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Overview of gout

Overview of gout

Gout is a chronic disease that involves the deposition of monosodium urate crystals in the body, in particular the joints, soft tissues and kidneys. The main symptoms of gout are joint pain and swelling, which may represent an initial or recurrent acute attack, chronic gouty arthritis, or an acute attack in a patient with underlying chronic gouty arthritis (see Clinical presentations of gout). The major manifestations of gout in the kidney are nephrolithiasis and chronic urate nephropathy; both of which can progress to chronic kidney disease.

Gout occurs when the serum uric acid concentration is sufficiently elevated (usually greater than 0.42 mmol/L [7 mg/dL]), and the solubility coefficient of monosodium urate exceeded, long enough for crystals to form in tissues. While the presence of hyperuricaemia is important in the diagnosis of gout, patients with acute gout may have a normal serum uric acid concentration (see Diagnosis of gout). Furthermore, the presence of hyperuricaemia does not necessarily indicate that gout is the explanation for a patient's symptoms. Patients can also have asymptomatic hyperuricaemia, which is a risk factor for developing gout (see Pathogenesis of and risk factors for gout).

The incidence of gout increases with age, and in women gout rarely occurs before menopause. Gout is rare in children; a diagnosis of gout in a child is not tenable unless the child has a genetic defect in urate metabolism.

The prevalence of gout is increasing worldwide, particularly in affluent countries such as Australia and New Zealand. In these countries, increasing prevalence relates to the ageing population, higher consumption of alcohol and fructose-sweetened drinks, other changes in dietary habits, and increasing rates of obesity. Certain ethnic groups have a higher prevalence of gout; in particular, the prevalence of gout is higher in indigenous populations, including in Australia and New Zealand.

Gout can be effectively treated and its complications prevented with adherence to lifelong urate-lowering therapy using a treat-to-target approach (see General management approach for gout); however, gout is often poorly managed in Australian primary care, with low rates of allopurinol prescribing, serum uric acid monitoring and achievement of serum uric acid targets. Patient adherence to urate-lowering therapy is also often suboptimal.

Pathogenesis of and risk factors for gout

Pathogenesis of and risk factors for gout

Serum uric acid concentration is the most important determinant of developing gout; the incidence of gout increases exponentially with serum uric acid concentrations greater than 0.54 mmol/L (9 mg/dL).

Uric acid is formed in the liver from dietary and endogenous purines. Consumption of purine-rich foods (particularly meat and seafood), alcohol (particularly beer and spirits) and fructose-sweetened drinks can increase serum uric acid concentration and the risk of gout in susceptible individuals. Disorders involving a high cell turnover (eg haematological malignancies, severe psoriasis) can also increase serum uric acid concentration and the risk of gout in susceptible individuals.

Uric acid is eliminated by the kidneys (two-thirds) and the gut (one-third). Drugs that inhibit the renal excretion of uric acid can increase serum uric acid concentration and the risk of gout in susceptible individuals. These drugs include thiazide diuretics (often taken as a combination product with an angiotensin

converting enzyme inhibitor or angiotensin II receptor blocker), loop diuretics and ciclosporin. Diuretics are the most important cause of secondary gout in middle-aged and older people.

Comorbidities including hypertension, chronic kidney disease, dyslipidaemia, type 2 diabetes and obesity are risk factors for gout. A high concentration of endogenous insulin, as seen in patients with obesity, also inhibits the renal excretion of uric acid.

Patients who are in a catabolic state (eg septic) or are dehydrated are at an increased risk of developing an acute attack of gout. This often occurs during or immediately following a period of hospitalisation.

Essentially any drug, condition or dietary change that causes a rapid rise or decrease in serum uric acid concentration can precipitate or prolong an acute attack of gout. This includes starting or increasing urate-lowering therapy for the long-term management of gout, or implementing other dietary changes for the management of gout (eg stopping excessive alcohol consumption).

Clinical presentations of gout

Clinical presentations of gout

Acute gout

Acute gout

The first acute attack of gout is usually monoarticular, and often occurs in the big toe (the first metatarsophalangeal joint) or other part of the foot. The joint is usually very painful, red and swollen. The first attack can be severe and may mimic septic arthritis; patients may present with fever, malaise, leucocytosis, and elevated inflammatory markers. If the acute attack is not treated, symptoms usually subside over a few days to 1 to 2 weeks.

In women, the first attack may be polyarticular, typically in the hands and with gouty tophi. The presentation may be an acute inflammation in joints already affected by arthritis (eg the distal or proximal interphalangeal joints).

Most patients who are not started on urate-lowering therapy will have a second acute attack of gout within 2 years. Ischaemic heart disease, hypertension and chronic kidney disease are independent risk factors for recurrent attacks. Recurrent attacks may be misdiagnosed as a sprain or other soft-tissue injury. Initially, recurrent attacks may be separated by long intervals of relatively normal joint function. Eventually, recurrent attacks occur more frequently, are of longer duration, and involve more joints.

Chronic gout

Chronic gout

If gout remains untreated with urate-lowering therapy, recurrent attacks may fail to resolve completely, slowly leading to a chronic crippling, destructive arthritis. Even in the absence of recognised recurrent attacks, urate crystals can deposit in the joints, soft tissues and kidneys, and can lead to joint damage and chronic kidney disease.

Chronic gout may be oligoarticular or polyarticular, and symmetrical involvement of the small joints of the hands can mimic rheumatoid arthritis and psoriatic arthritis. Serum uric acid concentration may also be elevated in psoriasis due to increased cell turnover, which further complicates the differential diagnosis of psoriatic arthritis.

Chronic gout may be the first diagnosed clinical presentation of gout in some patients because of unrecognised previous acute attacks. Patients with chronic gout can also experience acute attacks (ie acute-on-chronic gout).

Gouty tophi are frequently seen in patients with chronic gout, and are usually present in the elbows (olecranon bursae), knees (prepatellar bursae) and peripheral joints (eg the toes and fingers). Chronic tophaceous gout is destructive and, unless treated, may cause significant disability.

Diagnosis of gout

Diagnosis of gout

While a diagnosis of gout is suspected based on clinical assessment (see Clinical presentations of gout), a definitive diagnosis requires the identification of monosodium urate crystals under polarised microscopy in synovial (or bursal) fluid or tophi (see Joint aspiration in adults). Confirmation of the diagnosis is important because gout requires lifelong urate-lowering therapy. Microscopy and culture of the synovial (or bursal) fluid should also be undertaken to exclude infection. Once a definitive diagnosis of gout has been made, diagnostic aspiration is not required for recurrent attacks unless infection is suspected.

Aspiration of an affected joint, bursa or tophus is required to confirm the diagnosis of gout.

Serum uric concentration should be measured in all patients with suspected gout. However, the presence of hyperuricaemia alone is insufficient to diagnose gout and, in patients with acute gout, serum uric concentration may be normal. Other than the presence of tophi, individual clinical features (eg history of painful or swollen big toe, unilateral podagra) have a low diagnostic utility. Response to colchicine does not replace aspiration in the diagnosis of gout; it can support a diagnosis of crystal arthritis, but does not distinguish between gout and acute calcium pyrophosphate crystal arthritis.

Monosodium urate crystals are not seen on plain X-ray because they are not radiopaque; however, a plain X-ray may be useful to identify joint damage due to gout. In complex or difficult cases, specialists may use other imaging modalities in the diagnosis of gout, but these have not yet been fully validated.

In patients with suspected gout, renal function should be measured as impaired renal function is both a risk factor and a consequence of gout, and can affect treatment choice and dosing. A search for other secondary causes of gout should be undertaken as appropriate (see Pathogenesis of and risk factors for gout).

General management approach for gout

General management approach for gout

Management of gout involves:

- providing rapid symptom relief for acute attacks (see Management of acute gout)
- prescribing lifelong urate-lowering therapy, using a treat-to-target approach, to prevent further acute attacks and to prevent and treat the complications of gout, such as tophi, chronic kidney disease and chronic destructive arthritis
- prescribing prophylaxis to prevent gout flares when starting or increasing urate-lowering therapy (see Flare prophylaxis when starting or increasing urate-lowering therapy)
- addressing modifiable risk factors for gout and optimising the management of associated comorbidities (see Pathogenesis of and risk factors for gout), including closely monitoring and actively managing cardiovascular disease risk factors (see Cardiovascular disease risk stratification):
    - if drug therapy is contributing to gout (eg use of a thiazide or loop diuretic), switch to an alternative drug or reduce the dosage of the contributing drug if switching is not possible
    - losartan and fenofibrate have modest uricosuric effects and, if clinically appropriate, may be preferable for the treatment of hypertension and dyslipidaemia respectively in a patient with gout
    - low-dose aspirin can inhibit the excretion of uric acid and increase the risk of recurrent acute attacks of gout. However, given the substantial cardiovascular comorbidity associated with gout, low-dose aspirin should usually be continued with adjustment of urate-lowering therapy as necessary to achieve the target serum uric acid concentration
- providing patient education; components include:

- explanation of the nature of the condition, the likelihood of recurrent acute attacks and long-term damage to the joints and kidneys if urate-lowering therapy is not started, and the need for adherence to lifelong urate-lowering therapy
- advice on maintaining a healthy lifestyle (eg maintaining ideal body weight, exercising regularly, stopping smoking); and limiting the intake of alcohol (especially beer and spirits), fructose-sweetened drinks and purine-rich foods. However, while there is strong evidence that lifestyle factors increase the risk of gout, there is a lack of evidence that correcting these factors improves outcomes in patients with gout
- printed or online information that reinforces education messages; useful patient information leaflets on 'Gout' and 'Gout and diet' are available on the Arthritis Australia website [URL] [Note 1].

Note 1: Any management advice given in these patient information leaflets should be considered in the context of the recommendations in these guidelines.

Management of acute gout

Management of acute gout

In early disease, an acute attack of gout can subside spontaneously within a week, but patients usually seek medical advice. The aim of management is to provide rapid symptom relief. Nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids (local injection or systemic use) and low-dose colchicine are all effective in treating acute gout. Drug choice is influenced by patient factors (including comorbidities), potential drug interactions and adverse effects, and drug cost.

In terms of oral therapy, the NSAID indometacin has traditionally been used to treat acute attacks of gout because it is short-acting and the dose can be easily titrated according to symptomatic response; however, any NSAID may be used. For discussion on NSAID choice, see Choice of NSAID and approach to NSAID use in patients at increased risk of specific adverse effects. Evidence suggests that systemic corticosteroids (oral or intramuscular) are as effective as NSAIDs in the treatment of acute gout, but systemic corticosteroids have a lower incidence of acute adverse effects than NSAIDs. Colchicine is effective in reducing pain and inflammation in acute gout, but has a high frequency of adverse effects (mainly gastrointestinal) that limit its usefulness. Paracetamol may be useful as an analgesic adjunct, but is not recommended as monotherapy.

There are no randomised controlled trials investigating intra-articular or soft-tissue (eg bursal) corticosteroid injections for acute gout, but their use is supported by evidence of benefit in other types of inflammatory arthritis (eg rheumatoid arthritis) and the proven effectiveness of systemic corticosteroids in acute gout. Local corticosteroid injection is appropriate if the acute attack involves one or two joints (or bursae) and joint (or bursal) infection has been excluded. Aspiration of synovial (or bursal) fluid for microscopy and culture may be required to exclude infection (see Joint aspiration in adults). If a definitive diagnosis of gout has not yet been made, aspiration should be undertaken to confirm the diagnosis of gout and exclude infection before injecting the corticosteroid; however, unless there is a high clinical suspicion of infection (eg recent history of penetrating trauma), the corticosteroid can be injected before test results are available. Once a definitive diagnosis of gout has been made, aspiration to exclude infection is not required before local corticosteroid injection for recurrent attacks unless infection is suspected. For principles of use of local corticosteroid injections, see Principles of using local corticosteroid injections for musculoskeletal conditions in adults.

For rapid symptom relief in acute gout, use:

1 a local corticosteroid injection at up to a maximum of two affected sites (see Table 12.9 for example doses)

OR

1 an NSAID orally, until symptoms abate (typically 3 to 5 days) (see Table 12.7 for dosing; the upper end of the dosing range is often required) *gout, acute*

OR

1 prednis(ol)one 15 to 30 mg orally, daily until symptoms abate (typically 3 to 5 days) [Note 2] *gout, acute*

OR

2 colchicine 1 mg orally initially, then 500 micrograms 1 hour later, as a single one-day course (total dose is 1.5 mg). *gout, acute*

The low-dose regimen of colchicine recommended above is as effective as higher-dose regimens and is significantly safer. Other low-dose regimens of colchicine may also be effective but their benefit has not been proven (eg 500 micrograms orally, 8- to 12-hourly until symptoms abate [maximum of 6 mg over 4 days]; reduce dosage in renal impairment). Other low-dose regimens may be considered if the patient's symptoms have not abated after the single one-day course; however, the total dose of colchicine given in an acute attack should not exceed 6 mg over 4 days.

Once the acute attack has settled, implement the other aspects of gout management (see General management approach for gout), including patient education and lifelong urate-lowering therapy. If patients are already taking urate-lowering therapy, advise them not to stop or change therapy during an acute attack because sudden changes in serum uric acid concentration can prolong or worsen the attack.
Avoid changes to urate-lowering therapy during an acute attack of gout.

Note 2: A single dose of intramuscular corticosteroid may be used as an alternative to oral therapy (eg in patients who are vomiting or unable to swallow tablets).

Long-term management of gout with urate-lowering therapy

Long-term management of gout with urate-lowering therapy

General considerations

General considerations

Lifelong urate-lowering therapy is recommended for all patients with a confirmed diagnosis of gout, but is especially important for patients who present with tophaceous gout, renal manifestations of gout, or chronic gouty arthritis.

Following an initial acute attack of gout, patients may be reluctant to start lifelong urate-lowering therapy. Patient education is pivotal to encourage starting therapy; see General management approach for gout for components of patient education. If patients decide not to embark on urate-lowering therapy, arrange regular follow-up appointments (eg at 6-monthly intervals) to monitor disease progression. Advise patients to return for review earlier if they have another acute attack of gout.

Titrate urate-lowering therapy using a treat-to-target approach.

Urate-lowering therapy is titrated using a treat-to-target approach. The aim of therapy is to lower serum uric acid to a concentration that:

- dissolves existing monosodium urate crystals in the joints, soft tissues and kidneys; and prevents the formation of new crystals
- reduces the frequency and severity of acute attacks, eventually leading to the absence of acute attacks
- resolves tophi.

The target serum uric acid concentration is less than 0.36 mmol/L (6 mg/dL) for patients with non-tophaceous gout, and less than 0.30 mmol/L (5 mg/dL) for patients with tophaceous gout. The presence of tophi indicates a higher urate load and necessitates a lower target serum uric acid concentration. Failure to adjust the dose of urate-lowering therapy to achieve the target serum uric acid concentration is a common reason for treatment failure. Once the target serum uric acid concentration has been achieved, urate-lowering therapy should be continued to maintain the target concentration.

Starting or increasing urate-lowering therapy is associated with a high risk of gout flare. Patients may be reluctant to take urate-lowering therapy because of a previous acute attack precipitated by starting or increasing therapy. Starting on a low dose of urate-lowering therapy minimises the risk of flares; the dose is then gradually increased until the target serum uric acid concentration is achieved. Flare prophylaxis is recommended for all patients starting or increasing urate-lowering therapy (see Flare prophylaxis when starting or increasing urate-lowering therapy). Advise patients of the high risk of gout flare and the recommended management as for an acute attack (see Management of acute gout).

Nonadherence to urate-lowering therapy also increases the risk of flare and is another common reason for treatment failure. Nonadherence to treatment is a particular problem in patients with gout because of the presence of relatively normal joint function between acute attacks initially, the complexity of the initial management regimen, and a natural reluctance of patients to take lifelong medication. Patient education has an important role in encouraging treatment adherence.

There are no data on the optimal time to start urate-lowering therapy after an acute attack. Starting urate-lowering therapy has traditionally been delayed until the acute attack has resolved; however, starting urate-lowering therapy concurrently with treatment for the acute attack may be appropriate, provided that treatment for the acute attack is adequate and the patient is well informed about the risk of flare. This may be best done under specialist guidance.

Advise patients not to stop or change urate-lowering therapy during an acute attack because sudden changes in serum uric acid concentration can prolong or worsen the attack.

First-line urate-lowering therapy

First-line urate-lowering therapy

High-quality evidence indicates that allopurinol, a xanthine oxidase inhibitor, is effective in lowering serum uric acid concentration by reducing uric acid production in the body. There is strong consensus that **allopurinol should be used as first-line urate-lowering therapy:**

allopurinol 50 mg orally, daily for 4 weeks; then increase the daily dose by 50 mg every 2 to 4 weeks or by 100 mg every 4 weeks to achieve the target serum uric acid concentration, up to a maximum maintenance dose of 900 mg daily. *gout* _

Measure serum uric acid concentration monthly during the dose titration phase. The target serum uric acid concentration is less than 0.36 mmol/L (6 mg/dL) or, if tophi are present, less than 0.30 mmol/L (5 mg/dL). Patients with a higher baseline serum uric acid concentration are likely to need a higher allopurinol dose to achieve the target serum uric acid concentration. A substantial proportion of patients require allopurinol doses above 300 mg daily to achieve the target serum uric acid concentration; however, nonadherence should always be ruled out before increasing allopurinol to higher doses.

Renal impairment is not a contraindication to the use of allopurinol. The same (or lower) starting dose of allopurinol and the same (or slower) rate of up-titration to achieve the target serum uric acid concentration is recommended for patients with renal impairment, with close monitoring of renal function.

Allopurinol reduces the metabolism of azathioprine and mercaptopurine, increasing the risk of severe bone marrow toxicity. If possible, avoid the combination of allopurinol with either azathioprine or mercaptopurine. If these combinations cannot be avoided, reduce the dose of azathioprine or mercaptopurine to approximately one-quarter to one-third of the usual dose and monitor full blood count closely.

Adverse effects occur in less than 1% of patients treated with allopurinol. Skin rash is the most common adverse effect and may represent a maculopapular rash or allopurinol hypersensitivity syndrome. Allopurinol hypersensitivity syndrome is a rare, but potentially fatal, adverse effect comprising erythematous desquamating rash, fever, hepatitis, eosinophilia, and worsening renal function. The majority of cases of allopurinol hypersensitivity syndrome occur in the first 3 months of treatment. Risk factors for allopurinol hypersensitivity syndrome include use of a high starting dose and rapid up-titration, renal impairment, older age, and the presence of human leucocyte antigen (HLA)-B*5801 allele, which is more common in people of

Asian ethnicity, especially the Han Chinese. Allopurinol hypersensitivity syndrome is a contraindication to further exposure to allopurinol. Advise patients to stop allopurinol immediately and seek medical advice if a skin rash develops. Patients who develop a maculopapular rash alone may be treated with an allopurinol desensitisation program; refer patients to a specialist for desensitisation.

If the target serum uric acid concentration cannot be achieved with allopurinol monotherapy (eg the dose of allopurinol required to achieve the target concentration is not tolerated), probenecid (a weak uricosuric) may be added to allopurinol. Use:

probenecid 250 mg orally, twice daily for 1 week, then increase to 500 mg twice daily; then increase the daily dose by 500 mg every 4 weeks to achieve the target serum uric acid concentration, up to a maximum maintenance dose of 2 g daily in divided doses. *gout, first-line therapy*

The efficacy of probenecid declines with declining renal function, but some efficacy is retained down to a glomerular filtration rate of 30 mL/minute. Probenecid can increase the risk of urate nephrolithiasis and should be avoided in patients with known urate nephrolithiasis.

Once the patient is stable and the target serum uric acid concentration has been achieved, serum uric acid concentration can be checked annually to ensure the target concentration is maintained. Ongoing monitoring should also include renal function, liver biochemistry, and full blood count (in patients taking probenecid), as well as the frequency of gout attacks and, if applicable, tophi size.

Second-line urate-lowering therapies

Second-line urate-lowering therapies

Allopurinol is the treatment of choice to lower serum uric acid concentration in patients with gout (see First-line urate-lowering therapy); however, if allopurinol is contraindicated or not tolerated at any dose, the following second-line urate-lowering therapies are recommended: febuxostat (a xanthine oxidase inhibitor) or probenecid.

Instead of allopurinol, use:

1 febuxostat 40 mg orally, daily for 2 to 4 weeks; then increase the daily dose by 40 mg every 2 to 4 weeks to achieve the target serum uric acid concentration, up to a maximum maintenance dose of 120 mg daily [Note 3] *gout*

OR

2 probenecid 250 mg orally, twice daily for 1 week, then increase to 500 mg twice daily; then increase the daily dose by 500 mg every 4 weeks to achieve the target serum uric acid concentration, up to a maximum maintenance dose of 2 g daily in divided doses. *gout, second-line therapy*

Measure serum uric acid concentration monthly during the dose titration phase. The target serum uric acid concentration is less than 0.36 mmol/L (6 mg/dL) or, if tophi are present, less than 0.30 mmol/L (5 mg/dL).

Once the patient is stable and the target serum uric acid concentration has been achieved, serum uric acid concentration can be checked annually to ensure the target concentration is maintained. Ongoing monitoring should also include renal function, liver biochemistry (in patients taking febuxostat), and full blood count (in patients taking probenecid), as well as the frequency of gout attacks and, if applicable, tophi size.

Febuxostat is not recommended for patients with pre-existing major cardiovascular disease [Note 4]. Febuxostat should be used with caution in patients with hepatic impairment or moderate to severe renal impairment; seek specialist advice. Febuxostat is thought to behave similarly to allopurinol in reducing the metabolism of azathioprine and mercaptopurine, and increasing the risk of severe bone marrow toxicity. If possible, avoid the combination of febuxostat with either azathioprine or mercaptopurine. If these combinations cannot be avoided, reduce the dose of azathioprine or mercaptopurine and monitor full blood count closely.

The efficacy of probenecid declines with declining renal function, but some efficacy is retained down to a glomerular filtration rate of 30 mL/minute. Probenecid can increase the risk of urate nephrolithiasis and should be avoided in patients with known urate nephrolithiasis.

Note 3: The maximum daily dose of febuxostat in the Australian approved product information is 80 mg; however, daily doses of up to 120 mg are approved in other countries.

Note 4: For more information, see the Therapeutic Goods Administration (TGA) safety advisory.

Flare prophylaxis when starting or increasing urate-lowering therapy

Flare prophylaxis when starting or increasing urate-lowering therapy

Starting or increasing urate-lowering therapy is associated with a high risk of gout flare, so flare prophylaxis is recommended. Colchicine has the strongest evidence as a prophylactic drug for gout flares. Nonsteroidal anti-inflammatory drugs (NSAIDs) may be considered for patients in whom colchicine is contraindicated or ineffective. The potential benefit of NSAIDs should be weighed up against their potential harms, particularly in patients at high risk of harms (see Principles of NSAID use for musculoskeletal conditions in adults for more information). Oral corticosteroids are usually only used under specialist advice and are associated with long-term adverse effects (see Principles of immunomodulatory drug use for rheumatological diseases in adults). If a patient has had multiple recurrent attacks of gout despite prophylaxis, combination therapy with colchicine plus either an NSAID or prednis(ol)one may be required. Avoid concurrent use of NSAIDs and oral corticosteroids because of the significantly increased risk of gastrointestinal toxicity, and because NSAIDs are not likely to have additional benefit in patients taking oral corticosteroids.

To prevent gout flares, use:

1 colchicine 500 micrograms orally, once or twice daily. Reduce dosage in renal impairment *gout, flare prophylaxis*

OR

2 an NSAID orally (see Table 12.7 for dosing; the lower end of the dosing range is usually adequate) *gout, flare prophylaxis*

OR

3 prednis(ol)one 5 mg orally, daily. *gout, flare prophylaxis*

The optimal duration of flare prophylaxis is unclear, but the frequency of flares, the duration of gout and the presence and size of tophi should be taken into account. Evidence supports the use of flare prophylaxis for at least 6 months, but the presence of tophi may warrant prolonged flare prophylaxis. In general, flare prophylaxis should be continued until the patient has no further attacks and the target serum uric acid concentration has been achieved. Typically, this takes at least 6 months, but may take longer in some individuals.

If the patient has a gout flare, the recommended management is as for an acute attack (see Management of acute gout) and urate-lowering therapy should be continued. If the patient has a gout flare after prophylaxis has been stopped, restart prophylaxis and reassure patients that the urate-lowering therapy is working.

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Introduction to osteoarthritis

Introduction to osteoarthritis

Osteoarthritis is a chronic musculoskeletal condition that affects the joints and peri-articular structures. The changes of osteoarthritis can affect the whole joint, including the cartilage, bone, synovial lining and synovial fluid. The prevalence of osteoarthritis increases significantly with age and osteoarthritis affects more than 50% of people aged 65 years and older. Although symptoms are less common before the age of 40 years, osteoarthritis can also affect younger people. In these patients, osteoarthritis can have a significant impact on the ability to work, in addition to the impact on physical function and quality of life experienced by all people with osteoarthritis.

Osteoarthritis can affect any joint; however, the most commonly affected joints are those of the hands (particularly the distal interphalangeal joints and the first carpometacarpal joints), the cervical spine, the lumbar spine, and the knees and hips. Osteoarthritis can be monoarticular, oligoarticular or polyarticular. Osteoarthritis may occur secondary to another joint pathology, including major injury, inflammatory arthritis or infection; or it may be a primary condition, in which case it is more likely to be generalised (involve three or more joint sites) and have a stronger genetic link.

Osteoarthritis with calcium pyrophosphate deposition is discussed in Calcium pyrophosphate deposition.

Symptoms and clinical course of osteoarthritis

Symptoms and clinical course of osteoarthritis

The major symptoms of osteoarthritis are pain, stiffness and swelling, which can lead to impaired mobility and physical function. Deterioration in quality of life is common due to the physical and psychosocial impacts of the condition. Stiffness following inactivity or morning stiffness in osteoarthritis is usually of shorter duration than in rheumatoid arthritis. The joint swelling in osteoarthritis may be bony (hard) due to osteophyte formation and/or spongy (soft) due to effusion or synovial thickening. Soft-tissue swelling in osteoarthritis is usually not as great as that observed in rheumatoid arthritis.

Osteoarthritis usually follows a slowly progressive course and many patients have minimal disease progression; however, a sudden and severe deterioration in symptoms can occur. Symptoms can also fluctuate over many years. Patients with knee osteoarthritis are more likely to experience fluctuating symptoms, while patients with hip osteoarthritis tend to have a more progressive disease course and can deteriorate rapidly. Some patients with osteoarthritis only experience symptoms with physical activity rather than symptoms throughout the day. Knee osteoarthritis tends to be associated with greater disability than osteoarthritis of the other joints.

For specific discussion on hand osteoarthritis, see Osteoarthritis of the hand.

Pathogenesis of osteoarthritis

Pathogenesis of osteoarthritis

Osteoarthritis has traditionally been considered to have a noninflammatory aetiology; however, it has become increasingly recognised that inflammatory mediators (eg cytokines, prostaglandins) released from cartilage, bone and the synovium contribute to both the development and progression of osteoarthritis. Low-grade inflammation associated with obesity, insulin resistance, dyslipidaemia, hypertension and ageing may also

contribute to disease pathogenesis. Some patients with osteoarthritis have significant inflammation; late-onset rheumatoid arthritis is an important differential diagnosis in these patients.

There are multiple sources of nociception in osteoarthritis, including structures within and around the joint; the sources of nociception often fluctuate over time in an individual patient. Intra-articular sources of nociception include synovitis, subchondral bone changes (reported as bone marrow oedema on magnetic resonance imaging [MRI]), periosteum disruption associated with osteophyte formation, microfractures, ligament degeneration, and capsular distension with effusions. Peri-articular sources of nociception include inflammation of tendon, fascia or bursa; muscle spasm; and nerve pressure. For example, pes anserinus bursitis at the medial aspect of the knee is commonly associated with knee osteoarthritis. Although osteoarthritis is characterised by the loss of articular cartilage, this is not a source of nociception because articular cartilage contains no neural or vascular structures.

Central sensitisation can also contribute to the experience of pain and its sequelae in osteoarthritis.

Risk factors for osteoarthritis

Risk factors for osteoarthritis

Risk factors for the development and progression of osteoarthritis can vary depending on the affected joint; however, the majority of epidemiological and risk factor studies have been in patients with knee osteoarthritis and these findings are often generalised to osteoarthritis at other sites.

Obesity and injury are important modifiable risk factors for osteoarthritis (see also Weight loss). Malalignment is a potentially modifiable risk factor for osteoarthritis. Nonmodifiable risk factors for osteoarthritis are older age, female gender, and family history of osteoarthritis.

Certain occupations are associated with osteoarthritis of particular joints because of the physical load placed on the joint by the occupation. Examples of associations include farming and hip osteoarthritis, occupations involving repeated knee bending and/or lifting heavy objects and knee osteoarthritis, and occupations involving manual labour and hand osteoarthritis.

Psychosocial factors can influence the experience of osteoarthritis. People with lower education levels, lower socioeconomic status and psychological comorbidities tend to experience greater pain and disability. See also Psychological therapies.

Diagnosis of osteoarthritis

Diagnosis of osteoarthritis

The diagnosis of osteoarthritis is largely based on clinical assessment, which should include a thorough symptom history, physical examination, and functional and psychosocial assessment (see Symptoms and clinical course of osteoarthritis for a description of osteoarthritis symptoms).

Radiological findings of osteoarthritis are poorly correlated with osteoarthritis symptoms.

Radiological findings of osteoarthritis are common in asymptomatic individuals, particularly with increasing age, and in isolation do not indicate the need for management. Furthermore, even in symptomatic patients, radiological findings of osteoarthritis may not explain the patient's symptoms or reflect the severity of their symptoms. The majority of patients with osteoarthritis have stable radiological findings over at least 10 years regardless of clinical disease progression.

Laboratory investigations are usually not required for the diagnosis of osteoarthritis, and inflammatory markers are usually normal or only minimally raised.

The diagnosis of osteoarthritis can be complicated by the presence of comorbid rheumatological diagnoses, such as fibromyalgia and rheumatoid arthritis; these conditions are also differential diagnoses of

osteoarthritis.

General management approach for osteoarthritis

General management approach for osteoarthritis

Osteoarthritis is best managed by an integrated chronic disease model of care that supports multidisciplinary involvement and is underpinned by a biopsychosocial approach. Besides their general practitioner, based on the patient's needs, other members of the multidisciplinary team may include a physiotherapist, an exercise physiologist, a dietician, a psychologist, a nurse, an occupational therapist, a rheumatologist and/or an orthopaedic surgeon. The general practitioner is usually the care coordinator.

Patients with osteoarthritis should be followed up through all stages of the disease. There is no cure or proven disease-modifying treatment for osteoarthritis; the following goals of management are relevant at all stages of the disease and should be individualised to the patient:

- enable pain coping and, where possible, reduce symptoms
- maintain and optimise physical function
- maintain and optimise ability to perform daily activities (eg participation in social, recreational and occupational activities)
- minimise associated disability
- maximise health-related quality of life.

Figure 12.8 summarises the essential features of osteoarthritis management. Although not an exhaustive list, it should be considered the minimum standard of care for all patients. The evidence base for intervention in osteoarthritis largely comprises clinical trials in patients with knee osteoarthritis. A smaller number of trials have been performed for osteoarthritis of the hip and hand and very few for spinal osteoarthritis, in part because of the difficulties in defining the patient population. While there are specific considerations in the management of osteoarthritis at different joints, the essential features of management apply to osteoarthritis at any joint. For specific considerations in the management of hand osteoarthritis, see Osteoarthritis of the hand.

The majority of patients with osteoarthritis have at least one comorbid condition, including other rheumatological diagnoses. Patients with osteoarthritis are more likely than their age- and gender-matched peers to have hypertension, diabetes, depression and obesity. Comorbidities can impact, and be impacted by, osteoarthritis and its management. Therefore, optimising the management of comorbidities should be addressed in every osteoarthritis management plan.

Assessing the benefit of interventions in osteoarthritis can be challenging because of the nature of the disease. In placebo-controlled trials, benefit is often observed in the placebo group, which may be in part due to a natural fluctuation in osteoarthritis symptoms. Where a comparative benefit for an intervention has been shown, the average effect size is often only small or moderate, which may be in part due to the slow progression of the disease. Application of the evidence is further limited by many trials assessing only short-term outcomes for what is a chronic condition, and only assessing harms as a secondary outcome measure.

As the goals of osteoarthritis management are individualised and some patients experience a greater benefit from a given intervention than others, the benefit of a specific intervention experienced by an individual patient may be adequate for their needs. Because of the limitations in the evidence base and the variability in patient needs and responses to a given intervention, it is recommended that a trial approach is taken to the use of interventions in osteoarthritis. This involves regular assessment of an intervention against the goals of osteoarthritis management to determine if the intervention is safe and of adequate and continued benefit for that individual.

While oral analgesia may be considered for pain relief, it is not an inevitable component of the management of osteoarthritis. In particular, the risk of harms should be taken into account in the decision to initiate oral analgesia.

Figure 12.8 Essential features of osteoarthritis management

[NB1]

- Individualise the goals of management and the management plan through shared decision-making, taking into account the patient's affected joints, the stage and severity of their disease, their functional impairments, their risk factors for osteoarthritis, and their age, comorbidities and concomitant treatments.
- Educate and reassure the patient about the nature of the condition and provide support for self-management (see Patient education for and self-management of osteoarthritis).
- Optimise the management of comorbidities, including other rheumatological diagnoses.
- If the patient is overweight or obese, provide advice about weight loss and refer to services as required.
- Provide advice about exercise and refer to services as required.
- Provide advice about nonpharmacological interventions (see Physical treatments and Psychological therapies).
- If topical analgesia is needed, trial a topical NSAID or capsaicin.
- If oral analgesia is needed, both paracetamol and oral NSAIDs have a role (see Paracetamol and oral nonsteroidal anti-inflammatory drugs for further discussion).
- Organise regular clinical review to monitor goals of management, and modify goals and the management plan as needed. If there are concerns about the patient's progress, consider specialist referral.
- Following an adequate trial period, assess interventions against management goals:
    - Cease unhelpful or harmful treatments.
    - Optimise oral analgesia to enable physical function, rather than to abolish pain.
    - Osteoarthritis symptoms can fluctuate; if symptoms improve, trial a cessation of oral analgesia.

NSAIDs = nonsteroidal anti-inflammatory drugs

NB1: See also the Australian Commission on Safety and Quality in Health Care (ACSQHC) Osteoarthritis of the Knee Clinical Care Standard [URL].

For patients with persisting functional impairment and pain despite implementing the strategies in Figure 12.8, a trial of other interventions may be considered depending on the affected joints, and the stage and severity of the disease. These include intra-articular corticosteroid injections, intra-articular hyaluronan injections and duloxetine. Therapies for central sensitisation may be considered for patients with more widespread nonspecific pain (see Management of fibromyalgia). Options for end-stage disease include surgery and opioids. In all cases, patients should be encouraged to maintain lifestyle measures, such as exercise and weight loss.

Formal osteoarthritis chronic care programs have been established in some public and private care settings. These programs use an integrated multidisciplinary approach targeted to the patient's needs. Although these programs are evolving and not yet widely available, referral to such programs may be considered for patients who do not respond to the strategies in Figure 12.8, or who do not have access to co-located multidisciplinary care.

Patient education for and self-management of osteoarthritis

Patient education for and self-management of osteoarthritis

All patients with osteoarthritis, irrespective of the stage of the disease, should receive education about the condition and advice on self-management. Patient education and self-management advice can help reduce pain, and improve physical function and quality of life. It should be targeted to the needs of the patient, their general health literacy, and their stage of acceptance of the condition. Use positive and non-catastrophic language to empower patients to proactively and positively manage their osteoarthritis. When describing osteoarthritis to patients, avoid the use of negative terms such as ‘bone on bone’, ‘normal wear and tear’ and ‘cartilage erosion’.

Follow-up patient education and self-management advice at regular clinical review appointments is also recommended. This has been associated with symptom improvement in part because of better adherence to interventions, but also because of improved self-efficacy and coping.

Patient education should include discussion about:

- the likelihood of slow or minimal disease progression
- the fluctuating nature of osteoarthritis symptoms
- the poor correlation between symptoms and radiological findings of osteoarthritis
- modifiable risk factors for disease progression (see Risk factors for osteoarthritis)
- realistic management goals and expectations of treatment.

Strategies for self-management include:

- coping strategies for living with chronic pain (see also Psychological therapies)
- pacing physical activities (eg spreading physically hard jobs throughout the day with breaks in between to reduce sustained physical loading)
- lifestyle measures, such as exercise and weight loss
- use of physical aids (see Nonpharmacological management)
- strategies to minimise symptoms when performing activities of daily living (often referred to as joint protection techniques); specific strategies are recommended for hand osteoarthritis (see Osteoarthritis of the hand) and similar principles may be applied to osteoarthritis of the other joints
- topical or oral analgesia for evoked pain (see Topical nonsteroidal anti-inflammatory drugs and capsaicin and Paracetamol and oral nonsteroidal anti-inflammatory drugs)
- monitoring pain levels using a pain management diary [Note 1].

The success of patient education and self-management largely relies on consistency in the messages provided to patients. Allied health professionals who are trained in both the management principles of osteoarthritis and in health coaching and behavioural change can assist in the education process (eg occupational therapists, physiotherapists, podiatrists). Evidence does not support a benefit from formal self-management education programs; however, these are unlikely to be harmful.

Printed or online information is useful to reinforce education and self-management advice. Patient support organisations such as Arthritis Australia provide educational materials and participation in their activities may be valuable for social support; see [URL]. The ‘My Joint Pain’ [URL] and ‘painHEALTH’ [URL] websites also provide useful tips for self-management [Note 2].

Note 1: The *Helping you manage pain* diary is available from NPS MedicineWise [URL].

Note 2: These websites provide patient information; any management advice given on these websites should be considered in the context of the recommendations in these guidelines.

Lifestyle management of osteoarthritis

Lifestyle management of osteoarthritis

Exercise

Exercise

Exercise is important for all patients with osteoarthritis, irrespective of the affected joints or the stage or severity of the disease (including for patients awaiting surgery). Reported benefits of exercise include reduction in pain, and improvements in physical function and quality of life.

No specific exercise program has been proven to be substantially better than another in the management of osteoarthritis. The success of exercise depends on patient adherence to the program in the long term, so

choice of exercise program should take into account the patient's functional impairments, comorbidities, and physical activity preferences.

For osteoarthritis of the knee or hip, programs that incorporate aerobic exercise with functional and progressive lower limb muscle strengthening are generally recommended. These have been shown to be safe and effective, even among older patients. Strengthening and aerobic exercise should be undertaken at least 3 times per week. People with lower limb osteoarthritis have an increased risk of falls, so balance training should be incorporated as part of functional exercise. There is evidence that a program of strengthening, flexibility and functional exercises can delay the need for surgery in patients with hip osteoarthritis.

In terms of specific modes of exercise, there is evidence for both land-based exercises, including Tai Chi, and water-based exercises, such as aqua aerobics, for knee and hip osteoarthritis. An example exercise program for knee osteoarthritis can be found on the HANDI (The Handbook of Non-Drug interventions) website [URL].

For osteoarthritis of other joints, a functional exercise approach is recommended. For discussion of exercise for hand osteoarthritis, see Osteoarthritis of the hand.

Regular aerobic exercise has multiple well-recognised general health benefits that are relevant to patients with osteoarthritis. These include reduced risk of cardiovascular disease, weight loss, improved quality of life, improved mood and sleep patterns, and reduced risk of falling in older patients. Weight loss is particularly important because obesity is a modifiable risk factor for the development and progression of osteoarthritis.

Patients with osteoarthritis often need additional encouragement to undertake exercise because of joint pain and perceived instability. Reassure patients that some discomfort at the affected joint during exercise is likely and this does not indicate disease progression. Encourage patients using supportive and non-catastrophic language such as ‘hurt does not mean harm’ and ‘sore but safe’. Topical or oral analgesia may be required to facilitate exercise (see Topical nonsteroidal anti-inflammatory drugs and capsaicin and Paracetamol and oral nonsteroidal anti-inflammatory drugs).

Appropriate exercise can be undertaken safely in a variety of settings (eg home, gym, group class or under clinical supervision). Referral to an appropriate health professional (eg physiotherapist, exercise physiologist) may be beneficial to initiate and reinforce an exercise program; this may include prescribing a personalised program of simple exercises (eg swimming, walking) that the patient can do unsupervised. Involving the patient's social supports (eg spouse) in the exercise program may also improve outcomes.

Depending on their functional impairments and comorbidities, some patients may require clinician-guided exercise instruction and support, combined with cognitive and behavioural pain education. Physiotherapist-delivered exercise integrated with training in pain-coping skills has been demonstrated to improve functional outcomes compared with either intervention alone in patients with knee osteoarthritis.

Weight loss

Weight loss

Obesity is a risk factor for both the development and progression of knee osteoarthritis. The majority of patients with knee osteoarthritis are overweight or obese. Of those patients undergoing joint replacement surgery for knee osteoarthritis, 60% are reported as obese. Obesity also appears to be a risk factor for hip, hand and spinal osteoarthritis; 40% of patients undergoing joint replacement surgery for hip osteoarthritis are reported as obese.

Weight loss is recommended for all patients with osteoarthritis who are overweight or obese, irrespective of the affected joints or the stage or severity of the disease (including for patients awaiting surgery). There is strong evidence that weight loss is beneficial for knee osteoarthritis. Despite no good evidence that it helps hip or other forms of osteoarthritis, weight loss is still recommended because of the general health benefits.

Improvement in osteoarthritis symptoms and physical function is proportional to the percentage of weight loss. A range of weight loss targets has been identified as necessary for a clinically significant improvement; a

reasonable target is a more than 5% weight reduction. Reduction in pain and improvement in physical function are greater if exercise and weight loss are combined. For information on weight loss strategies, see Management of overweight patients. Refer patients to weight management services if appropriate.

Nonpharmacological management of osteoarthritis

Nonpharmacological management of osteoarthritis

Physical treatments

Physical treatments

Physical treatments are often used as adjunctive therapy in the management of osteoarthritis; however, apart from exercise, physical treatments have a limited role in osteoarthritis management because of a lack of evidence, weak or unclear evidence of benefit, or evidence suggesting they are not effective. However, because some patients report a benefit and these interventions are unlikely to be harmful, a trial may be reasonable based on patient preference.

In patients with knee or hip osteoarthritis, thermotherapy (application of heat or cold), or the use of a walking stick may reduce pain and enable physical activity. In patients with patellofemoral osteoarthritis, there is limited evidence that medially directed taping of the patella may provide short-term pain relief. Taping should not be used in isolation and is most useful as an adjunct to encourage patients to start their exercise program. Long-term use of taping may be limited by local skin reactions. There is also some evidence to support the use of a patellofemoral brace for pain relief in patients with patellofemoral osteoarthritis and this may be considered as an alternative to taping.

Evidence suggests that acupuncture, transcutaneous electrical nerve stimulation (TENS), lateral heel wedge insoles, manual therapy, magnets and valgus braces are not effective in the management of osteoarthritis.

For discussion of physical treatments for hand osteoarthritis, see Osteoarthritis of the hand.

Psychological therapies

Psychological therapies

Patients with osteoarthritis who live with chronic pain, functional impairment and impaired quality of life are likely to experience a negative psychological impact. Psychological impairments may increase disability, affect adherence to self-management strategies and reinforce central sensitisation. Psychological therapies (eg cognitive behavioural therapy) may be useful to address psychological impairments and pain coping. Recent data also suggest a potential benefit from internet-delivered pain-coping programs.

For more information on psychological techniques for chronic pain, see Psychological techniques for managing pain. Treat specific psychological diagnoses if present (eg depression or anxiety).

Pharmacological management of osteoarthritis

Pharmacological management of osteoarthritis

Topical nonsteroidal anti-inflammatory drugs and capsaicin

Topical nonsteroidal anti-inflammatory drugs and capsaicin

Topical nonsteroidal anti-inflammatory drugs (NSAIDs) and capsaicin can be considered as an adjunct to other treatment strategies and as part of short-term self-management.

Topical NSAIDs have been shown to have a small benefit in pain relief compared to topical placebo preparations in studies up to 12 weeks and mainly in patients with knee osteoarthritis. Because of minimal systemic absorption, topical NSAIDs are considerably safer than oral NSAIDs and limited evidence suggests they have similar efficacy to oral NSAIDs in patients with osteoarthritis. If a trial of a topical NSAID is considered appropriate, use:

a topical NSAID applied directly to the painful area, up to 4 times daily (see Table 12.7 for available topical preparations). *arthritis, osteoarthritis*

Topical capsaicin has also been shown to have a small benefit in pain relief compared to topical placebo preparations in studies up to 12 weeks. The main adverse effect is a transient burning at the site of application, which decreases over time. If a trial of topical capsaicin is considered appropriate, use:

capsaicin 0.025% cream applied directly to the painful area, 3 to 4 times daily. *arthritis, osteoarthritis*

Paracetamol and oral nonsteroidal anti-inflammatory drugs

Paracetamol and oral nonsteroidal anti-inflammatory drugs

Both paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) have a role in oral analgesia for osteoarthritis symptoms.

Oral NSAIDs are more effective than paracetamol and can improve symptoms in most patients. However, oral NSAIDs also have a greater potential for harm, particularly in older people, who are the population most commonly affected by osteoarthritis. For patients at low risk of harms from NSAID use, a trial of an oral NSAID may be considered first line (see Principles of NSAID use for musculoskeletal conditions in adults for more information on assessing the risk of harms from NSAID use). Avoid first-line use of oral NSAIDs in all other patients.

Only consider using an oral NSAID first line for patients at low risk of harms from NSAID use.

The evidence for paracetamol in osteoarthritis is mainly from older clinical trials and all in patients with knee or hip osteoarthritis. The evidence indicates that on average paracetamol has small, but statistically significant, short-term benefits compared to placebo; there are differing interpretations of the clinical significance of this, but an individual patient may experience adequate benefit for their needs. Paracetamol also has a more favourable safety profile compared to other oral analgesics. Therefore, a trial of paracetamol remains appropriate for any patient requiring oral analgesia for osteoarthritis symptoms.

For patients with symptoms evoked by exercise or other physical activity, consider a trial of ‘as necessary’ paracetamol or oral NSAID. Use:

1 paracetamol 1 g orally, 4- to 6-hourly as necessary, up to a maximum of 4 g daily *arthritis, osteoarthritis* _

OR

1 paracetamol modified-release 1.33 g orally, 8-hourly as necessary

OR (for patients at low risk of harms from NSAID use)

1 an NSAID orally (see Table 12.7 for dosing). *arthritis, osteoarthritis*

For patients with symptoms that persist throughout the day, consider a trial of regular dosing, rather than ‘as necessary’ dosing.

Ensure the duration of the trial is adequate and assess treatment response against the goals of management. Goals related to physical function should be the focus; explain to the patient that the aim is to reduce, rather than abolish, pain so that physical function can be maintained.

If response to paracetamol is inadequate, a judicious trial of NSAID use may be considered instead of, or in combination with, paracetamol. This decision should be based on an assessment of the benefit–harm profile for an NSAID in the individual patient.

Do not continue paracetamol and/or oral NSAIDs if there is no benefit or treatment is harmful. Osteoarthritis symptoms can fluctuate; if symptoms improve, consider a trial of cessation of oral analgesia.

Intra-articular injections

Intra-articular injections

A single **intra-articular corticosteroid injection** may provide symptom relief lasting from 4 to 12 weeks in patients with knee osteoarthritis; however, most trials supporting the use of intra-articular corticosteroid injections have been reported to have a high or unclear risk of bias. Because of their rapid onset of action, intra-articular corticosteroid injections may be useful if patients have to travel or participate in an important occasion; they may also enable participation in strengthening exercises. Knee injections are easily performed with landmark guidance; radiological guidance, such as ultrasound, does not increase the effectiveness of the injection. Intra-articular corticosteroid injection may be repeated at 3-monthly intervals if needed; evidence suggests that repeat injections are effective and do not alter disease progression.

Small randomised controlled trials have shown that a single intra-articular corticosteroid injection may provide pain relief for up to 12 weeks in hip osteoarthritis; however, these injections are logistically difficult to administer because radiological guidance is needed.

For principles of use and example doses of local corticosteroid injections, see Principles of using local corticosteroid injections for musculoskeletal conditions in adults.

Intra-articular hyaluronan can be given as a single injection or as a weekly injection for 3 to 5 weeks depending on the preparation. The evidence for intra-articular hyaluronan injection in patients with knee osteoarthritis is inconsistent because of the range of preparations studied and the quality and design of the studies. Conclusions of systematic reviews have been conflicting, and larger trials in which participants were adequately blinded reported only a small and clinically insignificant benefit. Intra-articular corticosteroid injection provides greater short-term benefits in knee osteoarthritis than intra-articular hyaluronan injection, but pain relief from intra-articular hyaluronan injection may last slightly longer in patients who respond. Intra-articular hyaluronan injection may be associated with temporary worsening of osteoarthritis symptoms, and the unit cost of intra-articular hyaluronan injection is much higher than the unit cost of intra-articular corticosteroid injection. As with intra-articular corticosteroid injections, hyaluronan injections into the knee joint are easily performed using landmark guidance. Small studies of intra-articular hyaluronan injections have been conducted in hip, ankle and shoulder osteoarthritis with conflicting results.

Intra-articular injections of platelet-rich plasma, adipocyte cell suspensions and mesenchymal stem cells are being increasingly used for the treatment of osteoarthritis. Despite the favourable conclusions of systematic reviews of intra-articular injections of platelet-rich plasma, the results should be interpreted with caution because the individual studies in the reviews were generally at high risk of bias. The evidence to support the use of adipocyte cell suspensions and mesenchymal stem cells is also weak. None of these treatments is recommended.

For discussion of intra-articular injections for hand osteoarthritis, see Osteoarthritis of the hand.

Duloxetine

Duloxetine

Duloxetine has been shown to reduce pain and improve physical function compared to placebo in patients with chronic pain due to knee osteoarthritis. Evidence suggests that duloxetine may have a similar efficacy to oral nonsteroidal anti-inflammatory drugs (NSAIDs), but head-to-head comparisons are lacking. Duloxetine has also been shown to be an effective adjunct to oral NSAIDs. The duration of the studies ranged from 10 to

16 weeks. Duloxetine may be considered for patients with knee osteoarthritis who have persisting functional impairment and pain despite implementing the strategies in Figure 12.8.

If a trial of duloxetine is considered appropriate, use:

duloxetine 30 mg orally, daily for 1 week, then increase to 60 mg daily. Maximum daily dose is 120 mg.
arthritis, osteoarthritis _

Opioids

Opioids

Opioids have a very limited role in the management of osteoarthritis because of modest, if any, benefits and a significant risk of harms.

Opioids may be considered for patients with severe persisting functional impairment due to pain, despite maximal conservative management (see General management approach for osteoarthritis); this may include patients awaiting surgery or in whom surgery is not possible. Opioids are not recommended for osteoarthritis of the hand.

If opioids are used, they should be prescribed on a short-term trial basis, as part of an overall pain management strategy, with clear goals and regular review of treatment response and adverse effects. Before starting an opioid, a plan for ceasing ineffective therapy should be in place and discussed with the patient. If treatment response is inadequate, caution should be exercised when increasing the dose of opioids as there is an increased risk of harm and potentially no added benefit. Prolonged use of opioids indicates the need for specialist assessment. See Opioids for more information.

Studies up to 1 year in patients with knee or hip osteoarthritis indicate that tapentadol may have a more favourable safety profile than oxycodone; however, the long-term safety of tapentadol is not known and the same precautions as for other opioids should be applied to tapentadol.

Complementary medicines in osteoarthritis

Complementary medicines in osteoarthritis

Fish oil, glucosamine and chondroitin are commonly used treatments for osteoarthritis.

There are no placebo-controlled trials of **fish oil** in the management of osteoarthritis. A recent trial compared an anti-inflammatory dose of fish oil with a low dose of fish oil in patients with knee osteoarthritis and found a reduction in pain and improvement in physical function in both groups, but the anti-inflammatory dose of fish oil offered no benefit over low-dose fish oil [Note 3].

Although the combination of **glucosamine** and **chondroitin** has been suggested to have a disease-modifying effect in knee osteoarthritis, there is inadequate evidence to support its use for this purpose. In terms of symptom benefit, the evidence for glucosamine is inconsistent because of the range of different brands studied; however, large randomised controlled studies of glucosamine suggest that the benefit is no greater than placebo. The evidence for chondroitin is unclear, but limited evidence suggests it may have a small to moderate benefit compared to placebo. There is conflicting evidence regarding a symptom benefit with the combination of glucosamine and chondroitin in patients with painful knee osteoarthritis, with some studies suggesting a small benefit and others showing no benefit.

For patients with osteoarthritis who want to trial these therapies, the usual dosages are glucosamine sulfate 1500 to 2000 mg orally, daily, and chondroitin sulfate 800 to 1200 mg orally, daily. An appropriate trial duration is 3 to 6 months. Most formulations of glucosamine are prepared from shellfish and should not be used in patients with significant seafood allergy. There may be variation in the effect between different brands because of the range of sources used and different methods of processing.

There is no evidence for krill oil in the management of osteoarthritis, and there is inadequate evidence to support the use of turmeric (active ingredient is curcumin) or Ayurvedic medicine.

Note 3: Hill CL, March LM, Aitken D, Lester SE, Battersby R, Hynes K, et al. Fish oil in knee osteoarthritis: a randomised clinical trial of low dose versus high dose. Ann Rheum Dis 2016;75(1):23-9. [URL]

Surgery for osteoarthritis

Surgery for osteoarthritis

Surgical options for hip and knee osteoarthritis include osteotomy and joint replacement. Refer patients for surgery if they have severe persisting functional impairment and/or pain despite maximal conservative management (see General management approach for osteoarthritis). Timely referral is important (ie before significant functional decline occurs). Around 30% of patients with knee osteoarthritis will require surgery, and this figure is likely to be higher for patients with hip osteoarthritis. For discussion of surgery for hand osteoarthritis, see Osteoarthritis of the hand.

Patients referred for surgery should be advised of the realistic degree of reduction in pain and improvement in physical function that can be expected from surgery. Weight change following surgery is variable and obesity can persist for a large proportion of patients postoperatively.

While awaiting surgery, patients should be encouraged to persist with lifestyle measures, such as weight loss and exercise, as a higher preoperative level of functioning may improve outcomes from surgery and will enable better participation in postoperative rehabilitation. Weight loss before surgery is often recommended because obesity increases the risk of perioperative complications, delays the benefits of surgery, and is associated with higher rates of surgical revision. Management of patients who are awaiting joint replacement is discussed in The Royal Australian College of General Practitioners (RACGP) management guide on referral for joint replacement [Note 4].

Arthroscopic lavage and/or debridement are not recommended for osteoarthritis of the knee, and partial meniscectomy is not recommended for degenerative meniscal tears (with or without underlying osteoarthritis), because these treatments have not been found to be more effective than placebo or exercise, and have the potential for harm. There are no randomised controlled trials of arthroscopy for hip osteoarthritis.

Note 4: The RACGP management guide on referral for joint replacement is available at the RACGP website [URL].

Osteoarthritis of the hand

Osteoarthritis of the hand

In osteoarthritis of the hand, the most commonly affected joints are the distal interphalangeal joints and the first (thumb) carpometacarpal joints. Affected distal interphalangeal joints may go through a painful inflammatory phase, lasting from a few months to a few years, which then settles leaving residual bony deformity (Heberden nodes) that does not significantly impact on physical function. Primary generalised nodal osteoarthritis is a subtype of osteoarthritis that can involve multiple distal and proximal interphalangeal joints, and can have a significant impact on physical function. Thumb-based carpometacarpal osteoarthritis can occur in isolation or as part of primary generalised nodal osteoarthritis. It usually has a significant impact on physical function.

Relatively few randomised controlled trials have been conducted for osteoarthritis of the hand; however, there is evidence that conservative management can prevent the need for surgery. For initial management, the following interventions may be beneficial:

- strategies to minimise symptoms when performing activities of daily living (often referred to as joint protection techniques) (see Figure 12.9)
- assistive devices as needed for performing activities of daily living (eg tap turner), based on an assessment of the patient's abilities
- splints for thumb-based carpometacarpal osteoarthritis [Note 5]
- strengthening and stretching hand exercises
- application of heat.

If needed, the above interventions can be combined with topical or oral analgesia (see Topical nonsteroidal anti-inflammatory drugs and capsaicin and Paracetamol and oral nonsteroidal anti-inflammatory drugs). Opioids are not recommended for osteoarthritis of the hand.
Figure 12.9 Strategies to minimise symptoms of hand osteoarthritis when performing activities of daily living

[NB1]

- Distribute the weight of lifted objects over several joints (eg spread the load over two hands).
- Avoid repetitive thumb movements and putting strain on the thumb.
- Avoid a prolonged grip in one position.
- Use as large a grip as possible.
- Reduce the effort needed to do a task (eg use labour-saving gadgets, avoid lifting heavy objects, and reduce the weight of what is lifted).
- Conserve energy by planning activities (eg organise tasks more efficiently) and pacing them (eg take regular short breaks).

NB1: More information on these strategies can be found on the HANDI (The Handbook of Non-Drug interventions) website [URL]

Source: Dziedzic K, Nicholls E, Hill S, Hammond A, Handy J, Thomas E, et al. Self-management approaches for osteoarthritis in the hand: a 2x2 factorial randomised trial. Ann Rheum Dis 2015;74(1):108-18. [URL]

Intramuscular corticosteroids can reduce inflammation and improve symptoms in patients with primary generalised nodal osteoarthritis; however, their use is not recommended because of the lack of long-term effectiveness data and the potential for long-term adverse effects. Evidence suggests intra-articular corticosteroid injections and intra-articular hyaluronan injections are not more effective than placebo for carpometacarpal osteoarthritis, including thumb-based carpometacarpal osteoarthritis. The suggested benefit of intra-articular corticosteroids in interphalangeal osteoarthritis requires confirmation.

There is insufficient evidence to recommend hydroxychloroquine, methotrexate or sulfasalazine for osteoarthritis of the hand, although they are sometimes considered for inflammatory and erosive osteoarthritis. These drugs should only be started in consultation with a rheumatologist.

Surgery may be considered for advanced thumb-based carpometacarpal joint osteoarthritis if pain and functional impairment persist despite maximal conservative management. However, the evidence for benefit of surgery is inconclusive.

Note 5: Information on splints for hand osteoarthritis can be found on the HANDI (The Handbook of Non-Drug interventions) website [URL].

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Undifferentiated polyarthritis in adults

Undifferentiated polyarthritis in adults

Assessing undifferentiated polyarthritis

Assessing undifferentiated polyarthritis

The principal differential diagnoses in patients with recent-onset inflammatory polyarthritis are rheumatoid arthritis and a self-limiting arthritis, which is often due to viral infection. The clinical features of **viral arthritis** may be indistinguishable from early rheumatoid arthritis. For patients whose arthritis remits, a definitive diagnosis is not always achieved and, often, their arthritis is presumed to have a viral cause. Most cases of viral arthritis resolve spontaneously within 12 weeks; follow-up from recent-onset polyarthritis clinics shows that a significant proportion of episodes of recent-onset polyarthritis resolve within 12 months.

If **rheumatoid arthritis** is suspected, prompt action is critical so that diagnosis and disease-modifying therapy are not delayed; early suppression of inflammation can prevent irreversible joint damage and impact long-term prognosis.

Urgently refer any patient with suspected rheumatoid arthritis to a specialist.

Urgently refer any patient with suspected rheumatoid arthritis to a specialist (see also Diagnosis of rheumatoid arthritis). Rheumatologists often have fast-track triage systems for these patients and strongly encourage direct contact by general practitioners to expedite referral or to obtain advice on treatment (eg before starting prednisolone).

Helpful tests for recent-onset polyarthritis include:

- full blood count
- erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP)
- rheumatoid factor (RF) and antibodies to cyclic citrullinated peptides (CCP) (see Diagnosis of rheumatoid arthritis)
- antinuclear antibodies (ANA) (see Antinuclear antibody testing for inflammatory connective tissue diseases)
- serum uric acid, liver biochemistry, serum creatinine and urinalysis
- viral serology (see Viral arthritis).

If symptoms are of acute onset, consider tests for infection (eg blood cultures).

Iron studies and chest X-ray may be considered in some circumstances.

Managing undifferentiated polyarthritis

Managing undifferentiated polyarthritis

Specific treatment of polyarthritis depends on the diagnosis. If a specific diagnosis is suspected, treatment should be tailored accordingly. The management of various types of polyarthritis is discussed in Rheumatoid arthritis, Viral arthritis, Osteoarthritis, Spondyloarthritides, including psoriatic arthritis and Inflammatory connective tissue diseases.

While awaiting diagnostic confirmation (eg through the results of investigations, disease evolution or specialist consultation), undifferentiated polyarthritis is treated according to the severity of symptoms. Advise

patients with undifferentiated polyarthritis to stop smoking. Stopping smoking can improve response to therapy and may attenuate disease progression. See Smoking cessation for more information on assessment of patients' smoking and advice on smoking cessation.

For **mild to moderate inflammatory joint pain**, nonsteroidal anti-inflammatory drugs (NSAIDs) are most commonly used because of their known efficacy in treating pain, stiffness and swelling associated with established inflammatory rheumatological disease. Use:

an NSAID orally (see Table 12.7 for dosing). *arthritis, undifferentiated polyarthritis (adult)*

The potential benefits of an NSAID should be weighed against its potential harms, particularly in patients at high risk of harms (see Principles of NSAID use for musculoskeletal conditions in adults).

Although paracetamol is generally less effective than NSAIDs for moderate to severe pain, its more favourable safety profile justifies recommending it as a first-line analgesic for mild to moderate musculoskeletal pain. Paracetamol has little, if any, anti-inflammatory effect. Paracetamol may be used **in combination with** an NSAID, or **instead of** an NSAID if an NSAID is contraindicated or not tolerated. Use:

1 paracetamol 1 g orally, 4- to 6-hourly, up to a maximum of 4 g daily *arthritis, undifferentiated polyarthritis (adult)*

OR

1 paracetamol modified-release 1.33 g orally, 8-hourly.

There is evidence to suggest that fish oil has a mild anti-inflammatory effect. However, it may take up to 3 months for maximal effectiveness, so it may be necessary to co-prescribe fish oil with an NSAID and/or paracetamol initially. Use:

fish oil at least 2.7 g (omega-3) orally, daily (see Table 12.8 for preparations). *arthritis, undifferentiated polyarthritis (adult)*

See Principles of fish oil use for musculoskeletal conditions in adults for more information.

For patients with **severe symptoms and associated impaired function**, low-dose prednis(ol)one may be required. However, starting prednis(ol)one before specialist review may delay subsequent diagnosis. There should always be a plan for early withdrawal because long-term use is not justified in this setting. If considered essential for rapid symptom relief, use:

prednis(ol)one 5 to 15 mg orally, daily. *arthritis, undifferentiated polyarthritis (adult)*

Early specialist review is crucial if prednis(ol)one is ineffective at a dose at the upper end of the range.

Intramuscular administration of corticosteroids is sometimes used, based on a theoretical reduction in overall corticosteroid exposure compared to oral therapy. A single dose of intramuscular corticosteroid has a prolonged effect (up to 8 weeks) and repeat doses are often unnecessary.

If intramuscular therapy is indicated, the usual dosage is:

methylprednisolone acetate 120 mg intramuscularly, as a single dose. *arthritis, undifferentiated polyarthritis (adult)*

Although NSAIDs and prednis(ol)one can rapidly control inflammation, they are inadequate to prevent joint damage and achieve disease control. Seek urgent specialist advice if joint inflammation is still present at 12 weeks, because treatment with a disease-modifying antirheumatic drug (DMARD) should be considered. Seek urgent specialist advice if joint inflammation is still present at 12 weeks.

Methotrexate (in combination with folic acid) can be given in the setting of early undifferentiated polyarthritis that is not controlled with the above regimens or that recurs on withdrawal of prednis(ol)one. It should be dosed once weekly at the dose used for rheumatoid arthritis (see Conventional synthetic disease-

modifying antirheumatic drugs for dosage). Methotrexate appears to be particularly beneficial for preventing progression to erosive definitive rheumatoid arthritis in the presence of antibodies to cyclic citrullinated peptides (CCP). The immediate or subsequent initiation of one or more DMARDs would generally be on the advice of a specialist, who would also facilitate the withdrawal of prednis(ol)one. NSAIDs are often continued even after a DMARD is started, but the aim is to reduce or withdraw both NSAIDs and prednis(ol)one.

Undifferentiated monoarthritis in adults

Undifferentiated monoarthritis in adults

Assessing undifferentiated monoarthritis

Assessing undifferentiated monoarthritis

Common causes of monoarthritis include infection (ie septic arthritis), trauma and crystal deposition disease (see Gout and Calcium pyrophosphate deposition). Septic arthritis is a rheumatological emergency that requires immediate referral. Conditions that usually involve multiple joints, such as reactive arthritis (eg following *Chlamydia trachomatis* or *Neisseria gonorrhoeae* infection), can also initially present as a monoarthritis. Other less common noninflammatory causes of pain in a single joint include haemarthrosis, juxta-articular fracture and osteonecrosis.

Joint aspiration is the most critical diagnostic procedure and can exclude significant joint inflammation. Consider also nucleic acid amplification testing (NAAT) (eg polymerase chain reaction [PCR]) of urine samples if sexually transmitted infection is possible. Cultures of other sites (blood, cervix, urethra, pharynx) may also be indicated if gonococcal infection is possible, and susceptibility testing should be performed because of regional differences in the susceptibility of *N. gonorrhoeae* and emerging resistance to ceftriaxone.

Plain X-ray is indicated if the monoarthritis is associated with trauma. If initial imaging is normal but the suspicion of a fracture or acute internal derangement remains, more specialised imaging may be warranted.

In the setting of suspected acute septic arthritis, plain X-ray is rarely useful because it generally shows only soft-tissue swelling; the destructive changes of septic arthritis usually take 10 to 14 days to become apparent. If a swollen joint does not settle with treatment with an anti-inflammatory drug (eg an NSAID or prednisolone), then plain X-ray may be considered to detect unsuspected underlying pathology, including fracture, osteomyelitis, avascular necrosis, chondrocalcinosis or a tumour.

In undifferentiated monoarthritis, blood tests are usually nonspecific. However, an elevated erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP) concentration supports the diagnosis of an infective or inflammatory condition. There are several traps in interpreting blood tests:

- A normal white cell count does not exclude infection, especially in old or immunosuppressed patients.
- Blood cultures are only positive in about 50% of cases of nongonococcal septic arthritis.
- Serum uric acid concentration may be normal in patients with acute gout. Conversely, hyperuricaemia alone is insufficient to diagnose gout.
- Testing for autoantibodies such as rheumatoid factor (RF) and antinuclear antibody (ANA) is rarely helpful in an acute monoarthritis.

Diagnostic clues and potential pitfalls with monoarthritis are shown in Figure 12.6.

Figure 12.6 Diagnostic clues and potential pitfalls with monoarthritis

Haemarthrosis

- Suspect haemarthrosis in anticoagulated patients with acute monoarthritis, particularly in the weightbearing or glenohumeral joints. Haemarthrosis can occur even when the international normalised ratio (INR) is in the therapeutic range.

- For patients with recurrent haemarthrosis due to haemophilia, expert advice should be sought from a haematologist before joint aspiration because the patient will need coagulation factors.
- Haemarthrosis in an elderly patient may be associated with acute synovitis secondary to calcium pyrophosphate deposition.

Trauma

- Even minimal trauma can cause an articular fracture in an osteoporotic patient.
- Trauma can precipitate flares of crystal deposition disease.

Fever

- Temperature can be normal in patients with septic arthritis (20% are afebrile) or increased in patients with crystal deposition disease or other inflammatory processes.

Septic arthritis

- Immunosuppressed patients may have a more indolent presentation of septic arthritis, with only mild pain or swelling.
- Septic arthritis is not necessarily excluded by finding two or three involved joints; 10 to 20% of patients have an oligoarticular presentation.
- Presence of crystals in synovial fluid does not exclude sepsis.
- Infection in people who inject drugs often occurs in atypical sites, such as the sternoclavicular, costochondral, shoulder, vertebral or sacroiliac joints.
- False-negative synovial fluid culture results can be seen in patients previously treated with antibiotic therapy.

If a chronic inflammatory monoarthritis remains undiagnosed after 8 weeks, refer the patient to a specialist to determine whether synovial biopsy is indicated to exclude rare causes, such as malignancy or chronic fungal or mycobacterial infections.

Managing undifferentiated monoarthritis

Managing undifferentiated monoarthritis

In general, therapeutic aspiration of large tense joint effusions will provide pain relief and reduce potential damage from increased pressure within the joint capsule (see also Joint aspiration in adults). If symptoms persist and the diagnosis remains unclear, re-aspiration after 1 or 2 days is reasonable.

Specific treatment of monoarthritis depends on the diagnosis. If a specific diagnosis is suspected, treatment should be tailored accordingly.

Septic arthritis, even if the diagnosis is only suspected, requires urgent hospital referral. See Septic arthritis for a discussion of management (including antibiotic regimens).

For management of monoarthritis associated with **crystal deposition disease**, see Gout or Calcium pyrophosphate deposition.

Traumatic (nonfracture) monoarthritis will be helped by rest, the application of ice, simple analgesia and gentle mobilisation.

Inflammatory monoarthritis where sepsis is not suspected can be treated with intra-articular corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) (see Principles of analgesic and anti-inflammatory drug use for musculoskeletal conditions in adults).

Undifferentiated oligoarthritis in adults

Undifferentiated oligoarthritis in adults

An oligoarticular presentation is most suggestive of a spondyloarthritis (including ankylosing spondylitis, psoriatic arthritis, reactive arthritis and enteropathic arthritis) or seronegative arthritis. However, conditions that usually present as single-joint arthritis (infection, gout) can also cause oligoarthritis, as can still-evolving polyarthritis.

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Introduction to neck pain

Introduction to neck pain

Neck pain is a common condition affecting one in twenty people worldwide at any time. It causes substantial disability and is the fourth greatest contributor to global disability. It is more common in women than men, and the prevalence peaks at around 45 years of age.

Pain experienced in the neck region can originate from structures of the cervical spine, or can be referred from sources in the head, chest, shoulder or arm. Neck pain can also be associated with headaches (see Cervicogenic headache in Classifying headaches).

Most episodes of neck pain cannot be attributed to a specific cause and are acute and self-limiting (see Nonspecific neck pain). Acute torticollis (also known as 'wry neck') is a common form of acute neck pain involving abnormal muscle contraction and loss of neck rotation; it is managed as for acute nonspecific neck pain. Other causes of acute neck pain include cervical radiculopathy and acute calcium pyrophosphate crystal arthritis (see Calcium pyrophosphate deposition). A specific form of neck pain can occur in patients with rheumatoid arthritis (see Neck pain and rheumatoid arthritis).

Although serious pathology is rare in patients presenting with neck pain in primary care, clinical suspicion of such pathology should be raised by the presence of alerting features (see Table 12.19).

Assessment of neck pain

Assessment of neck pain

In a patient presenting with neck pain, restricted cervical range of movement and local tenderness indicate that the pain is of local origin, but does not enable a precise anatomical diagnosis. However, a physical examination is still important to identify alerting features of serious pathologies (see Table 12.19) and neurological signs, and to exclude nonspinal causes of neck pain.

The prevalence of asymptomatic degenerative changes in the cervical spine is high and increases with age. In patients with neck pain who do not have neurological symptoms or signs, and who do not have alerting features of a serious spinal pathology, further investigation is usually not necessary. This represents the vast majority of patients seen in primary care.

If a serious spinal pathology is suspected clinically, magnetic resonance imaging (MRI) is the preferred investigation. If MRI is not available, computed tomography (CT) may be useful, but may be associated with significant radiation exposure.

For assessment of patients with neck pain who have neurological symptoms or signs, see Assessment of cervical radiculopathy and Cervical myelopathy.

Nonspecific neck pain

Nonspecific neck pain

Introduction

Introduction

In patients who present for care for a new episode of nonspecific neck pain, improvement is often rapid, irrespective of the cause of the episode, and over half of patients fully recover within 3 months. However, half to two-thirds of patients still report some pain and disability at 1 to 5 years, either in the form of recurrent acute episodes or chronic pain. The severity of pain and disability at onset are the only well-established prognostic factors for nonspecific neck pain.

Whiplash-associated disorder refers to nonspecific neck pain caused by an acceleration–deceleration force to the neck, usually from a motor vehicle collision. In whiplash-associated disorder, most symptom improvement occurs in the first 3 months and then symptoms plateau; about half of patients still experience some symptoms at 6 to 12 months. The main prognostic factor for whiplash-associated disorder is the severity of initial symptoms, including sensory, motor and psychological components. Evidence indicates that parameters related to the impact of the collision (eg direction of impact, seating position, awareness of impending collision, being stationary when hit) have no effect on outcome.

For assessment of patients with neck pain, see Assessment of neck pain. Imaging has no utility in patients with nonspecific neck pain, but may be considered if neurological symptoms or signs are present or a serious pathology is suspected clinically (see Table 12.19).

Acute nonspecific neck pain

Acute nonspecific neck pain
General management approach for acute nonspecific neck pain

As most patients with acute nonspecific neck pain improve rapidly, minimal intervention is required beyond patient education and reassurance of favourable prognosis. Oral analgesia may be required for pain relief (see Pharmacological management of acute nonspecific neck pain).

Patient education should include an explanation of the nature of the pain, and advice to stay active (see Lifestyle and nonpharmacological management of acute nonspecific neck pain). Reassure patients that a serious underlying cause for their pain is very unlikely and the outcome is generally favourable, although some patients experience persisting symptoms that can still be present at 6 to 12 months. Assess and address any misconceptions the patient may have about the nature of the pain, as well as fear-avoidance behaviour. Printed or online information that reinforces these messages is useful to supplement advice provided by the clinician [Note 1].

If there is **persisting pain** that is not improving by 4 to 6 weeks, reassess the patient for serious pathologies (see Table 12.19) including cervical myelopathy, as well as cervical radiculopathy and nonspinal causes of neck pain; see Assessment of neck pain. In patients with persisting nonspecific neck pain, it is important to identify and manage any psychosocial factors that may be contributing to the persistence of pain.

Note 1: Patient information on neck pain can be found on the painHEALTH website [URL]. Any management advice given on this website should be considered in the context of the recommendations in these guidelines.

Lifestyle and nonpharmacological management of acute nonspecific neck pain

Staying active: Encourage patients with acute nonspecific neck pain to stay active and to avoid protecting their neck from movement. Pacing of activities, and/or resuming usual activities and work in a graded manner may be required. Reassure patients that although some pain with activity is likely, this does not imply damage to the spine (ie ‘hurt does not mean harm’). Oral analgesia may be required to facilitate staying active (see Pharmacological management of acute nonspecific neck pain).

Reassure patients and encourage them to maintain usual activities.

Exercise: Neck exercises are commonly recommended for acute nonspecific neck pain; however, there are no trials evaluating their efficacy and most patients with acute nonspecific neck pain recover rapidly with

minimal intervention.

Passive physical treatments: Passive physical treatments alone have a limited role in the management of acute nonspecific neck pain, including in whiplash-associated disorder. Although the evidence to support their use is limited, some patients report temporary pain relief from thermotherapy (application of heat or cold), massage, spinal mobilisation and upper thoracic spine manipulation. A trial of these treatments may be considered as part of an overall management approach that includes patient education and re-introduction of physical activity (see General management approach for acute nonspecific neck pain).

Low-level laser therapy, transcutaneous electrical nerve stimulation (TENS) and cervical spine manipulation are not recommended for acute nonspecific neck pain because evidence does not support a benefit.

Evidence suggests that collars are ineffective for reducing pain or improving physical function for acute nonspecific neck pain, including in whiplash-associated disorder.
Pharmacological management of acute nonspecific neck pain

Ensure other components of acute nonspecific neck pain management, in particular patient education and reassurance (see General management approach for acute nonspecific neck pain), have been implemented before considering pharmacological management.

Explain to the patient that the goal of pharmacological management is to reduce, rather than abolish, pain so that physical function can be maintained. Oral analgesia can be useful to facilitate exercise and staying active, but advise patients that some pain with activity is likely and reassure them that this does not imply damage to the spine.

A trial of a nonsteroidal anti-inflammatory drug (NSAID) is recommended for short-term pain relief. Use:

an NSAID orally (see Table 12.7 for dosing). *neck pain*

The potential benefits of an NSAID should be weighed against its potential harms, particularly in patients at high risk of harms (see Principles of NSAID use for musculoskeletal conditions in adults for more information).

The efficacy of paracetamol in neck pain has not been studied in clinical trials. However, because of its favourable safety profile, a trial of paracetamol may be considered if NSAIDs are contraindicated or not tolerated. Use:

1 paracetamol 1 g orally, 4- to 6-hourly as necessary, up to a maximum of 4 g daily *neck pain*

OR

1 paracetamol modified-release 1.33 g orally, 8-hourly as necessary.

For patients with pain that persists throughout the day, or if there is inadequate response to ‘as necessary’ dosing, consider a trial of regular rather than ‘as necessary’ dosing of oral analgesia.

The efficacy of tricyclic antidepressants (TCAs) in neck pain has not been studied in clinical trials. A trial of a TCA may be considered if pain is not adequately relieved with other measures and is persisting beyond 2 to 3 weeks. TCAs may be particularly useful if pain is interfering with sleep. To reduce the risk of drowsiness during the day, start at a low dose and increase the dose slowly as tolerated and if needed; an example regimen is:

amitriptyline 10 to 25 mg orally, in the early evening; increasing the daily dose by up to 25 mg every 2 to 4 weeks as tolerated and according to response, up to a maximum maintenance dose of 50 mg each evening. *neck pain*

If drowsiness during the day is a concern, nortriptyline and doxepin are the preferred TCAs. TCAs should be used with care in older patients and in patients with cardiovascular disease.

Although commonly prescribed, opioids have a very limited role in the management of acute nonspecific neck pain. The efficacy of opioids in neck pain has not been studied in clinical trials and they are associated with a significant risk of harms. Opioids may be considered for patients with severe pain that is not adequately relieved with other measures and is interfering with their ability to function. If opioids are used, they should be prescribed on a short-term trial basis, as part of an overall pain management strategy, with clear goals and regular review of treatment response and adverse effects. Before starting an opioid, a plan for ceasing ineffective therapy should be in place and discussed with the patient. If treatment response is inadequate, caution should be exercised when increasing the dose of opioids as there is an increased risk of harm and potentially no added benefit. Prolonged use of opioids indicates the need for specialist assessment. See Opioids for more information.

Muscle relaxants are not recommended for acute nonspecific neck pain because there is only limited evidence to support their use, and their potential harms may outweigh any potential benefits. Drowsiness, dizziness, increased risk of falls and dependency are common adverse effects.

Chronic nonspecific neck pain

Chronic nonspecific neck pain
General management approach for chronic nonspecific neck pain

Chronic nonspecific neck pain has been poorly studied. Management should follow the same principles as for other types of noninflammatory chronic pain and should be based on an integrated biopsychosocial approach (see General principles of chronic pain management).

Exercise is recommended for all patients with chronic nonspecific neck pain (see Lifestyle and nonpharmacological management of chronic nonspecific neck pain). Exercise should be combined with education about the nature of the pain. Reassure the patient that although some pain with activity is likely, this does not imply damage to the spine (ie ‘hurt does not mean harm’).

Some patients with chronic nonspecific neck pain require ongoing oral analgesia (see Pharmacological management of chronic nonspecific neck pain).

Multidisciplinary rehabilitation programs may be considered for patients with chronic nonspecific neck pain. These programs aim to simultaneously address all components (physical, psychological and social) of the patient's pain experience. The key psychological intervention is cognitive behavioural therapy (CBT). There is moderate-quality evidence that CBT is better than other interventions for addressing fear of neck movement, but it may not provide other benefits. See Cognitive behavioural therapy for pain management for more information.

Evidence does not support a role for surgery in chronic nonspecific neck pain. For the specific indication of lateral atlanto-axial osteoarthritis, observational data suggest that posterior C1-C2 fusion may offer symptom relief if other measures have failed. Lateral atlanto-axial osteoarthritis is characterised by severe unilateral neck pain, often radiating into the suboccipital region, and severe unilateral movement restriction.

Lifestyle and nonpharmacological management of chronic nonspecific neck pain

Exercise: Exercise is a central component in the management of chronic nonspecific neck pain, but the optimal program and mode of exercise has not been defined. Generally, a program that includes stretching, strengthening and proprioceptive retraining exercises is recommended. Proprioceptive retraining involves slow neck movements following a moving target. Also consider postural education, postural exercises and ergonomic advice. It is also important to encourage a general exercise program including walking, gym or water-based exercise.

Collars and pillows: Wearing a soft collar during the day is not useful for chronic nonspecific neck pain. Using more than one pillow, unless for the management of other medical conditions, is generally not recommended. Patients who experience neck pain or stiffness on waking may benefit from having a supporting pillow, or a small towel rolled inside a pillowcase, placed under their neck, or from wearing a soft collar or a thick scarf to bed. However, none of these strategies has been evaluated in clinical trials.

Other passive physical treatments: Low-level laser therapy, intermittent traction and acupuncture may provide short-term pain relief for chronic nonspecific neck pain. There is only limited evidence of short-term benefits for manual therapies (eg spinal manipulation or mobilisation) in chronic nonspecific neck pain, and ongoing manual therapy is not recommended. These passive physical treatments should only be considered as part of an overall management approach (see General management approach for chronic nonspecific neck pain).

Ultrasound, infrared light and continuous traction are ineffective for chronic nonspecific neck pain.
Pharmacological management of chronic nonspecific neck pain

Some patients with chronic nonspecific neck pain require ongoing oral analgesia, depending on their degree of pain. Oral analgesia can be used to facilitate exercise, which is thought to be more effective in the longer-term control of pain. The drugs and doses used for oral analgesia are as for acute nonspecific neck pain (see Pharmacological management of acute nonspecific neck pain). Monitor treatment response and adverse effects, and periodically consider a trial of treatment cessation.

Injection and ablation therapies for chronic nonspecific neck pain

Various types of injections have been used to treat chronic nonspecific neck pain, including trigger point injections at sites of maximal tenderness with corticosteroid, botulinum toxin or dry needling; however, there is no evidence that these therapies provide definite benefit.

Injection and ablation techniques targeting putative structural causes of chronic neck pain, such as the cervical facet joints, are sometimes used. Pain relief from injection of local anaesthetic into the putatively painful joint(s), or from blocking their nerve supply via medial branch blocks, may identify the source of neck pain and provide the rationale for percutaneous radiofrequency denervation. The proponents of these techniques assert that meticulous identification of appropriate patients is required and that these techniques should only be undertaken by skilled treatment providers in specialist centres. Decisions to investigate chronic nonspecific neck pain for therapeutic purposes should be coordinated by specialists; current evidence does not justify widespread use of this approach.

Cervical radiculopathy

Cervical radiculopathy

Introduction

Introduction

Cervical radiculopathy is due to compression or irritation of nerve roots in the cervical spine. The C7 and C6 nerve roots are most frequently involved. Most cases of cervical radiculopathy are due to degenerative changes in the cervical spine and/or lateral disc herniation. Rare noncompressive causes include herpes zoster (shingles), malignancy, nerve root infarction and demyelination.

Cervical radiculopathy may be associated with spinal cord compromise, so careful neurological examination and appropriate imaging are required to exclude myelopathy (see Cervical myelopathy).

Cervical radiculopathy is more common in men than women, and the incidence peaks between 50 and 54 years of age. In general, cervical radiculopathy has a favourable prognosis, with most people starting to improve within 4 weeks and many recovered within 6 months.

Assessment of cervical radiculopathy

Assessment of cervical radiculopathy

Patients with cervical radiculopathy typically describe severe pain radiating from the neck down one arm, but pain may radiate down both arms. Pain is often accompanied by neurological symptoms or signs (eg

paraesthesia, numbness, weakness). Symptoms and signs may occur in a dermatomal distribution; however, this is often nonspecific because of the extensive overlap of dermatomes. A full neurological examination of the upper limbs should be undertaken. Reduced triceps reflex suggests C7 or C8 involvement while reduced biceps and brachioradialis reflexes suggest C5 or C6 involvement.

Several physical tests have been described for diagnosing cervical radiculopathy. These include the neck compression test (Spurling manoeuvre) and the shoulder abduction test. The neck compression test is performed by extending the neck and rotating it to the affected side, then applying downward pressure on the head. The result is positive if pain is provoked. This test has a high specificity, but a low sensitivity, for cervical radiculopathy. It should never be performed in patients with rheumatoid arthritis, suspected metastatic disease or myelopathy. The shoulder abduction test is performed by placing the palm of the affected arm on top of the head while seated. The result is positive if pain relief is obtained. This test has a low to moderate sensitivity, but a moderate to high specificity, for cervical radiculopathy.

Early imaging (before 6 to 8 weeks) is usually not required for cervical radiculopathy unless a serious pathology (see Table 12.19), including cervical myelopathy, is suspected clinically or there is a progressive neurological deficit or concern about a neurological deficit. Magnetic resonance imaging (MRI) is the preferred imaging modality.

Management of cervical radiculopathy

Management of cervical radiculopathy

If cervical myelopathy has been excluded, the management of cervical radiculopathy is similar to the management of acute nonspecific neck pain (see General management approach for acute nonspecific neck pain).

Wearing a semi-hard collar during the day combined with rest for 3 to 6 weeks, or a supervised graded exercise program combined with home exercises for 6 weeks, may be beneficial for acute symptoms (lasting less than 1 month). There is limited evidence that adding cervical traction to exercise is beneficial. Neither cervical spine manipulation nor foraminal nerve root injections are recommended because the risk of harms outweighs any potential benefits.

There is limited evidence that a short course of prednis(ol)one reduces pain and improves physical function in patients with cervical radiculopathy, although the optimal dosage and duration of treatment are not defined. An example dosage is:

prednis(ol)one 30 mg orally, daily for 5 to 10 days, then taper the dose over 1 to 3 weeks to stop. *cervical radiculopathy* _

Surgical consultation is indicated for all patients with a progressive neurological deficit, or for any patient if there is concern about a neurological deficit. Surgical consultation may be considered for patients with severe persisting arm pain at 6 to 8 weeks despite nonsurgical management, provided imaging identifies nerve root compression that is concordant with the patient's clinical features and could be corrected with surgery. Limited evidence from open trials comparing surgery to nonsurgical management suggests surgery results in better short-term outcomes; longer-term outcomes (up to 2 years) are similar.

Cervical myelopathy

Cervical myelopathy

Cervical myelopathy results from a midline disc herniation compressing the spinal cord in the cervical region. This condition occurs more commonly in the older age group. It requires surgical decompression to prevent progressive and permanent neurological damage; urgently refer patients with suspected cervical myelopathy for neurosurgical assessment.

Urgently refer patients with suspected cervical myelopathy for neurosurgical assessment.

Patients with cervical myelopathy present with difficulties walking and have long-tract signs on examination, including unsteady gait, loss of proprioception and a positive Romberg sign. Lhermitte phenomenon (paraesthesia occurring with neck flexion) may be present, but is not specific for myelopathy. Patients may also have weakness, hyperreflexia or hyporeflexia, upgoing plantar responses, and/or sensory loss with a sensory level. Imaging is required for cervical myelopathy; magnetic resonance imaging (MRI) is the preferred imaging modality.

Neck pain and rheumatoid arthritis

Neck pain and rheumatoid arthritis

Patients with rheumatoid arthritis can develop neck pain due to cervical spine involvement. This usually occurs in the context of longstanding disease, but rarely can occur as an early feature of rheumatoid arthritis. Cervical spine involvement may be associated with atlanto-axial instability, which is important to identify and manage. With the advent of more effective disease-modifying antirheumatic drugs (DMARDs), the prevalence of atlanto-axial instability is declining.

Atlanto-axial instability arises through erosive damage to the complex ligament and joint structures that link the atlas (C1) to the axis (C2). In severe cases, the odontoid peg, normally constrained against the inside of the ring of C1, moves backwards relative to C1 and compresses the upper spinal cord. Clinically, this is often preceded by upper neck pain, typically in the suboccipital region and often unilateral. Symptoms and signs of upper motor neurone deficits occur later and indicate the need for urgent neurosurgical assessment (see Cervical myelopathy). In patients with concurrent severe peripheral joint disease, detection of subtle neurological deficits, such as weakness and lower limb reflex changes, may be difficult.

Any clinical suspicion of atlanto-axial instability should prompt further investigation, including lateral plain X-ray of the cervical spine in flexion and extension. These investigations may reveal an increased distance in the atlanto-dens interval. Abnormalities on these investigations, or the presence of any neurological symptoms or signs, require further assessment with magnetic resonance imaging (MRI) or, if unavailable, computed tomography (CT). MRI or CT should be performed in a specialist centre, ideally with rheumatological and neurosurgical input.

Atlanto-axial instability is an absolute contraindication to cervical spine manipulation. Advise patients with known atlanto-axial instability to avoid excessive or uncontrolled movements of the neck (eg when having their hair washed at the hairdresser). Appropriate precautions should be taken in patients with atlanto-axial subluxation who are receiving general anaesthesia.

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Introduction to calcium pyrophosphate deposition

Introduction to calcium pyrophosphate deposition

Calcium pyrophosphate deposition is a disease of the older patient, with the mean age at presentation reported to be between 65 and 75 years.

Calcium pyrophosphate deposition occurs when excessive calcium pyrophosphate production results in local supersaturation and subsequent crystallisation. Deposition of calcium pyrophosphate dihydrate crystals occurs almost exclusively in the joints and is the most common cause of chondrocalcinosis (cartilage calcification).

Calcium pyrophosphate deposition is often asymptomatic, but can present clinically as:

- osteoarthritis with calcium pyrophosphate deposition
- acute calcium pyrophosphate crystal arthritis (formerly known as pseudogout), which is the most common cause of an acute monoarthritis in the older patient
- chronic calcium pyrophosphate crystal inflammatory arthritis (formerly known as pseudorheumatoid arthritis).

See Clinical presentations of calcium pyrophosphate deposition for further discussion.

Risk factors for calcium pyrophosphate deposition

Risk factors for calcium pyrophosphate deposition

The main risk factors for calcium pyrophosphate deposition are increasing age and the presence of osteoarthritis.

Other risk factors for calcium pyrophosphate deposition may include previous joint injury, primary hyperparathyroidism, haemochromatosis and hypomagnesaemia. Checking serum calcium, ferritin and magnesium concentrations may be considered, particularly in younger patients with calcium pyrophosphate deposition. Although correction of these risk factors may not affect the course of the joint disease, it is important to prevent other complications.

Loop diuretics, but not thiazide diuretics, appear to be associated with the development of acute calcium pyrophosphate crystal arthritis.

Evidence does not support familial aggregation for chondrocalcinosis, but family history could relate to earlier onset of clinical disease.

Clinical presentations of calcium pyrophosphate deposition

Clinical presentations of calcium pyrophosphate deposition

Acute calcium pyrophosphate crystal arthritis presents as an acutely inflamed joint, mimicking gout. The knee and the wrist are the most commonly affected sites, a point of difference from gout, but the disease may involve other joints and tendons. Acute attacks can be accompanied by fever and leucocytosis, mimicking septic arthritis.

A rare manifestation of acute calcium pyrophosphate crystal arthritis is the ‘crowned dens’ syndrome, which affects females more commonly than males. It presents as acute neck pain and stiffness, often accompanied by fever and elevated inflammatory markers. Typically, there is periodontoid ‘crown-like’ calcification above the dens. This can be observed on coronal views on cervical computed tomography (CT) scan, but is not typically visible on plain X-rays.

Acute calcium pyrophosphate crystal arthritis may also present as pseudoneuropathic joint disease, with severe destruction resembling a Charcot joint.

Chronic calcium pyrophosphate crystal inflammatory arthritis refers to the occasional presentation of chronic oligoarthritis or polyarthritis with inflammatory features, and superimposed flares. It may involve the knees, second and third metacarpophalangeal joints, wrists, shoulders, elbows, hips and midtarsal joints. Chronic calcium pyrophosphate crystal inflammatory arthritis should be considered in the differential diagnosis of rheumatoid arthritis in older adults.

Osteoarthritis with calcium pyrophosphate deposition may be distinguished from osteoarthritis without calcium pyrophosphate deposition by the presence of more osteophytes, the involvement of different joints, and more inflammatory features.

Diagnosis of calcium pyrophosphate deposition

Diagnosis of calcium pyrophosphate deposition

A definitive diagnosis of calcium pyrophosphate deposition is made by identifying calcium pyrophosphate dihydrate crystals in synovial fluid (see Joint aspiration in adults). The synovial fluid may contain both monosodium urate and calcium pyrophosphate dihydrate crystals—if identified, seek specialist advice. Microscopy and culture of the synovial fluid should also be undertaken to exclude septic arthritis.

While the presence of chondrocalcinosis supports the diagnosis of calcium pyrophosphate deposition, it is neither highly sensitive nor specific. Furthermore, the finding of chondrocalcinosis on X-ray does not necessarily indicate the presence of clinical disease; it may be asymptomatic without need of management. The incidence of chondrocalcinosis increases with age: from 65 to 74 years the incidence is 15%, from 75 to 84 years it is 36%, and after the age of 84 years it is almost 50%. Chondrocalcinosis most commonly affects fibrocartilage (particularly the knee and triangular cartilage of the wrist) but may also occur in hyaline cartilage (mainly knee and glenohumeral joints) as linear opacities separate from, and often parallel to, subchondral bone. The location of the chondrocalcinosis is important for determining its relevance to clinical disease. For example, chondrocalcinosis involving the triangular cartilage of the wrist is much more likely to be associated with clinical disease than chondrocalcinosis involving the knee.

Ultrasound has promising utility in the diagnosis of calcium pyrophosphate deposition; it may be useful to detect hyperechoic lesions in hyaline and fibrous cartilage, tendons, bursa and/or joints, but further study is needed before it can be recommended.

Management of calcium pyrophosphate deposition

Management of calcium pyrophosphate deposition

There is a lack of evidence to guide the optimal management of acute calcium pyrophosphate crystal arthritis and current management recommendations are based on extrapolating the evidence from treatment of acute gout. As patients with acute calcium pyrophosphate crystal arthritis are often older and more likely to have age-related comorbidities (eg chronic kidney disease), intra-articular corticosteroid injection may be the safest treatment option (after excluding septic arthritis). Other treatment options include nonsteroidal anti-inflammatory drugs (NSAIDs), systemic corticosteroids and colchicine; see Management of acute gout for principles of drug use and dosing.

Currently, no treatment has been demonstrated to prevent or slow calcium pyrophosphate crystal deposition, prevent recurrent acute attacks or treat chronic disease. However, treatment options that may be trialled

include NSAIDs, colchicine and hydroxychloroquine.

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Introduction to assessing musculoskeletal symptoms in children and adolescents

Introduction to assessing musculoskeletal symptoms in children and adolescents

Musculoskeletal symptoms are common in children and adolescents. In the majority of cases, they are noninflammatory in nature and management is centred on providing reassurance and education regarding their cause (see Noninflammatory musculoskeletal pain in children and adolescents). The challenge for general practitioners is to distinguish between noninflammatory conditions and a systemic inflammatory disease or other serious pathology (eg malignancy, infection, fracture). See Pattern of musculoskeletal involvement for general advice on distinguishing between inflammatory and noninflammatory symptoms; additional detail on making this distinction in children and adolescents is included in history, examination and investigations.

Inflammatory rheumatological diseases in children and adolescents include:

- juvenile idiopathic arthritis (JIA), including enthesitis-related arthritis and psoriatic arthritis
- connective tissue diseases, such as juvenile dermatomyositis and systemic lupus erythematosus (SLE)
- systemic vasculitides and other inflammatory syndromes, such as immunoglobulin A vasculitis (formerly known as Henoch–Schönlein purpura), Kawasaki disease, periodic fever syndromes and acute rheumatic fever.

Accurate diagnosis is aided by careful attention to particular features on history and examination, and judicious subsequent investigations, if necessary. Early diagnosis and prompt treatment may avert or minimise permanent joint damage and disability, and are crucial if a significant pathology is suggested.

Assessing musculoskeletal symptoms in children and adolescents: history

Assessing musculoskeletal symptoms in children and adolescents: history

A thorough history can help determine whether the problem is **articular** or **nonarticular** in origin; **inflammatory** or **noninflammatory** in nature; **acute** (days to weeks) or **chronic** (months); **oligoarticular** (up to 4 joints) or **polyarticular** (more than 4 joints) and/or **axial** (spinal and sacroiliac joints). In children and adolescents with musculoskeletal symptoms, important aspects of history include:

- site of pain—articular pain is common in juvenile idiopathic arthritis (JIA), while nonarticular pain may occur in a wide range of conditions, including pain amplification syndromes, fracture and malignancy
- duration of symptoms—in a child or adolescent with arthritis, longstanding symptoms are more likely to be due to JIA than acute symptoms. Acute symptoms are more likely to be caused by reactive arthritis, subacute osteomyelitis with joint involvement, or septic arthritis
- variation in symptoms over the day—stiffness after inactivity (especially in the morning) suggests an inflammatory pathology, whereas pain after activity suggests a noninflammatory cause. In toddlers, morning stiffness may manifest as wanting to be carried on waking or crying with morning nappy changes
- degree of interference with daily activities—symptoms that interfere with daily activities strongly suggest a significant underlying pathology. Such interference may manifest as withdrawal from play, sporting or hobby activities; apparent loss of motor skills (eg a toddler stopping walking); or absence from school

- change in pattern of sleep—night pain that wakes the child suggests a serious underlying pathology
- presence of systemic features—fever, malaise, fatigue, weight loss, skin rash or persistent diarrhoea are alerting features of a systemic pathology
- recent history of infection or antibiotic use—reactive arthritis is a differential diagnosis
- history of infectious contacts—a history of tuberculosis infection or environmental exposure may be relevant in a child or adolescent with arthritis in a single joint; tuberculous arthritis is a differential diagnosis
- family history of rheumatological disease—particularly relevant with the spondyloarthritides, but may also be a clue to pain 'role models' in pain amplification syndromes.

Assessing musculoskeletal symptoms in children and adolescents: examination

Assessing musculoskeletal symptoms in children and adolescents: examination

In combination with a thorough history, a comprehensive examination can help determine the origin, nature, duration and distribution of musculoskeletal symptoms. In children and adolescents with musculoskeletal symptoms, important aspects of examination include:

- examination of joints for swelling or, in the absence of swelling, two of the following:
    - pain at the extremes of joint range of movement ('stress pain')
    - loss of range of motion
    - joint-line tenderness.

  These are the cardinal clinical features of an inflammatory arthritis and their absence excludes inflammatory joint disease as the basis for joint symptoms. Joints affected by inflammatory arthritis may not always be symptomatic, so it is important to examine all joints
- detection of signs of chronicity—localised muscle wasting, leg length inequality or fixed flexion deformity suggest longstanding joint inflammation
- detection of extra-articular features—specific patterns of extra-articular features are associated with some inflammatory rheumatological diseases; for example, psoriatic rash and nail pitting with psoriatic arthritis; synechiae secondary to uveitis with juvenile idiopathic arthritis (JIA), particularly the oligoarticular form; pallor, mouth ulcers, rash, alopecia or muscle weakness with connective tissue diseases
- examination of growth parameters such as weight, height and body mass index (considered in the context of pubertal status)—significant deviations from normal percentiles are an alerting feature of a systemic pathology
- elicitation of features suggestive of a pain amplification syndrome—multiple tender points, extreme hyperaesthesia and bizarre gait patterns are characteristic of a pain amplification syndrome.

Assessing musculoskeletal symptoms in children and adolescents: investigations

Assessing musculoskeletal symptoms in children and adolescents: investigations

Only a limited number of rheumatological conditions can be confirmed definitively by a specific investigation. In most instances, investigations can be corroborative; however, they can also be misleading if used out of context. Importantly, pathology testing or imaging should only be undertaken in patients with signs or symptoms suggestive of a specific diagnosis.

Useful investigations in the assessment of children and adolescents with a suspected inflammatory rheumatological disease include:

- erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP) concentration, full blood count (FBC)—elevation of the acute phase reactants CRP and ESR can help confirm inflammation; however, it is possible to have an inflammatory rheumatological disease without abnormalities in these tests.

FBC may identify differential diagnoses such as leukaemia (suggested by the presence of peripheral blasts or cytopenias). An elevated white cell count suggests infection rather than inflammation
- tests for evidence of preceding streptococcal infection, such as antistreptolysin-O titre (ASOT)—indicated in children or adolescents with migratory polyarthritis, in whom rheumatic fever is a possible diagnosis (see Acute rheumatic fever for more information on diagnosis)
- serum ferritin concentration—often markedly elevated (greater than 1000 micrograms/L) in systemic arthritis, out of proportion to its role as an acute phase reactant
- other biochemical assessments (eg muscle enzyme levels, liver biochemistry, kidney function tests) and/or serological testing for connective tissue disease (eg antinuclear antibodies [ANA], antibodies to double-stranded DNA [dsDNA], antibodies to extractable nuclear antigens [ENA])—indicated if there are features of multisystem disease on history or examination
- urinalysis—checking for proteinuria and/or haematuria is useful for evaluating possible vasculitis or connective tissue disease; checking for sterile pyuria is useful for evaluating possible reactive arthritis
- plain X-ray—may be indicated for conditions where bone changes are expected (eg fracture, the osteochondritides [including Perthes disease], osteomyelitis, tarsal coalition), but is usually not helpful in the initial assessment of a synovitis
- ultrasound—can be useful for differentiating tendon sheath from joint inflammation and also in synovitis of the hip
- radionuclide bone scan and magnetic resonance imaging (MRI)—may be indicated in specific situations, particularly in differentiating the mimics of juvenile idiopathic arthritis (JIA) and/or bone inflammation
- synovial fluid aspiration—detection of a microbial pathogen on nucleic acid amplification testing (NAAT) (eg polymerase chain reaction [PCR]) or culture of synovial fluid is diagnostic of infection, and synovial fluid aspiration should be performed in children or adolescents with suspected septic arthritis as part of acute management in hospital. Local or general anaesthesia may be required, depending on the affected joint and the patient's age. Crystal deposition disease is extremely rare in childhood; therefore, aspiration for microscopy alone is not usually helpful in the differential diagnosis of an inflammatory arthritis in children.

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- McGhee JL, Kickingbird LM, Jarvis JN. Clinical utility of antinuclear antibody tests in children. BMC Pediatr 2004;4:13. www.ncbi.nlm.nih.gov/pubmed/15245579

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Introduction to immunomodulatory drug use for rheumatological diseases in adults

Introduction to immunomodulatory drug use for rheumatological diseases in adults

The goal of immunomodulatory therapy in inflammatory rheumatological diseases is sustained remission; cure is usually not possible and patients generally require ongoing immunomodulatory therapy. The immunomodulatory drugs used in rheumatology are systemic corticosteroids, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), biological disease-modifying antirheumatic drugs (bDMARDs) and targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs). Regular monitoring of disease activity and adjustment of immunomodulatory therapy is required to achieve disease targets; where appropriate, specific advice is included in the clinical topics.

The management of patients with inflammatory rheumatological disease is complex and an integrated multidisciplinary approach is often required. The general practitioner can support the interventions of the rheumatologist (eg by monitoring adherence and managing residual symptoms), as well as proactively prevent, screen for and manage comorbidities (eg cardiovascular disease, depression) and adverse effects (eg infections) associated with inflammatory rheumatological disease and its treatment.

When an immunomodulatory drug is prescribed, the patient or the patient's carer should be provided with information about the goals of treatment, potential adverse effects and how to minimise them, screening requirements before and during treatment, and the importance of monitoring. This topic includes practical information on using these drugs for rheumatological diseases in adults. For comprehensive drug information, including precautions, contraindications, adverse effects and drug interactions, consult an appropriate drug information resource. Patient medicine information sheets for many of the drugs used in rheumatology can be accessed from the Australian Rheumatology Association website [URL].

General approach to immunomodulatory drug use for rheumatological diseases in adults

General approach to immunomodulatory drug use for rheumatological diseases in adults

Untreated active systemic inflammatory disease is associated with an increased risk of infection, as is treatment with immunomodulatory therapy. The relative risk of infection varies between individual immunomodulatory drugs and is greatest in patients treated with high-dose corticosteroids, biological disease-modifying antirheumatic drugs (bDMARDs), targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs) and combination therapy. Clinicians must always be alert to the possibility of infection (including opportunistic infection), particularly because the usual symptoms and signs of infection (eg fever) are often absent in patients treated with immunomodulatory drugs. If a patient develops symptoms or signs of infection, withhold disease-modifying antirheumatic drug (DMARD) therapy until a thorough assessment is completed. The DMARD is usually restarted once the infection has resolved. In contrast, corticosteroids should not be withheld, even if infection is confirmed. If the patient has severe infection and hypothalamic–pituitary–adrenal axis suppression, the corticosteroid dose may need to be increased; see Glucocorticoid-induced hyperglycaemia. Discuss any serious infection with the treating specialist.

DMARD therapy should be withheld in patients who are acutely unwell (eg dehydration, renal impairment) and specialist advice should be sought.

Considerations before starting immunomodulatory therapy

Considerations before starting immunomodulatory therapy

Before starting immunomodulatory therapy, it is important to:

- screen the patient for active infection (see Screening for infection and vaccination for further details)
- check for history of tuberculosis infection and environmental exposure (see Screening for infection and vaccination for details on tuberculosis testing and treatment)
- assess vaccination status (see Screening for infection and vaccination for further details)
- assess the patient's serology and, as appropriate, consider vaccination, treatment or prophylaxis (see Screening for infection and vaccination for recommendations)
- perform investigations to determine kidney, liver and bone marrow function, as well as chest X-ray. The results of these investigations may influence the choice of immunomodulatory drug and its dosing regimen, and provide a baseline measurement against which future results can be compared
- check for history of malignancy, including melanoma [Note 1]
- discuss reproductive health, including contraception, with patients of childbearing potential (see also Immunomodulatory drug use and reproductive health)
- perform a medication review and, if necessary, consult an appropriate drug interactions resource
- determine the frequency of monitoring required, and communicate this to the patient and other healthcare practitioners involved in their care. The specialist will determine the appropriate monitoring regimen based on the adverse effect profile of the immunomodulatory drug(s) used and patient factors (eg disease activity, comorbidities). Monitoring is most frequent in the first 3 to 6 months of therapy and after dose increases because adverse effects are more likely. Once the patient's drug regimen and disease activity are stable, the frequency of monitoring can be reduced, but should not stop completely.

For further detail, see systemic corticosteroids (Table 12.3), conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) (Table 12.4), biological disease-modifying antirheumatic drugs (bDMARDs) (Table 12.5) and targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs) (Table 12.6).

Note 1: Data on the risk of malignancy with immunomodulatory therapy are conflicting and incomplete. While malignancy risk is known to be drug specific, the particular risk posed by individual immunomodulatory drugs has not been elucidated. For example, Australian data suggest an increased risk of melanoma in patients with rheumatoid arthritis treated with methotrexate. However, it is not clear whether the increased risk relates to treatment with methotrexate or the disease process, and international studies have not replicated these findings. The choice of immunomodulatory drug in a patient with a history of malignancy requires shared decision-making between the patient and their specialists, and should be informed by the benefit–harm profile of the treatment options in the individual patient.

Considerations throughout immunomodulatory therapy

Considerations throughout immunomodulatory therapy

When reviewing the patient after immunomodulatory therapy has started, it is important to:

- ask about adherence to immunomodulatory therapy
- assess disease activity to determine whether the immunomodulatory therapy is effective—where appropriate, advice on specific disease targets is included in the clinical topics; the general practitioner should refer the patient back to the rheumatologist if these targets are not met
- assess for adverse effects
- monitor kidney, liver and bone marrow function according to the schedule determined. This is not required for patients treated with corticosteroid or hydroxychloroquine monotherapy
- ensure that vaccinations remain up to date (see Screening for infection and vaccination)
- assess patients who present with fever, cough, systemic symptoms or unexplained illness for opportunistic infection, including tuberculosis or fungal infection
- continue to screen for and optimise the management of osteoporosis, residual pain and other common comorbidities (eg cardiovascular disease, diabetes, depression)

- maintain vigilance for malignancy and ensure that malignancy screening that is appropriate for the patient's age and gender remains up to date; this might include skin checks every 6 to 12 months (depending on skin type and sun exposure) to detect early skin cancer. Encourage patients to monitor their skin for new or changing lesions. If malignancy is detected, immunomodulatory therapy may need to be interrupted—seek specialist advice
- for patients planning travel, refer to an infectious diseases or travel medicine specialist for travel advice (vaccination, prevention and treatment of infection).

For further detail, see systemic corticosteroids (Table 12.3), conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) (Table 12.4), biological disease-modifying antirheumatic drugs (bDMARDs) (Table 12.5) and targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs) (Table 12.6).

Screening for infection and vaccination in adults with rheumatological diseases

Screening for infection and vaccination in adults with rheumatological diseases

The optimal approach to screening, vaccination and antimicrobial prophylaxis to minimise the risk of infection in patients with inflammatory rheumatological diseases is not known; the following recommendations offer a practical approach based on expert consensus. For guidance on when to give antimicrobial prophylaxis (eg *Pneumocystis jirovecii* pneumonia [PJP] prophylaxis) for patients taking corticosteroids or immunomodulatory drugs, see Assessing the need for antimicrobial prophylaxis in immunocompromised adults without HIV infection.

Screen patients for infection before starting immunomodulatory therapy. Take a detailed infection history, considering potential bacterial (including latent or active tuberculosis), fungal, viral (including herpes simplex, varicella-zoster, hepatitis B and C, and HIV), and parasitic infections. Consider the environmental risk of tuberculosis (eg contact with tuberculosis patients, at-risk country of origin, prolonged stay in or plans to travel to an endemic area) or other infections (eg history of prolonged stay in or plans to travel to the tropics or areas where Strongyloides stercoralis or Burkholderia pseudomallei are endemic). Perform a thorough physical examination, looking for signs of active infection. Treat any active infection identified before starting immunomodulatory therapy. In patients treated with immunomodulatory therapy, clinicians should remain alert to the possibility of infection (including opportunistic infection)—see General approach to immunomodulatory drug use for advice on managing immunomodulatory therapy in patients who develop infection.

Assess the patient's **vaccination history** (including Bacille Calmette-Guérin [BCG]) and **serology**. In particular, perform hepatitis B and C virus serology in all patients [Note 2] ; perform HIV serology if the patient's history suggests they are at risk of HIV infection; and consider varicella-zoster serology, particularly in patients planned for treatment with tofacitinib.

Perform a tuberculin skin test (Mantoux) or tuberculosis-specific interferon gamma release assay (IGRA) for all patients who are likely to be treated with a biological disease-modifying antirheumatic drug (bDMARD) or targeted synthetic disease-modifying antirheumatic drug (tsDMARD) (with the exception of apremilast) [Note 3] .

Patients with latent **tuberculosis** (TB) are at increased risk of reactivated infection when they are treated with immunomodulatory drugs. For patients found to have latent TB infection, seek expert advice. Similarly, patients with **hepatitis B** are at increased risk of reactivated infection when they are treated with immunomodulatory drugs. For information about hepatitis B prophylaxis in patients taking immunomodulatory drugs, see Hepatitis B and patients undergoing cancer chemotherapy or immunosuppression.

To minimise the risk of **vaccine-preventable infections**, ensure all patients with inflammatory rheumatological disease are kept up to date with recommended vaccines (including influenza and pneumococcal vaccines) [Note 4] . If vaccination is necessary, it is ideally performed before starting

immunomodulatory therapy because the safety of live vaccines, and immunological response to both live and inactivated vaccines, may be reduced in immunosuppressed patients. However, if immediate treatment of rheumatological disease is required, immunomodulatory therapy should not be delayed so that vaccination can be completed. Nor should inactivated vaccines be withheld after immunomodulatory (including bDMARD) therapy is started, even though immunological response may be reduced. If there is uncertainty about the level of immunosuppression or when vaccine administration may be safe, seek specialist advice.

The patient's risk of exposure to vaccine-preventable infections can be further reduced by ensuring their household contacts are kept up to date with recommended vaccines.

Live vaccines (measles, mumps, rubella, varicella, zoster, yellow fever, Japanese encephalitis, Bacille Calmette-Guérin [BCG], oral typhoid) should not be given to patients already taking an immunomodulatory drug; they should be given at least 4 weeks before starting therapy to minimise the risk of adverse effects and vaccine-related disease. The exceptions are varicella and zoster vaccines, which can be given to patients treated with low-level immunosuppression but should not be administered to highly immunosuppressed patients [Note 5] [Note 6] .

Inactivated vaccines should ideally be given at least 2 weeks before starting immunomodulatory therapy for maximal immunogenicity. When inactivated vaccines are given to patients treated with immunomodulatory therapy, larger or repeat doses are sometimes required. Alternatively, revaccination can be considered (usually after 3 months) for patients who have achieved only a low antibody titre—seek specialist advice.

COVID -19 vaccination is recommended for people taking immunomodulatory drugs despite this population not being assessed in vaccine clinical trials. It is not usually necessary to interrupt immunomodulatory drug therapy for COVID-19 vaccination. However, consideration must be given to the timing of vaccination in relation to treatment with some drugs (eg abatacept, rituximab). For further detail, including advice on the use of specific immunomodulatory drugs at the time of vaccination and preferred vaccine(s) for individual patients, see An Australian Living Guideline for the Pharmacological Management of Inflammatory Arthritis and the accompanying Australian clinician guide for the use of immunomodulatory drugs in autoimmune rheumatic diseases at the time of COVID-19 vaccination.

Also see 'Vaccination for people who are immunocompromised' in the *Australian Immunisation Handbook* [URL].

For detailed advice about vaccination of patients with inflammatory rheumatological diseases, see the Australian recommendations [Note 7].

For patients planning travel, refer to an infectious diseases or travel medicine specialist for travel advice (vaccination, prevention and treatment of infection).

Note 2: Detailed information about testing for hepatitis B virus is provided in the National HBV testing policy [URL].

Note 3: False-negative results can occur in patients who have an acute systemic illness or are immunosuppressed. If the patient has risk factors for latent tuberculosis infection or there is clinical suspicion of tuberculosis, consider repeating the screening test after 1 to 3 weeks.

Note 4: For recommended vaccinations, see the *Australian Immunisation Handbook* [URL].

Note 5: Low-level immunosuppression is defined as prednis(ol)one less than 20 mg/day or equivalent; methotrexate up to 0.4 mg/kg/week; azathioprine up to 3 mg/kg/day.

Note 6: See the *Australian Immunisation Handbook* [URL] for recommendations for the use of varicella and zoster vaccines. For seronegative patients without reliable history of chickenpox or shingles, give varicella vaccine; for seropositive patients, consider zoster vaccine.

Note 7: Wong PKK, Bagga H, Barrett C, Hanrahan P, Johnson D, Katrib A, et al. A practical approach to vaccination of patients with autoimmune inflammatory rheumatic diseases in Australia. Internal Medicine Journal 2017;47(5):491-500. [URL]

Immunomodulatory drug use and reproductive health in adults with rheumatological diseases

Immunomodulatory drug use and reproductive health in adults with rheumatological diseases

The choice of immunomodulatory therapy in patients of childbearing potential needs to be carefully considered—seek specialist advice. For many immunomodulatory drugs there is a paucity of data to inform treatment decisions. Collaborative decision-making involving the patient, rheumatologist, general practitioner and, as necessary, other specialists (eg obstetric drug information service providers [Note 8]) is crucial.

When immunomodulatory therapy is initiated in **men or women of childbearing potential**, consider the effect of the drug on long-term fertility (such as premature gonadal failure with cyclophosphamide), as well as the need for effective contraception (such as when a teratogenic drug is used).

In **men and women who are planning pregnancy**, choice of therapy should take into account the impact of the drug on fertility. In women who are planning pregnancy or pregnant, choice of therapy should also take into account the safety of the drug in pregnancy, as well as the need to implement measures that may reduce the risk of harms (such as folic acid supplementation for patients treated with sulfasalazine or therapeutic drug monitoring for patients treated with ciclosporin). The risks of immunomodulatory therapy to the fetus or infant must be balanced against the risks associated with poor disease control if therapy is discontinued. Ideally, these factors should be considered before pregnancy is planned, to ensure that drug therapy can be continued throughout the perinatal period.

For **women who are breastfeeding**, consideration should be given to the compatibility of the drug with breastfeeding. Ideally, this should be considered before pregnancy is planned, to ensure that therapy can be continued throughout the perinatal period.

There are some data to suggest that the following drugs may, with appropriate precautions, be safely used in pregnancy: azathioprine, ciclosporin, hydroxychloroquine, prednis(ol)one, sulfasalazine and tumour necrosis factor (TNF) inhibitors. Specific information on the use of these and other immunomodulatory drugs in patients of childbearing potential (including males) or pregnant or breastfeeding women, is available from the Australian Rheumatology Association [URL]. Guidelines are also available from the British Society for Rheumatology and British Health Professionals in Rheumatology [Note 9]. Breastfeeding compatibility recommendations and the Australian Therapeutic Goods Administration (TGA) pregnancy categorisation for individual drugs are accessible through the icons in drug recommendations. However, note that it is not intended that the TGA pregnancy category would be the sole basis of decision-making in the use of a drug during pregnancy, in part because it does not provide information about the balance of harms and benefits in a particular patient. Furthermore, the category does not indicate the stage(s) of fetal development that might be affected by drug exposure and may not reflect the most up-to-date information about the drug's use in pregnancy.

Note 8: Contact details for obstetric drug information services available to health professionals and/or consumers in each Australian state (except Tasmania) are available from the TGA website [URL].

Note 9: Flint J, Panchal S, Hurrell A, van de Venne M, Gayed M, Schreiber K, et al. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. Rheumatology (Oxford) 2016; 55(9):1693-7. [URL]

Perioperative use of immunomodulatory drugs in adults with rheumatological diseases

Perioperative use of immunomodulatory drugs in adults with rheumatological diseases

When deciding whether to continue immunomodulatory therapy perioperatively, the potential consequences of postoperative infection should be weighed against the potential consequences of a perioperative flare in disease activity—seek specialist advice.

Seek specialist advice about the use of immunomodulatory drugs during the perioperative period.

Systemic corticosteroids must be continued perioperatively. Consider the need for higher doses if there is a risk of hypothalamic–pituitary–adrenal axis suppression (see Glucocorticoid-induced hyperglycaemia).

Most conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) can be safely continued perioperatively. However, cyclophosphamide should not be continued in patients having elective surgery. Experience at a single centre suggests that leflunomide increases the risk of early postoperative infections and wound-healing complications. This risk should be carefully weighed against the risk of disease flare if treatment is discontinued.

If disease-modifying antirheumatic drug (DMARD) therapy—such as a biological disease-modifying antirheumatic drug (bDMARD) or a targeted synthetic disease-modifying antirheumatic drug (tsDMARD)—is to be withheld, consider stopping it 3 to 5 half-lives before planned surgery. Confirm there is no postoperative infection and good wound healing has occurred before restarting therapy.

Immunomodulatory drug–specific considerations in adults with rheumatological diseases

Immunomodulatory drug–specific considerations in adults with rheumatological diseases

Classes of disease-modifying antirheumatic drugs (DMARDs) are summarised in Table 12.2.

Table 12.2 Classification of disease-modifying antirheumatic drugs (DMARDs)

Drug class	Drugs
conventional synthetic disease-modifying antirheumatic drugs (csDMARDs)	azathioprine, cyclophosphamide, ciclosporin, hydroxychloroquine, leflunomide, methotrexate, mycophenolate, sulfasalazine
biological disease-modifying antirheumatic drugs (bDMARDs)	abatacept, adalimumab, anakinra, belimumab, canakinumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, secukinumab, tocilizumab, ustekinumab
targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs)	apremilast, tofacitinib

The following tables give practical information on using systemic corticosteroids (see Table 12.3) and DMARDs (see Table 12.4 for csDMARDs, Table 12.5 for bDMARDs and Table 12.6 for tsDMARDs) to treat rheumatological diseases in adults; they do not provide comprehensive drug information. Prescribers should consider the balance of harms and benefits of each drug in an individual patient, taking into account adverse effects, precautions and contraindications, and possible drug interactions. For patients treated with combination therapy, refer to the considerations relevant to each drug. For guidance on when to give antimicrobial prophylaxis (eg Pneumocystis jirovecii pneumonia [PJP] prophylaxis) for patients taking corticosteroids or immunomodulatory drugs, see Assessing the need for antimicrobial prophylaxis in immunocompromised adults without HIV infection.

Table 12.3 Systemic corticosteroids in rheumatology: considerations for use

[NB1]

Before starting therapy:

- follow the recommendations in Considerations before starting immunomodulatory therapy

- identify comorbidities that might be exacerbated by corticosteroid therapy (eg diabetes, cardiovascular disease and its risk factors, depression, osteoporosis) and implement a plan for management and monitoring
- evaluate bone health and implement strategies to minimise bone density loss (see Preventing osteoporosis)

Throughout therapy:

- implement the recommendations in Considerations throughout immunomodulatory therapy; however, routine blood tests are not recommended with the exception of those needed to monitor the patient's disease
- regularly review corticosteroid therapy; to minimise adverse effects use the lowest dose and shortest treatment duration required to achieve treatment goals
- consider hypothalamic–pituitary–adrenal axis suppression (see Glucocorticoid-induced hyperglycaemia)
- in patients who are predisposed to diabetes or are treated with high doses or prolonged courses of systemic corticosteroids, monitor blood glucose concentrations (see Glucocorticoid-induced hyperglycaemia)
- monitor and actively manage risk factors for cardiovascular disease, especially with prolonged courses of corticosteroids at daily doses equivalent to 7.5 mg or more of prednis(ol)one (see Cardiovascular disease risk stratification)
- assess the need for antimicrobial prophylaxis in patients planned for treatment with high doses of corticosteroids (20 mg or more per day of prednis(ol)one [or equivalent]) for more than 2 weeks. For details, see Patients taking corticosteroid therapy

Other considerations:

- the systemic corticosteroids used in rheumatology are chosen for their anti-inflammatory (glucocorticoid) effects; equivalent dosages and duration of effect of glucocorticoids are given in Approximate relative potency and duration of effect of glucocorticoids
- the rate at which corticosteroids can be tapered depends on the starting dose and duration of corticosteroid use (which influences the risk of adrenal suppression) and the patient's risk of disease flare

NB1: Systemic corticosteroids commonly used in rheumatology are prednis(ol)one and methylprednisolone.

Table 12.4 Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) in rheumatology: considerations for use

- azathioprine, mercaptopurine, tioguanine
- cyclophosphamide
- ciclosporin
- hydroxychloroquine
- leflunomide
- methotrexate
- mycophenolate
- sulfasalazine

azathioprine, mercaptopurine, tioguanine

Before starting therapy:

- follow the recommendations in Considerations before starting immunomodulatory therapy
- perform TPMT genotype testing, because 1 in 300 individuals have a homozygous genetic mutation causing negligible enzyme activity. In these patients, severe myelosuppression occurs if the dose is not significantly reduced (eg giving 10% of the usual dose or increasing the dosing interval to 3 times weekly) [NB2]

Throughout therapy [NB1]:

- implement the recommendations in Considerations throughout immunomodulatory therapy
- check full blood count every 2 weeks during dose escalation, then every 4 to 6 weeks once a stable dose is achieved

Other considerations:

- during the first few weeks of therapy, azathioprine may cause hypersensitivity reactions that can be mistaken for a flare in the underlying illness

cyclophosphamide

Before starting therapy:

- follow the recommendations in Considerations before starting immunomodulatory therapy
- consider referral to a reproductive specialist to discuss fertility preservation
- perform urinalysis
- advise patients treated with oral cyclophosphamide to take their dose in the morning to reduce the risk of bladder toxicity
- advise all patients (while being treated with oral or intravenous cyclophosphamide) to maintain a fluid intake of 3 litres of water per day and report haematuria or dysuria

Throughout therapy [NB1]:

- implement the recommendations in Considerations throughout immunomodulatory therapy
- assess the need for antimicrobial prophylaxis—see Patients taking cyclophosphamide for a nonmalignant condition
- perform monthly urinalysis to check for haematuria and refer for cystoscopy if haemorrhagic cystitis is suspected [NB3]
- check kidney, liver and bone marrow function every 2 weeks for the first 3 months of treatment, then check monthly thereafter. Implement more frequent monitoring of bone marrow function if there is evidence of bone marrow toxicity and consider withholding the dose

Other considerations:

- perform yearly urinalysis, including urine cytology, once cyclophosphamide therapy has stopped to check for evidence of premalignant or malignant changes
- when possible, avoid use in patients of childbearing potential

ciclosporin

Before starting therapy:

- follow the recommendations in Considerations before starting immunomodulatory therapy
- measure kidney function, blood pressure, blood glucose concentration and fasting lipid levels

Throughout therapy [NB1]:

- implement the recommendations in Considerations throughout immunomodulatory therapy
- regularly assess kidney function, fasting lipid levels and blood pressure

Other considerations:

- acute kidney impairment associated with ciclosporin treatment is generally reversible if the dose is reduced or treatment stopped; however, chronic kidney impairment associated with long-term ciclosporin treatment is potentially irreversible
- plasma ciclosporin concentration monitoring is generally not performed when ciclosporin is used to treat rheumatological disease. However, ciclosporin has a narrow therapeutic index and plasma concentration monitoring may be useful; particularly if high doses are used, toxicity is suspected, or there is inadequate response (eg to rule out absorption problems and nonadherence)

hydroxychloroquine

Before starting therapy:

- follow the recommendations in Considerations before starting immunomodulatory therapy
- check for known history of G6PD deficiency. An alternative drug may be required in patients with G6PD deficiency
- perform baseline ophthalmological review (within 12 months of starting treatment)

Throughout therapy [NB1]:

- implement the recommendations in Considerations throughout immunomodulatory therapy; however, routine blood tests are not recommended with the exception of those needed to monitor the patient's disease
- repeat ophthalmological review yearly if treatment has continued for 5 years or longer [NB4]

leflunomide

Before starting therapy:

- follow the recommendations in Considerations before starting immunomodulatory therapy
- measure blood pressure and fasting lipid levels

Throughout therapy [NB1]:

- implement the recommendations in Considerations throughout immunomodulatory therapy
- regularly assess fasting lipid levels and blood pressure
- promptly investigate patients reporting new or worsening pulmonary symptoms

Other considerations:

- leflunomide and methotrexate have synergistic bone marrow, liver and pulmonary toxicity
- if reversal of leflunomide is required, use colestyramine washout (colestyramine 8 g orally, 3 times daily for 11 days)

methotrexate

Before starting therapy:

- follow the recommendations in Considerations before starting immunomodulatory therapy
- assess the patient's alcohol intake

Throughout therapy [NB1]:

- implement the recommendations in Considerations throughout immunomodulatory therapy
- promptly investigate patients reporting new or worsening pulmonary symptoms

Other considerations:

- methotrexate is given weekly rather than daily, and serious toxicity can occur if taken more frequently. The clinician and patient should agree on which day of the week the patient will take their methotrexate and this should be specified on the prescription
- folic acid and/or calcium folinate supplementation decreases the risk of adverse effects, including gastrointestinal adverse effects, liver transaminitis and mouth ulcers [NB5]. It should not be taken on the same day as the weekly methotrexate dose
- adverse effects can be limited by administering the methotrexate dose at night, splitting the weekly dose over 2 consecutive days (usually 12 hours apart) or administering the dose subcutaneously
- leflunomide and methotrexate have synergistic bone marrow, liver and pulmonary toxicity
- at the doses typically used in rheumatology, there is no risk of toxicity to close contacts of patients taking methotrexate and special precautions in handling bodily fluids are not required

mycophenolate

Before starting therapy:

- follow the recommendations in Considerations before starting immunomodulatory therapy

Throughout therapy [NB1]:

- implement the recommendations in Considerations throughout immunomodulatory therapy
- check full blood count every week for the first month of treatment, every 2 weeks for the second and third months, monthly for a further 9 months, then as clinically indicated

Other considerations:

- mycophenolate is available as mycophenolate mofetil and mycophenolate sodium (mycophenolic acid)

sulfasalazine

Before starting therapy:

- follow the recommendations in Considerations before starting immunomodulatory therapy
- check for known history of G6PD deficiency. An alternative drug may be required in patients with G6PD deficiency
- check for history of sulfonamide allergy

Throughout therapy [NB1]:

- implement the recommendations in Considerations throughout immunomodulatory therapy

G6PD = glucose-6-phosphodehydrogenase; TPMT = thiopurine methyltransferase

NB1: If the patient develops symptoms or signs of infection, withhold therapy until a thorough assessment is completed (see General approach to immunomodulatory drug use for more information).

NB2: TPMT genotype testing can help predict the risk of myelosuppression; however, a normal result does not rule out the possibility of bone marrow suppression and close monitoring of blood counts is still essential.

NB3: Accumulation of a toxic cyclophosphamide metabolite (acrolein) can lead to haemorrhagic cystitis, which is a contraindication to further cyclophosphamide therapy.

NB4: The risk of retinopathy is greater in patients older than 60 years of age, patients taking doses more than 6.5 mg/kg per day, patients taking hydroxychloroquine for more than 8 years, obese patients, patients who have kidney or liver disease, or patients with pre-existing eye disease. Consider more frequent ophthalmological review in these patients.

NB5: Folinic acid (available as calcium folinate) is the reduced form of folic acid; it is used in combination with folic acid when the response to folic acid is inadequate.

Table 12.5 Biological disease-modifying antirheumatic drugs (bDMARDs) in rheumatology: considerations for use

[NB1]

- abatacept
- adalimumab
- anakinra
- belimumab
- canakinumab
- certolizumab pegol
- etanercept
- golimumab
- infliximab
- rituximab
- secukinumab
- tocilizumab
- ustekinumab

abatacept (target: cytotoxic T-lymphocyte-associated protein 4)

Before starting therapy:

- follow the recommendations in Considerations before starting immunomodulatory therapy

Throughout therapy [NB2]:

- implement the recommendations in Considerations throughout immunomodulatory therapy

adalimumab (target: tumour necrosis factor)

Before starting therapy:

- follow the recommendations in Considerations before starting immunomodulatory therapy
- perform a baseline test for dsDNA antibodies
- check history of heart failure and demyelinating disorders (eg multiple sclerosis)

Throughout therapy [NB2]:

- implement the recommendations in Considerations throughout immunomodulatory therapy
- assess the need for antimicrobial prophylaxis—see Patients taking tumour necrosis factor inhibitors for a nonmalignant condition

anakinra (target: interleukin-1)

Before starting therapy:

- follow the recommendations in Considerations before starting immunomodulatory therapy; however, it is not known if anakinra increases the risk of reactivation of latent tuberculosis
- measure fasting lipid levels

Throughout therapy [NB2]:

- implement the recommendations in Considerations throughout immunomodulatory therapy
- regularly assess fasting lipid levels

belimumab (target: B-cell activating factor)

Before starting therapy:

- follow the recommendations in Considerations before starting immunomodulatory therapy
- assess for depression and suicidal ideation

Throughout therapy [NB2]:

- implement the recommendations in Considerations throughout immunomodulatory therapy
- monitor for the development of depression and suicidal ideation

canakinumab (target: interleukin-1)
Before starting therapy:

- follow the recommendations in Considerations before starting immunomodulatory therapy; however, it is not known if canakinumab increases the risk of reactivation of latent tuberculosis

Throughout therapy [NB2]:

- implement the recommendations in Considerations throughout immunomodulatory therapy

certolizumab pegol (target: tumour necrosis factor)
Before starting therapy:

- follow the recommendations in Considerations before starting immunomodulatory therapy
- perform a baseline test for dsDNA antibodies
- check history of heart failure and demyelinating disorders (eg multiple sclerosis)

Throughout therapy [NB2]:

- implement the recommendations in Considerations throughout immunomodulatory therapy
- assess the need for antimicrobial prophylaxis—see Patients taking tumour necrosis factor inhibitors for a nonmalignant condition

etanercept (target: tumour necrosis factor)
Before starting therapy:

- follow the recommendations in Considerations before starting immunomodulatory therapy
- perform a baseline test for dsDNA antibodies
- check history of heart failure and demyelinating disorders (eg multiple sclerosis)

Throughout therapy [NB2]:

- implement the recommendations in Considerations throughout immunomodulatory therapy
- assess the need for antimicrobial prophylaxis—see Patients taking tumour necrosis factor inhibitors for a nonmalignant condition

golimumab (target: tumour necrosis factor)
Before starting therapy:

- follow the recommendations in Considerations before starting immunomodulatory therapy
- perform a baseline test for dsDNA antibodies
- check history of heart failure and demyelinating disorders (eg multiple sclerosis)

Throughout therapy [NB2]:

- implement the recommendations in Considerations throughout immunomodulatory therapy
- assess the need for antimicrobial prophylaxis—see Patients taking tumour necrosis factor inhibitors for a nonmalignant condition

infliximab (target: tumour necrosis factor)

Before starting therapy:

- follow the recommendations in Considerations before starting immunomodulatory therapy
- perform a baseline test for dsDNA antibodies
- check history of heart failure and demyelinating disorders (eg multiple sclerosis)

Throughout therapy [NB2]:

- implement the recommendations in Considerations throughout immunomodulatory therapy
- assess the need for antimicrobial prophylaxis—see Patients taking tumour necrosis factor inhibitors for a nonmalignant condition

rituximab (target: B-cell antigen CD20)

Before starting therapy:

- follow the recommendations in Considerations before starting immunomodulatory therapy
- measure plasma immunoglobulins

Throughout therapy [NB2]:

- implement the recommendations in Considerations throughout immunomodulatory therapy
- measure plasma immunoglobulins before each treatment cycle
- assess the need for antimicrobial prophylaxis—see Patients taking rituximab for a nonmalignant condition

secukinumab (target: interleukin-17A)

Before starting therapy:

- follow the recommendations in Considerations before starting immunomodulatory therapy

Throughout therapy [NB2]:

- implement the recommendations in Considerations throughout immunomodulatory therapy

tocilizumab (target: interleukin-6)

Before starting therapy:

- follow the recommendations in Considerations before starting immunomodulatory therapy
- check for history of diverticulitis
- measure fasting lipid levels

Throughout therapy [NB2]:

- implement the recommendations in Considerations throughout immunomodulatory therapy
- regularly assess fasting lipid levels
- patients treated with tocilizumab can have normal CRP concentration in the presence of infection

ustekinumab (target: interleukin-12 and interleukin-23)

Before starting therapy:

- follow the recommendations in Considerations before starting immunomodulatory therapy

Throughout therapy [NB2]:

- implement the recommendations in Considerations throughout immunomodulatory therapy

CRP = C-reactive protein; dsDNA = double-stranded DNA

NB1: bDMARDs are produced in biological systems and have complex molecular structures. As a consequence, there are inherently minor variations between drug molecules, even between batches of the same drug. The term 'biosimilar' is used to refer to other brands of an already registered bDMARD (known as the biological reference drug). Biosimilars must have demonstrable similarity in physiochemical, biological and immunological characteristics, as well as efficacy and safety, to the biological reference drug. However, while changing from a bDMARD to one of its biosimilars, or vice-versa, is considered safe and efficacious, there are limited data to determine whether multiple changes (ie changing back to the product that was initially used or changing to another biosimilar) are appropriate. It is the consensus view of the Rheumatology Expert Group that both the generic and trade name of the bDMARD should be specified in the prescription to avoid unintended changes between products.

NB2: If the patient develops symptoms or signs of infection, withhold therapy until a thorough assessment is completed (see General approach to immunomodulatory drug use for more information).

Table 12.6 Targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs) in rheumatology: considerations for use

- apremilast
- tofacitinib

apremilast (target: phosphodiesterase-4)

Before starting therapy:

- follow the recommendations in Considerations before starting immunomodulatory therapy; however, investigations to exclude latent tuberculosis are not required because apremilast is not known to increase the risk of reactivation
- assess for depression and suicidal ideation

Throughout therapy [NB1]:

- implement the recommendations in Considerations throughout immunomodulatory therapy
- monitor for the development of depression and suicidal ideation
- monitor for weight loss

tofacitinib (target: Janus kinases)

Before starting therapy:

- follow the recommendations in Considerations before starting immunomodulatory therapy
- measure fasting lipid levels

Throughout therapy [NB1]:

- implement the recommendations in Considerations throughout immunomodulatory therapy
- regularly assess fasting lipid levels

NB1: If the patient develops symptoms or signs of infection, withhold therapy until a thorough assessment is completed (see General approach to immunomodulatory drug use for more information).

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Introduction to analgesic and anti-inflammatory drug use for musculoskeletal conditions in adults

Introduction to analgesic and anti-inflammatory drug use for musculoskeletal conditions in adults

Analgesics and anti-inflammatory drugs have an important role in providing symptom relief for acute and chronic musculoskeletal conditions; however, they should only be considered as part of an overall pain management strategy. Lifestyle measures and nonpharmacological therapies should always be considered as an alternative or adjunct to pharmacological management for conditions in which they have a proven benefit and/or a low risk of harms. For discussion of lifestyle measures and nonpharmacological therapies for specific musculoskeletal conditions, see the clinical topics. For an overview of nonpharmacological therapies for pain relief, see Chronic pain management strategies.

The pharmacological management of pain in musculoskeletal conditions requires careful consideration of the potential benefits and harms of treatments. Because evidence to guide the use of analgesics and anti-inflammatory drugs is often limited, and patient needs and responses vary, it is recommended that a trial approach is taken when using these drugs. This involves regular assessment of treatment against the goals of management to determine if the treatment is safe and of adequate and continued benefit for that individual. Unhelpful or harmful treatments should be stopped. In patients taking analgesics or anti-inflammatory drugs on an ongoing basis, periodically consider a trial of treatment cessation.

Clinicians should keep in mind that with the availability of single and combination analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) over-the-counter, patients may already have tried or be taking medications for symptom relief at the time they seek medical advice.

This topic covers practical information on using analgesic and anti-inflammatory drugs for musculoskeletal conditions in adults; advice on using these drugs for specific musculoskeletal conditions is given in the clinical topics. For comprehensive drug information, including precautions, contraindications, adverse effects and drug interactions, consult an appropriate drug information resource. Patient medicine information sheets for many of the drugs used in rheumatology can be accessed from the Australian Rheumatology Association website [URL].

Principles of nonsteroidal anti-inflammatory drug use for musculoskeletal conditions in adults

Principles of nonsteroidal anti-inflammatory drug use for musculoskeletal conditions in adults

General considerations

General considerations

The drug class of nonsteroidal anti-inflammatory drugs (NSAIDs) includes both nonselective cyclo-oxygenase (COX) inhibitors and COX-2–selective inhibitors (the latter group is sometimes referred to as coxibs). NSAIDs are commonly used for their analgesic and anti-inflammatory effects. No single NSAID has been shown to be more effective than any other, but some patients may respond better to one NSAID than to others. If a patient does not respond to the first NSAID trialled, generally one or two other NSAIDs should be trialled before confirming nonresponse to NSAIDs.

NSAIDs can cause gastrointestinal, cardiovascular and renal adverse effects. Important adverse effects of NSAIDs are summarised in Significant cardiovascular, gastrointestinal and renal adverse effects of NSAIDs.

The relative risk of individual adverse effects varies depending on the NSAID and on patient factors (see Choice of NSAID and approach to NSAID use in patients at increased risk of specific adverse effects). In general, the risk of harms increases with patient age, and dose and duration of treatment.

When considering the use of an NSAID, the potential benefits should be weighed against the potential harms for each patient. Principles of prescribing NSAIDs for musculoskeletal conditions are given in Figure 12.7. The dosages of oral NSAIDs for adults are summarised in Table 12.7.

For advice on NSAID use in pregnancy, see NSAIDs and reproductive health in women. For information on the use of NSAIDs in children, see Practical prescribing considerations for rheumatological diseases in children and adolescents; for paediatric dosages of oral NSAIDs, see Table 12.12.

Topical NSAIDs are commonly used for the treatment of local musculoskeletal conditions. NSAIDs that are available in a topical preparation are noted in Table 12.7. Because of their minimal systemic absorption, topical NSAIDs are considerably safer than oral NSAIDs; however, topical NSAIDs may only be useful for superficial sources of musculoskeletal pain.

Figure 12.7 Principles of prescribing NSAIDs for musculoskeletal conditions

- Consider lifestyle measures and nonpharmacological therapies if appropriate to reduce the need for NSAIDs.
- Consider using fish oil, paracetamol and topical NSAIDs to reduce the need for oral NSAIDs.
- Assess the benefit–harm profile for an NSAID in each patient:
    - Avoid NSAIDs in patients with active peptic ulcer disease or gastrointestinal bleeding.
    - Avoid NSAIDs in patients with an eGFR of less than 30 mL/minute. Avoid long-term use of NSAIDs in patients with an eGFR of 30 to 60 mL/minute unless there is no alternative treatment available and the patient has no other risk factors for acute kidney injury (see Patients who have an increased risk of renal toxicity).
    - Avoid NSAIDs in patients with cirrhosis (see Principles of analgesic use in patients with cirrhosis).
    - If possible, avoid NSAIDs in patients with established cardiovascular disease (eg heart failure, stroke) or at high risk of cardiovascular disease (see Cardiovascular disease risk stratification).
    - In particular, assess the need for NSAIDs in older people carefully (see NSAIDs and older people).
- Choose which NSAID to trial based on patient factors (see Choice of NSAID and approach to NSAID use in patients at increased risk of specific adverse effects).
- Use the minimum effective dose of NSAID for the shortest time possible.
- Do not use more than one NSAID at a time, except for co-administration with low-dose aspirin if it is clinically indicated for other reasons.
- If possible, avoid concurrent use of NSAIDs and systemic corticosteroids because of the significantly increased risk of gastrointestinal toxicity, and because NSAIDs are unlikely to have additional benefit in patients taking systemic corticosteroids [NB1].
- For patients with risk factors for increased gastrointestinal toxicity with an NSAID and/or who are likely to be treated with an NSAID long term, consider co-prescribing a PPI for prophylaxis and testing for *Helicobacter pylori* (see Patients who have an increased risk of gastrointestinal toxicity).
- Encourage patients taking an NSAID long term to address lifestyle risk factors for gastrointestinal toxicity (eg smoking, obesity) and cardiovascular disease (see Behavioural risk factor modification).
- Monitor treatment response, adverse effects and the ongoing need for an NSAID. Do not continue NSAIDs if there is no benefit or treatment is harmful. In patients taking an NSAID on an ongoing basis, periodically consider a trial of treatment cessation.

eGFR = estimated glomerular filtration rate; NSAIDs = nonsteroidal anti-inflammatory drugs; PPI = proton pump inhibitor

NB1: In patients currently taking an NSAID who require a short course of systemic corticosteroid, consider withholding the NSAID while the patient is treated with the corticosteroid. In patients currently taking a systemic corticosteroid who require acute anti-inflammatory treatment, consider temporarily increasing the dose of the corticosteroid instead of using an NSAID.

Table 12.7 Adult dosages of oral NSAIDs used for musculoskeletal conditions

[NB1]

Drug	Usual dose	Dose frequency [NB2]	Maximum daily dose
Nonselective COX inhibitors [NB3]			
diclofenac [NB4] *musculoskeletal conditions (adult)*	25 to 50 mg	2 or 3 doses per day	200 mg
ibuprofen [NB4] *musculoskeletal conditions (adult)*	200 to 400 mg	3 or 4 doses per day	2400 mg
indometacin *musculoskeletal conditions (adult)*	25 to 50 mg	2 to 4 doses per day	200 mg
ketoprofen (modified-release) *musculoskeletal conditions*	200 mg	1 dose per day	200 mg
ketorolac *musculoskeletal conditions*	10 mg	3 or 4 doses per day	40 mg
mefenamic acid *musculoskeletal conditions*	500 mg	3 doses per day	1500 mg
naproxen [NB5] *musculoskeletal conditions (adult)*	250 to 500 mg	2 doses per day	1250 mg
naproxen (modified-release) *musculoskeletal conditions (adult)*	750 to 1000 mg	1 dose per day	1000 mg
piroxicam [NB4] *musculoskeletal conditions (adult)*	10 to 20 mg	1 dose per day	20 mg
sulindac *musculoskeletal conditions*	100 to 400 mg	1 or 2 doses per day	400 mg
COX-2–selective inhibitors			
celecoxib *musculoskeletal conditions (adult)*	100 to 200 mg	1 or 2 doses per day	400 mg
etoricoxib *musculoskeletal conditions*	30 to 60 mg	1 dose per day	120 mg
meloxicam *musculoskeletal conditions (adult)*	7.5 to 15 mg	1 dose per day	15 mg

COX = cyclo-oxygenase; NSAIDs = nonsteroidal anti-inflammatory drugs

NB1: For indication-specific advice on the use of NSAIDs, see the clinical topics.

Drug	Usual dose	Dose frequency [NB2]	Maximum daily dose

NB2: With the exception of modified-release preparations, drugs that require more frequent daily dosing generally have a shorter half-life.

NB3: Aspirin is also a nonselective COX inhibitor, but is rarely used for anti-inflammatory purposes because of the significant risk of harms at the high dosages required for these effects.

NB4: This NSAID is also available as a topical gel.

NB5: Naproxen sodium is used in some preparations; 250 mg of naproxen is equivalent to 275 mg of naproxen sodium.

Choice of NSAID and approach to NSAID use in patients at increased risk of specific adverse effects

Choice of NSAID and approach to NSAID use in patients at increased risk of specific adverse effects

The relative risk of individual adverse effects varies between NSAIDs, so choice of NSAID is guided by patient factors.

If possible, avoid NSAIDs in patients with both an increased risk of gastrointestinal toxicity and an increased cardiovascular risk. If treatment with an NSAID is necessary for these patients, use a nonselective NSAID, ideally naproxen, and co-prescribe a proton pump inhibitor (PPI) for gastrointestinal prophylaxis (see discussion below).

Avoid NSAIDs in patients with cirrhosis (see Principles of analgesic use in patients with cirrhosis).

Patients who have an increased risk of gastrointestinal toxicity

Patients who have an increased risk of gastrointestinal toxicity

Risk factors for increased gastrointestinal toxicity with NSAID use include older age, history of upper gastrointestinal bleeding or peptic ulcer disease, *Helicobacter pylori* infection, the concomitant use of drugs that increase the risk of upper gastrointestinal bleeding or perforation (eg anticoagulants, antiplatelet drugs, selective serotonin reuptake inhibitors [SSRIs], serotonin and noradrenaline reuptake inhibitors [SNRIs], systemic corticosteroids), significant comorbidity, and smoking.

Avoid NSAIDs in patients with active peptic ulcer disease or gastrointestinal bleeding.

If treatment with an NSAID is necessary for a patient with risk factor(s) for increased gastrointestinal toxicity and/or if NSAID use is likely to be long term, consider the gastrointestinal risk of the NSAID, including the following factors:

- **Drug half-life**—NSAIDs with a longer half-life (eg piroxicam; see Table 12.7) are more likely to cause serious gastrointestinal complications.
- **COX-2–selectivity**—NSAIDs that selectively inhibit COX-2 (celecoxib, etoricoxib, meloxicam) have a lower risk of causing NSAID-induced gastrointestinal toxicity, but the risk is not completely eliminated and some COX-2–selective NSAIDs are only selective at low doses (eg meloxicam). COX-2–selective NSAIDs do not cause fewer dyspeptic symptoms than nonselective NSAIDs. The concomitant use of low-dose aspirin eliminates any upper gastrointestinal safety advantage of COX-2–selective NSAIDs.

For these patients, also consider co-prescribing a proton pump inhibitor (PPI) for prophylaxis, and testing for *H. pylori* infection. Limited data suggest using a COX-2–selective NSAID with a PPI provides the greatest gastrointestinal prophylaxis. For more information on prophylaxis and treatment of NSAID-induced ulcers, see NSAID-induced ulcers.

If NSAID use is likely to be long term, provide additional encouragement for patients to address lifestyle risk factors for gastrointestinal toxicity (eg smoking, obesity).

Patients who have an increased cardiovascular risk

Patients who have an increased cardiovascular risk

If possible, avoid NSAIDs in patients with established cardiovascular disease (eg heart failure, stroke) or at high risk of cardiovascular disease (see Cardiovascular disease risk stratification).

If treatment with an NSAID is necessary for patients who have an increased cardiovascular risk, consider the cardiovascular risk of the NSAID, including the following factors:

- Naproxen appears to confer the least cardiovascular risk of all the NSAIDs, but has a higher risk of gastrointestinal adverse effects.
- Diclofenac has a lower risk of gastrointestinal adverse effects, but a higher cardiovascular risk; avoid diclofenac in patients who have an increased cardiovascular risk.
- COX-2–selective NSAIDs have a higher risk of adverse vascular events (eg myocardial infarction). A single randomised controlled trial suggests celecoxib at low to moderate doses has no greater cardiovascular risk than naproxen or ibuprofen [Note 1]; however, this study has limitations and caution is still advised in the use of all COX-2–selective NSAIDs in patients at increased cardiovascular risk.

If NSAID use is likely to be long term, provide additional encouragement for patients to address lifestyle risk factors for cardiovascular disease (see Behavioural risk factor modification). In patients taking NSAIDs on an ongoing basis, cardiovascular disease risk factors should be closely monitored and actively managed.

Low-dose aspirin may reduce the increased cardiovascular risk associated with NSAIDs, but it increases the risk of gastrointestinal adverse effects. Advise patients who are prescribed low-dose aspirin for secondary prevention of vascular events to continue it regardless of their use of other NSAIDs.

Note 1: Nissen SE, Yeomans ND, Solomon DH, Luscher TF, Libby P, Husni ME, et al. Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. N Engl J Med 2016;375(26):2519-29. [URL]

Patients who have an increased risk of renal toxicity

Patients who have an increased risk of renal toxicity
General considerations

Risk factors for NSAID-induced acute kidney injury include pre-existing renal impairment; volume depletion (eg dehydration, sepsis) or effective arterial volume depletion (eg due to heart failure, cirrhosis, nephrotic syndrome); co-administration with angiotensin converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), diuretics or other nephrotoxic drugs; and older age. The risk of acute kidney injury is cumulative—for example, the risk is significantly increased if an NSAID is co-administered with an ACEI plus a diuretic, or if an older patient taking an NSAID develops an acute illness associated with dehydration.

For specific considerations with NSAID use in patients with pre-existing renal impairment, see Patients with chronic kidney disease.

If treatment with an NSAID is necessary for a patient with risk factor(s) for NSAID-induced acute kidney injury, NSAIDs with a short half-life are preferred (see Table 12.7). Nonselective NSAIDs and COX-2–selective NSAIDs have a similar risk of acute kidney injury. For patients with pre-existing renal impairment, see monitoring advice in Patients with chronic kidney disease. In patients with other risk factors for NSAID-induced acute kidney injury, check renal function periodically if NSAID use is ongoing.

Patients with chronic kidney disease

The use of NSAIDs in patients with chronic kidney disease requires particular consideration for three reasons. Firstly, in these patients, NSAIDs can cause an acute reduction in renal perfusion and glomerular filtration rate, which can lead to a reversible reduction in renal function, hyperkalaemia, or acute ischaemic kidney injury. This risk is significantly increased in patients concurrently taking ACEIs, ARBs and/or diuretics. Secondly, NSAIDs can increase blood pressure in patients with hypertension, a common comorbidity in patients with chronic kidney disease. Finally, long-term use of NSAIDs can increase the rate of progression of chronic kidney disease when used at higher doses or in patients with more severe chronic kidney disease. However, observational data in patients with mild to moderate chronic kidney disease taking standard doses of NSAIDs have been reassuring, with no evidence of a detrimental effect on renal function over time.

In all patients with chronic kidney disease in whom an NSAID is being considered, the potential benefits of an NSAID should be weighed against its potential harms, taking into account the degree of renal impairment and the presence of other risk factors for NSAID-induced acute kidney injury (see General considerations for risk factors).

Avoid NSAIDs in patients with an estimated glomerular filtration rate (eGFR) of less than 30 mL/minute. In patients with an eGFR of 30 to 60 mL/minute, avoid long-term use of NSAIDs unless there is no alternative treatment available and the patient has no other risk factors for acute kidney injury. Check renal function and blood pressure early after starting the NSAID to detect any acute change, and monitor closely if use is ongoing. Withhold the NSAID during any serious illness associated with risk of acute kidney injury. Even in patients with mild renal impairment (eGFR 60 to 90 mL/minute), use NSAIDs with caution if other risk factors for acute kidney injury are present and check renal function periodically if NSAID use is ongoing. In any patient with chronic kidney disease, use the minimum effective NSAID dose.

NSAIDs and older people

NSAIDs and older people

Older people are generally at increased risk of individual NSAID-related adverse effects (eg older age is a risk factor for increased gastrointestinal toxicity with NSAID use, a consideration in the calculation of absolute cardiovascular risk, and a risk factor for NSAID-induced acute kidney injury). Older patients are also more likely to have comorbidities and take other drugs that increase their risk of NSAID-related adverse effects.

Assess the need for NSAIDs in older people more carefully. NSAIDs with a short half-life are preferred in older patients (see Table 12.7), but see also the considerations for specific toxicity risks: Patients who have an increased risk of gastrointestinal toxicity, Patients who have an increased cardiovascular risk, and Patients who have an increased risk of renal toxicity.

NSAIDs and reproductive health in women

NSAIDs and reproductive health in women
Potential effects of NSAID use on conception

Recent studies have shown that intermittent, short-term NSAID use does not negatively affect fertility. While using an NSAID regularly or long term may lead to a temporary reduction in female fertility, the evidence for this effect is conflicting. Routinely withholding NSAIDs in people planning pregnancy is not recommended.

Potential harms of NSAID use during pregnancy

In general, NSAIDs should be avoided in pregnancy because of the risk of:

- miscarriage in early pregnancy; however, evidence of this effect is conflicting
- oligohydramnios via effects on fetal renal function when an NSAID is used after 20 weeks' gestation
- premature closure of the ductus arteriosus, and delayed labour and birth, when an NSAID is used after 30 weeks' gestation

- peripartum haemorrhage, especially with complicated deliveries, due to effects on maternal platelet function.

However, there continues to be a role for NSAID use during pregnancy in some circumstances; see Circumstances in which a nonselective NSAID may be used during pregnancy. When considering NSAID use in the perinatal period, consider the balance of potential harms and benefits of NSAID use, as well as other treatment options.

In general, NSAIDs should be avoided in pregnancy and must be avoided after 30 weeks' gestation.

COX-2–selective NSAIDs should be avoided from planned conception and throughout pregnancy because of a lack of data to demonstrate their safety.

A 2014 population-wide cohort study that adjusted for potential confounders found no increase in the risk of miscarriage in people taking NSAIDs in early pregnancy. However, guidelines still recommend avoiding NSAIDs or using NSAIDs with caution in pregnant people up to 8 weeks' gestation [Note 2] because of older data suggesting an increased risk of miscarriage in people taking NSAIDs in early pregnancy. A lack of controlling for increased maternal age in the study designs may have confounded the results.

Note 2: See the Australian Rheumatology Association *Prescriber's information on medications for rheumatic diseases in pregnancy* [URL]

Circumstances in which a nonselective NSAID may be used during pregnancy

There are limited circumstances in which nonselective NSAIDs may be used in people who are pregnant.

Low-dose aspirin (up to 150 mg orally, daily) can be continued throughout pregnancy and, indeed, has an established role in the prevention of pre-eclampsia in people at risk.

A nonselective NSAIDs may be used judiciously up to 30 weeks' gestation to treat conditions for which NSAIDs are known to be effective (eg ankylosing spondylitis, rheumatoid arthritis) if potential benefits are deemed to outweigh potential harms. Data suggest there is no increased risk of congenital malformations. However, they are best avoided after 20 weeks' gestation because of the risk of oligohydramnios via an effect on fetal renal function. If use for longer than 48 hours cannot be avoided in this period, use the minimum effective dose for the shortest time possible and consider ultrasound monitoring of amniotic fluid.

Nonselective NSAIDs can be used until 30 weeks' gestation if potential benefits outweigh potential harms. Consider amniotic fluid monitoring if used after 20 weeks' gestation.
NSAID use in people who are breastfeeding

If an NSAID is required in a breastfeeding patient, a short-acting NSAID is recommended (eg ibuprofen, diclofenac). Advice for individual NSAID compatibility with breastfeeding is accessible through icons in Table 12.7.

Principles of paracetamol use for musculoskeletal conditions in adults

Principles of paracetamol use for musculoskeletal conditions in adults

Although paracetamol is generally less effective than nonsteroidal anti-inflammatory drugs (NSAIDs) for musculoskeletal pain, its favourable safety profile in therapeutic doses justifies a trial of paracetamol first line for mild to moderate pain in most indications. Paracetamol may also be used to reduce the use of NSAIDs and thus the risk of NSAID adverse effects.

Adults with risk factors for glutathione depletion (eg decompensated cirrhosis, alcoholism, malnourishment, cachexia, frailty) may require reduced doses. See Principles of analgesic use in patients with cirrhosis. The differences in onset of action between paracetamol preparations are not clinically important for most

indications. Paracetamol preparations that require less frequent administration may be preferred for convenience.

Dose-related gastrointestinal, cardiovascular and renal adverse effects have been occasionally observed in patients taking paracetamol long term. Metabolite production in paracetamol overdose may lead to severe hepatic toxicity. Overdose from inadvertent ingestion of higher than recommended doses of paracetamol is a possibility, and patients should be advised to consider the paracetamol content of all medications. For more information on paracetamol toxicity, see Paracetamol poisoning: advice for primary care providers.

Patients taking paracetamol should be monitored for treatment response, adverse effects and the ongoing need for treatment. Do not continue paracetamol if there is no benefit or treatment is harmful. In patients taking paracetamol on an ongoing basis, periodically consider a trial of treatment cessation.

Principles of fish oil use for musculoskeletal conditions in adults

Principles of fish oil use for musculoskeletal conditions in adults

Fish oil contains the omega-3 long-chain polyunsaturated fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which have anti-inflammatory properties. Fish oil may also be used to reduce the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and thus the risk of NSAID adverse effects. Fish oil may take up to 3 months for maximal effectiveness, so it may be necessary to co-prescribe fish oil with other analgesics initially (eg an NSAID and/or paracetamol).

Numerous fish oil preparations are available with varying strengths of fish oil, omega-3, and EPA and DHA, including in combination with other active ingredients. For an anti-inflammatory effect, the recommended daily dose of total omega-3 (EPA + DHA) for adults is at least 2.7 g. The content of selected fish oil preparations and their minimum daily anti-inflammatory dose is given in Table 12.8. Cod liver oil is not recommended as a source of omega-3 because it contains cholesterol and, in the dose required for an anti-inflammatory effect, potentially toxic amounts of vitamins A and D.

The size and number of fish oil capsules required for daily dosing may not be tolerated by patients. An alternative is to use fish oil liquid; the palatability of fish oil liquid can be improved by using a ‘two-glass’ technique [Note 3].

Gastrointestinal adverse effects of fish oil include a ‘fishy’ aftertaste, heartburn and diarrhoea. Fish oil has been shown to have a low risk of harm in clinical trials assessing efficacy, but there is a theoretical risk of bleeding.

Table 12.8 Content of selected fish oil preparations and minimum daily anti-inflammatory dose for adults

[NB1] [NB2]

fish oil:

- 1 g capsules
- 1.5 g capsules
- 2 g capsules
- 1.5 g concentrated capsules
- 4.5 g/5 mL liquid
- 4.6 g/5 mL concentrated liquid

fish oil 1 g capsules	
EPA content	180 mg
DHA content	120 mg
Total omega-3 content (EPA + DHA)	300 mg
Minimum daily dose [NB3]	9 capsules

fish oil 1.5 g capsules

EPA content	270 mg
DHA content	180 mg
Total omega-3 content (EPA + DHA)	450 mg
Minimum daily dose [NB3]	6 capsules
fish oil 2 g capsules	
EPA content	360 mg
DHA content	240 mg
Total omega-3 content (EPA + DHA)	600 mg
Minimum daily dose [NB3]	5 capsules
fish oil 1.5 g concentrated capsules	
EPA content	540 mg
DHA content	360 mg
Total omega-3 content (EPA + DHA)	900 mg
Minimum daily dose [NB3]	3 capsules
fish oil 4.5 g/5 mL liquid	
EPA content	810 mg/5 mL
DHA content	540 mg/5 mL
Total omega-3 content (EPA + DHA)	1.35 g/5 mL
Minimum daily dose [NB3]	10 mL
fish oil 4.6 g/5 mL concentrated liquid	
EPA content	1.9 g/5 mL
DHA content	927 mg/5 mL
Total omega-3 content (EPA + DHA)	2.8 g/5 mL
Minimum daily dose [NB3]	5 mL

DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; omega-3 = omega-3 long-chain polyunsaturated fatty acids

NB1: Other preparations are available with different strengths of fish oil, omega-3, and EPA and DHA.

NB2: Cod liver oil is not recommended as a source of omega-3 because it contains cholesterol and, in the dose required for an anti-inflammatory effect, potentially toxic amounts of vitamins A and D.

NB3: This is calculated to give a daily dose of at least 2.7 g of total omega-3 (EPA + DHA) for anti-inflammatory effect.

Note 3: For information on this technique, see Cleland LG, James MJ, Proudman SM. Fish oil: what the prescriber needs to know. Arthritis Res Ther 2006;8(1):202. [URL]

Principles of using local corticosteroid injections for musculoskeletal conditions in adults

Principles of using local corticosteroid injections for musculoskeletal conditions in adults

Intra-articular injection, or injection into soft tissue, of a long-acting or depot corticosteroid can provide pain relief in musculoskeletal conditions. Because the potential benefits and harms of use vary with different musculoskeletal conditions and patient factors, local corticosteroid injections should only be given by, or under the supervision of, clinicians with appropriate training and experience. Radiological guidance does not increase the efficacy of local corticosteroid injections and is only required for joints that are difficult to access (eg hip joint).

Only corticosteroids specifically formulated for intra-articular injection or injection into soft tissue should be used for this purpose. Local anaesthetic may be used before, or mixed with, the corticosteroid. Example

doses of local corticosteroid injections for adults are given in Table 12.9. Triamcinolone hexacetonide is the most common local corticosteroid injection used in children; example doses of triamcinolone hexacetonide injection for children are given in Table 12.13.

The following factors may assist in choosing a local corticosteroid injection in adults:

- Betamethasone sodium phosphate plus betamethasone acetate is usually used for injection into smaller joints.
- Methylprednisolone acetate is crystalline and is formulated as a suspension; it is usually used for injection into larger joints.
- Triamcinolone acetonide is the least soluble injection and provides the longest duration of action (up to 21 weeks).

The following are absolute contraindications to local corticosteroid injection: infection of the skin at the injection site or systemic infection (because it may seed a deep infection) and infection of the joint or soft tissue (because it may worsen infection). Similarly, because of infection risk, local corticosteroid injection should not be given into a joint that is to be replaced less than 3 months before the planned surgery. Therapeutic anticoagulation is not a contraindication to local corticosteroid injection.

Systemic adverse effects of local corticosteroid injections include increase in blood glucose concentration for up to 48 hours, sleep disturbance and flushing. Local adverse effects of corticosteroid injections include temporary worsening of musculoskeletal symptoms, skin hypopigmentation and tissue atrophy. Although tendon rupture has been reported in patients injected with corticosteroids, a causal relationship is unproven. Peritendinous corticosteroid injections should be used with caution if the major weightbearing tendons (eg the patellar, tibialis posterior and Achilles tendons) are involved; consider seeking specialist advice. Septic arthritis is a rare but serious complication of intra-articular corticosteroid injections.

If local corticosteroid injection is effective for an extended duration (eg months), and in the absence of a safer therapeutic alternative, the injection may be repeated. A maximum of four injections per joint per year is recommended because of the risk of local tissue atrophy and systemic adverse effects. Avoid multiple injections involving the major weightbearing tendons.

For principles of use of systemic corticosteroids, see Principles of immunomodulatory drug use for rheumatological diseases in adults.

Table 12.9 Example doses of local corticosteroid injections for adults

[NB1] [NB2]

Corticosteroid:

- betamethasone sodium phosphate + betamethasone acetate 5.7 mg/mL
- methylprednisolone acetate 40 mg/mL
- triamcinolone acetonide 10 mg/mL
- triamcinolone acetonide 40 mg/mL
- triamcinolone hexacetonide 20 mg/mL

betamethasone sodium phosphate + betamethasone acetate 5.7 mg/mL *musculoskeletal conditions (local injection)*

small joint dose (eg hand)	0.25 to 0.5 mL
medium joint dose (eg wrist)	0.5 to 1 mL
large joint dose (eg knee)	1 to 2 mL
soft tissue dose (eg bursa)	1 mL

methylprednisolone acetate 40 mg/mL *musculoskeletal conditions (local injection)*

small joint dose (eg hand)	0.1 to 0.25 mL
medium joint dose (eg wrist)	0.25 to 1 mL
large joint dose (eg knee)	0.5 to 2 mL
soft tissue dose (eg bursa)	0.1 to 0.75 mL

triamcinolone acetonide 10 mg/mL *musculoskeletal conditions, local injection*

small joint dose (eg hand)	0.25 to 1 mL
medium joint dose (eg wrist)	1 mL
large joint dose (eg knee)	0.5 to 2 mL
soft tissue dose (eg bursa)	1 to 2 mL

triamcinolone acetonide 40 mg/mL

small joint dose (eg hand)	0.1 to 0.25 mL
medium joint dose (eg wrist)	0.25 mL
large joint dose (eg knee)	0.5 to 1 mL
soft tissue dose (eg bursa)	0.5 mL

triamcinolone hexacetonide 20 mg/mL [NB3] *musculoskeletal conditions, local injection (adult)*

small joint dose (eg hand)	0.1 to 0.3 mL
medium joint dose (eg wrist)	0.25 to 0.5 mL
large joint dose (eg knee)	0.5 to 1 mL
soft tissue dose (eg bursa)	0.5 to 1 mL

NB1: For indication-specific advice on the use of local corticosteroid injections, see the clinical topics.

NB2: These are example doses; the dose should be individualised for each patient depending on the size of the joint or soft-tissue lesion, the severity of the condition, the response obtained, and the patient's tolerance of the corticosteroid. The total volume of the injection administered will vary depending on the amount of local anaesthetic solution added.

NB3: Triamcinolone hexacetonide is not registered for use in Australia but is available via the Special Access Scheme.

Drugs that have limited use in the management of musculoskeletal conditions in adults

Drugs that have limited use in the management of musculoskeletal conditions in adults

Opioids

Opioids

Opioids, including tramadol and tapentadol, are often used to treat musculoskeletal pain because of concerns about paracetamol efficacy and nonsteroidal anti-inflammatory drug (NSAID) adverse effects; however, they in fact have a very limited role in the management of acute and chronic musculoskeletal conditions because of modest benefits and a significant risk of harms. Harms of opioids include tolerance, dependence, inadvertent (potentially fatal) overdose, cognitive effects, endocrinopathy, cardiovascular effects, falls, fractures, pruritus, dry mouth, anorexia, urinary retention and overflow incontinence, and constipation. Opioids have also been associated with an increased risk of hospitalisation for serious infection in patients with rheumatoid arthritis, and a significantly increased risk of all-cause mortality in patients with chronic

nonmalignant pain. Important short-term adverse effects of opioids are summarised in Adverse effects with short-term use of opioids and important long-term adverse effects of opioids are summarised in Adverse effects with long-term use of opioids.
Opioids have a very limited role in the management of musculoskeletal conditions.

Notwithstanding their modest benefits and significant risk of harms, opioids may be considered for severe musculoskeletal pain that is not relieved by other indicated measures (eg nonpharmacological therapies, paracetamol, NSAIDs, immunomodulatory drugs, analgesic adjuvants). The need for opioids should flag consideration of patient referral to a rheumatologist. If opioids are used, they should be prescribed on a short-term trial basis, as part of an overall pain management strategy, with clear goals and regular review of treatment response and adverse effects. Before starting an opioid, a plan for ceasing ineffective therapy should be in place and discussed with the patient. If treatment response is inadequate, caution should be exercised before increasing the dose as there may be no added benefit and an increased risk of harms.

Prolonged use of opioids for severe persisting musculoskeletal pain should only be undertaken in consultation with a rheumatologist to ensure that all alternative options have been explored and optimised. Most placebo-controlled trials of opioids in chronic pain have assessed only short-term effects, so evidence for long-term benefit is lacking. In patients with chronic pain, opioids may worsen pain and function, possibly by potentiating pain perception.

For patients already taking opioids, regular clinical review of the benefits and harms are recommended together with attempts at dose weaning and/or cessation if possible.

For further discussion on the use of opioids for pain, see Opioids in pain management.

Complementary medicines

Complementary medicines

Patients often initiate the use of complementary medicines for chronic pain. Some complementary medicines have been shown to provide no benefit in the treatment of pain, but for the majority of complementary medicines there is no evidence for or against benefit. The concentration of active ingredients in complementary medicines can vary between brands because of the range of sources used and different methods of processing. The role of glucosamine, chondroitin and other complementary therapies for osteoarthritis are discussed in Complementary medicines in osteoarthritis.

Complementary medicines can cause adverse effects or interact with conventional medicines. Patients often do not spontaneously disclose their use of complementary medicines so, as part of a thorough medication history, actively inquire about the use of complementary medicines, as well as over-the-counter and prescription medicines.

The National Institute of Health (US) website [URL] has links for health information and research about complementary medicines.

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Introduction to thoracic spine pain

Introduction to thoracic spine pain

Pain in the thoracic spine or upper back is defined as pain localised below the neck and above the costal margin. The thoracic spine is a complex structure with seven joints (one intervertebral joint, two zygapophyseal or facet joints, two costovertebral joints, two costotransverse joints) at each of 12 levels. Pain experienced in the thoracic spine can originate from the joints or other structures of the thoracic spine (eg the dura, intervertebral discs, vertebral bodies, muscles, thoracic nerves), or the underlying mediastinal viscera.

Thoracic spine pain is common, with a 1-year prevalence of 20% in adults. Higher rates are reported in adolescents, but this may reflect the focus of studies on this group.

Compared with low back pain, pain experienced in the thoracic spine is more commonly due to a serious underlying pathology (eg myocardial ischaemia, pulmonary embolism, vertebral fracture) (see Assessment of thoracic spine pain). Pain experienced in the thoracic spine may also be due to a nonspecific local musculoskeletal condition (see Nonspecific thoracic spine pain) or thoracic radiculopathy. Thoracic spine pain often coexists with neck pain and low back pain and is common after motor vehicle collisions. Other thoracic spine diagnoses associated with pain include diffuse idiopathic skeletal hyperostosis and Scheuermann disease.

The prognostic factors for thoracic spine pain have not been well studied, although occupational factors, age and mental health appear to be important.

Assessment of thoracic spine pain

Assessment of thoracic spine pain

It is important to exclude serious underlying medical and spinal pathologies in a patient presenting with thoracic spine pain. Patient history should focus on features that suggest an underlying disease of the heart, great vessels, lungs or oesophagus. These features include the site of pain, and aggravation of pain on movement, respiration and eating. Pain aggravated by movement and respiration can occur in both musculoskeletal and visceral (particularly pleural) causes of thoracic spine pain. Any suspicion of cardiac, pleural or respiratory disease should be fully evaluated before a diagnosis of nonspecific thoracic spine pain is made. Pain that is constantly present, including at night, and unrelieved by rest suggests invasion, distortion or inflammation of pain-sensitive structures. Spondyloarthritides (eg psoriatic arthritis, ankylosing spondylitis) and SAPHO syndrome (characterised by any combination of synovitis, acne, pustulosis, hyperostosis and osteitis) can affect joints in the upper thoracic region (eg sternoclavicular joint, manubriosternal joint) and therefore can also present with thoracic spine pain. Alerting features of serious pathologies in patients with spinal pain are given in Table 12.19.

Thoracic spine pain due to a nonspecific local musculoskeletal condition is suggested by pain that is constant in its location, dull or aching in character (but may have sharp exacerbations), and often related to specific movements or postures rather than exertion.

Thoracic radicular pain (pain due to compromise of the thoracic ventral spinal nerve roots) occurs less frequently than lumbar or cervical radicular pain. Thoracic radicular pain is typically perceived in the back and radiates around the chest wall and abdomen along the segmental dermatome of the thoracic ventral spinal nerves. The presence of thoracic radicular pain should alert the clinician to the possibility of systemic pathologies such as diabetic radiculopathy or, if skin rash is present, herpes zoster (shingles). Thoracic disc herniation is an uncommon cause of isolated radicular pain but, if present, may compromise the spinal cord

(myelopathy). Careful neurological examination and appropriate imaging is required to exclude myelopathy and the need for urgent surgical intervention.

Examination of the thoracic spine has limited utility in identifying specific painful structures, but may provide useful information about the aetiology of the pain. Physical examination should include:

- postural assessment for scoliosis and kyphosis, and visible muscle contraction or wasting
- assessment of the chest for skin rashes or scars
- assessment of range of movement (rotation, flexion and extension) and chest expansion
- palpation for tenderness and muscle contraction or spasm
- neurological examination, including sensory examination over the chest wall to determine if there is altered sensation in a dermatomal distribution or there is a sensory level, and assessment of the lower limbs for long-tract signs (specifically weakness, hyperreflexia or hyporeflexia, upgoing plantar responses and sensory loss).

The need for and type of investigations are guided by clinical assessment. If fracture is suspected, plain X-ray may be adequate. If the age of the fracture is uncertain, a bone scan may be useful to determine if the fracture is recent. For discussion of imaging in patients with radicular pain, see Thoracic radiculopathy. If myelopathy is suspected, magnetic resonance imaging (MRI) is indicated and should be obtained urgently if there are new or progressive neurological deficits.

Nonspecific thoracic spine pain

Nonspecific thoracic spine pain

The evidence to guide management of nonspecific thoracic spine pain is limited; the following recommendations are a reasonable approach.

If analgesia is required, use:

1 paracetamol 1 g orally, 4- to 6-hourly, up to a maximum of 4 g daily *back pain, thoracic spine*

OR

1 paracetamol modified-release 1.33 g orally, 8-hourly.

If response to paracetamol is inadequate, a nonsteroidal anti-inflammatory drug (NSAID) may be used **instead of, or in combination with**, paracetamol. Use:

an NSAID orally (see Table 12.7 for dosing). *back pain, thoracic spine*

The potential benefits of an NSAID should be weighed against its potential harms, particularly in patients at high risk of harms (see Principles of NSAID use for musculoskeletal conditions in adults for more information).

Nonpharmacological management of nonspecific thoracic spine pain involves a combination of stretching and mobilising exercises to restore range of movement (usually rotation and extension). A short course of manual therapy may assist patients with pain and mobility. There is no evidence to support the use of other physical treatments, such as electrotherapy and acupuncture, for thoracic spine pain.

Management of chronic nonspecific thoracic spine pain should follow the same principles as for other types of noninflammatory chronic pain and should be based on an integrated biopsychosocial approach (see General principles of chronic pain management). For patients with persistent pain that is interfering with their ability to function despite conservative management, consider referral to a pain specialist for targeted techniques.

Thoracic radiculopathy

Thoracic radiculopathy

The evidence base for management of thoracic radiculopathy is sparse.

For management of herpes zoster (shingles), see Shingles for antiviral therapy, and Acute pain associated with shingles (herpes zoster).

For management of diabetic radiculopathy, see Atypical diabetic neuropathies.

The clinical course of radiculopathy due to thoracic disc herniation has been poorly studied, but it is thought to have a more favourable prognosis than cervical or lumbar disc herniation. If myelopathy has been excluded (see Assessment of thoracic spine pain), initial management should be conservative, including analgesia (as for nonspecific thoracic spine pain) and local treatments (eg application of heat). Specific treatment for neuropathic pain is discussed in Neuropathic pain.

The indications for imaging for thoracic radiculopathy are not established; consider magnetic resonance imaging (MRI) if surgery is being contemplated, such as in patients with persisting or progressive neurological deficits or in patients with refractory pain.

Diffuse idiopathic skeletal hyperostosis

Diffuse idiopathic skeletal hyperostosis

Diffuse idiopathic skeletal hyperostosis (DISH) (also known as Forestier disease) is characterised by ligamentous ossification in the spine resulting in progressive stiffness and, sometimes, pain. In some patients, it may be asymptomatic. DISH typically affects the thoracic spine, but can also affect the cervical and lumbar spine. It can also cause enthesitis (inflammation at the sites of tendon and ligament attachment to bone) at peripheral sites. Ankylosing spondylitis is a differential diagnosis, but can be distinguished on the basis of radiographic appearance. The aetiology of DISH is unknown, but the condition is associated with metabolic disorders such as hyperuricaemia, dyslipidaemia, obesity, glucose intolerance and diabetes, as well as the use of oral retinoids.

There are no specific treatments for DISH and management is as for nonspecific thoracic spine pain, including analgesia and exercise. It is prudent to avoid vigorous manipulation of the spine in case this causes fracturing of ossified ligaments. Metabolic conditions associated with DISH should be managed as indicated; however, it is uncertain if this affects the progression of DISH. If DISH is associated with the use of an oral retinoid, treatment should be stopped.

Scheuermann disease

Scheuermann disease

Scheuermann disease is a condition of unknown aetiology that affects the developing intervertebral disc, typically in the thoracic spine, and is associated with kyphosis of the spine.

In most cases, radiographic findings of Scheuermann disease (endplate irregularity and Schmorl nodes in the thoracic vertebrae) are identified during investigation for back pain. However, the relationship between these findings and back pain is uncertain and likely to be weak. There are no specific treatments for Scheuermann disease and management is as for nonspecific thoracic spine pain. If kyphosis is severe, or associated with respiratory compromise, surgery may be warranted.

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Key references: Thoracic spine (upper back) pain

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Low back pain in pregnancy

Low back pain in pregnancy

Nonspecific low back pain occurs in 50 to 70% of pregnant women. It occurs more commonly in women with previous back pain, whether associated with pregnancy or not, but is not correlated with maternal weight or fetal size. The incidence of lumbar disc herniation resulting in radiculopathy in pregnancy is no higher than in the general population.

Prepregnancy fitness and continuation of a strengthening program throughout pregnancy reduce the likelihood of low back pain in pregnancy. If exercise is insufficient to control symptoms, use:

1 paracetamol 1 g orally, 4- to 6-hourly as necessary, up to a maximum of 4 g daily *back pain, low back (pregnancy)* _

OR

1 paracetamol modified-release 1.33 g orally, 8-hourly as necessary.

Pelvic pain in pregnancy

Pelvic pain in pregnancy

Pelvic pain arising from the sacroiliac joints and/or the pubic symphysis can be experienced in pregnancy, especially in women with high concentrations of relaxin. This pain may occur early in pregnancy. Appropriately graded strengthening and stabilising exercises, such as the use of a fit ball or water-based exercise, can be helpful and should be encouraged.

Changes in pubic symphysis width probably occur in most pregnant women, with a gap of up to 1 cm being considered normal. Rupture of the pubic symphysis (diastasis) can occur; especially in association with precipitate labour, cephalopelvic disproportion, pre-existing pelvic abnormality or excessive thigh abduction that can occur during delivery under epidural anaesthesia. The reported incidence of this condition is lessening as the number of forceps deliveries decreases. Pubic diastasis can be associated with severe suprapubic pain and may take months to several years to resolve.

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Introduction to low back pain

Introduction to low back pain

Low back pain or lumbar spine pain is defined as pain localised below the costal margin and above the inferior gluteal folds, with or without leg pain.

Most patients with low back pain seen in primary care will have a nonspecific local musculoskeletal condition with an acute and self-limited clinical course (see Nonspecific low back pain). Inflammation may occur as part of the repair process; however, it is a consequence of, rather than the cause of, the presentation. The term ‘mechanical back pain’ is sometimes used to describe nonspecific low back pain to highlight the exclusion of an underlying systemic inflammatory disease (eg ankylosing spondylitis) or other serious pathology (eg spinal infection, malignancy, fracture), but should not be used to infer a reliable relationship between symptoms and anatomical structures.

Low back pain associated with spinal nerve root involvement is typically due to a herniated lumbar disc (see Symptomatic lumbar disc herniation), but in older patients is usually due to lumbar canal or foraminal stenosis (see Symptomatic spinal canal stenosis).

Although serious pathology is rare in patients presenting with low back pain in primary care, clinical suspicion of such pathology should be raised by the presence of alerting features (see Table 12.19).

Assessment of low back pain

Assessment of low back pain

Clinical assessment

Clinical assessment

Nonspecific low back pain is poorly localised and often influenced by posture and movement. It may be associated with nonradicular leg pain that is also poorly localised and dull or aching in character; this is described as somatic referred pain.

Nerve root involvement is suggested by the presence of radicular pain. Lumbar radicular pain is often described by patients as a sharp, shooting or burning pain that radiates down the lateral or posterior side of one leg, or rarely both legs, often to the ankle or foot. It is sometimes associated with a ‘pins and needles’ sensation. Pain is often experienced in a dermatomal distribution and may be aggravated by coughing, sneezing or straining. Radicular leg pain may be associated with neurological symptoms or signs (eg weakness, dermatomal hyperaesthesia or hypoaesthesia, absent or reduced reflexes). The presence of radicular leg pain alone is not considered a serious pathology in the absence of severe or progressive neurological deficits. Radicular pain due to nerve root involvement in the lumbar spine is commonly referred to as ‘sciatica’, although nerve roots from L1 to L4 may also be involved. See also Assessment of symptomatic lumbar disc herniation and Assessment of symptomatic spinal canal stenosis.

In all patients with low back pain, consider and exclude serious pathologies; clinical suspicion of these is raised by the presence of alerting features (see Table 12.19). Any indication of cauda equina compression is a spinal emergency; immediately refer the patient to an emergency department for review by a neurosurgeon or spinal surgeon.

Any indication of cauda equina compression is a spinal emergency.

In patients with nonspecific low back pain, a precise anatomical diagnosis is usually not necessary, or possible with physical examination. However, a physical examination is still important to identify alerting features of serious pathologies and neurological signs, and to understand the patient's spinal movement patterns and limitations. Spinal symmetry, posture and flexibility, and spinal tenderness can be assessed with the patient standing. Firm digital palpation over spinous processes and paraspinal structures may reproduce the back and referred leg pain. Abdominal examination, pelvic examination, or assessment of hip irritability and range of movement is indicated if history suggests pathology in these areas.

Table 12.19 Alerting features ('red flags') of serious pathologies in patients with spinal pain

Serious pathology	Alerting features [NB1]
spinal infection (eg osteomyelitis, epidural abscess)	• symptoms and signs of infection (eg fever) • risk factors for infection (eg underlying disease, immunosuppression, penetrating wound, history of injecting drugs) • raised inflammatory markers (eg CRP, ESR) [NB2]
vertebral fracture	• history of significant trauma • history of minor trauma if: age older than 50 years, history of osteoporosis or taking corticosteroids
malignancy	• history of malignancy • age older than 50 years • failure to improve with treatment • unexplained weight loss • pain at multiple sites • pain at rest • symptoms in other body systems (eg cough, dysphagia)
visceral disease (eg pancreatitis, aortic aneurysm [leak or rupture])	• sudden onset of pain • absence of aggravating features (eg pain not aggravated by spinal movement) • associated collapse or hypotension • abdominal pain radiating to the back
cauda equina compression	• altered bladder and/or bowel function (eg urinary retention, faecal incontinence) • reduced sensation in the 'saddle' area • progressive bilateral foot or leg weakness
spinal cord pathology (myelopathy)	• a sensory level • weakness • hyperreflexia or hyporeflexia • upgoing plantar responses • sensory loss • see also cervical myelopathy
ankylosing spondylitis	• younger age (onset before 40 years) • symptom duration of longer than 3 months • prolonged morning stiffness and night pain • alternating buttock pain • improvement of symptoms with physical activity or exercise, and failure to improve with rest • response to NSAIDs

Serious pathology	Alerting features [NB1]

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; NSAIDs = nonsteroidal anti-inflammatory drugs

NB1: The presence of a single alerting feature is associated with a small increased likelihood of serious pathology compared with the presence of multiple alerting features.

NB2: ESR and CRP should only be measured if other alerting features for spinal infection are present.

Imaging

Imaging

Radiological findings are poorly correlated with symptoms in patients with low back pain. Many commonly reported abnormalities on lumbar spine imaging are physiological and not related to the experience of pain. For example, disc abnormalities, facet joint arthropathy, annular tears and spondylolisthesis occur frequently in adults without back pain. Giving patients a diagnostic label (eg a ruptured, torn, prolapsed or herniated disc) based on radiological findings is unhelpful and often leads to fear-avoidance behaviour, worsening disability and unwarranted further investigation and treatment.

Radiological findings are poorly correlated with symptoms in patients with low back pain.

Lumbar spine X-ray and magnetic resonance imaging (MRI) have no utility in patients with nonspecific low back pain, but may be considered to investigate serious pathologies if suspected clinically (see Table 12.19). Choice of investigation should be guided by the suspected pathology. MRI is superior to computed tomography (CT) and has a lower risk of harm because of less radiation exposure, but CT may be considered if MRI is contraindicated or unavailable. For discussion of imaging in patients with radicular pain, see Assessment of symptomatic lumbar disc herniation and Symptomatic spinal canal stenosis.

Nonspecific low back pain

Nonspecific low back pain

Introduction

Introduction

About 80% of people will experience an episode of nonspecific low back pain at some time in their lives, and it is most common between the ages of 35 and 55 years. Most episodes are acute and mild, but the prevalence of chronic severe, disabling pain increases with age (see Prognosis of nonspecific low back pain). Up to half of patients seek medical care, most in the primary care setting. Adolescents and children also experience nonspecific low back pain, and unresolved pain in youth is a predictor of pain in adulthood.

For assessment of patients with low back pain, see Assessment of low back pain. Lumbar spine imaging has no utility in patients with nonspecific low back pain, but may be considered if neurological symptoms or signs are present or a serious pathology is suspected clinically (see Table 12.19); see Imaging.

Risk factors for developing nonspecific low back pain include heavy physical work; frequent bending, twisting, or lifting; and prolonged static postures. Symptoms of depression and lifestyle factors (eg smoking, obesity, physical inactivity) are also associated with nonspecific low back pain. Exercise has a significant protective effect against nonspecific low back pain.

Prognosis of nonspecific low back pain

Prognosis of nonspecific low back pain

Low back pain is designated as acute if it persists for less than 12 weeks or chronic if it persists for longer than 12 weeks. The outcome of a single episode of nonspecific low back pain is generally favourable. Most patients have an acute course that improves rapidly (usually within 4 weeks) with no ongoing limitation in daily activities, and patients can resume normal physical function and return to work quickly regardless of whether the pain has fully resolved. However, many of these patients will have recurrent episodes of low back pain.

A small number of patients develop chronic nonspecific low back pain, which can be severe and disabling. Among those who present with chronic symptoms, two-thirds are still not fully recovered at 1 to 2 years. Therefore, early intervention to address risk factors for chronicity is important in patients with acute low back pain.

Risk factors for poor prognosis include a high level of pain and disability at presentation, leg pain, older age, poor general health, psychosocial factors (eg mental stress, anxiety, depression), and reduced cognition. For work-related prognostic factors, see Prevention of work-related disability. Misconceptions about the nature of the pain and unhelpful coping strategies can also contribute to poor prognosis; these include:

- belief that back pain is harmful to the spine
- belief that there is structural damage to the spine associated with spinal weakness or instability
- fear-avoidance behaviour and reduced activity and participation
- lowered mood and withdrawal from social interaction
- belief that passive treatment(s) alone rather than active participation will help.

Assessment of risk factors for poor prognosis may be aided by the use of validated tools, such as the STarT Back tool [Note 1] or Örebro Musculoskeletal Pain Questionnaire [Note 2]. Depending on the duration of symptoms at the time of presentation, some risk factors for poor prognosis may not be assessable initially.

Note 1: The STarT Back tool is available at [URL].

Note 2: Linton SJ, Boersma K. Early identification of patients at risk of developing a persistent back problem: the predictive validity of the Örebro Musculoskeletal Pain Questionnaire. Clin J Pain 2003;19(2):80-6. [URL]

General management approach for nonspecific low back pain

General management approach for nonspecific low back pain
Acute nonspecific low back pain

In acute nonspecific low back pain, the aims of management are to reduce pain, restore and maintain physical function, minimise disability and absence from work, and reduce the risk of chronicity.

In most patients with acute nonspecific low back pain, minimal intervention is required and symptoms resolve with appropriate patient education and reassurance of favourable prognosis. Oral analgesia may be required (see Pharmacological management of nonspecific low back pain), and massage or thermotherapy may be considered for pain relief based on patient preference (see Nonpharmacological management of nonspecific low back pain). To reassure patients and aid confidence in self-management, schedule a review appointment at 4 to 6 weeks and advise the patient to cancel the appointment in the likely event that their pain improves.

Patient education should include:

- an explanation of the nature of the pain and why imaging is not required—most back pain is caused by a simple strain of the back and a serious underlying cause is very unlikely; in most patients it is not possible to make a precise anatomical diagnosis on clinical or radiological grounds, or to identify a specific cause for the pain

- advice to stay active (see Staying active)
- encouragement to continue to work or to return to work as soon as possible (see Prevention of work-related disability)
- reassurance that recovery is likely to be quick even though pain may be severe
- an assessment and clarification of patient misconceptions about the nature of the pain, including addressing fear-avoidance behaviour and other unhelpful coping strategies that contribute to poor prognosis.

Printed or online information that reinforces these messages is useful to supplement advice provided by the clinician [Note 3]. Physiotherapists can have a role in patient education in acute nonspecific low back pain, and referral should be considered particularly for patients with risk factors for poor prognosis (see Prognosis of nonspecific low back pain).

If there is **persisting pain** that is not improving by 4 to 6 weeks, reassess the patient for serious pathologies (see Table 12.19). In patients with persisting nonspecific low back pain, early intervention to prevent progression to chronicity is important; use an integrated biopsychosocial approach to management that addresses risk factors for poor prognosis (see Prognosis of nonspecific low back pain). Components of management include:

- patient education and reassurance, including advice to stay active (see Staying active)
- support for continuing or returning to work (see Prevention of work-related disability)
- identification and management of psychosocial factors; consider cognitive behavioural therapy (see Nonpharmacological management of nonspecific low back pain) and treat specific diagnoses (eg depression or anxiety)
- exercise
- if required, oral analgesia (see Pharmacological management of nonspecific low back pain)
- if appropriate, massage or thermotherapy for pain relief (see Nonpharmacological management of nonspecific low back pain).

Chronic nonspecific low back pain

Management of chronic nonspecific low back pain should follow the same principles as for other types of noninflammatory chronic pain and should be based on an integrated biopsychosocial approach (see General principles of chronic pain management).

See also the components of management for persisting acute nonspecific low back pain (see Acute nonspecific low back pain); in particular, exercise is beneficial for chronic nonspecific low back pain and should be encouraged. Multidisciplinary rehabilitation programs aim to simultaneously address all components (physical, psychological and social) of the patient's pain experience. They may reduce pain and improve physical function; however, the ideal content and context for these programs, including the number and duration of sessions, is unclear.

Corticosteroid injections are not recommended for nonspecific low back pain, including putative facet joint pain, because evidence does not support a benefit.

Anaesthetic blocks or provocation techniques may be used to attempt to identify specific structures that may be responsible for low back pain. However, currently, there are no proven treatment options for patients with chronic low back pain in whom such investigations suggest a nociceptive input from discs or sacroiliac joints. There is limited evidence that percutaneous radiofrequency facet denervation provides pain relief in the small number of individuals demonstrated to have isolated facet joint pain. The proponents of these techniques assert that meticulous identification of appropriate patients is required and that these techniques should only be undertaken by skilled treatment providers in specialist centres. Decisions to investigate chronic nonspecific low back pain for therapeutic purposes should be coordinated by specialists; current evidence does not justify widespread use of this approach.

Evidence does not support a role for surgery in chronic nonspecific low back pain.

Note 3: Patient information on low back pain can be found on the WA Health Networks and painHEALTH websites. Any management advice given in these sources should be considered in the context of the recommendations in these guidelines.

Lifestyle management of nonspecific low back pain

Lifestyle management of nonspecific low back pain
Staying active

Encourage patients with nonspecific low back pain to stay active, including adopting normal movement and physical function as much as possible, and continuing or returning to work (see Prevention of work-related disability). Compared to bed rest, staying active reduces pain, disability and time off work, and increases the rate of recovery. Prolonged bed rest is harmful and should be discouraged. Adverse effects of bed rest include joint stiffness, prolonged pain, muscle wasting and bone demineralisation.

Reassure patients that although some pain with activity is likely, this does not imply damage to the spine (ie 'hurt does not mean harm'), and that staying active is not associated with recurrent episodes of low back pain. Oral analgesia may be required to facilitate staying active (see Pharmacological management of nonspecific low back pain).

Reassure patients and encourage them to maintain usual activities.

To assist patients with staying active, provide advice on techniques to minimise pain when getting out of bed and moving around; this advice may be provided by a physiotherapist. Encourage pacing of activities, and resuming usual activities and work in a graded manner.

Prevention of work-related disability

A large proportion of patients with nonspecific low back pain are able to continue their usual work without modification or restrictions, and work participation is important for recovery from nonspecific low back pain. Extended initial time off work is associated with prolonged work-related disability; fewer than half of patients who have been off work for 6 months will return to work and, after 2 years of work absenteeism, the chance of returning to work is negligible.

The patient's expectation of return to work is the most important predictor of return to work. Other barriers to returning to work and recovery from nonspecific low back pain include poor relations with colleagues, work-related mental stress, heavy physical work demands, the presence of compensation claims, and inappropriate work capacity certification from health professionals. Address work-related prognostic factors early to prevent prolonged disability; suggested questions for identifying these include:

- Have you had time off work in the past with back pain?
- What do you understand is the cause of your back pain?
- What are you expecting will help?
- How are your employers, colleagues, and family responding to your back pain?
- What are you doing to cope with back pain?
- Do you think that you will return to work? When?

The optimal approach to supporting the patient in returning to work includes:

- providing reassurance about returning to work and staying active
- understanding the patient's work context and job demands in relation to their physical capacity and beliefs
- understanding the employer's ability to accommodate the patient's needs
- communicating with the patient's employer to facilitate a prompt return to work; if necessary, return to work may require modifying the patient's duties and/or hours.

Exercise

Exercise is safe for the majority of patients with nonspecific low back pain. Graded exercise programs can assist in recovery by improving physical function and normalising central nervous system activity (which is often altered in people who experience chronic pain). Encouraging patients to exercise also reinforces positive beliefs about recovery, self-efficacy and physical capacity, and important messages about staying active and resuming usual activities in a graded manner. Maintaining exercise after the resolution of an acute episode of nonspecific low back pain may reduce the frequency of recurrent episodes.

Many different exercise programs have been advocated for the treatment of nonspecific low back pain, including exercises in a specific direction (direction-biased exercise programs, eg flexion or extension), exercises to strengthen the trunk stabilising muscles, and exercises to improve flexibility or enhance aerobic fitness. Given the wide range of potentially appropriate exercise modes and dosages, it is difficult to draw definite conclusions about the comparative effectiveness of specific programs. Data suggest exercise that promotes whole-body, compound movements (eg squats, lunges, step-ups) and is functionally oriented is more beneficial than non-functional exercise (eg specific stabilising exercises). Furthermore, isolated non-functional exercise may reinforce misconceptions about the nature of the pain and fear-avoidance behaviour in the longer term.

In this context, a pragmatic approach to exercise for nonspecific low back pain is recommended based on the practice points in Figure 12.14. Appropriately guided exercise programs can be undertaken independently, in a group, or as part of an existing fitness program. Consider referral to a physiotherapist particularly for patients with risk factors for poor prognosis (see Prognosis of nonspecific low back pain). In the short term, some patients may require specific movement re-education or exercise based on their clinical presentation (eg severity of pain, anxiety related to pain). This approach may also be needed for patients who do not recover within a clinically reasonable time frame.

Oral analgesia may be required to facilitate exercise (see Pharmacological management of nonspecific low back pain).

Figure 12.14 Practice points for recommending exercise for patients with nonspecific low back pain

- Emphasise to the patient that it is safe and helpful to move. Bracing and avoiding normal movements is unhelpful in the long term. Using phrases like ‘hurt does not mean harm’, ‘sore but safe’, and ‘your spine is strong’ may be helpful. Some patients may benefit from individualised education about their beliefs, fears and pain experience.
- Exercise programs should be individualised, taking into account the patient's physical activity preferences, beliefs and specific functional impairments.
- Exercise programs should include stretching, strengthening and aerobic exercises that are functionally oriented.
- Starting with gentle movements is the first step. These might include water-based walking, land-based walking, gentle swimming and floor stretches that encourage the spine to move in its normal planes. Activity should be graded by the duration of time spent exercising, rather than the pain experienced.
- As the patient's tolerance to activity over longer periods of time increases, the mode, frequency and/or intensity of activity can be progressed.
    - Functional exercises can be introduced to encourage large muscle group activation (eg squats, lunges, step-ups).
    - Exercise that patients enjoy (eg yoga, Pilates, walking, cycling) can be gradually introduced (eg start at 15 to 20 minutes' duration and then increase).
- In the later stages of rehabilitation, more dynamic and higher-load exercises can be performed.

Nonpharmacological management of nonspecific low back pain

Nonpharmacological management of nonspecific low back pain

Passive physical treatments alone have a limited role in the management of nonspecific low back pain. Although the evidence to support their use is limited, some patients report temporary pain relief from **thermotherapy** (application of heat or cold) and **massage**. A trial of these treatments may be considered as part of an overall management approach that includes patient education and re-introduction of physical activity (see General management approach for nonspecific low back pain).

The following passive physical treatments are not recommended for nonspecific low back pain because evidence does not support a benefit: acupuncture, spinal manipulative therapy, lumbar supports, transcutaneous electrical nerve stimulation (TENS), laser therapy, traction, electromyographic biofeedback, therapeutic ultrasound or short-wave diathermy.

Preliminary studies of motion-sensor biofeedback indicate a benefit in low back pain, but further data are required before this therapy can be recommended.

Cognitive behavioural therapy (CBT) helps patients develop adaptive coping behaviours and strategies to self-manage their pain. CBT is effective for persisting and chronic nonspecific low back pain and should be considered early if psychosocial factors are identified. See Cognitive behavioural therapy for pain management for more information.

Pharmacological management of nonspecific low back pain

Pharmacological management of nonspecific low back pain

Ensure other components of nonspecific low back pain management, in particular patient education and reassurance (see General management approach for nonspecific low back pain), have been implemented before considering pharmacological management.

Explain to the patient that the goal of pharmacological management is to reduce, rather than abolish, pain so that physical function can be maintained. Oral analgesia can be useful to facilitate exercise and staying active, but advise patients that some pain with activity is likely and reassure them that this does not imply damage to the spine.

A trial of a nonsteroidal anti-inflammatory drug (NSAID) is recommended for short-term pain relief. Use:

an NSAID orally (see Table 12.7 for dosing). *back pain, low back*

The potential benefits of an NSAID should be weighed against its potential harms, particularly in patients at high risk of harms (see Principles of NSAID use for musculoskeletal conditions in adults for more information).

Evidence indicates that paracetamol is ineffective for nonspecific low back pain. However, individual patients may experience a benefit and, because of its favourable safety profile, a trial of paracetamol may be considered if NSAIDs are contraindicated or not tolerated. Use:

1 paracetamol 1 g orally, 4- to 6-hourly as necessary, up to a maximum of 4 g daily *back pain, low back*

OR

1 paracetamol modified-release 1.33 g orally, 8-hourly as necessary.

For patients with pain that persists throughout the day, or if there is inadequate response to ‘as necessary’ dosing, consider a trial of regular rather than ‘as necessary’ dosing of oral analgesia.

Oral corticosteroids are occasionally used as part of an analgesic strategy for acute nonspecific low back pain, but evidence does not support a benefit. Given the significant adverse effects of long-term corticosteroid use, oral corticosteroids should not be used for chronic nonspecific low back pain.

Although commonly prescribed, opioids have a very limited role in the management of nonspecific low back pain. Evidence for efficacy of opioids in acute low back pain is lacking. In chronic low back pain, opioids provide only modest short-term pain relief and evidence for long-term efficacy is lacking. Opioids are associated with a significant risk of harms. Opioids may be considered for patients with severe pain that is not adequately relieved with other measures and is interfering with their ability to function. If opioids are used, they should be prescribed on a short-term trial basis, as part of an overall pain management strategy, with clear goals and regular review of treatment response and adverse effects. Before starting an opioid, a plan for ceasing ineffective therapy should be in place and discussed with the patient. If treatment response is

inadequate, caution should be exercised when increasing the dose of opioids as there is an increased risk of harm and potentially no added benefit. Prolonged use of opioids indicates the need for specialist assessment. See Opioids for more information.

Studies up to 1 year in patients with chronic low back pain indicate that tapentadol may have a more favourable safety profile than oxycodone; however, the long-term safety of tapentadol is not known and the same precautions as for other opioids should be applied to tapentadol.

There is no evidence that muscle relaxants are effective for persisting or chronic nonspecific low back pain. In the acute setting (used for less than 4 days), there is evidence that muscle relaxants may reduce pain and muscle tension, and increase mobility, but their potential harms may outweigh any potential benefits. Drowsiness, dizziness, increased risk of falls and dependency are common adverse effects.

Symptomatic lumbar disc herniation

Symptomatic lumbar disc herniation

Introduction

Introduction

Lumbar disc herniation is often asymptomatic; up to 36% of people without a history of back pain have a herniated disc on imaging and this finding is more common in older people. While lumbar disc herniation can cause spinal nerve root compression, evidence indicates that nerve root compression alone is insufficient to cause symptoms and that inflammation is also important. The prevalence of symptomatic lumbar disc herniation is between 1 and 3%, with the highest prevalence reported in patients between 30 and 50 years of age. Most herniated discs occur at the L4 to L5 level; disc herniations above this level are more common in people over 55 years of age.

In symptomatic lumbar disc herniation, the herniated portion of the disc may regress over time. Most patients who present for care improve rapidly (within 2 weeks); 80% of patients recover within 8 weeks and 95% of patients recover within a year. Prognostic factors in symptomatic lumbar disc herniation have not been well studied.

Assessment of symptomatic lumbar disc herniation

Assessment of symptomatic lumbar disc herniation

Nerve root involvement is suggested by the presence of radicular leg pain (see Clinical assessment). Pain may be worse in certain positions, such as sitting.

A positive straight-leg raise test is highly sensitive (around 91%) for nerve root involvement, but has a low specificity (around 26%). A positive straight-leg raise test is defined as reproduction of radicular leg pain when the affected leg is elevated to less than 60 degrees with the ankle dorsiflexed and the knee fully extended. A positive crossed straight-leg raise test is highly specific (around 88%) for nerve root involvement, but has a low sensitivity (around 29%). A positive crossed straight-leg raise test is defined as reproduction of radicular leg pain when performing a straight-leg raise test on the contralateral side. Early referral to a specialist should be considered if the diagnosis is uncertain.

Neurological symptoms and signs aiding the localisation of possible nerve root involvement are given in Table 12.20. Any indication of cauda equina compression is a spinal emergency; immediately refer the patient to an emergency department for review by a neurosurgeon or spinal surgeon. Alerting features of other serious pathologies in patients with spinal pain should also be excluded (see Table 12.19).

Any indication of cauda equina compression is a spinal emergency.

X-rays are not useful for symptomatic lumbar disc herniation. The diagnosis can be confirmed by magnetic resonance imaging (MRI) or, if not available, computed tomography (CT); however, early imaging (before 6 to 8 weeks) is unnecessary unless there are severe or progressive neurological deficits or there is concern about a neurological deficit.

Table 12.20 Symptoms and signs of nerve root involvement at different spinal levels

Level	Reduced muscle power	Reduced sensation	Reduced or absent reflex	Other
L3 or L4	knee extension	anterior and lateral aspects of thigh	knee jerk	
L5	dorsiflexion of big toe and ankle	particularly dorsum of foot	ankle jerk	
S1	plantar flexion of ankle	particularly lateral aspect and sole of foot	ankle jerk	
cauda equina	progressive bilateral foot or leg weakness	'saddle' area		altered bladder and/or bowel function (eg urinary retention, faecal incontinence)

Management of symptomatic lumbar disc herniation

Management of symptomatic lumbar disc herniation

Conservative management is generally recommended in the first 6 to 8 weeks. Management is essentially the same as for nonspecific low back pain (see General management approach for nonspecific low back pain). Patients should be given adequate explanation about the condition including its cause, lack of need for early diagnostic imaging, and the expected outcome.

Encourage patients to continue with usual activities; however, some activity modification will be necessary to avoid provoking pain. Physical treatments such as massage, acupuncture, exercise and traction are of unknown efficacy, and the safety of spinal manipulation in patients with significant radicular symptoms is uncertain.

Translumbar, transsacral or transforaminal (or 'nerve root') epidural corticosteroid injections may provide short-term pain relief in some patients; however, the average improvement in pain is small. A 15-day course of oral corticosteroids may improve physical function, but has little effect on pain. There is no evidence to support the use of intradiscal corticosteroid injection or chemonucleolysis of the disc with chymopapain injection. Drugs that are indicated for neuropathic pain (eg tricyclic antidepressants, gabapentin, pregabalin) may be useful for radicular pain, which could be considered to be a neuropathic pain; however, evidence from high-quality randomised controlled trials is lacking.

Surgical consultation is indicated for all patients with severe or progressive neurological deficits, or for any patient if there is concern about a neurological deficit. Surgical consultation should be considered for patients with severe persisting leg pain at 6 to 8 weeks despite conservative management, provided there is concordance between radiological findings and neurological signs. Surgery results in more rapid recovery than conservative management; however, long-term outcomes are similar in patients who have early surgery and those who have prolonged conservative management followed by surgery if needed. Potential harms from surgery include complications from anaesthesia, infection, and neurological damage.

Symptomatic spinal canal stenosis

Symptomatic spinal canal stenosis

Introduction

Introduction

Spinal canal stenosis is the narrowing of the vertebral or intervertebral canal and is often multifactorial. The lower three lumbar levels are most frequently affected. Spinal canal stenosis can be asymptomatic and is detected on imaging in over 20% of people older than 60 years of age without a history of back pain.

The clinical course of symptomatic spinal canal stenosis is variable, and can be unpredictable, with flares and stable periods over time. Approximately 50% of patients remain clinically stable, while 25% deteriorate over time and the remaining 25% improve over time. Despite the common perception of a progressive course, patients with mild to moderately symptomatic spinal canal stenosis have a favourable outcome in 30 to 50% of cases.

Assessment of symptomatic spinal canal stenosis

Assessment of symptomatic spinal canal stenosis

Symptomatic disease generally presents with low back pain radiating to the buttocks and legs, and is usually bilateral. Patients can also present with leg pain alone and no back pain. Pain may be aggravated by walking or standing, and relieved by sitting or leaning forward (neurogenic claudication or pseudoclaudication); this must be distinguished from the similar symptoms of claudication due to arterial insufficiency. Radicular leg pain in a single dermatomal distribution is more suggestive of single nerve root compression (see Symptomatic lumbar disc herniation).

Progressive bilateral foot or leg weakness, reduced sensation in the ‘saddle’ area, and altered bladder and/or bowel function (eg urinary retention, faecal incontinence) indicate the possibility of cauda equina compression. Any indication of cauda equina compression is a spinal emergency; immediately refer the patient to an emergency department for review by a neurosurgeon or spinal surgeon. Alerting features of other serious pathologies in patients with spinal pain should also be excluded (see Table 12.19).

Any indication of cauda equina compression is a spinal emergency.

In patients with suspected symptomatic spinal canal stenosis, the diagnosis can be confirmed by magnetic resonance imaging (MRI) or, if not available, computed tomography (CT).

Management of symptomatic spinal canal stenosis

Management of symptomatic spinal canal stenosis

Most commonly used treatments for symptomatic spinal canal stenosis are of unproven benefit. Conservative treatments include physical therapy and exercise. Epidural corticosteroid injection is often considered; however, recent evidence does not demonstrate a benefit. Oral corticosteroids are not effective for symptomatic spinal canal stenosis.

Surgical consultation is indicated for all patients with severe or progressive neurological deficits, or for any patient if there is concern about a neurological deficit. Surgical consultation should be considered for patients with severe persisting pain despite conservative management. Surgery may have an early benefit compared to conservative management; however, the long-term effects are uncertain. The risk of harms from surgery increases with advancing age, comorbidity and concurrent fusion.

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Key references: Introduction to nonspecific low back pain

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Introduction to fibromyalgia

Introduction to fibromyalgia

In contrast to inflammatory connective tissue syndromes, chronic diffuse noninflammatory soft-tissue pain is very common. No consistent measurable investigational abnormality has yet been found and the best way to define this problem is still debated. Fibromyalgia is the current preferred term for the common and well-defined clinical syndrome of chronic widespread noninflammatory musculoskeletal pain accompanied by a variety of typical symptoms including fatigue, sleep disturbance and cognitive clouding.

The pathophysiology of fibromyalgia is complex and remains poorly understood. Altered levels of neurotransmitters in the cerebrospinal fluid (CSF), as well as various abnormalities on functional imaging studies, have been demonstrated in patients with fibromyalgia. These findings suggest that central nervous system mechanisms (including central sensitisation) are fundamental to the development of the multiple symptoms of fibromyalgia.

The absence of laboratory or imaging abnormalities can be challenging for both patients and practitioners, particularly if a simple biomedical causal model to explain the patient's symptoms has been sought. A more nuanced biopsychosocial understanding of fibromyalgia is preferred; however, it should be understood that this does not imply that symptoms are a direct consequence of psychological distress.

See Diffuse amplified musculoskeletal pain for information on paediatric fibromyalgia.

Assessment of fibromyalgia

Assessment of fibromyalgia

Pain in fibromyalgia is typically widespread and may be experienced in both soft tissues and joints. While pain severity often fluctuates, it rarely follows the consistent diurnal pattern seen in inflammatory disorders. Patients may present with regionalised pain related to a recent event, but a detailed history often reveals a more extensive pain history. Some individuals may be genetically predisposed to widespread pain, and a history of ‘growing pains’ or other painful disorders in childhood is not uncommon.

While chronic widespread musculoskeletal pain is the hallmark of fibromyalgia, patients typically experience a variety of other symptoms including cognitive clouding (known as ‘fibrofog’), fatigue, impaired concentration, sleep dysfunction, depression, and gastrointestinal and urogenital dysfunction and discomfort (irritable bowel and irritable bladder). Sleep dysfunction may be both a consequence of widespread pain and a contributor to its persistence. Practitioner time and patience are required to thoroughly evaluate the patient's fibromyalgia symptoms in the context of their individual life-course and sociocultural setting.

A thorough general physical and musculoskeletal examination should be performed in all patients. There are no physical examination findings specific to fibromyalgia; however, soft-tissue tenderness to pressure is typically diffuse. While the location and severity of tenderness varies between patients, some anatomical locations (eg lateral epicondyles, trapezius muscles, anserine bursae) are tender in the majority of patients with fibromyalgia. The presence of allodynia (pain induced by normal touch) should be sought in both history and examination; pain induced by inflation of a sphygmomanometer cuff is a useful screening tool. Dermographism is seen in some patients.

Diagnostic criteria have been developed that incorporate both widespread pain and other symptoms typical of fibromyalgia; a formal tender point count is not required.

The diagnosis of fibromyalgia is not confirmed by the results of investigations, although normal C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) reassure both patient and doctor that significant inflammatory disease is unlikely to be the cause of symptoms.

Since fibromyalgia frequently coexists with other rheumatological diseases, a complete clinical evaluation of a patient with musculoskeletal pain should seek evidence of joint inflammation as well as the more diffuse soft-tissue tenderness typical of fibromyalgia.

Any change in the nature or pattern of symptoms needs a thorough assessment to avoid missing the onset of a comorbid illness.
Thoroughly assess any change in the nature or pattern of symptoms.

Consider referral to a rheumatologist if the diagnosis is uncertain or the patient's presentation is atypical (see When to refer a patient with fibromyalgia to a specialist).

Management of fibromyalgia

Management of fibromyalgia

General management approach

General management approach

Effective management of fibromyalgia requires a clear diagnosis, thorough patient education informed by a contemporary understanding of pain neuroscience, and an individualised management plan developed collaboratively by the patient and their treating clinician(s).

Patient education regarding the concept of chronic pain and principles of self-management is an effective component of overall management. It is often helpful to include people who are significant in the patient's life (eg a partner, relative or friend) in the process of education and self-management. The patient should be reassured that the condition is not damaging to joints or soft tissues and will not be associated with significant morbidity. Fibromyalgia can be likened to an alarm system that has become oversensitive and is generating its alarm under conditions that offer no threat to the tissues. Interventions in fibromyalgia aim to muffle the alarm so that it is less intrusive upon other activities (see Lifestyle and nonpharmacological management of fibromyalgia and Pharmacological management of fibromyalgia). Helpful points to discuss with a newly diagnosed patient may include:

- The pain experienced by the patient is real but is not caused by tissue damage.
- Fibromyalgia is not a progressive or deforming disease.
- Fibromyalgia is frustrating and, because symptoms fluctuate, the patient may feel like they are taking two steps forward and one step back.
- The chronic pain experienced in fibromyalgia can affect the way the patient feels, but this does not necessarily indicate a problem with their mental health.
- The overarching goal of management is not to achieve a pain-free state but rather to enable the patient to manage their pain so that it does not limit their function.

Printed or online information is useful to reinforce education provided by the clinician [Note 1].

Some patients may need specialist referral (see When to refer a patient with fibromyalgia to a specialist).

Comorbid rheumatological conditions (eg osteoarthritis, rheumatoid arthritis or inflammatory connective tissue disease) need appropriate management.

Note 1: Patient information on fibromyalgia can be found on the painHEALTH website. Any management advice given on this website should be considered in the context of the recommendations in these guidelines.

Lifestyle and nonpharmacological management of fibromyalgia

Lifestyle and nonpharmacological management of fibromyalgia

Regular **graded aerobic exercise** has been shown to reduce pain and fatigue and improve quality of life scores in patients with fibromyalgia. Patients are often physically deconditioned at presentation and may have tried and failed a previous exercise regimen. A graded exercise program should be advised, beginning with very light aerobic exercise, for example walking or exercise in water. The program should prescribe a slow incremental increase in exercise duration and intensity over a realistic time frame of several months. Importantly, the program should be graded by the duration of time spent exercising rather than the pain experienced, to reduce the risk of unhelpful cycles of overexertion followed by inactivity.

The practitioner may also help to design strategies to reduce situational stresses, identify coping strategies that help the individual manage their pain, and provide guidance and support for goal setting. Cognitive behavioural therapy (CBT) may improve pain and function in patients with fibromyalgia. Attention to good sleep practices is also of value. There are some data to suggest that mindfulness-based approaches may also be beneficial in fibromyalgia.

Mutual support from those similarly affected can have a positive effect. The state affiliate organisations of Arthritis Australia maintain fibromyalgia support groups (see the Arthritis Australia website for contact details).

Pharmacological management of fibromyalgia

Pharmacological management of fibromyalgia

Drug therapy is a component of fibromyalgia management; however, it may yield only modest benefits, so is best employed in conjunction with lifestyle and nonpharmacological management. Multiple drugs may need to be trialled sequentially because patients with fibromyalgia commonly experience unpleasant adverse effects or may have an inadequate response to treatment. The tolerability of drug therapy in fibromyalgia is often improved by starting treatment at a low dose and slowly increasing the dose in small increments. As with nonpharmacological interventions, realistic goal setting is recommended, focusing on functional improvement rather than abolition of pain.

Tricyclic antidepressants (TCAs), gabapentinoids, and some serotonin and noradrenaline reuptake inhibitors (SNRIs) have been shown to reduce pain in fibromyalgia; however, at the time of writing these drugs (with the exception of milnacipran) are not approved by the Australian Therapeutic Goods Administration (TGA) for this indication.

Low-dose TCAs are often used as first-line therapy because they have few major adverse effects and, in addition to reducing pain, may improve sleep. The goal of therapy is to achieve a dose that is beneficial without causing daytime drowsiness; this is best achieved with the use of a low starting dose, with small incremental dose increases. Dose adjustments should not usually be made more frequently than monthly; however, if treatment is well tolerated but response is poor, more frequent dose increases (eg fortnightly) can be considered. Amitriptyline and dosulepin (dothiepin) are the most commonly used TCAs for the treatment of fibromyalgia; suitable regimens are:

1 amitriptyline 10 to 25 mg orally, in the early evening; increasing the daily dose by up to 25 mg every 2 to 4 weeks as tolerated and according to response, up to a maximum maintenance dose of 50 mg each evening *fibromyalgia* _

OR

1 dosulepin (dothiepin) 25 mg orally, in the early evening; increasing the daily dose by up to 25 mg every 2 to 4 weeks as tolerated and according to response, up to a maximum maintenance dose of 75 mg each evening. *fibromyalgia* _

If low-dose TCAs are ineffective or poorly tolerated, consider a gabapentinoid or SNRI. Drug choice is influenced by patient factors (including comorbidities; eg an SNRI may be preferred in patients with comorbid depression), potential drug interactions and adverse effects (eg an SNRI may be preferable in obese patients), and drug cost.

If a gabapentinoid is preferred, use:

1 gabapentin 100 to 300 mg orally, in the early evening; increasing to 3 times daily as tolerated and according to response, up to a maximum maintenance dose of 2400 mg daily in 3 divided doses. Do not increase the dose more frequently than every 4 days *fibromyalgia* _

OR

1 pregabalin 25 to 75 mg orally, in the early evening; increasing to twice daily after 3 to 7 days and then increasing slowly as tolerated and according to response, up to a maximum maintenance dose of 450 mg daily in 2 divided doses. *fibromyalgia* _

Individual patient responses to gabapentin and pregabalin can differ; it is reasonable to switch between them if response to one is inadequate.

If an SNRI is preferred, use:

duloxetine 30 mg orally, daily; increasing after 1 month to 60 mg daily and then increasing as tolerated and according to response, up to a maximum maintenance dose of 60 mg twice daily. *fibromyalgia* _

Evidence also supports the use of milnacipran for the treatment of fibromyalgia. However, evidence for the effectiveness of other SNRIs (eg desvenlafaxine, venlafaxine) in fibromyalgia is lacking.

Combination therapy can be used but should be employed with caution. The need for combination therapy should flag consideration for specialist referral.

Analgesia with paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs) is generally only moderately helpful, if at all. Opioids should not be used because they have a significant risk of harm and are rarely of overall benefit.

When to refer a patient with fibromyalgia to a specialist

When to refer a patient with fibromyalgia to a specialist

While fibromyalgia does not cause tissue damage, it is a chronic condition that is often difficult to bear. It is sufficiently common that general practitioners need to be equipped with strategies for assessment and management. Rheumatological assessment can help confirm the diagnosis, exclude alternative diagnoses, and assist the patient to understand and deal with their condition; however, it is not necessary for every patient. Referral should be considered if the patient has an atypical presentation or refractory symptoms. When abnormal mood or adjustment disorders are a feature, psychological or psychiatric assessment may be advisable.

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Key references: Fibromyalgia

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Raynaud phenomenon

Raynaud phenomenon

Introduction

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Raynaud phenomenon is caused by vasospasm of the digits, usually in response to cold exposure or stress. It presents as episodic blanching, cyanosis and then erythema of the digits. The condition is often painful. While Raynaud phenomenon is a common condition, particularly in females, it should be differentiated from the more common complaint of diffusely cold and/or mottled hands that is not associated with a disease process. In the latter situation, the hands recover quickly and evenly.

Raynaud phenomenon can be a primary condition or can occur secondary to a connective tissue disease (eg systemic sclerosis) or other disease (eg arthrosclerosis, malignancy). Suspect an underlying connective tissue disease in a patient with other common clinical features of a connective tissue disease (eg arthralgia, fatigue), an elevated erythrocyte sedimentation rate (ESR), a positive antinuclear antibody (ANA), and abnormal nailfold capillaries on inspection under magnification (eg dilation, capillary dropout, haemorrhage).

Secondary Raynaud phenomenon may cause digital ischaemia (see Digital ischaemia for management).

Management of Raynaud phenomenon

Management of Raynaud phenomenon

In patients with secondary Raynaud phenomenon, optimise the management of the underlying disease. See Inflammatory connective tissue diseases for information on the management of connective tissue diseases.

In all cases of Raynaud phenomenon, advise patients to avoid cold exposure. In the absence of an underlying cause, the use of gloves and warm clothing is often sufficient to control symptoms. Strongly encourage patients to stop smoking. Avoid the use of beta blockers in patients with Raynaud phenomenon because they can worsen symptoms.

In more severely affected patients, particularly those with an underlying connective tissue disease, vasodilator drugs may be used to reduce vasospasm. For first-line therapy, use a dihydropyridine calcium channel blocker:

1 amlodipine 5 to 10 mg orally, daily *Raynaud phenomenon*

OR

1 felodipine modified-release 2.5 to 20 mg orally, daily *Raynaud phenomenon*

OR

1 nifedipine modified-release 30 to 120 mg orally, daily. *Raynaud phenomenon*

Second-line therapy includes topical glyceryl trinitrate (transdermal patches or ointment), angiotensin II receptor blockers, phosphodiesterase-5 inhibitors, alpha blockers, and selective serotonin reuptake inhibitors (SSRIs). Combination therapy with drugs from different classes may be used. Sympathectomy is seldom indicated.

Digital ischaemia

Digital ischaemia

Introduction

Introduction

Digital ischaemia, typically manifesting as digital ulceration, may occur due to secondary Raynaud phenomenon. In patients with Raynaud phenomenon that is secondary to systemic sclerosis, digital ulcers may occur as a consequence of the combined effects of severe Raynaud phenomenon and calcinosis. Ulcers occur over the tips of the digits and also at sites of trauma, such as over the extensor surfaces of contracted digits.

Other causes of digital ischaemia include thromboembolic disease, systemic vasculitis, hyperviscosity, and Buerger disease.

Management of digital ischaemia

Management of digital ischaemia

In patients with digital ischaemia, optimising the management of Raynaud phenomenon as well as the underlying disease is important (see Raynaud phenomenon).

Digital ulcers require protection and regular dressings using preparations such as povidone-iodine. Moisture-donating dressings to soften dry eschar, followed by debridement to allow healing, may be required. If ulcers fail to heal, excision of substantial underlying calcinosis may be necessary.

Suspect infection if ulcers become increasingly painful, red and swollen. For management of infected digital ulcers, see Cellulitis and erysipelas. It is important to remain alert to the possibility of infection spreading to cause septic arthritis or osteomyelitis. For management of septic arthritis, see Septic arthritis, and for management of osteomyelitis, see Osteomyelitis.

Adequate analgesia should be given (see Using analgesics to manage acute pain).

If ulcers are refractory to treatment, admission to hospital may be necessary for administration of a potent vasodilator, such as intravenous alprostadil or iloprost, under the supervision of an experienced clinician.

Critical digital ischaemia or necrosis is a digit-threatening event that can occur in patients with secondary Raynaud phenomenon due to an underlying connective tissue disease. Critical digital ischaemia is a medical emergency that always requires urgent specialist assessment, and usually requires hospital admission. Potent vasodilators, such as intravenous alprostadil or iloprost, are often beneficial. Anticoagulants are used if there is evidence of recent vascular thrombosis or thromboembolism. Antibiotics are required if there is associated infection. Patients with digital ischaemia can recover well with adequate therapy, so surgical amputation should be a last resort.

Key references: Raynaud phenomenon and digital ischaemia

Key references: Raynaud phenomenon and digital ischaemia

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Introduction to systemic vasculitides

Introduction to systemic vasculitides

Vasculitis is an inflammatory process affecting blood vessel walls. The vasculitides are a heterogeneous group of uncommon diseases ranging from self-limited cutaneous vasculitides to catastrophic life- and organ-threatening systemic vasculitides. The systemic vasculitides are addressed here. The cutaneous vasculitides leukocytoclastic vasculitis and urticarial vasculitis are addressed in the Dermatology guidelines.

The systemic vasculitides are thought to have an autoimmune pathogenesis. Blood vessel inflammation can result in occlusion, stenosis or aneurysm, leading to organ damage through haemorrhage or infarction. The kidneys and/or lungs are often affected and the severity and extent of their involvement is closely related to the disease prognosis.

The specific systemic vasculitides can be characterised by the size and type of affected blood vessels (see Table 12.18); however, their classification is evolving. Serology and organ involvement are increasingly recognised in the classification of these conditions.

Diagnosis of systemic vasculitides

Diagnosis of systemic vasculitides

The features of a systemic vasculitis may be nonspecific. Although all vasculitic syndromes are rare, a systemic vasculitis should be suspected in any patient with an unexplained persistent inflammatory state (eg fever, weight loss, night sweats, fatigue, malaise, raised inflammatory markers). Specific clinical features may suggest a particular vasculitic syndrome (see Table 12.18), but diagnosis can be complex and up to 40% of patients do not fit the classical description for any of the specific vasculitides. Urgently refer any patient with a suspected systemic vasculitis to a specialist.

Urgently refer any patient with a suspected systemic vasculitis to a specialist.

Some infections (eg sepsis, endocarditis) may have a similar clinical presentation to a systemic vasculitis. Other differential diagnoses are malignancy, use of illicit drugs such as cocaine and amfetamine, cholesterol embolisation, cryoglobulinaemia and atrial myxoma.

For most of the systemic vasculitides, diagnosis is confirmed by the identification of vascular inflammation in a biopsy of affected tissues. The choice of tissue or organ for biopsy is directed by the clinical presentation. For vasculitis affecting larger blood vessels that cannot be easily accessed for biopsy, such as the aorta or splanchnic vasculature, imaging may confirm the diagnosis without the need for biopsy.

Serological tests, such as antineutrophil cytoplasmic antibody (ANCA), are helpful in diagnosis but should only be performed if the patient's clinical presentation suggests a specific vasculitis for which serological confirmation is needed. For example, ANCA testing should be considered in patients with a vasculitic rash, acute glomerulonephritis, pulmonary haemorrhage, or refractory ear, nose and throat symptoms.

See also specific considerations in the diagnosis of each systemic vasculitis.

Table 12.18 Classification of systemic vasculitides

[NB1]

Systemic vasculitis	Key clinical features
Large-vessel vasculitides (often affect the aorta and/or its major branches)	
Takayasu arteritis	• upper limb claudication • absent pulses, arterial bruits, hypertension
giant cell arteritis [NB2]	• jaw claudication, severe headache, scalp tenderness • diplopia or visual loss • polymyalgia rheumatica • systemic symptoms such as weight loss, fever and malaise
Medium-vessel vasculitides (predominantly affect the main visceral arteries and their branches)	
polyarteritis nodosa	• palpable purpura, livedo reticularis • peripheral neuropathy • intestinal and liver ischaemia • renal vasculopathy
Kawasaki disease [NB3]	• occurs almost exclusively in children • see Figure 12.13
Small-vessel vasculitides (predominantly affect small intraparenchymal arteries, capillaries, venules or arterioles)	
ANCA-associated vasculitides	
microscopic polyangiitis	• acute, rapidly progressive glomerulonephritis • pulmonary haemorrhage • palpable purpura
granulomatosis with polyangiitis (formerly known as Wegener granulomatosis)	• sinusitis, nasal disease and subglottic stenosis • otitis media, hearing loss and ear pain • pulmonary infiltrates and nodules, haemoptysis and pleuritis • glomerulonephritis
eosinophilic granulomatosis with polyangiitis (formerly known as Churg–Strauss vasculitis)	• asthma • pulmonary and blood eosinophilia • mononeuritis multiplex • palpable purpura, skin infarcts, nodules over pressure areas • focal, segmental necrotising glomerulonephritis • granulomatous infiltration of the myocardium, coronary vasculitis
Immune-complex vasculitis	
immunoglobulin A vasculitis (formerly known as Henoch–Schönlein purpura)	• occurs predominantly in children • nonthrombocytopenic purpura • colicky abdominal pain • large-joint arthritis • renal vasculopathy

ANCA = antineutrophil cytoplasmic antibody

NB1: This table only lists the systemic vasculitides discussed in this topic; other specific systemic vasculitides have been defined, including vasculitis associated with other inflammatory syndromes (eg cryoglobulinaemia, Behçet syndrome).

NB2: Giant cell arteritis typically affects the cranial arteries, including the ophthalmic artery.

NB3: Kawasaki disease typically affects the coronary arteries.

General management approach for systemic vasculitides

General management approach for systemic vasculitides

Introduction

Introduction

Systemic vasculitides require specialist management. While a general approach to management can be described, its application varies for each of the systemic vasculitides. Consider both the following general management approach and the advice for the specific vasculitis. Immunoglobulin A vasculitis and Kawasaki disease are exceptions because their management is distinctly different from the general approach outlined here; see instead Immunoglobulin A vasculitis and Kawasaki disease.

If a systemic vasculitis is strongly suspected, treatment must start immediately, without waiting for diagnostic confirmation (ie biopsy or other investigations). Systemic vasculitis is treated with corticosteroids and, in some circumstances, disease-modifying antirheumatic drugs (DMARDs). Corticosteroids are the mainstay of treatment and must be continued for the duration of treatment. In all cases, the aim of therapy is to induce (see Inducing remission in systemic vasculitides) and maintain (see Maintaining remission in systemic vasculitides) remission of disease activity. Remission is defined as:

- the absence of clinical features of vasculitis
- resolution of organ changes, or stabilisation of organ structure and function
- normalisation of inflammatory markers.

Patients taking immunomodulatory drugs are at increased risk of infections. It is important to exclude infection before starting immunomodulatory therapy, and clinicians must always be alert to the possibility of infection (including opportunistic infection), particularly because the usual symptoms and signs (eg fever) are often absent. For other considerations in the management of corticosteroid and DMARD therapy (including adverse effects associated with long-term therapy, monitoring, screening for infection, and vaccination), see Principles of immunomodulatory drug use for rheumatological diseases in adults.

For guidance on when to give antimicrobial prophylaxis (eg Pneumocystis jirovecii pneumonia [PJP] prophylaxis) for patients taking corticosteroids or immunomodulatory drugs, see here.

Inducing remission in systemic vasculitides

Inducing remission in systemic vasculitides
Patients with disease affecting a major organ or body system

For patients with disease affecting a major organ or body system (eg glomerulonephritis, pulmonary haemorrhage, intestinal ischaemia, sight-threatening eye disease, neuropathy), intensive induction therapy is indicated. The regimens used for intensive induction therapy vary between the specific vasculitides, and depend on the organ affected and the extent to which it is affected. Regimens include:

- high-dose corticosteroids
- high-dose corticosteroids plus cyclophosphamide
- high-dose corticosteroids plus rituximab.

High-dose corticosteroid therapy is typically intravenous methylprednisolone followed by high-dose oral prednis(ol)one (usually 1 mg/kg up to 60 mg daily). When intravenous methylprednisolone cannot be started immediately, start treatment with high-dose oral prednis(ol)one instead and continue until intravenous methylprednisolone can be started.

If treatment with cyclophosphamide is indicated, see Principles of immunomodulatory drug use for rheumatological diseases in adults for considerations for use, especially in patients of childbearing potential.

For patients with microscopic polyangiitis or granulomatosis with polyangiitis, rituximab is an alternative to cyclophosphamide for intensive induction therapy. Rituximab is generally used when these patients have not responded to cyclophosphamide or have had a major toxicity from cyclophosphamide, or in women who wish to conceive in the future and are concerned about the effect of cyclophosphamide on fertility.

For patients with rapidly progressive glomerulonephritis or pulmonary haemorrhage, adjunctive plasma exchange may be used.
Patients with disease not affecting a major organ or body system

For patients with disease not affecting a major organ or body system (eg upper airway, skin or joint involvement), intensive induction therapy is not required, but treatment must still be started urgently. Treatment regimens must include high-dose oral prednis(ol)one (usually 1 mg/kg up to 60 mg daily) with or without another immunomodulatory drug (eg azathioprine, methotrexate or mycophenolate). For patients with microscopic polyangiitis or granulomatosis with polyangiitis, combination therapy is recommended—high-dose prednis(ol)one in combination with methotrexate or mycophenolate is preferred.

All patients with disease not affecting a major organ or body system should be frequently monitored for major organ involvement, particularly kidney disease, because this warrants more intensive treatment.

Maintaining remission in systemic vasculitides

Maintaining remission in systemic vasculitides

When remission has been achieved, prednis(ol)one is tapered and continued at the lowest effective dose (usually 5 mg orally, daily). The rate of tapering depends on the clinical and inflammatory marker response, and the development of corticosteroid adverse effects. Generally the daily prednis(ol)one dose should be reduced to 5 mg within 6 months of achieving remission. Neither the optimal nor the maximum duration of therapy is known; however, to reduce the risk of relapse, maintenance therapy should be continued for a minimum of 2 years once remission is achieved.

Long-term corticosteroid therapy can cause significant adverse effects. The risk of adverse effects must be balanced against the risk of relapse with inadequate treatment. Use the lowest dose and shortest duration of therapy necessary to control disease and prevent relapse. See Principles of immunomodulatory drug use for rheumatological diseases in adults for information on adverse effects associated with long-term corticosteroid use (such as bone density loss) and advice on how to minimise and monitor for such complications.

To allow lower corticosteroid doses to be used, prednis(ol)one is usually used in combination with another immunomodulatory drug (eg azathioprine or methotrexate) for maintenance of remission. For patients with microscopic polyangiitis or granulomatosis with polyangiitis, rituximab or mycophenolate may be used in combination with prednis(ol)one as an alternative steroid-sparing drug [Note 1] . Rituximab is mainly limited to use in patients who received it as induction therapy; however, the dosing regimens for induction and maintenance therapy are different. Cyclophosphamide is not used for maintenance therapy because of toxicity associated with long-term use.

After remission of disease activity is achieved, monitor all patients with systemic vasculitis for evidence of disease recurrence.

Note 1: At the time of writing, rituximab is not approved by the Australian Therapeutic Goods Administration (TGA) for maintenance therapy for microscopic polyangiitis or granulomatosis with polyangiitis. See the TGA website for current information [URL].

Takayasu arteritis

Takayasu arteritis

Takayasu arteritis is a systemic vasculitis that affects large blood vessels, typically the aorta and its major branches. It typically occurs in early adulthood and females are more commonly affected than males. Systemic features (eg fever, malaise, weight loss) occur in only 20 to 40% of patients. Most patients present with features of vascular insufficiency such as upper limb claudication, absent pulses, arterial bruits or hypertension. Patients with Takayasu arteritis are antineutrophil cytoplasmic antibody (ANCA)–negative.

Takayasu arteritis is thought to have distinct inflammatory and ischaemic phases; however, these can overlap. The vascular changes seen in the inflammatory phase are potentially reversible with treatment, but it can be difficult to distinguish active inflammation from irreversible vascular changes (such as stenosis). Specialised vascular imaging (magnetic resonance imaging or positron emission tomography) can aid this distinction and may be a useful adjunct to clinical assessment and measurement of inflammatory markers.

If active inflammation is suspected, treatment is recommended (see General management approach for systemic vasculitides). Patients with Takayasu arteritis generally require treatment with high-dose corticosteroid therapy; the appropriate route of administration and dosage depends on the disease severity.

Concurrent treatment of hypertension is important (see Elevated blood pressure). It is unclear if antiplatelet drugs such as aspirin are beneficial. Vascular surgery may be required for irreversible obstructive lesions; when possible, it is preferable to delay surgery until active inflammation is controlled.

Polyarteritis nodosa

Polyarteritis nodosa

Polyarteritis nodosa is a systemic vasculitis that affects small to medium arteries. It typically occurs in middle-aged or older adults and males are more commonly affected than females. The clinical presentation of polyarteritis nodosa includes prominent systemic features, as well as features due to the involvement of specific organs or tissues. Typical systemic features include fever, anorexia, weight loss, myalgia and arthralgia. The most commonly affected organs and tissues are the skin, nerves, gastrointestinal tract and kidneys. Features of skin involvement include cutaneous or subcutaneous nodules, palpable purpura, livedo reticularis and skin infarction. Neurological involvement is usually restricted to the peripheral nerves, with a sudden onset of pain and tingling progressing to a motor deficit. The involvement of many nerves evolves into a pattern of polyneuropathy. Intestinal and liver ischaemia can cause abdominal pain, infarction, haemorrhage and liver function abnormalities. Kidney impairment can occur due to vascular ischaemic nephropathy, and malignant hypertension can occur if the renal artery is affected; the glomerulus is rarely affected. End-stage chronic kidney disease can occur.

About 30% of patients with polyarteritis nodosa are positive for hepatitis B surface antigen, and these patients should be considered for antiviral therapy before starting, or stopping, immunomodulatory therapy. See Hepatitis B and patients undergoing cancer chemotherapy or immunosuppression for more information, including treatment recommendations. Classical polyarteritis nodosa is antineutrophil cytoplasmic antibody (ANCA)–negative.

Diagnosis is based on biopsy of affected tissues. Typical sites for biopsy are the sural nerve (particularly if nerve conduction studies demonstrate involvement), symptomatic muscle, or affected skin. Kidney biopsy may reveal arteritis (compared to glomerulonephritis in microscopic polyangiitis). Angiography is useful if no tissue is available for biopsy, and has an increased yield in patients with abdominal symptoms or abnormal liver biochemistry.

Management should follow the principles outlined in General management approach for systemic vasculitides. For polyarteritis nodosa **without evidence of major organ or body system involvemen**t (eg disease affecting the skin only, disease characterised by systemic symptoms only) the standard treatment is high-dose prednis(ol)one as recommended for patients with disease not affecting a major organ or body system. For disease **affecting a major organ or body system** (eg patients with polyneuropathy, kidney or liver involvement) intravenous methylprednisolone is used instead. Cyclophosphamide is added if a visceral organ is affected or if disease is progressive despite adequate corticosteroid therapy. In the maintenance

phase, combination therapy with prednis(ol)one and another immunomodulatory drug is almost always required (see Maintaining remission in systemic vasculitides).

Microscopic polyangiitis

Microscopic polyangiitis

Microscopic polyangiitis is a systemic vasculitis that predominantly affects small blood vessels. The mean age of occurrence is between 65 and 75 years. Microscopic polyangiitis often presents as an acute, rapidly progressive glomerulonephritis, and may be associated with pulmonary haemorrhage and skin lesions such as palpable purpura. Systemic features such as fever may be present before more specific symptoms. Nearly all patients with microscopic polyangiitis are antineutrophil cytoplasmic antibody (ANCA)–positive.

Most patients with microscopic polyangiitis have impaired kidney function and nephritic urinary sediment (including red cells and red cell casts); however, kidney biopsy is usually required to confirm the diagnosis. Prognosis is worse in patients with significant kidney impairment, pulmonary haemorrhage or other end-organ damage, or who have persistently positive ANCA serology despite treatment.

Management of microscopic polyangiitis should follow the principles outlined in General management approach for systemic vasculitides. Most patients have disease affecting a major organ or body system and require intensive induction therapy.

Granulomatosis with polyangiitis

Granulomatosis with polyangiitis

Granulomatosis with polyangiitis (formerly known as Wegener granulomatosis) is a systemic vasculitis that predominantly affects small to medium blood vessels and typically occurs in middle-aged adults. It is a multisystem disease characterised by necrosis, granuloma formation and vasculitis of the ear, nose and throat, and lower respiratory tract. Involvement of the ear, nose and throat can manifest as sinusitis, nasal disease, subglottic stenosis (which is almost pathognomonic), otitis media, hearing loss, and ear pain. Oral lesions can also occur. Lower respiratory tract involvement manifests as pulmonary infiltrates and nodules, haemoptysis and pleuritis. About 75% of patients develop glomerulonephritis. The onset of kidney involvement can be acute and can occur at any time in the course of the disease; it can progress to chronic kidney failure. Uncommonly, an orbital mass (usually an extension of disease affecting the sinus) or necrotising scleritis occurs; these presentations suggest sight-threatening disease, which requires intensive treatment.

Most patients with granulomatosis with polyangiitis have a positive antineutrophil cytoplasmic antibody (ANCA) with the cytoplasmic (cANCA) staining pattern and anti-proteinase-3 (PR-3) specificity. The diagnosis is confirmed by biopsy of affected tissue.

Management of granulomatosis with polyangiitis should follow the principles outlined in General management approach for systemic vasculitides. Most patients require intensive induction therapy. In rare cases, patients have limited disease that does not affect a major organ (eg isolated sinus disease) and treatment can be started with high-dose oral prednis(ol)one in combination with another immunomodulatory drug (eg methotrexate or mycophenolate). Once remission is achieved, a combination of prednis(ol)one and another immunomodulatory drug is usually required to maintain remission.

Historically, trimethoprim+sulfamethoxazole monotherapy was used to treat disease limited exclusively to the upper airway. However, it is not thought to be as effective at achieving or maintaining remission as treatment with prednis(ol)one, with or without another immunomodulatory drug, and should not be used alone. Trimethoprim+sulfamethoxazole (160+800 mg orally, twice daily) may be added to the patient's maintenance regimen; it should be used with caution in patients treated with methotrexate and in patients with renal impairment because there is an increased risk of toxicity.

Eosinophilic granulomatosis with polyangiitis

Eosinophilic granulomatosis with polyangiitis

Eosinophilic granulomatosis with polyangiitis (formerly known as Churg–Strauss vasculitis) is a systemic vasculitis that predominantly affects small to medium blood vessels and typically occurs in middle-aged adults. Patients with eosinophilic granulomatosis with polyangiitis often have a history of atopy or asthma. Systemic features are common and include fever, anorexia and weight loss. Asthma is the most common respiratory feature, but pulmonary infiltrates and diffuse interstitial changes, including eosinophilic infiltration, are also common. Mononeuritis multiplex commonly occurs. Skin manifestations include palpable purpura, skin infarcts and nodules over pressure areas. Coronary vasculitis or granulomatous infiltration of the myocardium occurs in up to 50% of cases, and myocardial infarction and congestive cardiac failure are major causes of mortality in eosinophilic granulomatosis with polyangiitis. Focal, segmental necrotising glomerulonephritis, often with crescent formation, occurs in approximately 20% of patients.

Blood eosinophilia of greater than 1×10^9/L (normal range less than 0.6×10^9/L) is characteristic. A positive antineutrophil cytoplasmic antibody (ANCA) with a perinuclear (pANCA) staining pattern is seen in approximately one-third of patients. Diagnosis is based on a suggestive clinical picture, as well as the identification of small necrotising granulomas or necrotising vasculitis with frequent eosinophils in a biopsy of affected tissue (such as the lung). Elevated creatinine indicates a poor prognosis.

Management should follow the principles outlined in General management approach for systemic vasculitides. Eosinophilic granulomatosis with polyangiitis is highly responsive to corticosteroids.

Immunoglobulin A vasculitis

Immunoglobulin A vasculitis

Introduction

Introduction

Immunoglobulin A (IgA) vasculitis (formerly known as Henoch–Schönlein purpura) is the most common vasculitis in children, in whom it is predominantly a self-limiting disease. It is not a common vasculitis in adults; however, if affected, adults are more likely to develop severe and/or progressive kidney disease.

IgA vasculitis affects small blood vessels, producing a leucocytoclastic vasculitis with a classic triad of nonthrombocytopenic purpura (typically on the lower limbs extending to the buttocks), colicky abdominal pain and large-joint arthritis. The arthritis can cause significant pain and swelling, but can also resolve relatively rapidly.

The most significant consequence of IgA vasculitis is nephritis due to IgA immune complex deposits in the glomerulus (vasculitic IgA nephropathy). It can occur up to 6 months after the initial presentation of IgA vasculitis, but the majority of cases are seen within 3 months. The nephritis is usually self-limiting and resolves fully over weeks to months, but severe glomerular inflammation can lead to permanent scarring, which occasionally progresses to chronic or even end-stage kidney disease. Progression to chronic kidney disease can occur shortly or even years after an apparent full recovery, and is most likely in patients who present with a mixed nephritic–nephrotic syndrome or nephrotic syndrome.

General management approach for IgA vasculitis

General management approach for IgA vasculitis

All patients with immunoglobulin A (IgA) vasculitis (formerly known as Henoch–Schönlein purpura) need to be monitored for the development of nephritis because even significant kidney involvement can be subclinical. See Monitoring for vasculitic IgA nephropathy for the recommended monitoring regimen. It is crucial that early morning urinalysis and blood pressure monitoring are performed regularly so that kidney involvement is promptly identified and, as necessary, investigated and treated. Kidney biopsy may be

indicated if there is evidence of significant kidney involvement. The severity of nephritis that warrants intervention is uncertain because of the lack of high-quality randomised controlled trials. However, based on the available evidence and expert opinion, immunomodulatory therapy is indicated if significant vasculitic or crescentic changes are seen on kidney biopsy, particularly in the presence of severe clinical manifestations.

Treatment of **abdominal** and **articular** manifestations of IgA vasculitis is largely symptomatic; use analgesics (such as paracetamol) and nonsteroidal anti-inflammatory drugs (NSAIDs). For principles of NSAID use in children and adolescents, see Practical prescribing considerations for rheumatological diseases in children and adolescents and for paediatric dosages of oral NSAIDs, see Table 12.12. For principles of use and adult dosages of oral NSAIDs, see Principles of NSAID use for musculoskeletal conditions in adults. Corticosteroids can relieve pain and inflammation and can be trialled in patients with severe abdominal or joint pain. If corticosteroids are indicated, prednis(ol)one is usually used at a dosage of 1 to 2 mg/kg up to 60 mg orally, per day; tapering the dose to stop may be required. See also Practical prescribing considerations for rheumatological diseases in children and adolescents and Principles of immunomodulatory drug use for rheumatological diseases in adults.

Well-controlled clinical trials have shown that corticosteroids do not reduce the risk of developing **nephritis** and they should not be used for this purpose. However, corticosteroids (including intravenous methylprednisolone) are sometimes used by nephrologists to treat patients with nephritis depending on clinical features and changes on kidney biopsy.

Avoid concurrent use of NSAIDs and oral corticosteroids because of the significantly increased risk of gastrointestinal toxicity, and because NSAIDs are not likely to have additional benefit in patients taking oral corticosteroids.

Monitoring for vasculitic IgA nephropathy

Monitoring for vasculitic IgA nephropathy

The monitoring regimen outlined below is based on a clinical pathway developed for use in children with immunoglobulin A (IgA) vasculitis (formerly known as Henoch–Schönlein purpura) [Note 2] , but it is also likely to represent a reasonable approach for adult patients, who are more likely to have kidney involvement. Monitoring should continue while there is an increased risk of nephritis, in particular the first 3 months after presentation and/or a recurrent flare.

For all patients with IgA vasculitis but **without evidence of significant nephritis** (normotensive patients either without abnormalities on urinalysis or with isolated microscopic haematuria only), monitor according to the following schedule:

- weekly measurement of blood pressure and early morning urinalysis for the first month
- fortnightly measurement of blood pressure and early morning urinalysis for the second and third months
- once-off measurement of blood pressure and early morning urinalysis at 6 and 12 months.

If isolated microscopic haematuria persists at 12 months, continue to measure blood pressure and perform early morning urinalysis once yearly. If there is a flare of cutaneous or gastrointestinal symptoms of IgA vasculitis, restart the monitoring schedule from the beginning.

For patients with IgA vasculitis who develop **hypertension, macroscopic haematuria or proteinuria** while being monitored, or who have these features at baseline, the following approach is suggested:

- detailed clinical review, including measurement of height, weight and blood pressure, and the following investigations:
    - urine microscopy and protein–creatinine ratio on an early morning sample
    - blood tests for albumin, creatinine, urea and electrolytes, full blood count, coagulation profile, anti-deoxyribonuclease B antibodies and antistreptolysin-O titre
    - particularly if the diagnosis of IgA vasculitis is not certain, measurement of antinuclear antibodies (ANA), antibodies to double-stranded DNA (dsDNA), antineutrophil cytoplasmic

antibodies (ANCA), immunoglobulins and complement concentration (C3 and C4)

- discuss with a nephrologist if any of the following features are present:
    - acute nephritic syndrome, suggested by the presence of macroscopic haematuria, proteinuria, oedema, hypertension and oliguria
    - nephrotic syndrome, suggested by a urinary protein–creatinine ratio greater than 250 mg/mmol, a serum albumin less than 25 g/L and the presence of oedema
    - macroscopic haematuria for 5 consecutive days
    - urinary protein–creatinine ratio greater than 250 mg/mmol for 4 weeks (measured weekly), or urinary protein–creatinine ratio greater than 250 mg/mmol for less than 4 weeks (measured weekly) but which has increased on repeat testing
    - abnormal renal function
    - confirmed hypertension
- if the patient has proteinuria that does not warrant nephrology review based on the features above, continue to monitor disease activity. Nephrology review is recommended if there is persistent elevation of urinary protein–creatinine ratio of:
    - greater than 100 mg/mmol for 3 months
    - greater than 50 mg/mmol for 6 months.

Note 2: Tizard EJ, Hamilton-Ayres MJ. Henoch Schönlein purpura. Arch Dis Child Educ Pract Ed 2008;93(1):1-8. [URL]

Kawasaki disease

Kawasaki disease

Introduction

Introduction

Kawasaki disease is a systemic vasculitis that typically affects the coronary arteries. It occurs almost exclusively in children and is usually seen before 5 years of age. It is the most important cause of acquired cardiac disease in children in developed countries.

Diagnosis of Kawasaki disease

Diagnosis of Kawasaki disease

The diagnosis of Kawasaki disease is based on criteria outlined in Figure 12.13. Incomplete cases (ie patients who do not fulfil the strict criteria for diagnosis of Kawasaki disease but develop coronary artery lesions) are relatively common, especially under 1 year of age; the diagnosis should be considered in any child with unexplained fever for 5 or more days associated with *any* of the cardinal clinical features listed in Figure 12.13. Other disease features may include preceding diarrhoeal illness, aseptic meningitis, sterile pyuria, uveitis, or hydropic distension of the gallbladder.

Figure 12.13 Criteria for the diagnosis of Kawasaki disease

The diagnosis of Kawasaki disease is based on the presence of fever for 5 or more days, as well as four or more of the following cardinal clinical features during the course of the illness, or fewer than four cardinal clinical features plus coronary artery lesions on echocardiogram:

- bilateral nonexudative conjunctivitis
- cervical lymphadenopathy (greater than 1.5 cm diameter), usually unilateral
- polymorphous rash
- changes to the lips and oral cavity including erythema, cracked lips and strawberry tongue
- changes in the extremities:
    - in the acute phase, erythema of palms and soles and oedema of hands and feet
    - in the subacute phase, desquamation of hands and feet.

Management of Kawasaki disease

Management of Kawasaki disease

The risk of coronary aneurysms in patients with Kawasaki disease is reduced (from around 30% to around 3%) by intravenous infusion of immunoglobulin. The usual dosage is:

intravenous immunoglobulin (IVIg) 2 g/kg intravenously, as a single slow infusion over 10 to 12 hours. *Kawasaki disease*

The infusion may be repeated if the fever persists, or recurs 36 hours or more after the completion of the initial infusion. If fever persists or recurs following a second dose of intravenous immunoglobulin, intravenous methylprednisolone is used. The usual dosage is:

methylprednisolone sodium succinate 30 mg/kg up to 1000 mg intravenously, over 1 hour, daily for up to 3 consecutive days. *Kawasaki disease* _

While the patient remains febrile, high-dose aspirin is typically used. In theory, it may have synergistic anti-inflammatory properties in combination with intravenous immunoglobulin, with a potential benefit on coronary vascular inflammation. However, direct evidence of a reduction in the risk of coronary artery lesions is lacking. Various doses of aspirin have been used in febrile patients, ranging from 30 to 100 mg/kg/day, given in four divided doses over 24 hours. Doses at the higher end of the range are used overseas, whereas doses at the lower end of the range are usually used locally. High-dose aspirin is generally continued for 48 hours after the fever resolves.

Low-dose aspirin is used once the fever has resolved, when marked thrombocytosis is typical; the usual dosage is:

aspirin 3 to 5 mg/kg orally, daily. *Kawasaki disease* _

Low-dose aspirin is continued until follow-up echocardiography has been performed, typically 6 weeks after the resolution of fever. Aspirin may be stopped if no coronary artery lesions are detected. However, if lesions are detected, aspirin should be continued, and ongoing surveillance of the coronary arteries is necessary.

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Key references: Systemic vasculitides: introduction

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Introduction to limb conditions

Introduction to limb conditions

In the clinical assessment of any limb condition, consider and exclude features that suggest an underlying systemic inflammatory disease or other serious pathology (see Assessing peripheral musculoskeletal symptoms in adults and Assessing musculoskeletal symptoms in children and adolescents).

Soft-tissue conditions of the limbs can be broadly grouped by the affected tissue; management principles are outlined for the following groups of soft-tissue conditions:

- muscle strain or tear
- tendinopathy
- ligament sprain or tear.

The management of the following specific conditions are also discussed:

- rotator cuff disease
- adhesive capsulitis (frozen shoulder)
- lateral and medial epicondylar tendinopathies (tennis elbow and golfer's elbow)
- de Quervain tenosynovitis
- carpal tunnel syndrome
- flexor tenosynovitis (trigger finger)
- hip joint conditions
- greater trochanteric pain syndrome
- patellofemoral pain syndrome
- prepatellar bursitis
- chronic exertional compartment syndrome
- medial tibial stress syndrome
- tear of the Achilles tendon
- plantar fasciitis.

Specific radiological findings discussed are femoroacetabular impingement and hip labral tears, and degenerative meniscal tears.

For common noninflammatory musculoskeletal conditions in children and adolescents, see Noninflammatory musculoskeletal pain in children and adolescents. Perthes disease, slipped capital femoral epiphysis and irritable hip are important mimics of juvenile idiopathic arthritis in the lower limbs. For more information on these conditions, see Important mimics of juvenile idiopathic arthritis in the lower limbs.

Management principles for muscle strain or tear

Management principles for muscle strain or tear

Muscle strain or tear is an acute injury to muscle caused by excessive tension or lengthening. It is both aetiologically and mechanistically different from delayed-onset muscle soreness.

The initial management of a muscle strain or tear is (see Table 12.21). Although the benefit of is supported by widespread use in practice, the effectiveness of this approach has not been proven in randomised controlled trials.

If analgesia is required, first-line treatment is paracetamol. Nonsteroidal anti-inflammatory drugs (NSAIDs) may be used in combination with paracetamol. There is a theoretical risk of NSAIDs inhibiting muscle repair through negative effects on satellite cell populations. For this reason, NSAIDs should not be used for more than 48 hours for acute muscle injury. See Principles of NSAID use for musculoskeletal conditions in adults for more information on NSAID use and dosing. Opioids are rarely indicated for acute muscle injury and are associated with a significant risk of harms.

Exercise is important for rehabilitation of the injured muscle to prevent recurrence of injury, although the optimal time to start exercise is unclear. Depending on the patient's functional impairments and their expectations for recovery, referral to an appropriate physical therapist (eg a physiotherapist) may be indicated. A supervised rehabilitation program is particularly important for patients who participate in significant physical activity or who have specific functional goals.

To reduce the risk of injury recurrence, advise patients who participate in significant physical activity to avoid returning to full pre-injury activity until they achieve near-full pre-injury flexibility and 85 to 90% of pre-injury power in the affected muscle. A gradual return to activity is recommended, with both the duration and intensity of activity gradually increased over the course of the healing process (usually 5 to 8 weeks).

The following therapies are not recommended because of insufficient evidence of benefit in the management of acute muscle injury, and inadequate study of treatment harms: autologous conditioned serum, platelet-rich plasma, platelet-rich fibrin matrix, Traumeel (a homeopathic preparation allegedly containing traces of botanical and mineral ingredients), Actovegin (extracts of calf blood), and dry needling.

Table 12.21 RICE therapy

Therapy [NB1]	Details
Rest	rest so that pain is not provoked, but some physical activity is maintained. Continue for up to 48 hours
Ice	apply ice packs to the affected area for 10 minutes every 1 to 2 hours. Continue for up to 48 hours. There is a risk of cold burn if ice is applied directly to the skin
Compression	use compression bandaging, if practical. Continue for up to 48 hours
Elevation	elevate the limb to reduce swelling. Continue for as long and as often as necessary

NB1: Heat and massage are contraindicated in the first 48 hours following injury.

Management principles for tendinopathy

Management principles for tendinopathy

Tendinopathy is primarily a degenerative condition of the tendon. Tendinopathy can be associated with microtears of the tendon, but these should be distinguished from acute major tendon tears.

Assess patients with tendinopathy for modifiable predisposing factors and biomechanical abnormalities that may be amenable to correction (eg posture, motor control). Advise patients to avoid or modify activities that aggravate discomfort or place high loads on the affected tendon.

For most tendinopathies, rest is not recommended because complete unloading of the tendons is not helpful. Referral to an appropriate physical therapist (eg a physiotherapist) for a progressive loading program can assist in treatment and rehabilitation. If undertaken, progressive loading programs should start with isometric loading followed by eccentric or eccentric-concentric loading. If patients do not respond to a well-supervised 6-month rehabilitation program, refer to a specialist.

Paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) are often used for short-term pain relief. Peritendinous corticosteroid injections are sometimes used for pain relief and the effect usually lasts up to 6 weeks. They should be used with caution in tendinopathy involving major weightbearing tendons such as the patellar, tibialis posterior and Achilles tendons. Consider seeking specialist advice and avoid multiple injections. Neither NSAIDs nor corticosteroids appear to alter the pathology in tendinopathy. See Principles of NSAID use for musculoskeletal conditions in adults for more information on NSAID use and dosing. See

Principles of using local corticosteroid injections for musculoskeletal conditions in adults for principles of use and example doses of local corticosteroid injections.

The following therapies are not recommended because of insufficient evidence of benefit in the management of tendinopathy, and inadequate study of treatment harms: stem cells, autologous conditioned serum, platelet-rich plasma, platelet-rich fibrin matrix, polidocanol, prolotherapy and dry needling.

Management principles for ligament sprain or tear

Management principles for ligament sprain or tear

Acute ligament injuries are usually caused by distraction forces that lengthen the ligament beyond its normal elastic limit. They range from virtually asymptomatic minor sprains to complete tears.

The initial management of acute ligament injuries is (see Table 12.21). Although the benefit of is supported by widespread use in practice, the effectiveness of this approach has not been proven in randomised controlled trials.

Nonsteroidal anti-inflammatory drugs (NSAIDs) reduce pain and shorten time to recovery in acute ligament sprains, particularly in acute ankle ligament sprain. See Principles of NSAID use for musculoskeletal conditions in adults for more information on NSAID use and dosing.

Consider referral to an appropriate physical therapist (eg a physiotherapist) for acute ligament injuries, particularly more severe injuries. Physical therapy includes restoration of range of motion, proprioception training, local muscle strengthening, and functional exercises. For acute ankle ligament sprains, supportive taping during the early phase of return to activity is useful.

Prolotherapy is not recommended for the management of acute or chronic ligament sprains because of insufficient evidence of benefit and inadequate study of treatment harms.

Rotator cuff disease

Rotator cuff disease

Introduction

Introduction

Rotator cuff disease is the most common cause of shoulder pain. The rotator cuff comprises the supraspinatus, infraspinatus, subscapularis and teres minor muscles and tendons; these muscles and tendons surround the glenohumeral joint, and facilitate movement and provide stability to the joint. Rotator cuff disease refers to all symptomatic disorders of the rotator cuff regardless of the anatomical location; it includes rotator cuff tears, tendinopathy, and impingement (compression) of the rotator cuff. The latter may be associated with subacromial bursitis.

The aetiology of rotator cuff disease is multifactorial. Risk factors include acromial abnormalities that result in narrowing of the subacromial space, increasing age, overuse, smoking and obesity. Symptomatic rotator cuff disease is common in young people who participate in sports involving overhead activity (eg swimming). It is also common in middle-aged and older people, who are more likely to sustain full-thickness rotator cuff tears. Asymptomatic rotator cuff tears are present in 4% of people younger than 40 years of age and in over 50% of people older than 60 years of age. A significant number become symptomatic over time.

The clinical course of rotator cuff disease is not well understood. About 25% of new episodes resolve fully within 1 month and nearly 50% resolve within 3 months; however, persistence of symptoms or recurrence of symptoms within a year of initial presentation can occur in 40 to 50% of people, and many partial-thickness rotator cuff tears progress to full-thickness tears over time. Progression of rotator cuff disease can lead to rotator cuff arthropathy, a form of glenohumeral osteoarthritis.

Diagnosis of rotator cuff disease

Diagnosis of rotator cuff disease

The diagnosis of rotator cuff disease is usually made by history and physical examination, without the need for investigations.

In rotator cuff disease, involvement is usually unilateral and pain is felt in the affected shoulder and/or lateral aspect of the upper arm. Night pain, interrupted sleep if lying on the affected side, and a painful arc are hallmarks of the condition. Symptoms may be subacute; painful weakness and atrophy suggest significant rotator cuff tears. Rapid onset of intense pain suggests calcific tendinitis due to deposition of calcium in the tendon, although sometimes calcium deposits do not cause symptoms.

Movement loss in rotator cuff disease is isolated and depends on the rotator cuff tendon involved; this can be identified by stressing specific rotator cuff tendons. Assuming the patient is able to completely relax their shoulder girdle muscles, the passive range of shoulder movements are generally painless and unrestricted in rotator cuff disease. This finding can assist in differentiating rotator cuff disease from adhesive capsulitis and glenohumeral osteoarthritis.

Scapula dysfunction (through malpositioning of the glenoid fossa) and acromioclavicular joint osteoarthritis (through narrowing of the subacromial space) may contribute to rotator cuff disease, so these pathologies should also be considered in the diagnosis. In acromioclavicular joint osteoarthritis, pain is typically felt on top of the shoulder and is worse in full abduction or if reaching across the body. The acromioclavicular joint is tender and an osteophyte may be palpable.

Plain X-rays are not useful in the majority of cases of rotator cuff disease. They may be considered to demonstrate calcific deposits if calcific tendinitis is suspected clinically, to identify abnormal acromial morphology or osteophytes if acromioclavicular joint osteoarthritis is suspected clinically, or to exclude other causes of shoulder pain (eg glenohumeral osteoarthritis if suspected clinically, fractures and/or dislocations in the setting of trauma).

Although frequently ordered, the diagnostic utility of ultrasound scans for rotator cuff disease is unknown. Abnormalities reported on ultrasound are common in asymptomatic individuals so, even if identified in a symptomatic patient, these findings may not explain the patient's symptoms. Furthermore, these findings may lead to inappropriate management and/or delay correct diagnosis and management. Ultrasound is not recommended for the diagnosis of shoulder pain suggestive of rotator cuff pathology on clinical assessment.

Do not use ultrasound to investigate shoulder pain if clinical assessment suggests rotator cuff pathology.

Management of rotator cuff disease

Management of rotator cuff disease

The evidence for commonly used treatments for rotator cuff disease is limited; however, a reasonable management approach includes analgesia if required and exercise. Advise patients to avoid or modify activities that aggravate discomfort or place high loads on the affected tendon. See also Management principles for tendinopathy.

Analgesia

If analgesia is required, oral analgesia and/or subacromial corticosteroid injection may be considered. If oral analgesia is indicated, use:

1 paracetamol 1 g orally, 4- to 6-hourly, up to a maximum of 4 g daily *rotator cuff disease* _

OR

1 paracetamol modified-release 1.33 g orally, 8-hourly.

If response to paracetamol is inadequate, a nonsteroidal anti-inflammatory drug (NSAID) may be used **instead of, or in combination with**, paracetamol. Use:

an NSAID orally (see Table 12.7 for dosing). *rotator cuff disease*

The potential benefits of an NSAID should be weighed against its potential harms, particularly in patients at high risk of harms (see Principles of NSAID use for musculoskeletal conditions in adults for more information).

Subacromial corticosteroid injection is useful for rapid pain relief, particularly for night pain, but its effect may only last a few weeks and a repeat injection may be needed. Subacromial corticosteroid injection can be helpful in alleviating pain in calcific tendinitis, although this has not been proven in randomised controlled trials. Ultrasound guidance for injection into the subacromial space is not recommended because it provides no additional benefit compared to non–radiologically guided injection. For principles of use and example doses of local corticosteroid injections, see Principles of using local corticosteroid injections for musculoskeletal conditions in adults.

Other analgesic therapies that may be considered for rotator cuff disease include suprascapular nerve block and acupuncture. There is preliminary evidence that suprascapular nerve block relieves pain from rotator cuff disease for up to 12 weeks. Acupuncture can provide transient pain relief.

Opioids are seldom required for rotator cuff disease. If patients have severe pain that is not adequately relieved with other measures, reconsider the diagnosis and consider the possibility of rotator cuff arthropathy.
Exercise

Consider referral to an appropriate physical therapist (eg a physiotherapist). A reasonable exercise recommendation for rotator cuff disease includes range of motion and strengthening exercises for the rotator cuff and scapular stabilising muscles. The aim of these exercises is to improve shoulder strength and function in the longer term. Adding manual therapy to exercise is unlikely to provide additional benefit.

Other treatments

Physical treatments other than exercise have a limited role in the management of rotator cuff disease. Extracorporeal shock wave therapy may reduce pain, improve function, and resolve calcifications in calcific tendinopathy, but is not beneficial in cases of non-calcific tendinopathy. Based on low-quality evidence, therapeutic ultrasound may have short-term benefits over placebo in calcific tendinitis, and low-level laser therapy may have short-term benefits over placebo in rotator cuff disease.

Platelet-rich plasma injections are not recommended for the treatment of rotator cuff disease or as an adjunct to surgery for rotator cuff disease because of insufficient evidence of benefit and inadequate study of treatment harms.

Surgery for rotator cuff disease may be considered after 3 to 6 months of appropriate conservative management if there is progressive weakness suggestive of a full-thickness rotator cuff tear, or if symptoms are severe and persisting regardless of the presence of a tear. Surgical removal of calcific deposits may relieve persistent pain due to calcific tendinitis.

Adhesive capsulitis (frozen shoulder)

Adhesive capsulitis (frozen shoulder)

Introduction

Introduction

Adhesive capsulitis (frozen shoulder) is the most common cause of shoulder pain after rotator cuff disease. It is estimated to affect 2 to 5% of the general population and 10 to 20% of patients with diabetes. It is most common in people between 50 and 60 years of age, and affects women slightly more often than men.

The aetiology and pathophysiology of adhesive capsulitis is poorly understood. Adhesive capsulitis generally has a self-limiting course that lasts 2 to 3 years. It classically evolves through three overlapping phases:

- **an initial, painful phase** usually lasting between 2 and 9 months. This phase is characterised by the insidious development of diffuse, severe and disabling shoulder pain. Pain is worse at night and patients are unable to sleep lying on the affected side
- **an intermediate, stiff (frozen) phase** lasting between 4 and 12 months. In this phase, stiffness and severe loss of shoulder movement predominate. Pain is less pronounced but still present, particularly at the end of the free range of shoulder movement
- **a recovery phase** lasting between 5 and 24 months, during which time there is a gradual return of shoulder movement.

The diagnosis of adhesive capsulitis is predominantly made by history and physical examination. While many conditions cause shoulder pain, adhesive capsulitis can be distinguished by the presence of severe global passive movement loss; movement loss occurs in all planes including abduction, flexion, internal rotation and, especially, external rotation. In the initial, painful phase of adhesive capsulitis, before global passive movement loss is apparent, differentiating between adhesive capsulitis and rotator cuff disease can be difficult.

Management of adhesive capsulitis

Management of adhesive capsulitis

In each phase of adhesive capsulitis, management is directed at symptoms. If pain and stiffness persist despite conservative management, consider specialist referral.

Initial, painful phase

Advise patients to avoid or modify activities that aggravate discomfort. Avoid manual therapies and high-load shoulder exercises in the initial, painful phase because they can intensify pain.

In all phases of this condition, but particularly in the initial, painful phase, adequate analgesia is important. For analgesia, use:

1 paracetamol 1 g orally, 4- to 6-hourly, up to a maximum of 4 g daily *adhesive capsulitis (frozen shoulder)*

OR

1 paracetamol modified-release 1.33 g orally, 8-hourly.

If response to paracetamol is inadequate, a nonsteroidal anti-inflammatory drug (NSAID) may be used **instead of, or in combination with**, paracetamol. Use:

an NSAID orally (see Table 12.7 for dosing). *adhesive capsulitis (frozen shoulder)*

The potential benefits of an NSAID should be weighed against its potential harms, particularly in patients at high risk of harms (see Principles of NSAID use for musculoskeletal conditions in adults for more information). Limited evidence suggests that topical NSAIDs are ineffective for adhesive capsulitis.

Other options for analgesia in adhesive capsulitis include oral corticosteroid therapy or intra-articular corticosteroid injection. Oral corticosteroid therapy provides rapid pain relief, and improves function and range of motion, but the effect may not be maintained beyond 6 weeks. Benefits from oral corticosteroids have been reported in patients who have had symptoms for up to 6 months. The usual dosage is:

prednis(ol)one 30 mg orally, daily for 3 weeks, then taper the dose over 2 weeks to stop. *adhesive capsulitis (frozen shoulder)*

In patients with diabetes, monitor blood glucose concentration and adjust diabetes treatment as required. Avoid concurrent use of NSAIDs and oral corticosteroids because of the significantly increased risk of

gastrointestinal toxicity, and because NSAIDs are not likely to have additional benefit in patients taking oral corticosteroids.

Intra-articular corticosteroid injection may be useful for rapid pain relief, but may have a short duration of effect. Limited evidence suggests that a second or third injection may be useful for recurrence of pain. Local corticosteroid injection may cause a transient increase in blood glucose concentration, but usually no adjustment to diabetes treatment is necessary. For principles of use and example doses of local corticosteroid injections, see Principles of using local corticosteroid injections for musculoskeletal conditions in adults.

Opioids have a very limited role in the management of adhesive capsulitis because of a lack of evidence for efficacy and a significant risk of harms. Opioids may be considered for patients with severe pain that is not adequately relieved with other measures and is interfering with their ability to function. If opioids are used, they should be prescribed on a short-term trial basis, as part of an overall pain management strategy, with clear goals and regular review of treatment response and adverse effects. Before starting an opioid, a plan for ceasing ineffective therapy should be in place and discussed with the patient. If treatment response is inadequate, caution should be exercised when increasing the dose of opioids as there is an increased risk of harm and potentially no added benefit. Prolonged use of opioids indicates the need for specialist assessment. See Opioids for more information.

Intermediate, stiff (frozen) and recovery phases

In the intermediate, stiff (frozen) and recovery phases, continue activity modification and analgesia as required (see Initial, painful phase). A reasonable exercise recommendation includes strengthening and active range-of-motion exercises. The aim is to gradually increase range of motion.

Arthrographic distension (hydrodilation) of the glenohumeral joint may provide sustained pain relief, and improve function and range of motion in the intermediate, stiff phase. It involves injection of a combination of local anaesthetic, corticosteroid and saline into the joint under radiological guidance. The procedure can be performed with minimal sedation and may be repeated if needed. Following arthrographic joint distension, the combination of manual therapy and exercise may improve patient-reported treatment success and active range of motion, but does not provide additional benefit over arthrographic distension alone in terms of pain or function.

Arthroscopic capsular release may be considered in refractory cases.

Lateral and medial epicondylar tendinopathies (tennis elbow and golfer's elbow)

Lateral and medial epicondylar tendinopathies (tennis elbow and golfer's elbow)

Lateral epicondylar tendinopathy (tennis elbow) is a common condition, particularly in patients between 40 and 50 years of age. It is thought to be an overload injury of the common extensor tendons at their origin at the lateral epicondyle. In spite of the title ’tennis elbow’, tennis is a direct cause in only 5% of cases. Medial epicondylar tendinopathy (golfer's elbow) is a similar, but less common condition, involving the common flexor tendons at their origin at the medial epicondyle.

Both conditions are characterised by pain and tenderness over the epicondyle, and pain on resisted movements. In lateral epicondylar tendinopathy, pain occurs on resisted dorsiflexion of the wrist and/or middle finger. In medial epicondylar tendinopathy, pain occurs on resisted volar flexion of the wrist. Pain at night and stiffness, particularly in the morning and after periods of inactivity, may occur.

The diagnosis of these conditions is usually made by history and physical examination, without the need for investigations. Myriad changes in the tendons on ultrasound scans and magnetic resonance imaging (MRI) may be present in asymptomatic individuals so, even if identified in a symptomatic patient, these findings may not explain the patient's symptoms.

Both conditions are generally self-limiting and many patients recover within 1 year; however, symptoms can persist beyond 2 years in some patients.

Management of lateral and medial epicondylar tendinopathies

Management of lateral and medial epicondylar tendinopathies

Reassure patients about the generally favourable prognosis of these conditions. Consider the impact of the condition on the patient's ability to perform daily activities (eg participation in social, recreational and occupational activities) and on their mental health.

A reasonable management approach includes analgesia if required and exercise. Advise patients to avoid or modify activities that aggravate discomfort or place high loads on the affected tendon. See also Management principles for tendinopathy.

Analgesia

Analgesia

If analgesia is required, topical or oral nonsteroidal anti-inflammatory drugs (NSAIDs) may provide short-term pain relief. Use:

1 an NSAID orally (see Table 12.7 for dosing) *epicondylar tendinopathies, lateral or medial (tennis or golfer's elbow)*

OR

1 a topical NSAID applied directly to the painful area, up to 4 times daily (see Table 12.7 for available topical preparations). *epicondylitis, lateral or medial (tennis or golfer's elbow)*

The potential benefits of an NSAID should be weighed against its potential harms, particularly in patients at high risk of harms (see Principles of NSAID use for musculoskeletal conditions in adults for more information).

Local corticosteroid injection may be considered instead of, or in combination with, an NSAID. Local corticosteroid injection can provide pain relief for 6 to 12 weeks. The injection may be repeated if needed. A rebound effect or worsening of symptoms after initial favourable response may occur. For principles of use and example doses of local corticosteroid injections, see Principles of using local corticosteroid injections for musculoskeletal conditions in adults.

Exercise

Exercise

A reasonable exercise recommendation for lateral and medial epicondylar tendinopathies is a progressive loading program for the affected tendon incorporating functional upper limb exercise. Stretching and strengthening exercises at the elbow are commonly used and are not harmful; they may be considered as a self-management strategy.

Other treatments

Other treatments

There is limited evidence to support the use of a range of physical treatments other than exercise in the management of lateral and medial epicondylar tendinopathies. These treatments include the application of ice or heat; the use of an elbow brace, strap or taping; the use of a wrist splint; manual therapy; laser therapy; and acupuncture.

Evidence does not support the use of ultrasound or extracorporeal shock wave therapy for lateral and medial epicondylar tendinopathies.

Surgery may be considered in the small subset of patients with persisting symptoms despite conservative management, but well-conducted trials comparing surgery with placebo or a nonsurgical control group are lacking.

De Quervain tenosynovitis

De Quervain tenosynovitis

De Quervain tenosynovitis affects the abductor pollicis longus and extensor pollicis brevis tendons at the distal end of the radius. Pain and swelling occur over the radial aspect of the wrist, extending to the thumb. De Quervain tenosynovitis often occurs in people who perform repetitive manual tasks. It can occur in pregnancy or, more commonly, in the postpartum period. In the postpartum period, it is probably caused by repeated radial and ulnar deviation of the wrist during gripping movements (eg during breastfeeding).

The diagnosis of de Quervain tenosynovitis is usually made by history and physical examination, but an ultrasound scan may be useful if there is uncertainty about the diagnosis.

Treatment options for de Quervain tenosynovitis include local corticosteroid injection, splinting and/or nonsteroidal anti-inflammatory drugs (NSAIDs). The choice of treatment(s) depends on patient factors, including patient preference.

Local corticosteroid injection is very effective in relieving pain and is more effective than NSAIDs or splinting. Injection can be repeated if symptoms recur. Give the injection into the tendon sheath along the radial aspect of the wrist. For principles of use and example doses of local corticosteroid injections, see Principles of using local corticosteroid injections for musculoskeletal conditions in adults. Local corticosteroid injection can be used in women who are pregnant or breastfeeding.

Resting the thumb is considered an effective treatment; however, this can be difficult for patients to implement, especially in the postpartum period, so splinting to immobilise the base of the thumb is often recommended. Splinting is usually used continuously for 6 weeks and then use is slowly reduced.

NSAIDs may provide pain relief, but should not be given in late pregnancy (beyond 32 weeks' gestation). If treatment with an NSAID is appropriate, use:

1 an NSAID orally (see Table 12.7 for dosing) *de Quervain tenosynovitis*

OR

1 a topical NSAID applied directly to the painful area, up to 4 times daily (see Table 12.7 for available topical preparations). *de Quervain tenosynovitis*

The potential benefits of an NSAID should be weighed against its potential harms, particularly in patients at high risk of harms (see Principles of NSAID use for musculoskeletal conditions in adults for more information). For advice on the use of NSAIDs in women who are pregnant or breastfeeding, see NSAIDs and reproductive health in women.

NSAIDs should not be used in pregnant women beyond 32 weeks' gestation.

Surgical release of tendons may be effective for refractory de Quervain tenosynovitis, but is rarely required.

Carpal tunnel syndrome

Carpal tunnel syndrome

Introduction

Introduction

Carpal tunnel syndrome refers to entrapment of the median nerve in the carpal tunnel at the wrist. It presents with paraesthesia, pain, and numbness in the fingers and thumb, in the distribution of the median nerve. Carpal tunnel syndrome is generally idiopathic, but can be associated with pregnancy, diabetes, hypothyroidism, rheumatoid arthritis, and overuse of the forearm muscles.

Carpal tunnel syndrome in pregnant women mostly occurs in the second and third trimesters. Symptoms commonly recur in subsequent pregnancies and later in life, especially around menopause. It is thought to be associated with the fluid retention that occurs in pregnancy.

The clinical course of carpal tunnel syndrome is not well understood. The condition resolves spontaneously in up to one-third of patients and may resolve with treatment of the underlying medical condition, if present. If associated with pregnancy, it usually resolves within 4 weeks of delivery.

Suspect carpal tunnel syndrome in any patient with persistent hand pain, particularly if it is nocturnal and dysaesthetic in quality. Nerve conduction studies can confirm an entrapment median neuropathy at the wrist, thereby excluding alternative diagnoses such as C6 radiculopathy.

Management of carpal tunnel syndrome

Management of carpal tunnel syndrome

Management of carpal tunnel syndrome includes treatment of the underlying medical condition, if present. Treatment choice for symptomatic relief depends on patient factors, including patient preference.

Nonsteroidal anti-inflammatory drugs (NSAIDs) may provide pain relief, but should not be given in late pregnancy (beyond 32 weeks' gestation). If treatment with an NSAID is appropriate, use:

an NSAID orally (see Table 12.7 for dosing). *carpal tunnel syndrome*

The potential benefits of an NSAID should be weighed against its potential harms, particularly in patients at high risk of harms (see Principles of NSAID use for musculoskeletal conditions in adults for more information). For advice on the use of NSAIDs in women who are pregnant or breastfeeding, see NSAIDs and reproductive health in women.

NSAIDs should not be used in pregnant women beyond 32 weeks' gestation.

Injection of corticosteroid into the carpal tunnel provides symptomatic relief, especially if inflammatory arthritis is also present. Benefit has been demonstrated for at least 1 month after injection. A second injection may be appropriate. Local corticosteroid injection can be used in women who are pregnant or breastfeeding, and is preferred over the use of NSAIDs if pharmacological management for pain relief is required in pregnant women. For principles of use and example doses of local corticosteroid injections, see Principles of using local corticosteroid injections for musculoskeletal conditions in adults.

Splinting and hand braces may provide short-term symptomatic relief for patients with carpal tunnel syndrome. Elevating the forearm on a pillow at night can also give symptomatic relief.

Evidence indicates that diuretics (including in pregnancy-induced carpal tunnel syndrome), magnets, laser acupuncture and chiropractic treatment have no benefit. There is insufficient evidence to support the use of gabapentin, amitriptyline, therapeutic ultrasound, exercise or mobilisation for carpal tunnel syndrome.

Do not use diuretics for carpal tunnel syndrome.

Patients should be referred for surgery if they do not respond to conservative management, or if they have progressive sensory or motor deficits or moderate to severe electrodiagnostic abnormalities. However, surgery should be avoided in pregnant women if possible because symptoms almost always resolve following delivery.

Flexor tenosynovitis (trigger finger)

Flexor tenosynovitis (trigger finger)

Introduction

Introduction

Flexor tenosynovitis (trigger finger, including the thumb) is most common in patients between 50 and 60 years of age. Gradually, or in some cases acutely, abnormality of the flexor tendon causes a painful click as the patient flexes and extends the digit. The patient may present with locking of the affected digit in a flexed position, and this may require gentle passive manipulation to release the digit into extension. Crepitus and/or a nodule may be palpable. Differential diagnoses include Dupuytren contracture and, in patients with multiple digit involvement, underlying systemic inflammatory disease (eg spondyloarthritides, rheumatoid arthritis) and chronic infection (eg mycobacterial infection).

A variety of causes for flexor tenosynovitis have been suggested, including repetitive finger movements, compressive forces at the A1 pulley (an annular ligament near the metacarpal head), and repetitive trauma. The incidence of flexor tenosynovitis is higher in patients with diabetes; patients with type 1 diabetes are more likely to have multiple digit involvement and treatment is difficult in these patients.

The clinical course of flexor tenosynovitis is not well understood. In idiopathic cases, the condition may resolve spontaneously.

Management of flexor tenosynovitis

Management of flexor tenosynovitis

Management of flexor tenosynovitis includes treatment of the underlying medical condition, if present.

Nonsteroidal anti-inflammatory drugs (NSAIDs) may provide pain relief. Use:

an NSAID orally (see Table 12.7 for dosing). *flexor tenosynovitis (trigger finger)*

The potential benefits of an NSAID should be weighed against its potential harms, particularly in patients at high risk of harms (see Principles of NSAID use for musculoskeletal conditions in adults for more information).

Splinting aims to reduce or remove tendon excursion through the A1 pulley for long enough to allow the tenosynovitis to resolve. Various methods of splinting may be beneficial, but none of these has been studied in randomised controlled trials.

Local corticosteroid injection in the region around the A1 pulley is a highly effective treatment, with reported success rates of 50 to 70% in randomised controlled trials. Injection may be particularly effective if a well-defined nodule is palpable, or if symptoms have been present for less than 6 months. For principles of use and example doses of local corticosteroid injections, see Principles of using local corticosteroid injections for musculoskeletal conditions in adults.

Surgery may be considered for patients with persisting symptoms despite conservative management. Success rates of over 90% have been reported, with a low complication rate.

Hip joint conditions

Hip joint conditions

Patients use the word ‘hip’ to refer to a number of anatomical structures, so when patients complain of hip pain, care must be taken to define the precise anatomical location of their pain. Patients with true hip joint

pathology usually present with groin and/or anterior thigh pain, which may extend down to the knee. Occasionally, patients may present with referred knee pain only. Hip joint pathology rarely refers pain to the lateral thigh; other diagnoses, such as greater trochanteric pain syndrome, back pain and diabetic amyotrophy (see Atypical diabetic neuropathies), should be considered in patients presenting with isolated pain in this area. In patients with hip joint pathology, passive movements of the hip are often painful and/or limited.

Acute pain secondary to hip joint pathology in an adult could be osteoarthritis or inflammatory arthritis (see Assessing peripheral musculoskeletal symptoms in adults). Consider the possibility of osteoarthritis in patients with risk factors for osteoarthritis (see Risk factors for osteoarthritis). In patients presenting with hip-girdle pain and stiffness, consider the possibility of polymyalgia rheumatica.

In patients with severe groin and/or anterior thigh pain but normal hip movements, consider the possibility of avascular necrosis or stress fracture. Avascular necrosis of the head of the femur is relatively uncommon, but the atraumatic form should be suspected in patients with recognised risk factors, such as the use of systemic corticosteroids or excessive alcohol consumption. Post-traumatic cases are associated with fracture of the head or the neck of the femur. Stress fractures may be seen in patients with risk factors for osteoporosis (see Risk factors for osteoporosis and fractures) or patients who participate in recurrent, vigorous physical activity.

In older patients, consider the possibility of a fracture of the neck of the femur. This is usually due to trauma. Patients have an inability to weightbear and present with an externally rotated, shortened leg.

Femoroacetabular impingement and hip labral tears

Femoroacetabular impingement and hip labral tears

Femoroacetabular impingement (FAI) and hip labral tears are primarily radiological findings and are poorly correlated with symptoms. FAI is characterised by abnormal contact between the proximal femur and the acetabulum. Two types of FAI have been described—pincer impingement (caused by an overcovered acetabulum) and cam impingement (caused by an aspherical femoral head). The prevalence of FAI in the general population is uncertain; the prevalence estimates of cam hip shape morphology ranged from 5 to 75% across three studies that included nonrepresentative subgroups of the general population, 19 studies of different clinical populations and eight studies in professional athletes. Higher prevalence was not demonstrated in athletes or symptomatic patients. Hip labral tears are also seen in high prevalence in asymptomatic people.

The clinical and long-term significance of these radiological findings, including the relationship between FAI and osteoarthritis, is unclear. There are no proven effective treatments for FAI and hip labral tears, and any interventions should be undertaken with caution.

Greater trochanteric pain syndrome

Greater trochanteric pain syndrome

Lateral thigh pain is often given the name ‘trochanteric bursitis’, but many cases involve pathology of the gluteus medius and/or minimus tendons (with or without bursal pathology); these are collectively referred to as greater trochanteric pain syndrome. A differential diagnosis is pain referred from the low back along the L2 and L3 dermatomes (see Low back pain).

There are few randomised controlled trials to guide the management of greater trochanteric pain syndrome. Initial management is usually exercises to improve the tensile strength of the gluteus medius and minimus tendons. Some patients may benefit from a specific exercise program to address muscle imbalance contributing to compression loading of the gluteal tendons. Encourage patients to persist with exercise even if symptom relief is achieved with analgesia because exercise is important to prevent recurrence of symptoms. Advise the patient to avoid compression of the gluteal tendons over the greater trochanter (eg avoid leg-crossing, hip-hanging, and side-lying in bed). If necessary, a pillow can be placed between the knees when sitting or lying down to reduce compression.

Nonsteroidal anti-inflammatory drugs (NSAIDs) may provide pain relief in early cases. Use:

an NSAID orally (see Table 12.7 for dosing). *greater trochanteric pain syndrome*

The potential benefits of an NSAID should be weighed against its potential harms, particularly in patients at high risk of harms (see Principles of NSAID use for musculoskeletal conditions in adults for more information).

For patients with more severe symptoms (night pain, impaired physical function, inability to lie on the side), consider local corticosteroid injection. Local corticosteroid injection can relieve pain and improve the patient's ability to undertake an exercise program; local corticosteroid injection may be considered instead of, or in combination with, an NSAID. Give the corticosteroid injection at the point of maximum tenderness. Ultrasound guidance for injection into the trochanteric bursa is not recommended because it provides no additional benefit compared to non–radiologically guided injection. A repeat injection may be given if needed but, in general, local corticosteroid injections should not be performed more than twice per year. For principles of use and example doses of local corticosteroid injections, see Principles of using local corticosteroid injections for musculoskeletal conditions in adults. Failure to have any response to local corticosteroid injection should raise suspicion of a gluteal tear or alternative diagnosis.

Degenerative meniscal tears

Degenerative meniscal tears

Most people aged 50 years and older will have some radiological findings of osteoarthritis in their knees, and roughly a quarter will have some degenerative changes in the menisci; the prevalence of these findings increases with age. These findings are common in both people with and without knee pain. Therefore, in people aged 50 years and older with knee pain, abnormalities reported on magnetic resonance imaging (MRI) may not necessarily explain their symptoms and MRI is not recommended. Management of knee pain in people aged 50 years and older with degenerative meniscal tears is the same as for those without this finding (see General management approach for osteoarthritis).

Patellofemoral pain syndrome

Patellofemoral pain syndrome

Patellofemoral pain syndrome refers to idiopathic pain arising from the anterior knee or patellofemoral region. The pain has an insidious onset and is generally felt anteriorly. Running, walking up or down stairs, and prolonged sitting may aggravate the pain. An effusion is uncommon. Risk factors for patellofemoral pain syndrome include female gender, obesity, and joint laxity. Biomechanical abnormalities that may be associated with patellofemoral pain syndrome include excessive pronation of the subtalar joint, weak quadriceps and tight hamstrings, tight lateral patellar retinaculum, and a laterally placed tibial tuberosity.

Patellofemoral osteoarthritis is often clinically identical to the patellofemoral pain syndrome and is the most common cause of retropatellar pain in the older patient.

Individually tailored conservative care, with a focus on graduated functional lower limb exercise and reduction of aggravating activities, is the mainstay for management of patellofemoral pain syndrome. The evidence to support the use of other physical treatments is limited; these include patellofemoral joint mobilisation, medial patellar taping, external patellar bracing and the use of foot orthoses.

If analgesia is required, paracetamol may provide pain relief. Use:

1 paracetamol 1 g orally, 4- to 6-hourly, up to a maximum of 4 g daily *patellofemoral pain syndrome*

OR

1 paracetamol modified-release 1.33 g orally, 8-hourly.

If response to paracetamol is inadequate, a nonsteroidal anti-inflammatory drug (NSAID) may be used **instead of, or in combination with**, paracetamol. Use:

an NSAID orally (see Table 12.7 for dosing). *patellofemoral pain syndrome*

The potential benefits of an NSAID should be weighed against its potential harms, particularly in patients at high risk of harms (see Principles of NSAID use for musculoskeletal conditions in adults for more information).

Prepatellar bursitis

Prepatellar bursitis

The prepatellar bursa is located anterior to the patella and is the most frequently symptomatic bursa around the knee joint. Prepatellar bursitis presents as a painful, tender superficial swelling over the patella, often after acute or chronic trauma. Gout and septic bursitis are differential diagnoses.

Kneepads should be used by those who kneel frequently to prevent prepatellar bursitis.

Mild cases of traumatic prepatellar bursitis can be managed with rest, application of ice, compression bandaging, and nonsteroidal anti-inflammatory drugs (NSAIDs). Advise patients to avoid traumatic compression.

If NSAIDs are indicated, use:

an NSAID orally (see Table 12.7 for dosing). *prepatellar bursitis*

The potential benefits of an NSAID should be weighed against its potential harms, particularly in patients at high risk of harms (see Principles of NSAID use for musculoskeletal conditions in adults for more information).

In more severe or refractory cases, or if inflammatory or septic bursitis is suspected, aspiration of bursal fluid for analysis and culture is required. For management of gout, see Gout. Management of septic bursitis requires urgent hospital referral (see Septic bursitis). If infection has been excluded, local corticosteroid injection is appropriate. For principles of use and example doses of local corticosteroid injections, see Principles of using local corticosteroid injections for musculoskeletal conditions in adults.

Chronic exertional compartment syndrome

Chronic exertional compartment syndrome

Pain originating in the anterior or deep posterior muscle compartment of the lower leg is common in those who exercise, and may be caused by a chronic exertional compartment syndrome. If examined immediately after activity, the area is tender and firm to touch.

Initial management of chronic exertional compartment syndrome is conservative. Nonsteroidal anti-inflammatory drugs (NSAIDs) may provide short-term pain relief. Use:

an NSAID orally (see Table 12.7 for dosing). *compartment syndrome, chronic exertional*

The potential benefits of an NSAID should be weighed against its potential harms, particularly in patients at high risk of harms (see Principles of NSAID use for musculoskeletal conditions in adults for more information).

Other conservative measures include reducing or stopping activities that lead to pain, changing the exercise program, stretching, and correction of foot biomechanical abnormalities if appropriate. These measures should be tried for 2 to 3 months, but are usually only successful if accompanied by stopping or significantly

reducing athletic activity. Many patients with chronic exertional compartment syndrome are not willing to give up athletic activity, so fasciotomy may be required.

Medial tibial stress syndrome

Medial tibial stress syndrome

Medial tibial stress syndrome (formerly known as shin splints) presents as exercise-related pain at the lower third to half of the medial tibial border. It is most likely due to a stress lesion at the fascial insertion of the medial soleus, tibialis posterior or flexor digitorum longus at the medial tibial border.

Medial tibial stress syndrome is difficult to treat and there is no strong evidence for any intervention. Rest is an important component of management, but can be difficult for patients to implement. There is little evidence for the use of nonsteroidal anti-inflammatory drugs (NSAIDs), but they may provide short-term pain relief. Use:

an NSAID orally (see Table 12.7 for dosing). *medial tibial stress syndrome*

The potential benefits of an NSAID should be weighed against its potential harms, particularly in patients at high risk of harms (see Principles of NSAID use for musculoskeletal conditions in adults for more information).

Evidence indicates that low-energy laser treatment, stretching and strengthening exercises, sports compression stockings, leg braces and pulsed electromagnetic fields have no benefit in medial tibial stress syndrome. There is insufficient evidence to recommend the use of iontophoresis, phonophoresis, ice massage, ultrasound, periosteal pecking and extracorporeal shockwave therapy for medial tibial stress syndrome.

Tear of the Achilles tendon

Tear of the Achilles tendon

Complete tear of the Achilles tendon typically occurs in males older than 40 years of age, usually during rapid acceleration (eg while playing tennis). It has also been described as an adverse effect of fluoroquinolone antibiotics (eg ciprofloxacin), generally in patients older than 60 years of age. It presents with acute pain and/or loss of function in the posterior aspect of the lower leg.

All complete tendon ruptures merit immediate surgical consultation. In acute tendon ruptures, conservative management (casting or functional brace with a heel lift for 6 to 8 weeks) or surgery may be considered. Surgery followed by intensive rehabilitation may reduce the rate of re-rupture when compared with conservative management, but has a higher risk of other complications. If conservative management is used, it should include functional rehabilitation.

Partial tear of the Achilles tendon presents with acute pain, often with a history of Achilles tendinopathy. Management is as for tendinopathy; see Management principles for tendinopathy.

Plantar fasciitis

Plantar fasciitis

Plantar fasciitis presents with pain at the anteromedial aspect of the calcaneus; the pain is worst during the first steps taken in the morning and improves during the day. Plantar fasciitis may represent an enthesopathy associated with one of the spondyloarthritides. Most cases that are not associated with a spondyloarthritis resolve within 1 year with conservative management. Heel spurs are a common incidental X-ray finding and are not related to the experience of pain.

Advise patients with plantar fasciitis to avoid or modify aggravating activities, and to avoid walking in flat shoes or barefoot. Conservative management of plantar fasciitis involves stretching and strengthening the calf

muscles, stretching the fascia, use of a heel cup or cushion, and ice massage after aggravating activity that cannot be avoided or modified. The evidence to support the use of these interventions is limited, but they are reasonable low-cost approaches. Orthoses, night splints and Low-Dye taping also have limited evidence for efficacy. Extracorporeal shock wave therapy has not been proven to be of benefit in the management of plantar fasciitis.

Nonsteroidal anti-inflammatory drugs (NSAIDs) may provide pain relief. Use:

an NSAID orally (see Table 12.7 for dosing). *plantar fasciitis*

The potential benefits of an NSAID should be weighed against its potential harms, particularly in patients at high risk of harms (see Principles of NSAID use for musculoskeletal conditions in adults for more information).

Corticosteroid injection into the region of the attachment may provide short-term pain relief. For principles of use and example doses of local corticosteroid injections, see Principles of using local corticosteroid injections for musculoskeletal conditions in adults.

If patients do not respond to a well-supervised 6-month rehabilitation program, refer to a specialist.

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Key references: Management principles for muscle strain or tear

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Key references: Management principles for tendinopathy

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Behçet syndrome

Behçet syndrome

Overview of Behçet syndrome

Overview of Behçet syndrome

Behçet syndrome is uncommon in Australia, but the prevalence is high in countries that formed the ancient silk route (eg Turkey, Iran, Japan). Although Behçet syndrome is often classified as a systemic vasculitis, vasculitis is only present in up to 25% of patients.

Key clinical features of Behçet syndrome are recurrent oral and genital ulceration, and ocular inflammation. Both anterior and posterior chambers of the eye can be involved. Severe uveitis occurs relatively commonly and can lead to blindness, so prompt referral of patients with Behçet eye disease to an ophthalmologist is essential and may be sight saving.

Promptly refer patients with Behçet eye disease to an ophthalmologist.

Around 5% of patients with Behçet syndrome have neurological involvement, leading to pyramidal, sensory and cerebellar signs. Patients with Behçet syndrome are also prone to developing superficial venous thrombophlebitis and more rarely deep vein thrombosis. An episodic oligoarthritis that is mild and nondeforming can occur and commonly affects the knees; aspiration of affected joints reveals sterile inflammatory fluid. Many other manifestations occur, including gastrointestinal ulceration causing colicky abdominal pain, diarrhoea and bleeding, and a pathergy reaction, in which simple trauma causes papule or pustule formation at the site of injury within a few hours.

There are no specific laboratory or serological findings for Behçet syndrome.

Always consider the diagnosis of herpes simplex infection in patients who present with oral or genital ulceration, even in patients with an apparent recurrent episode of Behçet syndrome.

Management of Behçet syndrome

Management of Behçet syndrome

Behçet syndrome requires specialist management. The aim of treatment is to suppress inflammation and preserve organ function while minimising toxicity from immunomodulatory therapy. Various immunomodulatory drug regimens are used to treat disease affecting major organs or body systems (eg central nervous system disease, large-vessel disease, gastrointestinal disease). Large-vessel involvement may lead to aneurysms, which may need surgical repair.

Some manifestations (eg oral and genital ulceration, arthritis) can be managed in primary care.

For treatment of **acute oral or genital ulceration**, use:

1 triamcinolone acetonide 0.1% paste applied to lesions, 2 to 3 times daily *Behcet syndrome* _

OR

2 prednis(ol)one 10 to 15 mg orally, daily until pain is controlled (typically 5 days), then taper the dose over 1 to 2 weeks to stop. *Behcet syndrome* _

For recurrent episodes of ulceration, the treatment course may be repeated. See Principles of immunomodulatory drug use for rheumatological diseases in adults for information on adverse effects associated with long-term corticosteroid use (such as bone density loss) and advice on how to minimise and monitor for such complications.

Topical pimecrolimus has been used to treat recurrent acute genital ulceration (in combination with colchicine for prevention) [Note 1]. Data suggest it may reduce healing time and pain.

For **prevention of oral or genital ulceration**, use:

colchicine 500 micrograms orally, once or twice daily. Reduce dosage in renal impairment. *Behcet syndrome*

Full blood count should be monitored in patients taking colchicine long term.

Apremilast is effective in treating and preventing oral ulcers, and can reduce disease activity and improve quality of life. For resistant cases of oral and genital ulcers, other drugs used include azathioprine, interferon alfa and infliximab. Azathioprine is used for the prevention of oral and genital ulcers, whereas interferon alfa and infliximab can be used for both prevention and treatment.

For treatment of **arthritis** associated with Behçet syndrome, use:

colchicine 500 micrograms orally, once or twice daily. Reduce dosage in renal impairment.

For resistant arthritis, other drugs used include azathioprine, interferon alfa and infliximab.

Note 1: At the time of writing, topical pimecrolimus is not approved by the Australian Therapeutic Goods Administration (TGA) for treatment of genital ulcers in Behçet syndrome. See the TGA website for current information [URL].

Adult-onset Still disease

Adult-onset Still disease

Overview of adult-onset Still disease

Overview of adult-onset Still disease

Adult-onset Still disease is a rare disease of unknown cause with manifestations in many body systems. It is characterised by a vigorous systemic inflammatory response. Adult-onset Still disease affects men and women equally, and typically presents in early adulthood. The equivalent disease in children is known as systemic arthritis.

The most common clinical features of adult-onset Still disease are arthralgia, arthritis, fever, sore throat and rash. Approximately one-half of patients have abdominal pain and/or enlarged lymph nodes, spleen or liver. Approximately one-third of patients have pleurisy and/or pericarditis, which can be particularly painful.

The most common laboratory findings in adult-onset Still disease are marked neutrophil leucocytosis, elevated inflammatory markers, abnormal liver biochemistry and a very high serum ferritin concentration. Serum ferritin can be extremely elevated (in the tens of thousands compared with the normal range of 15 to 400 micrograms/L) and may be useful in monitoring disease activity in combination with inflammatory markers.

Adult-onset Still disease is not associated with autoantibodies and the diagnosis is supported by negative antinuclear antibodies (ANA) and negative rheumatoid factor (RF). Biopsy is nonspecific.

Diagnosis of adult-onset Still disease requires both exclusion of conditions with similar presentations (especially infection and malignancy, particularly lymphoma) and consistency with clinical criteria (eg

spiking fever for 1 week or longer, arthralgia or arthritis for 2 weeks or longer, characteristic transient erythema during febrile episodes).

A third of patients have an acute, self-limiting disease course lasting less than 1 year. A further third have one or more flares, with complete symptom resolution between episodes. The final third have chronic disease characterised by development of persistent, destructive polyarthritis.

Management of adult-onset Still disease

Management of adult-onset Still disease

Treatment of adult-onset Still disease depends on the organs involved and disease severity. Urgently refer patients with life-threatening manifestations, such as cardiac tamponade or pneumonitis, to an emergency department for specialist review and treatment with intravenous methylprednisolone.

Urgently refer patients with life-threatening manifestations of adult-onset Still disease to an emergency department.

Some manifestations can be managed in primary care.

For musculoskeletal symptoms or fever, use:

an NSAID orally (see Table 12.7 for dosing). *adult-onset Still disease*

The potential benefits of a nonsteroidal anti-inflammatory drug (NSAID) should be weighed against its potential harms, particularly in patients at high risk of harms (see Principles of NSAID use for musculoskeletal conditions in adults for more information).

If response to NSAIDs is inadequate, use instead:

prednis(ol)one 10 to 25 mg orally, daily. *adult-onset Still disease*

Once disease manifestations are controlled, slowly withdraw prednis(ol)one while carefully monitoring disease activity; however, some patients may require ongoing corticosteroid therapy because the course of adult-onset Still disease is highly variable. See Principles of immunomodulatory drug use for rheumatological diseases in adults for information on adverse effects associated with long-term corticosteroid use (such as bone density loss) and advice on how to minimise and monitor for such complications.

Patients with chronic symptoms that have not responded to an NSAID and corticosteroid require specialist referral; only anecdotal evidence is available to guide management. Treatment generally involves the addition of a conventional synthetic disease-modifying antirheumatic drug (csDMARD), such as methotrexate. In severe refractory disease, cyclophosphamide or a biological disease-modifying antirheumatic drug (bDMARD) may be considered.

Periodic fever syndromes

Periodic fever syndromes

Overview of periodic fever syndromes

Overview of periodic fever syndromes

Familial Mediterranean fever is the most common of the periodic fever syndromes (also known as autoinflammatory syndromes). Other periodic fever syndromes include hyperimmunoglobulinaemia D syndrome, tumour necrosis factor receptor–associated periodic syndrome and familial cold-induced urticaria syndrome. All involve recurrent fevers in association with other features such as rash, arthritis, serositis, adenitis, conjunctivitis, changes in hearing and elevated inflammatory markers.

The diagnosis of periodic fever syndromes is complex and often delayed, with the majority of recurrent fevers in children remaining undiagnosed. Consider the possibility of a periodic fever syndrome in any patient with recurrent, self-limiting fevers, particularly if they follow a pattern and are accompanied by other recurring features. The combination of a patient's clinical features and the duration of fever provides clues to the likely periodic fever syndrome. The diagnosis of some periodic fever syndromes may be confirmed by genetic testing.

Refer any patient with a suspected periodic fever syndrome to a rheumatologist or other specialist experienced in the diagnosis and management of these conditions.

Familial Mediterranean fever

Familial Mediterranean fever

Familial Mediterranean fever is caused by a genetic mutation and predominantly occurs in Turkish, Armenian and Arabic ethnic groups. It can occur at any age, although 80% of cases present during childhood, often in children younger than 5 years.

Common features of familial Mediterranean fever include:

- fever—usually lasting 1 to 3 days
- arthritis—affecting large joints with a monoarticular or oligoarticular distribution, and of acute onset and short duration
- polyserositis—typically peritoneal or pleuritic
- rash—area of erysipelas-like rash on trunk or limbs
- marked elevation of inflammatory markers (C-reactive protein, erythrocyte sedimentation rate).

Less common features include headache, microscopic haematuria, and a vasculitic rash similar to that of immunoglobulin A vasculitis. A small number of patients have a more persistent pattern of arthritis, in a distribution similar to that of a spondyloarthritis (eg asymmetric, affecting large joints of the lower limbs).

Without therapy, the frequency of attacks varies from weeks to months.

Colchicine is recommended for the treatment of familial Mediterranean fever and should be continued lifelong if tolerated. It is very effective at both reducing the frequency of attacks and protecting against the development of amyloidosis, which is the main complication of familial Mediterranean fever. In children and adults, the usual dosage is:

colchicine 0.5 to 2 mg orally, daily. Reduce dosage in renal impairment. *familial Mediterranean fever* _

To limit the occurrence of early adverse effects, start treatment with the lowest dose and slowly titrate up until disease control is achieved. In young children, the maintenance dose of colchicine is usually at the lower end of the dose range. Full blood count should be monitored in patients taking colchicine long term.

Cryoglobulinaemia

Cryoglobulinaemia

Overview of cryoglobulinaemia

Overview of cryoglobulinaemia

Cryoglobulins are serum immunoglobulins that reversibly precipitate in the cold. Cryoglobulins most commonly develop in response to chronic infections with lymphotropic viruses such as HIV or hepatitis C. Other causes are lymphoproliferative disorders (eg chronic lymphatic leukaemia, multiple myeloma) and connective tissue diseases (eg Sjögren syndrome). Cryoglobulins can cause disease varying from minor skin manifestations to life-threatening vasculitic and kidney disease.

Cryoglobulins cause clinical manifestations by forming aggregates that lodge in blood vessels, causing local ischaemia, or by activating local inflammatory cascades, typically through the complement system. The most common manifestation of cryoglobulinaemia is a purpuric rash on the lower limbs. Although less common, arthralgia, weakness and liver disease occur in approximately one-half of patients. About one-third of patients have kidney involvement. Rarer manifestations are Raynaud syndrome and peripheral neuropathy. Cryoglobulinaemia can cause an organ-threatening vasculitis.

Testing for cryoglobulins, assessment of kidney function and exclusion of glomerulonephritis are important when evaluating patients with suspected cryoglobulinaemia. To determine the underlying cause, patients should have serum electrophoresis (to identify multiple myeloma) and immunoelectrophoresis (to identify chronic lymphatic leukaemia), and serology for hepatitis C and B, HIV and rheumatoid factor (RF). Inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are usually elevated. The need for other investigations depends on the underlying disease.

Management of cryoglobulinaemia

Management of cryoglobulinaemia

Cryoglobulinaemia requires specialist management. Treatment is related to disease severity and involves management of the underlying disease (eg hepatitis C) as well as the cryoglobulinaemia itself. Managing the underlying disease controls associated cryoglobulinaemia; however, immediate intensive immunomodulatory therapy is also required to control cryoglobulinaemia affecting the kidneys, liver or nerves, or other organ-threatening vasculitic disease. Rituximab is beneficial in severe cryoglobulinaemic vasculitis and can be continued long term in most patients. Some patients require plasmapheresis.

Immunoglobulin G4–related disease

Immunoglobulin G_4–related disease

Immunoglobulin G_4 (IgG_4)–related disease is a recently described, systemic, immune-mediated disease that affects multiple organs. The spectrum of IgG_4-related disease includes conditions previously thought to be isolated to a single organ (eg autoimmune cholangitis, autoimmune pancreatitis). Common presentations include aortitis, retroperitoneal fibrosis and orbital pseudotumour. Diagnosis is usually based on an elevated serum IgG_4 and histopathological analysis of a tissue sample. IgG_4-related disease is an important differential diagnosis of many inflammatory, infectious and malignant diseases (eg granulomatosis with polyangiitis, microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis, pancreatic cancer, primary sclerosing cholangitis, cholangiocarcinoma).

In the initial inflammatory phase of IgG_4-related disease, corticosteroids are effective and are first-line therapy. If patients require long-term high-dose corticosteroid therapy to prevent relapse, consider alternative immunomodulatory therapy (eg azathioprine, mycophenolate). Detailed international guidelines on the management of IgG_4-related disease are available [Note 2].

Note 2: Khosroshahi A, Wallace ZS, Crowe JL, Akamizu T, Azumi A, Carruthers MN, et al. International consensus guidance statement on the management and treatment of IgG4-related disease. Arthritis Rheumatol 2015;67(7):1688-99. [URL]

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Polymyalgia rheumatica

Polymyalgia rheumatica

Introduction

Introduction

Polymyalgia rheumatica is an inflammatory condition characterised by bilateral aching and stiffness of the shoulders and hip-girdle area caused by low-grade synovitis. Morning stiffness is the hallmark of the disease. Patients complain of an inability to turn over in bed and of great difficulty getting out of bed. The stiffness tends to improve after a hot shower, and with activity. The onset of symptoms can be sudden or gradual.

Polymyalgia rheumatica occurs almost exclusively in people older than 50 years; its incidence increases with age. It is more common in women than men.

Diagnosis of polymyalgia rheumatica

Diagnosis of polymyalgia rheumatica

There are no specific diagnostic tests for polymyalgia rheumatica; diagnosis is based on clinical presentation and elevated erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP) concentration. Polymyalgia rheumatica is unlikely if ESR is normal; however, up to 20% of patients have a normal ESR at diagnosis. If ESR and/or CRP are not clearly elevated, and onset of symptoms is recent, retest in 1 to 2 weeks. For a summary of features of polymyalgia rheumatica, see Table 12.17.

Polymyalgia rheumatica is overdiagnosed, particularly in patients younger than 50 years, in whom the diagnosis is almost always incorrect. Fibromyalgia, myalgias due to drugs such as statins, or Parkinson disease may be misdiagnosed as polymyalgia rheumatica, especially if ESR is spuriously elevated. Before making a diagnosis, exclude disorders that can mimic the presentation, such as rotator cuff disease or greater trochanteric pain syndrome. The features of polymyalgia rheumatica may be vague and nonspecific; in patients with systemic features such as weight loss, fevers, malaise and generalised pain and stiffness, exclude infection and malignancy (especially myelodysplasia).

Rapid response to corticosteroid therapy at the usual starting dose (eg prednis(ol)one 15 mg orally, daily) is a good diagnostic indicator of polymyalgia rheumatica. Reconsider the diagnosis if corticosteroid therapy fails to achieve prompt symptomatic relief and a decrease in inflammatory markers.

Urgently refer any patient with suspected giant cell arteritis to a specialist.

About 15% of patients with polymyalgia rheumatica also have giant cell arteritis. Urgently refer patients with suspected giant cell arteritis to a specialist (including patients with polymyalgia rheumatica who have jaw claudication, severe headache, visual symptoms, scalp tenderness or malaise because these are classic symptoms of giant cell arteritis); see Giant cell arteritis for more information.

Table 12.17 Features of polymyalgia rheumatica

Features that are usually present	• age older than 50 years • bilateral shoulder aching • elevated ESR and/or CRP concentration
Supportive features	**clinical**

- morning stiffness lasting longer than 45 minutes
- hip-girdle discomfort or limited range of motion
- absence of involvement of joints other than the hip and shoulder

laboratory

- absence of RF and antibodies to CCP

CCP = cyclic citrullinated peptides; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; RF = rheumatoid factor

Management of polymyalgia rheumatica

Management of polymyalgia rheumatica
General management approach for polymyalgia rheumatica

A long course of a corticosteroid is needed to successfully treat polymyalgia rheumatica and, even with appropriate treatment, relapse is common. Rapid tapering of the corticosteroid dose significantly increases the risk of relapse, which often results in higher overall corticosteroid exposure because increased doses and slower tapering are required to treat relapsed disease. To reduce the risk of relapse, slowly taper the dose of corticosteroid until it can be stopped; smaller and more frequent dose reductions are more effective at preventing relapse than larger and less frequent dose reductions. Tapering regimens shown to reduce the risk of relapse use continuous corticosteroid therapy for 12 months or more; avoid regimens that taper and stop corticosteroid therapy within 9 months. See Pharmacological management of polymyalgia rheumatica for advice on individualising the corticosteroid regimen.

Avoid regimens that taper and stop corticosteroid therapy within 9 months. Treatment is usually required for 12 months or more.

Long-term corticosteroid therapy can cause significant adverse effects. The risk of adverse effects must be balanced against the risk of relapse with inadequate treatment. Use the lowest dose and shortest duration of therapy necessary to control disease and prevent relapse. See Principles of immunomodulatory drug use for rheumatological diseases in adults for information on adverse effects associated with long-term corticosteroid use (such as bone density loss) and advice on how to minimise and monitor for such complications.

In specific circumstances, methotrexate is added to corticosteroid therapy for its corticosteroid-sparing effect (see Pharmacological management of polymyalgia rheumatica).

In addition to drug therapy, patients should be encouraged to stay active and undertake gentle exercise. The goal of the exercise regimen should be to gradually increase the amount of time spent exercising.

Pharmacological management of polymyalgia rheumatica

Individualise the rate of corticosteroid tapering according to the patient's circumstances, including disease activity (as indicated by the patient's symptoms and inflammatory markers) and corticosteroid adverse effects.

An example regimen for the treatment of polymyalgia rheumatica is:

prednis(ol)one 15 mg orally, daily for 4 weeks; then reduce daily dose by 2.5 mg every 4 weeks to 10 mg daily; then reduce daily dose by 1 mg every 4 to 8 weeks to stop. *polymyalgia rheumatica* _

Do not reduce the dose if the patient has signs of active disease, such as recurrence of symptoms or persistently elevated inflammatory markers.

Although ESR and CRP may help identify deterioration in the patient's condition, they are not specific measures of disease activity and should always be considered in the context of the patient's symptoms. If an asymptomatic patient has elevated inflammatory markers, consider alternative pathologies (eg infection) and

retest after 4 weeks. Transient rises in ESR or CRP typically do not indicate relapse. Furthermore, it is normal for these markers to increase slightly as the corticosteroid dose is reduced. Check ESR and CRP monthly for the first 3 months of therapy, then every 2 to 3 months thereafter or as clinically indicated.

If the patient has a flare of musculoskeletal or systemic symptoms during tapering, determine if symptoms are due to relapse; this should include measurement of inflammatory markers. Advise patients that transient symptoms, such as aching and influenza-like symptoms, are expected as the corticosteroid dose is reduced and, unless advised otherwise by their doctor, they should persist with planned dose reductions. In the absence of clinician-assessed relapse, the risks associated with prolonging corticosteroid therapy are likely to outweigh its benefits.

If assessment suggests relapse (eg symptoms for more than a few days, persistently or significantly elevated inflammatory markers that cannot be explained by another pathology), revert to the previously effective corticosteroid dose and begin a slower taper; consider referring the patient to a specialist. Specialist referral is also required if corticosteroid therapy is poorly effective, not tolerated, cannot be tapered, or is needed beyond 18 months.

Although evidence to support the use of methotrexate as a corticosteroid-sparing drug is conflicting, international guidelines support its use and it is frequently used in practice (particularly in patients who relapse, need prolonged corticosteroid therapy, or develop early or severe corticosteroid adverse effects). The methotrexate dose is adjusted on the basis of clinical response and adverse effects. For considerations in the management of methotrexate therapy (including monitoring, screening for infection, and vaccination), see Principles of immunomodulatory drug use for rheumatological diseases in adults.

The usual dosage of methotrexate is:

methotrexate 10 mg orally, **on one specified day once weekly**, increasing up to 25 mg orally or subcutaneously, **on one specified day once weekly** *polymyalgia rheumatica*

PLUS

folic acid 5 to 10 mg orally, per week (preferably not on the day methotrexate is taken). *polymyalgia rheumatica*

The use of tumour necrosis factor (TNF) inhibitors is not recommended; evidence suggests they are not as effective as methotrexate in allowing the corticosteroid dose to be reduced in patients with polymyalgia rheumatica.

Giant cell arteritis

Giant cell arteritis

Introduction

Introduction

Giant cell arteritis (formerly known as temporal arteritis or cranial arteritis) is a systemic vasculitis that typically affects the cranial arteries, including the ophthalmic artery. However, it can affect other large blood vessels, including the aorta and its major branches. Giant cell arteritis occurs almost exclusively in people older than 50 years, and more commonly in women than men. Its incidence increases with age and peaks in people aged 70 to 79 years.

Diagnosis of giant cell arteritis

Diagnosis of giant cell arteritis

The classic symptoms of giant cell arteritis include jaw claudication (which is almost pathognomonic), severe headache, polymyalgia rheumatica (in about 50% of cases), visual symptoms (commonly diplopia or visual

loss), scalp tenderness and malaise. Physical examination reveals temporal artery abnormality (eg the artery is tender, enlarged, difficult to compress, nodular or pulseless) in 50% of cases. Elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) concentration are common in giant cell arteritis, but ESR may be normal initially. The features of giant cell arteritis may be vague and nonspecific; in patients with systemic features such as weight loss, fevers, malaise and generalised pain and stiffness, exclude infection and malignancy (especially myelodysplasia).
Urgently refer any patient with suspected giant cell arteritis to a specialist.

Urgently refer any patient with suspected giant cell arteritis to a specialist because a delay in treatment can result in serious consequences such as blindness or ischaemic events. Giant cell arteritis should be suspected if any of the classic symptoms (jaw claudication, severe headache, visual symptoms, scalp tenderness, or malaise) develop in a patient with polymyalgia rheumatica or a history of polymyalgia rheumatica.

Temporal artery biopsy is a specific test for giant cell arteritis, so can help avoid unnecessary long-term treatment (and its associated toxicities). Diagnostic histological changes persist for at least 1 week after treatment is started, so—although biopsy must be performed promptly if giant cell arteritis is suspected—treatment should not be delayed until biopsy is performed.

When a biopsy is performed it is imperative to obtain an adequate sample (at least 2 cm) and to have the sample comprehensively assessed (multiple sections should be examined), because giant cell arteritis may present with 'skip' lesions. However, there is no benefit in performing a contralateral biopsy if the initial biopsy was of adequate length and comprehensively assessed but did not reveal arteritis; the result is unlikely to be different. Up to 20% of patients with giant cell arteritis do not have temporal artery involvement. If the diagnosis is strongly suspected in a patient with a negative temporal artery biopsy result, vascular imaging of the aorta and its major branches is usually performed to confirm the diagnosis.

Management of giant cell arteritis

Management of giant cell arteritis

Giant cell arteritis requires specialist management. Similar to polymyalgia rheumatica, giant cell arteritis is treated with a long course of corticosteroid; however, higher initial dosing is required. Corticosteroid therapy often needs to be continued for 2 years or more, and it would be uncommon to stop therapy before 18 months. Because long-term corticosteroid therapy can cause significant adverse effects, the lowest dose and shortest duration of therapy necessary to control disease and prevent relapse should be used. See Principles of immunomodulatory drug use for rheumatological diseases in adults for information on adverse effects associated with long-term corticosteroid use (such as bone density loss) and advice on how to minimise and monitor for such complications.

If the diagnosis of giant cell arteritis is strongly suspected, pre-emptive treatment should be started immediately, without waiting for histological confirmation. The same is true for any patient with, or with a history of, polymyalgia rheumatica who develops classic symptoms of giant cell arteritis.

Immediately start treatment, without waiting for histological confirmation, if there is a strong clinical suspicion of giant cell arteritis.

Patients **with** evolving visual loss or a recent history of transient visual loss require initial treatment with intravenous methylprednisolone; the usual dosage is:

methylprednisolone sodium succinate 0.5 to 1 g intravenously, over 1 hour, daily for 3 days, then switch to oral prednis(ol)one as below. *giant cell arteritis*

For patients **without** evolving visual loss or a recent history of transient visual loss, treatment is with oral prednis(ol)one; the usual dosage is:

prednis(ol)one 40 to 60 mg orally, daily (in two divided doses if necessary for symptom control) for a minimum of 4 weeks, continue until symptoms and abnormalities in inflammatory markers resolve; then reduce daily dose by 10 mg every 2 weeks to 20 mg daily; then reduce daily dose by 2.5 mg every 2 to 4

weeks to 10 mg daily; then reduce daily dose by 1 mg every 4 to 8 weeks, provided there is no relapse, to stop. *giant cell arteritis*

Dose adjustments should be advised by the specialist. Relapse is common during corticosteroid tapering and dose reductions should not be undertaken if the patient has signs of active disease (such as recurrence of symptoms or persistently elevated inflammatory markers that cannot be explained by another pathology). ESR and CRP are usually checked monthly for the first 3 months of therapy, then every 2 to 3 months thereafter or as clinically indicated.

To prevent ischaemic events, including ophthalmic vascular thrombosis, use aspirin **concurrently** with corticosteroid therapy. Use:

aspirin 100 mg orally, daily. *giant cell arteritis*

Methotrexate may be used in combination with corticosteroid therapy initially, or as a corticosteroid-sparing drug in patients who need prolonged high-dose corticosteroid therapy or who develop early or severe corticosteroid adverse effects. The methotrexate dose is adjusted on the basis of clinical response and adverse effects. For considerations in the management of methotrexate therapy (including monitoring, screening for infection, and vaccination), see Principles of immunomodulatory drug use for rheumatological diseases in adults.

The usual dosage of methotrexate is:

methotrexate 10 mg orally, **on one specified day once weekly**, increasing up to 25 mg orally or subcutaneously, **on one specified day once weekly** *giant cell arteritis*

PLUS

folic acid 5 to 10 mg orally, per week (preferably not on the day methotrexate is taken). *giant cell arteritis*

There is evidence for the efficacy of tocilizumab, in combination with prednis(ol)one, in the treatment of giant cell arteritis. While its exact place in therapy is not yet clear, tocilizumab is likely to represent a treatment option for patients with giant cell arteritis refractory to the combination of prednis(ol)one and methotrexate, or who have intolerable corticosteroid adverse effects [Note 1].

Note 1: At the time of writing, tocilizumab is not approved by the Australian Therapeutic Goods Administration (TGA) for treatment of giant cell arteritis. See the TGA website for current information [URL].

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Key references: Polymyalgia rheumatica

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Key references: Giant cell arteritis

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Introduction to rheumatoid arthritis

Introduction to rheumatoid arthritis

Rheumatoid arthritis is a chronic autoimmune disease characterised by persistent synovitis, systemic inflammation and the presence of autoantibodies. Persistent joint inflammation can lead to the development of bony erosions, cartilage and tendon degradation, and joint deformity. In about 40% of patients, inflammation also occurs at other sites (eg skin, eyes, lungs, heart, kidneys, blood vessels, salivary glands, central and peripheral nervous systems, and bone marrow). The pathophysiology of rheumatoid arthritis involves various cytokines, effector cells and signalling pathways; tumour necrosis factor, interleukin-6 and interleukin-1 appear to be the key cytokine mediators of the disease process.

The prevalence of rheumatoid arthritis is about 1%, with women more commonly affected than men. The risk of developing rheumatoid arthritis may be increased by genetic factors; the most established genetic link is the human leucocyte antigen DR4 (HLA-DR4). A healthy lifestyle (eg avoiding smoking, maintaining ideal body weight, eating a healthy diet) decreases the likelihood of developing rheumatoid arthritis.

Rheumatoid arthritis has the potential to cause disability and death; however, the prognosis has substantially improved in the last 20 years due to early use of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and the availability of biological disease-modifying antirheumatic drugs (bDMARDs).

Diagnosis of rheumatoid arthritis

Diagnosis of rheumatoid arthritis

It can be difficult to definitively diagnose rheumatoid arthritis in the early phase of an inflammatory arthritis (see Undifferentiated polyarthritis in adults); however, prompt diagnosis is crucial because of the need for early treatment with disease-modifying therapy to prevent irreversible joint damage. Urgently refer any patient with suspected rheumatoid arthritis to a specialist. Rheumatologists often have fast-track triage systems for these patients and general practitioners are strongly encouraged to make direct contact to expedite referral or to obtain advice on treatment. The appropriate time frame for referral is further influenced by the results of investigations (see below).

Urgently refer any patient with suspected rheumatoid arthritis to a specialist.

The diagnosis of rheumatoid arthritis is made on the basis of clinical presentation, in association with autoantibodies and evidence of systemic inflammation (eg elevated erythrocyte sedimentation rate and C-reactive protein concentration). Other features suggestive of rheumatoid arthritis are given in Figure 12.10. The most commonly affected joints include the wrists, metacarpophalangeal joints, proximal interphalangeal joints and metatarsophalangeal joints. The carpometacarpal and distal interphalangeal joints are not typically affected. Other large joints may also be affected by rheumatoid arthritis.

Detection of rheumatoid factor (RF) and antibodies to cyclic citrullinated peptides (CCP) can help resolve diagnostic uncertainty in patients with suspected rheumatoid arthritis. While RF is present in about 70% of patients with established rheumatoid arthritis, it is detected less frequently in early disease. Antibodies to CCP are usually present before the development of symptoms and have a 96% specificity for rheumatoid arthritis. However, up to 30% of patients with rheumatoid arthritis never develop RF or antibodies to CCP and are said to have seronegative disease.

For symptomatic patients who have RF or antibodies to CCP, immediate referral to a specialist is required because early joint damage is likely. For patients who do not have RF or antibodies to CCP but have

persistently swollen joints, referral should be made within 6 weeks of symptom onset.
Figure 12.10 Features suggesting rheumatoid arthritis

- family history of inflammatory arthritis
- early morning stiffness lasting longer than 1 hour
- swelling in five or more joints
- symmetry of the areas affected
- bilateral compression tenderness of the metatarsophalangeal joints
- RF positivity
- anti-CCP antibody test positivity
- symptoms present for longer than 6 weeks
- bony erosions evident on X-rays of the wrists, hands or feet (uncommon in early disease)
- raised inflammatory markers, such as CRP or ESR, in the absence of infection
- presence of rheumatoid nodules

CCP = cyclic citrullinated peptide; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; RF = rheumatoid factor

Prognosis of patients with rheumatoid arthritis

Prognosis of patients with rheumatoid arthritis

Key indicators of poor prognosis in patients with rheumatoid arthritis are listed in Figure 12.11. No single feature is entirely reliable in determining prognosis. Patients with poor prognosis should be intensively managed, and treatment should be started as early as possible, as it should for all patients with rheumatoid arthritis.

Figure 12.11 Key indicators of poor prognosis in patients with rheumatoid arthritis

- a high RF titre and/or a positive anti-CCP antibody test
- sustained raised inflammatory markers (CRP or ESR)
- swelling in more than 20 joints
- impaired function early in disease
- bony erosions evident on X-rays early in disease
- smoking

CCP = cyclic citrullinated peptide; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; RF = rheumatoid factor

General management approach for rheumatoid arthritis

General management approach for rheumatoid arthritis

Patients with rheumatoid arthritis require integrated, multidisciplinary care that is designed to manage the broad spectrum of patient needs in a timely manner. All patients should have an individualised management plan that is negotiated between the patient, their specialist and general practitioner, and other health professionals involved in their care (eg physiotherapist, occupational therapist, podiatrist, psychologist). The management plan should include support for self-management, including advice on managing symptom exacerbations until specialist review.

The goal of rheumatoid arthritis management is to maximise long-term health-related quality of life by:

- controlling symptoms
- normalising physical function
- enabling participation in social and work-related activities
- preventing joint damage
- minimising cardiovascular complications.

Management of rheumatoid arthritis involves:

- inducing clinical remission as early as possible (see Inducing and maintaining clinical remission in patients with rheumatoid arthritis)
- maintaining clinical remission (see Inducing and maintaining clinical remission in patients with rheumatoid arthritis)
- developing an individualised self-management plan for early management of an exacerbation of inflammatory joint pain while awaiting specialist review
- proactively inquiring about and managing pain, fatigue and mood disturbances (see Managing symptoms in patients with rheumatoid arthritis)
- optimising the patient's immune status, including ensuring that recommended vaccinations are up to date, because both rheumatoid arthritis and its treatment can increase the risk of infection (see Screening for infection and vaccinations in adults with rheumatological diseases)
- monitoring for drug adverse effects, including appropriate blood tests (see Principles of immunomodulatory drug use for rheumatological diseases in adults)
- monitoring for and managing potential complications of rheumatoid arthritis, including atherosclerosis, osteoporosis, depression, vasculitis, peptic ulcer disease, lung disease, neuropathy and atlanto-axial involvement (see Neck pain and rheumatoid arthritis). Systemic inflammation is the main contributor to the increased risk of developing atherosclerosis in patients with rheumatoid arthritis, but other risk factors for cardiovascular disease should be closely monitored and actively managed (see Cardiovascular disease risk stratification)
- educating the patient about their disease and its management, the need for long-term treatment, and appropriate lifestyle management. Printed or online information is useful to reinforce education provided by the clinician. Patient support organisations such as Arthritis Australia provide educational materials, and participation in their activities may be valuable for social support [URL]. The 'painHEALTH' website also provides useful tips for self-management [URL] [Note 1]
- evaluating the impact of rheumatoid arthritis treatment on the patient's reproductive health. For general advice on the use of immunomodulatory drugs in patients of childbearing potential, see Immunomodulatory drug use and reproductive health in adults with rheumatological diseases. For advice on nonsteroidal anti-inflammatory drugs (NSAIDs) and reproductive health, see NSAIDs and reproductive health in women.

For specific advice on the management of patients treated with immunomodulatory drugs, see Principles of immunomodulatory drug use for rheumatological diseases in adults.

Note 1: This website provides patient information; any management advice given on this website should be considered in the context of the recommendations in these guidelines.]

Inducing and maintaining clinical remission in patients with rheumatoid arthritis

Inducing and maintaining clinical remission in patients with rheumatoid arthritis

General considerations

General considerations

Induction and maintenance of clinical remission of rheumatoid arthritis requires specialist management. Disease activity is monitored and used to adjust therapy to attain clinical remission; this approach is known as 'treat to target'. Clinical remission is defined as all of the following:

- symptom relief
- normalisation of inflammatory markers
- the absence of joint swelling.

Disease-modifying antirheumatic drugs (DMARDs) reduce or eradicate synovitis and thus prevent joint damage. To induce clinical remission of rheumatoid arthritis and prevent joint damage, therapy with

conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) should be started as soon as possible; treatment choice can be complex and combination therapy may be required. Corticosteroids are often combined with csDMARDs during the induction stage of treatment to provide rapid symptom relief. Patients with an inadequate response to csDMARDs may require treatment with a biological disease-modifying antirheumatic drug (bDMARD) or a targeted synthetic disease-modifying antirheumatic drug (tsDMARD) (see Biological and targeted synthetic disease-modifying antirheumatic drugs).

While the aim of management is for the patient to have normal inflammatory markers and no swollen joints, decisions to escalate DMARD therapy should also be informed by comorbidities, patient preference and drug toxicity. Clinical remission (as defined above) can be achieved in up to 40% of patients. Most patients need to be maintained on treatment indefinitely because rheumatoid arthritis rarely goes into drug-free remission and may be more difficult to control if it recurs after stopping treatment. Even patients with well-controlled disease may have persisting symptoms (see Managing symptoms in patients with rheumatoid arthritis for advice on the management of pain and fatigue).

Disease activity is routinely monitored at a frequency tailored to the patient's disease severity and stage of treatment. Measures of inflammation and patient-reported outcomes should be considered in the assessment of disease activity and together should inform decisions about adjusting DMARD therapy. Inflammation is most reliably assessed by the number of swollen or tender joints as well as the inflammatory markers C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR); neither measure should be used alone. Patient-reported outcomes include pain, physical function, psychological health, sleep patterns, relationships, and participation in social and work-related activities. These outcomes can be measured formally or informally. Examples of formal assessment tools are the Stanford health assessment questionnaire (HAQ) and the routine assessment of patient index data-3 (RAPID3) questionnaire. Patient-reported pain without evidence of inflammation suggests that the pain may be caused by joint damage, central sensitisation or other painful processes (see Residual joint pain in patients in clinical remission). Joint damage is usually assessed throughout the disease course by plain X-rays and ultrasound. Magnetic resonance imaging (MRI) may occasionally be used by specialists.

Rheumatoid factor (RF) and antibodies to cyclic citrullinated peptides (CCP) are not used to monitor disease activity.

Conventional synthetic disease-modifying antirheumatic drugs

Conventional synthetic disease-modifying antirheumatic drugs

Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) are used by specialists to induce and then maintain clinical remission of rheumatoid arthritis.

The initial induction strategy is determined by disease severity, prognosis and patient factors, such as age, childbearing status, and comorbidities. Therapy may be with either a single csDMARD or a combination of csDMARDs, with or without a corticosteroid. Methotrexate is the drug of choice for most patients, and should form the backbone of the regimen when combination therapy is required. It may be used in combination with other csDMARDs (leflunomide, sulfasalazine, hydroxychloroquine) for patients with active disease and significantly impaired function, or if there are indicators of poor prognosis (see Figure 12.11). If methotrexate is contraindicated or not tolerated, leflunomide is often substituted. Monotherapy with hydroxychloroquine or sulfasalazine may be used if the patient has low-grade inflammation, few affected joints and no indicators of poor prognosis.

Methotrexate is the drug of choice for most patients.

When csDMARD therapy is started, disease activity is regularly monitored and therapy adjusted to achieve clinical remission. A response to csDMARDs should be apparent within 12 weeks. If remission is not achieved despite an adequate dose of csDMARD, adjustment of the csDMARD regimen is considered (eg switching to a different combination regimen, addition of a second or third csDMARD to an existing regimen).

For considerations in the management of csDMARD therapy (including monitoring, screening for infection, and vaccination), see Principles of immunomodulatory drug use for rheumatological diseases in adults.

The usual dosage of methotrexate is:

methotrexate 10 mg orally, **on one specified day once weekly**, increasing up to 25 mg orally or subcutaneously, **on one specified day once weekly** *arthritis, rheumatoid*

PLUS

folic acid 5 to 10 mg orally, per week (preferably not on the day methotrexate is taken). *arthritis, rheumatoid*

The usual dosage of leflunomide is:

leflunomide 10 to 20 mg orally, daily. *arthritis, rheumatoid*

The usual dosage of sulfasalazine is:

sulfasalazine (enteric-coated) 500 mg orally, twice daily, increasing gradually up to 1.5 g twice daily. *arthritis, rheumatoid*

The usual dosage of hydroxychloroquine is:

hydroxychloroquine 200 to 400 mg orally, daily. *arthritis, rheumatoid*

When disease control has been achieved and maintained with csDMARD therapy, the csDMARD dose may be reduced to the lowest dose that maintains disease control. Dose reductions should only occur in consultation with the treating specialist, and usually take place after corticosteroid therapy has been completely tapered.

If remission is not achieved or significant disease activity persists after trialling csDMARD combination therapy, specialist review is required for consideration of treatment with a biological disease-modifying antirheumatic drug (bDMARD) or a targeted synthetic disease-modifying antirheumatic drug (tsDMARD).

Corticosteroids

Corticosteroids

Corticosteroids have anti-inflammatory and disease-modifying effects in rheumatoid arthritis. Because of their rapid onset of action, corticosteroids are often used by specialists to achieve rapid symptom control at presentation, or during an exacerbation of disease, while awaiting a response to conventional synthetic disease-modifying antirheumatic drug (csDMARD) therapy (which can often take between 6 and 12 weeks).

Parenteral administration of corticosteroids is sometimes used, based on a theoretical reduction in overall corticosteroid exposure compared to oral therapy. A single dose of intramuscular corticosteroid has a prolonged effect (up to 8 weeks) and repeat doses are often unnecessary.

If intramuscular therapy is indicated, the usual dosage is:

methylprednisolone acetate 120 mg intramuscularly, as a single dose. *arthritis, rheumatoid*

Intravenous therapy is sometimes used by specialists for severe flares.

If oral therapy is indicated, the usual initial dosage is:

prednis(ol)one 5 to 15 mg orally, daily. *arthritis, rheumatoid*

Although corticosteroids are effective, significant adverse effects limit their use. When disease remission is achieved, the dose of corticosteroid should be slowly tapered until the corticosteroid can be stopped.

Unfortunately, this is not possible in all patients.

See Principles of immunomodulatory drug use for rheumatological diseases in adults for information on adverse effects associated with long-term corticosteroid therapy (such as bone density loss) and advice on how to minimise and monitor for such complications.

Intra-articular corticosteroid injections are effective if a small number of accessible joints are involved, and can minimise the use of systemic corticosteroids. For principles of use and example doses of local corticosteroid injections, see Principles of using local corticosteroid injections for musculoskeletal conditions in adults.

Biological and targeted synthetic disease-modifying antirheumatic drugs

Biological and targeted synthetic disease-modifying antirheumatic drugs

Biological disease-modifying antirheumatic drugs (bDMARDs) and targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs) are used by specialists for the treatment of rheumatoid arthritis if remission is not achieved, or significant disease activity persists, after trialling conventional synthetic disease-modifying antirheumatic drugs (csDMARDs). They are usually used in combination with csDMARD therapy. Several bDMARDs, with different mechanisms of action, are available. At the time of writing, tofacitinib is the only tsDMARD indicated for rheumatoid arthritis.

Patients taking bDMARDs or tofacitinib are at increased risk of infections. Clinicians must always be alert to the possibility of infection (including opportunistic infection), particularly because the usual symptoms and signs (eg fever) are often absent. For other considerations in the management of bDMARD or tofacitinib therapy (including monitoring, screening for infection, and vaccination), see Principles of immunomodulatory drug use for rheumatological diseases in adults.

The first-line bDMARDs are generally considered to be equally efficacious and drug choice is influenced by patient preference regarding route of administration and dosing frequency. The usual dosages for first-line bDMARDs (listed in alphabetical order) are:

abatacept 500 to 1000 mg intravenously, as a single dose at 0, 2 and 4 weeks, and thereafter every 4 weeks *arthritis, rheumatoid*

OR

abatacept 125 mg subcutaneously, once weekly

OR

adalimumab 40 mg subcutaneously, every 2 weeks *arthritis, rheumatoid*

OR

certolizumab pegol 400 mg subcutaneously, as a single dose at 0, 2 and 4 weeks, and thereafter 200 mg every 2 weeks *arthritis, rheumatoid*

OR

certolizumab pegol 400 mg subcutaneously, as a single dose at 0, 2 and 4 weeks, and thereafter every 4 weeks

OR

etanercept 50 mg subcutaneously, once weekly [Note 2] *arthritis, rheumatoid*

OR

golimumab 50 mg subcutaneously, every 4 weeks *arthritis, rheumatoid*

OR

infliximab 3 mg/kg intravenously, as a single dose at 0, 2 and 6 weeks, and thereafter every 8 weeks *arthritis, rheumatoid*

OR

tocilizumab 8 mg/kg intravenously, every 4 weeks *arthritis, rheumatoid*

OR

tocilizumab 162 mg subcutaneously, once weekly [Note 3] .

If response to initial drug choice is inadequate, an alternative first-line bDMARD may be used.

Rituximab is reserved for use by specialists when first-line bDMARD, specifically tumour necrosis factor inhibitor, therapy has failed. The two doses (1 g by intravenous infusion) are given 2 weeks apart. For patients who respond to the initial rituximab course, treatment may be repeated (usually after 6 to 12 months) depending on disease activity.

The tsDMARD tofacitinib is an alternative to first-line bDMARD therapy. The usual dosage is:

tofacitinib 5 mg orally, twice daily. *arthritis, rheumatoid*

Note 2: An alternative regimen is: etanercept 25 mg subcutaneously, twice weekly.

Note 3: At the time of writing, tocilizumab is not available on the Pharmaceutical Benefits Scheme (PBS) for subcutaneous use for treatment of rheumatoid arthritis. See the PBS website for current information [URL].

Managing symptoms in patients with rheumatoid arthritis

Managing symptoms in patients with rheumatoid arthritis

Pain

Pain
General considerations

Pain is common in patients with rheumatoid arthritis, even when disease-modifying antirheumatic drugs (DMARDs) are used. It may result in substantial disability in some patients. Pain may be due to joint inflammation or noninflammatory causes, such as peripheral sensitisation from joint damage or central sensitisation.

Exclude serious conditions, such as avascular necrosis, fracture, infection, malignancy or vasculitis, if pain is associated with an alerting feature. Alerting features include fever, weight loss, malaise, acute severe pain (different to usual rheumatoid arthritis pain), focal or diffuse muscle weakness, history of significant trauma, night pain, neurogenic pain or claudication, a single hot and swollen joint, and rash.

Assessment of pain severity (using a visual analogue scale or numerical rating scale), and its impact, and the cause of pain is important to guide management (see also Assessing a patient with pain).

Consider referring patients with persisting inflammatory joint pain to their specialist for adjustment of the DMARD regimen. Acute inflammatory joint pain suggestive of an exacerbation of disease activity should be managed according to the patient's individualised self-management plan until they can be reviewed by their specialist.

Residual joint pain in patients in clinical remission

If a patient with well-controlled disease (ie in clinical remission) experiences ongoing pain, it is likely to be noninflammatory in nature.

If osteoarthritis is thought to be responsible for the patient's residual symptoms, see Pharmacological management of osteoarthritis for management advice.

Management of noninflammatory residual joint pain associated with rheumatoid arthritis should follow the same principles as for other types of noninflammatory chronic pain (see General principles of chronic pain management). Combine nonpharmacological and pharmacological strategies, tailored to the individual patient. Factors that influence treatment choice include patient comorbidities, adverse effects, the potential for dependence, patient preference, likelihood of adherence to treatment, and cost.

Nonpharmacological strategies for residual noninflammatory joint pain include: rest and pacing activities, thermotherapy, splints/orthoses, exercise therapy, cognitive behavioural therapy (CBT), transcutaneous electrical nerve stimulation (TENS), psychotherapy, and relaxation, mindfulness and meditation. Although these strategies may provide pain relief, there is limited evidence to support their use. For more information on these strategies, see Chronic pain management strategies.

When analgesia is indicated, the primary goals of management are to improve function and reduce disability, not just reduce the intensity of pain. Before escalating analgesia, consider and address biopsychosocial and environmental factors that may be contributing to the patient's experience of pain. Continuing to increase the dose of analgesia or introducing multiple drugs may increase the risk of harms without additional benefit.

If a nonsteroidal anti-inflammatory drug (NSAID) is indicated, use:

an NSAID orally (see Table 12.7 for dosing). *arthritis, rheumatoid*

The potential benefits of an NSAID should be weighed against its potential harms, particularly in patients at high risk of harms (see Principles of NSAID use for musculoskeletal conditions in adults for more information).

Evidence suggests fish oil has a mild anti-inflammatory effect in rheumatoid arthritis. For patients with mild residual joint pain, it is a reasonable treatment option because of its low risk of harms. Use:

fish oil at least 2.7 g (omega-3) orally, daily (see Table 12.8 for preparations). *arthritis, rheumatoid*

Fish oil may take up to 3 months for maximal effectiveness, so it may be necessary to co-prescribe fish oil with an NSAID initially. See Principles of fish oil use for musculoskeletal conditions in adults for more information.

If neuropathic pain or fibromyalgia are contributing significantly to the patient's pain, consider adding a drug effective for these conditions to the analgesic regimen; see Commonly used adjuvants or Pharmacological management of fibromyalgia.

For patients with severe pain, consider referral to a rheumatologist or pain management specialist. Structural joint damage or coexistent osteoarthritis may require joint replacement surgery.

Opioids have a very limited role in the management of pain associated with rheumatoid arthritis because of modest, if any, benefits and a significant risk of harms. Opioids may be considered for patients with severe pain that is not adequately relieved by other analgesics (eg paracetamol plus an NSAID) and is interfering with their ability to function. If opioids are used, they should be prescribed on a short-term trial basis, as part of an overall pain management strategy, with clear goals and regular review of treatment response and adverse effects. Before starting an opioid, a plan for ceasing ineffective therapy should be in place and discussed with the patient. If treatment response is inadequate, caution should be exercised when increasing the dose of opioids. Prolonged use of opioids indicates the need for specialist assessment. See Opioids for more information.

If opioids are used, they should be prescribed on a short-term trial basis with regular review of treatment response and adverse effects.

Systemic corticosteroids are not recommended for the routine management of chronic pain in patients with rheumatoid arthritis in the absence of signs or symptoms of inflammation.

Fatigue

Fatigue

Fatigue is a common complaint in patients with rheumatoid arthritis. Consider and manage potential contributors to fatigue, such as anaemia, hypothyroidism, drug adverse effects, depression, insomnia due to underlying pain, or loss of muscle mass. See Conditions commonly associated with fatigue for more information on the assessment of patients with fatigue.

There are no pharmacological treatments for fatigue in rheumatoid arthritis. There is some evidence that physical activity (eg pool-based therapy, yoga, dynamic strength training, stationary cycling, low-impact aerobics, Tai Chi) and psychosocial interventions (eg cognitive behavioural therapy, mindfulness) have a small benefit, but the optimal treatment strategy is not yet established.

Lifestyle management of rheumatoid arthritis

Lifestyle management of rheumatoid arthritis

Exercise

Exercise

Land- and water-based aerobic exercises are beneficial for patients with rheumatoid arthritis at all stages of disease. Regular aerobic exercise improves physical function, helps maintain ideal body weight and also benefits psychological and cardiovascular health. Low-impact land exercise (eg stationary cycling, walking) or low- to moderate-intensity water-based exercise is preferred for patients with painful joints or high disease activity. Strengthening (anaerobic) exercise is also recommended to prevent muscle wasting. Weightbearing exercise improves bone health.

Patients may worry that rheumatoid arthritis disease activity is increased by exercise. Although some pain with exercise can be expected, patients should be reassured that the benefits of exercise significantly outweigh the risks.

Diet

Diet

The role of diet in rheumatoid arthritis remains controversial. Several studies have shown that dietary modifications including strict vegan diets, gluten-free diets and the Mediterranean-style diet produce small reductions in rheumatoid arthritis symptoms. However, no single diet results in consistent improvement for all patients with rheumatoid arthritis. The Mediterranean-style diet, characterised by a high consumption of fruit, vegetables, cereals and legumes, a little red meat but more fish, olive oil as the main source of fat, and a moderate intake of wine, appears to be the most universally accepted dietary intervention; it has the added benefit of weight control and reducing cardiovascular risk.

Smoking cessation

Smoking cessation

All patients with rheumatoid arthritis should be strongly advised to stop smoking. Not only is smoking linked to the development of rheumatoid arthritis, it is also linked to poor prognosis and is a predictor of poor

response to therapy. Smoking also increases the risk of developing cardiovascular disease in a patient group already at increased risk. Patient resources and help for smoking cessation are available from the Quitnow website [URL]. See Smoking cessation for more information on assessment of patients' smoking and advice on smoking cessation.

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Introduction to inflammatory connective tissue diseases

Introduction to inflammatory connective tissue diseases

The connective tissue diseases are a group of chronic diseases characterised by systemic inflammation (probably of autoimmune pathogenesis) and perpetuated by unknown factors (probably both genetic and environmental). The connective tissue diseases include:

- systemic lupus erythematosus (SLE)
- Sjögren syndrome
- systemic sclerosis
- mixed connective tissue disease
- immune-mediated myopathies, including juvenile dermatomyositis and dermatomyositis in adults.

The diagnosis of a connective tissue disease is predominantly based on clinical assessment. The connective tissue diseases share many clinical features, in particular arthralgia, myalgia, fatigue, Raynaud phenomenon and sicca symptoms. This makes the diagnosis of a specific connective tissue disease difficult, particularly early in the course of the disease before specific clinical features develop. Some patients have an illness that remains mild and poorly defined for many years, or never progresses to a specific connective tissue disease (see Management of the patient with a positive ANA and mild, nonspecific symptoms for more information).

While identifying the presence of antinuclear antibodies (ANA) is useful to support a diagnosis of a connective tissue disease in patients with a suggestive clinical presentation, interpretation of the ANA result is complex (see Antinuclear antibody testing for inflammatory connective tissue diseases for more information).

Antinuclear antibody testing for inflammatory connective tissue diseases

Antinuclear antibody testing for inflammatory connective tissue diseases

General information

General information

Antinuclear antibodies (ANA) is a generic term for autoantibodies to nuclear and other cellular elements (known as autoantigens). Little is known about how autoantigens, or their interaction with ANA, are linked to human disease; however, the presence of ANA is an important feature of connective tissue diseases.

When to test for antinuclear antibodies

When to test for antinuclear antibodies

ANA testing should only be undertaken in patients with signs or symptoms suggestive of a connective tissue disease. While identifying the presence of ANA is useful to support a diagnosis of a connective tissue disease in patients with a suggestive clinical presentation, ANA may also be present in patients with other autoimmune diseases (eg thyroid disease) and in healthy individuals—ie ANA testing has a high sensitivity, but a low specificity, for connective tissue diseases. Therefore, the diagnostic value of a positive ANA result depends on the pretest probability of a connective tissue disease.

Do not undertake ANA testing in patients without signs or symptoms suggestive of a connective tissue disease.

The presenting symptoms of a connective tissue disease may be commonplace and nonspecific (eg fatigue, pain, paraesthesia, dry eyes). A thorough patient history is essential to distinguish between symptoms likely due to a connective tissue disease and those likely due to a busy lifestyle, somatisation or other causes (see also The achey, tired patient). However, it may still be difficult to determine the need for ANA testing.

Patients whose only symptom is fatigue do not need ANA testing.

The following scenarios are examples of the diagnostic utility of ANA testing based on patient history:

- **ANA testing is often useful** in a young woman who presents with intermittent small joint arthralgia, definite alopecia, Raynaud phenomenon or serositis (eg pleurisy), or a combination of these features. In this instance, a positive ANA result is likely to be clinically significant (ie unlikely to be a false positive result) and a negative ANA result is likely to rule out the diagnosis of a connective tissue disease.
- **ANA testing is *not* useful** in a patient with a long history of fatigue, generalised constant pain, and nonspecific abdominal or neurological symptoms (eg tension headaches, dizziness, paraesthesia). In this instance, neither a positive nor a negative ANA result changes the likelihood that the patient has a connective tissue disease sufficiently for ANA testing to be helpful.

The ANA result is unlikely to change over time, so there is no benefit in repeating the test if the patient's clinical presentation has not changed.

The need for further testing for specific autoantibodies should be guided by the result of the ANA test (ie testing should occur in a two-step process). See Significance of antinuclear antibody tests for further discussion.

Significance of antinuclear antibody tests

Significance of antinuclear antibody tests

The screening immunoassay for ANA involves the microscopic demonstration of antibody binding to cellular elements in laboratory cell lines. Results are reported in two components: the quantity of ANA in the serum (expressed as a titre) and the pattern of antibody binding (staining pattern).

The higher the ANA titre, the higher the likelihood of a connective tissue or other autoimmune disease (eg thyroid disease). Low ANA titres (up to 1:160) are common in healthy individuals and the frequency increases with age. In the absence of definite clinical features of a connective tissue disease, a low ANA titre is unlikely to be clinically significant. The significance of intermediate ANA titres depends on the clinical context, and an intermediate titre does not necessarily indicate the presence of disease. While the presence of ANA is expressed as a positive result, low ANA titres may be expressed as a negative result. The cut-off value for a negative result depends on the laboratory.

Most ANA staining patterns (eg homogeneous or speckled) are subjective and nonspecific for a connective tissue disease; however, the centromere and nucleolar patterns are linked to systemic sclerosis. The recently described anti-DFS70 antibodies have a dense fine speckled (DFS) ANA staining pattern and are significantly more common in healthy individuals than in people with a connective tissue disease. Even when anti-DFS70 antibodies are present in high titre, provided it is the only antibody, the likelihood of a connective tissue disease is very low in patients with mild, nonspecific symptoms and long-term follow-up is not required in these individuals. The DFS pattern can be mistaken for a homogeneous pattern, so it should be specifically looked for if suspected (eg in a patient with a positive ANA, but mild, nonspecific symptoms).

If there is a high clinical suspicion of a connective tissue disease and the patient has a positive ANA, it is appropriate to test for specific autoantibodies to aid the diagnosis of a particular connective tissue disease. Table 12.14 lists common tests and the prevalence of specific autoantibodies in connective tissue diseases. Most specific autoantibody tests have intermediate sensitivity and specificity, and are of limited diagnostic

utility if considered in isolation. Therefore, the tests undertaken should be guided by the patient's clinical presentation. Also consider assessment for organ involvement and specialist referral in these patients.

For management of patients with a positive ANA and mild, nonspecific symptoms, see Management of the patient with a positive ANA and mild, nonspecific symptoms.

In patients with a negative ANA or low ANA titre, do not undertake further investigation for connective tissue diseases (eg testing for antibodies to double-stranded DNA [dsDNA] or extractable nuclear antigens [ENAs]) unless clinical suspicion of systemic lupus erythematosus (SLE) or other connective tissue disease remains high. The coincidental association of fatigue and lethargy with a low ANA titre is probably the commonest reason for the misdiagnosis of SLE.
Do not test for antibodies to dsDNA or ENA in patients with a negative ANA or low ANA titre unless clinical suspicion of SLE or other connective tissue disease remains high.Table 12.14 Common tests and prevalence of specific autoantibodies in connective tissue diseases

[NB1] [NB2]

- dsDNA
- phospholipid
- ENAs:
    - Ro (SS-A)
    - La (SS-B)
    - Smith (Sm)
    - U_1RNP
    - Scl-70 (topoisomerase I)
    - RNA polymerase III
    - Jo1
    - centromere

dsDNA	
Prevalence in normal population	2 to 5%
Prevalence in patients with SLE	60%
Prevalence in patients with other connective tissue diseases	rare
phospholipid [NB3]	
Prevalence in normal population	5%
Prevalence in patients with SLE	5 to 10%
Prevalence in patients with other connective tissue diseases	common in antiphospholipid syndrome [NB4]
ENA: Ro (SS-A)	
Prevalence in normal population	1 to 2%
Prevalence in patients with SLE	40%
Prevalence in patients with other connective tissue diseases	common in Sjögren syndrome
ENA: La (SS-B)	
Prevalence in normal population	less than 1%
Prevalence in patients with SLE	15%
Prevalence in patients with other connective tissue diseases	common in Sjögren syndrome
ENA: Smith (Sm)	
Prevalence in normal population	less than 1%
Prevalence in patients with SLE	10 to 50%

Prevalence in patients with other connective tissue diseases	rare
ENA: U_1RNP	
Prevalence in normal population	less than 1%
Prevalence in patients with SLE	uncommon
Prevalence in patients with other connective tissue diseases	common in mixed connective tissue disease
ENA: Scl-70 (topoisomerase I)	
Prevalence in normal population	less than 1%
Prevalence in patients with SLE	rare
Prevalence in patients with other connective tissue diseases	common in diffuse systemic sclerosis
ENA: RNA polymerase III	
Prevalence in normal population	less than 1%
Prevalence in patients with SLE	rare
Prevalence in patients with other connective tissue diseases	25% in diffuse systemic sclerosis (particularly in scleroderma renal crisis)
ENA: Jo1	
Prevalence in normal population	less than 1%
Prevalence in patients with SLE	rare
Prevalence in patients with other connective tissue diseases	common in antisynthetase syndrome [NB5]
ENA: centromere	
Prevalence in normal population	less than 1%
Prevalence in patients with SLE	rare
Prevalence in patients with other connective tissue diseases	common in limited systemic sclerosis

ANA = antinuclear antibodies; dsDNA = double-stranded DNA; ENAs = extractable nuclear antigens; SLE = systemic lupus erythematosus

NB1: Do not test for antibodies to dsDNA or ENA in patients with a negative ANA or low ANA titre unless clinical suspicion of SLE or other connective tissue disease remains high.

NB2: The tests undertaken should be determined by the patient's clinical presentation.

NB3: Antiphospholipid antibodies include lupus anticoagulant, anticardiolipin, and anti-beta-2-glycoprotein 1.

NB4: Antiphospholipid syndrome can occur secondary to connective tissue diseases, or as a primary syndrome.

NB5: Antisynthetase syndrome is an inflammatory myopathy associated with fever, interstitial lung disease, polyarthritis, ‘mechanic's hands’ and Raynaud phenomenon.

Management of the patient with a positive ANA and mild, nonspecific symptoms

Management of the patient with a positive ANA and mild, nonspecific symptoms

Some patients have a positive antinuclear antibody (ANA) in intermediate or higher titre (eg titre of 1:640 or more), but present with mild, nonspecific symptoms (eg arthralgia). Only 10% of these patients will go on to develop a definable connective tissue disease and this will usually occur within 24 months. The remaining

90% of patients will continue to have mild, nonspecific symptoms that do not fit a particular diagnosis. In all patients, avoid inappropriate use of diagnostic labels to limit patient anxiety and inaccurate prognosis.

For patients with mild, nonspecific symptoms, treatment is directed at clinical features (see Management of common clinical features of inflammatory connective tissue diseases).

Clinically reassess all patients after 12 months. Only repeat ANA testing and specific autoantibody tests (see Table 12.14) if the patient develops new symptoms or signs that are more suggestive of a connective tissue disease. Refer patients with a suspected connective tissue disease to a specialist. If there has been no change in the patient's clinical presentation after 12 months, determine the need for ongoing monitoring based on individual patient factors.

Management of common clinical features of inflammatory connective tissue diseases

Management of common clinical features of inflammatory connective tissue diseases

Arthralgia, myalgia and arthritis

Arthralgia, myalgia and arthritis

Arthralgia and myalgia are more common than arthritis in connective tissue diseases, and erosive joint damage is rare.

For arthralgia and myalgia, use:

1 paracetamol 1 g orally, 4- to 6-hourly, up to a maximum of 4 g daily *connective tissue disease*

OR

1 paracetamol modified-release 1.33 g orally, 8-hourly.

If response to paracetamol is inadequate or for arthritis symptoms, a nonsteroidal anti-inflammatory drug (NSAID) may be used **instead of, or in combination with,** paracetamol. Use:

an NSAID orally (see Table 12.7 for dosing). *connective tissue disease*

The potential benefits of an NSAID should be weighed against its potential harms, particularly in patients at high risk of harms (see Principles of NSAID use for musculoskeletal conditions in adults for more information).

While there is evidence suggesting that fish oil has a mild anti-inflammatory effect in patients with systemic lupus erythematosus (SLE), fish oil is a reasonable treatment option for arthritis in any connective tissue disease because of its low risk of harms. Use:

fish oil at least 2.7 g (omega-3) orally, daily (see Table 12.8 for preparations). *connective tissue disease*

Fish oil may take up to 3 months for maximal effectiveness, so it may be necessary to co-prescribe fish oil with an NSAID and/or paracetamol initially. See Principles of fish oil use for musculoskeletal conditions in adults for more information.

If the above drugs are insufficient to control symptoms, refer the patient to a specialist as conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) may be necessary. csDMARDs can take weeks to months to become effective. Drugs used include hydroxychloroquine or, for severe arthritis, methotrexate. Dosages are adjusted depending on clinical response and adverse effects. For considerations in the management of csDMARD therapy (including monitoring, screening for infection, and vaccination), see Principles of immunomodulatory drug use for rheumatological diseases in adults.

The usual dosage of hydroxychloroquine is:

hydroxychloroquine 200 to 400 mg orally, daily. *connective tissue disease: arthralgia, myalgia and arthritis*

The usual dosage of methotrexate is:

methotrexate 10 mg orally, **on one specified day once weekly**, increasing up to 25 mg orally or subcutaneously, **on one specified day once weekly** *connective tissue disease*

PLUS

folic acid 5 to 10 mg orally, per week (preferably not on the day methotrexate is taken). *connective tissue disease*

For patients with severe arthritis, concurrent prednis(ol)one may be necessary to control symptoms until csDMARDs become effective. The usual dosage is:

prednis(ol)one 5 to 15 mg orally, daily. *connective tissue disease*

Avoid doses of prednis(ol)one greater than 15 mg daily in patients with systemic sclerosis because there is a risk of precipitating scleroderma renal crisis. See Principles of immunomodulatory drug use for rheumatological diseases in adults for information on adverse effects associated with long-term corticosteroid therapy (such as bone density loss) and advice on how to minimise and monitor for such complications. Taper and stop corticosteroids as soon as symptoms are controlled.

Fatigue

Fatigue

Fatigue is a common problem in patients with a connective tissue disease and is difficult to manage. Consider and manage other causes of fatigue that may be present in a patient with a connective tissue disease, such as infection, psychosocial factors or iron deficiency (see Conditions commonly associated with fatigue for more information on the assessment of patients with fatigue). Patients who have anaemia of chronic disease associated with an elevated serum ferritin concentration should not be treated with iron supplementation. Iron supplementation is only indicated in cases of demonstrated iron deficiency (see Iron deficiency for more information).

Fatigue associated with a connective tissue disease can be helped by regular aerobic exercise. Hydroxychloroquine may be used by specialists. The usual dosage of hydroxychloroquine is:

hydroxychloroquine 200 to 400 mg orally, daily. *connective tissue disease: fatigue*

For considerations in the management of hydroxychloroquine therapy (including monitoring, screening for infection, and vaccination), see Principles of immunomodulatory drug use for rheumatological diseases in adults.

Raynaud phenomenon and digital ischaemia

Raynaud phenomenon and digital ischaemia

For treatment of Raynaud phenomenon and digital ischaemia, see Raynaud phenomenon and digital ischaemia.

Sicca symptoms

Sicca symptoms

Sicca symptoms (eg dry eyes and/or dry mouth) are due to dry mucosal membranes. Sicca symptoms can be a feature of any connective tissue disease, but are usually most severe in Sjögren syndrome and systemic sclerosis. Severe mucosal membrane dryness can cause ulceration and scarring; specialist referral is recommended. Sicca symptoms can also occur in people without a connective tissue disease, particularly older people; in this case, symptoms are not usually progressive and are not associated with antinuclear antibody (ANA) positivity.

Advise patients with sicca symptoms to:

- wear sunglasses outdoors to avoid wind-drying effects on the eyes
- avoid dry and heated air, cigarette smoke, and drugs with anticholinergic effects (eg tricyclic antidepressants, antiparkinsonian drugs)
- ensure adequate oral hydration and good dental hygiene, including regular dental review, to prevent dental caries (see Management of dental caries)
- be aware of the need for extra care to avoid damage to the eyes and mouth if undergoing surgery.

For **dry eyes**, ocular lubricants (artificial tears) should be used frequently. Multiple preparations are available, including drops, gels and ointments. Eye drops need to be applied several times a day. Gels and ointments are retained in the eye for longer and require less frequent administration than drops; however, they are associated with some blurring of vision and can leave a crust on the eyelashes. Gels and ointments may be most useful at night because of better tolerance and longer duration of effect. A trial of several different preparations may be required to determine the most effective and best tolerated preparation for an individual patient. Patients may become sensitised to the preservatives in multi-use eye drops or gels, especially if they are using them more than three or four times daily. Switch these patients to preservative-free single-use vials.

In severe cases of dry eyes, ciclosporin eye drops can improve tear flow. Ciclosporin eye drop preparations are not widely available and must be prescribed by an ophthalmologist. Surgical insertion of punctal plugs into the lacrimal duct is sometimes tried for symptomatic relief.

Dry mouth is difficult to treat and available preparations are often poorly tolerated. Available preparations include sprays, mouthwashes and gels, as well as artificial saliva. A trial of several different preparations may be required to determine the most effective and best tolerated preparation for an individual patient. For more information, see Dry mouth.

For **dry vagina**, lubricant jellies are recommended. If the woman is postmenopausal, consider the use of intravaginal estrogen (see Intravaginal estrogen therapy for treatment recommendations).

Systemic lupus erythematosus

Systemic lupus erythematosus

Introduction

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that has the potential to affect almost any organ in the body and cause generalised and systemic symptoms. The prevalence of SLE in Australia ranges from 19 to 93 per 100 000 people, with prevalence at the higher end of the range reported in Indigenous Australians. Females are more commonly affected by SLE than males. SLE may develop at any age, but peak incidence is during childbearing years (15 to 45 years of age) in women.

The clinical course of SLE is often one of remission and relapse (flare). The prognosis of SLE depends on the nature and severity of organ involvement. Patients who present with and continue to have mild symptoms in early disease are generally unlikely to progress to more severe disease. Patients with a younger age of onset and certain ethnic groups (eg Asians, Indigenous Australians) have an increased risk of more severe disease.

Modern treatments have improved the 5-year survival of SLE to around 95%; however, the mortality rate is still higher in patients with SLE compared to the general population, with atherosclerotic cardiovascular disease the major cause of mortality in patients with SLE. Early diagnosis and regular follow-up remain essential to improving outcomes in patients with SLE.

See also Cutaneous lupus erythematosus.

Diagnosis of systemic lupus erythematosus

Diagnosis of systemic lupus erythematosus

The American College of Rheumatology developed classification criteria for SLE to identify homogeneous groups of patients for research purposes; however, these criteria have been adopted internationally to aid the diagnosis of SLE (see Table 12.15). Four of the eleven criteria are required for classifying a patient as having SLE. These criteria do not replace clinical judgement in the diagnosis of SLE. For discussion on the role of antinuclear antibody (ANA) testing in the diagnosis of connective tissue diseases, see Antinuclear antibody testing for inflammatory connective tissue diseases.

The common presenting symptoms of SLE are musculoskeletal symptoms, fatigue and rash. Patients can also present with manifestations due to involvement of an organ that is uncommonly affected by SLE, which may delay the diagnosis. In SLE, organs are often affected sequentially rather than concurrently. SLE can coexist with other organ-specific autoimmune disease, such as thyroid or liver disease, which can predate the development of generalised or systemic symptoms.

Table 12.15 American College of Rheumatology classification criteria for systemic lupus erythematosus

Criterion	Definition
malar rash	malar erythema, flat or raised
discoid rash	erythematous raised patches with keratotic scaling and follicular plugging
photosensitivity	rash as an unusual reaction to sunlight
oral ulcers	oral or nasopharyngeal ulcers, usually painless
arthritis	nonerosive arthritis involving two or more peripheral joints with tenderness, swelling or effusion
serositis	pleurisy or pericarditis
renal features	proteinuria or cellular casts
neurological and neuropsychiatric features	seizures or psychosis
haematological features	haemolytic anaemia, leucopenia, lymphopenia or thrombocytopenia
immunological features	presence of anti–double-stranded DNA (dsDNA) antibody, anti–Smith (Sm) antibody, or antiphospholipid antibodies
antinuclear antibody positive	antinuclear antibody positivity in the absence of drugs known to cause drug-induced lupus

Adapted with permission from the 1997 Update of the 1982 American College of Rheumatology Revised Criteria for Classification of Systemic Lupus Erythematosus. © [1997] American College of Rheumatology. Available at www.rheumatology.org/Practice-Quality/Clinical-Support/Criteria/ACR-Endorsed-Criteria.

General management approach for systemic lupus erythematosus

General management approach for systemic lupus erythematosus

The management of SLE is best undertaken by a multidisciplinary approach with specialist involvement. Pharmacological treatment of SLE is determined by the organ involved and the severity of inflammation (see Management of clinical features of systemic lupus erythematosus).

Urgently refer patients with severe organ- and/or life-threatening disease to a specialist centre for management. Immunomodulatory drugs are usually required (see Table 12.16 for drugs used and usual

dosages). Treatment choice and dosing are complex and individualised for each patient; combination therapy may be required and various combinations are used in practice.
Urgently refer patients with severe organ- and/or life-threatening disease to a specialist centre for management.

Hydroxychloroquine has been shown to reduce the risk of flare and is recommended for most patients with SLE. Hydroxychloroquine can also improve lipid levels, which is beneficial because SLE is a risk factor for premature atherosclerotic cardiovascular disease. Systemic corticosteroids are commonly used for severe organ- and/or life-threatening disease in SLE, but they are usually not required for mild disease. The role of biological disease-modifying antirheumatic drugs (bDMARDs) in SLE is unclear. Studies of rituximab in heterogeneous SLE patient populations that assessed diverse clinical outcomes did not show a benefit, but rituximab may have a role in certain patient subgroups (eg refractory lupus nephritis). Belimumab has been shown to be beneficial as an add-on therapy in SLE. With the exception of systemic corticosteroids, the immunomodulatory drugs can take several months to become effective.

When immunomodulatory drugs are used in high doses, their adverse effects may complicate assessment of disease activity (eg hypomania can occur with high-dose corticosteroid therapy, abnormal liver biochemistry can occur with methotrexate). For more information on drug adverse effects, see Principles of immunomodulatory drug use for rheumatological diseases in adults.

Another common dilemma is distinguishing between disease flare and infection due to immunosuppression; inflammatory markers are elevated in both situations. C-reactive protein (CRP) may be more elevated than erythrocyte sedimentation rate (ESR) in the presence of infection. There is also individual patient variation in the pattern of elevation of these markers, so knowing each patient's pattern is helpful. Disease flare may be accompanied by a rise in antibodies to double-stranded DNA (dsDNA) and a reduction in C3 and C4 complement components; these may be helpful biomarkers for imminent flare in patients with this pattern. However, changes in treatment based solely on rising disease markers is not recommended.

For reproductive health considerations in women with SLE, see Reproductive health in women with systemic lupus erythematosus.

For discussion of SLE in children, see Systemic lupus erythematosus in children.

Table 12.16 Immunomodulatory drugs used by specialists for severe organ- and/or life-threatening disease in systemic lupus erythematosus

[NB1]

Drug	**Usual dosage [NB2]**
Corticosteroids	
methylprednisolone sodium succinate *systemic lupus erythematosus*	various intravenous dosing protocols used
prednis(ol)one *systemic lupus erythematosus*	25 to 60 mg orally, daily
Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs)	
azathioprine *systemic lupus erythematosus*	1.5 to 2.5 mg/kg orally, daily
cyclophosphamide *systemic lupus erythematosus*	50 to 100 mg orally, daily (up to 2 mg/kg orally, daily) various intravenous dosing protocols used

ciclosporin *systemic lupus erythematosus*	1.5 to 3 mg/kg orally, daily in two divided doses
hydroxychloroquine *systemic lupus erythematosus*	200 to 400 mg orally, daily
methotrexate *systemic lupus erythematosus*	10 mg orally, on one specified day once weekly, increasing up to 25 mg orally or subcutaneously, on one specified day once weekly [NB3]
mycophenolate mofetil *systemic lupus erythematosus*	500 to 3000 mg orally, daily in two divided doses
mycophenolate sodium *systemic lupus erythematosus*	180 to 720 mg (mycophenolic acid) orally, twice daily
Biological disease-modifying antirheumatic drugs (bDMARDs)	
belimumab *systemic lupus erythematosus*	10 mg/kg intravenously, as a single dose at 0, 2 and 4 weeks, and thereafter every 4 weeks
rituximab *systemic lupus erythematosus*	two doses of 1 g intravenously, given 2 weeks apart
Other	
intravenous immunoglobulin (IVIg) *systemic lupus erythematosus*	various intravenous dosing protocols used

NB1: For considerations in the management of immunomodulatory therapy (including monitoring, screening for infection, and vaccination), see Principles of immunomodulatory drug use for rheumatological diseases in adults.

NB2: These are usual dosages; the dosage should be individualised for each patient depending on disease severity and organ damage, clinical response and adverse effects to treatment, and patient factors (eg renal function).

NB3: Methotrexate should be taken in combination with folic acid 5 to 10 mg orally, per week (preferably not on the day methotrexate is taken).

Management of clinical features of systemic lupus erythematosus

Management of clinical features of systemic lupus erythematosus
Arthralgia, myalgia and arthritis

For management of arthralgia, myalgia and arthritis, see Arthralgia, myalgia and arthritis.

Raynaud phenomenon and digital ischaemia

For treatment of Raynaud phenomenon and digital ischaemia, see Raynaud phenomenon and digital ischaemia.

Mucosal and cutaneous features

Oral ulcers usually require only topical treatment. Local anaesthetic preparations provide symptomatic relief. Topical corticosteroids can promote healing if the ulceration is prolonged or severe. For more information, see Recurrent aphthous ulcerative disease.

For information on specific cutaneous manifestations of SLE, see leukocytoclastic vasculitis and urticarial vasculitis in the Dermatology guidelines.

Systemic features

For management of fatigue, see Fatigue.

Fever due to active SLE is rare and is associated with changes in inflammatory markers (erythrocyte sedimentation rate [ESR] and/or C-reactive protein [CRP] elevation, and complement reduction). Coexistent infection must *always* be actively excluded.

Weight loss can also occur if SLE remains untreated.

If SLE is associated with significant systemic symptoms, organ involvement is likely. Specific organ involvement may be identified when appropriate investigations are performed (eg urinalysis on midstream sample, full blood count, liver biochemistry).

Serosal features

Serositis is common in SLE, both as pleurisy and pericarditis. Rarely, peritoneal inflammation can present as acute abdominal pain, making the differential diagnosis difficult.

Acute severe serositis requires specialist management; patients with pericardial or pleural effusion respond rapidly to intravenous methylprednisolone.

In mild serositis, nonsteroidal anti-inflammatory drugs (NSAIDs) may be sufficient to control pain. Use:

an NSAID orally (see Table 12.7 for dosing). *systemic lupus erythematosus*

The potential benefits of an NSAID should be weighed against its potential harms, particularly in patients at high risk of harms (see Principles of NSAID use for musculoskeletal conditions in adults for more information).

More persistent or recurrent serosal inflammation may require specialist management with prednis(ol)one in combination with one or more of hydroxychloroquine, methotrexate or azathioprine. Hydroxychloroquine may also be used to reduce the frequency of flares of serositis.

Haematological features

Immune-mediated cytopenia is well described in SLE and can involve red blood cells, white blood cells and/or platelets. Minor reductions in blood cell counts do not necessarily require treatment. If cytopenia is progressive, or the numbers are reduced sufficiently to be of clinical concern, refer patients to a specialist for treatment.

For modest reductions in blood cell counts, options for immunomodulatory therapy include prednis(ol)one, azathioprine, cyclophosphamide and mycophenolate. Combination therapy may be required. Profound or progressive cytopenia may require high-dose corticosteroid therapy (intravenous methylprednisolone or high-dose oral prednis(ol)one), or the removal of the destructive antibody with intravenous immunoglobulin (IVIg), rituximab or plasma exchange.

Vascular features

Vasculitis of arterioles and/or venules can involve virtually any target organ in SLE and requires specialist management. When severe it can result in thrombosis within the affected vessel. As the pathogenesis of vasculitis is inflammatory, treatment is with prednis(ol)one, azathioprine and/or other immunomodulatory drugs.

See also Antiphospholipid syndrome and Neurological and neuropsychiatric features.

SLE is a risk factor for premature atherosclerotic cardiovascular disease, and atherosclerotic cardiovascular disease is the major cause of mortality in patients with SLE. Other risk factors for cardiovascular disease should therefore be closely monitored and actively managed in patients with SLE (see Cardiovascular disease risk stratification).

Antiphospholipid syndrome

Some women with SLE and antiphospholipid antibodies (see Table 12.14) will develop features of antiphospholipid syndrome (APS) (ie arterial thrombosis, venous thrombosis, miscarriage and/or thrombocytopenia). However, the risks are so low that treatment is not advised in the absence of symptoms. Routine screening of women with SLE for antiphospholipid antibodies may provoke unnecessary anxiety and is not recommended. APS can also occur in men with SLE and in patients without SLE (primary APS).

Suspect APS in any patient who presents with apparently unprovoked or resistant venous thrombosis, in patients less than 50 years of age presenting with stroke, and in women presenting with recurrent first trimester miscarriages or an unexplained second or third trimester fetal loss.

APS should be managed in consultation with a specialist centre. APS is treated with one or more of low-dose aspirin, heparin or warfarin. Warfarin should not be used in pregnancy.

Renal features

The histological classification of glomerular involvement in SLE is complex, and both vascular and interstitial lesions can occur. Mild forms of glomerular disease, indicated by low levels of haematuria (less than 200 000 glomerular red blood cells/mm^3), have a good prognosis and generally do not require treatment. Heavier haematuria and/or significant proteinuria require urgent assessment of renal function and referral to a specialist centre for consideration of renal biopsy. Treatment choice depends on histological classification and disease severity, but treatment usually includes high-dose prednis(ol)one plus either mycophenolate or cyclophosphamide. Other immunomodulatory drugs that may be used include azathioprine, rituximab and ciclosporin.

Aggressive control of associated hypertension and lipid levels improves renal outcomes; for more information, see Elevated blood pressure and Dyslipidaemia.

Hepatic features

Abnormal liver biochemistry is common in patients with SLE. Exclude organ-specific autoimmune liver disease associated with specific antibodies (eg smooth muscle antibody) and primary biliary cholangitis with antimitochondrial antibody (see Autoimmune hepatitis and Primary biliary cholangitis). Refer patients with progressive or persistent abnormal liver biochemistry to a specialist centre for consideration of liver biopsy.

Neurological and neuropsychiatric features

Headache and migraine are the most common neurological symptoms of SLE. Any suspicion of more serious neurological or neuropsychiatric features of SLE should prompt specialist referral.

Small-vessel cerebral vasculopathy is a common manifestation of central nervous system disease in SLE, and presents as slow cognitive decline. Depression or thought disorders may be associated with cognitive decline and, in addition to treatment for SLE, specific treatment for the psychiatric disease is indicated. Small- or large-vessel cerebral vasculopathy with arterial or venous thrombosis can be associated with antiphospholipid syndrome, and is treated with anticoagulation.

Seizures can be associated with any cause of cerebral ischaemia.

Cerebral vasculitis is rare and is usually associated with other systemic inflammatory manifestations. It carries a grave prognosis, even with aggressive treatment.

Transverse myelitis occurs rarely.

Reproductive health in women with systemic lupus erythematosus

Reproductive health in women with systemic lupus erythematosus

The use of estrogen-containing oral contraceptive pills can induce a flare of SLE in some women. Patients with SLE who are taking an estrogen-containing oral contraceptive pill should be monitored clinically. After 3 months of use of an estrogen-containing oral contraceptive pill, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and double-stranded DNA (dsDNA) should be measured. If a significant flare occurs, consider alternative contraceptive options.

Pregnancy can induce a flare of SLE in some women. The strongest predictor of flare is disease activity in the 6 months preceding conception. Therefore, the risk of flare is minimised by ensuring disease inactivity (as assessed by ESR, CRP and dsDNA) before conception. Antiphospholipid syndrome can cause miscarriage in pregnant women; see Antiphospholipid syndrome. The treatment of SLE in pregnant women is guided by specialist advice. Despite hydroxychloroquine being listed as a Therapeutic Goods Administration (TGA) category D drug [Note 1], it is generally recommended that hydroxychloroquine be continued throughout pregnancy. For more information on immunomodulatory drug use and reproductive health, see Immunomodulatory drug use and reproductive health in adults with rheumatological diseases.

Studies of postmenopausal hormone replacement therapy (HRT) indicate that it is not associated with a significant increase in flares of SLE. However, if the patient still wishes to avoid systemic HRT and their menopausal symptoms are predominantly genitourinary (eg vaginal atrophy), intravaginal estrogen treatment may be used (see Intravaginal estrogen therapy for treatment recommendations).

Note 1: TGA pregnancy categories are explained in Australian categorisation of drugs in pregnancy.

Systemic lupus erythematosus in children

Systemic lupus erythematosus in children

The criteria for diagnosis of SLE in children are the same as in adults (see Table 12.15); however, multisystem involvement is more common in children. Renal or central nervous system involvement occurs in approximately 70% and 30% of cases respectively.

The management of SLE in children is best undertaken by, or in conjunction with, a paediatric rheumatologist. Many children with SLE require treatment with systemic corticosteroids and other immunomodulatory drugs; treatment choices are similar to those in adults with SLE (see Management of clinical features of systemic lupus erythematosus). All children with SLE should be started on hydroxychloroquine, which has a role in reducing rates of disease flare and improving lipid levels. For significant disease manifestations, such as kidney disease, moderate- to high-dose corticosteroid therapy is usually necessary. Corticosteroids can have an impact on growth and, importantly, the normal dramatic accrual in bone density that occurs during the preteen and early teen years, which is when paediatric SLE tends to present. Corticosteroid-induced changes in body habitus (eg Cushingoid features, hair loss, striae) can also have a profound psychological impact on adolescents. Adherence to therapy can therefore be difficult (see also Practical prescribing considerations for rheumatological diseases in children and adolescents).

The peripubertal ovary is more resistant to cyclophosphamide-induced failure than the adult ovary, but testicular function can be affected in males. Alternative immunomodulatory drugs to cyclophosphamide include azathioprine, mycophenolate and rituximab; these drugs have an increasing role as first-line treatment for significant disease manifestations.

Sjögren syndrome

Sjögren syndrome

Introduction

Introduction

Sjögren syndrome is a chronic autoimmune disease associated with lymphoid infiltration of the exocrine glands, particularly the salivary and lacrimal glands, leading to secretory gland dysfunction and, usually severe, sicca symptoms. In severe cases, the dryness can cause salivary gland enlargement and calculus formation, and can affect the trachea causing dry cough and/or hoarse voice. Rarely, loss of gastrointestinal exocrine function can cause pancreatic dysfunction or pancreatitis, and atrophic gastritis.

Sjögren syndrome may be primary, or secondary when it occurs in association with rheumatoid arthritis or another connective tissue disease such as systemic lupus erythematosus (SLE) or systemic sclerosis. Primary Sjögren syndrome predominantly affects females, and the usual age of onset is between 40 and 50 years.

In addition to glandular features, patients with primary Sjögren syndrome often have fatigue, arthralgia and a nonerosive arthritis, as well as Raynaud phenomenon. A wide spectrum of other extra-glandular features may occur due to lymphoid infiltration of the kidney, lung, skin, muscle, stomach and liver, and should prompt specialist referral.

Although Sjögren syndrome is considered a benign disorder, it can very rarely transform into a lymphoid malignancy, primarily of B cell origin; persistent glandular swelling or abnormal weight loss should prompt further investigation.

Diagnosis of Sjögren syndrome

Diagnosis of Sjögren syndrome

A diagnosis of Sjögren syndrome is strongly suggested by significant and persistent sicca symptoms (eg severe dry eyes necessitating the use of ocular lubricants several times a day), in association with polyclonal hypergammaglobulinaemia, a positive antinuclear antibody (ANA), and the presence of antibodies to Ro (SS-A) and La (SS-B). For discussion on the role of ANA testing in the diagnosis of connective tissue diseases, see Antinuclear antibody testing for inflammatory connective tissue diseases. A raised erythrocyte sedimentation rate (ESR), a positive rheumatoid factor (RF) and anaemia of chronic disease are common in Sjögren syndrome.

Ocular abnormality due to Sjögren syndrome is confirmed by a Schirmer tear test (to demonstrate reduced tear production), and rose bengal staining and slit-lamp examination (to show keratitis).

The presence of lymphocytic infiltrate in the minor salivary glands on lip biopsy is diagnostic of Sjögren syndrome. However, this investigation is usually only undertaken by specialists to confirm the diagnosis of Sjögren syndrome in the absence of antibodies to Ro and/or La.

Management of Sjögren syndrome

Management of Sjögren syndrome

There is no cure for Sjögren syndrome, and treatment largely consists of symptomatic relief and patient education. For management of common clinical features such as sicca symptoms, arthralgia, arthritis, fatigue and Raynaud phenomenon, see Management of common clinical features of inflammatory connective tissue diseases.

Systemic sclerosis

Systemic sclerosis

Introduction

Introduction

Scleroderma is an uncommon condition in which excessive collagen deposition leads to fibrosis or thickening of the skin. The localised form, morphoea, is limited to the skin (see Morphoea). The systemic form, systemic sclerosis, is characterised by vascular abnormalities, inflammation and fibrosis of the skin, but also a range of other organs. Raynaud phenomenon (generally the first symptom) and a positive antinuclear antibody (ANA) are usual. For discussion on the role of ANA testing in the diagnosis of connective tissue diseases, see Antinuclear antibody testing for inflammatory connective tissue diseases.

Systemic sclerosis is rare in childhood, but morphoea is more common.

Systemic sclerosis has two disease variants defined by the extent of skin involvement:

- **limited cutaneous disease (limited systemic sclerosis)**, which is often associated with calcinosis, Raynaud phenomenon, oesophageal dysmotility, sclerodactyly, telangiectasia (previously defined by the acronym CREST) and a positive anti-centromere antibody
- **diffuse cutaneous disease (diffuse systemic sclerosis)**, which is typically more rapidly progressive and associated with more severe systemic involvement, such as interstitial lung disease and scleroderma renal crisis. Antibodies to Scl-70 (topoisomerase I) or RNA polymerase III may be present.

The prognosis for patients with systemic sclerosis depends on their age, gender, disease variant and the severity of systemic involvement. Males have a poorer outcome. Average survival from the first symptom is 30 to 40 years for limited disease, and 15 to 20 years for diffuse disease. Cardiopulmonary involvement is the leading cause of death.

Common cancers are twice as common in patients with systemic sclerosis compared to the general population, and occur with increased frequency around the time of diagnosis in patients with the RNA polymerase III antibody. In a patient with newly diagnosed systemic sclerosis with the RNA polymerase III antibody, clinical vigilance for malignancy is important.

Management of systemic sclerosis

Management of systemic sclerosis

Management of systemic sclerosis is directed at clinical features, and is best undertaken by a multidisciplinary approach with specialist involvement. Physiotherapists and other allied health professionals have an important role in the management of patients with systemic sclerosis.

Arthralgia, myalgia and arthritis

For management of arthralgia, myalgia and arthritis, see Arthralgia, myalgia and arthritis.

Raynaud phenomenon and digital ischaemia

For treatment of Raynaud phenomenon and digital ischaemia, see Raynaud phenomenon and digital ischaemia.

Skin fibrosis

Skin fibrosis is a defining clinical feature of systemic sclerosis. The skin may initially be pruritic, swollen and oedematous (scleroedematous stage). Thickening of the skin usually follows. In late stages, the skin may become atrophic with loss of sebaceous glands and hair follicles.

General hand, foot and nail care are important at all stages of skin fibrosis. Regular application of emollients (eg sorbolene cream) and avoidance of soaps can be useful.

In the scleroedematous stage, pruritus may be helped by oral antihistamines. Low-dose prednis(ol)one may also provide some symptom relief. Avoid doses of prednis(ol)one greater than 15 mg daily in patients with

systemic sclerosis because there is a risk of precipitating scleroderma renal crisis.

Immunomodulatory drugs used by specialists to treat the underlying disease include oral cyclophosphamide, mycophenolate and methotrexate. The evidence for these drugs varies. Oral cyclophosphamide reduced the extent of skin involvement in systemic sclerosis in a randomised controlled trial, and mycophenolate has been beneficial in case series. Methotrexate is used in practice despite limited evidence to support its use.

Maintaining range of motion of the hand is important from the time of diagnosis, and a simple exercise program is recommended. Facial exercises, especially mouth opening, are also important and there is some evidence to suggest facial exercises can improve eating, speaking and dental hygiene. If skin fibrosis is widespread, general range-of-motion exercises are recommended. These can be in the form of a gym program, hydrotherapy, a walking program, or a home-based exercise program. Hydrotherapy may not be suitable if skin ulcers are present and may cause worsening of Raynaud phenomenon. Aerobic exercise can improve lung function and peripheral circulation in patients with systemic sclerosis.

If foot problems limit mobilisation, consider referral to an orthotist or podiatrist. An orthosis (to reduce pressure on an overused area of the foot) or custom-made shoes may relieve pain and prevent worsening of ulcers.

Digital calcinosis

The management of painful, extruding digital calcinosis is difficult. Despite reports that warfarin, calcium channel blockers and colchicine may be effective, there are no drugs of established value. Recurrent surgical excision of calcinotic deposits may be necessary.

Sicca symptoms

For management of sicca symptoms, see Sicca symptoms.

Fatigue

For management of fatigue, see Fatigue.

Oesophageal dysmotility

Oesophageal dysmotility, with symptoms of gastro-oesophageal reflux, is common in all patients with systemic sclerosis. If associated with aspiration, it may worsen outcomes of systemic sclerosis–associated interstitial lung disease.

Management of oesophageal dysmotility is best undertaken in consultation with a gastroenterologist. Proton pump inhibitors (PPIs) are the mainstay of drug treatment and high doses may be required. There are no effective prokinetic drugs for oesophageal dysmotility. Nonpharmacological measures include elevating the head of the bed, eating soft food and small meals, and drinking liquids with meals. Advise patients to avoid smoking, alcohol and the use of opioids. Repeated endoscopy may be needed for oesophageal dilation for stricture. Severe reflux may require referral to a surgeon with expertise in antireflux procedures.

Gastric and small bowel involvement

Delayed gastric emptying (with nausea and bloating) and impaired intestinal transit due to systemic sclerosis may respond to domperidone.

Nonspecific looseness of stools or diarrhoea is frequent in patients with systemic sclerosis. It is best managed with a trial of avoidance of irritant foods in consultation with a dietitian, or with a trial of an antidiarrhoeal drug such as loperamide. Use:

loperamide 2 mg orally, 2 to 3 times daily as necessary. *systemic sclerosis, bowel involvement* _

Frequent loose foul-smelling fatty bowel motions suggest malabsorption with bacterial overgrowth; see Small intestinal bacterial overgrowth for management. Severe malabsorption may eventually require parenteral nutrition in consultation with a specialist centre.

Repeated endoscopy may be needed for argon laser treatment of bleeding vascular ectatic lesions of the stomach or intestine.

Large bowel involvement

Involvement of the large bowel in systemic sclerosis may result in altered bowel habits, such as constipation, faecal impaction with or without faecal overflow, and incontinence with or without rectal prolapse. Symptoms can be difficult to manage and advice from an incontinence therapist is useful in refractory cases. Regular use of laxatives or enemas may be necessary for constipation (see Functional constipation). In severe cases, biofeedback techniques, anal plugs or sacral nerve stimulation may be helpful. Rectal prolapse requires surgical repair.

Interstitial lung disease

Interstitial lung disease, or pulmonary fibrosis, is frequent in systemic sclerosis, but is more likely to be clinically significant in diffuse disease. Together with pulmonary arterial hypertension, interstitial lung disease is the commonest cause of death in patients with systemic sclerosis. As there may be few symptoms of pulmonary involvement, regular monitoring is important; see screening recommendations outlined in Pulmonary arterial hypertension.

Interstitial lung disease requires management in a specialist centre. The optimal management of interstitial lung disease in patients with systemic sclerosis is uncertain. Treatment may not be required for patients with indolent disease, but is indicated for patients who are likely to develop rapidly progressive or life-threatening disease; however, it can be difficult to identify which patients need treatment. Treatment may be appropriate for patients with: respiratory symptoms and recent disease onset, restrictive disease on pulmonary function tests or more than 20% lung involvement on high-resolution computed tomography (CT) scan, progressive decline in lung volume or diffusing capacity of the lungs for carbon monoxide (DLCO) on pulmonary function tests, and/or other disease manifestations warranting immunomodulatory treatment.

The aim of treatment is to improve respiratory function, but immunomodulatory drugs have only modest benefits. The nonspecific interstitial pneumonitis (NSIP) pattern of disease can be more responsive to therapy than the usual interstitial pneumonitis (UIP) pattern of disease more typically seen in idiopathic pulmonary fibrosis. If treatment is indicated, a trial of immunomodulatory therapy (cyclophosphamide or mycophenolate) with or without low-dose prednis(ol)one is used. Doses of prednis(ol)one greater than 15 mg daily should be avoided in patients with systemic sclerosis because there is a risk of precipitating scleroderma renal crisis.

Pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) occurs in 10 to 15% of patients with systemic sclerosis, regardless of whether they have diffuse or limited disease. PAH typically develops insidiously in patients without clinically significant interstitial lung disease, but it may occur secondary to interstitial lung disease with associated destruction of the pulmonary vascular bed. Initial symptoms of PAH can be subtle and easily misinterpreted as other manifestations of systemic sclerosis (eg mild breathlessness on exertion, dizziness, palpitations or generalised weakness).

PAH or interstitial lung disease may be quite advanced when dyspnoea develops; annual screening with echocardiogram and pulmonary function tests is recommended for early identification. Echocardiogram may demonstrate changes suggestive of PAH, such as elevated systolic pulmonary arterial pressure, but this is dependent on obtaining an adequate tricuspid regurgitant jet, which can be absent in up to 25% of people. Right heart catheterisation and high-resolution computed tomography (CT) scan of the chest should be performed when clinical suspicion of cardiopulmonary disease is high (eg unexplained deterioration in exercise capacity). Right heart catheterisation is essential for diagnosis of PAH, and to exclude other causes of elevated pulmonary arterial pressure (eg left ventricular diastolic dysfunction, shunts).

Refer all patients with suspected PAH to a specialist centre for management. Specific therapies for proven PAH include endothelin receptor antagonists (bosentan, ambrisentan, macitentan), phosphodiesterase-5 inhibitors (sildenafil, tadalafil) and prostanoids (iloprost, epoprostenol). These therapies have a symptomatic benefit and may have a survival benefit. Response to treatment should be assessed every 6 months with a 6-

minute walk test and echocardiogram. For endothelin receptor antagonists, monitor liver biochemistry and full blood count regularly.

Specific therapies for PAH have strict eligibility criteria for access on the Pharmaceutical Benefits Scheme (PBS). Although only monotherapy is PBS-funded, combinations of these drugs are often used under other funding arrangements. Selexipag, an oral prostacyclin agonist, and riociguat, a guanylate cyclase stimulator, are newer drugs for PAH and, at the time of writing, are not available on the PBS [Note 2]. The role of anticoagulation remains uncertain.

Note 2: See the PBS website for current information [URL].

Scleroderma renal crisis and hypertension

Scleroderma renal crisis (renal failure associated with accelerated hypertension) is a medical emergency. It can develop over a few days, and was the leading cause of death in patients with diffuse systemic sclerosis before the widespread use of angiotensin converting enzyme inhibitors (ACEIs). Scleroderma renal crisis usually occurs in the first 2 years following diagnosis of systemic sclerosis and may be the presenting symptom of the disease. Use of corticosteroids is a risk factor for scleroderma renal crisis; avoid doses of prednis(ol)one greater than 15 mg daily in patients with systemic sclerosis.

Check blood pressure in any patient with symptoms of hypertension, such as headache, dizziness or visual disturbance. Patients may also present with acute pulmonary oedema. Increase in blood pressure may be asymptomatic so regular screening for hypertension is required. In patients with diffuse disease, especially those with the RNA polymerase III autoantibody, check blood pressure several times a week in the first 2 years following diagnosis. Patients may be advised to purchase a home blood pressure monitor to enable self-monitoring.

Increase in blood pressure may be asymptomatic so regular screening for hypertension is required.

Suspect accelerated hypertension and scleroderma renal crisis in any patient with an increase in blood pressure of 30 mmHg or more above baseline. Urgently refer the patient to a specialist and treat immediately with an ACEI while awaiting specialist review. Captopril is the preferred ACEI because it is short-acting and can be rapidly titrated. The aim of treatment is to restore blood pressure to baseline as soon as possible. This approach improves survival, but many patients still require long-term dialysis and renal transplantation.

Any presentation of hypertension, even mild hypertension, should be treated as it can rapidly escalate to accelerated hypertension in patients with systemic sclerosis. An ACEI is the antihypertensive of choice in these patients; for principles of use and dosing, see Approach to drug therapy for blood pressure reduction. There is no evidence that commencing an ACEI before the development of hypertension improves outcomes in patients with systemic sclerosis.

Mixed connective tissue disease

Mixed connective tissue disease

Mixed connective tissue disease combines features of systemic lupus erythematosus (SLE), systemic sclerosis and polymyositis, and some features of rheumatoid arthritis. The female to male ratio is high (up to 16:1) and the age of onset is typically between 20 and 30 years.

Symptoms of mixed connective tissue disease may occur concurrently or, more commonly, evolve sequentially. The clinical presentation is likely to be oedema of the hands, inflammatory arthritis, Raynaud phenomenon, sclerodactyly and myositis. The arthritis is usually nonerosive but rheumatoid factor (RF) may be positive in 50 to 70% of patients, making the differentiation of rheumatoid arthritis and mixed connective tissue disease difficult. Mixed connective tissue disease is defined by clinical features and the presence of antibody to U_1RNP, and often to Ro (SS-A) and La (SS-B) as well (see Table 12.14).

Ten-year survival of mixed connective tissue disease is around 96%. Patients with pulmonary arterial hypertension (PAH) have a poor prognosis. A high U_1RNP titre correlates with a low incidence of renal

disease.

Because of small numbers of patients and the diversity of their clinical presentations, there are no controlled trials of treatments for mixed connective tissue disease. For treatment of PAH, see Pulmonary arterial hypertension. Angiotensin converting enzyme inhibitors (ACEIs) are indicated for treating hypertension, as in systemic sclerosis (see Scleroderma renal crisis and hypertension). Standard therapy for SLE and rheumatoid arthritis–like manifestations includes methotrexate and hydroxychloroquine (see General management approach for systemic lupus erythematosus).

Juvenile dermatomyositis

Juvenile dermatomyositis

Introduction

Introduction

Juvenile dermatomyositis is a systemic vasculopathy that primarily affects the muscle and skin. The clinical course is variable. Some children have a monophasic illness; others experience a relapsing pattern, which increases the potential for morbidity from both the disease and its therapy.

Diagnosis of juvenile dermatomyositis

Diagnosis of juvenile dermatomyositis

The cardinal clinical features of juvenile dermatomyositis are proximal weakness and a characteristic heliotrope rash affecting the face and limbs. Typically, patients also have abnormal nailfold capillaries, reflecting the vasculopathy underlying this disease.

Investigations for juvenile dermatomyositis include measurement of muscle enzyme levels (which are elevated in patients with the disease) and magnetic resonance imaging (MRI) of the pelvic girdle musculature (which reveals diffuse inflammatory changes on T2-weighted images in patients with the disease). Abnormalities on electromyogram and muscle biopsy are also present in patients with juvenile dermatomyositis, but MRI has obviated the need for these investigations in patients with typical clinical features. Dermatomyositis in children is not associated with neoplasia and investigations to exclude occult malignancy are not necessary.

Management of juvenile dermatomyositis

Management of juvenile dermatomyositis

The management of juvenile dermatomyositis is best undertaken by, or in conjunction with, a paediatric rheumatologist. The goal of management in all patients, including those with relapsing disease, is recovery of muscle strength and function. Juvenile dermatomyositis is treated with high-dose corticosteroids (intravenous methylprednisolone or high-dose oral prednis(ol)one) with doses tapered in response to recovery of muscle strength. Normalisation of muscle enzyme levels tends to occur before clinical response and, in itself, does not guide therapy. The concurrent use of methotrexate or ciclosporin improves the primary disease and reduces total exposure to corticosteroids. Other therapies include intravenous immunoglobulin (IVIg) and rituximab. In patients with severe vasculopathy involving the gastrointestinal tract or skin with severe ulceration and bleeding, cyclophosphamide is frequently used in combination with high-dose corticosteroids.

Development of subcutaneous calcification is an important complication of juvenile dermatomyositis and may be more common in poorly controlled disease. No treatment has been consistently reported to be of benefit for subcutaneous calcification, but spontaneous resolution can occur. Surgical excision may be necessary for symptomatic localised lesions.

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Overview of juvenile idiopathic arthritis

Overview of juvenile idiopathic arthritis

Juvenile idiopathic arthritis (JIA) (commonly referred to as juvenile arthritis) is the internationally accepted nomenclature for inflammatory arthritis beginning before 16 years of age and present for at least 6 weeks, for which no underlying cause can be found after appropriate investigation. It is the most common rheumatological disease in childhood, affecting approximately 1 in 1000 children. The spectrum of differential diagnoses of JIA is broad, ranging from noninflammatory conditions through to malignancy. A thorough assessment by a practitioner confident with this diagnosis, and its differentials, is recommended before starting long-term therapy (see also Assessing musculoskeletal symptoms in children and adolescents). For important mimics of JIA in the lower limbs, see Important mimics of juvenile idiopathic arthritis in the lower limbs.

JIA may present with several patterns of joint involvement and extra-articular disease, which may evolve over the disease course. Clinical presentations of JIA and their prevalence are given in Table 12.11.

The long-term management of children and adolescents with JIA is best undertaken by, or in conjunction with, a paediatric rheumatologist. The holistic care of children and adolescents with JIA typically involves a multidisciplinary team, in which the general practitioner has a key role in providing family support, managing the general health of the child and monitoring medication. During the transition in late adolescence from paediatric to adult services, general practitioners are well placed to manage areas of care such as immunisations, starting contraception and, if relevant, stopping smoking. Input from allied health professionals (eg physiotherapists, occupational therapists, orthotists, dietitians) when required is also important. Support from social workers and/or nurse educators can help families come to terms with the diagnosis and its treatment requirements, obtain disability entitlements, and liaise with schools. For more detailed information about multidisciplinary care of children with JIA, see the Australian standards of care [Note 1].

Table 12.11 Clinical presentations of juvenile idiopathic arthritis and their prevalence

Clinical presentation	Prevalence in patients with juvenile idiopathic arthritis
oligoarthritis—4 or fewer joints affected in the first 6 months of disease. Two subtypes occur: • persistent oligoarthritis—4 or fewer joints involved throughout the disease course • extended oligoarthritis—more than 4 joints involved after the first 6 months of disease	50 to 60%
polyarthritis (rheumatoid factor negative)—more than 4 joints affected in the first 6 months of disease, in the absence of rheumatoid factor	10 to 30%
polyarthritis (rheumatoid factor positive)—more than 4 joints affected in the first 6 months of disease, in the presence of rheumatoid factor (detected on at least two occasions 3 months apart)	2 to 7%
systemic arthritis	4 to 17%
enthesitis-related arthritis	3 to 11%
psoriatic arthritis	2 to 11%
undifferentiated arthritis	11 to 21%

Note 1: Munro J, Murray K, Boros C, Chaitow J, Allen RC, Akikusa J, et al. Australian Paediatric Rheumatology Group standards of care for the management of juvenile idiopathic arthritis. J Paediatr Child Health 2014;50(9):663-6. [URL]

Investigations in patients with juvenile idiopathic arthritis

Investigations in patients with juvenile idiopathic arthritis

In patients with juvenile idiopathic arthritis (JIA), the following tests are useful to classify disease (see Table 12.11) and assess the risk of disease complications:

- antinuclear antibodies (ANA)—ANA is commonly detected in children or adolescents with JIA, but is also found in up to 15% of healthy children. ANA positivity is a risk factor for the development of asymptomatic anterior uveitis, particularly in oligoarticular disease
- rheumatoid factor (RF) and antibodies to cyclic citrullinated peptides (CCP)—a minority of children or adolescents with polyarthritis are RF positive. Similar to its prognostic role in adults with rheumatoid arthritis, RF positivity in children and adolescents suggests poor prognosis. Antibodies to CCP are generally only found in patients who are RF positive; their role in the diagnosis and classification of JIA is yet to be determined
- human leucocyte antigen B27 (HLA-B27)—HLA-B27 is a diagnostic feature of enthesitis-related arthritis, but it is not useful in isolation because it is also present in about 10% of Caucasians. The significance of a positive test result is determined by the patient's clinical presentation; in a child or adolescent with symptoms suggestive of an enthesopathy, a positive result is likely to be significant.

Do not use ANA, RF, antibodies to CCP, or HLA-B27 to screen for juvenile idiopathic arthritis because these tests may be positive in healthy children.

These tests should not be used to screen for JIA because they may be positive in healthy children.

Juvenile idiopathic arthritis: oligoarthritis

Juvenile idiopathic arthritis: oligoarthritis

Introduction

Introduction

Oligoarthritis is most common in girls and typically presents in preschool-aged children, with involvement of large joints in the lower limb. Leg length discrepancy, as a result of stimulation of the growth plate adjacent to the affected joint, and flexion contractures may occur in this group if knee arthritis remains poorly controlled.

Screening for asymptomatic anterior uveitis

Screening for asymptomatic anterior uveitis

All patients with juvenile idiopathic arthritis (JIA) are at risk of developing asymptomatic anterior uveitis, with the exception of patients with enthesitis-related arthritis. Patients with oligoarthritis are at particular risk; up to 30% of patients will develop uveitis in the first 7 years of disease, particularly those who are positive for antinuclear antibody (ANA).

Although this form of uveitis is described as ‘asymptomatic’, it is only the ocular pain and redness characteristic of acute symptomatic anterior uveitis that are absent. Symptoms such as reduced visual acuity and photophobia occur, but are not reliably reported by younger children. Older children may be able to recognise these symptoms and, along with their parents, should be instructed to report them. Left undetected

or poorly controlled, anterior uveitis is potentially blinding, so regular slit-lamp screening examinations by an ophthalmologist or, in older children, an optometrist are essential.

The screening interval and duration vary according to the form of JIA, age at onset of disease and ANA status. Children with ANA-positive oligoarthritis or ANA-positive polyarthritis with an onset at 6 years of age or younger have the highest risk of uveitis. These patients should be screened every 3 months for the first 4 years of their disease course; the frequency of screening is then gradually reduced so that after 7 years of disease screening occurs yearly. Screening patients with JIA at lower risk of asymptomatic anterior uveitis typically involves reviews every 6 to 12 months until the age of 10 to 12 years. Patients with enthesitis-related arthritis do not require screening because they develop acute symptomatic, rather than asymptomatic, anterior uveitis.

Management of oligoarthritis

Management of oligoarthritis

Nonsteroidal anti-inflammatory drugs (NSAIDs) are often used in the initial management of oligoarthritis to reduce pain and stiffness. They will rarely resolve the arthritis and usually only have a short-term role while more definitive measures are arranged. For paediatric dosages of oral NSAIDs, see Table 12.12. See also Practical prescribing considerations for rheumatological diseases in children and adolescents.

The definitive treatment of oligoarthritis is intra-articular corticosteroid therapy, which—in most situations—should only be initiated on specialist advice. The most effective drug is triamcinolone hexacetonide [Note 2], which may induce remission in injected joint(s) for 6 to 12 months or longer. Example paediatric doses of triamcinolone hexacetonide for intra-articular injection are given in Table 12.13. In children younger than 6 years or in whom multiple joints are being injected, injections should be performed under general anaesthesia. In older children, sedation and/or analgesia (eg midazolam and/or inhaled nitrous oxide) is generally an acceptable alternative to general anaesthesia.

Serial casting and/or splinting may be used in conjunction with intra-articular corticosteroid therapy if flexion contractures are present.

For patients with frequent relapses of oligoarticular disease or who develop extended oligoarticular disease (ie follow a polyarticular course after the first 6 months of disease), the use of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) should be considered (see Management of rheumatoid factor negative polyarthritis for advice on drug choice and dosing).

Table 12.12 Paediatric dosages of oral NSAIDs used for rheumatological diseases

Drug	Dosage	Oral formulations available
naproxen [NB1] *musculoskeletal conditions (child)*	5 to 7.5 mg/kg twice daily (maximum 1000 mg/day)	suspension, tablet (including modified-release formulation) [NB2]
indometacin *musculoskeletal conditions (child)*	0.5 to 1 mg/kg 2 to 3 times daily (maximum 200 mg/day)	capsule
piroxicam *musculoskeletal conditions (child)*	0.2 to 0.4 mg/kg once daily (maximum 20 mg/day)	capsule, dispersible tablet
meloxicam *musculoskeletal conditions (child)*	0.15 to 0.3 mg/kg once daily (maximum 15 mg/day) [NB3]	capsule, tablet

Drug	Dosage	Oral formulations available
ibuprofen *musculoskeletal conditions (child)*	10 mg/kg 3 to 4 times daily (maximum 2400 mg/day)	capsule, suspension, tablet
diclofenac *musculoskeletal conditions (child)*	1 to 1.5 mg/kg twice daily (maximum 150 mg/day)	capsule, tablet
celecoxib *musculoskeletal conditions (child)*	2 to 4 mg/kg twice daily (maximum 200 mg/day)	capsule

NSAIDs = nonsteroidal anti-inflammatory drugs

NB1: Naproxen sodium is used in some preparations; 250 mg of naproxen is equivalent to 275 mg of naproxen sodium.

NB2: Modified-release formulations of naproxen should not be used for acute pain, but can be considered for older children with persistent pain who have been stabilised on an immediate-release formulation.

NB3: Data indicate that a 0.25 mg/kg once-daily meloxicam dose is not superior to a 0.125 mg/kg once-daily dose.

Table 12.13 Example doses of triamcinolone hexacetonide injection for children

[NB1] [NB2]

Dose of triamcinolone hexacetonide 20 mg/mL		
Small joint (eg hand)	Medium joint (eg wrist)	Large joint (eg knee)
0.03 to 0.05 mL for PIP joints 0.05 to 0.1 mL for MCP and MTP joints	0.025 mL/kg up to 0.5 mL	0.05 mL/kg up to 1 mL

MCP = metacarpophalangeal; MTP = metatarsophalangeal; PIP = proximal interphalangeal

NB1: These are example doses; the dose should be individualised for each patient depending on the size of the joint, the severity of the condition, the response obtained, and the patient's tolerance of the corticosteroid.

NB2: Triamcinolone hexacetonide is not registered for use in Australia but is available via the Special Access Scheme.

Note 2: Triamcinolone hexacetonide is not registered for use in Australia but is available via the Special Access Scheme.

Juvenile idiopathic arthritis: polyarthritis (rheumatoid factor negative)

Juvenile idiopathic arthritis: polyarthritis (rheumatoid factor negative)

Introduction

Introduction

Rheumatoid factor negative polyarthritis may affect both large and small joints, often in a symmetrical pattern.

Although asymptomatic anterior uveitis is less common in rheumatoid factor negative polyarthritis than in oligoarthritis, regular slit-lamp screening examinations are still required (see Screening for asymptomatic anterior uveitis for information on screening interval and duration).

Management of rheumatoid factor negative polyarthritis

Management of rheumatoid factor negative polyarthritis
General management approach

Pharmacological management of polyarthritis aims to induce clinical remission as early as possible and to maintain disease remission once it is achieved. Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) are the mainstay of therapy and should be started early with specialist advice. Biological disease-modifying antirheumatic drugs (bDMARDs) are used in children and adolescents with inadequate response to first-line csDMARD therapy.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used early in the disease course to manage pain and stiffness while awaiting a response to csDMARD therapy, which may take up to 12 weeks. For paediatric dosages of oral NSAIDs, see Table 12.12. Intra-articular corticosteroid therapy may have a role in relieving pain in specific joints, particularly if joint positioning or mobility is poor (eg subtalar joint). See also Practical prescribing considerations for rheumatological diseases in children and adolescents.

For children and adolescents with confirmed disease who have significant pain and stiffness despite the use of an NSAID at an appropriate dose, an oral corticosteroid may be started while awaiting response to csDMARD therapy. In most situations, this should only be done after seeking specialist advice. If considered appropriate, use:

prednis(ol)one 0.25 to 1 mg/kg up to 60 mg orally, daily. *arthritis, polyarthritis (child)*

Patients started on corticosteroids should be reviewed frequently and the dose tapered according to response.

Conventional synthetic disease-modifying antirheumatic drugs

Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) are used by specialists to induce and then maintain clinical remission of arthritis. Methotrexate is the preferred csDMARD for most patients and may also be useful for the management of chronic uveitis. Leflunomide has been demonstrated to have similar efficacy to methotrexate. Sulfasalazine has a limited role in the treatment of patients with polyarthritis; it is most often used for children with enthesitis-related arthritis. Hydroxychloroquine has been demonstrated not to have the same efficacy as other csDMARDs, but is sometimes used in milder cases, or in combination with other csDMARDs.

The specialist will determine the appropriate approach to monitoring, screening for infection, and vaccination based on the adverse effect profile of the immunomodulatory drug(s) used and patient factors (eg disease activity, comorbidities). See also Practical prescribing considerations for rheumatological diseases in children and adolescents.

The usual paediatric dosage of methotrexate is:

methotrexate 10 to 20 mg/m^2 up to 25 mg orally or subcutaneously, **on one specified day once weekly** [Note 3] [Note 4] *arthritis, polyarthritis (child)*

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folic acid 5 mg orally, once weekly (preferably not on the day methotrexate is taken) [Note 5]. *arthritis, polyarthritis (child)*

The usual paediatric dosage of leflunomide is:

leflunomide: *arthritis, polyarthritis (child)*

child less than 20 kg: 10 mg orally, on alternate days

child 20 to 40 kg: 10 mg orally, daily

child more than 40 kg: 20 mg orally, daily.

The usual paediatric dosage of sulfasalazine is:

sulfasalazine 5 mg/kg up to 500 mg orally, twice daily, increasing over 2 to 4 weeks to 15 to 20 mg/kg up to 1.5 g twice daily. *arthritis, polyarthritis (child)*

The usual paediatric dosage of hydroxychloroquine is:

hydroxychloroquine 3 to 5 mg/kg up to 400 mg orally, daily. *arthritis, polyarthritis (child)*

Note 3: Oral bioavailability of methotrexate plateaus above 15 mg. If doses higher than 15 mg are ineffective, subcutaneous administration could be considered.

Note 4: Nausea can be reduced by splitting the methotrexate dose over 2 consecutive days (usually 12 hours apart) or administering methotrexate subcutaneously, as well as by folic acid supplementation.

Note 5: Folic acid can be formulated as a solution by a pharmacist. For formulation details, see the *Australian Pharmaceutical Formulary and Handbook* (APF), 23rd edition, 2015.

Biological disease-modifying antirheumatic drugs

Biological disease-modifying antirheumatic drugs (bDMARDs) are used by specialists to treat children and adolescents with inadequate response to first-line therapy with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs). In the small group of children and adolescents with difficult-to-control polyarthritis, treatment with a bDMARD can minimise polypharmacy and reduce the need for prolonged corticosteroid therapy.

The specialist will determine the appropriate approach to monitoring, screening for infection, and vaccination based on the adverse effect profile of the immunomodulatory drug(s) used and patient factors (eg disease activity, comorbidities). See also Practical prescribing considerations for rheumatological diseases in children and adolescents.

At the time of writing, adalimumab, etanercept and tocilizumab are the only bDMARDs available on the Pharmaceutical Benefits Scheme (PBS) for polyarticular juvenile idiopathic arthritis (JIA). The usual paediatric dosages (listed in alphabetical order) are:

adalimumab (child 2 years or older and less than 15 kg: 10 mg; 15 kg to less than 30 kg: 20 mg; 30 kg or more: 40 mg) subcutaneously, every 2 weeks *arthritis, polyarthritis (child)*

OR

etanercept (child 2 years or older) 0.8 mg/kg up to 50 mg subcutaneously, once weekly *arthritis, polyarthritis (child)*

OR

etanercept (child 2 years or older) 0.4 mg/kg up to 25 mg subcutaneously, twice weekly

OR

tocilizumab (child 2 years or older and less than 30 kg: 10 mg/kg; 30 kg or more: 8 mg/kg) intravenously, every 4 weeks. *arthritis, polyarthritis (child)*

Juvenile idiopathic arthritis: polyarthritis (rheumatoid factor positive)

Juvenile idiopathic arthritis: polyarthritis (rheumatoid factor positive)

Introduction

Introduction

Rheumatoid factor positive polyarthritis occurs mainly in older children and adolescents. Similar to rheumatoid arthritis in adults, it has the potential for early progression to erosive disease, nodules and significant functional disability.

Children with rheumatoid factor positive polyarthritis are at low risk of developing uveitis; however, regular slit-lamp screening examinations are still required (see Screening for asymptomatic anterior uveitis for information on screening interval and duration).

Management of rheumatoid factor positive polyarthritis

Management of rheumatoid factor positive polyarthritis

Management of rheumatoid factor positive polyarthritis is the same as for patients with rheumatoid factor negative polyarthritis, particularly in regards to the early initiation of conventional synthetic disease-modifying antirheumatic drug (csDMARD) therapy with the aim of achieving early disease remission (see Management of rheumatoid factor negative polyarthritis).

Juvenile idiopathic arthritis: systemic arthritis

Juvenile idiopathic arthritis: systemic arthritis

Introduction

Introduction

Systemic arthritis (formerly known as Still disease) shares clinical and laboratory similarities with the rarer adult equivalent, adult-onset Still disease. The clinical presentation of systemic arthritis is dominated by systemic features such as:

- quotidian fever
- evanescent salmon pink rash (Still rash), which is usually nonpruritic
- hepatosplenomegaly and/or lymphadenopathy
- polyserositis.

Arthritis is necessary for diagnosis but can be preceded by systemic features by weeks or even months. Arthritis can present with an oligoarticular or polyarticular distribution, but typically progresses to a polyarticular course. Growth retardation (independent of corticosteroid use) and anaemia of chronic disease commonly coexist with the arthritis.

A markedly elevated serum ferritin concentration (greater than 1000 micrograms/L) is common. Although not pathognomonic for systemic arthritis, it suggests the diagnosis.

Macrophage activation syndrome is a well-recognised complication of systemic arthritis. It is characterised by fever, splenomegaly, abnormal clotting profile (mimicking disseminated intravascular coagulation), cytopenias and extreme hyperferritinaemia. Urgently refer children or adolescents with this complication to a centre of expertise.

Urgently refer children with macrophage activation syndrome to a centre of expertise.

Children and adolescents with systemic arthritis are at very low risk of developing uveitis; however, regular slit-lamp screening examinations are still required (see Screening for asymptomatic anterior uveitis for information on screening interval and duration).

Management of systemic arthritis

Management of systemic arthritis

Systemic arthritis requires specialist management.

Most children and adolescents with systemic arthritis are treated with nonsteroidal anti-inflammatory drugs (NSAIDs) for symptom relief (see Table 12.12 for paediatric dosages of oral NSAIDs).

Many children and adolescents will require corticosteroid therapy to control systemic features. To obtain initial disease control, intravenous methylprednisolone may be used. The usual dosage is:

methylprednisolone sodium succinate 15 to 30 mg/kg up to 1000 mg intravenously, over 1 hour, daily for 3 consecutive days. *arthritis, systemic (child)*

A once-monthly dose of methylprednisolone may be given until the disease is controlled.

For ongoing oral therapy, use:

prednis(ol)one 0.5 to 1 mg/kg up to 60 mg orally, daily. *arthritis, systemic (child)*

Long-term corticosteroid therapy can cause significant adverse effects; the risk of adverse effects must be balanced against the risk of disease complications with inadequate treatment. Once disease control is achieved, taper the dose of oral corticosteroid. Consider tapering to alternate-day dosing to limit adverse effects. Children should be monitored for the development of adverse effects associated with long-term corticosteroid use and, if appropriate, measures should be implemented to minimise these adverse effects.

Ciclosporin may have a role in controlling active systemic features, especially in children or adolescents with subtle features of macrophage activation syndrome. It is used in combination with corticosteroids. The usual dosage is:

ciclosporin 1.5 to 2.5 mg/kg orally, twice daily. *arthritis, systemic (child)*

Children or adolescents who continue to have active polyarthritis despite treatment with a corticosteroid, or in whom arthritis recurs as the corticosteroid dose is tapered, should be treated with methotrexate in combination with folic acid. The dosages used are the same as for polyarthritis (see Management of rheumatoid factor negative polyarthritis).

For patients dependent on corticosteroid therapy (with or without ciclosporin) for control of systemic features, or those with ongoing active polyarthritis despite the use of methotrexate, biological disease-modifying antirheumatic drugs (bDMARDs) may be considered. At the time of writing tocilizumab is the only bDMARD available on the Pharmaceutical Benefits Scheme (PBS) for this indication [Note 6]. The usual dosage is:

tocilizumab (child less than 30 kg: 12 mg/kg; child 30 kg or more: 8 mg/kg) intravenously, every 2 weeks. *arthritis, systemic (child)*

Alternative bDMARDs for systemic arthritis are anakinra and canakinumab.

In a significant number of patients with systemic arthritis, the systemic features eventually settle and the course of their disease becomes that of a polyarthritis. In these patients, the disease-modifying antirheumatic drugs (DMARDs) used for polyarthritis—particularly methotrexate, adalimumab and etanercept—may be used as alternatives to tocilizumab (see Management of rheumatoid factor negative polyarthritis).

The specialist will determine the appropriate approach to monitoring, screening for infection, and vaccination based on the adverse effect profile of the immunomodulatory drug(s) used and patient factors (eg disease activity, comorbidities). See also Practical prescribing considerations for rheumatological diseases in children and adolescents.

Note 6: See the PBS website for current information [URL].

Juvenile idiopathic arthritis: enthesitis-related arthritis

Juvenile idiopathic arthritis: enthesitis-related arthritis

Introduction

Introduction

Enthesitis-related arthritis is the only form of juvenile idiopathic arthritis (JIA) that predominantly occurs in males, typically presenting in late childhood or adolescence. The classic sites for enthesitis (inflammation at the sites of tendon and ligament attachment to bone) are the Achilles tendon and plantar fascial attachment into the calcaneus, the poles of the patellae, and the greater trochanters. Hip involvement early in the disease course or isolated severe disease of the midfoot is relatively common.

Similar to adults with ankylosing spondylitis, children and adolescents with enthesitis-related arthritis may experience symptomatic acute anterior uveitis; this is distinct from the asymptomatic anterior uveitis of the young child with oligoarthritis. See Clinical features of ankylosing spondylitis for information on acute anterior uveitis and its management.

Patients with enthesitis-related arthritis may have extra-articular features. As for other spondyloarthritides, enthesitis-related arthritis is associated with extra-articular diseases. Consideration should be given to whether extra-articular symptoms in a patient with enthesitis-related arthritis are due to the disease itself or a comorbid disease (eg bowel symptoms may warrant consideration of comorbid inflammatory bowel disease) (see Spondyloarthritides, including psoriatic arthritis for more information).

As in ankylosing spondylitis, human leucocyte antigen B27 (HLA-B27) positivity is typical in children with enthesitis-related arthritis. Ankylosing spondylitis will develop in a subset of children with enthesitis-related arthritis.

Management of enthesitis-related arthritis

Management of enthesitis-related arthritis

Nonsteroidal anti-inflammatory drugs (NSAIDs) may improve symptoms of peripheral arthritis and enthesitis (see Table 12.12 for paediatric dosages of oral NSAIDs). In enthesitis-related arthritis, indometacin is often the NSAID of choice.

Intra-articular corticosteroid injections can be useful for peripheral arthritis if a small number of accessible joints are involved; however, the effect may be of shorter duration than in younger children with other forms of JIA.

Early use of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) by specialists may be appropriate, particularly for patients with poor response to NSAIDs and/or intra-articular corticosteroid therapy. Sulfasalazine is often used initially. Methotrexate may be effective for peripheral arthritis; it should be given in combination with folic acid. The dosages used are the same as for polyarthritis (see Conventional synthetic disease-modifying antirheumatic drugs).

The biological disease-modifying antirheumatic drugs (bDMARDs) adalimumab and etanercept are effective for both joint and entheseal disease; they are used by specialists. The dosages used are the same as for polyarthritis (see Biological disease-modifying antirheumatic drugs). Infliximab is also effective for

treatment of enthesitis-related arthritis, but at the time of writing it is not available on the Pharmaceutical Benefits Scheme (PBS) for this indication [Note 7].

Physical therapy is important to maintain flexibility and pelvic girdle strength, and orthoses are used to assist any subtalar involvement or to cushion painful entheses.

Note 7: See the PBS website for current information [URL].

Juvenile idiopathic arthritis: psoriatic arthritis

Juvenile idiopathic arthritis: psoriatic arthritis

Introduction

Introduction

Psoriatic juvenile idiopathic arthritis (JIA) can present at any age, with either an oligoarticular or polyarticular distribution. The presence of a psoriatic rash and nail pitting gives a definite diagnosis; dactylitis (inflammation of a whole finger or toe) is a suggestive feature. A family history in a first-degree relative should be sought, although family history is not sufficient for diagnosis in the absence of the clinical features.

Regular slit-lamp screening examinations for asymptomatic anterior uveitis should follow the same frequency as for oligoarthritis (see Screening for asymptomatic anterior uveitis for information on screening interval and duration).

Management of psoriatic arthritis

Management of psoriatic arthritis

Management of psoriatic arthritis depends on the number of actively involved joints. For patients with oligoarthritis, see Management of oligoarthritis for suggested management. For patients with polyarthritis, see Management of rheumatoid factor negative polyarthritis for suggested management.

For dactylitis, a corticosteroid injection along the tendon sheath followed by regular physical and occupational therapy can be helpful, particularly if fingers are involved.

Important mimics of juvenile idiopathic arthritis in the lower limbs

Important mimics of juvenile idiopathic arthritis in the lower limbs

The following conditions are specific to children and may mimic juvenile idiopathic arthritis in the lower limbs. It is important to recognise and appropriately manage these conditions.

Perthes disease

Perthes disease

Perthes disease occurs in children aged 3 to 12 years and is more common in boys. Patients present with hip or groin pain and limp, but referred pain to the knee may also occur or may be the only symptom. Hip abduction and internal rotation are limited.

If Perthes disease is suspected, perform a hip X-ray and, if the diagnosis is confirmed, refer the patient to an orthopaedic surgeon. Pending specialist review, physical activity should be restricted and weightbearing reduced by the use of crutches if possible.

Slipped capital femoral epiphysis

Slipped capital femoral epiphysis

Slipped capital femoral epiphysis most commonly affects adolescent boys. Patients present with limp and hip or groin pain that may radiate to the knee. The leg is externally rotated and abducted, with limited internal rotation.

Urgently refer patients with radiographically confirmed slipped capital femoral epiphysis to an orthopaedic surgeon.

If slipped capital femoral epiphysis is suspected, perform a hip X-ray and, if a slip is identified, urgently refer the patient to an orthopaedic surgeon. Pending specialist review, physical activity should be restricted and weightbearing reduced by the use of crutches if possible.

Irritable hip

Irritable hip

Irritable hip, or transient synovitis of the hip, is a self-limiting, unilateral condition that occurs in children aged 3 to 8 years. Patients present with hip or groin pain and limp, and hip abduction and internal rotation are limited. Occasionally, patients may refuse to weightbear. Patients are afebrile and appear well; they may have a history of recent upper respiratory tract infection.

Patients with irritable hip have normal X-ray, full blood count and erythrocyte sedimentation rate (ESR). However, a hip X-ray may be useful to exclude bony pathology, and ultrasound may be useful to confirm hip effusion.

Symptoms of irritable hip and septic arthritis overlap; if there is any doubt about the diagnosis, seek orthopaedic review.

Irritable hip is treated with nonsteroidal anti-inflammatory drugs (NSAIDs) (see Table 12.12 for paediatric dosages of oral NSAIDs). Symptoms usually improve significantly over 24 to 48 hours and generally resolve within a week.

Key references: Juvenile idiopathic arthritis

Key references: Juvenile idiopathic arthritis

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Overview of spondyloarthritides

Overview of spondyloarthritides

The spondyloarthritides are related inflammatory arthropathies including:

- axial spondyloarthritis, including ankylosing spondylitis
- reactive arthritis
- enteropathic arthritis
- psoriatic arthritis.

For management of psoriatic arthritis in children and adolescents, see Juvenile idiopathic arthritis: psoriatic arthritis. For management of other spondyloarthritides in children and adolescents, see Juvenile idiopathic arthritis: enthesitis-related arthritis.

The spondyloarthritides share clinical (see Figure 12.12) and radiological features, and many clinicians now consider spondyloarthritis to be a single disease with clinical features in the peripheral joints, spine, entheses, skin, gastrointestinal tract and other organs. Enthesitis (inflammation at the sites of tendon and ligament attachment to bone) is the hallmark of all spondyloarthritides and can occur in numerous locations. It most commonly affects the heels (Achilles tendinitis and plantar fasciitis), anterior chest wall and pelvis.

The spondyloarthritides share a genetic link with human leucocyte antigen B27 (HLA-B27).

A comparison of features of spondyloarthritides is given in Table 12.10.

Some patients have features suggestive of an axial spondyloarthritis, but do not meet the formal classification criteria for ankylosing spondylitis. While these patients have often been described as having ‘undifferentiated spondyloarthritis’, the term ‘nonradiographic axial spondyloarthritis’ has more recently been used; however, a proportion of these patients will progress to overt ankylosing spondylitis. Management of nonradiographic axial spondyloarthritis is the same as for ankylosing spondylitis (see General management approach for ankylosing spondylitis); lifestyle management is particularly important in these patients.

Figure 12.12 Clinical features of spondyloarthritides

Articular and peri-articular features

- enthesitis (inflammation at the sites of tendon and ligament attachment to bone)
- spondylitis (inflammation of the spine) characterised by sacroiliitis (inflammation of sacroiliac joints)
- peripheral arthritis that, characteristically:
  - is oligoarticular
  - is asymmetrical
  - affects the lower limbs
  - affects large joints
- dactylitis (inflammation of a whole finger or toe, ‘sausage digits’)

Possible extra-articular features

- psoriasis-like skin and nail lesions
- conjunctivitis or acute anterior uveitis
- chronic gastrointestinal inflammation
- chronic genitourinary inflammation

Table 12.10 Comparison of features of spondyloarthritides

- Ankylosing spondylitis
- Reactive arthritis
- Enteropathic arthritis
- Psoriatic arthritis

Ankylosing spondylitis [NB1]	
age of onset	adolescence to 40 years of age
gender distribution	predominantly males
onset	gradual
prevalence of HLA-B27	more than 90%
prevalence of articular involvement	spine—100%
	peripheral joints—up to 20%
prevalence of extra-articular involvement	eyes—up to 30% (acute anterior uveitis)
	heart, blood vessels or lungs—1 to 4%
	skin and/or nails—less than 20%
	gastrointestinal tract—IBD in 7%; subclinical gastrointestinal inflammation in up to 66%
	genitourinary tract—rare
Reactive arthritis	
age of onset	childhood to middle age
gender distribution	predominantly males, but 1:1 for reactive arthritis following a gastrointestinal infection
onset	acute
prevalence of HLA-B27	75%
prevalence of articular involvement	spine—less than 50%
	peripheral joints—90%
prevalence of extra-articular involvement	eyes—up to 33% (conjunctivitis)
	heart, blood vessels or lungs—uncommon
	skin and/or nails—streptococcal infection of the skin and soft tissues can trigger reactive arthritis; skin lesions can also be a disease manifestation
	gastrointestinal tract—bacterial gastrointestinal tract infection is a common trigger, but symptoms have usually resolved before the onset of arthritis; gastrointestinal symptoms are an uncommon disease manifestation
	genitourinary tract—bacterial genitourinary tract infection is a common trigger; genitourinary symptoms are also a common disease manifestation
Enteropathic arthritis	
age of onset	childhood to middle age
gender distribution	1:1
onset	variable
prevalence of HLA-B27	more than 25% with peripheral arthritis
	60% with sacroiliitis and spondylitis

prevalence of articular involvement	spine—common; spinal inflammation is typically independent of intestinal disease activity peripheral joints—common; peripheral joint inflammation is often associated with intestinal inflammation eyes—in patients with IBD, less than 15% (acute anterior uveitis) heart, blood vessels or lungs—rare
prevalence of extra-articular involvement	skin and/or nails—uncommon gastrointestinal tract—IBD usually precedes the diagnosis of arthritis; however, arthritis may occasionally present first genitourinary tract—uncommon
Psoriatic arthritis	
age of onset	childhood to middle age [NB2]
gender distribution	1:1
onset	variable
prevalence of HLA-B27	24% with peripheral arthritis more than 60% with sacroiliitis and spondylitis
prevalence of articular involvement	spine—up to 20% peripheral joints—95% eyes—50% (conjunctivitis) heart, blood vessels or lungs—rare
prevalence of extra-articular involvement	skin and/or nails—extremely common gastrointestinal tract—increased incidence of IBD genitourinary tract—rare

HLA-B27 = human leucocyte antigen B27; IBD = inflammatory bowel disease

NB1: The features of nonradiographic axial spondyloarthritis are similar to the features of ankylosing spondylitis.

NB2: For patients younger than 16 years, see Juvenile idiopathic arthritis: psoriatic arthritis for a disease overview, as well as advice on management.

Ankylosing spondylitis

Ankylosing spondylitis

Introduction

Introduction

Ankylosing spondylitis affects up to 0.5% of the population and occurs predominantly in men.

The human leucocyte antigen B27 (HLA-B27) is found in more than 90% of patients with ankylosing spondylitis, but it is not a useful diagnostic indicator in isolation because it is also present in about 10% of the normal Australian population. The presence of HLA-B27 confers a risk of approximately 8% of

developing ankylosing spondylitis in that individual; this risk is increased to 20% if, in addition, a first-degree relative has ankylosing spondylitis.

Ankylosing spondylitis follows a chronic relapsing and remitting course. Disease severity varies considerably between patients.

See Table 12.10 for comparative features of ankylosing spondylitis and other spondyloarthritides.

Clinical features of ankylosing spondylitis

Clinical features of ankylosing spondylitis

Inflammation in ankylosing spondylitis is centred in the spine (spondylitis). It predominantly affects the sacroiliac joints (sacroiliitis) initially, before involving other areas of the spine, usually the lumbar spine and then the thoracic and cervical spine. Enthesitis (inflammation at the sites of tendon and ligament attachment to bone) is a hallmark of the disease. Dactylitis (inflammation of a whole finger or toe) and extra-articular features also occur.

Spondylitis results in pain and stiffness of the spine; in ankylosing spondylitis it is characterised by:

- a gradual onset before the age of 40 years
- a duration of symptoms of longer than 3 months
- prolonged morning stiffness and night pain
- improvement with physical activity or exercise, and failure to improve with rest
- response to nonsteroidal anti-inflammatory drugs (NSAIDs).

Sacroiliitis manifests as stiffness and pain in the buttock, sometimes radiating into the thigh. Alternating buttock pain is characteristic.

Following inflammation and ossification of the axial entheses, the spine progressively stiffens (ankylosis). Involvement of the costovertebral joints leads to reduced chest expansion. With time, abnormal posture and impaired function may occur. Spinal osteoporosis is common; suspect fracture in patients with longstanding disease and a sudden increase in spinal pain.

Peripheral enthesitis and peripheral arthritis occur less commonly. In ankylosing spondylitis, peripheral enthesitis usually affects the heels (Achilles tendinitis and plantar fasciitis) and the peripheral arthritis is usually oligoarticular, asymmetrical and predominantly affects the lower limbs. Arthritis of the hips and shoulder joints (including the acromioclavicular and sternoclavicular joints) occurs in some patients and can be disabling. Arthritis of the costochondral joints of the chest wall can occur and may be associated with more severe disease.

The most common extra-articular feature of ankylosing spondylitis is acute anterior uveitis, which is experienced by up to 30% of patients at some point. Advise patients to seek medical advice immediately if they experience sudden onset of unilateral eye pain, photophobia and increased lacrimation. Conjunctival injection around the rim of the iris is a characteristic finding. Urgently refer any patient with suspected acute anterior uveitis to an ophthalmologist. Treatment involves corticosteroid eye drops and mydriatics to reduce inflammation and prevent sequelae such as synechiae.

Urgently refer any patient with suspected acute anterior uveitis to an ophthalmologist.

Less common extra-articular features of ankylosing spondylitis include aortic insufficiency secondary to aortitis, cardiac conduction defects, and apical pulmonary fibrosis.

Diagnosis of ankylosing spondylitis

Diagnosis of ankylosing spondylitis

History and physical examination give the most useful information in the diagnosis of ankylosing spondylitis (see Clinical features of ankylosing spondylitis). Inflammatory markers such as erythrocyte sedimentation

rate (ESR) and C-reactive protein (CRP) are usually elevated at some point, but have a limited role in diagnosis and disease monitoring because they do not always correlate with disease activity. However, an elevated CRP concentration in early axial spondyloarthritis is associated with an increased risk of eventual structural damage to the axial skeleton, as seen on X-rays of the sacroiliac joints and spine.

Plain X-rays can assist in assessing the extent of joint and entheseal involvement and damage, as well as the rate of disease progression, but changes may not occur for some years.

Magnetic resonance imaging (MRI) is a sensitive tool for detecting axial inflammation, but the inflammatory lesions typical of ankylosing spondylitis ('bone oedema') are also frequently seen in healthy individuals. MRI is best used as an adjunct to careful clinical assessment by an experienced clinician. Other imaging modalities, particularly those that involve ionising radiation such as computed tomography (CT) and radionuclide bone scans, should not be used because they do not add further diagnostic information.

The following features are predictive of poor prognosis in ankylosing spondylitis:

- hip involvement
- age younger than 16 years at the onset of symptoms
- presence of three of the following factors within 2 years of the onset of symptoms:
    - ESR greater than 30 mm/hour or CRP concentration greater than 6 mg/L
    - limitation of spinal movement
    - dactylitis (inflammation of a whole finger or toe)
    - peripheral oligoarthritis
    - inadequate symptom relief from nonsteroidal anti-inflammatory drugs (NSAIDs).

Refer all patients with suspected ankylosing spondylitis to an appropriate specialist for accurate diagnosis and initiation of treatment.

General management approach for ankylosing spondylitis

General management approach for ankylosing spondylitis

The goal of ankylosing spondylitis management is to maximise long-term health-related quality of life by:

- controlling symptoms and inflammation
- normalising physical function
- enabling participation in social and work-related activities
- preventing progressive structural damage
- minimising cardiovascular complications.

All patients with ankylosing spondylitis should be advised to stop smoking (see Smoking cessation), exercise and use nonsteroidal anti-inflammatory drugs (NSAIDs) for symptom control, irrespective of whether other treatments are used.

Patient education, especially at diagnosis, is important to encourage participation in a long-term exercise program and to introduce coping strategies to address possible psychosocial impacts of the disease. An integrated biopsychosocial approach is recommended to address issues such as workforce participation, socialisation, sexual function, and sleep. Printed or online information is useful to reinforce education [Note 1] .

Local corticosteroid injections may be used for peripheral arthritis or enthesitis.

When treatment with the combination of exercise and an NSAID is inadequate to control symptoms, or disease is severe, disease-modifying therapy is added. The choice of drug depends on the site(s) of disease activity.

Biological disease-modifying antirheumatic drugs (bDMARDs) are effective in the treatment of axial inflammation and enthesitis. They are used by specialists to treat patients with severe and/or axial disease.

Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) have a limited role in the treatment of ankylosing spondylitis because they have no effect on axial inflammation or enthesitis. They may be used by specialists in patients with predominantly peripheral arthritis.

Note 1: Patient information on ankylosing spondylitis can be found on the painHEALTH website [URL]. Any management advice given on this website should be considered in the context of the recommendations in these guidelines.

Lifestyle management of ankylosing spondylitis

Lifestyle management of ankylosing spondylitis
Exercise

Exercise is an essential component of management for all patients with ankylosing spondylitis. The aim is to maintain and optimise physical function by improving the mobility of the spine and peripheral joints, as well as improving strength, posture, chest expansion and aerobic fitness. Exercise is also important for mental health.

Consistent participation in exercise is important, particularly for spinal mobility, and patients should be encouraged to participate in exercise they enjoy. In general, most types of exercise are safe for patients with ankylosing spondylitis. However, the appropriateness of high-impact exercise, contact sport, jarring activities or heavy lifting should be considered on a case-by-case basis; particularly in patients who have complications of ankylosing spondylitis such as spinal ankylosis, impaired balance or mobility, osteoporosis or cardiorespiratory complications.

Mobility goals should be informed by the patient's disease course. In early, well-controlled disease, an appropriate goal may be to restore full range of spinal mobility and normal posture. In more advanced disease, however, the goal may be to maintain the patient's existing movement range.

Referral to a health professional with appropriate expertise (eg physiotherapist) may be beneficial to initiate and reinforce an exercise program. Some example exercises can be found on the website of the United Kingdom National Ankylosing Spondylitis Society [URL].

Australian consensus recommendations on the use of exercise for ankylosing spondylitis have recently been published [Note 2] .

Note 2: Millner JR, Barron JS, Beinke KM, Butterworth RH, Chasle BE, Dutton LJ, et al. Exercise for ankylosing spondylitis: An evidence-based consensus statement. Semin Arthritis Rheum 2015;45(4):411-27. [URL]

Smoking cessation

All patients with ankylosing spondylitis should be strongly advised to stop smoking because smoking is associated with a poor disease prognosis. Patient resources and help for smoking cessation are available from the Quitnow website [URL]. See Smoking cessation for more information on assessment of patients' smoking and advice on smoking cessation.

Pharmacological management of ankylosing spondylitis

Pharmacological management of ankylosing spondylitis
Nonsteroidal anti-inflammatory drug use for ankylosing spondylitis

In combination with exercise, nonsteroidal anti-inflammatory drugs (NSAIDs) are the cornerstone of management of ankylosing spondylitis, with NSAIDs used first line for the treatment of pain and inflammation.

While the symptomatic benefit of NSAIDs is well established, there is conflicting evidence regarding the role of regular NSAID use in slowing spinal ankylosis. In general, NSAIDs are only used for symptom control in

ankylosing spondylitis.

Use:

an NSAID orally (see Table 12.7 for dosing). *ankylosing spondylitis*

Patients with ankylosing spondylitis often benefit from taking NSAIDs in the evening to minimise night pain and morning stiffness. It is not unusual to use the upper end of the recommended dosage range.

The risk of harms from NSAID use in patients with ankylosing spondylitis is generally low because the disease typically affects younger adults; some data show that NSAID-related harms may not differ from placebo in the short term. Furthermore, the risk of harms is generally outweighed by the benefits of use because of the proven efficacy of NSAIDs in the treatment of ankylosing spondylitis. NSAIDs are preferred over other analgesics, particularly opioids, because of their favourable benefit–harm profile in this setting. See Principles of NSAID use for musculoskeletal conditions in adults for more information.

Biological disease-modifying antirheumatic drug use for ankylosing spondylitis

Biological disease-modifying antirheumatic drugs (bDMARDs) are used by specialists for patients with axial disease that has not responded adequately to exercise and nonsteroidal anti-inflammatory drugs (NSAIDs). The tumour necrosis factor (TNF) inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab) are most commonly used. In most patients bDMARDs are highly effective at decreasing disease activity and increasing function. However, convincing data about long-term disease modification and prevention of ankylosis are lacking.

Patients taking bDMARDs are at increased risk of infections and clinicians must always be alert to the possibility of infection (including opportunistic infection), particularly because the usual symptoms and signs (eg fever) are often absent. For other considerations in the management of bDMARD therapy (including monitoring, screening for infection, and vaccination), see Principles of immunomodulatory drug use for rheumatological diseases in adults.

The TNF inhibitors are generally considered to be equally efficacious in the management of ankylosing spondylitis, and drug choice is influenced by patient preference regarding route of administration and dosing frequency. For patients with ankylosing spondylitis and comorbid inflammatory bowel disease, TNF inhibitors other than etanercept may be preferred because etanercept has been shown to be ineffective in the management of inflammatory bowel disease. The bDMARD secukinumab, an interleukin-17 inhibitor, is effective in the treatment of ankylosing spondylitis and is an alternative treatment option.

The usual dosages used for ankylosing spondylitis (listed in alphabetical order) are:

adalimumab 40 mg subcutaneously, every 2 weeks *ankylosing spondylitis*

OR

certolizumab pegol 400 mg subcutaneously, as a single dose at 0, 2 and 4 weeks, and thereafter 200 mg every 2 weeks *ankylosing spondylitis*

OR

certolizumab pegol 400 mg subcutaneously, as a single dose at 0, 2 and 4 weeks, and thereafter every 4 weeks

OR

etanercept 50 mg subcutaneously, once weekly [Note 3] *ankylosing spondylitis*

OR

golimumab 50 mg subcutaneously, every 4 weeks *ankylosing spondylitis*

OR

infliximab 5 mg/kg intravenously, as a single dose at 0, 2 and 6 weeks, and thereafter every 6 weeks *ankylosing spondylitis* _

OR

secukinumab 150 mg subcutaneously, as a single dose at 0, 1, 2, 3 and 4 weeks, and thereafter every 4 weeks. *ankylosing spondylitis* _

Some bDMARDs with other molecular targets (eg the interleukin-12/23 inhibitor, ustekinumab) are effective in the treatment of ankylosing spondylitis, but are not yet part of standard treatment.

Recent data support the efficacy of bDMARDs in severe nonradiographic axial spondyloarthritis that is unresponsive to exercise and NSAIDs, particularly in patients with objective markers of inflammation (elevated erythrocyte sedimentation rate or C-reactive protein concentration, or bone oedema on magnetic resonance imaging). If used, the dosages are the same as for ankylosing spondylitis [Note 4] .

Note 3: An alternative regimen is: etanercept 25 mg subcutaneously, twice weekly.

Note 4: At the time of writing, bDMARDs are not approved by the Australian Therapeutic Goods Administration (TGA) for treatment of nonradiographic axial spondyloarthritis. See the TGA website for current information [URL].

Corticosteroid use for ankylosing spondylitis

Oral corticosteroids (eg prednis(ol)one) have a limited role in the management of ankylosing spondylitis.

Intra-articular corticosteroid injections may be used for peripheral arthritis if a small number of accessible joints are involved. Radiologically guided corticosteroid injections into sacroiliac joints may be beneficial for sacroiliitis. Peritendinous corticosteroid injections may be beneficial for enthesitis. They should be used with caution in enthesitis involving major weightbearing tendons such as the Achilles tendons; consider seeking specialist advice and avoid multiple injections. For principles of use and example doses of local corticosteroid injections, see Principles of using local corticosteroid injections for musculoskeletal conditions in adults.

Intravenous methylprednisolone is used rarely by specialists for patients with severe systemic disease.

Conventional synthetic disease-modifying antirheumatic drug use for ankylosing spondylitis

Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) may be effective for peripheral arthritis, but should not be used to treat spondylitis because they have no effect on axial inflammation. Since spondylitis is the predominant symptom of ankylosing spondylitis, csDMARDs are rarely required. They may be used by specialists in the small number of patients with predominantly peripheral arthritis.

There is limited evidence to guide csDMARD choice in peripheral arthritis in ankylosing spondylitis. Sulfasalazine is the drug of choice in most patients because of its stronger evidence base and more favourable adverse effect profile. If sulfasalazine is contraindicated or not tolerated, treatment options include methotrexate or leflunomide. Methotrexate is preferred over leflunomide because of greater experience with its use.

For considerations in the management of csDMARD therapy (including monitoring, screening for infection, and vaccination), see Principles of immunomodulatory drug use for rheumatological diseases in adults.

The usual dosage of sulfasalazine is:

sulfasalazine (enteric coated) 500 mg orally, daily, increasing gradually up to 1.5 g twice daily. *ankylosing spondylitis* _

Sulfasalazine doses up to 4 g per day are sometimes used in patients with comorbid inflammatory bowel disease.

The usual dosage of methotrexate is:

methotrexate 10 mg orally, **on one specified day once weekly**, increasing up to 25 mg orally or subcutaneously, **on one specified day once weekly** *ankylosing spondylitis* _

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folic acid 5 to 10 mg orally, per week (preferably not on the day methotrexate is taken). *ankylosing spondylitis* _

The usual dosage of leflunomide is:

leflunomide 10 to 20 mg orally, daily. *ankylosing spondylitis* _

Reactive arthritis

Reactive arthritis

Introduction

Introduction

Reactive arthritis is an inflammatory, postinfective disease that typically presents 1 to 3 weeks after an infection. It has an annual incidence of about 30 per 100 000 people. Reactive arthritis following genitourinary infection occurs predominantly in males, most commonly between 20 and 40 years of age. The most common genitourinary pathogen associated with reactive arthritis is *Chlamydia trachomatis*. Reactive arthritis following gastrointestinal infection affects males and females equally. The most common enteric pathogens are *Salmonella typhimurium, Shigella flexneri, Yersinia enterocolitica* and *Campylobacter jejuni*. Streptococcal infections can also be followed by reactive arthritis.

In some patients, a history of triggering infection may be absent, but a diagnosis of reactive arthritis can still be made based on clinical presentation.

In up to 80% of patients with reactive arthritis, the arthropathy settles within 6 months (see Acute reactive arthritis), while the remaining 20% have chronic reactive arthritis. Some patients will experience recurrent episodes of acute reactive arthritis, which should be managed as acute reactive arthritis.

See Table 12.10 for comparative features of reactive arthritis and other spondyloarthritides.

Clinical features of reactive arthritis

Clinical features of reactive arthritis

The clinical presentation of reactive arthritis may include one or more of the triad of arthritis, conjunctivitis and urethritis.

The arthritis is typically an inflammatory peripheral arthropathy with an asymmetrical oligoarticular distribution, predominantly affecting the lower limbs. Dactylitis (inflammation of a whole finger or toe) is a common feature, and enthesitis (inflammation at the sites of tendon and ligament attachment to bone) can occur. The articular symptoms typically develop at least 1 week after an infective illness; this temporal relationship may help to distinguish reactive arthritis from joint infection (see Septic arthritis or Viral arthritis). While *Streptococcus pyogenes* does not cause reactive arthritis, rheumatic fever is also a postinfective arthritis and should be considered in high-risk populations (see Acute rheumatic fever).

Extra-articular features of reactive arthritis include:

- conjunctivitis in up to 33% of cases. Acute anterior uveitis can occur, although less commonly than with ankylosing spondylitis (see Clinical features of ankylosing spondylitis for more information on

acute anterior uveitis and its management)
- genitourinary inflammation, including urethritis, prostatitis and balanitis
- keratoderma blennorrhagica. This is a pustular hyperkeratotic rash typically affecting the palms and soles of the feet, which is histologically identical to pustular psoriasis.

Management of reactive arthritis

Management of reactive arthritis
Acute reactive arthritis

Although reactive arthritis typically presents after an infection has resolved, active infection or asymptomatic infection may still be present at the time of the arthritis diagnosis. Further investigation may be required to distinguish persistent infection from the inflammatory manifestations of reactive arthritis (eg urethritis). Treat active infection as indicated. If an asymptomatic sexually transmitted infection is suspected, see Principles of sexually transmitted infection management for advice on investigation, treatment and contact tracing.

The treatment of acute reactive arthritis (duration of less than 6 months) depends on the extent and severity of joint involvement, and the nature of any extra-articular involvement.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are effective at treating mild to moderate peripheral arthritis and spondylitis. Use:

an NSAID orally (see Table 12.7 for dosing). *arthritis, reactive*

The potential benefits of an NSAID should be weighed against its potential harms, particularly in patients at high risk of harms (see Principles of NSAID use for musculoskeletal conditions in adults for more information).

Intra-articular corticosteroid injections are effective for severe peripheral arthritis if a small number of accessible joints are involved. Peritendinous corticosteroid injections may be beneficial for enthesitis. They should be used with caution in enthesitis involving major weightbearing tendons such as the Achilles tendons; consider seeking specialist advice and avoid multiple injections. For principles of use and example doses of local corticosteroid injections, see Principles of using local corticosteroid injections for musculoskeletal conditions in adults.

Oral corticosteroids may be required for severe articular and extra-articular disease, provided active infection has been excluded. The usual dosage is:

prednis(ol)one 10 to 50 mg (depending on severity) orally, daily until symptoms improve, then taper the dose to stop. *arthritis, acute reactive* _

See Principles of immunomodulatory drug use for rheumatological diseases in adults for information on adverse effects associated with long-term corticosteroid therapy (such as bone density loss) and advice on how to minimise and monitor for such complications.

Topical corticosteroids may be needed for ocular inflammation.

Chronic reactive arthritis

Up to 20% of patients with reactive arthritis may develop chronic arthritis (ie persisting beyond 6 months).

All patients with chronic spondylitis or peripheral arthritis should be advised to exercise (see the advice on exercise in ankylosing spondylitis). Nonsteroidal anti-inflammatory drugs (NSAIDs) are used for symptom control. The combination of exercise and NSAIDs is continued throughout the disease course, irrespective of whether other treatments are used. For more information on the use of NSAIDs, including dosage, see Nonsteroidal anti-inflammatory drug use for ankylosing spondylitis.

Intra-articular and peritendinous corticosteroid injections may be used for peripheral arthritis and enthesitis, respectively. Peritendinous injections should be used with caution in enthesitis involving major

weightbearing tendons such as the Achilles tendons; consider seeking specialist advice and avoid multiple injections. Radiologically guided corticosteroid injections into sacroiliac joints may be beneficial for sacroiliitis. For principles of use and example doses of local corticosteroid injections, see Principles of using local corticosteroid injections for musculoskeletal conditions in adults.

When treatment with exercise and an NSAID is inadequate to control symptoms, or disease is severe, disease-modifying therapy may be added. The choice of drug depends on the site(s) of disease activity. The conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) are often used by specialists to treat peripheral arthritis, although strong evidence is lacking. See Conventional synthetic disease-modifying antirheumatic drug use for ankylosing spondylitis for doses. csDMARDs are relatively ineffective in the treatment of enthesitis. Biological disease-modifying antirheumatic drugs (bDMARDs) may be effective in refractory cases of chronic reactive arthritis; however, there is little evidence to support their use. They should only be used by specialists after persistent infection has been excluded. See Biological disease-modifying antirheumatic drug use in ankylosing spondylitis for doses.

Enteropathic arthritis

Enteropathic arthritis

Introduction

Introduction

Enteropathic arthritis is an inflammatory arthropathy that occurs in conjunction with inflammatory bowel disease, specifically Crohn disease and ulcerative colitis. Enteropathic arthritis is the most common extra-intestinal feature of inflammatory bowel disease; up to 20% of patients may develop axial and/or peripheral spondyloarthritis.

See Table 12.10 for comparative characteristics of enteropathic arthritis and other spondyloarthritides.

Clinical features of enteropathic arthritis

Clinical features of enteropathic arthritis

In patients with enteropathic arthritis, the clinical features of spondylitis (inflammation of the spine) and sacroiliitis (inflammation of sacroiliac joints) are indistinguishable from those of ankylosing spondylitis. Like the other spondyloarthritides, the peripheral arthritis is oligoarticular, asymmetrical and predominantly affects the lower limbs. Enthesitis (inflammation at the sites of tendon and ligament attachment to bone) may be seen at the Achilles tendon and plantar fascia insertion.

Other extra-intestinal features of inflammatory bowel disease that can be seen in conjunction with enteropathic arthritis include:

- ocular complications, especially acute anterior uveitis, but also conjunctivitis and episcleritis (see Clinical features of ankylosing spondylitis for more information on acute anterior uveitis and its management)
- cutaneous lesions, such as erythema nodosum (Crohn disease) and pyoderma gangrenosum (ulcerative colitis).

The spondyloarthritis may precede the clinical presentation of inflammatory bowel disease. As a general rule, spondylitis disease activity is independent of intestinal disease activity, whereas peripheral arthritis disease activity is often associated with intestinal inflammation.

Management of enteropathic arthritis

Management of enteropathic arthritis

Consideration should be given to the effects of pharmacological therapy used to manage enteropathic arthritis on the patient's underlying inflammatory bowel disease, as well as the effects of therapy used to manage inflammatory bowel disease on the patient's arthritis. Whenever possible, a drug that is effective for both indications should be used to avoid unnecessary polypharmacy. For guidance on the management of inflammatory bowel disease, see Inflammatory bowel disease.

All patients with spondylitis or peripheral arthritis should be advised to stop smoking (see the advice on smoking cessation in ankylosing spondylitis), exercise (see the advice on exercise in ankylosing spondylitis) and, if tolerated, use nonsteroidal anti-inflammatory drugs (NSAIDs) for symptom relief (see Nonsteroidal anti-inflammatory drug use for ankylosing spondylitis). NSAIDs aggravate inflammatory bowel disease in some patients.

Intra-articular corticosteroid injections may be used for peripheral arthritis if a small number of accessible joints are involved. Radiologically guided corticosteroid injections into sacroiliac joints may be beneficial for sacroiliitis. Peritendinous corticosteroid injections may be beneficial for enthesitis. They should be used with caution in enthesitis involving major weightbearing tendons such as the Achilles tendons; consider seeking specialist advice and avoid multiple injections. For principles of use and example doses of local corticosteroid injections, see Principles of using local corticosteroid injections for musculoskeletal conditions in adults.

When treatment with the combination of exercise and an NSAID is inadequate to control symptoms, or disease is severe, disease-modifying therapy is added. The choice of drug depends on the site(s) of disease activity. For patients with peripheral arthritis, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) may be considered by specialists. Sulfasalazine, azathioprine and methotrexate are preferred because they are widely used to treat inflammatory bowel disease. Biological disease-modifying antirheumatic drugs (bDMARDs)—usually tumour necrosis factor (TNF) inhibitors—may be effective in the treatment of enteropathic arthritis; however, there is no direct evidence to support their use. The choice of bDMARD should take into account the drug's effect on inflammatory bowel disease—for example, a TNF inhibitor other than etanercept may be preferred because etanercept has been shown to be ineffective in the management of inflammatory bowel disease.

Psoriatic arthritis

Psoriatic arthritis

Introduction

Introduction

Psoriatic arthritis affects 0.04 to 0.1% of the population and typically presents in young to middle-aged adults. Males and females are affected equally. The reported prevalence of inflammatory arthritis in people with psoriasis varies widely from 6% up to 42%. In about 67% of patients, psoriasis is present before the onset of the arthropathy, whereas in approximately 15% of patients the arthritis precedes the skin disease by more than one year.

See Table 12.10 for comparative characteristics of psoriatic arthritis and other spondyloarthritides.

Psoriatic arthritis is associated with an increased risk of cardiovascular disease.

Refer all patients with suspected psoriatic arthritis to an appropriate specialist for accurate diagnosis and initiation of treatment.

For psoriatic arthritis in children, see Juvenile idiopathic arthritis: psoriatic arthritis.

Clinical features of psoriatic arthritis

Clinical features of psoriatic arthritis

In most patients with psoriatic arthritis, the arthropathy affects peripheral joints alone and may present with dactylitis (inflammation of a single finger or toe) or enthesitis (inflammation at the sites of tendon and ligament attachment to bone). The following patterns of joint involvement are recognised:

- oligoarticular peripheral arthritis—occurs in 50% of patients; involves up to five joints. Over time many patients with an initially oligoarticular presentation will develop polyarticular disease
- polyarticular peripheral arthritis—occurs in 30% of patients; may resemble rheumatoid arthritis
- predominant sacroiliitis (inflammation of the sacroiliac joints) and spondylitis (inflammation of the spine)—occurs in up to 10% of patients. The sacroiliitis is usually asymmetrical. On plain X-ray the syndesmophytes are typically 'chunky', often with noncontiguous involvement of vertebrae
- predominant distal interphalangeal joint involvement in both hands and feet—occurs in 5% of patients. The distal interphalangeal joints involved are usually associated with severe psoriatic nail involvement
- arthritis mutilans—occurs in up to 5% of patients. It presents as osteolysis or dissolution of bone affecting the small joints of the hands and feet and adjacent phalanges, resulting in shortening of digits, and flail joints. This pattern of involvement is more commonly seen in females.

The extra-articular features common to the spondyloarthritides may occur with psoriatic arthritis (see Figure 12.12). Ocular inflammation most commonly presents as conjunctivitis, although up to 7% of patients can develop iritis.

Markers of poor prognosis in psoriatic arthritis are:

- juvenile or young adult onset
- extensive psoriatic skin disease
- failure to respond to nonsteroidal anti-inflammatory drugs (NSAIDs)
- polyarticular presentation.

Management of peripheral psoriatic arthritis

Management of peripheral psoriatic arthritis
General management approach

Consideration should be given to the effects of pharmacological therapy used to manage psoriatic arthritis on the patient's underlying psoriatic skin disease, as well as the effects of therapy used to manage psoriatic skin disease on the patient's arthritis. Whenever possible, a drug that is effective for both indications should be used to avoid unnecessary polypharmacy. See Psoriasis for guidance on the management of psoriasis (including primary care treatment and considerations such as psychological health). Ensure good disease control, even in patients with only one or two joints involved, because the arthritis can be destructive.

In addition to lifestyle management, as recommended for ankylosing spondylitis, the following pharmacological treatments may be used. In monoarticular or oligoarticular disease, nonsteroidal anti-inflammatory drugs (NSAIDs) and intra-articular corticosteroid injections are often used first line; disease-modifying antirheumatic drugs (DMARDs) are used for resistant or progressive cases. In polyarticular disease, DMARD therapy is required. For more information on DMARD therapy, see Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), Biological disease-modifying antirheumatic drugs (bDMARDs) and Targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs).

As psoriatic arthritis is associated with an increased risk of cardiovascular disease, advise patients about lifestyle modification, and monitor and actively manage risk factors for cardiovascular disease (see Cardiovascular disease risk stratification).

Nonsteroidal anti-inflammatory drug use for peripheral psoriatic arthritis

Nonsteroidal anti-inflammatory drugs (NSAIDs) are effective in managing pain and inflammation in peripheral psoriatic arthritis. Use:

an NSAID orally (see Table 12.7 for dosing). *arthritis, peripheral psoriatic*

The potential benefits of an NSAID should be weighed against its potential harms, particularly in patients at high risk of harms (see Principles of NSAID use for musculoskeletal conditions in adults for more information). Fish oil may have an NSAID-sparing effect (see Principles of fish oil use for musculoskeletal conditions in adults for more information).

Corticosteroid use for peripheral psoriatic arthritis

Intra-articular corticosteroid injections play a significant role in the management of monoarticular or oligoarticular peripheral arthritis. Intra-articular corticosteroid injections may result in long-term suppression of arthritis in the injected joint, avoiding the need for disease-modifying antirheumatic drug (DMARD) therapy. For principles of use and example doses of local corticosteroid injections, see Principles of using local corticosteroid injections for musculoskeletal conditions in adults.

Avoid using oral corticosteroids in patients with psoriatic arthritis because a flare of skin disease can occur when the dose is reduced. Topical corticosteroids are often recommended to control skin disease.

Conventional synthetic disease-modifying antirheumatic drug use for peripheral psoriatic arthritis

The conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) methotrexate, sulfasalazine and leflunomide are established therapies used by specialists for psoriatic arthritis, and may benefit both the arthritis and skin disease.

There is limited evidence to guide csDMARD choice in peripheral psoriatic arthritis, and comparative efficacy data are lacking. Drug choice may be influenced by patient factors (including comorbidities), drug interactions, adverse effects and cost. The risk of abnormalities in liver biochemistry may be higher in patients with psoriatic arthritis than in other inflammatory arthropathies.

For considerations in the management of csDMARD therapy (including monitoring, screening for infection, and vaccination), see Principles of immunomodulatory drug use for rheumatological diseases in adults.

The usual dosage of methotrexate is:

methotrexate 10 mg orally, **on one specified day once weekly**, increasing up to 25 mg orally or subcutaneously, **on one specified day once weekly** *arthritis, peripheral psoriatic* _

PLUS

folic acid 5 to 10 mg orally, per week (preferably not on the day methotrexate is taken). *arthritis, peripheral psoriatic* _

The usual dosage of sulfasalazine is:

sulfasalazine (enteric coated) 500 mg orally, daily, increasing gradually up to 1.5 g twice daily. *arthritis, peripheral psoriatic* _

The usual dosage of leflunomide is:

leflunomide 10 to 20 mg orally, daily. *arthritis, peripheral psoriatic* _

Ciclosporin has been demonstrated in clinical trials to benefit psoriatic arthritis and skin disease. Dose-limiting adverse effects are significant, especially renal impairment and hypertension.

Other csDMARDs, including azathioprine, gold and hydroxychloroquine, have been used in the treatment of psoriatic arthritis, with anecdotal evidence of benefit. Caution is recommended with the use of hydroxychloroquine in psoriatic arthritis because of the risk of inducing a severe flare of skin disease.

Biological disease-modifying antirheumatic drug use for peripheral psoriatic arthritis

The biological disease-modifying antirheumatic drugs (bDMARDs) that inhibit tumour necrosis factor (TNF), adalimumab, certolizumab pegol, etanercept, golimumab and infliximab, are effective in the treatment

of psoriatic arthritis and psoriatic skin disease. They are used by specialists for psoriatic arthritis when csDMARDs are not effective or are poorly tolerated.

The TNF inhibitors are generally considered to be equally efficacious in peripheral psoriatic arthritis and drug choice is influenced by patient preference regarding route of administration and dosing frequency. For patients with psoriatic arthritis and comorbid inflammatory bowel disease, TNF inhibitors other than etanercept may be preferred because etanercept has been shown to be ineffective in the management of inflammatory bowel disease.

The usual dosages of the TNF inhibitors used for psoriatic arthritis (listed in alphabetical order) are:

adalimumab 40 mg subcutaneously, every 2 weeks *arthritis, peripheral psoriatic* _

OR

certolizumab pegol 400 mg subcutaneously, as a single dose at 0, 2 and 4 weeks, and thereafter 200 mg every 2 weeks *arthritis, peripheral psoriatic* _

OR

certolizumab pegol 400 mg subcutaneously, as a single dose at 0, 2 and 4 weeks, and thereafter every 4 weeks _

OR

etanercept 50 mg subcutaneously, once weekly [Note 5] *arthritis, peripheral psoriatic* _

OR

golimumab 50 mg subcutaneously, every 4 weeks *arthritis, peripheral psoriatic* _

OR

infliximab 5 mg/kg intravenously, as a single dose at 0, 2 and 6 weeks, and thereafter every 8 weeks. *arthritis, peripheral psoriatic* _

Some bDMARDs with molecular targets other than TNF (eg the interleukin-12/23 inhibitor ustekinumab, the interleukin-17 inhibitor secukinumab) are effective in the treatment of psoriatic arthritis, as well as psoriatic skin disease. Comparative data to the TNF inhibitors are lacking. Given the longer experience with TNF inhibitors, bDMARDs with other molecular targets are likely to play a role in the management of patients for whom TNF inhibitors are ineffective, poorly tolerated, or contraindicated.

The usual dosage of ustekinumab for psoriatic arthritis is:

ustekinumab 45 mg subcutaneously, as a single dose at 0 and 4 weeks, and thereafter every 12 weeks [Note 6] . *arthritis, peripheral psoriatic* _

The usual dosage of secukinumab for psoriatic arthritis is:

secukinumab 150 mg subcutaneously, as a single dose at 0, 1, 2, 3 and 4 weeks, and thereafter every 4 weeks [Note 7] . *arthritis, peripheral psoriatic* _

Patients taking bDMARDs are at increased risk of infections and clinicians must always be alert to the possibility of infection (including opportunistic infection), particularly because the usual symptoms and signs (eg fever) are often absent. For other considerations in the management of bDMARD therapy (including monitoring, screening for infection, and vaccination), see Principles of immunomodulatory drug use for rheumatological diseases in adults.

Note 5: An alternative regimen is: etanercept 25 mg subcutaneously, twice weekly.

Note 6: An increased ustekinumab dose (90 mg rather than 45 mg) can be considered for patients weighing more than 100 kg; however, it is not clear if this dose is more effective than standard dosing. More frequent maintenance dosing (up to every 8 weeks) has been used in patients with plaque psoriasis, with or without comorbid psoriatic arthritis, whose response to treatment was inadequate. At the time of writing, increased doses of ustekinumab are not available on the Pharmaceutical Benefits Scheme (PBS) for treatment of psoriatic arthritis. See the PBS website for current information [URL].

Note 7: For patients who have not responded to treatment with a TNF inhibitor or who have comorbid moderate to severe plaque psoriasis, an increased secukinumab dose (300 mg rather than 150 mg) is used.

Targeted synthetic disease-modifying antirheumatic drug use for peripheral psoriatic arthritis

The targeted synthetic disease-modifying antirheumatic drug (tsDMARD) apremilast is effective in treating psoriatic arthritis, as well as psoriatic skin disease. While it appears to be well tolerated, there is limited clinical experience with its use and its place in the treatment of psoriatic arthritis is not yet determined.

Management of psoriatic spondylitis

Management of psoriatic spondylitis

Spondylitis in psoriatic arthritis is typically milder than in ankylosing spondylitis, but the same management principles apply; see General management approach for ankylosing spondylitis.

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Introduction to viral arthritis

Introduction to viral arthritis

Symmetrical polyarthritis is a well-recognised manifestation of infection with the following viruses:

- alphaviruses (Ross River virus, Barmah Forest virus, and chikungunya virus)
- flaviviruses (dengue virus, Zika virus, and yellow fever virus)
- parvovirus B19
- rubella virus (and its vaccine, which is an attenuated form of the virus)
- hepatitis B and C viruses
- HIV.

Herpesviruses (eg Epstein–Barr virus, cytomegalovirus, varicella-zoster virus), adenovirus and enterovirus can also cause arthritis, but this occurs less frequently because these viruses have a low predilection for the joints.

Alphaviruses and flaviviruses are transmitted by arthropod vectors (typically mosquitoes). Measures to minimise the potential for mosquito bites (eg using insect repellent, and wearing long trousers and long-sleeved shirts in the evening) may be helpful in preventing infection with these viruses.

Most cases of viral arthritis are self-limiting and do not require investigations, specific treatment or specialist referral. Management is focused on patient reassurance and symptomatic relief.

Diagnosis of viral arthritis

Diagnosis of viral arthritis

The diagnosis of viral arthritis is largely based on clinical assessment. Investigations are usually not required unless there is uncertainty about the diagnosis at presentation or the patient has persisting symptoms.

Clinical assessment

Clinical assessment

Arthritis due to a viral infection most commonly presents as a symmetrical polyarthritis, but the presentation can vary depending on the virus. Arthritis is rarely the only symptom of a viral infection and may not be the presenting symptom. Patients who have a viral infection typically also present with influenza-like symptoms, including myalgia, fever, headache and red eyes. Maculopapular rash is also common. Gastrointestinal symptoms (eg abdominal pain, diarrhoea) and lymphadenopathy are less common. In most cases of viral arthritis, symptoms peak at 1 to 2 weeks and are largely resolved by 6 weeks; however, occasionally, arthritis and myalgia persist for several months.

The main differential diagnosis of viral arthritis is early rheumatoid arthritis because this also presents as a symmetrical polyarthritis; however, in rheumatoid arthritis, symptoms are likely to be persisting without improvement or worsening at 6 weeks. See Diagnosis of rheumatoid arthritis for features suggesting rheumatoid arthritis, and see Undifferentiated polyarthritis in adults for approach to diagnosis and management of patients with an undifferentiated polyarthritis.

Monoarthritis is rarely due to a viral infection; promptly investigate a patient presenting with monoarthritis for other conditions, such as septic arthritis or gout, before considering a diagnosis of viral arthritis (see

Undifferentiated monoarthritis in adults).

Investigations

Investigations

Routine testing for all viruses that may be associated with arthritis is not recommended because testing is of limited clinical utility. Test results can be difficult to interpret, often a causative pathogen cannot be identified and, even if a pathogen is identified, this is unlikely to change management.

If testing for specific viruses is deemed necessary, this should be informed by the clinical presentation and the presence of risk factors (eg history of exposure to infected individuals or children with 'slapped cheek' rash [parvovirus B19], insect bites, administration of the rubella vaccine, history of injecting drugs, sexual history, history of travel). In patients with hepatitis B or C viral infection, or HIV infection, arthritis can occur during seroconversion. Testing for hepatitis B or C virus or HIV should be performed if infection is suspected clinically because these viruses have broader health implications and can be specifically treated. Arthritis can also occur in chronic hepatitis C infection.

If viral serology is performed, confirmation of a recent viral infection requires an appropriate change in paired acute and convalescent serology. The acute sample should ideally be collected within 1 week of symptom onset, and the convalescent sample should be collected 14 to 21 days after symptom onset. Testing for both immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies is recommended. Although there are virus-specific IgM and IgG antibody tests, cross-reactions with related viruses are not uncommon, particularly in those with a past history of related viral infection or vaccination. Furthermore, IgM antibodies may persist for up to 2 years following viral exposure and their presence may not reflect recent acute infection. False positive results can also occur in evolving inflammatory diseases.

While rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibody testing are useful in the differential diagnosis of rheumatoid arthritis (see Diagnosis of rheumatoid arthritis), early testing (eg before 6 weeks) is unlikely to be helpful in patients with clinical features of a viral infection (eg arthritis in combination with myalgia, fever and a maculopapular rash). Early testing increases the likelihood of a false positive result because RF can also be present in viral arthritis. Although RF is usually only present at low titre and transient in viral arthritis, it can be present for up to 6 months. It is uncommon for anti-CCP antibody testing to be positive in viral arthritis.

Management of viral arthritis

Management of viral arthritis

There are no antiviral drugs available for the treatment of viral arthritis and, as most cases of viral arthritis are self-limiting, no specific treatment is required. Reassure patients about the favourable prognosis of the condition.

For relief of musculoskeletal symptoms, nonsteroidal anti-inflammatory drugs (NSAIDs) are recommended first line. Use:

an NSAID orally (see Table 12.7 for dosing). *arthritis, viral*

The potential benefits of an NSAID should be weighed against its potential harms, particularly in patients at high risk of harms (see Principles of NSAID use for musculoskeletal conditions in adults for more information).

Paracetamol may be used for symptom relief **in combination with** an NSAID, or **instead of** an NSAID if an NSAID is contraindicated or not tolerated. Use:

1 paracetamol 1 g orally, 4- to 6-hourly, up to a maximum of 4 g daily *arthritis, viral*

OR

1 paracetamol modified-release 1.33 g orally, 8-hourly.

Corticosteroids are not recommended for the treatment of viral arthritis unless symptoms are disabling and the patient has a contraindication or intolerance to NSAIDs. If indicated, use a short course of low-dose therapy. An example dosage is:

prednis(ol)one 10 mg orally, daily for up to 2 weeks. *arthritis, viral*

Treatment with disease-modifying antirheumatic drugs (DMARDs) is discouraged because onset of effect takes several weeks and viral arthritis symptoms have usually resolved by this time.

If symptoms are not improving by 6 weeks or, regardless of improvement, if significant symptoms persist beyond 12 weeks, reconsider a possible diagnosis of rheumatoid arthritis (see Diagnosis of rheumatoid arthritis) and refer patients to a specialist.

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Key references: Viral arthritis

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