Rheumatology

A Clinical Handbook

SECOND EDITION

Mohsin Azam
Gabriel Samanta
Ash Samanta

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Contents

Additional self-assessment questions are available on the Resources tab at:

www.scionpublishing.com/Rheum2.

Preface to the second edition

It is now ten years since the first edition of *Rheumatology – a clinical handbook* was published. Over the years, I have received comments from medical students, newly qualified doctors, trainees in rheumatology and consultant colleagues, who have said how much they enjoyed going through this text. Phrases used have been "a very useful little book", "highly informative", "well set out and sign-posted", "easy to read" and "contains key information". Whilst such encouraging reports are extremely gratifying, at the same time they serve as reminders that the reputation of this book can only be maintained if it is updated, which is what this new edition achieves.

I am very pleased that Mohsin Azam has remained as an author. Mohsin was one of the authors of the original version, at which time he was a medical student in Leicester. He is now a Principal GP in North London. Despite his extremely busy schedule, Mohsin has generously given up much of his time to contribute to developing the new edition, for which I am very grateful.

I am delighted to welcome Gabriel Samanta as a new member to the team of authors. In the interests of openness and transparency I must declare that Gabriel is my son and is a medical student at Imperial College London. Despite his ongoing studies and working on a project as part of his course, he has researched and updated all chapters to provide a first draft which Mohsin and I have carefully reviewed. Gabriel deserves to be commended not only for his hard work but also for his courage and tenacity in working under the watchful (and nagging) influence of his dad!

Earlier readers of *Rheumatology – a clinical handbook* will observe that the format is as before. This is because of the positive feedback received in the past, wherein much credit was placed upon the layout of the chapters and on the colour coding, headings and signposting, all of which were regarded as particularly useful. All chapters have been reviewed and revised as required. The principal changes are updating in respect of new substantive material, immunological investigations, relevant blood tests, imaging, and new treatments that include biologics as well as other pharmacological therapies for inflammatory conditions. The latest version of relevant clinical guidelines is provided, and self-assessment questions (with answers available on the publisher's website) have been refined.

Our sincerest thanks go to Scion Publishing, to Jonathan Ray for his persistent but gentle nudges that have been inspirational reminders to the authors, to Jonathan's team for their guidance and help throughout the process, and to my many colleagues in Rheumatology who have ungrudgingly provided advice in their specialist areas. I hope that the second edition is received with the same warmth as before.

Ash Samanta
Emeritus Consultant Rheumatologist,
University of Leicester

Preface to the first edition

In my experience of teaching rheumatology at undergraduate (and postgraduate) level for over thirty years, there is one consistent response that I have come across from medical students. This is a general fear of rheumatology. The reason many students regard rheumatology as mysterious and arcane is because of a lack of understanding about what rheumatology covers, as well as a somewhat fuzzy knowledge of the various conditions that are encompassed within rheumatology.

Some years ago I thought it might be helpful for medical students (at the University of Leicester) if I put together what I termed 'revision notes' for rheumatology. I would often encourage students to offer any suggestions for change but the reality was that no-one ever did. A couple of years ago, two bright young medical students, Ahmad Al-Sukaini and Mohsin Azam (who are co-authors of this text) approached me after one of my lectures and came up with a number of ideas, and the revision notes were updated in due course. They also suggested putting together a short book that would be more comprehensive than just brief notes, and that would flag key issues in rheumatology for undergraduate medical students. Their enthusiasm, effort and assistance are to be strongly commended.

According to surveys we carried out at the University of Leicester, students wholeheartedly agreed that a rheumatology 'guide' would be of benefit to them and to junior doctors. Their preference was to use bullet point formatting and an approach that would be succinct and highly focused, as opposed to the more conventional paragraphs and narrative writing. We have also used a wide range of pedagogic features, including summary tables, illustrations and mnemonics throughout. Furthermore, the size of the book was important – it had to be one that could be carried around easily. To test student knowledge and reinforce learning, questions were devised within the framework used by examiners. Single Best Answer (SBA) and Extended Matching Questions (EMQs) are increasingly being utilized by medical school examiners to explore understanding of a topic and it is essential that students familiarize themselves with these types of question. The questions, together with their answers, can be found online, as mentioned at the end of the Contents.

We took up this challenge and have put together this text with the aim of covering rheumatology in a clear and concise manner. The content thoroughly encompasses the current medical school curriculum in the UK and we hope that this text will be highly beneficial to medical students for furthering their knowledge, as well as a revision guide for undergraduate examination purposes. We also hope that it will assist newly qualified junior doctors and serve as a quick reference guide for clinics and ward-based work. The concise and coherent format of this book is likely to appeal to other healthcare professionals who require a working knowledge of rheumatology.

Finally, I would say that this text is not intended to replace any of the standard erudite text books in rheumatology that have already been published. It is designed to focus the mind, provide concise guidance, and encourage further exploration of rheumatology.

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January 2014

Acknowledgments

We would like to place on record our sincere gratitude to the team at Scion Publishing Ltd, particularly Dr Jonathan Ray and Ms Clare Boomer, for their great support, encouragement and patience.

Please refer to the Appendix for acknowledgment to the copyright holders of the many images in the book.

Dedications

To my son Yasin and daughter Elanur – you bring so much joy and warmth into my life. M.A.

For my family, and the friends who create 'home'. G.S.

For my 'long-suffering' family. A.S.

Abbreviations

ACA	anti-centromere antibody
ACE	angiotension-converting enzyme
ACR	American College of Rheumatology
ALP	alkaline phosphatase
ANA	antinuclear antibodies
ANCA	antineutrophil cytoplasmic antibodies
APS	antiphospholipid syndrome
ARF	acute renal failure
AS	ankylosing spondylitis
AxSpA	axial spondyloarthropathies
BMD	bone mineral density
BMI	body mass index
BP	blood pressure
CBT	cognitive behavioural therapy
CCF	congestive cardiac failure
CCP	cyclic citrullinated peptide
CK	creatine kinase
CNS	central nervous system
CPPD	calcium pyrophosphate disease
CRP	C-reactive protein
CSS	Churg–Strauss syndrome
CT	computerized tomography
CVE	cerebrovascular event
CVS	cardiovascular system
CXR	chest X-ray
DAS	Disease Activity Score
DEXA	dual-energy X-ray absorptiometry
DIP	distal interphalangeal
DM	dermatomyositis
DMARD	disease-modifying antirheumatic drug
DNA	deoxyribonucleic acid
DVT	deep vein thrombosis
ECG	electrocardiogram
EDTA	ethylenediaminetetraacetic acid
EMG	electromyography
ERA	endothelin-1 receptor antagonists
ESR	erythrocyte sedimentation rate
EULAR	European Alliance of Associations for Rheumatology
FBC	full blood count
FDG	fluorodeoxyglucose
FRAX	Fracture Risk Assessment Tool
FSH	follicle-stimulating hormone
GBM	glomerular basement disease
GCA	giant cell arteritis
GCS	glucocorticosteroid
GI	gastrointestinal
GORD	gastro-oesophageal reflux disease
GPA	granulomatosis with polyangiitis
GU	genitourinary
HAART	highly active antiretroviral treatment
Hb	haemoglobin
HBV	hepatitis B virus
HLA	human leucocyte antigen
HRT	hormone replacement therapy
HSP	Henoch–Schönlein purpura
IBD	inflammatory bowel disease
IHD	ischaemic heart disease
IL	interleukin
ILAR	International League of Associations for Rheumatology
IV	intravenous
JIA	juvenile idiopathic arthritis
JRA	juvenile rheumatoid arthritis
LDH	lactate dehydrogenase
LFT	liver function test
MAS	macrophage activation syndrome
MCP	metacarpophalangeal
MCTD	mixed connective tissue disease
ME/CFS	myalgic encephalomyelitis / chronic fatigue syndrome
MI	myocardial infarction
MMF	mycophenolate mofetil
MMP	metalloprotease

MPA	microscopic polyangiitis
MRI	magnetic resonance imaging
MSK	musculoskeletal
MSU	monosodium urate
MTP	metatarso-phalangeal
NICE	National Institute for Health and Care Excellence
NSAID	non-steroidal anti-inflammatory drug
OA	osteoarthritis
PAN	polyarteritis nodosa
PCV	packed cell volume
PDE	phosphodiesterase
PE	pulmonary embolism
PIP	proximal interphalangeal
PM	polymyositis
PMR	polymyalgia rheumatica
PPI	proton pump inhibitor
PsA	psoriatic arthritis
PTH	parathyroid hormone
RA	rheumatoid arthritis
ReA	reactive arthritis
RF	rheumatoid factor
RFT	renal function test
ROS	reactive oxygen species
SCAR	severe cutaneous adverse reaction
SI	sacroiliac
SLE	systemic lupus erythematosus
SpA	spondyloarthropathy
SS	Sjögren's syndrome
SSc	systemic sclerosis
SUA	serum uric acid
TB	tuberculosis
TFT	thyroid function test
TNF	tumour necrosis factor
USS	ultrasound scan
UTI	urinary tract infection
VTE	venous thromboembolism
WCC	white cell count
WG	Wegener's granulomatosis
WHO	World Health Organization
XOi	xanthine oxidase inhibitor

Chapter 1

Introduction

What is rheumatology?

Rheumatology is a multidisciplinary branch of medicine that encompasses the investigation, diagnosis and management of patients with arthritis and other musculoskeletal conditions. This includes many disorders affecting joints, bones, muscles and soft tissues. A significant number of musculoskeletal conditions also affect other organ systems and occur as part of a systemic autoimmune disease. The main rheumatological disorders are summarized in *Fig. 1.1* and will be covered in significant depth.

The rheumatology multidisciplinary team (MDT) consists of a variety of disciplines that work together with the aim of providing optimal care to sufferers via a holistic approach (*Fig. 1.2*). The team consists of many healthcare professionals including consultant rheumatologists, general practitioners (GPs), occupational therapists, orthopaedic surgeons, physiotherapists, psychiatrists, specialist nurses and many more.

Rheumatologists are specialists who deal with a wide range of rheumatic diseases. They assess overall function, including physical and mental wellbeing and level of independence. They also manage results of advanced imaging and lab tests, treatment options and the need for further assessment and management, such as referrals to other healthcare providers.

Outline of the book

Chapter 2

For each condition the following will be covered:

- ***Pathophysiology***: the information surrounding the pathophysiology of rheumatology disorders is constantly evolving and there is still so much that remains to be understood. Up-to-date resources were used with the intention of keeping this section simple and concise and not overlooking the clinical aspects of rheumatology!
- ***Epidemiology and risk factors***: attention has been paid to the incidence / prevalence of the rheumatology disorders so that students are aware of the very common, less common and rare disorders. Where possible, risk factors are arranged in a descending order of importance via a simple to follow table, to highlight the most important risk factors for students to learn.
- ***Clinical features***: a variety of pedagogical features such as X-rays, photographs and illustrations have been used, as well as **red flags** indicated by  , and mnemonics in **green**. Red flags or alarm systems refer to symptoms which are suggestive of significant pathology and should therefore not be missed or neglected. These devices are aimed at enabling students to have a greater understanding of the features to look out for and also as an aid to information retention.
- ***Diagnosis and investigations***: this element is centred on the diagnostic pathway – history taking, physical examination, investigations and possible differential diagnoses. It is conveyed in an easy to follow box format. Wherever relevant, up-to-date clinical guidelines, including those from the National Institute for Health and Care Excellence (NICE), the European Alliance of Associations for Rheumatology (EULAR) and the American College of Rheumatology (ACR), were utilized. *Chapter 4* has also been created specifically for investigations, to provide further detail of the various tests performed in rheumatology.

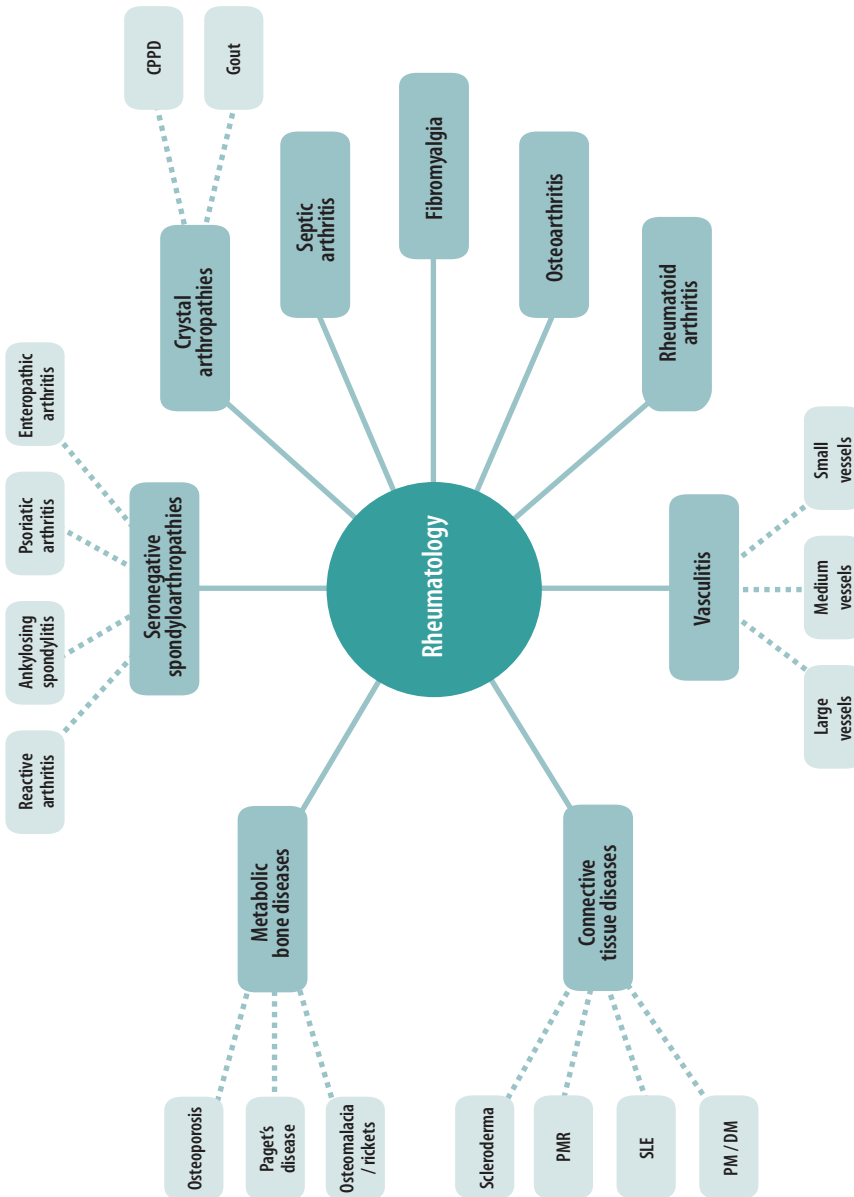

Fig. 1.1: An outline of the main rheumatological disorders.

- ***Management***: this part also utilizes clinical guidelines. Flowcharts, tables and diagrams are used to convey information more effectively and render it more memorable. *Chapter 5* covers the main pharmacological agents of rheumatology in further detail.
- ***OSCE tip / rapid diagnosis / clinical fact box:*** wherever applicable, extra information is provided in the form of tips for the OSCE examination, empirical diagnostic features to form a 'rapid diagnosis' and important clinical facts for students to be aware of.

Self-assessment questions conclude each specific condition section. These are designed for students to check that they have understood and grasped the material.

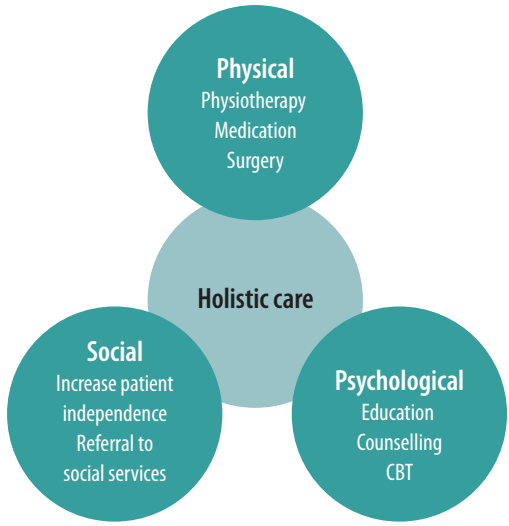

Fig. 1.2: An MDT holistic approach outline to rheumatology.

Chapter 3

This chapter consists of two important and common conditions in rheumatology which present during early life: vitamin D deficiency including both rickets and osteomalacia and juvenile idiopathic arthritis. The same longitudinal format is used as above.

Chapter 4

It may be advisable to read this before embarking on the main rheumatological conditions text (*Chapter 2*), as it provides a basic understanding of the three principal investigations used in rheumatology to reach a definitive diagnosis: blood tests, imaging and synovial fluid analysis.

Chapter 5

This should be used as a cross-reference with *Chapter 2*, in order for students to gain a deeper understanding of the way in which pharmacological agents work, as well as the side-effects and contraindications. It provides information about commonly used agents

including analgesics, corticosteroids, osteoporosis agents, DMARDs and biological agents. This section also includes '**DO**' and '**DO NOT**' boxes so that students are aware of the essentials and common pitfalls, respectively, when prescribing pharmacological agents.

Chapter 6

This focuses on the key points of history taking and performing clinical examinations, with particular emphasis on the GALS and hand examination, so that students have a thorough structure to follow and therefore do not panic when it comes to the dreaded OSCE examinations!

Additional questions in the form of single best answer questions (SBAs) and extended matching questions (EMQs) have been made available online as a free resource to complement the material in the book. To access the questions and answers, click on the Resources tab at www.scionpublishing.com/Rheum2.

Chapter 2

Specific conditions

2.1 Rheumatoid arthritis

Rheumatoid arthritis (RA) is a **chronic systemic inflammatory** disorder which primarily affects joints that are lined with **synovium**. It is typically characterized by a **symmetrical**, occasionally **deforming**, **peripheral polyarthritis**. Because it is a **systemic disease**, it can also affect the whole body, including the heart, lungs and eyes. Cardiovascular disease is the leading cause of mortality in RA.

Pathophysiology

- The actual cause of RA is not entirely understood.
- It is likely that **genetically susceptible** individuals, e.g. HLA-DRB1 carriers, are exposed to an environmental antigen or factors (such as tobacco smoke, occupational dust) resulting in self-stimulation of the immune system **(autoimmunity)**.
- The immune response cross-reacts with the **host tissue (synovial membrane)** resulting in **inflammation** of the **synovial membrane (synovitis)** that lines **joints** and **tendon sheaths**. This gives rise to **synovial hypertrophy**.
- **T-cells** seem to be the most important mediators of the disease. They stimulate the immune system via the release of a variety of **inflammatory cytokines**, most importantly **TNF-α**, **IL-1**, **IL-17**, and **IL-6**, resulting in a **pro-inflammatory state** (*Fig. 2.1.1*). There may also be a deficit in the regulation or apoptosis of T-cells, contributing to pathogenesis.
- **Synovial macrophages, fibroblasts and autoreactive B-cells** are the drivers of RA and produce autoantibodies (**rheumatoid factor** and **anti-citrullinated protein antibodies**) (**RF** and **anti-CCP**). They are the primary generators of TNF-α and other inflammatory cytokines.
- This process can ultimately lead to **cartilage damage** and **bone destruction** by activating osteoclasts, resulting in periarticular osteopenia, bone erosions, and generalized osteoporosis.
- Bone formation is also reduced as **osteoblast** maturation is suppressed by **TNF-α**.

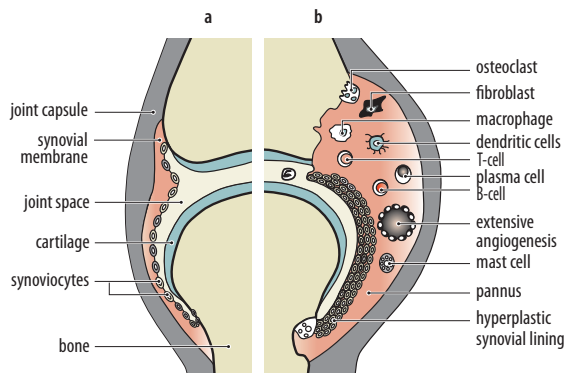

Fig. 2.1.1: (a) Normal healthy joint with thin synovial membrane and **(b)** an RA joint. Various inflammatory cells, such as T-cells, macrophages and plasma cells, infiltrate the synovial membrane to make it hyperplastic. Ultimately it develops into a 'pannus' which migrates onto and into articular cartilage and underlying bone.

Epidemiology and risk factors

- **Prevalence**: there are approximately 680 000 people with RA in the UK (~1%).
- **Incidence**: approximately 1.5 men and 3.6 women are diagnosed with RA per 10 000 people per year in the UK.
- Certain risk factors have been linked to RA (*Table 2.1.1*).

Table 2.1.1: Risk factors for RA	
Gender	• **Before menopause**, RA is **3 times** more common in **women** than men; after menopause the distribution is similar.
Age	• Rheumatoid arthritis can affect any age group, but the age of onset is often **30–50 years**.
Familial	• Estimated to account for **60%** of disease susceptibility.
Genetic	• There are strong associations between **HLA-DR4 and HLA-DR1** and RA, which may be **familial or non-familial (sporadic)**.
Environmental factors	• **Smoking (2.5–3.5× risk)**, infection (there may be a relationship with EBV or *P. gingivalis*), diet, microbiome and hormonal.

Clinical features

The **S** factor:

1. **S**tiffness in the morning typically >1 hour
2. **S**ymmetrical joint pain
3. **S**wollen joints (polyarthritis)
4. **S**mall joints of the hand, feet and wrist (mainly affected)
5. **S**ex: female:male ratio is 3:1
6. **S**peed: **quick onset** over weeks to **months**
7. **S**pecific signs for the hand:
   a. ***Early***: swollen metacarpophalangeal (MCP), proximal interphalangeal (PIP), wrist or metatarso-phalangeal (MTP) joints.
   b. ***Later*** (*Fig. 2.1.2a*): **boutonnière deformity** (flexion of the PIP and hyperextension of the distal interphalangeal (DIP) joints), **swan neck deformity** (hyperextension of PIP and flexion of DIP joints), **Z-thumb** (hyperextension of the interphalangeal joint, and fixed flexion and subluxation of the MCP joint) and **ulnar deviation** (subluxation of proximal phalanges towards the ulnar side).
8. **S**everal extra-articular **manifestations** (*Fig. 2.1.3*).

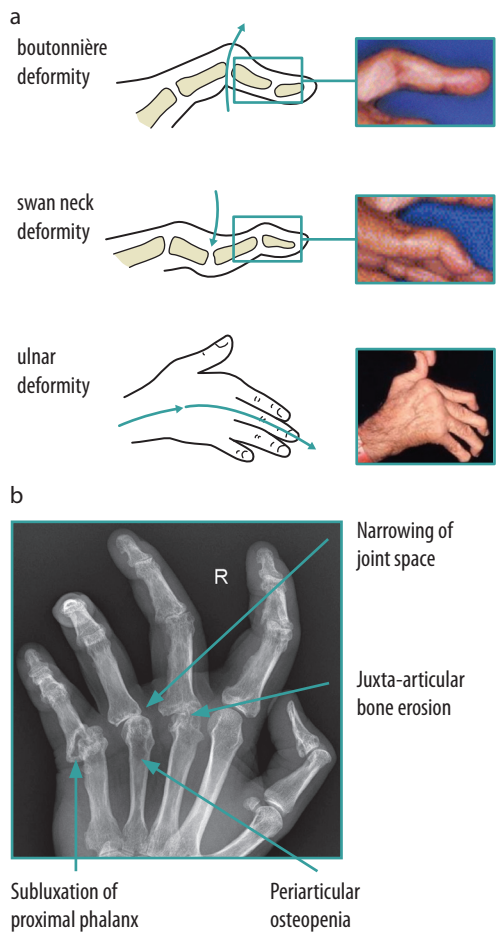

Fig. 2.1.2: **(a)** Late specific signs of RA; **(b)** Late X-ray features of RA.

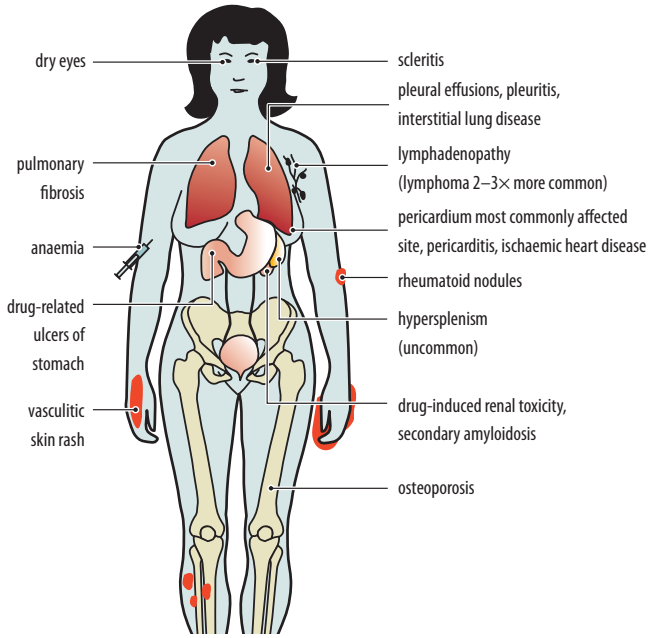

Fig. 2.1.3: The extra-articular manifestations of the disease can occur at any age after onset and occur more commonly in males, despite RA being more common in females. Extra-articular organs may involve the skin, eyes, heart, lungs and kidneys.

OSCE tips: RA vs OA clinical features!

- **RA** usually presents symmetrically, osteoarthritis (**OA**) usually presents with asymmetrical joint pain
- **RA** morning stiffness usually >1 hour, **OA** stiffness usually <30 minutes
- **OA** is worse on movement, **RA** is not
- **RA** is more likely to involve the distal small joints (MCP, PIP and MTP), whereas **OA** is likely to affect larger joints (hip, knee, shoulder)
- Common age of onset for **RA** is 20–40 years and >50 years for **OA**
- **RA** onset is relatively rapid (weeks to months), **OA** typically years
- **RA** presents with systemic symptoms, **OA** doesn't
- **RA** tends to be worse in the morning; **OA** is worse after activities, especially towards the end of the day

Diagnosis and investigations (see *Table 2.1.2*)

All people suspected of having RA should be referred for specialist assessment.

	Diagnosis	Prognostic indicators
Hx	• Pain duration (usually ≥6 weeks), morning stiffness >1 hour	• Activity limitations, comorbidities, risk factors such as smoking and family history
Ex	• ≥3 swollen tender joints, symmetrical joint involvement, subcutaneous nodules	• Extra-articular manifestations (*Fig. 2.1.3*)
Ix	• ↑ **Serum rheumatoid factor (RF)** • ↑ **Anti-cyclic citrullinated peptide antibodies (anti-CCP)** • ↑ **Erythrocyte sedimentation rate (ESR) / C-reactive protein (CRP)** **Note:** *RF has ↑ sensitivity and ↓ specificity; anti-CCP has ↑ specificity and ↓ sensitivity*	• **Full blood count**: ↑ platelet count, ↑ serum ferritin, anaemia of chronic disease • **Renal and liver function tests** • **X-ray**: chest, hands (*Fig. 2.1.2b*) and feet • **MRI**: identify synovitis early • **Ultrasound**: joint effusion, Baker's cysts and synovial swelling/hypertrophy
DDx	• Psoriatic arthritis • Connective tissue disease, e.g. systemic lupus erythematosus (SLE)	• Reactive arthritis • Polymyalgia rheumatica

Table 2.1.2: The 2010 American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR) criteria

The most recent criteria for the diagnosis of RA are the 2010 ACR and the EULAR criteria. A total score of ≥6 is diagnostic of RA.	Score
A. Joint involvement:	
1 large joint	0
2–10 large joints	1
1–3 small joints (with or without involvement of large joints)	2
4–10 small joints (with or without involvement of large joints)	3
B. Serology:	
Negative RF and negative anti-CCP	0
Low-positive RF or low-positive anti-CCP	2
High-positive RF or high-positive anti-CCP	3
C. Acute phase reactants:	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
D. Duration of symptoms:	
<6 weeks	0
≥6 weeks	1

Note: The 2010 EULAR and ACR criteria replaced the 1987 ACR criteria as they focus on features at an earlier stage of the disease that are associated with persistent and/or erosive disease, rather than defining the disease by its late-stage features. As a result, this refocuses attention on the important need for earlier diagnosis and therefore earlier treatment.

Management

The aim of management in RA is to reduce/slow the joint inflammation and disease progression to maintain the patient's lifestyle. Early use of **disease-modifying antirheumatic drugs (DMARDs)** and **biological agents** improves the long-term outcome of the disease. Treatment should be started **within 3 months** of symptom onset, based on NICE NG100 (2018, updated 2020).

- Refer urgently to a **rheumatologist**, in order to prevent irreversible destruction of joint(s) if:
  - the **small joints of the hand and feet** are affected
  - more than one joint is affected
  - there has been a delay of 3 months or longer between the onset of symptoms and seeking medical advice.
- Consider NSAID and PPI in the interim.
- Specialists usually start with a conventional DMARD **(cDMARD)** monotherapy and short-term **corticosteroids** (bridging if appropriate).
- Emphasis should be placed on reaching a clinical effective dose rather than on the choice of DMARD.
- If the disease is severe and a combination of **cDMARDs** have not been sufficient, biologic DMARDs (**bDMARDs**) may be offered.
- The disease activity of RA should be monitored by measuring **CRP** and the **DAS28 score** (*Box 2.1.1*). The aim is to reduce the **DAS28 score below 3**. However, DAS28 score may be subjective and is highly examiner-dependent.
- Patient-driven composite tools such as **RAPID3** can also be used as they are more time-efficient and may provide a more reliable measurement of change over time.
- DMARDs need monitoring (generally every 3 months once stable) and frequently include: FBC, LFT and U & E.

Non-pharmacological management

- Encourage regular exercise: aerobic activities, flexibility and muscle strength exercises, **core stability exercise**, **balance rehabilitation**, promotion of lifestyle physical activity, smoking cessation, healthy balanced diet.
- People with RA should have access to a **multidisciplinary team** such as **specialist nurses**, **physiotherapists**, **occupational therapists** and **podiatrists**.

Pharmacological: see *Table 2.1.3*

Surgery:

- Consider the following for surgical opinion if they do not respond to non-surgical management:
  - **Persistent pain** due to joint damage or other identifiable soft tissue cause
  - **Worsening joint function**
  - **Progressive deformity**
  - **Persistent localized synovitis**.

Table 2.1.3: Pharmacological management of rheumatoid arthritis

cDMARDs	• Are **first-line** • Early DMARD treatment (ideally within 3 months from symptom onset) is associated with better long-term prognosis • **Methotrexate**, **sulfasalazine**, **leflunomide** and **hydroxychloroquine** are the most commonly used • NICE recommends a combination of DMARDs, including methotrexate and at least one other DMARD, plus short-term glucocorticoids (if not contraindicated)
Corticosteroids	• Rapid reduction in **symptom onset** and **inflammation** • Can be given via **intra-muscular**, **intra-articular** and **oral routes** • NICE recommends a combination of DMARD ± a short course of bridging prednisolone
NSAIDs	For **symptomatic relief** and also to **reduce inflammation**, e.g. **ibuprofen**, **naproxen**, **diclofenac**
Biological agents (bDMARDs) (TNF-α inhibitors, B-cell blockers, and anti-IL-1 & IL-6 agents). Indications: after the failure of 2 conventional non-biological DMARDs. Failure is measured objectively using DAS28 (indicated by a score >5.1)	
TNF-α inhibitors	• Usually indicated when there is an inadequate response to at least 2 DMARDs (including methotrexate) • Block the pivotal action of TNF-α, a key cytokine in the pathogenesis of RA • Include **infliximab**, **adalimumab** and **etanercept** • Very **expensive** and used in **severe cases (high DAS28 score)** • Should normally be used in combination with methotrexate • Risks include reactivation of tuberculosis (TB)
B-cell blockers	• **Rituximab** is a **monoclonal antibody** • It works by targeting the **B-cell surface marker**, **CD-20** • It is given via IV infusions 2 weeks apart • A combination of **rituximab** and **methotrexate** is recommended as an option for the treatment of adults with RA who are intolerant of other DMARDs or whose response to them is inadequate
Anti IL-1 & IL-6 agents	• Like TNF- α, IL-1 and IL-6 are pro-inflammatory cytokines which are heavily involved in the disease process • **Anakinra** is an **IL-1 receptor antagonist** • **Tocilizumab** is an **anti-IL-6 receptor monoclonal antibody** • On the balance of its clinical benefits and cost-effectiveness, anakinra is not recommended for the treatment of rheumatoid arthritis
JAK inhibitors	• **Tofacitinib** and **baricitinib** are **JAK inhibitors** • Block cytokines via inhibition of **Janus kinases** • Targeted synthetic DMARDs that can be given in tablet form • Risk of thrombotic events, and infection (immunosuppression)

- Surgical procedures may include:
  - **Joint prosthesis**: **hip** and **knee**
  - **Arthroscopy**: remove abnormal synovium, cartilage and eroded bone
  - **Tendon reconstruction**: restore function when tendon ruptured.

Box 2.1.1: The Disease Activity Score (DAS)28

- It assesses **tenderness and swelling at 28 joints** (see *Fig. 2.1.4*), **ESR**, and patients' **self-reported symptom** severity, to calculate a disease activity score.
  DAS28 score of:
  >5.1 = high disease activity
  3.2–5.1 = moderate disease activity
  <3.2 = low disease activity
  <2.6 = remission
- ***A decrease in DAS28 score by***:
  0.6 points or less = poor response
  >1.2 points = moderate or good response
  (depending on whether an individual's DAS28 score at the end point is above or below 3.2, respectively)

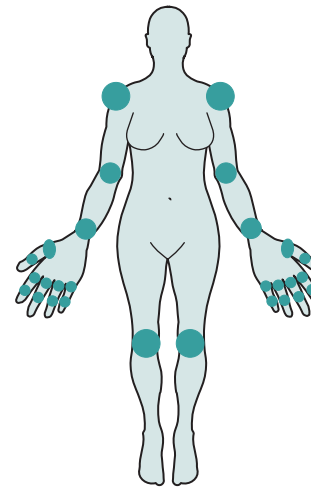

Fig. 2.1.4: The 28 joints (MCPs, PIPs, wrists, elbows, shoulders and knees) that are examined in calculating DAS28.

Self-assessment

A 45 year old woman complains of symmetrical pain and swelling of her MCP joints. You think that a diagnosis of RA is likely.

1. What specific questions would you like to ask her?
2. Name two hand deformities that can be caused by RA.
3. What blood tests would you initially perform, and what might they show?
4. Name four extra-articular manifestations of RA.
5. The blood tests confirm a diagnosis of RA. Which group of pharmacological agents would be most appropriate in preventing disease progression? Name the most used drug in this group and its main side-effects.
6. Name two ways of monitoring response to treatment.

Answers to self-assessment questions are to be found on the Resources tab at www.scionpublishing.com/Rheum2.

2.2 Osteoarthritis

Osteoarthritis (OA) is the **most common form of arthritis** and is a major cause of **impaired mobility**. It is a chronic condition which occurs when damage triggers repair processes resulting in **cartilage damage** and **joint space narrowing** leading to **pain**, **functional limitation** and **impaired quality of life**. It can affect any joint but the **hip**, **knee**, **lumbar** or **cervical spine**, and **wrist joints** are most commonly affected.

Pathophysiology

- OA is viewed as a **metabolically dynamic process** where there is an imbalance between joint breakdown and sufficient repair process.
- Normal joint articulating cartilage, **hyaline cartilage**, undergoes turnover in which 'worn out' collagen and other matrix components are degraded and replaced by **chondrocyte cells**.
- Both **genetic and environmental** factors can stimulate **apoptosis** of chondrocytes, disrupting the normal repair mechanism and thereby causing cartilage damage, or **hypertrophy and cluster** of the chondrocytes, increasing production of enzymes, which degrade the matrix and 'use up' **proteoglycans**. The cartilage swells due to the breakdown of **proteoglycans**, making it more vulnerable to damage.
- Certain **cytokines** (e.g. **IL-1** and **TNF-α**) and **protease enzymes** (e.g. **metalloproteinase**) increase in the cartilage, which triggers osteoarthritic changes through direct cartilage damage. They activate **osteoblasts** and **osteoclasts**.
- Eventually, cartilage destruction exposes underlying bone, resulting in abnormal **subchondral bone growth (subchondral sclerosis)**, **osteophytes** and **bone cysts** (*Fig. 2.2.1*).
- In OA, the synovium becomes inflamed and swells, which leads to synovial cell proliferation. This may be accentuated by **calcium phosphate** and **calcium pyrophosphate dihydrate crystals** which are released by the cartilage. This **increases** intra-articular pressure and stimulates **nociceptors (pain)**. This may overlap with pseudogout (*Sec. 2.8*).
- The articular capsule may become fibrotic which may lead to pathological weakness in the bridge of the joint and surrounding muscles.

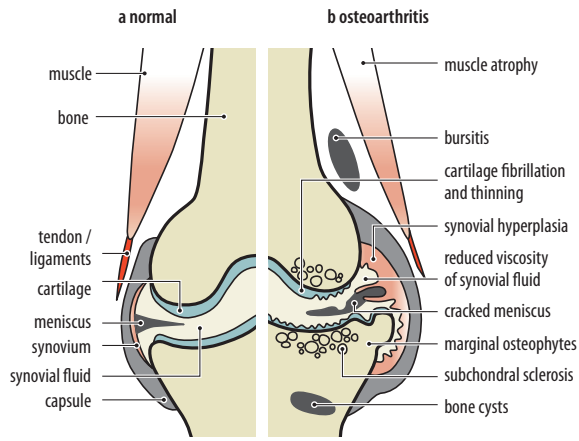

Fig. 2.2.1: (a) Normal joint **(b)** OA joint.

Epidemiology and risk factors

- Worldwide estimates indicate that there are approximately 429 people per 100 000 with OA.
- Approximately a third of women and nearly a quarter of men aged 45–64 have sought treatment for OA in the UK.

Fig. 2.2.2: Bony enlargements of the DIP joints (Heberden's nodes) and PIP joints (Bouchard's nodes) due to osteophyte formation.

Table 2.2.1: Risk factors for OA

Systemic risk factors		Mechanical risk factors	
Age	• Risk increases with age; partly due to age-related changes such as ligament laxity (ligaments are joint protectors). There is a reduction in normal repair response.	**Obesity**	• Places mechanical stress on joint cartilage.
Gender	• Polyarticular OA is more common in women. • A high prevalence in post-menopausal women suggests a role for sex hormones.	**Injury**	• Ligament damage or fractures can lead to abnormal stress on joint cartilage.
		Joint damage	• Joint damage due to underlying disease, e.g. RA, Paget's disease, varus and valgus deformity or trauma (secondary OA).
Family history	• 40–60% of 'common OA' is thought to have a hereditary component. This is joint-specific.	**Joint site**	• Weight-bearing joints are at higher risk.
Bone density	• ↑ bone density e.g. Paget's disease ↑ risk of OA. • ↓ bone density e.g. osteoporosis ↓ risk of OA.	**Occupation**	• Cleaners have ↑ risk of hip, knee and shoulder OA. • Hairdressers have ↑ risk of hand OA. • Farmers have ↑ risk of hip OA.

Clinical features

- Clinical features depend on the joint sites affected (*Table 2.2.2*).

  Symptoms: **joint pain** – usually gradual onset, worse on movement, load bearing and at the end of the day, **joint stiffness** – in the morning or after rest for <30 minutes, **reduced joint function** and **joint instability**.

  Signs: **periarticular tenderness**, **crepitus**, ↓ range of movement, **muscle wasting**, **joint deformity** and **instability**, squaring of the thumb, swelling of the hands (**Bouchard's nodes** and **Heberden's nodes**; *Fig. 2.2.2*), mild **synovitis** and **effusion**.

Table 2.2.2: American College of Rheumatology (ACR) criteria for hand, hip and knee OA	
Nodal OA	Nodal OA or primary generalized OA commonly affects post-menopausal women. There is hand pain, aching, or stiffness for most days of the prior month. Heberden's and Bouchard's nodes in ≥2 joints are characteristic of nodal OA. EULAR has released classification criteria for hand OA based on the same criteria, with the addition of age, number of joints with osteophytes, and X-ray findings.
Hip OA	Hip pain for most days of the prior month. Categorized largely radiographically: femoral and/or acetabular osteophytes and radiograph hip joint-space narrowing.
Knee OA	Commonly presents in obese women ≥38 years of age. There is knee pain for most days of the prior month, crepitus on movement, morning stiffness ≤30 minutes and bony enlargement of the knee on examination.

Diagnosis and investigations

Hx

- **Joint pain** (worsened by exercise & relieved by rest) and **stiffness** (morning / after rest).
- **Reduced joint function** and **joint instability**.
- Ask about **risk factors** e.g. family history and trauma.

Ex

- **Look** → pain on movement, muscle wasting and limp/antalgic gait.
- **Feel** → periarticular tenderness, swelling of joints, mild synovitis and effusion, and absence of systemic features, e.g. fever.
- **Move** → pain on movement, ↓ range of movement, joint deformity, joint instability and crepitus.

Ix

- **Blood tests**: ESR and CRP are usually normal, RF and anti-CCP negative.
- **Joint aspiration**: sterile, straw-coloured, viscous fluid; white cell count (WCC) may be slightly elevated.
- **X-ray ('LOSS')**: **L**oss of joint space, **O**steophytes, **S**ubchondral sclerosis, **S**ubchondral cysts (*Figs 2.2.3* and *2.2.4*). This also helps with grading the severity of OA.
- **MRI**: can demonstrate early thinning of cartilage.
- **Arthroscopy**: cartilage loss and erosion.

DDx

Large joint involvement:

- Monoarticular inflammatory arthropathy
- Chronic infection e.g. tuberculosis
- Calcium pyrophosphate disease (CPPD) (if knee is involved)

Small polyarticular joint involvement:

- RA

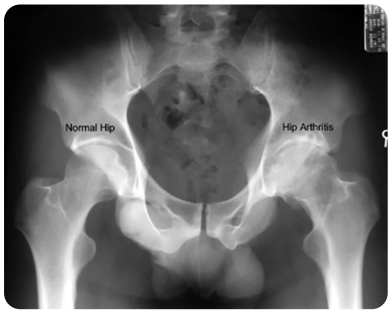

Fig. 2.2.3: X-ray of an individual with a normal right hip and a left hip with OA demonstrating reduced joint space, subchondral cysts and subchondral sclerosis.

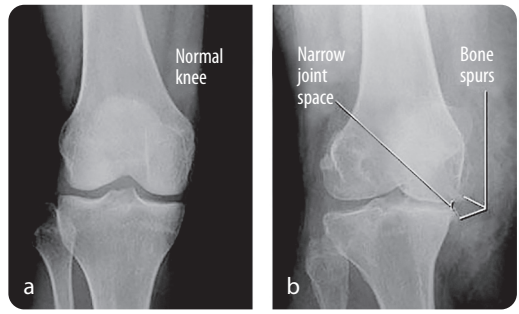

Fig. 2.2.4: X-ray of **(a)** a normal joint and **(b)** an osteoarthritic knee which shows reduced joint space and bony spurs (osteophytes).

OSCE tips: Specific questions to ask someone with suspected OA

- **Presenting complaint** → Joint pain worse on exercise or after rest? Is there morning stiffness? If so, for how long? Reduced joint function and stability? Weight-bearing joint(s)? Particular joint(s) that is 'overused'?
- **Predisposing factors** → e.g. history of trauma?
- **Past medical history** → Secondary causes e.g. RA and Paget's disease?
- **Family history** → Family history of OA?
- **Social history** → Current/previous occupation? How are their symptoms impacting them?

Management (NICE guidelines, 2022)

- Management of OA includes non-pharmacological management (*Table 2.2.3*), pharmacological pain relief (*Fig. 2.2.5*) and surgical intervention.

Table 2.2.3: Non-pharmacological management of OA

Education and advice	Education, advice and access to information are core treatments which should be offered to everyone with OA (www.versusarthritis.org). Self-management programmes should be encouraged.
Exercise	Exercise should be a core treatment for people with OA and should consist of local muscle strengthening and general aerobic fitness.
Weight loss	Should be a core treatment for OA individuals who are obese or overweight. Behaviour change techniques should be used.
Aids and devices	Advice on appropriate footwear should be given as part of core treatment for people with lower limb OA. In some cases people with biomechanical joint pain or instability may be considered for bracing / joint supports / insoles / walking sticks / frames if exercise is ineffective.

Table 2.2.3: Non-pharmacological management of OA *(continued)*	
Physiotherapy and occupational therapy	Manual joint manipulation may be useful for some individuals with hip and knee OA. Advice should be given on modifiable work-related factors. Occupational therapy assessment for any adjustments at work or in the home.
Psychosocial support	Motivational coaching, pain coping and goal setting.

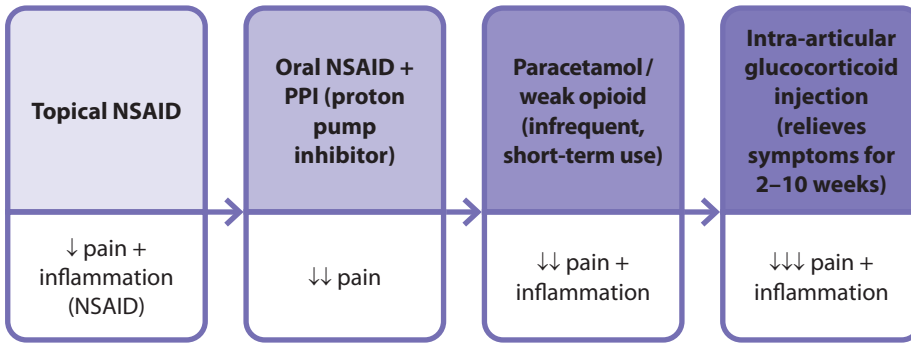

Fig. 2.2.5: Pharmacological management of OA.

- Surgical intervention is indicated when joint symptoms have a substantial impact on the patient's quality of life and medical management has failed. Scoring tools, age, gender and BMI should not be used to exclude patients from surgery.
  - **Replacement of joint** – the most common operations are to replace hip, knee, and base of thumb joints. The ankle joint can be fused or replaced.
  - **Arthroscopy lavage and debridement are not recommended as per current evidence-based guidance** (https://doi.org/10.1136/bjsports-2017-j1982rep) (2018).

Self-assessment

A 68 year old female has been complaining of bilateral hip pain for the last 6 weeks. An X-ray is then performed (*Fig. 2.2.6*).

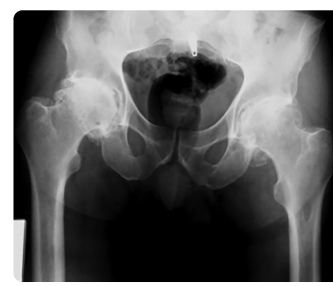

Fig. 2.2.6: X-ray of pelvis.

1. Describe four abnormalities you may see in the X-ray.
2. What pharmacological agents would you begin with? If these don't work, what is your next plan of action?
3. Name three non-pharmacological management options for OA.
4. She returns to your clinic some months later complaining that the medications are not working. What are the indications for surgical intervention and what procedure should be performed?

Answers to self-assessment questions are to be found on the Resources tab at www.scionpublishing.com/Rheum2.

2.3 Septic arthritis

Septic arthritis is the **acute infection** (usually **bacterial**) of a **native** or **prosthetic joint**. Since septic arthritis can lead to **rapid joint destruction**, immediate accurate diagnosis and treatment are essential. Any joint can be affected, particularly the **lower limb joints**, most commonly the **hip** and **knee**. The presentation is typically mono-/oligo-arthritis (bacterial causes) but can be polyarthritis (viral causes).

Pathophysiology

- Septic arthritis usually occurs due to the spread of bacteria from another site to the joint:
  - The most common route of spread is **haematogenous** (**respiratory** or **urinary tract infection**). Highly vascularized joints lack a limiting basement membrane, making them more vulnerable.
  - Other routes include **local tissue infection** (**cellulitis** and **osteomyelitis**), **penetrating trauma** and **inoculation** (skin opportunistic pathogens may spread when there is a break in the skin).
- Release of **cytokines by osteoclasts and synovial macrophages** leads to hydrolysis of **proteoglycans** and **collagen**. **Cartilage destruction** and eventual **bone loss** (if left untreated) begin within 48 hours, and are caused by direct invasion by the causative agent resulting in increased intra-articular pressure.
- **Bacteria** are the most common causative pathogens (*Fig. 2.3.1*). **Viruses** and **fungi** rarely cause septic arthritis.

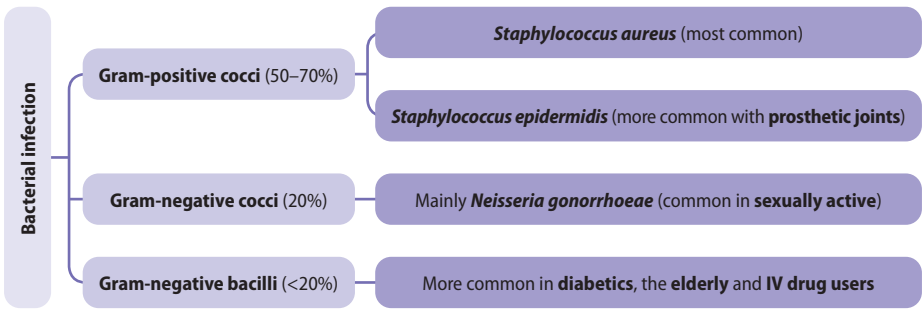

Fig. 2.3.1: Causative bacteria of septic arthritis.

Epidemiology and risk factors

- The estimated incidence of septic arthritis in the UK is 7.8 cases per 100 000 of the population (2016) (https://doi.org/10.1093/rheumatology/kew323).

Table 2.3.1: Risk factors for septic arthritis	
Prosthetic joint	• Incidence is 10 × higher. Early infection is most likely due to *Staphylococcus aureus*, whereas delayed infection is due to coagulase-negative staphylococcus and Gram-negative aerobes.
Rheumatoid arthritis	• Incidence is 4 × higher.
Diabetes mellitus	• Diabetic patients have increased risk of infection; this can often be linked to foot ulcers.
Low socioeconomic status	• Poverty and malnutrition, and those abusing alcohol and drugs.
Age	• Extremes of age (<15 and >80).
Intravenous drug use	• Transfer of pathogenic organisms via haematogenous spread; joints of the spine are more often affected.
Osteomyelitis	• Osteomyelitis from penetrating injuries can spread to joint.
Intra-articular injection / aspiration	• Transfer of pathogenic skin organisms directly into joint.

Clinical features

Rapid diagnosis: Septic arthritis in children (Kocher criteria for a child with a painful hip)

- Non-weight-bearing on affected side
- Raised ESR and/or CRP
- Fever
- Raised WCC

Probability that child has septic arthritis: 4/4 = 99%, 3/4 = 93%, 2/4 = 40%, 1/4 = 3%

- Usually **one joint** is affected (approx. 90% of the time). Less commonly two or more joints may be affected at the same time due to the spread of bacteria.
- The **knee** is the most common site of infection (**>50%**), followed by the **hip** (more common in **children**), then the **shoulder**, **wrist**, **elbow** and **ankle**. Other joints are rarely affected, but hand and foot may be infected after bacterial infection following piercing trauma.
- **Symptoms / signs include**:
  - **Extremely painful, red (erythema), swollen joint (acute).**
  - **Muscle spasm** resulting in **joint immobility**.
  - **Systemic features** – tachycardia, fever, rash, malaise, anorexia.
  - **Loosening of the implant** (chronic infection in prosthetic joint).
  - **Reduced passive joint mobility**.
- The clinical picture may be partially masked in the **elderly**, **immunocompromised**, those with **RA** and **IV drug users**.

Diagnosis and investigations

Hx

- **Presenting complaint**: extreme pain, overlying skin is red, swollen joint and fever (60%). In most cases of septic arthritis there is a rapid onset of symptoms (<2 weeks) and only one joint is affected.
- **Past medical history**: e.g. diabetes, RA and other risk factors (*Table 2.3.1*).
- **Social history**: low socioeconomic status and IV drug use.
- **Sexual history**: gonorrhoeal infection.

Ex

- **Look** → signs of erythema, swelling and obvious effusion.
- **Feel** → tenderness, warmth and effusion.
- **Move** → marked limitation of movements and inability to bear weight.
- Presence of **systemic features** (fever, malaise, rash and tachycardia).

Ix

- **Aspiration of the joint (image-guided if available)**: to obtain a sample of synovial fluid. Synovial fluid is sent for immediate Gram stain, WCC, culture and polarized light microscopy (to rule out gout / CPPD). May show presence of microorganisms; WCC is often raised. Subsequent culture reveals organism type and sensitivities to antibiotic therapy.
- **Blood culture**: presence of microorganisms; reveals organism type and sensitivities to antibiotic therapy.
- **Blood test**: ↑ESR, WCC and CRP. Electrolyte and liver function tests can be performed to indicate whether there is systemic sepsis.
- **X-ray**: usually normal but may reveal any underlying joint disease at presentation, e.g. RA. May show effusion and narrowing of joint space due to cartilage destruction.
- **Ultrasound**: may show presence of synovial thickening or effusion to guide aspiration.
- **CT with contrast and MRI**: useful for determining extent of infection.
- Other investigations to find the source of infection may be useful, such as **MSU or urethral swabs**.

DDx

- Gout
- Pseudogout
- Acute exacerbation of OA
- Bursitis
- Flare-up of RA
- Transient non-specific synovitis (hip)
- Reactive arthritis
- Haemarthrosis

Management

Antibiotics

- **Empirical antibiotics** (initially **IV**) whilst waiting for synovial fluid joint analysis (refer to local guidelines and consult microbiologist).
- The choice of empirical therapy depends on the most likely causative organism:
  - **Flucloxacillin** (0.5–1 g/6 hours IV for 4–6 weeks) for ***Staphylococcus aureus*** and **vancomycin** for **MRSA**.
  - If **penicillin-allergic** then **IV vancomycin** should be given (dose variable adjusted to trough level (15–20 mg/L)).
  - **Cefotaxime** (1 g every 12 hours IV for 4–6 weeks) for **gonococcal** or **Gram-negative bacteria**.
- Other antibiotics may be indicated and added, depending on the results of culture and sensitivity testing.
- Antibiotic therapy (initially IV then later oral) should be continued for at least **1 week and longer where clinically indicated**.

Non-pharmacological management

- **Orthopaedic review** for the consideration of **arthrocentesis**, **lavage** and **debridement**, particularly if **prosthetic joint** is affected.
- **Joint immobilization** followed by **physiotherapy**.
- **Regular review** and **examination** of the affected joint as well as follow-up blood tests for inflammatory markers.

Self-assessment

A 9 year old boy presents with an acute red, swollen hip and is unable to walk. You suspect that he has septic arthritis.

1. What findings would you expect on examination?
2. What is the most common route of spread in septic arthritis?
3. Name three risk factors of septic arthritis.
4. An aspiration of the joint is performed to obtain a sample of synovial fluid. What tests should be performed on the sample?
5. What is the most likely causative organism for sepsis in this case?
6. What suitable empirical antibiotic would you prescribe?

Answers to self-assessment questions are to be found on the Resources tab at www.scionpublishing.com/Rheum2.

Introduction to spondyloarthropathies

- Spondyloarthropathies are a group of inflammatory arthropathies which include the following conditions ('**PEAR**'):
  - **P**soriatic arthritis (*Sec. 2.4*)
  - **E**nteropathic spondyloarthropathies – associated with inflammatory bowel disease and GI bypass surgery (this condition is not discussed any further in this book)
  - **A**nkylosing spondylitis (*Sec. 2.5*)
  - **R**eactive arthritis (*Sec. 2.6*)
- The spondyloarthropathies frequently overlap and have several clinical features in common:
  - **Rheumatoid factor negative** (seronegative)
  - **HLA-B27 association** – HLA-B27-positive individuals have a 20-fold increased risk of developing a spondyloarthropathy
  - **Axial arthritis** – arthritis of the spine and sacroiliac joints
  - **Asymmetrical large joint oligoarthritis** (<5 joints) or **monoarthritis**
  - **Enthesitis** – inflammation of the site of tendon or ligament insertion e.g. plantar fasciitis and Achilles tendinitis
  - **Dactylitis** ('sausage digit') – inflammation of the entire digit as a result of soft tissue oedema, and tenosynovial and joint inflammation
  - **Extra-articular manifestations** – these differ from RA, e.g. inflammatory bowel disease (IBD) and iritis

The European Spondyloarthropathy Study Group criteria for spondyloarthropathy 1991

Inflammatory spinal pain, or **synovitis** (asymmetric, predominantly in the lower extremities) and one or more of the following:

- **Family history**: first-degree or second-degree relative with **ankylosing spondylitis**, **psoriasis**, **acute iritis**, **reactive arthritis** or **IBD**
- Past or present **psoriasis**
- Past or present **IBD**
- Past or present pain alternating between the two buttocks
- Past or present spontaneous **enthesitis** on examination
- Episode of diarrhoea occurring within one month before onset of arthritis
- **Non-gonococcal urethritis** or **cervicitis** occurring within one month before onset of arthritis
- **Sacroiliitis** (meeting the criteria shown in *Fig. 2.5.2*)

2.4 Psoriatic arthritis

Psoriatic arthritis (PsA) is a **chronic inflammatory arthritis** and the most common type of **seronegative oligoarthritis**. PsA is unique compared to other **seronegative spondyloarthritides** in that the **small joints** of the **hand** are commonly affected. A variety of joint patterns are recognized in PsA, although these may overlap. It affects up to 25% of people with psoriasis; the risk correlates to the severity of psoriasis.

Pathophysiology

- The pathogenesis of PsA remains poorly understood.
- Like other autoimmune joint diseases, **genetically susceptible individuals** are exposed to an **environmental trigger** (**bacteria**, **stress**, or **entheseal-related peptide**) which may then activate the immune system.
- This results in **T-cell infiltration** and **chemokine / cytokine** release, and hyperplasia of the synovium.
- The process is amplified by **angiogenesis**, **cellular infiltration (B cells and macrophages)**, **and fibrosis** of involved tissues.
- **Human leucocyte antigen (HLA)** and other genes may determine the exact pattern of tissue involvement.
- **Plasmacytoid cells may play a key role in the pathogenesis of PsA**.
- **Osteoclast activity** is also increased in PsA, leading to **bone remodelling**.

Epidemiology and risk factors

- The prevalence of PsA in the UK is approximately 0.3%.
- Incidence has been observed in studies to be around 16 per 100 000 people in the UK.
- Men and women are equally affected.

Table 2.4.1: Risk factors for PsA

Psoriasis	**Strongest risk factor**. Skin psoriasis may occur **before** (**70%**), **after** (**15%**), or at **same time as** (**15%**) joint symptoms.
Hereditary	Approx. **30%** of individuals with psoriasis or PsA have first-degree relatives with psoriasis or PsA. There is an association between **HLA-B27** and PsA.
Joint or tendon trauma	A small number of PsA patients may recall trauma prior to the onset of their arthritis.
HIV	The prevalence of PsA is higher in patients with HIV compared to the general population.
Age	More common in individuals aged **30–55** but can occur at any age.
Ethnicity	PsA is more common in **Caucasians** than Africans or Asians.

Clinical features

- A variety of PsA patterns of joint involvement are recognized (*Table 2.4.2*).