Inflammatory Arthritis

Inflammatory arthritis affects about 3% of the population and consists of the conditions rheumatoid arthritis, spondyloarthropathy and connective tissue disorders.
Rheumatoid arthritis (RA) currently affects 450,000 people in the UK and 12,000 new cases are diagnosed annually.
The management of RA has undergone significant change over the last decade. In the past, the diagnosis was often delayed and caused considerable disability – 40% of the sufferers of RA had suffered health-related work loss within three to five years of diagnosis.[1] In addition to pain and disability, people with RA can have overwhelming fatigue as a result of the systemic inflammation, altered physical functioning and low mood.
Early diagnosis of inflammatory arthritis and the prompt treatment with disease-modifying drugs has been shown to improve outcomes.[2]
This module will outline some of the presenting features of inflammatory arthritis and cover the presentations of the different categories of arthritis
It will also cover the investigations which are necessary to make a diagnosis and the primary care management of these patients.
It will also give advice on when to refer for a specialist opinion.

When should inflammatory arthritis be considered?
Inflammatory arthritis, and particularly RA, is more common in women and has two peaks of incidence around middle age (30-45) and in older people over 70 years of age.
It can present quite insidiously and the symptoms can mimic a viral infection, with joint aching and fatigue. It can also be quite acute in onset.
Cardinal features are:

- Morning stiffness – this should be longer than 30 minutes and is often several hours in those badly affected, and can prevent patients from being able to get up in the morning in time for work and can make it difficult for them to dress and eat.
- Stiffness tends to wear off as the day progresses but will return in the evening when the person sits down to rest.
- Joint pains are of course associated with inflammatory arthritis, but are also common in other disorders such as osteoarthritis.
- The presence of soft, fluctuant swelling around the joint, which is tender to palpation, is the hallmark of synovitis.
- Patients with inflammatory arthritis feel unwell with fatigue and depression but will often attribute this to something else.

RA is more common in smokers, as they have a more severe disease course and are more at risk of cardiovascular comorbidities.

What features would suggest an inflammatory arthritis?
Soft, fluctuant swelling of the joints of the hands is suggestive of synovitis and

inflammatory arthritis. Rheumatoid arthritis classically affects the metacarpophalangeal joints (MCP) and proximal interphalangeal joints (PIP) in a symmetrical distribution, and the metatarsophalangeal joints (MTP) and interphalangeal joints in the foot.

Psoriatic arthritis can affect the distal interphalangeal (DIP) joints and there are often nail changes of psoriasis present as well.

Both types of arthritis can cause painful swelling of the wrists and other synovial joints.

- Structural deformities of the spine, such as scoliosis, are unlikely to have been caused by rheumatoid arthritis, and spondyloarthropathy can cause a kyphosis but this is a late feature of the disease.
- OA classically affects the DIP joints, causing Heberden's nodes, but these are hard and bony and seldom soft and fluctuant.

The metacarpal and metatarsal squeeze tests are painful in inflammatory arthritis.

Diagnosing inflammatory arthritis

- Inflammatory arthritis causes joint pain and swelling with tenderness on palpation.
- Metacarpal and metatarsal squeeze tests may be positive.
- The patient will experience morning stiffness lasting more than 30 minutes (less than 30 minutes with joint pain could be due to OA).
- The patient will experience fatigue and systemic upset.

Other important features to note in the history are:

- Family history as all types of inflammatory arthritis can run in families.
- Ask about previous episodes of joint pain and inflammation, as the patient may have had sub-acute presentations and experienced similar problems in the past and forgotten about them, or thought they were not connected.
- Ask about skin rashes, in particular psoriasis, as approximately 20% of people with psoriasis will develop joint inflammation and features of psoriatic arthropathy.
- Ask about features of inflammatory bowel disease (IBD) (diarrhoea, bloody stools, abdominal pain and weight loss), as spondyloarthropathy is associated with IBD.
- Reactive arthritis happens in some people after infections with chlamydia and some gut infections such as salmonella. Ask about these infections, which the patient may not have realised are causative.
- Unusual skin rashes may be vasculitis and vasculitis can be a sign of inflammatory arthritis or connective tissue disorder.

NICE recommendation for referral

The NICE guidelines for the management of rheumatoid arthritis in adults recommend the following:[3]

Refer for specialist opinion anyone with suspected persistent synovitis of undetermined cause. Refer urgently if any of the following apply:

- The small joints of the hands or feet are affected.
- More than one joint is affected.
- There has been a delay of three months or longer between onset of symptoms and seeking medical advice.

Refer urgently any person with suspected persistent synovitis of undetermined cause, even if their blood tests show a normal acute-phase response or negative rheumatoid factor.

NICE recommends that blood tests are undertaken, but that negative tests

should not stop a referral being made. Therefore, it is most sensible to refer a patient immediately that arthritis is suspected to avoid any delay, and also to start investigations at this point so that results will be available once the patient is assessed in specialist care.

It has been discovered that there is a window of opportunity in the first 12 weeks of onset of inflammatory arthritis, where starting disease modifying medication (DMARDs) can actually abort the disease progression and potentially halt it, thereby greatly improving the long-term prognosis for patients.[4]

Where there has been a delay in starting DMARD therapy, the patient has a worse outcome with more joint damage and disability.

Investigations for inflammatory arthritis

The investigation of someone with suspected inflammatory arthritis should always include tests for FBC, as the person may have a normochromic, normocytic anaemia of chronic disease.

Inflammatory markers are useful if elevated. Normal inflammatory markers should not be taken as an indication that the person does not have inflammatory arthritis. In the early stages of RA, when very few joints are inflamed, the load of inflammatory tissue is not large enough to raise the ESR and CRP.

Some forms of spondyloarthropathy do not cause elevation of the inflammatory markers by much.

Rheumatoid factor (RF) is positive in about 80% of patients with rheumatoid, but can be positive in many other conditions. In elderly people, RF and other auto-antibodies such as ANA can be positive spuriously. Therefore RF can be quite unreliable, particularly in older patients.

Anti-CCP antibodies are immunoglobulins which react against citrullinated C peptides, particularly in synovial tissue. Smoking causes citrullination of proteins in the lung, explaining pulmonary involvement in some patients with RA.

Anti-CCP is far more sensitive and specific than RF – it is about 90% sensitive and 90% specific for RA and the presence of both RF and anti-CCP indicates a more aggressive form of RA, with erosive potential and more joint damage.

New diagnostic criteria for RA were recently developed in 2010 by a consensus group of rheumatologists in the USA and Europe.[5]

The criteria are printed in the box below and must only be used for patients with at least one swollen and painful joint showing evidence of synovitis. This prevents mistakenly diagnosing degenerative arthritis as RA. A score of 6 or more is required for a definite diagnosis. More weight is given to swelling of the small joints of the hands and feet and for synovitis which persists more than six weeks. This may sound counter-intuitive with the NICE guidelines recommending urgent referral, but the guidelines mention referral for those with persistent synovitis only.

Many types of viral infections can cause transient synovitis which settles in a couple of weeks and should not be confused with RA.

2010 diagnostic criteria for the diagnosis of rheumatoid arthritis

Target population (who should be tested?) – patients who:
1) Have at least one joint with definite clinical synovitis (swelling)
2) With the synovitis not better explained by another disease
Classification criteria for RA (score-based algorithm: add score of categories A–D;a score of 6/10 is needed for classification of a patient as having definite RA):

Joint Distribution (0-5)	
1 Large Joint	0
2-10 medium /large joints	1
1-3 small joints (large joints not counted)	2
4-10 small joints (large joints not counted)	3
>10 joints (at least one small joint)	5
Serology	
Negative RF AND negative ACPA	0
Low positive RF OR low positive ACPA	2
High positive RF OR high positive ACPA	3
Symptom Duration	
< 6 Weeks	0
> 6 weeks	1
Acute Phase Reactants	

Normal CRP AND normal ESR/PV	0
Abnormal CRP OR abnormal ESR/PV	1

Back pain is common and 60-80% of us will have back pain at some point in our lives. A 35-year-old lady is most likely to have simple mechanical back pain, but it is always necessary to rule out red flags such as cauda equina lesions (ask about bladder and bowel function and loss of perineal sensation), and malignancy (nocturnal pain that is severe).
It is also necessary to establish whether this pain is inflammatory in nature. Inflammatory back pain occurs in spondyloarthropathy. Spinal spondyloarthropathy is classically called ankylosing spondylitis and affects about 1% of the population.
It is difficult to diagnose in the early stages and there can be up to a 10-year delay in diagnosis from first presentation with features of inflammatory back pain. Modern treatments such as biologic drugs can prevent progression of the disease, and it is important to recognise these patients early in the disease, so that biologic drugs can be started.

Features of inflammatory back pain

- Age at onset of back pain – <45 years (peak age of onset 15-35 years)
- Back pain lasting more than three months (possibly intermittent)
- Night pain
- Early morning pain and stiffness lasting more than one hour
- Pain improves with exercise
- Tenderness/inflammation over SIJs (often seen as alternating buttock pain)

Insidious onset (often distinguishes from mechanical back pain)

Spondyloarthropathy

Patients with spondyloarthropathy have a reduced range of spinal movement in at least two different planes. This means that spinal flexion will be reduced (ask the patient to touch their toes) and spinal side or lateral bend (ask the patient to slide their hand down the side of their leg) will be reduced.
An average 35-year-old should be able to touch their toes and slide the hand to below the knee in the plane at 90 degrees to toe touching.
Of course, in elderly patients loss of spinal movement may be common due to OA.
Spinal flexion is measured in the modified Schobers test

Schober's test

With the patient standing, mark two crosses on the spine 10cm apart, just above the sacral dimples which are where the SIJs lie. Ask the patient to touch their toes; the crosses should stretch out to lie 15cm apart in someone with normal spinal flexion (assuming they are young and fit). An increase of less than 5cm is abnormal and indicates reduced spinal flexion.
In addition to a loss of spinal flexion, the patient with spondyloarthropathy will also lose a degree of chest expansion due to stiffness in the thoracic spine and reduced elevation of the ribs on inspiration. In a normal person, chest expansion should be four to five inches.

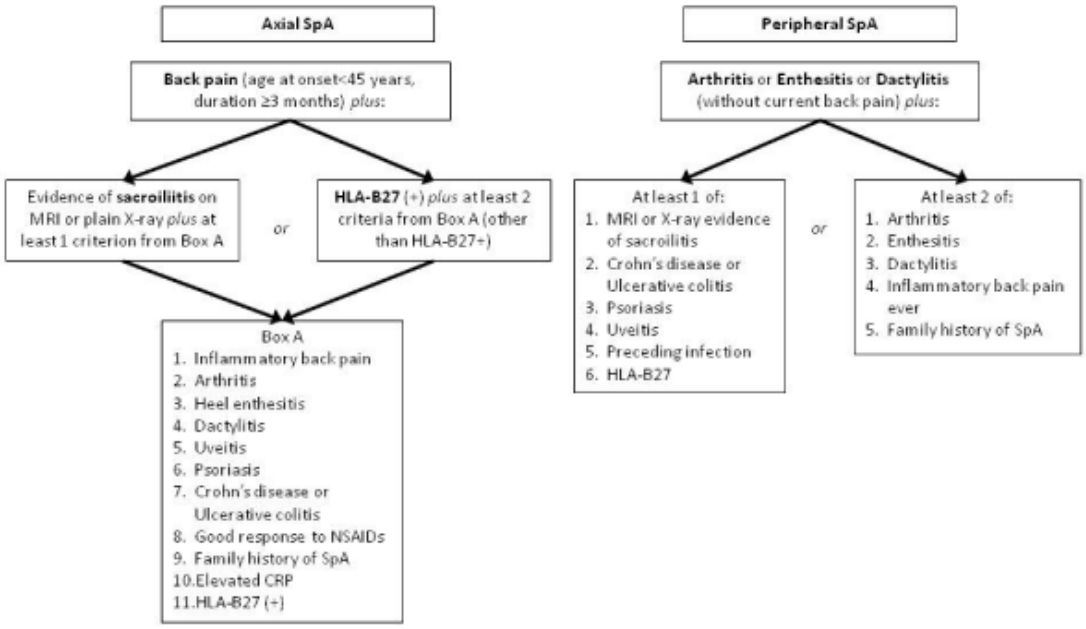
Patients with spondyloarthropathy often have enthesitis, which is inflammation of tendons where they attach to bones. The achilles tendon is the one most commonly involved and examination of the area may reveal tenderness at the tendon insertion and some swelling and heat in the area. The plantar fascia is

also commonly involved (one cause of plantar fasciitis) and the tendons of the rotator cuff in the shoulder and the medial and lateral epicondyles at the elbow.
A late feature of ankylosing spondylitis is pulmonary fibrosis, particularly at the lung apices and lung auscultation may reveal this, or more commonly, a loss of ventilation of the lower lung zones due to poor chest expansion.

Spondyloarthropathies
The spondyloarthropathies are a group of diseases associated with the genetic type HLAB27.
Patients with psoriasis and IBD (ulcerative colitis and Crohn's disease) can develop features of spondyloarthropathy.
Reactive arthritis is an acute arthropathy that develops in patients who are HLAB27 positive and have had a recent infection with chlamydia, salmonella or other gut bacterial pathogens.
In patients with psoriasis, about 20% will go on to develop joint pain and swelling and features of spondyloarthropathy, including spinal disease.
Some patients with spondyloarthropathy will develop anterior uveitis in the eye. Juvenile arthritis is also a form of HLAB27-associated spondyloarthropathy.

New classification of spondyloarthropathy
ASAS, the Assessment of Spondyloarthritis International Society, have recently re-classified spondyloarthropathy .
The diagnosis of ankylosing spondylitis has been replaced by a group of diseases called axial spondyloarthropathy (SpA). Axial means associated with the spine. All other types of SpA are called peripheral as they affect peripheral joints.
Dactylitis is a form of joint inflammation affecting a whole digit, causing swelling of a whole finger or toe, also known as 'sausage digit' because of the swelling of the whole digit.

ASAS criteria for the classification and diagnosis of SpA



The features of early spondyloarthropathy are not always visible on spinal X-rays. It can take up to 10 years for the features of sacro-ileitis to be visible on standard radiographs and as discussed above, the patient may have already developed a spinal deformity by the time the disease is diagnosed.
MRI scans are much more useful in showing up the early features of disease, which are bony oedema around the SIJs, bony sclerosis of the SIJ (also called sacro-ileitis), early calcification of the spinal ligaments and spinal fusion. Pathognomonic lesions, called Romanus lesions, are seen at the anterior vertebral body corners, causing 'squaring off' of the vertebral bodies. Changes at the SIJ are often the earliest features seen on MRI scans, so it is important to request scans in addition to standard spinal MRI protocols, which don't usually image the SIJ.
HLAB27 is likely to be positive in about 90% of patients with ankylosing spondylitis, but is also common in the normal population. In the UK, approximately 10% of the normal population will be HLAB27 positive. This does not mean that they have spondyloarthropathy.
Do not refer patients who are HLAB27 positive for a rheumatology opinion unless they have some other features of spondyloarthropathy, such as enthesitis or inflammatory back pain.

Features of axial spondylarthropathy

- Axial spondyloarthropathy is often diagnosed late ; there can be a delay of more than 10 years before a diagnosis of spinal disease is made.
- The advent of biologic treatments for SpA has meant that early diagnosis is imperative to allow drugs to be started and the disease arrested.
- Patients often present with inflammatory back pain, the features of which are insidious onset in patients under 45, nocturnal pain, prolonged early morning stiffness, alternating buttock pain, relieved by exercise

and worse after rest.
- X-rays do not show up the features of early spondylorthroopathy.
- MRI scanning of the spine and SIJ are the investigations of choice.
- Patients will have reduced spinal movements in two separate planes and a loss of chest expansion.
- Spondyloarthropathies are associated with HLAB27, psoriasis, IBD and some genitourinary bacterial infections (reactive arthritis).

Practical tip

- Ask patients with back pain which part of the day is best or worse for them. In mechanical back pain, the pain tends to be worse at the end of the day after exercise/activity. For patients with inflammatory back pain, the pain is much worse in the morning with associated stiffness.
- Patients with inflammatory back pain will have difficulty turning over in bed because of pain and stiffness.
- Ask about the associated diseases with inflammatory back pain – psoriasis, ulcerative colitis and Crohn's, anterior uveitis, enthesitis, previous joint swelling and pain (arthritis).
- Plantar fasciitis is a form of enthesitis. Bilateral sudden onset plantar fasciitis with no apparent cause is unusual and can be an indication of developing spondyloarthropathy.
- A tape measure is a useful tool to measure chest expansion and spinal flexion.
- One of the ASAS criteria is response to NSAIDs. Axial spondyloarthropathy is one of the few reasons to treat a patient with long-term NSAIDs, as they are disease-modifying in this situation and slow progression of the spinal disease.

DMARDS

Drugs such as methotrexate and hydroxychloroquine are DMARDS. Other commonly used DMARDS are sulphasalazine, leflunomide, azathioprine and steroids.
NICE recommends starting the patient on a combination of DMARDs as this brings the disease under control more quickly. It is common to prescribe steroids initially as well.
Please note that methotrexate is given as a weekly dosage, along with folic acid.
All DMARDs can have side-effects because they often work by impairing cell division, and affect the tissues in the body that are undergoing the most cell division (the gut, mucous membranes and hair follicles, and bone marrow). They have the potential to cause mouth ulcers, nausea, vomiting and diarrhoea, plus hair loss. The co-prescription of folic acid reduces these side-effects to some extent.
DMARDs also have the potential to reduce blood cell counts, and blood tests are done fortnightly initially to screen for low white cell count, low platelet count and anaemia. A very low white cell count predisposes to bacterial sore throats, so any patient on DMARDs who presents with a sore throat should have an urgent FBC undertaken.
Most DMARDs can also upset liver function and regular LFTs are performed as part of the monitoring regime.

Practical tip

If a patient has severe side effects from DMARDs, it is a good idea to seek guidance from the rheumatology unit. Most units will have a telephone advice line, usually for patients, but also just as accessible to health professionals.
Nausea, vomiting and diarrhoea with methotrexate is often treated by increasing the dose of folic acid, sometimes to an everyday dosage, apart from the day when the methotrexate is taken.
When writing prescriptions for methotrexate, write which day the patient should take the drug (for example, Tuesdays) on the FP10 to prevent confusion with a daily dosage.
Also, only prescribe methotrexate as 2.5mg tablets. Tablets in 10mg are available, but there have been several occasions when patients mixed up 2.5 and 10mg tablets and overdosed on this potentially very dangerous drug.
A useful patient leaflet on methotrexate is available from the National Patient Safety Agency. All patients should be given a copy of this when they start the drug.
Guidelines on the prescription of DMARDs and the schedules of monitoring are available at the British Society for Rheumatology website.

Lupus

Lupus is a connective tissue disorder affecting mostly women and particularly women of African extraction. The incidence in the UK is about five per 100,000. The presenting features are often poorly defined, as in this lady, and it can take many years to diagnose.
Some of the more specific features are sun-sensitivity, butterfly facial rash over the cheeks, Raynaud's phenomenon, arthritis and alopecia.
There are often associated blood dyscrasias such as low WCC and low platelet count. Pericarditis and pleurisy are also common in lupus and can be the features which prompt a blood test for ANA, as in this case.
ANA is usually positive in lupus patients and in patients with other connective tissue disorders such as scleroderma.
Further analysis of the ANA antibodies into extractable nuclear antigens (ENAs) by the pathology lab, further defines the CT disorders. Lupus is diagnosed in the case of positive Ro and La ENAs. Sjogren's disease often has a positive anti- Ro or a positive anti-La.

Practical tip

ANA can be positive in older patients who do not have a connective tissue disorder (similar to RF). So it is unwise to measure ANA levels in patients unless there is good evidence to suggest a connective tissue disorder, such as new onset Raynaud's, butterfly skin rash, or low WCC.
Raynaud's phenomenon can be primary and starts in childhood, in which case it is not associated with a connective tissue disorder. Approximately 80% of Raynaud's cases are primary, and 20% of cases are secondary, develop later in life, and are associated with a connective tissue disorder.
Lupus can take many years to manifest and patients are often wrongly diagnosed with fibromyalgia before the true disease becomes apparent.
Lupus is a lifelong disease. It can cause nephritis and kidney failure. Regular assessment of the urine for blood and protein is imperative in the monitoring of patients with lupus.