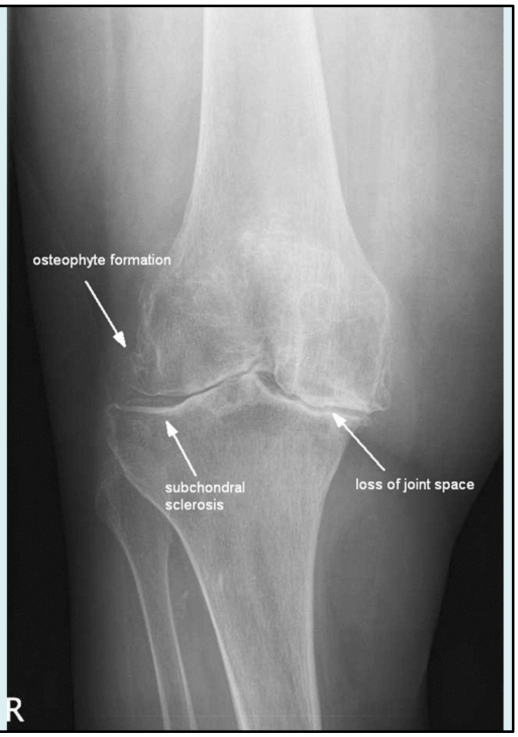
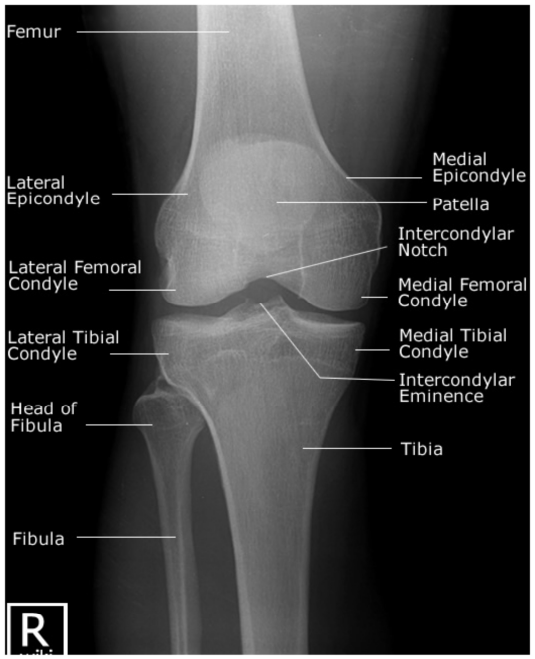
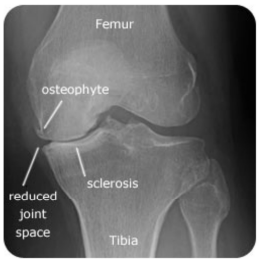
Right knee pain and stiffness in a seronegative patient

A 65-year-old man presented to his primary care provider complaining of **right knee pain and stiffness**. The patient indicated that the pain began approximately two months previously and had gotten **progressively worse.** His knee also had often **swelled after activity.** The pain and swelling were partially relieved by **ibuprofen.** Physical examination revealed a **varus alignment of the knees** with a **mild effusion of the right knee**. There was **tenderness to palpation of the anteromedial joint line**. **Decreased range of motion** in his right knee. Standing anteroposterior **X-rays** revealed **joint-space narrowing,** medial and lateral **osteophytes**, **subcondral sclerosis**. *Rheumatoid factor and ANA were negative*. The patient was diagnosed with **osteoarthritis** (OA) and was educated about conservative OA management. He was given a two-week prescription for a **nonsteroidal anti-inflammatory drug**. The patient was instructed to take **acetaminophen for pain, up to 4 grams a day**, once the swelling had resolved. The patient was instructed about a **home exercise program**. Follow-up with the patient two months later revealed that he has decreased pain and increased range of motion in his right knee. The patient states he takes acetaminophen as needed at night for pain relief to help him sleep. He has been able to partially resume his active lifestyle with the exception of running, for which he has substituted running on an exercise bicycle.




Femur
Lateral Epicondyle
Lateral Femoral Condyle
Lateral Tibial Condyle
Head of Fibula
Fibula
Medial Epicondyle
Patella
Intercondylar Notch
Medial Femoral Condyle
Medial Tibial Condyle
Intercondylar Eminence
Tibia
R


Femur
osteophyte
sclerosis
reduced joint space
Tibia

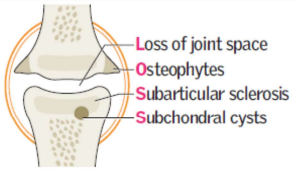
Osteoarthritis (OA)

Osteoarthritis (OA) is the commonest joint condition. ♀:♂≈3:1, onset typically >50yrs. It is usually primary (generalized), but may be secondary to joint disease or other conditions (eg haemochromatosis, obesity, occupational).

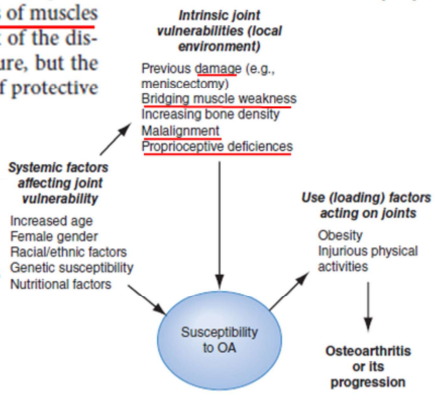
OA is joint failure, a disease in which all structures of the joint have undergone pathologic change, often in concert. The pathologic sine qua non of disease is hyaline articular cartilage loss, present in a focal and, initially, nonuniform manner. This is accompanied by increasing thickness and sclerosis of the subchondral bony plate, by outgrowth of osteophytes at the joint margin, by stretching of the articular capsule, by mild synovitis in many affected joints, and by weakness of muscles bridging the joint. In knees, meniscal degeneration is part of the disease. There are numerous pathways that lead to joint failure, but the initial step is often joint injury in the setting of a failure of protective mechanisms.

degeneration of articular cartilage attributable to
(a) trauma and/or loading factors,
(b) structural/mechanical imbalances,
(c) Bridging muscle weakness
(d) Proprioceptive deficiencies

degeneration of articular cartilage → Inflammation
↓
Subarticular sclerosis
Osteophytes
Bony swelling and Nodes
↓
Synovitis, enthesititis, bridging muscle atrophy
↓
Reduced mobility
Joint failure



Risk factors for osteoarthritis (OA)



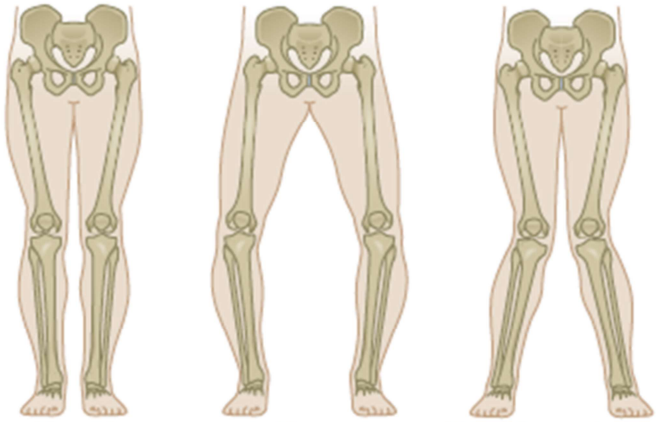


FIGURE 394-5 The two types of limb malalignment in the frontal plane: varus, in which the stress is placed across the medial compartment of the knee joint, and valgus, which places excess stress across the lateral compartment of the knee.

Signs and symptoms *Localized disease* (usually knee or hip): pain on movement and crepitus, worse at end of day; background pain at rest; joint gelling—stiffness after rest up to ~30min; joint instability. *Generalized disease* (primary OA): with Heberden's nodes ('nodal OA', seen mainly in post-menopausal ♀), commonly affected joints are the DIP joints, thumb carpo-metacarpal joints and the knees. There may be joint tenderness, derangement and bony swelling (Heberden's nodes at DIP, Bouchard's nodes at PIP), ↓range of movement and mild synovitis. Assess effect of symptoms on occupation, family duties, hobbies and lifestyle expectations.

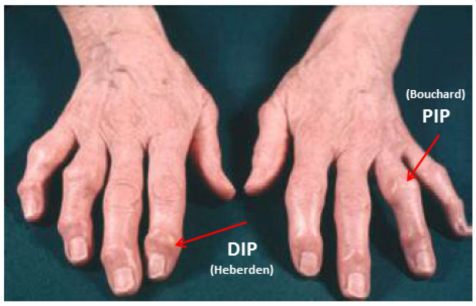
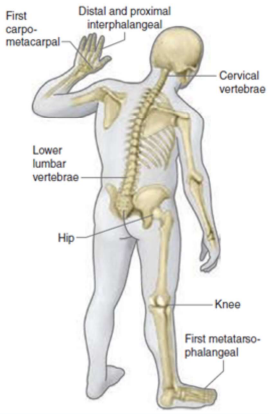


FIGURE 394-2 **Severe osteoarthritis of the hands** affecting the distal interphalangeal joints (Heberden's nodes) and the proximal interphalangeal joints (Bouchard's nodes). There is no clear bony enlargement of the other common site in the hands, the thumb base.

Joints commonly affected by osteoarthritis.



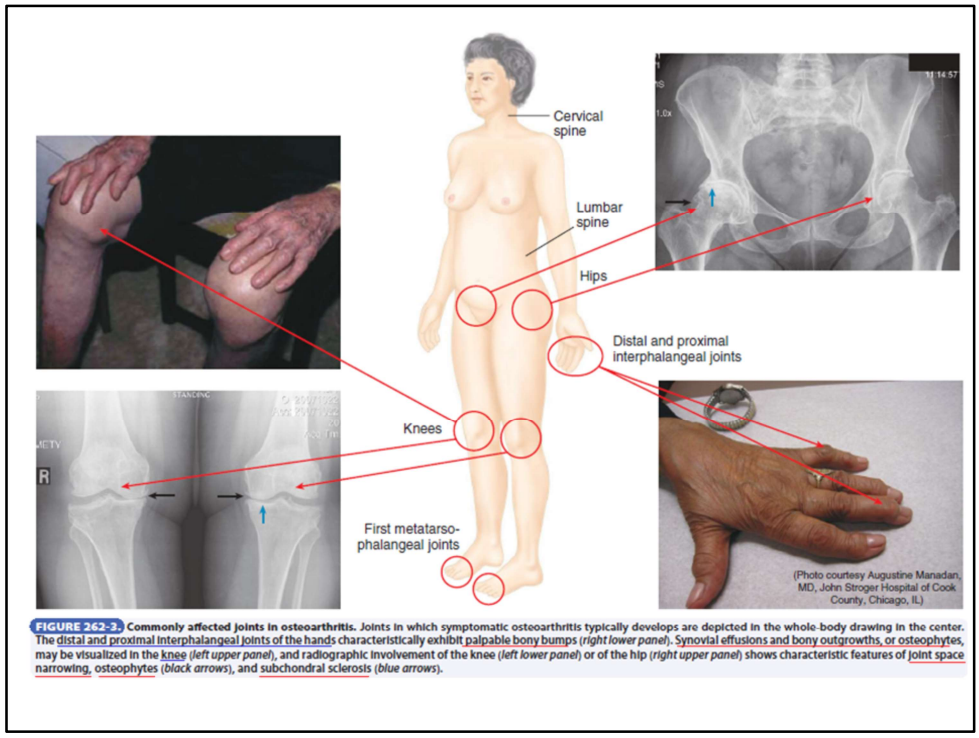


FIGURE 262-3 **Commonly affected joints in osteoarthritis.** Joints in which symptomatic osteoarthritis typically develops are depicted in the whole-body drawing in the center. The distal and proximal interphalangeal joints of the hands characteristically exhibit palpable bony bumps (*right lower panel*). Synovial effusions and bony outgrowths, or osteophytes, may be visualized in the knee (*left upper panel*), and radiographic involvement of the knee (*left lower panel*) or of the hip (*right upper panel*) shows characteristic features of joint space narrowing, osteophytes (*black arrows*), and subchondral sclerosis (*blue arrows*).

Management[6] *Core treatments:* Exercise to improve local muscle strength and general aerobic fitness (irrespective of age, severity or comorbidity). Weight loss if overweight. *Analgesia:* Regular paracetamol ± topical NSAIDs. If ineffective use codeine or short-term oral NSAID (+PPI)—see BOX. Topical capsaicin (derived from chillies) may help. Intra-articular steroid injections temporarily relieve pain in severe symptoms. Intra-articular hyaluronic acid injections (viscosupplementation) are as effective as NSAIDs or steroid injection, but are much more expensive.[7] Glucosamine and chondroitin products are not recommended. *Non-pharmacological:* Use a multi-disciplinary approach, including physiotherapists and occupational therapists. Try heat or cold packs at the site of pain, walking aids, stretching/manipulation or TENS. *Surgery:* Joint replacement (hips, or knees) is the best way to deal with severe OA that has a substantial impact on quality of life.

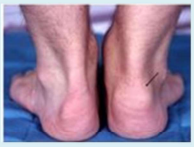
Topical NSAIDs for acute musculoskeletal pain in adults

Cochrane Database of Systematic Reviews 2015, Issue 6. Art. No.: CD007402.

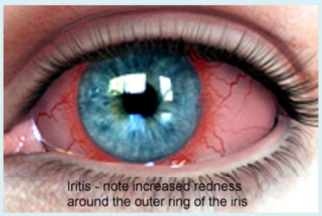
Topical NSAIDs provided good levels of pain relief in acute conditions such as sprains, strains and overuse injuries, probably similar to that provided by oral NSAIDs. Gel formulations of diclofenac (as Emugel®), ibuprofen, and ketoprofen, and some diclofenac patches, provided the best effects. Adverse events were usually minimal.

Low back pain and stiffness in a young men

A 20-year-old man presents to his primary care physician with **low back pain and stiffness** that has persisted for **more than 3 months**. There is no history of obvious injury but he is a very avid sportsman. **His back symptoms are worse when he awakes** in the morning, and the stiffness lasts more than 1 hour. **His back symptoms improve with exercise.** He has a desk job and finds that **sitting for long periods of time exacerbates his symptoms**. He has to get up regularly and move around. His back symptoms also wake him in the second half of the night, after which he can find it difficult to get comfortable. He normally takes an **anti-inflammatory drug** during the day, and finds his stiffness is worse when he misses a dose. He has had **2 bouts of iritis** in the past.



Enthesitis (Insertion of Achilles Tendon at Calcaneus) Right Heel



Iritis - note increased redness around the outer ring of the iris

Tenderness and swelling over bilateral Achilles tendons in a young boy

A **17-year-old boy** presents with an 18-month history of **pain in his right ankle and both heels**, with early morning stiffness and fatigue. He was forced to give up sport, and walking short distances is proving difficult due to heel pain. Examination reveals marked **tenderness and swelling over bilateral Achilles tendons**.

BMJ, Feb 2016

SERONEGATIVE SPONDYLOARTHROPATHIES

- ankylosing spondylitis (AS)
- psoriatic arthritis
- reactive arthritis
- arthritis associated with inflammatory bowel disease
- undifferentiated spondyloarthropathy.

These disorders are noted for who have sacroiliitis. **male** predominance, onset usually **before age 40**, inflammatory arthritis of the **spine** and **sacroiliac joints**, asymmetric oligoarthritis of large peripheral joints, **enthesopathy** (inflammation of where ligaments, tendons, and joint capsule insert into bone), **uveitis** in a significant minority, the **absence of autoantibodies** in the serum, and a striking association with **HLA-B27**. HLA-B27 is positive in up to 90% of patients with ankylosing spondylitis and 75% with reactive arthritis. HLA-B27 also occurs in 50% of the psoriatic and inflammatory bowel disease patients

The pathogenesis of AS is immune-mediated, but there is little direct evidence for antigen-specific autoimmunity, and there is evidence to suggest more of an **autoinflammatory pathogenesis**. Uncertainty remains regarding the primary site of disease initiation. The dramatic response of the disease to therapeutic blockade of tumor necrosis factor α (**TNF-α**) indicates that this cytokine plays a central role in the immunopathogenesis of AS. *More* recent evidence strongly implicates the **interleukin (IL) 23/IL-17** cytokine pathway in AS pathogenesis.

ANKYLOSING SPONDYLITIS

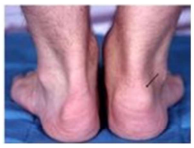
- Chronic low backache in young adults, generally worst in the morning.
- Progressive limitation of back motion and of chest expansion.
- Transient (50%) or persistent (25%) peripheral arthritis.
- Anterior uveitis in 20–25%.
- Diagnostic radiographic changes in sacroiliac joints.
- Negative serologic tests for rheumatoid factor and anti-CCP antibodies.
- HLA-B27 testing is most helpful when there is an intermediate probability of disease.

1 Ankylosing spondylitis (AS) is a chronic inflammatory disease of the spine and sacroiliac joints, of unknown aetiology. *Prevalence:* 0.25–1%. *Men present earlier:* ♂:♀ ≈ 6:1 at 16yrs old, and ~2:1 at 30yrs old. ~90% are HLA B27 +ve (see BOX 2).

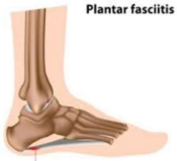
Symptoms and signs: The typical patient is a man <30yrs old with gradual onset of low back pain, worse at night, with spinal morning stiffness relieved by exercise. Pain radiates from sacroiliac joints to hips/buttocks, and usually improves towards the end of the day. There is progressive loss of spinal movement (all directions)—hence ↓thoracic expansion. See p542–4 for tests of spine flexion and sacroiliitis. The disease course is variable; a few progress to kyphosis, neck hyperextension (question-mark posture; fig 1), and spino-cranial ankylosis. Other features include enthesitis (see BOX 1), especially Achilles tendonitis, plantar fasciitis, at the tibial and ischial tuberosities, and at the iliac crests. Anterior mechanical chest pain due to costochondritis and fatigue may feature. Acute iritis occurs in ~⅓ of patients and may lead to blindness if untreated (but may also have occurred many years before, so enquire directly). AS is also associated with osteoporosis (up to 60%), aortic valve incompetence (<3%) and pulmonary apical fibrosis.

Early sacroiliitis

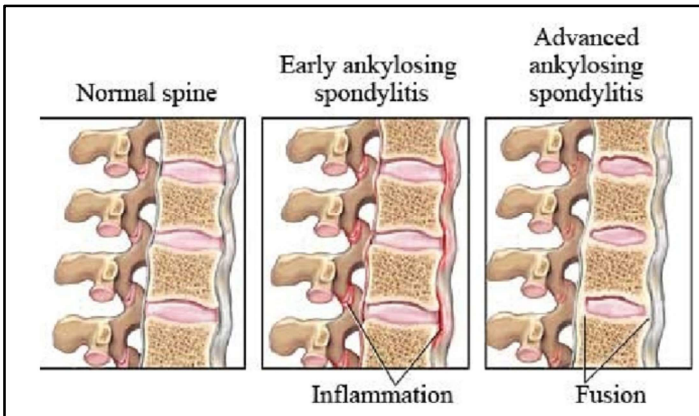

Iritis - note increased redness around the outer ring of the iris

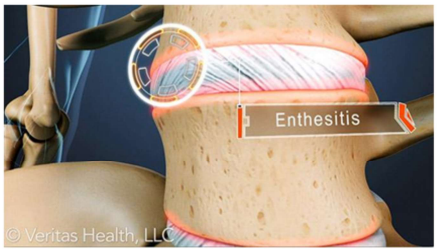

Enthesitis (Insertion of Achilles Tendon ; Calcaneus) Right Heel

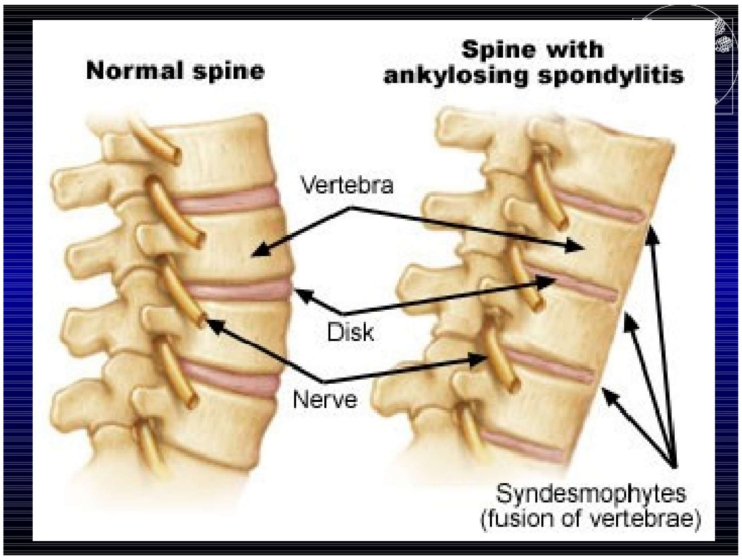
Question mark posture, or suppliant posture - loss of lumbar lordosis, fixed kyphosis, compensated extension cervical spine, protruberant abdomen.



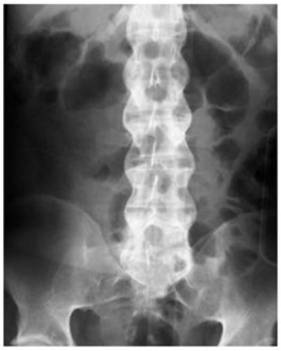
Inflammation of the plantar fascia

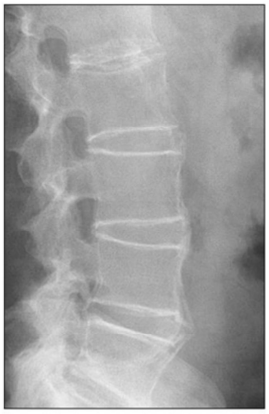

Normal spine
Early ankylosing spondylitis
Advanced ankylosing spondylitis
Inflammation
Fusion

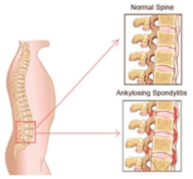

Enthesitis
© Veritas Health, LLC


Normal spine
Spine with ankylosing spondylitis
Vertebra
Disk
Nerve
Syndesmophytes
(fusion of vertebrae)

Radiograph of the lumbar spine in a patient with AS







Ossification of the annulus fibrosus in the lumbar spine has resulted in the formation of marginal syndesmophytes in a gradually ascending pattern ("bamboo spine").

Tests: Diagnosis is clinical, supported by imaging (MRI is most sensitive and better at detecting early disease).[40] Sacroiliitis is the earliest X-ray feature, but may appear late: look for irregularities, erosions, or sclerosis affecting the lower half of the sacroiliac joints, especially the iliac side. Vertebral syndesmophytes are characteristic (often T11–L1 initially): bony proliferations due to enthesitis between ligaments and vertebrae. These fuse with the vertebral body above, causing ankylosis. In later stages, calcification of ligaments with ankylosis lead to a 'bamboo spine' appearance. *Also:* FBC (normocytic anaemia), ↑ESR, ↑CRP, HLA B27+ve (not diagnostic).

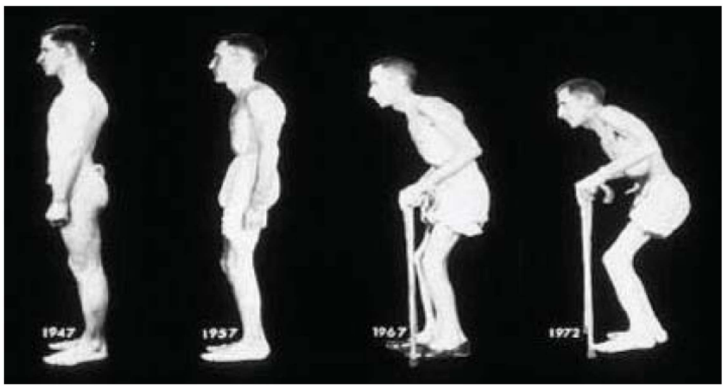
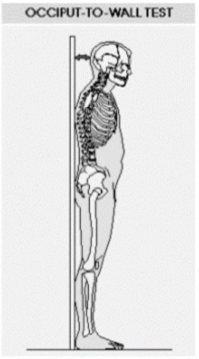


Fig 1. Progression of disease and effect on posture in severe ankylosing spondylitis.

Occiput To Wall Distance / Flesche Test

❑The severity of cervical flexion deformity in ankylosing spondylitis can be assessed by measuring the occiput to wall distance (**Flesche test).**
❑With the patient standing erect, the heels and the buttocks are placed against a wall; the patient is then instructed to extend his or her neck maximally in an attempt to touch the wall with the occiput.
❑The distance between the occiput and the wall is a measure of the degree of flexion deformity of the cervical spine.

- The occiput to wall distance should be zero



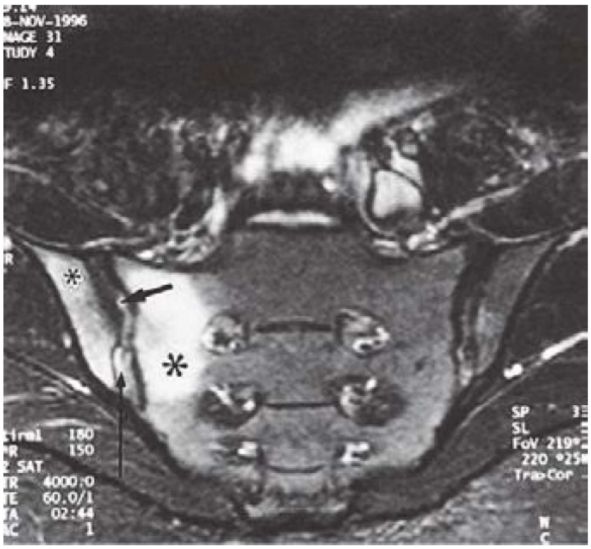


FIGURE 384-1 **Early sacroiliitis in a patient with ankylosing spondylitis,** indicated by prominent edema in the juxtaarticular bone marrow (*asterisks*), synovium and joint capsule (*thin arrow*), and interosseous ligaments (*thick arrow*) on a short tau inversion recovery (STIR) magnetic resonance image. *(From M Bollow et al: Zeitschrift für Rheumatologie 58:61, 1999. Reproduced with permission.)*

Management: Exercise, not rest, for backache, including intense exercise regimens to maintain posture and mobility—ideally with a physiotherapist specializing in AS. NSAIDs (eg ibuprofen or naproxen, if no CI—see p547) usually relieve symptoms within 48h, and they may slow radiographic progression.[41] TNFα blockers etanercept, adalimumab and golimumab are indicated in severe active AS if NSAIDs fail (p549).[42] Local steroid injections provide temporary relief. Surgery includes hip replacement to improve pain and mobility if the hips are involved, and rarely spinal osteotomy. There is increased risk of osteoporotic spinal fractures (consider bisphosphonates).

Prognosis: There is not always a clear relationship between the activity of arthritis and severity of underlying inflammation (as for all the spondyloarthritides). Prognosis is worse if ESR >30; onset <16yrs; early hip involvement or poor response to NSAIDs.[43]

Question mark posture, or suppliant posture - loss of lumbar lordosis, fixed kyphosis, compensated extension cervical spine, protruberant abdomen.

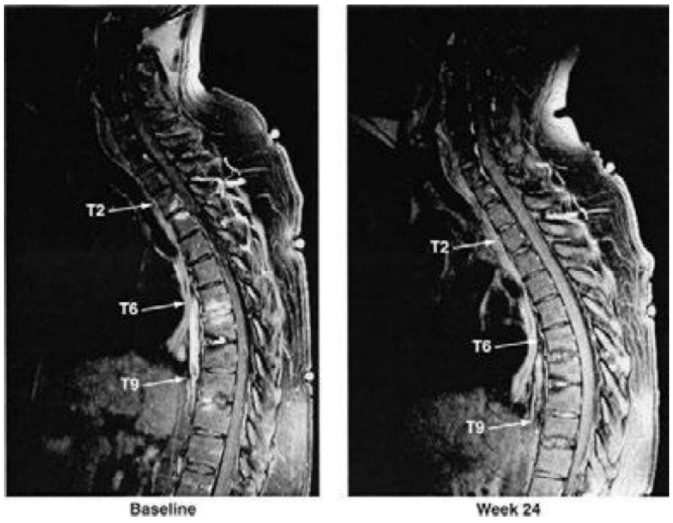
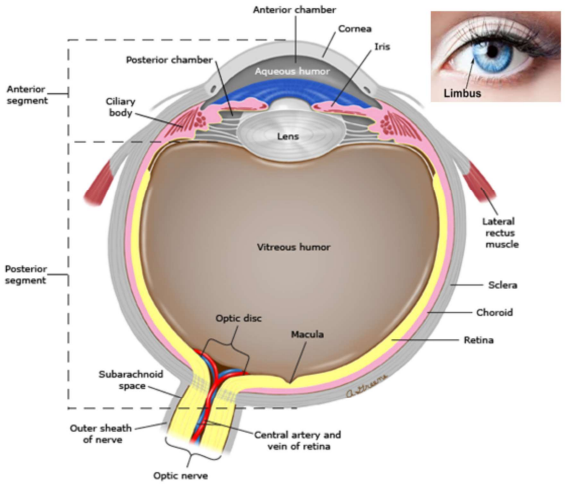


FIGURE 384-2 Spinal inflammation (spondylodiskitis) in a patient with ankylosing spondylitis and its dramatic response to treatment with infliximab. Gadolinium-enhanced T1-weighted magnetic resonance images, with fat saturation, at baseline and after 24 weeks of infliximab therapy. *(From J Braun et al: Arthritis Rheum 54:1646, 2006.)*

Acute Anterior Uveitis

- Anterior uveitis is the most common form of uveitis, 90% of all cases. It may produce pain and redness, that is primarily noted at the **limbus** (the junction between the cornea and the sclera).The degree of visual loss associated with anterior uveitis is variable.
- Posterior and intermediate uveitis – is more likely to be painless, but may result in nonspecific visual changes.
- Panuveitis – inflammation is detected simultaneously in the anterior chamber, vitreous, and retina or choroid.
- More than 50-60% of anterior uveitis are HLA B27 positive;
- Acute anterior uveitis can be associated with systemic immune mediated diseases, traumatic, infective or idiopathic.



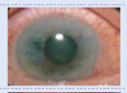
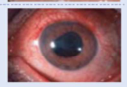
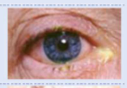
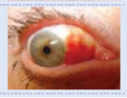
Classification by location

Anterior uveitis	Anterior chamber	Iritis Iridocyclitis Anterior cyclitis
Intermediate uveitis	Vitreous	Pars planitis Posterior cyclitis Hyalitis
Posterior uveitis	Retina or choroid	Focal, multifocal, or diffuse choroiditis Chorioretinitis Retinochoroiditis Retinitis Neuroretinitis
Panuveitis	Anterior chamber, vitreous and retina or choroid	

Systemic immune-mediated causes of uveitis

Ankylosing spondylitis
Behçet's disease
Blau syndrome
Crohn's disease
Drug or hypersensitivity reaction
Interstitial nephritis
Juvenile idiopathic arthritis
Kawasaki's disease
Multiple sclerosis
Neonatal onset multisystem inflammatory disease
Psoriatic arthritis
Reactive arthritis
Relapsing polychondritis
Sarcoidosis
Sjögren's syndrome
Sweet syndrome
Systemic lupus erythematosus
Ulcerative colitis
Vasculitis
Vitiligo
Vogt-Koyanagi-Harada syndrome

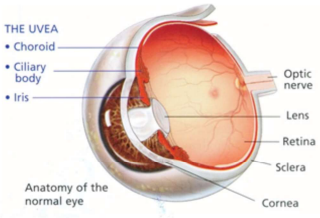
Differential diagnosis of a red eye

	Conjunctiva	Iris	Pupil	Cornea	Anterior chamber	Intraocular pressure	Treatment	Appearance
Acute glaucoma	Both ciliary and conjunctival vessels injected. Entire eye is red. See *OHCS* p430.	Injected	Dilated, fixed, oval	Steamy, hazy	Very shallow	Very high	Refer. IV acetazolamide + pilocarpine drops (miotic); Peripheral iridotomy.	
Anterior uveitis (iritis)	Redness most marked around cornea, which doesn't blanch on pressure. Usually unilateral. *Causes:* AS, RA, Reiter's•, sarcoidosis, herpes simplex, herpes zoster, and Behçet's disease. NB: a similar scleral appearance but without papillary or anterior chamber involvement may be *scleritis* (eg RA, SLE, vasculitis).	Injected	Small, irregular due to adhesions between the anterior lens and the pupil margin	Normal	Turgid	Normal	Refer. Steroid eye drops (eg 0.5% prednisolone) + mydriatic (eg cyclopentolate 0.5%).	
Conjunctivitis	Often bilateral. Conjunctival vessels injected, greatest toward fornices, but blanching on pressure. Mobile over sclera. Purulent discharge.	Normal	Normal	Normal	Normal	Normal	Most do not require treatment. Consider chloramphenicol ointment or drops.	
Subconjunctival haemorrhage	Bright red sclera with white rim around limbus. *Causes:* BPT; leptospirosis; bleeding disorders; trauma; snake venom; haemorrhagic fevers.	Normal	Normal	Normal	Normal	Normal	Looks alarming but resolves spontaneously. Check BP if elderly; Refer if traumatic; On warfarin?	

Granulomatous disorders Syphilis, TB, sarcoidosis, leprosy, brucellosis, and toxoplasmosis may inflame either the front chamber (anterior uveitis/iritis) or back chamber (posterior uveitis/choroiditis). Refer to an ophthalmologist.

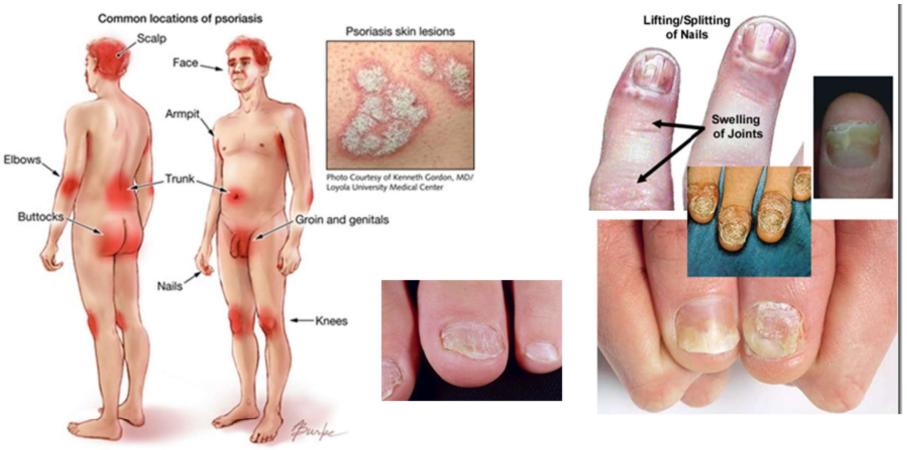
Systemic inflammatory diseases may manifest as iritis in ankylosing spondylitis and Reiter's•; *conjunctivitis* in Reiter's; *scleritis* or *episcleritis* in RA, vasculitis and SLE. Scleritis in RA and Wegener's• may damage the eye. Refer urgently if eye pain. Giant cell arteritis causes optic nerve ischaemia presenting as sudden blindness.

Keratoconjunctivitis sicca is a reduction in tear formation, tested by the Schirmer filter paper test (<5mm in 5min). It causes a gritty feeling in the eyes, and a dry mouth (xerostomia from ↓ saliva production). It is found on its own (Sjögren's syndrome), or with other diseases, eg SLE, RA, sarcoidosis. ℞: artificial tears/saliva (eg Tears Naturale®, hypromellose drops, Saliveze® oral spray).



Anatomy of the normal eye

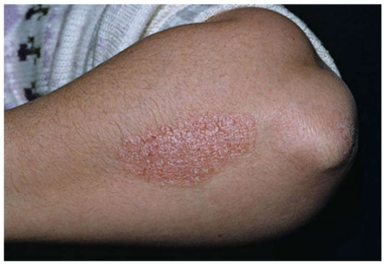
3 Psoriatic arthritis (*OHCS* p594) Occurs in 10–40% with psoriasis and can present before skin changes. Patterns are: •Symmetrical polyarthritis (like RA); •DIP joints; •Asymmetrical oligoarthritis; •Spinal (similar to AS); •Psoriatic arthritis mutilans (rare, ~3%, severe deformity). *Radiology:* Erosive changes, with 'pencil-in-cup' deformity in severe cases. Associated with nail changes in 80%, synovitis (dactylitis—see BOX 1), acneiform rashes and palmo-plantar pustulosis. *Management:* NSAIDs, sulfasalazine, methotrexate and ciclosporin. Anti-TNF agents are also effective.

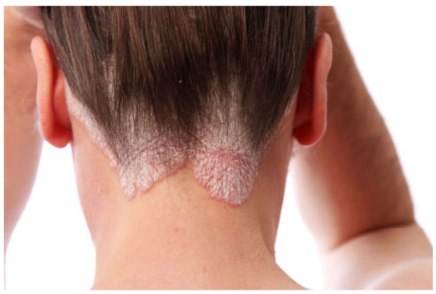


Psoriatic arthritis	M = F	30-55	<20 percent RF+	10 percent of those with psoriatic arthritis will have an RA-like distribution (MCPs, PIPs, wrists). Cutaneous psoriasis will be evident in the vast majority of cases.

PSORIASIS

Psoriasis is one of the most common dermatologic diseases, affecting up to 2% of the world's population. It is an immune-mediated disease clinically characterized by erythematous, sharply demarcated papules and rounded plaques covered by silvery micaceous scale. The skin lesions of psoriasis are variably pruritic. Traumatized areas often develop lesions of psoriasis (the *Koebner* or isomorphic phenomenon). In addition, other external factors may exacerbate psoriasis, including infections, stress, and medications (lithium, beta blockers, and antimalarial drugs).

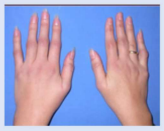
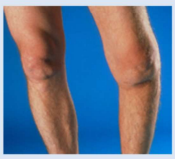
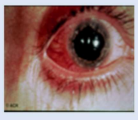
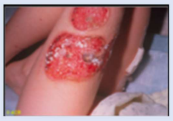
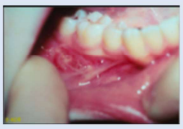
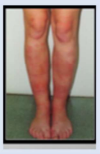
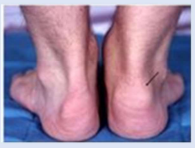
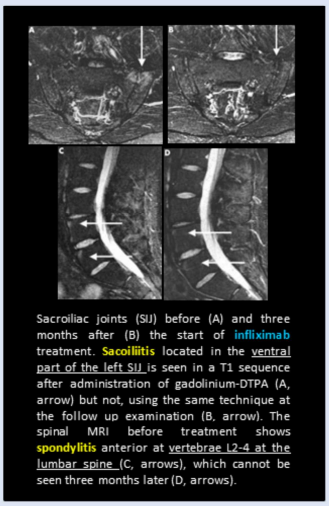




2 Enteric arthropathy *Associations:* Inflammatory bowel disease, GI bypass, coeliac and Whipple's disease (p730). Arthropathy often improves with the treatment of bowel symptoms (beware NSAIDs). Use DMARDs for resistant cases.

20 percent of patients with Crohn's disease or ulcerative colitis (more likely in patients with large bowel disease) will develop enteric arthropathy:

- **Peripheral arthritis**
  - **Asymetric oligoarthritis**
  - **Seronegative RA-like polyarthritis**
- **Spondylarthritis**
- **Sacroilitis**
- **Enthesitis (heel pain)**
- **oral ulcerations**
- **Uveitis**
- **Pyoderma gangrenosum**
- **Erythema nodosum**

Sacroiliac joints (SIJ) before (A) and three months after (B) the start of **infliximab** treatment. **Sacoiliitis** located in the ventral part of the left SIJ is seen in a T1 sequence after administration of gadolinium-DTPA (A, arrow) but not, using the same technique at the follow up examination (B, arrow). The spinal MRI before treatment shows **spondylitis** anterior at vertebrae L2-4 at the lumbar spine (C, arrows), which cannot be seen three months later (D, arrows).

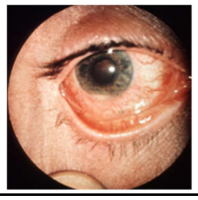
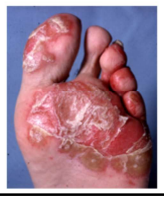
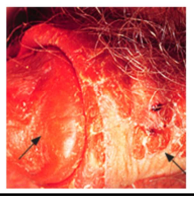
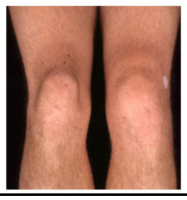
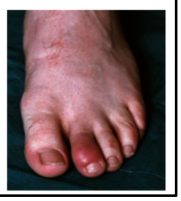
Reactive arthritis **is conventionally defined as an arthritis that arises following an infection, although the pathogens cannot be cultured from the affected joints.** It is generally regarded as a form of spondyloarthritis. **Gastrointestinal and urogenital pathogens** could be considered causative. These included Chlamydia trachomatis, Yersinia, Salmonella, Shigella, and Campylobacter. Escherichia coli, Clostridium difficile, and Chlamydia pneumoniae can be added to the list.

Two major clinical features can be identified:

- An **interval** ranging from several days to weeks between the antecedent infection and arthritis.
- **A typically mono- or oligoarticular pattern of the arthritis, often involving the lower extremities, and sometimes associated with dactylitis (sausage digits) and enthesitis (heel pain)**

1. **Conjunctivitis and anterior uveitis.** Conjunctival injection and anterior uveitis (iritis) with hypopyon.
2. Erythematous, scaly plaques of **keratoderma blennorrhagicum**.
3. **Circinate balanitis** characterized by shallow ulcers on the glans penis and the shaft of the penis (arrows). The lesions are generally asymptomatic.
4. Asymmetrical swelling of left knee due to **reactive arthritis**. The patellar borders are effaced and there is suprapatellar fullness.
5. **Sausage like swelling** of the left second toe.

4 Reactive arthritis A *sterile* arthritis, typically affecting the lower limb ~1-4 weeks after urethritis (p416; *Chlamydia* or *Ureaplasma* sp.), or dysentery (*Campylobacter*, *Salmonella*, *Shigella*, or *Yersinia* sp.). It may be chronic or relapsing. *Also there may be* iritis, keratoderma blenorrhagica (brown, raised plaques on soles and palms), circinate balanitis (painless penile ulceration secondary to *Chlamydia*), mouth ulcers and enthesitis. *Reiter's syndrome*[44] is a triad of urethritis, arthritis, and conjunctivitis. *Tests:* ESR & CRP↑. Culture stool if diarrhoea. Infectious serology. Sexual health review. X-ray may show enthesitis with periosteal reaction. *Management:* There is no specific cure. Splint affected joints acutely; treat with NSAIDs or local steroid injections. Consider sulfasalazine or methotrexate if symptoms >6 months. Treating the original infection may make little difference to the arthritis.

Shared features of the spondyloarthropathies

The spondyloarthropathies show much overlap, with several features in common:

1. Seronegativity (= rheumatoid factor -ve).
2. HLA B27 association—see BOX below.
3. 'Axial arthritis': pathology in spine (spondylo-) and sacroiliac joints.
4. Asymmetrical large-joint oligoarthritis (ie <5 joints) or monoarthritis.
5. Enthesitis: inflammation of the site of insertion of tendon or ligament into bone, eg plantar fasciitis, Achilles tendonitis, costochondritis.
6. Dactylitis: inflammation of an entire digit ('sausage digit'), due to soft tissue oedema, and tenosynovial and joint inflammation.
7. Extra-articular manifestations: eg iritis (anterior uveitis), psoriaform rashes, oral ulcers, aortic valve incompetence, inflammatory bowel disease.

NB Behçet's syndrome (p708) can also present with uveitis, skin lesions and arthritis and is not always associated with gross oral or genital ulcerations.

HLA-B27 disease associations[45]

The HLA system plays a key role in immunity and self-recognition. More than one hundred HLA B27 disease associations have been made, yet the actual role of HLA B27 in triggering an inflammatory response is not fully understood. ~5% of the UK population are HLA B27 positive—most do not have any disease. The chance of an HLA B27 positive person developing spondyloarthritis or eye disease is 1 in 4. Common associations include:

Ankylosing spondylitis: 88% of all those with AS are HLA B27 positive.
Acute anterior uveitis: 50-60% are HLA B27 positive.
Reactive arthritis: 60-85% are HLA B27 positive.
Enteric arthropathy: 50-60% are HLA B27 positive.
Psoriatic arthritis: 60-70% are HLA B27 positive.

Lyme disease[347] is a tick-borne (fig 1) infection caused by *Borrelia burgdorferi*. *Signs:* ►≤75% remember the tick bite. The 1st sign is usually erythema migrans; a circular rash (*OHCS* p587 fig 3) occurring in ~80%, which begins at the site of a tick bite after 3-30d (p564). It gradually expands, reaching up to 30cm across. Its centre may clear as it enlarges (bull's-eye appearance). *Also:* fatigue, chills, fever, headache, muscle and joint pain, lymphadenopathy, myocarditis; heart block; meningitis; ataxia; amnesia; cranial nerve palsies; neuropathy; lymphocytic meningoradiculitis (Bannwarth's syndrome). *Diagnosis* is based on symptoms, physical findings, and a history of exposure to infected ticks. Lab tests are not needed in presence of erythema migrans.[348] *℞:* Skin rash: doxycycline 100mg/12h PO (amoxicillin or penicillin V if <8yrs or pregnant) for 14-21d. Later complications: high-dose IV benzylpenicillin, ceftriaxone. *Prevention:* Keep limbs covered; use insect repellent; tick collars for pets; check skin often when in risky areas. Vaccination is available, eg if living in high-risk areas. Advice differs on prophylaxis after a tick bites. A single dose of doxycycline 200mg PO given within 72h of a bite is effective prophylaxis; in highly endemic areas, this may be worthwhile (eg if risk >1%). *Removing ticks:* Use fine (tick-removing) tweezers to grasp the tick very close to the skin. With a steady motion, pull the tick's body away; clean with soap and water. Don't worry if the tick's mouthparts remain in the skin—they won't transmit Lyme disease.[349] Skin complications: acrodermatitis chronica atrophicans (ACA; skin is as 'thin as cigarette paper'); borrelia lymphocytoma manifests, eg as a blue/red discolouration of the earlobe.

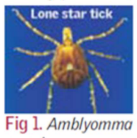
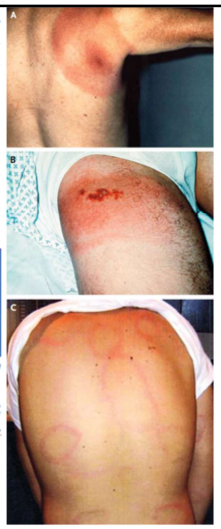


Fig 1. *Amblyomma americanum.*
© Prof S. Upton; Kansas Univ.



Types of Erythema Migrans.

Panel A shows a single erythema migrans lesion,

Panel B shows vesicula erythema migrans, and

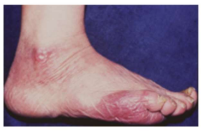
Panel C shows multiple erythema migrans lesions.

Serologic tests for the diagnosis of B. burgdorferi infection are generally of little use in patients with erythema migrans. Two-tier serologic testing for antibodies to B. burgdorferi is recommended (a quantitative test, usually an enzymelinked immunosorbent assay [ELISA] of the concentration of antibodies to B. burgdorferi and, if results are positive or equivocal, a Western blot); however, it has poor sensitivity in patients with erythema migrans during the acute phase (positive results in only 25 to 40% of patients without evidence of dissemination)

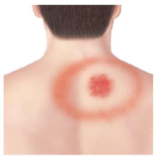
Erythema migrans (fig 7) Presents as a small papule at the site of a tick bite which develops into a spreading large erythematous ring, with central fading. It lasts from 48h to 3 months and there may be multiple lesions in disseminated disease. *Cause:* The rash is pathognomonic of Lyme disease and occurs in ~80% of cases (p430).

There are three stages of Lyme infection:

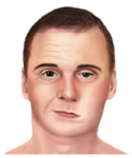
- Stage 1 disease is a localized infection, presenting about a week after the tick bite with erythema migrans (a macular rash), lymphadenopathy, and associated fever and headache.
- Stage 2 disease occurs several days to weeks after the appearance of erythema migrans. Some patients may develop a more widespread rash, and after several weeks or months around 15% of untreated cases develop neurological complications such as meningitis, encephalitis, cranial or peripheral neuritis, or radiculopathies. About 5% of patients develop cardiac involvement. Myalgia and arthritis may also occur at this stage.
- Stage 3 disease commonly causes a chronic arthritis (usually of the knees), but may also cause chronic encephalomyelitis and other neurological disorders or acrodermatitis chronica atrophicans. The evidence for persistent infection at this stage is lacking.



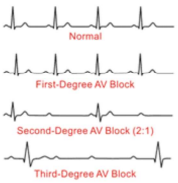
Erythema migrans



Facial paralysis (Bell's palsy)



Fluctuating AV block



Asimetric chronic arthritis

acrodermatitis chronica atrophicans

Manifestations, brief clinical case definitions, and recommended diagnostic approach for the diagnosis of Lyme borreliosis in routine clinical practice

	Primary diagnostic testing	Supporting diagnostic testing	Supporting clinical findings
Erythema migrans			
Expanding red or bluish-red patch (≥5 cm in diameter),* with or without central clearing Advancing edge is typically distinct, often intensely coloured, and not noticeably raised	Diagnosis on the basis of history and visual inspection of the skin lesion Laboratory testing not needed or recommended If lesion is atypical, then acute-phase and convalescent-phase serological testing† are recommended because of insensitivity of acute phase testing‡	Culture or PCR of a skin biopsy specimen useful in research studies, but not needed for routine clinical practice	Tick bite at site; regional lymphadenopathy in North American patients
Lyme neuroborreliosis			
In adults, mainly meningo-radiculitis, meningitis, and peripheral facial palsy; rarely encephalitis, myelitis; very rarely cerebral vasculitis In children, mainly meningitis and peripheral facial palsy	Pleocytosis and demonstration of synthesis of intrathecal antibodies to *Borrelia burgdorferi* sensu lato§ Serological testing† usually positive at time of presentation; if negative, test convalescent phase sera (2–6 weeks later)	Detection of Lyme borrelia by culture or PCR of cerebrospinal fluid Intrathecal synthesis of total IgM, IgG, or IgA	Recent or concomitant erythema migrans
Cardiac Lyme borreliosis (a rare manifestation)			
Acute onset of atrioventricular (I–III) conduction disturbances, rhythm disturbances, and sometimes myocarditis or pericarditis Alternative explanations should be excluded	Serological testing† usually positive, but if negative and clinical suspicion strong, test convalescent phase sera (2–6 weeks later)	None recommended (Detection of Lyme borrelia by culture or PCR from endomyocardial biopsy restricted to research studies)	Recent or concomitant erythema migrans, neurological disorders, or both
Lyme arthritis			
Recurrent attacks or persisting objective joint swelling in one or more large joints Alternative explanations should be excluded	Serological testing† As a rule, high concentrations of specific serum IgG antibodies present	Synovial fluid analysis Detection of *B burgdorferi* sensu lato by PCR of synovial fluid or tissue	Previous other well-defined Lyme borreliosis manifestations
Acrodermatitis chronica atrophicans			
Long-standing red or bluish-red lesions, usually on the extensor surfaces of extremities Initial doughy swelling Lesions eventually become atrophic Possible skin induration and fibroid nodules over bony prominences	Serological testing† As a rule, high concentrations of specific serum IgG antibodies present	Histology Detection of *B burgdorferi* sensu lato by culture or PCR from skin biopsy useful in research studies, but not for routine clinical practice	Previous other well-defined Lyme borreliosis manifestations

Data from reference 45. *If less than 5 cm in diameter, a history of tick bite, a delay in appearance after the tick bite of at least 2 days, and an expanding rash at the site of the tick bite is needed. †Two-tier serological testing is recommended, but newer first tier and immunoblot assays are increasingly incorporating the same peptides or recombinant immunodominant antigens of *Borrelia burgdorferi* sensu lato—whether doing the second tier immunoblot still increases overall specificity of serological testing is less clear. ‡As a rule, initial and follow up samples have to be tested in parallel to avoid misinterpreting changes caused by inter-assay variation. §In early cases, intrathecally produced specific antibodies might still be absent.

Lancet 2012; 379: 461-73

The diagnosis of **early Lyme disease** can be made solely on **clinical grounds** if the characteristic **erythema migrans** (EM) lesion is present in a patient who lives in or has recently traveled to an area that is endemic for Lyme disease.The patient with a characteristic EM lesion will likely be seronegative, since the lesion appears prior to development of a diagnostic, adaptive immune response. Laboratory testing is neither required nor recommended.

In contrast to the negative serology at the time of the appearance of the EM lesion, by the time the patient has findings of **early disseminated extracutaneous disease** (eg, lymphocytic meningitis, facial palsy, radiculoneuropathy, carditis with heart block), **serologic tests are typically positive**, as they are in patients with late Lyme disease.

Serologic testing should be performed in patients who meet all of the following criteria:

- A recent history of having resided in or traveled to an **area endemic for Lyme disease** or
  and
- A **risk factor for exposure to ticks**
  and
- **Symptoms consistent with early disseminated disease or late Lyme disease** (eg, meningitis, radiculopathy, mononeuritis, cranial nerve palsy, arthritis, carditis)

Serologic testing for Lyme disease should **not** be performed in the following settings:

- In patients with an EM rash. Patients with skin rashes consistent with EM who reside in or have recently traveled to an endemic area should be treated for Lyme disease.
- For screening of asymptomatic patients living in endemic areas
- For patients with non-specific symptoms only (eg, fatigue, myalgias/arthralgias). The use of serologic testing in populations with a low pre-test probability of Lyme disease results in a greater likelihood of false-positive test results than true positive test results.

Clinical manifestations of Lyme disease

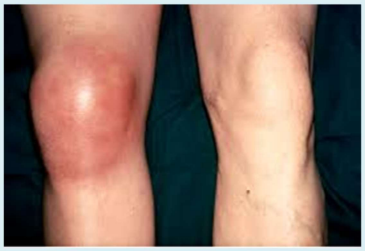
Early localized disease, occurring a few days to one month after the tick bite*
Erythema migrans - occurs in approximately 80 percent of patients
Associated symptoms and signs may include: fatigue, malaise, fever, lethargy, mild headache, mild neck stiffness, myalgias, arthralgias, regional lymphadenopathy
Early disseminated disease¶, occurring weeks to months after the tick bite*Δ
Carditis - about 1 percent of patients reported to the CDC◊
Manifestations include AV nodal block, mild cardiomyopathy or myopericarditis
Neurologic disease - occurs in approximately 15 percent of untreated patients◊
Manifestations include lymphocytic **meningitis**, **cranial neuropathy** (most often facial, can be bilateral), **peripheral neuropathy**; rarely myelitis or encephalitis
Musculoskeletal involvement - occurs in approximately 60 percent of untreated patients◊
Manifestations include **migratory arthralgias**
Skin involvement - **multiple erythema migrans lesions**Δ, borrelial lymphocytoma (in Europe)
Lymphadenopathy - regional or generalized
Eye involvement§ - conjunctivitis, iritis, choroiditis, vitritis, retinitis
Liver disease - liver function test abnormalities, hepatitis
Kidney disease - microhematuria, asymptomatic proteinuria
Late or chronic disease¶, occurring months to years after the tick bite*
Musculoskeletal symptoms - approximately 60 percent of untreated patients develop intermittent monoarticular or oligoarticular **arthritis**; approximately 10 percent of untreated patients develop persistent monoarthritis, usually affecting the knee
Neurologic disease - incidence has not been established
Peripheral neuropathy or encephalomyelitis (both rare)
Cutaneous involvement - **acrodermatitis chronica atrophicans**, morphea/localized scleroderma-like lesions (both described only in Europe)

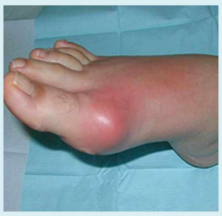
* Only about 25 percent of patients with erythema migrans recall the tick bite that transmitted Lyme disease.
¶ Can occur in the absence of any prior features of Lyme disease.
Δ The multiple erythema migrans lesions of early disseminated disease typically occur days to weeks following infection.
◊ Incidence following treated erythema migrans is not known but is very low.
§ Observation based on individual case reports.

Acute monoarthritis in a patient with metabolic syndrome

A 48-year-old man comes to your office complaining of *severe right knee pain for 8 hours. He states that the pain, which **started abruptly** at 2 AM and woke him from sleep, was quite severe—so painful that even the weight of the bed sheets on his knee was unbearable. By the morning, the knee had become **warm**, **swollen,** and **tender.** He prefers to keep his knee bent, since straightening the knee causes the pain to worsen. He has never had pain, surgery, or injury to his knees. **A year ago**, he did have some ***pain and swelling at the base of his great toe on the left foot**, which was not as severe as this episode, and resolved in 2 or 3 days after taking ibuprofen. His only medical history is ***hypertension**, which is controlled with **hydrochlorothiazide**. He is a nonsmoker, and reports moderate social alcohol use. He is overweight with a ***waist circumference is 110 cm**. On examination, his temperature is 37.5°C, heart rate 104 bpm, and blood pressure 136/78 mm Hg. His head and neck examinations are unremarkable, his chest is clear, and his heart is tachycardic but regular, with no gallops or murmurs. **His right knee is swollen, with a moderate effusion, and appears erythematous, warm, and very tender to palpation**. He is unable to fully extend the knee because of pain. He has no other joint swelling, pain, or deformity, and no skin rashes.

What is the most likely diagnosis?
What is your next step?
What is the best initial treatment?
What is the best approach to prevent further attack?





CFIM n° 21

Acute monoarthritis in a patient with metabolic syndrome

A 48-year-old man comes to your office complaining of **severe right knee pain for 8 hours**. He states that the pain, which started abruptly at 2 AM and woke him from sleep, was quite severe—so painful that even the weight of the bed sheets on his knee was unbearable. By the morning, the knee had become **warm**, **swollen,** and **tender.** He prefers to keep his knee bent, since straightening the knee causes the pain to worsen. He has never had pain, surgery, or injury to his knees. **A year ago**, he did have some **pain and swelling at the base of his great toe on the left foot**, which was not as severe as this episode, and resolved in 2 or 3 days after taking ibuprofen. His only medical history is **hypertension**, which is controlled with hydrochlorothiazide. He is a nonsmoker, and reports moderate social alcohol use. He is overweight with a **waist circumference is 110 cm**. of On examination, his temperature is 99.4°F, heart rate 104 bpm, and blood pressure 136/78 mm Hg. His head and neck examinations are unremarkable, his chest is clear, and his heart is tachycardic but regular, with no gallops or murmurs. **His right knee is swollen, with a moderate effusion, and appears erythematous, warm, and very tender to palpation**. He is unable to fully extend the knee because of pain. He has no other joint swelling, pain, or deformity, and no skin rashes.

What is the most likely diagnosis? *Most likely diagnosis: Acute monoarticular arthritis, likely crystalline or infectious, most likely gout because of history.*

What is your next step? *Aspiration of the knee joint to send fluid for cell count, culture, and crystal analysis.*

What is the best initial treatment? *Best initial treatment: If the joint fluid analysis is consistent with infection, he needs drainage of the infected fluid by aspiration and administration of antibiotics. If analysis is suggestive of crystal-induced arthritis, he can be treated with colchicine, nonsteroidal anti-inflammatory drugs (NSAIDs), or corticosteroids.*

What is the best approach to prevent further gout attack? *Stop* hydrochlorothiazide. *Start Allopurinol 3 weeks after acute attack.*

CFIM n° 21

Patterns of presentation of arthritis

Monoarthritis	Oligoarthritis (≤5 joints)	Polyarthritis (>5 joints involved)	
Septic arthritis	Crystal arthritis	*Symmetrical:*	*Asymmetrical:*
Crystal arthritis (gout, CPPD)	Psoriatic arthritis	Rheumatoid arthritis	Reactive arthritis
Osteoarthritis	Reactive arthritis, eg *Yersinia, Salmonella, Campylobacter*	Osteoarthritis	Psoriatic arthritis
Trauma, eg haemarthrosis	Ankylosing spondylitis Osteoarthritis	Viruses (eg hepatitis A, B & C; mumps)	
		Systemic conditions[1] (can be either)	

1 Connective tissue disease (eg SLE and relapsing polychondritis), sarcoidosis, malignancy (eg leukaemia), endocarditis, haemochromatosis, sickle-cell anaemia, familial Mediterranean fever, Behçet's.

▸▸ Exclude septic arthritis in any acutely inflamed joint, as it can destroy a joint in under 24h (p546). Inflammation may be less overt if immunocompromised (eg from the many immunosuppressive drugs used in rheumatological conditions) or if there is underlying joint disease. Joint aspiration (p543) is the key investigation, and if you are unable to do it, find someone who can.

Some important rheumatological investigations

Joint aspiration is the most important investigation in any monoarthritic presentation (see also *OHCS* p708). Send synovial fluid for urgent white cell count, Gram stain, polarized light microscopy (for crystals, p550) and culture. The risk of inducing septic arthritis, using sterile precautions, is <1:10,000.[2] Look for blood[1], pus, and crystals (gout or CPPD crystal arthropathy; p550). ►Do not attempt joint aspiration through inflamed and potentially infected skin (eg through a psoriatic plaque).

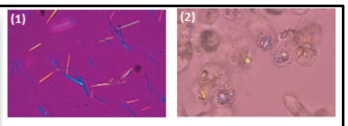
Synovial fluid in health and disease

	Appearance	*Viscosity*	*WBC/mm³*	*Neutrophils*
Normal	Clear, colourless	↔	≤200	None
Osteoarthritis	Clear, straw	↑	≤1000	≤50%
Haemorrhagic[1]	Bloody, xanthochromic	Varies	≤10,000	≤50%
Acutely inflamed:				
• *RA*	Turbid, yellow	↓	1–50,000	Varies
• *Crystal*	Turbid, yellow	↓	5–50,000	~80%
Septic	Turbid, yellow	↓	10–100,000	>90%

Blood tests FBC, ESR, urate, U&E, CRP. Blood culture for septic arthritis. Consider rheumatoid factor, anti-CCP, ANA, other autoantibodies (p555), and HLA B27 (p552) —as guided by presentation. Consider causes of reactive arthritis (p552), eg viral serology, urine chlamydia PCR, hepatitis and HIV serology if risk factors are present.

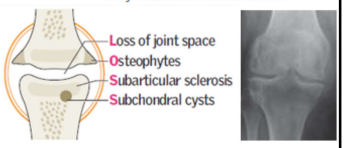
Radiology Look for erosions, calcification, widening or loss of joint space, changes in underlying bone of affected joints (eg periarticular osteopenia, sclerotic areas, osteophytes). Characteristic X-ray features for various arthritides are shown in figs 1–3. Irregularity of the lower half of the sacroiliac joints is seen in spondyloarthritis. Ultrasound and MRI are more sensitive in identifying effusions, synovitis, enthesitis and infection than plain radiographs—discuss further investigations with a radiologist. Do a CXR for RA, vasculitis, TB and sarcoid.

1 Eg trauma, tumour or haemophilia.

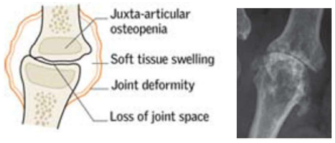


(1) **Needle-shaped monosodium urate crystals** found in gout, displaying negative birefringence under polarized light. (2)**Rhomboid-shaped calcium pyrophosphate dihydrate crystals** in **P**seudogout, showing **P**ositive birefringence in polarized light.

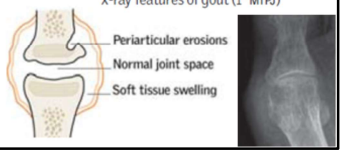
x-ray features of osteoarthritis.



x-ray features of rheumatoid arthritis (MCPJ)

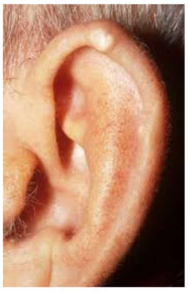


x-ray features of gout (1st MTPJ)



Crystal arthropathies: gout[32]

Gout typically presents with an acute monoarthropathy with severe joint inflammation (fig 1). >50% occur at the metatarsophalangeal joint of the big toe (podagra). Other common joints are the ankle, foot, small joints of the hand, wrist, elbow or knee. It can be polyarticular. It is caused by deposition of monosodium urate crystals in and near joints, precipitated, for example, by trauma, surgery, starvation, infection or diuretics. It is associated with raised plasma urate. In the long term, urate deposits (= tophi, eg in pinna, tendons, joints; see fig 2) and renal disease (stones, interstitial nephritis) may occur. *Prevalence:* ~1%. ♂:♀ ≈ 4:1.



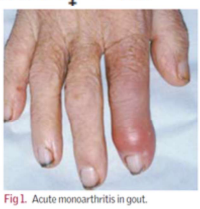


Fig 1. Acute monoarthritis in gout.

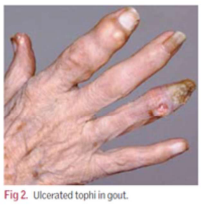
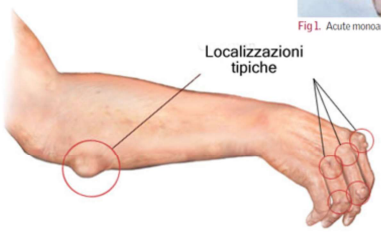


Fig 2. Ulcerated tophi in gout.



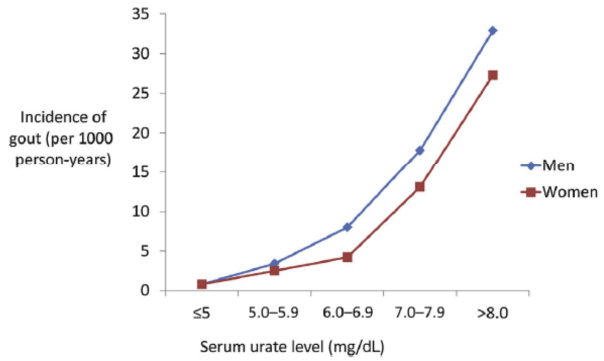
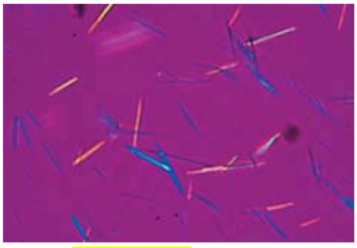


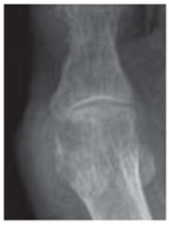
Fig. 1. Increasing incidence of gout in men and women with serum urate level. (*Data from* Bhole V, de Vera M, Rahman MM, et al. Epidemiology of gout in women: fifty-two-year followup of a prospective cohort. Arthritis Rheum 2010;62:1069–76.)

Differential diagnoses Exclude septic arthritis in any acute monoarthropathy (p546). Then consider haemarthrosis, CPPD (below) and palindromic RA (p548).

Causes Hereditary, ↑dietary purines, alcohol excess, diuretics, leukaemia, cytotoxics (tumour lysis). *Associations:* Cardiovascular disease, hypertension, diabetes mellitus and chronic renal failure (see p694).[32] Gout is a marker for these, therefore seek out and treat if needed.

Investigations Polarized light microscopy of synovial fluid shows *negatively birefringent* urate crystals (fig 3). Serum urate is usually raised but may be normal.[33] Radiographs show only soft-tissue swelling in the early stages. Later, well-defined 'punched out' erosions are seen in juxta-articular bone (see fig 3 on p543). There is no sclerotic reaction, and joint spaces are preserved until late.





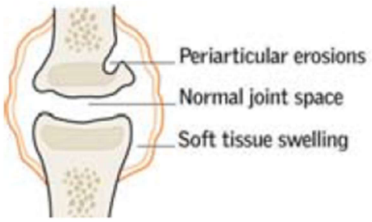


Fig 3. Needle-shaped monosodium urate crystals found in gout, displaying negative birefringence under polarized light.

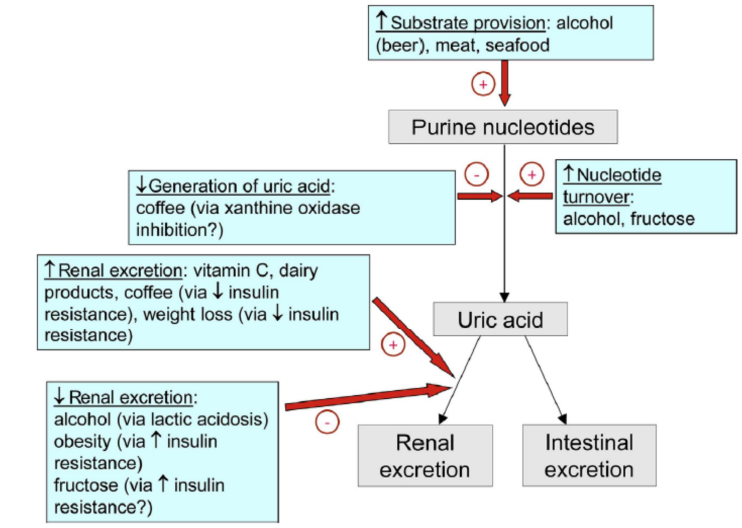


Fig. 2. Proposed mechanism of action of lifestyle factors in the etiology of hyperuricemia and gout. ↑, Increased; ↓, decreased.

The relationship between obesity, insulin resistance and gout

- Adiposity leads to insulin resistance which leads to hyperinsulinemia, leading to inhibition of excretion urate by the kidney leading to hyperuricemia, hence gout.

Influence of food on urate concentrations

↑Alcohol, ↑ Sugar-sweetened beverages (fructose)
↑ Red meat, ↑ Seafood ↑ Tomato
alcohol and fructose rapidly increases serum urate by generation of urate through hepatic metabolism.
↓Coffee, ↓ Dairy

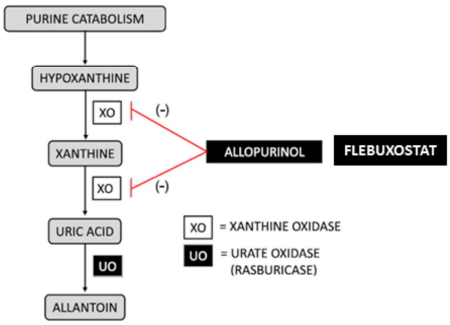
2012 American College of Rheumatology Guidelines for Management of Gout

Treatment of acute gout[34] Use high-dose NSAID or coxib (eg *etoricoxib* 120mg/24h PO).[35] Symptoms should subside in 3-5d. If CI (eg peptic ulcer; heart failure; anticoagulation), *colchicine* (0.5mg/6-12h PO) is effective but slower to work (note new *BNF* guidelines of max 6mg per course). **NB:** in renal impairment, NSAIDs and colchicine are problematic. Steroids (oral, IM or intra-articular) may also be used.[36] Rest and elevate the affected joint. Ice packs and 'bed cages' can be effective.

Prevention Lose weight. Avoid prolonged fasts, alcohol excess, purine-rich meats and low-dose aspirin (↑serum urate). *Prophylaxis:* Start if >1 attack in 12 months, tophi or renal stones. The aim is to ↓ attacks and prevent damage caused by crystal deposition. Use *allopurinol* and titrate from 100mg/24h, increasing every 2 weeks until plasma urate <0.3mmol/L (max 300mg/8h). SE: rash, fever, WCC↓. Introduction of allopurinol may trigger an attack so wait until 3 weeks after an acute episode, and cover with regular NSAID (for up to 6 weeks) or colchicine (0.5mg/12h PO for up to 6 months). Avoid stopping allopurinol in acute attacks once established on treatment. *Febuxostat* (80mg/24h) is an alternative if allopurinol is CI or not tolerated. It ↓ uric acid by inhibiting xanthine oxidase (SE: ↑ LFTs) and is more effective at reducing serum urate than allopurinol (although the number of acute attacks is the same).[37] Uricosuric drugs ↑ urate excretion. They are rarely used in patients who under-excrete uric acid or who are resistant to other treatment (eg sulfinpyrazine).

<5 mg/dl

✓**Asymptomatic hyperuricemia** is not routinely treated because of expense and the potential drug toxicity. However, patients should be monitored closely for the development of complications if the serum uric acid level is at least 12 mg/dL in men or 10 mg/dL in women. In these patients, antihyperuricemic therapy should be considered.



Urate-lowering drugs

An increasing number of urate-lowering drugs are available. There are three main classes (table 3): drugs that inhibit urate production (xanthine oxidase inhibitors), such as allopurinol and febuxostat; drugs that normalise renal urate excretion (uricosurics), including probenecid, benzbromarone, and the newer URAT1 inhibitor lesinurad; and drugs that catalyse the conversion of urate to the more water soluble and readily excretable allantoin (recombinant uricases), such as pegloticase and rasburicase.

A xanthine oxidase inhibitor, usually allopurinol, is given as first-line therapy.[3] Allopurinol is rapidly metabolised to its active metabolite, oxypurinol, which is cleared by the kidney. Although head-to-head studies have shown that febuxostat is more effective than allopurinol, these studies have all been of fixed-dose allopurinol (maximum dose 300 mg daily), and higher doses have not been compared with febuxostat in clinical trials.[119,120] This restriction in allopurinol doses is a result of concerns about allopurinol hypersensitivity syndrome with higher doses, particularly in patients with kidney impairment. However, several factors contribute to the syndrome, including higher starting doses,[121] the presence of HLA-B*5801,[122] kidney impairment,[123] and concomitant use of diuretics.[124] The risk factors, mechanisms, and ways to minimise the risk of allopurinol hypersensitivity syndrome have been more extensively reviewed elsewhere.[125] The syndrome typically occurs within the first 8 weeks of therapy.[123] The starting dose of allopurinol could be important and the maximum starting dose of allopurinol is recommended to be no higher than 100 mg daily (reduced to 50 mg daily in those with moderate-to-severe chronic kidney disease).[3] There is increasing evidence that, in patients who tolerate allopurinol, the dose can be safely increased to more than 300 mg per day with a treat to target serum urate approach, even in patients with kidney impairment.[126] Although larger studies about the safety of this approach are underway, the American College of Rheumatoloy recommendations support the start low, go slow treat to target approach with allopurinol, with appropriate monitoring.[3]

Febuxostat is predominantly metabolised in the liver and therefore dose reduction is not necessary in patients with mild-to-moderate kidney impairment. In patients with severe kidney impairment (ie, estimated glomerular filtration rate <30 mL/min per 1·73 m^2), data are more limited. A study[127] of 70 patients with stage 3b–5 chronic kidney disease without gout showed that 10 mg febuxostat daily increasing to 60 mg daily over 12 weeks was safe and effective in achieving target serum urate in 70% of patients. Febuxostat is less cost-effective as first-line therapy compared with allopurinol.[128]

The uricosurics are second-line urate-lowering therapy for patients who do not reach target serum urate concentrations with a xanthine oxidase inhibitor.[3]

Pegloticase, which is given as an intravenous infusion every 2 weeks, is typically reserved for patients with severe, refractory gout in whom target serum urate concentrations are not achieved or who cannot tolerate oral urate-lowering therapy.

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	Allopurinol	Febuxostat
Mechanism of action	Xanthine oxidase inhibitor: prevents urate production	Xanthine oxidase inhibitor: prevents urate production
Metabolism and excretion	Metabolised by aldehyde oxidase to oxypurinol, which is excreted predominantly by the kidneys	Hepatic: conjugation by uridine diphosphate-glucuronosyltransferase enzyme and oxidation to active metabolites by CYP1A2, CYP2C8 and CYP2C9; excreted via the kidneys
Contraindications	Hypersensitivity to allopurinol	Use with caution in heart failure and ischaemic heart disease
Clinically important drug interactions	Azathioprine increases 6-mercaptopurine concentrations, resulting in myelosuppression; warfarin (increased anticoagulant effects); diuretics (possible increased risk of allopurinol hypersensitivity syndrome)	Azathioprine increases 6-mercaptopurine concentrations, resulting in myelosuppression
Dosing	50–900 mg daily (maximum of 800 mg approved by US FDA), which should be titrated to achieve target serum urate*	40–120 mg daily (maximum of 80 mg approved by US FDA), which should be titrated to achieve target serum urate
Important side-effects	Gout flares when initiating treatment, rash, allopurinol hypersensitivity syndrome	Gout flares when initiating treatment, abnormal liver function tests
Monitoring	Serum urate, renal and liver function	Serum urate, renal and liver function
Special considerations	Dose escalation above renal based doses and above 300 mg daily to achieve target serum urate can be done with appropriate monitoring of renal and liver function and education about rash	Hypersensitivity might occur rarely in patients with prior allopurinol hypersensitivity
Anti-inflammatory prophylaxis when commencing drug	Yes	Yes

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Treatment of acute flares

Although colchicine has been used for many years, it has been studied in only two randomised controlled trials for acute gout flares.[135,136] Low dose colchicine commenced within 12 h of a flare (1·2 mg immediately followed by 0·6 mg after 1 h) is as effective as high dose (1·2 mg immediately followed by 0·6 mg hourly for 6 h) and is associated with substantially fewer adverse effects, particularly gastrointestinal adverse effects.[136] Thus, low dose colchicine is the preferred option. The dose of colchicine should be further reduced in patients with kidney impairment and those receiving cytochrome P450 3A4 inhibitors (eg, diltiazem, verapamil, clarithromycin) or p-glycoprotein inhibitors (eg, ciclosporin).[137] Colchicine should also be used with caution in those with liver disease or taking statins.

NSAIDs are usually effective in acute flares, although might be contraindicated in patients with kidney impairment, cardiovascular disease, or a history of gastrointestinal disease. The selective cyclo-oxygenase 2 (COX2) inhibitors are as effective as traditional NSAIDs but are associated with fewer adverse effects, particularly gastrointestinal adverse effects.[138] In general, NSAIDs and selective COX2 inhibitors should be used at full dose for the shortest period.

For patients with several comorbidities, corticosteroids can be the most appropriate therapeutic option. When only one or two joints are involved, intra-articular corticosteroids can be effective. Oral prednisolone (35 mg daily) is as effective as 500 mg naproxen twice a day, with no noteworthy differences in adverse effects during 5 days of treatment.[139]

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	Recommendation
Indications for urate-lowering therapy	Established diagnosis of gout and either tophi (detected by physical examination or imaging), frequent acute gout flares (>1 per year), stage 2 chronic kidney disease or worse, or past urolithiasis
Target serum urate	<360 µmol/L (6 mg/dL) minimum; for severe or tophaceous disease, concentrations <300 µmol/L (5 mg/dL) might be necessary
Serum urate monitoring	Monthly until target serum urate achieved; 6 monthly thereafter to ensure maintenance of target
Drug treatment of acute flares	Non-steroidal anti-inflammatory drug, colchicine, or corticosteroid
Anti-inflammatory prophylaxis during initiation of urate-lowering therapy	Low dose colchicine or non-steroidal anti-inflammatory drug (third line: low dose corticosteroids) for at least 6 months, or until 3 months after achieving target serum urate if no tophi are present, or until 6 months after achieving target if tophi are present—whichever is greatest
Urate-lowering treatment options	Xanthine oxidase inhibitor (eg, allopurinol, febuxostat) are first line; uricosurics (eg, probenecid) are second line; uricases (eg, pegloticase) are third line if oral urate-lowering therapy is unsuccessful
Education	Patients should be educated about the rationale for long-term urate-lowering therapy and risk of flares during initiation of urate-lowering therapy, and be provided with an action plan for flare management and healthy lifestyle advice
Comorbidity screening	Type 2 diabetes, cardiovascular disease, hypertension, dyslipidaemia, chronic kidney disease, obesity, and obstructive sleep apnoea should be screened for

Based on the 2012 American College of Rheumatology gout management guidelines.[3,101]

Table 2: **Principles of gout management**

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GOTTA

ATTACCO ACUTO

FANS

- **Indometacina** *Indoxen* cps 25-50 mg *Liometacen* fl polv+solv 50mg/2 ml
  50 mg/8h per 2 giorni quindi 25 mg/8h per 3 giorni
- **Naproxene** *Naprosyn* cpr 500 mg; bust 500 mg
  500 mg 2-3 volte/die
- **Diclofenac** *Voltaren*, *Dicloreum* cpr 50-100-150; fl 75mg/3ml
  50 mg 3 volte/die

Inibitori Selettivi delle COX-2

- **Etoricoxib** *Arcoxia, Algix* cpr 30-60-90-120 mg

Colchicina cpr 0.5-1 mg

Cortisonici

- **Prednisone** *Deltacortene* cpr 25 mg

TERAPIA CRONICA

Allopurinolo *Zyloric* cpr 100-300 mg, bust 300 mg

Febuxostat *Adenuric* cpr 80-120 mg

Gout classically progresses through four stages:

Stage 1 is **asymptomatic hyperuricemia**. Patients have elevated uric acid levels without arthritis or kidney stones. The majority of patients with hyperuricemia never develop any symptoms, but the higher the uric acid level and the longer the duration of hyperuricemia, the greater the likelihood of the patient developing gouty arthritis.

Stage 2 is **acute gouty arthritis**, which most often involves the acute onset of severe **monoarticular pain**, often occurring at night, in the first MTP joint, ankle, or knee, with rapid development of joint swelling and erythema and sometimes associated with systemic symptoms such as fever and chills. This usually follows decades of asymptomatic hyperuricemia. Attacks may last hours or up to 2 weeks.

Stage 3 is **intercritical gout**, or the period between acute attacks. Patients are generally completely asymptomatic. However, 60% to 70% of patients will have another acute attack within 1 to 2 years. The presence of these completely asymptomatic periods between monoarthritic attacks is so uncommon, except in crystalline arthritis, that it is often used as a diagnostic criterion for gout.

Stage 4 is **chronic tophaceous gout**, which usually occurs after 10 or more years of acute intermittent gout. In this stage, the intercritical periods are no longer asymptomatic; the involved joints now have chronic swelling and discomfort, which worsens over time. Patients also develop subcutaneous tophaceous deposits of monosodium urate.

Gout (Lancet 2016)

- Gout is a chronic disease of deposition of monosodium urate crystals, which form in the presence of increased urate concentrations.
- Although environmental factors contribute to hyperuricaemia, renal and gut excretion of urate is central to regulation of serum urate, and genetic factors are important.
- Activation of the NLRP3 inflammasome and release of interleukin 1β have key roles in initiation of acute gout flares.
- A "treat to target serum urate" approach is essential for eff ective gout management; long-term lowering of serum urate to less than 360 µmol/L leads to crystal dissolution and ultimately to suppression of flares.
- An allopurinol dose-escalation strategy is frequently eff ective for achieving treatment targets, and several new urate-lowering drugs are also available. Worldwide, rates of initiationand continuation of urate-lowering therapy are very low, and, consequently, achievement of serum urate targets is infrequent. Strategies to improve quality of gout care are needed.

Tumour lysis syndrome Rapid cell death on starting chemotherapy for rapidly proliferating leukaemia, lymphoma, myeloma, and some germ cell tumours can result in a rise in serum urate, K^+, and phosphate, precipitating renal failure. Prevention is key, with good hydration and *allopurinol* started 24h before chemotherapy (300mg/12h PO if good renal function; if creatinine >100µmol/L give 100mg on alternate days).[25] Haemodialysis may be needed in renal failure. A more potent uricolytic agent is *rasburicase* (recombinant urate oxidase) 200µg/kg/d IVI for 5–7d.[26]

- *Tumour lysis syndrome:* Caused by a massive destruction of cells leading to K^+↑, urate↑ and renal injury. *Risk*↑ if: LDH↑, creatinine↑, urate↑, wcc >25×10^9/L.[65] *Prevention:* high fluid intake + allopurinol pre-cytotoxics. For those at high risk of cell lysis, recombinant uricase (rasburicase) may be given. Seek advice.

Laboratory Definition of Tumor Lysis Syndrome Using the Cairo-Bishop Classification

LABORATORY TUMOR LYSIS SYNDROME
Uric acid $\geq$ 8 mg/dL ($\geq$ 476 μmol/L) or 25% increase from baseline
Potassium $\geq$ 6 mEq/L ($\geq$ 6 mmol/L) or 25% increase from baseline
Phosphorus $\geq$ 6.5 mg/dL ($\geq$ 2.1 mmol/L) or 25% increase from baseline
Calcium $\leq$ 7 mg/dL ($\leq$ 1.75 mmol/L) or 25% decrease from baseline
CLINICAL TUMOR LYSIS SYNDROME
Creatinine $\geq$ 1.5 times the upper limit of normal
Cardiac arrhythmia or sudden death
Seizure

NOTE. Two or more laboratory changes must be observed within 3 days before or 7 days after cytotoxic therapy.

Adapted from Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. *Br J Haematol*. 2004;127:3–11, with permission from Blackwell Publishing Group.

Table 1
Cairo-Bishop definition of LTLS and CTLS

LTLS[a]	
Potassium	≥6 mEq/L or 25% increase from baseline
Uric acid	≥8 mg/dL or 25% increase from baseline
Phosphorous	≥6.5 mg/dL (children), ≥4.5 mg/dL (adults), or 25% increase from baseline
Calcium	≤7 mg/dL or 25% decrease from baseline
CTLS[b]	
Renal involvement	Creatinine ≥1.5 × ULN
Cardiac involvement	Arrhythmia/sudden death
Neurologic involvement	Seizure

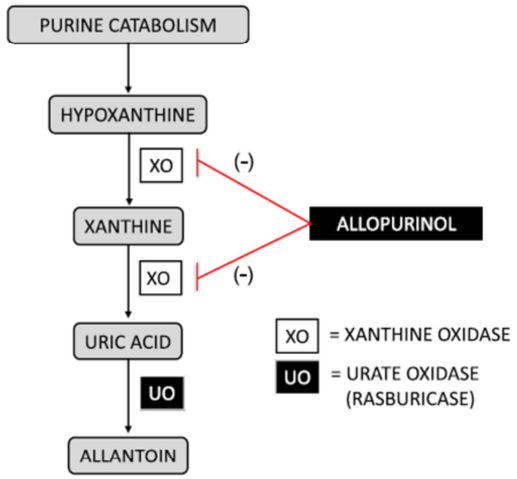

Fig. 1. Purine catabolism pathway. Purines are metabolized into hypoxanthine, which is then further broken down into xanthine and uric acid via the enzyme xanthine oxidase (XO). Allopurinol blocks the action of XO by competitive inhibition leading to decreased production of uric acid. Urate oxidase (rasburicase) oxidizes uric acid into allantoin, which is 5 to 10 times more soluble in water than uric acid. Urate oxidase is not present in humans.

TABLE 3. Treatment of Metabolic Derangements in TLS

PROBLEM	INTERVENTION	DOSAGES	COMMENTS
Renal insufficiency and hypovolemia	Intravenous fluids	Normal saline, 3 L/m^2 daily	Use with caution if decreased systolic function
	Dialysis		For fluid-unresponsive oliguric renal failure or patients with CHF
Hyperuricemia	Allopurinol	100 mg/m^2 per dose orally every 8 h (maximum daily dose: 800 mg)	Drug-drug interactions with 6-MP and azathioprine; only effective for prophylaxis
	Rasburicase	0.15-0.2 mg/kg/d iv	Contraindicated in pregnancy and G6PD deficiency; costly
Hyperphosphatemia	Minimize phosphate intake	Minimal consumption of dairy and bread products	
	Phosphate binders (aluminum hydroxide or aluminum carbonate)	30 mL orally every 6 h	
	Dialysis		If no response to oral therapy
Hyperkalemia	Insulin (regular)	10 U iv	
	Dextrose	50 mL of 50% dextrose iv push, then infuse 50-75 mL of 10% dextrose over 1 h	
	Albuterol	20 mg nebulized	
	Dialysis		If no response to other therapy
	Calcium gluconate	1000 mg iv	If hyperkalemic EKG changes are noted
Hypocalcemia	Calcium gluconate	1000 mg iv (no faster than 200 mg/min)	Use with caution in severe hyperphosphatemia

6-MP indicates 6-mercaptopurine; CHF, congestive heart failure; EKG, electrocardiogram; G6PD, glucose-6-phosphate dehydrogenase; iv, intravenously; TLS, tumor lysis syndrome.

Crystal arthropathies: Calcium pyrophosphate deposition (CPPD)

CPPD is an umbrella term used to describe different patterns of disease including:[38]

- *Acute CPP crystal arthritis* (previously pseudogout) like gout it causes an acute monoarthropathy typically of larger joints in elderly patients. It is usually spontaneous and self-limiting, but can be provoked by illness, surgery or trauma.
- *Chronic CPPD* inflammatory RA-like (symmetrical) polyarthritis and synovitis.
- *Osteoarthritis with CPPD* chronic polyarticular osteoarthritis with superimposed acute CPP attacks.

Risk factors Old age, hyperparathyroidism (see p214), haemochromatosis (see p262), hypophosphataemia (see p693).

Tests Polarized light microscopy of synovial fluid shows weakly positively birefringent crystals (fig 4). It is associated with soft tissue calcium deposition on x-ray.

Management Acute attacks: cool packs, rest, aspiration and intra-articular steroids. NSAIDs (+PPI) ± *colchicine* 0.5–1.0mg/24h (used with caution) may prevent acute attacks. Methotrexate and hydroxychloroquine have a role in chronic CPPD.[39]

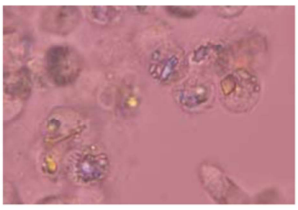

Fig 4. Rhomboid-shaped calcium pyrophosphate dihydrate crystals in Pseudogout, showing Positive birefringence in polarized light.

Severe knee pain and swelling with fever in a patient with rheumatoid arthritis

A 37-year-old woman developed a symmetrical polyarthritis. A test for rheumatoid factor was positive and erosive changes were seen on X-ray confirming a **clinical diagnosis of RA**. The arthritis followed an **aggressive course** with **poor response to a variety of disease-modifying antirheumatic drugs** and she became increasingly disabled due to severe destructive changes in the knees, wrists and shoulders. A moderate dose of **prednisolone** was introduced at the age of 42, with some symptomatic improvement in her joints and she was referred to an orthopaedic surgeon with a view to knee replacements. However, 1 month before her orthopaedic appointment she presented to the **emergency department** with a **painful swollen right knee**. On examination **she was unwell, febrile (38°C) and had a hot, red right knee with a sizable effusion**. 80ml of **purulent synovial fluid was aspirated** from the joint and microscopy of the fluid revealed numerous Gram-positive cocci. A diagnosis of ***septic arthritis*** was made on a background of severe RA and steroid therapy. She was treated with **high-dose antibiotics** and **the joint was washed out via an arthroscope**. **Culture** of blood and synovial fluid grew Staphylococcus aureus. She received 6 weeks antibiotic treatment in total together with vigorous physiotherapy. Her knee, however, was significantly worsened by the infection and she could no longer straighten the leg or walk more than a few yards. **Joint replacement was deferred for 6 months to reduce the risk of infection in the prosthesis.**

CFIM n° 21

Patterns of presentation of arthritis

Monoarthritis	Oligoarthritis (≤5 joints)	Polyarthritis (>5 joints involved)	
Septic arthritis	Crystal arthritis	*Symmetrical:*	*Asymmetrical:*
Crystal arthritis (gout, CPPD)	Psoriatic arthritis	Rheumatoid arthritis	Reactive arthritis
Osteoarthritis	Reactive arthritis, eg *Yersinia, Salmonella, Campylobacter*	Osteoarthritis	Psoriatic arthritis
Trauma, eg haemarthrosis	Ankylosing spondylitis Osteoarthritis	Viruses (eg hepatitis A, B & C; mumps)	
		Systemic conditions[1] (can be either)	

1 Connective tissue disease (eg SLE and relapsing polychondritis), sarcoidosis, malignancy (eg leukaemia), endocarditis, haemochromatosis, sickle-cell anaemia, familial Mediterranean fever, Behçet's.

▸▸ Exclude septic arthritis in any acutely inflamed joint, as it can destroy a joint in under 24h (p546). Inflammation may be less overt if immunocompromised (eg from the many immunosuppressive drugs used in rheumatological conditions) or if there is underlying joint disease. Joint aspiration (p543) is the key investigation, and if you are unable to do it, find someone who can.

Septic arthritis

▸▸Consider septic arthritis in any acutely inflamed joint, as it can destroy a joint in under 24h. Inflammation may be less overt if immunocompromised (eg from medication) or if there is underlying joint disease. The knee is affected in >50% cases.

Risk factors Pre-existing joint disease (especially rheumatoid arthritis); diabetes mellitus, immunosuppression, chronic renal failure, recent joint surgery, prosthetic joints (where infection is particularly difficult to treat), IV drug abuse, age >80yrs.[8]

Investigations Urgent joint aspiration for synovial fluid microscopy and culture is the key investigation (p543), as plain radiographs and CRP may be normal. The main differential diagnoses are the crystal arthropathies (p550). Blood cultures may be helpful for guiding antibiotic choice later.

Ask yourself "How did the organism get there?" Is there immunosuppression, or another focus of infection, eg from indwelling IV lines, infected skin, or pneumonia (present in up to 50% of those with pneumococcal arthritis)?[9]

Treatment If in doubt start empirical IV antibiotics (after aspiration) until sensitivities are known. Common causative organisms are *Staph. aureus*, streptococci, *Neisseria gonococcus* and Gram -ve bacilli. Follow local guidelines for antibiotic choice. Consider flucloxacillin 1g/6h IV (*clindamycin* if penicillin allergic); *vancomycin* 1g/12h IV if MRSA (or history of MRSA); or *cefotaxime* 1g/8h IV if gonococcal or Gram -ve organisms suspected.[10] If HIV +ve, look for atypical mycobacteria and fungi. Antibiotics are required for a prolonged period but there is no consensus on which route or for how long they should be continued (eg ~2 weeks IV, then 2-4 weeks PO)—ask a microbiologist.[11] Ask for orthopaedic advice for consideration of arthrocentesis, lavage and debridement, especially if there is a prosthetic joint involved.[12] This may be done arthroscopically (eg for knee) or open under GA (eg for hip; this allows for biopsy—helpful in TB). Splint for ≤48h, give adequate analgesia and consider physiotherapy.

Disseminated gonococcal infection

- Disseminated gonococcal infection (DGI) results from bacteremic spread of the sexually transmitted pathogen, **Neisseria gonorrhoeae.**
- Patients with DGI usually present with one of two syndromes: **purulent arthritis** alone or a triad of **tenosynovitis, dermatitis, and polyarthralgias** without frank arthritis. Patients with the syndrome of polyarthralgias often have systemic symptoms such as fever, chills, and malaise. Those with purulent arthritis alone usually have involvement of the knees, wrists, or ankles without any systemic symptoms. When present, polyarthritis is typically asymmetric.
- The possibility of DGI should be considered in individuals (particularly those **younger than 40 years or sexually active with multiple partners**) who present with **acute polyarthralgias, polyarthritis**, or joint pain concerning for septic arthritis.
- The diagnosis is made by **identification of N. gonorrhoeae** (either through molecular testing or culture) in a nonmucosal site (blood, synovial fluid, skin).

Differential diagnosis of some systemic causes of arthritis

	Gonococcal arthritis	Reactive arthritis (formerly Reiter's syndrome)	Rheumatoid arthritis	Psoriatic arthritis
Age	Young	Young	Middle	Middle
Gender	Female>male	Male>female	Female>male	No effect
Onset	Abrupt	Abrupt	Insidious	Insidious
Joint number	Monoarthritis or oligoarthritis	Oligoarthritis	Polyarthritis	Oligoarthritis
Symmetry of arthritis	No	No	Yes	No
Sausage digits	No	Yes	No	Yes
Back pain	No	Yes	No	Yes
Urethritis	Yes	Yes	No	No
Skin lesions	Pustular, nodular, or vesicular	Palms and soles in 10 percent	Subcutaneous nodules	Psoriasis
Gonococcus identified on testing	Yes	No	No	No