

## Chapter 9

# The rheumatological long case

It's better to be dead, or even perfectly well, than to suffer from the wrong affliction.

Ogden Nash (1902–71)

### NOTES ON THE RHEUMATOLOGY LONG CASE

Joint and mobility problems are common in long-case patients, even when this is not the central abnormality. Elderly and obese patients often have osteoarthritis (OA), which limits their ability to exercise and lose weight. A modified GALS (gait, arms, legs and spine) assessment can be a quick way to identify the importance of these matters to the patient (and to the long case itself).

#### Ask:

1. Have you been troubled by pain or stiffness in your back or muscles or joints? Where?
2. How are you affected by this? Can you walk up and down stairs? Can you get out of a chair easily? Can you dress and wash yourself?

#### Examine:

1. **Gait:** get the patient to walk to the end of the room, turn around and come back. Note the length of stride, smoothness of walk and turning around, stance, heel strike and arm swing. Is walking painful? Hemiplegic, Parkinsonian, foot drop and other neurological gaits should be obvious.
2. **Arms, legs and spine:**
  - a. From behind – look at the spine for scoliosis, muscle bulk of the shoulders, paraspinal muscles, gluteal muscles and calves; the iliac crests for loss of symmetry.
  - b. From the side – look for normal lordosis and thoracic kyphosis. Ask the patient to bend; look for normal separation of lumbar spinous processes.
  - c. From in front – look for asymmetry or wasting of major muscle groups (shoulders, arms and quadriceps). Is there deformity of the knees, ankles or feet?

When arthritis seems likely to be an important part of the case, take the time to test movement. Look for restricted, asymmetrical or painful movements.

1. **Spine** – rotation: ‘Turn your shoulders as far as you can to the right, and now to the left’; lateral flexion: ‘Slide your hand down the side of the leg on the right side, and now on the left’. Cervical spine – lateral flexion: ‘Bend your right ear down towards your shoulder; now on the other side’; flexion and extension: ‘Look up and back as far as you can; now put your chin on your chest’.
2. **Shoulders (acromioclavicular, glenohumeral, sternoclavicular joints)** – ‘Put your right hand on your back and reach up as far as you can as if to scratch your back; now the left’; ‘Put your hands up behind your head and your elbows as far back as you can’.
3. **Elbows (extension)** – ‘With your elbows straight, put your arms down beside you’.
4. **Hands and wrists** – ‘Straighten out your arms and hands in front of you’. Look for fixed flexion deformity of the fingers and swelling and deformity of the hands and wrists or wasting of the small muscles of the hands. ‘Turn your hands up the other way’: look at the palms for swelling or muscle wasting. Is supination smooth and complete? Is there external rotation of the shoulder used to make up for limited supination? Test for grip strength: ‘Squeeze my fingers as hard as you can’. Test finger joints: ‘Touch the tip of each finger with your thumb’.
5. **Legs and hips** – ‘Lie down on the bed for me’. Look at leg length and, if suspicious, measure true leg length from anterior superior iliac spine to medial malleolus and apparent length from umbilicus to medial malleolus. Test knee flexion: ‘Bend your knee and pull your foot up towards your bottom’. Meanwhile, put your hand on the patella and feel for crepitus. Test for osteoarthritis of the hip by internally rotating the hip. Flex the knee to 90° and move the foot laterally. Pain and limitation of movement occur early with osteoarthritis.
6. **Feet** – look for arthritic changes especially at the metatarsophalangeal (MTP) joints, bunions, swelling, calluses, etc.

The examination will have to be varied for very immobile patients, but with practice it can be performed rapidly.

## Possible lines of questioning

1. What was your assessment of *this* patient’s general mobility and ability to cope with normal activities?
2. Did he or she have a normal gait?
3. Could he or she get up easily from a chair?
4. Did he or she need any walking aids? Were they adequate in your opinion?

Remember the patterns of joint involvement (Table 9.1).

## Rheumatoid arthritis (RA)

This is the most common of the inflammatory arthritides and is a very common long case in which the diagnosis is usually straightforward and the patient has many physical signs. The peak incidence of the onset of rheumatoid arthritis is in the fourth decade of life and it is three times as common in women as in men. There may be a family history and there is an association with human leukocyte antigen (HLA)-DR4 (70%).

Table 9.1 Patterns of joint involvement

CONDITION	PATTERNS	CLUES
Rheumatoid arthritis (RA)	Symmetrical – wrists, MCPs, PIPs, MTPs with or without large joints	Never DIPs, CMC or temporomandibular joints
Axial spondyloarthropathy	Large joints – lower limb, spine, SI joints	Not hand small joints
Psoriatic	1. Like RA 2. Large joint lower limb 3. DIPs or PIPs or both 4. Arthritis mutilans	Psoriatic rash, nail changes Dactylitis Enthesitis
Gout	Asymmetrical – CMCs, DIPs, PIPs, big toe MTP	Tophi Rare in young women
Osteoarthritis (OA)	Asymmetrical – CMCs, DIPs, PIPs, big toe MTP (often first affected)	Swelling is bony, not boggy
SLE	Symmetrical – PIPs, MCPs, sometimes large joints	Rashes

MCP = metacarpophalangeal; PIP = proximal interphalangeal; DIP = distal interphalangeal; CMC = carpo-metacarpal; SI = sacroiliac; SLE = systemic lupus erythematosus.

If left untreated, the disease leads to progressive and irreversible joint damage and deformity (Fig 9.1a). Life expectancy is reduced by 10 years.

### The history

1. Ask when the diagnosis was made and whether diagnosis seems to have been delayed – the onset of RA in patients over the age of 60 is associated with a worse prognosis for those who are rheumatoid factor (RF) positive. Delay in diagnosis and treatment also leads to a worse outcome.
2. Ask about the presenting features – most patients present with vague generalised symptoms, such as fatigue, anorexia and non-specific musculoskeletal pains; a minority present with obvious oligoarticular arthritis; a few present with severe constitutional symptoms and acute arthritis. Morning stiffness that lasts for more than an hour and continues for more than 6 weeks is characteristic of inflammatory arthritis, but not of osteoarthritis.
3. Ask about the initial treatment.
4. Ask about the disease progression and which joints have been involved. The lumbar spine is never involved and the distal interphalangeal joints are only rarely affected.
5. Enquire about the alterations in treatment over time and any complications encountered.
6. Ask about the non-articular features of the disease:
  - a. skin – Raynaud's phenomenon, leg ulcers (Fig 9.1b)
  - a. eyes – dry eyes (and mouth; Sjögren's syndrome), scleritis, episcleritis or scleromalacia perforans, cataracts (caused by steroids); iritis does not occur
  - b. sore throat, hoarseness or neck pain – suspect cricoarytenoid joint disease; recurrent headaches at the base of the skull or arm tingling from C1–2 subluxation (obtain a lateral flexion cervical spine X-ray)
  - c. lungs – dyspnoea due to diffuse interstitial lung disease or pleural effusion, pain as a result of pleuritis



**Figure 9.1** Rheumatoid arthritis: (a) Joint damage and deformity in the hand; (b) leg ulcer.

(a) W R Frontera, J K Silver and T D Rizzo. *Essentials of physical medicine and rehabilitation*, 3rd edn. Fig. 41.1A. Saunders, Elsevier, 2015, with permission. (b) T P Habif. *Clinical dermatology*, 5th edn. Fig 3.66. Mosby, Elsevier, 2009, with permission.

- d. heart – chest pain due to pericarditis, valve disease (from rheumatoid nodules), increased atherosclerosis
  - e. renal – drug use, amyloid (all rare)
  - f. nervous system – peripheral neuropathy, mononeuritis multiplex, cord compression (due to cervical spine involvement (C1–2 subluxation) or rheumatoid nodules), entrapment neuropathy (particularly carpal tunnel syndrome)
  - g. blood – anaemic symptoms due to chronic disease, iron deficiency (from blood loss), folate deficiency (diet), Felty's syndrome (rheumatoid arthritis with leukopenia and splenomegaly, and non-healing leg ulcers)
  - h. systemic – fever, weight loss, fatigue
  - i. vasculitic – digital arteritis, ulcers, mononeuritis multiplex, pyoderma gangrenosum.
7. Ask about drug complications:
    - a. aspirin (pain or nausea, gastric erosions or peptic ulcers causing bleeding, tinnitus)
    - b. NSAIDs (ulceration, renal impairment, increased cardiac risk)
    - c. methotrexate (MTX) is often used and has a number of side-effects that need to be monitored (hepatic and pulmonary toxicity, low white cell count and thrombocytopenia); the patient should know not to drink alcohol while taking MTX – an alternative drug (to MTX, not alcohol) is leflunomide (side-effects: diarrhoea, alopecia, liver toxicity)
    - d. penicillamine (nephrotic syndrome, thrombocytopenia, rashes, mouth ulcers, alteration in taste and, rarely, systemic lupus erythematosus (SLE), polymyositis, myasthenia gravis, Goodpasture's syndrome or pulmonary infiltration)
    - e. cyclosporin – monitor renal function and blood pressure
    - f. hydroxychloroquine (nausea, pigmentation, bull's eye retinopathy – need regular ophthalmological review)
    - g. sulfasalazine (rash, nausea, haematological abnormalities, abnormal liver function tests, reversible oligospermia)
    - h. anti-tumour necrosis factor (TNF) monoclonal antibody or other biological disease-modifying agent (increased risk of infections including reactivation of TB, positive ANA, lymphoma and demyelination)
    - i. steroids.
  8. Ask about the major current problem – such as decreasing hand function, paraesthesiae, severe pain, etc.
  9. Find out about the current activity of the disease. This can be assessed historically by asking about the number of joints that have recently been involved with active synovitis, the severity and duration of early-morning stiffness (very important), functional ability, changes in weight and the degree of systemic ill health. A severe course is more likely if there is the early appearance of rheumatoid nodules, an insidious onset and constitutional symptoms.
  10. Enquire about past medical history, especially regarding peptic ulceration, drug reactions or renal disease.
  11. Enquire about social background – ability to cope at home, ability to climb steps, independence in daily activities, ability to perform fine-motor activities, the work environment, availability of support services. Smoking is a risk factor for rheumatoid arthritis, particularly in developing anti-CCP (cyclic citrullinated peptide) positive rheumatoid arthritis. The risk falls after smoking is stopped.
  12. Ask about a family history (first-degree relatives) of rheumatoid arthritis, lupus, blood clots, diabetes (type 1), thyroid disease and miscarriages. Other types of autoimmune disease may be present in close relatives.

The examination (Table 9.2)

A thorough general examination is important. In addition to assessing for synovitis in every joint, look particularly at the following:

- 1. general appearance – steroid complications, weight; remember that the pain arises mostly from the joint capsule and that acutely inflamed joints are held in the flexed position to increase the volume of the capsule and reduce pain
- 2. the hands – including vasculitis and hand function; the wrist joints are almost always affected
- 3. the arms – the elbow and shoulder joints, rheumatoid nodules and axillary node enlargement
- 4. the face – check the eyes for Sjögren’s syndrome, scleritis, episcleritis, scleromalacia perforans, cataracts, anaemia and signs of hyperviscosity in the fundi; enlarged parotid glands (Sjögren’s syndrome); the mouth (dryness, dental caries, ulcers); listen for a hoarse voice and palpate the temporomandibular joints (crepitus); *note*: rheumatoid arthritis does not cause iritis
- 5. the neck – for signs of cervical spine involvement
- 6. the chest – the heart for pericarditis, conduction defects, and aortic and mitral regurgitation; the lungs for pleural effusion, fibrosis, nodules, infarction and Caplan’s syndrome
- 7. the abdomen – for splenomegaly and epigastric tenderness
- 8. the hips and knees

Table 9.2 Rheumatoid arthritis	
<b>1. GENERAL INSPECTION</b> Cushingoid appearance Weight	<b>6. CHEST</b> Heart – pericarditis, valve lesions Lungs – effusion, fibrosis, infarction, infection, nodules (and Caplan’s syndrome) Tuberculosis (steroids)
<b>2. HANDS (EXAMINE ALL JOINTS)</b>	<b>7. ABDOMEN</b> Splenomegaly (e.g. Felty’s syndrome) Epigastric tenderness (drugs) Inguinal nodes
<b>3. ARMS</b> Entrapment neuropathy (e.g. carpal tunnel) Subcutaneous nodules Elbow joint Shoulder joint Axillary nodes	<b>8. HIPS</b>
<b>4. FACE</b> Eyes – dry eyes (Sjögren’s), scleritis, episcleritis Scleromalacia perforans Cataract (steroids, chloroquine) Fundi – hyperviscosity Face – parotids (Sjögren’s) Mouth – dryness, ulcers, dental caries, temporomandibular joint (crepitus)	<b>9. KNEES</b>
<b>5. NECK</b> Cervical spine Cervical nodes	<b>10. LOWER LIMBS</b> Ulceration (vasculitis) Calf swelling (ruptured synovial cyst) Peripheral neuropathy Mononeuritis multiplex Cord compression
	<b>11. FEET</b>
	<b>12. OTHER</b> Urine – protein, blood (drugs, vasculitis, infection, amyloidosis) Rectal examination (blood)



9. the lower legs – for ulcers, calf swelling (ruptured Baker's cyst), neuropathy, mono-neuritis multiplex and signs of cord compression
10. the feet
11. the peripheral nervous system – for peripheral neuropathy or mononeuritis multiplex (caused by vasculitis)
12. the skin – for cutaneous vasculitis (ischaemic ulcers on the legs or brown discoloured areas in the nail beds; *note*: exclude psoriasis)
13. urine analysis – for protein and blood, and rectal examination for blood (if there is a history suggestive of NSAID complications).

### Differential diagnosis

Consider the differential diagnosis of a deforming symmetrical chronic polyarthropathy:

1. rheumatoid arthritis
2. psoriatic arthropathy and other seronegative spondyloarthropathies
3. chronic tophaceous gout (rarely symmetrical)
4. primary generalised osteoarthritis
5. SLE (usually but not always non-deforming).  
Remember that the causes of arthritis plus nodules include:
  1. rheumatoid arthritis (seropositive)
  2. SLE – rare
  3. rheumatic fever (Jaccoud's arthritis) – very rare
  4. amyloid arthropathy (most usually in association with multiple myeloma); *note*: gouty tophi and xanthoma may sometimes be confused.

### Investigations

To support the diagnosis (remembering that this is primarily a clinical diagnosis; see Table 9.3), investigations include:

1. **serological tests**
  - a. rheumatoid factor (RF) – 70% of patients are seropositive; patients may at first be seronegative and seroconvert later. (*Note*: Most patients are RF positive if they have nodules or associated vasculitis; remember that more than 10% of well people over the age of 65 have RF and that it is commonly found in association with infections and other inflammatory conditions, in relatives of patients with rheumatoid arthritis and transiently after some vaccinations.)
  - b. anti-citrullinated cyclic peptide (anti-CCP) – this is more specific (97%); it is associated with a more severe disease course and erosive disease
2. **X-ray films of involved joints** – changes to look for are:
  - a. soft-tissue swelling
  - b. symmetrical joint space narrowing (OA causes asymmetrical narrowing) (Figs 9.2 and 9.3) and erosions
  - c. juxta-articular osteoporosis
  - d. marginal joint erosions (Fig 9.4).

Investigations used to assess the activity of the disease include:

  1. ESR or CRP – remember that the differential diagnosis of a raised ESR in rheumatoid arthritis includes:
    - a. active disease
    - b. amyloidosis
    - c. infection
    - d. Sjögren's syndrome

**Table 9.3 Criteria for the diagnosis of rheumatoid arthritis in newly presenting cases (2010 ACR/ EULAR RA criteria)**

Target population (who should be tested?) – patients:	
1. who have at least one joint with definite clinical synovitis (swelling)	
2. with the synovitis not better explained by another disease	
<b>CLASSIFICATION CRITERIA FOR RA</b> (score-based algorithm: add score of categories A–D; a score of $\geq 6/10$ is needed for classification of a patient as having definite RA)	<b>SCORE</b>
<b>A. JOINT INVOLVEMENT</b>	
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
>10 joints (at least one small joint)	5
<b>B. SEROLOGY (AT LEAST ONE TEST RESULT IS NEEDED FOR CLASSIFICATION)</b>	
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
<b>C. ACUTE-PHASE REACTANTS (AT LEAST ONE TEST RESULT IS NEEDED FOR CLASSIFICATION)</b>	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
<b>D. DURATION OF SYMPTOMS</b>	
<6 weeks	0
$\geq 6$ weeks	1
ACPA = anti-citrullinated protein antibody; RF = rheumatoid factor.	
© 2010 American College of Rheumatology and European League Against Rheumatism. Rheumatoid Arthritis Classification Criteria 2010. <i>Arthritis and Rheumatism</i> 2010; 62(9):2569–81.	

2. haemoglobin measurement – the severity of normochromic anaemia usually correlates with activity
3. anti-CCP, and RF titres
4. the presence of progressive erosions on serial X-ray films.

### Treatment

1. Remember that the aim of modern treatment is to induce complete remission of the disease by suppressing the inflammatory process. This means early diagnosis and introduction of disease-modifying antirheumatic drugs (DMARDs). The traditional DMARDs will control the disease effectively for many patients, but the newer biological therapies allow many more patients to have the disease controlled. The general principles of treatment include:
  - education





**Figure 9.2** Cervical spine X-ray of a patient with rheumatoid arthritis. Note the erosions and loss of joint space. Special views are needed to exclude erosion of the odontoid process.

Figure reproduced courtesy of The Canberra Hospital.

- physiotherapy, including exercise and splinting of the joints to prevent deformity
- occupational therapy
- smoking cessation
- rest of inflamed joints
- drug treatment aimed at reducing pain and inflammation (with aspirin, other NSAIDs or COX-2 inhibitors) and at preventing progression of the disease. The gastrointestinal toxicity of the traditional NSAIDs (i.e. peptic ulceration) is reduced by the COX-2 inhibitors; however, all can cause dyspepsia and renal disease (e.g. acute interstitial nephritis) and worsen renal function in patients with diabetic or atherosclerotic kidney disease; all NSAIDs are associated with an increased risk of myocardial infarction. If there is aspirin allergy, sodium salicylate is an alternative.



**Figure 9.3** (a) X-ray of the pelvis of a patient with rheumatoid arthritis; note the severe destructive changes on both sides – very different from (b). (b) Osteoarthritis of the left hip; note the asymmetrical loss of joint space.

Figures reproduced courtesy of The Canberra Hospital.

2. The use of DMARDs is now recommended early on for patients with active progressive disease, especially if there is evidence of joint destruction ([Table 9.4](#)). These drugs include:
  - methotrexate (MTX)
  - sulfasalazine
  - hydroxychloroquine
  - cyclosporin
  - leflunomide
  - azathioprine
  - penicillamine
  - gold (oral or injected).



**Figure 9.4** X-ray of the chest of a patient with rheumatoid arthritis involving the shoulder; note the erosions of the humeral heads with subluxation and erosions of the distal clavicles.

Figure reproduced courtesy of The Canberra Hospital.

**Table 9.4 Risk factors for destructive disease**

1. High-titre RF or positive anti-CCP
2. Constitutional symptoms
3. Insidious onset
4. Erosions early on X-ray
5. Rheumatoid nodules early
6. HLA-DR4

These medications have a slow onset of action (weeks for methotrexate to months for gold). There is evidence that they can lead to healing of bone erosions. Monitoring should include:

- full blood count
  - urine testing for proteinuria
  - specific tests for certain drugs, such as liver function tests for methotrexate, or ophthalmological examination and assessment of visual fields for hydroxychloroquine.
3. Methotrexate is the most commonly used of these drugs; it can be given orally or intramuscularly, usually 10–25 mg weekly, but starting with a low dose. It is usually better tolerated than the other DMARDs and is often the drug of first choice and given early in the course of the disease to decrease inflammation and sometimes the development of synovitis. MTX may sometimes cause an increase in the number of rheumatoid nodules. It can be given alone or in combination with hydroxychloroquine and sulfasalazine. Folic acid is given daily to decrease the risk of side-effects of MTX, especially mouth ulcers. Safety monitoring includes full blood count and liver function tests. Adverse reactions include rash, abnormal liver function tests

(transaminases), leukopenia, thrombocytopenia and interstitial lung disease. It should not be given to patients with glucose-6-phosphate dehydrogenase deficiency.

- 4. Alternative agents in use include leflunomide (a pyrimidine antagonist that inhibits the proliferation of T cells).
- 5. The biological agents are generally second-line treatments because of their cost, but their use has increased greatly recently. Table 9.5 shows the current prescribing rules for these drugs, while Table 9.6 lists their side-effects and precautions for their use.

Table 9.5 Rules for use of biological agents for the treatment of rheumatoid arthritis
<ul style="list-style-type: none"><li>1. Failure of at least 6 months of treatment with a traditional DMARD</li><li>2. Treatment must include MTX and combinations of hydroxychloroquine, leflunomide or sulfasalazine</li></ul>

Table 9.6 Side-effects and precautions for use of biological agents
<ul style="list-style-type: none"><li>1. Local reactions at injection sites (usually mild)</li><li>2. Infusion reactions – nausea, flushing, headache or palpitations (often well managed with antihistamines)</li><li>3. Delayed infusion reactions – fatigue, rash, arthralgia and myalgia (may require steroid use or cessation of treatment)</li><li>4. Increased risk of serious infections – patients should avoid undercooked eggs and meat (<i>Listeria</i> and <i>Salmonella</i> organisms)</li><li>5. Reactivation of TB (screen for TB before use – Mantoux, interferon gamma (IFN-<math>\gamma</math>), chest X-ray)</li><li>6. Contraindicated for patients with active hepatitis B or C</li><li>7. Contraindicated for patients receiving immunosuppression</li><li>8. Live vaccines are contraindicated</li><li>9. Possible increased incidence of non-melanoma skin cancers</li><li>10. Not recommended in pregnancy, though no evidence of problems</li></ul>

There are two main types of biological agents: the TNF (tumour necrosis factor) inhibitors and the non-TNF inhibitors.

THE TNF INHIBITORS

These drugs block the activation of TNF- $\alpha$ , which is an inflammatory cytokine found in the synovium of RA patients. Suppression of synovitis with these agents can almost completely prevent joint and bone destruction. All the TNF inhibitors have to be given by intravenous infusion or subcutaneous injection. The five drugs currently available (Table 9.7) are equally effective and can be used in combination with methotrexate. Failure to respond occurs in 30% of patients and for them it is worth trying another drug in the same class or a non-TNF inhibitor.

Table 9.7 Currently available TNF inhibitors for adults with RA
<ul style="list-style-type: none"><li>1. Infliximab: IV infusion initially 3 mg/kg at 0, 2 and 6 weeks and then 8-weekly (with MTX)</li><li>2. Adalimumab: SC injection 40 mg 2nd-weekly</li><li>3. Certolizumab pegol: SC injection of 400 mg at 0, 2 and 4 weeks, then every 4th week</li><li>4. Etanercept: SC injection 25 mg twice weekly or 50 mg weekly</li><li>5. Golimumab: SC injection 50 mg every 4th week (with MTX)</li></ul>

### THE NON-TNF INHIBITORS

These DMARDs inhibit proinflammatory cytokines other than TNF (see [Table 9.8](#) for a list of currently available drugs).

**Table 9.8 Currently available non-TNF inhibitors and side-effects**

1. Abatacept: a T cell co-stimulation inhibitor; monthly IV infusion or subcutaneous injection (hypersensitivity reactions, increased risk of serious infections)
2. Anakinra: an interleukin 1 (IL-1) receptor antagonist; daily SC injection (injection site reactions, neutropenia). Less effective than the other drugs in this class
3. Rituximab: antibody against CD20 B cell antigen; two 1000 mg IV infusions 2 weeks apart (infusion reactions, serious infection – URTI, UTI, sinusitis, progressive multifocal leukoencephalopathy)
4. Tocilizumab: IL-6 inhibitor; monthly IV infusion 8 mg/kg (URT, neutropenia, increased lipids abnormal LFTs)
5. Tofacitinib: Janus kinase inhibitor (increased risk of infections including herpes zoster, liver dysfunction)

URT = upper respiratory tract infection; UTI = urinary tract infection; LFT = liver function test.

## HINTS

### Drugs

1. Drugs are safe if monitored.
2. SLE should always be treated with hydroxychloroquine.
3. Avoid big doses of steroids in scleroderma patients (see [Table 9.9](#)).
4. Methotrexate is useful for any form of bad joint disease.
5. Ankylosing spondylitis should be treated with NSAIDs first.
6. Patients on biological agents may have serious infections without the usual signs.
7. If a patient is unwell, consider stopping a disease-modifying agent but do not stop steroids.

**Table 9.9 What drugs to use in rheumatoid arthritis and other autoimmune conditions**

RHEUMATOID ARTHRITIS	ANKYLOSING SPONDYLITIS	SCLERODERMA
MTX with or without: hydroxychloroquine, sulfasalazine, leflunomide, prednisone	NSAIDs and exercise Try different NSAID	Treat Raynaud's MTX
No better after 6 months: add biological agent	No better at 3 months: add biological agent	If getting worse, ILD or cardiac involvement: cyclophosphamide, autologous stem cell transplant Keep steroid dose below 15 mg
<i>Note:</i> Always screen for TB and hepatitis B and C (serology) before using a biological agent.		
MTX = methotrexate; ILD = interstitial lung disease.		

6. The main indications for steroid use are:
  - new or uncontrolled disease as a bridge until suppressive treatment with slow-acting DMARDs becomes effective
  - vasculitic complications of rheumatoid arthritis (where high doses are needed)
  - chronic low-dose treatment, which may be justifiable in the elderly
  - local steroid injections for acute involvement of a joint (these may give prolonged relief from pain and swelling, and improve function).
7. Surgery may be very effective treatment for severely diseased joints. Hip, shoulder and knee replacements are the most successful operations. Arthroplasty and relief of contractures can be of value, especially in the hands.

The prognosis of this chronic, but often intermittent, disease varies. Only a small minority of patients have no permanent joint problems 10 years after diagnosis, and half have a disability that interferes with work by this time. The greater the number of involved joints at the outset and the more abnormal the inflammatory markers, the worse is the prognosis. Life expectancy is reduced by up to 7 years as a result of the increased risk of gastrointestinal bleeding, the increased risk of infection and a threefold increased risk of atherosclerosis. The use of methotrexate has been shown to halve excess mortality, including that from cardiovascular disease.

At each visit, assess the patient for disease activity and function (Box 9.1).

#### Box 9.1 Routine assessment of patients with RA

1. Fatigue
2. Morning stiffness
3. Weight loss
4. Functional limitations
5. Acute-phase reactants (ESR, CRP)

#### PREGNANCY AND RHEUMATOID ARTHRITIS

The disease tends to abate during pregnancy but, in order to reduce the risk of fetal toxicity and assist conception, some drugs should be adjusted:

- Methotrexate should be stopped 3 months before conception.
- Leflunomide should be stopped until it is no longer detectable in the serum.
- Sulfasalazine can cause reversible oligospermia and men should stop this 3 months before conception.
- Aspirin and NSAIDs can interfere with implantation; they can be used in the second trimester, but later in pregnancy can cause premature closure of the ductus arteriosus and interfere with labour.
- Steroids increase the risk of maternal diabetes and cleft palate in the baby.
- The safety of biological agents is uncertain.
- Methotrexate should not be used by breastfeeding mothers.
- NSAIDs and low-dose steroids are considered safe for breastfeeding mothers.

## Possible lines of questioning

1. What is your impression of the activity of *this* patient's disease?
2. Has he or she a good understanding of the side-effects of these disease-modifying drugs?
3. How severely affected is *this* patient's mobility?
4. Would you recommend changes to drug or other treatment for *this* patient?
5. What is the history of steroid use for *this* patient?
6. Is there evidence of osteoporosis?

## Osteoarthritis

This common problem will affect many long-case patients. It may not be the main medical problem, but it may be one that affects the patient's life severely. It affects 80% of people over 55 years of age, and 95% of people over 65. It is associated with obesity and diabetes, and may be one of the reasons a patient cannot exercise and lose weight. It should be possible from the history and examination to distinguish this from an inflammatory arthritis, although many patients may have both.

Osteoarthritis involves synovial joints. Weight-bearing joints (the hip and the knee and the proximal interphalangeal (PIP) and distal interphalangeal (DIP) joints of the hands and the first MTP of the foot are most often affected (Fig 9.5). There is usually loss of articular cartilage, meniscal damage, laxity of surrounding ligaments, formation of osteophytes and changes to subchondral bone.

Risk factors include obesity (for the knee especially), a family history and joint injury, which can be repetitive or acute.



**Figure 9.5** Osteoarthritis of the hand.

A Stevens, J S Lowe and I Scott. *Core pathology*, 3rd edn. Fig. 24.17. Elsevier Ltd, 2009, with permission.



## The history

Ask:

1. How long has the arthritis been a problem?
2. Has there been swelling or inflammation of the joints (suggesting an inflammatory arthritis rather than osteoarthritis)?
3. What joints have been involved? – DIP, shoulders, hips, knees and proximal MCP joints are often affected.
4. Are the joints stiff in the morning? – patients with osteoarthritis do not have much morning stiffness.
5. Is there a family history?
6. Have there been injuries to the joints (e.g. from playing sport)?
7. Has the patient been able to lose weight?
8. What limitations are there with respect to mobility and exercise?
9. Are walking sticks or frames needed?
10. How does the patient manage around the house – ADLs, etc.?
11. Is he or she able to drive or work?
12. What treatment has been tried – drug treatment, joint injections, exercise and physiotherapy, alternative treatments, surgery, weight loss?
13. What drugs have been used?
14. Have there been side-effects, especially from NSAIDs?
15. Have these treatments helped?

## The examination

1. Examine the joints that have been giving the patient problems.
2. Look for deformity, loss of range of movement, ligamentous laxity, scars from previous surgery, joint pain on movement.
3. Test joint function (e.g. by getting the patient to walk).
4. Look at the effectiveness of walking aids.

## Management

### NON-PHARMACOLOGICAL

Many treatments will probably have been tried but consider:

1. exercise:
  - a. stretching and mobility exercises can help maintain joint range of motion
  - b. aquatic exercise may be possible for patients with severe restriction
  - c. exercise bicycle so that exercise is not weight-bearing
  - d. supervised or group exercise works better for reduction of pain than independent exercise at home
2. use of mobility aids:
  - a. a stick used in the opposite hand
  - b. knee braces and foot orthoses
3. loss of weight – this is the most important modifiable risk factor for osteoarthritis. A 10% loss of weight achieved by diet and exercise has been shown to reduce symptoms by 50%.

### DRUG TREATMENT

1. **NSAIDs** are the usual first-line treatment. They are probably somewhat more effective than paracetamol, but at the expense of their well-known gastrointestinal and cardiovascular side-effects. Using a proton pump inhibitor with a NSAID reduces GI bleeding risk in older patients (>60 years) or those with a history of peptic ulcer. There is no good information about the optimal duration of treatment.

2. **Paracetamol** (up to 4 g/day) has been a common choice for osteoarthritis because of concerns about NSAID side-effects. There is not much evidence, however, that it is more effective than placebo, especially for knee pain, and there have been concerns about acute liver failure with large doses (>4 g daily).
3. **Topical NSAIDs** have been shown to be useful for knee and hand arthritis and seem safer than oral NSAIDs. Topical capsaicin can be a useful adjunct.
4. **Intra-articular injections of steroids** give 1–2 weeks of relief and improve mobility. They are useful for acute exacerbations. Frequent use can cause cartilage and joint damage and involve some risk of infection.
5. **Opioids** can be given topically or orally and are more effective than placebo for knee arthritis, but the benefits are modest. Their use is associated with more adverse events than is the case with NSAIDs. These include cardiovascular events, fractures and an increased mortality.
6. **Duloxetine** is a centrally acting serotonin reuptake inhibitor. It has been shown to be superior to placebo and can be used in combination with NSAIDs.

### SURGERY

Joint replacement can be very helpful when other treatment has failed. Arthroscopic procedures have not been shown to be effective for knee arthritis beyond what medical treatment can achieve.

### COMPLEMENTARY MEDICINES

1. The most commonly used of these drugs is glucosamine. It seems no more effective than placebo in controlled trials.
2. Fish oil and chondroitin have similarly failed to show advantages over placebo for knee pain.

## Possible lines of questioning

1. How would you manage *this* obese patient with severe osteoarthritis of the knees?
2. What would advise *this* woman with hip arthritis and a history of ischaemic heart disease about the use of NSAIDs?
3. How would you assess *this* patient's surgical risk and likely postoperative course for knee replacement surgery?

## Ankylosing spondylitis (spondyloarthritis, SPA)

Patients with this chronic condition are more commonly seen as short cases, but the problem may form part of a long-case patient's problems.

The classification of this group of diseases is in a state of flux. The term axial spondyloarthropathy now includes:

- ankylosing spondylitis
- reactive arthritis
- psoriatic arthritis and spondylitis
- enteropathic arthritis and spondylitis
- juvenile-onset spondyloarthritis.

The axial skeleton, peripheral joints and extra-articular structures are affected (Fig 9.6).



**Figure 9.6 (a and b) Ankylosing spondylitis.**

H N Herkowitz, S R Garfin, F J Eismont et al. *Rothman-Simeone the spine*, 6th edn. Fig. 35.1. Saunders, Elsevier, 2011, with permission.

In some populations 90% of patients are HLA-B27 positive. Between 1% and 6% of people with HLA-B27 have the disease.

It affects men two to three times as often as women and rarely begins after the age of 45 – the median age of diagnosis is 23.

### The history

The patient will be likely to know the diagnosis. Ask:

1. The age of diagnosis and symptoms leading up to the diagnosis:
  - Lower aching back pain with some hours of morning stiffness is common. Pain tends to occur over the lower back, buttocks and posterior thighs.
  - Nocturnal exacerbation is often a feature of ankylosing spondylitis.
  - There may be tenderness over bony processes including the spinous processes, ischial tuberosities, iliac crests, greater trochanters, costochondral junctions and heels.
  - Thirty per cent of patients develop hip and shoulder pain.
  - Asymmetrical peripheral joint involvement occurs in a similar proportion
2. How was the diagnosis made – X rays, MRI, or HLA assessment (see [Table 9.10](#))?
3. What treatment has been used? Find out:
  - which drugs, if any, have been used
  - whether they have helped with symptoms
  - whether the patient knows if radiological and serological test results have improved
  - whether there have been problems with side-effects (see p. 233)
  - whether joint surgery has been required (e.g. hip replacement)
  - whether other manifestations of the disease required treatment (e.g. uveitis and topical steroids).
4. How has this debilitating disease affected the patient's ability to work, exercise and perform ADLs? What symptoms are present at the moment? How limited is the patient by these?

5. How is the treatment being monitored?
6. Have there been features of reactive arthritis – urethritis, conjunctivitis?
7. Has the patient psoriasis?
8. Has there been a diagnosis of inflammatory bowel disease?
9. Has there been testing for HIV infection? Reactive arthritis and psoriatic arthritis exacerbations are associated with HIV infection.
10. Were the symptoms preceded by gastrointestinal or genitourinary infections? Reactive arthritis is often preceded by such infections.
11. The extra-articular manifestations include:
  - uveitis (40%)
  - aortic regurgitation
  - symptoms of cauda equina syndrome (late)
  - upper lobe interstitial lung disease (late).

### Diagnosis

Persistent back pain in a young person that is worse at night should suggest the diagnosis. The presence of associated features and raised inflammatory markers makes the diagnosis more likely (Table 9.10). The most important differential diagnosis is malignancy.

Find out whether the patient knows the results of any of these investigations.

**Table 9.10 Diagnosis of axial spondyloarthritis**

1. Age less than 45
2.  $\geq 3$  months of back pain
3. HLA-B27 plus two or more of:
  - inflammatory back pain
  - heel pain (enthesitis)
  - uveitis
  - dactylitis (diffuse swelling of digits – toes or fingers)
  - inflammatory bowel disease
  - family history of SPA or HLA-B27
  - elevated CRP
  - response to NSAIDs
4. Sacroiliitis on X ray or MRI.\*

\*MRI shows three or more corner inflammatory lesions in two slices or more.

### The examination

Examine the patient as set out for the short-case ankylosing spondylitis (p. 489).

### Management

1. An exercise program is usually recommended to help the patient maintain flexibility.
2. Non-steroidal anti-inflammatories have been shown to relieve symptoms and slow radiographic progression.
3. For the many patients who progress despite this treatment, anti-TNF- $\alpha$  treatment with infliximab or etanercept has been very successful in improving symptoms and markers of disease activity. Even patients with severe deformity have obtained improvement. The doses used are similar to those used for rheumatoid arthritis.
4. Find out whether these drugs have been used, whether they helped symptoms, any side-effects, if joint surgery is being considered, and how the disease is affecting the patient's life (and family).

## Possible lines of questioning

1. What precautions and advice would you give *this* patient before starting anti-TNF $\alpha$  treatment?
2. What is your assessment of *this* patient's functional state?

## Systemic lupus erythematosus

This multisystem disorder occurs usually in patients between 20 and 40 years of age.

- Women are more often affected than men (8:1) and there is an increased incidence in families (monozygotic twins have a 50% concordance).
- There are associations with HLA-DR2, with HLA-DR3, and with homozygous deficiencies of the early components of complement.
- It presents diagnostic as well as long-term management problems. The diagnosis requires at least four of the 11 published criteria either currently or in the past (Table 9.11). Fewer than four criteria are often labelled 'possible lupus'. Non-specific positive autoimmune tests with some evidence of inflammation can be referred to as 'undifferentiated connective tissue disease'.

Table 9.11 American Rheumatism Association criteria for SLE

1. Malar rash – sparing the nasolabial folds
2. Discoid rash
3. Photosensitivity rash
4. Oral ulcers
5. Arthritis – non-erosive and affecting two or more peripheral joints
6. Serositis – pleurisy or pericarditis, with audible rub, effusion or ECG changes
7. Renal disorder – persistent proteinuria > 0.5 g/day or cellular casts
8. Neurological disorder – seizures or psychosis not related to drugs or metabolic abnormalities
9. Haematological disorder – haemolytic anaemia, leukopenia (<4000/ $\mu$ L), lymphopenia (<2000/ $\mu$ L), thrombocytopenia (<100 000/ $\mu$ L)
10. Immunological disorder – anti-DNA antibodies in abnormal titre, or anti-Smith (anti-Sm) antibody, or positive anti-phospholipid antibodies
11. Antinuclear antibody disorder – abnormal ANA titre >1:160

Note: Four or more manifestations of the 11 must be present serially or simultaneously.

## The history

1. Ask about the presenting symptoms (Table 9.12):
  - a. general symptoms – malaise (nearly all patients), weight loss (60%), nausea and vomiting (50%), thrombosis of veins or arteries (15%)
  - b. musculoskeletal symptoms (95%) – arthralgia, arthritis (typically symmetrical and non-erosive), myalgia and myositis
  - c. dermatological symptoms (85%) – skin rash, alopecia, oral and nasal ulcers
  - d. fever (77%)
  - e. neuropsychiatric symptoms (60%) – delirium, dementia, convulsions, chorea, neuropathy, loss of vision (optic neuritis), stroke, headache, symptoms resembling multiple sclerosis, anxiety and depression

- f. renal tract symptoms (50%) – haematuria, oedema, renal failure (just about any type of glomerulonephritis)
- g. respiratory tract symptoms (45%) – pleurisy
- h. cardiovascular symptoms (40%) – pericarditis, myocarditis, valvular lesions, premature coronary artery disease (increased atherosclerosis)
- i. haematological symptoms (50%) – lymphadenopathy, anaemia
- j. gastrointestinal symptoms (30%) – nausea, diarrhoea, pseudo bowel obstruction, perforation
- k. thrombophlebitis, recurrent abortions or fetal death in utero (suggests antiphospholipid syndrome)
- l. sicca symptoms (secondary to Sjögren's syndrome)
- m. reduced ADL and ability to work as a result of the effect of this chronic and relapsing disease on the patient's life.

**Table 9.12 Summary of systems review for SLE**

1. Aphthous ulcers	6. Dry eyes and mouth
2. Serositis	7. Thrombosis
3. Raynaud's	8. Miscarriages
4. Alopecia	9. Nephritis
5. Photosensitivity rashes	

2. Ask about any drug history (e.g. procainamide, hydralazine – causes of an SLE-like syndrome) (Table 9.13). Remember, newer antiarrhythmic and antihypertensive drugs have made classical drug-induced lupus less common and typically the symptoms resolve rapidly with cessation of the drug; autoantibody levels (anti-histone) diminish slowly. Anti-TNF drugs can also cause a lupus-like syndrome with a positive ANA and anti-double-stranded DNA (anti-dsDNA); minocycline and hydralazine do this too, but with these drugs ANCA (antineutrophil cytoplasmic antibody) is positive as well.

**Table 9.13 Drugs inducing SLE**

1. Procainamide (most patients are ANA positive within 1 year; 15–20% develop SLE)
2. Hydralazine (most patients are ANA positive within 1 year; 5–10% develop SLE)
3. Isoniazid*
4. Methyldopa*
5. Penicillamine*
6. Chlorpromazine*
7. Anticonvulsants,* particularly phenytoin (not sodium valproate)
<i>Note:</i> There is an increased incidence of drug-induced lupus in slow acetylators who will develop a positive ANA and clinical manifestations sooner than rapid acetylators. Drug-induced lupus is more common in the elderly because of the more frequent use of drugs in this group. There is usually no renal or nervous system disease, no antibody to dsDNA and improvement may occur if the drug is withdrawn.
*Rarely cause overt SLE, but ANA is commonly positive.

3. Ask about any treatment given and any complications of treatment.
4. Ask about problems during pregnancy and use of contraception. Pregnancy is especially risky if the disease is active. Progesterone or low-dose oestrogen contraception is advisable.

- 5. Ask about protection from sunlight. This reduces the risk of photosensitivity rashes and flares of systemic disease.
- 6. Enquire about the family history.
- 7. Enquire about the patient’s understanding of the implications of this chronic and incurable disease and its prognosis. Remember, though, that current treatment allows a 90% 10-year survival rate compared with 50% 30 years ago.

The examination (Table 9.14)

Table 9.14 Systemic lupus erythematosus	
<b>1. GENERAL INSPECTION</b> Cushingoid Weight Mental state	<b>5. CHEST</b> Cardiovascular system – endocarditis Respiratory system – pleural effusion, pleurisy, pulmonary fibrosis, collapse or infection
<b>2. HANDS</b> Vasculitis Rash Arthropathy (symmetric polyarthritis)	<b>6. ABDOMEN</b> Hepatosplenomegaly
<b>3. ARMS</b> Livedo reticularis Purpura Proximal myopathy (SLE, steroids)	<b>7. HIPS</b> Aseptic necrosis
<b>4. HEAD</b> Alopecia, lupus hairs Eyes – scleritis, cytooid lesions, etc. Mouth – ulcers (painless), infection Rash (e.g. butterfly) – spares nasolabial folds Cranial nerve lesions Cervical adenopathy	<b>8. LEGS</b> Feet – small joint synovitis Rash Proximal myopathy Cerebellar ataxia Neuropathy (uncommon) Mononeuritis multiplex
	<b>9. OTHER</b> Urine analysis (proteinuria) Blood pressure (hypertension) Temperature chart

- 1. Inspect the patient for weight loss and Cushingoid appearance (because of steroid treatment) and assess the patient’s general mental state.
- 2. Examine all the skin for a classical malar rash (Fig 9.7), a discoid erythematous raised rash (Fig 9.8), and a photosensitivity rash.  
Remember that discoid lupus erythematosus (DLE) occurs in 20% of SLE patients. This disfiguring skin disease leads to permanent hair loss with telangiectasia, scaling, circular erythematous lesions and follicular plugging. There is often destruction of skin appendages. DLE can occur without other features of SLE.
- 3. Look at the hands for vasculitis, which can produce nail-fold infarcts and ischaemia or gangrene, and rash (e.g. photosensitivity, diffuse maculopapular rash).
- 4. Look for Raynaud’s phenomenon and arthropathy (fusiform swelling of the PIP joints or synovitis, possibly in a rheumatoid arthritis distribution – 10% develop swan-neck deformity and ulnar deviation of the fingers). This non-erosive arthropathy is referred to as Jaccoud’s arthritis.
- 5. Look at the forearms for livedo reticularis and purpura as a result of vasculitis or thrombocytopenia. Test for proximal myopathy caused by actual disease or secondary to steroid treatment.
- 6. Inspect the head. Look for alopecia. Lupus hairs are characteristic: they occur above the forehead and are short, broken hairs that grow back quickly after hair loss (except in patients with DLE).





**Figure 9.7** Malar rash in SLE (face).

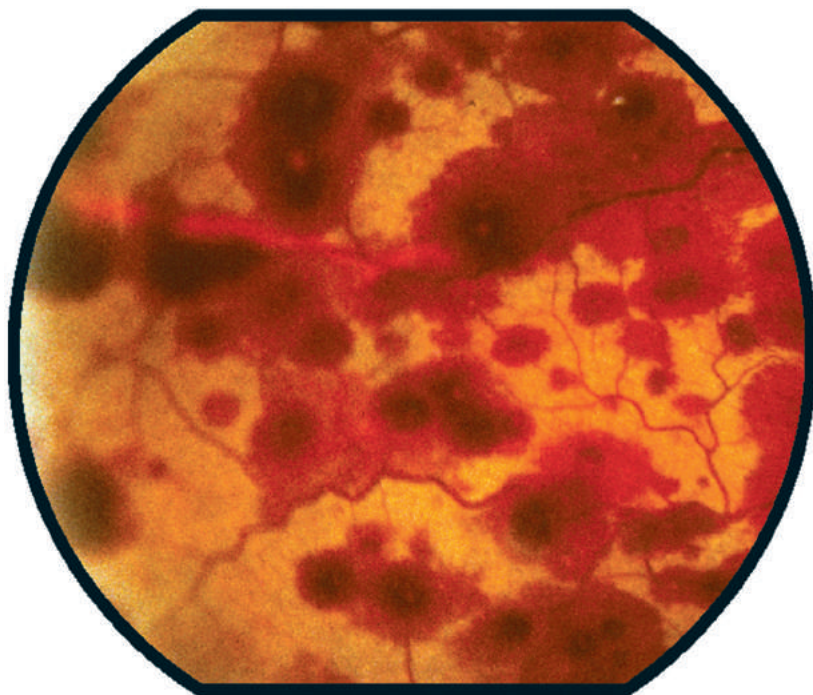
B J Beck. Mental disorders due to a general medical condition. *Comprehensive clinical psychiatry*. Ch 21:257–81. On-line Archives of Rheumatology, 2008, with permission.



**Figure 9.8** Discoid lupus rash. Note sparing of the proximal interphalangeal joints, a typical SLE feature.

M Dall'Era. *Kelley's textbook of rheumatology*. Saunders, Elsevier, 2013, with permission.

7. Look at the eyes for keratoconjunctivitis sicca and for pale conjunctivae due to anaemia, and look at the fundi for cytooid lesions (hard exudates secondary to vasculitis) (Fig 9.9).
8. Look in the mouth for ulcers and infection. Note any facial rash (butterfly photosensitivity rash (30%), discoid lupus or diffuse maculopapular rashes). Feel the cervical and axillary nodes.
9. Examine the chest. In the cardiovascular system, note signs of pericarditis or murmurs (Libman–Sacks endocarditis is a very uncommon cause of clinical signs).



**Figure 9.9** Cytoid lesions in fundi. This patient also has a haemorrhagic fundus from SLE.

L Yannuzzi. *The retinal atlas*. Ch 6. Elsevier 2010, with permission.

10. In the respiratory system, note signs of pleural effusion, pleuritis, interstitial lung disease or atelectasis.
11. Examine the abdomen for splenomegaly (usually mild) and hepatomegaly. Feel for abdominal tenderness.
12. Examine the hips for signs of aseptic necrosis.
13. Examine for proximal weakness in the legs, cerebellar ataxia, hemiplegia and transverse myelitis. Assess mental status (cognitive changes, even psychosis).
14. Also examine for neuropathy (mainly sensory) and mononeuritis multiplex, as well as thrombophlebitis and leg ulceration.
15. Look at the urine analysis for evidence of renal disease (haematuria and proteinuria).
16. Take the blood pressure (it may be elevated in renal disease). Also look at the temperature chart for fever, indicating active disease or secondary infection.

### Investigations

1. Diagnosis depends on a combination of the symptoms, signs and laboratory test results (see [Tables 9.11](#), [9.12](#) and [9.15](#)). Almost all cases are ANA positive, which is very sensitive but not specific (if ANA negative, check Sjögren's syndrome A/B (SSA/SSB) antibodies). Very specific tests for SLE are anti-dsDNA (including titre, 100% specific) and anti-Smith (anti-Sm – positive virtually only in SLE).
2. Patients who do not fit the criteria may have another connective tissue disease. Mixed connective tissue disease (MCTD) is suggested by the overlapping clinical

**Table 9.15 Antibodies associated with connective tissue and other autoimmune diseases**

DISEASE	ANTIBODIES ASSOCIATED
Systemic lupus erythematosus	Anti-single-stranded DNA (anti-ssDNA) – not specific (useless!) Anti-dsDNA (70%) – high titres are specific Anti-Smith (30%) – specific for lupus Anti-RNP (30% in low titre) – high titre in MCTD Anti-Ro-SS-A (30%) – associated with primary Sjögren's syndrome, congenital heart block; can cause nephritis Anti-SS-B (15%) – associated with Sjögren's syndrome Antihistone (drug-induced SLE usually from hydralazine, or procainamide; 95%) Antiphospholipid (50%) – include anticardiolipin and lupus anticoagulant Antierythrocyte (60%) – occasionally causes anaemia Antilymphocyte (70%) – possible leukopenia
Systemic sclerosis	Anticentromere (lcSSc: 70%) Antinucleolar, anti-Scl-70 (dcSSc; ILD 30%) Anti-RNP, anti-SS-A (dcSSc, PAH, myositis) Antinuclear antigen (90%) Anti-PM-Scl (myositis) Anti-Th / To (lcSSc, PAH)
Sjögren's syndrome	Anti-SS-A (70%), anti-SS-B (60%)
MCTD	Anti-U1-RNP (100%)
Polymyositis and dermatomyositis	Anti-Jo-1 (polymyositis: 30%; dermatomyositis: 30%) Anti-Mi2 (10% dermatomyositis) Anti-SRP (aggressive disease)
Granulomatosis with polyangiitis (GPA)	Proteinase 3 ANCA (90% sensitivity and specificity)
Goodpasture's	Glomerular basement membrane (90% sensitivity and specificity)
Graves' disease	TSH-receptor (sensitivity 80%, specificity 95%)
Idiopathic thrombocytopenic purpura (ITP)	GpIIb / IIIa (sensitivity 80%, specificity 90%)
Primary biliary cirrhosis	Anti-mitochondrial (sensitivity 90%, specificity >90%)
lcSSc = limited cutaneous systemic sclerosis; dcSSc = diffuse cutaneous systemic sclerosis; MCTD = mixed connective tissue disease; PAH = pulmonary arterial hypertension; ILD = interstitial lung disease; RNP = ribonucleoprotein; ANCA = antineutrophil cytoplasmic antibody; Sm = Smith; SRP = signal recognition protein; TSH = thyroid-stimulating hormone.	

features of scleroderma, polymyositis and SLE and the presence of characteristic antibodies to nuclear ribonucleoprotein (nRNP), which is one of the extractable nuclear antigens. Anti-nRNP is present in high titre and produces a speckled pattern on fluorescent antibody testing in patients with MCTD. When these patients are followed for many years, they may start to resemble patients with progressive systemic sclerosis or SLE, or may continue with a relatively undifferentiated connective tissue disease.

## HINTS

Features of mixed connective tissue disease include:

1. Overlapping features of SLE, polymyositis, and systemic sclerosis
2. High titre of anti-U1-RNP antibodies
3. Pericardial effusion
4. Raynaud's, swollen hands, fatigue and arthritis
5. Pulmonary arterial hypertension (PAH) is main cause of death
6. Treat symptoms with steroids, antimalarials, NSAIDs, and immunosuppression (cyclophosphamide for PAH)

3. MRI scans and lumbar puncture (increased protein and mononuclear cells) may be indicated if central nervous system lupus is suspected. Central nervous system symptoms often correlate poorly with serological measures of the activity of the disease. Do not miss bacterial meningitis in SLE.
4. Haematological tests:
  - a. Anaemia – normochromic, normocytic and related to the chronic inflammatory processes – is very common. Immune haemolytic anaemia is less common and the Coombs' test then gives a positive result.
  - b. The ESR tends to be elevated but the CRP is often normal, except during episodes of serositis.
  - c. Leukopenia (especially lymphopenia) occurs in over half the patients and may be caused by antibody directed against leukocytes.
  - d. The lupus anticoagulant and anticardiolipin antibodies, or both, are found in about 10% of cases. Characteristically, there is a prolonged partial thromboplastin time with kaolin (PTTK), which is not corrected by the addition of normal plasma. It is associated with thrombosis rather than bleeding.
  - e. Thrombocytopenia occurs in 15% of cases and is associated with anti-platelet antibodies.
5. Immunological tests:
  - a. The characteristic abnormalities are the presence of autoantibodies (see [Table 9.15](#)). ANAs are present in 99% of cases and are usually detectable from the time of onset of symptoms. The antigens involved include ssDNA and dsDNA, SS-A and SS-B, and Sm antigen (an acidic nuclear protein). Many antibodies persist even when the disease is quiescent. Antibodies to dsDNA and Sm are the most specific for SLE and are therefore the most useful diagnostically. The latter, however, is not very sensitive.
  - b. Complement abnormalities are usual during exacerbations of the disease, with a reduction in total haemolytic complement (CH50) and in the components of the classical pathway (C3 and C4). The combination of a low CH50 and normal C3 suggests an inherited deficiency of complement components and is strongly associated with SLE. The finding of high levels of anti-dsDNA and lower complement levels is usually associated with active disease and especially renal involvement.
  - c. Positive RF occurs in 10% of cases at low titre. Skin biopsy in SLE can be helpful; positive immunofluorescence of the basement membrane in involved skin occurs in 95% of patients.

## Treatment

Current work suggests that appropriate treatment to suppress exacerbations of SLE will prolong life. Many patients have mild disease without life-threatening complications.

The prognosis of SLE is generally good. There is a 90% 10-year survival rate; the major causes of death are infections, renal failure, lymphoma and myocardial infarction.

1. Arthralgias, myalgia and fever respond to rest and NSAIDs.
2. Exposure to sunlight should be avoided and sunscreen used.
3. Hydroxychloroquine is very effective for skin and joint manifestations, reduces the risk of renal involvement and improves survival. Annual retinal and visual field examinations must be performed in patients on this drug because of the cumulative risk of retinal toxicity. Although it is a category D drug, it is often used in pregnancy where its benefits outweigh the risks.
4. Raynaud's phenomenon may respond to calcium channel antagonists.
5. Steroids are indicated for central nervous system involvement, pericarditis, myocarditis, pleurisy, severe haemolytic anaemia and thrombocytopenia. Use of high initial doses with gradual reduction once improvement occurs is the proper method of treatment.
6. Hypercoagulability (thrombotic episodes and antiphospholipid antibodies) should be treated with warfarin for life, with a target INR of 2.5–3.
7. Management of renal disease is difficult. Renal biopsy usually shows abnormalities, but often only mild changes. Virtually any type of glomerulonephritis may occur. Renal biopsy is indicated early on if there is any clinical or biochemical evidence of renal disease or if the urine sediment is abnormal. Four main groups of biopsy abnormalities can be identified:
  - mesangial proliferation
  - focal glomerulonephritis
  - diffuse proliferation
  - membranous proliferation.

Mesangial proliferation has the best prognosis – disease is unlikely to progress. Diffuse proliferative glomerulonephritis has the worst prognosis and aggressive treatment (e.g. high-dose pulse steroids plus cyclophosphamide) is recommended. Membranous proliferation has a low rate of response to treatment. SLE is not a contraindication to dialysis or renal transplant in those patients who develop renal failure, but there is a higher than average risk of graft failure.

8. Calcium and vitamin D supplements should be offered to protect against osteoporosis. Bisphosphonates should be considered if long-term steroid treatment is likely.
9. Azathioprine is indicated as a steroid-sparing agent. Methotrexate can also be used, particularly if arthritis is prominent.

Cyclophosphamide is a more toxic alternative. Intermittent pulses of cyclophosphamide may be helpful. These agents are particularly indicated in active glomerulonephritis.

10. Mycophenolate is now accepted in treatment guidelines as a less toxic alternative to cyclophosphamide in the treatment of renal lupus. A number of new biological agents are being tested in clinical trials. Autologous stem cell transplant is also an experimental treatment.
11. Anti-B cell treatment has been used for SLE. Rituximab and belimumab have shown modest efficacy. They are currently available under special access schemes. A few patients have a dramatic response to these drugs.
12. Exacerbations of lupus may occur in pregnancy and postpartum.
  - Hydroxychloroquine should be continued throughout pregnancy as there are better outcomes for mother and baby.
  - Spontaneous abortions are common in women with antiphospholipid antibodies. Treatment with anticoagulation (heparin plus low-dose aspirin – never prescribe warfarin) may be effective in reducing the risk of abortion.

- Steroids may be used in pregnancy because, except for dexamethasone, these do not cross the placenta.
  - Women with the anti-Ro (SSA/SSB) antibody may have babies with permanent complete heart block and transient erythematous rashes.
  - Cervical dysplasia is common and women younger than 26 years should be offered human papilloma virus vaccine.
13. Improved survival has meant that cardiovascular complications are now the most common cause of death. This is probably due to the chronic inflammation associated with the disease. Aggressive control of cardiovascular risk factors and particularly avoidance of smoking is very important.
- The risk of lymphoma is also increased and screening may be indicated.

### Possible lines of questioning

1. What would you advise *this* woman with SLE if she asks about the risks of pregnancy to her and her baby?
2. What does she see as the main problem with her health?
3. Do you think the disease is active at the moment?
4. What are her cardiovascular risk factors? How would you attempt to modify them?

## Systemic vasculitis

Patients with a systemic vasculitic illness will often be used for the long-case examination because of the complex nature of these illnesses and the frequent need for hospital admission. The fact that these illnesses tend to affect multiple body systems across numerous specialties is ideal for testing candidates' general approach to internal medicine. The majority of cases seen in the examination will have a vasculitis such as granulomatosis with polyangiitis (Wegener's granulomatosis), giant cell arteritis or polyarteritis nodosa. Occasionally, less common adult vasculitides, such as eosinophilic granulomatosis with polyangiitis (EGPA) (Churg–Strauss syndrome) or microscopic polyarteritis, will be encountered.

The long-case examination for the patient with systemic vasculitis requires the candidate to take a careful history and examine the patient in a thorough general manner, as well as to look for specific abnormalities in each disease. Candidates will be expected to have a good knowledge of the various investigative tools available to diagnose vasculitis. The course of treatment will invariably be discussed in this type of case, particularly the side-effects of long-term medications and likely prognosis.

### The history

In most cases, the onset of a systemic vasculitic illness is subacute rather than acute. The patient has often seen several practitioners before a diagnosis is made. The history will be critical in determining the diagnosis if the patient has a systemic vasculitis and presents a diagnostic problem, or indeed if there are significant management issues.

1. First, ask about the systemic features that would suggest a vasculitic illness: fatigue, malaise, fever, myalgia and arthralgia will be very frequent in these patients. Ask about vasculitic skin rash, which would normally be in the form of palpable purpura. Ask about the pattern of joint involvement.



2. Next ask about a history of renal disease, particularly hypertension or renal failure, and any gastrointestinal symptoms.
3. **Granulomatosis with polyangiitis (GPA)** – the new name for Wegener's granulomatosis (small or medium-sized vessel inflammation causing a pulmonary–renal syndrome): the upper and lower respiratory tract are almost invariably involved and frequent symptoms include:
  - nasal congestion
  - rhinorrhoea
  - bloody nasal discharge
  - cough (which is initially a dry cough, but may evolve into haemoptysis)
  - breathlessness.
4. **Giant cell arteritis:** patients are generally in the sixth, seventh or eighth decade of life. About 20% of patients with polymyalgia rheumatica develop giant cell arteritis. The usual specific symptoms are:
  - severe bitemporal headache
  - less commonly, visual disturbance (e.g. diplopia) or visual loss
  - jaw claudication (quite specific), scalp tenderness or occasionally tongue claudication. Other focal neurological symptoms can also occur.
5. **Polyarteritis nodosa** (medium-sized arteries): the specific symptoms depend on which arteries are involved – coronary arteries, mesenteric arteries or renal arteries. Suspect this possibility if there are multiple systems involved (e.g. foot drop with chest and abdominal pain). Ask about risk factors for hepatitis B (recently acquired in one-third of cases).
6. **Eosinophilic granulomatosis with polyangiitis (EGPA)** (small vessels causing a pulmonary–renal syndrome): this is the new name for Churg–Strauss vasculitis; patients almost invariably have asthma first, then a peripheral eosinophilia. Ask about a previous history of:
  - asthma
  - allergic rhinitis, nasal polyps
  - eczema
  - cough and breathlessness
  - peripheral nervous system disease, in the form of either symmetrical peripheral neuropathy or mononeuritis multiplex.
7. **Microscopic polyarteritis (polyangiitis)** (small vessels causing a pulmonary–renal syndrome): the major problem is usually with renal impairment and lung disease, which may not have any specific symptoms. Systemic symptoms of vasculitis are generally very prominent.
8. **Mixed essential cryoglobulinaemia** (small vessels due to rheumatoid factor bound to IgG): patients present with:
  - palpable purpura of the extremities
  - Raynaud's disease
  - arthritis
  - neuropathy.
 Hepatitis C is common.

### The examination

1. The patient with systemic vasculitis usually looks unwell. Check for fever, sinus tachycardia, pallor and signs of recent weight loss.
2. Look for livedo reticularis (a net-like pattern – Fig 9.10). The differential diagnosis includes cholesterol atheroembolism after a vascular procedure, antiphospholipid





**Figure 9.10** Livedo reticularis and erythematous macules of the forearms.

J Dion. Livedo reticularis and erythematous macules of the forearms indicating cutaneous microscopic polyangiitis. *American Journal of Medicine* 2010; 123(11), with permission.

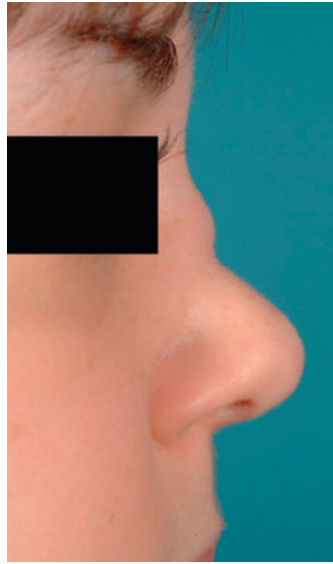
syndrome and vasculitis. Other mimics of vasculitis include atrial myxoma, bacterial endocarditis and thrombotic thrombocytopenic purpura (TTP).

3. Other physical signs will be more specific to the actual underlying illness:
  - **Granulomatosis with polyangiitis:** look for the classical collapse of the nasal septum (a saddle-shaped nose (Fig 9.11), which also occurs in relapsing polychondritis). There may be evidence of tachypnoea and crackles throughout the lung field. Fluid overload may occur in the setting of worsening renal failure.
  - **Giant cell arteritis:** tender and indurated temporal arteries will often be present. There may be abnormal eye signs if there is retinal involvement. Focal neurological signs should be sought.
  - **Polyarteritis nodosa:** there may be evidence of painful skin nodules in rare cases, as well as palpable purpura and livedo reticularis. Look for mononeuritis multiplex.
  - **EGPA:** look for signs of allergic disease, such as swollen nasal turbinates, nasal polyps and evidence of bronchospasm. Examine the peripheral nervous system carefully, looking for single nerve lesions or symmetrical peripheral neuropathy generally affecting the lower limbs.
  - **Microscopic polyarteritis:** urinalysis is the key – look for any evidence of proteinuria or haematuria.
  - **Mixed essential cryoglobulinaemia:** look for Raynaud's disease, palpable purpura and peripheral neuropathy. Assess for signs of liver disease (hepatitis C).

## Investigations

Investigations will be critical in determining the diagnosis in systemic vasculitis.

1. In most cases a biopsy of affected tissue is the most reliable way of making the diagnosis; other investigations will raise the suspicion that vasculitis is the problem and direct the clinician to a suitable biopsy site.



**Figure 9.11** Saddle-shaped nose deformity in granulomatosis with polyangiitis (Wegener's granulomatosis).

H S Bennett. Restylane – a temporary alternative for saddle nose deformity in nasal Wegener's granulomatosis – how we do it. *British Journal of Oral and Maxillofacial Surgery* 2010; 49(4), with permission.

2. It will often be necessary to exclude systemic infection, malignancy or generalised autoimmune disease.
3. In vasculitis, the ESR is invariably raised, often at levels of  $>70$  mm/h. There is frequently a normochromic normocytic anaemia and there may be neutrophilia. The platelet count may be elevated.
4. Renal function will often be impaired in granulomatosis with polyangiitis, polyarteritis nodosa and microscopic polyarteritis.
5. Abnormal liver function tests, particularly elevated transaminase levels, may be found in granulomatosis with polyangiitis and in polyarteritis nodosa. Liver function abnormalities are also reported in giant cell arteritis.
6. Urine abnormalities will often be found in the form of urinary casts and the presence of dysmorphic red blood cells in the urine, particularly in granulomatosis with polyangiitis, microscopic polyarteritis and polyarteritis nodosa.
7. The chest X-ray will often show a bilateral diffuse interstitial abnormality in granulomatosis with polyangiitis (see Fig 16.31a and b, p. 436) and a peripheral fluffy, patchy infiltrative pattern in EGPA.
8. **Granulomatosis with polyangiitis:** the critical investigation is the antineutrophil cytoplasmic antibody (c-ANCA). This will be present in a vast majority of cases of granulomatosis with polyangiitis. Further testing of this antibody will reveal the presence of anti-pr3 antibodies. The presence of a typical clinical syndrome with a positive c-ANCA and pr3 antibodies is virtually diagnostic of granulomatosis with polyangiitis. The need for a tissue biopsy may be avoided if these tests are positive. Occasionally, patients with upper airways disease only will not have a positive c-ANCA test.
9. **Giant cell arteritis:** diagnosis depends on a positive tissue sample. Don't delay starting steroids to make a definite diagnosis (the biopsy can be done within 2 weeks

of starting steroids). Temporal artery biopsy should reveal the diagnosis as long as a generous biopsy is taken by the surgeon, but the artery on the other side may need to be sampled in some cases.

- 10. **Polyarteritis nodosa:** tissue samples are often not available. Many organs may be involved (Table 9.16). If symptoms or signs point this way, a biopsy of nerve, muscle or testis may be diagnostic; renal biopsy is not helpful. Angiography is sometimes helpful in this illness, particularly of the mesenteric arteries, but possibly also of the coronary arteries. Bead-like aneurysmal dilatation of the arteries is suggestive of polyarteritis.

Table 9.16 Clinical findings in patients with polyarteritis nodosa		
SITE	CLINICAL PROBLEM	PREVALENCE (%)
Muscles and joints	Myalgia, arthritis	65
Kidneys	Hypertension, renal impairment	60
Gut	Nausea, vomiting, abdominal pain, bowel, liver or pancreatic infarcts	45
Peripheral nervous system	Mononeuritis multiplex, peripheral neuropathy	50
Central nervous system	Strokes and seizures	25
Skin	Purpura, infarcts, Raynaud's phenomenon	40
Heart	Cardiac failure, infarction, pericarditis	35
Genitourinary	Ovarian, testicular pain or infarction	20

- 11. **EGPA:** 50% of patients will have a positive perinuclear (p) ANCA test. The other important diagnostic tool is the tissue biopsy, which will reveal intense eosinophilia. Sural nerve biopsy will sometimes be required in the setting of neuropathy and this will show vasculitis.
- 12. **Microscopic polyarteritis:** this is characterised by a positive p-ANCA result. This antibody is directed against myeloperoxidase. Renal biopsy is usually necessary to establish the diagnosis.
- 13. p-ANCA is rare in other inflammatory diseases, but common in patients with vasculitis (c-ANCA is specific for granulomatosis with polyangiitis). ANCA titres do not correspond with the clinical severity of the patient's illness and they may be only markers of disease. Remember that p-ANCA tests may be positive (but myeloperoxidase (MPO) negative) in other conditions including inflammatory bowel disease, autoimmune hepatitis and primary sclerosing cholangitis, as well as in health (5%).

Treatment

Systemic vasculitis will generally require aggressive immunosuppressive medication. Failure to suppress the vasculitis aggressively can result in permanent injury, progressive deterioration and death.

- 1. **Granulomatosis with polyangiitis (deadly if untreated):** high-dose corticosteroids and daily oral cyclophosphamide should be instituted. Trimethoprim-sulfamethoxazole is adjunctive therapy. Biological agents are being investigated for treatment of granulomatosis with polyangiitis. Rituximab shows the most promise, but should not be used at this stage unless other agents have failed.

2. **Giant cell arteritis:** high-dose oral corticosteroids are required, typically for 1–2 years.
3. **Polyarteritis nodosa:** the untreated 5-year survival rate is less than 20%. A combination of high-dose prednisone and cyclophosphamide will usually be very effective (90% long-term remission). Treatment may often be discontinued after remission is obtained and the long-term prognosis is very good. Interferon alpha, or the antiviral drug vidarabine, may help to induce remission if there is associated hepatitis B infection.
4. **EGPA:** the eosinophilic vasculitis of the Churg–Strauss syndrome is generally very steroid responsive, but occasionally other cytotoxic agents need to be used. Steroids alone have been shown to increase the 5-year survival rate from 25% to 50%.
5. **Microscopic polyarteritis:** corticosteroids combined with immunosuppressive agents are usually required, with renal support in patients who develop renal failure.
6. The duration of treatment for all of these vasculitic illnesses needs to be individualised. Patients with giant cell arteritis can come off treatment after about 2 years, but some have disease for several years. Most of the other diseases will require maintenance therapy.
7. Patients often suffer the effects of long-term steroid therapy and immunosuppression, such as osteoporosis, hypertension, diabetes and accelerated vascular disease. Prevention should be aggressively pursued. Infection (e.g. *Pneumocystis pneumonia*) is common in this group and can be serious or fatal.
8. Patients on cyclophosphamide need careful monitoring of their blood count and careful counselling to ensure adequate fluid intake and avoid haemorrhagic cystitis. They also deserve an annual urinalysis for haematuria once therapy is ceased; haematuria may indicate the development of bladder cancer.

## Possible line of questioning

How would you monitor *this* patient for problems with his or her drug treatment?

## Antiphospholipid antibody syndrome

Antiphospholipid antibody syndrome is a disease that not infrequently requires patients to be admitted to hospital for its various complications. It may therefore crop up as a long case in the examination. The disease can be either primary or secondary. The secondary form is usually a complication of other autoimmune conditions, the most common of which is SLE. The main antibody in this disease is directed against the phospholipid–beta<sub>2</sub>-glycoprotein 1 complex, on which it exerts a procoagulant effect. It has also been described in HIV infection.

### The history

Patients with antiphospholipid antibody syndrome commonly suffer thrombosis (Table 9.17).

1. Ask about venous thromboses. The most common site is the deep lower limb or pelvic veins, but the axillary veins can be involved.
2. Ask about arterial thromboses. Stroke and myocardial infarction are the most common arterial complications.

**Table 9.17 Clinical manifestations of the antiphospholipid antibody syndrome**

1. Cardiac – myocardial infarction, valvular heart disease, pulmonary hypertension
2. Haematological – haemolytic anaemia, thrombocytopenia, migraine, epilepsy, transverse myelopathy
3. Renal – renal vein thrombosis
4. Endocrine – Addison's disease (adrenal vein thrombosis)
5. Neurological – cerebral ischaemia (stroke, multi-infarct dementia)
6. Gastrointestinal – bowel ischaemia
7. Obstetric – recurrent abortions, intrauterine growth retardation
8. Dermatological – livedo reticularis, ulcers

3. Enquire about a history of recurrent first-trimester and later abortion. Antiphospholipid antibody syndrome is far more common in females and otherwise unexplained first-trimester abortions are characteristic of this disease. Other obstetric complications include intrauterine growth retardation and an increased tendency for hypertension in pregnancy.
4. Ask about bleeding problems associated with thrombocytopenia, skin changes (especially livedo reticularis), central nervous system complications such as migraine and chorea, and eclampsia or pre-eclampsia with the HELLP syndrome:  
**Haemolysis, Elevated Liver enzymes, Low Platelets**
5. Ask about features of the underlying disorder, such as SLE, which suggest the patient has a secondary form of antiphospholipid antibody syndrome.

### The examination

Unless the patient has an active thrombosis, there are unlikely to be any abnormal physical signs. Look especially for:

1. signs of any associated autoimmune diseases, particularly skin rashes and joint abnormalities in SLE, and dry eyes and mouth in Sjögren's syndrome
2. livedo reticularis rash on the lower limbs
3. heart murmurs from sterile valve vegetations.

### Investigations (see also pp. 190–2)

1. The detection of IgG anticardiolipin antibodies is diagnostic for the antiphospholipid antibody syndrome if the antibodies are in high titre and found in the correct clinical context. IgM anticardiolipin antibodies may be detected, although these are less specific.
2. The lupus inhibitor is a related antibody (both are antibodies to phospholipid) that confers an even greater risk of thrombosis and pregnancy complications. The lupus inhibitor is also associated with a prolonged activated partial thromboplastin time (APTT) not corrected in a mixing study.
3. Antibodies to beta<sub>2</sub>-glycoprotein-1 ( $\beta_2$ -GP-1) in high titre may be present in the appropriate clinical setting.
4. In patients with suspected antiphospholipid antibody syndrome it is worth checking the ANA and other autoimmune serology as indicated, as well as measuring the platelet count. The Venereal Disease Research Laboratory (VDRL) test may be falsely positive.

### Treatment

1. Any patient with thrombotic complications of the antiphospholipid antibody syndrome should be considered for treatment with anticoagulants for life (consider whether the benefits exceed the risks for individual patients).

2. The patient with anticardiolipin antibodies but no clinical abnormalities presents a difficult clinical situation. There are no data to support routine anticoagulation in this situation, but clearly there is a risk of arterial thrombosis.
3. The patient who has had obstetric problems in the past but no history of thrombosis also presents a dilemma for clinicians. The literature supports the use of anticoagulation therapy only in those with anticardiolipin antibodies or lupus inhibitor in whom a thrombotic complication has previously occurred.
4. Women who have suffered recurrent abortion will require treatment during pregnancy. Low-molecular-weight heparin would normally be used throughout the pregnancy, with the addition of low-dose aspirin. There is no good evidence that corticosteroids improve survival of the fetus.

## Systemic sclerosis (scleroderma)

### Definitions

- Limited cutaneous systemic sclerosis (lcSSc) is characterised by skin changes of the distal extremities and the face.
- CREST is a subset of lcSSc
- Diffuse cutaneous systemic sclerosis (dsSSc) involves skin involvement proximal to the elbows and knees.

This is a progressive disease of multiple organs. Although rare it crops up commonly in examinations. It is more common in women than in men (5:1). The 5-year survival at diagnosis is only 70%. Asian patients have a higher incidence of diffuse disease and of interstitial lung disease. There is a slightly increased risk of disease for people who have a first-degree relative affected.

### The history

1. Ask about symptoms:
  - a. dermatological symptoms – Raynaud's phenomenon (commonly the first symptom), tight skin, disability from sclerodactyly
  - b. arthritis – arthropathy in a rheumatoid distribution, carpal tunnel symptoms
  - c. gastrointestinal symptoms – dysphagia, heartburn (oesophagitis), diarrhoea (malabsorption)
  - d. renal tract symptoms – hypertension, chronic kidney disease, scleroderma renal crisis
  - e. respiratory symptoms – symptoms of interstitial lung disease, pleurisy, known diagnosis of pulmonary hypertension
  - f. cardiac symptoms – symptoms of pericarditis, palpitations (arrhythmias), symptoms of cardiac failure (dilated cardiomyopathy)
  - g. other symptoms – erectile dysfunction, hypothyroidism, history of non-melanoma skin cancer.
2. Consider the differential diagnosis (Table 9.18). Graft versus host disease can mimic scleroderma. Also ask about a history of exposure to polyvinyl chloride (PVC), L-tryptophan (eosinophilic myalgia syndrome) and drugs (e.g. bleomycin, pentazocine). Nephrogenic systemic fibrosis can occur in dialysis patients exposed to gadolinium during an MRI. Also ask about drugs likely to aggravate Raynaud's phenomenon (e.g. beta-blockers); a possible association with silicone breast implants seems to have been negated. Don't miss diabetic-induced skin thickening.



Table 9.18 Differential diagnosis of scleroderma
These rare conditions are not associated with Raynaud's or antinuclear antibodies:
1. Eosinophilic fasciitis
2. Morphea
3. Scleroderma
4. Nephrogenic systemic fibrosis
5. Diabetic cheiroarthropathy

3. Ask about treatment received (e.g. D-penicillamine) and side-effects thereof (see Table 9.21).
4. Enquire about degree of disability – function at home, ability to work, financial security.
- Scleroderma may be classified as limited or diffuse. Limited disease means involvement of the skin up to the elbows (and may include the face) without chest, abdominal or internal organ involvement, except for the oesophagus. These patients are usually anticentromere positive.

**HINTS**

- Limited cutaneous systemic sclerosis (face, hands and feet) is associated with a risk of pulmonary arterial hypertension.
- Diffuse cutaneous scleroderma is associated with the risk of interstitial lung disease, serositis and acute renal failure (scleroderma renal crisis).

In CREST (typically a more limited form of scleroderma, usually with oesophageal involvement, which causes dysphagia), sclerodactyly is usually limited to the distal extremities and/or face. The signs are:

**Calcinosis** (calcific deposits in subcutaneous tissue at the ends of the fingers) (Fig 9.12)

**Raynaud's phenomenon** (resulting in loss of tissue pulp at the ends of the fingers)

**(o)Esophageal involvement**

**Sclerodactyly** (tightening of the skin on the fingers) (Fig 9.13)

**Telangiectasia.**

Progressive pulmonary fibrosis (ILD) is more common in patients with diffuse disease, but pulmonary hypertension is six times more common in patients with limited disease; it tends to occur late in the course of the disease. Patients with rapidly progressing dyspnoea are more likely to have pulmonary hypertension than ILD. These lung conditions are the main causes of mortality for scleroderma patients.

Localised scleroderma is called *morphea*. It presents as single or multiple plaques of skin induration.

**The examination (see Table 9.19)**

1. Make a general inspection for weight loss (due to malabsorption or dysphagia).
2. Look at the hands. Look for the signs of limited scleroderma. These include sclerodactyly (tightening of the skin of the fingers – see Fig 9.13) with extension up to the elbow, telangiectasia, finger tapering, pitting scars, signs of calcinosis (calcific deposits in subcutaneous tissue at the ends of the fingers – see Fig 9.12) and the effects of Raynaud's phenomenon (loss of tissue pulp at the ends of the fingers).





**Figure 9.12** X-ray of the hands showing marked calcinosis (arrows).

Figure reproduced courtesy of The Canberra Hospital.



**Figure 9.13** Sclerodactyly.

W D James, T Berger, D Elston. *Andrews' diseases of the skin: clinical dermatology*, 11th edn. Fig 8-25. Saunders, Elsevier, 2011, with permission.

**Table 9.19 Systemic sclerosis**

<p><b>1. GENERAL APPEARANCE</b></p> <p>'Bird-like' facies</p> <p>Weight loss (malabsorption)</p> <p>Anaemia (malabsorption, bleeding from a watermelon stomach)</p> <p><b>2. HANDS</b></p> <p>CREST – calcinosis, atrophy of distal tissue pulp (Raynaud's), sclerodactyly, telangiectasia</p> <p>Dilated capillary loops</p> <p>Small joint arthropathy and tendon crepitus</p> <p>Fixed flexion deformity</p> <p>Hand function</p> <p><b>3. ARMS</b></p> <p>Oedema (early) or skin thickening and tightening</p> <p>Pigmentation</p> <p>Vitiligo</p> <p>Hair loss</p> <p>Proximal myopathy</p> <p><b>4. HEAD</b></p> <p>Alopecia</p> <p>Eyes – loss of eyebrows, anaemia, dryness (Sjögren's), difficulty with closing</p> <p>Mouth – dryness, puckered, difficulty with opening</p>	<p>Pigmentation</p> <p>Telangiectasia</p> <p><b>5. DYSPHAGIA</b></p> <p>Ask patient about swallowing</p> <p><b>6. CHEST</b></p> <p>Tight skin ('Roman breast plate')</p> <p>Heart – cor pulmonale from pulmonary hypertension, pericardial effusion, pericarditis, failure, arrhythmias, ischaemia</p> <p>Lungs – fibrosis, reflux pneumonitis, chest infections, lung carcinoma, vasculitis</p> <p><b>7. LEGS</b></p> <p>Skin lesions</p> <p>Vasculitis</p> <p>Small joint arthropathy</p> <p>Patellar crepitus</p> <p><b>8. OTHER</b></p> <p>Blood pressure (hypertension in renal involvement)</p> <p>Urine analysis (proteinuria)</p> <p>Temperature chart (infection)</p> <p>Stool examination (steatorrhea)</p> <p>Cancer elsewhere (non-melanoma skin cancer)</p>
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Nail-fold capillaroscopy is useful, but few have the skill. The presence of dilated tortuous vessels (giant loops) almost always indicates an underlying connective tissue disorder of some sort. Assess hand function.

- Look at the arms for skin changes and assess proximal weakness (myositis).
- Examine the head. Note any alopecia. Look at the face for 'salt-and-pepper' pigmentation, loss of wrinkling, 'bird-like' or 'mouse-like' facies (because of puckering of the mouth) and telangiectasia. Check for any difficulty in closing the eyes, dryness of the eyes (Sjögren's syndrome) and pale conjunctivae (anaemia). Check for any difficulty opening the mouth wide and for dryness and puckering of the mouth.
- Look at the chest for the 'Roman breast plate' effect as a result of skin tightening.
- Examine the cardiovascular system for pericarditis, arrhythmias, cor pulmonale and cardiac failure (due to myocardial fibrosis).
- Examine the respiratory system for interstitial lung disease, reflux pneumonitis, infection, lung carcinoma and vasculitis.
- Look for jaundice and xanthelasma (primary biliary cirrhosis occurs rarely with CREST). Scratch marks may be visible from pruritis.
- Look at the legs for vasculitis and ulceration.
- Take the blood pressure.
- Check the urine analysis and temperature charts.

### Investigations

- The ESR may be raised. Anaemia may be present owing to chronic disease, iron deficiency (secondary to bleeding from oesophagitis), folate or vitamin B<sub>12</sub> deficiency (secondary to malabsorption), or a microangiopathic haemolytic anaemia, which is usually associated with acute renal crises.

2. Hypergammaglobulinaemia (particularly IgG) is present in 50% of cases. Rheumatoid factor is present in 25% and ANA is found in most cases. Anti-Scl-70 is positive in a minority with diffuse scleroderma. Anticentromere antibody is particularly associated with CREST (up to 70%) (see Table 9.15).
3. Investigations for malabsorption and dysphagia may be necessary.
4. Assess visceral involvement with chest X-ray films, gastroscopy or oesophageal manometry, depending on the clinical presentation.
5. Regular screening for ILD and pulmonary hypertension should be routine:
  - a. respiratory function tests, high-resolution CT of the chest for ILD
  - b. echocardiography and, if pulmonary arterial hypertension is suspected, a right heart catheter and 6-minute walk test.

### Treatment

This debilitating chronic disease will expose the patient to the need for recurrent investigations and adjustments to treatment. These matters need careful explanation from the outset. Prognosis is worse in men and those with renal or late-onset disease. Patients with skin and gut involvement, but without other organ disease, have the best prognosis.

1. Symptomatic treatment includes avoiding vasospasm (by avoiding smoking, beta-blockers and cold weather). Aggressive treatment of reflux with proton pump inhibitors is important to prevent the formation of oesophageal strictures. Nifedipine, phenoxybenzamine, prazosin or methyldopa may help Raynaud's phenomenon. The prostacyclin analogue iloprost has shown promise for Raynaud's phenomenon in scleroderma. Morphea may respond to ultraviolet-A (UVA) light.
2. Artificial tears are useful for dry eyes and NSAIDs may help with joint symptoms.
3. Treat malabsorption (particularly bacterial overgrowth, with antibiotics).
4. D-penicillamine (an immunosuppressant drug that also interferes with collagen cross-linking) may be helpful for skin disease and may improve survival. It has been usual to start treatment with a low dose. Randomised studies have shown no advantage of higher doses. The drug has a number of severe side-effects (Table 9.20). Monthly full blood counts are usually recommended.

**Table 9.20 Side-effects of D-penicillamine**

SEVERE	MORE MINOR
Glomerulonephritis and nephrotic syndrome	Alteration of taste
Myasthenia gravis	Skin rashes
Thrombocytopenia	Fever
Leukopenia	Nausea
Aplastic anaemia	Anorexia

5. Cyclophosphamide is used if there is lung involvement and may improve other complications of the disease, especially if used early. Treatment is usually given for 9 months.
6. Pericarditis, inflammatory myopathy and early interstitial lung disease may respond to steroids.
7. A number of drugs are now approved for the treatment of pulmonary arterial hypertension (PAH) in scleroderma patients (Table 9.21).

Table 9.21 Drugs approved for the treatment of pulmonary arterial hypertension

1. Endothelin receptor antagonists: bosentan and ambrisentan
2. Phosphodiesterase inhibitors: sildenafil and tadalafil
3. Prostanoids: intravenous epoprostanol and inhaled iloprost

- 8. Aggressive treatment of hypertension to prevent renal failure is vital – ACE inhibitors are the drug class of choice. An ACE inhibitor is often given to patients even with abnormal renal function to prevent or treat hypertensive renal crises. Dialysis is not contraindicated. A sudden increase in blood pressure should prompt investigations for acute renal failure and microangiopathic haemolytic anaemia, which occur in renal crises.
- 9. Many other drugs have been tried for patients with scleroderma, including angiotensin receptor blockers, selective serotonin reuptake inhibitors, serotonin antagonists, topical nitrates and platelet inhibitors. There are no controlled trials showing that treatment can reverse the course of the disease.

**HINT**

Early diagnosis and treatment of ILD and PAH improve the prognosis; regular screening is most important.