of CAD and the nontraditional risk factors related to their disease.

[2]Apart from the known effects of smoking on CAD, it increases the severity of the rheumatoid arthritis, which can lead to atypical manifestation of the CAD and increasing the difficulty of the early detection (Tables 16.3 and 16.4).

Table 16.3 Prevalence of traditional risk factors

Prevalence	Smoking	Hypertension	DM	Dyslipidemia	Obesity
RA	↑↑	↑	↑↑	↑↑	↑
SLE	↑	↑↑	↑	↑	↑
General population	↑	↑	↑	–	↑

Table 16.4 Effects of traditional risk factors on RA

Effects of	RA
Smoking	↑RA development ↑ RF and ACPA-positive RA ↑worse prognosis
Hypertension	↑more than the general population, it is unclear whether it is from under diagnosis or from under treatment ↑BP from NSAIDs, chronic corticosteroids, leflunomide, and cyclosporine
DM	Possible association between RA and insulin resistance Can predict a new cardiovascular event
Dyslipidemia	↓ or ↑ Total lipid ↓ or ↑ LDL ↓↓HDL Can predate the diagnosis of RA
BMI	↑BMI and obesity = ↑other traditional risk factors = ↑worse prognosis = CVD ↓BMI and cachexia = acute inflammation

that subsequently lead to endothelial dysfunction, a decrease in endothelial progenitor cells, and arterial stiffness, which are the constitutes of accelerated atherosclerosis observed in RA patients [18]. These patients are greatly susceptible to CAD (myocardial infarction and angina), heart failure, pericarditis, myocarditis, atrial fibrillation, valvular heart disease, and cardiac amyloidosis.

16.2.1.1 Pericarditis

Pericarditis is the most common cardiac manifestation in RA, which is usually an asymptomatic disease. Clinical pericarditis is observed in around 4% of the patients [21], which is lower than the autopsy proven one that occurs in around 30%–50% of patients with RA [22]. Patients with RA are more likely to develop pericardial effusion than the ones without RA by ten times [23]. Most of the patients develop the pericardial effusion after the onset of the arthritis; however, RA was diagnosed after pericardial effusion in a minority of patients [3]. The variables associated with the development of extra-articular manifestations including pericarditis are as follows: male gender, presence of increased serum concentrations of rheumatoid factor, joint erosions, subcutaneous nodules, number of disease-modifying antirheumatic drugs (DMARD), presence of nail fold lesions, and any other extra-articular feature 1 year before the time of the diagnosis, or treatment with corticosteroids at the time of the diagnosis [21].

Patients with findings of edema, shortness of breath, chest pain, raised jugular venous pressure, pericardial rub, and paradoxical pulse were found to have 100% mortality rate within 2 years [4]. In patients with pericardial effusion, the diagnosis of RA was mainly clinical without the need for invasive procedure [3]. Biologic agents are now considered one of the cornerstones of RA therapy associated with the development of pericardial effusion mostly within 4 months of the start of the infliximab and etanercept [24]. Purulent pericardial effusion was reported in patients receiving infliximab and etanercept [25, 26].

Treatment: Although most of the evidence came from patients with immune-mediated pericarditis, it can be extrapolated to the RA-associated pericarditis as follows:

1. Asymptomatic disease usually diagnosed accidently will resolve spontaneously.
2. Symptomatic disease therapy includes the following:
   - Nonsteroidal anti-inflammatory drug (NSAID) is the mainstay therapy for idio-

pathic pericarditis, and the two agents that proved their efficacy are ibuprofen and indomethacin [27].

- Corticosteroids: low- to moderate-dosage prednisone (0.2–0.5 mg/kg per day) for 4 weeks and then slowly tapered, if the patient is intolerant to aspirin or NDSAID or with pericardial effusion [27].
- Colchicine: in patients with acute and recurrent pericarditis in addition to aspirin or NSAID in the dose of 0.5 mg twice daily in patients >70 kg and 0.5 mg once daily in patients ≤70 kg [27].
- If previous medical treatment fails, there is growing evidence for oral azathioprine, intravenous human immunoglobulins, and anakinra [27].
- Tocilizumab was reported to be successful too [28, 29].
- Surgical management includes pericardiocentesis, pericardiectomy, or pericardiotomy in the cases of hemodynamic compromise, cardiac tamponade, or constrictive pericarditis.
- Biologic-agents-associated pericarditis should be stopped and treated accordingly [24].
- Purulent pericarditis with biologic agents should be stopped and antibiotic therapy to be used accordingly [25, 26].

16.2.1.2 Myocardial Involvement

Myocarditis is less common than RA-associated pericarditis. It was found in 19% of patients with RA based on post-mortem study where the majority were females with active arthritis; however, most of the patients with myocarditis were clinically asymptomatic [30].

Cardiomyopathy with finding of left ventricle hypertrophy (LVH) was found in around 37% of asymptomatic RA patients by echocardiography [31]. The pathohistological finding was either diffuse or focal inflammation of the myocardium [32].

Diagnosis: The left ventricle function is usually evaluated with echocardiography, but it has a limited role in the evaluation of myocardium involvement. Cardiac magnetic resonance imaging (CMR) is helpful as noninvasive evaluation tool for myocarditis as it shows increased T2-weighted edema ratio (ER) score suggesting myocardial tissue edema. It has a role too in identifying the chronicity of myocarditis [33].

Treatment: Conventional therapy to support the left ventricle function is generally used. High-dose prednisolone (60 mg) daily for 2 months, tapered over 4 months followed by maintenance dose, normalizes the left ventricle ejection fraction and the gallium uptake [34].

Antimalarials-Induced Cardiotoxicity

Hydroxychloroquine and chloroquine are medications initially used as antimalarial treatment. They found to be effective as disease-modifying antirheumatic drugs. Hydroxychloroquine-induced cardiotoxicity has been reported in patients with RA [35].

Risk factors: Old age, female sex, long duration of therapy, high daily dose, preexisting cardiac disease, or renal impairment [35].

Presentation: Features of systolic dysfunction and prolonged QT interval were reported too [35].

Diagnosis:

(a) Echocardiography shows diffuse thickening ventricular walls [35].
(b) CMR: Shows areas of patchy gadolinium enhancement. It is important to differentiate it from other causes of cardiomyopathy [35].
(c) Endomyocardial biopsy: Shows enlarged and vacuolated cells, and the presence of myeloid and curvilinear bodies within the cardiac myocytes [35].

Treatment: Mainly withdrawal of the antimalarial agents and conventional heart failure treatment if needed [35].

16.2.1.3 Heart Failure

It is a clinical syndrome that is two times higher in RA patients than the general population [36].

Associations: Rheumatoid factor positivity was associated with higher risk of congestive heart failure [36].

Causes: Patients with RA develop heart failure mostly due to ischemic cardiomyopathy,

drug-induced myopathy (e.g., antimalarial drugs), rheumatoid nodule, NSAID use, or amyloidosis.

Treatment: Treat the underlying cause and conventional heart failure treatment. Avoid the use of tumor necrosis factor-alpha (TNF alpha) inhibitors especially the high doses (10 mg/kg) in NYHA classes 3 and 4 heart failure [37]. In patients with congestive heart failure and RA, the combined use of synthetic DMARDs, non-TNF biologic, or tofacitinib over TNF inhibitors is recommended [38].

16.2.1.4 Coronary Artery Disease (CAD)

Patients with rheumatoid arthritis (RA) have a reduced life expectancy when compared with the general population, where cardiovascular death is considered the leading cause of mortality in patients with RA; it is responsible for approximately half the deaths observed in RA [8]. Epidemiologic studies have shown that this increased mortality is largely attributable to cardiovascular diseases, primarily CAD. Considerable evidence suggests that inflammation plays a role in the pathogenesis of atherosclerosis [10]. The prevalence of cardiovascular comorbidity is difficult to assess accurately because CAD has a tendency to remain silent in the rheumatoid patient, but deaths from CVD occur earlier than in the general population. It has also been suggested that the increased risk of CAD in RA precedes the onset of clinical rheumatoid disease [17].

Traditional risk factors for atherosclerosis, such as smoking, hypercholesterolemia, hypertension, DM, and sedentary lifestyle, may be more common in RA than in the population as a whole but do not account for all of the increase in the disease. Currently, there is a large body of evidence that a chronic inflammatory state can enhance the harmful effects of some traditional risk factors, such as the association between systemic inflammation and arterial wall stiffness in hypertension or the proatherogenic lipid profile (high LDL and lipoprotein (a) low HDL) seen with increasing rheumatoid disease activity. The burden of addressing CAD in RA is therefore divided between rigorous control of traditional risk factors and effective disease control through immunosuppression [39]. The more extended the span of the RA and the utilization of TNF alpha inhibitors are, there is a chance for improvement of atherosclerosis [40]. The two are a surrogate for the seriousness of the illness and a presence of coronary calcification [41]. Male gender and severe inflammatory state (high inflammatory markers and disease activity score) are usually associated with atherosclerosis [42].

Factors influencing cardiovascular disease in rheumatoid arthritis:

- **Oxidized LDL** (oxLDL) and antibodies to oxidized LDL are both established as significant risk factors for CVD in RA. It has been consistently observed that the levels of oxLDL are higher in patients with active disease [39].
- **C-reactive protein:** Higher levels of CRP are associated with CVD in non-RA patients [39]. Treatment of CAD with statins or angiotensin-converting enzyme (ACE) inhibitors has been demonstrated to lower CRP levels [39]. Attention was specifically focused on high-sensitivity CRP (hsCRP). Raised hsCRP is found in hypertension, smoking, and DM, as well as CAD.

  In RA baseline, CRP predicts cardiovascular mortality [43], and the molecule acts directly in a pro-inflammatory manner at a range of sites. For example, CRP activates vascular endothelial cells to express adhesion molecules in a dose-dependent manner, and CRP activates monocyte chemotactic protein-1 (MCP-1), which can be inhibited by statins and fenofibrates [39].
- **Homocysteine**: Homocysteine is increasingly regarded as an epiphenomenon of CAD rather than a causative factor [39].

Elevated levels of homocysteine have been associated with CAD in the general population as well as in reduced levels of various vitamins including folate and B6 [39]. It has also been shown that homocysteine is present in higher concentrations in the joints of RA patients, where it may enhance production of pro-inflammatory cytokines such as IL-1 and thus act as a driver for

joint damage; it may also accelerate atherosclerosis in a similar manner [44].

- **Physical disability due to rheumatoid arthritis***:* Poor functional status, especially in the lower limbs, is a powerful predictor of mortality in RA, while regular exercise is known to have beneficial effects on the cardiovascular system. Exercise capacity is also inversely related to the presence of metabolic syndrome [45]. Patients with chronic RA have physical disabilities, which prevent them from taking regular exercise. This influences CAD in several ways; the presence of CAD usually causes delay in the individual's presentation to clinician since reduced physical activity may not exacerbate symptoms. The delay in presentation would also prevent treatment at an earlier stage of CAD, even with the lack of CVD, physical disability would still stop adequate exercise.
- **Leptin and the adipocytokines***:* Leptin is an adipokine that functions both as a hormone and a cytokine. It is produced by the adipose tissue, and its main role appears to be to reduce food intake and to stimulate the sympathetic nervous system. It is known to stimulate inflammatory cytokine production, and to have direct deleterious effects on articular cartilage. It is also known to cause endothelial dysfunction, oxidative stress, and platelet aggregation and to be elevated in RA; while fasting has been implicated as a means of reducing leptin levels and improving RA disease activity [39]. Leptin has the potential to play a key role linking obesity, inflammation, and cardiovascular damage.

Prevention of CAD in RA.

Since it is generally similar to prevention in patients without RA [46], here are some important points to prevent CAD in RA patients.

One needs to:

- Stop smoking.
- Measure fasting blood glucose annually or in the event of significant weight gain especially in patients taking steroids. In already diabetic patients, the steroids should be kept in the lowest dose.
- Monitor blood pressure for RA patients before beginning medications and then at regular intervals for patients using NSAID, cyclosporine, and corticosteroids. NSAIDs reduce the antihypertensive effects of diuretics, β-blockers, and angiotensin-converting enzyme inhibitors, but it is less likely to interfere with calcium channel blockers [47]. In those group of patients either to increase the dose of the antihypertensive medications or to use a calcium channel blocker.
- Manage hypercholesterolaemia according to recommendation for the general population.
- Manage obesity as well as weight loss.
- Supplement the diet with fish oil that is rich in omega-3 fats, because this has demonstrated efficacy in the treatment of RA, facilitated reduction of NSAIDs use and reduced cardiovascular mortality risk [48].
- Diagnose and treat RA early:
  - Methotrexate: shown to decrease cardiovascular mortality among RA patients [49].
  - TNF inhibitors: shown to decrease the risk of MI among patients who have controlled synovitis within 6 months of treatment [50].

16.2.1.5 Rheumatoid Nodule

Valvular nodule is 10 times higher in RA patients than the general population [23].

Incidence: Echocardiographic evidence of aortic valve nodule was observed less than mitral valve nodule in the rate 0.3% vs. 0.6% among RA patients [31], respectively.

Presentation: Differs according to the site of the nodule, as it causes functional impairment, such as arrhythmias and valve disease [51]. It was associated with complete atrioventricular (AV) block necessitating pacemaker as it involves the AV node [52, 53].

Treatment: According to the presentation.

16.2.2 SLE

It is a multisystem autoimmune disease with a strong female predilection.

Cardiovascular morbidity and mortality is a frequent complication, particularly in females aged 35–44 years, where the risk of myocardial infarction is raised 50-fold [54]. The cardiac morbidity is the most common cause of death in SLE patients, which is around 25% of deaths in SLE [55].

The heart is one of the most frequently affected organs in systemic lupus erythematosus (SLE), where any part can be affected, including the pericardium, myocardium, coronary arteries, valves, and the conduction system. In addition to pericarditis and myocarditis, high incidence of CAD has become increasingly recognized as cause of mortality, especially in older adult patients and those with long-standing SLE [56].

Pericarditis is the most common cardiac abnormality in SLE patients, but lesions of the valves, as well as myocardium and coronary vessels, may all occur. In the past, cardiac manifestations were severe and life threatening, often leading to death. Therefore, they were frequently found in postmortem examinations. Nowadays, cardiac manifestations are often mild and asymptomatic. However, they can be frequently recognized by echocardiography and other noninvasive tests (Echocardiography is a sensitive and specific technique in detecting cardiac abnormalities, particularly mild pericarditis, valvular lesions, and myocardial dysfunction). Therefore, echocardiography should be performed periodically on SLE patients [57].

16.2.2.1 Pericarditis

The most common clinical cardiovascular manifestation of SLE.

Prevalence: Echocardiographic evidence of pericardial effusion was detected in 27% of SLE patients, where most of them had asymptomatic disease [58]. Lupus pericarditis occurs predominantly in females in around 92% [59] which is mostly due to main predominance of SLE in females.

Associations: Mostly associated with active SLE in 93% and involvement of other organs with SLE in 72% [59]. In the absence of renal failure, constrictive pericarditis or pericardial effusion is rarely reported [60]. Patients with tamponade had lower serum level of C4 in comparison to the ones who did not develop tamponade [61].

Clinical presentation: Ranges from asymptomatic to pericardial effusion [58] to cardiac tamponade in 16% [59].

Diagnosis: Either by the presence of pericardial effusion by echocardiography only or the presence of 2 out of 4 of the following (Retrosternal pain, pericardial friction rub, widespread ST-segment elevation, and new/worsening pericardial effusion) among SLE patients [59].

Treatment: The treatment of lupus pericarditis is mainly derived from immune-mediated pericarditis, as previously mentioned in the RA section, where it responded well to NSAID and corticosteroids [59]. High-dose corticosteroids, complete drainage, and pericardial window were used for treating patients with large pericardial effusion/tamponade [61, 62].

16.2.2.2 Myocarditis

Effects: SLE is associated with the increase in the left ventricle mass, and this would be even more if SLE was associated with hypertension (HTN) [63].

Associations: The association is strong between lupus myocarditis with the presence of myositis but weak with the presence of the antibodies to nuclear ribonucleoprotein (RNP) [64]. High SLE Disease Activity Index is an independent risk factor in the development of lupus myocarditis [5], where anticardiolipin IgG and lupus anticoagulant were positive in patients with severe symptoms [65].

Clinical features: It ranges from asymptomatic disease discovered accidently to symptomatic heart failure and sudden death [5].

Diagnosis: Echocardiography: Most patients suffered from wall motion abnormalities (WMA), whereas less than 50% of lupus myocarditis patients showed decrease in the left ventricle ejection fraction after the exclusion of other causes of myocarditis [5].

Treatment: Conventional treatment of heart failure [5]. Immunosuppressive therapy (high-dose systemic corticosteroids with subsequent dose tapering, intravenous immunoglobulin, plasmapheresis, or cyclophosphamide) showed

improvement in heart failure symptoms, EF, and the WMA of the heart [5]. After corticosteroids therapy, the EF improved up to a mean of 49.5% after around 7 months of follow-up from a mean of 33.8% [66]; one article reported normal EF after follow-up [67]. Refractory lupus myocarditis can be treated with rituximab [68]. Intravenous "pulse" cyclophosphamide was used in patient with lupus myocarditis refractory to corticosteroids, and it showed improvement in heart failure symptoms and EF from 19% to 63% [69]. Mycophenolate mofetil was effective in a case series [70]. Intravenous immunoglobulin was effective in the treatment of patients with severe lupus myocarditis in conjunction with corticosteroids and cyclophosphamide [65]. One rare case report showed that plasmapheresis and extracorporeal membrane oxygenation (ECMO) were effective in lupus myocarditis [71].

16.2.2.3 Coronary Artery Disease (CAD)

Prevalence: The prevalence of the angina, myocardial infarction, and sudden cardiac death was found to be 8.3% as per a Johns Hopkins SLE cohort study [9]. Another study found more than 50-fold risks of MI in young women 35–44 years old when compared to the control group [11].

Risk Factors

(a) **Traditional risk factors for atherosclerosis.**
It has an increased prevalence in patients with SLE as hypertension, DM, premature menopause, sedentary lifestyle, and high homocysteine level [12].

(b) **Inflammation-related risk factors.**
- High disease activity and elevated level of CRP [13].
- In lupus nephritis, it was found that patients with long-term lupus nephritis had frequent episodes of cardiac lesions, mainly cardiac infarctions [72].
- Low serum levels of C3, antiphospholipid antibodies (APL), and elevated levels of antibodies to anti-ds DNA were found to be independent predictors of thrombosis. Hydroxychloroquine is protective against future thrombosis in those patients [73].
- Several autoantibodies such as anti-DNA, APL, anti-SSA (Ro antibodies), and anti-endothelial cell antibodies present in patients with SLE can mediate cardiac damage [74].
- Old age at diagnosis of SLE [9, 11].
- Longer duration of SLE [9, 11].
- Longer duration of steroid therapy [9].
- High levels of oxidized low-density lipoprotein cholesterol and homocysteine [9].

Preventions of CAD in SLE.
To prevent CAD, one has to:

- Control the traditional risk factors, to use the statins according to the guidelines for the general population, and to control blood pressure aggressively.
- Improve the lipid profile by using hydroxychloroquine as it lowers the level of the cholesterol in the blood, especially in patients taking steroids [75], and it is associated with a reduced risk of DM [76].
- Minimize the use of steroids.

16.2.2.4 Endocarditis (Libman–Sacks Endocarditis)

It was first described by Libman and Sacks in 1942 after they discovered valvular lesions in four patients with SLE.

Prevalence: Echocardiographic evidence was detected in around 11% of patients with SLE [77].

Associations: It was found to be associated with longer SLE duration and activity, thrombosis, stroke, thrombocytopenia, and antiphospholipid syndrome [77]. Its coexistence with antiphospholipid antibodies (APLs) increases the risk of thromboembolic complications, especially stroke [78].

Pathology: Since the main involved valve is the mitral followed by the aortic [78], the left side is mainly more involved than the right. Therefore, the main dysfunction is regurgitation; stenosis is rarely found [78].

Diagnosis: Echocardiography: It is manifested as valve vegetations, thickening, and/or

regurgitation [79]. Transesophageal echocardiography (TEE) was found to be more sensitive than transthoracic echocardiography (TTE) for the detection of echocardiographic findings [79]; for example, valvular thickening was found higher with TEE at 70% vs. 52% with TTE [79].

How to differentiate it from infective endocarditis? Infective endocarditis is an uncommon complication of SLE, yet at the same time, it should be in the differential diagnosis as both diseases can be presented with fever and valvular vegetation. Three laboratory tests can help differentiate between them to a degree, and these are the white blood cell count (WBC), the CRP level, and the antiphospholipid antibody (APL) level [80]. The test results show that the WBC is expected to be low during lupus flare and high during infection, CRP is high with infection and suppressed during lupus flare, and the aPL is high in SLE and unlikely to be positive in infection [80].

Treatment

The control of the SLE disease activity is important with the use of the corticosteroids. Although the use of corticosteroid is not beneficial for the valve lesion, it is important to control underlying diseases [78]. The corticosteroids, on the other hand, were noted to be associated with fibrosis and severe dysfunction (e.g., mitral valve insufficiency) after high doses of corticosteroid are used [81, 82]. Patients with Libman–Sacks Endocarditis, who suffered from a thromboembolic event, are recommended to be on life-long anticoagulation to prevent further episodes [78]. Accordingly, conventional treatment of heart failure and valvular lesion as needed is crucial.

16.2.3 Systemic Sclerosis (SSc)

Widespread vascular lesions, fibrosis of the skin, and internal organs characterize a connective tissue disease. More than half of the patients with SSc, who underwent autopsy, were found to have significant cardiac abnormalities [37]. Cardiac involvement is recognized as a poor prognostic factor when clinically evident, with a 5-year mortality rate is around 75% [83]. Primary myocardial involvement is common in SSc; increasingly, evidence strongly suggests that myocardial involvement is related to repeated focal ischemia leading to myocardial fibrosis with irreversible lesions. Reproducible data have shown that this relates to microcirculation impairment with abnormal vasoreactivity, with or without associated structural vascular abnormalities. Consistently, atherosclerosis and macrovascular coronary lesions do not seem to be increased in SSc. Myocardial involvement leads to abnormal systolic, diastolic left ventricular dysfunction, and right ventricular dysfunction. Sensitive and quantitative methods have demonstrated the ability of vasodilators—including calcium channel blockers and angiotensin-converting enzyme inhibitors—to improve both perfusion and function abnormalities. By that, they emphasize the critical role of microcirculation impairment [84].

Asymmetric hypertrophy of the interventricular septum with signs of sub-aortic obstruction consistent with hypertrophic obstructive cardiomyopathy was evident in echocardiogram in patients with diffuse SSc. Hypertrophic cardiomyopathy is associated with the human lymphocyte antigen HLA DR3 [85], and this may provide a possible link with SSc as this HLA phenotype is common in the latter condition [85].

16.2.3.1 Myocardial Fibrosis

Prevalence: Around 66% of patients with SSc based on MRI [86]. The presence of the left ventricle (LV) dysfunction (ejection fraction (EF) <55%) was reported in around 5.4% among SSC patients [1].

Pathology: Patchy distribution of myocardial fibrosis is pathognomonic [87]; Foci of contraction band necrosis (mostly due to the recurrent vasospasm of the small vessels of the heart) is found in all parts of the myocardium mainly in the subendocardial area [88]. Asymptomatic patients with impaired coronary flow reserve did not show stenotic lesions of the major epicardial coronary arteries [89]. Contrarily, symptomatic patients (e.g., angina) with SSc had evidence of CAD in similar rate to the symptomatic ones without SSc [90].

Associations: There is association between the high volume of fibrosis and Raynaud's phenomenon duration of 15 years or more and

abnormal Holter study results [86]. Male sex, old age, presence of digital ulcerations, and myositis were associated with higher prevalence of LV dysfunction [1].

Diagnosis

(a) Echocardiography: Most patients had LV hypertrophy in around 22.6%, followed by LV diastolic dysfunction in around 17.7%, and a rare percent of LV systolic dysfunction in around 1.4%, in the absence of the pulmonary arterial hypertension [91].
(b) Heart MRI: Delay enhancement MRI can identify areas of fibrosis in a significant number of patients [86].

Treatment

Vasodilators (e.g., calcium channel blockers and angiotensin-converting enzyme (ACE) inhibitors) showed improvement of the myocardial perfusion and halting of the disease progression [92]. Patients showed radiological improvement in myocardial perfusion and function after the administration of nifedipine (60 mg daily) for 14 days [93]. Among SSc patients, it was found that the ones treated with calcium channel blockers (CCB) have less reduced LVEF [1]; the cardiac protective effect of CCB still needs to be established.

16.2.3.2 Myocardial Ischemia

SSc is an independent risk factor for acute myocardial infarction with no protective effect was noted with the immunosuppressive therapy [6].

16.2.3.3 Pericarditis

Prevalence: Symptomatic pericardial disease is observed in around (5–16%) of the patients, which is lower than the autopsy proven one and was demonstrated in around (33–72%) of SSc patients [94]. Symptomatic pericarditis in patients with limited scleroderma is more than the patients with diffuse scleroderma, which was observed at the rate of 30% vs. 16%, respectively [2].

Associations: Symptomatic pericarditis is associated with pulmonary hypertension [95], while cardiac tamponade and heart failure are associated with poor prognosis [87].

Presentation: It is usually asymptomatic [2], yet it can rarely be present with large symptomatic pericardial effusion [2]. The large pericardial effusion usually occurs after the clinical and laboratory manifestations of the scleroderma [2], but still it can happen before, so it is part of the differential diagnosis of pericardial effusion [96]. Renal failure can be presented in the setting of large pericardial effusion and constrictive pericarditis [87].

Laboratory: exudative pericardial effusion pattern with predominance of mononuclear cells [97].

Treatment: In the setting of pericarditis, NSAID and corticosteroids were effective [94], and with the presence of active inflammation, immunosuppressive therapy may have a role [94].

Conventional heart failure treatment is helpful [94]. Cardiac tamponade is to be treated accordingly, e.g., pericardiocentesis [87]. Constrictive pericarditis is to be treated accordingly, e.g., diuretics, sodium and fluid restriction, and/or pericardial stripping [87].

16.2.4 Antiphospholipid Syndrome

Antiphospholipid syndrome (APS) is a systemic autoimmune disease associated with arterial and venous thrombotic events and recurrent fetal loss. The heart is a target organ in APS.

Endocardial disease, intracardiac thrombosis, myocardial involvement including CAD and microvascular thrombosis, as well as pulmonary hypertension, have all been described in APS patients. Valvular involvement is the most common manifestation with a prevalence of 82% detected by transesophageal echocardiography. Symmetrical—nodular thickening of the mitral and/or aortic valves—is characteristic. Anticoagulant/antiplatelet treatment is ineffective in terms of valvular lesion regression [98]. Some patients require cardiac valve replacement. However, patients with APS have shown an increased perioperative morbidity and mortality. Intracardiac thrombosis,

although a rare complication, can cause pulmonary and systemic emboli [98].

16.2.4.1 Aspirin and APS

The primary prophylaxis of thrombosis with low dose aspirin (81 mg) in asymptomatic, persistently antiphospholipid antibody (APL)-positive individuals was not beneficial when compared to placebo [99]. SLE patients with persistent positive lupus anticoagulant (LA) antibody are at high risk of thrombosis, and primary prophylaxis with low-dose aspirin and hydroxychloroquine is recommended [100].

16.2.5 Ankylosing Spondylitis (AS)

It is a chronic inflammatory condition that usually affects young men, mainly affecting the spine and the sacroiliac joints and, to lesser extent, the peripheral joints. Cardiac dysfunction and pulmonary disease are well known and commonly reported extra-articular manifestation associated with ankylosing spondylitis (AS). The cardiac manifestations were reported in around 2–10% [101], and it may reach up to 30% [102] of patients with AS—mostly conduction defects and aortic insufficiency [101]. The cardiac manifestation is mostly observed in patients with long-term AS and peripheral joint involvement [103]. AS has also been reported to be specifically associated with aortitis, aortic valve diseases, conduction disturbances, cardiomyopathy, and CAD. There is no difference between the type of rheumatic therapy and its use among patients with AS, who have myocardial infarction versus who does not [101].

16.2.5.1 Aortic Involvement

It was first described in 1973 AD by Bulkley and Roberts during autopsy examination of patients with AS that had congestive heart failure due to severe aortic regurgitation [104]. It is an important topic, because if patients with AS developed chest pain, you should rule out aortic dissection.

Prevalence: Echocardiographic evidence of aortic regurgitation was mostly mild and was observed in around 3–13% of patients with AS [60]. Positive HLA-B27 patients with aortic regurgitation around half of them do not have clinical features of rheumatic disease [105].

Pathology: Arteritis around the aortic root and valve due to inflammatory process with platelets aggregation lead to tissue thickening [104]. There is fibrous growth of the intimal layer that leads to aortic root dilatation [104]. Increase in stiffness of the aorta and decreased global myocardial performance are features of AS and correlate with the disease activity and its duration [106].

Diagnosis: Echocardiography: TEE showed aortic root thickening, increased stiffness, dilatation, and nodularities of the aortic cusps. The first two were the most common findings [107]. Valve regurgitation was seen in around half of the patients [107].

16.2.5.2 Myocardial Involvement

Prevalence: Diastolic dysfunction was found at the rate of 20% [108] ranging to 50% [109], while systolic dysfunction was affected less than that in around 18% of AS patients [110].

Pathology: It was found to have an increase in myocardial inflammation and the connective tissue/myocyte rate, which will give the picture of the increase in diffuse interstitial connective tissue [110].

Presentation: Diastolic dysfunction in AS is usually not severe enough to cause diastolic heart failure [111]. Rarely, were LV systolic dysfunction and hypertrophy reported in the absence of significant aortic regurgitation [48].

16.2.5.3 Conduction Abnormalities

It is the most common finding in AS patients, and it usually precedes the other cardiac findings [102].

Prevalence: Conduction abnormalities were observed in around 2–20% of AS patients [60]. Around half of the positive HLA-B27 patients with conduction abnormalities do not have clinical features of rheumatic disease [105].

Pathology: Inflammatory process leads to damage of the interventricular septum wall, and AV node dysfunction is secondary to the compromise of the arterial supply to the AV node [112].

Another factor is the autonomic nervous system abnormalities that can lead to conduction defects and arrhythmias at the end [113].

Associations: Disease duration is associated with the prolongation of the PR and the QRS intervals [112]. Conduction abnormalities occur more frequently in patients with positive HLA-B27 [105].

Types:

1. Supraventricular extrasystoles and ventricular extrasystoles are very common findings among AS patients [102].
2. Prolonged QRS interval in about 29.2% of AS patients [112].
3. First-degree atrioventricular (AV) block in around 4.6% of AS patients [112].
4. Complete right bundle branch block (RBBB) in around 0.8% of AS patients [112].
5. Left anterior hemiblock 0.8% of AS patients [112].

16.2.6 Psoriatic Arthritis

The increased risk of clinical and subclinical CVD is mostly due to accelerating atherosclerosis, and the incidence of mortality in CAD was similar to that of RA [114]. Patients with psoriatic arthritis have higher occurrences of CVD risk factors and CAD, peripheral vascular disease, and congestive heart failure [115].

16.2.6.1 Arrhythmias

Incidence: Patients with psoriasis were found to have higher risk of developing arrhythmia than the normal population at the rate of 15.41 per 1000 person-years, and this was even higher among patients with psoriatic arthritis [116].

16.2.6.2 CAD:

Incidence: The incidences of myocardial infarction is 5.13 per 1000 person-years, while it is 5.13 for severe psoriasis, which is higher than the general population [7]. The new events of heart failure were higher among psoriasis patients, especially among the severe psoriasis group than the general population [117].

Associations: Severe psoriasis is associated rationally with a higher risk of death, specifically cardiovascular being the most common cause [118]. CAD is associated with young patients [7, 119], psoriatic arthritis [119], and/or severe psoriasis [7, 119]. Severe psoriasis has higher risk of CAD and stroke [119].

Pathology: Metabolic diseases, such as obesity and diabetes mellitus, are more among psoriasis patients, which may play a role in the development of atherosclerosis in addition to the inflammatory process [120].

Prevention: Treatment with methotrexate and TNF alpha inhibitors therapy appears to lower the rates of CAD among patients with psoriasis [120].

16.2.7 Systemic Vasculitis

CVD is significantly involved in different types of systemic vasculitis, ranging from large to small vessel vasculitis (see Chap. 20 on "Vasculitis and Rheumatology").

16.3 The Accelerated Atherosclerosis Effects on CAD in Rheumatologic Diseases

This can be called an immune system-mediated inflammatory process as the immune cells can be found within atherosclerotic plaques, and inflammation activates this process.

(Table 16.5 shows the major contributing factors for atherosclerosis in different rheumatologic diseases).

16.4 Metabolic Syndrome and Rheumatological Diseases

The concept of metabolic syndrome was first recognized by Raven when he discussed that insulin resistance has a central role in type 2 DM, hypertension, and CAD [121]. Later, it became known as metabolic syndrome. The major components

Table 16.5 : Atherosclerosis in rheumatologic diseases

Disease	Contributed factors	
All	• Active prolonged inflammatory process. • Vascular endothelial dysfunction and injury. • ↑ Oxidized LDL (oxLDL) engulfed by macrophages to form foam cells • Immune dysregulation by ↑ CD4+ T cells that lack surface CD28 molecule (CD4 + CD28−), which infiltrate the atherosclerotic plaques and display a high pro-inflammatory and tissue-damaging potential; this promotes vascular injury. • ↑Beta 2 glycoprotein I (B2GPI) is present along with CD4 lymphocytes in the plaque cells which increase the lesion area. • The plague secretes interleukins, tumor necrosis factor-α (TNF), and platelet-derived growth factor for more expansion of the lesion. • ↑Anti-oxLDL, (aCL) antibodies, anti-β2GPI antibodies when there is extensive atherosclerosis.	
Disease	**Contributed factors**	**Subclinical detection**
RA	• Endothelial dysfunction. • Traditional risk factors. • Depletion of endothelial progenitor cells.	Preclinical atherosclerosis can be detected by: 1. B mode-carotid ultrasound: • IMT (intimal medial thickness). • See atherosclerotic plague by echolucency and calcific acoustic shadowing. 2. CT scan of coronary arteries: • Presence of calcification. • Extent of calcification. 3. Arterial stiffness: • Pulse wave velocity (PWV). • Pulse wave analysis (PWA). 4. Elevated CRP.
SLE	• Traditional risk factors. • Depletion of endothelial progenitor cells. • Inflammation. • Metabolic changes in SLE: Renal dysfunction and early menopause. • Antiphospholipid antibodies.	
APS	• Possible involvement of antiphospholipid antibodies (APL) in the pathogenesis of atherosclerosis. • Positive APL is associated with arterial atherosclerosis which will develop into thrombosis at coronary, carotid, and lower peripheral arteries. • Positive lupus anticoagulant (LA) is associated with venous thrombosis.	
Systemic sclerosis	• Endothelial injury and its activation can lead to loss of vasomotor function and vasoconstriction. • Myofibroblasts develop from activated vascular muscles and cause thickening of the intima, lumen narrowing, and irreversible fibrosis. • It may also induce formation of intravascular thrombosis.	
Ankylosing spondylitis	• There are very limited studies. • Inflammation is a possible contributed risk. • Endothelial dysfunction.	• No difference in IMT compared with the general population. • Impaired flow-mediated dilatation and coronary flow reserve.
Vasculitis	• There is inflammatory cells infiltration in the layers of arterial wall.	• Variable.

of metabolic syndrome include dyslipidemia, central obesity, insulin resistance, and hypertension [122]. The major components are not occurring concurrently; as it was found that insulin sensitivity will predict the increase in waist circumference (obesity), and the latter will predict the remaining components, e.g., dyslipidemia and hypertension [123]. The adipose tissue is acting as endocrine organ by the secretion of the pro-inflammatory factors called adipokines. Insulin resistance has a role in the development of CVD (probably due to the adipokines from the adipose tissue) [124] as it has a role in the enhancement of vascular inflammation and endothelial dysfunction [125]. Different adipokines have been recognized in metabolic syndrome with rheumatic diseases, and their effects were emphasized (see Table 16.6).

Patients with rheumatic diseases are under the pressure of chronic inflammation mainly with

Table 16.6 The effects of different adipokines on rheumatologic diseases [154]

Rheumatic disease	Adipokines			
	Leptin	Adiponectin	Visfatin	Resistin
RA	↑, pro-inflammatory	↑, Synovitis	↑, Radiographic joint damage	↑, Disease activity and joint destruction
PsA	Controversial	Controversial	Controversial	–
PsA	–	–		–
AS	Marker of disease activity??	–	Controversial	–
Gout	–	–	–	–
OA	↑, cartilage destruction	Controversial	↑, degradation of collagen	–

RA and SLE. Many patients with rheumatic diseases—mainly RA, SLE, and AS—have been diagnosed with metabolic syndrome [14–16].

Here, we will discuss the rheumatic diseases and its relationship with metabolic syndrome.

16.4.1 RA

It was initial to associate insulin sensitivity to be lower in RA patients compared to osteoarthritis patients [126]. Later, it was found that the main factors of insulin resistance in RA are obesity and disease activity [127]. The prevalence of metabolic syndrome among RA patients ranges from 44% to 53% [15, 128]. Such patients were found to have higher disease activity than those without metabolic syndrome with low level of high-density lipoprotein cholesterol [15]. Its presence is associated with higher systemic inflammatory marker and glucocorticoids use [129]. Patients with RA, who were diagnosed with metabolic syndrome, were found to have higher risk of coronary artery calcification [128].

16.4.2 SLE

Non-diabetic patients with SLE were found to have significant decrease in sensitivity to insulin, and around 18% of them were diagnosed with metabolic syndrome [130]. The prevalence of metabolic syndrome among SLE patients ranges from 16% to 32.4% [14, 131, 132]. SLE patients have higher fasting insulin level, and cardiovascular risk factors were also elevated among the last group [133]. Metabolic syndrome was associated with higher level of C-reactive protein, homocysteine, lipoprotein, and cholesterol [14] . Metabolic syndrome and CVD among SLE patients were associated with prolonged SLE duration and increased cumulative organ damage [131]. Lupus nephritis, high corticosteroid doses, Korean and Hispanic ethnicity were associated with metabolic syndrome in SLE patients [132]. The use of hydroxychloroquine was associated with protective effect of CVD [131].

16.4.3 AS

The prevalence of metabolic syndrome among AS is around 45.8% [16], whereas low AS disease activity is not associated with accelerated atherosclerosis [134].

16.4.4 Psoriasis

Psoriasis is associated with DM. The prevalence of DM was higher with severe psoriasis than mild psoriasis in the rate of 7.1% vs. 4.4%, respectively [135]. The prevalence of metabolic syndrome among psoriatic patient ranges from 15% to 35.5% [136–138]. Psoriatic patients are prone to the development of the main components of metabolic syndrome (e.g., DM and hypertension) [139]. Treating psoriasis was found to be associated with improvement in the metabolic risk biomarkers, such as high-sensitivity CRP, adiponectin, and the oral glucose tolerance test [140].

16.4.5 Gout

The initial association of gout with metabolic syndrome was with the close association of hyperurecemia and the components of metabolic syndrome (e.g., hypertension, insulin resistance, and obesity) was noted [141]. Elevated uric acid levels among gout patients can be associated with insulin resistance since renal clearance is inversely related with insulin resistance [142]. The prevalence of metabolic syndrome among gout patients ranges from 44% to 88% [143–145].

16.5 The Various Medications that Are Being Used in the Management of Rheumatologic Disease that Have Variable Effects on CAD

It is important to mention these factors because managing clinicians may not pay attention to these effects as they focus mainly on the activity of the rheumatologic disease.

16.5.1 NSAIDs[3]

- The risks of major cardiovascular events—such as myocardial infarction, stroke, and death—appear to increase to a similar degree by the use of most nonselective NSAIDs at high doses. The exception is naproxen, which does not increase such risk [146].
- All of the COX-2 selective inhibitors (coxibs) appear to increase the risk of ischemic cardiovascular disease in a dose-dependent fashion. Recent data showed that naproxen, celecoxib, and ibuprofen did not differ in the risk of the cardiovascular mortality, but naproxen was less than the last two for the risk of the gastrointestinal bleeding [147]. Certain COX-2 inhibitors are associated with twofold increase in CAD risk.
- COX inhibition leads to CAD with two possible mechanisms:
  - It can interfere with normal platelet and endothelial vasodilator functions.
  - It can cause hypertension.
- All (NSAIDs) can increase blood pressure in both normotensive and hypertensive individuals. Its use may reduce the effect of all antihypertensive drugs except calcium channel blockers.

  (Figure 16.1 summarizes the effects of NSAIDs on the cardiovascular system)

16.5.2 Glucocorticoids (GC)

This medication is known to have serious noxious effects by increasing blood pressure, insulin resistance, body weight, and fat distribution. There is an excess risk of cardiovascular morbidity and mortality when the drug is used in high cumulative doses and for a long duration. There is 68% of increased risk of myocardial infarction among RA patients treated with GCs [148]. Cushing disease is associated with accelerated atherosclerotic vascular disease [149].

16.5.3 Methotrexate

Many studies have demonstrated that its use has been associated with a beneficial reduction in CVD events among patients with systemic inflammation diseases primarily from RA [49]. It is known to decrease homocysteine level. RA patients who used methotrexate have lower LDL levels, significant increase in mean HDL, and decrease in carotid artery intima-media thickness, compared with baseline values.

16.5.4 TNF Biologic DMARDs

- A large study showed significant reduction in fatal and nonfatal CVD outcomes associated

[3]The association of nonsteroidal anti-inflammatory drugs (NSAIDs) with cardiovascular morbidity and mortality in patients with RA is still controversial.

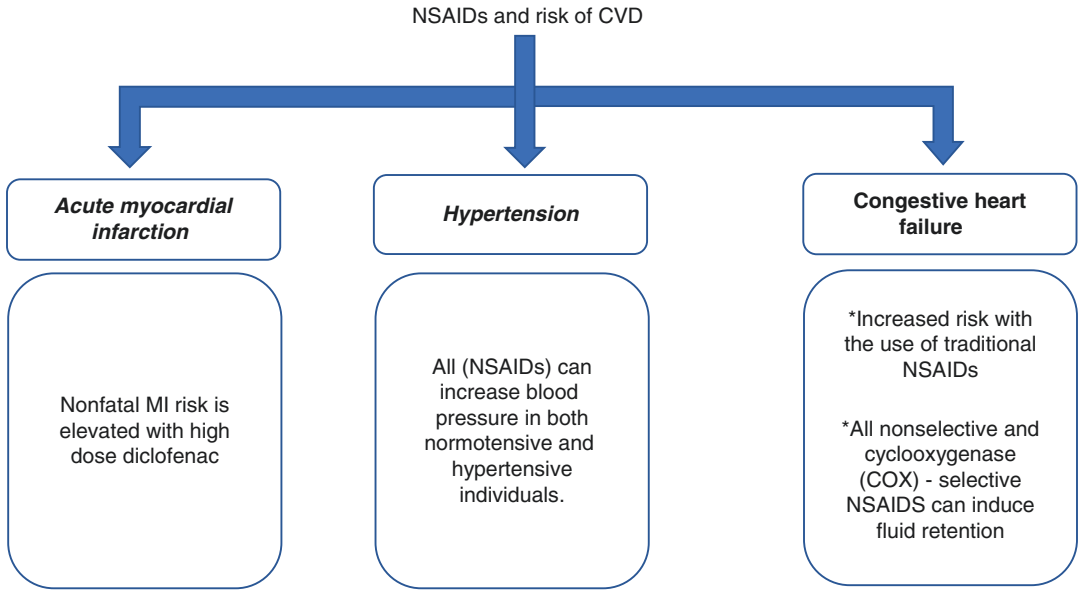

Fig. 16.1 NSAIDs and risk of CVD

with TNF inhibitors, but this remains controversial.

- The cardiovascular benefit of TNF inhibitors may be limited to patients with RA whose synovitis responds to these agents. Patients whose disease activity was reduced by TNF inhibitor therapy within the first 6 months of treatment had markedly decreased risk of myocardial infarction compared with those who continued to have active disease.
- It was associated with a significant increase in both total cholesterol and HDL with no change in regard to the atherogenic index [150].

16.5.5 Non-TNF Biologic DMARDs

- Rituximab has no significant effect on CVD, with no positive outcome on lipid profile or endothelial dysfunction.
- Tocilizumab is associated with beneficial low CRP after early introduction, but it has unclear worse effect regarding elevation of total cholesterol, LDL [151, 152] when used for years, even though it does not increase CVD events. Tofacitinib is also associated with increased level of LDL [153].

In summary, for the prevention of CAD in rheumatologic diseases, we should do the following:

- Traditional CAD risk factors control.
- Early diagnosis and management of CAD.
- Long follow-up for CAD complications.
- Early diagnosis and management of rheumatologic disease with strict control of the disease activity.

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Appendix 1

Note about tables and figures

*** Diagnostic markers of CVD in rheumatologic disease** (including CAD): we have a table that summarizes the workup needed for the detection of CVD in each group of patients with rheumatologic disease (Table 16.A.1).

*** Management and control of CVD risk factors** (Including CAD): The control and the prevention of the risk factors for CVD and what we also call traditional risk factors for CAD are summarized in Table 16.A.2.

Table 16.A.1 Diagnostic markers of CVD in rheumatologic disease

	Diagnosis of CVD	
AIRDs	Disease	Investigation
RA	MI	• ECG and cardiac enzymes: Mainly troponins and CK MB. • Echocardiogram.
	Congestive heart failure	• Echocardiogram. • Chest X-rays. • CBC, serum electrolytes, BUN, creatinine, liver function test, and fasting blood sugar. • Elevated B-type natriuretic peptide (BNP) levels are not specific for left ventricular systolic dysfunction, and may be reduced by concomitant diuretic and angiotensin-converting enzyme inhibitor therapy, limiting sensitivity [155] • Exercise stress tests.
	Peripheral arterial disease	• Clinical investigation of arterial stiffness to look for incompressibility and obstruction and performing: – PWV: Pulse wave velocity. – PWA: Pulse wave analysis. • Ankle-brachial systolic pressure index (ABI), • Exercise testing (ABI) if rest (ABI) is normal. • Contrast arteriography is the gold standard.
SLE	• Pericardium: Mostly asymptomatic, pericarditis or effusion.	• ECG findings: Diffuse ST-elevation and T-wave abnormalities. • Pericardiocentesis if significant pericardial effusion, fever (to rule out concomitant infections) or failed medical treatment. • Low antinuclear antibodies (ANA), phagocytic cells containing nuclei (LE cells), low complement levels, and immune complexes in effusion.
	Myocardium: Mainly myocarditis	• ECG findings: Prolonged PR intervals, ST and T-wave abnormalities. • Echocardiography. • MRI. • Myocardial biopsy.
	Endocardium and valves	• Echocardiography if a new murmur is detected or changing in cardiac function. • Blood culture and echocardiography if fever or new heart murmur. • Transesophageal Doppler echocardiography produces high-resolution images of the cardiac valves and is superior to transthoracic echocardiography in the detection of valve abnormalities. • Libman-sacks endocarditis is typically asymptomatic. However, the verrucae can fragment and produce systemic emboli, and infective endocarditis can develop on already damaged valves [156]..
	Conduction defects	• Preconception or early prenatal testing for anti-Ro/SSA and anti-La/SSB antibodies and periodic monitoring for the development of heart block in the fetus. .
Systemic sclerosis	Pulmonary arterial hypertension Myocardium	• ECG: Look for tachyarrhythmia. • Chest X-ray. • Doppler echocardiogram: – Rhythm. – Conduction disturbance. – Cardiac chambers and valves (morphology and function). – Pulmonary arterial pressure. • Cardiac pulmonary stress test. • Cardiac catheterization for better diagnosis of pulmonary hypertension. • MRI. • Nuclear studies of myocardial function and perfusion .
AS & PsA	Different CVDs	• Clinical assessment. • ECG. • Cardiac enzymes. • Echocardiogram.

(continued)

Table 16.A.1 (continued)

AIRDs	Diagnosis of CVD	
	Disease	Investigation
APS	IHD	• Clinical assessment. • ECG. • Cardiac enzymes.
	Valvular disease	• Clinical: Asymptomatic regurgitation. • Echocardiogram: Vegetation and marked thickening.
	Pseudo-endocarditis	• Clinical: Fever, murmur, and splinter hemorrhage. • Echocardiogram with the presence of mitral valve nodules and mitral regurgitation. • High APL titer. • Blood culture is negative for infection.
	Peripheral artery disease	• Ankle-brachial index at lower extremities is abnormal.
	DVT	• Clinical assessment. • Duplex ultrasound. • D-dimer for exclusion in low probability cases..
	Intracardiac thrombus	• Not common and misdiagnosed. • Clinical: Angina-like pain. • Exercise test: Positive. • Angiogram: Normal coronary arteries.
Inflammatory myopathies	CVDs are rare	• ECG: Conduction defects and arrhythmia. • Specific marker is the level of cardiac isoform troponin-I. • Creatine kinase (CK)-MB is not a specific cardiac marker, so it is not helpful.
Vasculitis	According to the type	• ECG and echocardiogram. • Contrast-enhanced cardiac MRI. • BNP. • ANCA.

Table 16.A.2 Management and control of CVD risk factors [157]

Health parameters	Maintenance
Dyslipidemia	• Annual lipid profile screening is recommended. • Statin use decreases TC and LDL levels, which lower the risk of cardiovascular events; give if it is indicated. • In high-risk patients who use statins, the goal of LDL-C level: < 70 mg/dL. .
DM	• Monitoring of blood glucose (fasting and random). • Annual screening of hemoglobin A1c in patients with active disease and chronic corticosteroid use. • Treatment of DM as guidelines.
Hypertension	• Early blood pressure monitoring when there is a risk from medication. • Regular monitoring of blood pressure and start treatment as guidelines. • Control level of blood pressure, the goal: <140/90 mmHg.
Smoking	• Cessation is strongly recommended to improve disease activity and therapy effectiveness of RA, and its benefit on lowering CVD events is probable.
Obesity	• Regular monitoring of BMI. • Waist to hip ratio. • Encouragement of healthy diet. • Body mass index goal: 18.5–24.9 kg/m^2. • Waist circumference goal: Women 35 inches (89 cm), men 40 inches (102 cm).
Physical activity	Goal: At least 30 min per day, minimum 3–4 times a week

*** Preventive tips for using common medications in rheumatologic disease:** As we recognize the numerous and various medications that are being used in the management of rheumatologic diseases that are being associated with adverse effects on the CV system and CAD so here we tried to have a summary of preventive tips to use while using them in those patients as shown in Table 16.A.3.

* The use of **aspirin:** there are no specific rules for its use in rheumatologic disease as the rules applied in those patients are the same as the general population. Figure 16.2 is a simple diagram showing the approach to use it.

* The use of **statin**s: There are no specific rules for its use in rheumatologic disease as the rules applied in those patients are the same as the general population. We have here a simple diagram based on the latest guidelines from the American Heart Association (AHA) that was released in 2013 (Fig. 16.3).

Table 16.A.3 Medications of rheumatologic disease and the preventative measures

Medication	Disease	Effects on CVD
Glucocorticoids	RA SLE	• Reduced doses will lower the risk of CAD. • Calcium and vitamin D should be given. • Since the risk is dose-dependent, it is a must to keep the duration of using steroids as short as possible and the dose as minimal as possible. • A close surveillance of blood pressure and modification of antihypertensive regimens is recommended when the patient is hypertensive and is receiving moderate to high doses of GCs. • Increased cardiovascular disease was associated with glucocorticoid use at doses ≥7.5 mg/day of prednisone or its equivalent [158].
Methotrexate	RA	• Folic acid supplementation to correct homocysteine level. • It is advisable to continue using it as indicated as a DMARD. • Its CVD benefit is not fully approved, but a definitive result will come out from further studies which may prove the hypothesis of CVD as an inflammatory mechanism, and it can be beneficial in chronic CVD management.
TNF blockers	RA AS	• Annual lipid screening is recommended when the risk of lipid disturbance is there. • Inpatients with RA, it is recommended to continue using TNF inhibitors as biologic DMARD therapy. • Anti-TNF biologic (infliximab) is not recommended in patient with NYHA class 3 or 4 cardiac failure with an ejection fraction of ≤50% due to a worsening effect of infliximab on the cardiac function. • Check pulse wave velocity and analysis for possible transient improvement of vascular morbidity. • TNF blockers may decrease CVD involvement and atherosclerosis in ankylosing spondylitis, but no strong evidence.
Non-TNF	RA	• More, larger studies are needed to clear the risky-beneficial nature of these medications and their effects over the CVD.
NSAIDS	RA AS	• Effective for pain management, but it is wise to be cautious about the cardiovascular side effects of NSAIDs especially in patients with high CVD risk factors. • Extra caution regarding the dose, risk factors, and comorbidity status.
Statins	SLE	For primary and secondary prevention (as evident by the last AHA guidelines 2013) [159] • Anti-inflammatory effect. • Lowering LDL-C and CRP. • Antithrombotic effect. • Immuno-modulating effect.
Aspirin	SLE APS	Should be indicated in SLE if no contraindication: • History of CAD. • Ongoing risk factors like HTN, DM, high cholesterol, and smoking. • Prophylactic low-dose aspirin in patients with thrombosis-free and -positive APL.

(continued)

Table 16.A.3 (continued)

Medication	Disease	Effects on CVD
Anticoagulation therapy	APS	• In patients with first event of venous thrombosis (INR: 2.0–3.0). • In patients with recurrent venous or arterial thrombosis, give intensive therapy (INR: 3.0–4.0). • It is recommended to give antiplatelet therapy with anticoagulation therapy (controversial).
Antimalarial agents	SLE APS	• Anti-inflammatory effect. • Anticoagulant effect. • For lipid profile improvement. • Prophylactic dose in patients with thrombosis-free positive APL in APS.
Cyclophosphamide	SLE	• It is the standard treatment of severe SLE with organ involvement, e.g., myocarditis. • It is recommended to give pulse steroids and pulse cyclophosphamide.
Calcium channel blockers	SSc	• Nifedipine and Diltiazem use with caution as they are contraindicated in MI and angina as they are causing reflex tachycardia.
Endothelin receptor antagonist	SSc	• Bosentan for relieving dyspnea and improvement of 6 min walk test (6MWT) [160].
Prostacyclin analogues	SSc	• Iloprost for widening narrow blood vessels and better blood circulation. • Ventavis inhaled solution for stage 3 or 4 pulmonary hypertension.
Sidenafil	SSc	• For improvement of hemodynamics .

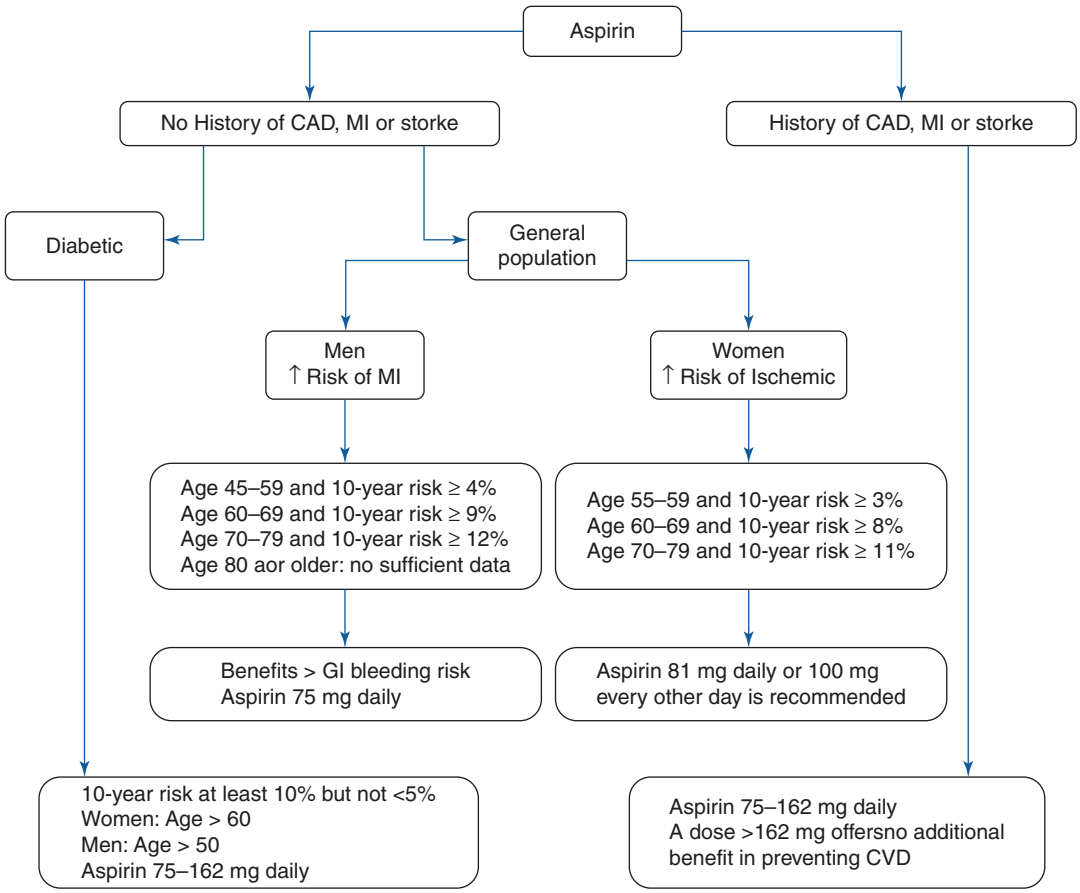
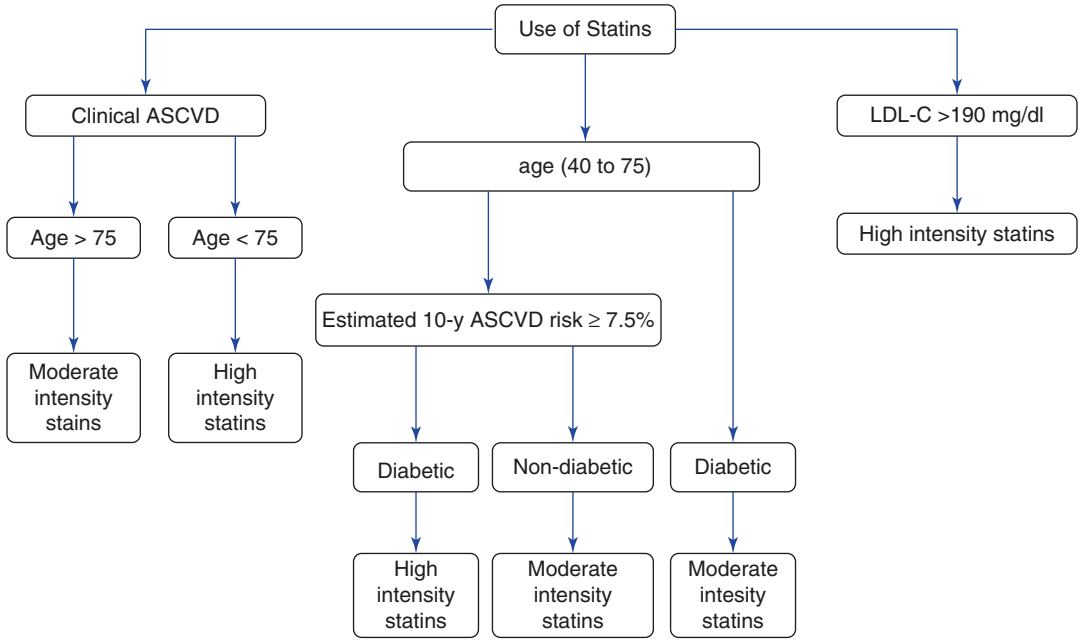


Fig. 16.2 The use of aspirin for primary and secondary prevention of CAD [161]



High Intensity Statins Therapy
- Atorvastatin 40–80 mg
- Rosuvastatin 20–40 mg

Moderate Intensity Statin Therapy
- Atorvastatin 10–20 mg
- Rosuvastatin 5–10 mg
- Simvastatin 20–40 mg
- Pravastatin 40–80 mg
- Lovastatin 40 mg
- Fluyastatin XL 80 mg
- Fluyastatin 40 mg
- Pitavastatin 2–4 mg

Fig. 16.3 The use of the statins for management of CAD [159]

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Gestational Rheumatology

17

Hanan Al-Osaimi and Areej Althubiti

17.1 Introduction

There are changes that occur in the maternal organ systems due to increased demands of pregnancy. Most of the rheumatic disorders occur in the reproductive age group. The hormonal changes that occur during pregnancy may mimic the signs and symptoms of rheumatic disorders thereby making the diagnosis difficult. Rheumatological disorders need to be diagnosed and treated at least 6 months before the onset of pregnancy; otherwise they may have considerable effect on the prognosis of the disease. This is particularly evident in cases of SLE and antiphospholipid antibody syndrome. Therefore, pregnancy is a crucial issue that needs to be clearly addressed in details in all female patients in the reproductive age group having some of the rheumatological disorders.

There are two concerns in these patients. The first one is the effect of the disease activity on pregnancy, and the second is the influence of pregnancy on the disease. That explains why pregnancy should be planned carefully at least 6 months of remission before attempting pregnancy. This is supported with close follow-up for the disease activity during pregnancy. Therefore, managing pregnant patients with rheumatic disease can be very challenging. The simple explanation is the combination of aggravation of disease by pregnancy, the aggravation of pregnancy by disease, and the use of special medications in pregnancy. A successful pregnancy requires achievement of multiple biological steps from "conception, embryogenesis, placental and fetal development, maternal-fetal communication to labor and delivery" [1].

17.2 Objectives

By the end of this chapter, you should be able to:

1. To discuss the physiology of pregnancy.
2. To discuss systemic lupus erythematosus flare manifestations and management during pregnancy.
3. To diagnose and manage antiphospholipid syndrome during pregnancy.
4. To discuss neonatal lupus erythematosus pathophysiology and management.
5. Review management of other common rheumatologic diseases during pregnancy.

17.3 Physiology of Pregnancy

There are added burden by the mother, the fetus, and the placenta during pregnancy. All of these should be met by the mother's organ systems.

H. Al-Osaimi (✉)
King Fahad Armed Forces Hospital,
Jeddah, Saudi Arabia

A. Althubiti
Saudi Commission for Health Specialties,
Riyadh, Saudi Arabia

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Thus, there are certain cardiovascular, hematological, immunological, endocrinal, and metabolic changes that happen in the mother in normal pregnancy.

17.3.1 Changes in Cardiovascular System

The most important physiological changes that happen in pregnancy are the increase in cardiac output and retention of sodium and water. These changes result in significant increase in blood volume and reduction in systemic vascular resistance and blood pressure. Such changes start as early as fourth week of pregnancy, reaching their highest level during the second trimester, and then remain relatively constant until delivery. As the increase in the red cell volume is proportionately much less than the increase in plasma volume, there is hemodilution (physiological anemia) by the end of second trimester [2].

The increased level of plasma erythropoietin is responsible for balanced increase in the red cell mass. The physiological anemia that happens in pregnancy reduces the cardiac work load and helps for enhanced placental perfusion by decreasing the blood viscosity. It also decreases the risk of thrombosis in uteroplacental circulation. The increased blood volume also defends against the usual blood loss in the peripartum period.

Cardiac output increases by 30–50% during normal pregnancy. This is as a result of increase in the preload owing to rise in blood volume, decrease in afterload due to decrease in systemic vascular resistance, and increase in the maternal heart rate. The cardiac output and systemic vascular resistance steadily return to non-pregnant levels over a period of 3 months postpartum [3].

17.3.2 Hematological Changes

The total white cell count is increased up to 40%, and the platelet count gradually declines till the term, while they do not fall below 100,000/cu mm. This is expected as a result of dilutional effect, increased destruction, and turnover [4].

17.3.3 Changes in Coagulation System

Pregnancy is linked with changes in several coagulation factors that result in a 20% reduction of prothrombin and the partial thromboplastin times creating a hypercoagulable state. This acts as a double-edged sword, both for protection (e.g., hemostasis contributing to reduced blood loss at delivery) and increased risk (e.g., thromboembolic phenomenon). Venous thrombosis in pregnancy happens in approximately 0.7 per 1000 women and is three- to fourfold higher in the puerperium than during pregnancy. The risk is amplified in women with underlying inherited thrombophilia (e.g., factor V Leiden or the prothrombin gene mutation) [5].

17.3.4 Changes in the Maternal Immune System

The local modification of the maternal immune system is accountable for the successful coexistence between the mother and the fetus/placenta expressing both maternal (self) and paternal antigens. The cell-mediated adaptive immune responses are reduced, bypassed, or even eliminated. However, the antibody-mediated immunity is reformed, while the natural immunity (innate immunity) remains intact which continues to offer the host defense against infection. During insemination, the transforming growth factor β1 (TGF-β1), found in the seminal fluid, excites the production of granulocyte-macrophage colony-stimulating factor (GM-CSF) and enrolment of inflammatory cell infiltrates in the uterus [6].

During implantation of the fertilized ovum, the majority of the lymphocytes infiltrating the decidua are typical uterine natural killer (NK) cells which are CD56++, CD16-, and CD3- and express various receptors. Uterine decidua and the fetoplacental unit produce large number of cytokines which contribute to shift of the immune response from T helper 1 (Th1) to T helper 2 (Th2) response. While there are many specific mechanisms for immunological protection

against the fetus, the most essential one is altered HLA expression [7].

17.3.5 Changes in the Endocrine Glands

Maternal changes in pregnancy involve the hypothalamus, pituitary, parathyroid, adrenal glands, and ovaries to adapt the needs of the fetal-placental-maternal unit. The hypothalamus still controls much of the endocrine system through hypothalamic-pituitary axis, directly affecting the function of the abovementioned endocrine organs.

(a) **Hypothalamus:** These hormones released from hypothalamus are available in high concentrations in portal circulation where they are biologically active. The circulating concentrations of many of these hormones are also raised in pregnancy due to placental production of identical or variant hormones [8].

The most important changes are seen in the following hormones:

Gonadotropin-releasing hormone (GnRH) level increases during pregnancy. The main source is the placenta and exerts a main role in placental growth and function. Corticotropin-releasing hormone (**CRH**) from hypothalamus is engaged in stress response in pregnancy and delivery. It is also released by the placenta, chorionic trophoblasts, amnion, and decidual cells. The placental CRH do not stimulate adrenocorticotropic hormone (ACTH) secretion but helps in induction of labor. Besides CRH the gestational tissues also secrete urocortin which shares the same function as that of placental CRH. The urocortin-2 also controls the tone of vascular endothelium which also plays a major role in parturition [9].

(b) **Pituitary Gland:** Anterior lobe of pituitary gland expands threefold during gestation because of hypertrophy and hyperplasia of lactotrophs. It needs minimum 6 months after delivery to return to normal size. Follicle-stimulating hormone (FSH), luteinizing hormone (LH), and thyroid-stimulating hormone (TSH) levels are decreased, while growth hormone (GH), ACTH, and prolactin (PRL) levels are increased mainly due to the synthesis by the placenta.

The serum PRL concentration increases due to increase estradiol during pregnancy, reaching the maximum at delivery to prepare the breast for lactation. The plasma sodium concentration drops by 5 meq/L due to resetting of osmoreceptors as a result of increased levels of human chorionic gonadotropin (HCG). Oxytocin level increases steadily during gestation and is involved in parturition and lactation. There is increase in thyroxin-binding globulin (TBG) but TSH (along with triiodothyronine (T3) and thyroxin (T4)) is in the normal range [10].

The renin-angiotensin-aldosterone system is stimulated during pregnancy due to reduction in peripheral vascular resistance and blood pressure, but there is a gradual decline in vascular responsiveness to angiotensin II. The aldosterone level increases by four- to sixfold, and the blood pressure usually reduces by 10 mmHg. Relaxin, a vasodilator factor produced by the placenta and aldosterone, is critical in sustaining sodium balance in the setting of peripheral vasodilatation. During pregnancy there is an increase in the levels of maternal and placental ACTH, cortisol-binding protein, atrial natriuretic peptide (ANP), plasma rennin activity (PRA), sex hormone-binding protein, and testosterone levels [11].

17.4 Systemic Lupus Erythematosus

17.4.1 Introduction

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease occurring in young women in their childbearing age. It is one of the most common rheumatological conditions encountered in pregnancy with considerable influence on its outcome. It mainly affects the skin, joints, blood, kidney, and other organs. Pregnancy can have influence on the disease, and

the disease also has considerable influence on pregnancy.

The annual incidence of SLE is 3 cases per 100,000 population out of which 90% belong to the female gender. Asians and African Americans found to have more severe disease with renal involvement. The thrombotic complications are seen in 10% of these cases [12]. SLE is a hypercoagulable state due to antiphospholipid antibodies and increase in certain procoagulants due to inflammation and platelet hyperfunction. This further leads to thrombogenesis by multiple-hit theory. The factors which increase thrombosis risk also encourage pregnancy loss in lupus.

17.4.2 Influence of Pregnancy on SLE

SLE patients experience different kinds of pregnancy related complications more than non-SLE women. One of the common pregnancy-related complications are pregnancy-induced hypertension (PIH); preeclampsia (blood pressure ≥ 140/90 mmHg after 20 weeks of gestation and proteinuria ≥300 mg/24 hrs), eclampsia (preeclampsia plus seizures), HELLP syndrome (**h**emolysis, **e**levated **l**iver enzymes, and **l**ow **p**latelets), and gestational diabetes [13].

17.4.3 Lupus Flares

The risk of lupus flare is enlarged if the woman has had active lupus in the last 6 months of pregnancy. Therefore, quiescent disease at the onset of pregnancy offers optimum protection against the occurrence of flare during pregnancy [14]. Lupus may flare through any trimester of pregnancy or postpartum period. The flares are usually mild mainly involving the joints, skin, and blood. Some of the physiological changes of pregnancy can simulate the symptoms of the active disease such as palmar erythema, arthralgia, myalgia, and lower limb edema.

The laboratory data specific for lupus flare as compared to pregnancy data include rising titer of anti-double strand DNA antibodies, presence of red blood cell casts in the urine, positive direct Coombs test, and presence of antiplatelet antibody with thrombocytopenia. Complement levels can be in natural range as complement levels increase during pregnancy due to estrogen-induced hepatic synthesis of complements. Hence, it is important to differentiate lupus flare from pregnancy-related complications and physiological changes of pregnancy [15].

Previous studies have suggested that several factors may increase the risk of preeclampsia in pregnancies complicated by SLE. These factors include preexisting hypertension, renal insufficiency, presence of APS, as well as active SLE [16]. The differentiating features of preeclampsia from lupus nephritis are mentioned in Table 17.1.

17.4.4 Lupus Nephritis (LN)

Lupus pregnancies with long-standing LN are at high risk of spontaneous abortions and increased perinatal and maternal mortality. However, the outcome of pregnancy in patients with stable LN at conception is relatively favorable. Remission in lupus nephritis has been defined as stable renal function, a serum creatinine within the normal range, urinary red cells below 5/high power field, proteinuria below 0.5 g/day, and ideally normal

Table 17.1 Broad guidelines to differentiate lupus nephrites from preeclampsia

Parameter	Active lupus nephritis	Preeclampsia
High BP	Present or absent	Diastolic BP > 90 mmHg
Proteinuria	• >500 mg/24 h if normal baseline • Doubling if >500 mg/24 h at baseline. • Occur before third trimester.	• >300 mg/24 h if normal baseline • Occur during third trimester.
Edema	Present/absent	Present/absent
Active sediment	Present/absent	Absent
Uric acid	Normal or elevated	Elevated
C3, C4	Low	Normal
Anti-ds DNA abs	Rising	Absent

serum complement component 3 (C_3) levels for the last 12–18 months [17]. LN flare can be associated with other findings of active lupus such as serositis, arthritis, and high titers of anti-DNA antibodies. The proteinuria of preeclampsia decreases after delivery but not that of active lupus patient.

17.4.5 Influence of SLE on Pregnancy

SLE patients are as fertile as the overall female population [18]. Reduced fertility rate is seen in patients with active disease on high-dose steroids, patients with proven renal disease, and patients with moderate to severe renal failure. End-stage renal disease resulting from LN can lead to amenorrhea. However, amenorrhea in renal patients may also be because of ovarian failure from cyclophosphamide use or of autoimmune origin [19].

Lupus flares can occur at any time during pregnancy with potential adverse effects on the conception. Lupus flares happen more commonly throughout pregnancy and postpartum period more than in non-pregnant SLE patients. Increase in lupus activity is seen at least in 1/3 cases in pregnancy. Therefore, for a better outcome of lupus pregnancy, it is important to control disease activity and to achieve clinical remission for at least 6 months before pregnancy [20].

Adverse live-birth outcome was significantly correlated with low pre-gestational serum albumin level, elevated gestational anti-dsDNA antibody, and diabetes mellitus. Spontaneous abortion was directly correlated with low levels of pre-gestational serum albumin, positive anticardiolipin IgA, anti-B_2-glycoprotein IgM, and anti-La antibodies. The risk of obstetric complications and maternal mortality is high in patients with active LN associated with preexisting hypertension [21].

17.4.6 Hypercoagulability in SLE

Pregnancy itself is a hypercoagulable state with fetal demise, thrombosis, and preeclampsia being associated with factor V Leiden mutation, prothrombin gene mutation 20210A, and deficiencies of anti-thrombin III, protein C, and protein S [22]. Pregnancy complications in SLE are rather common with maternal hypertensive complications occurring in 10–20%, preterm births in 20%, fetal growth restriction occurring in about 28%, and an average drop in fetal growth weight to around 16%. The increased stillbirth rate in SLE is fourfold greater than the general population [23]. Hence, SLE-specific thrombophilic factors are additive to the background of pregnancy-related hypercoagulability (multiple hits). Collectively, this encourages the occurrence of worse fetal outcomes in lupus.

Hypercoagulability in SLE is due to multiple factors (multiple-hit theory)

(a) Lupus-specific procoagulant factors-APLA (antiphospholipid antibodies).
(b) Other lupus-specific factors include antibodies to factor XII, prothrombin, and annexin V [24].
(c) Lupus nonspecific factors.
(d) Non-lupus-related procoagulant factors.

Chronic inflammation happening in SLE patients contributes to the occurrence of thrombosis. The factors responsible for this state can be summarized into:

1. Elevated or activated procoagulant factors—factors 2, 7, 8, 9, and 10, VWF, and fibrinogen.
2. Reduced anticoagulant factors—protein C, S, antithrombin III.
3. Inhibition of fibrinolysis – PAI-1 elevation, hyperhomocysteinemia.
4. Elevated ESR, CRP, high-sensitivity CRP (HsCRP), complement activation, fibrinogen.
5. Increase in proinflammatory cytokines: IL-1, IL-6, tumor necrosis factor (TNF), and vascular endothelial growth factor (VEGF) [24].

17.4.6.1 Platelet Activation

The prothrombotic effects of antiphospholipid antibodies occur through different mechanisms. They include platelet activation, endothelial cell activation with resultant upregulation of adhesion molecules and production of thromboxane A2, and stimulation of monocytes to make tissue factor.

Ultimately, all this will enhance clotting and vasoconstriction. Tissue factor activates the extrinsic coagulation system, while tissue plasminogen activator (tPA) activates fibrinolysis. Tissue factor pathway inhibitor activity is diminished in SLE, and this is correlated with elevated levels of tissue factor and subsequent hypercoagulability [25].

17.4.6.2 Lupus Platelets

Inflammatory process in SLE leads to release of tissue factor which further leads to platelet activation. The antiphospholipid antibodies bind to activated platelet membrane ultimately leading to hyperfunction of platelets similar to sticky platelet syndrome. Hyperfunction of platelets in SLE is one of the important factors in causation of thrombosis [26].

17.4.6.3 Laboratory Workup

In general, more than basic tests are needed to evaluate the full range of possibly disrupted clotting mechanisms. This involves testing for lupus-specific antiphospholipid antibodies and other hemostatic markers of coagulation. The lupus-specific antibodies include lupus anticoagulant, anticardiolipin antibodies, and anti-β-2 glycoprotein-1 antibodies. These antiphospholipid antibodies are a heterogeneous group of antibodies identified by various laboratory techniques; each of them has some problems with standardization, specificity, interpretation, and quality control [27]. The target antigens for these different antibodies involve prothrombin and negatively charged phospholipids [28].

Apart from antiphospholipid antibodies, a coagulation risk laboratory profile also necessitates to be checked in lupus patients with thrombosis and fetal loss. Such profile includes testing for fibrinogen, factor VII, factor VIII, tPA, PAI-1, plasminogen activity, von Willebrand factor activity and antigen, protein C activity, protein S activity, homocysteine, and high-sensitivity C-reactive protein (Hs-CRP) [29].

17.4.6.4 High-Risk Clinical Scenarios

Selecting SLE patients for a coagulation assessment is well recognized for those with a thrombosis or fetal loss but is not well outlined for those who are at risk but have not yet had an event. Therefore, patients who have had an event should obviously be selected for a coagulation workup. The high-risk scenarios which needed workup are given in Table 17.2.

Table 17.2 High-risk lupus pregnancy

High-risk lupus pregnancy	
Renal involvement	High-dose steroid therapy
Cardiac involvement	Pre-estrogen therapy
Pulmonary hypertension	Pre-tamoxifen therapy
Interstitial lung disease	Pre-organ transplantation
Active lupus disease	Chronic inflammation
Multiple pregnancy	Immobility
Pre-vascular procedures (stent placements, etc.)	Immunosuppressive therapy (cyclophosphamide, methotrexate, etc.)
Extractable nuclear antigens (Ro, La)	Multiple antiphospholipid antibodies

17.4.6.5 Management of Lupus Pregnancy

Ideally, management of lupus pregnancy should begin before the onset of pregnancy. Thus, at preconception counseling, the physician not only estimates the risk profile of the patients but also reviews their drugs. The aim is to avoid known teratogenic drugs, to discontinue certain medications, and to initiate other drugs. This had been the golden goal to protect the mother and fetus from adverse effects of these medications. Hence, it is important to monitor the mother for at least 6 months before attempting conception. This is to assure a better outcome in lupus pregnancy.

There is a need for different subspecialists like rheumatologist, obstetrician, nephrologist, and neonatologist, to come together in managing such high-risk lupus pregnancy with close monitoring.

A) Management Issues

Once results are positive for pregnancy, we should have a baseline assessment of the disease activity, severity of the disease, and major organ involvement.

- Prenatal care visits: Every 4 weeks up to 20 weeks, then every 2 weeks until 28 weeks, and then weekly until delivery [Table 17.3].

Table 17.3 Guidelines in the assessment of pregnant patients with lupus

First trimester	• Baseline CBC, electrolytes, serum creatinine, liver enzymes, uric acid.
	• Fasting blood glucose, fasting lipid profile if at high risk, for example, if patient is nephritic or on steroids.
	• Normal antenatal checkup.
	• ANA, anti-dsDNA, anti-Ro and anti-La, antibody titers.
	• Complements levels (C_3,C_4,CH_{50}).
	• Anticardiolipin antibodies, lupus anticoagulant, and β_2 glycoprotein.
	• Urinalysis, 24-hour urine collection for measurement of protein and creatinine clearance.
Second trimester	• Baseline laboratory studies.
	• Anti-dsDNA.
	• Complement levels (C_3, C_4, CH_{50}), urinalysis.
	• Obstetric ultrasound: Every 4 weeks from 20 weeks of gestation until delivery "to monitor fetal growth".
	• Mother with positive anti-Ro and/or anti-La antibodies, serial fetal echocardiography between 16 and 18 weeks of gestation.
Third trimester	• Repeated laboratory studies.
	• Urinalysis, 24-hour urine protein collection if proteinuria is present.
	• Weekly fetal non-stress test (NST) and/or biophysical profile (BPP) scoring from 28 weeks gestation.
	• Fetal Doppler ultrasonography to be done in presence of intrauterine growth restriction.
Each visit	• Careful blood pressure measurement.
	• Urine dipstick for proteinuria.

Owing to the advancement of treatment interventions, more and more women with SLE are able to become pregnant. Pregnancy outcomes have improved noticeably over the last 40 years, with a decrease in pregnancy loss rate from a mean of 43% in 1960–1965 to 17% in 2000–2003 [30].

Pregnant patients with SLE on immunosuppressive therapy should receive prophylaxis for infection (including antibiotics for invasive procedures) and immunization with influenza and pneumococcal vaccine.

Other goals to achieve in managing a lupus pregnancy are:

1. Checking for high-risk clinical settings.
2. Performing coagulation risk lab profile in high-risk cases.
3. Assessment of the number and degree of procoagulant hits.
4. Prevention of thrombosis and adverse fetal outcomes.
5. Treatment of active lupus disease.
6. Treatment of hypercoagulable state.
7. Ensuring safety of medications used in treatment of the disease.

Treatment of hypercoagulable state:

1. Thromboprophylaxis for acute high-risk conditions.
2. Chronic prophylaxis for thrombosis prevention.
3. Full treatment dose anticoagulation therapy for thrombosis.

Thromboprophylaxis is controversial for patients with positive antiphospholipid antibodies (aPLs) but without any clinical history of thrombosis. However, evaluating risk of thrombosis by evaluating the multiple hits with a full thrombophilia profile would provide good support for deciding on intensity and type of thromboprophylactic treatment. For example, in pregnant SLE patients who are positive for lupus anticoagulant, it is recommended to use low-dose molecular weight or unfractionated heparin during pregnancy because neither can cross the placenta [31].

Treatment for acute arterial or venous thrombosis consists of an initial course of unfractionated or low molecular weight heparin followed by long-term treatment with warfarin to keep the international normalized ratio (INR) between 2.0 and 3.0. Heparin-type drugs or, more recently,

one of the newer thrombin or factor Xa inhibitors can be used. For arterial thrombosis (stroke, myocardial infarction), addition of antiplatelet agents (low-dose aspirin, clopidogrel 75 mg) may be helpful, particularly if platelet hyperfunction is present [32]. Treatment for antiphospholipid syndrome (APS) is detailed in the section of antiphospholipid syndrome.

B) Treatment of Active Lupus Activity

SLE is common in women in the childbearing age. Physicians should be competent in the safe use of medications at preconception, conception, and during lactation. They should also be competent in addressing the effects of certain drugs on infants. The Food and Drug Administration (FDA) has a classification system for pregnancy risk. The pharmacological management of SLE could be puzzling as it has an unpredictable clinical course, with different organ system involvement and the absence of clear understanding of disease pathogenesis [33].

As hypertensive disorders of pregnancy are the leading cause of maternal mortality and morbidity, the target blood pressure of less than 140/90 is to be achieved. The safer antihypertensive drugs in pregnancy based on the evidence relate to parenteral hydralazine or labetalol and oral labetalol, nifedipine, or methyldopa [34]. Treatment with low doses of aspirin during pregnancy would be indicated in women with SLE, APS, hypertension, history of preeclampsia, and renal disease. Low dose of aspirin is safe throughout pregnancy. Women who took aspirin had a significantly lower risk of preterm delivery than those treated with placebo, but there is no significant difference in perinatal mortality [35].

NSAID should be used in the lowest effective dose and should be withdrawn before 8 weeks of expected date of delivery [36]. Nevertheless, because of the shared character of inhibition of prostaglandin synthesis, adverse effects like constriction of the ductus arteriosus in utero, renal dysfunction in the neonate, persistent pulmonary hypertension, increased maternal blood loss, and prolongation of pregnancy and labor are all possible when administered to pregnant patients.

Hydroxychloroquine (HCQ) is now considered an extremely essential therapeutic choice in the treatment of lupus. These drugs are highly effective for discoid lupus erythematosus (DLE) cutaneous lesions. HCQ improves photosensitive skin lesions and prevents lupus flares [37]. Studies have confirmed that HCQ can preclude renal and central nervous system lupus. It also exerts the role of a prophylactic agent against some of the major comorbidities of SLE and its treatment, namely, hyperlipidemia, diabetes mellitus, and thrombosis [38]. More recently, chloroquine and HCQ have been shown to improve survival in a cohort of 232 SLE patients after adjusting for patient characteristics and disease activity [39]. It has been recently suggested that HCQ may affect TLR9 (toll-like receptor 9) activation and IFN-alpha production. From all of these perspectives, this drug is now considered an extremely essential therapeutic choice in the management of lupus.

Steroids are used in pregnant SLE, and safety is not a major concern for their use in pregnancy based on the clinical indication. But one needs to look into the maternal morbidity it causes like maternal hypertension, gestational diabetes, infection, weight gain, acne, and proximal muscle weakness. Consequently, close monitoring is essential with the use of the lowest possible dose of corticosteroid needed to control disease flare along with vitamin D and calcium supplement [40].

There are few immunomodulator drugs that are used in SLE patients such as cyclophosphamide, methotrexate, mycophenolate mofetil, cyclosporine, **azathioprine**, and rituximab. The use of these drugs needs a thorough discussion with the pregnant lupus patient before starting them. As most of these drugs are classified by FDA as pregnancy risk category B and few as category X or D, they need to be shifted to azathioprine which is found to be safe in pregnancy [41]. Plasmapheresis and intravenous immunoglobulin (IVIG), the other two modalities of treatments used in lupus patients, are safe in pregnancy, but they are costly with very few indications.

C) Delivery

SLE is not an indication for delivery by cesarean section, and one should allow for vaginal delivery as much as possible [42]. There should be a team approach to the pregnant women with SLE. This is to guarantee a safe vaginal delivery and allow performing a cesarean section for obstetric indications only. The indications for cesarean section are the same as in other conditions.

D) Puerperium

The optimum management does not stop with the birth of a healthy baby. Actually, postpartum period should be addressed as high risk for pregnant lupus patients with several possible complications. The mother can suffer a lupus flare. Several studies have confirmed the postpartum period is specifically high risk for increased lupus activity. A close surveillance in the first 4 weeks after delivery is thus warranted, especially in patients with recent activity or with a previous history of severe disease. However, no specific prophylactic therapy, such as increasing the dose of steroid, is recommended. Thromboembolic risk is also high during the puerperium [43].

SLE is a chronic multisystem disease occurring in young women in their childbearing age. Therefore, the collaboration of rheumatologists and obstetricians who are experienced in high-risk pregnancies management is essential for managing pregnant patients with SLE. The aim is to have successful outcomes for both the disease and the pregnancy. Some manifestations of normal pregnancy can be misinterpreted as signs of lupus activity. Thus, understanding of pregnancy and lupus interaction has resulted in better approaches of monitoring and treating this particular clinical condition.

17.5 Antiphospholipid Syndrome in Pregnancy

17.5.1 Introduction

APS or Hughes' syndrome is a multisystem autoimmune disorder with hypercoagulable state characterized by thrombosis (arterial, venous, or small blood vessels) or some obstetric complications (recurrent spontaneous abortions, stillbirth, preterm delivery, or severe preeclampsia) in the presence of antiphospholipid antibodies [44]. In 50% of the cases, it is primary (PAPS), and in the rest, it is secondary (SAPS) to any autoimmune disease particularly SLE.

APS is the most common cause of acquired thrombophilia and is a known risk factor for the development of deep vein thrombosis (DVT) with or without pulmonary embolism, new strokes in individuals below the age of 50, and recurrent fetal loss [45]. APS is seen in 0.5% in the general population and 1–5% in healthy women of childbearing age. The antiphospholipid antibodies are present in 30–40% of SLE patients, and up to a third of these patients develop clinical manifestations of APS, especially venous or arterial thromboses. Majority of these patients (85–90% of the cases) are seen in the females in the reproductive age group [46].

17.5.2 Diagnostic Criteria

The 1999 Sapporo criteria is replaced by revised Sydney criteria in 2006. Since then many research work was done, but the criteria remain the same as in 2006 [47].

The clinical criteria include any of the followings:

1. Vascular (arterial, venous, or small vessel) thrombosis excluding superficial thrombosis.
2. Pregnancy morbidity.
   (a) ≥1 unexplained deaths of a morphologically normal fetus at or beyond ≥10 gestational weeks (GW)
   (b) ≥1 premature births of a morphologically normal neonate ≤34 GW due to severe preeclampsia, eclampsia, or severe placental insufficiency
   (c) ≥3 unexplained consecutive spontaneous abortions ≤tenth GW (Excluding anatomic or hormonal defects or maternal/paternal chromosomal causes).

The laboratory criteria include the presence of any one of the three antibodies on two occasions at least 12 weeks apart. They are lupus anticoagulant (LA), anticardiolipin antibodies (aCL-IgG or IgM), or anti-β_2-glycoprotein 1 antibody (aβ_2GP1-IgG or IgM). LA is to be tested 2–3 weeks after discontinuation of warfarin.

One clinical criteria and one antibody test are required for diagnosis of APS.

The aPL should be in medium or high titers at least tested twice >12 weeks apart. The strict objective criteria laid down for each clinical criterion should be fulfilled for the diagnosis of APS. aPLs are not only seen in APS (primary or secondary) but also in other diseases (syphilis, Lyme disease, CMV, EBV, HIV, HCV, and varicella) or patients on phenothiazines or even in normal general population. Therefore, the tests for aPL need to be repeated and established that these aPLs are persistently elevated and in medium or high titers to separate the APS patients from other causes of elevated aPL [47].

17.5.3 Pathogenesis of APS

Thrombotic and non-thrombotic mechanisms (inflammatory complement mediated) were proposed to explain the clinical manifestations in obstetric APS. In the last decade, the non-thrombotic mechanism proved to be the most important one causing cellular activation of endothelial cells, neutrophils, monocytes, and platelets leading to upregulation of tissue factor (TF) ultimately activating the coagulation pathway [48].

Obstetric APS complications are explained by three mechanisms:

17.5.3.1 Thrombosis (Thrombosis of Vessels and Placenta)

The main target antigens described in patients with APS include anti-β2GP1/cardiolipin, prothrombin, and annexin V which accounts for more than 90% of antibody-binding activity. The other targeted antigens are thrombin, protein C, protein S, thrombomodulin, tissue plasminogen activator, kininogens, prekallikrein, factor VII/VIIa, factor XI, factor XII, complement component C4, heparan sulfate proteoglycan, heparin, and oxidized low-density lipoproteins [49].

Negatively charged phospholipids exposed on the outer side of cell membranes attract the main autoantigens. This is happening excessively under special circumstances such as injury, apoptosis (e.g., endothelial cell), or after activation (e.g., platelets) [49]. The aPL acts on the clotting regulatory proteins like annexin A5, prothrombin, factor X, protein C, and plasmin, thereby promoting thrombosis [50]. Anti-β2GP1 disrupts the anticoagulant annexin A5 shield on trophoblast and endothelial cell monolayers causing a procoagulant state which subsequently leads to infarction and thrombosis of the placenta [49]. The activated platelets by aPL lead to increased expression of GPIIb/IIIa followed by synthesis of thromboxane A2 thereby causing a procoagulant state [51].

17.5.3.2 Defective Placentation

Defective placentation is either due to impairment of invasion of trophoblast or inhibition of endometrial angiogenesis. Anti-β2GP1 is the most important antibody responsible for this mechanism. This antibody directly binds to the maternal decidua causing exposure of the cell membrane of the syncytiotrophoblast followed by injury, apoptosis, inhibition of proliferation, and formation of syncytia [52]. This results in defective secretion of growth factors and decreased production of human chorionic gonadotropin (HCG), thereby causing impaired invasion of trophoblast [52]. The aPL binds to human endometrial epithelial cells (HEEC) on maternal side inhibiting angiogenesis [53]. Endometrial angiogenesis and decidualization are fundamental prerequisites for successful implantation and placental development.

17.5.3.3 Inflammation

A physiological development of pregnancy requires a fine regulation of the maternal immune response during implantation of embryo. Acute inflammatory events are recognizable causes of adverse pregnancy outcomes through proinflammatory mediators, such as complement, tumor

necrosis factor-alpha (TNF-alpha), and chemokines [54].

The aPLs induce an inflammatory response leading to compliment activation (both classical and alternate pathways with excessive generation of C3a and C5a), activation of endothelial cells and monocytes, upgrading of TF and release of inflammatory mediators like intracellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM), selectins, TNF-alpha, and interleukins (ILs) resulting in poor pregnancy outcome [55]. A new probable mechanism of aPL-mediated fetal loss linking TF and complement activation has been recently explained. TF, best known as the primary cellular initiator of blood coagulation, also contributes to different biological processes. Although APS is a thrombophilic disorder, it needs a triggering factor popularly known as "second hit" (inflammation, tobacco, estrogens, etc.) to complete the cascade of thrombosis [56].

PAPS is a hereditary condition without a known cause and more often seen in patients with genetic marker HLA-DR7. SAPS is secondary to a known autoimmune disease, out of which the commonest is SLE. Other diseases where it could also be seen are rheumatoid arthritis, scleroderma, Sjogren's syndrome, Behcet's disease, psoriatic arthritis, and temporal arteritis. It is also common in individuals with genetic markers: HLA-B8, HLA-DR2, and HLA-DR3, and it is also seen more in blacks, Hispanics, and Asians [57].

17.5.4 Treatment

17.5.4.1 Low-Dose ASA (LDA): Either Alone or Combined with Heparin

Pregnant women with aPL positivity should be stratified in order to administer the optimal treatment. The recommended treatment of established APS in pregnancy generally consists of aspirin combined with heparin. LMWHs are at least as effective as unfractionated heparin and are safer [58]. The rationale of this combination is that aspirin may inhibit aPL-mediated hypercoagulopathy in the intervillous space of the placenta. Heparin on the other hand may prevent aPLs from interfering with cytotrophoblast migration and promote blastocyst implantation in addition to prevention of venous thrombosis [59].

Prophylaxis and treatment of pregnancy with positive aPLs are shown in the flow chart (Fig. 17.1).

17.5.4.2 Aspirin/Heparin-Resistant APS (AHR-APS)

At least 20% of the patients do not respond to the recommended treatment, and there is no approved treatment for this group of patients. Nevertheless, since recurrence of thrombotic events occurs despite the therapy and thrombosis cannot account for all of the histopathological findings in placenta from women with APS, other suggested mechanisms of reproductive impairment were expected to be involved [60] in obstetrical APS. The most essential mechanism for heparin to protect placenta in APS emerges to be its ability to prevent the binding of aPL antibodies to trophoblast cells. Recent studies showed that heparin also acts by inhibiting the endometrial angiogenesis and now several trials go on to demonstrate the beneficial effects of neutralizing antibodies by using synthetic peptides using β2GPI epitopes [61].

The AHR cases, which are approximately 20%, need to be approached differently. If they are resistant to conventional treatment of aspirin and heparin (unfractionated), it is better to give LMWH, particularly tinzaparin, which is found to be more effective or switch to fondaparinux with vitamin D supplements. If still not effective, the next step is to add high-dose HCQ (400–800 mg/day) or low-dose prednisolone (10–15 mg/day). Further resistance is counteracted by adding prednisolone to HCQ. If it is found still to be ineffective, then add pentoxifylline or IVIG in order for the treatment to be more effective.

Apart from these drugs, there are others which are being tried in resistant cases of APS. These include the combination of antiplatelet agents like aspirin and dipyridamole (adenosine uptake inhibitor), rituximab, homocysteine, direct thrombin inhibitors (dabigatran), oral direct fac-

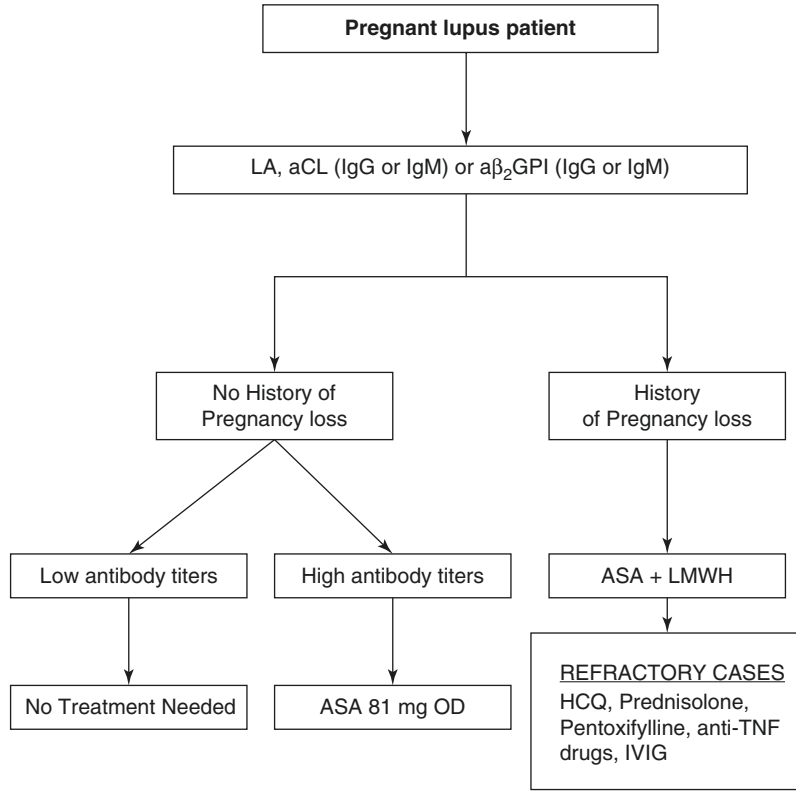

Fig. 17.1 Flow Chart for Management of Aps Pregnant Patient (R. Handa, 2006) (aCL=anti-cardiolipin antibody; LA=lupus anticoagulant; αβ2GP1=anti-β2 – Glycoprotein 1 antibody; HCQ=Hydroxy Choloroquin; anti-TNF drugs = Anti-Tumor Necrotic Factor drugs; IVIG=Intravenous Immunoglobulin)

tor Xa inhibitors (rivaroxaban or apixaban), dilacept (an adenosine uptake inhibitor, similar to dipyridamole) [62], defibrotide (a single-stranded DNA derivate), and histone deacetylase inhibitors which act to inhibit endothelial or monocyte TF expression [63].

17.5.5 Conclusion

APS is a preventable and treatable thrombophilic multisystem autoimmune disorder causing two clinically important manifestations, namely, thrombosis and obstetric complications like recurrent consecutive spontaneous abortions, stillbirths, premature deliveries, and pregnancy-induced hypertension. It is a commonly prevalent disorder which needs high index of suspicion to diagnose early and offer prophylactic and therapeutic management. The cornerstone of management is low-dose aspirin with or without heparin based on the popular theory of thrombosis. Recently inflammatory theory is gaining more importance, and accordingly management by drugs other than aspirin with heparin seems to play a prominent role in the future. However, this requires well-designed double-blind placebo-controlled randomized trials.

17.6 Neonatal Lupus Erythematosus

17.6.1 Introduction

Neonatal lupus erythematosus (NLE) or neonatal lupus syndrome is a rare syndrome seen in 1–2% of neonates with autoantibodies to SSA/Ro, SSB/La, and/or U1 RNP passively transferred transplacentally from the mother. Such a mother is either asymptomatic or having manifestations of SS, SLE, or other systemic rheumatic disease. NLE is distinguished by cutaneous, cardiac, or rarely both clinical manifestations.

17.6.2 Pathogenesis and Clinical Features

The skin manifestation is appreciated at least in 30% of these patients. This may present in the form of periorbital annular erythematous plaques later spreading to other areas of the face, scalp, trunk, and extremities. It is non-scarring and non-atrophic and usually transient lasting for days to months. The cardiac manifestation is seen in up to 60% of the patients. It is mainly in the form of complete congenital heart block (CHB). This is irreversible and associated with cardiomyopathy in at least 10% of the cases. CHB is also associated with higher morbidity and mortality. Almost all the patients with cardiac lupus require permanent pacemaker. The recurrence rate of NLE is as much as 25% in the following pregnancies. There has been better understanding of etiopathogenesis of the disease in the recent past due to rapid development in field of medicine [64].

NLE is presumed to result from transplacental passage of maternal anti-SSA/Ro and/or anti-SSB/La autoantibodies. These autoantibodies enter the myocardial cell resulting in exaggerated apoptosis. This leads to expression of these antibodies on the surface of the cardiocyte. It is postulated that resident cardiocyte participates in physiologic clearance of apoptotic cells. However, clearance is now inhibited by opsonization through these maternal autoantibodies. This results in accumulation of these apoptotic cells promoting inflammation and stimulating macrophages. Consequently, these macrophages secrete cytokines mainly transforming growth factor-beta (TGF-β) that stimulate fibroblast proliferation. Ultimately, this leads to fibrosis of the conduction system (causing CHB) or myocardium (leading to cardiomyopathy or endocardial fibroelastosis) or both [65, 66].

Presentation in the neonate could be in the form of bradycardia, intermittent cannon waves in the neck, varying intensity of first heart sound, intermittent gallops, and murmurs. The newborn is at greatest risk with a rapid atrial rate, often 150 beats/min or faster, and a ventricular rate less than 50 beats/min with junctional or atrioventricular (AV) nodal escape or ectopic rhythm. First- or second-degree heart block found in infants at birth can progress to CHB [67]. It may take just 1 week for a neonate to develop CHB from a normal PR interval. Therefore, weekly fetal echocardiography is essential between 16 and 24 weeks. The diagnosis of NLE is made when a fetus or newborn of a mother with anti-SSA/Ro and/or anti-SSB/La or anti-RNP antibodies develops heart block and/or the typical rash or hepatic or hematologic manifestations in the absence of other causes.

Women who test positive for SSA/Ro and SSB/La autoantibodies may benefit from more intense evaluation for fetal heart block. This requires frequent fetal echocardiographic testing weekly from the 16th through the 26th week of pregnancy and then every other week until 32 weeks. The most vulnerable period for the fetus is during the period from 18 to 24 weeks gestation. Normal sinus rhythm can progress to complete block in 7 days during this high-risk period. New onset heart block is less likely from 26 to 30 weeks, and it rarely develops after 30 weeks of pregnancy. Fetoscope auscultation to detect heart blocks by detecting bradycardia, biophysical profile scoring, and non-stress testing can also be used to diagnose CHB [68].

17.6.3 Treatment of Congenital Heart Block

The ultimate treatment for CHB is prevention as once it is diagnosed, medical treatment seems to be less favorable. Testing for culprit antibodies is essential prior to initiating therapy for a presumed case of neonatal cardiac lupus (NCL) as there are cases of heart block not associated with anti-SSA/Ro and SSB/La antibodies. The incidence of CHB is only 2% in the offspring of unselected anti-Ro antibody positive mothers. Therefore, the preventative therapy cannot be recommended for this group. Yet, in women with a previous child with CHB, the risk is greater, in the range of 17–19%. Graham Hughes has suggested that in this group of patients, maternal administration of intravenous immunoglobulins (**IVIG**) may cut the risk of recurrences. Another

possible strategy to avoid recurrence in subsequent pregnancies is immune suppression with **fluorinated steroids**, which cross the placenta. However, the toxicity of these agents prevents their use as a preventative therapy [69]. *A case-control study proposed that using HCQ, a toll-like receptor (TLR) inhibitor may decrease the risk of NCL related to anti-SSA/SSB antibodies* [67].

Treatment of different degrees of heart blocks is variable. Complete heart block is permanent, and nothing could reverse it even with glucocorticoid therapy [70]. On the other hand, second-degree heart block may be reversible. Unfortunately, it may progress to complete heart block despite therapy [71]. The clinical consequence of first-degree heart block is uncertain, since development from first-degree block to more advanced heart block in untreated fetuses has not been reported.

Fluorinated glucocorticoids such as dexamethasone and betamethasone, which are not inactivated by placental 11-beta hydroxysteroid dehydrogenase, may suppress the associated pleuropericardial effusion or hydrops and may improve outcomes. Fluorinated glucocorticoids are also considered for signs of a more global cardiomyopathy. Maternal dexamethasone in conjunction with transplacental β-adrenergic stimulation for bradycardia in fetus with HR of <55 beats/mt was reported to be effective in CHB [67].

Many children with CHB (33–53%) require pacing as newborns. There is a long-term risk of sudden death. From this perspective, the majority of patients are paced by the time they reach adult life [72]. Neonatal cutaneous lupus requires mainly avoidance of sun exposure and use of sunblock and hydrocortisone cream. There is usually no need for systemic steroids in these patients. Systemic antimalarials, on the other hand, are not recommended due to slow onset of action in a transient illness and due to its potential toxicity in infants [73].

17.6.4 Conclusion

NLE is due to passive transplacental transfer of maternal IgG autoantibodies (SSA/Ro, SSB/La or U1RNP) to the fetus. It is seen in 1–2% of these neonates. It can cause transient and self-limiting cutaneous lupus that usually does not require treatment. It can also manifest as CHB which is usually permanent requiring pacemaker in most of the patients. They are susceptible for cardiomyopathy either as a direct effect of the disease or due to right ventricular pacing which also adds to mortality at least by 10%. The diagnosis is made by identifying autoantibodies to SSA or SSB or U1 RNP in the mother. The diagnosis of CHB is made mainly in utero by periodic fetal echocardiography from 16 weeks onwards.

The outcome of heart blocks in general is not a favorable one. The mortality is considered high among children with CHB detected in utero than those detected after birth. The mortality is high mainly in the first year and particularly more in the first 3 months of life. Many aspects of the pathogenic mechanisms are discovered, but more research is needed. This is to help prevent this disease and provide better therapies for these patients.

17.7 Rheumatoid Arthritis (RA) and Pregnancy

17.7.1 Introduction

Rheumatoid arthritis (RA) is an autoimmune disease that is favorably influenced by pregnancy but classically flares after delivery [74]. The restructuring effect of pregnancy on RA has been well-known since 1938. Improvement of RA symptoms usually occurs in the first trimester and probably increases as pregnancy advances.

17.7.2 Effect of Pregnancy on RA

Pregnancy and postpartum period associated with changes in sex hormone levels, glycosylation of immunoglobulins, and cortisol level. One of the important immunological modifications during pregnancy is the Th_1/Th_2 shift. This is happening because of the progressive increase of progesterone and estrogens during pregnancy.

They reach their peak level in the third trimester of gestation. At high levels, estrogens seem mainly to suppress Th_1 cytokine and stimulate Th_2-mediated immunological responses as well as antibody production. For this reason, Th_1-mediated diseases, like RA, tend to improve [75]. Also changes in the percentage of IgG molecules lacking the terminal galactose units in the oligosaccharide chains attached to H2 regions have been tested as a probable explanation for ameliorating of RA during pregnancy. The percentage of agalactosyl IgG (Gal-o) varies with the age in normal healthy individuals. However, in patients with RA, Gal-o levels exceed normal values [76]. The levels of the glucocorticoids closely follow with the clinical improvement of RA in pregnancy. There is a progressive rise in total plasma cortisol levels with advancing gestation. The plasma concentration of free/active form of cortisol almost doubles in pregnant females as compared to the non-pregnant ones [77].

17.7.3 Effects of RA on Pregnancy

Women with well-controlled RA have a pregnancy outcome that is equivalent to the general obstetric population. Furthermore, disease activity and prednisone use during pregnancy were both adversely associated with birth weight. Only higher disease activity was associated with a lower birth weight, whereas the effect of prednisone on birth weight was mediated by shortening of the gestational age at delivery [1, 78]. The short- and long-term desirability of pregnancy needs to be always considered in women with RA in their reproductive age. This is extremely vital while choosing disease-modifying antirheumatic drugs (DMARDs). Educating both women and men about appropriate contraception is a key to avoiding unplanned pregnancies while taking a DMARD that is teratogenic and/or has unknown safety profile during pregnancy. A strategy for RA management during pregnancy is necessary as well for the health of the mother to reduce possible toxicity to the fetus [79].

The safe strategy to be used in managing RA in those planning pregnancy is as follows:

(a) Patients in remission—Review and adjust the medications compatible with pregnancy.
(b) Patients with active disease—Delay pregnancy till improvement is achieved with adequate treatment.

In RA, antepartum evaluation should include in addition to detailed history and musculoskeletal examination a careful examination of upper airway and cervical spine. A lateral cervical spine radiograph should be obtained in case a pregnant patient is affected by severe erosive disease or presence of neck symptoms or duration of the disease for more than 10 years. This film should be with flexed neck to exclude atlanto-axial anterior subluxation [80]. Extreme caution should be taken while managing the airway of these patients for any surgical intervention.

17.8 Sjogren's Syndrome (SS) and Pregnancy

Sjogren's syndrome (SS) is a chronic autoimmune inflammatory disease that can present either alone, primary Sjogren's syndrome (PSS), or in the context of an underlying connective tissue disease (secondary SS). It may occur at any age but mainly affects women in the fourth decade of life with a female-to-male ratio of 9:1 [32]. It is important to notice that the systemic form may be associated with other autoimmune disease, for example, RA in 30% of cases, SLE in 10%, and scleroderma in 1% autoimmune thyroid disease, chronic hepatitis, or lymphatic system disorders. Furthermore, systemic SS is characterized by anti-Ro/SSA 70–80%, and afflicted pregnancies may be exposed to high risk of CHB, cardiomyopathy, and neonatal lupus. These risks in some reports have been higher than in patients with SLE [81].

PSS can occur in all age groups, including children. Pregnancy complications due to the presence of anti-Ro/SSA and anti-La/SSB autoantibodies in the maternal serum are well recog-

nized as NLE and CHB. Reports on pregnancy outcomes beyond these two disorders are rare in PSS in contrast to the situation in SLE and APS. Pregnancy outcome in PSS has not been thoroughly studied but has in overall not been considered to be associated with adverse fetal outcome [82]. Data on pregnancy outcome in PSS are few and conflicting. In the past decades, the paucity of reports maybe related to the fact that PSS doesn't usually become clinically apparent until the fourth decade of life. However, the advanced maternal age of the first pregnancy has been discovered recently to explain the increased impact on pregnancies complicated by PSS [83].

17.9 Systemic Sclerosis (SSc) and Pregnancy

Systemic sclerosis (SSc) is a chronic autoimmune disorder with approximate female-to-male ratio of 5:1. Reports of pregnancies in SSc are rare owing to the low prevalence of the disease. The onset of the disease is usually after the fourth decade of life [84]. Most physicians concur that SSc women have a high probability of successful pregnancy if careful planning, close monitoring, and appropriate therapy are implemented. Moreover, retrospective case-control studies showed less ominous outcomes [85]. Still, an increased occurrence of preterm births and small full-term infants, compared to the controls, was noticed. Symptoms related to SSc particularly Raynaud's phenomenon improves during pregnancy, but esophageal reflux worsens. After pregnancy, some women with diffuse SSc had increased skin thickening [85].

The exertional dyspnea is particularly worse in the third trimester as the uterus increases in size. It is essential to rule out pulmonary hypertension during preconception counseling [86]. The extreme danger in pregnant SSc women is the occurrence of renal crisis, secondary to acute onset severe hypertension that can be fatal for both mother and child. It can be puzzled with preeclampsia and HELLP syndrome. However, in contrast to preeclampsia, delivery of the fetus does not affect the hypertension or renal dysfunction. Elevation of blood pressure in these patients, even mild, should be considered possibly serious, yet pregnancy itself does not appear to increase the risk of renal crisis.

Renal crisis is more prevalent in patients with early diffuse SSc (within 5 years from symptom onset). Risk factors include the presence of anti-topoisomerase, anti-RNA polymerase III antibodies, and exposure to high doses of corticosteroids. Preeclampsia rate does not seem to be increased in SSc patients [85]. Angiotensin-converting enzyme inhibitors (ACEI) are a life-saving treatment in hypertensive renal crisis in patients with SSc despite their association with congenital malformations and kidney dysfunction in the infant [86].

History of a renal crisis during a previous pregnancy should delay the following pregnancy until the disease has been stabilized. This usually takes around 3–5 years from the onset of symptoms. These women are usually treated with nifedipine to maintain good control of blood pressure. Delivery is usually recommended if appropriate antihypertensives fail. ACEI may be initiated during pregnancy in severe cases after appropriate counseling about the risk of congenital abnormalities [86]. High rate of complications during pregnancy is seen in women with history of significant interstitial lung disease, scleroderma renal crisis, early diffuse SSc with rapid onset, or moderate-severe pulmonary arterial hypertension (PAH).

If a patient with SSc wishes to continue with pregnancy after applicable counseling of risks, aggressive monitoring and co-management with experts in renal and pulmonary disease are mandatory. Medications such as ACEI and prostaglandins which conduct high risk for congenital malformations with higher incidence of other fetal toxicities need to be considered. The benefits to both mother and fetus may overshadow known risks of antenatal exposure [87]. Previous events of renal crisis are not a complete contraindication for future pregnancy. It is recommended that a woman postpone several years until her disease is stable before trying to conceive. A trial without ACEI prior to pregnancy is suggested to deter-

mine if blood pressure can be effectively controlled with substitute antihypertensive medications [88].

Labor and delivery are susceptible period in these cases. Some patients may need prolonged observation in the hospital following delivery to monitor for acute cardiovascular collapse in case of PAH [87]. In SSc, a thorough search should be conducted for systemic dysfunction, namely, renal disease, systemic hypertension, PAH, cardiac dysfunction, and fetal distress. Close surveillance should be performed for arterial pulses, peripheral venous access, extent of Raynaud's involvement, and special positioning needs [80].

17.10 Vasculitis and Pregnancy

17.10.1 Introduction

There are profound immune and endocrine changes which happen during pregnancy. The physiological increase of cortisol, progesterone, estradiol, and testosterone during the third trimester of pregnancy seems to lead to Th2 cytokine polarization both at systemic level and at the feto-maternal interface.

The following issues should be taken into consideration while counseling the patient with vasculitis for pregnancy:

(a) Patients should receive a mode of contraception at least while receiving high dose of cytotoxic medications.
(b) Pregnancies should be planned when the disease is in remission.
(c) Strict monitoring is recommended for patients during gestation and postpartum periods by multidisciplinary team.
(d) In case of disease relapse on adequate treatment, aggressive management should be recommended.
(e) Pregnancy complicated by the onset of vasculitis particularly has worse prognosis.

In patients with systemic vasculitis, the risk of thromboembolic events is increased [24].

Table 17.4 Effect of pregnancy on the course of systemic vasculitis [90]

Status of disease at conception		
Type of vasculitis	Active	Inactive
GPA	Frequent flares—Risk of maternal death	Rare flares (25%)
PAN	Frequent flares	Rare flares (25%)
MPA	Risk of maternal death	Frequent flares (50%)
EGPA	Frequent flares (50%) (asthma, mononeuritis multiplex, skin rash)	Rare flares (25%)
TA	High risk of maternal morbidity and fatality in patients with severe aortic valvular diseases or aortic aneurysm	Rare flares (25%)
BD	Frequent improvement (50%)	Rare flares (25%)

(*GPA* granulomatous polyangiitis, *PAN* polyarteritis nodosa, *MPA* microscopic polyangiitis, *EGPA* eosinophilic granulomatous with polyangiitis, *TA* Takayasu's arteritis, *BD* Behcet's disease)

17.10.2 Large Vessel Vasculitis

17.10.2.1 Behcet's Disease (BD)

Systemic vasculitides are infrequent diseases characterized by an abundant variety of symptoms, ranging from mild to life-threatening manifestations. Pregnancy is more frequent in vasculitis that have onset at younger age and affect the female gender such as Takayasu's arteritis (TA) and Behcet's disease (BD) [89, 90]. BD is an inflammatory disorder of unknown etiology that affects mostly young adults. It involves the oral and genital mucosae as well as the eyes, joints, and central nervous system (CNS). Furthermore, arterial and/or venous thrombosis also may occur during the course of BD. This has been connected with considerably increased morbidity. Limited data are available concerning the impact of pregnancy on the course of BD (Table 17.4) [90].

Although BD appears to improve during pregnancy, disease flare consists mainly of oral and genital ulcerations. Mucocutaneous ulcerations seem to predominate during the second

and third trimesters of pregnancy. Life-threatening complications such as thrombosis or CNS lesions can happen as well. The postpartum period is still a vulnerable period. The global risk of obstetric complications in patients with BD is similar to that in the overall population. However, the risk of miscarriage seems to be increased in patients with a history of vascular involvement. The use of colchicine is safe in pregnant women with BD and could even reduce the risk of disease flares. Other medications like azathioprine and glucocorticoids can also be used during pregnancy, seemingly without an increased risk of complications. Pregnancy is consequently a viable option for women who have BD [91].

BD activity may vary between pregnancies in the same patient. It has to be noted that remission and exacerbation both have been reported during pregnancy. Relapses occur most frequently in the first trimester. They represent primarily mucocutaneous findings with ocular and thrombotic complications being rare. Active disease does not seem to worsen maternal or fetal outcome. Maternal BD has not been linked to an increased rate of miscarriage, pre-maturity, fetal anomalies, or neonatal BD. Pregnant patients who suffer from genital ulcers at the time of delivery may benefit from cesarean section. Patients should continue to be monitored postpartum as the disease might flare according to several reports [92]. Pregnancy is a hypercoagulable state; therefore anticoagulation is recommended in women with prior history of thrombosis.

Most infants born to mothers with BD are generally healthy. Reports of neonatal BD have appeared infrequently in the literature. While some have proposed that the mechanism of disease of neonatal BD is similar to that of NLE, there is no evidence of any transplacental transfer or maternal antibodies [93]. Most of the reports of neonatal BD have portrayed a transient disease with spontaneous resolution [93].

17.10.2.2 Takayasu's Arteritis

TA is a granulomatous vasculitis that affects large vessels such as the aorta, its major branches, and pulmonary arteries. TA manifests at a younger age, typically affecting the women of childbearing age. Fertility appears not to be affected. Neither the fetal mortality nor spontaneous abortion rates are increased in TA, but the incidence of low birth weight is increased. Maternal complications include accelerated hypertension, heart failure, and stroke [94].

It is obligatory to tightly control blood pressure (BP) using both noninvasive (BP measurement at upper and lower limbs and Doppler flow if pulses are not palpable) and invasive procedures (intra-arterial monitoring through arterial cannulation). This is mandated particularly when BP values cannot be accurately measured due to multiple vascular stenosis. In order to prevent BP increase during vaginal pushing, spinal analgesia should be given, and BP monitoring should be continued at least 24–48 h after delivery. This is due to the hemodynamic changes that occur in the postpartum period which might promote aortic dissection.

Aortic valvular disease has been reported as a risk factor for maternal morbidity in patient with TA. The baseline cardiac function should be assessed at the onset of pregnancy and monitored through pregnancy [95]. In postpartum period, antibiotics should be given to prevent bacterial endocarditis in patients with aortic insufficiency and/or luminal narrowing of the aorta and its branches [89].

The indications for cesarean section in TA are mainly for [19]:

1. Obstetrical reasons.
2. Mild disease but with elevated systolic BP despite adequate medical treatment at the time of labor.
3. Presence of one or more complications like retinopathy, secondary hypertension, aortic insufficiency, aortic/arterial aneurysm, and non-recordable BP in both arms.
4. Severe complications of TA like heart failure or dysrhythmias.

Disease relapse during pregnancy are generally treated with prednisone 1 mg/kg/day until the disease control is obtained. Then prednisone can be tapered to the lowest possible effective dose. In

refractory cases, the use of azathioprine is recommended. Hypertension has to be managed very aggressively with ∝ − methyldopa, Ca-channel blocker, or hydralazine. ACEIs are contraindicated because of their high incidence of fetal toxicity [92].

17.10.3 Medium Vessels Vasculitis

17.10.3.1 Polyarteritis Nodosa (PAN)

PAN is a disorder characterized by necrotizing inflammation of medium size or small arteries. In patients with PAN, prevalent manifestations are general symptoms like malaise, fever and fatigue, musculoskeletal pain and arthralgias, mucocutaneous findings, and gastrointestinal manifestations [95]. Peripheral neuropathy especially mononeuritis multiplex is common as well [95]. Approximately 30% cases of PAN are associated with co-infection with hepatitis B. Like other forms of vasculitis, PAN can be associated with hypertension, abdominal pain, and proteinuria simulating some of the more common complications of pregnancy [90].

Some patients have a medium vessel vasculitis that is restricted to the skin. This form of vasculitis, known as cutaneous PAN, generally does not evolve to the systemic form [90]. Worsening of a mild form of vasculitis in a pregnant patient may be treated effectively with glucocorticoids alone. Use of cyclophosphamide is required in the presence of life-threatening manifestations particularly bowel infarction, CNS, and/or cardiac involvement [95].

17.10.4 Small Vessels Vasculitis

17.10.4.1 Granulomatosis with Polyangiitis (GPA) (Wegner's Granulomatosis)

Pregnancies in women with GPA are uncommonly observed. The disease peaks after the age of 40, and it affects mainly the upper respiratory tract, the lungs, and the kidneys. The relapse or worsening of renal involvement in the late pregnancy can be difficult to differentiate from preeclampsia. There are few useful parameters in this regard with active urine sediment indicating GPA nephritis [96]. Premature delivery is a common complication of pregnancy in patients with GPA, particularly in those with active disease during gestation. In case of insufficient response to corticosteroids, azathioprine can be used. Cyclophosphamide may be considered for life-threatening manifestations occurring during the second or third trimester of pregnancy [96].

17.10.4.2 Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss Syndrome)

Eosinophilic granulomatosis with polyangiitis (EGPA) formerly known as Churg-Strauss syndrome is a disorder characterized by pulmonary and systemic small vessel vasculitis, extravascular granulomas, and hypereosinophilia occurring in patients with asthma and allergic rhinitis [96]. Pregnancy is not a common event in EGPA due to various reasons such as the rarity of the disease, the peak incidence of the disease around the fifth decade, and male preponderance [97].

EGPA relapse was reported in 50% of women who conceived, while the disease was in remission. The commonly observed manifestations during the relapse were worsening of asthma, mononeuritis multiplex, and skin rash. Patients with disease onset during pregnancy are considered as unfortunate as they had a very poor prognosis. Cases of fulminant EGPA associated with pregnancy may be caused by decrease or discontinuation of the medications in use. This is in addition to the loss of lung capacity associated with pregnancy, which may further exacerbate the existing bronchospasm [90]. Treatment of EGPA relapses during pregnancy consists of the use of prednisone with adjusted doses according to the severity of disease manifestations. In EGPA patients, special care should be given to monitor bronchospasm during pregnancy and postpartum period [96].

17.11 Polymyositis (PM)/ Dermatomyositis (DM) and Pregnancy

Women in reproductive age group are rarely affected by PM/DM as the onset of the disease is over the age of 45 years. Data for such diseases are extremely limited. Patients are encouraged to achieve and maintain stable disease prior to conception. It is recommended obviously to have the disease totally quiescent as active muscle weakness adversely affects both pregnancy and labor. The typical guidelines applied while using medications during pregnancy in other rheumatic diseases should be applied again in these diseases. Medications that are contraindicated in pregnancy would need to be substituted prior to conception [1].

The fetal prognosis matches activity of the maternal disease. In patients with preexisting quiescent disease, little clear risk to the mother or fetus is observed. This is in contrast to new onset of disease or exacerbation during pregnancy for which a significantly worse outcome is noted [98]. Treatment with corticosteroids, azathioprine, and intravenous immunoglobulin may be suitable for active myositis during pregnancy. It is observed that patients with PM are sensitive to non-depolarizing muscle relaxants and the use for their antagonist drugs may cause muscle weakness and severe arrhythmias. Steroid-induced myopathy may lead to an increased sensitivity to neuromuscular blocking drugs and an unpredictable response. All these are important clinical vignettes that should be taken care of while dealing with these patients particularly during anesthesia. Other important aspects to be considered in the anesthetic management are respiratory insufficiency, risk of aspiration, arrhythmias, cardiac failure, and hyperkalemia [99].

Disease activity and underlying cardiopulmonary involvement should be thoroughly evaluated in affected patients with PM/DM. In the presence of muscle weakness, spirometry should be done to evaluate respiratory muscles involvement. Chronic aspiration due to pharyngeal weakness may lead to pulmonary diffusion deficits. An ECG should be done to exclude conduction abnormalities and arrhythmias [80]. Echocardiogram and full cardiac evaluation may be required accordingly.

17.12 Spondyloarthritis and Pregnancy

Ankylosing spondylitis (AS) is a chronic, progressive autoimmune disease, mainly involving sacroiliac joint, vertebral column, and peripheral joints. It is also complicated with some other manifestations including uveitis and the aortic valve lesions in the heart [100, 101]. Pregnancy may occur in patients with this disease as the peak incidence of AS is in the 25–34 years of age group [102]. Pregnancy has been observed to significantly improve peripheral arthritis and uveitis in most patients, but there is deterioration in 25% of patients with predominantly axial disease in pregnancy [100]. As with other rheumatic disease, there is an increased risk of flares in postpartum period [100].

Clinicians who are taking care of a pregnant patient with this disease need to be concerned for few issues. These include the method of delivery, the optimal choice of labor analgesia, and the type of anesthesia to be provided in the event of cesarean section. Possible pelvic joint ankylosis associated with AS can interfere with a normal spontaneous vaginal delivery. The potential cardiac involvement in AS may also have an influence on the mode of delivery. Although aortic regurgitation correlated with AS is often asymptomatic, even trivial valvular disease may cause decompensation in the pregnant patient. Other cardiac involvements in AS which have been reported include proximal aortitis, mitral regurgitation, and conduction defects. Preanesthetic evaluation should include a careful physical examination of the chest and cardiovascular systems as well as a baseline electrocardiogram. Transthoracic echocardiography may be used to evaluate the abnormal findings of the heart in the clinical examination [90]. However, it might be considered as a baseline for patients with long-lasting disease.

Pulmonary involvement in AS have also been described. A restrictive pattern of lung function is seen due to costochondral rigidity and flexion deformity of the thoracic spine.

Placement of epidural anesthesia in these patients may be technically difficult. This could be related to calcification of interspinous ligaments, formation of bony bridges between the vertebrae, or ankylosis of the vertebral column with restriction in lumbar flexion. General anesthesia is sporadically necessary in patients with AS. Involvement of the cervical and temporomandibular joint or cricoarytenoid arthritis may cause obstacles with tracheal intubation. Moreover, loss of normal neck flexibility with increasing osteoporosis predisposes the spine to fracture, even with minor trauma. An awake fiberoptic intubation should be considered whenever a difficult intubation is anticipated or ankylosis of the spine is expected [102].

17.13 Conclusion

As rheumatic diseases affect women during the childbearing age, every pregnancy for those patients should be considered as high risk and should be strictly monitored by meticulous antenatal evaluation. It is essential to know the effect of each disease on pregnancy and vice versa. Therefore, the physician should focus on the prepregnancy planning, fertility, medications use, and fetal complications and need to continue the care through the postpartum and lactation periods.

Most of the complications of these diseases during pregnancy can be prevented. This can be achieved by carefully planning the pregnancy during the inactive phase of the disease and timely discontinuation of harmful medications used in these disorders. However, pregnancy can still be threatened by active disease, presence of autoantibodies, and severe affection of major organ involvement by the disease. Therefore, the management of these rheumatic diseases in pregnancy needs a multidisciplinary approach by the rheumatologist, obstetrician, neonatologist, and at times other specialists (nephrologist, hematologist, etc.). This is to support these unfortunate patients from all dimensions to have a healthy child [103].

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18 Perioperative Management of Patients with Rheumatic Diseases

Manal Alotaibi, Khaled Albazli, Lina Bissar, and Hani Almoallim

18.1 Introduction

The aim of this chapter is to present a simple approach to the assessment of patients with different rheumatologic diseases, especially rheumatoid arthritis (RA), before undergoing orthopedic surgery. Perioperative assessment confirms an early diagnosis of the patient's medical condition and comorbidities, overall health, and the assessment of the risk factors associated with the proposed interventions. Perioperative assessment allows for proper postoperative management of complications. It can also aid in the management of high-risk drugs used by rheumatologic patients such as disease-modifying antirheumatic drugs (DMARD), antiplatelets, and corticosteroids. The assessment also supports postoperative plans and patient education [1–3].

18.1.1 Objectives

1. To present a comprehensive preoperative medical evaluation for patients with rheumatologic disorders before undergoing orthopedic surgery.
2. To clarify the assessment of specific clinical issues in patients with RA and systemic lupus erythematosus (SLE).
3. To present the perioperative management of medications for patients with rheumatologic disorders before undergoing orthopedic surgery.
4. To clarify how to follow-up and educate the patient postoperatively.

18.2 The Preoperative Medical Evaluation

18.2.1 History Taking

Detailed information should be obtained. There are several components of the history that should

M. Alotaibi
Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Internal Medicine Department, College of Medicine, Umm Al-Qura University, Makkah, Saudi Arabia
e-mail: manal.alotaibi@northwestern.edu

K. Albazli
Department of Medicine, Faculty of Medicine in Al-Qunfudhah, Umm Al-Qura University, Makkah, Saudi Arabia

The George Washington University School of Medicine and Health Sciences, Washington, DC, USA

L. Bissar (✉)
Department of Medicine, King Faisal Specialist Hospital and Research Center (General Organization), Jeddah, Saudi Arabia
e-mail: lbissar@kfshrc.edu.sa

H. Almoallim
College of Medicine, Umm Al-Qura University, Makkah, Saudi Arabia
e-mail: hmmoallim@uqu.edu.sa

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be outlined. These include the patient's age, duration of rheumatologic disorder, current functional level, specific joint involvement with arthritis, any extra-articular manifestations of the disease, current medications including DMARDs and previous use of steroids, previous complications associated with surgery, and any comorbidities like hypertension and/or diabetes mellitus.

18.2.2 Physical Examination

Obviously, for any rheumatic disease patients, there should be specific focus on the musculoskeletal system during the physical examination. This should include posture, location and pattern of joint involvement, gait, and range of motion (ROM) of the examined joints. Furthermore, underlying disorder must be identified. The skin should also be assessed for any manifestations suggestive of an underlying rheumatologic diseases that may impact skin integrity.

18.2.3 Investigations

The following tests may be considered along with routine tests:

- A complete blood count for an examination of possible drug related hematologic side effects. This may include anemia due to gastric or duodenal irritation, leukopenia, and/or pancytopenia from massive bone marrow suppression. This is essential in situations where significant blood loss is expected, such as total hip replacements.
- A complete renal profile, liver enzymes, and liver function tests to screen for DMARDs side effects.
- A urinalysis and urine culture should be obtained. It is important to rule out urinary tract infections in patients undergoing total joint arthroplasty [4, 5].
- A 12-lead electrocardiogram (ECG) is necessary as a baseline cardiovascular evaluation for patients undergoing surgeries. ECG is recommended in men over the age 40 and women over 50 having major surgery. This is essential even in the absence of history or physical exam findings.
- Chest x-ray is necessary as a baseline for pulmonary evaluation. It is indicated for patients over the age 50 undergoing major joint or spine surgery. This is even in the absence of symptoms and/or signs suggestive of active pulmonary disease [6, 27].

18.2.4 Assessment of Specific Clinical Problems in Patients with RA

18.2.4.1 Cardiovascular

Special focus should be made to risk stratify RA patients for coronary artery disease. Many contributing factors including accelerated atherosclerosis put RA patients at high risk for cardiac morbidity and mortality. RA patients presenting for orthopedic surgery for any kind of procedure and/or intervention should receive careful preoperative cardiac risk stratification. There are several measures to be taken. Dipyridamole thallium scintigraphy (DTS) conducted preoperatively is found to be most useful to stratify selected nonvascular surgery patients at intermediate or high risk by clinical assessment [6–9, 28].

18.2.4.2 Pulmonary

Multiple pulmonary complications including fibrosis, bronchiolitis, and pleuritis can have significant impact on RA patients. Serial pulmonary function test (PFT) among patients with RA is recommended. This can help in early detection of defected ventilation. [10]

18.2.4.3 Cricoarytenoid Arthritis

This is a common involvement in RA patients. It places concerns of complicated intubation or obstructed airway after surgery. Most patients are asymptomatic, but despite that they may present with symptoms such as hoarseness, sore throat, and/or difficult inspiration. Therefore, it is extremely essential to avoid intraoperative musculoskeletal trauma in patients with RA by applying generous padding during joint positioning and by avoiding sudden movements of the neck and torso [11, 23–26].

Table 18.1 Perioperative management of antirheumatic drugs

Antirheumatic drug	Comments
Methotrexate (MTX)	• There is no increased risk of infection or other postoperative complications in patients with RA who continued MTX. • Continue the current dose of methotrexate for patients undergoing elective total hip arthroplasty (THA) or total knee arthroplasty (TKA). • Withheld the week before and the week after surgery if there are additional concerns regarding the perioperative safety of MTX such as renal insufficiency or if a more complex surgical intervention is required. • MTX should be reinstated as soon as the patient is stable postoperatively. • MTX treatment should be discontinued until full recovery if prolonged surgery or artificial respiration is anticipated or in case of pulmonary complications, to reduce the risk of pneumonia [30, 31].
TNF blockers	• It is recommend stopping TNF blockers use 1 to 4 weeks before surgery, proportional to the drugs half-lives. • Withhold TNF blockers and other biologic agents prior to surgery in patients undergoing elective THA or TKA, and schedule the surgery at the end of the dosing cycle. • Treatment may be restarted at minimum 14 days postoperatively if there is no evidence of infection and once wound healing is satisfactory [32].
Tocilizumab	• Infection rates attributed to tocilizumab are comparable to those associated with other biologic DMARDs. • Discontinuing tocilizumab 11 to 13 days before surgery, based on the drug half-life, is a safe approach to perioperative therapy [31, 33].
SLE specific medications: Mycophenolate mofetil Azathioprine Cyclosporine Tacrolimus	• Withhold their current doses 1 week prior to surgery in all patients with stable SLE undergoing THA or TKA. • Continue their current doses through the surgical period in all patients with severe SLE undergoing THA or TKA.
Rituximab	• Rituximab has been shown to be safe in patients with prior recurrent bacterial infections. • Compared with TNF blockers, rituximab is associated with a lower risk for bacterial infections, which are the primary concern in perioperative management, although the presence of low immunoglobulin levels in a small proportion of patients raises the infection risk. • Elective surgery can be arranged in the 7th month from the last given dose [31].
Abatacept	• The risk of infection in patients treated with abatacept is not significantly increased over baseline non-biologic-treated RA patients. • Abatacept is administered either as a monthly infusion or a weekly subcutaneous injection, and conservative timing of surgery should be at the end of the dose cycle [31].
Steroid	• In general, limiting minimal doses of steroids preoperatively should be considered to prevent impairment of wound healing and surgical site infections. • Chronic use of steroid also increases the potential risk of subversive consequences of an inadequate adrenal response [31].

18.3 Perioperative Drug Management

18.3.1 Perioperative Management if Antirheumatic Drugs [12–16]

(See Table 18.1)

18.3.2 Perioperative Management of Other Systemic Medications [12–14, 16, 17]

(See Table 18.2)

Table 18.2 Perioperative management of medications

Category	Medications and treatments	Comment
Cardiac	Continue most medications through surgery Continue most antihypertensive drugs through surgery with sips of water, or consider non-oral forms Consider transdermal, IV, or sublingual equivalents Avoid abrupt withdrawal of beta-blockers and alpha-blockers **Diuretics** It is recommended that diuretics be continued in patients with heart failure, but rapid diuresis before surgery must be avoided **Nitroglycerin** Nitrates should be continued if in use. Perioperative nitroglycerin use for the prevention of adverse ischemic events in high-risk patients may be considered **ACE inhibitors** It is recommended that ACE inhibitors be continued during non-cardiac surgery in stable patients with LV systolic dysfunction **Beta-blockers** Continuation of beta-blockers is recommended in patients previously treated with beta-blockers because of ischemic heart disease (IHD), arrhythmias, or hypertension Beta-blockers should be considered for patients scheduled for intermediate-risk surgery if their blood pressure is not controlled Heart-rate-reducing calcium channel blockers, particularly diltiazem, may be considered before non-cardiac surgery in patients who have contraindications to beta-blockers **Antiplatelet therapy** Continue aspirin around the time of surgery in patients at moderate- to high-risk for cardiovascular events Stop aspirin 7 to 10 days Before surgery in patients at low risk for cardiovascular events. Usually may safely resume 24–48 h postoperatively	Most patients can safely have surgery as long as the systolic BP is less than 180 and the diastolic BP is less than 110, and there is no evidence of end organ damage Correct electrolyte disturbances before surgery Patients taking aspirin and NSAID may have a higher risk for developing perioperative bleeding complications

Endocrine	**Thyroid disease** Continue thyroid supplements with sips of water Reduce L-thyroxine dose by 20% for long-term parenteral use, if applicable **Corticosteroids** For moderate stress procedures (total joint replacement), it is a good practice to provide: 1. intraoperatively: Hydrocortisone 50 mg intravenously 2. postoperative day 1: Hydrocortisone 20 mg intravenously every 8 h for 3 doses 3. postoperative day 2: Return to preoperative glucocorticoid dose or parenteral equivalent. The glucocorticoid target is 50 to 75 mg per day of hydrocortisone equivalent for 1 or 2 days **Diabetes mellitus** [34] The sole use of sliding scale insulin in the inpatient hospital setting is Discouraged More stringent goals, such as 110–140 mg/dL (6.1–7.8 mmol/L) may be appropriate for selected patients, as long as this can be achieved without significant hypoglycemia All patients with type 1 and type 2 diabetes should be transitioned to scheduled subcutaneous insulin therapy at least 1–2 h before discontinuation of continuous insulin infusion Type 1 diabetes mellitus, critically ill patients, or those going through major surgery require an intravenous insulin therapy for achieving the desired glucose range of 140–180 mg/dL (7.8–10 mmol/L) without increasing risk for severe hypoglycemia. Strict glycemic control in critically ill patient is detrimental by increasing mortality and should be avoided For non-critically ill patients or those undergoing minor surgery, the preferred method for maintaining glucose control is to schedule subcutaneous insulin with basal, nutritional, and correction components. There is no clear evidence for specific blood glucose goals Pre-meal blood glucose target is 140 mg/dL (7.8 mmol/l) and random blood glucose is 180 mg/dL (10.0 mmol/l). More stringent targets may be appropriate in stable patients with previous tight glycemic control. Less stringent targets may be Appropriate in those with severe Comorbidities Type 2 diabetes controlled with diet usually does not require perioperative therapy; however, blood sugars must be checked and short-acting insulin as a correction dose may be given Type 2 diabetes treated with oral agents or non-insulin injectable should hold their hypoglycemic agents on the morning of surgery. Blood sugar should be checked and correction dose of short-acting insulin may be administered subcutaneously Glucose must be monitored for all patients and for patients on therapies associated with increased risk for hyperglycemia, including high-dose glucocorticoid therapy	Prolonged anesthetic effect after surgery may suggest hypothyroidism All patients with diabetes admitted to the hospital should have their diabetes clearly identified in the medical record, and an order for blood glucose monitoring, with results available to all members of the health care team A plan for preventing and treating hypoglycemia should be established for each patient to avoid risky situations Obtaining an HbA1c on patients with diabetes admitted to the hospital should be considered if the result of testing in the previous 2–3 months is not available Obtaining an A1C in Patients with risk factors for Undiagnosed diabetes who Exhibit hyperglycemia in the Hospital Patients with hyperglycemia in the hospital who do not have a prior diagnosis of diabetes should have appropriate plans for follow-up testing and care documented at discharge A hypoglycemia management Protocol should be adopted and implemented by each hospital or hospital system A plan for preventing and treating hypoglycemia should be established for each patient Episodes of hypoglycemia in the hospital should be documented In the medical record and Tracked

(continued)

Table 18.2 (continued)

Category	Medications and treatments	Comment
Gastrointestinal and hepatic	Malabsorption, dysmotility of bowel, and hepatic dysfunction may significantly alter pharmacodynamics of perioperative medications including anesthetic	Nutritional status and liver disease must be assessed and monitored preoperatively History of risk factors for hepatitis B or C and history of alcohol use should be determined
Renal	Perioperative renal function is the best predictor of postoperative renal failure Nephrotoxic drugs are to be avoided Urine volume status, output, adequate perfusion, and drug levels should be monitored if applicable Less nephrotoxic induction protocols should be used Nephrology consultation should be considered in patients with worsening renal function or decreased urine output	Patients with chronic kidney diseases (CKD) may have multi-organ dysfunction, general disability, and specific problems associated with renal replacement therapy (RRT) In patients with mild-to-moderate CKD, surgical trauma and perioperative hemodynamic instability may precipitate acute kidney injury
Rheumatologic	**NSAIDs** 1. To be stopped 1–3 days before surgery depending on half-life. 2. They can be started again postoperatively for pain relief. 3. May continue the use of COX2 inhibitors. **Codeine, oxycodone, methadone** Are to be continued until morning of surgery, and then decision is up to the anesthesiologist to determine narcotic use intraoperatively **DMARDs** see below	Patients with severe SICCA syndrome, an autoimmune disease, also known as Sjogren syndrome, which classically combines dry eyes, dry mouth, and another disease of connective tissue such as RA (most common), lupus, scleroderma, or polymyositis require lubricant eye drops
Hematology	Anticoagulation can be associated with increased risk of bleeding, especially in the immediate postoperative period In major orthopedic surgery, physicians should consider low-molecular-weight heparin (LMWH) as venous thromboprophylaxis 12 h prior to surgery and extend to 35 days after surgery In patients who require temporary interruption of a vitamin K antagonists (VKA) before surgery: 1. VKAs should be stopped 5 days before surgery 2. VKAs should be resumed 12 to 24 h after surgery when there is adequate homeostasis In patients who are receiving bridging anticoagulation with therapeutic-dose SC LMWH and are undergoing high-bleeding-risk surgery: 1. the last preoperative dose of LMWH should be administered 24 h before surgery 2.LMWH can be resumed 48 to 72 h after surgery 3. IV unfractionated heparin (UFH) should be stopped 4 to 6 h before surgery Erythropoietin, with or without iron supplement, is recommended preoperatively in patients with a baseline Hct < 34% to avoid or reduce allogeneic blood transfusion preoperatively	Patients may have anemia that places them at risk for requiring blood transfusion during major surgeries associated with significant blood loss Anemia in RA patients is a common and dynamic condition that may increase the patient's risk for myocardial ischemia. Physicians should consider autologous blood transfusion requirements well in advance of surgery
Neurology	To continue anti-convulsion therapy Treatment with atropine may precipitate delirium in Parkinson's disease	Delirium is a predictor of poor outcome (i.e., potentially preventable) Formal assessment of preoperative cognitive function can help target prevention efforts by identifying high-risk patients
Miscellaneous	Ask about nonprescription drugs including dietary and herbal supplements Recommend smoking cessation and Offer behavioral support combined with nicotine replacement therapy or varenicline Alcohol and illicit drug use should be considered possible Asymptomatic bacteriuria in patients undergoing total joint arthroplasty must be treated to avoid risk Among HIV positive patients, perioperative management should include hands-on pharmacy support	Patient may be unaware of pregnancy Patient's fears and expectations should be explored

18.3.3 DVT Prophylaxis

- Meta-analysis showed that extended-duration prophylaxis against deep vein thrombosis (DVT) with low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) in patients with major hip or knee replacement surgery can reduce the risk of symptomatic venous thromboembolism significantly [18].
- There are many options for the prevention of venous thromboembolism in patients undergoing elective hip or knee arthroplasty and who are not at increased risk beyond that of the surgery itself for venous thromboembolism or bleeding. Prophylaxis should be started after surgery (specific timing given separately for each drug) and continued for 28–35 days for hip patients and 10–14 days for knee patients: dabigatran, fondaparinux, LMWH, rivaroxaban, and UFH (for patients with renal failure) are all options [18, 19, 35].
- It has to be considered that the benefit here is associated with increased risk of minor bleeding but with no excess major bleeding [18].
- In patients undergoing hip fracture surgery (HFS), it is recommended to use one of the following rather than no antithrombotic prophylaxis for a minimum of 10 to 14 days: LMWH, fondaparinux, LDUH, adjusted-dose VKA, or aspirin.
- There are specific considerations for patients undergoing major orthopedic surgery, total hip arthroplasty (THA), total knee arthroplasty (TKA), hip fracture surgery (HFS), and receiving LMWH as thromboprophylaxis; it is recommended to start either 12 h or more preoperatively or 12 h or more postoperatively, rather than within 4 h or less preoperatively or 4 h or less postoperatively [19, 36].
- It has to be noted that in patients undergoing THA or TKA, irrespective of the concomitant use of an intermittent pneumatic compression device (IPCD) or length of treatment, it is suggested to use LMWH in preference to the other agents recommended as alternatives: fondaparinux, apixaban, dabigatran, rivaroxaban, low-dose UFH, adjusted-dose vitamin K antagonist (VKA), or aspirin.

18.3.4 Prophylactic Antibiotics [20, 29]

- Prophylactic antibiotics are needed for RA patients who will be undergoing long procedures especially patients with TKA, joint replacement, and prosthetic joints. This is to prevent surgical site infections.
- Obviously, antibiotics must be administered to patients undergoing surgery in an infected area with a high bacteremia risk.
- Cefazolin or cefuroxime antibiotics are the antibiotic of choice and should be given 30 to 60 min before skin incision.
- In case of a confirmed ß-lactam allergy, vancomycin may be used. It should be started within 2 h prior to incision.
- The dose of antibiotic varies according to patient's weight; for patients >80 kg, the doses of cefazolin should be doubled.
- It has to be noted that additional intraoperative doses of antibiotic might be needed. It should be given for prolonged procedures and if there is significant blood loss during the procedure.
- Prevention of wound infection is essential. This can be prevented after surgical repair of closed fractures by a single dose of cephalosporin.
- Prophylactic antibiotics should be stopped within 24 h of the end of surgery.

18.4 Assessment of Specific Clinical Problems in Patients with SLE

Specific perioperative concerns must be considered for patients with SLE undergoing orthopedic surgery. This should include assessing risk factors for worse outcomes including smoking or use of oral contraceptive pills (OCP), adequate blood pressure (BP), and lipid control. It has to be noted that SLE patients undergoing both nonelective and elective hip and knee surgery have a high mortality and morbidity rate compared to RA patients [21].

It is also necessary to assess medication management around the operation time. SLE patients

have multiple organ involvement. This should be assessed as well including hematologic abnormalities, renal disease, and immune dysfunction, and thromboembolic disease. Moreover, a careful balance should be addressed in the risk assessment in patients with antiphospholipid antibody syndrome (APS). The aim is to evaluate these patients preoperatively to decrease the risk of major bleeding and the risk of a thromboembolic event.

18.5 Postoperative Follow-Up

There has to be a thorough postoperative risk assessment for the following patients:

- Carful follow-up for patients with RA and SLE assessing the risk of prosthetic joint infections, DVT, and pulmonary embolism. These patients have greater risk for the development of these complications postoperatively.
- Hospitalized patients with autoimmune disease have a high risk of postoperative venous thrombosis. These patients can be offered a regional anesthesia, as it reduces the postoperative DVT significantly.
- Patients with gout should be assessed for the risk of flare of gout postoperatively.
- There are special precautions for patients with Raynaud's phenomenon. Hypothermia must be avoided postoperatively and pressure ulcers must also be prevented [22].

18.6 Patient Education

To assure patients' safety, it is recommended to inform the patient of the following:

- Patients should be aware about the expected duration of movement limitations and options for pain control. This is immediately after the surgery and in the following weeks to months.
- They should also be aware about the importance of a comprehensive physical activity program following surgery.
- Each patient should be aware of the pain control plan. The associated fluctuation of pain with different medication withdrawal or institution must be explained.
- More details should be delivered to patients according to their needs, issues like possible drug-drug and/or drug-food interactions of new medication regimens. The classical and common examples are the potential risk of anticoagulant drugs and foods affecting potency of warfarin. Patients should be aware about any follow-up instructions including monitoring of laboratory investigations.
- Obviously, patients should be aware about the importance of early immobilization [22].

18.7 Physical Activity and Rehabilitation

Patients should undertake physical therapy since physical activities are essential for patients with rheumatologic disease. The major benefits are to prevent disabilities, restore function, and relieve pain. These activities should be evaluated preoperatively to verify consistency with treatment goals. These are greatly augmented by prescribed therapeutic exercises and functional activities. Special precautions should be given for patients with active inflammatory joint or soft tissue diseases. The therapeutic exercises should be balanced with essential rest periods for a successful treatment. The aim is usually dedicated at preserving or increasing functional level, decreasing pain and joint inflammation, and increasing range of motion and strength [22].

Figure 18.1 illustrates a summary of perioperative management of patients with rheumatic diseases.

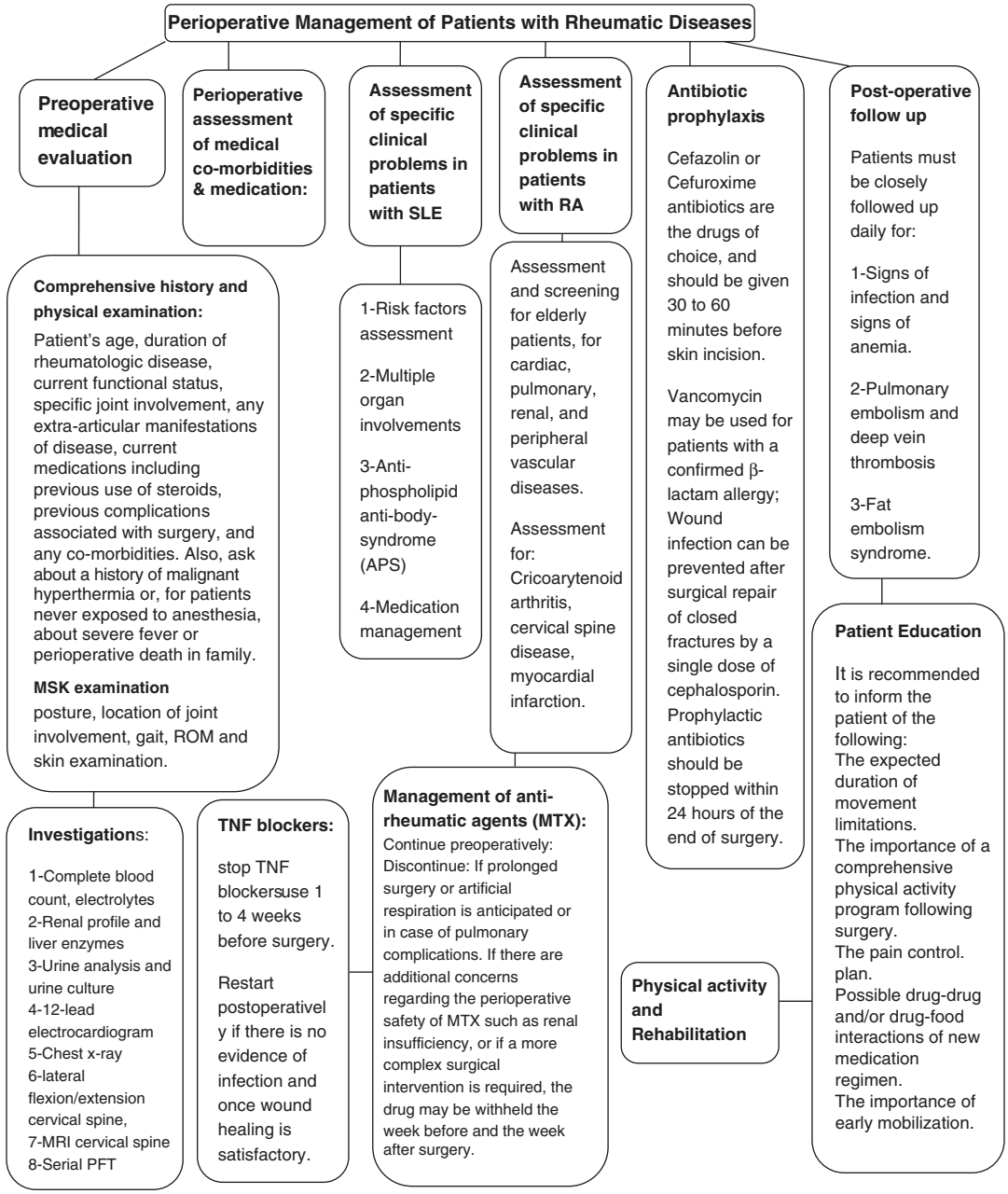

Fig. 18.1 Summary of the Perioprative Mangment of Patients with Rheumatic Diseases

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Eye and Rheumatology

19

Abdullah A Al-ghamdi

19.1 Introduction

The ocular involvement in rheumatology can be in a wide variety; it ranges from simple episcleritis to significant visual loss. Early detection followed by appropriate management can reserve vision. Ophthalmic involvement may occur in all of the rheumatic disorders. Ocular manifestation may be a presenting sign in some disorders, as in juvenile idiopathic arthritis (JIA), ankylosing spondylitis (AS), and Sjogren's syndrome (SjS), or can be a presenting sign with the systemic involvement as in systemic lupus erythematosus (SLE), polyarteritis nodosa (PAN), granulomatosis with polyangiitis (GPA), and systemic sclerosis. Thus ocular manifestations in rheumatologic diseases (Table 19.1) can be the link in approaching the diagnosis.

Detection of the ocular manifestations can be simple, yet the cooperation with ophthalmologists is crucial in some conditions. The major manifestations of ocular involvement in rheumatic disease include uveitis, scleritis, retinal vascular disease, neuro-ophthalmic lesions, orbital disease, keratitis, and SjS.(*).

Approximately 16% of patients with RA have ophthalmic manifestations including scleritis and peripheral ulcerative keratitis PUK, a condition characterized by inflammation and thinning of the peripheral cornea, which may lead to perforation and blindness. While in patients with Adamantiades-Behçet's disease (ABD) ocular involvement occurs in approximately 70%, and characterized by recurrent, explosive exacerbations of intraocular inflammation most commonly presenting as a posterior uveitis or panuveitis accompanied by a destructive retinal vasculitis, ocular or orbital involvement of Wegener's granulomatosis is seen in approximately 29–52% of the patients with PUK, corneal granuloma, episcleritis, necrotizing scleritis, or uveitis [1].

Concerning the ocular manifestations of rheumatic conditions, another aspect to shed light on is the side effects of medications used in the treatment of rheumatic diseases, for instance, one of the most serious side effects of hydroxychloroquine is toxicity in the eye.

In this chapter ocular manifestations of rheumatic diseases will be discussed along with historical points, basic ophthalmological examination, investigation, and management.

19.1.1 Objectives

By the end of this chapter, the reader is expected to construct an approach to the most common ocular presentations of rheumatic diseases, which

A. A. Al-ghamdi (✉)
Department of Ophthalmology and Otorhinolaryngology, Umm Alqura University, Makkah, Saudi Arabia
e-mail: aaaghamdi@uqu.edu.sa

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Table 19.1 Ocular involvement in rheumatic diseases

Rheumatic disease	Ocular involvement
Rheumatoid arthritis	Keratoconjunctivitis sicca Scleritis Episcleritis Ulcerative keratitis Superior oblique tendon sheath syndrome
Juvenile idiopathic arthritis	Uveitis
Systemic lupus erythematosus	Madarosis "loss of eyelashes" Keratoconjunctivitis sicca Scleritis Ulcerative keratitis Retinal vasculitis Optic neuropathy
Granulomatosis with polyangiitis	Scleritis Ulcerative keratitis Orbital inflammatory disease Nasolacrimal obstruction Dacryocystitis
Polyarteritis nodosa	Scleritis Ulcerative keratitis Orbital inflammatory disease Occlusive retinal periarteritis
Relapsing polychondritis	Scleritis Acute anterior uveitis
Systemic sclerosis	Eyelid tightening and Telangiectasia Keratoconjunctivitis sicca
Sjogren syndrome	Keratoconjunctivitis sicca Adie pupil
Giant cell arteritis	Arteritic anterior ischemic optic neuropathy is the most common TIA Central retinal artery occlusion Cilioretinal occlusion Ocular ischemic syndrome Diplopia
Psoriatic arthritis	Anterior uveitis Conjunctivitis Secondary Sjogren syndrome
Reiter syndrome	Conjunctivitis Acute anterior uveitis Keratitis Episcleritis Scleritis Papillitis Retinal vasculitis
Dermatomyositis	Eyelid heliotrope rash Periorbital edema and erythema Keratoconjunctivitis sicca Scleritis Cotton wool spot
Ankylosing spondylitis	Uveitisscleritis

include uveitis, eye dryness, corneal ulcer, scleritis, episcleritis, and ocular side effects of rheumatic medications.

19.2 Uveitis

Uveitis is the inflammation of the middle layer of the eye, which includes choroid posteriorly, ciliary body, and iris anteriorly. Uveitis is a common manifestation of rheumatic and immune-mediated disorders. The most common systemic immune disorders causing uveitis are spondyloarthritis (SpA). Those with HLA-B27-positive disease are likely to have earlier onset with more severe manifestations [2].

19.2.1 Approach to Uveitis

19.2.1.1 History

The main symptoms of anterior uveitis are eye pain and redness. These symptoms must be distinguished from other causes. Asking about constitutional symptoms and making systemic review in history aid you to target a specific diagnosis. Table 19.2 demonstrates the differential diagnosis of uveitis in terms of rheumatic diseases.

Sudden mood of onset, unilateral affection, and resolution of symptoms within few months with recurrence to the other eye are features suggestive for SpA (such as AS), reactive arthritis (ReA). Keep in mind that males are more common to be affected with SpA than females.

Insidious mood of onset, bilateral affection, and chronic duration are features suggestive for

Table 19.2 Differential diagnosis of acute uveitis in respect to systemic immune diseases

Juvenile idiopathic arthritis
Relapsing polychondritis
Ankylosing spondylitis
Reactive arthritis
Psoriatic arthritis
Systemic lupus erythematosus
Sjogren syndrome
Behçet's disease

psoriatic arthritis which is more common in females than males.

Bilateral affection with episodic attacks that do not resolve completely is a feature suggestive for Behçet's disease.

Insidious mood of onset, bilateral affection, and chronic duration in young children are features suggestive for JIA. Keep in mind that uveitis in JIA is commonly accompanied with other complications like band keratopathy (calcium deposition in corneal epithelium), posterior synechiae (which is iris adhesion to the lens), cataract, and glaucoma. Rule out other causes by asking about HIV infection and its risk factors and about the status of immune system to rule out CMV infection and tuberculosis.

19.2.1.2 Eye Examination

Presence of leukocytes in the anterior chamber by slit lamp examination is characteristic of anterior uveitis. A haze or flare may also be seen which represents protein accumulation in the anterior part of the eye. Direct visualization of active chorioretinal inflammation and the presence of leukocytes in the vitreous humor behind the eye lens can also be a sign for posterior uveitis. Inflammation in the anterior chamber, vitreous, and choroid or retina is termed panuveitis.

19.2.1.3 Treatment

In patients with systemic disease associated with uveitis, the treatment for the systemic disease may or may not be enough to control the uveitis [3]. Treatment for uveitis can be given systemically or delivered directly to the eyes.

The main use of local therapy is for the treatment of unilateral or asymmetric disease [3]. Topical glucocorticoids are for anterior uveitis. Periocular or intraocular injections of glucocorticoids (e.g., Kenacort injection) in posterior uveitis or panuveitis. A dilating drop such as scopolamine or cyclopentolate can relieve pain due to papillary muscle spasm.

Systemic treatment is generally reserved for resistant uveitis and in glaucoma patients, who cannot be treated with local injection. In addition, patients with bilateral disease are often treated with systemic therapy. A small percentage of patients with uveitis may require immunosuppressive medications. Absolute indications for their use include Behçet's syndrome, Vogt-Koyanagi-Harada syndrome, sympathetic ophthalmia, and rheumatoid sclerouveitis, while relative indications include intermediate uveitis, retinal vasculitis with central vascular leakage, chronic severe iridocyclitis or panuveitis, JRA-related iridocyclitis, and children with intermediate uveitis [4]. Additionally, patients who require a daily dose of 10 mg or more of prednisone to control their ocular inflammation may benefit from a glucocorticoid-sparing agent, such as an antimetabolite, as a safer long-term alternative [5]. Infliximab and adalimumab are antitumor necrosis factor-alpha (TNF-a) drugs. It can be very useful in patients refractory to conventional therapy. [6] Interferon-alpha appears capable of inducing disease remission in patients with Behçet's disease [3]. Rituximab, an anti-CD20 (i.e., anti-B-cell) monoclonal antibody has been reported to be effective in patients with refractory scleritis due to Wegener's disease [3].

19.3 Eye Dryness

Also known as keratoconjunctivitis sicca, it is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface, accompanied by increased osmolarity of the tear film and inflammation of the ocular surface [7, 8]. Dry eye is the most recognized ocular manifestations of SLE together with lupus retinopathy [1].

19.3.1 Approach to Dry Eye

19.3.1.1 History

A good history probably guides you to the possible underlying cause of the dry eye like medications, weather conditions, or systemic diseases. Symptoms of dry eye can be burning or foreign body sensation, eye irritation, redness or dryness, and/or blurred vision.

Table 19.3 Differential diagnosis of dry eye in respect to systemic immune-mediated diseases

Rheumatoid arthritis
Psoriatic arthritis
Sjogren syndrome
Systemic sclerosis
Systemic lupus erythematosus
Dermatomyositis

Contact lenses use, previous eye surgeries, chemical insult, Parkinson's disease, and familial history might give a hint about the possible cause of the dry eye.

Ocular dryness associated with mouth dryness increases the susceptibility of SjS, which can be a primary disorder or a secondary disorder of other systemic immune-mediated diseases. Table 19.3 shows the differential diagnosis of dry eye in terms of rheumatic diseases.

19.3.1.2 Eye Examination

Use the slit lamp to examine the lacrimal glands, the conjunctiva, and the eyelids to assess meibomian gland function. Examine ocular surface by fluorescein stain to look for corneal abrasions and assess corneal sensation.

Assessment of tear film is also an important step using tear break-up time, in which fluorescein stain is used to assess the stability of tear film or Schirmer's test, quantitative measurement of tear production by each eye.

19.3.1.3 Treatment

The treatment of dry eye deepened on the severity of the condition; it includes artificial tear substitutes, gels/ointments, topical cyclosporine and corticosteroids, systemic omega-3 fatty acids supplements, systemic cholinergic agonists, systemic anti-inflammatory agents, mucolytic agents, autologous serum tears, punctal plugs, and tarsorrhaphy [9].

19.4 Corneal Ulcer

Ulcers are primarily divided into infectious and noninfectious categories. Noninfectious ulcers include autoimmune, neurotrophic, toxic, and allergic keratitis, as well as chemical burns and keratitis secondary to entropion, blepharitis, and a host of other conditions.

Table 19.4 Differential diagnosis of ulcerative keratitis in respect to rheumatological diseases

Rheumatoid arthritis
Systemic lupus erythematosus
Granulomatosis with polyangiitis
Polyarteritis nodosa

19.4.1 Approach to Corneal Ulcer

19.4.1.1 History

Some patients are asymptomatic, while others present with mild symptoms of conjunctival swelling, hyperemia, and ocular irritation. There is a history of a systemic immune disorder such as RA, SLE, and GPA. It's essential that the treating rheumatologist manages the underlying immune condition. Examples of these immune conditions are listed in Table 19.4.

Moderate to severe ulcers can progress rapidly to melting and perforation.

19.4.1.2 Eye Examination

The appearance of noninfectious ulcers is often quite different from infectious lesions. Most notably, the underlying cornea is relatively clear without diffuse haziness or white blood cells. Sterile infiltrates smaller than 1 mm can be seen, as well as gray-white circumlimbal lesions.

19.4.1.3 Treatment

Sterile infiltrates are usually self-limiting and resolve within a week or two. If an ulcer does develop but is less than 2 mm, fairly round, and peripheral, without much stromal involvement or inflammation, it is most likely a sterile ulcer which is very responsive to topical steroids.

Although systemic immunomodulation is required, some topical measures, such as lubricating the surface, may be helpful. The clinician may also consider using topical cyclosporine to help heal the eye and immunosuppressant drops such as ascorbate to reduce the risk of stromal melting [10–14].

19.5 Scleritis

Around 50% of patients present with scleritis have underlying systemic diseases. GPA is the most common vasculitic disorder to manifest with scleritis.

19.5.1 Approach to Scleritis

19.5.1.1 History

Ask about pain; scleritis presents with severe piercing eye pain that may worsen at night and awaken patients from sleep with ipsilateral referral to head or face. Other symptoms include photophobia and redness. Severe eye and periorbital pain that is progressive and worsen in the early morning are features suggestive for necrotizing anterior scleritis. Severe pain and difficult to localize, diplopia, ocular pain upon eye movement, and reduced vision are features suggestive for posterior scleritis. In your history cover constitutional symptoms and systemic review to target rheumatic diseases and also previous ocular surgery are important. A list of rheumatic causes of scleritis is in Table 19.5.

19.5.1.2 Eye Examination

Signs of scleritis include tender globe, sclera, and episcleral edema. Slit lamp examination in advanced disease shows blood vessel closure with scleral thinning and a bluish discoloration. Diffuse ocular erythema and scleral edema with no nodules or necrosis are features suggestive for diffuse anterior scleritis. Areas of localized tender edema with deep episcleral vessel dilatation are features suggestive for nodular anterior scleritis. Keep in mind that the eye in anterior scleritis appears red while in isolated posterior scleritis the eye appears white but there are other important signs in posterior scleritis which are detected by fundoscopic examination like choroidal folds, annular choroidal detachment, retinal folds, exudative retinal detachment, retinal vasculitis, optic disc edema, and posterior uveitis. Posterior scleritis can also cause glaucoma.

Table 19.5 Differential diagnosis of scleritis in respect to systemic immune-mediated disease

Rheumatoid arthritis
Relapsing polychondritis
Systemic lupus erythematosus
Reactive arthritis

19.5.1.3 Treatment

Pain relief should be the goal of treatment. It could be achieved by topical lubricants, topical glucocorticoids, and oral NSAIDs. Treat the underlying disease. Azathioprine has been shown to be effective in the management of scleritis secondary to relapsing polychondritis. In necrotizing scleritis, cyclophosphamide is considered the treatment of choice. Infliximab has been used effectively in scleritis secondary to JIA, ankylosing spondylitis, Wegener granulomatosis, sarcoidosis, and Crohn disease [15].

19.6 Episcleritis

19.6.1 Approach to Episcleritis

19.6.1.1 History

Ask in your history about the mood of onset, eye redness and whether it is diffused or localized, and eye irritation because episcleritis usually manifests as an acute onset, localized or diffused eye redness, and/or irritation. Bilateral eye involvement may suggest an immune-mediated disease. Examples of these immune-mediated episcleritis are listed in Table 19.6.

19.6.1.2 Eye Examination

Shows vasodilatation of superficial episcleral vessels and episcleral edema.

19.6.1.3 Treatment

Treat the underlying disease. Pain relief should be the goal of treatment. It could be achieved by

Table 19.6 Differential diagnosis of episcleritis in respect to systemic immune-mediated disease

Rheumatoid arthritis
Systemic lupus erythematosus
Behçet's disease
Reiter syndrome
Inflammatory bowel disease

topical lubricants, topical NSAIDs [16], topical glucocorticoids, and oral NSAIDs.

19.7 Cataract

Cataract is defined as an opacity in the lens of the eye. In rheumatology practice, cataract results from the use of topical or systemic glucocorticoids for treatment of immune-mediated diseases. The lens of the eye is composed of layers like an onion. The outermost is the capsule, the layer inside the capsule which is the cortex, and the innermost layer which is the nucleus. A cataract may develop in any of these areas and is described based on its location in the lens shown in Fig. 19.1. Risk factors and symptoms can be reviewed in Tables 19.7 and 19.8.

19.7.1 Approach to Cataract

19.7.1.1 History

Ask about vision difficulties experienced by the patient that may limit their daily activities and other general health concerns affecting vision.

19.7.1.2 Eye Examination

It includes visual acuity measurement to determine to what extent a cataract may be limiting clear vision at distance and near, refraction to determine the need for changes in an eyeglass or contact lens prescription, as well as slit lamp examination to determine the extent and location of any cataracts. It would be better to evaluate the retina of the eye through a dilated pupil to exclude any retinal disease. It is also advisable to measure the intraocular pressure. Supplemental testing for color vision and glare sensitivity could be done.

19.7.1.3 Treatment

The treatment of cataracts is based on the level of visual impairment they cause. If a cataract affects vision only minimally, or not at all, no treatment may be needed. Patients may be advised to monitor for increased visual symptoms and follow a regular check-up schedule. In some cases, a change in eyeglass prescription may provide temporary improvement in visual acuity.

Table 19.7 Risk factors for cataract

Old age
Diabetes mellitus
Drugs, e.g., steroids and chlorpromazine
UV light radiation
Smoking
Alcohol
Nutritional deficiency

Table 19.8 Signs and symptoms of cataract

Blurred or hazy vision
Reduced intensity of colors
Increased sensitivity to glare from lights, particularly when driving at night
Increased difficulty seeing at night
Change in the eye's refractive error

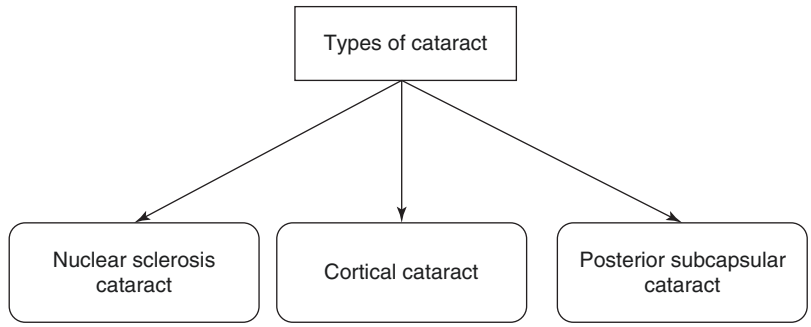

Fig. 19.1 Types of cataract

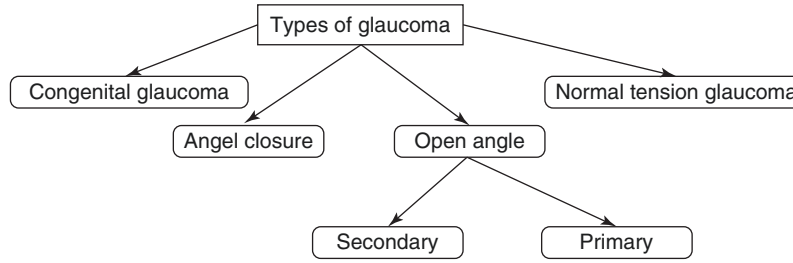

Fig. 19.2 Types of glaucoma

19.8 Glaucoma

Glaucoma is a group of eye disorders leading to progressive damage to the optic nerve. Like in cataract, glaucoma in rheumatology practice results from the use of topical or systemic glucocorticoids for treatment of immune-mediated diseases. It is usually associated with increased pressure inside the eye and is characterized by loss of optic nerve tissue resulting in loss of vision. Advanced glaucoma may even cause blindness. Figure 19.2 shows the types of glaucoma.

Table 19.9 Risk factors for glaucoma

Age	Increased risk after 60 years, after 40 years in people of African descent
Race	Increased risk in African race (open angle) and Asians (closed angle)
Family history	Increased risk in people who have siblings or parents with glaucoma
Medical conditions	Hypertension and heart diseases
Physical injury to the eye	Like blunt trauma
Some eye conditions	Retinal detachment, eye tumors, and eye inflammations, short axial length, and hypermetropia
Medications	Corticosteroid use

19.8.1 Approach to Glaucoma

19.8.1.1 History

Ask about any symptoms the patient is experiencing and the presence of any risk factors for glaucoma which are listed in Table 19.9.

19.8.1.2 Eye Examination

Measure visual acuity to determine the extent to which vision may be affected. Measurement of the pressure inside the eye is an essential step and can be done by tonometry or more preferably by applanation. Pachymetry to measure corneal thickness could be done for more accurate intraocular pressure estimation. Visual field testing, also called perimetry, is often done for glaucoma patients to check if the field of vision has been affected by glaucoma. Evaluation of the retina can be done to monitor any changes that might occur over time. Supplemental testing may include gonioscopy, a procedure to give clearer views of the angle anatomy.

19.8.1.3 Treatment

The treatment of glaucoma is aimed at reducing intraocular pressure. The most common first-line treatment of glaucoma is usually prescription eye drops that must be taken regularly. In some cases, systemic medications, laser treatment, or other surgery may be required. While there is no cure as yet for glaucoma, early diagnosis and continuing treatment can preserve eyesight. Patients need to continue treatment for the rest of their lives. Because the disease can progress or change silently, compliance with eye medications and eye examinations are essential, as treatment may need to be adjusted periodically. Early detection, prompt treatment, and regular monitoring can help to control glaucoma and therefore reduce the chances of progression vision loss.

19.9 Ophthalmologic Side Effects of Rheumatic Medications [17]

There are several ocular side effects of rheumatic medications (Table 19.10). It is well documented that corticosteroid use induces cataract and increases intraocular pressure causing glaucoma. Most common type of cataract induced by corticosteroids is posterior subcapsular cataract. The incidence of posterior subcapsular cataract is associated with dosage of steroids use and duration of treatment. In a number of randomized, controlled trials, the incidence of corticosteroid-induced cataracts reported to be ranging from 6.4% to 38.7% after oral corticosteroid use [18, 19]. Glaucoma incidence has been reported in

Table 19.10 Ocular side effects of medications used in rheumatic diseases

Steroids	Cataract Glaucoma
Indomethacin	Corneal opacity Blurred vision Retinopathy Pigmentary changes of the macula
Aspirin	Subconjunctival hemorrhages and hemorrhagic retinopathies following trauma (increases bleeding tendency)
Ibuprofen, naproxen, oxaprozin, and piroxicam	Increase bleeding tendencies Blurred vision Photophobia Decreases central vision Stevens-Johnson syndrome
Rofecoxib, celecoxib, valdecoxib, lumiracoxib, nimesulide, and etodolac which are NSAIDs selective for the inhibition of cyclooxygenase (COX)-2	Conjunctivitis Blurred vision
Sulfasalazine	Facial nerve palsy Blurred near vision
Abatacept	Eye irritation Allergic conjunctivitis Blurry vision Visual disturbance Eye pruritus
Rituximab	Conjunctivitis Transient ocular edema A burning sensations Loss of visual function
Interferon alfa	Retinal vascular abnormalities (retinal microvascular changes, presence of cotton wool spots, intraretinal hemorrhages, retinal detachment)
Methotrexate	Periorbital edema Ocular pain Blurred vision Photophobia Conjunctivitis Blepharitis Decreased reflex tear secretion Non-arteritic ischemic optic neuropathy
Bisphosphonates	Uveitis Scleritis
Chloroquine and hydroxychloroquine	Keratopathy Ciliary body dysfunction Lens opacities Outer retinal damage Pigmentary retinopathy

patients using oral, intravenous, eye drops, intranasal, or inhalational steroids.

Indomethacin is one of the most potent NSAIDs that has been associated with cases of corneal opacities and blurred vision, especially when used long term. Reports on ocular side effects from the usage of sulfasalazine are relatively few, including peripheral facial nerve palsy and blurred near vision in association with sulphasalazine treatment. Aspirin, ibuprofen, naproxen, oxaprozin, and piroxicam increase bleeding tendency which manifests in subconjunctival hemorrhages and hemorrhagic retinopathies following trauma.

Biologics are a new class of drugs which have become recently a choice to treat immune-mediated diseases. Abatacept is a biologic agent which causes eye irritation, allergic conjunctivitis, blurry vision, visual disturbance, and eye pruritus involving less than 1% of the drug users. Another biologic agent is rituximab. In a clinical study concerning the efficacy of rituximab in 222 patients with lymphoma, 9 of them reported ocular side effects, including conjunctivitis, transient ocular edema, a burning sensation, and a transient or permanent loss of visual function [20]. Interferon alfa is an antiviral which is used as immunomodulator and has shown effectiveness in treating rheumatic diseases. Side effects of interferon alfa include retinal vascular abnormalities (retinal microvascular changes, presence of cotton wool spots, intraretinal hemorrhages, retinal detachment). Mostly, the ocular changes are transient and asymptomatic [21].

Methotrexate is an antimetabolite which is used to treat several rheumatic diseases. Ocular side effects of methotrexate include periorbital edema, ocular pain, blurred vision, photophobia, conjunctivitis, blepharitis, decreased reflex tear secretion, and non-arteritic ischemic optic neuropathy. Bisphosphonates are used in patients with chronic inflammatory diseases or patients with osteoporosis. Their use has been reported to cause uveitis and scleritis.

Antimalarials such as chloroquine and hydroxychloroquine cause keratopathy, ciliary body dysfunction, lens opacities, outer retinal damage, and pigmentary retinopathy.

19.10 Antimalarial-Related Retinopathy

19.10.1 Approach to Antimalarial-Related Retinopathy

19.10.1.1 History

There are many factors that may contribute to hydroxychloroquine retinopathy. These factors include daily and cumulative dosage which is the most important, duration of treatment, renal or liver disease, patient's age, and prior retinal disease. The great majority of case reports of hydroxychloroquine toxicity occurred in individuals taking more than 6.5 mg/kg/day or chloroquine at 3 mg/kg/day, and most of the reports of hydroxychloroquine toxicity at lower doses occurred in individuals who took the drug for at least 5 years.

19.10.1.2 Eye Examination

Consists of a dilated posterior-segment examination, along with Amsler grid testing or automated perimetry. Baseline fundus photographs and fluorescein angiography (FA) are helpful in patients with preexisting macular pigmentary changes. The patients should repeat visual acuity testing every 6 months, screen the visual field, use the Amsler grid, and have a detailed funduscopy. Central threshold visual field testing is recommended for suspected optic neuropathy.

19.10.1.3 Treatment

The only treatment for antimalarial related retinopathy is stopping the offending medication with consultation of the rheumatologist who is taking care of the patient.

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Vasculitis and Rheumatology

20

Waleed Hafiz

20.1 Learning Objectives

By the end of this chapter, you should be able to:

- Discuss pathologic mechanisms underlying vasculitis.
- Review classification and nomenclature of vasculitis.
- Compose a diagnostic approach to a patient with vasculitis.
- Describe major forms of vasculitis.

Vasculitis is a clinicopathologic process characterized by inflammation and damage of blood vessels by leucocytes which leads to bleeding. Compromise of vascular lumen results in ischemia and necrosis of the tissues supplied by the involved vessels. Vasculitis can be a primary disease process, or it may be secondary to another underlying disease [1].

20.1.1 Pathologic Mechanisms Underlying Vasculitis

The exact mechanisms are unclear. However, three different models have been advanced [2]:

1. Pathogenic immune-complex formation and/or deposition
   (IgA vasculitis, hepatitis C-associated vasculitis, hepatitis B-associated vasculitis)
2. Production of antineutrophil cytoplasmic antibodies (ANCA)
   (Microscopic polyangiitis, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis)
3. Pathogenic T lymphocytic responses and granuloma formation
   (Giant cell arteritis, Takayasu's arteritis, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis)

The end result of these immunopathologic pathways is endothelial cell activation, with subsequent vessel obstruction and ischemia of dependent tissue. This may cause hemorrhage in the surrounding tissues and, in some cases, weakening of the vessel wall, which leads to the formation of aneurysms. For almost all forms of vasculitis, the triggering event initiating and driving this inflammatory response is unknown.

20.1.2 Classification of Vasculitis

Vasculitis is classified based on the predominant size of vessels affected. Types of vessels are

W. Hafiz (✉)
Faculty of Medicine, Umm Al-Qura University, Makkah, Saudi Arabia
e-mail: wahafiz@uqu.edu.sa

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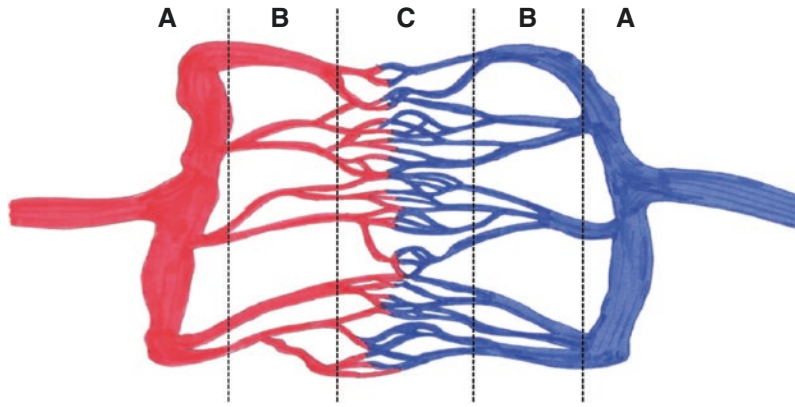

Fig. 20.1 Types of vessels that are defined by the 2012 Chapel Hill Consensus Conference nomenclature system. (**a**) Large vessels represents the aorta, its major branches and their corresponding veins. (**b**) Medium vessels are the visceral arteries, veins and their main branches. (**c**) Small vessels consist of interparenchymal arteries, arterioles, capillaries, venules and veins

defined in the (CHCC) 2012 [3, 4]. This is illustrated in Fig. 20.1.

20.1.3 The 2012 Chapel Hill Consensus Conference (CHCC) on Nomenclature of Vasculitis

The CHCC is a nomenclature system. It is neither a classification system nor a diagnostic system. It specifies the name that should be used for a specifically defined disease process. The following names are adopted by the CHCC 2012 on the nomenclature of vasculitides [4], and their definitions are presented in Table 20.1.

Large Vessel Vasculitis (LVV):
1. Takayasu's arthritis (TA).
2. Giant cell arthritis (GCA).

Medium Vessel Vasculitis (MVV):
1. Polyarteritis nodosa (PAN).
2. Kawasaki disease (KD).

Small Vessel Vasculitis (SVV):
1. Antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis:
   (a) Granulomatosis with polyangiitis (GPA).
   (b) Microscopic polyangiitis (MPA).
   (c) Eosinophilic granulomatosis with polyangiitis (EGPA).
2. Immune-complex-associated vasculitis:
   (a) Anti-glomerular basement membrane (Anti-GBM) disease.
   (b) Cryoglobulinemic vasculitis (CV).
   (c) IgA vasculitis (IgAV).
   (d) Hypocomplementemic urticarial vasculitis (HUV) (Anti-C1q).

Variable Vessel Vasculitis (VVV):
1. Behcet's disease (BD).
2. Cogan's syndrome (CS).

Single Organ Vasculitis (SOV):
1. Cutaneous leukocytoclastic angiitis.
2. Cutaneous arteritis.
3. Primary central nervous system vasculitis.
4. Isolated aortitis.

Vasculitis Associated with Systemic Disease:
1. Lupus vasculitis.
2. Rheumatoid vasculitis.
3. Sarcoid vasculitis.

Vasculitis Associated with Probable Etiology:
1. Hepatitis C-associated cryoglobulinemic vasculitis.
2. Hepatitis B-associated vasculitis.
3. Syphilis-associated vasculitis.
4. Drug-associated immune-complex vasculitis.
5. Drug-associated ANCA-associated vasculitis.
6. Cancer-associated vasculitis.

Table 20.1 Definitions adopted by the 2012 CHCC on the nomenclature of vasculitides [4]

CHCC2012 name	CHCC2012 definition
Large vessel vasculitis (LVV)	"Vasculitis affecting large arteries more often than other vasculitides. Large arteries are the aorta and its major branches. Any size artery may be affected. Page no. 6"
Takayasu arteritis (TAK)	"Arteritis, often granulomatous, predominantly affecting the aorta and/or its major branches. Onset usually inpatients younger than 50 years. Page no. 6"
Giant cell arteritis (GCA)	"Arteritis, often granulomatous, usually affecting the aorta and/or its major branches, with a predilection for the branches of the carotid and vertebral arteries. Often involves the temporal artery. Onset usually in patients older than 50 years and often associated with polymyalgia rheumatica. Page no. 6"
Medium vessel vasculitis (MVV)	"Vasculitis predominantly affecting medium arteries defined as the main visceral arteries and their branches. Any size artery may be affected. Inflammatory aneurysms and stenoses are common. Page no. 6"
Polyarteritis nodosa (pan)	"Necrotizing arteritis of medium or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules, and not associated with antineutrophil cytoplasmic antibodies (ANCAs). Page no. 6"
Kawasaki disease (KD)	"Arteritis associated with the mucocutaneous lymph node syndrome and predominantly affecting medium and small arteries. Coronary arteries are often involved. Aorta and large arteries may be involved. Usually occurs in infants and young children. Page no. 6"
Small vessel vasculitis (SVV)	"Vasculitis predominantly affecting small vessels, defined as small intraparenchymal arteries, arterioles, capillaries, and venules. Medium arteries and veins may be affected. Page no. 6"
ANCA-associated vasculitis (AAV)	"Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (i.e., capillaries, venules, arterioles, and small arteries), associated with myeloperoxidase (MPO)ANCA or proteinase 3 (PR3) ANCA. Not all patients have ANCA. Add a prefix indicating ANCA reactivity, e.g., MPO-ANCA, PR3-ANCA, ANCA negative. Page no. 6"
Microscopic polyangiitis (MPA)	"Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (i.e., capillaries, venules, or arterioles). Necrotizing arteritis involving small and medium arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs. Granulomatous inflammation is absent. Page no. 6"
Granulomatosis with polyangiitis (GPA)	"Necrotizing granulomatous inflammation usually involving the upper and lower respiratory tract, and necrotizing vasculitis affecting predominantly small to medium vessels (e.g., capillaries, venules, arterioles, arteries and veins). Necrotizing glomerulonephritis is common. Page no. 6"
Eosinophilic granulomatosis with polyangiitis (EGPA)	"Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium vessels, and associated with asthma and eosinophilia. ANCA is more frequent when glomerulonephritis is present. Page no. 6"
Immune complex vasculitis	"Vasculitis with moderate to marked vessel wall deposits of immunoglobulin and/or complement components predominantly affecting small vessels (i.e., capillaries, venules, arterioles, and small arteries). Glomerulonephritis is frequent. Page no. 6"
Anti-glomerular basement membrane disease (anti-GBM)	"Vasculitis affecting glomerular capillaries, pulmonary capillaries, or both, with GBM deposition of anti-GBM autoantibodies. Lung involvement causes pulmonary hemorrhage, and renal involvement causes glomerulonephritis with necrosis and crescents. Page no. 6"
Cryoglobulinemic vasculitis (CV)	"Vasculitis with cryoglobulin immune deposits affecting small vessels (predominantly capillaries, venules, or arterioles) and associated with serum cryoglobulins. Skin, glomeruli, and peripheral nerves are often involved. Page no. 6"
IgA vasculitis (IgAV)	"Vasculitis, with IgA1-dominant immune deposits, affecting small vessels (predominantly capillaries, venules, or arterioles). Often involves skin and gastrointestinal tract, and frequently causes arthritis. Glomerulonephritis indistinguishable from IgA nephropathy may occur. Page no. 6"

(continued)

Table 20.1 (continued)

CHCC2012 name	CHCC2012 definition
Hypocomplementemic Urticarial vasculitis (HUV) (anti-C1q vasculitis)	"Vasculitis accompanied by urticaria and hypocomplementemia affecting small vessels (i.e., capillaries, venules, or arterioles), and associated with anti-C1qantibodies. Glomerulonephritis, arthritis, obstructive pulmonary disease, and ocular inflammation are common. Page no. 6"
Variable vessel vasculitis (VVV)	"Vasculitis with no predominant type of vessel involved that can affect vessels of any size (small, medium, and large) and type (arteries, veins, and capillaries). Page no. 6"
Behcet's disease (BD)	"Vasculitis occurring in patients with Behcet's disease that can affect arteries or veins. Behcet's disease is characterized by recurrent oral and/or genital aphthous ulcers accompanied by cutaneous, ocular, articular, gastrointestinal, and/or central nervous system inflammatory lesions. Small vessel vasculitis, thromboangiitis, thrombosis, arteritis, and arterial aneurysms may occur. Page no. 6"
Cogan's syndrome (CS)	"Vasculitis occurring in patients with Cogan's syndrome. Cogan's syndrome characterized by ocular inflammatory lesions, including interstitial keratitis, uveitis, and episcleritis, and inner ear disease, including sensorineural hearing loss and vestibular dysfunction. Vasculitic manifestations may include arteritis (affecting small, medium, or large arteries), aortitis, aortic aneurysms, and aortic and mitral valvulitis. Page no. 6"
Single-organ vasculitis (SOV)	"Vasculitis in arteries or veins of any size in a single organ that has no features that indicate that it is a limited expression of a systemic vasculitis. The involved organ and vessel type should be included in the name (e.g., cutaneous small vessel vasculitis, testicular arteritis, central nervous system vasculitis). Vasculitis distribution may be unifocal or multifocal (diffuse) within an organ. Some patients originally diagnosed as having SOV will develop additional disease manifestations that warrant redefining the case as one of the systemic vasculitides (e.g., cutaneous arteritis later becoming systemic polyarteritis nodosa, etc.). Page no. 7"
Vasculitis associated with systemic disease	"Vasculitis that is associated with and maybe secondary to (caused by) a systemic disease. The name (diagnosis) should have a prefix term specifying the systemic disease (e.g., rheumatoid vasculitis, lupus vasculitis, etc.). Page no. 7"
Vasculitis associated with probable etiology	"Vasculitis that is associated with a probable specific etiology. The name (diagnosis) should have a prefix term specifying the association (e.g., hydralazine-associated microscopic polyangiitis, hepatitis B virus–associated vasculitis, hepatitis C virus-associated cryoglobulinemic vasculitis, etc.). Page no. 7"

20.1.4 How to Approach a Patient with Vasculitis?

20.1.4.1 A Case Scenario

A lady comes to the clinic with a rash over her legs. She is aged 32 years and for the last 6 months has been unwell, with intermittent fevers, loss of appetite, and fatigue. Recent blood tests show elevated erythrocyte sedimentation rate (ESR; 83 mm/h) and C-reactive protein (CRP; 46 mg/dL). Today she has palpable purpura on her lower legs. Urinalysis is positive for blood and protein.

What are the clinical clues to vasculitis?
What investigations will assist with a precise diagnosis?
How should the condition be treated and monitored?

Tables 20.2, 20.3 and 20.4 summarize history, physical examination findings (Fig. 20.3), and work-up of a patient presenting with suspected vasculitis. Figure 20.2 summarizes history taking from a patient presenting with suspected vasculitis. This includes review of systems, past medical history, and medication history. Figures 20.4, 20.5 and 20.6 show different mucocutaneous finding that can be present in a patient with vasculitis.

20.1.5 Major Forms of Vasculitis

20.1.5.1 Takayasu's Arteritis (TA)

TA primarily affects the aorta and its primary branches [5]. It is an uncommon form of vasculitis. Up to 90% of the cases are women of reproductive age, and it is more prevalent in Asia [6].

Table 20.2 What to ask a patient presenting with suspected vasculitis?

Non-specific systemic symptoms	Fever, weight loss, malaise, loss of appetite, and fatigue
Skin	Rash, palpable purpura, nodules, ulcers, and cutaneous or nailfold infarctions
Ocular symptoms	Pain, redness, diplopia, and visual loss
Neurological	Numbness, weakness, pain consistent with mononeuritis multiplex, transient ischemic attacks, and symptoms suggestive of stroke
Cardiac	Chest pain and dyspnea
Pulmonary	Chest pain, dyspnea, cough, and hemoptysis
Gastrointestinal	Abdominal pain and upper or lower gastrointestinal bleeding
Musculoskeletal	Arthralgias and arthritis
Renal	Hematuria
Past medical history	Systemic rheumatic diseases (systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome, scleroderma, dermatomyositis) Malignancies (lymphoma, leukemia) Hematological conditions (thrombotic thrombocytopenic purpura) Bronchial asthma, hyperactive airways Infections (HIV, viral hepatitis B or C)
Medication history	Hydralazine, propylthiouracil, thiazide, allopurinol, penicillin, gold, phenytoin, and sulfonamide

Table 20.3 What to look for when physically examining a patient with suspected vasculitis?

Skin	Palpable purpura, nodules, papules, ulcers, and digital ischemia
Pulse and blood pressure	Unequal pulses and high blood pressure (especially diastolic)
Face	Pallor, conjunctivitis, septal nasal perforation, and saddle nose deformity
Oral cavity and neck	Strawberry gums, oral ulcers, and cervical lymphadenopathy
Cardiac	Cardiac bruits
Pulmonary	Bilateral crepitations
Gastrointestinal	Abdominal tenderness
Musculoskeletal	Arthritis and migratory polyarthritis

Table 20.4 What are the laboratory tests that help ascertain the type of vasculitis?

CBC	Anemia, leukocytosis, leukopenia, thrombocytosis, and thrombocytopenia
Renal profile	Hyperkalemia and elevated creatinine
Hepatic profile	Abnormal if there is an underlying hepatitis
ANCA, RF, ANA, and cryoglobulins	Screening
Complements C3 and C4	Hypocomplementemia
Hepatitis and HIV serology	Rule out hepatitis B or C and HIV infection
Urinalysis	Active sediment or red blood cell casts
Inflammatory markers	Elevated ESR and/or CRP
Chest X-ray	Pulmonary involvement (nodules, infiltrates, cavities, etc.)
2D echocardiogram	Cardiac involvement
CT angiography/ MRA	Aneurysms, vascular irregularities, stenosis, and post-stenotic dilatation
Tissue biopsy	Identify the histopathology

The inflammation is characterized by thickening of the arterial wall. This can lead to narrowing, occlusion, or dilatation of the arteries [7].

The pathogenesis of TA is not clear. Presence of mononuclear cells is thought to cause active inflammation that leads to granuloma formation [8]. Aneurysms are formed due to laminal destruction. Arterial plaques were also found in patients with TA [9].

Systemic symptoms are manifested early in TA [10]. As the disease progresses, vascular involvement becomes evident. Subclavian artery stenosis proximal to the origin of the vertebral artery can lead to the so-called subclavian steal syndrome [11]. Ischemic ulcerations and gangrene may develop as results of vascular occlusion.

The differential diagnosis of TA includes fibromuscular dysplasia, excess ergotamine intake, Ehlers-Danlos syndrome, and GCA.

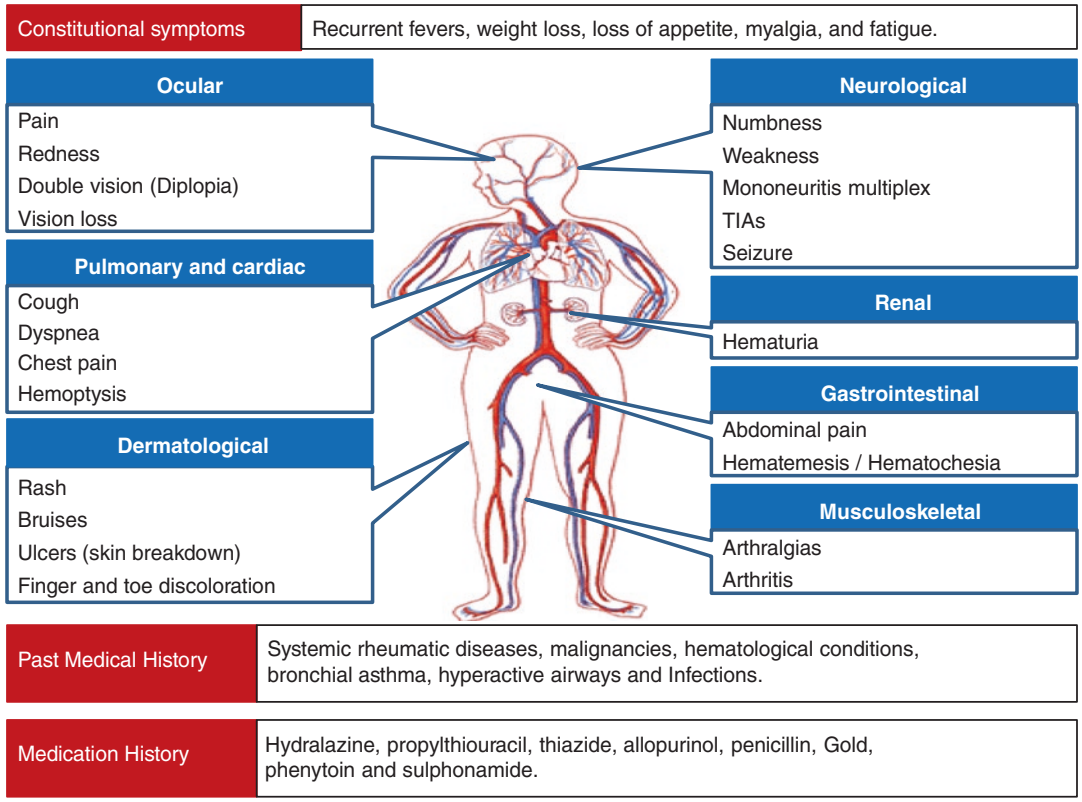

Fig. 20.2 History taking from a patient presenting with suspected vasculitis. This includes review of systems, past medical history and medication history

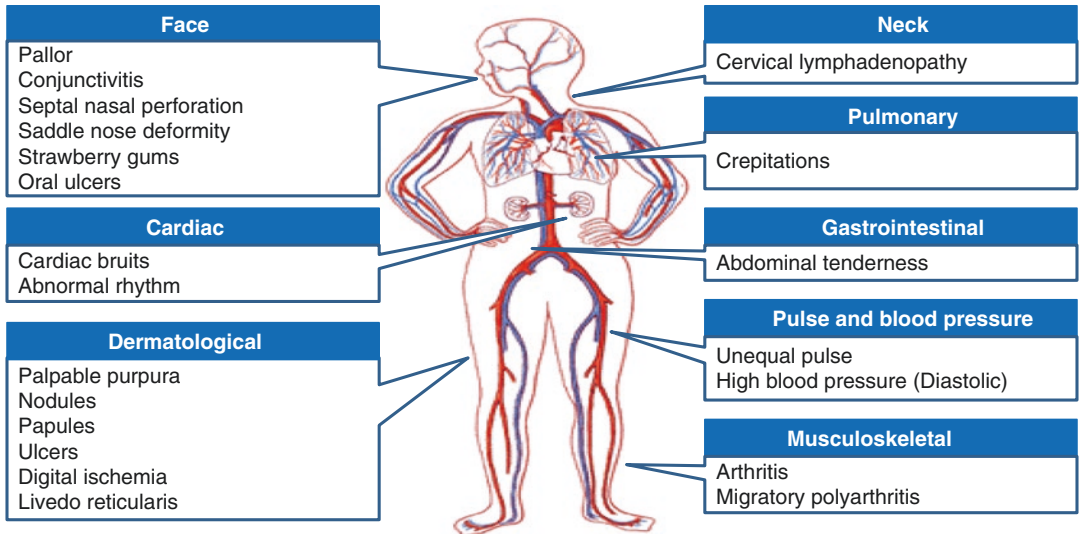

Fig. 20.3 Physical signs that should be checked for in a patient presenting with suspected vasculitis

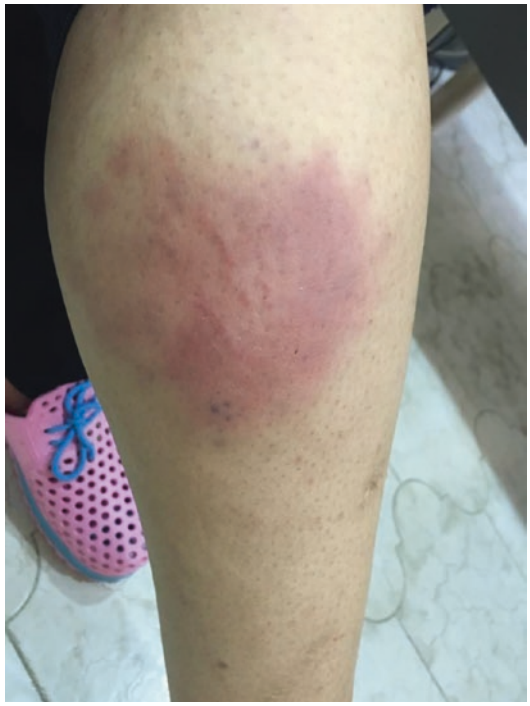

Fig. 20.4 Erythema nodosum in polyarteritis nodosa. Courtesy of Prof. Hani Almoallim

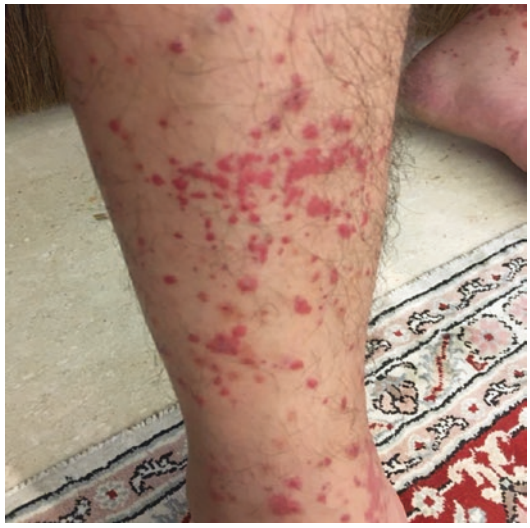

Fig. 20.5 Leukocytoclastic vasculitis with palpable purpura in a patient with immune-complex-associated small vessel vasculitis. Courtesy of Prof. Hani Almoallim

Glucocorticoids are the mainstay treatment. They reduce both systemic symptoms and disease progression [12]. Azathioprine, mycophenolate, methotrexate, tocilizumab, or leflunomide can be used in glucocorticoid-resistant cases, while cyclophosphamide is for those who have continued disease activity despite those medications [13, 14]. Percutaneous transluminal angioplasty or bypass grafts may be considered in late cases when irreversible arterial stenosis has occurred and when significant ischemic symptoms develop [15].

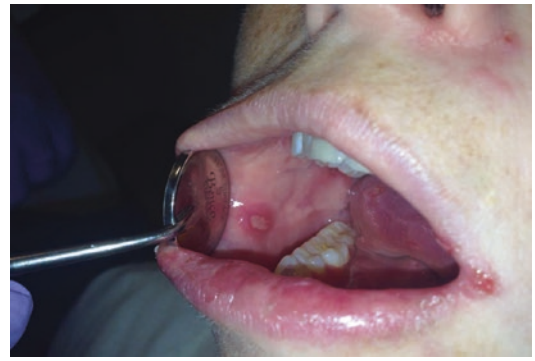

Fig. 20.6 Oral ulcer in a patient with Behcet's disease. Courtesy of Dr. Lujain Homeida

Table 20.5 summarizes CHCC12 definition, epidemiology, clinical manifestation, diagnostic studies, American College of Rheumatology (ACR) 1990 classification criteria, and treatment of TA.

20.1.5.2 Giant Cell Arteritis (GCA)

GCA is a vasculitis of large-sized vessels. Up to 90% of cases are above the age of 60 [16]. It affects the aorta and its major branches, mainly the carotid and vertebral arteries [17].

The pathogenesis of GCA is poorly understood. It is thought that an initial trigger (e.g., viral infection or other factor) activates monocytes in a susceptible host. These monocytes cause systemic symptoms. Release of inflammatory mediators and tissue injury may lead to fibrosis, scarring, and narrowing or occlusion of the arteries [18].

Symptoms of GCA start gradually but may manifest acutely in some patients. An efficient history should include questions about systemic symptoms, such as fever, fatigue, and weight loss; headache; jaw claudication, which is the most specific symptom of GCA; visual symptoms; and symptoms of polymyalgia rheumatica [19–21].

Table 20.5 Takayasu's arteritis (pulseless disease)

CHCC 2012 definition	Arteritis, often granulomatous, predominantly affecting the aorta and/or its major branches. Onset usually in patients younger than 50 years [4]
Epidemiology	Most common in Asia and in young women of reproductive age
Clinical manifestation	Phase 1: Inflammatory period (fever, arthralgias, weight loss) Phase 2: Vessel pain and tenderness, unequal pulses in extremities, bruits, limb claudication, hypertension, aortic aneurysm, and insufficiency Phase 3: Vessel fibrosis
Diagnostic studies	Elevated ESR (75%) and CRP Angiography and MRI/MRA: Stenosis, occlusion, irregularity, and aneurysms Biopsy: Pan arteritis, cellular infiltrates with granulomas, and giant cells
ACR 1990 Classification criteria	1. Age less than 40 at disease onset. 2. Claudication of extremities. 3. Decrease in brachial artery pulse. 4. Systolic BP difference by more than 10 mmHg between both arms. 5. Bruit over subclavian artery or aorta. 6. Arteriographic narrowing or occlusion. Presence of 3 out of 6 is 90.5% sensitive (se) and 97.8% specific (Sp) [3]
Treatment	Steroids: 40–60 mg/day initially, then slow tapering based on clinical and radiological response. Methotrexate, leflunomide, azathioprine, or tocilizumab for resistant cases. May consider antiplatelet therapy or surgical/endovascular revascularization

Table 20.6 Giant cell arteritis

CHCC 2012 definition	Arteritis, often granulomatous, usually affecting the aorta and/or its major branches, with a predilection for the branches of the carotid and vertebral arteries. Often involves the temporal artery. Onset usually in patients older than 50 years and often associated with polymyalgia rheumatica [4]
Epidemiology	90% are above 60 years, rare below 50 years, female/male ratio is 2:1
Clinical manifestation	Constitutional symptoms, headache, tender and pulseless temporal arteries, optic neuritis, diplopia, amaurosis fugax, blindness, jaw claudication, Raynaud's phenomenon, and thoracic aortic aneurysm
Diagnostic studies	Elevated ESR and CRP. Anemia Angiography, MRI/MRA: If aortic aneurysm is suspected Bilateral temporal artery biopsy: Vasculitis and granulomas
ACR 1990 Classification criteria	1. Age more than 50 at disease onset. 2. New headache. 3. Temporal artery tenderness or decreased pulse. 4. ESR more than 50 mm/h. 5. Biopsy: Vasculitis and granulomas. Presence of 3 out of 5 is 93.5% Se and 91.2% Sp [3]
Polymyalgia rheumatica	Seen in 50% of patients with GCA, 15% of patients with PMR develop GCA. Bilateral aching and morning stiffness for more than 30 min for more than 1 month, involving two of the following areas: Neck or torso, shoulders or proximal arms, hips or proximal thighs, and night time pain. Age at onset is usually more than 40
Treatment	Steroids: 40 to 60 mg/day and 10 to 20 mg/day for polymyalgia rheumatica. Taper down treatment based on clinical response. Monitor ESR and CRP Methotrexate and tocilizumab can be added as steroid-sparing agents

Temporal artery biopsy is the gold standard modality for the diagnosis of GCA. However, if the clinical suspicion is high or vision is threatened, high-dose glucocorticoid therapy should be started immediately. Appropriate measures to prevent glucocorticoid-induced osteoporosis should be taken [22]. Methotrexate is moderately effective as a glucocorticoid-sparing agent. Tocilizumab was recently granted a breakthrough designation status by the US Food and Drug Association for GCA based on positive results from a phase 3 clinical trial [23].

Table 20.6 summarizes CHCC12 definition, epidemiology, clinical manifestation, diagnostic

studies, ACR 1990 classification criteria, and treatment of GCA.

20.1.5.3 Polyarteritis Nodosa (PAN)

PAN is a systemic necrotizing arteritis of the medium-sized muscular arteries, with occasional involvement of small muscular arteries. It is not associated with the presence of ANCA. It is more common in men in the sixth decade of life [24].

PAN is mostly idiopathic, although hepatitis B virus infection, hepatitis C virus infection, and hairy cell leukemia are important in the pathogenesis of some cases. The pathogenesis is poorly understood. It is characterized by segmental transmural inflammation of muscular arteries which leads to fibrinoid necrosis and disruption of the elastic lamina. Unlike other forms of systemic vasculitis, it does not involve veins [25].

Like most types of vasculitis, patients with PAN present with systemic symptoms (fatigue, weight loss, weakness, fever, arthralgias) and signs of multisystem involvement (skin lesions, hypertension, renal insufficiency, neurologic dysfunction, and abdominal pain). PAN has a striking tendency to spare the lungs.

The differential diagnosis of PAN is broad, including infectious diseases that affect the vasculature or that are complicated by systemic vasculitis; noninfectious disorders, particularly those that can cause widespread arterial embolism, thrombosis, or vasospasm; and other systemic vasculitides.

Treatment of PAN depends on the severity of the disease. Mild disease can be treated with prednisolone at a dose of 1 mg/kg per day (maximum 60 to 80 mg/day) for approximately 4 weeks and then to be tapered based on clinical improvement [26]. Moderate to severe disease is treated with methotrexate, azathioprine, mycophenolate, or cyclophosphamide [26].

Table 20.7 summarizes CHCC12 definition, epidemiology, clinical manifestation, diagnostic studies, ACR 1990 classification criteria, and treatment of PAN.

Table 20.7 Polyarteritis nodosa

CHCC 2012 definition	Necrotizing arteritis of medium or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules and not associated with antineutrophil cytoplasmic antibodies (ANCAs) [4]
Epidemiology	More common in men. Average age at onset is 50. Strongly associated with HBV
Clinical manifestation	Constitutional symptoms, myalgias, arthralgias, arthritis, active urinary sediment, hypertension, renal impairment, peripheral neuropathy, mononeuritis multiplex, abdominal pain, GI bleeding, testicular pain, livedo reticularis, purpura, coronary arteritis, pericarditis, and Raynaud's phenomenon
Diagnostic studies	Elevated ESR and CRP. Leukocytosis. HbsAg is positive in about 30% ANCA is negative Angiography or CTA: Microaneurysms and focal vessel narrowing Biopsy of sural nerve, skin, or affected organ: Vasculitis, necrosis, and no granulomas
ACR 1990 Classification criteria	1. More than 4 kilograms of weight loss. 2. Livedo reticularis. 3. Testicular pain or tenderness. 4. Myalgias, weakness, and leg tenderness. 5. Mono or polyneuropathy. 6. Diastolic BP more than 90 mmHg. 7. Elevated BUN more than 40 mg/dL or Cr more than 1.5 mg/dL. 8. HBV. 9. Arteriographic abnormality. 10. Vasculitis on biopsy. Presence of 3 out of 10 is 82% Se and 87% Sp [3]
Treatment	Steroids: 40–60 mg/day initially and then slow tapering based on clinical and radiological response. Steroid-sparing agents for resistant cases. Antiviral therapy for HBV-related disease

20.1.5.4 Granulomatosis with Polyangiitis (GPA) and Microscopic Polyangiitis (MPA)

These are types of vasculitis that affect small vessels. They occur mostly in older adults, and both genders are equally affected. Both types are associated with ANCA and have similar features on renal histology (crescentic, pauci-immune glomerulonephritis) [27].

An initiating event (e.g., infection or drug) causes tissue injury and immune response [28]. This leads to production of ANCA. Up to 80% of the antigens observed in granulomatosis with polyangiitis are proteinase 3 (PR3) (c-ANCA), while myeloperoxidase (MPO) (p-ANCA) is observed in 10% of patients. About 70% of microscopic polyangiitis patients have positive ANCA which is mostly p-ANCA.

Patients typically present with constitutional symptoms that may last for weeks to months without evidence of specific organ involvement. Both types affect multiple systems including pulmonary, renal, ocular, neurologic, and hematologic [29].

The distinction of these types of small vessel vasculitis from other systemic rheumatic diseases is challenging. Differential diagnosis includes diseases with similar general clinical features like EGPA, similar lung and/or renal signs like anti-GBM disease, and/or positive ANCA serologies like renal-limited vasculitis.

Therapy has two components: induction of remission with initial immunosuppressive therapy and maintenance immunosuppressive therapy for a variable period to prevent relapse. Choice of drug regimen in induction of remission depends on the severity of the disease. Mild disease can be treated by a combination therapy with glucocorticoids and methotrexate, while cyclophosphamide or rituximab [30] is required to treat severe disease. Plasma exchange is added in case of glomerulonephritis or pulmonary hemorrhage [31, 32].

Tables 20.8 and 20.9 summarize CHCC12 definition, epidemiology, clinical manifestation, diagnostic studies, ACR 1990 classification criteria, and treatment of GPA and MPA.

Table 20.8 Granulomatosis with polyangiitis

CHCC 2012 definition	Necrotizing granulomatous inflammation usually involving the upper and lower respiratory tract and necrotizing vasculitis affecting predominantly small to medium vessels (e.g., capillaries, venules, arterioles, arteries, and veins). Necrotizing glomerulonephritis is common [4]
Epidemiology	Can occur at any age, but mostly in young and middle-aged adults
Clinical manifestation	Pulmonary: Sinusitis, rhinitis, nasal mucosal ulceration, saddle nose deformity, pleurisy, pulmonary infiltrates, nodules, hemorrhage, and hemoptysis Renal: Hematuria and glomerulonephritis Ocular: Episcleritis, uveitis, proptosis, corneal ulcers Neurological: Cranial and peripheral neuropathies and mononeuritis multiplex Hematological: Increase incidence of DVT/PE
Diagnostic studies	90% have positive ANCA (80 to 95% c-ANCA, remainder p-ANCA) CXR or CT chest: Nodules, infiltrates, cavities. CT sinus: Sinusitis Elevated BUN and creatinine, hematuria, proteinuria, and sediment with RBC casts Biopsy: Necrotizing granulomatous inflammation
ACR 1990 Classification criteria	1. Nasal or oral inflammation: Oral ulcers, purulent or bloody nasal discharge. 2. CXR showing nodules, fixed infiltrates or cavities. 3. Microscopic hematuria or urinary red cell casts. 4. Granulomatous inflammation on biopsy. Presence of 2 out of 4 is 88% Se and 92% Sp [3]
Treatment	Induction: Cyclophosphamide PO (2 mg/kg/day for 3 to 6 months or pulse 15 mg/kg/day every 2 to 3 weeks) or IV rituximab 375 mg/m^2 per week for 4 weeks and prednisolone 1 to 2 mg/kg/day taper over 6 to 18 months. If rapidly progressive glomerulonephritis, add plasma exchange Maintenance: Methotrexate or azathioprine for 2 years. Bactrim may prevent respiratory infections

Table 20.9 Microscopic polyangiitis

CHCC 2012 definition	Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (i.e., capillaries, venules, or arterioles). Necrotizing arteritis involving small and medium arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs. Granulomatous inflammation is absent [4]
Epidemiology	Not associated with HBV
Clinical manifestation	Similar to granulomatosis with polyangiitis but renal involvement is more common than pulmonary involvement
Diagnostic studies	70% have positive ANCA (almost all p-ANCA) CXR or CT chest: Nodules, infiltrates, cavities Elevated BUN and creatinine, hematuria, proteinuria, sediment with RBC casts, and dysmorphic RBCs Biopsy: Pauci-immune inflammation
ACR 1990 Classification criteria	None
Treatment	Induction: Cyclophosphamide PO (2 mg/kg/day for 3 to 6 months or pulse 15 mg/kg/day every 2 to 3 weeks) or IV rituximab 375 mg/m^2 per week for 4 weeks and prednisolone 1 to 2 mg/kg/day taper over 6 to 18 months. If rapidly progressive glomerulonephritis, add plasma exchange Maintenance: Methotrexate or azathioprine for 2 years. Bactrim may prevent respiratory infections

20.1.5.5 Eosinophilic Granulomatosis with Polyangiitis (EGPA)

EGPA is a multisystem disease characterized by allergic rhinitis, asthma, and prominent peripheral blood eosinophilia [33].

In this disease, ANCA is detected in about 50% of patients. The etiology of EGPA is unknown. However, genetic factors such as HLA-DRB4 are thought to play a role. Presence of ANCA produces an immune response, which then leads to eosinophilic infiltration and necrotizing granuloma [34].

Clinical features of EGPA develop in several phases: the prodromal phase which is characterized by presence of asthma and allergic rhinitis; the eosinophilic phase with eosinophilic infiltration of multiple organs; and the vasculitis phase that may be heralded by nonspecific constitutional symptoms [35].

Differential diagnosis includes aspirin-exacerbated respiratory disease, the eosinophilic pneumonias, allergic bronchopulmonary aspergillosis, the hyper-eosinophilic syndrome, and other ANCA-associated vasculitides.

Treatment of EGPA consists of induction of remission and maintenance of remission. For mild disease, induction can be achieved with high-dose glucocorticoids. Cyclophosphamide is added to glucocorticoids in severe disease. For maintenance of remission, azathioprine or methotrexate can be used [36].

Table 20.10 summarizes CHCC12 definition, epidemiology, clinical manifestation, diagnostic studies, ACR 1990 classification criteria, and treatment of EGPA.

20.1.5.6 IgA Vasculitis (IgAV)

IgA vasculitis, also previously called Henoch-Schönlein Purpura, is the most common systemic.

vasculitis of childhood. Up to 10% of IgA vasculitis occur in adults.

It is a self-limited disease and is characterized by the presence of the following: palpable purpura without thrombocytopenia and coagulopathy, arthralgias and/or arthritis, abdominal pain, and renal disease [37].

The underlying cause of IgA vasculitis is unknown. It is thought that IgA vasculitis represents an immune-mediated vasculitis that may be triggered by a variety of antigens, including various infections or immunizations [38].

Treatment of IgA vasculitis is supportive and should be directed toward adequate oral hydration, bed rest, and symptomatic relief of joint and abdominal pain. Nonsteroidal anti-inflammatory drugs can be used to alleviate joint or abdominal pain. Glucocorticoids are used for more severe cases [39].

Table 20.10 Eosinophilic granulomatosis with polyangiitis

CHCC 2012 definition	Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium vessels, and associated with asthma and eosinophilia. ANCA is more frequent when glomerulonephritis is present [4]
Epidemiology	Rare condition, can present at any age. Associated with HLA-DRB4
Clinical manifestation	Asthma and allergic rhinitis Eosinophilic infiltrative disease or pneumonia Systemic small vessel vasculitis with granuloma Neuropathy, glomerulonephritis Cardiac involvement: Coronary arteritis, myocarditis, and vascular insufficiency Dermatological: Palpable purpura, petechiae, and subcutaneous nodules
Diagnostic studies	50% have positive ANCA (c-ANCA or p-ANCA). Eosinophilia CXR: Shifting pulmonary infiltrates Elevated BUN and creatinine, hematuria, proteinuria, and sediment with RBC casts Biopsy: Microgranulomas with eosinophilic infiltrates
ACR 1990 Classification criteria	1. Asthma. 2. Eosinophilia more than 10%. 3. Mono- or polyneuropathy. 4. Migratory or transitory pulmonary infiltrates. 5. Paranasal sinus abnormality. 6. Extravascular eosinophils on biopsy. Presence of 4 out of 6 is 85% Se and 99.7% Sp [3]
Treatment	Induction: High-dose corticosteroids. Cyclophosphamide can be used if necessary Maintenance: Azathioprine or methotrexate

Table 20.11 summarizes CHCC12 definition, epidemiology, clinical manifestation, diagnostic studies, ACR 1990 classification criteria, and treatment of IgA vasculitis.

20.1.5.7 Cutaneous Leukocytoclastic Angiitis

Cutaneous leukocytoclastic angiitis, also previously called hypersensitivity vasculitis, is a form of single-organ vasculitis that involves cutaneous vessels of any size with no evidence of systemic vasculitis [4].

Table 20.11 IgA vasculitis

CHCC 2012 definition	Vasculitis, with IgA1-dominant immune deposits, affecting small vessels (predominantly capillaries, venules, or arterioles). Often involves skin and gastrointestinal tract and frequently causes arthritis. Glomerulonephritis indistinguishable from IgA nephropathy may occur [4]
Epidemiology	Males are affected more than females. Begins after an infection or drug exposure
Clinical manifestation	Palpable purpura on extensor surfaces and buttocks Polyarthralgias, abdominal pain, GI bleeding, microscopic hematuria and fever
Diagnostic studies	Normal platelet count Skin biopsy: Leukocytoclastic vasculitis with IgA and C3 deposition in vessel wall Renal biopsy: Mesangial IgA deposition
ACR 1990 Classification criteria	1. Palpable purpura. 2. Age less than 20 at disease onset. 3. Bowel angina. 4. Skin biopsy: Leukocytoclastic vasculitis with IgA and C3 deposition in vessel wall. Presence of 2 out of 4 is 87% Se and 88% Sp [3]
Treatment	Supportive, steroids, and disease-modifying antirheumatic drugs for renal involvement or severe disease

It is the most common type of vasculitis. It may be idiopathic, but it may be directly caused by drugs, infections, tumor antigens, and serum sickness.

It is difficult to distinguish cutaneous leukocytoclastic angiitis from other forms of vasculitis, particularly when confined to the skin. Many types of systemic vasculitis may present initially with cutaneous involvement, so careful evaluation is required.

Treatment of the underlying cause or withdrawal of the offending agent lead to resolution within a period of days to a few weeks. Glucocorticoids are preserved for progressive disease [40].

Table 20.12 Cutaneous leukocytoclastic angiitis

CHCC 2012 definition	A form of single-organ vasculitis, involves arteries or veins of any size in the skin that has no features indicating that it is a limited expression of systemic vasculitis [4]
Epidemiology	Most common type of vasculitis. Caused by drugs (e.g., penicillin, cephalosporins, phenytoin, allopurinol, aspirin, amphetamine, thiazide, chemicals and immunizations), by infections (e.g., streptococcal throat infection, bacterial endocarditis, and TB), tumor antigens, and serum sickness
Clinical manifestation	Palpable purpura, ulceration, transient arthralgias, fever, peripheral neuropathy
Diagnostic studies	Elevated ESR and eosinophils. Low complements Skin biopsy: Leukocytoclastic vasculitis with neutrophils. No IgA deposition
ACR 1990 Classification criteria	1. Age more than 16. 2. Medication taken at disease onset. 3. Palpable purpura. 4. Maculopapular rash. 5. Skin biopsy: Leukocytoclastic vasculitis with neutrophils. Presence of 3 out of 5 is 71% Se and 84% Sp [3]
Treatment	Withdrawal of the offending agent and rapid prednisolone taper

Table 20.12 summarizes CHCC12 definition, epidemiology, clinical manifestation, diagnostic studies, ACR 1990 classification criteria, and treatment of cutaneous leukocytoclastic angiitis.

20.1.5.8 Behcet's Disease (BD)

It is a type of vasculitis that can affect blood vessels of all sizes. It is characterized by recurrent oral aphthae and any of several systemic manifestations including genital aphthae, ocular disease, skin lesions, gastrointestinal involvement, neurologic disease, vascular disease, or arthritis. It is more common along the ancient silk road, which extends from Eastern Asia to the Mediterranean. It typically affects adults between the age of 20 and 40 with a similar prevalence between both genders [41].

The underlying cause of BD is unknown. It is thought that the immune response is triggered by exposure to an agent (e.g., infection, chemicals). It is also found to be associated with HLA-B51 [42]. Both cellular and humoral immunity responses are activated [43]. Endothelial dysfunction leads to inflammation and thrombus formation in BD [43].

Ocular, vascular, and neurological manifestations account for the greatest morbidity and mor-

Table 20.13 Behcet's disease

CHCC 2012 definition	Vasculitis occurring in patients with Behcet's disease that can affect arteries or veins. Behcet's disease is characterized by recurrent oral and/or genital aphthous ulcers accompanied by cutaneous, ocular, articular, gastrointestinal, and/or central nervous system inflammatory lesions. Small vessel vasculitis, thromboangiitis, thrombosis, arteritis, and arterial aneurysms may occur [4]
Epidemiology	Associated with HLA-B51. Highest prevalence in Turkey and other Asian countries
Classification criteria	1. Recurrent oral aphthous ulceration (at least 3 times a year). 2. Recurrent genital ulceration. 3. Eye lesion (uveitis, scleritis, optic neuritis). 4. Skin lesions (pustules, papules, erythema nodosum). 5. Positive pathergy test (skin prick with a sterile needle will produce a pustule). Presence of first criteria plus two or more of the others is 91% se and 96% Sp
Other clinical manifestation	Arthritis, focal neurological deficit, venous thrombosis, arterial stenosis, or aneurysm
Diagnostic studies	Ulcer biopsy Slit lamp and fundoscopic eye examination
Treatment	Mucocutaneous Mild: Colchicine, topical steroids, and dapsone Severe: Oral steroids, azathioprine, methotrexate, cyclosporine, and anti-TNF Arthritis: NSAIDs, colchicine, steroids, and anti-TNF Ocular: Steroids, azathioprine, infliximab, cyclosporine, and cyclophosphamide Vascular: High-dose steroids and cyclophosphamide. Then azathioprine for maintenance. Anticoagulation for venous thrombosis Neurological: Steroids, methotrexate, azathioprine, cyclophosphamide, and adalimumab. Anticoagulation for dural sinus thrombosis

tality in BD. Cutaneous and articular involvement are also common [44].

Treatment of BD depends on the severity of the disease. Mild disease can be treated with colchicine and oral glucocorticoids. Severe disease requires addition of immunosuppressive therapy such as cyclophosphamide, TNF-alpha blockers, and azathioprine [45].

Table 20.13 summarizes CHCC12 definition, epidemiology, clinical manifestation, diagnostic studies, ACR 1990 classification criteria, and treatment of BD.

The author of this chapter is grateful to Prof. Hani Almoallim and Dr. Lujain Homeida for providing some clinical images from their own collection.

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Diabetes and Rheumatology

21

Alaa Monjed

21.1 Introduction

Diabetes mellitus (DM) is a chronic disease characterized by persistent hyperglycaemia that happens as a result of a pancreatic insulin deficiency and/or insulin resistance. Its morbidity and mortality are primarily related to the resultant microvascular and macrovascular complications. Its prevalence has grown widely, which will result in higher rates of diabetic complications including rheumatic manifestations.

An improved understanding of the mechanisms through which diabetes alters connective tissue metabolism should lead to better preventive and therapeutic interventions. In this chapter, a brief summary about the pathophysiology of rheumatological manifestations in diabetes is outlined. A schematic classification of rheumatological manifestations in diabetic patients is demonstrated according to the region and according to the presence or absence of pain. This is followed by summarized review of these rheumatological manifestations of diabetes mellitus. It is obvious that these are not unique to diabetes mellitus as it may affect normal individuals, as well.

21.1.1 Objectives

The reader of this chapter should be able to:

1. Identify different diabetes related rheumatic complications.
2. Differentiate between rheumatic complications related to diabetes and those associated with other diseases.
3. Classify these rheumatic diseases based on the involved region and the underlying pathophysiology.
4. Assess diabetic patients with rheumatic complications clinically and select the appropriate diagnostic tests.
5. Manage diabetic patients with rheumatic complications.

21.2 Pathophysiology

The high glucose, high insulin milieu of diabetes affects many of the key cells and matrix components of connective tissues. For example, reactive oxygen species are increased in diabetes and certainly may mediate tissue damage [1]. Advanced glycosylation end products (AGEs) tend to accumulate in the long-lived proteins of connective tissues and may alter both extracellular matrix structure and function as well as cell viability [2]. Early glycosylation of skin collagen can be decreased by improving glycaemic

A. Monjed (✉)
College of Medicine, Umm Al-Qura University, Makkah, Saudi Arabia
e-mail: akrmonjed@uqu.edu.sa

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control [3, 4]. However, the long-term, cumulative damage due to the binding of advanced glycosylation end products to collagen is probably irreversible.

21.2.1 Classification of Rheumatological Manifestations in Diabetic Patients

Rheumatological diseases associated with diabetes mellitus can be classified according to:

1. The involved musculoskeletal structures as shown in the Fig. 21.1.
2. Painful or painless rheumatic diseases as shown in the Fig. 21.2.

21.3 Carpal Tunnel Syndrome

Carpal tunnel syndrome (CTS) is an entrapment neuropathy caused by compression of the median nerve resulting in pain and/or paraesthesia in thumb, index and middle finger.

21.3.1 Epidemiology

- *In diabetic patients*: CTS is common and estimated to occur in **14%** in patients without diabetic polyneuropathies and up to **30%** in those with diabetic polyneuropathies [5].
- It may be more common in those with prediabetes [6].
- More common in women than men [7].
- *In nondiabetics* with life expectancy of 70 years: **3–5%** in Men and **11%** in women are expected to develop CTS [7].

21.3.2 Approach to CTS

21.3.2.1 History

- *Numbness and tingling sensation:* it should be localized to the palmer aspect of the first to the fourth fingers and the distal palm. These symptoms usually happen at night and resolve by shaking (shake sign).
- *Pain:* usually at night, and over the ventral aspect of the wrist and radiated distally to the palm and fingers or proximally to the ventral forearm, resolved by flicking (flicking sign).

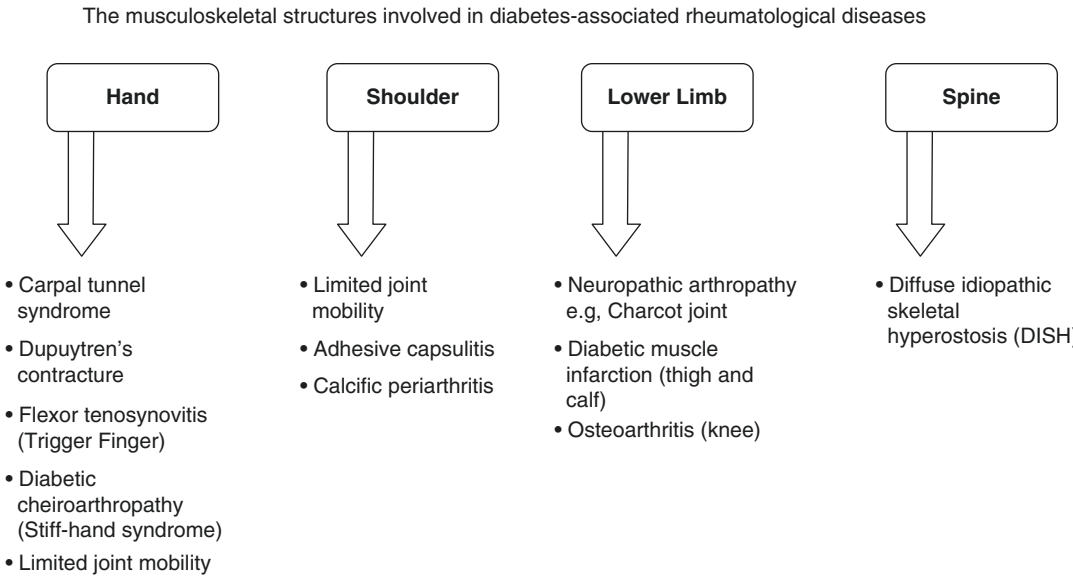

Fig. 21.1 The musculoskeletal structures involved in diabetes-associated rheumatological diseases

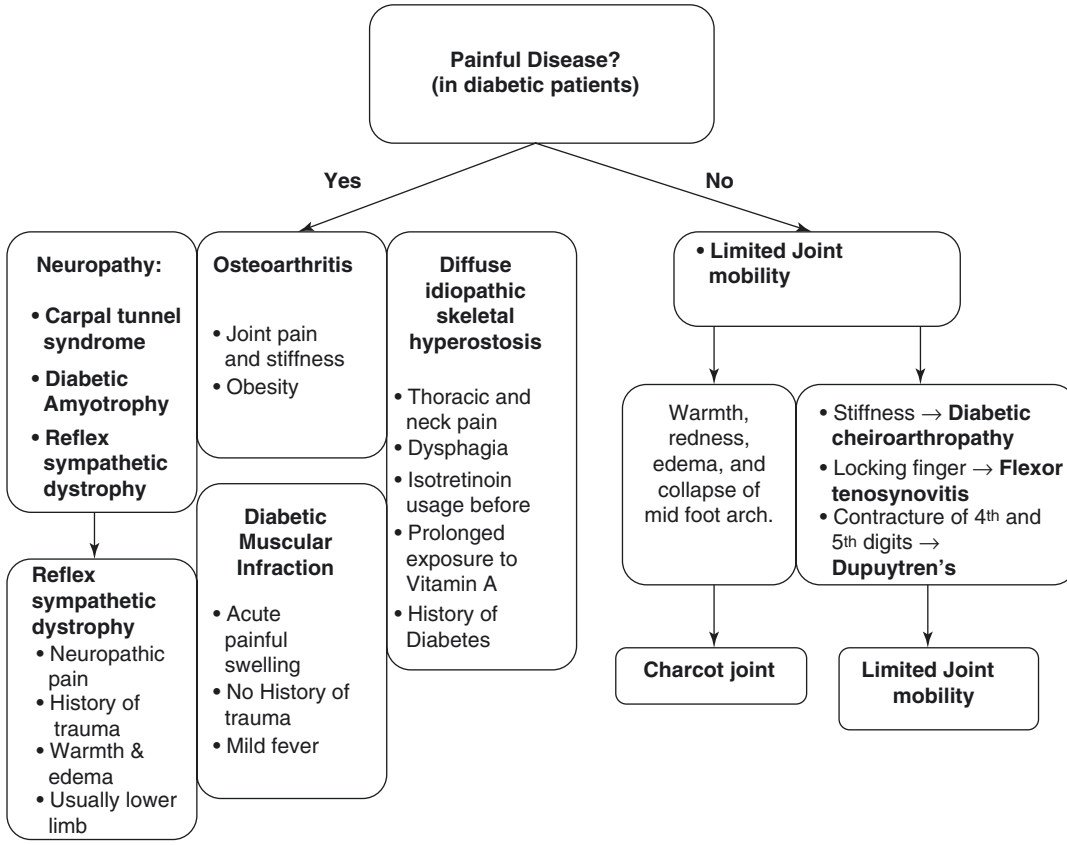

Fig. 21.2 Painful and painless rheumatic diseases associated with diabetes mellitus

- *Autonomic symptoms:* temperature and colour changes in the hand.
- *Weakness of thumb* abduction and opposition.

To exclude other causes of CTS, the following should be assessed for establishing the diagnosis (Table 21.1):

21.3.2.2 Physical Examination

- **Motor Examination:** wasting and weakness of the median-innervated hand muscles (LOAF); *first and second lumbricales*, *opponens pollicis*, *abductor pollicis brevis* and *flexor pollicis brevis* may be detectable and resulting in weak thumb abduction.
- **Sensory Examination:**
  - Decreased sensation in the median nerve distribution (from thumb through the middle of the fourth finger).
  - *Semmes-Weinstein monofilament testing or 2-point* discrimination, which may be more sensitive in picking up the sensory abnormality.
- **Special tests:**
  - *Phalen test (87% specificity and 84% sensitivity):* the patient has to hold his hands against each other in full palmer flexion; paraesthesia will happen within 30 to 120 s in this position.
  - *Tinel sign (89% specificity and 82% sensitivity):* gentle tapping over the median nerve in the carpal tunnel area causes tingling in the nerve's distribution.
  - *The carpal compression test* (*sensitivity 84%, specificity 82%*)**:** applying firm pressure directly over the carpal tunnel, usually with the thumbs, for up to 30 s will reproduce the symptoms.

Table 21.1 Causes of Carpal Tunnel Syndrome

Causes	Important Differentiating Tips
Diabetes	Numbness, neuropathy, retinopathy, nephropathy, and peripheral vascular disease
Rheumatoid Arthritis	Constitutional symptoms, polyarthritis, morning stiffness, positive RF and ACPA
Gout	Monoarthritis, hyperuricemia, monosodium urate crystals in synovial fluid, negative culture of joint fluid for microorganisms
Heart failure	Orthopnea, PND, ischemic heart disease, diabetes, Hypertension
Hyperthyroidism	Palpitation, heat intolerance, weight loss, goitre, suppressed TSH
Colles' fracture	History of trauma
Over use syndrome	Work related e.g. computer Users, typists, and musicians

Abbreviations: *RF*: Rheumatiod factor, *ACPA*: Anti-citrullinated protein antibodies, *PND*: Paroxysmal nocturnal dyspnea, *TSH*: Thyroid stimulating hormone

- *Hand elevation test (89% specificity and 87% sensitivity):* asking the patient to raise the affected hand and holding it in that position for 1 min. The test is positive when tingling and numbness happen in the median nerve distribution area.

21.3.2.3 Investigations

- Carpal tunnel syndrome is a clinical diagnosis.
- Lab tests are usually not helpful except for assessing glycaemic control.
- *Nerve conduction studies (NCS) and electromyography (EMG):* are the diagnostic tests that usually used to confirm the diagnosis, assess severity and rule out other abnormalities or conditions such as polyneuropathy, plexopathy and radiculopathy.
- Imaging studies are not routinely used:
  - *Ultrasound (sensitivity 64%):*
    It can demonstrate the thickening of the median nerve, the flattening of the nerve within the tunnel and the bowing of the flexor retinaculum, which are all features that indicate the presence of CTS.
  - *MRI (sensitivity 96%):*
    It demonstrates swelling of the median nerve and increased signal intensity on T2-weighted images, indicating accumulation of the axonal transportation, myelin sheath degeneration or oedema, which are suggestive of CTS.

21.3.3 Treatment

- *Conservative treatment:*
  - **Splinting:** splinting the wrist at night-time for a minimum of 3 weeks. Many off-the-shelf wrist splints seem to help.
  - **Steroid injection, nonsteroid anti-inflammatory drug and vitamin B6:** effective in reducing inflammation and oedema [8, 9].
- *Surgical release of carpal tunnel:*
  - This is performed more frequently among *patients with DM* and is estimated to be 4–14 times higher than the general population.
  - Success rate is more than 90%.

21.4 Reflex Sympathetic Dystrophy

Reflex sympathetic dystrophy (RSD), also known as complex regional pain syndrome I (CRPS I), is characterized by localized or diffuse neuropathic pain of the upper or lower extremity usually associated with swelling, vasomotor disturbances and trophic skin changes which include loss of hair, skin colour changes, temperature changes and skin thickening (autonomic involvement) [10].

21.4.1 Pathogenesis

The pathogenesis of RSD is unclear, but there are some theories that may explain it:

- Sympathetic nervous system dysfunction.
- Neurogenic inflammation.
- Central nervous system sensitization.
- Autoimmune condition.
- Limb ischaemia or ischaemia reperfusion injury.

21.4.2 Epidemiology

Incidence of RSD is 26.2 per 100,000person year in Netherlands 1996–2005, the highest incidence in women aged 61–70 years, with a female to male ratio 3.4:1 [11].

21.4.3 Approach to RSD

21.4.3.1 History

- *Neuropathic pain* following an injury (tissue trauma or bony fracture). It is described as burning, throbbing, aching, squeezing or shooting pain.
- *Vasomotor and sudomotor changes* in the affected limb (colour changes, temperature changes and excessive sweating).
- Ask about the possible precipitating factors or causes such as:
  - **Trauma** kor **immobilization** following trauma to limb.
  - **Bone fractures of extremities.**
  - **Diabetes mellitus.**
  - **Hyperthyroidism.**
  - **Hyperparathyroidism.**
  - **Nerve injury.**
  - **Medications**, e.g. ACE inhibitors.

21.4.3.2 Physical Examination

- **Skin**: may be shiny, swollen, thinned, erythematous or cyanotic, with scaling. Temperature may be increased or decreased.
- **Extremities:**
  - Joint may be stiff with decreased range of motion.
  - Signs of chronic lymphoedema.
- **Neurologically:**
  - Sensory changes and weakness may be present.
  - Tremor or dystonia in the affected limb.

21.4.4 Diagnosis Criteria (Table. 21.2)

21.4.5 Treatment

There are different medical and surgical treatment modalities, but they have no strong evidence to support their use.

- The best treatment of RSD is prevention by early mobilization following an injury or stroke and use of supplemental vitamin C for patients with wrist fractures [14, 15]. A typical dose is 500–1500 mg daily, and the duration is 50 days.
- Physical therapy.
- Medical therapy:
  - Analgesics, e.g., topical capsaicin cream.
  - Bisphosphonates.
  - Anticonvulsants, e.g., gabapentin.
  - Tricyclic antidepressant.
  - Vasodilator medication or percutaneous sympathetic blockades.
  - Glucocorticoids.
- Invasive therapy for non-improving on non-invasive therapy.
  - Regional sympathetic nerve block.
  - Electrical nerve stimulation.

Table 21.2 Diagnostic criteria of reflex sympathetic dystrophy, also known as complex regional pain syndrome

Bruehl's criteria[12]
Continuing pain disproportionate to any inciting event. **1. Patient must report at least 1 symptom in each of the 4 following categories** a) Sensory: hyperesthesia b) Vasomotor: temperature asymmetry, skin color changes or skin color asymmetry c) Sudomotor/edema: edema, sweating changes or sweating asymmetry d) Motor/trophic: decreased range of motion, motor dysfunction (weakness, tremor, dystonia) or trophic changes (hair, nail, skin) **2. Must display at least 1 sign in 2 or more of the following categories** e) Sensory: evidence of hyperalgesia (to pinprick) or allodynia (to light touch) f) Vasomotor: evidence of temperature asymmetry, skin color changes or asymmetry g) Sudomotor/edema: evidence of edema, sweating changes or sweating asymmetry h) Motor/trophic: evidence of decreased range of motion, motor dysfunction (weakness, tremor, dystonia) or trophic changes (hair, nail, skin)

Veldman's criteria[13]
1. Presence of 4 out of 5 symptoms: a) Diffuse pain during exercise b) Temperature differences between affected and unaffected extremity c) Color differences between affected and unaffected extremity d) Volume differences between affected and unaffected extremity e) Limitations in active range of movement of the affected extremity **2. Occurrence or increase of symptoms during or after use** **3. Symptoms in an area larger than the area of the primary injury**

– Sympathectomy.
– Spinal cord stimulation.

21.5 Flexor Tenosynovitis

Flexor tenosynovitis, also known as trigger finger, is a non-infectious inflammation of the flexor tendon sheath of the finger leading to finger blocking in flexion with failure of active extension.

21.5.1 Pathogenesis

Inflammation causes thickening of flexor tendon of the digit over metacarpal head and resistance to its entrance into the base of flexor tendon sheath, accompanied by constriction of the sheath. Flexors are stronger than extensors, so finger gets locked in a flexed position, as extensors cannot overcome the resistance of constriction.

21.5.2 Epidemiology

The prevalence of flexor tenosynovitis is estimated at 11% in diabetic patients, compared with less than 1% in nondiabetics [16]. The occurrence of flexor tenosynovitis correlates significantly with the duration of DM, but not with glycaemic control [16].

21.5.3 Approach to Flexor Tenosynovitis

21.5.3.1 History

- Locking of finger in a flexed position with a resistance to re-extension. It commonly involves thumb, the middle and ring fingers.
- Clicking of the locked digit and finger pain.

21.5.3.2 Physical Examination

- Local tenderness and palpable swelling at the base of the finger, where the tendon crosses over the metacarpal head.
- Pain usually gets worse by stretching the tendon in extension or by resisting flexion isometrically.
- *Prayer sign test:* the ability to flatten the hands together as in prayer, facilitating recognition of contractures in the metacarpophalangeal, proximal interphalangeal and distal interphalangeal joints.
- *Table top test:* assesses the ability to flatten the palm against the surface of a table, facilitating recognition of contractures in the metacarpophalangeal joints.

21.5.3.3 Investigations

- It is a clinical diagnosis.
- *Plain radiographs* are rarely done unless there is a history of trauma or inflammatory diseases. They may show calcification of the tendon but rarely occurs.

21.5.4 Treatment [17]

- Activity modifications to avoid the triggers.
- Splinting.
- NSAIDs.
- Steroid injections into tendon sheath.
- Surgical release.

21.6 Diabetic Muscular Infarction

It refers to spontaneous ischemic necrosis of skeletal muscles, unrelated to athero-embolism or occlusion of major arteries. Diabetic muscle infarction (DMI) is a rare but life threatening complication seen in patients with long-standing and poorly controlled diabetes. It is considered as one of the micro- and macrovascular complications of Diabetes.

21.6.1 Pathophysiology

DMI is more common in type I diabetes and most of the affected patients have multiple microvascular complications. Hyperglycaemia, with or without insulin resistance, has many potentially adverse effects on the arterial vasculature. It may also affect platelets functions and the levels of coagulation and thrombolytic factors leading to occlusion of arterioles and capillaries resulting in muscles necrosis and oedema.

21.6.2 Epidemiology

- More common with type I diabetes.
- Usually affecting women more than men.
- Usually associated with other complications of diabetes as nephropathy (70%), retinopathy (57%) and neuropathy (55%) [18]

21.6.3 Approach to DMI

21.6.3.1 History

- *Tender and swollen leg.*
- *Pain of an acute onset in the thigh and less commonly in the calf muscles over days.*
- *Autonomic symptoms: mild fever.*
- Ask about trauma: usually there is no history of trauma in DMI.
- Ask about suspected complications as recurrence or staph sepsis.
- Ask about the diabetes control and medication use.
- Ask about symptoms of nephropathy and retinopathy, e.g. urinary symptoms and vision problems.

21.6.3.2 Physical Examination

- Assessing the leg swelling: site, size, shape, tenderness and temperature.
- Any associated leg ulcers?
- Check the leg and upper limb arterial pulses.
- Look for signs of DM-related micro- and macrovascular complications such as retinopathy, neuropathy and cardiovascular abnormalities.

21.6.3.3 Imaging Studies

- **MRI:**
  - Shows a high intensity in the involved muscle as well as subcutaneous oedema and subfascial fluid (in T2-weighted sequences), in addition to loss of the normal fatty intramuscular septa with T1-weighted images (common finding) [19].
  - It is the diagnostic test of choice.
- **Ultrasonography**:
  - Finding of internal linear echogenic structures, absence of a predominant anechoic area and no evidence of internal motion can discriminate a diabetic muscle infarction from an abscess.
  - Venous Doppler ultrasound with compression to rule out venous thrombosis.
- **Arteriography:**
  - It may show atherosclerotic luminal narrowing. Generally, it is not used for diagnosis.

21.6.3.4 Muscle Biopsy (for Confirmation)

The primary pathological findings are muscle necrosis and oedema, but occlusion of arterioles and capillaries by fibrin may also be seen. It should be reserved for patients with atypical presentation, uncertain diagnosis or those who do not improve with medical treatment [20].

21.6.4 Treatment

- Rest and analgesics.
- Anti-platelet agents (ASA) and/or anti-inflammatory drugs.
- Surgical excision.

21.7 Adhesive Capsulitis (Frozen Shoulder)

Adhesive capsulitis, also known as frozen shoulder, is characterized by progressive painful restriction of the shoulder movements, especially external rotation and abduction. Typically, the pain of frozen shoulder in diabetics is less than that of nondiabetic patients.

21.7.1 Pathogenesis

The exact mechanism is unknown. It is thought that hyperglycaemia can lead to a faster rate of collagen glycosylation and cross-linking in the shoulder capsule, which will cause thickening and contraction of the capsule that result in a substantial decrease in capsular volume capacity.

21.7.2 Epidemiology

- The prevalence of frozen shoulder is estimated to be 2 to 5% of the general population [21, 22].
- Patients with diabetes mellitus are at a greater risk of developing frozen shoulder, with prevalence of 10 to 20% [23–25].
- Bilateral involvement is more frequent in diabetic patients than in nondiabetic subjects (33 to 42% vs. 5 to 20%) [26].
- Women are more often affected than men [27].

21.7.3 Approach to Frozen Shoulder

21.7.3.1 History

- Shoulder stiffness.
- Diffuse severe pain, even at night.
- Limitation of shoulder motion.
- *The followings should be obtained:*
  - Duration and location of pain.
  - Precipitating and relieving factors.
  - One shoulder or both are affected.
  - Any other joints involved.
  - Any strain, overuse or trauma.

Table 21.3 Frozen shoulder progression phases [22, 28]

Painful freezing phase	Adhesive phase	Resolution phase
▪ 10-36 weeks ▪ Pain and stiffness around the shoulder with no history of injury ▪ Constant pain with little response to NSAIDs	▪ 4-12 months ▪ Pain gradually subsides but still apparent at extremes ▪ Stiffness continues ▪ Near total loss of external rotation	▪ 12-42 months ▪ Spontaneous improvement in the range of motion ▪ Mean duration of overall impairment > 30 months

  - Prolonged immobilization.
  - Neck pain or radiation of pain into arms.
  - Neurologic symptoms in arms.

Frozen Shoulder May Progress Through Three Theoretical Phases [22, 28] (Table. 21.3).

21.7.3.2 Physical Examination

A stiff and painful glenohumeral joint makes it difficult to perform a complete shoulder examination.

- Look for swelling, redness and warmth.
- Check distal strength, sensation and pulses.
- Check for diffuse tenderness over anterior and posterior aspect of the shoulder.
- Lock for loss of active and passive motion in all planes especially on external rotation and abduction.
- Diagnosis is unlikely if complete abduction present on passive motion.

21.7.3.3 Imaging

- **Plain radiographs** are usually normal, so had limited diagnostic use.
- **Ultrasonography** is used either to confirm the diagnosis of frozen shoulder or to rule out other pathology of the rotator cuff and bursa. Findings associated with frozen shoulder may include [29]:
  - Thickening of the coracohumeral ligament and the soft-tissue structures in the rotator cuff interval.
  - Increased fluid in the tendon sheath of the long head of the biceps.
  - Increased vascularity around the intra-articular portion of the biceps tendon and the coracohumeral ligament.
- **MRI** shows a thickening of the joint capsule and the coracohumeral ligament. It is useful in some conditions like rotator cuff tendinopathy and concomitant glenohumeral osteoarthritis for accurate diagnosis.

21.7.4 Treatment

In most cases, frozen shoulder is a self-limited condition, although a complete resolution does not occur in many patients.

- Physical therapy.
- Nonsteroidal anti-inflammatory drugs (NSAIDs) and analgesics.
- Intra-articular steroid injections.
- Surgery in severe non-responding cases.

21.8 Neuropathic Osteoarthropathy (Charcot Joint)

Neuropathic osteoarthropathy, also known as Charcot osteoarthropathy, is a progressive destructive process affecting the bone and joint structures associated with various diseases in

which neuropathy occurs. However, DM is by far the most common aetiology.

21.8.1 Pathogenesis

The pathogenesis remains uncertain, but it is probably due to an underlying diabetic peripheral neuropathy and a combination of mechanical trauma and vascular factors. It may result from repeated trauma, often minor, in the setting of decreased sensation due to a sensory neuropathy, which results in increased damage with micro-fractures (Fig. 21.3).

21.8.2 Epidemiology

- Among the general diabetic population, neuroarthropathy is uncommon, affecting approximately 1 in 700 diabetic patients [30, 31].

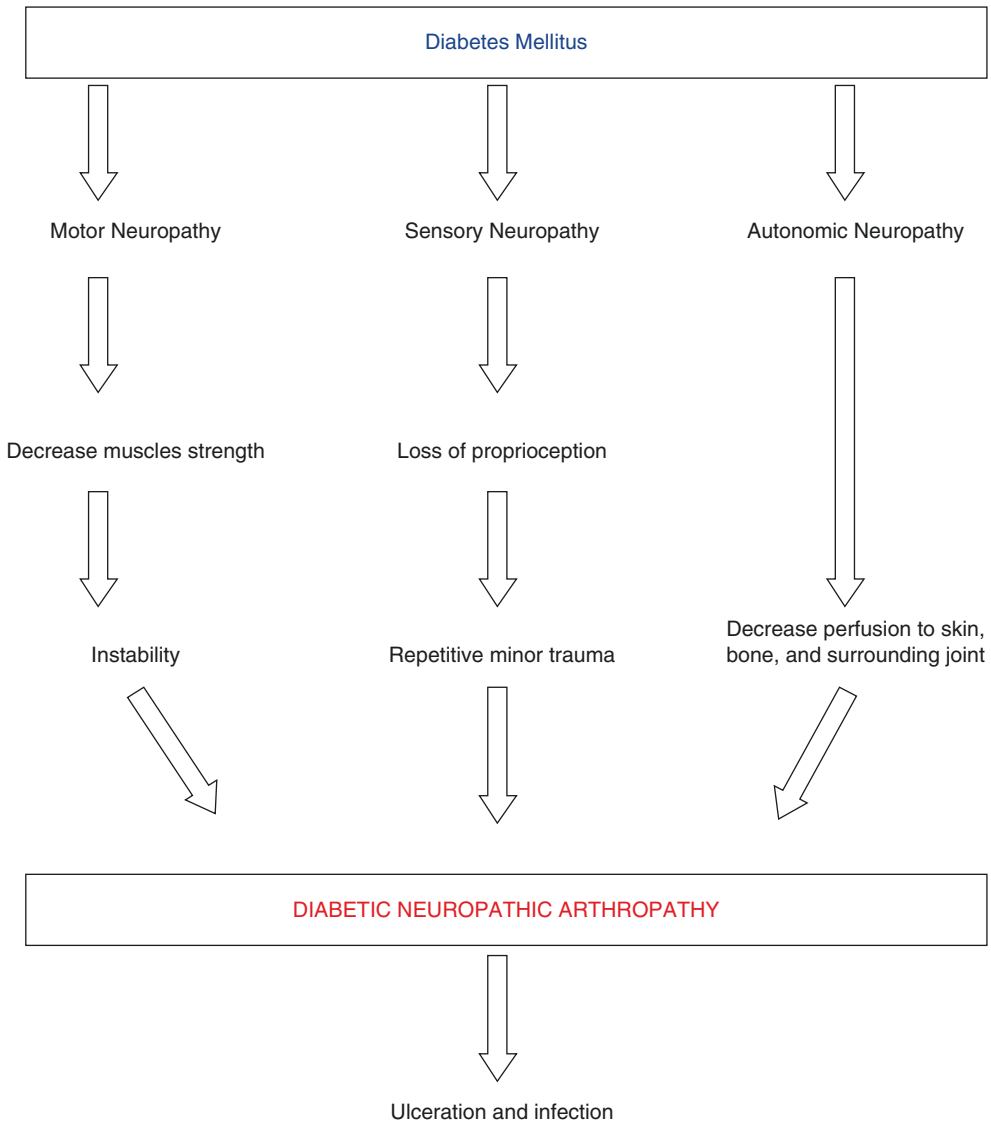

Fig. 21.3 Pathogenesis of diabetic neuropathic arthropathy

Table. 21.4 The Modified Eichenholtz System to Stage Charcot Joint Progression

Inflammatory (Stage 0)	Development (Stage 1)	Coalescence (Stage 2)	Remodeling (Stage 3)
▪ Localized swelling, erythema, and warmth ▪ No radiological abnormalities	▪ Persistent swelling, redness, and warmth ▪ Bony changes such as fracture, subluxation, dislocation ▪ Bony debris starts to appear radiologically	▪ Inflammatory signs decrease ▪ Radiological signs of fracture healing, bony debris resorption ▪ New bone formation	▪ Clinical inflammatory signs have settled ▪ Bony deformity ▪ Radiologically, may show mature fracture and decreased sclerosis

- Patients at risk are usually those who have longstanding diabetes (average duration 15 years) with peripheral neuropathy and are in their sixth or seventh decade [30, 31].

21.8.3 Approach to Charcot Joint

21.8.3.1 History

- Arthritis and swollen foot or ankle (although may occur in any joint).
- The **modified Eichenholtz system** was developed to stage the progression of Charcot joint and to recommend treatment based on the clinical stage and radiographic changes [32] (Table. 21.4).

21.8.3.2 Physical Examination

- **Serial X-rays with different findings according to the stage.**
  - Inflammatory stage: no radiological abnormalities.
  - Development stage: joint effusion, subluxation, bone destruction and osteochondral fragmentation.
  - Coalescence stage: periosteal new bone formation, subchondral sclerosis, resorption of debris, marginal osteophytes.
  - Remodelling stage: ankylosis or rounded bone ends, decreased sclerosis, decreased swelling.
- **MRI:** may show bone marrow oedema, bone bruising or microfractures.

21.8.4 Treatment

- Avoidance of weight bearing is the mainstay of treatment. It should be for at least 3 months or until erythema and oedema resolve accompanied by radiographic improvements.
- NSAIDs.
- Calcitonin and bisphosphonates may be added on to limb offloading. Their use has not been approved yet in the treatment of Charcot neuroarthropathy [35, 36].
- Surgical treatment may only be required when the conservative treatment fails or severe deformities developed.

(Table 21.5) Summary of the Most Common Rheumatological Diseases/Complications in Diabetic Patients.

21.9 Diabetes and Osteoporosis

Both diabetes and osteoporosis are prevalent diseases with significantly associated mortalities and morbidities. It has been well established that diabetic patients are at increased risk of osteoporosis and fractures, particularly at the hip.

Osteoporosis is defined as a combination of reduced bone mass and altered bone quality, with microarchitectural abnormalities, resulting in decreased bone strength with an increased risk of fractures [37, 38]. At present, the diagnosis of osteoporosis rests on bone mineral density

(BMD) measurement using dual-energy X-ray absorptiometry (DXA). The results are reported as the difference, in standard deviations (SDs), with the peak bone mass (−score). The World Health Organization (WHO) defines osteoporosis as a BMD -score of −2.5 or less [37–39].

Table 21.5 Summary of the Most Common Rheumatological Diseases/Complications in Diabetic Patients

	Rheumatological diseases		Pathophysiology	Symptoms	Investigations	Treatment
Rheumatological complication of diabetes	Syndromes of limited joint mobility	***Diabetic cheiroarthropathy (Stiff-hand syndrome)*** (8-50% among diabetics)	Binding of advanced *glycosylation end products* to collagen that is deposited around joints	- Painless stiffness of small joints in the hand - Decreased grip strength - Prayer sign test - Table top test	- Glucose level - Imaging: U/S MRI	- Improve glycemic control - NSAID - Corticosteroid injection - Physiotherapy - Surgery
		Dupuytren's contracture	Same as other limited joint, leading to fibroblastic proliferation and collagen deposition	- Finger stiffness, usually the 3rd & 4th digits in DM - Thickening or a palpable nodule in the palm - Loss of motion of the affected fingers	Clinical diagnosis	Mild disease: - physiotherapy Moderate: - corticosteroid injection Contracture: - surgery
		Trigger finger (Stenosing flexor tenosynovitis)	Inflammation of flexor tendons in hand leading to thickening	- Finger pain - Locking of finger in flexed position	- Clinical diagnosis - X- ray - Biopsy	- Active movement - Splinting - NSAIDs - Steroid injection
		Adhesive capsulitis (Frozen shoulder)	Same as other limited joint mobility	- Shoulder stiffness - Painful shoulder - Loss of motion	- Clinical diagnosis - U/S, MRI, and plain X-rays	- Physiotherapy - NSAID - Steroid injection - Surgery
	Neuropathy	***Neuropathic arthritis (Charcot joints)***	Mechanical and vascular factors resulting from diabetic peripheral neuropathy	- Arthritis - Swollen foot - Foot arch collapse	- Clinical diagnosis - X- ray - MRI	- Weight-bearing limitation - NSAIDs - Surgery
		Carpal tunnel syndrome (CTS)	Neuropathy of diabetes causes nerve compression	- Numbness - Pain - Weakness	- Phalen test - Tinnel test - Nerve conduction study+/-EMG	- Splinting - NSAIDs - Steroid injection - Surgery
		Diabetic Amyotrophy	Ischemic injury from a non-systemic micro vasculitis	- Acute local pain, followed by weakness in the proximal leg - Autonomic failure and weight loss	- CBC, FBS, HbA1C ESR - EMG, nerve conduction study - MRI and CT	- Tricyclic antidepressant - Steroids - Immunotherapy
		Reflex sympathetic dystrophy	Neuropathic complication of DM with autonomic symptoms	1st stage: burning throbbing pain & edema 2nd stage: ↑ edema & skin thickening 3rd stage: limitation of movement and contracture, waxy trophic skin changes, and brittle nails	- Autonomic tests - X-ray, CT, MRI - Bone scintigraphy	- Education - Physical therapy - Analgesics, corticosteroids, oral muscle relaxants, bisphosphonates, and calcium-channel blockers - Invasive: intravenous percutaneous sympathetic blockade, surgical sympathectomy, spinal cord stimulation, and amputation

(continued)

Table 21.5 (continued)

	Rheumatologic al diseases	Pathophysiology	Symptoms	Investigations	Treatment
Rheumatological complication of diabetes	**Diffuse idiopathic skeletal hyperostosis (DISH) (Non-inflammatory disease with calcification and ossification of spinal ligament and entheses)**	• **Etiology:** unknown, could be due to abnormal osteoblastic activity at the enthesis. • **Insulin-like growth factor-1, insulin, glucose, and growth hormone** are involved in the pathogenesis of osteoblastic activity in DISH. • **Other factors :** ➢ prolonged exposure to Vitamin A and fluoride. ➢ usage of Isotretinoin. ➢ Mechanical: Dextrocardia	• Neck, thoracic spine, low back, or extremities pain • Disability and spinal morning stiffness • May be associated with dysphagia, stridor, apnea, hoarseness, or thoracic outlet syndrome due to large anterior cervical osteophytes • O/E: ↓ range of spinal motion with tender entheses	• Radiologically: • Plain X-ray: ➢ Thoracic: longitudinal calcification and ossification ➢ Cervical: Hyperostosis with downward pointing spurs ➢ Lumbar: Hyperostosis with upward pointing spurs • CT: is more sensitive in detecting posterior calcifications	Symptomatic relief: • Physical therapy • Analgesia: NSAIDs or local steroid • Surgery: If dysphagia, myopathy, or thoracic outlet syndrome developed
	Criteria for diagnosis of DISH: • **Resnick and Niwayama Criteria:**[31] 1. Presence of longitudinal ossification and calcification on the anterior surface of at least, 4 consecutive vertebral bodies. 2. Absence of degenerative radiological changes in discs involved with preservation of intervertebral space. 3. Absence of apophyseal joint bony ankylosis and sacroiliac joint erosion or sclerosis. • **Utsinger Criteria:**[32] 1. Ossification, fine and ribbon-like wave, along the anterolateral aspect of at least 4 consecutive vertebrae. 2. Ossification on the anterolateral aspect of at least 2 consecutive vertebral bodies. 3. Presence of peripheral and symmetrical entheses pathology, involving heel, patella and olecranon, with new bone formation. 1 = definite, 2 or 3 = probably.				
	Diabetic Muscular Infarction	Hyperglycemia has many adverse effects on arterial vasculature as well as platelets and coagulation factors leading to occlusion of the vessels	• Painful and swollen leg: commonly involving thigh +/- calf muscles • Mild fever without infectious signs or symptoms • History of trauma • Compartment syndrome (less common)	• CK elevation • U/S • MRI • Muscle biopsy to confirm the diagnosis	• Analgesia • Anti-platelets (ASA) • NSAIDs • Surgical excision of infarcted tissues

ASA, asprin, *CBC*, complete blood count; *CK*, creatinine kinase; *CT*, computed tomography; *EMG*, electromyography; *ESR*, erythrocyte sedimentation rate; *FBG*, fasting blood glucose; *MRI*, magnetic resonance imaging; *NSAIDs*, non-steroidal anti-inflammatory drugs; *O/E*, on examination; *U/S*, ultrasound

21.9.1 Pathogenesis

Type I diabetes is associated with bone fragility and loss of bone mass, while type II diabetes, despite having a normal or an increased bone mineral density (BMD), is associated with bone quality deterioration that cannot be diagnosed by using dual-energy X-ray absorptiometry (DXA).

Box 21.1 Risk Factors for Fractures in Diabetic Patients [37, 40]

1. Type of diabetes I or II, poor glycaemic control, and risk of drug-induced hypoglycaemia.
2. Microvascular complications of diabetes, especially nephropathy and neuropathy.
3. Type I diabetes-associated diseases such as autoimmune hyperthyroidism, amenorrhea, eating disorders and celiac disease.
4. Increased risk of falls due to diabetes-related complications such as hypoglycaemia, poor vision and/or balance, autonomic orthostatic hypotension and arthropathy.
5. Vitamin D deficiency, which is more common in diabetics than general population.

21.9.2 Challenges in Diagnosing and Treating Diabetes-Related Osteoporosis

Although the risk has been well established, it remains underappreciated in the major international diabetes guidelines and by most clinicians caring for diabetic patients. There have been also insufficient studies evaluating the effectiveness and long-term safety of the available therapeutic antiporotic modalities to reduce the risk of fracture in patients with diabetes.

21.9.3 Approach to Diabetes-Related Osteoporosis

21.9.3.1 History

- Type of diabetes and glycaemic control (frequency of hyper- and hypoglycaemia).
- Symptoms of diabetes-related microvascular complications.
- Assess any risk for falls.
- Ask about any of the following risk factors that might increase the risk of osteoporotic fractures:
  - Previous history of fracture.
  - Parental history of hip fracture.
  - Smoking.
  - Alcoholism.
  - Steroid use.
  - Hyperthyroidism, celiac disease, hyperparathyroidism, vitamin D deficiency or rheumatoid arthritis.

21.9.3.2 Physical Exam

- Height measurement for any loss of height.
- Body mass index (low BMI < 19 kg/m^2).
- Back examination for kyphosis or point tenderness over a vertebra suggesting a compression fracture.
- Signs that may indicate increased fall risk (difficulty with balance or gait, orthostatic hypotension, lower extremity weakness and or neuropathy, poor vision or hearing).

21.9.3.3 Diagnosis

- Use the current osteoporosis guidelines for screening in patients with diabetes through using dual-energy X-ray absorptiometry (DXA) to measure the bone mineral density (BMD), but keep in mind the fracture risk is high in type II diabetes despite having normal or increased bone mineral density (BMD).
- Use the fracture risk assessment (FRAX) algorithm (www.shef.ac.uk/FRAX/), which is a validated tool used to estimate 10-year risks for major osteoporotic and hip fractures even if BMD is not measured [41]. It has been developed by the metabolic bone disease unit at the University of Sheffield.

21.9.3.4 Management of Osteoporosis on Diabetic Patients

- Maintain a good glycaemic control.
- Minimize hypoglycaemia as possible.
- Screening and prevention of diabetes-related complications.
- Avoid glitazones (TZDs).
- Identify patients with high risk of falls and prevent falls.
- Good supplementation with calcium (600–1200 mg/day) and vitamin D (at least 800–1000 IU/day).
- Use of specific antiporotic medication (bisphosphonates, denosumab or anabolic agent teriparatide) based on the recommendations of good clinical practice and the patients' factors.

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Soft Tissue Rheumatic Disorders

22

Roaa Mahroos and Hani Almoallim

22.1 Introduction

Soft tissue disorders are common focal pathological syndromes affecting soft tissue structures like tendons, ligaments, bursa, fascia, and the site of insertions of these structures to bones (enthesis). They are commonly encountered disorders in daily clinical practice particularly in outpatient settings. A systemic disease does not always accompany them;, however, they can be associated with spondyloarthritis. They are most likely caused by overuse, repetitive trauma, and occupational history. This chapter will present in a simplified approach different types of bursitis, tendinitis, enthesitis, and fasciitis encountered in clinical practice. The emphasis will be placed on diagnostic workup based on comprehensive history-taking skills and musculoskeletal (MSK) examination findings. Outlines of management principles will be reviewed as most of these disorders respond to conservative therapy (pain management, physiotherapy, and avoidance of aggravating movements) and it rarely needs surgical intervention. There are other soft tissue disorders discussed in "Diabetes and Rheumatology" Chap. 21. Detailed techniques of MSK examination of several of these disorders are discussed in Chap. 2.

22.1.1 Learning Objectives

By the end of this chapter, you should be able to:

- Discuss the anatomy and classification of common soft tissue disorders (bursa, ligaments, tendons, and fascia) that cause localized pain syndromes.
- Describe the clinical presentation of the most common types of soft tissue disorders.
- Construct a diagnostic approach for different types of soft tissue disorders.
- Outline management principles of these disorders.

22.1.2 Classification of Soft Tissue Disorders

A selective group of soft tissue disorders will be reviewed in this chapter based on the following classification (Fig. 22.1). It is based on the site of involvement of these structures. It is important to consider soft tissue disorders in the differential diagnosis of regional pain syndromes.

R. Mahroos (✉)
Doctor Samir Abbas Hospital (DSAH),
Jeddah, Saudi Arabia
e-mail: roaa.mahroos@dsah.sa

H. Almoallim
Medical College, Umm Al-Qura University (UQU),
Makkah, Saudi Arabia
e-mail: hmmoallim@uqu.edu.sa

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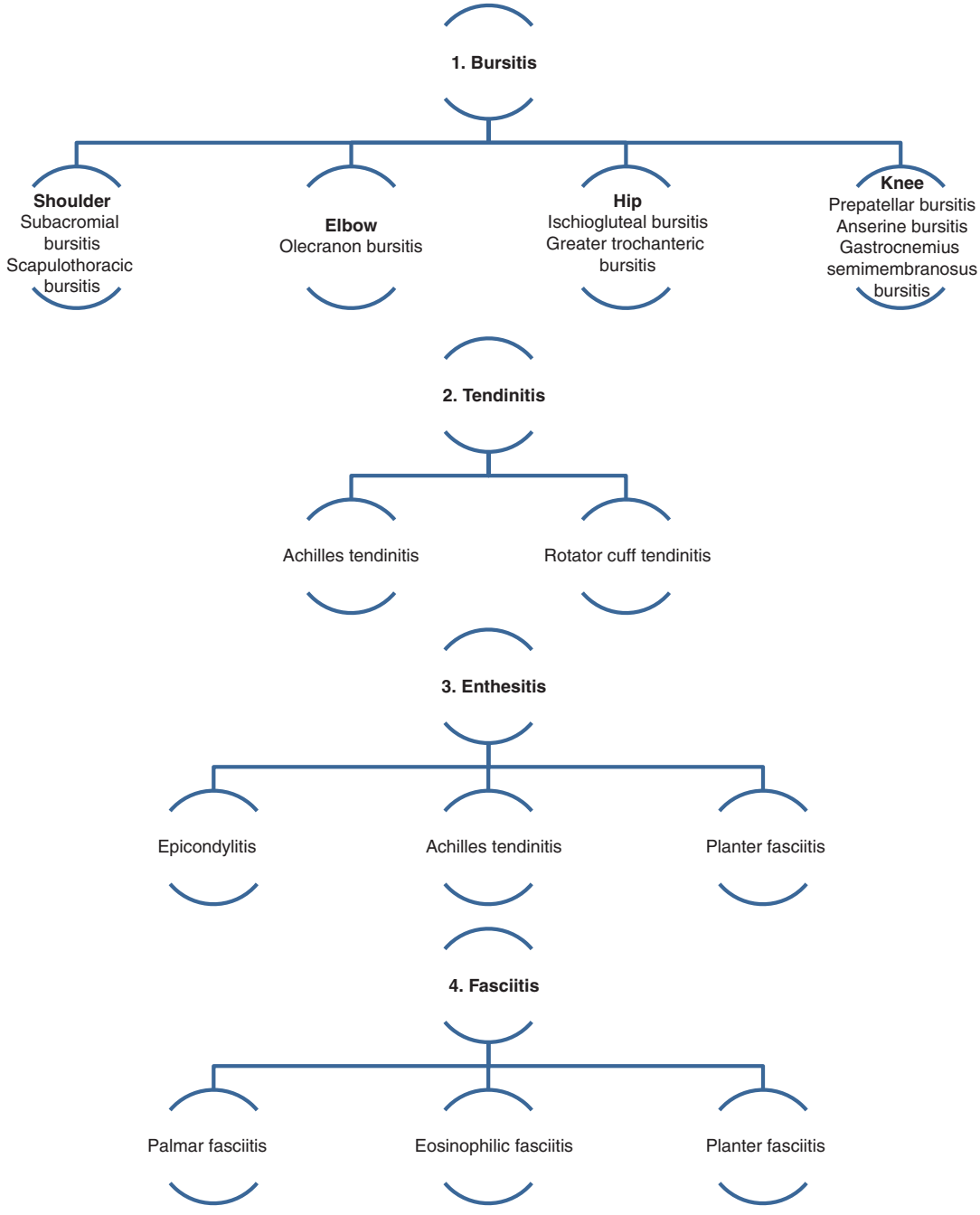

Fig. 22.1 Classification of soft tissue disease in rheumatology

22.1.3 Bursitis

It is important to realize the anatomical definition of a bursa in order to recognize the clinical presentation of bursitis. A bursa is simply the sac structure that is formed of two layers filled with synovial fluid that protects other structure underneath it from injuries caused by pressure. This sac acts as cushions. Bursitis is simply inflammation of this sac.

The most common sites are shoulder (subdeltoid, olecranon), hip (ischial tuberosity, trochanteric), knee (prepatellar bursa), and foot (retrocalcaneal) [1–9]. Table 22.1 represents a comprehensive a general review of the clinical presentation, investigation, and treatment of bursitis. Table 22.2 represents a review of specific types of bursitis.

22.1.4 Tendinitis

A tendon is a thick fibrous cord that attaches muscle to bone. Inflammation in the tendon is called tendinitis. The most common sites for ten-

Table 22.1 Review of the Bursitis history, physical examination, investigation, and treatment

History	• **Pain:** Assess duration, site, localization, increases with movement, relation to position, interferes with activity, recurrence, other joint pains, stiffness, and functional disability (at home, work, and leisure activities) • **Occupation:** Repetitive movement disorder that increase pressure in the joint and its surrounding soft tissue structures. For example, overhead lifting, pushing up elbows when arising from bed, carrying heavy objects, prolong sitting on hard surface, and repeated kneeling • **History of trauma:** Systemic review for evidence of a systemic disease (see Chap. 1) like rheumatoid arthritis (RA), crystal-induced arthritis (gout, pseudogout) and uremia • **History suggestive of infection:** Fever, (infective endocarditis, cellulitis), skin abrasions in superficial bursae (olecranon and prepatellar bursa) wounds, and diabetic, alcoholic [5–7] and immunosuppressed patients are at increased risk of septic bursitis [8, 9] • **Obesity**
Physical examination	• **Swelling:** Mainly superficial • **Tenderness:** With active range of motion (ROM) testing • **Reduced active ROM:** With less or no pain with passive ROM • **Local tenderness:** With palpation over the bursa • **In septic bursitis**: Fever, swelling, redness, tenderness, and hotness [10]
Investigations	1. **If history and physical examination** suggest septic bursitis a. CBC, blood culture, and glucose 2. **Bursa fluid aspiration:** [11] Deep bursa use US or MRI guided aspiration, and fluid for a. **Cell count:** Normal WBC: less than 200/ L. Noninflammatory WBC: 200–2000/ L. Inflammatory WBC: 2000–100, 000/ L. Septic bursitis WBC: may be exceeding 100, 000/ L b. **Gram stain and culture in liquid media**: [10] It is Positive in two-thirds of patients with septic bursitis [8]. The most common organisms: *Staphylococcus aureus* In about 80% of cases, [8, 9, 12, 13] streptococci beta-hemolytic strain, rare coagulase negative staph, *Enterococcus*, *E. coli*, and *Brucella*, or TB in subacute and chronic endemic areas c. Crystal analysis utilizing compensated polarized microscopy d. Bursa fluid glucose: Serum glucose ratio of <50% [14] 3. **Imaging typically not helpful in acute superficial bursitis:** a. Plain X-ray: When there is history of trauma or foreign body and to exclude crystal-induced arthritis particularly chondrocalcinosis b. CT or MRI: Particularly in septic bursitis to confirm the presence of abscesses or fluid collection

(continued)

Table 22.1 (continued)

Treatment	1. **Patient education** a. Avoid aggravating factors that increase joints pressure b. Joint protection program using cushion and pads c. Rest joint position to decrease pressure d. Weight reduction 2. **Pain control and decrease inflammation:** a. **NSAIDs** (see Chap. 4): selective cyclooxygenase 2 inhibitor (celecoxib 200 mg twice daily) or nonselective (naproxen 500 mg twice daily for few days in acute bursitis) b. **Local glucocorticoid injection:** after ruling out septic bursitis with negative culture there is limited data on efficacy and safety;, in general it is more effective than NSAID in speeding recovery, relieving pain, and preventing recurrence of olecranon and subacromial bursitis [7] long-acting glucocorticoid (methylprednisolone 40 mg for large bursa, subacromial or trochanteric, and 10 mg for small bursa, anserine or Ischia) mixed with equal amount of 1% lidocaine injection should not be repeated for 6–8 weeks c. Apply ice for 20 min 6–4 times per day d. Heat not more than 20 min **Septic bursitis:** treatment in immunocompetent or nondiabetic patients: Oral antibiotic (dicloxacillin or second-generation cephalosporin or clindamycin) for 10 days if there is improvement frequent aspiration of the bursa and continue antibiotic for 5 days post sterilization in severe cases and in immunosuppressed patients: IV broad-spectrum antibiotic to cover pseudomonal plus anti-methicillin-resistant *S. aureus* (MRSA) (vancomycin) for 2–3 weeks, till the culture and sensitivity results are available [15] repeat bursa drain and debridement or open surgical drain in deep bursitis

Table 22.2

Subacromial bursitis	
Anatomy	Subacromial bursa lies between acromion process and supraspinatus muscle at top of the humorous Bursitis results from inflammation of supraspinatus tendon
Action of supraspinatus muscle	Abduction of the shoulder
Symptoms	• severe pain at rest and movement of the affected shoulder • prevent active movement
Signs	• tenderness over the bursa just below the acromion • this may extend over deltoid muscle • tender and possibly restricted active ROM, while passive abduction is harmless with possibility of mild tenderness
Treatment	Pain is markedly relieved after injecting local anesthesia, immobilization, rest of the joint, and use of NSAIDs If not improving after 72 h, inject methylprednisolone 40 mg with lidocaine
Comment	It is associated with: • rotator cuff tear that presents with supraspinatus muscle weakness • polymyalgia rheumatic when it is usually bilateral
Scapulothoracic bursitis [2–4]	
Anatomy	The bursa is located in medial angle of scapula and adjacent to second and seventh ribs
Symptoms	Pain and popping sensation with scapulothoracic movement It increases with working overhead, pushing up, reaching up, and shoulder shrugging
Signs	Localize tenderness and crepitus with movement

Table 22.2 (continued)

Treatment	• spontaneous regression in most of the patients [1] • physiotherapy: Postural and scapular strengthening exercise [2] • US heat stretching test might help • if pain persists, glucocorticoid injections under fluoroscopy might be considered • surgery might be indicated in refractory cases [3]
Olecranon bursitis (student's elbow) [9–12]	
Anatomy	The bursa is located just over the extensor aspect of the extreme proximal end of the ulna
Aggravated positions	Leaning on elbow, repetitive forward leaning position, or any position where pressure is exerted on the bursa
Symptoms	Pain in the posterior point of the elbow with normal ROM
Signs	Tenderness, worsening of pain with elbow flexion, and swelling in posterior point of the elbow
Treatment	Consider bursal fluid aspiration if swollen to rule out septic and/or crystal-induced bursitis Treat underlying condition if sepsis or crystal-induced bursitis have been confirmed. Glucocorticoid injection is superior to NSAIDs in preventing recurrent bursitis [4] Referral to orthopedic surgery if recurrent with thick synovium
Ischiogluteal bursitis (Weaver's bottom)	
Anatomy	The bursa is located between gluteus medius muscle and ischial tuberosity
Symptoms	Pain in sitting and lying position. Also, pain in lower buttock after prolonged sitting On hard surfaces
Signs	Tenderness over ischial tuberosity
Treatment	NSAIDs, glucocorticoid injection, foam rubber cushion, and stretching with knee to chest exercise
Greater trochanteric bursitis	
Anatomy	The bursa is located between the tendon of gluteus medius and posterolateral prominence of greater trochanter This bursitis is more common in females rather than males
Symptoms	Night pain, lateral hip pain, 40% radiate to the lateral site of the thigh, worsening if lying on affected side, and patient cannot walk in severe case Iliotibial band syndrome (snapping hip) and leg length discrepancy predispose patients to develop trochanteric bursitis
Signs	• tenderness on lateral hip joint pain region over the greater trochanter • hip joint resisted hip abduction may reproduce symptoms • antalgic gait Notes: The differences between greater trochanteric bursitis and gluteus medius tendinopathy are gluteus medius tendinopathy causes pain and tenderness superior to the greater trochanter, positive Trendelenburg test, significant muscle weakness, and positive one—Leg mini-squat test, patient cannot complete a single repetition squat on affected leg to 60° Recommended X-ray: Lateral, anteroposterior, and frog-leg views to rule out other causes affecting hip joint itself
Treatment	Radiating radicular pains from the lower back need to be ruled out as well. Heat and passive stretching exercise with hip adduction can be tried with weight reduction and avoiding stairs Some resistant cases may need to be injected with glucocorticoid and lidocaine Spinal needles should be used in obese patients
Prepatellar bursitis (Housemaid's knee) [1–9]	
Anatomy	The bursa is located between the patella and the skin
Symptoms	Positive history of kneeling down frequently and/or history of trauma Anterior knee pain that increases with flexion Swelling may be observed
Signs	Tenderness over the patella. Swelling, hotness, and redness particularly in septic or crystal-induced bursitis
Treatment	Rule out septic bursitis and/or crystal-induced bursitis with bursal fluid aspiration Rest joint and avoid trauma. Glucocorticoid injection may be considered In refractory cases refer to surgery

(continued)

Table 22.2 (continued)

Anserine bursitis (Goose's foot)	
Anatomy	The bursa is located medially around 6 cm below the joint line at the attachment of medial collateral ligament to medial tibia It is the site of insertion of three tendons: gracilis, sartorius, and semitendinosus muscles
Symptoms	Risk factors: Positive history of repeated knee flexion in excessive running, stair climbing. More common in obese elderly females and/or with valgus knee alignment Pain at night over the upper tibia around 6 cm below medial joint line It is important to ask the patient to point with one finger the area of pain
Signs	Local tenderness over the exact anatomical location of the bursa. Rule out medial collateral ligament instability (see Chap. 2)
Treatment	Rest. Repeated knee bending should be avoided;, also avoid crossing the leg or frequent squatting positions Use pillow under the knee as a relaxation technique. Ice bags may be applied. NSAIDs can be used, and if there is no improvement after 6–8 weeks, local glucocorticoid injection can be considered.
Gastrocnemius semimembranosus bursitis (Baker's cyst)	
Anatomy	The bursa is located between gastrocnemius and semimembranosus muscles on the medial side distal to the crease in the popliteal fossa back of the knee Most common in adult from 35–70 years old, and it increases with age because the communications between the knee and bursa increase [16]
Symptoms	Asymptomatic accidental finding during physical examination or radiological investigation Posterior knee pain and stiffness that increase with activity Swelling or discomfort in prolong that standing and hyperflexion
Signs	Swelling in posterior aspect of the knee, more marked with knee extension Absence of swelling on knee flexion up to 45° (Foucher's sign) Ecchymosis below the medial malleolus (cresent's sign) in rupture baker's cyst
Causes	One third of causes is due to trauma. Two thirds of the causes are due to other diseases (osteoarthritis, rheumatoid arthritis, septic arthritis and meniscal tear)
Complication	Pseudothrombophlebitis, leg ischemia, compartment syndrome, nerve entrapment, and ruptured [17]
Treatment	Investigation by US or MRI Treat underlying disease If asymptomatic no treatment In arthrocentesis and intra-articular corticosteroid injection result in decrease size after 4 weeks by US follow-up [18] Direct cyst injection if it does not communicate with the joint Surgery is indicated in recurrences and lack of response to glucocorticoid injection

dinitis are around shoulder, elbow, and ankle joints. One of the pathophysiological mechanisms for tendinitis is micro-tears, affecting these tendons from repeated stressors like in overuse, or in traumatic situations.

In some situations where there is inflammation of the tendon sheath, the condition is called tenosynovitis. Table 22.3 represents a comprehensive, general review of the clinical presentation, investigation, and treatment of tendinitis.

Table 22.4 represents a review of rotator cuff tendinitis.

Tendinosis is a chronic proses associated with an atrophic and degenerative change of the tendon caused by recurrent tendinitis. US or MRI is required to diagnose it and to differentiate between different causes.

22.1.5 Rotator Cuff Tendinitis and Rotator Cuff Tear

Rotator cuff tendinitis (RCT) is a common type of tendinitis that affects the shoulder. The patient usually presents with lateral shoulder pain and limited active ROM. It is the most common cause of shoulder pain in clinical practice. A brief approach to shoulder pain is presented in Chap. 2. Table 22.4 represents a comparison between RCT and rotator cuff tear (RCTr) in terms of definition, diagnostic, and therapeutic interventions.

Table 22.3 Review of the tendonitis history, examination, diagnosis, treatment, and prevention

History	• **Localized pain** over the tendon with active movement particularly • **Limited activity** • **Occupation:** overuse and/or sporting activity, usually in middle age group of patients
Risk factors	Intrinsic • Age over 35 years and obesity • Biomechanical abnormalities: Mostly located in lower limbs (pes planus [flat foot], pes cavus, reduced planter dorsiflexion, pelvic inequality and kyphosis) • Previous tendinitis or rupture • Fluoroquinolones use [19] Extrinsic • Training error (sudden increase and inadequate rest) • Environmental (hard gym floors, frozen turf) • Poor equipment (inappropriate footwear) • Poor ergonomics excessive movement
Examination	• Localized tendon pain • Pain with tendon loading • Pain with passive stretching • Pain with active movement • Normal ROM on passive test • Muscle weakness in chronic tendinitis and tendon tear
Diagnosis	**US and MRI:** • Help to diagnose partial or complete tendon tear • Tendon thickness • To rule out other causes particularly if patient did not improve on treatment
Treatment	• Avoid aggravating activity • Apply ice over the tendon for 15 min 4–6 times daily • NSAIDs and local glucocorticoid injection in severe cases • Physiotherapy: Range of motion stretching and strengthening exercises, eccentric exercise, and aerobic fitness • Surgery: probably after 6 months if no improvement or acute tendon rupture

Table 22.4 Review of the tendonitis history, examination, diagnosis, treatment, and prevention [21, 22]

Anatomy	Rotator cuff muscles	Origin on scapula	Insertion on humerus
	Supraspinatus Subscapularis Infraspinatus Teres minor	Supraspinous fossa Subscapular fossa Infraspinous fossa Lateral border	Insertion on humerus Superior facet of greater tuberosity Lesser tuberosity Middle facet of greater tuberosity Inferior facet of greater tuberosity
Muscle action	Rotator cuff muscles	Mscle action	
	Supraspinatus Subscapularis Infraspinatus Teres minor	Abduction Internal rotation External rotation External rotation	
Definition	Rotator cuff tendinitis	Rotator cuff tear	
	Inflammation in the tendon	Injury in the tendon can be partial or complete tear	
Risk factors	Excessive overhead activity, repetitive stressful movement, obesity, anatomic variants, scapular instability, dyskinesia or hypermobility, old age, Chronic diseases (such as diabetes and hyperlipidemia), and Lifting heavy objects [19]. Acute tear can also occur with a fall or forceful injury.		
Symptoms	• Shoulder pain increasing with overhead activity • Shoulder pain could be laterally or posteriorly. It depends on the muscle involved • Limited shoulder movement particularly active ROM. • In the case of rotator cuff tear, muscle weakness is more pronounced, and patients can be asymptomatic.		
Signs	See (Chap. 2)		
Special tests	See (Chap. 2)		

(continued)

Table 22.4 (continued)

Investigations	Radiology: X-rays for tendon calcifications or bone deformation. US high sensitivity and/or MRI to confirm diagnosis, asses rotator cuff tear and degeneration.
Treatment	**Acutely**—if there is significant tear refer the patient to orthopedic surgery. In partial tear or tendinitis consider conservative therapy: • Avoid aggravating activity. • Apply ice over tendon for 15 mins 4–6 times daily. • NSAIDs. Local glucocorticoid inject with lidocaine may be considered. • Physiotherapy: Range of motion stretching and strengthening exercises. **Subacute treatment**—If no improvement is achieved within two to three months: • Glucocorticoids—subacromial glucocorticoid injection is a common treatment to controlling the symptoms [20].

Table 22.5 History, examination, diagnosis, and treatment of enthesitis

Sites	The common sites for enthesitis are in planter fascia at calcaneus and Achilles tendon in the heel. However, there is a scoring system to measure the extent of enthesitis in different body sites
Causes	Ankylosing spondylitis, reactive arthritis, psoriatic arthritis, inflammatory bowel disease (IBD), celiac disease, Whipple disease, acne-associated arthritis, fracture, trauma, and idiopathic secondary usually to repetitive trauma or mechanical misalignment or over weight History suggestive of SpA (see Chap. 1): Red eyes, pain with eyes movement, oral or genital ulcer, genital discharge, back pain or other joint pain, diarrhea or bloody diarrhea resent gastroenteritis, history of psoriasis, or family history of psoriasis
Symptoms	Pain that increases with activity and possibly swelling
Signs	• local tenderness increase with movement • swelling • warmth • decrease active ROM and stiffness • other sites: Iliac crest, greater trochanter, medial and lateral epicondyles in elbow, tibial tuberosities, plantus, costochondral junction, and humeral tuberosities • Most enthesitis in SpA is not detected at clinical examination
Investigations	**Special test:** HLA B 27 **X-ray:** Nonspecific finding: like intra-tendon focal edema, calcific deposit spars, soft tissue swelling, and thickening **US:** Better than clinical examination in the detection of enthesitis of the lower limbs in SpA. There are specific radiographic definitions for enthesitis at different body sites
Treatment	Exercise program Proper shoe wearing using custom made devices Occupation-related measures Local steroid injection in severe and resistant cases In SpA: NSAIDs can be tried first, no clear evidence of efficacy for sulfasalazine [23] and/or methotrexate [24] in enthesitis mainly presentation in SpA. However, several studies showed efficacy of anti-TNF-alpha therapy and IL-17 antagonists in severe enthesitis [25]

22.1.6 Enthesitis

It is inflammation at the site of insertion of ligaments, tendons, fascia, and articular capsules into the bone. It might be associated with pain at free nerve ending. It is the hallmark of spondyloarthritis (SpA) particularly when paravertebral ligaments are involved causing spondylitis. Extensive search for a systemic spondyloarthritic disease (see Chap. 1) should be sought in patients presenting with common enthesitis like Achilles tendinitis and plantar fasciitis [21, 22]. However, most of these enthesitis disorders have no systemic correlation, and they are induced by regional pathophysiological mechanisms. Table 22.5 represents a review about enthesitis. Tables 22.6, 22.7 and 22.8 summarize common enthesitis encountered in clinical practice: Achilles tendinitis, epicondylitis, and plantar fasciitis (Table 22.6).

Table 22.6 Achilles Tendonitis [21, 22]

Anatomy	It is the largest tendon in the body formed by the union of tendons of soleus and gastrogenemius muscles to form Achilles tendon. It inserts posteriorly at the calcaneus
Muscles action	Plantar flexion
Epidemiology	• patients are usually 30–40 years of age • males are equally affected like females • rupture Achilles tendon is five times more common in males
Risk factors	Excessive supination, increase intensity of training program and increasing time in training (basketball and football players), repetitive stress, obesity, male gender, previous history, mechanical factors: Pes planus and pes cavus deformities, over pronation of foot, and drugs—Fluoroquinolone or local glucocorticoid use
Symptoms	• pain with activity relieved after rest • pain 2–6 cm above insertion of the tendon, swelling, and possibly redness • in rupture Achilles tendon patient feels struck violently in the back of ankle or hears loud popping sound with severe pain • absence of pain dose not rule out Achilles tendon rupture
Signs	• gait and excessive foot supination. This is common with genu varaus deformity in the knee • examine the patient in prone position with feet hanging off at the end of the bed • inspect for bruising, swelling, and foot misalignment • palpation: Hotness, thick tendon or defect, edema, hematoma, tenderness 2–6 cm above calcaneus and compare it with the other side • palpate the tendon in while in dorsiflexion of the ankle, plantar flexion, and Neutral position • assess retrocalcaneal bursitis as one of the differential diagnosis for heel pain • crepitus in chronic tendinitis • assess for peripheral vascular disease (pulse, capillary refill, hair loss, and edema) Notes: The retrocalcaneal bursitis causes pain, fullness, or swelling proximal and anterior to the insertion of Achilles tendon in to the calcaneus The posterior tibial tendinitis causes pain in medial side of the ankle
Special tests	• **calf squeeze or (Thompson test):** Sensitivity of 96% and specificity of 93% [21] (see Chap. 2) • **Matles test:** Sensitivity of 88% and specificity of 85%: [21] The patient lies prone with knees flexed to 90°. Observe whether the affected foot is dorsiflexed or neutral (both are abnormal) compared with the uninjured side, where the foot should appear plantar-flexed
Investigations	**Radiology:** US and/or MRI to confirm diagnosis, monitor treatment response, and/or to assess why the patient is not responding if another diagnosis is missing
Treatment	Avoid aggravating activity, support Achilles tendon with bandage, apply ice, NSAIDs can be used, avoid glucocorticoid at it is associated with high risk of tendon rupture [22]. Consider corrections of mechanical defects by providing custom-made orthotics that provide arch support Consider rehabilitation and occupational therapy programs with eccentric exercise for around 12 weeks. Air heel brace cast can be used in severe cases Superficial heat and cold compressors Deep heat by (US and iontophoresis) Surgery can be considered in refractory cases after 3–6 months if no improvement all measures **Acute tendon rupture:** Apply ice, analgesic, rest the ankle, and consider immobilization trial in few degrees of plantarflexion. Consider surgical referral for partial ruputure: there is still no clear rule for surgical intervention

22.1.7 Achilles Tendinitis

See Table 22.6.

22.1.8 Epicondylitis [26, 27]

See Table 22.7

22.1.9 Fasciitis

A fascia is a layer of fibrous *connective tissue (collagen)* below the skin that covers underlying tissues (muscles, blood vessels, and nerves). Fasciitis is the inflammation of the fascia that causes fibrosis and loss of elasticity. The most common types of fasciitis are

Table 22.7 Lateral and medial epicondylitis

Types	**Lateral epicondylitis (tennis elbow):** 15 times more common than medial epicondylitis Females are equally affected like males	**Medial epicondyle (golfer elbow):** Less common
Definition	It is inflammation at bony origin for wrist extensors muscles (extensor carpi radialis brevis "inserted in posterior base of third metacarpal" and extensor digitorum communis), due to overuse. The elbow of the dominant arm is affected more	It is inflammation at bony origin for wrist flexors muscles (pronator teres and flexor carpi radialis)
Muscles action	Extensor and abductor of the hand at wrist joint	Flexors of fingers and thumb. Also, flexors and pronators of the wrist
Risk factors	**Age:** Player 30 years or older, smoking, obese, Tennis ball player **, Occupation:** Computer user and repeat movement for 2 h daily [27, 28]	
Physical exam	• localize tenderness in lateral epicondyle • pain on resisted wrist extension while elbow in flexion • pain in resisted supination and hand shaking • pain in resisted middle finger extension • Normal ROM of the elbow except in severe cases • few degrees of extension might be affected • examine radial nerve • in compression neuropathy the pain diffuses distally to epicondyle and is associated with muscle weakness	• Localized tenderness in medial epicondyle • Pain on resisted wrist flexion while elbow in extension • pain with resisted forearm pronation • examine ulnar nerve
Investigation	It is a clinical diagnosis and investigations are usually not required X-rays if indicated to look for osteophytes and calcification in epicondyle	
Treatment	Phase 1: Symptom less than 6 weeks • rest the joint and use splint • physiotherapy (eccentric exercise) • NSAID: There is limited evidence, oral NSAIDs helps to reduce pain and improve the function in 6 weeks [27], and there is limited benefit of topical NSAIDs in acute epicondylitis [29] Phase 2: If symptoms do not improve for 6–12 weeks • repeat 3 views X-ray to identify other possible causes • continue eccentric exercise • local injection of corticosteroid. If no improvement, repeat in 2–4 weeks for total of 2 Doses. Use of local corticosteroid injection in lateral epicondylitis improves many patient Symptoms in 6 weeks but does not prevent recurrences and long-term outcome worseness [30, 31] Phase 3: If symptoms do not improve after 12 weeks • do US and/or MRI Alternate treatment option might be considered as platelet-rich plasma injections, autologous blood injections, prolotherapy, extracorporeal shock wave therapy, and percutaneous needle tenotomy [32] • surgery if more than 6 months with failed conservative therapy including corticosteroid injection • 1. debridement +_ arthroscopic drain • 2. open debridement • 3. Pericutanous tenotomy	

planter fasciitis, palmar fasciitis, and eosinophilic fasciitis (these types can be secondary to autoimmune rheumatological diseases and malignancies).

22.1.10 Plantar Fasciitis

See Table 22.8.

22.1.11 Palmar Fasciitis

See Table 22.9.

22.1.12 Eosinophilic Fasciitis

See Table 22.10.

Table 22.8 Planter fasciitis anatomy, history, physical exam, investigation and treatment

Planter fasciitis	
Anatomy	It is a thick white tissue with longitudinal fibers attach to medial process of calcaneal tuberosity divide to five slips continuing forward to form fibrous of flexor sheathes on plantar aspect one for each toe
History	Age 40–60 years old Pain in planter region that worse when initiate walking during the first few steps in morning Aggravating factors: prolong standing or jumping, flat foot, high arch foot, heel spurs, running, excessive training during aerobic exercise and obesity [33, 34] Symptoms suggestive of SpA (see Chap. 1) [35]
Physical examination	• local tenderness • limited ankle dorsiflexion The examiner should dorsiflex the patient toes with one hand, then pull the plantar Fascia tight, and then palpate with thumb or index finger of other hand, the fascia From heel particularly the medial aspect where the plantar fascia originates to the Forefoot: Tenderness can be elicited
Investigations	• HLA-B27 and CRP if SpA is suspected • X-rays: Lateral and axial films to detect thickness, fat pad abnormality, heel spur And to rule out other causes • MRI in resistant cases [36] • US: 80% sensitivity and 88, 5% specificity to detect fascia thickening and edema [37]
Treatment	• 80% resolve spontaneously by 12 months • decrease physical activity and consider stretching exercise • arch support with custom made orthotics and avoid flat shoes • ice massage • NSAIDs can be tried for 2–3 weeks • inject with local glucocorticoid and lidocaine in resistant cases Mechanical defects should be corrected otherwise symptoms may recur • botulinum toxin injection might be considered • for resistant cases refer to surgery for cast and possible splint extracorporeal shock wave therapy • if still no response fasciotomy can be considered as 5–10% of cases ultimately required it

Table 22.9 Palmar fasciitis: definition, risk factors, symptoms, physical exam, investigation and treatment

Palmar fasciitis (palmar fibromatosis)	
Definition	Inflammation of the palmar fascia which causes fibrosis
Risk factors	Malignancy most common as ovarian cancer but can also be associated with breast, lung, pancreas, stomach, colon, and metastasis [38]
Symptoms	• Pain in palm with swelling: inability to close hands resulting in limitation of activity and function • joints pain • vasomotor symptoms • symptoms suggestive malignancy
Physical examination	• tenderness and swelling of bilateral palms with tight fascia and fibrosis (woody hands) • symmetrical polyarthritis and flexion deformity of the fingers • Nailfold capillary is normal
Investigations	• tissue biopsy shows extensive fibrosis with fibroblast and mononuclear cell infiltration • screening for malignancy
Treatment	• treat underlying malignancy if patient has metastasis and has poor prognosis • NSAIDs • corticosteroid • ganglion blockade

Table 22.10 Eosinophilic fasciitis definition, risk factors, symptoms, physical exam, investigation and treatment

Eosinophilic Fasciitis (Shulman's syndrome or diffuse fasciitis with eosinophilic)	
Definition	Inflammation of the fascia with eosinophils infiltration causes fibrosis in early stages
Risk factors	Hematological malignancy leukemia, myelodysplasia, and aplastic anemia [39]
Symptoms	Stage 1: • pitting edema bilaterally most involving both arms and legs with sparing fingers and toes • proximal area more than distal in the extremities • no Raynaud's phenomenon Stage 2: • sever induration of the skin and subcutaneous tissue with peau d's orange appearance • Groove sign is an induration due to retraction of the subcutaneous tissue along the superficial veins • mild myositis with normal CK level Stage3: • Neuropathy like carpal tunnel syndrome • flexion deformity of the digits • muscle atrophy • no sclerodactyly and normal nailfold capillary
Investigations	• CBC and peripheral blood film look for hematological malignancy • peripheral eosinophilia in 80% of the cases and the degree of eosinophilia does not correlate with disease activity • elevated ESR and CRP • aldolase can be elevated with normal CK • presence of polyclonal hypergammagloblinemia • tissue biopsy shows inflammation and fibrosis in all skin layers except the epidermis and eosinophils infiltration can be seen in early stages • MRI findings fascial thickening with enhancement
Treatment	• treat underlying causes • some patients may experience spontaneous improvement as the disease can be self-limited • complete remission can be seen after 2 years or more • high dose of prednisolone 20–60 mg/ day • in resistant cases use hydroxychloroquine and methotrexate
Poor prognostic factors	• young age at onset of the disease • trunk involvement

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23 Gastrointestinal Manifestations of Rheumatic Diseases

Hussein Halabi, Ammar AlDabbagh, and Amany Alamoudi

23.1 Objectives

- To describe gastrointestinal manifestations in rheumatic diseases.
- To construct a diagnostic and systemic approach to gastrointestinal symptoms in rheumatic diseases.
- To interpret laboratory, radiological, and endoscopic finding in patients with rheumatic diseases presenting with gastrointestinal manifestations.

23.2 Gastrointestinal Manifestations of Systemic Lupus Erythematosus (SLE)

SLE may involve any part of the gastrointestinal (GI) tract as well as the liver.

Some patients may develop GI manifestation at onset of the disease (42%), which may delay the diagnosis of SLE in those patients. Patients with SLE who present with GI symptoms may have these symptoms secondary to active disease, side effects with medications, or secondary to infectious process. The most common symptoms are nausea and vomiting (53%), anorexia (49%), and abdominal pain (19%) [1]. The prognosis in such cases depends on early recognition and proper management [2].

23.2.1 Oral Cavity Manifestations of SLE

Oral cavity manifestations can happen in 7–52% of SLE patients and are necessarily associated with disease activity. The abnormalities which are secondary to active lupus are usually erythematosus, discoid, and ulcerative and can be painful or painless [3].

There are no high-quality evidences to guide in the management of oral lupus lesions using systemic therapy.

Antimalarials, azathioprine, and corticosteroid are frequently used for the treatment of severe cases. Furthermore, thalidomide and cyclosporine are commonly used as alternative therapy as shown in some studies from Europe [3] (Fig. 23.1).

H. Halabi
Department of Internal Medicine, King Faisal Specialist Hospital and Research Center, Jeddah, Saudi Arabia

A. AlDabbagh (✉)
Internal Medicine, Gastroenterology and Hepatology Consultant, Jeddah, Saudi Arabia
e-mail: aaldabbagh@fakeeh.care

A. Alamoudi
Doctor Soliman Fakeeh Hospita, Jeddah, Saudi Arabia

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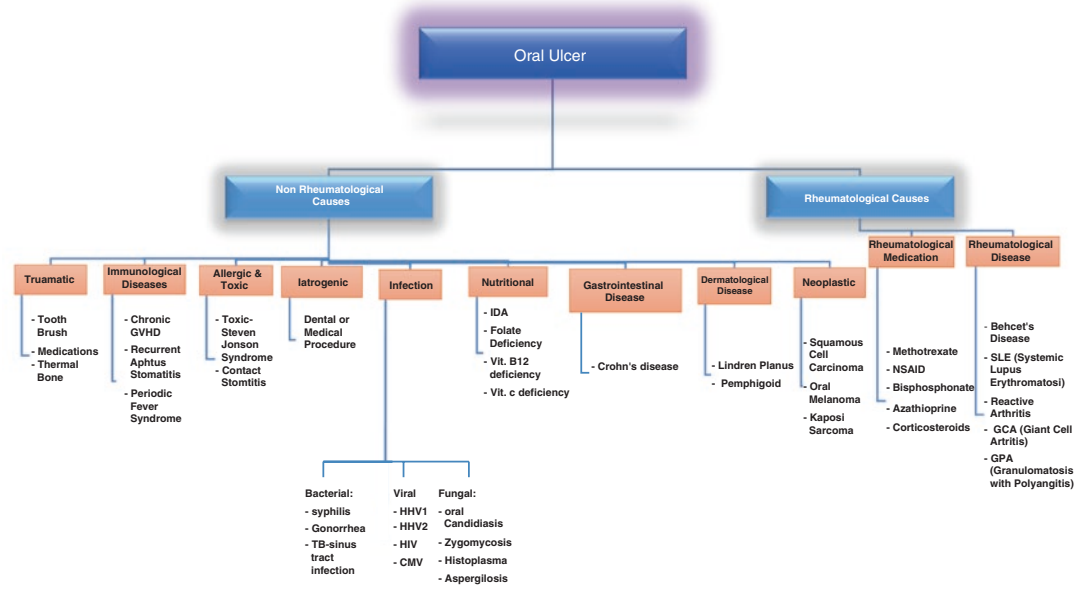

Fig. 23.1 Causes of oral ulcers

23.2.2 Esophageal Manifestations of SLE

Dysphagia, heartburn, and regurgitation are common among SLE patients.

Dysphagia may result from dysmotility disorder, heartburn, or reduced saliva production in case the patient has a secondary Sjogren's syndrome. The esophageal dysmotility may present in 21% to 72% of SLE patients [1].

Multiple factors may play a role in the motility changes which include inflammatory process in esophageal muscles, muscle atrophy, or ischemic vasculitis. Motility abnormalities may not be correlated to the symptoms or lupus [1]. SLE patients are at an increased risk of developing infectious esophagitis secondary to immunosuppression and pill-induced esophagitis. There are no high-quality evidences guiding the management of dysphagia and reflux in patients with SLE. Pharmacological agents, such as antacids, proton pump inhibitors, H2 blockers, or promotility agents, may play a therapeutic role [3].

23.2.3 Gastric Manifestations of SLE

In SLE patients who present with acute abdominal pain, perforating peptic ulcer may happen in 6% to 8% out of them. Physicians should consider *H. pylori* testing before initiating treatment with NSAIDs. Additionally, those patients may require to be on continuous gastroprotective agents such as proton pump inhibitors and H2 blocker.

23.2.4 Colonic and Small Bowel Manifestations of SLE

It is always challenging for physicians if SLE patients present with acute abdominal pain. The majority of SLE patients are taking corticosteroid and/or other immunosuppressive medications, which could mask some clinical signs of perforation and ischemia [3].

The most prevalent etiologies of acute abdominal pain in patients with SLE are mesenteric vasculitis, hepatobiliary disease, pancreatitis, gastroenteritis, and appendicitis. Acute abdominal pain in SLE patients is associated with relatively high mortality reaching 9.4% to 11% [1].

During flare of SLE, 53% of the patients who present with acute abdominal pain may have intestinal vasculitis, and their initial symptoms may include acute abdominal pain, nausea, and vomiting.

Intestinal vasculitis may lead to ischemic changes and infarction, and its affection may

range from superficial ulcerations to deeper layers which may cause penetration of the submucosa; in some cases GI bleeding may happen.

There are certain clinical and radiological signs that may alert physician for the possibility of bowel perforation which include low blood pressure, metabolic acidosis, high levels of serum lactate dehydrogenase, distended abdomen, and dilated intestines in abdominal radiograph.

Thumb printing represents edema of the submucosa or bleeding on a barium enema; this sign is considered specific for intestinal ischemia [3]. Colonoscopic findings may reveal inflammatory changes and/or ulcers, which may be irregular in shape or punched out. Three-phase abdominal Tc-99 m pyrophosphate scintigraphy can be utilized to show areas of active vasculitis. Mesenteric angiography may be used to rule out distinct type of vasculitis like polyarteritis nodosa which may be associated with diffuse irregularities of the small arteries in the intestine and renal arteries [1].

Treatment of lupus vasculitis includes treatment of underlying SLE and high doses of steroids, but in advanced cases, cyclophosphamide is usually given. Patient must be referred to general surgery because they should have a low threshold for early laparotomy in cases of acute abdomen [1].

In SLE patients, infection is considered one of the most common causes of mortality which could reach up to 28.5% [1, 3]. The majority of SLE patients are considered immunocompromised because of immune dysregulation associated with the disease itself and because most of the patient are being managed with immunosuppressant medications. Thus, they are at risk of certain kinds of infections such as CMV, *Salmonella* infection, pneumatosis cystoides intestinalis, and others.

In infection with *Salmonella*, the bacteria is usually isolated from blood rather than the stool sample. It is usually associated with febrile illness and abdominal pain and infrequently diarrhea [1].

Patients with pneumatosis cystoides intestinalis could have benign pneumoperitoneum. Conservative management may be sufficient, and some patients may require corticosteroids or intravenous cyclophosphamide [1].

Because of the similarity between clinical symptoms of SLE flares and those associated with infections, early identifications of underlying infections among SLE patients can be challenging [3].

One of the rare GI complications in patients with SLE is intestinal pseudo-obstruction (IPO), and it is defined as having symptoms and signs of intestinal obstruction with the absence of actual mechanic obstruction.

IPO can be diagnosed based on the clinical findings, abdominal radiograph, and manometry findings [4]. Management usually starts with conservative measures; in case of insufficient response, steroids and/or immunosuppressive drugs can be given as well as antibiotics specially the ones with prokinetic properties such as erythromycin. Octreotide may be used in refractory cases [1].

Protein-losing gastroenteropathy (PLE) is described as the presence of low levels of serum albumin secondary to losing proteins from the GI tract, and it's usually considered in patients with hypoalbuminemia with the absence of marked proteinuria, advanced hepatic disorders, impaired absorption, or poor oral intake [4]. The small intestines are commonly affected rather than the large intestines [1]. It commonly manifested as mild edema and may progress to ascites and pleural and pericardial effusions [4]. Radiological features of PLE may include prominent mucosal pattern (due to edema), speculation, and fragmentation or clumping of barium. Histological features may be normal or may show blunted villi or lymphangiectasia. Management of PLE includes corticosteroids, and some patients may require the use of cytotoxic medications; octreotide is occasionally used [1].

23.2.5 Pancreatic and Gallbladder Manifestations of SLE

Acute pancreatitis is an uncommon complication of SLE, and it might occur in 8% of patients with SLE, and patient may develop abdominal pain [1].

SLE patients with pancreatitis have a mortality rate of 27%. It is associated specially with neuropsychiatric and cardiac manifestations, hypocalcemia, low levels of the complements, and complications of pancreatitis [1]. The management of SLE-related pancreatitis, as with other causes of acute pancreatitis, is with intravenous fluids, pain control, and electrolyte correction.

Primary sclerosing cholangitis and autoimmune cholangiopathy have been reported in SLE patients. Acute acalculous cholecystitis may occur secondary to vasculitis or serositis, and it is commonly managed with surgical intervention [1] (Fig. 23.2).

23.2.6 Hepatic Manifestations of SLE

It was estimated in some studies after several years of follow-up periods that 9.3% to 59.7% of SLE patients may have an abnormal liver function test (LFT) [5]. Transaminitis is common among SLE patients and may be developed due to several etiologies which may include side effects of medications, infectious viral hepatitis, fatty liver disease associated with steroid use, hepatic congestion, primary liver disease, autoimmune hepatitis (lupoid hepatitis), or lupus hepatitis [6]. During SLE flare, 20% of the patients may have abnormal liver enzymes, while in 23% of the patients, the etiology of the abnormal liver tests is unknown [7]. SLE patients may have hepatomegaly in 39% to 40% of the cases, while splenomegaly may present in 6% of patients with SLE [1].

Autoimmune hepatitis (AIH) should be always considered in SLE patient with persistent elevated liver enzymes; undiagnosed AIH may progress rapidly to hepatic cirrhosis. Both diseases are associated with positive ANA; however, anti-smooth muscle antibody is associated

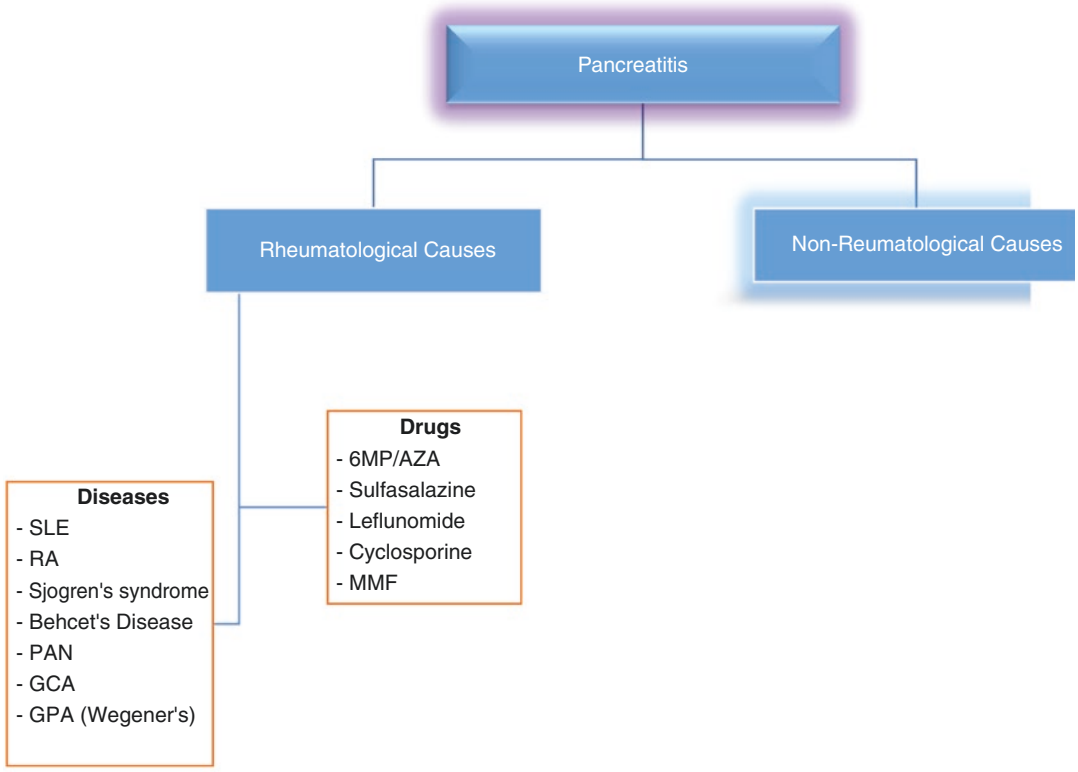

Fig. 23.2 Rheumatological causes of pancreatitis

with AIH and can help in distinguishing between AIH and lupus-associated hepatitis. On the other hand, anti-ribosomal P antibody was found to be positive in many patients (69%) with lupus hepatitis [7].

Patients with AIH are usually managed with corticosteroid initially, and some of them require other immunosuppressant medications [8].

Based on the current understanding of lupoid hepatitis, it can be defined as the presence of pathologic liver injury fitting a picture of chronic hepatitis, having a negative serum serology of the common viral infections associated with chronic hepatitis and the presence of positive ANA or LE cell preparation [9].

Luckily, there are some histological findings seen in liver biopsies which may be helpful for distinguishing lupus hepatitis from AIH. For instances, in AIH, interface hepatitis associated with lobular activity, rosetting of liver cells, or lymphoplasma cell infiltration can be seen in liver biopsy. On the other hand, in lupus hepatitis, the inflammation is usually lobular and occasionally periportal, with a paucity of lymphoid infiltrate [6].

SLE patient may have a secondary antiphospholipid syndrome (APS), which is described as the presence of antiphospholipid antibodies and recurrent arterial or venous thrombosis. Patients with APS have GI involvement such as Budd-Chiari syndrome, hepatic ischemia, and esophageal varices (secondary to portal vein thrombosis); esophageal involvement may occur as well which include necrosis with perforation (due to thrombosis), bowel ischemia, colonic ulcers, and pancreatitis [10].

Overlap syndrome can occur in which patient may have SLE with AIH or PBC with similar prevalence (2.7% to 15%) [7, 11].

23.2.7 Gastrointestinal Malignancies in Systemic Lupus Erythematosus

Several studies have looked at the malignancy rate among SLE patients. An international study which involved 16,409 SLE patients noted a modest increased risk of malignancy in SLE patients [12]. Multiple factors are possibly contributing to this slight increase of overall malignancy risk in those patients which include immune dysregulation in SLE which may lead to disturbance in abnormal proliferations and activation of T and B cells. Thus, abnormality in B cell proliferation may explain the presence of non-Hodgkin's lymphoma, a type of B cell lymphoma, in some SLE patients. Other factors are the use of immunosuppressive medications as well as the chronic inflammation associated with the disease itself [13].

The most frequently noted malignancies in SLE patients are non-Hodgkin's lymphoma, lung cancer, hepatobiliary malignancy, vulvar/vaginal malignancy, and thyroid malignancies, as well as cervical dysplasia [12].

On the other hand, there are some malignancies found to be decreased among patients with SLE such as breast and prostate cancer. Some proposed reason for this decrease in the rate of these malignancies may be related to circulating anti-DNA autoantibodies as well as certain cytokines mediated by HSP-27 [12].

23.3 Gastrointestinal Manifestations of Rheumatoid Arthritis (RA)

23.3.1 Dysphagia and Other Esophageal Manifestations of Rheumatoid Arthritis

Almost half of RA patients may have temporomandibular joint (TMJ) arthritis. Patients with TMJ arthritis may complain of pain and crepitus during chewing secondary to TMJ involvement which may correlate with RA activity. Atlantoaxial subluxation with evidences of spinal cord involvement may result in dysphagia; physicians should be aware of the high risk associated with endoscopy in such patients. Patients with juvenile RA (JRA) may complain of dysphagia secondary to cervical spine abnormality or to micrognathia, which occurs as a result of the loss of the mandibular condyles and retraction of the jaw [14]. Methotrexate, the cornerstone of treat-

ment of RA, can cause oral ulcers which might contribute to the difficulty in initiating swallowing or dysphagia.

Esophageal manifestations in RA may include esophageal dysmotility, reflux esophagitis, amyloidosis, and, rarely, esophageal varices due to Felty's syndrome.

Abnormal esophageal motility with a low peristaltic pressure in the lower two-thirds of the esophagus and reduced pressure in the lower esophageal sphincter lead to impaired peristalsis in patients with RA. These manifestations may occur in up to 62.5% of RA patients and can be associated with heartburn, dysphagia, and esophagitis. Esophageal dysmotility may be attributed to amyloidosis or to GI vasculitis, which occasionally can cause esophageal strictures from local ischemia [10, 14].

23.3.2 Gastric Manifestations of Rheumatoid Arthritis

Most of GI abnormalities in patient with RA are associated with the chronic use of NSAIDs and steroids. In 20% to 40% of the patients on NSAIDs, abnormal changes can be seen during endoscopic evaluations. Those patients are considered at a high risk of peptic ulcer disease and ulcerations in both small and large bowels [10].

In 30% and 60% of patients with RA, biopsy samples may show chronic superficial and atrophic gastritis. In addition, chronic atrophic gastritis can also be seen in patients with RA and associated secondary Sjogren's syndrome. Those patients may develop vitamin B12 deficiency and/or pernicious anemia [14]. NSAIDs are commonly prescribed for RA patient because of their effect for pain relief and for their anti-inflammatory properties; however, their use is associated with a wide range of GI manifestations, and patients may present with relatively mild symptoms such as dyspepsia and gastroduodenal ulcerations to a life-threatening ones such as GI bleeding, perforations, or obstructions. Gastropathy associated with NSAID use may direct physicians toward the use of a selective type of NSAIDs known as cyclooxygenase 2 inhibitors (COX-2), which in many trials proven its efficacy in reducing GI complications such as bleeding, perforations, or obstructions. Physicians may use alternative methods for GI protection with NSAID use such as prescribing proton pump inhibitor (PPI) or misoprostol combined with NSAIDs [15, 16].

23.3.3 Intestinal and Colonic Manifestations of Rheumatoid Arthritis

Small bowel findings in patients with RA may manifest as inflammatory changes which could result in blood and protein loss, ulcerations, and strictures. However, colonic and rectal involvement includes nonspecific colitis and rectitis, ulcerations, blood loss, diverticular complications, and perforation. The cecum and the right colon are the common sites of colon ulcerations which may complicate with a bleeding or perforations [10].

RA-associated vasculitis is an uncommon complication of RA; it can happen in 1% of the patients. Among RA patients with associated vasculitis, 20% of them may develop intestinal involvement. Patients at risk of RA vasculitis are those with long-standing erosive arthritis, positive rheumatoid factor with a high titer, and the presence of subcutaneous nodules.

Surprisingly, RA vasculitis may occur in patients with inactive joint disease. Furthermore, it can complicate with GI bleeding, ulcerations, bowel perforations, and small and large intestine infarctions [10, 15]. The prognosis in such patients is commonly poor, and the consequences may be fatal [17].

Long-standing RA may complicate with secondary amyloidosis which involves the GI tract as well as the liver. GI involvement may manifest as protein-losing enteropathy, colon ulcers, or esophageal strictures [18].

Pneumatosis cystoides intestinalis is rarely associated with RA [19]. GI side effects associated with use of NSAIDs do not merely involve the upper GI tract; it also can involve the lower GI tract [15].

Anti-gliadin IgG may be found in up to 47% of patients, specially in those with positive rheumatoid factor (IgA). Duodenal villous atrophy may present in some patients; however there are insufficient evidences to support the association between RA and celiac disease.

23.3.4 Hepatic Manifestations of Rheumatoid Arthritis

Enlarged liver may be seen in up to 22% of RA patients using scintigraphy scan, and it may be associated with elevated RF.

Spontaneous rupture of the spleen may occur with or without splenomegaly. RA may involve the capsule which could lead to this complication. Regarding laboratory investigations, patients with RA usually have normal levels of transaminases and bilirubin; however, alkaline phosphatase may be elevated in up to 18%–46%, while gamma glutamyl transaminase (GGT) may be elevated in 23%–77% of RA patient and it may correlate with RA activity.

In autopsy study, abnormal liver histology was found to be in 92% of RA patients and 65% of patients in a clinical study. The most prevalent histologic findings are periportal fibrosis, inflammatory changes in the portal tract, sinusoidal dilatation, amyloid, and rarely cirrhosis. These changes are usually mild and might correlate with RA activity.

RA has been commonly reported after an infection with hepatitis B or C. However, it is still unclear as to whether the virus triggers RA or the infections and RA occur at the same time. After following levels of HCV viral loads and liver function tests, it was found that the use of anti-TNF biological therapy in the treatment of RA may not cause a reactivation of chronic infection with HCV. On the other hand, anti-TNF may cause a reactivation of HBV. It is recommended for all patients with HBV who are planning to get anti-TNF to be started on the treatment for HBV at least 2 weeks before the initiation of anti-TNF.

In RA patients presenting with liver abnormalities, physicians should broaden the differential diagnosis to include side effects of a drug with hepatotoxicity, viral hepatitis, fatty liver, and autoimmune hepatitis (AIH).

Sulfasalazine can cause reversible liver injury but might recur if the drug was reintroduced.

Methotrexate hepatotoxicity was extensively reviewed and can cause steatosis, stellate cell hypertrophy, and hepatic fibrosis. Hepatic damage may increase with recurrent hepatic infections and concomitant use of the hepatotoxic drugs or alcohol [20].

23.3.5 Other Gastrointestinal Manifestations of Rheumatoid Arthritis

Rheumatoid vasculitis is classified as vasculitis associated with a systemic disease. It usually involves small- and medium-sized vessels affecting 1–5% of RA patients.

Intestinal involvement in rheumatoid vasculitis was described in another section (see Intestinal and Colonic Manifestations of Rheumatoid Arthritis).

In case of ruptured aneurysm, patients may develop abdominal pain and syncope. Regarding hepatic manifestations, rheumatoid vasculitis may lead to intrahepatic or subcapsular hematomas, infarction, or rupture [10, 21]. Management of rheumatoid vasculitis is based on only small observational studies and case reports.

The most commonly used agents are high-dose steroids, cyclophosphamide, and biological therapies.

Secondary amyloidosis can be caused by several diseases; however, RA is the most common cause of secondary amyloidosis. Patients at risk are those with poorly controlled and long-standing disease usually more than 5 years. Secondary amyloidosis may involve the GI tract in up to 22% of the cases. It may manifest as refractory diarrhea, malabsorption, protein-losing enteropathy, and abdominal pain [22–24].

Presence of splenomegaly, neutropenia, and RA makes the classic trial of Felty's syndrome which may present in 1% of RA patients. It is characterized by severe destructive arthritis,

rheumatoid nodules, enlarged lymph nodes, vasculopathy, skin ulcers, and hepatic abnormality which may include hepatomegaly in up to 68% of the cases and abnormal liver function tests in up to 56% of the patients which is a higher percentage compared to the one seen in uncomplicated RA.

23.4 Gastrointestinal Manifestations of Inflammatory Myositis

Inflammatory myopathies are distinct category of rheumatic diseases which usually present with a proximal myopathy; however they have different skeletal and other organ manifestations; dermatomyositis (DM), polymyositis (PM), and inclusion body myositis (IBM) are the main diseases in this category.

23.4.1 Symptomatology

Gastrointestinal manifestations of inflammatory myopathies include dysphagia, heartburn, bloating, nausea, and chronic constipation. Severe GI manifestations maybe secondary to inflammatory changes in bowel mucosa, resulting in erosions, ulcers, and perforations, are uncommonly seen in adult DM [25, 26].

23.4.2 Esophageal Manifestations of Inflammatory Myositis

Patients with inflammatory myopathies and esophageal involvement may develop uncoordinated swallowing, uncoordinated esophageal peristalsis, and hiatus hernia with reflux and stricture formation [27].

The most common GI symptoms in patients with inflammatory myositis are dysphagia—to solids and liquids—and heartburns [25]. They occur secondary to abnormalities in the pharynx and esophagus and in up to 32–84% of patients with myositis. The highest type of inflammatory myositis in the percentage is inclusion body myositis, and it is unfortunately the most refractory one [28]. The patient might present with symptoms including nasal speech, hoarseness of the voice, nasal regurgitation, and an inability to swallow a food bolus while the patient is on recumbent position due to the elimination of the effect of gravity; physical exam will be significant for tongue weakness, flaccid vocal cords, and poor palatal motion [27, 28]. The presence of esophageal manifestations is linked to unfavorable prognosis and a more severe disease.

Patients with reflux symptoms might respond to anti-reflux measures as well as treatment of inflammatory myopathy [25]. The use of steroids may improve esophageal dysfunction. In PM and DM, plasmapheresis may be effective for the treatment of dysphagia [29]. Intravenous immunoglobulin (IVIG) is usually considered in the refractory inflammatory myopathy, with consistent remission maintained in almost half of successfully treated patients with PM after discontinuation of therapy [30]. In IBM, IVIG may be effective as well if given with or without steroid in cases of severe dysphagia. Surgical intervention is usually needed in case of obstructive causes.

Cricopharyngeal myotomy is the most beneficial intervention for dysphagia in inflammatory myopathy [28], but dilatation may be attempted if surgery is contraindicated. Injection of botulinum toxin A into the cricopharyngeus may also eliminate the need for surgical myotomy [27, 29–31].

23.4.3 Gastric Manifestations of Inflammatory Myositis

Esophageal as well as gastric emptying can be delayed in PM and DM. Manometry may reveal reduced distal esophageal/gastric emptying implying malfunction of the smooth muscle of the upper GI tract [25]. Delayed gastric emptying, constipation, and boating all are common in patient with inflammatory myopathy which can be attributed to dysmotility disorders. Patients with inflammatory myopathies (6–60%)—specially DM—are at high risk of certain types of

malignancy [10]. There is a threefold increased risk for cancer of the stomach, pancreas, and colon [32]. The most common GI malignancies are gastric and colorectal adenocarcinoma [10].

23.4.4 Intestinal Manifestations of Inflammatory Myositis

Vasculitis may lead to ulcerations in the mucosa and possibly intestinal perforation. This is more common in childhood type of DM rather than adult type, in which all these features have been described throughout the GI tract from the esophagus to the large intestine. Pneumatosis cystoides intestinalis has been reported in DM and PM. There have been also some reports linking between PM and small bowel pseudo-obstruction and pseudomonal necrotizing enterocolitis [25] (Fig. 23.3).

23.4.5 Hepatic Manifestations of Inflammatory Myositis

Inflammatory myositis is occasionally misdiagnosed as a liver abnormality. Thus, this could result in a delay in delivering the appropriate management. Active muscle inflammation is commonly associated with an elevation of the levels of CK, aldolase, ALT, AST, and LDH. Higher levels of these enzymes are commonly seen in PM compared to DM and in males compared to females. Liver abnormality or biliary diseases should be suspected in case the levels of transaminases are higher than CK levels or when patients develop cholestatic picture [33] [9].

There are some case reports associating between PM and primary biliary cirrhosis (PBC); physicians may pay attention for patients with elevated alkaline phosphatase in light of the possible association [9].

23.5 Gastrointestinal Manifestations of Systemic Sclerosis

Gastrointestinal manifestations of systemic sclerosis are common, and they have an effect on prognosis, morbidity, mortality, and quality of life. They result from fibrosis and can affect several portions of the GI tract. GI involvement is the most frequent internal complication and accounts for about 10% of the presenting features in systemic sclerosis [34]. Furthermore, it is possibly the second most prevalent site of systemic sclerosis visceral damage [35]. In systemic sclerosis, women are affected 4.6 times more than men [36].The pathophysiology of SSc of the GIT is known only to a limited extent. It is due to fibrotic changes caused by an increase in the collagen deposition and other extracellular matrix components in the upper and lower GIT leading to dysmotility, malabsorption, malnutrition and

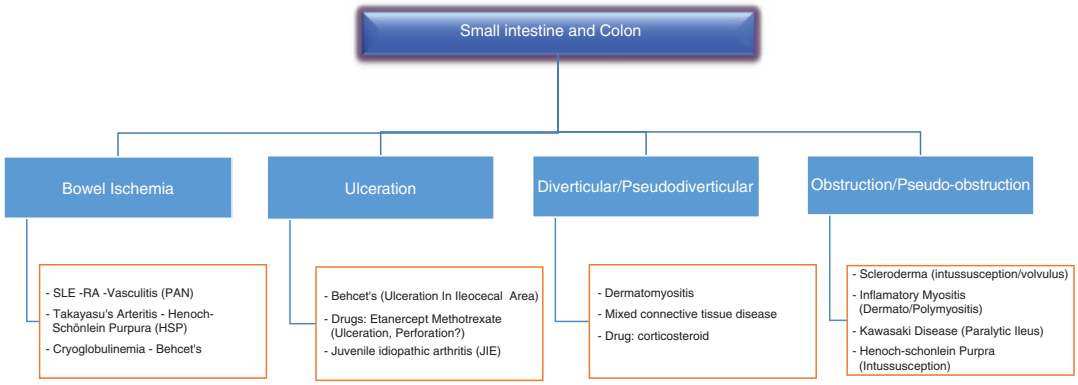

Fig. 23.3 Colonic and small intestinal manifestations of rheumatological diseases

dilation of the intestine [36], and alteration of the microvasculature, the autonomic nervous system, and the immune system. Sjogrin proposed a progression of sclerodermatous GI involvement: vascular damage (grade 0), neurogenic impairment (grade1), and myogenic dysfunction (grade2) with the replacement of normal smooth muscle by collagenous fibrosis and atrophy [35]. The most common organ involved in GI manifestation is the esophagus, followed by the anorectum and small bowel [34], but any portion of the tact can be involved in both limited and diffused SSc. Physicians should have a high level of suspicion for GI abnormality in SSc, because patients with SSc may have subclinical GI abnormalities, in 50% of patients with esophageal involvement and 20% of small intestine involvement [2]. The mortality rate secondary to GI complications is estimated in 6–12% of the cases [35].

The oropharyngeal involvement in patients with systemic sclerosis includes skin thickening, xerostomia, and swallowing difficulties (Fig. 23.4).

23.5.1 Esophageal Manifestations of Systemic Sclerosis

Esophageal manifestations in SSc may occur in up to 70 to 90% [2]. Asymptomatic esophageal changes may happen in 50% of the cases, Thus, early recognition is crucial in order to avoid the complications.

Esophageal manifestations of SSc may not always be symptomatic, but early diagnosis remains important as the delay may increase the risk of complications [35]. All the symptoms are related to esophageal motility disorder and gastroesophageal reflux. Symptomatic patients may complain of heartburn, dysphagia, or odynophagia and, with advanced dysphagia, may complain of food and fluid regurgitation. Gastric reflux may lead to esophageal damage through mild peptic esophagitis, and it could progress to erosions, bleeding, and prominent ulcerations.

Patients with SSc may develop esophageal stricture formation and fistulae, and an achalasia-like syndrome may result into higher risk of

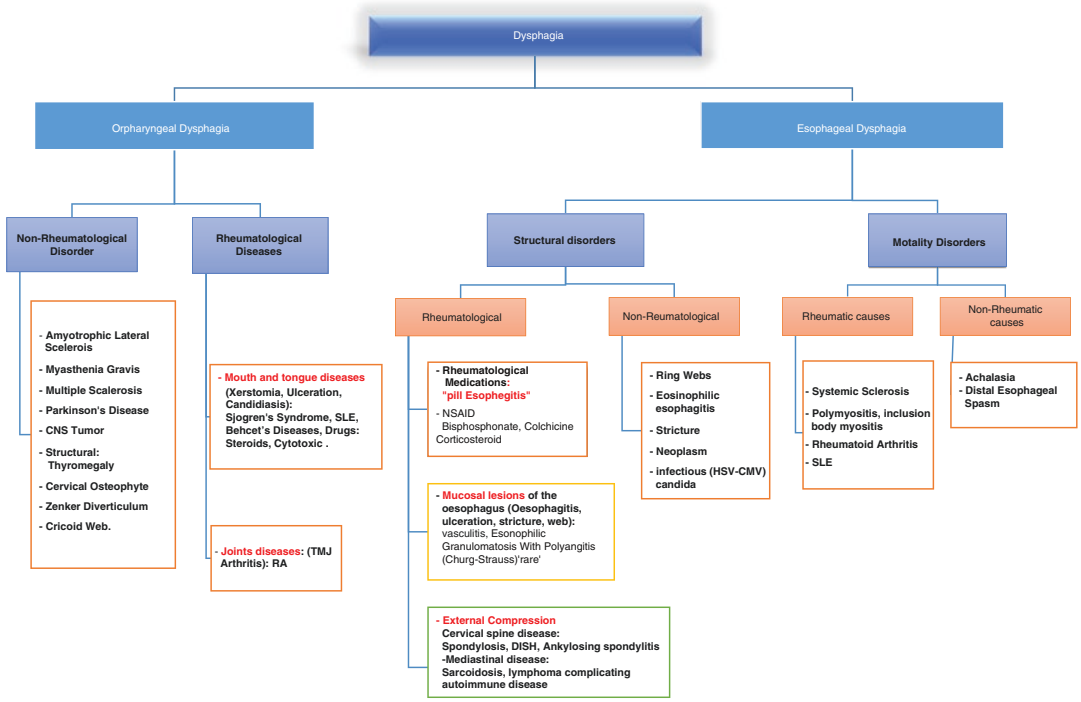

Fig. 23.4 Approach to dysphagia

developing Barrett's esophagus [35] and esophageal adenocarcinoma [34].

Barrett's esophagus happens when the normal stratified squamous epithelial lining of the distal esophagus undergoes metaplasia, with normal epithelial cells being replaced by an abnormal columnar epithelium including goblet cells. It has an incidence rate of 6.8–12.7% compared with that of the general population (less than 1%) [35]. Evaluation for esophageal involvement is guided by the patient's symptoms. EGD should be done in any patient with refractory heartburn, dysphagia, and odynophagia. Treatment with proton pump inhibitors for 6 months may result in complete resolution of inflammation [34].

23.5.2 Gastric Manifestations of Systemic Sclerosis (SSc)

Patients with SSc may have gastric involvement of the disease in 10–75% of the cases [37]. The most common finding among these patients with SSc is delayed gastric emptying [2] followed by iron deficiency anemia which may be found in 96% of patients with SSc, and it is mostly due to gastric antral vascular ectasia (GAVE); it is also called watermelon stomach [37]. GAVE has been found more in patients with early diffuse cutaneous SSc and late-onset anticentromere-positive limited cutaneous SSc [37]. The diagnosis of delayed gastric emptying is made by electrogastric graphic recording or by scintigraphy following a radiolabelled meal. GAVE can be diagnosed endoscopically with two unique findings, i.e., (i) classic "watermelon stomach" with prominent, flat, or raised erythematous stripes, radiating in a spoke-like fashion from the antrum to the pylorus, and (ii) "honeycomb stomach "where a coalescence of many round angiodysplastic lesions are formed in the antrum [37]. Prokinetic agents such as metoclopramide and domperidone are commonly used because of their effect on increasing the tone of contraction of gastric muscles. Patients who have insufficient response to these medications may be offered a low dose of erythromycin [35].

In patients with GAVE, in addition to measures for correcting anemia such as blood transfusion if indicated and iron supplementation, endoscopic laser ablation is found to be effective in up to 75% of cases [35]. Surgical antrectomy is usually not indicated. In refractory cases intravenous cyclophosphamide has been used with successful results [34].

23.5.3 Intestinal Manifestations of Systemic Sclerosis

SSc can involve the small and large bowel as well, including the rectum and the anus. Small intestine manifestations, in conjunction with hypomotility, cause malabsorption contributing to an increased incidence of bacterial overgrowth and pseudo-obstruction which can lead to severe malnutrition. Colonic involvement may include diarrhea, fecal incontinence, and bleeding [35]. Another complication which is associated with morbidity and mortality among SSc patients is the malabsorption syndrome, which is also linked to high disease activity. Small bowel bacterial overgrowth can be diagnosed by a positive breath test or jejuna aspirate cultures. In addition, the basic laboratory tests should be acquired for all SSc patients, including serum hemoglobin because it could indicate the presence of vitamin B12, folic acid, or iron deficiencies. In SIBO, levels of serum folic acid may be elevated due to the synthesis of folates by bacterial flora in the intestines. Additionally, serum albumin is frequently used to look for evidences of malnutrition; however, this might not be entirely accurate, because it is a negative phase reactant, which has poor sensitivity and specificity for malnutrition. Carotene levels in the serum may be utilized to screen for fat malabsorption [34].

The diagnosis of pseudo-obstruction can be done by scintigraphy or wireless motility capsule. Dilatation of intestinal loops is the most prominent radiographic feature in SSc when absence of peristalsis affects the duodenum and proximal jejunum. Teamwork among rheumatologists, nutritionists, and gastroenterologists is crucial in SSc patients with malnutrition and complicated GI disease. In case a patient with SSc present with picture of SIBO, a trial of appropriate antibiotics should be started for 10 days, regardless of the

result of breath testing. In patients with pseudo-obstruction, metoclopramide and domperidone can be tried. Subcutaneous octreotide may be considered for patients with refractory GI symptoms. In case patients failed all to abovementioned medications, parenteral nutrition or enteral feeding through jejunostomy might be considered [34].

23.5.4 Colonic and Anorectal Manifestations of Systemic Sclerosis

Constipation may occur in patients with SSc during early phase of colonic disease. Colonic telangiectasia and pseudodivirticula are common incidental findings and may cause anemia. Therapeutic options during early phases of constipation include bulk-forming laxatives which also might be helpful in the management of fecal incontinence. Reduction of rectal compliance may occur secondary to the deposition of collagen; this might complicate with anismus which can manifest as diarrhea. Patient may complain of severe urgency, and incontinence could occur which is usually mildly improved in medical therapy such as loperamide [35].

The anorectum can be affected in up to 50–70% of SSc patients, and 20% of cases may complicate with fecal incontinence. A recent study confirmed the involvement of the IAS in SSc patients, finding the IAS of SSc patients to be thin and atrophic compared with that of incontinent controls. Based on this finding, the most effective management of anorectal symptoms could be with sacral neuromodulation, which may be worth considering early in patients with SSc [34].

23.6 Gastrointestinal Manifestations of Behcet's Disease (BD)

Gastrointestinal manifestations of Behçet's disease are of great importance because they have been associated with morbidity and mortality. They follow the development of oral ulcers by 3.5 to 6 years [38].

23.6.1 Esophageal Manifestations of Behçet's Disease

Esophageal manifestations in BD are uncommon; it may occur in 2%–11% of the patients [38]. When the esophagus is involved, other GI parts may be involved as well in more than 50% of cases [39]. The most frequent symptoms include retrosternal chest pain, dysphagia, odynophagia, and upper and lower GI bleeding [40, 41]. Endoscopy may show single or multiple ulcers. Several complications may happen including stenosis and perforations [42]. Esophageal varices have also been reported [43].

Esophageal dysmotility may also occur in BD. In comparison to age-matched group, patients with BD may have a significantly lower esophageal pressure and relaxation [44]. In patients with BD, upper GI endoscopy is not routinely done; however, in some cases physicians may consider upper GI endoscopy and/or manometry for patients with symptoms suggestive of underlying esophageal abnormality.

23.6.2 Gastric Manifestations of Behçet's Disease

Gastric involvement in BD is uncommon. Patients may complain of abdominal pain or dyspepsia [43]. Ulcerations may be found during endoscopic evaluation; they may be isolated gastric ulcers, isolated duodenal ulcers, or mixed [45].

Uncommon findings may include Dieulafoy's lesions and gastric non-Hodgkin's lymphoma [43]. Gastroparesis has also been associated to BD in few case reports.

23.6.3 Intestinal and Colonic Manifestations of Behcet's Disease

Intestinal involvements in BD can be classified into two categories: small vessel disease in which ulcers are formed secondary to mucosal inflammation and large vessel disease which may result in bowel ischemia and infarction.

The ileocecal area is the most common site for intestinal lesions [45]. The rectum and anus are rarely involved [46].

Typically, intestinal lesions in BD are described as large (> 1 cm), round−/oval-shaped, deep ulcers in the ileocecal area [43]; this is based on the findings from a landmark study from Korea where a total of 94 patients with BD complicated with intestinal involvement were studied. Terminal ileum, ileocecal valve, and cecum were the most common sites for intestinal involvement representing 96% of the cases. The pattern of intestinal involvement includes localized single ulcer in 67% and localized multiple ulcers in 27% of the cases, while multiple segments and colonic involvement are found in only 6% of cases [47].

There are some other rare abnormalities in BD which may include the presence of strictures, formation of abscess and fistula, and bowel perforations [43]. Because the management is completely different and the presentation may be confused with BD, tuberculosis (TB) should be ruled out in patients living in geographic areas which are endemic with TB. In cases where it is difficult to differentiate between BD and intestinal TB, some experts recommend beginning 8-week trial of anti-tuberculosis antibiotics. Another mimicker of BD is Crohn's disease (CD), which is sometimes challenging for physicians to differentiate between the two, since both of them may present in young patients. However, colonoscopy may help reaching the diagnosis. Endoscopic findings in 235 patients with CD and BD were studied; the most predictive findings of BD using multivariate analysis were round-shaped ulcers, focal single and focal multiple ulcers "less than 6," and absence of cobblestone appearances [48].

In contrast, the lesions in CD are characteristically described as segmental, diffuse, and longitudinal, with the presence of cobblestone appearance. Both diseases (BD and CD) may have colitis and transmural enteritis, formation of fistulae, intestinal perforation, and GI bleeding, but if there are any signs of vasculitis in the specimen, this might indicate the presence of BD rather than CD [49]. One of the rare complications that may also affect the GI tract in patients with BD is AA amyloidosis, usually manifested with diarrhea and malabsorption. Involvement of the renal system with proteinuria could also occur and may progress to renal failure. In such cases, the mortality is relatively high reaching 50% [45] (Fig. 23.5).

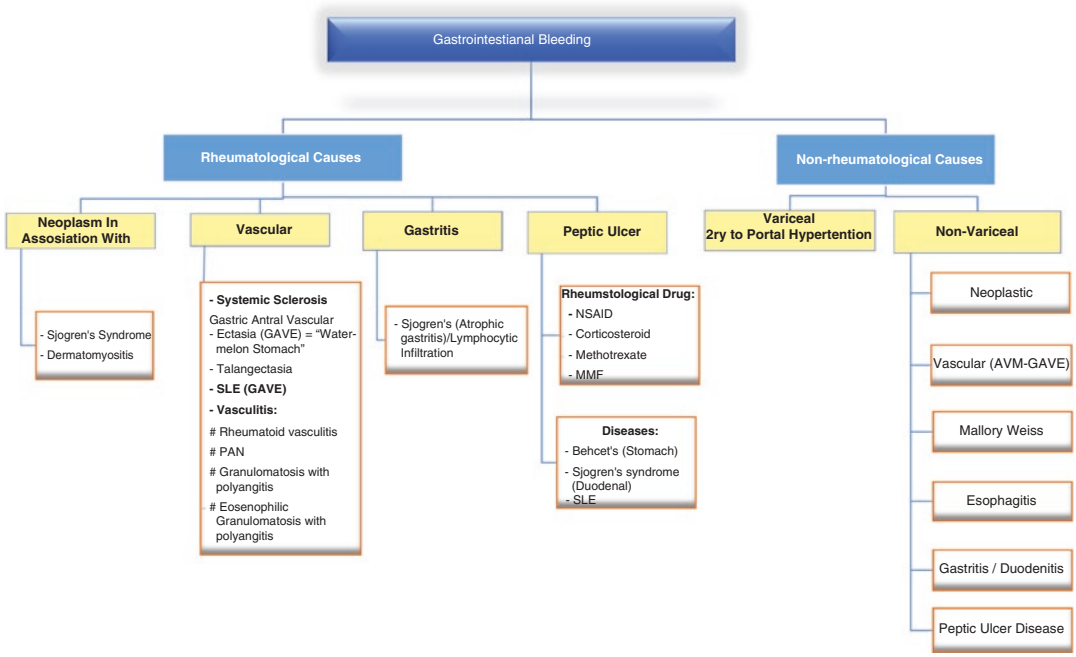

Fig. 23.5 Etiologies of gastrointestinal bleeding

23.6.4 Pancreatic Manifestations of Behcet's Disease

Pancreatic manifestation in BD is very rare. Only limited case reports of acute pancreatitis have been linked to BD. Chronic pancreatitis was reported in a patient with BD—however, this finding might be due to other etiology since the same patient was consuming high amount of alcohol [43, 50]. Because of the lack of sufficient evidence to associate BD with pancreatitis, in a patient with BD who presents with pancreatitis, workup for other etiologies must be done [45].

23.6.5 Hepatic Manifestations of Behcet's Disease

Budd-Chiari syndrome (BCS) is the most common hepatic manifestation in BD. It causes high mortality rate secondary to venous thrombosis that resulted from endothelial dysfunction. Its prevalence rates are between 1.3% and 3.2% [43–45].

The patient can present right upper quadrant abdominal pain, ascites, and hepatosplenomegaly. The course of disease can be acute, subacute, or chronic [39].

Acute BCS is associated with poor prognosis due to extensive venous thrombosis.

Budd-Chiari syndrome (BCS) can be treated medically, surgically, and /or by interventional radiology. Ascites can be treated by salt restriction and diuretics. Endoscopy is indicated for screening and treatment of varices. Cyclophosphamide and corticosteroids are the cornerstone for treatment of BCS in patients with BD. Anticoagulation is still controversial and is not recommended in the most recent European League Against Rheumatism guidelines [39, 43].

Other hepatic manifestations of BD include liver abscess, sclerosing cholangitis, and chronic hepatitis [43].

23.6.6 Visceral Arterial Involvement in Patients with Behcet's Disease

BD can involve arteries and veins of all sizes. The incidence of vascular involvement is 7%–29% with males predominant. Arterial involvement is rare, and patients can present fever, abdominal pain, pulsatile mass, or complications such as intestinal infarction or gastrointestinal bleeding [43, 51].

23.7 Gastrointestinal Manifestations of Vasculitis

23.7.1 Polyarteritis Nodosa (PAN)

23.7.1.1 Gastrointestinal Manifestations of Polyarteritis Nodosa

Polyarteritis nodosa (PAN) is a necrotizing vasculitis that affects medium-sized arteries. It is associated with hepatitis B virus (HBV) in about 7% of cases [52].

Gastrointestinal manifestations occur in 14% to 65% of patients with PAN, and it is a major cause of morbidity and mortality [53, 54].

The small bowel and gallbladder are most commonly affected from the GI tract [53]. The most common symptom is chronic abdominal pain which usually develops over weeks or months [52]. The pain is usually post-prandial, and it is caused by mesenteric ischemia and can be associated with nausea, vomiting, GI bleeding, or change in bowel habits. Ischemic colitis presents with abdominal pain and bloody diarrhea. If the ischemia was limited to the mucosa; submucosa ulceration and bleeding may occur, but transmural ischemia will cause necrosis of the bowel wall which may be complicated by infarction and perforation, and this is associated with a poor prognosis [55].

Patients should be referred to surgery if they developed signs of acute abdomen in the form of rebound, rigidity, or persistent tenderness.

Multiple hemorrhagic refractory ulcers involving the stomach, duodenum, and jejunum have also been reported. Colon involvement is manifested by deep ulcers complicated by perforation or ischemic pseudomembranous colitis. Systemic vasculitis involving the appendix is also reported, and it is most often caused by PAN [56].

23.7.1.2 Hepatic and Biliary Manifestations of Polyarteritis Nodosa

Liver can be involved in 16% to 56% of patients [52]. Clinical manifestations of liver diseases are rare in patients with PAN. In the liver biopsy, necrotizing vasculitis may be found. Hepatic arteriograms may show caliber changes with corkscrew vessels and distal microaneurysms. If the portal vein and hepatic arteries are involved, it can lead to liver infarction, atrophy of a liver, acute liver failure, or nodular regenerative hyperplasia. Rarely, hemobilia and subcapsular or intrahepatic hemorrhage occur if aneurysmal rupture occurs in the liver.

Ascites has been reported, and it is secondary to serositis rather than to liver diseases [56–58].

Vasculitis of the arteries supplying the small bile ducts causes intrahepatic sclerosing cholangitis which is characterized by periductal inflammation, fibrous collar around the ducts, and ductal proliferation. Acalculous gangrenous cholecystitis can be a complication of arteritis as well. Biliary strictures and intracholecystic hemorrhage occur rarely from the rupture of an aneurysm of the cystic arteries into the gallbladder lumen [52, 58].

23.7.1.3 Pancreatic Manifestations of Polyarteritis Nodosa

The pancreatic diseases are involved in 35% to 37% of the PAN cases.

Acute pancreatitis, pseudocysts, masses, and pancreatic infarcts were reported [52].

Diagnostic Modalities of Polyarteritis Nodosa

Arteriography is the initial modality that is used in the diagnosis of PAN, and it is positive in more than 60% of patients [53]. Typical arteriographic lesions in PAN are arterial saccular and fusiform microaneurysms, which are usually associated with stenotic lesions in the kidney and mesenteric and hepatic artery branches. The diagnosis of PAN can be established when characteristic angiographic changes are detected within the appropriate clinical picture, even without histologic confirmation [59].

Treatment

Corticosteroids along with cyclophosphamide are the cornerstone of treatment for hepatitis B- and C-negative PAN. Adding cyclophosphamide has shown to decrease the incidence of relapse, but it does not change the 10-year survival rate [60]. For life-threatening PAN, plasma exchanges can be used [61]. In patients with HBV-associated vasculitis, the use of anti-viral therapy in combination with corticosteroid and plasma exchanges is effective in controlling disease activity and in viral seroconversion.

The control of the viremia is also proven to help in preventing the development of cirrhosis and hepatocellular carcinoma.

Relapses are rare in HBV-related PAN and never occur when seroconversion has been achieved [62, 63].

Surgery is required for the complications, such as perforation/rupture, ischemia, or bleeding of the gastrointestinal organs or kidneys [59].

23.7.2 Granulomatosis with Polyangiitis—GPA (Formerly Named Wegener's Granulomatosis)

Granulomatosis with polyangiitis is manifested by necrotizing vasculitis and granulomatosis.

The disease can affect the upper and lower respiratory tract and the kidneys, with systemic involvement. GI tract can be involved in 10% to 24% of patients with GPA and is detected in an autopsy [64].

Vasculitis can cause local or diffuse pathologic changes including mesenteric ischemia, bleeding, submucosal edema, paralytic ileus, ulcerations, bowel obstruction, and perforation.

Upon studying a group of 62 patients with systemic small- and medium-sized vessel vasculitis and gastrointestinal tract manifestations, Pagnoux et al. found that the most frequent GI symptoms in patients with GPA were abdominal pain (97%), nausea or vomiting (34%), diarrhea (27%), GI bleeding in the form of hematemesis (6%), and hematochezia or melena (16%) [65].

Any part of the GI tract could be affected. The most commonly described pathologies are ulcer-

ations, intestinal ischemia, and perforations. Gastrointestinal manifestations can be the presenting symptom of GPA before the respiratory or renal involvement [64, 66, 67].

23.7.3 Eosinophilic Granulomatosis with Polyangiitis—EGPA (Formerly Named Churg-Strauss Syndrome)

The respiratory tract is almost constantly affected, but it can be a multi-systemic disease. GI involvement can be the presenting symptoms or present concurrently with the vasculitic phase, but it has a negative prognostic factor, especially if mesenteric ischemia or bowel perforation is present [68]. GI manifestations occur in 50% of patients with EGPA. Patients may present with nonspecific symptoms such as abdominal pain, vomiting, and diarrhea [69]. Pathologic findings include ulcers, mesenteric perforation, obstruction, and paralytic ileus with evidence of eosinophilia and granulomatosis. Because of the collateral blood supply in the GI tract, ischemic changes are rarely documented. Histologic vasculitis is rarely seen on endoscopic biopsy because submucosal vessels are too superficial to get adequate sample [68, 70].

Small bowel is the most commonly involved followed by the stomach and the colon [71]. Treatment of vasculitis includes steroids with cytotoxic medications for induction of remission. Depending on the degree of GI involvement, patients may require surgical interventions [68, 70].

23.7.4 Henoch-Schonlein Purpura (HSP)

Henoch-Schonlein purpura is a small-vessel IgA-dominant vasculitis involving the capillaries, venules, or arterioles [72]. It can affect adults but more commonly affect children and typically after upper respiratory tract infection. GI involvement occurs in 75–85% of HSP patients [72, 73]. The most common presenting symptom is abdominal pain and usually is peri-umbilical pain. Other GI manifestations include vomiting, GI bleeding, and paralytic ileus. Abdominal pain occurs because of extravasations of blood and fluid into the bowel wall, which can cause ulceration of the bowel mucosa and bleeding into the lumen. Upper gastrointestinal endoscopy should be considered in patients who develop GI bleeding. Fifty percent of patients may develop melena, and 15% hematemesis [74]. Endoscopy may show hemorrhagic erosions, ulcerations, or more commonly red, small ring-like petechiae in the second part of the duodenum. Petechiae in the descending colon is commonly seen in colonoscopy [74]. Computed tomography (CT) scan may reveal wall thickening with skipped areas, mesenteric edema, and vascular engorgement [75].

Severe GI complications of HSP are rare. Intussusception secondary to submucosal hematoma is the most common (1% to 5%). Intussusception should be suspected if the patient develops colicky abdominal pain that has suddenly increased in intensity and that is associated with bloody stools, and it can be diagnosed by abdominal ultrasonography [72, 74].

Other GI manifestations in HSP patients are protein-losing enteropathy, esophageal and ileal stricture, gastric and small bowel perforations, bowel ischemia, pancreatitis, cholecystitis, and appendicitis [73].

The prognosis for HSP is good with the exception of those patients who developed end-stage renal disease. Treatment of HSP with gastrointestinal involvement, including intussusception, bowel perforation or infarction, and severe bleeding, usually requires surgical intervention. Corticosteroids and immunosuppressive drugs can be used especially in patients with severe glomerulonephritis.

23.7.5 Behcet's Disease

Gastrointestinal involvement in Behcet's disease was discussed separately in a previous section of this chapter.

23.8 Gastrointestinal Manifestations of Spondyloarthropathies (SpA)

Spondyloarthritis (SpA) is a group of diseases sharing the clinical, radiological, and serological manifestations in addition to having a familial and genetic link. It consists of ankylosing spondylitis (AS), reactive arthritis, psoriatic arthritis (PsA), and SpA associated with IBD (IBD-associated SpA), as well as forms that do not meet the criteria of the definite categories of SpA and are thus known as undifferentiated SpA. The incidence of SpA in patients with IBD ranges between 17% and 39%. It is the most common extra-intestinal manifestation in IBD patients [76, 77]. Most importantly, the chronic type of inflammation may be considered as a risk factor for developing CD over time. Around 20% of the patients with chronic GI inflammation on baseline ileocolonoscopy evolved into overt IBD in a 5-year period [78].

23.8.1 Ankylosing Spondylitis (AS)

The pathogenesis of both SpA and IBD is a result of a complex interplay between the host (genetic predisposition), the immune system, and environmental factors [78].

There is a strong genetic link between HLA-B27 and AS. More than 90% of patients with AS are HLA-B27 positive. Furthermore, 25–78% of patients with IBD and AS are HLA-B27 positive. Recently, interleukin 23 receptor (IL23R) variants and the major histocompatibility complex (MHC) have been shown to be associated with AS and Crohn's disease [79].

Up to two-thirds of AS patients have subclinical GI involvement which is diagnosed either by endoscopy or histology features, and up to 5%–10% of cases of AS are associated with IBD [80].

Tumor necrosis factor inhibition (infliximab, adalimumab, etanercept, golimumab) can improve symptoms, signs, and the quality of life in several forms of SpA.

NSAIDs are widely used for the treatment of AS. The distal part of small bowel and colon are the major sites of side effects of NSAIDs, although the incidence of NSAID enteropathy or colopathy is lower than the upper GI tract and usually it is subclinical. However intestinal injuries induced by NSAIDs, including erosions, ulcerations, strictures, and intestinal perforations, are common. A randomized, controlled trial found that the mucosal breaks in a group who used NSAIDs plus omeprazole are more than the other group who used COX-2 inhibitors. This study showed a relative protection of using COX-2 inhibitors compared with non-selective NSAIDs plus omeprazole against small bowel injury [81]. Symptoms and signs are nonspecific such as bleeding from ulcers, anemia, hypoalbuminemia, bloody diarrhea, and signs of acute abdomen [80].

23.8.2 Psoriatic Arthritis (PsA)

Psoriatic arthritis (PsA) is a joint inflammation associated with skin manifestations and extra-articular involvement that affect the quality of life. PsA is considered as seronegative spondyloarthritis (SpA) [82, 83]. GI involvement such as ulcerative colitis and Crohn's disease is reported in 5–10% of the patients with subclinical course in up to two-thirds of the patients [82, 85]. Other GI manifestations such as GERD were also reported in some retrospective studies [82].

23.8.3 Reactive Arthritis

Reactive arthritis can occur after an enteric infection due to *Shigella*, *Salmonella*, *Yersinia*, and *Campylobacter* species with an incidence rate ranging from 2% to 33%. The presence of HLA-B27 genotype and *Yersinia* infection increase the risk of arthritis. Arthritis develops within 2–3 weeks after diarrhea and mainly involves the knee, ankle, wrist, and sacroiliac joints. It is diagnosed based on the clinical presentation and confirmed by positive stool culture or by rising of antibody titers.

Antibiotic treatment may be effective for diarrhea but not for arthritis [80, 84]. Steroids and azathioprine can be used in refractory cases.

23.8.4 IBD-Associated SpA

The onset of IBD can be preceded by SpA manifestations, but in some cases the intestinal inflammation is silent. Based on the European Spondyloarthropathy Study Group criteria, IBD is considered as a diagnostic criterion of SpA. The musculoskeletal involvement in patients with IBD can be divided into two clinical categories: axial (including sacroiliitis) and peripheral. Both categories can coexist in the same patient [85]. Other SpA manifestations such as enthesitis, tenosynovitis, dactylitis, or extra-articular manifestations (such as anterior uveitis) can also occur in IBD-associated SpA.

Axial involvement is present in 2–16% of patients with IBD and more common in Crohn's disease patients than in ulcerative colitis patients.

Axial manifestations are inflammatory back pain, isolated sacroiliitis, ankylosing spondylitis (AS), and non-radiographic spondyloarthritis. Inflammatory back pain is diagnosed clinically using the ASAS criteria. It is usually difficult to localize the pain, insidious in onset, and starts usually at rest, relieved by movement and associated with stiffness. It can be exacerbated by cough or sneezing. Patients with IBD-associated ankylosing spondylitis are found to be HLA-B27 positive in 50–80% of cases, which is less common than those with primary ankylosing spondylitis [79, 86, 87]. The clinical course is characterized by progressive spine involvement with syndesmophyte (bony growth) development and vertebral ankylosis. Isolated sacroiliitis is diagnosed by pelvic radiograph anteroposterior (AP) views or by MRI.

Physical exercise and physiotherapy have a role in maintaining the function and relieving symptoms. Medical treatment such as anti-inflammatory drugs (NSAIDs/COX-2 inhibitors) are the first-line treatment for symptomatic AS; however, TNFa inhibitors (adalimumab or infliximab) are usually used as a second line of treatment when there is inadequate control of the disease by NSAID [86, 87].

The peripheral manifestations of SpA can be seen in both Crohn's disease and ulcerative colitis with prevalence rate of 0.4–34.6% of IBD patients. It is more common in individuals with Crohn's disease. Peripheral arthropathies in inflammatory bowel disease (IBD) include arthritis, dactylitis, enthesitis, and arthralgia. Peripheral arthritis can be classified as type 1 and type 2 arthritis and can coexist with axial involvement.

Type 1 is an oligoarticular (<5 joints) peripheral arthritis usually affecting four or fewer joints that is usually persistent for 10 weeks and often associated with IBD relapses. In contrast, type 2 is a polyarticular arthritis (≥5 joints) affecting five or more small joints with persistent symptoms for months to years and not associated with IBD activity [79, 84, 87, 88].

Peripheral arthropathies are diagnosed clinically; on examination, signs of active arthritis in form of swelling and pain can be found. Erythema nodosum is usually associated with the type 1 arthritis, whereas uveitis is the most common extra-articular manifestation in patients with type 2 arthritis. Laboratory tests, such as C-reactive protein (CRP) and white blood cell count, reflect the bowel activity and cannot be used as a diagnostic tool. Furthermore, peripheral arthritis is not associated with HLA-B27 positivity.

The treatment of active IBD should always bring the attention to arthropathies, which usually occur during a relapse.

The treatment includes pain management such as paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), and/or cyclooxygenase-2 (COX-2) inhibitors.

Steroid injection can be used into the affected joint. For resistant peripheral arthritis in patients with IBD, sulfasalazine and tumor necrosis factor a (TNFa) inhibitors can be used [79, 86, 87].

23.9 Gastrointestinal Manifestations of Sjogren's Syndrome (SS)

SS is a chronic inflammatory disorder associated with autoimmune destruction of the exocrine glands, which leads to diminished glandular secretions causing a mucosal dryness. SS is classified to either primary or secondary. The primary

form accounts for approximately 50% of the cases. The secondary form occurs in association with other autoimmune diseases, most commonly RA. Because of the wide distribution of exocrine glands in the GI tract, SS can involve any part of the digestive system, including the salivary glands, mouth, esophagus, stomach, pancreas, hepatobiliary organs, small bowel, and colon.

23.9.1 Oral Manifestations of Sjogren's Syndrome

Oral involvement in SS is characterized mainly by dryness, causing a wide spectrum of symptoms, including mild-to-severe xerostomia with dysgeusia and tooth decay. SS patients report sensitivity to acid and spicy foods, parched mouth, difficulty chewing and swallowing dry food, fissures, atrophy, and papillae of the tongue and might present with accelerated or unusual tooth decay or tooth loss, hoarseness of voice, oral candidiasis, and nasal dryness. On examination, the oral mucous membranes might appear dull, parchment-like, adhering to the examining finger. Angular cheilitis and reduction in infralingual salivary pooling could be seen. Parotid and/or submandibular gland enlargement could be appreciated [89].

Treatment of dry mouth includes secretagogues and topical agents, which stimulate muscarinic receptors (pilocarpine and cevimeline) [90, 91].

23.9.2 Esophageal Manifestations of Sjogren's Syndrome

Dysphagia occurs in 30% to 81% of patients with SS. It is usually localized to the cervical esophagus/pharynx or midthoracic region [92].

Saliva is required for pharyngoesophageal transfer of a food bolus, and saliva reduction in SS might contribute to dysphagia. However, most authors find no relationship between dysphagia and salivary flow rates when tested and measured by the change in weight of a sponge after it is chewed [93].

Esophageal manometry is the key investigation and usually showed upper esophageal sphincter pressure. Some studies showed increased nonspecific motility abnormalities in SS [94, 95]. During endoscopy, mucosal atrophy can be seen throughout the entire length of the esophagus.

23.9.3 Gastric Manifestations of Sjogren's Syndrome

Dyspepsia is found in 15.6% to 23% of patients with primary Sjogren's syndrome. Chronic atrophic gastritis was found in 25% to 81% of patients with SS who underwent endoscopy. Consistent with this finding, hypopepsinogenemia was found in 69% of patients, with half of them having elevated serum gastrin [96, 97]. One of the main concerns in SS is the increased risk of the development of lymphoma, such as mucosa-associated lymphoid tissue lymphomas (MALT lymphoma), within the GI tract. Evaluation for malignancy by endoscopic studies is crucial whenever the SS patient reported symptoms of abdominal fullness or epigastric pain [98].

Treatment of *H. pylori* does not prove to reduce gastric lymphocytic infiltration, gastric atrophy, or dyspepsia in SS. B cell clonality was noted in both the parotid and gastric tissue from six patients with primary SS and gastric MALT lymphoma [96, 97].

Chronic inflammation and/or glandular atrophy study by immunohistochemistry might reveal a predominance of CD3+ T lymphocytes, mostly CD4 + 0.31 These findings are similar to that found in the salivary glands, suggesting that SS is a systemic disease affecting multiple organs [98].

23.9.4 Bowel and Colonic Manifestations of Sjogren's Syndrome

Documented intestinal involvement is rare to absent in large series. Abdominal discomfort occurs in up to 37% of patients with SS, nausea

5%, constipation 23%, diarrhea in 9%, and iron deficiency anemia due to malabsorption in up to5% [99, 100]. Duodenal ulcers, likely related to a decrease in saliva production and duodenal gland secretion reduction, both of them have been described in SS. Celiac disease occurred in 4.5% to 15% of patients as observed in two cohorts of primary SS [101].

An occasional association of inflammatory bowel disease (IBD) with SS was suggested in case reports [102]. A study that evaluated the presence of SS among a large cohort of IBD patients found that the prevalence of SS was 4.2% to 5.7%; SS was diagnosed 6 years after the diagnosis of IBD.

SS has been associated with intestinal pseudo-obstruction, colon cancer, and pneumatosis cystoides intestinalis. Vasculitis in SS is rare and can be associated with cryoglobulins, and it is often life-threatening, presenting with ischemic or infarcted bowel, leading to bowel gangrene and acute surgical abdomen [103, 104] (Fig. 23.6).

23.9.5 Pancreatic Manifestations of Sjogren's Syndrome

Pancreatitis was documented in 7% of patients with SS. It might present as autoimmune pancreatitis or chronic pancreatitis. There are multiple reported cases of SS with pancreatic calcifications. Enlarged pancreatic head suggestive of neoplasm and increased serum CA 19-9 antibodies in benign pancreatic processes had been also reported. Pancreatic exocrine insufficiency is not uncommon, and it is related to reduced gastric secretions and/or abnormal gallbladder function.

Primary sclerosing cholangitis (PSC) and secondary sclerosing cholangitis are associated with chronic pancreatitis and SS or sicca syndrome. Treatment depends on sclerosing cholangitis status and the degree of extrahepatic involvement. Immunomodulators (including steroids, azathioprine, and rituximab) are the mainstay of treatment for autoimmune sclerosing cholangitis with or without autoimmune pancreatitis. Endoscopic treatment is directed to therapeutic intervention to release the biliary obstruction and for tissue sampling. Liver transplantation is the treatment for end-stage liver disease due to sclerosing cholangitis or recurrent cholangitis [89, 105, 106].

23.9.6 Hepatic Manifestations of Sjogren's Syndrome

Liver involvement is the most common non-exocrine feature in primary SS. Hepatomegaly was found in 11–21% of patients with primary SS at the time of diagnosis. Abnormal liver function tests (LFTs) mainly cholestatic biochemical picture are detected in 30–60% of cases, but hepatocellular or mixed patterns may also be observed. The most common causes of liver dis-

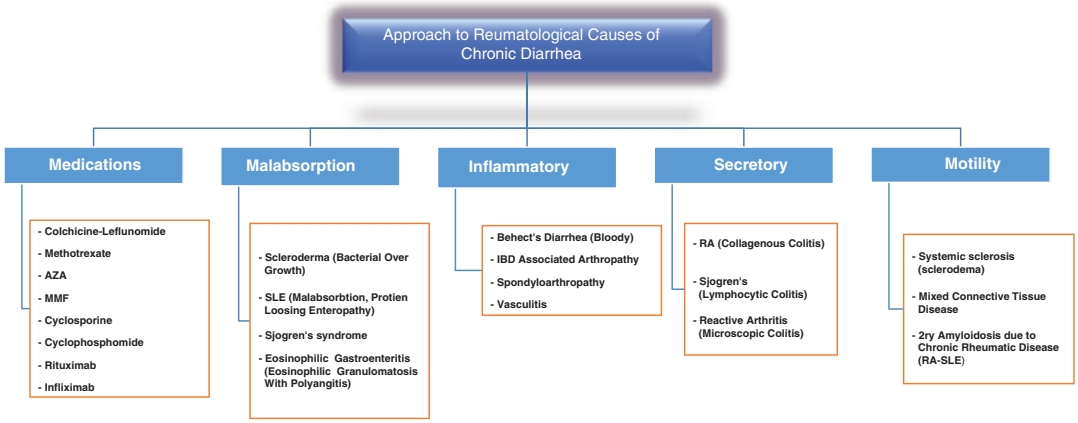

Fig. 23.6 Approach to rheumatological causes of chronic diarrhea

ease in SS are primary biliary cholangitis (PBC), autoimmune hepatitis (AIH), nonalcoholic fatty liver disease, and HCV. AIH or PBC is associated with pSS in 50% of cases [9, 107].

Iron overload might cause functional damage of the salivary glands leading to sicca syndrome, which responds to iron chelation. Idiopathic granulomatous hepatitis can also occur in association with SS [108].

B cell clonality was detected in the liver of 77.8% of the patients with SS who were specifically evaluated for this. There is no increased incidence of hepatic lymphoma in SS (except for SS-HCV), suggesting that the B cell clonality is a benign antigen-driven expansion [9, 108].

In regard to PBC, sicca complex is found in 35% to 77% of patients with PBC; in contrast, SS is found in 18% to 38% of patients. The degree of sicca components does not correlate with the duration or degree of liver disease or the presence of autoantibodies [107, 109].

It is worth mentioning that the salivary gland ducts of patients with PBC—independent of the presence of sicca symptoms—manifest a PBC-like immunohistochemical monoclonal AMA staining specific for the self-antigen pyruvate dehydrogenase. More recently, PBC was diagnosed in 7% of patients with pSS. Furthermore, with respect to the 92% of primary SS patients that were shown to have a positive test for anti-mitochondrial antibody (AMA), histopathology demonstrated histologic features consistent with PBC, suggesting the importance of AMA screening for SS patients, especially when clinically warranted, such as in the case of elevated alkaline phosphatase (ALP) and aminotransferases [110].

Autoimmune hepatitis is another concern in patients with SS as several studies have reported a higher prevalence of primary autoimmune liver diseases among patients with pSS [111, 112]. Autoimmune hepatitis is found in 1.7% of patients with primary SS. ANA titers of >1/80 are associated with the presence of anti-Ro/SSA and anti-La/SSB, whereas titers of 1/320 are associated with presence of anti-smooth muscle and anti-ribonuclear protein antibodies. SS has also been associated with autoimmune cholangiopathy, including IgG4 and non IgG4 diseases [111, 112].

HCV infection has an important link with SS; xerostomia is found in up to 35.7% of HCV patients. Patients with sicca syndrome and HCV are more expected to have neurological involvement, elevated transaminase levels, rheumatoid factor, and cryoglobulins and less likely to have anti-SSA/SSB antibodies compared with SS patients without HCV [113, 114].

Neoplasia is more common in SS-HCV, including both hepatocellular carcinoma and lymphoproliferative tumors. The most frequent involved organs of lymphoma in SS-HCV patients are the liver and exocrine glands, which are infrequently involved in patients with B cell non-Hodgkin's lymphoma [114].

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Pediatric Rheumatology

24

Reem Abdwani

24.1 Introduction

Musculoskeletal (MSK) complaints in children are common. However, not all MSK complaints are due to rheumatic diseases. Etiologies range from benign conditions to serious conditions requiring prompt attention. Therefore, a complete history and physical examination, in addition to essential investigations and imaging, is essential to distinguish rheumatic conditions from other diseases (Fig. 24.1). Most of the differential diagnoses have been covered in other chapters; however, besides trauma and infectious causes including septic arthritis and reactive arthritis, some common causes of non-rheumatic joint pain in children include the following:

Toxic synovitis of the hips is a common self-limited form of reactive arthritis usually occurs after an upper respiratory tract infection commonly affecting boys younger than 8 years. The child presents with painless limp or complains of pain in the groin, anterior thigh, or knee (referred pain). Unlike patients with septic arthritis, the child appears well, while the affected limb is held in a position of external rotation and flexion. Investigations are normal or show mild increases in inflammatory markers. Management is supportive with rest and analgesia.

Growing pain is benign short-lived vague pain limited to calf, thigh, and shin commonly affecting children between the ages of 3 to 10 years. Pain is severe in intensity, often occurs late in the day, or awakens the child at night. The child is otherwise well and asymptomatic during the day, having no functional limitations. The pain is intermittent in nature, with symptom-free intervals lasting days to months. There is often a family history of growing pains. Importantly, the physical examination, laboratory data, and radiological investigations are normal. Management consists of reassurance and supportive analgesia.

Childhood malignancies, such as leukemia, lymphoma, and neuroblastoma, may present with daytime and nighttime joint pain. Clinical characteristics include severe pain that is out of proportion to clinical findings, lack of morning stiffness, and the ability to localize the pain to the bone on palpation. Patient may have constitutional symptoms including fever, weight loss, and night sweats. Similarly, the presence of thrombocytopenia and high LDH may indicate the presence of malignancy.

Slipped capital femoral epiphysis (SCFE) is a condition in which the femoral head is displaced from femoral neck. It commonly affects overweight boys between the ages of 10 and 14 years or children with endocrine problems such as hypothyroidism or growth hormone deficiency. The complaint of hip pain may be acute or insidious and can frequently present with knee

R. Abdwani (✉)
Department of Pediatrics, Sultan Qaboos University, Seeb, Oman
e-mail: rmabdwani@squ.edu.om

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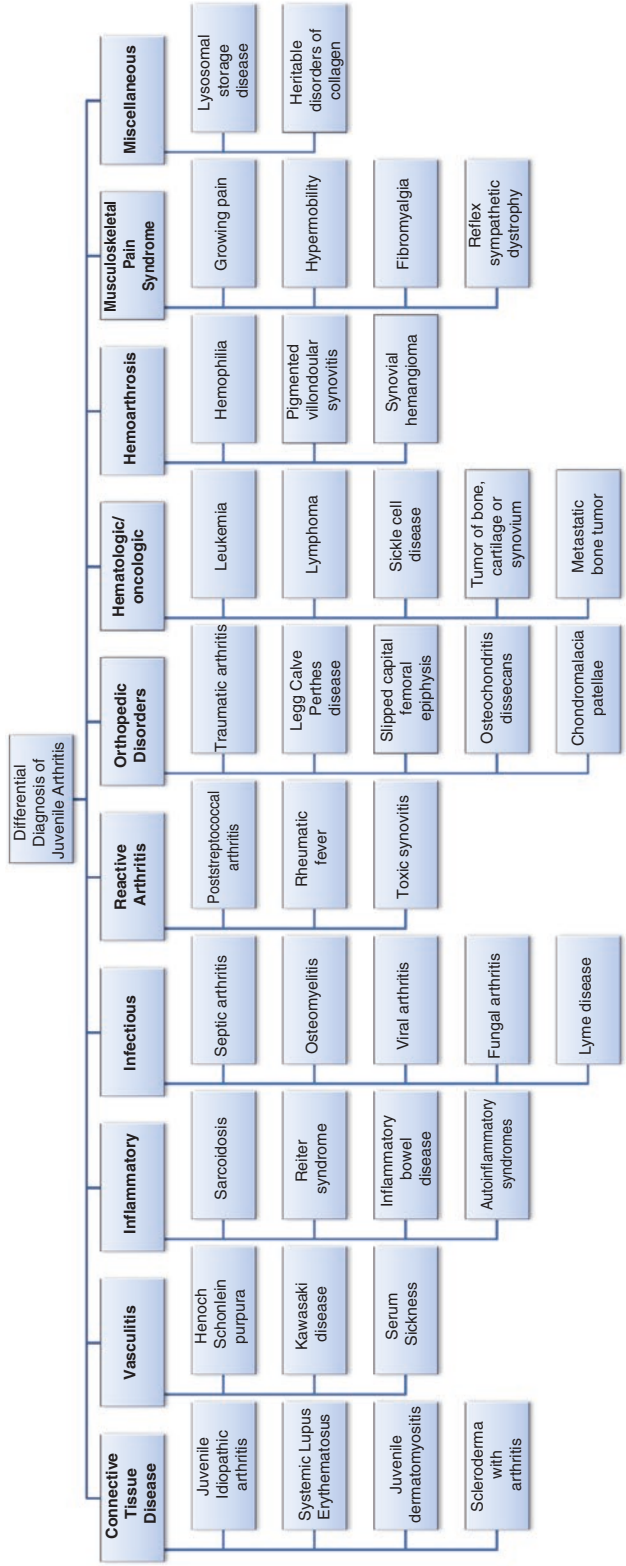

Fig. 24.1 Differential diagnosis of juvenile arthritis

pain. Examination reveals a flexed and externally rotated hip with painful and limited passive internal rotation. Diagnosis is radiological and patients should be placed on non-weight-bearing crutches until an urgent orthopedic consultation for a surgical intervention is made.

Legg Calve Perthes disease is self-limiting avascular necrosis of the femoral capital epiphysis commonly affecting boys from 4 to 10 years. Children present with painful limp and limited range of motion of the hip joint. Initial radiographs may be normal; therefore, MRI is more sensitive in detecting early disease. Patients should be kept non-weight-bearing until an urgent orthopedic referral. Treatment is aimed at maintaining the femoral head within the acetabulum, which can be achieved conservatively with abduction splints or casts or surgically with an osteotomy of the proximal femur.

24.2 Learning Objectives

By the end of this chapter, you should be able to:

- List common causes of non-rheumatic joint pain in children.
- Recognize some of the similarities and differences between childhood and adult onset rheumatic diseases.
- Distinguish the characteristic clinical features of juvenile idiopathic arthritis subtypes.
- Explore the classification criteria of pediatric vasculitis with emphasis on the clinical presentation and management of Kawasaki disease.
- Discuss the spectrum of autoinflammatory syndromes.

24.3 Pediatric Rheumatic Diseases

Children are not little adults. By acknowledging the similarities and difference between adult and childhood types of rheumatic diseases, it will be easier to identify those features that are characteristic of or specific to children. Many pediatric rheumatic diseases have different disease phenotypes, outcome measures, investigations, and treatment that are distinct from adult rheumatic diseases. The next sections will highlight the clinical features that are specific to pediatric rheumatic diseases.

24.4 Childhood Onset SLE

The diagnosis and treatment of childhood onset SLE (cSLE) is similar in many aspects to adult SLE (aSLE). However, differences in disease demographics, clinical presentation, disease course, and outcome exist between cSLE and aSLE.

Onset of SLE during childhood period occurs in 10–20% of all SLE cases. There is less female prediction in cSLE as the female to male ratio with pediatric SLE changes from 4:3 with disease onset during the first decade of life to 4:1 during the second decade to 9:1 in aSLE [1]. cSLE often presents with more acute and severe disease manifestation at the time of diagnosis with a higher frequency of renal, neurological, and hematological involvement, while cutaneous and musculoskeletal features are more common at disease onset in aSLE [2]. SLE Disease Activity Index (SLEDAI), at diagnosis and over disease course, tends to be much higher in cSLE [3]. Comparative studies support that cSLE is more often treated with high doses of corticosteroids and immunosuppressive medications than aSLE [4]. Despite improved survival rates in SLE patients, there remains substantial morbidity due to disease damage. cSLE is associated with more rapid accrual of damage than is SLE in adults, and it involves mostly ocular, renal, and musculoskeletal damages [4].

24.5 Juvenile Dermatomyositis

Adult and juvenile onset dermatomyositis share the hallmark clinical presentation of pathognomic skin rash and muscle weakness described in Chap. 8; however, each has distinct demographics, clinical features, and associated outcomes [5].

JDM is rare, with incidence of 2–4 per million children [6]. The mean age of onset of JDM is 7 years with 25% of patients presenting younger than 4 years of age [7]. The rash of JDM can be atypical, occurring anywhere in the body, and is more frequently associated with ulcerative change than in adults. Anti-p155/140 autoantibody is the most prevalent myositis specific antibody found in 30% of patients with JDM and is associated with cutaneous rash with skin ulceration, generalized lipodystrophy, low creatinine kinase levels, and a chronic course of disease [8].

The clinical course in JDM is monophasic (40–60%), chronic (40–60%), and polyphasic (>5%).

Predictors of chronic course include delay in treatment, higher skin disease activity at baselines, ongoing Gottron's papules and periungual nail fold capillary changes beyond 3 months of treatment [9]. In addition, the presence of subcutaneous edema on MRI at diagnosis and extensive myopathic and severe arteropathic changes on the initial muscle biopsy are predictors of a chronic illness course [9]. Approximately 20–47% of patients with JDM develop calcinosis at presentation or after many years of illness [10]. JDM has not been clearly associated with the development of malignancy which is a significant cause of mortality in adults with DM.

Treatment of JDM consists of combination of corticosteroids (2 mg/kg) with slow taper and methotrexate 15 mg/m^2 s/c. Other treatment modalities include cyclophosphamide for interstitial lung disease or vasculitis. IVIG, cyclosporine, mycophenolate mofetil, and rituximab are used in refractory cases.

24.6 Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis (JIA) is comprised of a heterogeneous group of several disease subtypes that are characterized by the onset of arthritis prior to the age of 16 years with symptoms that persist for more than 6 weeks after exclusion of other causes of juvenile arthritis Fig. 24.1. Arthritis is diagnosed in the presence of joint effusion or two or more of the following: limited range of movement, joint line tenderness, or painful range of movement and warmth. The current classification system by the International League of Associations for Rheumatology (ILAR) recognizes seven distinct subtypes of JIA, based on their presentation within the first 6 months [11]. The categories of JIA and their diagnostic criteria are defined in Fig. 24.2. There is evident heterogeneity with respect to demographic, genetic, and clinical features among the JIA subtypes, translating into heterogeneity in the responses to treatment.

Oligoarticular JIA is the most common subtype with relative frequency of 30–60% in Caucasian population with peak age at 1–3 years [11]. It is divided into two further subsets: persistent, if arthritis remains confined to four or fewer joints during the whole disease course, and extended, if arthritis spreads to more than four joints after the initial 6 months of illness. The arthritis affects medium to large size joints with the knee being most common joint affected followed by ankle and wrist. Both wrist and ankle arthritis in addition to elevated inflammatory markers (ESR) at disease onset have been recognized as predictors of an extended course [12]. The classic disease phenotype includes asymmetric arthritis, early disease onset, female predilection, high frequency of positive ANA, and high risk of uveitis [13]. Positive ANA represents a high-risk factor for development of chronic uveitis which occurs in 20–30% of oligoarticular JIA [14]. Chronic uveitis can be asymptomatic until the point of visual loss, making it crucial to undergo regular ophthalmologic screening (Fig. 24.3) [15].

Polyarticular JIA, subdivided into rheumatoid factor positive and rheumatoid factor negative, accounts for 10–30% of JIA cases occurring most commonly in young girls with an early peak between ages 1–4 years and a later peak of 6–12 years [11]. It is likely that the older group with rheumatoid factor positivity represents disease that is similar to adult rheumatoid arthritis. The arthritis tends to be symmetrical and involves large and small joints [16]. In contrast to oligoarticular JIA, systemic manifestation including low grade fever, anorexia, malaise, and growth failure can be present [16]. Chronic

International League of Associations for Rheumatology (ILAR) classification of JIA

Systemic-onset JIA	Systemic arthritis is diagnosed if there is arthritis in 1 or more joints with, or preceded by, fever of at least 2 weeks' duration. Signs or symptoms must have been documented daily for at least 3 days and accompanied by 1 or more of the following: evanescent rash, generalised lymphadenopathy, hepato/splenomegaly, serositis. (Exclusions are A, B, C, and D from the exclusion list below.)
Persistent or extended oligoarthritis	Oligoarthritis is diagnosed if there is arthritis affecting 1 to 4 joints during the first 6 months. Persistent oligoarthritis affects up to 4 joints throughout the course of the disease, and extended oligoarthritis affects more than 4 joints after the first 6 months of disease. (Exclusions are A, B, C, D, and E from the exclusion list below.)
RF-negative polyarthritis	Polyarthritis (RF-negative) is diagnosed if there is rheumatoid factor (RF)-negative arthritis affecting 5 or more joints during the first 6 months of disease. (Exclusions are A, B, C, D, and E from the exclusion list below.)
RF–positive polyarthritis	Polyarthritis (RF-positive) is diagnosed if there is RF-positive arthritis affecting 5 or more joints during the first 6 months of disease. Two or more RF tests (taken at least 3 months apart) are positive during the first 6 months of disease. (Exclusions are A, B, C, and E from the exclusion list below.)
Psoriatic JIA	Psoriatic arthritis is diagnosed if there is arthritis and psoriasis, or arthritis and at least 2 of the following: dactylitis, nail pitting, onycholysis, and/or family history of psoriasis (in a first-degree relative). (Exclusions are B, C, D, and E from the exclusion list below.)
Undifferentiated	Undifferentiated arthritis is diagnosed if there is arthritis that does not fulfil criteria in any of the above categories or that fulfils criteria for 2 or more of the above categories.

Exclusions

A	Psoriasis or history of psoriasis in patients or first-degree relatives.
B	Arthritis in HLA B27 positive males beginning after the age of 6 years.
C	Ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, acute anterior uveitis, or history ofoneof these disorders in first-degree relatives.
D	Presence of IgM rheumatoid factor on at least 2 occasions at least 3 months apart.
E	Presence of systemic JIA in patients.

Fig. 24.2 International League of Associations for Rheumatology (ILAR) classification of JIA

asymptomatic uveitis develops less frequently and is more common in RF negative polyarticular JIA [11]. Children with RF positive polyarthritis can develop similar complication to adult disease including rheumatoid nodules, Felty syndrome, rheumatoid vasculitis, and pulmonary disease in rare cases [17].

Systemic onset JIA accounts for 10% of cases of JIA with a broad peak of onset between 1 and 5 years, and it also occurs in adolescence and adulthood [11]. Children of both sexes are equally affected. [18] The systemic symptoms of fever, fatigue, and anemia may overshadow or proceed the arthritis by 6 weeks to 6 months. The arthritis is typically symmetrical and polyarticular and can be extensive and resistant to treatment. The systemic manifestation include fever spikes >38.5 °C occurring once or twice daily, which return to baseline or below temperatures. This inflammation is accompanied by a salmon colored evanes-

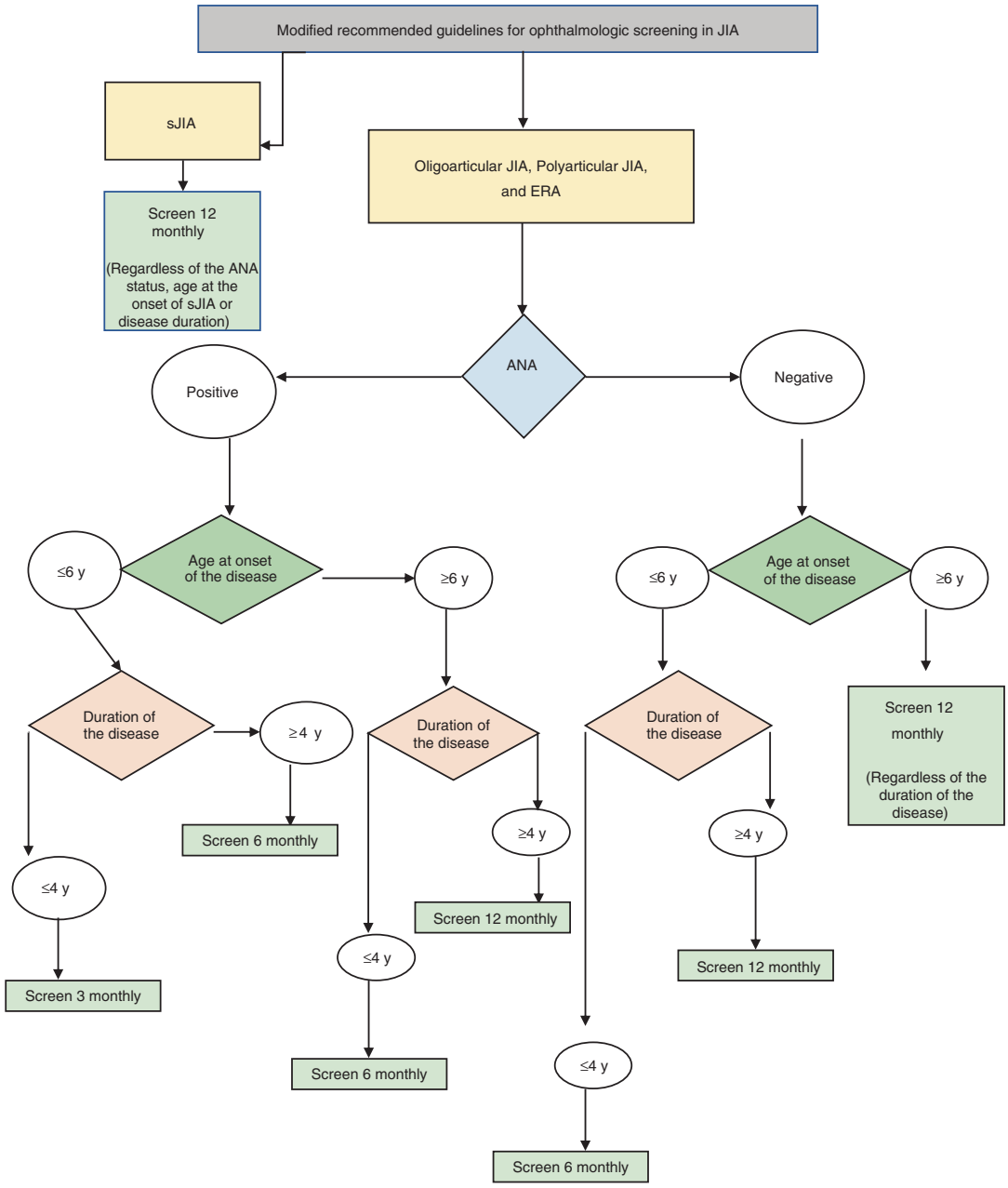

Fig. 24.3 Modified recommended guidelines for ophthalmologic screening in JIA

cent macular rash accompanying fever spikes. Extra-articular manifestation include serositis, hepatosplenomegaly, and lymphadenopathy. An infectious workup and a bone marrow aspirate are strongly considered before starting treatment. Systemic JIA is associated with macrophage activation syndrome (MAS), a potentially life-threatening complication which can manifest as a change in the fever pattern from intermittent to continuous and improvement in arthritis [19]. A recent classification criteria for MAS has been proposed [20] (Fig. 24.4).

Psoriatic JIA (PsA) affects 5% of patients with JIA and has a bimodal age of distribution in preschool years and in late childhood [11]. Psoriasis often begins after the onset of arthritis

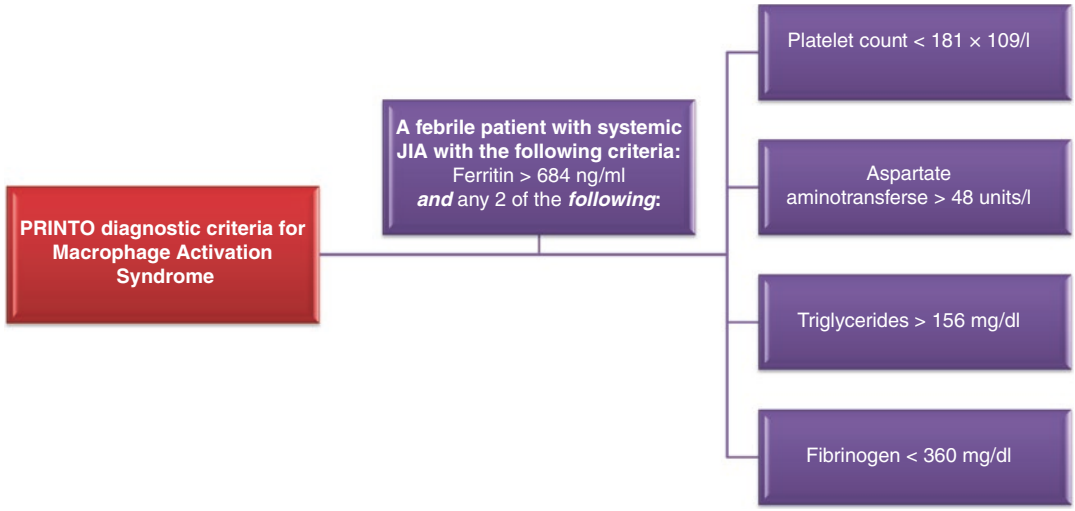

Fig. 24.4 New Classification Criteria for Diagnosis of Macrophage Activation Syndrome

in children and may not be evident [21]. The pattern of joint inflammation is clinically diverse [22, 23]. Disease at younger age of onset tends to have asymmetric involvement of large and small joints of hand and feet, which differentiates it from oligoarticular JIA [14]. Dactylitis, a clinical hallmark of the disease is also a common manifestation of younger children. Children with older age of onset, who are often HLA B27 positive, tend to develop enthesitis, spinal, and sacroiliac disease [22, 23]. Asymptomatic chronic anterior uveitis occurs in 15–20% of children with PsA and is associated with the presence of ANA [25]. Acute symptomatic anterior uveitis observed in adult patients, is rare in children [25].

Enthesitis-related arthritis (ERA) affects <5% of patients with JIA, characterized by the presence of arthritis and enthesitis, typically occurs in boys older than 6 years of age with positive HLA B27 [11]. In contrast to adult ankylosing spondylitis at presentation, axial involvement is not common, while sacroiliitis can be silent [26]. However, axial disease with symptomatic sacroiliitis becomes common within 5 years of diagnosis [27, 28]. Peripheral arthritis of the lower limbs and predominantly the hips is commonly seen [29]. The hallmark of ERA is enthesitis, with resultant pain and swelling at entheseal sites. Other distinguishing manifestation is tarsitis. Symptomatic anterior uveitis may develop in children with ERA, and this usually presents with significant eye pain and redness, which may be unilateral [20]. Although cardiopulmonary involvement is uncommon, aortic insufficiency has been reported.

Undifferentiated arthritis does not represent a distinct subset but includes patients who do not meet the criteria for any category or who meet the criteria for more than one subtype of JIA [30].

Laboratory and Imaging Studies: Most children with JIA have no laboratory abnormalities. Preliminary investigations should be aimed at excluding differential diagnosis (Fig. 24.5). Children with systemic JIA and polyarticular JIA commonly show evidence of inflammation with elevated inflammatory markers and anemia of chronic disease. A complete blood count and peripheral should be performed to exclude leukemia which can present as low WBC and platelet count. ANA should be performed to identify patients at higher risk for developing uveitis, while RF should be performed in polyarticular JIA to identify patients with worse prognosis.

Plain radiographs have limited ability to identify early erosive changes and have poor sensitivity to identify active synovitis. Ultrasound is well suited to assess synovitis, capture erosions, and guide local injections. MRI is able to identify early changes and most sensitive indicator of joint inflammation.

Treatment: The main stay of treatment of JIA aims at controlling inflammation, maintaining

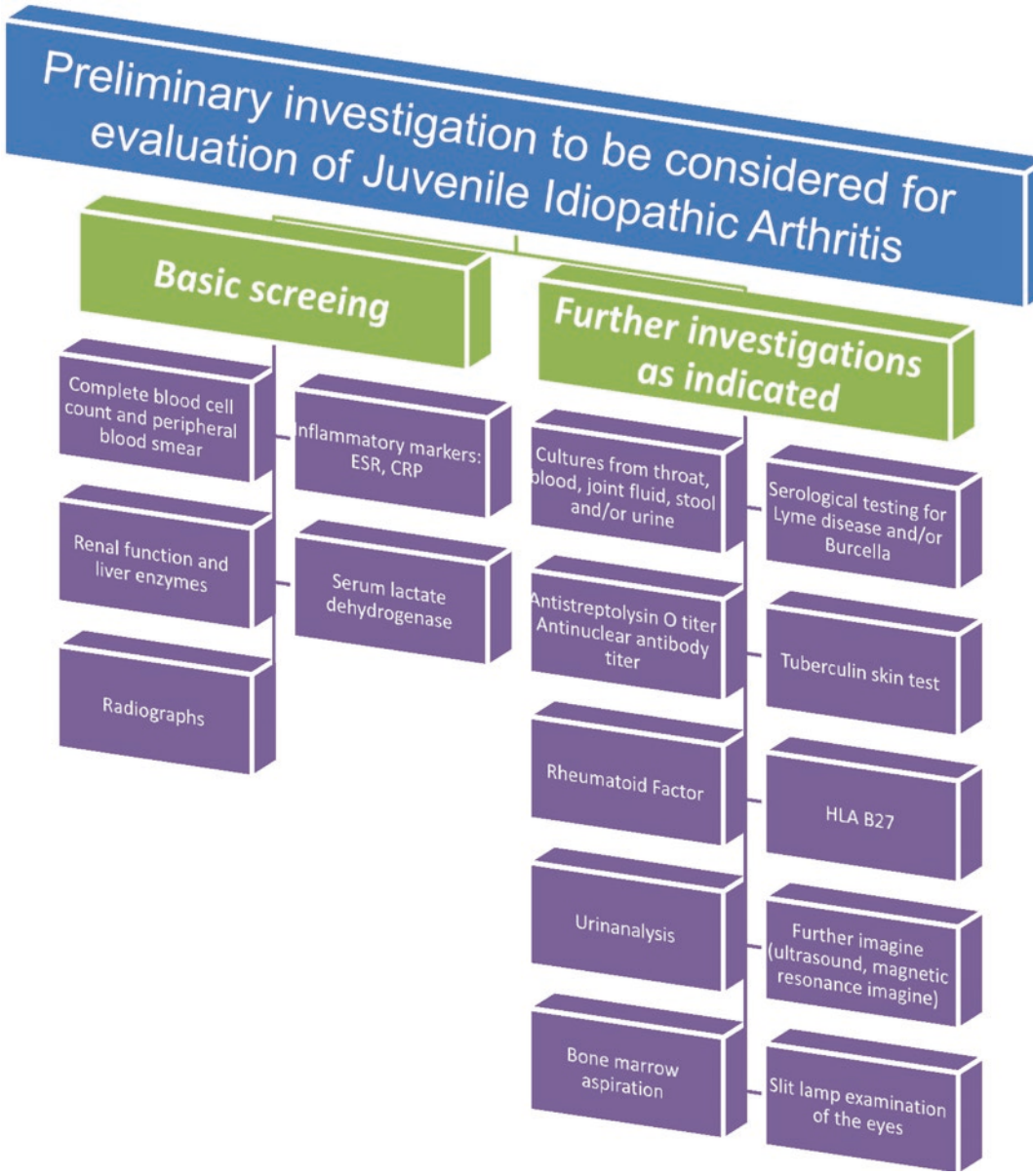

Fig. 24.5 Preliminary investigation to be considered for evaluation of Juvenile Idiopathic Arthritis

function, and preventing joint damage and blindness. This can be achieved through a multidisciplinary team comprising a pediatric rheumatologist, ophthalmologist, orthopedic surgeon, specialist nurse, physical therapist, occupational therapist, and psychologist. ACR treatment recommendations for JIA categories are outlined (Figs. 24.6 and 24.7).

First-line therapy in JIA consists of nonsteroidal anti-inflammatory drugs (NSAIDs). Only a few NSAIDs are approved for use in children: the most common are naproxen (15–20 mg/kg), ibuprofen (30–50 mg/kg), and indomethacin (1–4 mg/kg). There is limited data on the safety and efficacy of Cox 2 inhibitors [31]. Intra-articular corticosteroids (IAC) may also be used as first line in the treatment of Oligoarticular JIA [32]. Triamcinolone hexacetonide (TH) is the drug of choice for IAC. Due to its lower solubility, it has longer lasting duration of action than other

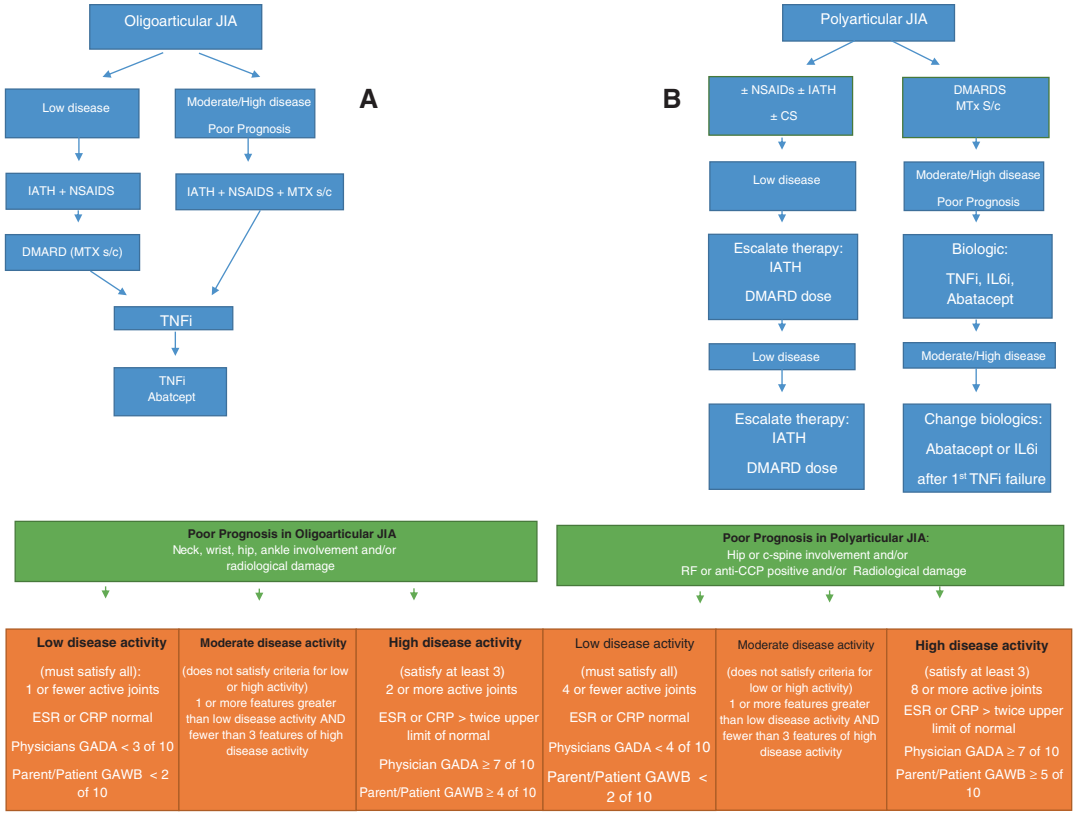

Fig. 24.6 Adopted from 2011 and 2019 American College of Rheumatology Recommendations for Treatment of Oligoarticular JIA (A) and Polyarticular JIA (B). CRP: C reactive protein; ESR: erytherocyte sedimentation rate; GADA: global assessement of overall disease activity; GAWB: global assessement of overall well-being; IATH: intra-articular trimcinolone hexacetonide

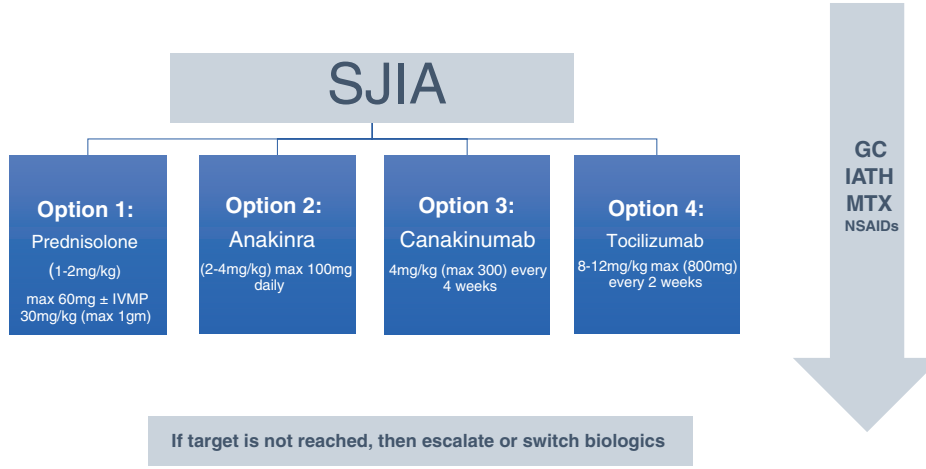

Fig. 24.7 Management of systemic juvenile idiopathic arthritis

preparations [33]. The dose of TH administered is1mg/kg (max 40 mg) for the knee joint or half of this dose for ankle and wrist [24]. The role of systemic corticosteroids is limited to the extra-articular manifestations of systemic arthritis and as a bridging therapy in severe polyarthritis awaiting the therapeutic effects of second-line agents or biologics.

Second-line therapy includes conventional disease modifying antirheumatic drugs (DMARDs). Methotrexate remains the most widely used at a dose of 10–15 mg/m2 per week either orally or subcutaneously. There is increased bioavailability of the drug in the subcutaneous route at higher doses, and increased efficacy after switching from oral to subcutaneous administration has been reported [34, 35]. Methotrexate should be continued for at least 6–12 months after achieving disease remission. No difference in the relapse rate was found between patients who were discontinued from methotrexate at 12 months vs. 6 months of disease remission [36]. Experience with leflunomide in JIA is limited but is an alternative option in case of intolerance [37].

Biologic DMARDs are shown to be highly safe and effective in the treatment of JIA as demonstrated in various randomized controlled studies with anti-TNF inhibitors (etanercept, adalimumab, infliximab), anti-CLA4 (abatacept), anti-IL1 (anakinra), and anti-IL-6 (tocilizumab) [38–42]. Stepwise treatment algorithms have been proposed by the ACR for treatment of oligoarticular JIA, polyarticular JIA, and systemic onset JIA. However, there is recent evidence to demonstrate the benefits of early aggressive therapy with both conventional and biologic DMARDs in treatment of JIA such as TREAT, STOP JIA, and BeST for Kids studies [43–45].

24.7 Childhood Vasculitis

Childhood vasculitis is often a challenging and complex as the diagnosis can be primary or secondary to infections, drugs, and other rheumatic diseases. If vasculitis is suspected, then the approach to history, physical examination, workup, and classification is similar to the approach used in adult vasculitis.

The EULAR/Pediatric Rheumatology European Society (PReS) consensus criteria for childhood onset vasculitis are listed in (Table 24.1) [46]. Of the primary vasculitides, Henoch Schönlein purpura (HSP) and Kawasaki disease (KD) are the most common, while the other vasculitides are observed rarely in childhood [46]. As other types of vasculitides have been previously described in Chap. 19, this section will focus on KD which is of particular interest to pediatric age group.

24.8 Kawasaki Disease

Kawasaki disease is an acute, self-limiting systemic vasculitis predominantly affecting the coronary arteries, causing coronary artery aneurysms (CAA) in 15–25% of untreated patients [47]. The disease has a diverse distribution worldwide with an ethnic bias toward Asians.

KD predominantly affects children younger than 5 years of age with peak age incidence at 2 years. Patients at extreme end of ages, younger than 3 months, or older than 5 years are affected less often but are at increased risk for CAA formation. Pathogenesis of KD is thought to be due to genetic factors and infectious triggers due to disease characteristics which include winter and spring seasonal variation, community outbreaks, increased risk in siblings, and higher risk in Asians even if they migrate to western countries [48, 49].

KD presents in children as unexplained fever for ≥5 days with the additional four out of the five characteristic clinical features described in Fig. 24.8. The diagnosis of incomplete KD can be made in children in presence of two to three of the principal clinical features, commonly occurring in young children. The evaluation algorithm of incomplete KD requires the presence of supportive laboratory evidence and echo cardiac findings (Fig. 24.9) [50]. The supplementary supporting laboratory criteria include three of the following: hypoalbuminemia <30 mg/dl, anemia for age, elevation of alanine aminotransferase, thrombocytosis after 7 days, leukocytosis >15,000/mm^3, and sterile pyuria ≥10 WBC/HPF. Diagnostic challenge

Table 24.1 EULAR/PRES Consensus Criteria for Childhood Vasculitis

Henoch-Schönlein purpura/IgA vasculitis

- Purpura or petechiae with lower limb predominance and at least one of the following:
  1. Arthritis or arthralgias
  2. Abdominal pain
  3. Histopathology demonstrating IgA deposition
  4. Renal involvement

Kawasaki disease

- *Fever that persists for at least 5 days plus at least 4 of the following:*
  1. Conjunctivitis
  2. Changes of the lips and oral cavity
  3. Cervical lymphadenopathy
  4. Rash
  5. Extremity changes

Childhood Polyarteritis Nodosa

- Histopathological or angiographic abnormalities plus one of the following:
  1. Skin involvement (livedo reticularis, nodules, infarcts)
  2. Myalgias
  3. Hypertension
  4. Peripheral neuropathy
  5. Renal involvement

Childhood-onset Takayasu arteritis

- Aneurysm or dilatation in the aorta or its main branches and pulmonary artery shown by angiography plus one of the following.
  1. Absent peripheral pulses or claudication
  2. Blood pressure discrepancy in any limb
  3. Bruits
  4. Hypertension
  5. Elevated acute phase reactants

Childhood-onset Granulomatosus with polyangiitis

- *Diagnosis requires 3 of the following 6 criteria:*
  1. Histopathological evidence of granulomatous inflammation
  2. Upper airway involvement
  3. Laryngo-tracheo-bronchial involvement
  4. Pulmonary involvement
  5. ANCA positivity
  6. Renal involvement

Primary CNS vasculitis

- Acquired neurological or psychiatric finding which can not be explained by other causes
- Histopathological or angiographic changes indicating vasculitis in CNS
- Absence of systemic vasculitis or any disease which could cause pathological changes

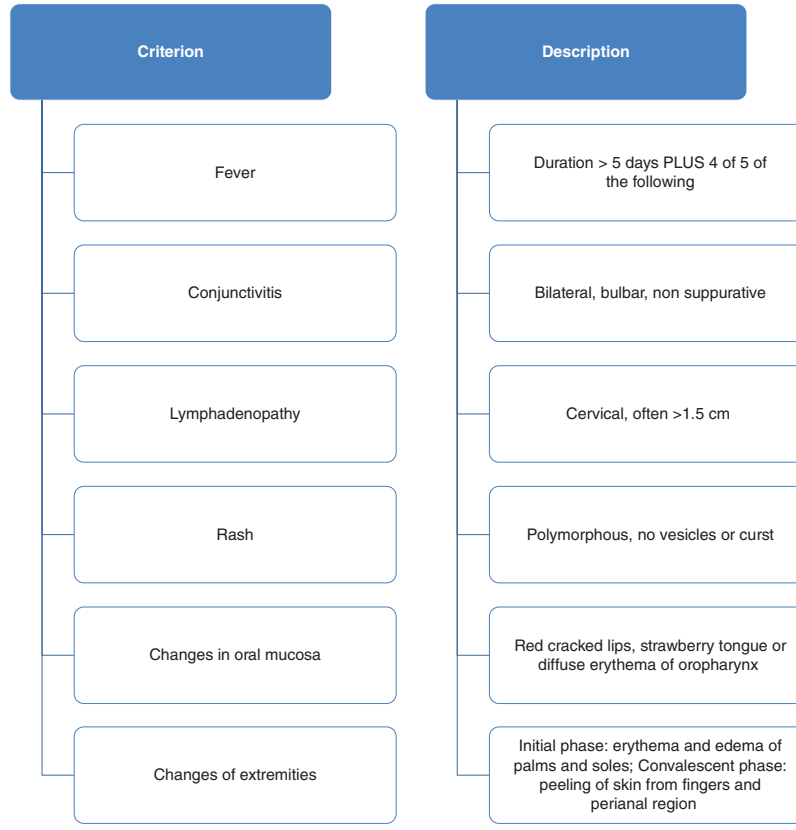

Fig. 24.8 Diagnostic Criteria for Kawasaki Disease

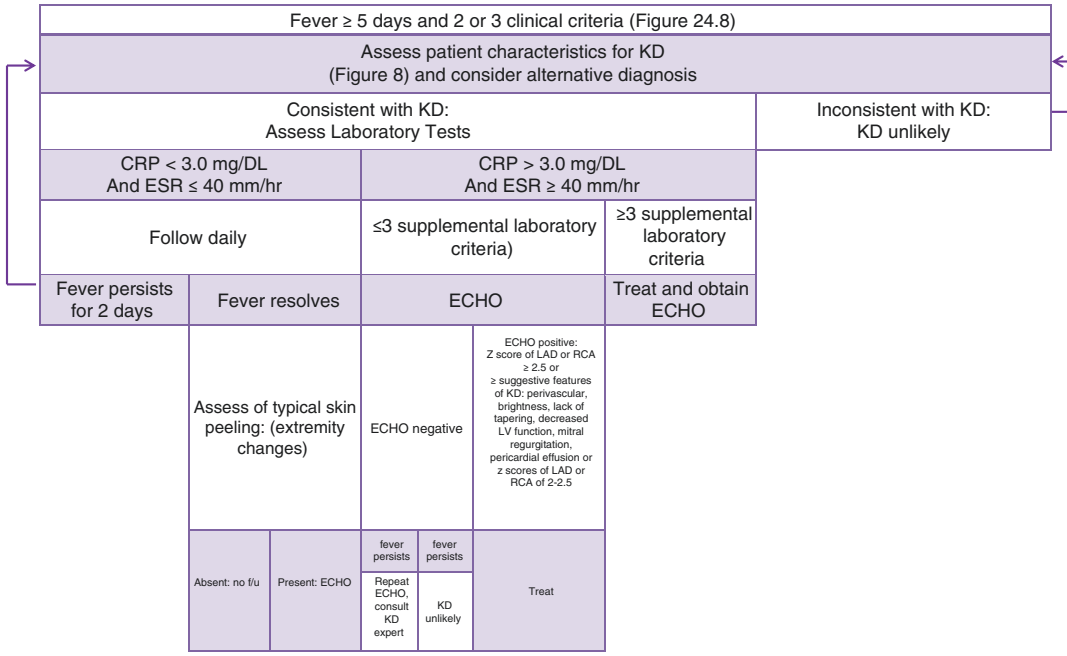

Fig. 24.9 American Heart Association Guidelines for Treatment of KD

Fig. 24.10 Differential diagnosis of KD:

often arises given the significant overlap in clinical feature with other pediatric illnesses in (Fig. 24.10). Treatment of KD as per the American Heart Association (AHA) treatment guidelines includes intravenous immune globulin (IVIG) 2gm/kg as single infusion and aspirin (30–50 mg/kg) [50]. Aspirin is then continued until resolution of fever by 48–72 hours before switching to low dose ASA (5 mg/kg) for 6 weeks and until inflammatory parameters normalize. However, approximately 20% of patients with KD fail to respond to initial treatment with IVIG. [50–52] The RAISE study has demonstrated that treatment of selected high-risk KD patients with IVIG/aspirin was associated with the development of CAA in 23% [53]. The Kobayashi scoring system has been developed in Japan to predict IVIG resistance and to identify children at highest risk of developing CAA (Table 24.2) [54]. Treatment of severe high-risk KD patients with IVIG/aspirin and corticosteroids in the primary therapy has sig-

nificantly reduced the development of CA [53, 55]. The United Kingdom has developed recent guidelines for the treatment of KD including patients with high-risk features (Fig. 24.11) suggesting a role for anti-TNF- α if systemic inflammation persists despite IVIG, aspirin, and corticosteroids. [56] Live vaccines should be delayed for at least 3 months following treatment with IVIG, mainly due potential lack of effectiveness and potential detrimental immune activation [7].

Table 24.2 Kobayashi Scoring System for Predicting IVIG Resistance

Kobayashi
Na < 133 mmol/L (2 points)
≤ 4 days of illness (2 points)
AST ≥ 100 U/L (1 point)
Platelet ≤ 30.0 x 10^4/mm^3 (1 point)
CRP ≥ 10 mg/dL (1 point)
Age ≤ 12 months (1 point)
≥ 80% neutrophils (2 points)
High Risk: ≥ 5 points

24.9 Autoinflammatory Syndromes

Autoinflammatory syndromes (AIS) are a growing cluster of heterogeneous disorders, characterized by recurrent attacks of unprovoked self-limited fever and systemic inflammation involving different sites such as skin, joints, gastrointestinal, or central nervous system. AA amyloidosis is the most serious long-term complication. AIS is secondary to abnormal activation of the innate immune system leading to overproduction of pro-inflammatory cytokines, such as interleukin (IL)-1β, and tumor necrosis factor (TNF)-α, which leads to pathological delay of inactivation of inflammatory response [57]. The spectrum of monogenic AIS, share overlapping wide range of clinical features as described in (Fig. 24.12) [58].

These syndromes should be suspected in patients, especially young children, typically with recurrent fever and/or with episodic multisystem inflammation, in the absence of infection.

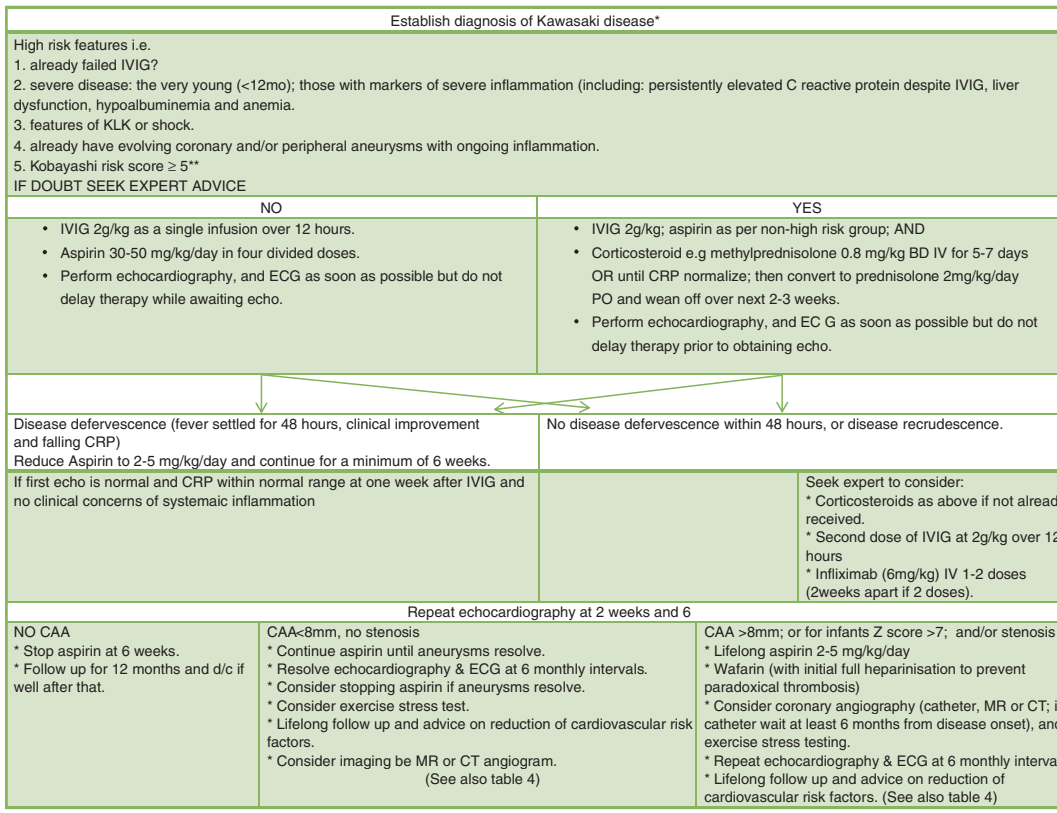

Fig. 24.11 Recommended clinical guideline for the management of Kawasaki disease in the UK

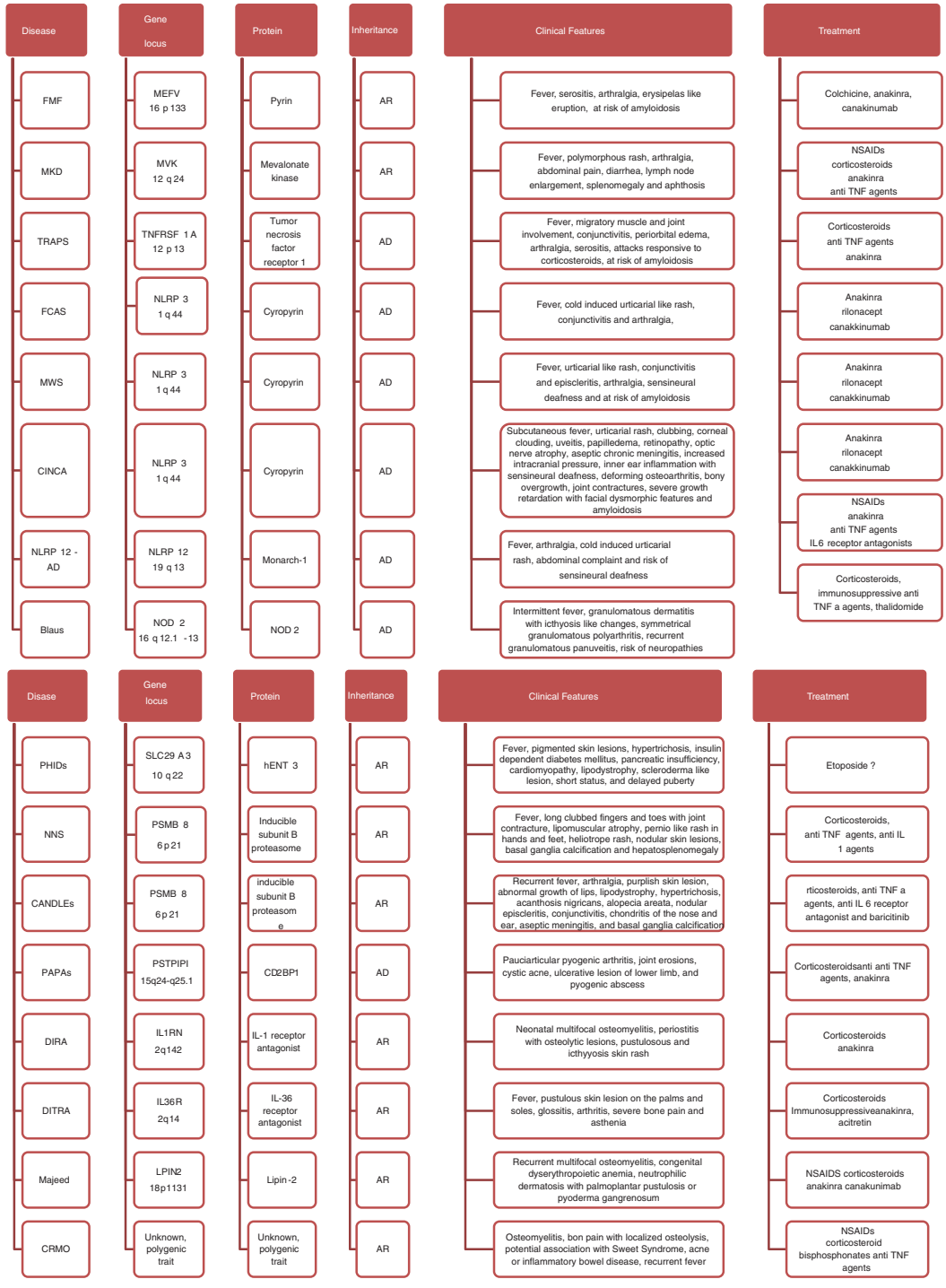

Fig. 24.12 Spectrum of autoinflammatory disease syndromes. AD: autosomal dominant, AR: autosomal recessive, BLAUs: Blau syndrome, CANDLEs: Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature, CINCAs: chronic infantile neurologic cutenous articular syndrome. CRMO chronic recurrent multifocal osteomyelitis, DIRA: deficiency of interleukin-1-receptor antagonist, DITRA: deficiency of IL-36 receptor antagonist, FCAS: familial cold auto-inflammatory syndrome; FMF: familial Mediterranean fever, MAJEEDs: Majeed syndrome, MKD: mevalonate kinase deficiency syndrome, MWS: Muckle-Wells syndrome, MLRP12-AD: NLRP12 associated auto-inflammatory disease, NNS: Nakojo-Nishimura syndrome, NSAIDs: non-steroidal anti-inflammatory drugs, PAPA: pyogenic arthritis, poderma gangrenosum and acne syndrome, PHID: pigmentary hypertrichosis and non-autoimmune insulin dependent diabetes mellitus syndrome, TRAPS: tumor necrosis factor receptor associated periodic syndrome

However, some occasionally AIS manifest as inflammation without fever and the inflammation can be persistent rather than episodic. The interval between attacks is variable, and the child remains completely well between febrile episodes. During attacks, laboratory tests are characterized by leukocytosis and elevation of acute phase reactants that normalize in the periods between fever episodes. A family history of these syndromes is often but not always obtained, including a history of unexplained deafness, renal failure, or amyloidosis. Initial workup for patients with AIS should be focused on ruling out serious conditions such as infection, malignancies, or immunodeficiency disorders. However, repeated attacks typically four to six attacks over an observation period of 9–12 months would require further genetic testing for AIS. Diagnosis of AIS can be challenging due to overlapping clinical features; however, AIS can be differentiated by age of onset, ethnicity, attack triggers, duration of attacks, disease-free intervals between attacks, clinical manifestations, and the response to therapy as described in (Table 24.3) [59, 60].

Table 24.3 Clues that help differentiate auto inflammatory syndromes

Age of onset	
At birth	NOMID, DIRA, FCAS
Infancy and first year of life	HIDS, FCAS, NLRP12
Toddler	PFAPA
Late childhood	PAPA
Most common of auto inflammatory syndromes to have onset in adulthood	TRAPS, DITRA
Variable (mostly in childhood)	All others
Ethnicity and geography	
Armenians, Turks, Italian, Sephardic Jaws	FMF
Arabs	FMF, DITRA (Arab Tunisian)
Dutch, French, German, Western Europe	HIDS, MWS, NLRP12
United States	FCAS
Can occur in blacks (West Africa origin)	TRAPS
Eastern Canada, Puerto Rico	DIRA
Worldwide	All others
Triggers	
Vaccines	HIDS
Cold exposure	FCAS, NLRP12
Stress, menses	FMF, TRAPS, MWS, PAPA, DITRA
Minor trauma	PAPA, MWS, TRAPS, HIDS
Exercise	FMF, TRAPS
Pregnancy	DITRA
Infections	All, especially DITRA
Attack duration	
< 24 h	FCAS, FMF
1-3 d	FMF, MWS, DITRA (fever)
3-7 d	HIDS, PFABA
> 7 d	TRAPS, PAPA
Almost always “in attack”	NOMID, DIRA
Interval between attacks	
3-6 wk	PFAPA, HIDS
> 6 wk	TRAPS
Mostly unpredictable	All others
Truly periodic	PFAPA, cyclic neutropenia
Useful laboratory tests	
Acute-phase reactants must be normal between attacks	PFAPA
Urine mevalonic acid is attack	HIDS
IgD > 100 mg/dL	HIDS

(continued)

Table 24.3 (continued)

Age of onset	
Proteinuria (amyloidosis)	FMF, TRAPS, MWS, NOMID
Response to therapy	
Corticosteriod dramatic	PFAPA
Corticosteriod partial	TRAPS, FCAS, MWS, NOMID, PAPA[a]
Colchicine	FMF, PFAPA (30% effective)
Cimetidine	PFAPA (30% effective)
Etanercept	TRAPS, FMF arthritis
Anti-IL-1 dramatic	DIRA (anakinra), FCAS, MWS, NOMID, PFAPA
Anti-IL-1 mostly	TRAPS, FMF
Anti-IL-1 partial	HIDS, PAPA

Abbreviations: DIRA, deficiency of the IL-1 receptor antagonist; DITRA, deficiency of the IL-36 receptor antagonist (generalized pustular psoriasis); FCAS, familial cold auto inflammatory syndrome; FMF, familial Mediterranean fever; HIDS, hyperimmunoglobulinemia D syndrome; IL, interleukin; MWS, Muckle-Wells syndrome; NLRP, nucleotide oligomerization domain-like receptor family, pyrin domain; NOMID, neonatal-onset multisystem inflammatory disorder; PAPA, pyogenic sterile arthritis, pyoderma gangrenosum, acne syndrome; PFAPA, periodic fever, aphthous stomatitis, pharyngitis, adenitis; TRAPS, tumor necrosis factor receptor-associated periodic syndrome

Adapted from: Rigante D, Lapalco G, Vitale A et al. Untangling the Web of Systemic Inflammatory Diseases. Mediators

[a] For intra-articular steroids

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Part III

Classification Criteria and Guidelines

25 Classification Criteria and Clinical Practice Guidelines for Rheumatic Diseases

Rola Hassan, Hanan Faruqui, Reem Alquraa, Ayman Eissa, Fatma Alshaiki, and Mohamed Cheikh

25.1 Introduction

Rheumatic diseases have many classification criteria and management guidelines that are continuously being updated in order to improve the quality of healthcare provision. With these ever-evolving criteria and guidelines, practicing clinicians need an easy way to get to the core of these updates and to retain them in an easy and memorable way. Classification criteria are meant to differentiate between similar diseases and also to confirm or rule out a certain disease based on inclusion and exclusion criteria. The diagnosis of rheumatic diseases can be challenging since many clinical signs and symptoms as well as many laboratory markers are not specific and can be positive in many diseases.

There is an important concept that should be addressed. It is that the use of these criteria is meant to be a guide rather than a sole diagnostic tool. It is an established practice that the diagnosis of rheumatic diseases relies heavily on clinical grounds. The importance of basic skills in rheumatology, namely, the comprehensive history and meticulous musculoskeletal (MSK) examination, cannot be overemphasized. This is obvious as there are no specific diagnostic tests for most rheumatic diseases. For this reason, it is essential to correlate the findings in history and MSK examination with laboratory, radiological, and sometimes histopathological findings to establish the diagnosis.

Guidelines and recommendations for the management of rheumatic diseases were developed to provide guidance based on the best available evidence. It cannot be applied in all situations since the availability of the equipment and medications as well as the patient's condition and ability plays a major role in the application of these guidelines. The physician has to apply the recommendations and guidelines in light of available circumstances and local health authorities' instructions. Such multifaceted decision-making may result in different guideline groups giving different strengths of recommendations for the same treatment. Therefore, all types of evidence, including evidence-based guidelines, need to be examined with care and common sense.

In this section, we will explain how to use the classification criteria for rheumatic diseases in clinical practice, the importance of having classification criteria and the advantage of updating the old ones. We will also cover the most recent

R. Hassan (✉)
Saudi Commission for Health Specialties, Riyadh, Saudi Arabia

H. Faruqui · R. Alquraa · A. Eissa
M. Cheikh
Doctor Soliman Fakeeh Hospital, Jeddah, Saudi Arabia
e-mail: mohamed.m.cheikh@gmail.com

F. Alshaiki
Department of Medicine, King Abdulaziz Hospital and Oncology Center, Jeddah, Saudi Arabia

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guidelines and recommendations for the management of the most common rheumatic diseases. This will be aided by the use of tables, graphs, and figures for simplification purposes to help in their application in research and clinical practice and to enhance the accessibility and practicality of this section.

25.2 Rheumatoid Arthritis Classification Criteria and Management Guidelines

25.2.1 Classification Criteria (Fig. 25.1)

Rheumatoid arthritis (RA) is the most common inflammatory arthritis. If left without treatment, RA can result in joint damage and functional disability. It is diagnosed clinically after the exclusion of other diseases if the symptoms and signs are suggestive. It should be suspected if patients present with inflammatory polyarthritis, after which a detailed history and physical examination, along with appropriate laboratory tests, will help in aiding or excluding this diagnosis.

The initial American College of Rheumatology (ACR) classification criteria for RA were developed in 1987. It was based on patients with established disease. To classify as having RA, the presence of four out of the seven items and the presence of symptoms for more than 6 weeks are required. There was limited practical value in this classification especially for diagnosing early disease. This limitation was corrected in the new (2010) ACR/EULAR (European League Against Rheumatism) classification criteria [1] which was formulated to increase the specificity and sensitivity in diagnosing early RA. These criteria take prognostic markers into account, which were not included in its predecessor. Patients can be identified earlier and started promptly on treat-

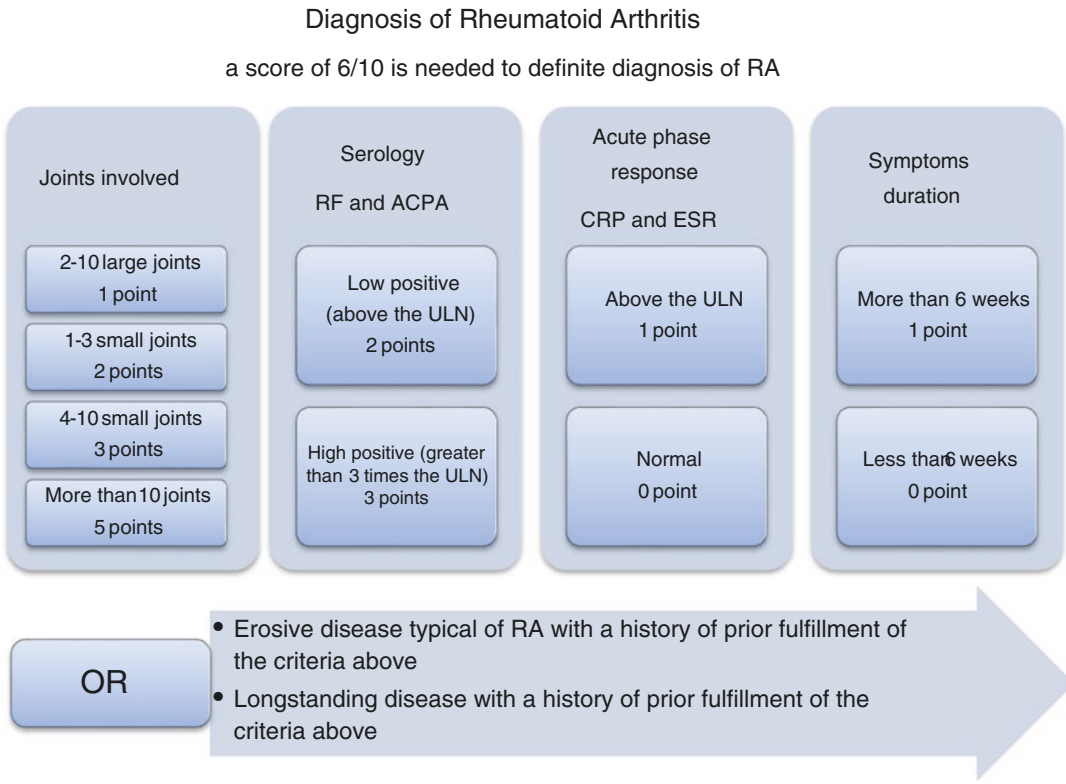


Fig. 25.1 Rheumatoid arthritis new classification criteria

ment with disease-modifying antirheumatic drugs (DMARDs), or they can be entered into clinical trials for promising new agents. It is the hope that these new criteria will help rheumatologists to care for patients with early arthritis and to tailor treatment according to their needs.

25.2.2 Management Guidelines [2] (Fig. 25.2)

The general approach to RA treatment has evolved remarkably in the last 10 years as there are an increasing number of effective DMARDs. The early introduction of DMARDs has become standard of care and depends upon early diagnosis that is facilitated by the 2010 ACR/EULAR classification criteria of RA to reach the target remission or in the very least low disease activity.

The 2013 International Task Force recommendations were designed to be based on evidence. They determined 14 recommendations instead of the 15 that were mentioned in the previous 2010 paper, published by the same institute. These recommendations addressed the use of methotrexate or a combination of DMARDs in the first phase, the use of anti-TNF or abatacept or tocilizumab in the second phase, and the use of tofacitinib after the use of at least one DMARD in the third phase.

Both 2010 and 2013 guidelines agreed on:

- The use of low-dose steroids initially.
- Early treatment with DMARD within the first 3–6 months and assessment every 3–6 months.
- Adjustment of treatment according to disease activity scales using the treat-to-target approach.

We have to consider the following in the application of the guidelines:

- Presence of poor prognostic factors.
- Presence of contraindications to methotrexate or other agents.
- The aim is to control the disease and to reach remission or low disease activity.

The 2016 update in the EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs Fig. 25.2.

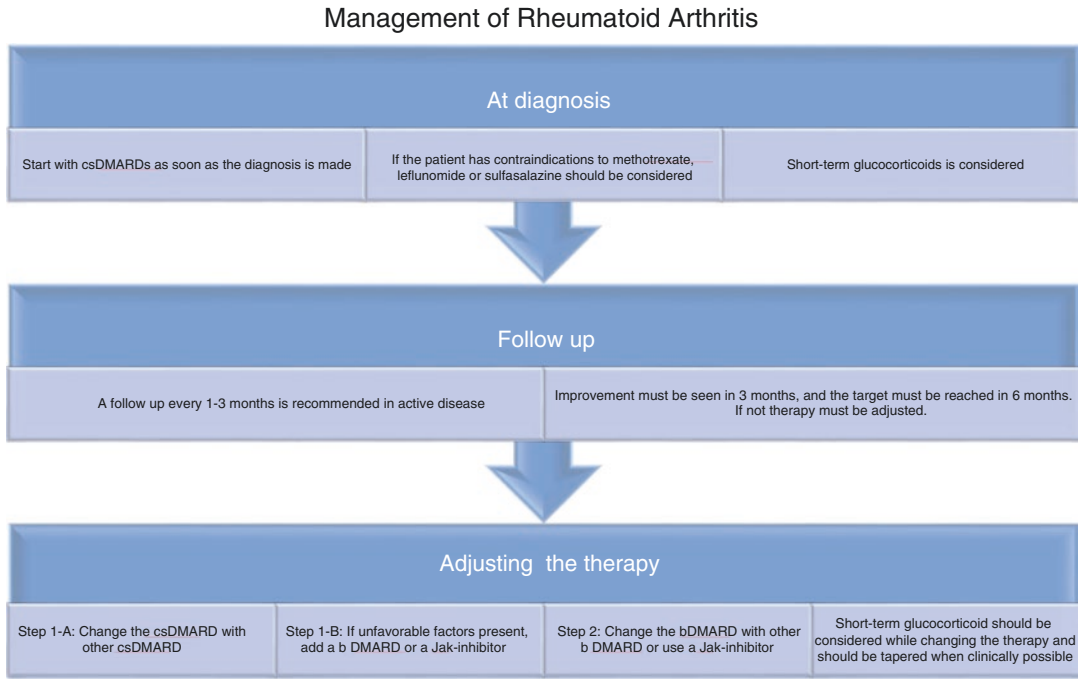


Fig. 25.2 Management of rheumatoid arthritis

25.3 Systemic Lupus Erythematosus Classification Criteria and Management Guidelines

25.3.1 Classification Criteria of Systemic Lupus Erythematosus (Fig. 25.3)

Systemic lupus erythematosus (SLE) is a multisystem disease that affects nearly every organ in the body. It can present with a wide array of clinical symptoms and signs and with variable disease courses. If left untreated in its early stages, the disease carries significant morbidity and mortality rates.

The Systemic Lupus International Collaborating Clinics (SLICC) represents a consensus group of SLE experts, who amended and validated the 1997 American College of Rheumatology classification criteria in 2012, to address many of the former's limitations (e.g., patients with biopsy-proven lupus nephritis still fail to fulfill the 1997 criteria). The first version

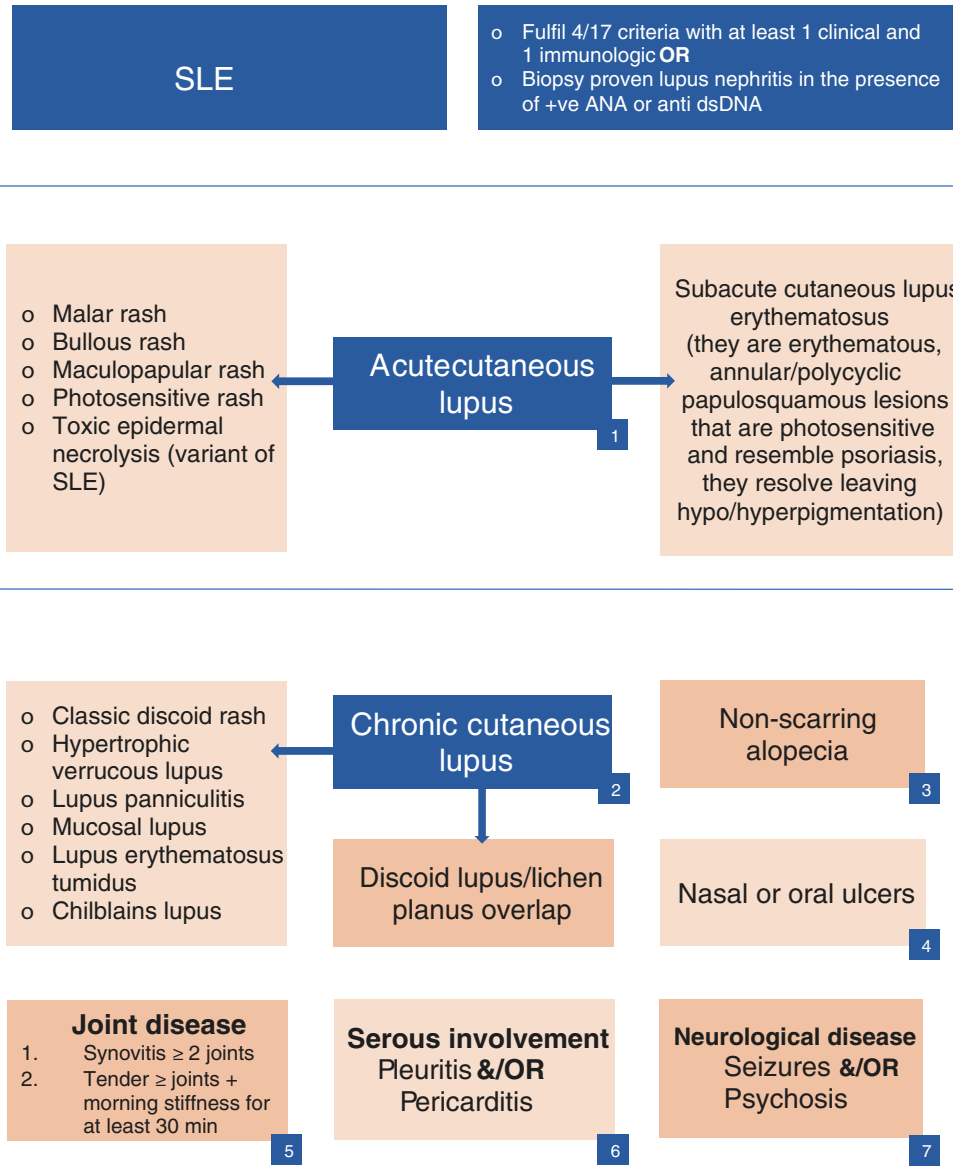


Fig. 25.3 The 2012 SLE SLICC criteria [4].

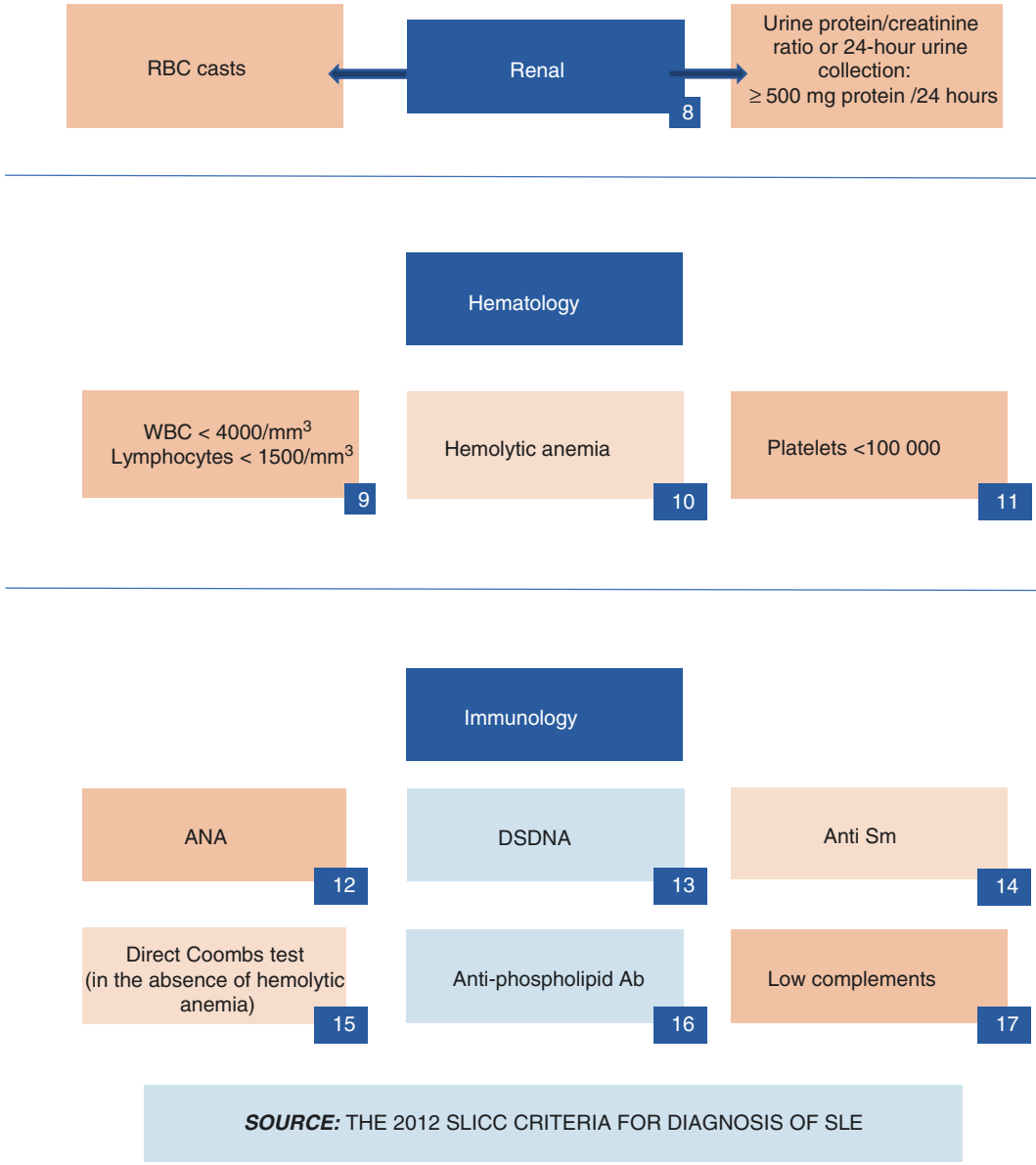


Fig. 25.3 (continued)

of the ACR criteria was introduced in 1982; it was last updated in 1997. These new criteria (SLICC) had greater sensitivity when compared to the 1997 criteria (97% vs 83%) but lower specificity (84% vs 96%) [3, 4]. Both the ACR and the SLICC criteria were initially developed as a way to categorize patients for research purposes, as its use by clinicians for diagnosis is limited by its imperfect sensitivity and specificity.

The 2012 SLICC criteria require the fulfillment of 4 out of the 17 criteria with a minimum of at least one clinical and one immunologic criterion. Lupus nephritis confirmed by biopsy with positive autoantibodies is also sufficient for classification [4].

The absence of an SLE diagnostic criteria and the wide variety of clinical manifestations make the diagnosis challenging and by exclusion. It

requires the appropriate gathering and interpretation of the patient's symptoms, physical signs, and diagnostic tools.

The recommendations for the treatment of SLE are based on an approach combining evidence as well as the opinions of experts in the field. Currently, the only major improvement was to create better protocols based on the use of existing medications, both traditional and biological. There is a newly approved drug for SLE by the name of belimumab. However, it has very limited post-marketing experience as patients with severe renal and central nervous system diseases were excluded from its original studies. It is expected that treatment algorithms will be changed in the future by biologic therapies.

It is important to point out that disease presentations and clinical manifestations vary widely in SLE and that treatment protocols should be thought out carefully and fitted to each patient's unique disease course and needs.

25.3.2 Management Guidelines for Systemic Lupus Erythematosus

The goals of treatment of systemic lupus erythematosus are the following:

1. Induction of remission: aiming to rapidly control disease activity for prolonged periods of time.
2. Maintenance therapy: aiming to retain remission or low disease activity and to prevent flares.
3. Adjunctive therapy: aiming to reduce the side effects of drugs employed to control disease activity and to control other SLE-associated conditions.

25.3.2.1 General Management Recommendations

The 2019 European League Against Rheumatism guidelines for the treatment of SLE without renal involvement include [5] the following (Figs. 25.4 and 25.5):

- Hydroxychloroquine (HQ) should be given to all SLE patients with a maximum dose of 5 mg/kg/day.
- Ophthalmological examination should be conducted at diagnosis time, after 5 years and then every year to screen for retinal toxicity associated with HQ.
- Oral steroids are to be given in cases of mild disease, while intravenous steroids are to be given in moderate/severe disease.
- It is recommended to keep chronic prednisone use under 7.5 mg daily (or its equivalent) and to stop it whenever possible.
- In patients who are not sufficiently controlled on HQ or those who need further steroid-sparing agents, immunosuppressive agents can be added. Methotrexate (MTX) is recommended for mild disease activity. Azathioprine (AZT), calcineurin inhibitors (CNI), and mycophenolate mofetil (MMF) are to be given for moderate disease activity, both as steroid-sparing agents and as initial therapies, while belimumab is used for refractory cases. MMF and cyclophosphamide (CYC) are recommended for induction of remission in severe disease activity, while rituximab (RTX) is used when disease response is poor.
- For cutaneous manifestations of SLE, first-line management includes topical steroids and CNI; systemic steroids can also be used, along with HQ. If patients do not respond to initial treatment, further choices should include MTX, retinoids, dapsone, and MMF. Rescue therapy with thalidomide can be considered after failure of all previous lines.
- Acute management of thrombocytopenia due to SLE (Plt < 30,000) includes the use of moderate−/high-dose steroids in combination with either AZT, MMF, or CYC. Intravenous immunoglobulins can also be used in case of poor initial response to steroids. For refractory cases, RTX therapy can be attempted. Last resort choices include thrombopoietin and splenectomy.
- Immunization against seasonal influenza yearly and pneumococcal vaccine (both PCV13 and PPSV23) every 3–5 years is recommended.

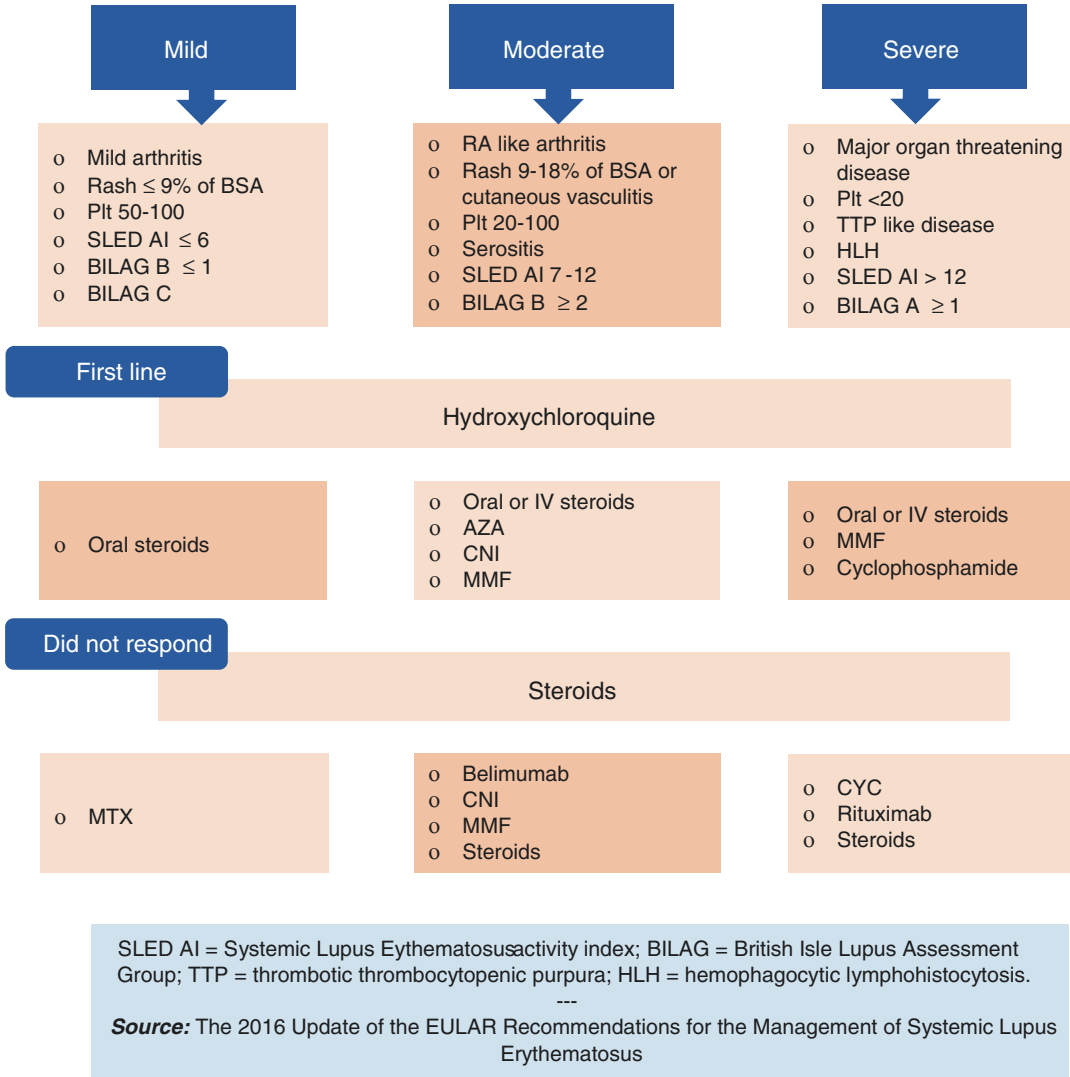


Fig. 25.4 Management of systemic lupus erythematosus without kidney involvement [5]

Recognizing certain clinical manifestations in SLE is crucial as proper treatment should be started promptly to salvage organ function. Lupus nephritis and neuropsychiatric lupus are considered to be the two most serious clinical manifestations of SLE. In the next section, we will introduce the latest published classification criteria and management guidelines for lupus nephritis and neuropsychiatric lupus.

25.3.2.2 Lupus Nephritis (LN)

It is estimated that during the first 10 years of diagnosis, 50–60% of SLE patients will develop renal disease. Kidney biopsy should be executed in most patients with SLE who have evidence of kidney involvement in order to establish the diagnosis of lupus nephritis and to classify the patient's renal disease according to its histopathology. This will help determine the disease's prognosis and the proper line of therapy that should ensue (see chapter "Renal System and Rheumatology") [6].

The lupus nephritis classification system was developed by the International Society of Nephrology (ISN) in 2003 [7]. This system appears to be associated with increased reproduc-

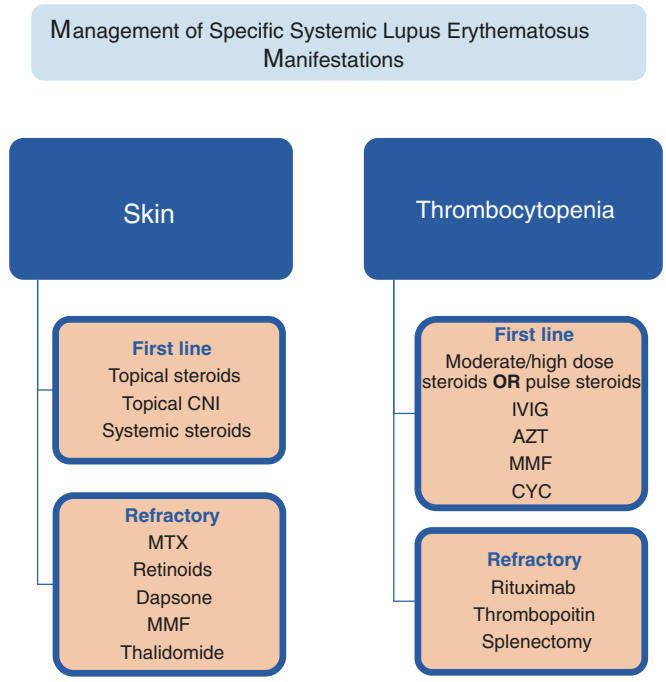


Fig. 25.5 Management of specific systemic lupus erythematosus manifestations [5]

Source: The 2016 Update of the EULAR Recommendations for the Management of Systemic Lupus Erythematosus

ibility compared with the modified 1974 WHO system [8]. The ISN classification system divides glomerular disorders associated with SLE into six different patterns (or classes) [7], each carrying distinct histopathological, clinical, and prognostic characteristics (Fig. 25.6).

The 2012 American College of Rheumatology guidelines for treatment of SLE with renal involvement include the following (Figs. 25.7, 25.8, 25.9, 25.10 and 25.11):

- Renal function monitoring should be done every 3 months in patients deemed at high risk of developing LN, including male patients, juvenile-onset SLE, and seropositivity for anti-C1q antibodies [5].
- The use of either MMF or low-dose CYC along with glucocorticoids is recommended for the induction of remission in Class III and IV LN. Both are equally efficient in controlling the disease with no clear superiority for one over the other [6].
- Higher doses of CYC can be used in LN if there is an increased risk of progressing to end-stage renal disease (decreased glomerular filtration rate, the presence of crescents or fibrinoid necrosis in the kidney biopsy) [5].
- Maintenance therapy with MMF or AZT is recommended for Class III and IV LN [6].
- Use of RTX or CNI along with glucocorticoids is recommended to treat resistant cases of Class III and IV LN that failed traditional therapy [6].
- Class V LN patients are recommended to use MMF only as the induction drug of choice with either MMF or AZT serving as maintenance therapy [6].
- Resistant cases of Class V LN are recommended to use CYC with glucocorticoids [6].
- Evaluation of disease activity every 6 months with modification of treatment options according to the ACR response criteria is recommended [9].

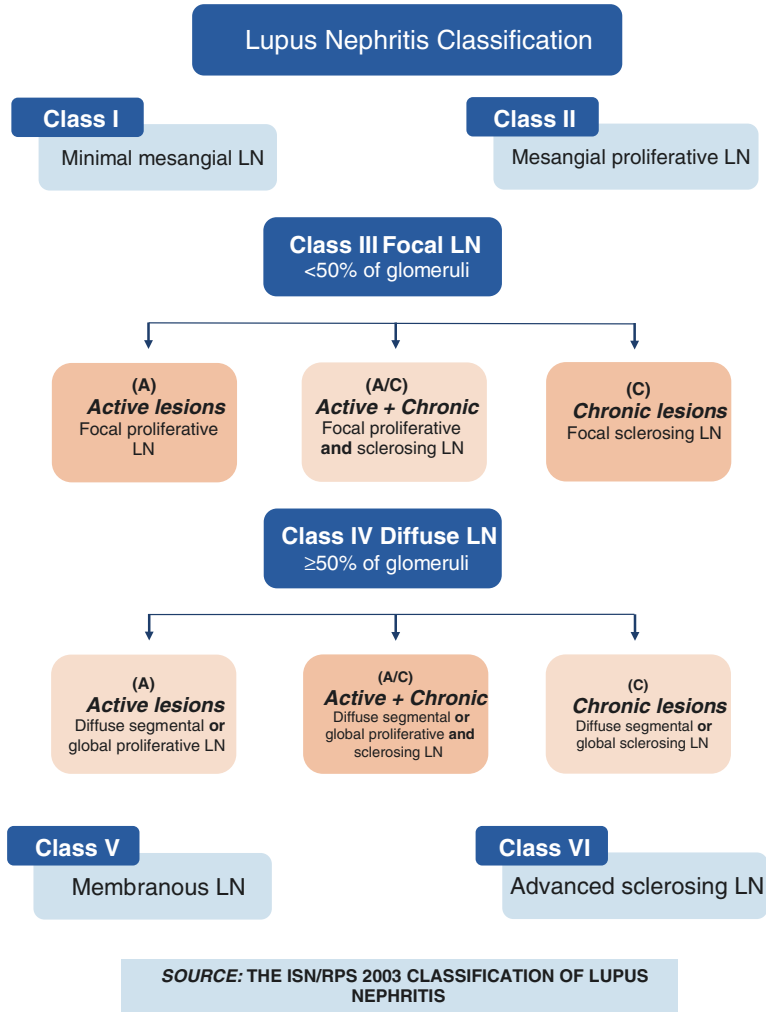


Fig. 25.6 The ISN/RPS 2003 classification of lupus nephritis [7].

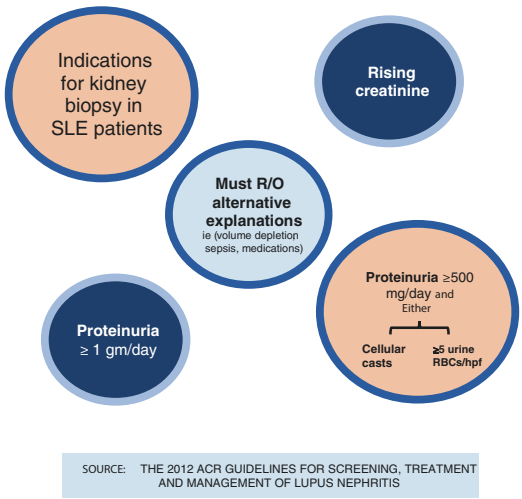


Fig. 25.7 The 2012 American College of Rheumatology indications for kidney biopsy in SLE patients [6]

- Early decrease in urine protein (≤1 gram at 6 months or ≤ 800 mg at 12 months) carries a favorable long-term prognosis [5].
- There are special considerations for lupus nephritis during pregnancy [6].
- There are special recommendations for adjunctive treatment of lupus nephritis [6].

25.3.2.3 Neuropsychiatric Lupus [10]

SLE is known to affect both the central nervous system (CNS) and peripheral nervous system. It is one of the most confusing manifestations of the disease, and it also carries one of the highest risks of morbidity and mortality. These manifestations may occur prior or during the disease course, with the commonest symptoms including headaches, psychiatric

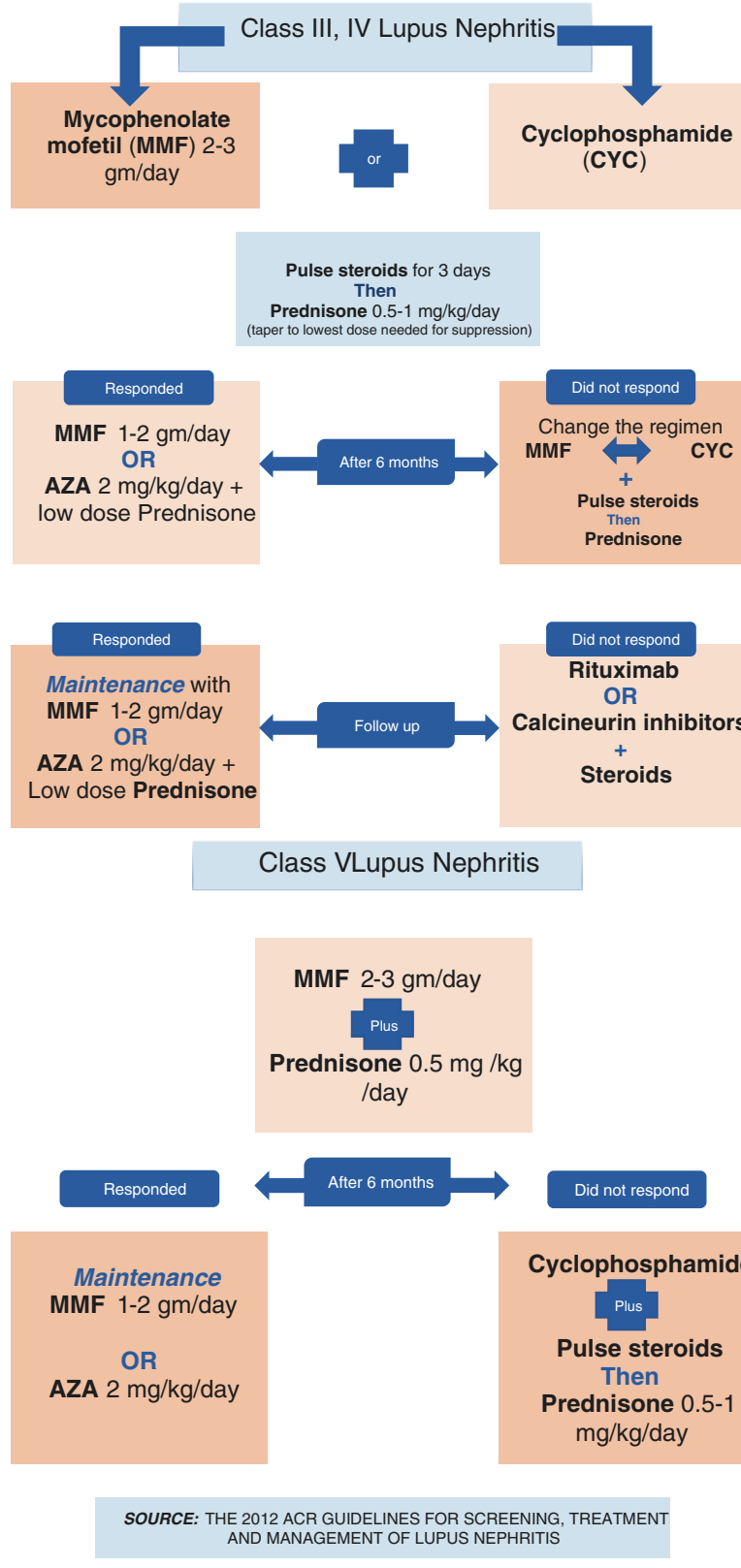


Fig. 25.8 The 2012 American College of Rheumatology guidelines for treatment of lupus nephritis [6]

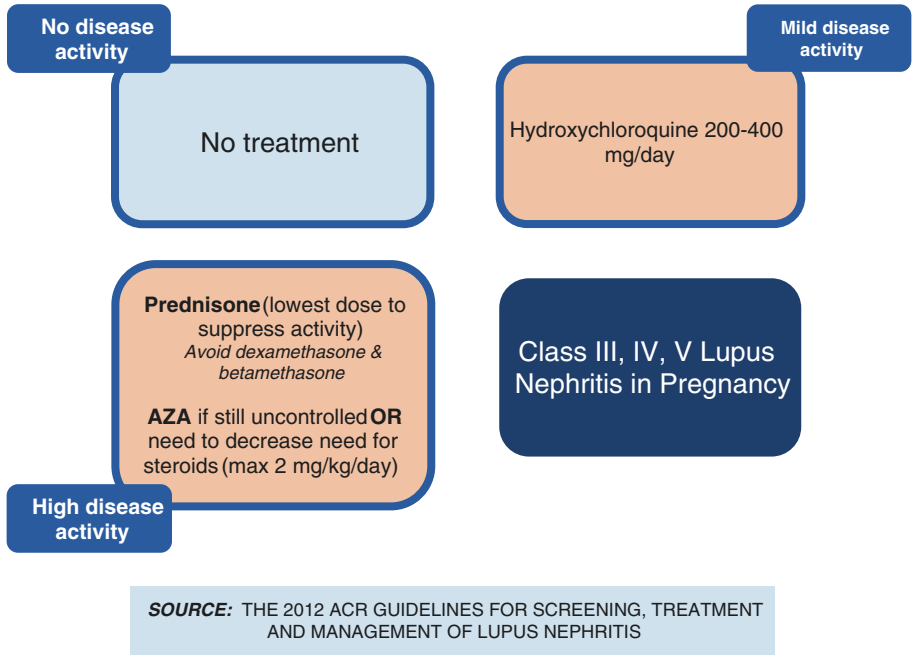


Fig. 25.9 The 2012 American College of Rheumatology guidelines for treatment of class III, IV, and V lupus nephritis in patients who are pregnant [6]

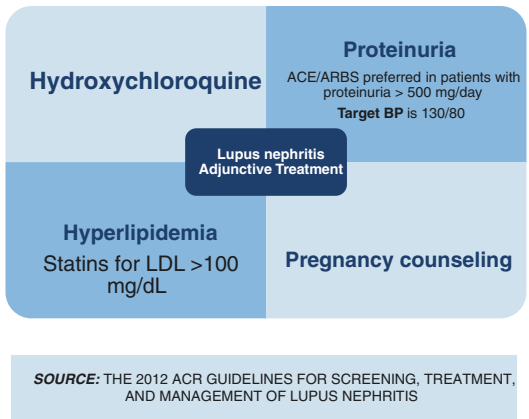


Fig. 25.10 The 2012 American College of Rheumatology guidelines for the adjunctive therapy of lupus nephritis [6]

mood disorders, and cognitive dysfunction. Neuropsychiatric lupus encompasses 19 neurologic and psychiatric syndromes; these were all classified and defined by the ACR. Recommendations for diagnostic testing were also included in these criteria (Figs. 25.12 and 25.13).

The pathogenesis, clinical manifestations, and assessments of neuropsychiatric lupus are very complex which make it difficult to design proper controlled trials; therefore, the treatment is strongly based on physicians' clinical experience. Treatment tends to vary with the manifestation, for example, stroke due to antiphospholipid antibodies is treated with anticoagulants, while cognitive defects may respond to steroids, antidepressants, and/or anxiolytics. There are no randomized clinical trials that have specifically examined these treatments. **Principle of management of NPSLE** (see Box 25.1, Figs. 25.14 and 25.15) [11].

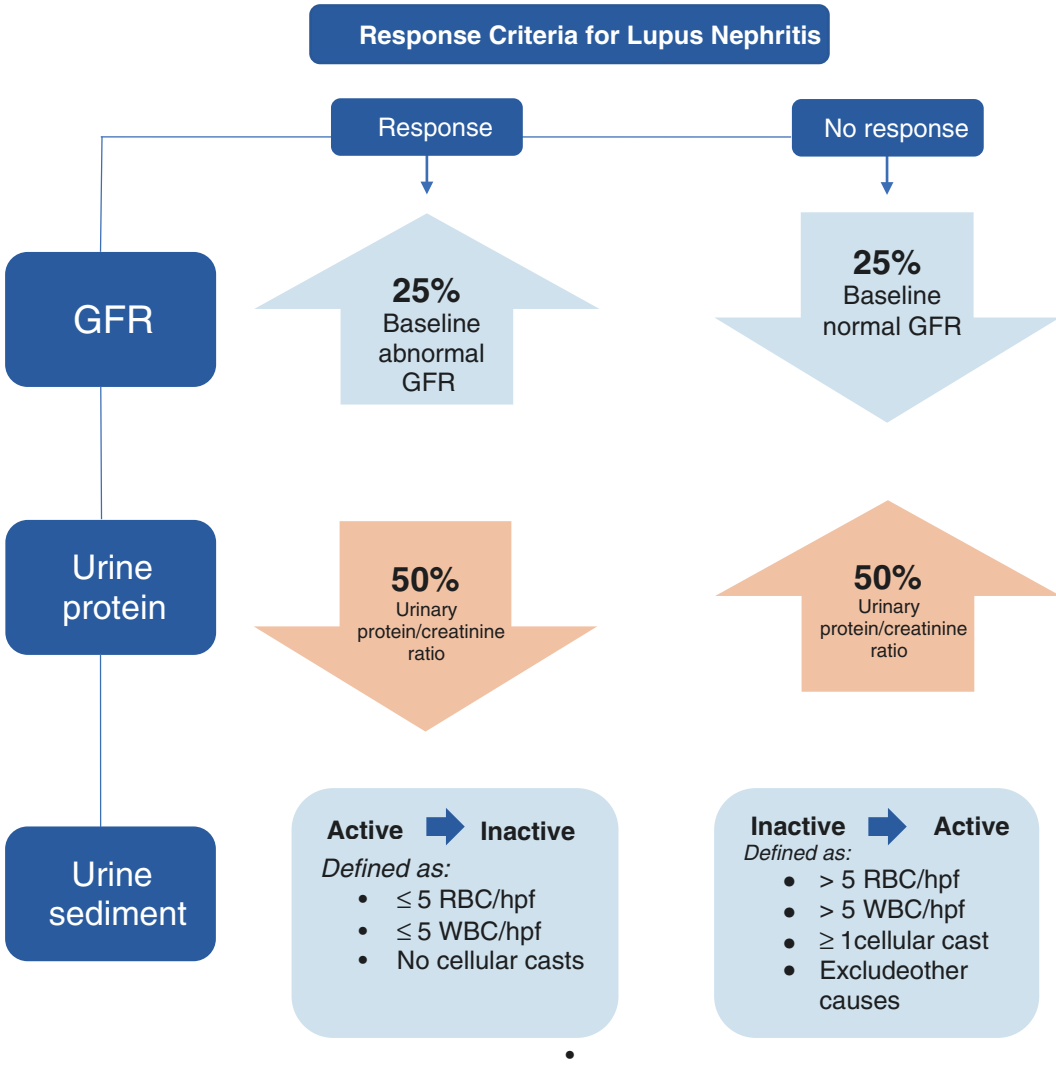


Fig. 25.11 The 2006 American College of Rheumatology response criteria for proliferative and membranous renal disease in SLE [9]

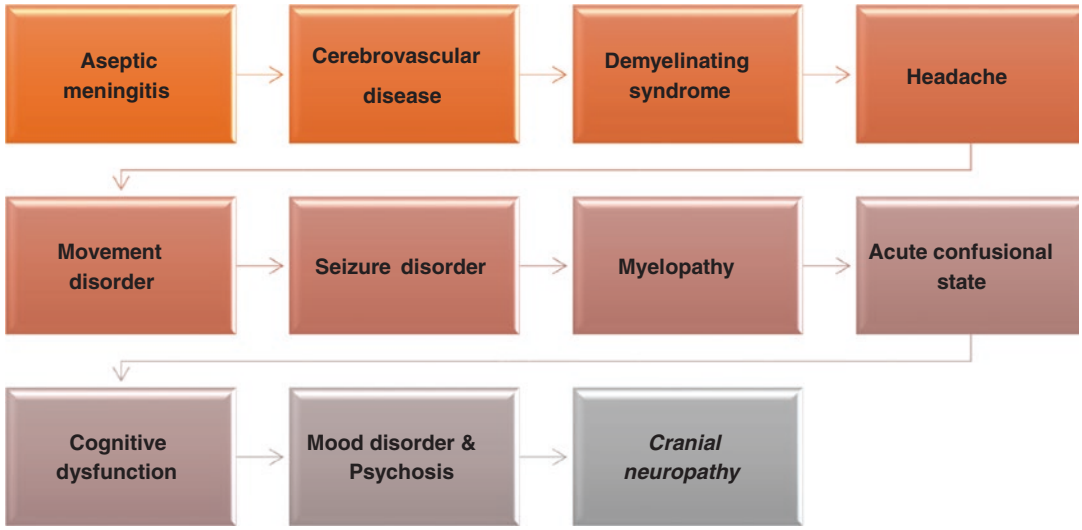


Fig. 25.12 Neuropsychiatric manifestations of systemic lupus erythematosus (Central nervous system)

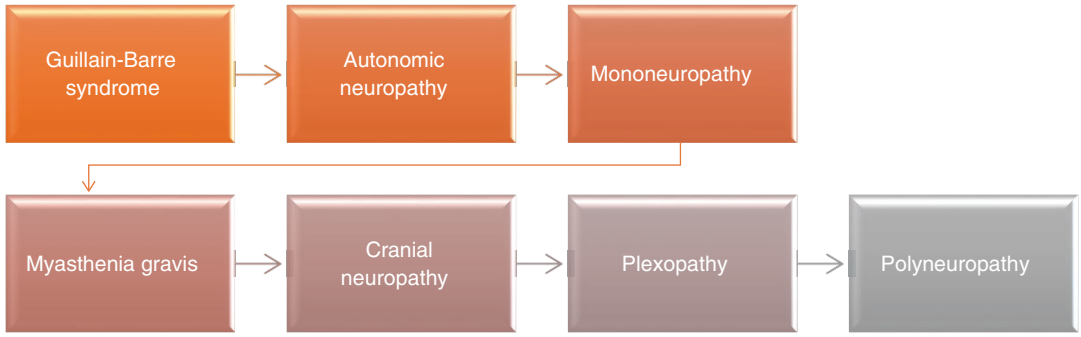


Fig. 25.13 Neuropsychiatric manifestations of systemic lupus erythematosus (peripheral nervous system)

Box 25.1 Principle of management of NPSLE

1-Sympomatic therapy include anticonvulsants, antidepressants and treatment of any aggravating factors
2-Antiplatelet/anticoagulation therapy:**Indicated when manifestations are related to antiphospholipid antibodies**
3-Glucocorticoids and immunosuppressive therapy are indicated after the exclusion of non-SLE causes if the neuropsychiatric manifestations were felt to reflect an immune inflammatory process (eg: acute confusional state, aseptic meningitis) after exclusion**of non-SLE-related causes**

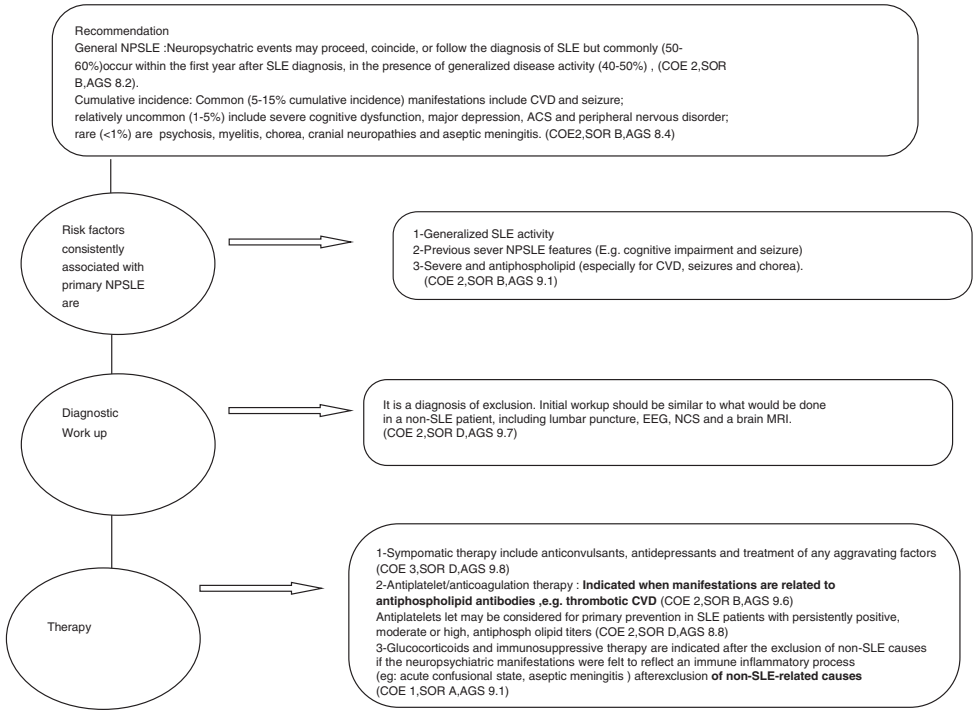


Fig. 25.14 EULAR Recommendation for the management of NPSLE. ACS, acute confusion state; AED, antiepileptic drugs; CNS, central nervous system; CSF, cerebrospinal fluid; CVD, cerebrovascular disease; DWI, diffusion-weighted imaging; FLAIR, fluid-attending inversion recovery sequence; NCS, nerve conduction studies; NPSLE, neuropsychiatric systemic lupus erythematosus; SLE, systemic lupus erythematosus; COE, category of evidence; SOR, strength of recommendation; AGS, agreement score

25.4 Antiphospholipid Syndrome Classification Criteria and Management Guidelines

25.4.1 Classification Criteria

Antiphospholipid syndrome (APS) is an autoimmune disease that mainly causes thrombosis of the patient's arteries and veins and may also lead to poor pregnancy outcomes. The presence of antiphospholipid antibodies (aPL) is associated with this disease. However, these antibodies can also be found in healthy individuals.

The definition has been discussed in several international meetings involving experts from different specialties (rheumatology, obstetrics, neurology, hematology, nephrology, etc.). Classification criteria were proposed in 1998 in Japan. It required positive antibodies testing and at least one clinical manifestation of APL. These criteria were initially intended to be used in research settings; however, they were also used by clinicians to decrease the rates of overdiagnosing this disease. Although these criteria helped to classify a homogenous group of patients for research purposes, they had some limitations when used in a clinical setting, as some patients who had clinically evident APL still failed to fulfill these classification criteria. The same group subsequently modified these criteria in 2006, in Sydney. The most significant modifications are outlined below [12]:

(a) Time between two positive antibodies results was lengthened to 12 weeks. This was done to detect persistent positivity.
(b) For the antibody anti-beta-2 glycoproteins, both IgG and IgM antibodies were added to the criteria.

There is a need to further understand the underlying pathogenic mechanisms that cause

APL. Further studies that develop more specific laboratory techniques to be able to detect those who are most at risk of developing thrombosis and poor pregnancy outcomes are also imperative. These techniques could also help with the recruitment of patients in clinical trials (see Fig. 25.16).

25.4.2 Management Guidelines

In the absence of solid guidelines derived from clinical trials, using prophylaxis as a management strategy is still controversial. The treatment of non-obstetric manifestations of APS is mostly the same regardless of the classification of APS (primary vs secondary). Current treatment of APS includes heparin and warfarin. Many patients with coexisting SLE are also treated with hydroxychloroquine, which may have some benefit for patients at risk of thrombosis; this is based on evidence from retrospective studies that suggest the presence of an association between the use of hydroxychloroquine and a reduced risk of thrombosis.

There are special recommendations regarding the treatment of catastrophic APS as well as for the management of APS during pregnancy. More well-designed, prospective research that tackles the management options for APL is required (Fig. 25.17) [13].

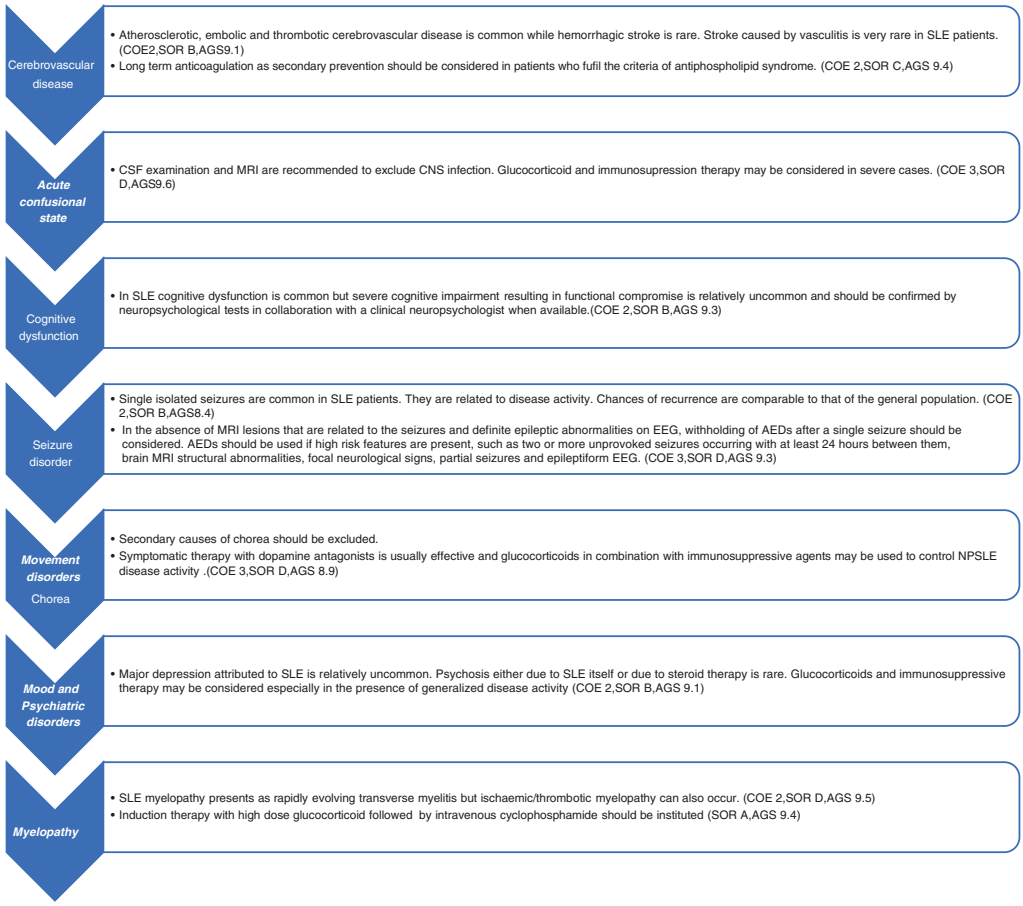


Fig. 25.15 EULAR Recommendation for the Management of Specific NPSLE disorder. ACS, acute confusion state; AED, antiepileptic drugs; CNS, central nervous system; CSF, cerebrospinal fluid; CVD, cerebrovascular disease; DWI, diffusion-weighted imaging; FLAIR, fluid-attending inversion recovery sequence; NCS, nerve conduction studies; NPSLE, neuropsychiatric systemic lupus erythematosus; SLE, systemic lupus erythematosus; COE, category of evidence; SOR, strength of recommendation; AGS, agreement score

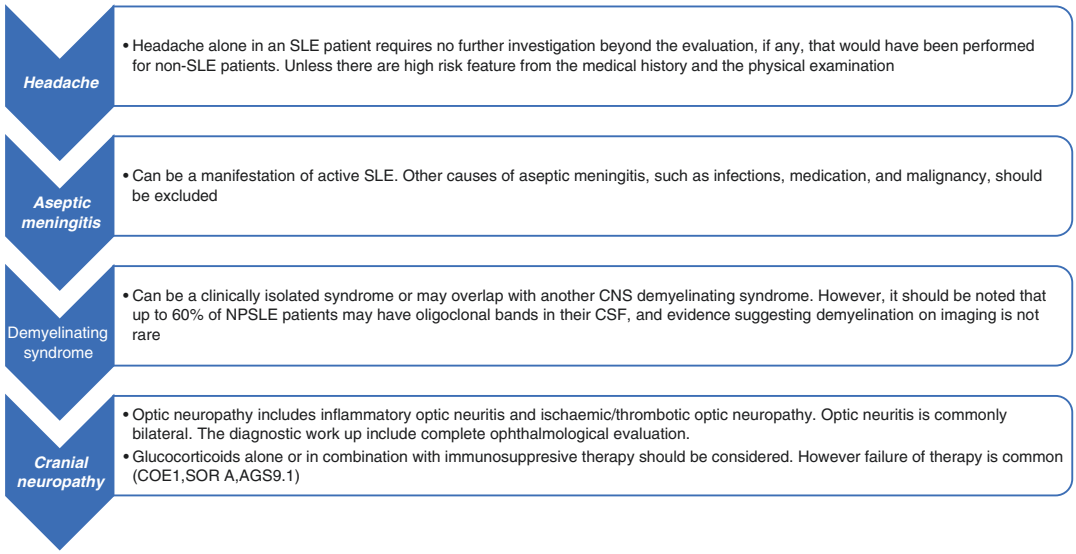


Fig. 25.15 (continued)

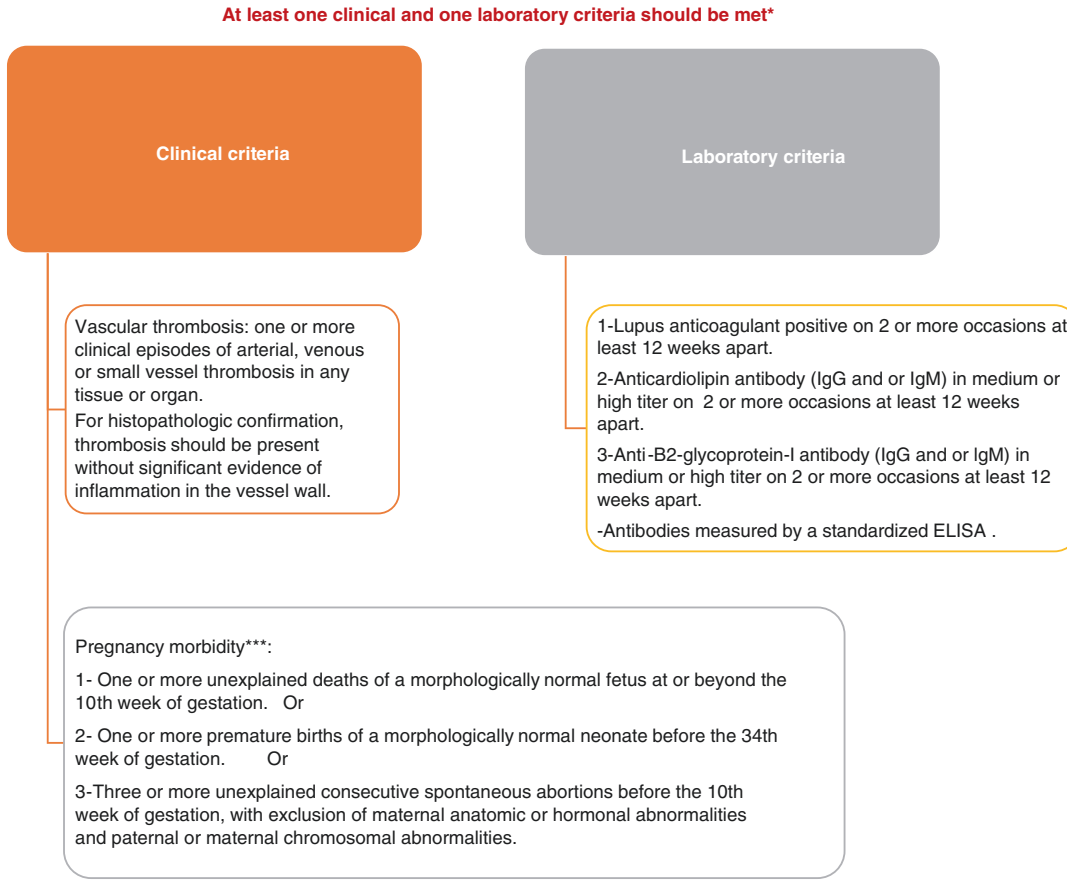


Fig. 25.16 Classification criteria for antiphospholipid syndrome (APS)

25.5 Vasculitis Classification Criteria and Management Guidelines

25.5.1 Classification Criteria (Fig. 25.18)

Vasculitides encompasses a group of heterogeneous yet uncommon conditions that can either occur secondary to another disease or arise on its own. Classification criteria of vasculitis generally include several organizing principles like the size of the involved vessel, type of involved vessel (artery, vein, capillary, etc.), underlying pathophysiology (primary vs secondary vasculitis), type of immune damage, and others.

There are no validated criteria for the diagnosis of vasculitis. However, the ACR presented classification criteria in 1990 for seven types of vasculitis. These criteria's main limitation was

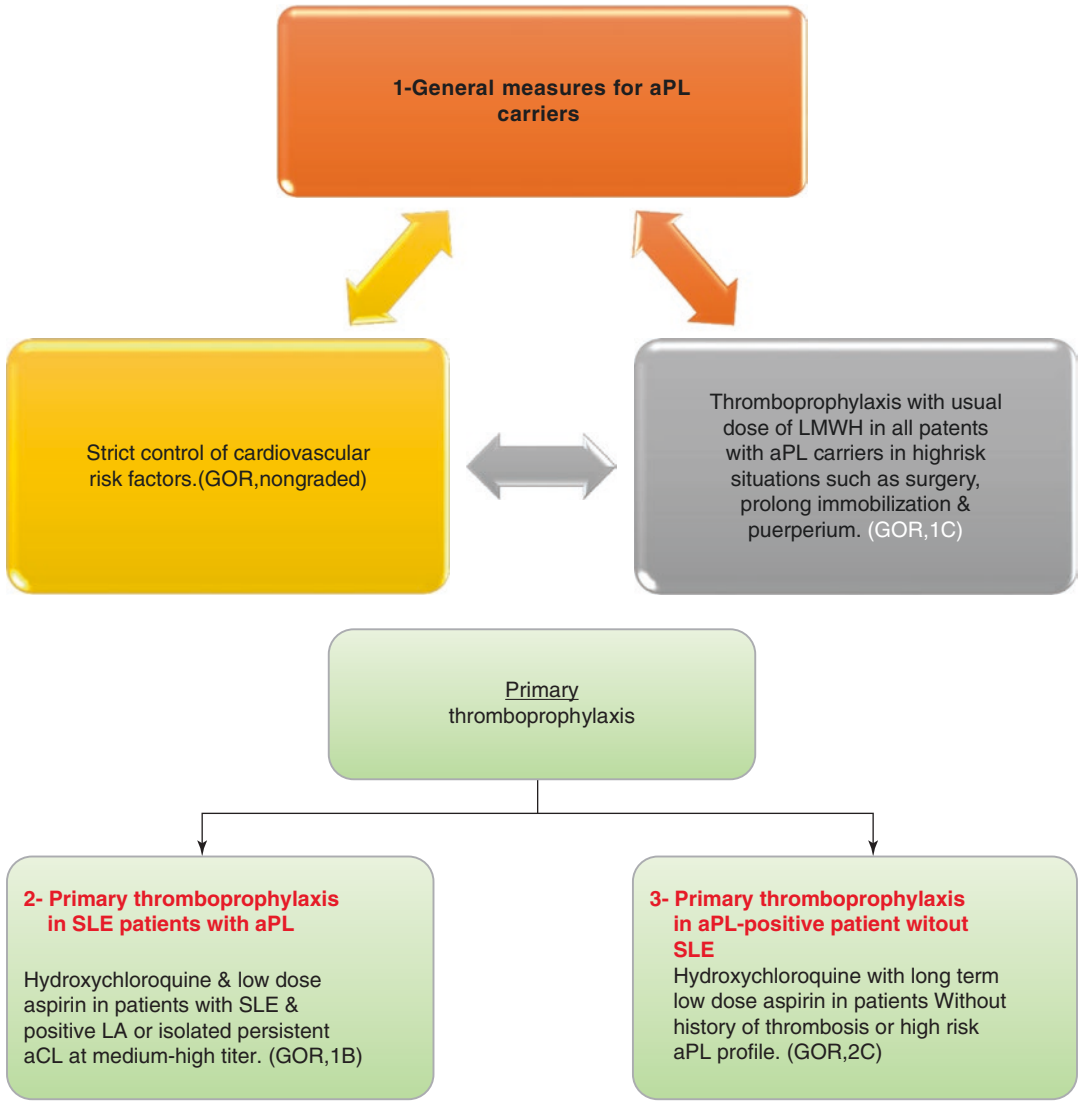


Fig. 25.17 Summary of Management Guideline for Antiphospholipid syndrome(APS)

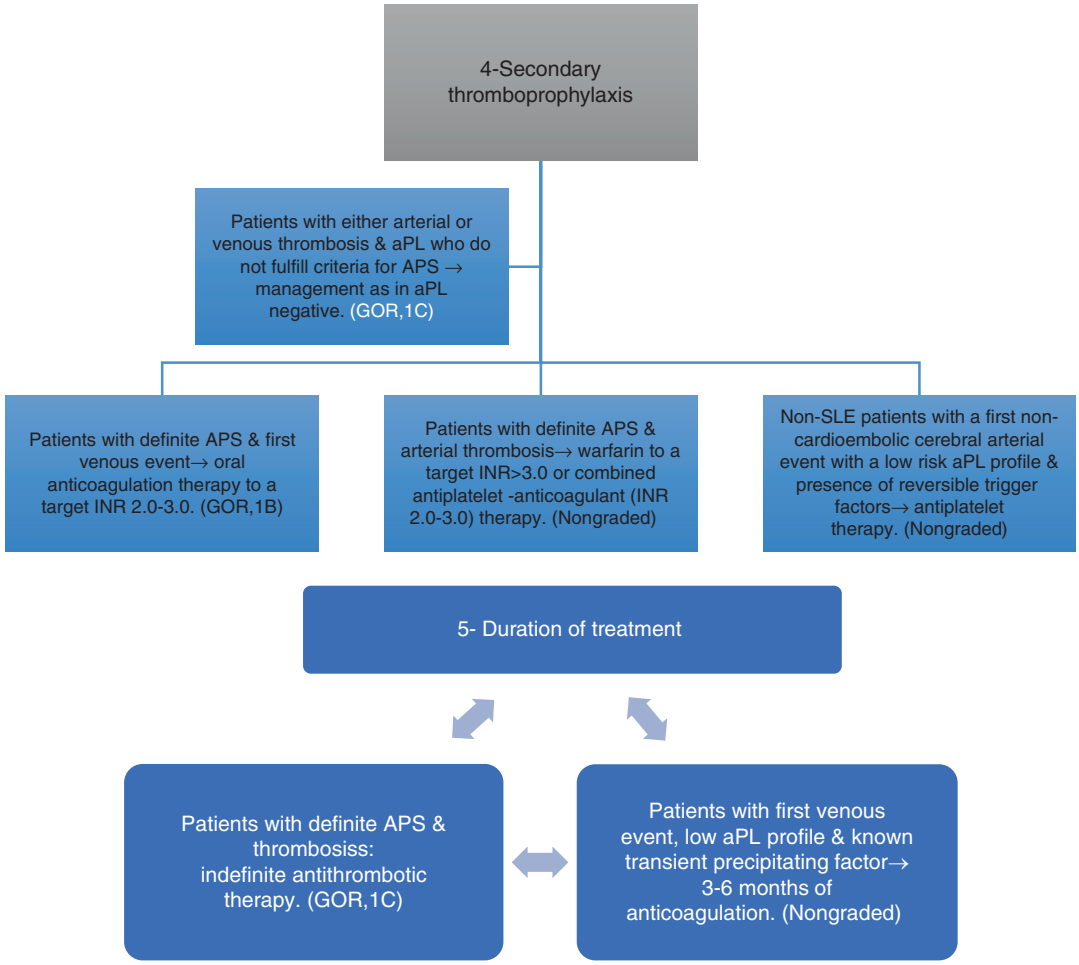


Fig. 25.17 (continued)

that it did not include microscopic polyangiitis or antineutrophil cytoplasmic antibodies (ANCA) [14].

The most widely used nomenclature system is the one introduced in 1994 and revised in 2012 by the Chapel Hill Consensus Conference (CHCC) [15], which included microscopic polyangiitis and replaced disease eponyms with names that were more representative of the disease's underlying pathophysiology. However, unlike the previously mentioned ACR criteria, the CHCC was not meant to be a classification or diagnostic criteria. Although, the ACR and CHCC definitions are widely used, there is no agreement about how it should be applied. Another set of classification criteria is the European Medicines Agency (EMA) criteria, which attempted to produce a consensus method for the application of both the ACR's and the CHCC's definitions of ANCA-associated vasculitis and polyarteritis nodosa in a clinical setting. They developed an algorithm which incorporates the ACR and CHCC definitions with both ANCA and surrogate markers to successfully classify this population of patients [16].

The most notable changes suggested by the 2012 CHCC are:

- Use of the term eosinophilic granulomatosis with polyangiitis (EGPA) instead of Churg-Strauss syndrome.
- Adoption of the term antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) instead of three disorders: microscopic

polyangiitis (MPA), granulomatosis with polyangiitis (GPA) (Wegener's), and EGPA.
- Use of the term immunoglobulin A (IgA) vasculitis instead of Henoch-Schönlein purpura.
- Use of the term cryoglobulinemic vasculitis in place of essential cryoglobulinemic vasculitis.
- Introducing a definition for hypocomplementemic urticarial vasculitis (HUV) (anti-C1q vasculitis).

(See chapter "Vasculitis and Rheumatology.")

Physicians should use these criteria with an understanding that they are still a work in progress and that they currently have limited value in clinical practice for diagnosing patients. The diagnosis of vasculitis should also always be confirmed by a tissue biopsy.

25.5.2 Management Guidelines

Management of vasculitis relies on the extent of involvement and severity of the vasculitis. For example, a mild drug-induced vasculitis would only require discontinuation of the offending drug. Systemic or more severe forms of vasculitis may require a short or more sustained course of glucocorticoids, a cytotoxic agent, or other medications.

Significant progress has been achieved over the last 30 years in terms of refining the manage-

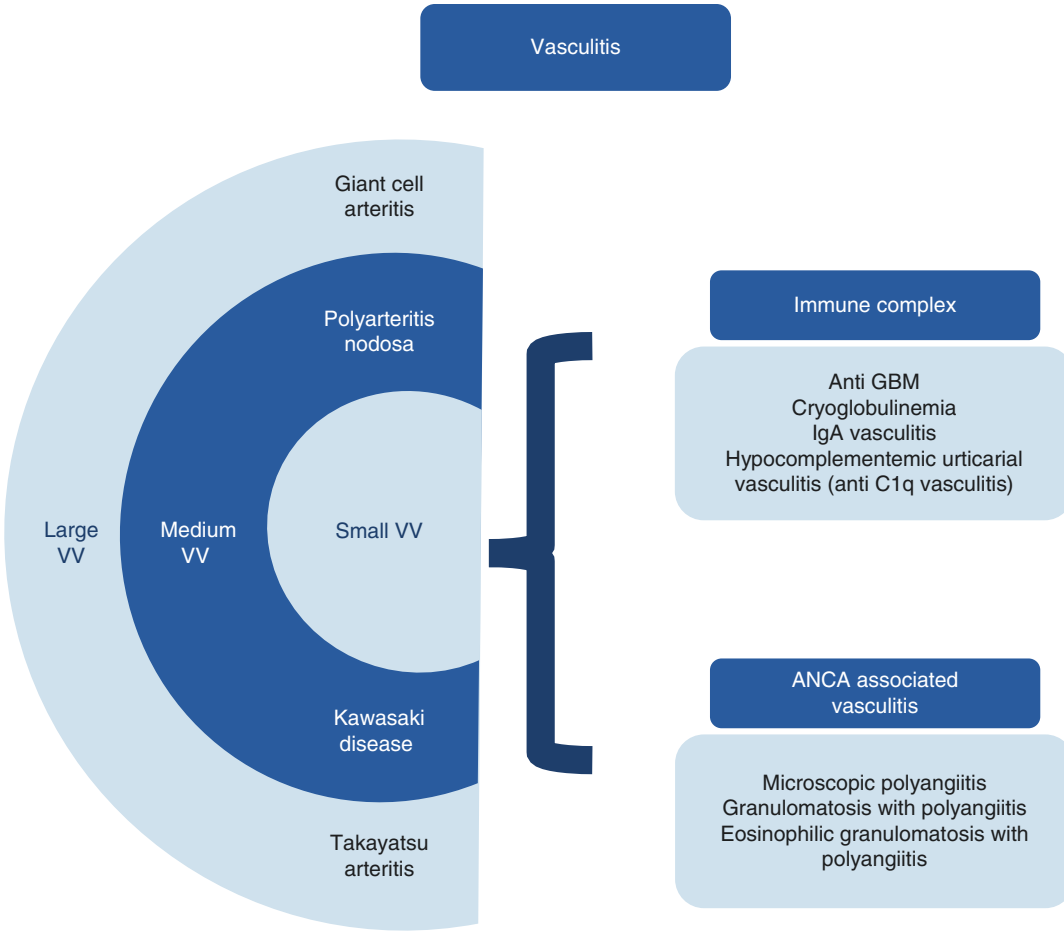


Fig. 25.18 The 2012 Chapel Hill classification criteria (HCCC) of vasculitis [15]

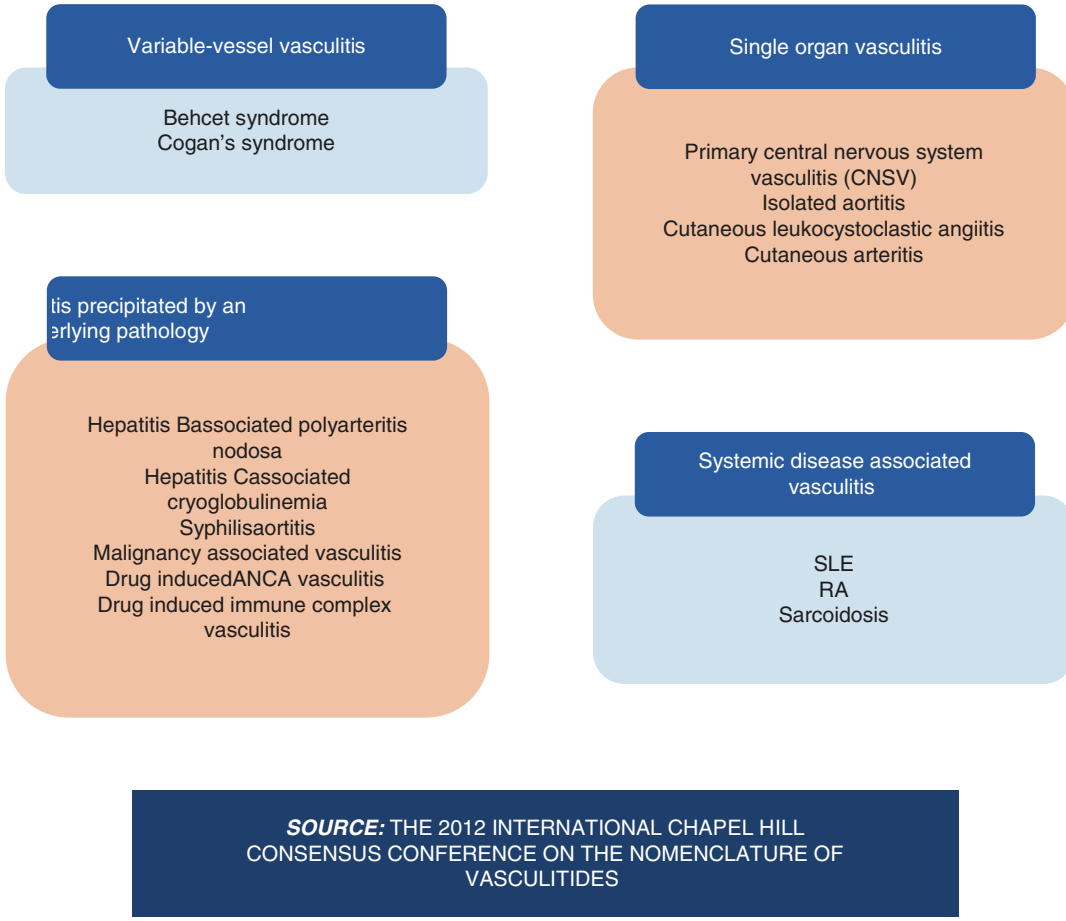


Fig. 25.18 (continued)

ment guidelines of immunosuppressive medications while keeping toxicities at a minimum. These advances have made diseases like ANCA-associated vasculitis (AAV) treatable and less fatal. Further advances are needed as there are still a proportion of patients that are going to develop symptoms that are refractory to all available therapies. Half of this patient population will also develop a relapse within 5 years of diagnosis, and toxicity from treatments given is still a significant contributor to mortality and chronic disability.

The introduction of biomarkers has also made it possible to determine disease activity and estimate risks of relapse. However, the key to adequately managing these patients should be by tailoring their immunosuppressive regimens to their individual needs.

The 2016 European League Against Rheumatism (EULAR)/European Renal Association (ERA)- European Dialysis and Transplant Association (EDTA) recommendations for the management of ANCA-associated vasculitis include the following [17] (Fig. 25.19):

- It is recommended to do a biopsy for all patients who are suspected to have vasculitis, or patients who are suspected to have relapsing vasculitis.
- Induction therapy of non-organ-threatening vasculitis should include a combination of

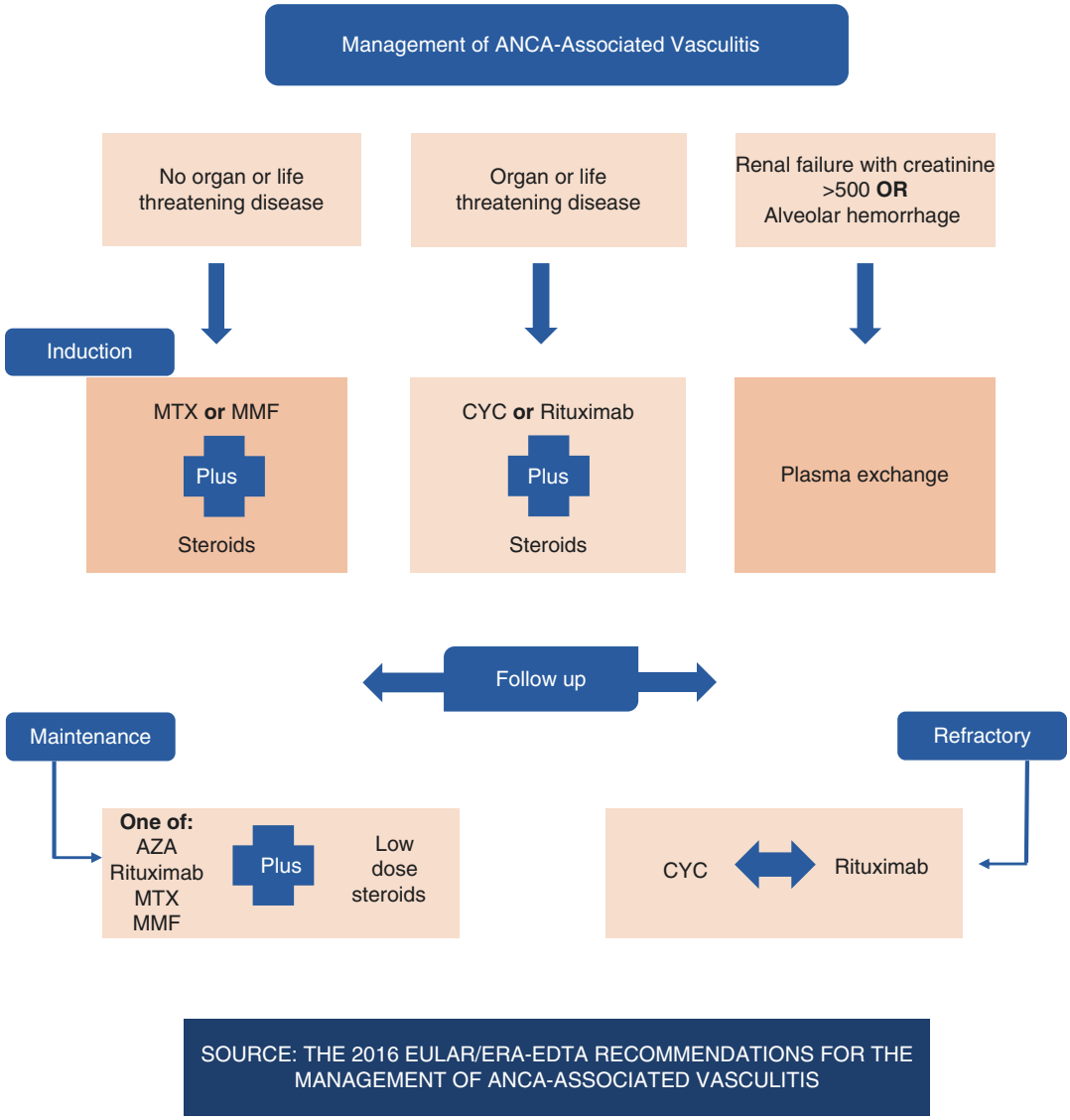


Fig. 25.19 The 2016 Eular/ERA-EDTA recommendations for the management of anca-associated vasculitis [17].

glucocorticoids and either methotrexate or mycophenolate mofetil.

- Induction therapy of organ-threatening vasculitis should include a combination of glucocorticoids and either cyclophosphamide or rituximab.
- Relapsing disease with organ-threatening vasculitis should be treated the same as new-onset organ-threatening vasculitis.
- Rapidly progressive glomerulonephritis, both new in onset and relapsing, should be treated with plasma exchange.
- Severe diffuse alveolar hemorrhage should also be treated with plasma exchange.
- For disease maintenance, it is recommended to use a combination of glucocorticoids with either azathioprine, methotrexate, mycophenolate mofetil, or rituximab. This treatment should be continued for a minimum of 24 months.
- For refractory cases, it is recommended to switch from cyclophosphamide to rituximab or from rituximab to cyclophosphamide.

25.5.3 Classification Criteria [18]

Polymyalgia rheumatica (PMR) is an inflammatory disorder that is mainly characterized by neck, shoulder, and hip girdle pain and morning stiffness. An association between PMR and giant cell arteritis (GCA) was found, which may represent a shared underlying pathogenic process.

In April of 2012, the ACR and EULAR convened and proposed PMR classification criteria that were designed to define its most important manifestations. [18].

Scoring-based criteria were made that outlined the following components:

- The presence of morning stiffness for more than 45 minutes (2 points).
- Pain in the hips with limited range of motion (1 point).
- The absence of rheumatoid factor and/or anti-citrullinated protein antibody (2 points).
- The absence of pain in the peripheral joints (1 point).

The interpretation of the PMR scoring algorithm after ruling out alternative conditions:

- The scoring scale is 0–6 (without ultrasound) and 0–8 (with ultrasound).
- A score of ≥4 (without ultrasound) or ≥ 5(with ultrasound) is suggestive of PMR.
- A score of >5 increases the sensitivity to 66% and specificity to 81%.
- Patients with a score of <4 make them less likely to have PMR.

Ultrasounds are the imaging of choice for PMR, as they are a great tool to discern between PMR and other non- inflammatory conditions. They also increase the specificity of diagnosis. These criteria need to be validated by other cohort studies as it is important to distinguish PMR from other conditions (see Table 25.1).

There are no clear guidelines for the treatment of PMR. The role of the early introduction of DMARDs in PMR is not entirely known. Currently, corticosteroids are the mainstay of treatment for PMR, although some randomized controlled trials have studied the use of immunosuppressant therapy. New trials are also studying the use of biologics with PMR (see Table 25.2) [19].

25.6 Spondyloarthritis Classification Criteria and Management Guidelines

25.6.1 Classification Criteria (Figs. 25.20, 25.21 and 25.22) (Table 25.3)

Spondyloarthritis (SpA) is an umbrella term that encompasses the following interconnected diseases: ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis, enteropathic-related spondylitis and arthritis, and

Table 25.1 Summary of EULAR/ACR 2012 classification criteria for Polymyalgia Rheumatica (PMR)

Criteria	Points without US(0-6)	Points with US (0-8)
Morming stifness duration >45 min	Two points	Two points
Hip pain or limited range of motion	One point	One point
Absence of RF or ACPA	Two point	Two points
Absence of other joint involvement	One point	One point
At least one shoulder with subdeltoid bursitis and/or biceps tenosynovitis and/or glenohumeral synovitis (either posterior or axillary) and at least one hip with synovitis and/or trochanteric bursitis	Not applicable	One point
Both shoulders with subdetoid burstis, biceps tenosynovitis or glenohumeral synovitis	Not applicable	One point

[a]A score of 4 or more is categorized as PMR in the algorithm without US and a score of 5 or more is categorized as PMR in the algorithm with US

Table 25.2 Summary of EULAR/ACR 2015 recommendation of management for Polymyalgia Rheumatica (PMR)

Management of Polymyalgia Rheumatica	
Initial glucocorticoid therapy: Prednisone 15mg daily with clinical response in 1 week and resolution of acute phase reactant in 3-4 weeks	
If no response	Dose may be increased by 5 mg day increments each week up to 30 mg/day
Follow up in 4-6 weeks	Gradual steroid tapering. Once the dose has fallen to 10 mg day, reduce the dose no faster than 1 mg per month
Relapse	• In patients who relapse while on glucocorticoids→increase glucocorticoid dose to lowest effective dose. • Relapse following discontinuation of glucocorticoids→resumption of glucocorticoids at the original dose at which control was achieved. • In patients who relapse several times→ interval between dose reductions should be increased to every two or three months.

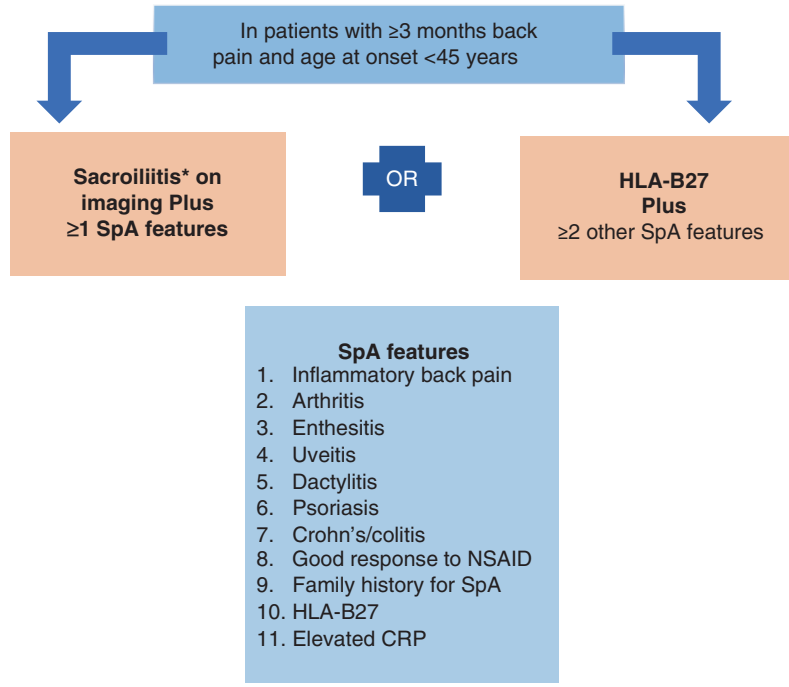


Fig. 25.20 ASAS classification criteria for axial spondyloarthritis (SpA)

undifferentiated SpA. There are many proposed classification criteria for SpA; however, they are more geared to be used in research contexts rather than clinical settings.

The most recent classification criteria developed by the Assessment of SpondyloArthritis international Society (ASAS) have determined that MRIs are the imaging modality of choice for the detection of axial and sacroiliac affection, as they are more sensitive than radiographs, especially for early disease. These changes were not mentioned in the modified New York criteria, the European Spondyloarthropathy Study Group criteria, and the Amor criteria for AS [20].

The ASAS group also proposed a definition for inflammatory back pain and criteria for classifying axial and peripheral spondyloarthritis. These criteria were designed to provide a diagnosis for patients in the early phases of their disease. The above mentioned advances were made to aid research into the use of biologic agents in early disease. ASAS also defined non-radiographic axial spondyloarthritis (nr-axSpA); this entity shares the same underlying genetic factors, disease course, and prognosis as the radiographic variant; however, it differs in its absence from detection by plain radiographs as well as a lesser degree of ossification and inflammation found both clinically and on MRIs.

25.6.2 Management Guidelines

Diagnosis of SpA is often delayed with many patients not receiving the appropriate treatment. Biological agents were found to halt the disease's progression and improve its prognosis. Treatment, however, should be tailored to each patient's specific needs [21].

ASAS-EULAR Recommendations for Management of SpA (2016 Update) [22] (Figs. 25.23 and 25.24).

The management of patients with AS should be specifically individualized for each patient according to the disease's severity and activity as well as the patient's general condition, function, disability, wishes, and expectations.

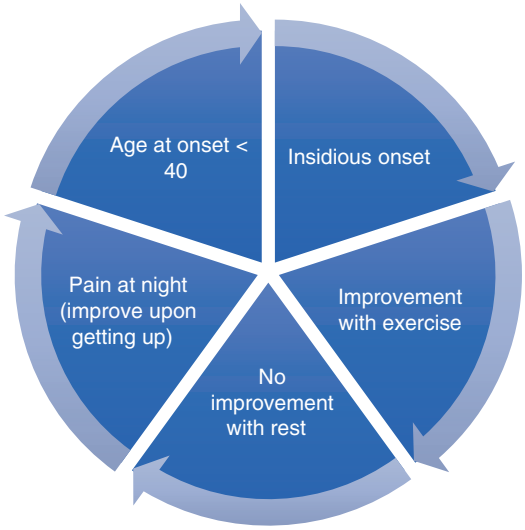


Fig. 25.21 Inflammatory back pain assessment ASAS expert criteria)

Monitoring of the patient's disease includes assessment by history, physical examination, laboratory investigation, and imaging modalities. Management options are then tailored based on this assessment and assigned to either nonpharmacologic, pharmacologic, or surgical approaches.

Nonpharmacologic strategy:

Education, regular exercise, and physiotherapy should be considered.

Pharmacologic strategy:

- Anti-inflammatory drugs are the first-line agents in patients complaining of pain and/or stiffness.
- Pain killers like paracetamol and opioids.
- Local steroid injections can be used if the patient is still in pain despite using anti-inflammatory medications.
- DMARDs can be used in extra-axial inflammatory joint pain.
- Anti-tumor necrosis factor (anti-TNF): for patients with axial disease, the use of the combination of DMARDs and anti-TNF is not necessary.
- Interleukin 17 and interleukin 12/23 inhibitors: they have been introduced in the recent ASAS-EULAR guidelines based on recent randomized controlled trials that show their efficacy in SpA.

Surgical strategy:

Total hip replacement and spinal surgery should be contemplated in patients with pain or disability that are refractory to treatment.

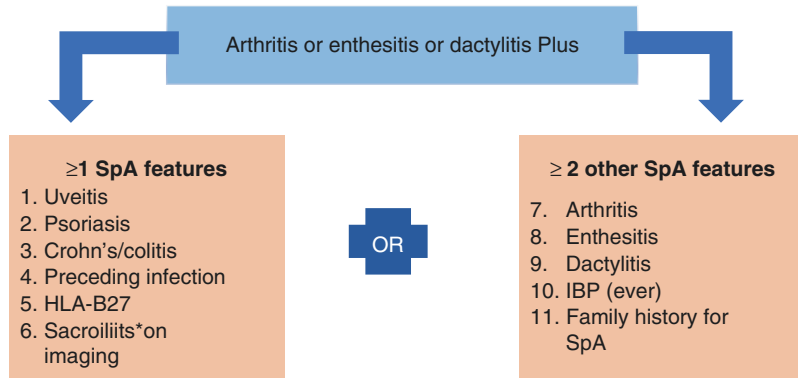


Fig. 25.22 ASAS classification criteria for peripheral spondyloarthritis (SpA)

Table 25.3 Definition of SpA features in the ASAS classification criteria for peripheral SpA

SpA feature	Definition
Entry criteria:	
Arthritis	Current peripheral arthritis compatible with SpA (usually asymmetric and/or predominant involvement of the lower limb), diagnosed clinically by a physician
Enthesitis	Current enthesitis, diagnosed clinically by a doctor
Dactylitis	Current dactylitis, diagnosed clinically by a doctor
Additional SpA features:	
IBP in the past[a]	IBP in the past according to the rheumatologist's judgement
Arthritis	Past or present peripheral arthritis compatible with SpA (usually asymmetric and/or predominant involvement of the lower limb), diagnosed clinically by a physician
Enthesis[b]	Enthesitis: Past or present spontaneous pain or tenderness on examination of an enthesis
Uveitis	Past or present uveitis anterior, confi rmed by an ophthalmologist
Dactylitis	Past or present dactylitis, diagnosed by a physician
Psoriasis	Past or present psoriasis, diagnosed by a physician
IBD	Past or present Crohn's disease or ulcerative colitis diagnosed by a physician
Preceding infection	Urethritis/cervicitis or diarrhea within 1 month before the onset of arhthritis, enthesitis or dactylitis
Family history for SpA	Presence in first-degree (mother, father, sisters, brothers, children) or second-degree (maternal and paternal grandparents, aunts, uncles, nieces, and nephews) relatives of any of the following: ankylosing spondylitis, psoriasis, acute uveitis, reactive arthritis or IBD
HLA-B27	Positive testing according to standard laboratory techniques
sacroiliitis by imaging	Bilateral grade 2–4 or unilateral grade 3–4 sacroiliitis on plain radiographs, according to the modified New York criteria, or active sacroiliitis on MRI according to the ASAS consensus definition

ASAS, Assessment of SpondyloArthritis International Society; HLA-B27, human leucocyte antigen B27; IBD, inflammatory bowel disease; IBP, inflammatory back pain; SpA, spondyloarthritis.
[a]Here, only IBP in the past is considered. In patients with current IBP (and concomitant peripheral manifestations), the ASAS classifi cation criteria for axial SpA should be applied
[b]Any site of enthesitis can be affected whereas in the ASAS classification criteria for axial SpA only enthesitis of the head is considered

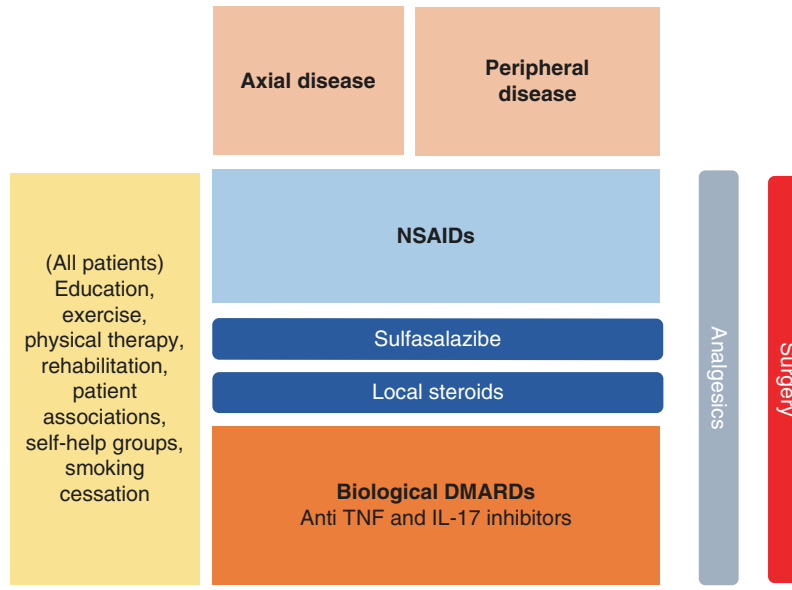


Fig. 25.23 ASAS-EULAR recommendations for the management of axial and peripheral spondyloarthritis) ASAS-EULAR recommendations for the treatment of patients with axSpA with bDMARDs.

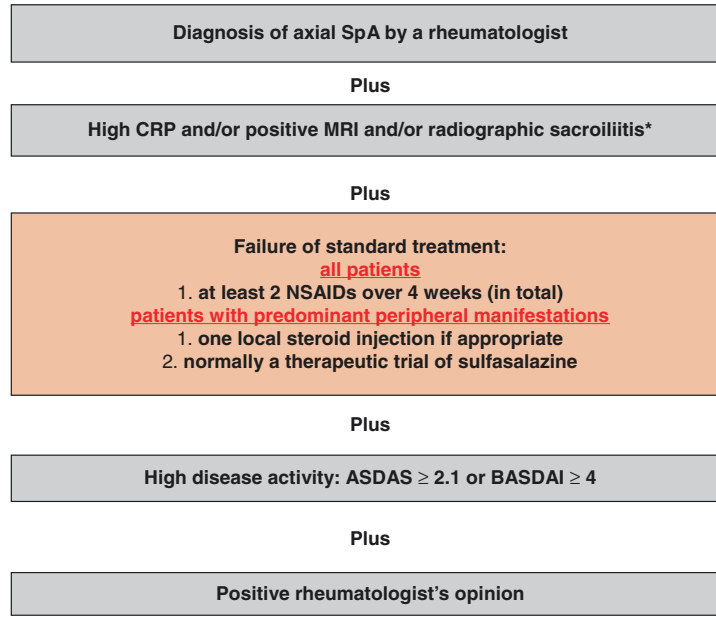


Fig. 25.24 ASAS-EULAR recommendations for the treatment of patients with axSpA with bDMARDs)

Table 25.4 Classification Criteria for Psoriatic Arthritis (CASPAR)

Classification criteria for psoriatic arthritis (CASPAR)		
Inflammatory articular disease (joint, spine or entheseal) with ≥ 3 of the following:		
1. Evidence of psoriasis: (one of a,b,c)	a. Current psoriasis	Psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist
	b. Personal history of psoriasis	A history of psoriasis that may be obtained from patient, family doctor, dermatologist, rheumatologist, or other qualified health-care provider
	c. Family history	A history of psoriasis in a first or second degree relative according to the patient's reporting
2. Psoriatic nail dystrophy	Typical psoriatic nail dystrophy including onycholysis, pitting and hyperkeratosis observed on current physical examination	
3. A negative rheumatoid factor	By any method except latex but preferably by ELISA or nephelometry, according to the local laboratory reference range	
4. Dactylitis (a or b)	a. Current swelling of entire digit b. A history of dactylitis recorded by a rhematologist	
5. Radiological evidence of juxta-articular new bone formation	III-defined ossification near joint margins (but excluding osteophyte formation) on plain X-rays of hands or feet	

25.7 Psoriatic Arthritis Classification Criteria and Management Guidelines (Table 25.4) (Fig. 25.25)

25.7.1 Classification Criteria

Psoriatic arthritis (PsA) is an inflammatory joint disease with heterogeneous presentation patterns representing different clinical subcategories. Many classification criteria have been put forth but they were not used widely and have not been validated. The presence of these different presentation patterns has made it difficult to propose and validate classification criteria for the diagnosis of PsA, especially with disease patterns like seronegative polyarthritis and psoriasis.

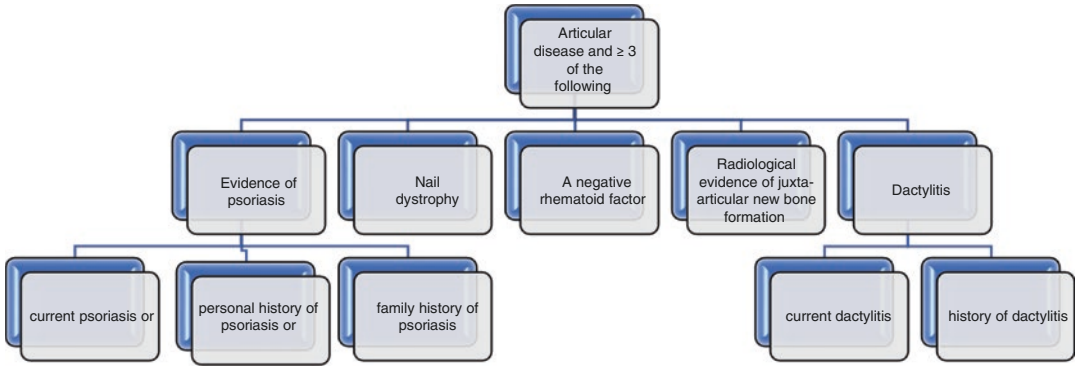


Fig. 25.25 Summary of the Classification Criteria of Psoriatic Arthritis

Older criteria, such as the Moll and Wright classification criteria for PsA that were proposed in 1973, do not offer a clear distinction between RA and PsA. The Fourni criteria that were proposed in 1999 were the first to be formulated based on patients' data; however, they require HLA-B27 positivity which excludes around 24% of patients who have the disease but test negative for HLA-B27. ClASsification for Psoriatic ARthritis (CASPAR) criteria are a congregation of international authorities who were successful in creating validated classification criteria in 2004. These criteria are highly sensitive and specific (specificity 99% and sensitivity 92%) and have allowed for the diagnosis of PsA even in the absence of arthritis if manifestations like dactylitis and enthesitis are present. PsA can also be diagnosed despite the presence of low RF positivity. The absence of psoriasis is allowed as these criteria incorporate family history; therefore, a diagnosis can be established if other typical features are present [23].

25.7.2 Management Guidelines

A list of ten recommendations were proposed for the management of articular and extra-articular features of PsA. Treatments mentioned comprise of NSAIDs, synthetic DMARDs, and biological therapies. These recommendations are aimed to give a combined evidence-based and expert opinion approach to tackle this disease in the most optimal way and to provide the best outcomes.

Summary of European League Against Rheumatism recommendations for the management of psoriatic arthritis with pharmacological therapies (2015) [24] (Fig. 25.26).

Table 25.5 The old ACR classification criteria for systemic sclerosis [26])

Criterion	Definition
Major criterion	Proximal scleroderma
Or two of the minor criterions:	
Minor criteria	1. Sclerodactyly 2. Digital pitting scars of fingers or loss of the distal finger pad 3. Bilateral basilar pulmonary fibrosis
The proposed criteria had a 97% sensitivity for definite systemic sclerosis and a 98% specificity	

25.8 Systemic Sclerosis Classification Criteria and Management Guidelines

25.8.1 Classification Criteria of Systemic Sclerosis (Tables 25.5, 25.6 and 25.7)

ACR developed classification criteria for systemic sclerosis (SSc) in 1980. One major and two minor criteria are required to diagnose SSc. As these criteria had a strong emphasis on skin manifestations

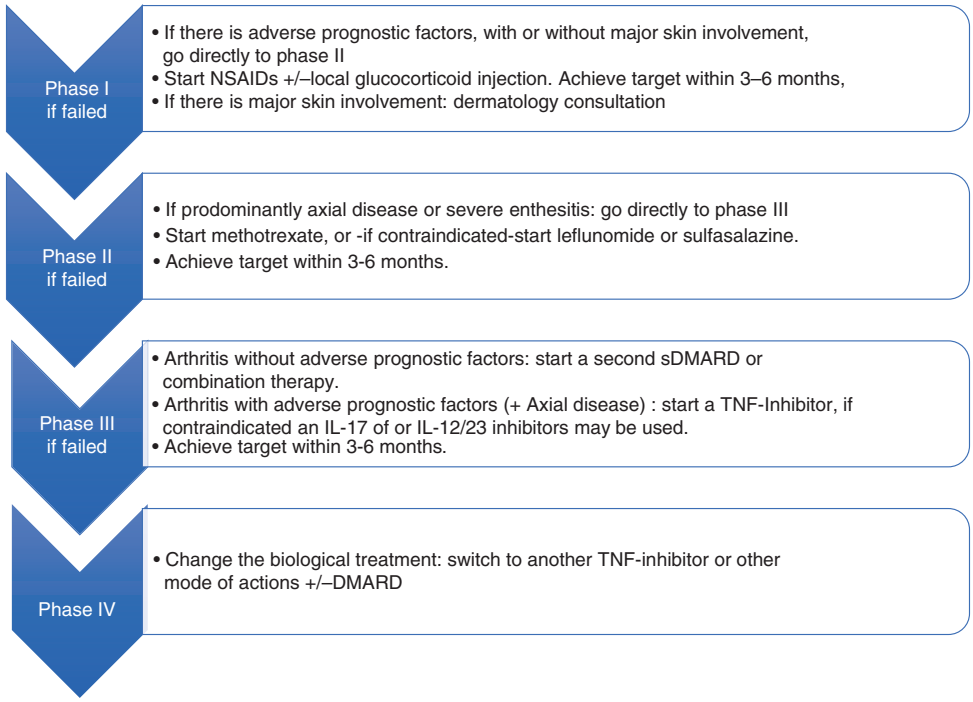


Fig. 25.26 Summary of EULAR 2015 recommendations for the management of psoriatic arthritis

Table 25.6 The American College of Rheumatology/European League Against Rheumatism criteria for the classification of systemic sclerosis (SSc)[a]

Manifestation	Additional manifestation	Weight/ score[b]
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints (sufficient criterion)	-	9
Skin thickening of the fingers (only count the higher score)	Puffy fingers	2
	Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	4
Fingertip lesions (only count the higher score)	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia	-	2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or interstitial lung disease (maximum score is 2)	-	2
Raynaud phenomenon	-	3
SSc-related autoantibodies (anticentromere, antitopoisomerase I [anti-Scl-70], anti-RNA polymerase III) (maximum score is 3)	-	3

[a]These criteria are applicable to any patient considered for inclusion in an SSc study. The criteria are not applicable to patients with skin thickening sparing the fingers or to patients who have a scleroderma-like disorder that better explains their manifestations (e.g., nephrogenic sclerosing fibrosis, generalized morphea, eosinophilic fasciitis, scleredema diabeticorum, scleromyxedema, erthromyaglis, porphyria, lichen sclerosis, graft-versus-host disease, diabetic cheiroarthropathy)
[b]The total score is determined by adding the maximum weight (score) in each category. Patients with a total score ≥ 9 are classified as having definite SSc

Table 25.7 Definitions of manifestations in the American College of Rheumatology/European League Against Rheumatism criteria of the classification of systemic sclerosis (SSc)

Manifestation	Definition
Skin thickening	Skin thickening or hardening not due to scarring after injury, trauma, etc.
Puffy fingers	Swollen digits: a diffuse, usually nonpitting increase in soft tissue mass of the digits extending beyond the normal confines of the joint capsule. Normal digits are tapered distally with the tissues following the contours of the digital bone and joint structures. Swelling of the digits obliterates these contours. Not due to other causes such as inflammatory dactylitis.
Fingertip ulcers or pitting scars	Ulcers or scars distal to or at the proximal interphalangeal joint not thought to be due to trauma or exogenous causes.
Telangiectasiae	Telangiectasiae are visible macular dilated superficial blood vessels, which collapse upon pressure and fill slowly when pressure is released. Telangiectasiae in a scleroderma-like pattern are round and well demarcted and founds on hands, lips, inside of the mouth, and/or are large mat-like telangiectasiae. Distinguishable from rapidly filling spider angiomas with central arteriole and from dilated superficial vessels.
Abnormal nailfold capillary pattern consistent with systemic sclerosis	Enlarged capillaries and/or capillary loss with or without pericapillary hemorrhages at the nailfold. May also be seen on the cuticle.
Pulmonary arterial hypertension	Pulmonary arterial hypertension diagnosed by right-sided heart catheterization according to standard definitions.
interstitial lung disease	Pulmonary fibrosis seen on high-resolution computed tomography or chest radiography, most pronounced in the basilar portions of the lungs, or occurrence of "Velcro" crackles on examination.

rather than the vascular or immunologic features that predate Raynaud's phenomenon, it became evident that it lacked proper sensitivity and specificity when it came to diagnosing early disease.

The ACR and EULAR collaborated to develop a revised classification criteria in 2013 to improve the older criteria's lower sensitivity and specificity rates in diagnosing early SSc and limited cutaneous SSc [25]. These criteria may be used for the inclusion of patients in SSc trials; however, it may be less efficient in patients with scleroderma-like syndromes.

25.8.2 Management Guidelines of Systemic Sclerosis (Table 25.8)

There is still a lot to be discovered in terms of the pathogenesis of SSc disorders. Treatment is challenging and no cure has yet been found. Previously, SSc trials were found to be subpar, with many based on single centers with insufficient recruitment numbers and poor randomization and control. They also did not take into account the many variable subsets and stages of the disease.

The past 10 years has witnessed significant advances in the field of SSc treatment, and many clinical trials have been documenting the efficacy of different treatment modalities. However, there are many obstacles that still stand in the way of conducting quality clinical trials, they include the following:

- SSc is an uncommon disease and can present with variable features.
- Progression rates vary between the different subsets of the disease.
- Treatment varies based on the organ that is involved.
- Disease monitoring measures are not very accurate in detecting slower incremental changes.

25.8.3 Dermatomyositis and Polymyositis Classification Criteria and Management Guideline

There have been many proposed classification criteria for dermatomyositis (DM) and polymyositis (PM). Brohan and Peter executed one of

Table 25.8 Summary of 2016 EULAR recommendations for treatment of systemic sclerosis, according to the organ involvement [26]

Digital ulcers in patients with SSc	Intravenous iloprost should be considered in the treatment of digital ulcers in patients with SSc.	A
	PDE-5 inhibitors should be considered in the treatment of digital ulcers in patients with SSc.	A
	Bosentan should be considered for reduction of the number of new digital ulcers in SSc, especially in patients with multiple digital ulcers despite use of calcium channel blockers, PDE-5 inhibitors or iloprost therapy.	A
SSc-PAH	Several ERA (ambrisentan, bosentan and macitentan), PDE-5 inhibitors (sildenafil, tadalafil) and riociguat have been approved in the treatment of PAH associated with CTDs. ERA, PDE-5 inhibitors or riociguat should be considered to treat SSc-related PAH.	B
	Intravenous epoprostenol should be considered for the treatment of patients with **severe** SSc-PAH (class III and IV).	A
	Prostacyclin analogues (iloprost, treprostinil) should be considered for the treatment of patients with SSc-PAH.	B
Skin and interstitial lung disease (SSc-ILD)	Methotrexate may be considered for treatment of skin manifestations of early diffuse SSc.	A
	Despite its known toxicity, cyclophosphamide should be considered for treatment of SSc-ILD, in particular for patients with SSc with progressive ILD.	A
	HSCT should be considered for treatment of selected patients with rapidly progressive SSc at risk of organ failure. In view of the high risk of treatment-related side effects and of early treatment-related mortality, careful selection of both patients and experienced medical teams are of key importance.	A
Scleroderma renal crisi (SRC)	Experts recommend immediate use of ACE inhibitors in the treatment of SRC.	C
	Because several retrospective studies suggest that glucocorticoids are associated with a higher risk of SRC, blood pressure and renal function should be carefully monitored in patients with SSc treated with glucocorticoids.	C
SSc-related gastrointestinal disease	Experts recommend that PPI should be used for the treatment of SSc-related GERD and for the prevention of oesophageal ulcers and strictures	C
	Experts recommend that prokinetic drugs should be used for the management of SSc-related symptomatic motility disturbances (dysphagia, GERD, early satiety, bloating, pseudo-obstruction, etc).	C
	Experts recommend the use of intermittent or rotating antibiotics to treat symptomatic small intestine bacterial overgrowth in patients with SSc.	D

CTD, connective tissue disease; ERA, endothelin receptor antagonists; EULAR, European League against Rheumatism; GERD, gastro-oesophageal reflux disease; HSCT, haematopoietic stem cell transplantation; PAH, pulmonary arterial hypertension; PDE-5, phosphodiesterase type 5; PPI, proton pump inhibitor; SRC, scleroderma renal crisis; SSc, systemic sclerosis; SSc-RP, Raynaud's phenomenon in patients with SSc

the earliest criteria in 1975, which had been used to aid in research for several decades. These criteria demanded the presence of typical skin manifestations and at least three out of four other criteria to meet the diagnosis of DM. Patients who were diagnosed with PM had to have met all four criteria in addition to the cutaneous features. As there are no highly specific autoantibodies, biopsy and histological proof remain important diagnostic tools. There are limitations with these criteria as research studies conducted on PM/DM are scarce, making the classification of these diseases difficult in addition to the poor understanding of the relationship between DM and PM.

The discovery of at least eight antisynthetase autoantibodies had allowed for significant advances in diagnosing DM and PM, especially as these autoantibodies were all associated with different manifestations of the disease (see chapter "Diagnostic Approach to Proximal Myopathy").

25.8.4 Summary of Polymyositis and Dermatomyositis Classification Criteria [27] (Fig. 25.27)

Management of inflammatory myositis is difficult due to the scarcity of randomized controlled trials and the fact that the disease is very uncommon. Treatment includes:

- Glucocorticoids, immunoglobulins, and the newly included mycophenolate mofetil.
- Mycophenolate mofetil and rituximab which were found to be efficient in refractory cases.
- Anti-tumor necrosis factor (anti-TNF) inhibitors which were also found to be useful in treating resistant cases.

In general, there are limited data upon which the base treatment recommendations for DM and PM are provided.

25.8.5 Sjögren's Syndrome Classification Criteria and Management Guidelines (Table 25.9)

The ACR proposed classification criteria for Sjögren's syndrome (SS). These criteria were based on evidence from the Sjogren's International Collaborative Clinical Alliance (SICCA) and also on the knowledge of field authorities; it is easily applicable and based mostly on objective testing.

At least two of the following items need to be present to diagnose SS:

- Positive serum anti-SSA and/or anti-SSB or positive rheumatoid factor plus antinuclear antibodies ≥1:320.
- Ocular staining score ≥ 3.
- Labial salivary gland biopsy showing focal lymphocytic sialadenitis with a focus score ≥ 1 foci/4 mm^2 [28].

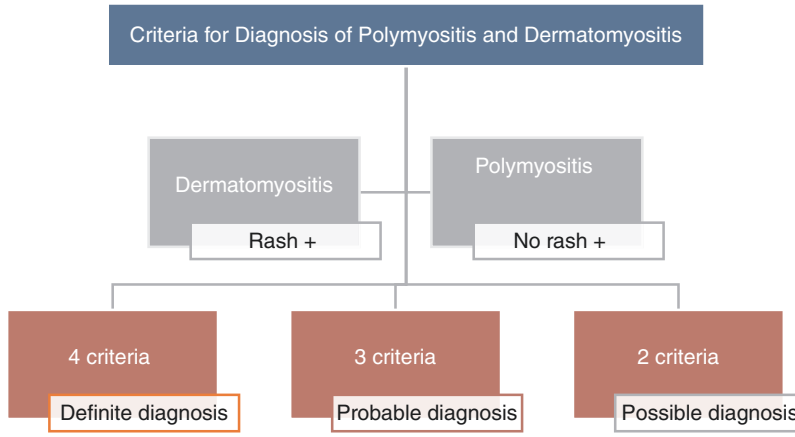
Table 25.9 ACR classification criteria for Sjogren's syndrome

Criteria of Sjogren disease	
3	Labial salivary gland with focal lymphocytic sialadenitis & focus score ≥1
3	Positive anti Ro/La
1	Ocular staining score ≥5
1	Schirmer's test ≤ 5mm/ 5minutes in at least 1 eye
1	Unstimulated whole saliva flow rate ≤0.1 ml /minute

• The criteria applies to those who meet the inclusion criteria with a score of at least 5 and to those who do not fulfil any of the exclusion criteria

• Exclusion criteria include:

• History of head and neck radiation treatment
• Active hepatitis c infection
• AIDS
• Sarcoidosis
• Amyloidosis
• Graft-verus-host diease
• IgG4-related diease



Inclusion criteria:	Symmetrical proximal muscle weakness
	Elevated muscle enzymes
	Characteristic EMG abnormalities
	Necrosis, phagocytosis, regeneration and inflammtion in the muscle biopsy
	Gottron's sign or heliotrope rash or papules in dermatomyositis
Exclusion criteria:	Motor neuron diease
	Myasthenia gravis
	Infectious causes
	Granulomatous disease
	Endocrine causes
	Toxic causes

Fig. 25.27 Criteria for the diagnosis of polymyositis and dermatomyositis

There is no single medication available that has been proven to be effective in SS in randomized controlled trials. Treatment at this moment is mainly symptomatic, supportive, and empiric.

In a subset of patients in which arthralgia is a major symptom, some clinicians prescribe antimalarials (hydroxychloroquine). More recently, biological therapies are studied for their potential efficacy in early SS. Therefore, proper patient detection in the early stages of the disease is important.

B-cell targeting with either rituximab or belimumab has been studied, and a study with epratuzumab is planned for the near future [29]. Until now, no immunomodulatory drugs have been proved to be effective in primary SS.

25.8.6 Behcet's Disease Classification Criteria and Management Guidelines

Behcet's disease (BD) is an inflammatory disease that runs a relapsing and remitting course. The pathogenesis is not entirely known and no conclusive diagnostic tests have been found. The diagnosis relies on clinical grounds.

A group of physicians responsible for the treatment of large numbers of patients with BD formed the International Study Group (ISG) and published the ISG criteria for diagnosis in 1990. The utility of the criteria is dependent on the prevalence of the syndrome in the background population; there may also be atypical patients

who do not fulfill the criteria. These criteria are meant for the classification of groups of patients participating in research programs to ensure comparability of the groups, and not for the diagnosis of the individual patients in clinical situations.

25.8.7 Diagnostic Criteria for Behcet's Disease, International Study Group for Behcet's Disease (1990) (Tables 25.10 and 25.11)

Treatment of BD is mainly based on evidence that were gleaned from case reports and case series with a paucity of randomized controlled trials. Management relies both on organ dysfunction and on the degree of dysfunction. As patients mostly have multisystemic dysfunction, management is thus dictated by the most critical organ that is involved.

Since 1998, there have been only a small number of advances in the quality of BD literature. These include significant benefits found in randomized trials of colchicine, mucocutaneous disease, and the introduction of anti-TNF-alpha therapy. Most current approaches with other medications are dictated primarily by extrapolation of the use of certain medications from their efficacy in other inflammatory conditions.

The EULAR and the task force of the EULAR Standing Committee for Clinical Affairs (ESCCA) proposed a list of treatment recommendations in 2008. This list was primarily derived from a systematic review that was conducted in 2006. The treatments of all facets of BD were outlined in nine recommendations. Recommendations regarding the management of ocular, mucocutaneous, and musculoskeletal were based on stringent evidence. However, manifestations that affect the vascular, neurological, and gastrointestinal systems were derived from data that is of a lesser quality, including open trials, observational studies, and expert opinions. There is a significant need for more research to cover all areas that are deficient in this disease [30].

25.8.8 Gout Classification Criteria and Management Guidelines [31] (Box 25.2)

Gout is considered to be one of the most common inflammatory arthritis. It is characterized by the deposition of monosodium urate crystals in the extracellular fluid. The diagnosis of gout is sug-

Table 25.10 Diagnosis criteria for Behcet's disease

Criteria of Behcet's diease	
2	Ocular lesions
2	Genital aphthosis
2	Oral aphthosis
1	Skin lesion
1	Neurological manifestations
1	Vascular manifestations
1	Positive pathergy test

• *4 points or more diagnose Behcet diease

Table 25.11 EULAR recommendations for the management of Behcet's disease

Managment of Behcet's diease	
Arthritis /ertyhaema nodosum	Cholchicine
Posterior eye diease	Corticosteriod & azathioprine(AZA)
Retinal diease	Ciclosporine or infliximab ±corticosteriod & AZA
Venous thrombosis	Immunosuppressive
Pulmonary or arterial aneurysms	Cyclophosphamide and corticosteriod
GI involvment	Sulfasalazine, corticosteriod, azathioprine, TNFα antagonist before surgery
CNS inlvoment	Corticosteriod, AZA, TNFα antagonist cyclophosphamide Ciclosporin A not recomended
Resistant cases	AZA, IFNα and TNFα antagonist

• *2008 EULAR recommendations of management for Behcet disease

gested by the presence of typical clinical features along with increased urate levels in the serum. However, coincidentally found high serum urate concentrations could also occur in other causes of acute arthritis.

The 2014 guidelines [31] provide practical recommendations which are supported by evidence-based practice in addition to the opinions of a large number of multinational expert rheumatologists. This is called the 3e (Evidence, Expertise, Exchange) Initiative.

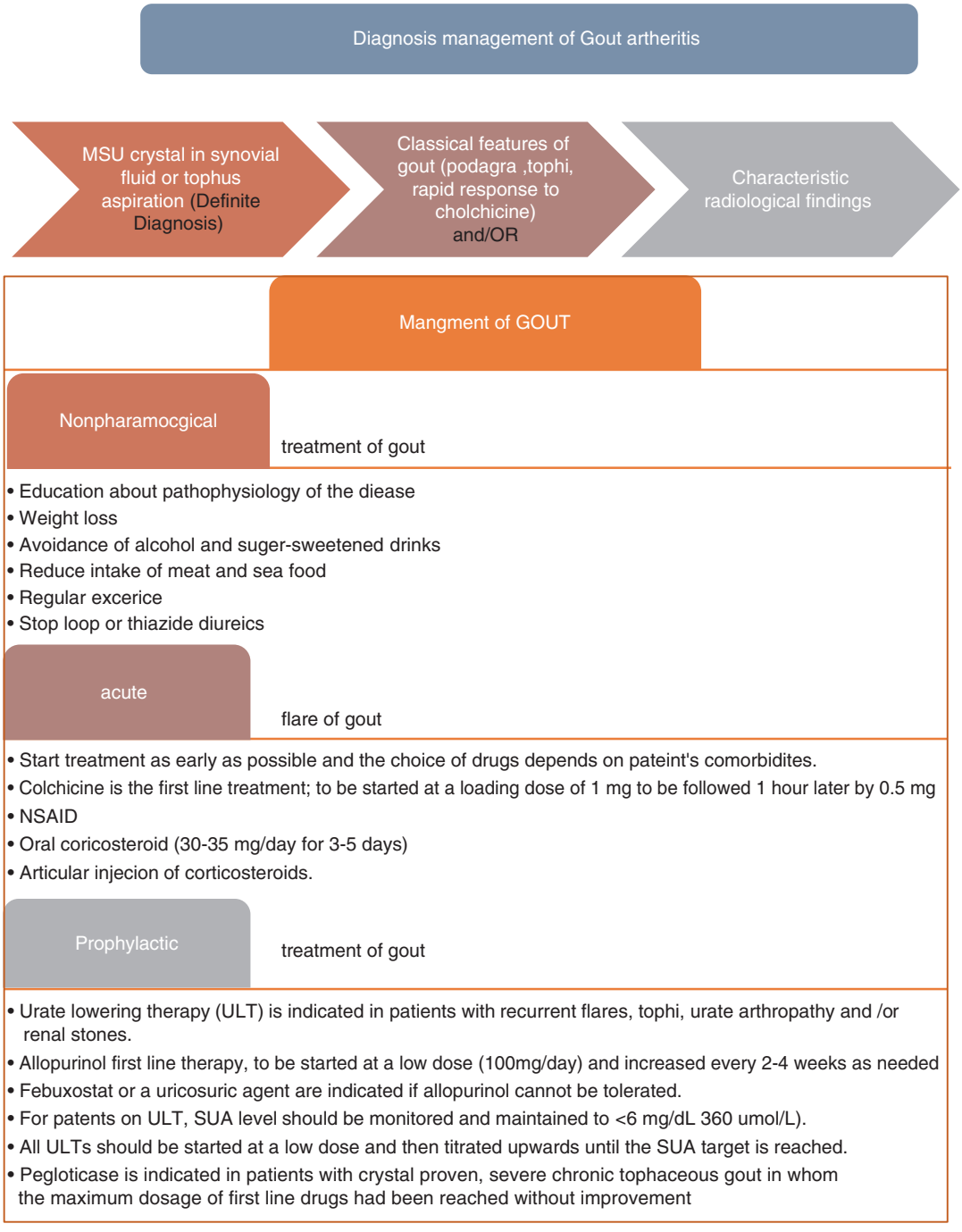
In these recommendations, they emphasize the finding of monosodium urate crystals in synovial fluid as a crucial step for definitive diagnosis of gout.

The 3e Initiative differs from the 2012 ACR guidelines in two recommendations:

1. Kidney function should be assessed in patients with high uric acid levels and/or gout. Measurements of the patient's cardiovascular risk factors are also suggested. In the previous 2012 guideline, it was not necessary to assess for cardiovascular risk factors or renal function status.
2. It was suggested that allopurinol be used as the first-line urate-lowering therapy.

All xanthine oxidase inhibitors were previously considered as first-line choices for therapy. However, now allopurinol is the first-line agent with alternatives including uricosurics or febuxostat. The use of uricase on its own can be used in severe and refractory cases where other lines were either exhausted or contraindicated.

It is important to mention the limitations of these guidelines. Three limitations were mentioned: first, there were no participants from other specialties like nephrology so, the applicability of these recommendations is not clear. Second, many recommendations have different statements with variable degrees of supporting evidence. Lastly, agreement on these recommendations was variable which suggests some degree of dispersion. However, around more than 80% of rheumatologists voted in support of these recommendations.



Box 25.2: 2016 EULAR recommendation of gout management

2016 EULAR recommendation of gout management

Box 25.2 Multinational Recommendations on the Diagnosis and Management of Gout

25.9 Osteoarthritis Classification Criteria and Management Guidelines

25.9.1 Classification Criteria (Fig. 25.28)

Osteoarthritis (OA) is a chronic musculoskeletal disease that often leaves the patients suffering from pain and disability. OA may be classified as primary or secondary. Optimal management requires early diagnosis.

The ACR formulated classification criteria for OA, and although they are highly specific when applied and allow for the discernment between patients with inflammatory arthritis and patients with osteoarthritis, they have lower sensitivity rates, especially if the differentiation between

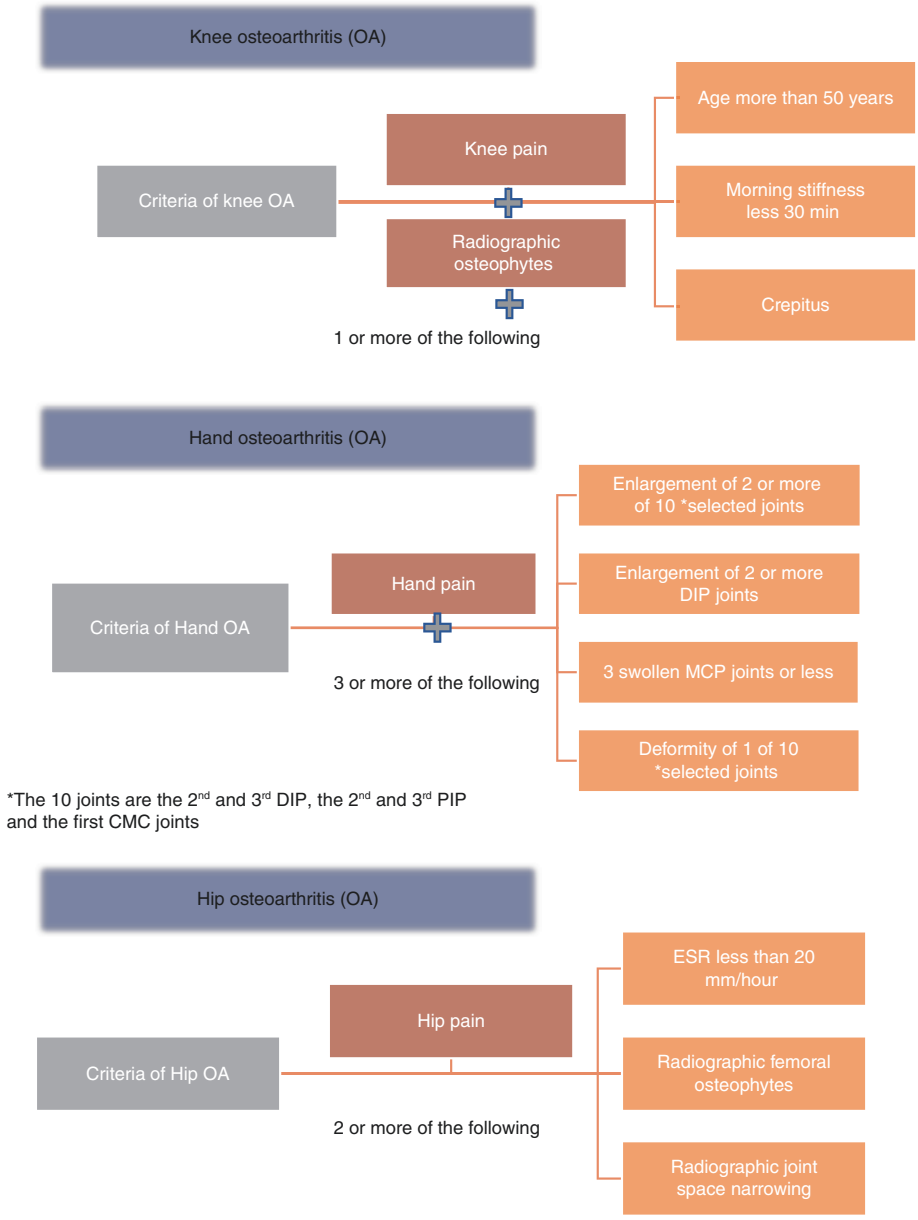


Fig. 25.28 ACR classification criteria for osteoarthritis (OA) [32, 33, 34]

patients who are in the early stages of their disease and healthy subjects is sought.

Another set of recommendations was developed by the EULAR which showed that hand and knee OA can be diagnosed using clinical assessment alone. The EULAR guidelines include ten recommendations which were derived from a systematic review of literature and the opinions of experts in the field. They stipulate that the presence of symptoms including knee pain, brief morning stiffness, and disturbances in functionality along with clinical signs including knee crepitus, limitation of range of motion, and enlargement of bones would suffice to make a diagnosis without the need to proceed for any imaging modalities. This approach would benefit primary care physicians the most. However, plain radiographs and further imaging can be done if the presentation is atypical or other differentials are considered.

25.9.2 Osteoarthritis Management Guidelines [35] (Figs. 25.29, 25.30 and 25.31)

Research regarding the management of osteoarthritis is still scarce. The disease is primarily managed using a consensus of opinions from experts in the field. The EULAR has formulated a list of treatment recommendations in 2010 which was derived from both experts' opinions and research evidence. The list covers the treatment of the hand, hip, and knee OA. In determining the strength of recommendation for any treatment, many factors other than efficacy need to be considered, including safety, cost, logistics of delivery, and the individual patient's acceptability.

25.9.2.1 Osteoporosis Classification Criteria and Management Guidelines [36–41] (Table 25.12) (Box 25.3) (Fig. 25.32)

Osteoporosis is characterized by decreased bone mass and disruption in musculoskeletal microarchitecture leading to bone fragility and higher risks of fracture. The disease often remains undetected until a fracture develops. Osteoporosis is confirmed either by the occurrence of a fragility fracture in the hip or spine or by confirmation of decreased bone density by bone mineral density (BMD) measurements. The definitions of osteopenia and osteoporosis based on BMD testing were defined by the World Health Organization (WHO).

Risk stratification for osteoporosis is imperative in all adults. BMD-independent factors that should be kept in consideration include older age, previous occurrences of fragility fractures, use of steroids, smoking and alcohol consumption, and a positive family history of fracture. There are recommendations about when to do BMD screening to detect osteoporosis and when to repeat BMD testing.

The Fracture Risk Assessment Tool (FRAX) was proposed by the WHO in 2008; this tool helps to determine the 10-year risk of hip fractures or major fragility fractures. However, as the association between decreased bone mass and fractures in premenopausal women is not as well studied as the one in postmenopausal women, bone mineral density criteria and management guidelines may not be as useful in the premenopausal women population.

Ruling out secondary causes of osteoporosis is imperative. Management guidelines include non-pharmacological lines of therapy and phar-

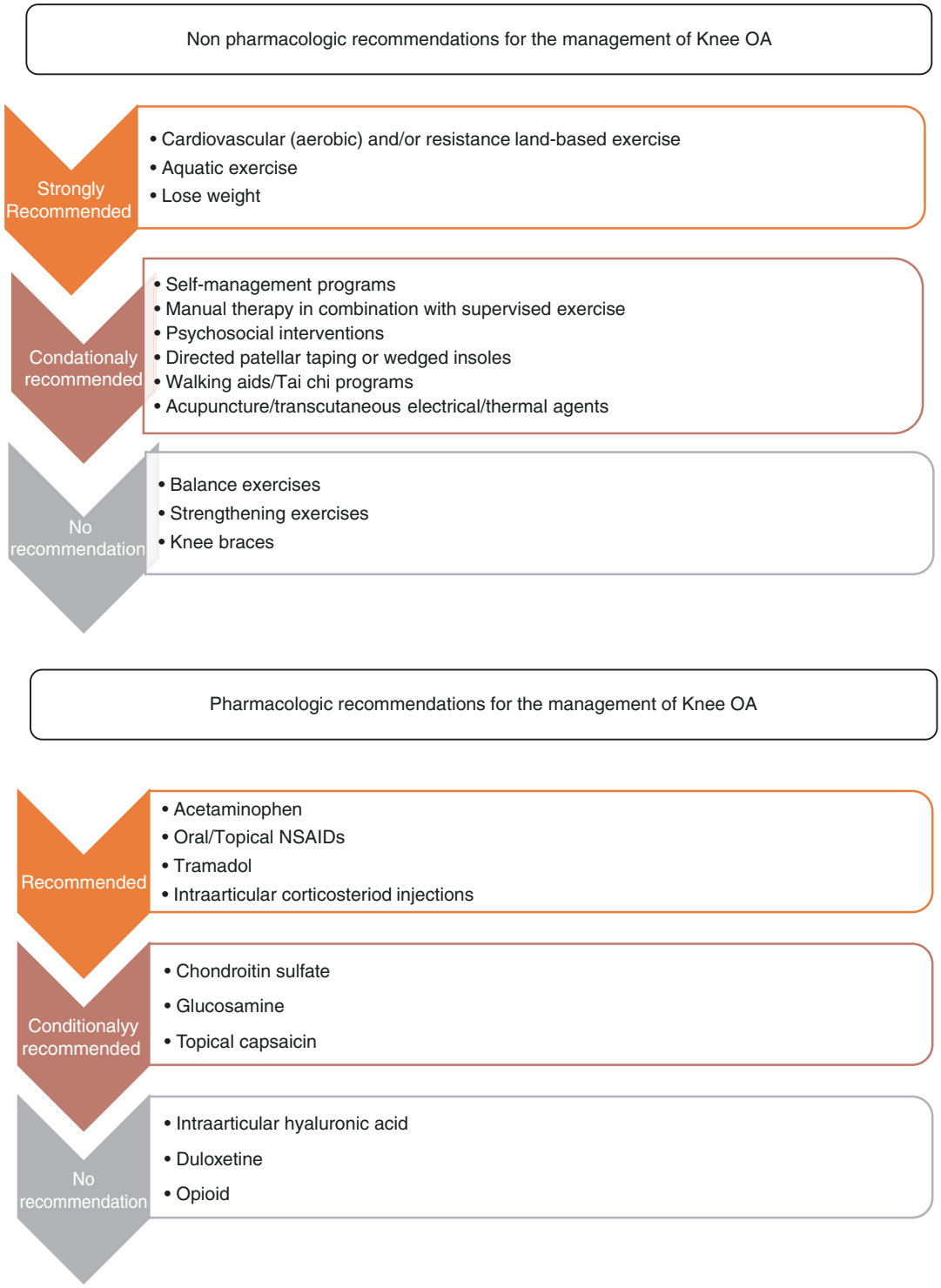


Fig. 25.29 Nonpharmacologic and pharmacological recommendations for the management of knee OA*

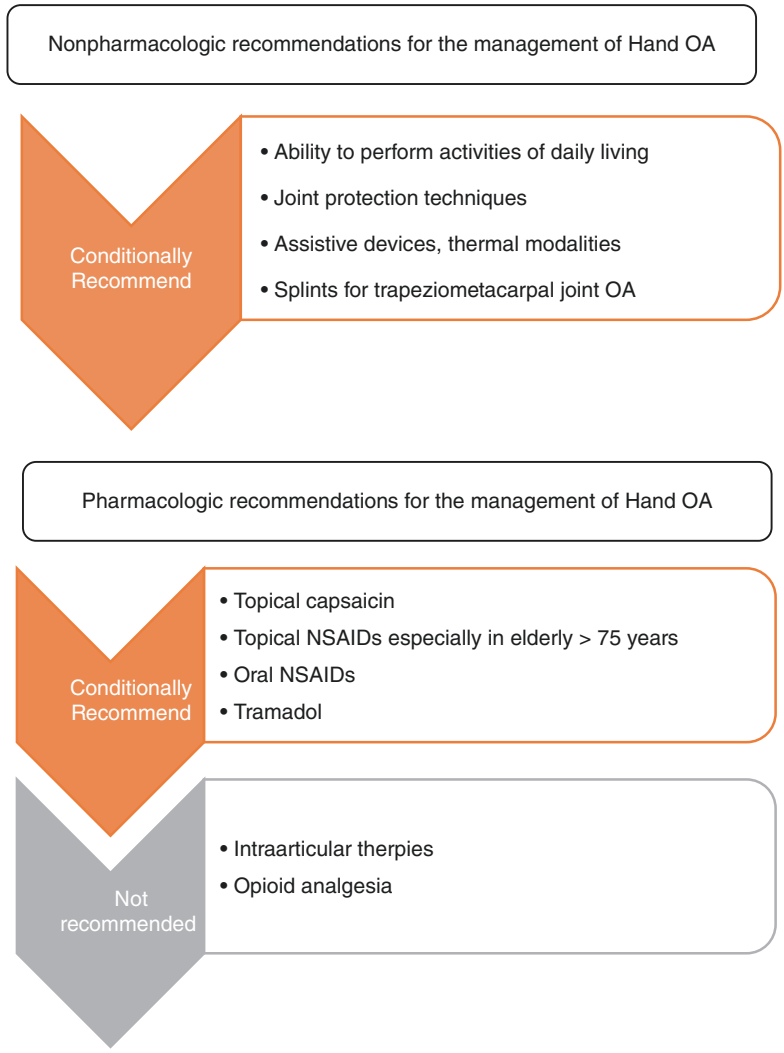


Fig. 25.30 Nonpharmacologic and pharmacological recommendations for the management of hand OA

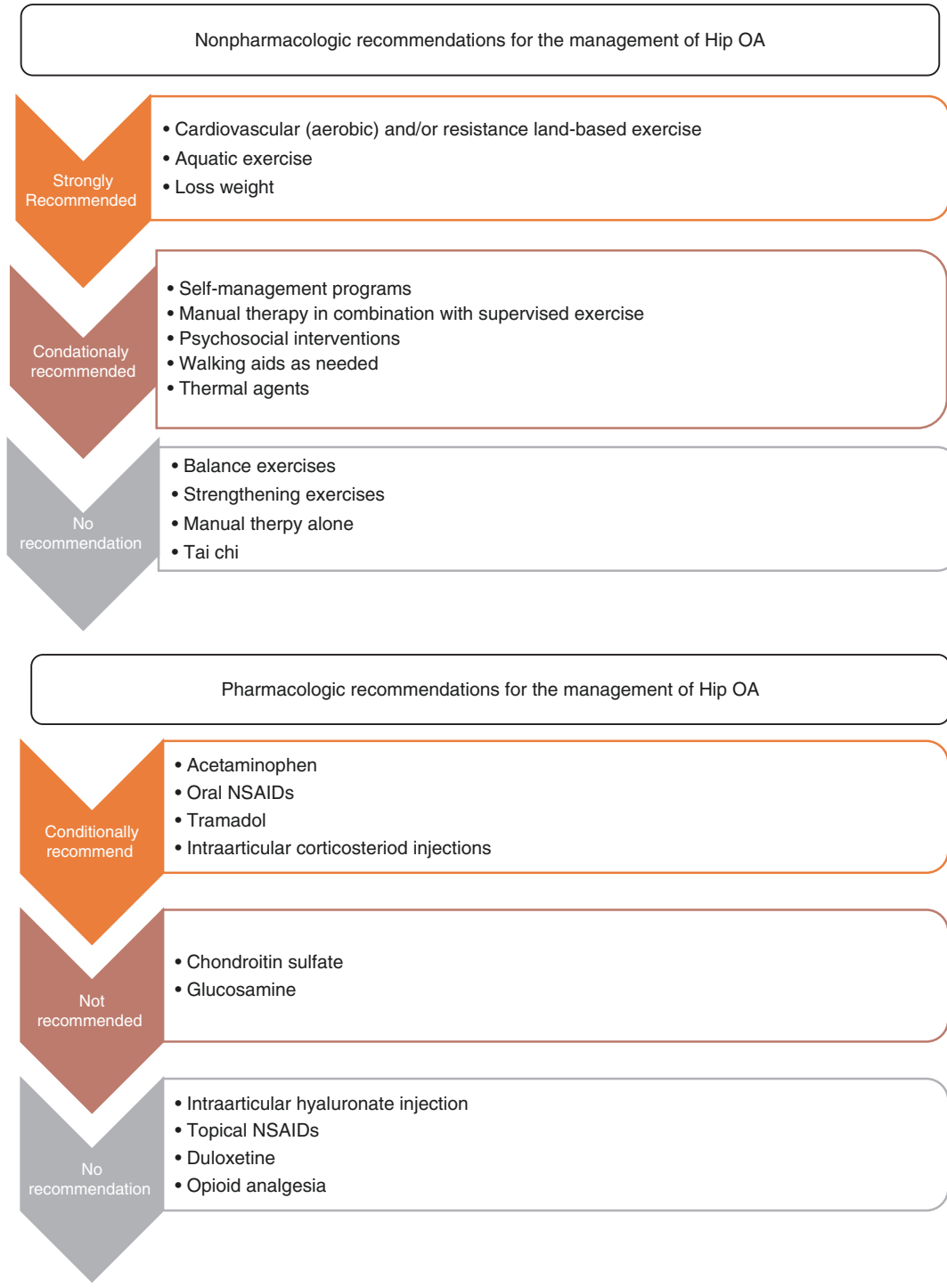


Fig. 25.31 Nonpharmacologic and pharmacological recommendations for the management of hip OA*

Table 25.12 Defining osteoporosis by BMD WHO definition of osteoporosis based on BMD

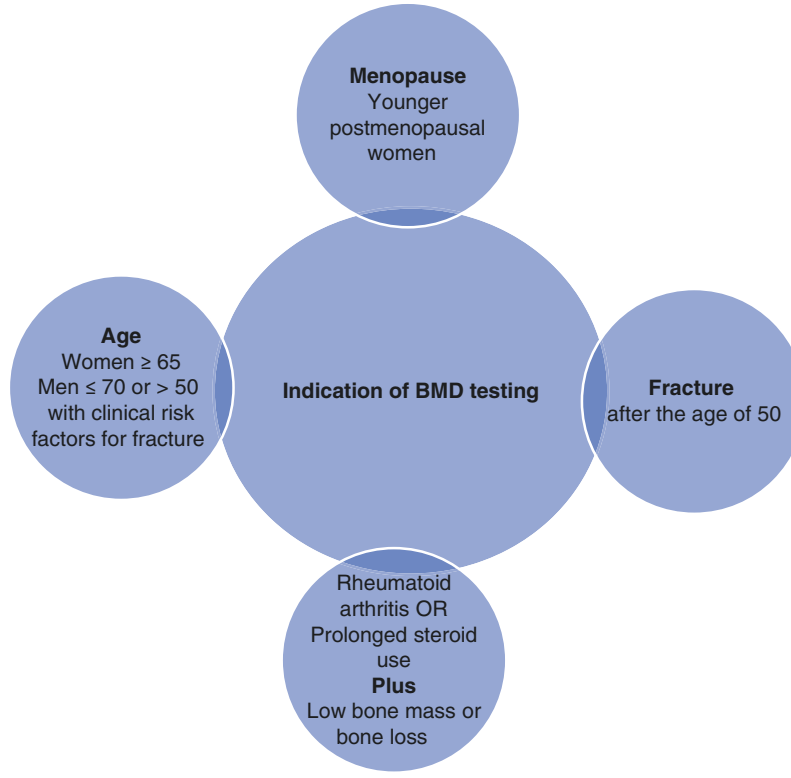
Classification	Normal	Osteopenia	Osteoporosis	Severe Osteoporosis
BMD (the SD of a young adult reference population)	Within 1 SD	1 to 2.5 below the SD	2.5 or more below the SD	2.5 or more below the SD
T-score	-1 and above	-1 to -2.5	-2.5 and below	-2.5 and below with a fracture

Box 25.3 Factors That Identify People Who Should Be Assessed for Osteoporosis

Risk Factors of Osteoporosis

- Age above 65 years
- Low body weight
- Early menopause
- Fractures: vertebral compression fracture, fragility fracture, family history of osteoporotic fracture.
- Disease: malabsorption syndromes, primary hyperparathyrodism, hypogonadism, rheumatoid arthritis, clinical hyperthyroidism.
- Medications: systemic glucocorticoid disease for more than 3 months, prolonged anticonvulsant therapy, chronic heparin therapy.
- Dietary: low calcium intake, excessive alcohol intake, excessive caffeine intake.
- Smoker
- Propensity to fall

Fig. 25.32 Indications for BMD testing



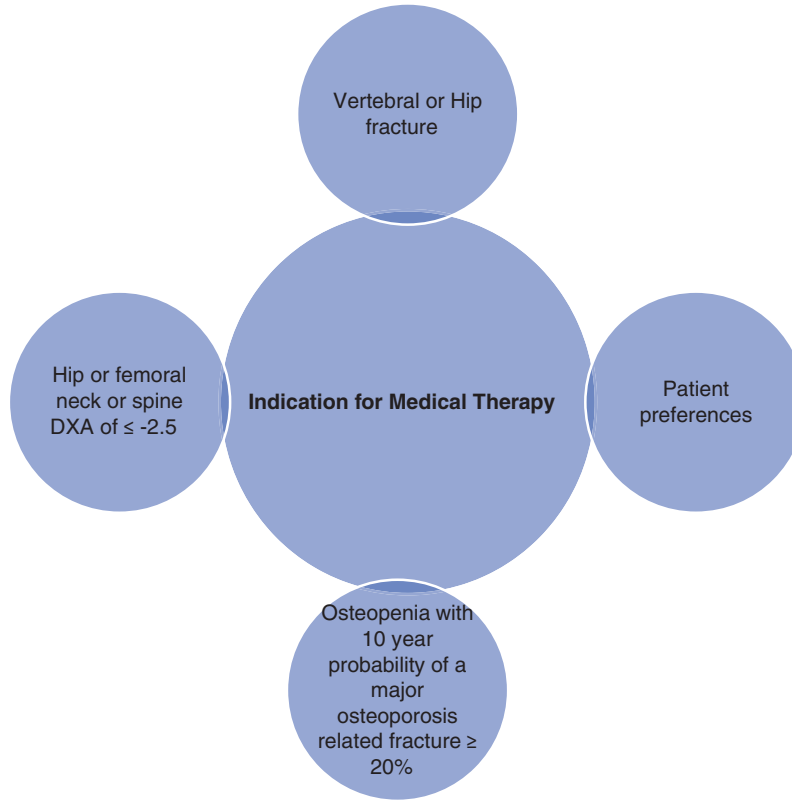


Fig. 25.33 Consider medical therapies based on the following

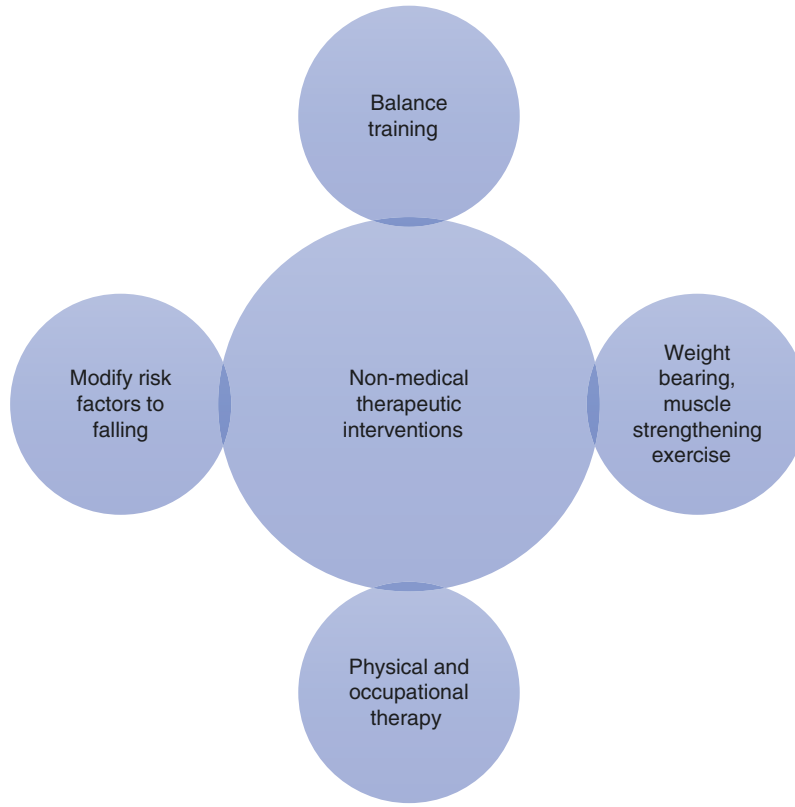


Fig. 25.34 Consider nonmedical therapeutic interventions

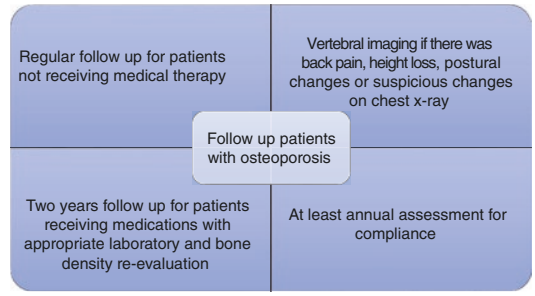


Fig. 25.35 Follow-up recommendations

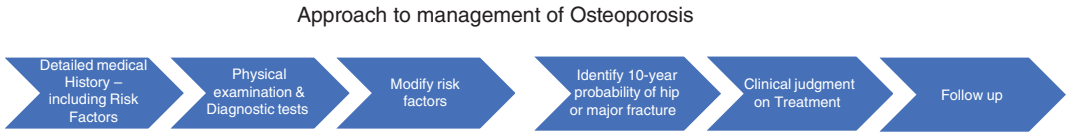


Fig. 25.36 Clinical approach to managing osteoporosis in postmenopausal women and men age 50 and older general principles (2013)

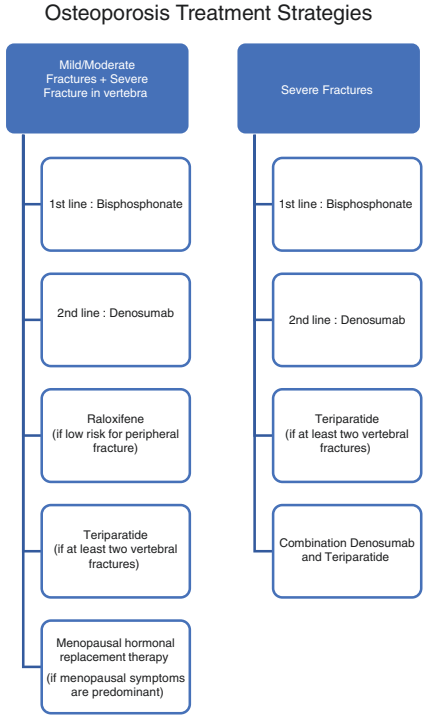


Fig. 25.37 Pharmacological treatment of postmenopausal osteoporosis

macological agents. Assessment and treatment of preventable risk factors is also advised.

Universal recommendations for all patients (Figs. 25.33, 25.34, 25.35, 25.36 and 25.37) (Box 25.4) include:

- Proper calcium and vitamin D dietary intake.
- Management of vitamin D deficiency.
- Weight-bearing exercises and exercises to improve muscle strength.
- Prevention of fall.
- Smoking cessation and limitation of alcohol consumption.

The treatment guidelines mentioned should be thought of as a guide in clinical practice. A thorough consideration of each patient's situation is imperative in making proper management decisions. These treatment guidelines should not stop physicians from offering therapies to those who do not meet the BMD (T-score ≤ -2.5) and FRAX diagnostic scores, or are not at a high enough risk of fracture despite decreased BMD, as every patient's needs should be assessed individually.

Box 25.4 Treatment Strategies for Postmenopausal Osteoporosis

Indications for treatment of osteoporosis related fractures	Severe fractures (vertebral fracture, proximal or distal femur, proximal humerus, pelvic and others) with T-score ≤ -1
	Non-severe fractures with T-score ≤ -2
	Risk factors for osteoporosis or high fall risk with T-score ≤ -3
	Risk factors for osteoporosis or high fall risk, T-score ≥ -3 and medical therapy is indicated by FRAX score.

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