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MARIETHA GRAHAM,
Tel. (012) 481-2010
E-mail: mariethag@samedical.org

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Approach to Arthritis: Clinical Guideline 2003

Principal authors: G M Mody, M Tikly, A A Kalla, O L Meyers

1. Objective

These guidelines have been developed to provide a practical approach to the differential diagnosis, investigation and management of monoarthritis/oligoarthritis and polyarthritis.

2. Abbreviations

ACR = American College of Rheumatology; CPPD = calcium pyrophosphate dihydrate; CRP = C-reactive protein; DIP = distal interphalangeal; ENA = extractable nuclear antigens; ESR = erythrocyte sedimentation rate; ESSG = European Seronegative Spondyloarthropathy Group; GALS = Gait, Arms or upper limbs, Lower limbs and Spine; HIV = human immunodeficiency virus; NSAIDs = non-steroidal anti-inflammatory drugs; OA = osteoarthritis; RA = rheumatoid arthritis; SAMA = South African Medical Association; SLE = systemic lupus erythematosus; TB = tuberculosis; WBC = white blood cell.

Please forward all comments to: **Private Practice Unit, South African Medical Association, PO Box 74789, Lynnwood Ridge, 0040 (tel. (012) 481-2073)**

3. Introduction

Pain in or around a joint is a common presenting symptom in primary care. In many cases the pain is due to overuse of a joint or minor injury and the condition is self-limited and resolves completely. However, in some cases it may represent a more serious local condition or the initial manifestation of a systemic disorder, which may lead to disability and deformity if the correct diagnosis and appropriate management is delayed. A detailed history and clinical examination are therefore necessary to establish a likely diagnosis and, where indicated, laboratory tests, X-rays and other special investigations are needed.

The American College of Rheumatology (ACR) has published 'Guidelines for the initial evaluation of the adult patient with acute musculoskeletal symptoms'.[1] Lipsky[2] has also published algorithms for the diagnosis and management of musculoskeletal complaints. This subject is also reported in the proceedings of a symposium 'Rheumatology Today: Pathways to Progress'.[3]

This review will only discuss the non-articular disorders briefly and will focus on the articular disorders to complement the accompanying guidelines on gout, rheumatoid arthritis (RA) and osteoarthritis (OA).

The approach to a patient with joint pain is shown in Fig. 1.

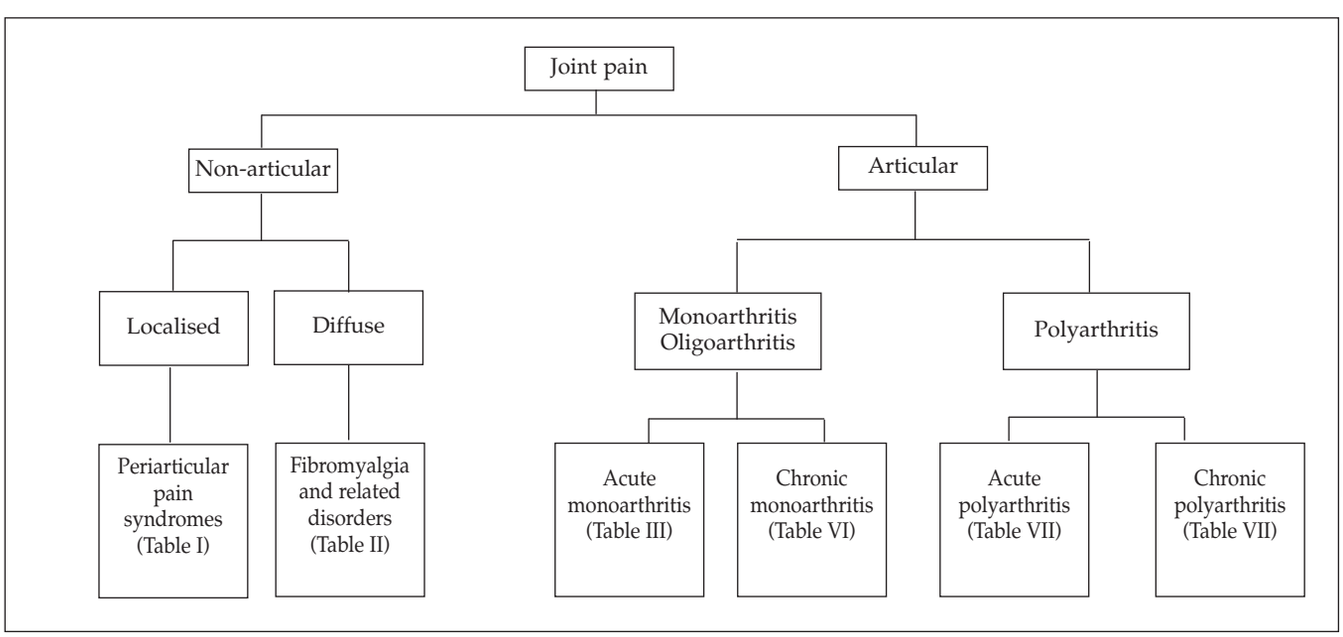

Fig. 1. Approach to a patient with joint pain.

4. Source of pain: articular or non-articular

One of the first decisions the clinician has to make is whether the source of the patient's symptoms is **articular** (due to pathology affecting the joint capsule, intra-articular ligaments, synovium, articular cartilage, periarticular bone or menisci) or **non-articular** (due to involvement of the muscle, tendon, extra-articular ligaments, bursa, fascia, nerves or bones).

4.1 Articular pain

Articular pain is usually deep-seated, poorly localised and present on active and passive movements. Sometimes the pain may be referred to specific sites, e.g. some patients with OA of the hip may only complain of knee pain. Swelling of the joint may be due to the presence of an effusion, synovial thickening or bony enlargement. On examination, crepitus, instability or deformity of the joint may be present.

4.2 Non-articular pain

Non-articular pain is usually localised to the affected anatomical structures. It is present on active movement and there is therefore limitation of active movement, while the passive range of movement is usually normal. There may be muscle weakness, and muscle wasting is present with chronic symptoms. However, there are no deformities of the joints.

5. Approach to a patient with non-articular pain

On the basis of the history and clinical examination, it is usually possible to determine whether the source of the pain is articular or non-articular.

Patients with non-articular pain may have localised, regional or diffuse pain.

5.1 Localised non-articular pain

Some of the more common clinical syndromes of localised non-articular pain are shown in Table I. The diagnosis can be confirmed by the history and local and regional examination, including assessment of active, passive and resisted movement, and specific manoeuvres to reproduce the symptoms.

5.2 Regional non-articular pain

Some patients have pain that may be felt in one or more regions of the body e.g. neck, shoulder, back, hip. These patients are considered to have myofascial pain syndromes, which are characterised by the presence of trigger points. Pressure over a trigger point is associated with referral of pain over a diffuse area in the same region. They respond to injection of the trigger points with local anaesthetics or corticosteroids.

Table I. Causes of localised non-articular pain

Shoulder	Rotator cuff tendinitis, bicipital tendinitis, calcific tendinitis, rotator cuff rupture
Elbows	Medial epicondylitis (golfer's elbow), lateral epicondylitis (tennis elbow), olecranon bursitis
Wrists and hands	De Quervain's tenosynovitis, carpal tunnel syndrome, flexor tenosynovitis (trigger finger), Dupuytren's contracture
Hip	Trochanteric bursitis
Knee	Anserine bursitis, prepatellar bursitis
Ankle and foot	Achilles tendinitis, plantar fasciitis, peroneal/tibialis posterior tenosynovitis, Morton's metatarsalgia

5.3 Diffuse non-articular pain

Some of the causes of diffuse aches and pains are summarised in Table II. Patients with **diffuse** aches and pains should have baseline investigations to exclude a connective tissue, malignant, metabolic or endocrine disorder. If patients have systemic features such as fever, weight loss, constitutional disturbances or inflammatory markers such as a raised erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) level, further investigations are mandatory to exclude a serious underlying disorder. In the absence of systemic features or inflammatory markers, it is necessary to consider conditions such as fibromyalgia or the benign hypermobility syndrome. The ACR has developed criteria for the diagnosis of fibromyalgia which include the presence of widespread pain of more than 3 months' duration with at least 11 of the 18 defined paired tender points.[4]

6. Approach to a patient with arthritis

Arthritis may be a manifestation of a wide spectrum of disorders ranging from infections such as human immunodeficiency virus

Table II. Causes of diffuse non-articular pain

Systemic features (fever, weight loss, lethargy, myalgia, increased ESR or CRP)
Polymyalgia rheumatica
Connective tissue diseases
Malignancy (myeloma, leukaemia)
Widespread pain with typical tender points
Fibromyalgia syndrome
Others
Benign hypermobility syndrome
Diffuse myofascial pain
Parkinson's disease
Hypothyroidism
Osteomalacia

(HIV) disease and septic arthritis, to crystal-associated arthritis, osteoarthritis or autoimmune diseases, to malignancies such as leukaemia and carcinoma. Some of the factors that help to determine the likely cause in an individual patient include the following:

- **onset** — acute or chronic
- features of an **inflammatory** or **non-inflammatory** disorder
- **pattern** of joint involvement — monoarticular, oligoarticular or polyarticular; symmetrical or asymmetrical
- **coexistent disorders**, e.g. inflammatory bowel disease, psoriasis, sarcoidosis.

The presence of symptoms for less than 6 weeks is usually classified as **acute**, while symptoms of more than 6 weeks' duration are classified as **chronic**.[5]

The characteristic features of **inflammatory** joint disorders include the presence of soft-tissue swelling, erythema and warmth, morning stiffness of more than 1 hour, systemic symptoms, raised ESR and CRP, anaemia and synovial fluid white blood cell (WBC) count > 2 x 10^9/l. **Non-inflammatory** joint disorders may be associated with bony swelling, morning stiffness < 60 minutes' duration, normal acute phase reactants and synovial fluid WBC count < 2 x 10^9/l.

In this article the causes of arthritis are classified according to the onset, i.e. **acute** or **chronic**, pattern of joint involvement, i.e. **monoarthritis** or **polyarthritis**, and age group, i.e. **child**, **adult** or **elderly.**

A simplified approach to the cause of arthritis in the vast majority of patients can be considered in five broad categories of **traumatic, inflammatory, infectious, degenerative** and **miscellaneous** causes (Fig. 2). Trauma and infection are discussed briefly under 'Acute monoarthritis'. Degenerative arthritis includes the peripheral and spinal involvement associated with OA. The inflammatory disorders include autoimmune disorders such as RA, crystal-associated disorders such as gout, and the spondyloarthropathies. RA, OA and gout are discussed in separate guidelines. The spondyloarthropathies, which are not discussed separately, are reviewed in greater detail in this article.

7. Approach to a patient with acute monoarthritis

Acute monoarthritis refers to the presence of acute pain and swelling developing in a single joint, usually within a few days, often as a result of an inflammatory process. These patients require immediate evaluation because of the possibility of an infectious arthritis, which can result in rapid destruction of the articular cartilage and lead to irreversible joint damage and disability. The subject of acute monoarthritis or monoarthritis has been reviewed.[5-10]

Some of the conditions which must be considered in a patient with monoarthritis are set out in Table III. Although the most common causes are infection, crystal-associated arthritis, trauma and OA, monoarthritis may occur as the presenting manifestation of almost any rheumatic disorder.

The assessment of a patient with acute monoarthritis presents a diagnostic challenge to the clinician. A detailed history and careful clinical examination are mandatory to identify any clues that may suggest a likely diagnosis. Laboratory investigations, including arthrocentesis and analysis of the synovial fluid, may help to establish a definite diagnosis such as gout or septic

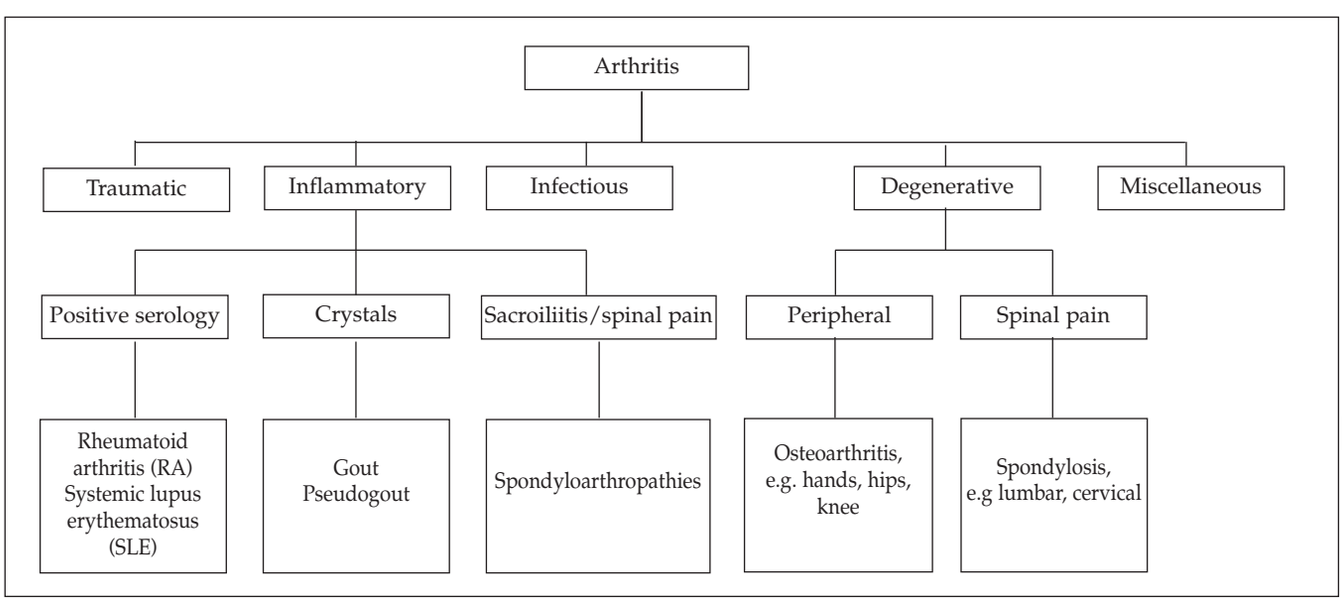

Fig. 2. Differential diagnosis of arthritis.

Table III. Differential diagnosis of acute monoarthritis

Disorder	Possible causes
Infection	Gonococcal arthritis, non-gonococcal septic arthritis, acute rheumatic fever, tuberculosis, HIV, hepatitis B, Lyme disease, fungal infection
Crystal arthritis	Gout, pseudogout, hydroxyapatite
Osteoarthritis	Primary or secondary
Trauma	Fracture, internal derangement, traumatic synovitis
Initial presentation of systemic diseases	RA, SLE, psoriatic arthritis, Reiter's syndrome, other spondyloarthropathies
Avascular necrosis	Corticosteroid therapy, chronic alcoholism
Tumours	Osteoid osteoma, pigmented villonodular synovitis, metastasis
Others	Foreign bodies, leukaemia, amyloidosis

arthritis. Sometimes it may not be possible to establish a specific diagnosis, and it is necessary to individualise the approach to management and consider whether empirical treatment or further investigations such as arthroscopy and synovial biopsy are appropriate.

There are differences in the age and sex distribution of some of the common conditions associated with monoarthritis. A useful approach to determine the most likely cause of monoarthritis is therefore to consider disorders that are most likely to occur in the different age groups as shown in Table IV. Patients may be broadly categorised as children, adults and the elderly. Acute septic arthritis (non-gonococcal), tuberculosis and trauma must be considered in all age groups.

Disorders which usually present in childhood include acute rheumatic fever, haemophilia and juvenile idiopathic arthritis. In young adults disorders such as gonococcal arthritis, HIV-associated arthritis and spondyloarthropathies such as reactive arthritis or Reiter's syndrome must be considered. In older patients, gout and OA also become important. The systemic inflammatory disorders such as RA and SLE may occasionally present with monoarthritis or oligoarthritis. The most important causes of arthritis in the elderly are OA and crystal-associated disorders such as gout and pseudogout.

Table IV. Age-related causes of monoarthritis

Children	Adults	Elderly
Septic arthritis	Septic arthritis (including gonococcal)	Septic arthritis
Tuberculosis	Tuberculosis	Tuberculosis
Trauma	Trauma	Trauma
Haemophilia	HIV infection	Gout
Rheumatic fever	Gout	Pseudogout
Child abuse	Spondyloarthropathies	Osteoarthritis
Leukaemia	Systemic diseases, e.g. RA,	
Juvenile idiopathic arthritis	SLE	
	Osteoarthritis	

8. Causes of monoarthritis

8.1 Infections

8.1.1 Non-gonococcal bacterial arthritis

The most common organism is *Staphylococcus aureus*, followed by streptococcal infection (non-group A, β-haemolytic streptococci and *Streptococcus pneumoniae*). These Gram-positive aerobes account for nearly 70% of all patients with non-gonococcal bacterial arthritis. Patients with prosthetic joints may also be prone to infection with *S. epidermidis*.[11] In addition to *S. aureus*, Gram-negative bacteria and anaerobes are an important consideration in intravenous drug users and immunocompromised patients.

The typical presentation is with fever, and acute pain and swelling of the joint. The joints most frequently involved are the hip and knee. The majority of patients present with monoarthritis, but oligoarticular and rarely polyarticular involvement may occur. The differential diagnosis of polyarthritis and fever has been reviewed by Pinals.[12]

Management includes the use of appropriate antibiotics, and closed (needle aspiration) or open drainage is usually necessary. Many strains of *S. aureus* are resistant to penicillin and methicillin.[13]

8.1.2 Gonococcal arthritis

Neisseria gonorrhoeae is the most common cause of bacterial arthritis in young adults. Gonococcal arthritis is commoner in women than in men. The typical presentation is with migratory arthralgia, which eventually leads to acute monoarthritis. Some patients may have tenosynovitis, a vesicular skin rash or oligoarticular involvement. The diagnosis is confirmed by the culture of *N. gonorrhoeae* in the joint fluid. The diagnostic yield is improved with immediate transport of the fluid to the laboratory. If gonococcal arthritis is suspected, gonococci may also be cultured from swabs of the urethra, rectum, cervix or pharynx.

Resistance to penicillin has been reported for strains of *N. gonorrhoeae* which produce gonococcal arthritis. A survey of 34 patients with gonococcal arthritis in Durban showed the presence of penicillinase-producing strains of *N. gonorrhoeae* in 56%.[14] Ceftriaxone is therefore recommended as initial empiric therapy in patients with suspected gonococcal arthritis.

8.1.3 HIV infection

The articular syndromes associated with HIV infection have recently been reviewed[15] and include arthralgia, the painful

articular syndrome, reactive arthritis, HIV-associated arthritis, septic arthritis and avascular necrosis. HIV infection may present as an acute monoarthritis, oligoarthritis or polyarthritis. The joints of the lower limb are most frequently involved. The joint fluid is usually sterile. These patients are also prone to develop septic arthritis, which may be due to common organisms such as *S. aureus* or other opportunistic infections.

8.1.4 Tuberculosis arthritis

The HIV epidemic and increase in the prevalence of extrapulmonary tuberculosis (TB) has led to a greater awareness of TB infection of the joints. The presentation is usually one of chronic monoarthritis. Concomitant pulmonary involvement is present in up to half the patients[16] and is more likely to occur in immunosuppressed patients and the elderly. The diagnosis is usually made by histology or culture of the synovium, although *Mycobacterium tuberculosis* may occasionally be cultured from the synovial fluid.

8.1.5 Arthritis associated with streptococcal infections

Patients with acute rheumatic fever may present with flitting arthralgia and develop monoarthritis or oligoarthritis. There has been a resurgence of acute rheumatic fever in certain Western communities and it is an important cause of valvular heart disease in South Africa. The diagnosis is made on the basis of the modified Jones criteria,[17] which include evidence of streptococcal infection on culture of the throat swab or the detection of streptococcal antibodies. An awareness of acute rheumatic fever is important in children and young adults as prophylactic therapy helps to prevent recurrent attacks. A form of reactive arthritis, resembling a spondyloarthropathy with mono- or oligoarticular involvement, has been reported with streptococcal infection.

8.1.6 Other infections

Arthritis has been reported with a variety of fungal infections such as sporotrichosis, cryptococcosis, blastomycosis and histoplasmosis. The presentation is usually chronic and the diagnosis is made on synovial biopsy.

Lyme disease, caused by infection with a spirochaete, *Borrelia burgdorferi*, follows exposure to ticks and must be considered in endemic areas. It may present with chronic monoarthritis or oligoarthritis and the diagnosis is confirmed by serological tests. South Africa is not an endemic area and no local cases of Lyme disease have been recorded. The results of serological tests must be interpreted with caution as they may be falsely positive.

Viruses such as hepatitis B and herpes simplex may also produce monoarthritis.

8.2 Crystal-associated arthritis

The classic presentation of acute gout with involvement of the first metatarsophalangeal joint, ankle, midfoot or knee is well known, but any joint may be involved. The initial attack is usually monoarticular but subsequent attacks may be polyarticular. The diagnosis is confirmed by the detection of negatively birefringent urate crystals on polarised light microscopy.

Acute pyrophosphate arthropathy or pseudogout occurs in the elderly and is caused by the presence of calcium pyrophosphate dihydrate (CPPD) crystals. The presentation may be asymptomatic (incidental chondrocalcinosis on X-rays), acute arthritis resembling gout, or chronic arthritis as seen with severe OA. The knees and the wrists are most commonly involved. Radiographs show the presence of calcification of the articular cartilage or chondrocalcinosis in the knee, wrist, pubic symphysis or spine. The diagnosis is made by the detection of CPPD crystals in the joint fluid or radiographic evidence of chondrocalcinosis.

8.3 Osteoarthritis

OA is usually a chronic progressive disorder with little clinical evidence of inflammation and the synovial fluid WBC count is usually $< 2 \times 10^9$/l. Patients may develop acute episodes of pain and swelling in the knee, first carpometacarpal joint, distal interphalangeal joints or first metatarsophalangeal joints.

8.4 Trauma

Acute pain and swelling of a joint such as the knee may be due to overuse during sporting or recreational activities or minor trauma, especially in patients with joint laxity. Trauma to a joint may also lead to internal derangement, haemarthrosis or fracture.

8.5 Avascular necrosis

Avascular necrosis occurs most frequently at the hips, but other sites such as the shoulder, knees and ankles may be involved. The commonest cause is corticosteroid therapy, but other secondary causes must be considered. One of the common causes of hip pain in adult males is avascular necrosis secondary to chronic alcoholism. Patients usually present with severe joint pain with limitation of movement.

8.6 Haemarthrosis

Haemarthrosis may occur with trauma, with haemophilia or deficiency of other clotting factors, or in patients on anticoagulant therapy. A fracture should always be suspected in patients with haemarthrosis if there are fat globules in the synovial fluid.

8.7 Foreign body response

An acute synovitis may follow penetrating injuries from wood fragments, thorns or other foreign materials.

8.8 Monoarticular presentation of systemic diseases

Patients with distinct rheumatic disorders such as RA, SLE and spondyloarthropathies (e.g. Reiter's syndrome, ankylosing spondylitis, psoriatic arthritis) may also present with monoarthritis and they must be considered in the differential diagnosis.

8.9 Miscellaneous

Disorders such as sarcoidosis, amyloidosis, haemochromatosis, leukaemia, lymphoma and carcinoma may also occasionally present with monoarthritis.

9. Clinical assessment of monoarthritis

9.1 History

A history of previous attacks of arthritis will support a diagnosis of gout or a non-infective inflammatory rheumatic disorder. Previous chronic joint pain may suggest the possibility of pre-existing OA.

An acute presentation is usually associated with septic arthritis, gout and trauma. A less acute presentation is usually seen with infections such as TB, OA and inflammatory rheumatic disorders such as psoriatic arthritis and reactive arthritis.

A history of trauma implies that mechanical derangement (torn menisci or ligaments) and fracture need to be considered in the differential diagnosis. A previous penetrating injury suggests a possible foreign body reaction. An infectious cause should be considered in patients with fever, tick bite, sexual risk factors and parenteral drug use. Symptoms such as diarrhoea and urethritis or cervicitis suggest reactive arthritis.

Precipitating events such as recent surgery suggest gout, while corticosteroid use may be associated with infection or avascular necrosis.

The site of involvement may also provide a clue, as the distal interphalangeal joint may be involved with psoriasis or OA, the first metatarsophalangeal joint with gout and the first carpometacarpal joint with OA.

9.2 Physical examination

The history and physical examination will indicate whether the symptoms are caused by pathology within the joint or whether a periarticular structure such as a tendon, ligament or bursa is involved. A variety of periarticular syndromes may mimic monoarthritis and some of the commoner syndromes in the upper and lower limbs are shown in Table I.

The systemic examination may lead to the detection of clinical findings that suggest a particular diagnosis. Some of the systemic features, e.g. involvement of the skin or eyes, and the associated rheumatic diseases are summarised in Table V. HIV infection should be suspected in patients with a history of diarrhoea or weight loss, or if oral thrush or lymphadenopathy are noted on clinical examination.

Table V. Systemic features of monoarthritis

Feature	Disease
Skin	Juvenile idiopathic arthritis, psoriatic arthritis, Reiter's syndrome, sarcoidosis, rheumatic fever, gonococcal infection
Nails	Psoriasis
Nodules	Gout, RA, hyperlipidaemia
Mouth ulcers	SLE, Behcet's syndrome, Reiter's syndrome
Eyes	Reiter's syndrome, ankylosing spondylitis, juvenile idiopathic arthritis
Gastrointestinal	Colitic arthritis, Reiter's syndrome
Heart	Reiter's syndrome, ankylosing spondylitis, infective endocarditis
Respiratory	Tuberculosis, sarcoidosis

9.3 Investigations

If an infection is suspected, initial investigations are aimed at trying to confirm the diagnosis. Blood cultures, urethral and cervical swabs and urine and stool cultures should be taken. Arthrocentesis and detailed synovial fluid analysis should be performed. A wet preparation of synovial fluid should be examined for the presence of crystals. The diagnostic work-up of a patient with monoarthritis or polyarthritis, based on synovial fluid analysis, is shown in Fig. 3.

Haematological and biochemical tests may show leucocytosis, a bleeding tendency or raised serum uric acid. Other tests such as rheumatoid factor, autoantibodies such as antinuclear antibodies and antibodies to extractable nuclear antigen and HLA B27 may be necessary, depending on the clinical picture.

Radiographs of the affected joints may help in the diagnosis of fractures, tumours, and pre-existing chronic diseases such as OA or chondrocalcinosis. The majority of patients with early inflammatory arthritis show no radiological changes except soft-tissue swelling.

A magnetic resonance imaging scan may be of value when the source of the pathology is uncertain as it may localise the pathology to the joint, surrounding tissue or bone. It may also help to identify meniscal tears or ligament damage. It is usually not required initially for the vast majority of patients.

- The initial laboratory investigations will depend on the most likely differential diagnosis based on the age, sex, history and findings on clinical examination.
- The use of groups of tests such as the 'arthritis screen' or 'arthritis panel' is not required in most patients.
- Tests for extractable nuclear antigens (ENA) should not be

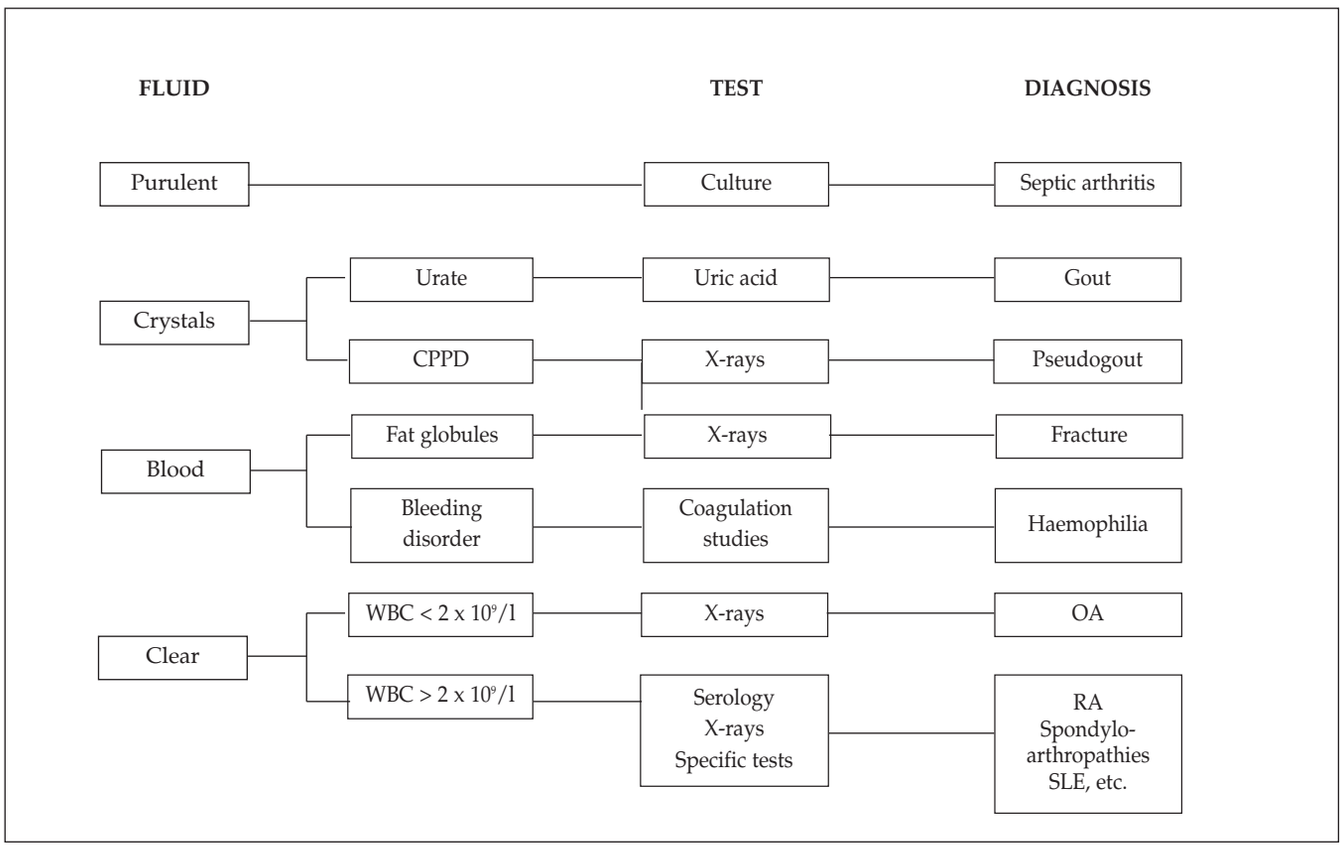

Fig. 3. Role of synovial fluid analysis in the diagnosis work-up of a patient with arthritis.

part of the screening tests for patients with arthritis. They are useful if a connective tissue disease is diagnosed on clinical examination or if the anti-nuclear test if positive.

9.4 Management

Patients with severe acute monoarthritis require hospitalisation if septic arthritis is suspected, significant disability is present, systemic features such as fever are present or the diagnosis is uncertain.

It may be possible to establish a definite diagnosis based on the history, physical examination and laboratory investigations including synovial fluid analysis.

An infectious arthritis will require treatment with appropriate antibiotics and repeated aspiration and drainage may be necessary. If, however, an infection is considered likely but not confirmed on Gram staining, appropriate empiric antibiotic therapy (depending on the suspected organism) should be initiated at the onset while awaiting the results of confirmatory tests. If an infection is still not excluded, synovial biopsy may be necessary to exclude conditions such as TB and gonococcal infection.

Patients with gout, OA or inflammatory synovitis associated with psoriatic arthritis or RA usually respond to non-steroidal anti-inflammatory drugs (NSAIDs). If the response is inadequate, intra-articular corticosteroids are of value.

Traumatic synovitis due to overuse during sports or recreational activities usually responds to rest, NSAIDs, physical treatment and the avoidance of precipitating factors. If the symptoms persist, an arthroscopy will help to exclude conditions such as meniscal injury, internal derangement of the knee or pigmented villonodular synovitis.

Despite the above investigations and management, there will be some patients in whom no definite diagnosis can be established. They may respond to treatment with intra-articular steroids, which may sometimes need to be repeated.

10. Chronic monoarthritis

Some patients who present with acute monoarthritis do not improve with the above management and progress to develop chronic monoarthritis. Others may present for the first time with a history of joint pain for 6 weeks or longer (sometimes even months or years). The common causes of chronic monoarthritis are shown in Table VI.

In some patients the diagnosis can easily be made on history and clinical examination and confirmed by laboratory tests and

Table VI. Causes of chronic monoarthritis

Chronic infection — tuberculosis, fungal, HIV
OA
Spondyloarthropathies such as psoriatic arthritis, ankylosing spondylitis, Reiter's syndrome, inflammatory bowel disease
RA — atypical presentation
Chronic gout or pseudogout
Trauma with internal derangement
Neuropathic joint
Pauciarticular juvenile idiopathic arthritis
Idiopathic

radiographs. Patients with OA involving the knees or first carpometacarpal joints may have swelling, tenderness, crepitus and limitation of movement and the typical radiographic features are noted on X-rays. Radiographs also help to diagnose an unsuspected fracture, avascular necrosis, chondrocalcinosis, a neuropathic joint and the presence of erosive changes suggestive of an inflammatory process due to gout, RA or even a chronic infection such as TB.

If a patient with chronic monoarthritis initially presented with acute monoarthritis, it is still necessary to consider an inadequately treated pyogenic infection or a chronic infection such as TB. The synovial fluid analysis should be repeated and evaluated as above for evidence of an infection and the presence of crystals, and to determine whether the synovial fluid is inflammatory or non-inflammatory.

If the diagnosis is not apparent on history, clinical examination, assessment of radiographs, synovial fluid analysis and simple laboratory tests, further investigations are necessary. An arthroscopy and synovial biopsy for culture and histology are necessary to exclude TB or inadequately treated infection. An arthroscopy will also help to diagnose knee injuries such as a meniscal tear, a foreign body reaction, rarer disorders such as pigmented villonodular synovitis, or even malignant disorders.

A small proportion of patients will remain undiagnosed despite extensive investigations. Some of them may later resolve completely, others may later develop features of inflammatory rheumatic disorders such as RA or a spondyloarthropathy, while the remainder will remain undiagnosed and require long-term monitoring.

The course of monoarthritis has been reported in several studies.[18-21] Blocka and Sibley[21] reported the clinical course of undiagnosed chronic monoarthritis in a series of 38 patients who were seen over a mean period of 24.6 months. A diagnosis became apparent in 12 patients (spondyloarthropathy in 6 and RA in 3, while 1 each had OA, erosive arthropathy and a glomus tumour). Of the remaining 26 undiagnosed patients, 10 resolved completely while the remaining 16 had persistent arthritis.

11. Approach to a patient with polyarthritis

Polyarthritis refers to the presence of inflammation in five or more joints. A likely cause for inflammatory polyarthritis can be suspected on history and clinical examination and confirmed by laboratory tests and radiographic assessment.

Features on history and clinical examination that assist in the differential diagnosis of polyarthritis are the onset, duration, pattern of joint involvement, distribution of the involved joints and the presence of systemic manifestations such as fever, skin rashes and eye involvement.

11.1 Causes of polyarthritis

Some of the common causes of polyarthritis are shown in Table VII.

Table VII. Causes of polyarthritis

Infection
Viral, e.g. hepatitis B, rubella, parvovirus B19, HIV
Bacterial, e.g. gonococcal and non-gonococcal septic arthritis
Inflammatory
RA
SLE, mixed connective tissue disease
Spondyloarthropathies, e.g. psoriatic arthritis, reactive arthritis, ankylosing spondylitis, arthritis associated with inflammatory bowel disease
Juvenile idiopathic arthritis
Crystal-associated arthritis
Polyarticular gout, pyrophosphate arthropathy
Degenerative
Generalised OA
Metabolic and miscellaneous
Hypertrophic pulmonary osteoarthropathy
Leukaemia, lymphoma
Hypothyroidism, haemochromatosis
Sarcoidosis

11.2 Clinical assessment of a patient with polyarthritis

In most patients it is possible to ascertain the likely cause of the polyarthritis based on the history and clinical examination. Information about the onset, duration and pattern of arthritis, the distribution of the joints involved and the presence of systemic features provide useful clues to the possible aetiology in an individual patient. A careful clinical assessment therefore remains the most important part of the diagnostic work-up, and the results of laboratory tests may provide information to support a particular diagnosis.

A comprehensive examination of the musculoskeletal system is also necessary to detect any affected joints. The GALS approach,

i.e. Gait, Arms or upper limbs, Lower limbs and Spine, is recommended to ensure that all the joints are examined.

11.2.1 Onset and duration of polyarthritis

Polyarthritis due to bacterial and viral infection usually has an acute onset. Many of the post-viral arthritis syndromes have a benign course and usually resolve within 6 weeks. The wide spectrum of articular manifestations with HIV infection includes acute and chronic polyarthritis. Bacterial infections usually present with monoarthritis or oligoarthritis, but polyarthritis may occur. It usually resolves within 6 weeks unless there is a delay in diagnosis and institution of appropriate antibiotic therapy.

Acute polyarthritis may be the initial presenting manifestation of many of the well-defined chronic inflammatory rheumatic diseases such as RA, SLE and spondyloarthropathies. In the early stages it is not always possible to establish a definite diagnosis as arthritis may be the only manifestation. Later, systemic manifestations may develop and laboratory tests may become positive, enabling a definite diagnosis to be made.

11.2.2 Pattern of arthritis

The pattern of joint involvement may be additive, migratory or intermittent.[22]

The **additive** pattern of arthritis is typically seen in inflammatory disorders such as RA, SLE and psoriatic arthritis. There is persistent inflammation in the affected joints and the disease spreads to involve other joints.

Intermittent arthritis is usually seen in crystal-associated arthropathies such as gout and pseudogout. The acute attacks of arthritis are episodic — they usually resolve completely and then recur.

In **migratory** arthritis, the affected joints usually subside completely and new joints become involved, e.g. acute rheumatic fever and gonococcal arthritis.

11.2.3 Distribution of involved joints

Involvement of the distal interphalangeal (DIP) joints is characteristic of patients with psoriatic arthritis and OA. Symmetrical involvement of the wrists and small joints of the hands occurs in RA, SLE, psoriatic arthritis and arthritis associated with HIV infection. Involvement of the axial skeleton (including sacroiliac joints and spine) and peripheral arthritis (asymmetrical and especially lower limb involvement) suggests a spondyloarthropathy such as ankylosing spondylitis, reactive arthritis and psoriatic arthritis. Enthesopathies such as Achilles tendinitis, plantar fasciitis and medial and lateral epicondylitis are commonly seen in the spondyloarthropathies.

11.2.4 Systemic features

Fever occurs in patients with SLE, bacterial infections including rheumatic fever and infective endocarditis, and Still's disease. Some of the systemic manifestations and associated disorders are shown in Table V, e.g. skin rashes may occur with psoriatic arthritis, SLE, Reiter's syndrome and sarcoidosis. Involvement of various organ systems such as the heart, lung, kidneys and brain may occur with SLE, RA, Wegener's granulomatosis and HIV infection.

12. Spondyloarthropathies

The spondyloarthropathies are a group of inflammatory joint diseases sharing certain clinical, radiological and genetic features. The characteristic features of the spondyloarthropathies are shown in Table VIII.

Table VIII. Characteristic features of the spondyloarthropathies

Musculoskeletal
Sacroiliitis or spondylitis
Peripheral arthritis — typically asymmetrical and involving the lower limbs
Enthesopathy at axial and peripheral sites
Extra-articular features
Involvement of skin, eyes, heart
Genetic features
Strong association with HLA B27
Aggregation within families
Absence of rheumatoid factor and nodules

An enthesis is the site of attachment of a tendon, ligament or articular capsule to bone. Pathological changes at this site are regarded as enthesopathy, e.g. Achilles tendinitis, plantar fasciitis. Enthesopathy is the pathogenic mechanism that contributes to the radiographic changes seen in the spine and sacroiliac joints. Sacroiliitis and spinal pain are associated with an inflammatory backache, the characteristic features of which are shown in Table IX.

Table IX. Features of an inflammatory backache

Onset below 40 years
Insidious onset
Duration of more than 3 months (episodic)
Associated morning stiffness
Improvement with exercise

The spectrum of diseases included within the spondyloarthropathies is shown in Table X.

The European Seronegative Spondyloarthropathy Group (ESSG) has proposed criteria for the diagnosis of a spondyloarthropathy as shown in Table XI.

Table X. Spectrum of the spondyloarthropathies

Ankylosing spondylitis
Psoriatic arthritis
Reactive arthritis
Arthritis associated with inflammatory bowel disease
Whipple's disease
Behcet's disease
Juvenile spondyloarthropathy
Undifferentiated spondyloarthropathy

The most important feature of a spondyloarthropathy is the presence of inflammatory spinal pain (inflammatory backache) or asymmetrical lower limb arthritis. If either of these is present with any one of the 7 characteristics shown in Table XI, a diagnosis of spondyloarthropathy can be made. If a patient fulfils the criteria for any of the spondyloarthropathies such as ankylosing spondylitis, reactive arthritis/Reiter's syndrome, psoriatic arthritis or arthritis associated with inflammatory bowel disease, they are diagnosed as having one of these well-defined disorders. If a patient does not fulfil the criteria for any of the above diseases, the patient is diagnosed as having an undifferentiated spondyloarthropathy.

A comparison of the characteristics of patients with ankylosing spondylitis and related disorders is shown in Table XII.

13. Diagnosis of a patient with polyarthritis

The diagnosis of a patient with polyarthritis is based on the history and findings on clinical examination and supported by laboratory tests and radiographic examination.

Table XI. Classification criteria for spondyloarthropathies[23]

Inflammatory spinal pain OR Synovitis (asymmetrical or predominantly in lower limbs)
AND
Any one or more of the following:
Positive family history Ankylosing spondylitis, psoriasis, uveitis or reactive arthritis or inflammatory bowel disease in first- or second-degree relatives
Psoriasis Past or present psoriasis diagnosed by a physician
Inflammatory bowel disease Past or present Crohn's disease or ulcerative colitis diagnosed by a physician and confirmed by radiographic examination and endoscopy
Urethritis, cervicitis or acute diarrhoea Occurring within 1 month before arthritis
Alternating buttock pain Past or present pain alternating between the right and left gluteal areas
Enthesopathy Past or present spontaneous pain or tenderness at the insertion of Achilles tendon or plantar fascia
Sacroiliitis Bilateral grade 2 - 4 or unilateral 3 - 4

The investigation of a patient with polyarthritis will depend on the most likely diagnosis based on history and clinical examination.

Table XII. Comparison of ankylosing spondylitis and related disorders

Characteristics	Ankylosing spondylitis	Reactive arthritis	Psoriatic arthropathy	Enteropathic arthropathy
Age at onset	Young adult	Young to middle age adult	Any age	Any age
Sex ratio	Predominantly male	Predominantly male	Equally distributed	Equally distributed
Type of onset	Gradual	Acute	Variable	Gradual
Sacroiliitis	> 95%	20%	20%	10%
Symmetry of sacroiliitis	Symmetrical	Asymmetrical	Asymmetrical	Asymmetrical
Peripheral joint involvement	25%	90%	> 95%	Occasional
HLA-B27 (in caucasians)	> 90%	75%	20% (50% with sacroiliitis)	5% (50% with sacroiliitis)
Eye involvement	25 - 30% (uveitis)	Common (conjunctivitis)	Occasional	Occasional
Cardiac involvement	1 - 4%	5 - 10%	Rare	Rare
Skin or nail involvement	None	Common	Very common	None

The laboratory tests may include the following:

- full blood count
- acute phase reactants – ESR, CRP
- serum uric acid
- urea and creatinine
- liver function tests
- urine microscopy and chemistry
- rheumatoid factor
- antinuclear factor and other auto-antibodies
- synovial fluid analysis
- synovial biopsy in selected patients.

Radiographs may not be of value in the early stages as they only show soft-tissue swelling. Characteristic radiographic findings of the affected joint are seen with established RA, OA, gout and spondyloarthropathies.

The most common causes of polyarthritis with the characteristic articular manifestations, extra-articular manifestations, laboratory findings and radiographic changes are shown in Table XIII.

14. Management of polyarthritis

The management of a patient with polyarthritis will depend on the cause. In some patients a definitive diagnosis is not possible in the early stages of the disease. If an infection has been excluded or is unlikely, the patient will be treated symptomatically with analgesics and non-steroidal anti-inflammatory drugs together with other non-pharmacological measures. If the disease is progressive, specific therapy with urate-lowering drugs, disease-modifying antirheumatic drugs and oral or intra-articular steroids may be necessary, depending on the diagnosis.

Table XIII. Differential diagnosis of chronic polyarthritis

Disease	Joint manifestations	Extra-articular manifestations	Laboratory tests	Radiographic changes
RA	• Symmetrical polyarthritis involving wrists and small joints of the hands and feet • Typical deformities with established disease	• Rheumatoid nodules, cutaneous vasculitis • Involvement of eyes, lungs, heart and peripheral nerves	• Positive RF in 70-80%	• Soft-tissue swelling • Juxta-articular osteoporosis • Marginal erosions
SLE	• Symmetrical polyarthritis similar to RA • Usually non-deforming	• Raynaud's, alopecia, malar rash, mouth ulcers, photosensitivity • Also cardiac, respiratory renal and neuropsychiatric manifestations	• Antinuclear antibodies and DsDNA • Anti-Sm and other autoantibodies • Haemolytic anaemia, leucopenia, lymphopenia, thrombocytopenia, urinary abnormalities	• Soft-tissue swelling • Usually non-erosive
Psoriatic arthritis	• Pattern variable including oligoarticular, polyarticular (resembling RA), DIP, spinal and sacroiliac (similar to AS) and arthritis mutilans	• Skin lesions • Pitting of nails and dystrophic nail changes	• Increase in prevalence of HLA B27	• Sacroiliitis • Syndesmophytes • Erosive arthritis • Enthesopathy
Spondylo-arthropathies	• Asymmetrical lower limb arthritis of larger joints, sacroiliac and spine • Enthesopathy	• Involvement of eyes, skin, heart	• Increased prevalence of HLA B27	• Sacroiliitis • Syndesmophytes • 'Bamboo' spine
Polyarticular gout	• 1st MTP, ankle, mid-foot, knee • Upper limbs less often	• Tophi	• Raised uric acid • Coexistent diseases	• Erosive arthropathy • Tophaceous deposits in bones and joints
Generalised OA	• DIP, PIP, and CMC joints, hip, knee, 1st MTP • Cervical and lumbar spine	• Nil	• Nil	• Joint space narrowing • Osteophytes • Sclerosis of joint margin • Sub-chondral cysts

DIP = distal interphalangeal; AS = ankylosing spondylitis; MTP = metatarsophalangeal; CMC = carpometacarpal; PIP = proximal interphalangeal.

The principles of management, goals of therapy, non-pharmacological measures, drug therapy and surgery are discussed in the guidelines on gout, OA and RA.

15. Disclaimer

This national clinical guideline is for reference and education only and is not intended to be a substitute for the advice of the appropriate health care professional or for independent research and judgement. SAMA relies on the source of the national clinical guideline to provide updates and to notify us if the guideline protocol becomes outdated. SAMA accepts no responsibility or liability arising from any information contained in or any error in or omission from the protocol or from the use of any information contained in it.

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Annexure A: Methodology

This project was initiated by SAMA. On the recommendation of the South African Rheumatism and Arthritis Association (SARAA), Professor G M Mody was mandated with the task of developing the guidelines and invited the following to contribute to the process: R Asherson, D Bouwer, S Brighton, B Cassim, D Gotlieb, A A Kalla, O L Meyers, A Stanwix and M Tikly.

The Approach to Arthritis: Clinical Guideline was drawn up by G M Mody, M Tikly, A A Kalla and O L Meyers.

This project was funded by MSD and Searle in terms of an unrestricted educational grant.

On 3 and 4 December 1999, a nationally representative arthritis consensus meeting was held in Gauteng. Participants were invited as representatives of professional government and consumer groups with an interest in the arthritis field. Each organisation so invited, nominated its own representatives. All participants received a copy of a draft guideline developed previously together with the relevant references before the meeting. A neutral chairperson chaired the meeting. The purpose of the meeting was to consider the content of the draft guideline and to either endorse or amend the document. The proceedings were audio-recorded and transcribed for future reference.

The endorsement document was revised according to the proceedings of the national consensus meeting and was circulated to all participants and many other interested persons.

Amendments to this endorsement draft were made where there was sufficient need as indicated by the comments received. The document as revised was submitted to the SAMA Guideline Committee for endorsement according to the set criteria. Once endorsed, the guideline was sent for publication to the *South African Medical Journal*.

The grants were made in accordance with the SAMA code of sponsorship, which precludes attempts by sponsors to influence, unethically, the content of the guideline. All funds were paid directly into SAMA's accounts and all disbursements were made from that fund.

Annexure B: Consensus Group for Arthritis Guidelines

South African Medical Association: F J Milne (Chairperson); Arthritis Foundation: O L Meyers; Representatives of the Authoring Group (SARAA): A A Kalla, D Gotlieb, G Mody, S Brighton, O L Meyers; DENOSA: G Brown; Department of Health: Directorate Pharmacy (EDL): J Ludick, Directorate Chronic Disease: C Kotzenberg; National Osteoporosis Foundation: C Schnitzler; National Pathology Group: P Cole; Pain Management Society of SA and SAMA Nominee: P Dessein; Radiological Society of SA: P du Plessis; SAMA: Centre for Quality Care: V Pinkney-Atkinson; SAMA Nominee: D Kastanos; SA Academy of Family Practice: S Namane; SA Association of Occupational Therapists: T Pistorius; SA Orthopaedic Association: N J G Maritz; SA Society of Physiotherapy: H Gardener; Society for General and Family Practitioners: J Fourie; **Observer delegates:** MSD: M Combrink, B Crouse, S Nkalashe, B Prinsloo; Searle: M Doveton, G Hirsch, G Muir, L Wiggil; Medscheme: H Seftel.

Hyperuricaemia and Gout: Clinical Guideline 2003

Principal authors: O L Meyers, B Cassim, G M Mody

Summarised Guideline

1. Definition

1.1 Hyperuricaemia

Hyperuricaemia is physicochemically defined as the concentration of urate in the plasma that exceeds the solubility limits of monosodium urate of 0.415 mmol/l. In epidemiological studies, hyperuricaemia is defined as a level of uric acid above the mean ± 2 standard deviations of a healthy population (> 0.42 mmol/l).

1.2 Gout

Gout is a clinical syndrome that results from the deposition of monosodium monohydrate crystals. Their shedding into the joint leads to recurrent arthritis and their accumulation in cartilage, tendons, bursae and bones leads to the formation of tophi.

2. Uric acid metabolism

The amount of urate in the body is the net result of the amount produced and the amount excreted. Uric acid is the metabolic end product of endogenous and ingested purine metabolism. Uric acid excretion occurs via the kidneys (approximately two-thirds) and the bowel (approximately one-third). In the kidney, four processes are involved: glomerular filtration, presecretory reabsorption, secretion and post-secretory reabsorption. Ten per cent of the filtered urate is excreted.

3. Epidemiology

- Serum urate levels vary with age and gender. Children have serum urate concentrations well below adult levels. The levels begin to rise during puberty to reach adult levels. In women the levels continue to remain low until the menopause, when they rise and approximate the levels in men.
- The peak age of onset of gout is 40 - 50 years. Gout is rare before 30 years in men, in premenopausal women and in children.
- The distribution of gout is worldwide. In South Africa, surveys have shown higher urate levels in urban Tswana compared with rural Tswana. Previously gout was uncommon in South African blacks, but it is now commonly seen in clinical practice.

Please forward all comments to: **Private Practice Unit, South African Medical Association, PO Box 74789, Lynwood Ridge, 0040 (tel. (012) 481-2073)**

4. Causes of hyperuricaemia

Hyperuricaemia can be classified as genetic or acquired, and further subdivided as being due to overproduction or under-excretion of uric acid.

5. Clinical syndromes

5.1 Gout

5.1.1 Acute gout

- A precipitating factor such as trauma, infection, rapid weight loss, surgery, excessive purine-rich food intake or alcohol may be found.
- Of first attacks 80% are monoarticular, affecting the lower limb joints, usually the first metatarsophalangeal (MTP) joint, tarsus, ankle or knee. The first MTP joint is involved in about 50% of first attacks and it will be involved at some stage in > 90% of patients with gout.
- In the elderly woman, who is frequently on diuretics and has mild renal insufficiency, the initial attack is often polyarticular.
- Complete resolution of the initial attack usually occurs within 5 – 7 days, even if untreated.

5.1.2 Intercritical or interval gout

Once the acute attack has resolved the patient enters this phase and at this stage the causes for hyperuricaemia should be looked for and eliminated if possible.

5.1.3 Chronic tophaceous gout

Patients in whom gout is undiagnosed, untreated or poorly treated will eventually develop tophaceous gout, which is characterised clinically and radiologically by the deposition of urate in the joints, tendons, bursae, cartilage and bone.

5.2 Renal disease

The renal problems associated with hyperuricaemia are nephrolithiasis, chronic urate nephropathy and acute uric nephropathy.

Nephrolithiasis may precede the onset of gout or occur in patients who have never had gout. The risk for nephrolithiasis is positively correlated with the level of the serum urate and increased uricsuria. Urate nephropathy is a late manifestation

of gout and is a rare cause of renal insufficiency.

Acute uric acid nephropathy (the tumor lysis syndrome) is due to massive uric acid overproduction and increased urinary uric acid excretion following tumour lysis by cytotoxics or radiotherapy. It can be prevented by adequate hydration, use of diuretics and prophylactic allopurinol therapy in high-risk patients.

6. Investigations

The investigation of gout involves the measurement of the serum uric acid (which may be normal during the acute attack), analysis of synovial fluid or tophaceous material (where possible), and measurement of the 24-hour urinary uric acid excretion. The renal function should be assessed and patients should be screened for dyslipidaemia and diabetes mellitus. X-rays of the hands and the feet may show tophaceous deposits in the soft tissues, joints and bones.

Diagnosis

The definitive diagnosis is made by the demonstration of monosodium urate crystals in synovial fluid or in a suspected tophus.

7. Management of hyperuricaemia and gout

7.1 Asymptomatic hyperuricaemia

Only a small number of patients with hyperuricaemia will develop gout. A search for the cause of hyperuricaemia should be instituted and corrected where possible.

7.2 Treatment of the acute attack

The therapeutic options for the prompt and safe termination of the acute attack are colchicine, non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. **Urate lowering therapy should not be started during the acute attack of gout because it can prolong or worsen the acute attack**. The therapeutic agents used to treat the acute attack will not lower the serum urate or influence the long-term course of the disease.

7.2.1 Non-steroidal anti-inflammatory drugs (NSAIDs)

The NSAIDs are now the treatment of choice for acute gout. Their use is limited by their side-effects, especially renal and gastrointestinal.

7.2.2 Colchicine

Colchicine is effective and is given in a dose of 1 mg immediately followed by 0.5 mg 2-hourly to a maximum of 6 mg or until side-effects such as abdominal cramps or diarrhoea occur or the acute attack has settled. Colchicine is most effective if it is started within 24 hours of the onset of the acute attack.

7.2.3 Corticosteroids

Corticosteroids are very effective in treating the acute attack and they are especially useful when NSAIDs are contraindicated. They can be given parenterally or orally.

7.3 Correction of hyperuricaemia and long-term management

Once the acute attack has settled, it is necessary to identify any of the possible causes of hyperuricaemia and try to modify or correct them. These factors include gradual weight reduction, dietary modification, reducing or stopping diuretics if possible, avoiding low-dose salicylates if possible, and reducing or stopping the intake of alcohol.

7.3.1 Prophylactic therapy

Patients who need urate lowering drugs should receive prophylactic colchicine or NSAIDs until the urate levels are reduced. Colchicine is used in a dose of 0.5 – 1.0 mg daily and NSAIDs may be used at standard doses. The dosage will need to be reduced in the presence of concomitant diseases.

7.3.2 Reduction of hyperuricaemia in gout

Despite modification of lifestyle, weight reduction and correction of risk factors, many patients will require urate lowering agents.

The indications for urate lowering therapy are:

- persistently raised uric acid levels
- more than two attacks of gout
- the presence of tophi
- a willingness to continue lifelong therapy.

Before starting urate lowering therapy, prophylactic therapy should be given to prevent acute flares while the urate levels are being reduced. The therapeutic options to reduce the uric acid are the uricosuric drugs, which promote urate renal clearance, and allopurinol, a xanthine oxidase inhibitor, which inhibits the production of uric acid.

7.3.2.1 Uricosuric drugs

The uricosuric drugs are probenecid and sulphinpyrazone. Their greatest risk is nephrolithiasis, which can be prevented by maintaining a high urine volume and alkalinising the urine (sodium bicarbonate 1 g 3 - 4 times daily or Citro-Soda 10 ml 3 times daily). These drugs are indicated in the following circumstances:

- low or normal urinary uric acid excretion
- creatinine clearance over 80 ml/min
- no history of nephrolithiasis
- age under 60 years
- do not require low-dose salicylate for vascular disease.

Benzamarone is a potent uricosuric and is given in a daily dose of 50 – 100 mg daily. **It has recently been withdrawn from the South African market due to reports of serious hepatotoxicity.** The starting dose of probenecid is 250 mg twice daily. Control of hyperuricaemia with probenecid is

achieved in 60 - 80% of patients with 1 - 2 g daily. Sulphinpyrazone is administered in a dose of 50 mg twice daily and the dose may be increased to 200 - 400 mg daily.

7.3.2.2 Allopurinol

Allopurinol and its metabolite, oxypurinol, are competitive inhibitors of xanthine oxidase. The specific indications for allopurinol therapy are:

- tophaceous gout
- increased excretion of uric acid (over-producers)
- renal insufficiency
- nephrolithiasis
- where uricosuric agents are either ineffective or there is hypersensitivity
- patients over the age of 60 years
- prophylaxis for the tumour lysis syndrome.

The starting dose is 50 - 100 mg daily, which can be increased to a usual maintenance dose of 300 mg daily. In renal insufficiency, dose reduction will be necessary. Allopurinol is generally well tolerated and the most frequent adverse effect is a maculopapular erythematous rash (rarely toxic epidermal necrolysis), and rarely the allopurinol hypersensitivity syndrome. Serious drug interactions may occur with azathioprine and mercaptopurine.

8. Referral of patients

Special therapeutic situations, which often require referral to a rheumatologist, include:

- the patient with chronic renal insufficiency
- allopurinol hypersensitivity
- the patient with tophaceous gout
- gout in a transplant patient
- diagnostic uncertainty
- refractory gout (where more than 300 mg of allopurinol is needed or the patient fails to respond to therapy).

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Full Guideline

1. Objective and scope

These guidelines have been developed to:

- provide an understanding of gout
- promote the cost-effective management of gout by doctors and other health care providers.

2. Abbreviations

ACTH = adrenocorticotrophic hormone; ATP = adenosine triphosphate; ESR = erythrocyte sedimentation rate; FBC = full blood count; GFR = glomerular filtration rate; MTP = metatarsophalangeal; NSAID = non-steroidal anti-inflammatory drug.

3. Introduction

Gout has been recorded since antiquity and the clinical presentation described by Hippocrates is still applicable today. The development of effective therapy has made it possible to control the disease, thus reducing the morbidity and preventing disability. Unfortunately, the delay in diagnosis and institution of appropriate therapy results in unnecessary suffering for many patients.

4. Definition

4.1 Hyperuricaemia

Definition: a plasma (serum) concentration > 0.42 mmol/l.

The definition is based on physicochemical, epidemiological and disease-related criteria. Physicochemically, it is defined as the concentration of urate in the plasma that exceeds the solubility limits of monosodium urate of 0.415 mmol/l. In epidemiological studies hyperuricaemia is defined as a level above the mean ± 2 standard deviations of a healthy randomly selected caucasian population (95% will have serum urate concentrations < 0.42 mmol/l).[1]

The consequences of hyperuricaemia are:

- Attacks of acute arthritis (gout).
- Accumulations of uric acid crystals to form tophi.
- Uric acid nephrolithiasis and nephropathy.

The risk of these complications increases with increasing serum urate concentrations > 0.42 mmol/l.[2]

4.2 Gout

Gout is a clinical syndrome that results from the deposition of

monosodium monohydrate crystals. Their shedding into the joint leads to recurrent arthritis and their accumulation in cartilage, tendons, bursae and bones leads to the tophi.

5. Uric acid metabolism

The amount of urate in the body is the net result of the amount produced and the amount excreted. The uric acid pool of a normal adult man is about 7.2 mmol, which is double that of a woman, in the steady state. There is an approximately 60% daily turnover.

5.1 Uric acid production

Uric acid is the metabolic end-product of endogenous/ ingested purine metabolism.

The purine nucleotides (guanylic, adenylic and inosinic acid) are degraded by the enzyme xanthine oxidase to uric acid which circulates as the urate anion. Normal humans have urate concentrations close to the theoretical limit of solubility and regularly excrete urine supersaturated with respect to uric acid.

5.2 Uric acid excretion

- Human cells lack the enzyme uricase and cannot metabolise uric acid to the more water soluble allantoin. Homeostasis is therefore dependent upon elimination through the gut and the kidneys.[1]
- Urate entry into the bowel is a passive process dependent upon the serum urate concentration. Complete uricolysis depends upon intestinal micro-organisms. About one-third is eliminated by the bowel.
- Urinary excretion accounts for two-thirds of the daily excretion. Four processes are involved: glomerular filtration, presecretory reabsorption, secretion and post-secretory reabsorption. Ten per cent of filtered urate is excreted.[3]
- Diabetic ketoacidosis, starvation, alcohol intoxication, lactic acidosis and salicylate intoxication are accompanied by the accumulation of organic acids that compete with urate for tubular secretion and cause hyperuricaemia.[3]
- Low-dose salicylate and pyrazinamide also inhibit tubular secretion of urate.[3]
- Diuretics cause hyperuricaemia by volume depletion and increasing urate reabsorption.[4]

6. Epidemiology

- Serum urate levels vary with age and gender. Children have serum urate concentrations well below adult levels. Levels begin to rise during puberty to reach adult levels. In women, levels continue to remain low until the menopause, after which they rise and approximate the levels in men.[5]
- Gout is the most common form of inflammatory joint disease in men.[6]
- The peak age of onset is 40 - 50 years.
- Gout is rare before 30 years in men, in premenopausal women and in children.
- The distribution is worldwide (regional variations are environmentally and genetically determined). The incidence of gout is 2.6 - 2.7/1 000 in the USA and the UK.[3,7]
- In South Africa surveys have shown higher urate levels in urban Tswana[8] compared with rural Tswana.[9] Previously gout was uncommon in South African blacks, but it is now frequently seen in clinical practice.[10] Secondary or acquired gout is commoner in South African black men than in Caucasians in the UK, in whom primary gout is more common.[11]

7. Causes of hyperuricaemia (Table I)

Hyperuricaemia can be classified as genetic or acquired and further subdivided as overproduction or under-excretion of uric acid.

8. Clinical syndromes

The three classic stages in the natural history of progressive urate deposition disease are acute gouty arthritis, interval or intercritical gout and chronic tophaceous gout.

8.1 Gout

8.1.1 Acute gout

A precipitating factor(s) such as trauma, infection, rapid weight loss, surgery, excessive purine-rich food intake or alcohol may

Table I. Causes of hyperuricaemia

Genetic (primary)	Overproduction (20%)	
	Reduced excretion (80%)	
Acquired (secondary)	Overproduction	
	Nutritional	High-purine foods
	Haemopoietic	Haematological malignancies
		Haemolytic anaemia
	Systemic disease	Psoriasis
	Drugs	Cytotoxic agents
	Under-excretion	
	Dietary	Alcohol
	Renovascular	Any renal disease
		Hypertension
	Drugs	Diuretics, pyrazinamide, ethambutol, cyclosporin, levodopa, low-dose salicylate
	Metabolic	Lactic acidosis, diabetic ketoacidosis

be found.[1] The acute attack is often a dramatic event with the following features:

- An intense inflammatory reaction characterised by severe pain, swelling, redness, warmth and disability reaching maximal severity within 12 - 48 hours.[12]
- Of first attacks 80% are mono-articular, affecting the lower limb joints, usually the first metatarsophalangeal (MTP) joint, the tarsus, ankle or knee.[13] In 50% of first attacks the first MTP joint is involved, and it will be involved in > 90% of patients with gout at some time.
- In the elderly woman, who is frequently on diuretics and has mild renal insufficiency, the initial attack is frequently polyarticular.[14,15]
- Polyarticular gout is usually seen after years of gout and in the tophaceous phase.[16] The initial presentation in black men is frequently polyarticular.[11]
- Signs of inflammation often extend beyond the affected joint to other joints and into the surrounding tissues which may give the impression of a polyarthritis or cellulitis. The inflammatory reaction may start in the connective tissues as a true aseptic cellulitis. Less intense 'petite attacks' may occur.
- **THE SERUM URATE LEVEL MAY BE NORMAL DURING THE ACUTE ATTACK.**[17]
- The signs of acute inflammation are accompanied by a fever, an elevated leucocyte count and a high erythrocyte sedimentation rate (ESR) which mimics a microbial infection of the joint or the connective tissue diseases.[18]
- Complete resolution of the initial attack usually occurs within 5 - 7 days even if untreated. Later in the course of the disease the attacks last longer and they are often less painful.[19]

8.1.2 Intercritical or interval gout

Once the acute attack has resolved the patient enters this phase, which is characterised by the following:[3]

- Hyperuricaemia. It is during this stage that causes for hyperuricaemia should be looked for and eliminated if possible.
- Intermittent acute attacks.
- Most untreated patients will have a second attack within 2 years. Attacks will gradually merge into a chronic polyarticular disease with tophi.

8.1.3 Chronic tophaceous gout

Patients in whom gout is undiagnosed, untreated or poorly treated will eventually develop tophaceous gout, which is characterised clinically and radiologically by the deposition of urate in the joints, tendons, bursae, cartilage and bone.

- The interval between the first attack and the first appearance of small tophi is about 10 years.[20]
- Accelerated tophus development occurs in poorly compliant men, elderly women on diuretics and organ transplantation recipients who are treated with cyclosporin[21] and who are often also taking diuretics.
- Tophi may be the presenting manifestation without preceding acute arthritis or the intercritical phase.
- Tophi in bones and joints may contribute to joint damage.
- Tophi are generally not painful, but they may become inflamed and ulcerate, discharging large amounts of chalky urate which resembles pus. The ulcers take a long time to heal.

8.2 Renal disease

The renal problems associated with hyperuricaemia are nephrolithiasis, chronic urate nephropathy and acute uric acid nephropathy.[3]

8.2.1 Nephrolithiasis

- Nephrolithiasis may precede the onset of gout or it may occur in patients who have never had gout.[3]
- The risk for nephrolithiasis is positively correlated with the level of the serum urate and increased uricosuria.
- Mixed, calcium oxalate or calcium phosphate stones may also occur.
- The factors that favour urate stone formation are the renal load of uric acid, dehydration with a reduced urine volume, and a low urinary pH. An acid urine encourages the formation of insoluble uric acid.[3]

8.2.2 Chronic urate nephropathy

- Urate nephropathy is a late manifestation of gout and it is a rare cause of renal insufficiency.[22]
- The nephropathy is characterised by deposits of uric acid crystals surrounded by giant cells in the medullary interstitium. It is either clinically silent or produces mild proteinuria, hypertension and rarely renal insufficiency.[22]
- Renal insufficiency in gout is common, but it is generally due to the co-morbid conditions such as hypertension, urinary infection and vascular disease.

8.2.3 Acute uric acid nephropathy (the tumour lysis syndrome)

- This is due to massive uric acid overproduction and increased urinary uric acid excretion following tumour lysis by cytotoxics or radiotherapy, or occurs during the 'blastic phase' of leukaemia or lymphoma before treatment.[23] It may also occur following prolonged seizures or vigorous exercise with heat stress. Uric acid is precipitated in the renal tubules.

- There is acute oliguric renal insufficiency and the diagnosis is supported by the finding of a uric acid/creatinine ratio of > 1 in a random urine specimen, hypocalcaemia and hyperphosphataemia and hypertension.[3]
- The management is to anticipate its development and to ensure adequate intravenous hydration and use of diuretics. The prior use of allopurinol is prophylactic. The urine should be kept alkaline. Haemodialysis may be required.

8.2.4 Associated conditions

Some medical conditions are associated with gout because they cause hyperuricaemia but the association is not only because of hyperuricaemia.

- There is a strong association of obesity with hyperuricaemia either because of dietary excess or because it reduces urate excretion.[24]
- Hypertension is associated with hyperuricaemia in four ways:[3]
  - Hypertension reduces the renal clearance of urate.
  - The renal damage by interstitial microtophi may lead to secondary renovascular hypertension.
  - Excessive alcohol consumption may cause both hypertension and hyperuricaemia.
  - Diuretics used to treat hypertension reduce urate clearance.
- Hypertriglyceridaemia is frequently associated with gout. The mechanism is not known.[25]
- The association of gout with vascular disease is probably dependent upon hypertension, obesity, platelet adhesiveness and dyslipidaemia.[26]
- An association with diabetes mellitus has been suggested but the mechanism is not clear.[27]

9. Investigations

- Serum uric acid is measured colorimetrically or enzymatically. There is great inter-laboratory variation. The serum uric acid may be normal during an acute attack of gout and it is not essential for the diagnosis of acute gout.[12]
- Examination of synovial fluid or material from a suspected tophus for the crystals of monosodium urate provides the definitive diagnosis of gout. The fluid should be examined microscopically and examined under polarised light to demonstrate the negative birefringent crystals.[28] A Gram stain should be done if an infection is suspected. If the diagnosis is still uncertain, a biopsy may be useful to make the diagnosis.
- Twenty-four-hour urinary urate excretion is used to identify those subjects who have hyperuricosuria or those who are underexcretors of uric acid.[29] It is theoretically a good way to determine whether allopurinol or uricosuric drugs should be used, but it is not often used in practice. If a uricosuric drug is to be used this measurement should be done before starting such therapy.
- Renal function should be assessed by measuring the serum creatinine/blood urea. If these results are elevated a formal creatinine clearance should be performed because the result will determine the treatment options.
- Screening for dyslipidaemia and diabetes mellitus should be done. A full blood count (FBC) will provide information about haemopoietic diseases. Rarer causes of hyperuricaemia can be screened for according to the clinical information.
- X-rays of the hands and the feet will provide evidence of tophaceous deposits in the soft tissues, joints and bones. Soft-tissue swelling may be the only abnormality in the early stage of the disease. X-rays are only indicated at this stage to exclude other causes such as a fracture if the clinical picture is not typical. Eccentric soft-tissue swelling/densities which may calcify may be detected in chronic gout. Bone erosions with overhanging and well-defined edges may occur in the joint or in the para-articular region.[30]

10. Diagnosis

The only definitive diagnosis is the demonstration of monosodium urate crystals in synovial fluid or the synovial fluid phagocytes or the demonstration of these crystals in a suspected tophus. If a tissue biopsy is required the tissue must be sent to the laboratory in alcohol.[28]

Where this is not possible the typical clinical manifestations such as the rapidity of the onset and the evolution and the redness of the skin overlying the affected joint may be used to make the diagnosis. This will always remain presumptive.[4]

11. Management of hyperuricaemia and gout

11.1 Asymptomatic hyperuricaemia

Asymptomatic hyperuricaemia is frequently seen because of the use of multiphasic screening programmes in hospitals and clinics. There is no reason to treat asymptomatic hyperuricaemia because:

- Only a small number of such subjects will develop gout whatever the level.
- The risk of nephrolithiasis is low.[22]
- No significant renal insufficiency can be attributed to the hyperuricaemia alone.[22]

- The only need for intervention is where the tumour lysis syndrome may be anticipated.
- A search for the cause of hyperuricaemia should be instituted. Obesity, dyslipidaemia, diabetes mellitus, hypertension and vascular disease are co-morbid conditions which contribute to hyperuricaemia, or are associated with it.
- Hyperuricaemic individuals should be reviewed serially and treated for specific indications, e.g. gout, tophi, etc.

11.2 Treatment of the acute attack

The algorithm for the management of acute gout is shown in Fig. I.

The therapeutic options for the prompt and safe termination of the acute attack are colchicine, the non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids.

URATE LOWERING THERAPY SHOULD NOT BE STARTED DURING THE ACUTE ATTACK OF GOUT BECAUSE IT CAN PROLONG OR WORSEN THE ACUTE ATTACK.

THE THERAPEUTIC AGENTS USED TO TREAT THE ACUTE ATTACK WILL NOT LOWER THE SERUM URATE, NOR WILL THEY INFLUENCE THE COURSE OF THE DISEASE.

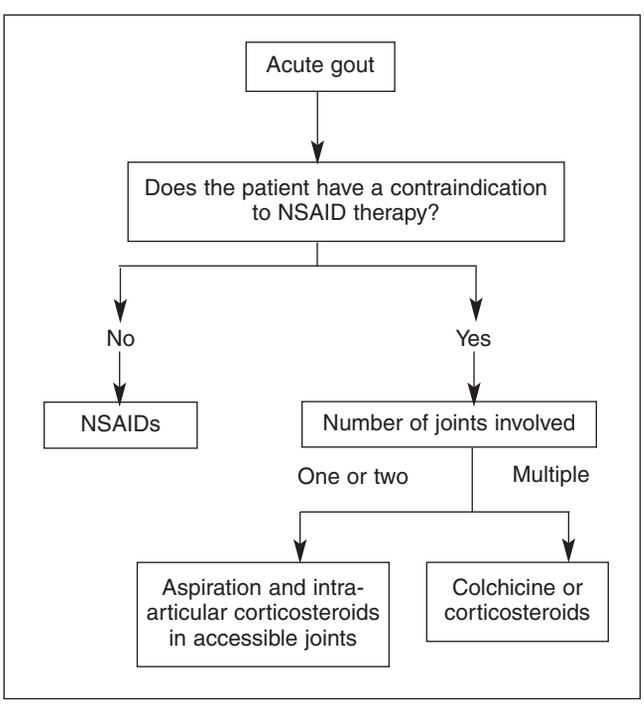

Fig. 1. Approach to the management of acute gout.

11.2.1 NSAIDs

- The NSAIDs are now the treatment of choice for acute gout unless there are contraindications to their use.[31]
- Most of the currently available NSAIDs may be used.
- Maximum doses must be started and continued for 24 hours after complete resolution, whereafter the dose is tapered. Intramuscular NSAIDs may also be used.
- NSAID use is limited by their side-effects, especially renal and gastrointestinal. Factors associated with an increased risk of side-effects are:[32,33]
  - age ≥ 65 years
  - a history of a previous peptic ulcer
  - impaired renal function
  - poorly compensated heart failure
  - hepatic dysfunction
  - concomitant use of anticoagulant therapy.

If there are contraindications to their use, colchicine or corticosteroids may used.

11.2.2 Colchicine

Colchicine is effective in about two-thirds of patients. It is given in doses of 1 mg immediately followed by 0.5 mg 2-hourly to a maximum of 6 mg or until side-effects occur. It is most effective if it is started within 24 hours of the onset of the acute attack.[34] Intravenous use is not recommended.[35] About 80% will develop side-effects (nausea, vomiting, diarrhoea and abdominal pain) before clinical improvement occurs. A narrow benefit-toxicity ratio limits its use.[36]

11.2.3 Corticosteroids

Corticosteroids are very effective in treating the acute attack and are especially useful when NSAIDs are contraindicated. They can be given parenterally or orally.[36,37]

- **Parenteral corticosteroids**. They may be given intramuscularly or intra-articularly unless an infection is suspected. Intra-articular steroids (methylprednisolone, betamethasone) are used when the affected joint(s) is accessible.[38] The intramuscular route is useful in the post-operative situation. Intravenous use is rarely required.
- **Oral corticosteroids.** Oral administration may be used for patients with polyarticular gout or those in whom NSAIDs are contraindicated or ineffective.[36] A dose of prednisone (0.5 mg/kg daily) is given for the first 48 hours; thereafter the dose is reduced by 5 mg daily. Prophylactic colchicine (0.5 - 1.0 mg daily) started before the steroid course ends will prevent a flare. Adrenocorticotrophic hormone (ACTH) is an expensive drug which has also been used.[37]

11.3 Correction of hyperuricaemia and long-term management

Once the acute attack has settled it is necessary to identify any possible causes of hyperuricaemia and try to modify or correct them. These factors include gradual weight reduction, dietary modification, reducing or stopping diuretics if possible, avoiding low-dose salicylate if possible, and reducing or stopping the intake of alcohol.[31]

11.3.1 General measures

11.3.1.1 Patient education

Non-compliance is one of the major factors leading to failure of therapy. It is the responsibility of the doctor to inform the patient fully about the nature of the disease. An important distinction must be drawn between the treatment of the acute attack and the long-term treatment of the hyperuricaemia. The patient must understand that treating the acute attack will not prevent recurrences or the long-term complications.

11.3.1.2 Diet (Table II)

The purine content of the diet may contribute only about 0.06 mmol to the serum urate concentration. The diet should be modified to contain moderate amounts of purines. Caloric restriction is more important than purine restriction.

Excess fructose leads to increased degradation of adenosine triphosphate (ATP) to uric acid.[39]

Table II. Purine content of food and beverages

High (best to avoid)
Liver, kidney, anchovies, sardines, herring, mussels, bacon, codfish, scallops, trout, haddock, veal, venison, turkey, alcoholic beverages
Moderate (may eat occasionally)
Asparagus, beef, bouillon, chicken, crab, duck, ham, kidney beans, lentils, lima beans, mushrooms, lobster, oysters, pork, shrimp, spinach

11.3.1.3 Obesity

Obesity is associated with increased production and decreased excretion of uric acid.[24] Weight reduction should be gradual because starvation may cause ketosis which decreases urate clearance.[3] Reduction of weight may be sufficient to return the uric acid levels to normal.

11.3.1.4 Alcohol

Alcohol ingestion increases the production of uric acid and decreases its clearance. Some alcoholic beverages, particularly beer, contain large amounts of purines.[40] Patients should be advised to stop or reduce their alcohol intake, depending upon the severity of the hyperuricaemia.

11.3.1.5 Modification of drug therapy

Thiazide and the loop diuretics lead to a contraction of the plasma volume and reduce the excretion of uric acid.[4] Low-dose salicylate, tuberculostatic drugs such as pyrazinamide and ethambutol, and niacin decrease uric acid excretion.[3]

These drugs may need to be withdrawn or the dose modified. In severe congestive cardiac failure where it is impossible to stop the diuretics, allopurinol is used to treat the hyperuricaemia.

11.3.2 Prophylactic therapy

In those patients who will need urate lowering drugs, prophylactic colchicine or NSAIDs should be started and continued while the urate levels are reduced. The prophylaxis should be continued until the serum urate is normal and the patient has not had any attacks for 1 - 3 months.[3]

Colchicine is used in a dose of 0.5 - 1.0 mg daily.[41] Patients with renal insufficiency or patients on long-term therapy may develop a colchicine-induced neuromyopathy.[42] The dose of colchicine will need to be adjusted in renal insufficiency. If not contraindicated, a NSAID may be used at standard doses for prophylaxis.[43]

11.3.3 Reduction of hyperuricaemia in gout

The algorithm for the management of hyperuricaemia and gout is shown in Fig. 2.

The urate levels should be serially monitored after life style modification, weight reduction and elimination of risk factors where possible. If the uric acid is still elevated despite the

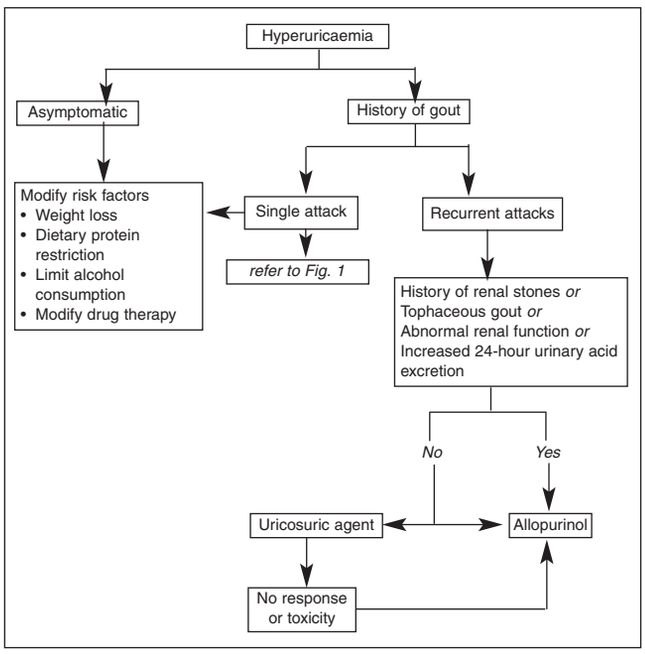

Fig. 2. Approach to the management of hyperuricaemia and gout.

above measures, patients will require urate lowering agents to control their hyperuricaemia. **These drugs must not be used until all the signs of inflammation have cleared.**

The indications for urate lowering therapy are:[20]

- Persistently raised uric acid levels
- More than two attacks of gout
- The presence of tophi
- A willingness to continue lifelong therapy.

The extra-cellular fluid is saturated with urate at a concentration of 0.415 mmol/l. Reducing the urate levels below 0.415 mmol/l will lead to dissolution of the crystals and a reduction of the urate pool. The aim of therapy is to reduce the serum urate to less than 0.30 mmol/l,[20] particularly in tophaceous gout.

Before starting this therapy the patient should be given prophylactic therapy to prevent acute flares while the urate levels are being reduced.[31]

The therapeutic options are the uricosuric drugs, which promote urate renal clearance, and allopurinol, a xanthine oxidase inhibitor, which reduces the production of uric acid.

11.3.3.1 Uricosuric drugs

The uricosuric drugs are benzbromarone, probenecid and sulphinpyrazone.

Their greatest risk is nephrolithiasis. This can be prevented by maintaining a high urine volume and alkalinising the urine (sodium bicarbonate 1 g 3 - 4 times daily or Citrosoda 10 ml 3 times daily).

These drugs are indicated for patients who:[13]

- are excreting less than or normal amounts of uric acid
- have a creatinine clearance over 80 ml/min
- have no history of nephrolithiasis
- are under the age of 60 years
- do not require low-dose salicylate for vascular disease.

Probenecid. The starting dose is 250 mg twice daily. Control of hyperuricaemia is achieved in 60 - 80% of patients taking 1 - 2 g daily respectively. It is well tolerated, with a few adverse effects such as gastrointestinal complaints, hypersensitivity and skin rashes.[3]

Sulphinpyrazone. The starting dose is 50 mg twice daily increasing to 200 - 400 mg daily. Adverse effects are gastrointestinal complaints, and rarely bone marrow suppression.[3]

Benzbromarone. Recent reports of serious hepatotoxicity have led to its withdrawal from the market in South Africa. It is still available in a fixed drug combination with allopurinol. There are no scientific data on its safety in this combination.

11.3.3.2 Allopurinol

Allopurinol and its metabolite oxypurinol is a competitive inhibitor of xanthine oxidase. The long half-life of oxypurinol allows for a single daily dose.

The specific indications for allopurinol therapy are:

- tophaceous gout
- increased excretion of uric acid (over-producers)
- renal insufficiency
- nephrolithiasis
- where uricosuric agents are either ineffective or there is hypersensitivity
- patients over the age of 60 years
- for the prophylaxis of the tumour lysis syndrome.

The starting dose is 50 - 100 mg daily which can be increased to a usual maintenance dose of 300 mg daily. Occasionally larger doses are necessary.[31]

It is effective in renal insufficiency but dose adjustments will be necessary, e.g. the maximum dose is 100 mg every 2 - 3 days when the creatinine clearance is 10 ml/min, 100 mg daily where the clearance is 30 ml/min, and 200 mg daily where the clearance is 60 ml/min.[45]

Allopurinol is generally well tolerated and the most frequent adverse effect is a maculopapular erythematous rash (rarely a toxic epidermal necrolysis). The most serious adverse effect is the allopurinol hypersensitivity syndrome, which is characterised by fever, vasculitis, eosinophilia, bone marrow suppression, hepatic dysfunction and interstitial nephritis.[46] This is a very serious illness with a mortality of 25%. It often occurs in patients who are taking thiazide diuretics and who have mild renal insufficiency.[47]

There are a few potentially serious drug interactions, notably with concomitant azathioprine and mercaptopurine which depend upon xanthine oxidase for their inactivation.[48,49] Dangerous levels of these drugs may be reached. This is important in the transplant patient. Allopurinol is contraindicated under such therapeutic circumstances.

The concomitant use of ampicillin and allopurinol causes skin rashes in 20% of patients. Patients who are generally well controlled on stable doses of allopurinol should not stop their therapy during the occasional acute attack of gout.

11.4 Special therapeutic situations

- **The patient with chronic renal insufficiency (consult a rheumatologist and/or a nephrologist).** Gout is rare in renal insufficiency, but patients with gout may develop impaired renal function due to co-morbid diseases. Acute attacks of gout are best treated with corticosteroids, orally or parenterally. Urate lowering is best achieved with allopurinol with dose adjustments.

- **Allopurinol hypersensitivity (consult a rheumatologist).** Desensitisation schemes are available but they are not always successful.[43]
- **The patient with tophaceous gout (consult a rheumatologist/orthopaedic surgeon/plastic surgeon).** Tophaceous gout will often respond to allopurinol and where appropriate to a combination of allopurinol and a uricosuric drug. With adequate treatment tophi will resorb provided they are not calcified. Surgical clearance will help to reduce the urate pool and facilitate treatment. Wound healing is a problem.
- **Gout in a transplant patient (consult a rheumatologist).** Many of these patients have renal insufficiency. The causes are multifactorial and include the use of cyclosporin.[21] The use of NSAIDs is contraindicated and the best treatment for acute attacks is corticosteroid, orally or parenterally. Urate lowering is a problem because there are several constraints: patients with GFR below 50 ml/min will not respond to the uricosuric drugs. Allopurinol may potentiate the action of azathioprine.[48] Allopurinol is either contraindicated or the dose of azathioprine may require a 50 - 70% reduction with frequent monitoring of the white cell count. The therapeutic margin between leucopenia and adequate immunosuppression is dangerously low.
- **Other problems best referred to a rheumatologist include:**
  - diagnostic uncertainty
  - refractory gout (where more than 300 mg of allopurinol is needed or the patient fails to respond to therapy).

12. Disclaimer

This national clinical guideline is for reference and education only and is not intended to be a substitute for the advice of the appropriate health care professional or for independent research and judgement. SAMA relies on the source of the national clinical guideline to provide updates and to notify us if the guideline protocol becomes outdated. SAMA accepts no responsibility or liability arising from any information contained in or any error in or omission from the protocol or from the use of any information contained in it.

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Annexure A: Methodology

This project was initiated by SAMA. On the recommendation of the South African Rheumatism and Arthritis Association (SARAA), Professor G M Mody was mandated with the task of developing the guidelines and invited the following to contribute to the process: R Asherson, D Bouwer, S Brighton, B Cassim, D Gotlieb, A A Kalla, O L Meyers, A Stanwix and M Tikly.

The draft for the Hyperuricaemia and Gout: Clinical Guideline 2003 was drawn up by O L Meyers, B Cassim and G M Mody.

This project was funded by MSD and Searle in terms of an unrestricted educational grant.

On 3 and 4 December 1999, a nationally representative arthritis consensus meeting was held in Gauteng. Participants were invited as representatives of professional government and consumer groups with an interest in the arthritis field. Each organisation so invited, nominated its own representatives. All participants received a copy of a draft guideline developed previously together with the relevant references before the meeting. A neutral chairperson chaired the meeting. The purpose of the meeting was to consider the content of the draft guideline and to either endorse or amend the document. The proceedings were audio-recorded and transcribed for future reference.

The endorsement document was revised according to the proceedings of the national consensus meeting and was circulated to all participants and many other interested persons.

Amendments to this endorsement draft were made where there was sufficient need as indicated by the comments received. The document as revised was submitted to the SAMA Guideline Committee for endorsement according to the set criteria. Once endorsed, the guideline was sent for publication to the *South African Medical Journal*.

The grants were made in accordance with the SAMA code of sponsorship, which precludes attempts by sponsors to influence, unethically, the content of the guideline. All funds were paid directly into SAMA's accounts and all disbursements were made from that fund.

Annexure B: Consensus Group for Arthritis Guidelines

South African Medical Association: F J Milne (Chairperson); Arthritis Foundation: O L Meyers; Representatives of the Authoring Group (SARAA): A A Kalla, D Gotlieb, G Mody, S Brighton, O L Meyers; DENOSA: G Brown; Department of Health: Directorate Pharmacy (EDL): J Ludick, Directorate Chronic Disease: C Kotzenberg; National Osteoporosis Foundation: C Schnitzler; National Pathology Group: P Cole; Pain Management Society of SA and SAMA Nominee: P Dessein; Radiological Society of SA: P du Plessis; SAMA: Centre for Quality Care: V Pinkney-Atkinson; SAMA Nominee: D Kastanos; SA Academy of Family Practice: S Namane; SA Association of Occupational Therapists: T Pistorius; SA Orthopaedic Association: N J G Maritz; SA Society of Physiotherapy: H Gardener; Society for General and Family Practitioners: J Fourie; **Observer delegates:** MSD: M Combrink, B Crouse, S Nkalashe, B Prinsloo; Searle: M Doveton, G Hirsch, G Muir, L Wiggil; Medscheme: H Seftel.

Osteoarthritis: Clinical Guideline 2003

Principal authors: S Brighton, G M Mody, M Tikly, D Bouwer

Summarised Guideline

1. Definition

Osteoarthritis (OA) is not a single disease but rather the final common pathway of a heterogenous group of conditions which result in joint failure. The disease process involves the entire joint, including the articular cartilage, subchondral bone, ligaments, capsule, synovial membrane and periarticular tissues. Ultimately the articular cartilage degenerates with fibrillation, fissures, ulceration and full-thickness loss of the joint surface.

2. Introduction

OA was previously considered to be simply 'wear and tear' of the joint, but awareness of the burden of OA, a better understanding of the pathogenesis and advances in molecular medicine have led to a resurgence of interest in the disease.

3. Diagnosis

The diagnosis of OA of the hips and knees is based on the finding of characteristic clinical, laboratory and radiographic features of pain in the affected joint, erythrocyte sedimentation rate less than 20 mm/h and radiographic changes of osteophytes, joint space narrowing, subchondral sclerosis and cyst formation.

4. Epidemiology

The prevalence of OA varies depending on the site of OA and whether the diagnosis is based on radiographic criteria alone or in combination with clinical criteria.

5. Classification of Osteoarthritis (OA)

OA is classified into idiopathic (no known cause) and secondary (associated with a variety of predisposing conditions). Idiopathic OA is further classified into localised or generalised, when there is involvement of three or more joint areas.

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6. Risk factors

Risk factors are categorised as susceptibility and mechanical factors.

6.1 Susceptibility factors

The factors which increase the susceptibility to OA include age, gender and hormone, race, obesity, genetic factors, nutritional factors and joint hypermobility, while there is an inverse relationship with osteoporosis.

6.2 Mechanical factors

The mechanical factors which increase the risk of OA are injuries to the joint, cartilage and ligament, certain occupations which require regular knee bending, crawling or carrying heavy loads and any abnormalities in the shape of the joint.

7. Pathology and pathogenesis

OA develops when there is excessive load on normal cartilage and subchondral bone or where a normal load is applied to abnormal bone or cartilage.

8. Burden and impact of OA

The increased proportion of elderly people in most communities is associated with increased health care costs. Costs are directly related to medication and surgery and there are also indirect costs due to reduced working hours, unemployment and early retirement.

9. Clinical features of OA

9.1 Symptoms

The symptoms of OA include pain on movement, stiffness, reduction of joint movement and functional impairment.

9.2 Signs

The signs are joint swelling due to bone thickening, wasting of adjacent muscles, tenderness along the joint line, crepitus on movement and reduced range of movement, joint instability and deformity (in advanced disease).

9.3 OA at specific sites

9.3.1 OA of the knee

Knee OA most commonly affects the middle aged and elderly, especially females, who often have OA at other sites especially

the hands. The commonest site is the medial compartment. Symptoms include pain on walking, stiffness, particularly after immobility, and difficulty going up and down stairs. Signs include painful limitation of flexion, joint line tenderness and coarse crepitus. Small effusions and periarticular soft-tissue lesions may be seen. The course of the disease is variable, usually progressing slowly over many years. Acute flares of joint pain are common. Surgery is indicated for patients with severe pain or deformities and significant limitation of function.

9.3.2 OA of the hip

The sex incidence is nearly equal, with a slight male predominance in some studies. Pain is felt in the groin or anterior thigh but may be referred to a much wider area including the buttock and knee and may be mistaken for knee pathology. Initially pain is present on walking but later there may be night pain or pain at rest. Activities of daily living, e.g. walking, bending, climbing stairs, are affected. Patients have painful restriction of movement, particularly internal rotation. Pain on the lateral thigh is often due to trochanteric bursitis. The course of hip OA is usually slowly progressive but some patients may have rapid progression with severe disability.

9.3.3 OA of the hand

Heberden's nodes are bony swelling of the superio-lateral aspect of the distal interphalangeal (DIP) joints. Bouchard's nodes are bony swelling over the posterior interphalangeal (PIP) joints of the fingers. Cysts often form over the affected joints and may exude a jelly-like material. Disability is usually associated with activities of fine finger movements. Hand OA predominantly affects the carpometacarpal (CMC) joints at the base of the thumbs and fingers with the DIP joints being involved more than the PIP joint of the fingers. The metacarpophalangeal (MCP) joints are less frequently involved. Hand OA has a strong genetic predisposition and is more common in women than men.

10. Management

The goals of management are:

- education of the patient
- relief of the pain and stiffness
- improvement of function
- modification of the disease process.

Management must be individualised, taking into account the following factors:

- the patient's knowledge, attitudes and motivation
- the age and general medical condition of the patient
- co-morbid diseases and their therapy
- constitutional factors such as obesity and muscle weakness
- availability and costs of different treatment modalities.

Pain is a major factor and the source of the pain should be found. The pain may be referred, e.g. from the hip or spine. Local pain arises from within the joint due to involvement of the synovium, subchondral bone or articular capsule. Periarticular pain arises from adjacent muscles, ligaments, tendons or bursae.

Management of OA includes non-pharmacological, pharmacological and surgical approaches.

10.1 Non-pharmacological

Non-pharmacological management includes patient education, weight loss, exercises, modification of footwear, use of orthoses and assistive devices, physiotherapy and occupational therapy.

10.1.1 Patient education

The patient must be educated about the symptoms, natural history, therapeutic options and adverse effects of drugs. Patients should be encouraged to participate in their own 'self-management' so as to modify or control the impact of the disease on their physical health and improve their ability to cope with the disease.

10.1.2 Obesity

Obesity is a major risk factor for the development of knee OA. Reduction of the body mass index by two units may reduce the risk of OA by 50%. Obese women with unilateral OA of the knee are at a greater risk of developing OA of the opposite knee. Weight loss must be emphasised both in prevention and slowing the disease process and delaying the need for surgery.

10.1.3 Exercise

The importance of exercise must be emphasised to the patient. The exercise programme should include complete active range of motion with periods of weight bearing and non-weight bearing. The exercise programme should include muscle strengthening exercises as well as aerobic exercises. Aerobic exercises should include walking, which is readily available, and aquatic exercises. The exercise programme should be one that the patient can continue unsupervised at home.

10.1.4 Physiotherapy

Physiotherapists play an important role in relieving pain and stiffness, motivating the patient and designing specific exercise programmes.

10.1.5 Occupational therapy

Occupational therapists help patients to cope with their illness and provide advice and assistive devices to improve function and prevent deformities.

10.1.6 Assistive devices, orthoses, taping of the patella and footwear

Patellar taping has been shown to reduce pain from the patello-femoral joint, but its value awaits confirmation in further studies. Walking aids such as walking sticks should be used in

the contralateral hand to relieve load on the involved weight-bearing joint. A variety of other orthoses are available to relieve load on a joint. A knee brace or neoprene sleeve may be prescribed. Heel wedges may help to correct biomechanical abnormalities and relieve knee pain.

10.2 Pharmacological therapy

10.2.1 Analgesics

Paracetamol is effective but a meta-analysis of trials shows that non-steroidal anti-inflammatory drugs (NSAIDs) produce significantly greater improvement in both pain at rest and pain on motion. Paracetamol is inexpensive, well tolerated and effective in doses up to 4 g daily and is recommended as the initial drug of choice in all forms of OA. Although paracetamol is one of the safer analgesics it must be used with caution in the presence of liver disease and alcohol abuse. It is the analgesic of choice in patients with impaired kidney function, but in very high doses it can cause interstitial nephritis. Recent reports show some gastric irritation at doses exceeding 2 g daily.

10.2.2 Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs have analgesic and anti-inflammatory properties and are effective in patients with OA. They are used in patients with inadequate response to analgesics alone. Pain relief is apparent in a few days with further improvement over a few weeks. There is individual variation in the response by patients to different preparations. Traditional NSAIDs are associated with an increased risk of gastrointestinal complications. Risk factors for gastro-intestinal tract (GIT) bleeding on traditional NSAIDs are:

- age 65 and over
- history of peptic ulcer or upper GIT bleeding
- concomitant use of oral corticosteroids or anticoagulants
- smoking and alcohol consumption
- the use of low-dose aspirin for cardiovascular prophylaxis.

The recent introduction of selective COX-2 inhibitors has been reported to reduce the risk of GIT complications. It is essential that renal function is monitored in elderly patients as all NSAIDs can impair renal function in patients with hypertension, congestive heart failure, on diuretics or angiotensin-converting enzyme (ACE) inhibitor therapy, and aged over 65 years.

The traditional NSAIDs as well as the COX-2-specific inhibitor drugs may cause oedema and a rise in blood pressure. The use of COX-2-specific inhibitor drugs or gastro-protective agents with conventional NSAIDs is recommended in patients at high risk for GIT complications.

10.2.3 Topical creams and ointments

- Topical preparations of NSAIDs are effective and should be tried when one or a few joints are involved, particularly for patients intolerant of oral NSAIDs.
- Capsaicin cream depletes tissue reserves of substance P with a decreased pain signal. It causes an initial burning sensation and must be used regularly to prevent the build-up of substance P.

10.2.4 Intra-articular corticosteroid injections

There is a significant benefit from intra-articular steroid injections. Injections should not be repeated more than three times a year. The response to the injections is significantly better if the joint is rested for about 24 hours after the injection. Side-effects are sepsis, post-injection flares of pain, atrophy of subcutaneous tissue and systemic effects such as facial flushing. The risk of sepsis is low provided an aseptic technique is used.

10.2.5 Newer therapies

Newer therapeutic agents include the use of intra-articular hyaluronic acid (hyaluronan) and oral glucosamine sulphate and chondroitin sulphate.

10.3 Surgery

Arthroscopy with joint lavage is of value in mild to moderate OA of the knee. Joint replacement surgery should be considered in patients with severe symptoms and disability despite adequate pharmacological and non-pharmacological measures.

10.4 Management of OA at specific sites

10.4.1 OA of the hips

Non-pharmacological therapy. Exercises should aim to maintain at least 30° of flexion, full extension and strengthen the abductors and extensors. A suggested programme is non-weight bearing, non-impact aerobic exercises, e.g. bicycle, rowing machine, etc and later weight bearing activities, e.g. walking. Walking aids, e.g. a cane, can be used. Patients not adequately controlled should be considered for total joint arthroplasty.

10.4.2 OA of the knee

Soft-tissue lesions, for instance bursitis around the knee, must be excluded as a cause of the patient's symptoms. Always examine the hip to exclude referred pain to the knee. Taping the patella and a light knee brace can be considered. Strengthening of the quadriceps muscles is associated with significant improvement in knee pain and function.

10.4.3 OA of the hand joints

Early OA of the hand joints might look like rheumatoid arthritis (RA) to the inexperienced observer, but the typical joint distribution of DIP and PIP joints with bony swelling favours OA. Radiological changes of osteophytes at the DIP joints (Heberden's nodes) and at the PIP joints (Bouchard's nodes) are typical of OA. OA of the CMC joint of the thumb starts with pain on straining the thumb, e.g. a gripping action;

later there is almost continual pain, which decreases with stiffening of the joint. Overloading the joints, e.g. tight gripping, and carrying weight with the fingers must be avoided. Intra-articular steroid injections help to relieve pain in the thumb CMC joint. Surgery may be necessary in a few patients who have persistent pain.

11. Disclaimer

This national clinical guideline is for reference and education only and is not intended to be a substitute for the advice of the appropriate health care professional or for independent research and judgement. SAMA relies on the source of the national clinical guideline to provide updates and to notify us if the guideline protocol becomes outdated. SAMA accepts no responsibility or liability arising from any information contained in or any error in or omission from the protocol or from the use of any information contained in it.

Full Guideline

1. Objective

This guideline has been developed to

- provide an understanding of osteoarthritis, and
- promote the cost-effective management of osteoarthritis by doctors and other health care providers.

2. Abbreviations

ACR = American College of Rheumatology; BMI = body mass index; CMC = carpometacarpal; COX = cyclo-oxygenase; DIP = distal interphalangeal; EULAR = European League of Associations for Rheumatology; HA = hyaluronic acid; HRT = hormone replacement therapy; IL-1 = interleucin 1; MMPS = matrix metalloproteinases; MCP = metacarpophalangeal; MTP = metatarsophalangeal; NSAID = non-steroidal anti-inflammatory drug; OA = osteoarthritis; PIP = proximal interphalangeal; RA = rheumatoid arthritis; TIMPs = tissue inhibitor of metalloproteinases.

3. Introduction

Osteoarthritis (OA) is the commonest joint disorder in the world and one of the most important causes of disability in the elderly. OA was previously considered to be a 'wear and tear' phenomenon or degenerative disease, and as a result attracted little research interest. Recently there has been a resurgence of interest in the epidemiology and pathogenesis of OA. The change has been driven by two fundamental factors. Firstly, there is a greater awareness of the burden of OA with the increasing elderly population, especially in Western communities. Secondly, advances in molecular medicine have led to a better understanding of the pathogenesis of OA. As a result of our better understanding of the interplay of various enzymes, cytokines and growth factors, there are now increased prospects for developing disease-modifying agents in OA.

The American College of Rheumatology (ACR) has published guidelines for the management of OA of the hip[1] and knee.[2] The ACR has subsequently published the 2000 update[3] for the medical management of OA of the hip and knee. The European League of Associations for Rheumatology (EULAR) has also published guidelines for the management of OA of the knee.[4]

4. Definition

OA is not a single disease but rather the final common pathway of a heterogeneous group of conditions, which result in joint failure.

OA is characterised by a focal softening and disintegration of articular cartilage, which is accompanied by the proliferation of new bone. The radiographic changes include joint space narrowing, subchondral sclerosis and cyst formation, and marginal osteophytes.

In 1994 a workshop entitled 'New Horizons in Osteoarthritis', sponsored by various professional organisations in the USA, defined OA as follows: 'Osteoarthritis is a group of overlapping distinct diseases, which may have different etiologies but with similar biologic, morphologic, and clinical outcomes. The disease processes not only affect the articular cartilage, but involve the entire joint, including the subchondral bone, ligaments, capsule, synovial membrane, and periarticular muscles. Ultimately, the articular cartilage degenerates with fibrillation, fissures, ulceration, and full-thickness loss of the joint surface.'[5]

5. Diagnosis and classification criteria

The diagnosis of osteoarthritis of the hip and knee is based on the findings of characteristic clinical, laboratory and radiographic features of:

- pain in the affected joint
- erythrocyte sedimentation rate < 20 mm/h (in the absence of infection)
- radiographic changes of osteophytes, joint space narrowing, subchondral sclerosis and cyst formation.

The ACR has proposed criteria for the classification of OA of the hips,[6] knees[7] and hands.[8] The aim of developing the classification criteria was to encourage uniformity in the reporting of studies on OA and facilitate comparison of the

results of different studies on epidemiology, natural history and outcome, and response to therapy.

The ACR classification criteria for OA of the hip are:[6]

Hip pain

+

2 of the following 3 features:

- erythrocyte sedimentation rate < 20 mm/h
- radiographic femoral or acetabular osteophytes
- radiographic joint space narrowing.

The ACR classification criteria for OA of the knees are:[7]

Knee pain and radiographic osteophytes

+

at least one of the following:

- age > 50 years
- morning stiffness ≤ 30 minutes in duration
- crepitus on motion.

The ACR classification criteria for OA of the hands[8] were modified by Silman and Hochberg[9] and are shown in Table I.

Table I. ACR classification of OA of the hand[9]

Clinical

1. Hand pain, aching, or stiffness for most days of prior month
2. Hard-tissue enlargement of ≥ 2 of 10 selected hand joints*
3. Fewer than 3 swollen MCP joints
4. Hard-tissue enlargement of 2 or more DIP joints
5. Deformity of 2 or more of 10 selected hand joints

Osteoarthritis present if items 1, 2, 3, 4 or 1, 2, 3, 5 are present. Sensitivity is 92% and specificity is 98%.

* 10 selected hand joints include bilateral 2nd and 3rd DIP joints, 2nd and 3rd PIP joints and 1st CMC joints.

MCP = metacarpophalangeal; DIP = distal interphalangeal.

6. Epidemiology

The prevalence of OA varies depending on the site of OA and whether the diagnosis is based on radiographic criteria alone or in combination with clinical criteria.

Radiographic OA of the hand was found in approximately 32.5% of adults in the USA[10] and in 75% of women aged 60 - 70 years in a Dutch study.[11] The prevalence of radiographic knee OA was 33% in people aged 63 years and over in the Framingham Study.[12]

The prevalence of symptomatic knee OA was 9.5% in the elderly in the Framingham Study[10] while a prevalence of 15% was reported in a British population over 55 years.[13] Symptomatic hip OA varied from 0.7% to 4.4% of adults, and symptomatic hand OA occurred in approximately 27.3% of females and 18.3% of males in Britain.[14]

7. Classification of OA

A 'Workshop on Etiopathogenesis of Osteoarthritis' has classified OA into idiopathic and secondary types.[15] Idiopathic OA is further classified as being localised, or generalised when there is involvement of three or more joint areas.

In idiopathic or primary OA there is no known cause, while secondary OA is associated with a variety of predisposing conditions. The sites of localised idiopathic OA are shown in Table II and some of the different conditions, which may be associated with secondary OA, are shown in Table III.

8. Risk factors

The risk factors for OA may be categorised as susceptibility factors and mechanical factors.[16]

Table II. Classification of primary OA

Localised		
1.	Hands	DIP and PIP joints, 1st carpometacarpal joints
2.	Feet	1st MTP joint (hallux valgus and rigidus)
3.	Knee	Medial, lateral and patello-femoral compartments
4.	Hip	Superior pole, medial pole, concentric
5.	Spine	Apophyseal joints, intervertebral disc, ligaments
6.	Others	Shoulder, temporo-mandibular, acromioclavicular, wrist, sacroiliac, ankle
Generalised		Involvement of 3 or more joint areas

DIP = distal interphalangeal; PIP = proximal interphalangeal; MTP = metatarsophalangeal.

Table III. Causes of secondary OA

1. **Trauma or surgery**
   e.g. major fractures, post menisectomy, occupation or sport-related injury
2. **Anatomical or developmental**
   e.g. slipped femoral epiphyses, congenital dislocation of hip, Perthes' disease, bone dysplasias, leg length inequality, hypermobility syndrome
3. **Metabolic or endocrine**
   e.g. ochronosis, acromegaly, hyperparathyroidism
4. **Secondary to inflammatory diseases**
   e.g. rheumatoid arthritis, crystal deposition diseases
5. **Miscellaneous**
   e.g. endemic (Mseleni joint disease), osteonecrosis, Paget's disease and neuropathic

8.1 Susceptibility factors

8.1.1 Age

The prevalence of OA increases with age. In a radiographic survey, OA was present in 2% of women aged < 45 years, 30% in the 45 - 64 year age group and 68% in those over 65 years.[17] Studies on the biological characteristics of cartilage from patients with OA and normal elderly people have shown differences with respect to the water concentration and the amount of proteoglycans, collagen, enzymes and enzyme inhibitors. Other factors such as mechanical injury, disturbances of proprioception,[18] or metabolic disturbances rather than ageing alone therefore contribute to the increased prevalence of OA with increasing age.

8.1.2 Gender and hormones

OA of the distal interphalangeal (DIP) joints, first carpometacarpal (CMC) joint and knees is commoner in women, while OA of the hips is commoner in men. The predominance of OA in women, especially after the menopause, suggested that OA might be hormonally mediated. Recent epidemiological studies show that hormone replacement therapy (HRT) is associated with a reduction in the risk of knee and hip OA.[19-22] All these studies showed an inverse relationship between HRT and the prevalence of OA. Further supportive evidence is obtained from studies that reported a stronger inverse association of HRT with long-term users of HRT rather than short-term users or non-users.[19,20] The association was stronger when the analysis was restricted to patients with more severe OA or bilateral radiographic OA.

8.1.3 Race

The prevalence of OA varies among different racial groups. A low prevalence of radiographic hip OA has been reported among black populations in Jamaica, South Africa, Nigeria and Liberia (1 - 4%) compared with European populations (7 - 25%).[10] Clinical Heberden's nodes are also infrequent in the black population in South Africa.[23]

8.1.3.1 South African experience

Mseleni joint disease was first reported in 1973 in the Mseleni area on the western side of Lake Sibiya in northern KwaZulu-Natal.[24] It is characterised by irregularity of the joint surface, OA or protrusio acetabulae.[25] The joints most frequently affected are the hips, knees, ankles and wrists. It is commoner in females (female/male ratio 7:2) and occurs radiologically at all ages. The disease tends to be familial, but a genetic or environmental factor has not as yet been identified.[26]

8.1.4 Obesity

Overweight persons have been consistently shown to have a higher risk of knee OA in population studies. A survey in the USA showed that the risk of radiographic OA of the knee was increased fourfold in women with a body mass index (BMI) > 30 compared with women with a BMI < 25.[27] There is an increased risk of both tibiofemoral and patellofemoral OA. Obesity has been shown to precede rather than follow knee OA.[28]

A reduction of weight is associated with a lower risk of OA. In the Framingham Study, a weight loss of 5 kg in women of normal height with a BMI of more than 25 was associated with a greater than 50% reduction in the risk of developing knee OA.[29] Obesity also increased the odds of disease progression in patients with established knee OA. In patients with established knee OA, weight loss was also associated with significant symptomatic improvement.[30]

8.1.5 Genetic factors

There is a strong familial tendency for generalised nodal OA, which commonly begins in the perimenopausal period in women.

Family studies of members with premature polyarticular OA have shown a number of gene mutations of the collagen 2A1 gene.[31] This genetic defect is directly responsible for the development of OA.

8.1.6 Osteoporosis

Deformation of the subchondral bone during impact loading protects the articular cartilage from damage.[32] Dequeker *et al*.[33] found an inverse relationship between osteoporosis and OA in 53 of 67 studies reviewed. Patients with osteoporosis may have more deformable bone and therefore have a lower prevalence of OA.[34] Patients with OA have higher bone mineral density than age-matched controls, even at sites distant from the joint affected by OA.[35,36]

8.1.7 Nutritional factors

Felson and Zhang[37] reviewed the association between nutritional factors and OA. Reactive oxygen species have been implicated in the pathogenesis of OA.[38] Patients in the Framingham Osteoarthritis Study who had the lowest tertile of vitamin C intake had a three-fold greater risk of progression of knee OA, joint space loss and onset of knee pain compared with patients with a higher intake.[39]

Vitamin D is active in the remodelling of bone and may also affect the occurrence and progression of OA. In the Framingham Osteoarthritis Study, patients with radiographic OA who had the lowest tertile of serum 25-hydroxyvitamin D had a much higher rate of radiographic progression.[40]

8.1.8 Hypermobility

Hypermobility occurs in a small proportion of healthy people and may also be associated with rare inherited disorders of collagen. Hypermobility is associated with a wide spectrum of soft-tissue lesions and premature OA.[41]

8.2 Mechanical factors

8.2.1 Joint injury/occupation/recreational activities

Major injury to a joint is associated with damage to the

articular cartilage, which leads to progressive changes associated with OA. In the knee, injury to the cruciate ligament and meniscal tears or previous total menisectomy are associated with an increased risk of OA.

Repetitive use of a joint with certain occupational activities may be associated with an increased risk of OA. There is an increased prevalence of hand OA in cotton mill and textile workers,[42,43] and farmers have an increased risk of OA of the hip.[44] Occupations that require regular knee bending, crouching or crawling and carrying heavy loads are associated with an increased prevalence of knee OA.[27,45,46] A review of six recent studies further supports the association of occupation and OA.[47]

A review of the studies on the risk of running and OA of the knees and hips produces conflicting results.[10] In runners, some of the factors that contribute to the differences are failure to include patients who had stopped running as a result of hip or knee problems, failure to identify patients who may have a history of a major injury to the joint, and lack of long-term follow-up. The increased risk of knee OA in soccer players can often be related to known injuries such as cruciate ligament tears and menisectomy.[45,48] In the Framingham study, the level of physical activity correlated with the risk of developing radiographic knee OA in the elderly.[37]

8.2.2 Shape of the joint

Abnormality of the shape of the hip in childhood disorders such as Perthes' disease, slipped capital epiphysis and congenital dislocation of the hip are associated with hip OA. Mild variants of acetabular dysplasia in Caucasians may account for the relatively higher prevalence of OA of the hip in Caucasian populations, but this suggestion has not been confirmed in Asians.[49]

9. Pathology and pathogenesis

The primary target of OA is the hyaline articular cartilage, but the subchondral bone has also been suggested as the site of the initiating event. In the articular cartilage, the most prominent changes are seen in the load-bearing areas. In the early stages the cartilage is thicker than normal, but as the disease progresses the cartilage becomes thinner and softer and there are vertical clefts or fibrillation of the surface. Ulcers develop on the cartilage and may extend to the bone. There is some repair of the cartilage, but it is unable to withstand mechanical stress.[50]

OA develops when there is excessive load on normal articular cartilage and subchondral bone or when a normal load is applied to abnormal bone or cartilage.[17]

Weight-bearing joints are subjected to repeated localised high loads. The soft tissue in the region of the joints, namely the muscles, tendons and ligaments as well as the subchondral bone, play a major role in dissipating these loads. The cartilage itself dissipates the mechanical loads placed upon it by its special properties, namely compressibility, elasticity, and self-lubrication.

The major constituents of articular cartilage are type II collagen, proteoglycans, chondrocytes and water. The collagen can withstand compressive and shearing forces and proteoglycans attract and retain water. Any factors that cause disruption of the collagen will result in OA. Chondrocytes play a role in maintaining a balance between the synthesis and degradation of the cartilage matrix. They have the ability to upregulate the production of proteoglycans and other cartilage matrix proteins. They also produce matrix metalloproteinases (MMPS) such as collagenase and stromelysin, which degrade the cartilage matrix. Chondrocytes also synthesise enzymes known as tissue inhibitor of metalloproteinases (TIMPs), which modulate the action of MMPS.

10. Burden and impact of OA

Yelin[51] has reviewed the economic impact of OA. The increased proportion of elderly people in Western communities is associated with increasing health care costs for musculoskeletal complaints including OA. In the USA, musculoskeletal conditions accounted for $4 billion in total costs or 0.7% of gross national product in 1963[52] compared with $124 billion or 2.5% of gross national product in 1988.[53]

The costs of the illness are related to direct costs for medical care and indirect costs mainly due to lost wages from reduced hours of work or stopping work. A survey of patients with OA by Gabriel *et al*.[54] found that about 11% of patients had reduced working hours, 9% were unable to get a job, and 14% retired early.

Although the costs associated with rheumatoid arthritis (RA) are greater than those with OA, the higher prevalence of OA results in a greater impact on the economy. Further studies are needed to assess the economic impact of OA and the need for health care services, including hospitalisation for surgical procedures such as hip and knee arthroplasty.

11. Clinical features of OA

The main symptoms and signs of OA are shown in Table IV.

11.1 Symptoms

11.1.1 Pain

Initially patients experience an aching pain associated with the use of a joint or movement and relieved by rest. With progression of the disease, the pain becomes persistent and may be present at rest or at night.

There is no consistent correlation between the severity of pain and radiographic changes except in advanced OA when

Table IV. Symptoms and signs of OA

Symptoms
Pain – related to use, rest pain, night pain
Stiffness – early morning stiffness (< 30 min), after inactivity
Reduced movement
Functional impairment
Signs
Crepitus
Tenderness – joint line, periarticular
Bony swelling
Mild inflammation with effusion
Reduced movement
Joint deformity
Muscle wasting/weakness

the pain is usually more severe. The correlation of pain with radiographic change is best at the hip and then the knee, compared with the hand and spine.

A variety of factors may contribute to pain in OA, and these are shown in Table V with the associated mechanisms. Some patients may develop a periarticular disorder such as bursitis or tendinitis that may contribute to their pain.

Table V. Causes of joint pain in OA

Source	Mechanism
Synovium	Inflammation
Subchondral bone	Medullary hypertension, microfractures
Osteophyte	Stretching of periosteal nerve ending
Ligaments	Stretch
Capsule	Inflammation, distension
Muscle	Spasm

11.1.2 Stiffness

Patients may experience early morning stiffness, but it usually lasts for less than 30 minutes compared with RA where it may be prolonged in active disease. Stiffness may also occur after a period of inactivity. Patients experience difficulty with initiating movement and the stiffness usually improves once the joint is mobile.

11.1.3 Reduced joint movement

Patients are often unable to flex or extend their joints fully as a result of capsular thickening, formation of osteophytes, deformity of the articular surface and rarely synovial inflammation.

11.1.4 Functional impairment

The limitation of function depends on which joint is affected and the severity of the OA. Patients may experience difficulty with mobility or activities of daily living, especially with hip or knee OA.

11.2 Signs

The joint appears swollen, and this is usually due to bony thickening. There may be wasting of adjacent muscles.

On examination there may be tenderness along the joint line. Tenderness may be localised to a periarticular region, suggesting a tendinitis or bursitis. Synovial thickening and effusion may be present.

Crepitus may be present on movement of the joint. Patients with advanced OA may have a reduced range of movement, joint instability and deformity.

There may be weakness of the muscles adjacent to the affected joint.

11.3 OA at specific sites

11.3.1 OA of the knee joint

The three major compartments of the knee joint are the medial tibio-femoral, lateral tibio-femoral and patello-femoral compartments.

OA of the knees usually occurs in:

- younger people, often men, who have isolated knee disease which is related to a previous injury or operations such as menisectomy
- middle-aged and older people, predominantly female, who often have OA at other joint sites such as the hands. Obesity is very strongly associated with knee OA.

The symptoms of OA are pain on walking, stiffness of the joint especially after a period of immobility, and difficulty with going up and down stairs. On examination there may be evidence of wasting of the quadriceps muscles, bony swelling, tenderness, painful limitation of flexion and coarse crepitus. Tenderness may also be elicited in the periarticular region such as the medial joint line at the site of insertion of the medial collateral ligament or over the upper part of the tibia in association with soft-tissue swelling due to anserine bursitis. Small effusions may also be present. Medial compartment OA is the commonest variant of primary OA and often results in a varus deformity. In patients with patello-femoral OA, anterior crepitus, abnormal movement and tracking of the patella as well as tenderness on patella compression may be present.

The course of OA is variable. Usually the disease evolves slowly over a period of many years. There may sometimes be spontaneous improvement in symptoms, but there is usually no regression of the radiographic changes. The course of the illness is punctuated by acute flares which may last days or weeks and be associated with signs of inflammation. Progressive increase in pain and deformity will require surgery.

11.3.2 OA of the hip

OA of the hip has a roughly equal sex incidence, but some studies report a higher incidence in men. OA of the hip may be classified as primary or secondary or it can be classified

according to the area of involvement within the joint (superior pole, medial pole or concentric). OA has also been classified as hypertrophic (osteophyte formation and subchondral sclerosis) or atrophic (little or no new bone formation).

Pain from the hip is typically felt in the groin (femoral nerve distribution), but may also be referred over a wider area including the lateral thigh and buttock (sciatic nerve distribution), the anterior thigh and knee (obturator nerve distribution) and down the leg as far as the ankle.

Occasionally pain may be maximal at the knee with little pain in the region of the hip. Initially pain is worse on walking only but subsequently there is pain at rest and also at night. Stiffness is a common symptom. Activities of daily living that are affected include bending, walking, climbing up stairs or getting in and out of a car.

On examination there is painful restriction of movement with internal rotation of the hip in flexion initially being the movement most affected. There may also be tenderness in the region of the groin. Some patients may have pain and tenderness over the greater trochanter, which is worse on lying on the affected side and suggests the presence of trochanteric bursitis. With progression of OA there may be evidence of wasting of the gluteal and anterior thigh muscles with a Trendelenburg gait due to weakness of the abductor muscles. There may also be ipislateral shortening of the leg due to upward migration of the femoral head, or more commonly to an adduction deformity.

The natural history of osteoarthritis of the hip is variable. In patients with the atrophic form there may be rapid progression of symptoms resulting in severe disability. However, in patients with the hypertrophic form, the disease is slowly progressive because new bone formation stabilises the joint.

11.3.3 OA of the hand

OA predominantly affects the CMC joints at the base of the thumb and the DIP joints more than the PIP joints. The metacarpophalangeal (MCP) joints are infrequently involved.

OA of the hand is far more common in women than in men. The disease usually starts in middle age and there is strong evidence of a genetic predisposition and an association with knee disease and obesity. The hallmarks of interphalangeal joint OA are the presence of bony swelling over the supero-lateral aspect of the DIP joints (Heberden's nodes) and over the PIP joints (Bouchard's nodes). They are often tender and may develop cysts which may exude a colourless jelly-like material. As the disease progresses there may be instability of the joints, limitation of flexion and occasionally effusion in the joint. The disability associated with hand OA is seen most frequently in activities that require fine finger movement.

OA at the base of the thumb is associated with pain and tenderness along the radial aspect of the wrist. There is tenderness over the base of the first CMC joint and crepitus on movement. As the disease progresses there is an adduction deformity of the metacarpal which gives the appearance of 'squaring' of the thumb base. There may also be associated hyper-extension at the MCP joints. Patients may experience difficulty with the pinch grip and with opening bottles and jars. De Quervain's tenosynovitis may mimic first CMC joint OA and is associated with swelling and tenderness along the radial border of the wrist and hand. It shows a good response to local steroids and must therefore be distinguished from OA of the first CMC joint.

Radiographs of the thumb joint and interphalangeal joints show the typical features of OA which include loss of joint space, osteophytes, subchondral sclerosis and cysts.

In the early stages, the disease usually waxes and wanes and patients may have evidence of inflammatory flares in which the joints become warm and tender. Subsequently the flares tend to subside, the swelling becomes firm or bony and the joint may be fixed with a reduction of movement.

12. Management

The management of OA has recently been outlined in an excellent review.[55] An algorithm for the management of OA is shown in Fig. 1.

The **goals** of management are:

- education of the patient
- relief of pain and stiffness
- improvement of function
- modification of the disease process.

The principles of management and the role of the various modalities of treatment will be outlined here. However, management will need to be individualised for each patient,[56] and the following factors will need to be taken into consideration when planning a successful programme:

- the patient's knowledge, attitude and motivation
- the age and general medical condition of the patient
- co-morbid diseases and their therapy, e.g. hypertension, kidney disease, peptic ulcers
- constitutional factors such as obesity and muscle weakness
- availability and costs of the different treatment modalities.

Pain is one of the major symptoms for which patients seek medical attention. It is therefore essential to determine the source of the pain so that appropriate therapy can be provided. The pain may be:

- **referred pain**, e.g. patients with hip OA may present with knee pain and patients with spinal diseases may present with hip pain
- **local pain**, arising from within the joint due to involvement of the synovium, subchondral bone, articular capsule
- **periarticular pain**, due to involvement of adjacent muscles, ligaments, tendons or bursae.

The management of OA includes the following modalities:

- **non-pharmacological**
- **pharmacological**
- **surgery.**

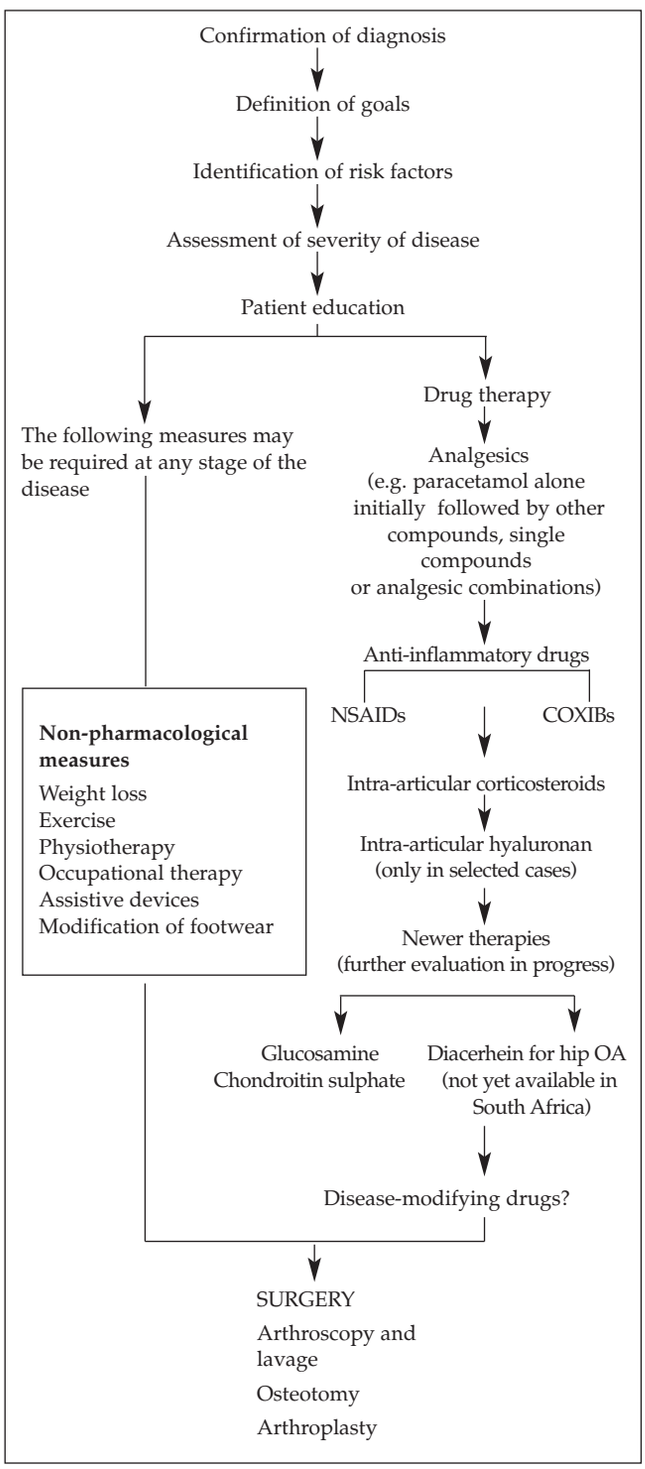

Fig. 1. Management of OA.

12.1 Non-pharmacological

Non-pharmacological management of OA has been the subject of recent excellent reviews and includes patient education, weight loss, exercises, modification of footwear, use of orthoses and assistive devices, physiotherapy and occupational therapy.[3,57-59]

12.1.1 Patient education

- It is important for patients and their families to have an understanding of OA, early in the course of the disease.[57] They should be informed about the symptoms, the natural history, therapeutic options, and adverse effects of drugs.
- The objectives of the educational programme are to achieve one or more of the goals outlined earlier.
- Patients are encouraged to participate in their 'self-management' so that they can modify or control the impact of the disease on their physical health status and improve their ability to cope with the disease.

Education may take various forms including the following:

- Educational materials from the Internet or agencies such as the Arthritis Foundation of South Africa.
- Educational information provided by health care professionals, either individually or in small group meetings or public lectures.
- Books on the Arthritis Self Help Programmes or Arthritis Self Help Courses conducted by the Arthritis Foundation of South Africa.
- A recent survey has shown that social support via telephone contact can contribute to significant improvement in both pain and function.[60]

12.1.2 Weight loss

The following are some of the key observations that have been recorded regarding the effect of body weight on OA:

- Epidemiological studies have shown that obesity is a major risk factor for the development of hip and knee OA.[61]
- Obesity has been shown to precede the onset of OA in the Framingham Study[28,62] and a reduction of the body mass index (BMI) by 2 units is associated with a 50% reduction in the risk of developing OA.[29]
- Women with unilateral knee OA who are obese are at greater risk of progression of structural damage in the affected knee and also at a greater risk of developing OA in the unaffected knee.[63]
- Weight reduction has been shown to reduce pain and improve function in OA.[64-66]

Overweight patients should therefore be encouraged to participate in a weight management programme which should include a low-calorie diet and aerobic exercises. Appetite suppressants may sometimes be necessary. The surgical risk is reduced in patients who are able to lose weight before surgery.

12.1.3 Exercise

Cartilage is avascular and aneural, requiring regular motion and compression for adequate nutrition and stimulation of remodelling and repair. Daily exercises that include complete active range of motion and periods of weight-bearing and non-weight-bearing, are recommended to maintain the integrity of the cartilage.

- Weakness of the quadriceps muscles is reported in patients with knee OA compared with age-matched controls.[67] Quadriceps weakness may be due to disuse atrophy and contributes to pain and disability.[68,69]
- Quadriceps weakness has also been detected in patients with radiographic features of OA who do not have a history of knee pain.[67] Some authors have suggested that muscle weakness and dysfunction may predispose to the development of OA,[67,70] and muscle strengthening exercises have a role in its prevention as well as its management.
- Exercise programmes are effective in the management of OA.[71,72] A review of the randomised controlled trials in OA has shown that exercises are of value.[73] Minor[74] has provided recommendations for a programme of exercises in patients with hip and knee OA. The exercise programme should include muscle strengthening exercises and aerobic exercises. Muscle strengthening exercises should include isotonic and isometric exercises with resistance. Aerobic exercises should include walking, as it is readily accessible, and aquatic exercises.
- Patients should be taught an exercise programme that they can continue at home as supervised hospital- or clinic-based programmes are impractical in the long term. Unfortunately many patients discontinue their exercises by 12 months, and follow-up contact is required to improve adherence to the programme.
- Recommendations for exercises should be part of the comprehensive management and must consider any functional limitation and disability, due either to inactivity or to the disease itself.[74]

12.1.4 Physiotherapy

The physiotherapist plays an important role in the management of OA by helping to relieve pain, improve function and prevent or correct deformities. The physiotherapist can also help to initiate and co-ordinate an exercise programme to prevent muscle wasting or strengthen muscles that are already weak. Patients with more severe disease can be assisted with mobilisation and advised about the use of appropriate walking aids.

12.1.5 Occupational therapy

The occupational therapist determines the impact of OA on the patient's activities of daily living, which include self care, household tasks, work or recreational activities. They are also able to provide advice and recommend assistive devices to help relieve pain, improve function and prevent deformities. Patients may benefit by using a walking aid, shoe insert, knee brace or splint, depending on the site affected. Patients with hip and knee OA may benefit from the use of a raised toilet seat or bath seat and will also feel more confident with additional handrails. Pain relief can also be obtained by correct advice about positioning and stretching of limbs. Depending on the site and severity of the OA and associated symptoms and disability, it may be necessary to recommend modification of the work environment to reduce disability.

12.1.6 Assistive devices, orthoses, taping of the patella and footwear

Patellar taping has been shown to reduce pain in patello-femoral OA[75] but these observations have not been confirmed in a larger study.[76] The rationale for the use of medial patella taping is that it alters the forces acting on the patella during quadriceps contraction. However, this theory has been questioned by others, who feel that the taping influences patellar tracking by increasing the proprioceptive input.

The use of a walking aid, such as a walking stick or crutches, helps to relieve stress on the painful affected weight-bearing joint. The walking aid should be used in the contra-lateral hand. The walking stick should be of correct height and should extend to the level of the proximal wrist crease when the patient stands upright with the arms at the side.[1] Some patients are reluctant to use a walking stick as they feel that they may be perceived as being infirm and lose their independence.

A variety of orthoses are also available and are used to provide pain relief in weight-bearing joints such as the knee. Knee braces help to provide stability, correct malalignment and reduce the abnormal forces on the knee. Malalignment associated with knee OA may lead to deformity of the hind-foot, which may improve with the use of functional foot orthoses. A neoprene sleeve or valgus brace may be prescribed for knee OA, but the brace is usually more effective in patients with advanced OA.[77,78]

Lateral heel wedged insoles may help to correct the biomechanical abnormalities and relieve pain associated with knee OA.[79]

12.2 Pharmacological therapy

The pharmacological therapy of OA has recently been reviewed[80-82] and includes the use of analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), intra-articular corticosteroids, intra-articular hyaluronan and oral nutripharmaceuticals such as glucosamine sulphate and chondroitin sulphate.

12.2.1 Systemic analgesics

The primary indication for drug therapy in OA is the relief of pain, and analgesics therefore are recommended as initial therapy. The initial use of analgesics is supported by the

observation that although inflammation plays a role in the pathogenesis of OA, pain may arise from structures such as the periosteum, subchondral bone, joint capsule and intra- and periarticular ligaments as well as periarticular tendons and associated muscles. The relief of mild to moderate pain with simple analgesics such as paracetamol is comparable with that obtained with NSAIDs.[83-85] However, a meta-analysis of trials comparing simple analgesics with NSAIDs in patients with knee OA noted that patients treated with NSAIDs had significantly greater improvement in both pain at rest and pain on motion.[86]

Paracetamol has both central and peripheral modes of action and readily penetrates the central nervous system at therapeutic doses. It is readily available, inexpensive, well tolerated and effective in doses up to 4 g daily and is recommended as the initial drug of choice in all patients with OA. Paracetamol has a near linear dose response curve for analgesia which reaches a plateau at 1 000 mg. The maximum recommended dose is 1 g 4 times daily.

Even though paracetamol is one of the safest analgesics, it may be associated with clinically serious adverse effects, especially at high doses. It should be used with caution in patients with liver disease and should be used in lower doses or avoided in patients with excessive alcohol intake.[87,88]

High-dose paracetamol can prolong the half-life of warfarin sodium and therefore careful monitoring of the prothrombin time is necessary in patients on concomitant warfarin sodium therapy.[89,90] Although paracetamol can cause chronic interstitial nephritis when consumed in large doses over a long period of time, it is still recommended as the analgesic of choice in patients with impairment of kidney function.[91]

A recent epidemiological survey noted that patients on high-dose paracetamol are also at high risk for upper gastrointestinal complications compared with patients on traditional NSAIDs.[92] They found that patients on more than 2 g daily of paracetamol had an adjusted relative risk for serious gastrointestinal complications that was intermediate between that for low and medium doses of NSAIDs. They suggest that this effect is due to the weak inhibition of cyclo-oxygenase (COX) 1 with paracetamol in doses of more than 2 g daily. These observations are of interest and concern and require confirmation, as the use of higher doses of paracetamol has been based on its reported better safety profile.

Other analgesics may be used singly or in combination with paracetamol in patients who are unable to tolerate NSAIDs and do not respond to paracetamol alone. Patients with hip OA showed a better response to a combination of paracetamol and codeine than paracetamol alone, but adverse effects such as nausea, vomiting, dizziness and constipation are common.[93] Another study of acute pain in hip or knee OA showed that paracetamol and dextropoxyhene was better tolerated than paracetamol and codeine, although their efficacy was similar.[94] Although other analgesic combinations have not been evaluated in controlled clinical trials, their trial is recommended in individual patients.

Tramadol is an analgesic with opiod receptor activity and also inhibits the uptake of serotonin and norepinephrine, both of which contribute to its analgesic effect. It has been shown to be comparable to ibuprofen in patients with hip and knee OA[95] and is useful in patients with OA whose symptoms are inadequately controlled with NSAIDs alone.[96]

The comparison of paracetamol and NSAIDs in two recent studies was reviewed by Shamoon and Hochberg[97] and showed that paracetamol and ibuprofen were comparable in efficacy in patients with mild to moderate pain but that ibuprofen was significantly superior in patients with severe pain[98] and diclophenac was superior to paracetamol for both pain and function assessed by different validated outcome measures.[99] Patients have also shown a greater preference for NSAIDs over paracetamol in two other recent studies.[100,101]

12.2.2 NSAIDs

NSAIDs produce their anti-inflammatory effects by blocking cyclo-oxygenase, the enzyme responsible for the conversion of arachidonic acid to prostaglandins.[102] The identification of two separate isoforms of cyclo-oxygenase, COX-1 and COX-2, has improved our understanding of the effects and adverse effects of traditional NSAIDs.[103] COX-1 is a ubiquitous constitutive isoenzyme that is responsible for physiological functions of the prostaglandins, such as protection of the gastric mucosa and maintenance of renal function. The COX-2 isoenzyme is inducible and is produced in response to inflammatory stimuli and produces prostaglandins that mediate pain and inflammation.[104] These observations provided the stimulus for the development of compounds that selectively inhibit the COX-2 isoenzyme, and led to the availability of celecoxib and rofecoxib.

NSAIDs have analgesic and anti-inflammatory properties and are effective in patients with OA,[80,105-107] and are used if there is inadequate response to analgesics alone. They provide comparable pain relief in OA and there is no consistent evidence to show the superiority of one agent over another.[105,107]

Pain relief is usually apparent within a few days with further improvement over a few weeks. There is also a great variability in patient response to NSAIDs. If the relief of symptoms is inadequate after 2 - 4 weeks, an alternative NSAID should be tried. A large proportion of patients who initially showed a response to a particular NSAID will later discontinue their NSAID and only about 5 - 20% of patients continue with the same NSAID a year later.[108] The combination of NSAIDs is generally not recommended as there is no synergistic beneficial effect but there is an increased risk of toxicity.

Traditional NSAIDs have been widely used in the

management of OA. As the majority of patients are elderly, there is an increased risk of toxicity, especially gastrointestinal complications such as peptic ulcers, perforation and bleeding, and nephrotoxicity including oedema, hypertension and renal insufficiency.

Epidemiological data show that among persons aged 65 years and older, 20 - 30% of all hospitalisations and deaths due to peptic ulcer disease are related to the use of NSAIDs.[109-111] The risk factors for upper gastro-intestinal bleeding in patients on NSAIDs are:[112-114]

- age ≥ 65 years
- history of peptic ulcer disease or upper gastro-intestinal bleeding
- concomitant use of oral corticosteroids
- concomitant use of anticoagulants
- smoking and alcohol consumption.

The use of low-dose aspirin for cardiovascular prophylaxis also increases the risk of gastrointestinal complications.

Elderly patients have a progressive physiological decline in renal function. NSAIDs also reduce renal perfusion, and it is therefore essential to monitor renal function closely in the elderly. The risk factors for the development of renal insufficiency in patients on NSAIDs are:[80]

- age ≥ 65 years
- hypertension
- congestive heart failure
- use of diuretics
- use of angiotensin-converting enzyme inhibitors.

The other adverse effects of NSAIDs include skin rashes of varying severity, hepatotoxicity, bone marrow toxicity and adverse reproductive outcomes.[115,116]

The COX-2-specific inhibitors, celecoxib and rofecoxib, have been shown to be superior to placebo and comparable in efficacy to traditional NSAIDs (naproxen v. celecoxib and ibuprofen and diclofenac v. rofecoxib) in patients with hip and knee OA.[117-122] They are both associated with a lower incidence of gastroduodenal ulcers than comparator NSAIDs in endoscopic studies.[123-124] Two large randomised controlled trials with about 8 000 patients in each study showed that celecoxib and rofecoxib are both associated with a significantly lower risk for symptomatic and complicated gastroduodenal ulcers in patients with OA and RA who were not on aspirin.[125-126] The COX-2-specific inhibitors do not have a clinically significant effect on bleeding time or platelet aggregation and are especially useful in the pre- and perioperative management of patients with OA.[80]

Other adverse effects of traditional NSAIDs such as oedema, rise in blood pressure and impairment of renal function, are also seen with celecoxib and rofecoxib. Patients on warfarin therapy require careful monitoring and NSAIDs (including COX-2-specific inhibitors) should be avoided in patients with congestive heart failure and significant renal insufficiency.

An increased number of cardiovascular thrombotic events were reported in patients on rofecoxib in the VIGOR Study.[126] Patients who are prescribed low-dose aspirin for cardiovascular prophylaxis will need to continue taking it whether they are on traditional NSAIDs or COX-2-specific inhibitors.

The strategies for the management of patients with increased risk for gastrointestinal toxicity who require anti-inflammatory medication include the use of COX-2-specific inhibitors, traditional NSAIDs combined with gastroprotective agents, intra-articular corticosteroids or intra-articular hyaluronan.

The use of gastroprotective agents is recommended in patients on conventional NSAIDs who are at high risk for upper gastrointestinal complications.[127] Misoprostol has been shown to reduce the incidence of gastrointestinal complications when used in a dose of 200 µg 3 or 4 times daily, but diarrhoea and flatulence may be a problem in some patients.[128,129] Proton pump inhibitors such as omeprazole have also been shown to be effective in preventing NSAID gastropathy, while H_2-blockers are not as effective.[130-131]

12.2.3 Topical creams and ointments

12.2.3.1 Non-steroidal anti-inflammatory drug ointments. Topical preparations of NSAIDs are widely used by patients with musculoskeletal symptoms including OA. A review of trials using topical NSAIDs has shown that they are effective in relieving symptoms in OA when compared with oral NSAIDs.[132-135] Topical preparations should be tried when one or a few joints are involved or in patients in whom NSAIDs are contraindicated, who cannot tolerate them or who are reluctant to take them.

12.2.3.2 Capsaicin. Capsaicin is a naturally occurring alkyl vanillylamide from the fruits of plants of the capsicum genus. The use of topical capsaicin cream four times daily depletes the tissue reserves of substance P with a decreased pain signal. Substance P is a chemoattractant for neutrophils and monocytes, and stimulates synovial cells to produce prostaglandins and collagenase, which are mediators of joint inflammation in OA. The use of capsaicin in OA has been reviewed by Brandt and Bradley.[136] Capsaicin has been shown to be effective in providing pain relief when used alone[137] or as adjunctive therapy with analgesics or NSAIDs.[138,139] Capsaicin should be considered for OA of the knees or hands, but has also been used at other sites. The patient must be warned of a local burning sensation initially. Capsaicin has to be used regularly to prevent the build up of substance P.

12.2.4 Intra-articular corticosteroid injections

The efficacy of intra-articular steroids in knee OA has been

recorded in many studies, which were reviewed by Ayral.[81] Recent studies have demonstrated a significant short-term benefit of steroids over placebo, ranging from 1 to 4 weeks.[140-144] The possible reasons for the difference between the short-term benefit reported in controlled studies and the sustained response by many patients in clinical practice has been addressed by Creamer.[145] They are that the dose of steroids used in the studies was less than usually used in clinical practice, patients often receive more than one injection while studies were restricted to a single injection, and there is a large placebo response, which varied from 36% to 86% in some studies.[146,147]

Several studies of patients with knee OA failed to identify any predictors of response to intra-articular steroids apart from the possible presence of an effusion.[148-150] The use of intra-articular steroids is recommended for the management of disease flares where pain is accompanied by effusion. A study of patients with hip OA suggested that patients with a purely atrophic radiographic pattern respond less well than those with a hypertrophic or mixed bone response.[151]

Injections of steroids should not be performed more than 3 or 4 times a year because of the risk of progressive damage to the cartilage by injection of weight-bearing joints. However recent studies suggest that the risk of cartilage degradation is minimal[152-155] except in the presence of chronic effusions.[156]

Studies of patients with inflammatory arthritis have shown that the duration and degree of response is significantly greater after a period of rest following an intra-articular steroid injection.[157,158] Although the effect of post-injection rest has not been studied in OA, bed rest for at least 24 hours is recommended after lower limb injections, and the use of a rigid bandage or splint for injection of the first CMC joint or finger joints.[81]

Some patients with OA may have pain arising from periarticular structures such as the ligament or capsulo-meniscal junction. They have localised tender points which respond to infiltration of local steroids.[159]

The side-effects of intra-articular steroids are sepsis, post-injection flares, atrophy of subcutaneous tissue, systemic effects such as facial flushing, and very rarely anaphylaxis.[160] The risk of sepsis is low, depending on the experience of the doctor, and was reported as 1/77 300 in a French study of 69 rheumatologists.[161] Acute inflammation of the joint may develop within 6 - 12 hours after an injection, but it usually settles spontaneously within 1 - 3 days.[162] However, an infection or crystal-associated arthritis should be considered if it persists. Atrophy of the skin and subcutaneous tissue and changes in pigmentation may occur in about 1% of patients.[163] Skin changes are most likely to occur with longer acting steroid preparations, injection of superficial joints or if there is extravasation or leakage into the soft tissues.

12.2.5 Newer therapies

12.2.5.1 Hyaluronic acid/hyaluronans

Hyaluronic acid (HA) is synthesised by synoviocytes, fibroblasts and chondrocytes and is a major constituent of the synovial fluid and articular cartilage. The concentration of HA is reduced in patients with OA. Viscosupplements of HA by intra-articular injection have been promoted to treat patients with OA by restoring the viscoelasticity of the synovial fluid. The use of HA has been the subject of many recent reviews.[81,164-166]

Several clinical trials suggest that HA is superior to placebo[167] and comparable with NSAIDs[168] in patients with knee OA. It has also been reported to be of value in hip OA.[169] Hyaluronic acid is administered as a course of 3 or 5 weekly injections, depending on the preparation used. It has been considered to be useful for both pain reduction and functional improvement.[4] Some patients may develop an acute arthritis or pseudoseptic reactions.

Relief of symptoms may last from 6 months to a year. It is of very little value in patients with severe OA and in patients with effusion. As HA is not superior to NSAIDs or intra-articular corticosteroids, it has been proposed as a therapeutic alternative in patients with moderate OA with little or no effusion who have failed to respond to non-pharmacological measures, analgesics or intra-articular steroids and who are either unable to tolerate NSAIDs or have contraindications to them.

Some patients may benefit from a repeat course of injections if symptoms recur. However, there is no conclusive evidence in humans to show that HA halts the progression of OA.[166]

12.2.5.2 Glucosamine sulphate and chondroitin sulphate

Glucosamine sulphate and chondroitin sulphate are considered to have a beneficial effect on cartilage and are widely used in the management of OA, although their efficacy has not been proven.[170] They are postulated to increase the formation and regeneration of cartilage as occurs with naturally occurring glucosamine and chondroitin. Glucosamine is one of the principal substrates in the biosynthesis of glycosaminoglycans, proteoglycans and hyaluronidase. Glucosamine undergoes acetylation and is then sulphated into keratin sulphate, heparan sulphate and hyaluronan. Keratan sulphate and hyaluronate are necessary to maintain the structural and functional integrity of articular cartilage. They enable the articular cartilage to avidly bind water and absorb pressure.[170] Chondroitin sulphate is part of the proteoglycan molecule and contributes to the resilience of the cartilage together with collagen and non-collagenous glycoproteins.[170]

Studies of cultured human chondrocytes suggest that glucosamine sulphate might improve chondrocyte biosynthesis[171] and inhibit enzymes that degrade cartilage.[172, 173] However, there are no animal studies to show that ingested glucosamine sulphate and chrondroitin sulphate are incorporated into articular cartilage.[174]

Recent prospective controlled studies have shown that glucosamine sulphate[175] and chondroitin sulphate[176] provide a small to moderate improvement in pain and function compared with placebo and provide pain relief comparable to NSAIDs. The 3-year prospective study with glucosamine also showed a disease-modifying effect with slowing of radiographic progression.[175] However, the finding of a disease-modifying effect with preservation of cartilage is still controversial as the radiographic techniques used to assess knee OA in this study (standard antero-posterior knee X-ray) have been questioned as being unreliable as changes in the joint space width can be altered significantly by relief of joint pain.[177] The National Institute of Health is currently conducting a 3-year randomised controlled trial comparing glucosamine sulphate, chondroitin sulphate, a combination of these and celecoxib with a placebo.

12.2.5.3 Diacerhein

Diacerhein, a purified compound with an anthroquinonic structure, has been shown to have beneficial effects on the cartilage in animal models of OA.[178,179] It differs from conventional NSAIDs and corticosteroids as it does not have any effect on cyclo-oxygenase but inhibits the effects of interleukin-1 (IL-1) on chondrocytes.[180] IL-1 plays an important role in the pathophysiology of OA and degradation of cartilage.

Diacerhein is effective in patients with hip OA.[178,181,182] An 8-week double-blind, placebo-controlled study showed that diacerhein was as effective as tenoxicam in providing symptomatic relief but had a slower onset of action, usually about 6 weeks.[178] A survey of 207 patients with knee and hip OA showed that the addition of diacerhein to standard OA therapy produced a good or excellent response in 60% of patients compared with 26% of patients who received standard therapy alone.[181] A recent 3-year prospective study showed that diacerhein may have a chondoprotective or structure-modifying effect in hip OA as there was a slowing of progression of joint space narrowing.[182]

Diacerhein is not available in South Africa.

12.3 Surgery

Referral to a surgeon is necessary if patients require assessment for their condition, e.g. where the symptoms are not typical, and when they have failed to respond to non-pharmacological and pharmacological measures.

- **Arthroscopy**. Arthroscopy and joint lavage is of value in patients with mild to moderate OA of the knee.
- **Joint replacement surgery**. Hip and knee arthroplasty produces excellent results and should be considered in patients who have severe symptoms and disability despite adequate non-pharmacological and pharmacological measures.
- **Other surgery**. Patients with OA of the first CMC joint or first MTP joint may require surgery such as fusion of these joints.

12.4 Management of OA at specific sites

The principles of management and role of the various non-pharmacological, pharmacological and surgical measures are discussed above.

This section will emphasise a few measures that need to be considered for specific sites.

12.4.1 Management of OA of the hips

12.4.1.1 Non-pharmacological therapy

The goal of an exercise programme is to maintain at least 30º of flexion and full extension of the hip as well as to strengthen the hip abductors and extensors.

OA of the hip commonly results in decreased range of motion, particularly internal rotation and extension. Reduced hip range of motion is associated with decreased walking speed.

The other critical requirement for reduction of impact loading on the joint cartilage is adequately conditioned muscle mass. It is necessary to include muscular conditioning in the form of concentric and eccentric strength and endurance at functional speeds.

Patients are advised to commence with non-weight-bearing or non-impact weight-bearing exercises, e.g. bicycle, rowing machine, health walker or aquatic exercises for the initial aerobic exercise period when pain and joint vulnerability limit weight-bearing exercises. They can later proceed to weight-bearing activities, e.g. walking, as safety and tolerance permit, and avoid steep gradients.

Aerobic activity for persons with OA includes range-of-motion and strengthening exercises as warm-up activities in a gradually progressive aerobic walking programme. The patient must at all times walk at a speed that does not produce increased pain at the time of the activity or afterwards.

A walking aid may be of value, depending on the severity of the symptoms and disability.

12.4.1.2 Pharmacological therapy — as above

Diacerhein has potential for structure-modifying effect and requires further evaluation.

12.4.1.3 Surgical treatment

Patients with severe symptomatic OA who have pain that has not adequately responded to medical and non-pharmacological methods should be referred for surgical opinion. Total joint arthroplasty provides marked pain relief and functional improvement in most patients with OA of the hip.

12.4.2 Management of OA of the knee

Periarticular disorders such as anserine and infrapatellar or prepatellar bursitis must be excluded. The hip must always be examined as referred pain from the hip to the knee and vice versa is well described.

12.4.2.1 Non-pharmacological therapy

Patients with patello-femoral OA may get relief by taping the patella on the medial side. A lightweight knee brace may be of benefit in patients with tibio-femoral disease, particularly with lateral instability.

The principles of exercise therapy for the knee are similar to those for the hip. The goal of exercise therapy is to maintain a flexion range of 90° which is required for getting up from a chair.

Conditioning exercises have been found to be feasible and effective in OA of the knee. The strengthening of the quadriceps muscles with either isometric, isotonic or resistive exercises is associated with significant improvement in quadriceps strength, knee pain and function. Weight reduction and the use of a walking aid must be considered where appropriate.

12.4.2.2 Pharmacological therapy

The role of glucosamine as a structure modifying agent requires further evaluation and the results of the National Institute of Health study are awaited.

12.4.2.3 Surgery

Arthroscopic joint lavage and conservative debridement is worth considering for non-end-stage disease that has not responded to comprehensive conventional medical management. Little advantage can be expected in patients with advanced disease. Therapeutic effects of lavage in OA could derive from several mechanisms, the most likely being the removal of potentially phlogistic cartilage fragments.

High tibial osteotomy for early medial compartment OA of the knee has been shown to produce satisfactory results in 85% of knees, at 6-year follow-up.[183] This operation is indicated in patients under 60 years of age. Obesity is a relative contraindication.

Knee replacement gives excellent results in the end-stage osteoarthritic knee.

12.4.3 OA of the small hand joints

12.4.3.1 Clinical assessment

Typically, PIP and DIP OA becomes symptomatic in the 5th decade. It may be clinically difficult to distinguish from RA in the early stages, but the characteristic joint distribution should point to the correct diagnosis. RA seldom involves the DIP joints. Later, typical radiological changes of joint space narrowing and osteophytes are seen.

The natural course of PIP and DIP disease is characterised by pain in the 5th decade, stabilising in the 6th decade and a relatively painless 7th decade, but with finger deformities.

OA of the CMC joint of the thumb typically starts with an aching in the joint with exacerbation after straining the joint, e.g. with a tight gripping action. Later almost continual pain is encountered, and in advanced disease loss of the web space is seen.

12.4.3.2 Non-pharmacological therapy

Non-pharmacological therapy requires the patient to avoid mechanically overloading the joint, e.g. with tight gripping actions or carrying heavy objects with the fingers such as a heavy shopping basket. The use of a splint may also provide symptomatic relief.

12.4.3.3 Pharmacological treatment

Intra-articular corticosteroids can be very effective at the CMC joint of the thumb but if more than 3 injections per year are required, surgery should be considered. Intra-articular injections of the PIP and DIP joints may be considered but are often technically difficult due to the osteophytes surrounding the joint line.

Surgery to the DIP and PIP joints has been disappointing.

13. Disclaimer

This national clinical guideline is for reference and education only and is not intended to be a substitute for the advice of the appropriate health care professional or for independent research and judgement. SAMA relies on the source of the national clinical guideline to provide updates and to notify us if the guideline protocol becomes outdated. SAMA accepts no responsibility or liability arising from any information contained in or any error in or omission from the protocol or from the use of any information contained in it.

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Annexure A: Methodology

This project was initiated by SAMA. On the recommendation of the South African Rheumatism and Arthritis Association (SARAA), Professor G M Mody was mandated with the task of developing the guidelines and invited the following to contribute to the process: R Asherson, D Bouwer, S Brighton, B Cassim, D Gotlieb, A A Kalla, O L Meyers, A Stanwix and M Tikly.

The draft for the Osteoarthritis: Clinical Guideline 2003 was drawn up by S Brighton, G M Mody, M Tikly and D Bouwer.

This project was funded by MSD and Searle in terms of an unrestricted educational grant.

On 3 and 4 December 1999, a nationally representative arthritis consensus meeting was held in Gauteng. Participants were invited as representatives of professional government and consumer groups with an interest in the arthritis field. Each organisation so invited, nominated its own representatives. All participants received a copy of a draft guideline developed previously together with the relevant references before the meeting. A neutral chairperson chaired the meeting. The purpose of the meeting was to consider the content of the draft guideline and to either endorse or amend the document. The proceedings were audio-recorded and transcribed for future reference.

The endorsement document was revised according to the proceedings of the national consensus meeting and was circulated to all participants and many other interested persons.

Amendments to this endorsement draft were made where there was sufficient need as indicated by the comments received. The document as revised was submitted to the SAMA Guideline Committee for endorsement according to the set criteria. Once endorsed, the guideline was sent for publication to the *South African Medical Journal*.

The grants were made in accordance with the SAMA code of sponsorship, which precludes attempts by sponsors to influence, unethically, the content of the guideline. All funds were paid directly into SAMA's accounts and all disbursements were made from that fund.

Annexure B: Consensus Group for Arthritis Guidelines

South African Medical Association: F J Milne (Chairperson); Arthritis Foundation: O L Meyers; Representatives of the Authoring Group (SARAA): A A Kalla, D Gotlieb, G Mody, S Brighton, O L Meyers; DENOSA: G Brown; Department of Health: Directorate Pharmacy (EDL): J Ludick, Directorate Chronic Disease: C Kotzenberg; National Osteoporosis Foundation: C Schnitzler; National Pathology Group: P Cole; Pain Management Society of SA and SAMA Nominee: P Dessein; Radiological Society of SA: P du Plessis; SAMA: Centre for Quality Care: V Pinkney-Atkinson; SAMA Nominee: D Kastanos; SA Academy of Family Practice: S Namane; SA Association of Occupational Therapists: T Pistorius; SA Orthopaedic Association: N J G Maritz; SA Society of Physiotherapy: H Gardener; Society for General and Family Practitioners: J Fourie; **Observer delegates:** MSD: M Combrink, B Crouse, S Nkalashe, B Prinsloo; Searle: M Doveton, G Hirsch, G Muir, L Wiggil; Medscheme: H Seftel.

Rheumatoid Arthritis: Clinical Guideline 2003

Principal authors: A A Kalla, A Stanwix, D Gotlieb, R A Asherson, G M Mody

Summarised Guideline

1. Objective

- To promote a better understanding of rheumatoid arthritis (RA) and the rationale for the use of the various forms of therapy.
- To provide guidelines for the efficient and cost-effective management of RA.

2. Introduction

RA is associated with a significant morbidity and mortality and has a major economic impact on society. The availability of newer and more effective forms of therapy will further revolutionise the management and improve the outcome of RA.

3. Definition

RA is an autoimmune disease of unknown aetiology characterised by chronic symmetrical, inflammatory, erosive polyarthritis and is associated with a variety of extra-articular manifestations.

4. Epidemiology

RA has been reported worldwide in all ethnic groups. The overall prevalence of RA in Caucasians is 1%. The incidence of RA may be lower and the disease less severe in rural sub-Saharan Africans and in Caribbean blacks. The female to male ratio is approximately 3:1.

5. Aetiology

The aetiology of RA is unknown but is probably multifactorial. One of the major genetic factors is the HLA DR4 antigen, which is present in about 70% of Caucasians with RA compared with 20 - 30% of controls.

Please forward all comments to: **Private Practice Unit, South African Medical Association, PO Box 74789, Lynnwood Ridge, 0040 (tel. (012) 481-2073)**

6. Pathology and pathophysiology

The pathological changes in RA are swelling of the synovial membrane with infiltration by lymphocytes, plasma cells and macrophages; hyperplasia and hypertrophy of the synovial membrane; and the formation of inflammatory granulation tissue (pannus) which leads to erosion of the articular cartilage and bony surface and subsequently fibrous and, occasionally, bony ankylosis.

7. Diagnosis of rheumatoid arthritis

According to the American College of Rheumatology (ACR) criteria, the presence of swelling of a joint due to either synovial thickening or effusion must be observed by a doctor and be present for at least 6 weeks in order to exclude self-limited conditions such as viral-associated arthritis. For classification purposes a patient shall be said to have RA if at least 4 of 7 criteria are present. A test for rheumatoid factor RF must be performed in all patients with suspected RA.

8. Extra-articular features of RA

A wide spectrum of extra-articular manifestations may be seen in patients with RA. Subcutaneous nodules may be detected along bony prominences and along tendon sheaths. Common sites for the presence of nodules are the extensor aspects of the upper forearm, olecranon bursa, occiput, buttock and tendons of the hands and legs. Subcutaneous nodules are usually associated with a positive RF. Multiple organs may be affected.

9. Natural history

In view of the variable course of RA, numerous attempts have been made to identify factors that indicate a poor prognosis so that these patients may receive more intensive therapy early in the course of the disease. In the early stages there is marked inflammation of the joints with minimal evidence of joint destruction. Later in the course of the disease, there is likely to be severe joint destruction if there is inadequate suppression of inflammation in the early stages of the disease.

10. Measures of outcome and remission

The cumulative effect of joint destruction over time has many consequences which are referred to as dimensions of outcome. Outcome is measured by different dimensions including disability, discomfort, side-effects, monetary costs and death.

11. Impact and burden

The previously held belief that RA was a disease with a good prognosis which could be controlled by conservative regimens is contrary to the current experience of health professionals, health care funders, patients and their families. We now recognise that RA has a major impact on the patient and society as it may lead to increased mortality, significant pain, fatigue, disability and functional loss and substantial psychological and social effects. The economic consequences of RA include direct costs, indirect costs and intangible costs.

12. Initial evaluation of the patient

A detailed examination of the musculoskeletal system is mandatory at initial assessment. The clinical examination must include assessment of all the peripheral joints as well as the spine. Practitioners involved in the care of patients with RA should be familiar with the systematic examination of the musculoskeletal system. The examination of the joints must include assessment for signs of inflammation such as swelling, warmth, tenderness, the range of movement of the joints and the presence of deformities.

13. Assessment of disease activity

Assessment of disease activity in RA is based on:

- history (duration of early morning stiffness, time to onset of fatigue, night pain)
- physical examination (presence of joint swelling, tenderness)
- laboratory tests — erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)
- functional assessment (ability to function independently with respect to self-care, vocational and avocational activities).

The progression of RA is best assessed on serial radiographs of the hands and feet. Radiographs of selected involved areas such as the cervical spine (including flexion and extension views), knees or other joints should be performed if clinically indicated.

14. Management

At initial presentation it is essential to confirm the diagnosis, assess the extent and activity of the disease and detect any extra-articular manifestations.

14.1 Goals of treatment

We know that uncontrolled synovial inflammation leads to joint damage early in the course of the disease. Early initiation of disease-modifying antirheumatic drug (DMARD) therapy is therefore essential to suppress inflammation. The goals of treatment are to alleviate pain and inflammation in order to keep the joints mobile and to prevent deformity and destruction of the joint.

14.2 Non-pharmacological

It is the responsibility of the doctor to initiate the process of informing the patient about the disease, once the diagnosis of RA has been made. The goals of rehabilitation interventions are to control pain, prevent deformity, preserve or improve function and prevent disability. This is achieved by the interaction of a multidisciplinary team which includes a rheumatologist, orthopaedic surgeon, nurse, physiotherapist, occupational therapist, orthotist, podiatrist, and social worker. The physiotherapist (PT) plays an important role in the education of the patient, management of acute and non-acute disease, as well as pre- and postoperative assessment and management. The occupational therapist assesses and treats the patient's level of functioning in terms of personal management, work and leisure activities.

14.3 Pharmacological

The pharmacological therapies available for the treatment of RA are used for symptomatic relief and to modify the natural progression of the disease. Many patients require analgesics for control of pain, but they do not have any effect on suppressing inflammation or modifying the disease. In the treatment of RA, non-steroidal anti-inflammatory drugs (NSAIDs) are the first line of therapy. Although they are effective for pain relief and control of inflammation, they do not alter the course of the disease and should be used in conjunction with DMARDs. Any patient who has persistent synovitis, with or without joint damage, should have DMARD therapy started promptly to prevent or slow further damage. While DMARDs have certain common characteristics, they differ in their efficacy, side-effect profile and onset of action, which varies from 1 to 6 months before a clinical response is evident.

Methotrexate (MTX) has become the dominant DMARD and is among the best studied long-term agents in patients with RA. Experience with MTX has shown that up to 80% of patients respond within the first 12 weeks of treatment. Approximately 30% of patients will discontinue MTX due to toxicity. If the aspartate aminotransferase (AST) is elevated above the upper limit of normal in half the tests over a year or if there is a decrease in albumin (in the setting of well-controlled RA), then a liver biopsy should be considered if MTX is to be continued. Sulphasalazine (SSZ) is introduced slowly over the first month to avoid problems of nausea and gastrointestinal (GI) irritability — starting 0.5 g daily for 1 week, then 1 g daily for 1 week (divided doses), then 1.5 g daily for 1 week (divided doses), and thereafter 1 g twice a day. The use of chloroquine is generally for milder disease or in

combination therapy and it takes about 3 - 6 months to demonstrate efficacy. Many patients require low-dose oral glucocorticoid (GC) therapy initially (7.5 - 10 mg daily) and the dosage should be reduced and gradually stopped if possible. High-dose oral therapy, given in reducing doses over a 3 - 4 week period is required for specific indications, e.g. certain extra-articular manifestations of RA. GCs are a major risk factor for osteoporosis. Treatment consists of elemental calcium 1 g daily and calciferol (vitamin D) 50 000 units weekly combined with antiresorptive therapy in the form of hormone replacement therapy and/or bisphosphonates.

There are two TNF α-antagonists which have been used in RA (infliximab and etanercept). Leflunomide is a newer immunomodulatory drug which inhibits pyrimidine synthesis. It is of value in patients who are also unresponsive to or cannot tolerate MTX. Newer monoclonal antibodies are being developed, including anakinra, a recombinant human form of interleukin-1 receptor antagonist (IL-1Ra), which acts by blocking the binding of IL-1α and IL-1β to IL-1 receptor, thereby preventing the activation of target cells.

Many patients with RA require multiple drugs for the management of associated conditions such as depression, diabetes mellitus, hypertension, cardiac failure and gastropathy. Combination DMARD therapy is also being increasingly advocated.

14.4 Surgery

Surgical management of patients with RA should be viewed as part of the continuum of their treatment. Surgical management varies depending on the ACR anatomic stage of joint destruction. Anaesthesia of the patient with RA can be extremely hazardous. In patients with RA, anaesthesia is safest in a specialist environment.

14.5 Refractory RA

Management of patients with refractory RA is one of the major challenges in modern rheumatology. For practical purposes, patients may be considered as having refractory RA when they have failed to respond to conventional DMARDs such as chloroquine, salazopyrine and MTX, either singly or in combination. The biological agents (tumour necrosis factor (TNF) antagonists) or leflunomide are useful in these patients.

15. Women's health issues

15.1 Fertility

RA has no adverse effect on fertility. Reproductive processes are normal in patients with RA and the usual investigations would be necessary to ascertain the cause for infertility.

15.2 Pregnancy

RA tends to improve during pregnancy and there is therefore a reduced need for drug therapy during the gestational period. CSs in low dose are generally safe in pregnancy and may be needed to control symptoms.

15.3 Lactation

Many of the drugs used to treat RA are excreted in breast-milk and the DMARDs should be deferred until breast-feeding has stopped, while NSAIDs should be used with caution.

15.4 Menopause

RA may start in the menopausal period and many patients with onset in adult life will reach the menopause.

16. Disclaimer

This national clinical guideline is for reference and education only and is not intended to be a substitute for the advice of the appropriate health care professional or for independent research and judgement. SAMA relies on the source of the national clinical guideline to provide updates and to notify us if the guideline protocol becomes outdated. SAMA accepts no responsibility or liability arising from any information contained in or any error in or omission from the protocol or from the use of any information contained in it.

Full Guideline

1. Abstract

Rheumatoid arthritis (RA) is a chronic inflammatory polyarthritis, which if untreated or inadequately treated, results in the destruction of joints and severe functional disability. Although the major effects of the disease are on the joints, it may be accompanied by a variety of extra-articular manifestations.

RA affects approximately 1% of the population in most parts of the world. It is one of the leading causes of disability and has a major impact on the utilisation of health care resources. Recent advances in our understanding of the pathogenesis of the disease and the availability of more effective forms of therapy have emphasised the need for early diagnosis and the institution of aggressive medical therapy to suppress inflammation and prevent joint destruction.

2. Abbreviations

ACR = American College of Rheumatology; ALT = alanine aminotransferase; AST = aspartate aminotransferase; AZA = azathioprine; COX = cyclo-oxygenase; CRP = C-reactive

protein; CS = corticosteroid; CXR = chest X-ray; DMARD = disease-modifying antirheumatic drug; ESR = erythrocyte sedimentation rate; FBC = full blood count; FC = functional class; GC = glucocorticoid; GGT = gamma-glutamyl transpeptidase; GI = gastrointestinal; GIT = gastrointestinal tract; HAQ = Health Assessment Questionnaire; HIV = human immunodeficiency virus; HLA = human leucocyte antigen; IA = intra-articular; IL-1 = interleukin-1; MCP = metacarpophalangeal; MCV = mean cell volume; MTP = metatarsophalangeal; MTX = methotrexate; NSAID = non-steroidal anti-inflammatory drug; PG= prostaglandin; PIP = proximal interphalangeal; PPI = proton pump inhibitors; PT = physiotherapist; RA = rheumatoid arthritis; RF = rheumatoid factor; SF-36 = short form 36; SSZ = sulphasalazine; TNF = tumour necrosis factor; TNF∝ = tumour necrosis factor alpha;
TNFR = tumour necrosis factor receptor; WHO =World Health Organisation.

3. Objective

The objective of this guideline is to:

- promote a better understanding of RA and the rationale for the use of the various forms of therapy
- provide guidelines for the efficient and cost-effective management of RA.

4. Introduction

RA is associated with a significant morbidity and mortality and has a major economic impact on society. As a result, increasing attention has focused on strategies to initiate early and appropriate therapy to suppress inflammation and prevent joint destruction. The availability of newer and more effective forms of therapy will further revolutionise and improve the management of RA. It is important to ensure that currently available modalities of management are utilised optimally to achieve a favourable outcome.

The American College of Rheumatology (ACR) has published general guidelines for the management of RA,[1] monitoring of drug therapy in RA,[2] and monitoring therapy with methotrexate.[3]

5. Definition

RA is an autoimmune disease of unknown aetiology characterised by chronic symmetrical, inflammatory, erosive polyarthritis, and is associated with a variety of extra-articular manifestations.

6. Epidemiology

RA has been reported worldwide in all ethnic groups. The overall prevalence of RA in Caucasians is 1%. The incidence of RA may be lower and the disease less severe in rural sub-Saharan blacks and in Caribbean blacks.[4] The female/male ratio is approximately 3 : 1.

The majority of patients develop the disease between the age of 35 and 50 years.

Epidemiological surveys in South Africa have shown that the prevalence of RA in an urban black population was 0.9%,[5] which is similar to the prevalence of approximately 1% reported in Caucasians in other parts of the world. However, a significantly lower prevalence of 0.12% was reported in the rural Tswana population.[6] A lower prevalence of RA was also reported among the rural Xhosa[7] and rural coloured populations.[8]

A survey of 256 patients with RA in South Africa among Caucasians, coloureds and blacks showed that the female/male ratio was 2.8 : 1 and there was no significant difference among the races.[9] The mean age at onset of RA was significantly younger in blacks (36.5 years) than in coloureds (38.9 years) and Caucasians (44.2 years).[9]

7. Aetiology

The aetiology of RA is unknown, but is probably multifactorial. Twin and family studies have shown that genetic factors do play a role. Approximately 10% of patients with RA may have an affected first-degree relative.[10] One of the major genetic factors is the HLA DR4 antigen which is present in about 70% of Caucasians with RA compared with 20 - 30% of controls.[11] This association has been confirmed in many parts of the world; however, Israeli Jews and Asian Indians show an association with HLA DR1.[12,13]

Genetic studies in South Africa have confirmed a significant association of HLA DR4 with RA among Zulus,[14] Caucasians and coloureds[15] and other African blacks.[16]

A variety of infectious agents have been studied as possible triggering agents in genetically susceptible hosts, but most of the findings have been disappointing and the nature of the triggering agent therefore remains elusive.[17]

8. Pathology and pathophysiology

The pathological changes in RA are swelling of the synovial membrane with infiltration by lymphocytes, plasma cells and macrophages; hyperplasia and hypertrophy of the synovial membrane; and the formation of inflammatory granulation tissue (pannus), which leads to erosion of the articular cartilage and bony surface and subsequently fibrous and, occasionally, bony ankylosis.

The presentation of an antigen to the macrophages leads to the activation of T cells which trigger the immune response and inflammation, and stimulate the B cells to produce antibodies such as rheumatoid factor (RF). The large number

of T cells, primarily with an activated/memory phenotype, in the synovium is a strong indication that they have a key role to play in the pathogenesis of RA. The T cells play an important role in the pathogenesis of RA and large amounts of T-cell-derived cytokines are found in the synovial fluid and membrane. The hyperplasia of the synovial lining cells and the formation of pannus leads to the production of cytokines such as tumour necrosis factor alpha (TNF∝) and interleukin-1, interleukin-6, matrix metalloproteinases (e.g. collagenases) and prostaglandins (PGs), which result in the irreversible destruction of cartilage and subchondral bone.[18] The PGs are important mediators of inflammation, but suppression of PG activity alone is not sufficient to inhibit the progressive joint destruction characteristic of the disease.

9. Diagnosis of RA

The ACR criteria for the classification of RA are shown in Table I.[19] According to the criteria, the joint swelling due to either synovial thickening or effusion must be observed by a doctor and be present for at least 6 weeks in order to exclude self-limited conditions such as viral-associated arthritis. For classification purposes a patient shall be said to have RA if at least 4 of the 7 criteria are present. Criteria 1 through 4 must have been present for at least 6 weeks.

In the early stages of RA, patients may present with constitutional disturbances such as fatigue, malaise and weight loss. Patients who have florid synovitis with obvious swelling of the joints present little difficulty on clinical assessment. However, in the early stages, synovitis may be difficult to assess and may not be detected by an inexperienced observer. The experience from early arthritis clinics in several overseas centres suggests that many patients will turn out not to have RA and their symptoms will resolve over 6 - 12 weeks.

Patients with the fibromyalgia syndrome can have severe joint pain in the absence of synovitis, leading to a misdiagnosis of early RA, and they may receive inappropriate treatment. Thus referral to a rheumatologist or physician experienced in rheumatic diseases is advisable, to confirm the diagnosis before embarking on a long-term plan of management.

A test for RF must be performed in all patients with suspected RA. It is positive in about 80% of patients with RA.[20] It is therefore still possible to make a diagnosis of RA in the absence of a positive RF. There are many causes of a false-positive test, including chronic infections such as infective endocarditis and tuberculosis as well as other connective tissue diseases.[20] A positive RF may be present in about 15% of the elderly and in about 5% of normal subjects.[21] Seronegative RA has a somewhat better prognosis than seropositive RA.[22]

10. Extra-articular features of RA

A wide spectrum of extra-articular manifestations may be seen in patients with RA. Subcutaneous nodules may be detected along bony prominences and along tendon sheaths. Common sites for the presence of nodules are the extensor aspects of the upper forearm, olecranon bursa, occiput, buttock and tendons of the hands and legs. Subcutaneous nodules are usually associated with a positive RF. They are detected in about 25% of RA patients, although they have been reported less often in African blacks.[23]

Some of the common extra-articular manifestations of RA are shown in Table II.

Table I. The 1987 revised criteria for the classification of RA* (Adapted from Arnett *et al*.[19])

Criterion	Definition
1. Morning stiffness	Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement
2. Arthritis of 3 or more joint areas	At least 3 joint areas simultaneously have had soft-tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints
3. Arthritis of hand joints	At least 1 area swollen (as defined above) in a wrist, MCP, or PIP joints
4. Symmetrical arthritis	Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry)
5. Rheumatoid nodules	Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxtaarticular regions, observed by a physician
6. Serum RF	Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in < 5% of normal control subjects
7. Radiographic changes	Radiographic changes typical of rheumatoid arthritis on postero-anterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localised in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify)

*For classification purposes a patient shall be said to have RA if he/she has satisfied at least 4 of these 7 criteria. Criteria 1 through 4 must have been present for at least 6 weeks.
PIP = proximal interphalangeal; MCP = metacarpophalangeal; MTP = metatarsophalangeal.

Table II. Common extra-articular manifestations of RA

Skin	
	Subcutaneous nodules, cutaneous vasculitis, skin rashes due to drug toxicity
Cardiac	
	Pericardial effusion, valvulitis
Pulmonary	
	Pleural effusion, pulmonary fibrosis, pulmonary nodules, Kaplan's syndrome (rheumatoid nodules associated with pneumoconiosis), bronchiolitis obliterans
Haematological and reticulo-endothelial	
	Anaemia, neutropenia with splenomegaly (Felty's syndrome), lymphadenopathy, thrombocytosis (with active disease or gastrointestinal bleeding)
Eye	
	Keratoconjunctivitis sicca (Sjogren's syndrome), episcleritis, scleritis, scleromalacia perforans
Neurological	
	Entrapment, e.g. carpal tunnel syndrome
	Peripheral sensory or sensorimotor neuropathy
	Mononeuritis multiplex
	Myelopathy associated with atlantoaxial instability

11. Natural history

The natural history of RA is variable. A small proportion of patients have low-grade inflammation which is not progressive and responds to non-steroidal anti-inflammatory drugs (NSAIDs). However, as shown in Fig. 1, the vast majority of patients have episodes of exacerbation and remission which, if untreated, lead to progressive joint destruction and impaired function.[24]

Fig. 2 is a graphic representation of the natural history of

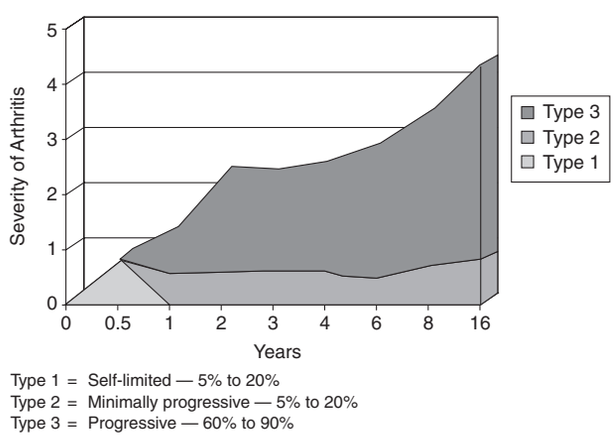

Fig. 1. Clinical course of RA (adapted from Pincus[25]).

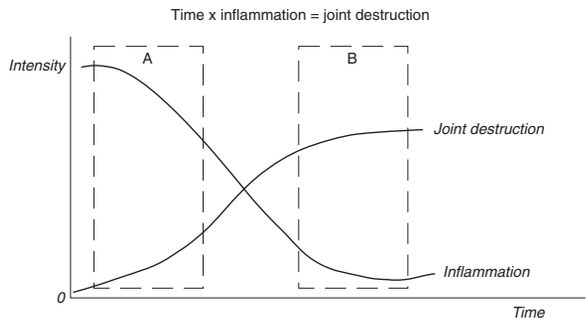

Fig. 2. Natural history of RA.

RA showing the variation in the extent of inflammation and progression of joint destruction during the course of RA.

In the early stages there is marked inflammation of the joints with minimal evidence of joint destruction (Fig. 2 – A). Studies using magnetic resonance imaging have shown that joint erosions may occur as early as 12 weeks and may reach a maximum within 2 years.[26] Disease-modifying drug therapy should therefore be initiated at this stage to suppress inflammation and prevent destruction of cartilage and bone.

Later in the course of the disease, there is likely to be severe joint destruction if there is inadequate suppression of inflammation in the early stages of the disease (Fig. 2 – B). Some patients still have significant inflammation of the joints and require disease-modifying drug therapy. However, usually there is less severe inflammation and the symptoms are related to joint destruction (secondary osteoarthritis) which may require surgery.

In view of the variable course of RA, numerous attempts have been made to identify factors that indicate a poor prognosis so that these patients may receive more intensive therapy early in the course of the disease. Factors associated with a poor prognosis are summarised in Table III.[27] Patients with RA who have persistent, inflammatory, symmetrical polyarthritis of the hands and feet are more likely to have a worse outcome.[28] These patients usually carry the HLA DR4 epitope.[28]

Table III. Factors associated with a poor prognosis[27]

Early age of onset
High-titre RF
Marked elevation of ESR and CRP
> 20 swollen joints
Early radiographic detection of erosion
Severe functional disability at presentation
Genetic markers
Extra-articular disease

ESR = erythrocyte sedimentation rate; CRP = C-reactive protein.

12. Measures of outcome and remission

The cumulative effect of joint destruction over time has many consequences, which are referred to as dimensions of outcome. The World Health Organisation (WHO) developed the concept of impairment, disability and handicap.[29] Inflammation causes an impairment in the form of limited motion or deformities, which cause disability such as difficulty with daily activities or work, resulting in the handicap as an inability to fulfil an appropriate role in society. More recently, the WHO has developed a revised International Classification of Functioning which will be available for future use.

Outcome is measured by different dimensions including disability, discomfort, side-effects, monetary costs and death.[30-33] Health status and quality of life can be measured by instruments such as the Health Assessment Questionnaire (HAQ)[30] and short form 36 (SF-36)[34] which are self-administered questionnaires covering the dimensions of physical, social and emotional functioning. There is significant correlation between the ACR functional classification[35] (Table IV) and the HAQ score.

Table IV. Criteria for the classification of functional status in RA[35]

Class I	Completely able to perform usual activities of daily living (self-care, vocational and avocational)
Class II	Able to perform usual self-care and vocational activities, but limited in avocational activities
Class III	Able to perform usual self-care activities, but limited in vocational and avocational activities
Class IV	Limited in ability to perform usual self-care, vocational and avocational activities

Disability can easily be assessed using the ACR Functional Status Classification (Table IV) and should be assessed at 6-monthly intervals. This simple classification categorises the disability with respect to self-care, function at work and the ability to participate in recreational activities.[35] Usual self-care activities (include dressing, feeding, washing, grooming and using the toilet), avocational activities (recreational and/or leisure) and vocational (work, school, homemaking) activities are patient-desired and age- and sex-specific.

Table V. ACR criteria for remission in RA[36]

1. Morning stiffness < 15 minutes
2. No fatigue
3. No joint pain
4. No joint tenderness or pain on rotation
5. No soft-tissue swelling of joints or tendon sheaths
6. ESR (Westergren) < 30 mm/ h (females) or < 20 mm/h (males)

Exclusions: Vasculitis, pericarditis, pleurisy, myocarditis, unexplained fever, weight loss

Remission is present if a minimum of 5 features are present for at least 2 consecutive months, in the absence of systemic disease.

ESR = erythrocyte sedimentation rate.

The goal of therapy is to induce remission as defined by the ACR[36] in terms of clinical and laboratory variables (Table V). The criteria for remission are very stringent and most patients do not achieve a total remission despite aggressive therapy. The response to therapy is therefore assessed by improvement in activity variables including the swollen joint count, tender joint count, patient's own assessment of pain, disease activity and physical function, physician's assessment of disease activity and level of the acute phase reactants.[37] The extent of improvement can be expressed as a percentage change from baseline (20%, 50%, 70%), referred to as ACR20, ACR50 or ACR70.

The ACR has also classified the anatomical grades of joint deterioration on X-rays in four stages, as set out in Table VI.

Table VI. ACR classification of joint deterioration

Stage I	X-rays reveal no bone and cartilage erosions
Stage II	Osteopenia has developed with or without slight subchondral bone or cartilage destruction
Stage III	There is obvious destruction of bone and cartilage
Stage IV	End stage with fibrosis or bony ankylosis

13. Impact and burden

Callahan[38] has recently reviewed the impact and burden of RA.[38] The previously held belief that RA was a disease with a good prognosis which could be controlled by conservative regimens is contrary to the current experience of health professionals, health care funders, patients and their families. We now recognise that RA has a major impact on the patient and society, as it may lead to increased mortality,[39-41] significant pain, fatigue, disability and functional loss, and substantial psychological and social effects.[40] The economic impact of RA is difficult to determine accurately, but was estimated to be $14 billion per year in 1992 in the USA[38] and is projected to be about $95 billion in 2000.

The economic consequences of RA include direct costs, indirect costs and intangible costs.[38]

- **Direct costs:**
  - are related to the provision of medical care such as hospitalisation, medication, diagnostic tests and physician costs
  - are shown to be related to the functional status of the patient, with higher costs for more severe disease.
- **Indirect costs:**
  - are estimated to be 3 - 4 times higher than the direct costs
  - include loss of income as a result of reducing or stopping work

- include the fact that patients with RA are more likely to have stopped working or reduced their work hours, resulting in a drop in their household income, than healthy people or patients with osteoarthritis.

- **Intangible costs:**
  - are related to pain, loss of function and impaired quality of life
  - include pain, depression, anxiety, limitation in performance of household, social, recreational and sexual activities, and changes in appearance resulting from deformity
  - include effects on psychological well being, measured in terms of depression, coping strategies, anxiety, cognitive change and learned helplessness. Psychological distress is commoner among RA patients than patients with other chronic disease.[37]

The risk associated with RA is related to the significant morbidity and increased mortality. Patients with RA who have severe disability (functional class (FC) III or IV) have mortality rates comparable to those seen in patients with triple-vessel coronary artery disease and Hodgkin's disease.[42] The average lifespan of patients with RA is 6 - 7 years less than age-matched controls without RA.[39] Factors contributing to the poor outcome are disease-related complications, co-morbid disease, cardiovascular disease and infections.[39-41,43]

The benefit of therapy needs to be evaluated against the risk associated with the disease. The beneficial effect of NSAIDs and disease-modifying antirheumatic drugs (DMARDs) compared with placebo has been confirmed in many studies. The toxicity associated with the use of DMARDs compared with that of NSAIDs is less than previously suspected.[44] Regular and careful monitoring of patients will further reduce the risk of serious adverse events.

A risk-benefit assessment of the risk of the disease and the potential toxicity associated with therapy has led to a revolutionary remodelling of the conventional pyramidal approach to the management of RA.[45] Previously there was a delay in initiating DMARD therapy. However, the current approach is to introduce DMARDs early in the course of the disease in order to suppress inflammation and prevent joint damage. Combinations of DMARDs are often necessary to achieve a remission and to prevent radiological and functional deterioration.[46] Such regimens are also effective in refractory RA.

14. Initial evaluation of the patient

The essential components of the initial evaluation of patients are summarised in Table VII.

Table VII. Initial evaluation

Symptoms	Distribution of joint pain, morning stiffness, fatigue, disability
Examination	Synovial and tendon inflammation, mechanical joint problems and extra-articular manifestations
Investigations	
Laboratory	FBC, ESR, CRP, rheumatoid factor, urinalysis, creatinine, electrolytes, AST, ALT, albumin
Radiograph	Hands, feet (A-P views) and selected involved joints

FBC = full blood count; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; AST = aspartate aminotransferase; ALT = alanine aminotransferase; A-P = anteroposterior.

14.1 Musculoskeletal examination

- A detailed examination of the musculoskeletal system is mandatory at initial assessment.[47]
- Peripheral joint examination should include assessment for signs of inflammation such as swelling, warmth, tenderness or reduction in the range of movement and the presence of deformities. It is important to ascertain whether swelling is due to synovial thickening, effusion or bony enlargement.
- Joints such as the hip or cervical spine do not show any swelling and the involvement of these joints is detected by tenderness on movement or limitation of movement.
- Involvement of periarticular structures such as muscles, ligaments or tendons may also contribute to pain and impaired function, e.g. flexor tenosynovitis may also contribute to pain, swelling and limitation of movement.
- Factors that contribute to limitation of movement include synovial inflammation, tenosynovitis, muscle weakness, contractures or mechanical damage.

14.2 Radiology

- The progression of RA is best assessed on serial radiographs of the hands and feet. Radiographs of selected involved areas such as the cervical spine (including flexion and extension views), knees or other joints should be performed if clinically indicated.
- The cervical spine should be carefully assessed in the patient with neck pain. Atlantoaxial instability is an important cause of neck pain and will be missed if lateral flexion/extension views are not requested. Careful neurological examination should always be performed in the RA patient with neck pain. In addition, the anaesthetist will need to be aware of the presence of atlantoaxial subluxation in patients with long-standing disease who require surgery under general anaesthesia.

15. Assessment of disease activity

Assessment of disease activity in RA is based on the

- history (duration of early morning stiffness, time to onset of fatigue, night pain)

- physical examination (presence of joint swelling, tenderness)
- laboratory tests erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)
- functional assessment (ability to function independently with respect to self-care, vocational and avocational activities).

Improvement is not uniform in all variables, as some measures improve while others may persist. It is assumed that suppression of the inflammation will improve outcome, but evidence suggests that radiological changes may worsen in spite of improvement in standard measures of disease activity.[48] The ESR is more accessible but not as sensitive as the CRP in detecting a therapeutic response. Persistent elevation of either is predictive of cumulative damage.

16. Management

The management of RA is summarised in Fig. 3, and the goals of treatment in Table VIII.

Table VIII. Goals of treatment

Relief of pain and inflammation
Prevention of irreversible joint damage
Preservation of function or improvement of disability if present
Improvement of quality of life
Alteration of the natural history of the disease

16.1 Goals of treatment

At initial presentation it is essential to confirm the diagnosis, assess the extent and activity of the disease and detect any extra-articular manifestations. It is preferable for the patient to be referred to a rheumatologist or physician experienced in treating rheumatic diseases at this stage to confirm the diagnosis and formulate a plan of management, which will need to be individualised according to the activity and severity of the disease. In patients with early disease, the aim of therapy is to try to achieve a complete remission to enable patients to return to a normal lifestyle. However, if patients present with established disease and deformities, a programme of rehabilitation is initiated to improve function and prevent further progression of the disease.

We know that uncontrolled synovial inflammation leads to joint damage early in the course of the disease. Therefore early initiation of DMARD therapy is essential to suppress inflammation. Regular follow-up and monitoring for disease progression is necessary.

The management of RA is summarised in Table IX.

Table IX. Management of RA

Non-pharmacological
Patient education
Role of nurse practitioner
Physiotherapy
Occupational therapy
Pharmacological
Analgesics
NSAIDs
DMARDs
Corticosteroids
Newer therapies
Surgery

16.2 Non-pharmacological

16.2.1 Patient education

It is the responsibility of the doctor to initiate the process of informing the patient about the disease, once the diagnosis of RA has been made. The educational process is extended and reinforced by other members of the health care team. Social agencies such as the Arthritis Foundation of South Africa are able to supply educational materials that provide an understanding of the disease and the role of various modalities of therapy. Arthritis self-help groups are also available in some of the major centres and help to empower patients to play an

Table X. Educational topics for patients with RA

Nature of the disease process
Basic knowledge of anatomy of the joint
Cause of RA is unknown
Chronic nature of the illness and variable course
Systemic nature of the illness
Treatment
Role of non-pharmacological measures
Suppression of inflammation and relief of pain
Induction of remission and prevention of long-term joint destruction
Benefits and adverse effects of the various forms of drug therapy
Role of surgery, where indicated
Need for continuous long-term monitoring and follow-up
Behaviour modification
Role of rest during episodes of acute inflammation
Importance of exercise to preserve function
Beneficial effects of joint protection techniques and devices
Avoidance of weight gain
Job modification, if necessary
Emotional support
Alleviation of any guilt felt by the patient
Alteration of body image due to deformity
Difficulty with sexual activity
Involvement of family and employer

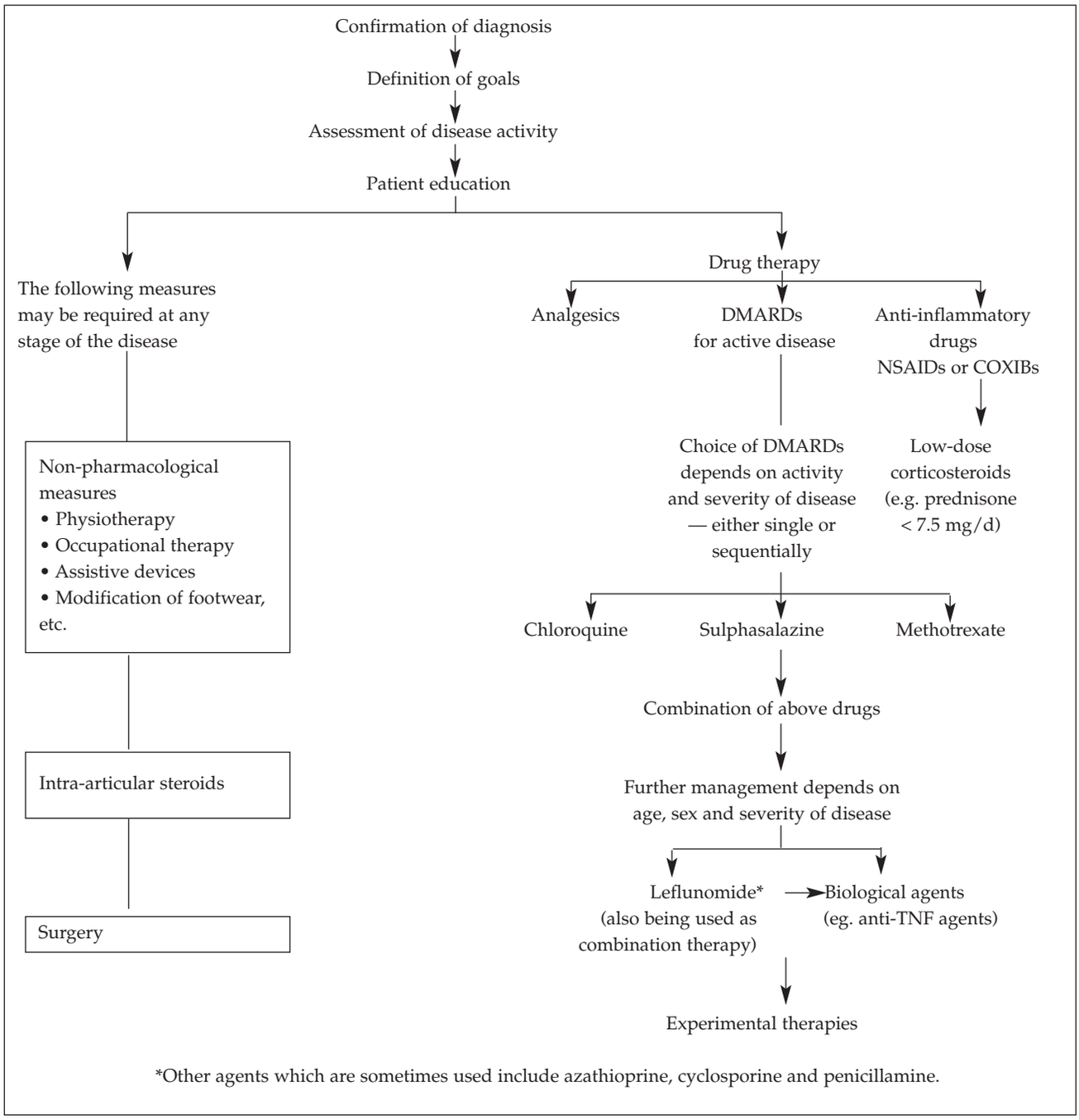

Fig. 3. Management of RA. This algorithm serves as a guide. In individual patients, depending on their age, sex, severity of the disease and functional status, it may be necessary to progress more rapidly to aggressive therapy.

active role in the management of their disease.

Some of the educational topics that need to be addressed are shown in Table X and include:

- an understanding of the nature of the basic disease process
- the role of the various forms of therapy
- the need for behaviour modification according to the symptoms and disability
- the need for emotional support.

16.2.2 Role of the multidisciplinary team

The consequences of RA are pain, functional impairment and disability. Physiotherapy and occupational therapy are part of the comprehensive management of RA. The goals of rehabilitation interventions are to control pain, prevent deformity, preserve or improve function and prevent disability. This is achieved by the interaction of a multidisciplinary team which includes a rheumatologist, orthopaedic surgeon, nurse,

physiotherapist (PT), occupational therapist, orthotist, podiatrist, and social worker.

16.2.2.1 The rheumatology nurse practitioner

A trained rheumatology nurse is able to provide care for patients using a combination of skills such as supporting, helping, teaching and counselling. Nursing activities may include the following:

- assessing the patient's acceptance and knowledge of disease and therapy
- providing education to the patient and the family
- identifying patient-focused problems and providing a plan of care
- recognising psychological problems affecting the patient and providing counselling and support
- assessing and monitoring the progress of disease
- assessing the response to therapy and monitoring for adverse reactions.

16.2.2.2 Physiotherapy

The PT plays an important role in the education of the patient, management of acute and non-acute disease, and pre- and postoperative assessment and management.

- Education
  - knowledge of disease
  - role and benefits of physiotherapy.
- Acute disease (or flare-up)
  - pain/inflammation management, including ice, electrotherapy modalities and rest, e.g. knee backslab
  - deformity prevention, e.g. positioning to avoid flexion deformity especially hip, knee, elbow and wrist
  - prone lying and static exercises to opposing muscles
  - no pillows under the knees, since this will encourage flexion deformities.
- Non-acute disease
  - reduce pain, e.g. ice/heat electrotherapy modalities
  - prevent/correct deformities — positioning and active exercise, e.g. gluteus and quadriceps
  - maintain or increase range of movement, e.g. knee needs 90° to get out of chair, hip needs 45° for stairs
  - strengthen muscles to protect joints (endurance and strength).
- Exercise (non-weight-bearing)
  - swimming (hydrotherapy)
  - stationary cycling.
- Positive correction
  - antigravity muscles.
- Gait correction
  - identify problems and treat.
- Advice on appropriate walking aids
  - unloads joint
  - increases endurance.
- Pre- and postoperative management
  - arthroplasty (contraindications, appropriate exercise programme)
  - synovectomy
  - osteotomy — appropriate mobilisation
  - arthrodesis.

16.2.2.3 Occupational therapy

The occupational therapist assesses and treats the patient's level of functioning in terms of personal management, work and leisure activities.

A holistic approach is used to prevent deformity, preserve or improve function and prevent disability.

The various modalities of therapy include the following:

- Prevention of deformity.
  - design and construct resting splints to prevent and correct deformities
  - joint protection techniques applied in a functional position to prevent deformity
  - adaptation of personal and work environment to prevent deformity
  - prescribe appropriate assistive devices to prevent deformities.
- Improve function
  - design and construct functional splints to maximise hand function
  - ergonomic adaptations in work and home environment
  - treatment of psychosocial symptoms as a result of RA (coping with RA, stress management, sexual counselling)
  - postoperative hand therapy
  - prescribe appropriate assistive devices to improve function
  - education on joint protection, energy conservation and time management.
- Monitor level of function.

The holistic approach of occupational therapy to physical and psychological problems prevents further disability at an optimal level of independence. The skilled therapist is able to discuss matters relating to sexual activity and difficulties in performance openly with the patient. Both partners may require advice and education about sexual technique in the presence of joint pain and/or deformity.

16.3 Pharmacological

The pharmacological therapies available for the treatment of RA are used for symptomatic relief and to modify the natural progression of the disease. Pain is a significant symptom and its origin may be multifactorial. Relief of pain and suppression of inflammation usually require a combination of analgesic and anti-inflammatory drugs. Management strategies often require the use of multiple drugs. DMARDs are necessary to halt progression of the disease and prevent joint destruction. Many patients with RA require multiple drugs for the management of associated conditions such as depression, diabetes mellitus, hypertension, cardiac failure and gastropathy. Combination DMARD therapy is also increasingly being advocated.[46]

16.3.1 Analgesics

- Many patients require analgesics for control of pain, but they do not have any effect on suppressing inflammation or modifying the disease.
- Salicylate-containing analgesics should be avoided, especially when NSAIDs are used concurrently.
- Start with the simple analgesics (paracetamol) before proceeding to compounds containing codeine or propoxyphene preparations. Tramadol is a very effective analgesic in controlling recalcitrant pain, but it should be limited to short-term use only.[49,50]

16.3.2 NSAIDs

In the treatment of RA, NSAIDs are the first line of therapy. Although they are effective for pain relief and control of inflammation, they do not alter the course of the disease and should be used in conjunction with DMARDs. There are no significant differences in efficacy among the NSAIDs, although there are some differences in the incidence of side-effects irrespective of the route of administration.[51] The choice of NSAID is based on a combination of cost, duration of action, physician experience, patient preference, route and frequency of administration. Analgesic effects of NSAIDs are prompt in onset, but a reduction in signs of inflammation may take up to 2 weeks. A wide spectrum of adverse effects may occur with NSAIDs (Table XI), but the majority of them are uncommon. All systems can be affected, but the most important are the gastrointestinal (GI) and renal side-effects.

In order to reduce GI toxicity, patients should take NSAIDs with food. Co-prescription of gastroprotective agents, e.g. misoprostol[52] or proton pump inhibitors (PPIs), are indicated in patients with risk factors for GI bleeding, which include:

- age ≥ 65 years
- history of peptic ulcer disease or upper GI bleeding or perforation
- concomitant use of oral corticosteroids
- concomitant use of anticoagulant
- smoking and alcohol consumption.

Patients should always be informed about the potential symptoms of gastric irritation or bleeding, and be instructed to stop the medication and contact the physician in the event of serious problems.

Table XI. Adverse reactions to NSAIDs

GI
Nausea, vomiting, diarrhoea, constipation
Gastropathy — mucosal irritation, erosions, peptic ulceration
Major GI haemorrhage, penetrating ulcers
Small-bowel erosions
Hepatotoxicity (rare)
Renal
Interstitial nephritis and changes in renal perfusion
Oedema
Hypertension may be aggravated
Central nervous system
Headaches, psychosis, tremor
Aseptic meningitis, tinnitus, vertigo
Haematological
Anaemia, bone marrow hypoplasia, reduced platelet aggregation
Autoimmune haemolytic anaemia
Hypersensitivity
Asthma, urticaria, rashes, photosensitivity
Stevens-Johnson syndrome
Drug interactions, e.g warfarin

The NSAIDs are known to produce their anti-inflammatory effects and their adverse effects as a result of the inhibition of the cyclo-oxygenase (COX) enzyme.[53] However, recent research has shown that there are two COX isoenzymes, called COX-1 and COX-2. COX-1 is a constitutive enzyme responsible for physiological functions such as protection of the gastric mucosa, maintenance of renal function and platelet aggregation. COX-2 is an inducible enzyme produced by many different cells in response to inflammation. These observations led to the development of selective COX-2 inhibitors called Coxibs, which produce the anti-inflammatory effects without affecting the physiological functions mediated by the COX-1 isoenzyme. There are currently two Coxibs in clinical practice, celecoxib and rofecoxib. They have been extensively investigated[54-57] and have been shown to have a lower incidence of GI toxicity. Their efficacy is comparable to conventional NSAIDs. However, like conventional NSAIDs, they may be associated with sodium and water retention resulting in oedema and a rise in the blood pressure. They should be considered as first choice especially in elderly patients, those with a previous peptic ulcer, and patients on concurrent corticosteroids or warfarin therapy. However, there are cost limitations to their general use. Patients at risk for ischaemic heart disease and requiring low-dose aspirin should not be denied such treatment. However, in such cases the gastroprotective effects of the Coxibs is negated.

Renal prostaglandins have an important role in the maintenance of the physiological function of the kidney. NSAIDs inhibit the renal prostaglandins and increase the risk of nephrotoxicity, especially in the elderly, patients on diuretics, and patients with pre-existing renal disease, congestive cardiac failure, cirrhosis, coronary artery disease, or any altered physiological state in which renal blood flow is being maintained by compensatory vasodilatation. In order to prevent renal toxicity in at-risk patients, the NSAID should be started in modest doses. In rare instances, severe hepatotoxicity has been seen with diclofenac.

The following principles underline the use of NSAIDs:

- Consider whether a NSAID is necessary, i.e. active inflammation, or whether an analgesic alone will suffice. If

RA is active, a NSAID is required.
- Become familiar with a few preparations, their dosage, side-effects and drug interactions.
- Start with a low dose and then increase to the maximum dose before changing to another NSAID.
- Allow 10 - 14 days with a drug before changing medication.
- Avoid combining NSAIDs as the side-effects are additive.
- Where possible, especially in the elderly and in patients with coexistent conditions, e.g. renal disease, hypertension or cardiac failure, consider alternative agents, e.g. low-dose corticosteroids or Coxibs.

16.3.3 DMARDs

Recent surveys have shown that progressive joint damage occurs early in the course of the disease,[58-60] emphasising the importance of starting DMARD therapy early.[61] The goal of treatment is to suppress inflammation before joint damage occurs. Any patient who has persistent synovitis, with or without joint damage, should start DMARD therapy promptly to prevent or slow further damage. While DMARDs have certain common characteristics, they differ in their efficacy, side-effect profile and onset of action, which varies from 1 to 6 months before a clinical response is evident. Before initiating DMARD therapy, the patient should be made aware of the risks and benefits, the need for long-term therapy and the importance of monitoring side-effects. The initiation, choice and continuation of the specific DMARD should be made in consultation with a rheumatologist or physician with experience in treating rheumatic diseases.

- **Benefit assessment.** DMARDs have been shown to be superior to placebo in the treatment of RA. They result in relief of pain, reduction of swelling, improvement in laboratory measures of activity, improvement in function and slowing of radiological progression. Regular evaluation of the response to therapy and modification when necessary is essential to achieve the most favourable outcome.
- **Risk assessment.** Untreated RA is associated with significant morbidity. Patients with severe disability have mortality rates comparable to those in patients with triple-vessel coronary artery disease and Hodgkin's lymphoma.[42] These observations, together with the relative safety of DMARDs, have revolutionised our approach to the management of RA and have led to the earlier initiation of aggressive medical therapy.[44]

The choice of DMARD will depend on:[61]
- extent of disease activity
- presence of poor prognostic markers
- availability of facilities for monitoring of adverse events
- cost of medication
- the toxicity profile of the agent
- compliance and presence of co-morbid diseases
- the physician's experience in administering and monitoring the drug therapy.

Patients may show an initial response to the selected DMARD, but vigilant monitoring is necessary for evaluating adverse events and detecting a flare of the disease, which will require review of the DMARD therapy. This may require either the addition or substitution of a DMARD. A rheumatologist/specialist physician is able to assist with decision-making at this stage.

Tachyphylaxis, the phenomenon of initial efficacy followed by breakthrough of the disease, usually occurs within 2 years of initiating treatment, although recent reports have shown sustained benefit from continuous methotrexate (MTX) therapy, even after 7 - 8 years of follow-up.[62,63] The mechanisms of tachyphylaxis are poorly understood.

The use of DMARDs in RA is summarised in Tables XII - XV.

Table XII. MTX summary

Preparation
Injectable or oral preparation.

Dosage
Starting dose is 7.5 - 10 mg weekly increasing dose versus response up to 25 mg weekly
Approximately 4 - 6 weeks for response to start
Doses should be administered in the evening to avoid nausea
Use folic acid with the drug to reduce side-effects

Caution
Use with caution in established/active liver disease, renal impairment, significant lung disease and alcohol abuse
Increased side-effects are noted with obesity, diabetes and the elderly

Toxicity
Nausea, diarrhoea, rashes, alopecia, mouth ulcers and stomatitis
More severe effects include marrow suppression, liver toxicity and pulmonary toxicity (pneumonitis)

Monitoring
Chest X-ray before start of therapy
Routine monitoring must be done using FBC and liver function assessments – AST, ALT, GGT and FBC. Blood tests must be done at baseline, then monthly for 3 months, and thereafter 4 - 12-weekly, depending on results
If liver enzyme levels are persistently increased, consider biopsy if the drug is to be continued
Liver biopsy is not considered essential for baseline assessment, or for routine follow-up after a predetermined total dose. Guidelines are now available for follow-up and need for biopsy[3]

16.3.3.1 MTX

MTX has become the dominant DMARD and is among the best-studied long-term agent in patients with RA. Experience with MTX has shown that up to 80% of patients respond within the first 12 weeks of treatment. Improvement is

Table XIII. SSZ summary

Preparation: Oral
- An enteric preparation may reduce GI side-effects

Dosage
- Progressive dose increase — starting 0.5 g daily for 1 week, then 1 g daily for 1 week, then 1.5 g daily for 1 week, and thereafter 1 g bd. The dose can be increased to 3 g if inadequate response
- Response takes between 1 and 6 months
- Contraindicated in sulphonamide allergy, severe hepatotoxicity and haematological disease
- Adverse events are reported more frequently in the first 3 months of use and have a generally low profile with no long-term effects reported. The drug is generally well tolerated. Dose reductions are usually effective for minor side-effects

Mild side-effects include:
- GI discomfort, with nausea, vomiting, loss of appetite, abdominal pain
- Skin rashes and allergic manifestations are common
- Headaches, mood alterations
- Reduced sperm counts may be seen — reversible

Rare severe problems requiring drug withdrawal include:
- Marrow suppression
- G-6-PD deficiency-related anaemia with haemolysis
- Nephrotoxicity
- Hepatotoxicity
- Pulmonary toxicity
- Major allergic rashes – including Stevens-Johnson syndrome

Monitoring
- Baseline FBC and liver function assessment including AST, ALT, GGT and urinalysis
- Monitoring must be done monthly for 3 months and then every 3 months, depending on the results

Table XIV. Chloroquine summary

Preparation: Oral
- Chloroquine salts. Tablets: sulphate, phosphate (hydroxychloroquine unavailable in South Africa)

Dosage
- Chloroquine base – 4 mg/kg daily. Average 200 mg daily 5 times per week
- Dose reductions must be considered in the elderly
- Once stabilised, dose reductions can be considered by reducing frequency of administration
- Take with food to improve bioavailability and reduce nausea

Contraindicated in patients with pre-existing retinopathy.

Side-effects
- Nausea
- Rash and photosensitivity. Skin pigmentation may develop in sun-exposed areas
- Diarrhoea
- Neuromyopathy is reported rarely
- Fundal defects with maculopathy, especially peripheral vision and reduced night vision

Monitoring
- Ophthalmological assessment is required on a 6 - 12-monthly basis
- Baseline assessment is required within the first 6 months
- The safety profile enables the drug to be used in remote areas, as no haematological monitoring is required

maintained for up to 7 years in the majority of patients who continue with therapy.[62,63] Toxicity rather than lack of efficacy accounts for discontinuation in most cases. MTX has been shown to retard radiological progression. Advantages relate to the ease of once weekly dosing and the low cost of the drug. Disadvantages relate to the need for regular blood monitoring and adverse effects.

The mechanisms of action are complex. MTX inhibits dihydrofolate reductase and other folate-dependent enzymes. Co-administration of folic acid does not diminish efficacy, but reduces side-effects in the majority of patients. The anti-inflammatory effect is probably mediated by adenosine and the toxicity by homocysteine metabolism. Bioavailability is the same whether the drug is given as a solution, tablet or subcutaneous or intramuscular injection. Food does not affect bioavailability. Absorption is generally good but variable, and switching from oral to parenteral preparations can sometimes improve response. Patients with renal insufficiency (creatinine > 200 µmol/l) and the elderly have a higher risk of toxicity and require closer surveillance if they are used.

16.3.3.1.1 Dosing (2.5 mg yellow tablet)
- The efficacy is dose-dependent.
- Average dose range is 7.5 - 25 mg once a week depending on the patient's body mass, renal function, activity of disease and tolerance.
- Subcutaneous/intramuscular MTX is an option when there is intolerance or lack of effect with oral therapy.
- If the arthritis is not controlled by 20 - 25 mg MTX weekly for 3 months, the addition of a further agent should be considered.
- Folate is generally co-administered at a dose of 5 mg twice weekly.

16.3.3.1.2 Toxicity issues

Approximately 30% of patients will discontinue MTX due to toxicity.
- **Liver**
  - Clinically serious liver disease is rare in RA patients receiving weekly MTX.
  - Routine surveillance liver biopsy is not advised.
  - Potential risk factors include obesity, diabetes, alcohol intake, prior history of hepatitis B or C.
  - If the aspartate transaminase (AST) is elevated above the upper limit of normal in half the tests over a year, or there is a decrease in albumin (in the setting of well-controlled RA), a liver biopsy should be considered if

Table XV. Composite summary of DMARD therapies

Drug	Dose	Main side-effects	Monitoring required	Time to benefit
Methotrexate	7.5 - 25 mg weekly	Nausea Diarrhoea Skin rash, alopecia Stomatitis Marrow suppression Liver toxicity Pneumonitis	FBC and LFT at baseline, at 1 month, and thereafter 4 - 12-weekly Baseline CXR	1 - 2 months
Sulphasalazine	1 g 8 - 12-hourly	Nausea, vomiting Abdominal pain Skin rashes Stevens-Johnson syndrome Headaches Mood alterations Reduced sperm counts Marrow suppression G-6-PD deficiency anaemias	Baseline FBC LFT Urinalysis Monthly for 3 months Then every 3 - 6 months	2 - 6 months
Antimalarials Chloroquine sulphate Chloroquine phosphate	4 mg/kg	Rash/photosensitivity/skin pigmentation Nausea/diarrhoea Neuromyopathy Macular damage	Ophthalmological assessment 6 - 12-months	2 - 6 months
Oral gold Auranofin	3 mg 12-hourly	As for injectable gold (infrequent) Diarrhoea	FBC and urinalysis 4 - 12-weekly	3 - 6 months
D-penicillamine	150 - 750 mg daily	Rash/stomatitis/diarrhoea Metallic taste Autoimmune syndromes Nephrotoxicity Marrow suppression	FBC and urinalysis 2-weekly for the first month, then 4-weekly	3 - 6 months
Azathioprine	50 - 150 mg daily	Bone marrow suppression GI intolerance Hepatotoxicity Lymphoproliferative disorders	FBC 1 - 2-weekly initially and then monthly LFT especially AST, ALT and GGT 6-monthly	2 - 3 months
Infliximab	3 - 10 mg/kg IVI every 8 weeks	Injection site reaction Severe infection, e.g. disseminated tuberculosis	FBC monthly CXR	A few days to 4 months
Etanercept	25 mg subcutaneous twice a week	Acute or chronic infections	Monitor for injection site reactions, monthly FBC	A few days to 12 weeks
Leflunomide	100 mg daily for 3 days, then 20 mg daily	Diarrhoea, alopecia, rash, hepatotoxicity	As for methotrexate. Also, no procreation for 2 years after discontinuation	4 - 12 weeks

MTX is to be continued.

- **Lung**
  - The strongest risk factors are age, pre-existing lung disease, previous use of DMARDs, low serum albumin and diabetes mellitus.
  - A chest X-ray before the initiation of MTX is recommended.
  - A rare but serious complication is pneumonitis, which is not related to the duration or dosage of MTX.
  - Characteristic symptoms are shortness of breath, dry cough, fatigue and fever.
  - If MTX-induced lung injury is suspected and the chest X-ray shows an abnormal diffuse interstitial infiltrate, MTX should be discontinued and the patient referred for specialist care, which would include therapy with corticosteroids.
- **Infections**
  - MTX may increase the risk of common bacterial infections, herpes zoster and opportunistic infections.
  - MTX should be discontinued during any active infection.
- **Malignancy**
  - Unconfirmed reports have appeared on the possible association with lymphoproliferative malignancies and melanoma.
  - Some studies have shown a negative association between malignancy and MTX use.
- **GI**

  Stomatitis, anorexia, abdominal pain, nausea, vomiting, loss of weight or diarrhoea occasionally lead to discontinuation. They usually improve with MTX dose reduction, supplemental folate, evening dosing, splitting the dose into 12-hour intervals (up to 3 doses within a 24-hour period), or changing from the oral to the parenteral route.
- **Other**
  - Macrocytosis is a common finding and an increasing mean cell volume (MCV) may precede a bone marrow crisis or merely reflect folate deficiency. Bone marrow suppression, including pancytopenia (white cell count < 3.5 x 10^9/l, haemoglobin < 10 g/dl, platelets < 150 x 10^9/l), may rarely develop. The latter usually responds to folinic acid rescue and supportive measures, including transfusion, steroids and haematological growth factors.
  - Alopecia and skin rashes may occasionally lead to withdrawal.
  - Methotrexate may be associated with the development of new nodules, especially in the hands.

16.3.3.1.3 Monitoring

- If the initial regular laboratory screening tests do not reveal any adverse effects, 2 - 3-monthly monitoring has been found to be adequate in most patients.
- More frequent testing is necessary in older patients and those with pre-existing complicating factors, or if abnormalities are detected on early follow-up.

Baseline investigations

- full blood count (FBC) and platelets
- CRP or ESR
- alkaline phosphatase, AST/alanine transferase (ALT), albumin, gamma-glutamyl transpeptidase (GGT)
- creatinine
- hepatitis B and C serology and HIV screening in high-risk setting
- chest X-ray.

Follow-up investigations

- 4 weeks after starting MTX — FBC/platelets, AST/ALT, CRP/ESR
- 4 - 8-weekly (as above)
- if stable, then 8 - 12-weekly
- 3 - 6-monthly — albumin, creatinine, urine dipstix
- if in high-risk setting, revert to 4 - 8-weekly.

16.3.3.2 Sulphasalazine

Sulphasalazine (SSZ) consists of two agents — a sulfur (sulfapyridine) and a salicylate component. The drug is introduced slowly over the first month to avoid problems of nausea and GI irritability – starting 0.5 g daily for 1 week, then 1 g daily for 1 week (divided doses), then 1.5 g daily for 1 week (divided doses), and thereafter 1 g twice a day. A reduction in radiological erosions has been reported with SSZ.[64]

16.3.3.3 Antimalarials

These are chloroquine salts. They are generally regarded as milder drugs. Chloroquine is generally used for milder disease or in combination therapy, and it takes about 3 - 6 months to demonstrate efficacy. Double-blind studies show reduced joint swelling and early morning stiffness in 60 - 80% of patients.

Chloroquine is often used in combination with MTX and has been shown to reduce MTX toxicity in such patients.[65]

16.3.3.4 D-penicillamine

D-penicillamine has also been shown in trials to be effective in RA. Response takes 3 - 6 months. Approximately 60% of patients respond, but there is no significant effect on radiological progression and there is a relatively higher toxicity profile.

Doses recommended include starting at 150 mg for 3 months and if there is no response increasing by 150 mg every 4 - 8 weeks to a maximum dose of 750 mg daily. Do not use concurrently with meals and in particular not with iron or antacid preparations. It is generally recommended that the drug be taken in the evening, preferably on an empty stomach.

16.3.3.5 Sodium aurothiomalate/auranofin

- **Injectable gold** (sodium aurothiomalate) has been used in RA for over 50 years. **It has been withdrawn from the market and is not available in South Africa.** It was administered by intramuscular injection with an initial test

dose of 10 mg followed by 50 mg weekly to a total of 1 g. Thereafter it was given monthly in a dose of 50 mg. Adverse effects included skin rashes, nephrotoxicity and bone marrow depression. It was therefore necessary to monitor the full blood count and urine before injection.

- **Auranofin** (oral gold) is used in mild disease, and has a high incidence of side-effects including diarrhoea, nausea and skin rashes. The more serious side-effects on the bone marrow and kidney are uncommon.

16.3.3.6 Leflunomide

Leflunomide is an immunomodulatory drug that inhibits pyrimidine synthesis. It is of value in patients who are unresponsive to or unable to tolerate MTX. Leflunomide has been shown to be more effective than placebo and has similar efficacy to SSZ and MTX in RA. It has been used in combination with either SSZ or MTX. Radiographic progression is significantly slower with leflunomide and SSZ than placebo. The adverse effects include diarrhoea, nausea, alopecia, rash and weight loss.[66-68] Liver function abnormalities are also encountered and careful monitoring of the full blood count and liver enzymes is mandatory. Its use should be confined to rheumatologists or physicians with an interest in rheumatology. It is contraindicated in pregnancy. Avoid pregnancy for 2 years after discontinuation. Washout using cysteine infusion may be necessary.

Leflunomide (Arava) is now registered for use in South Africa.

16.3.3.7 Biological agents

Advances in our understanding of the pathogenesis of RA and the pivotal role of proinflammatory cytokines such as tumour necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1) led to the development of targeted therapy to control inflammation in RA. Currently TNF-α antagonists and IL-1 receptor antagonists are used in clinical practice, while numerous other biological agents are being evaluated in clinical trials.[69-74]

16.3.3.7.1 Tumour necrosis factor-α antagonists

TNF-blocking agents have been widely used in patients with active RA who have failed to respond to conventional DMARDs. The two compounds in current use are etanercept and infliximab.[75-80]

Etanercept is a dimeric fusion protein consisting of extracellular ligand binding portion of the human 75 kilodalton (p75) tumour necrosis factor linked to the FC portion of IgG1. Etanercept binds to TNF and blocks its interaction with the cell surface TNF receptors, thus modulating the biological responses that are induced or regulated by TNF.[73] It is administered by subcutaneous injection in a dose of 25 mg twice weekly. It is associated with mild to moderate cutaneous reaction (erythema and/or itching, pain or swelling) at the site of injection.

Infliximab is a chimeric (mouse/human) monoclonal anti-TNF-α antibody which is administered by intravenous infusion. A single infusion of the antibody is associated with marked suppression of disease activity in up to 80% of RA patients and the benefit is sustained for 2 - 8 weeks. It is associated with the formation of antibodies and combination with MTX results in a lower prevalence of antibody formation. The adverse effects include infusion reaction such as chills, pruritus, urticaria, headaches, diarrhoea, skin rashes, pharyngitis, rhinitis and upper respiratory and urinary tract infection.

Infliximab is currently registered for use in South Africa.

Adalimumab is a humanised anti-TNF-α monoclonal antibody, which has also been extensively studied and found to be effective in RA with a relatively good safety profile. It is currently not registered for use in South Africa. There are also a number of other TNF blockers, which are undergoing clinical trials at present.

Efficacy. All the TNF blockers have been known to be effective in controlling pain and inflammation in RA. They are associated with significant improvement in the functional status and response may be seen as early as 4 weeks after initiating therapy. They are also associated with slowing of radiographic progression. Although they are effective when used as monotherapy, they are usually combined with MTX as there is an even greater response to combination therapy.

Adverse effects. The long-term effects of blocking TNF are not completely understood. Apart from cutaneous reactions with etanercept and infusion reactions with infliximab, a number of other adverse effects have been seen. A number of patients develop a positive antinuclear antibody, antibodies to dsDNA and anti-cardiolipin antibody, but a lupus-like disease is only rarely reported. Other uncommon adverse effects which have been reported include pancytopenia, aplastic anaemia and demyelinating-like disorders. Post-marketing surveillance has drawn attention to an increased prevalence of infections such as tuberculosis and other opportunistic infections. Many of the patients had extrapulmonary or disseminated tuberculosis. As a result, screening for latent tuberculosis is now recommended. TNF blocker therapy should not be initiated in the presence of active infection. The association of TNF blockers with lymphoma or other malignancies has not been confirmed.

The British Society for Rheumatology working party provided guidelines for the use of biological agents in the treatment of RA by rheumatologists,[81] as follows:

A. Patients must fulfil the ACR criteria for the diagnosis of these diseases.
B. Patients must have active disease as indicated by the following:
   1. Six or more swollen and tender joints
   2. Elevated ESR or CRP above the normal for that laboratory
   3. Signs of active disease should be present at two visits at

least one month apart.

C. Failure of standard DMARD therapy
   1. Previous use of at least 3 DMARDs serially or in combination
   2. DMARDs should have been given a trial of at least 6 months, at least 2 of which are at therapeutic level for that drug
   3. DMARDs include methotrexate, chloroquine, sulphasalazine, azathioprine, cyclosporin, cyclophosphamide, penicillamine and leflunomide.

Note that infliximab should be infused at a supervised facility with appropriately trained staff and resuscitation equipment available.

The high cost of biological agents at present will limit their widespread use. As tuberculosis is very common in South Africa, strict vigilance and monitoring is necessary.

16.3.3.7.2 Interleukin 1 receptor antagonist

Anakinra, a recombinant human form of interleukin-1 receptor antagonist (IL-1Ra), acts by blocking the binding of IL-1∝ and IL-1β to IL-1 receptor, thereby preventing the activation of target cells. At a dose of 150 mg administered as a once-daily subcutaneous injection it has been shown to be superior to placebo in randomised, controlled clinical trials, in improving the clinical signs and symptoms, as assessed by the ACR 20 criteria.[82] Anakinra also reduces radiographic progression compared with placebo,[83] and combination with MTX produces an effect superior to the use of MTX alone.[84] The commonest adverse effect is injection-site reaction, which occurs most frequently in the first 4 weeks and may disappear in days to weeks. It should be used with caution in patients with co-morbid disease, especially asthma or chronic obstructive pulmonary disease. Anakinra should not be given to patients with any type of active infection, and concern remains about malignancy and the risk of serious infections, such as tuberculosis.

Anakinra is not currently available in South Africa.

16.3.3.8 Cyclosporine

Cyclosporine is considered a more toxic drug and has largely been used as combination therapy with MTX.[85] It has major side-effects, including hypertension and renal toxicity. Careful monitoring of the drug level is required. Cyclosporine use is limited by cost and toxicity and is impractical for general use. It should be considered in patients with drug resistance and in severe intractable disease. Cyclosporine should be reserved for use strictly by rheumatologists.

16.3.3.9 Azathioprine

Azathioprine (AZA) is a purine antagonist and is used in resistant disease. The dosage is 1.5 - 3 mg/kg daily and the usual recommended dose is 50 - 150 mg daily. It should not be used with allopurinol.

Side-effects include:

- bone marrow suppression
- infections
- gastrointestinal intolerance
- hypersensitivity hepatitis with cholestasis.

Malignancy risks. Malignancy has not been reported at doses used in the treatment of the rheumatic diseases, although it has been reported in transplant patients treated with AZA.

16.3.3.10 Other agents

Some studies suggest that minocycline is of value, especially in early, mild disease. An improvement in clinical and laboratory parameters has been reported.

Recent data on the use of minocycline in early RA reported a greater remission rate in patients treated early (within the first year) with minocycline.[75,76] Radiological progression has not been retarded with the use of minocycline.

The dose is 100 mg twice daily and a beneficial response may be seen after 3 - 6 months. It is not widely used at present.

16.3.4 Corticosteroids/glucocorticoids

Many patients require low-dose oral therapy initially (7.5 - 10 mg daily) and this dosage should be reduced and the drug gradually withdrawn if possible. High-dose oral therapy, given in reducing doses over a 3 - 4-week period, is required for specific indications such as certain extra-articular manifestations of RA.

Glucocorticoids (GCs) were first used for RA over 50 years ago, but there is still controversy about the risks versus the benefits.[77-79] Low-dose corticosteroid (CS) therapy in RA seems safe and effective, but high-dose CS is associated with many of the adverse effects which may add to the overall burden of the underlying disease. GCs are effective in suppressing inflammation in RA. Their routine use is precluded by long-term side-effects. GCs may be used systemically or locally, bearing in mind the following:

- GCs should **not** be used as monotherapy except under special circumstances.
- They are used in the short term to suppress disease activity while awaiting the beneficial effects of DMARDs ('bridge' therapy), during acute 'flares' of RA, or to cover certain special situations/life-threatening systemic complications of the disease.
- GCs should be considered when NSAIDs are contraindicated (e.g. gastropathy, renal impairment).
- GCs should be considered in active disease during pregnancy
- Parenteral (intramuscular/intravenous/intra-articular) therapy may occasionally be necessary to suppress acute 'flares' of the disease.

Intra-articular (IA) GCs. Infection should always be excluded prior to IA therapy. An aseptic technique should be used. Injections of GC into joint and periarticular structures (e.g. tendon sheath) are safe and effective in suppressing

inflammation and relieving symptoms.

The same joint should, generally, not be injected more frequently than 3 - 4 monthly.

Repeated injection of the same joint requires revision of the patient's systemic drug therapy.

GC-induced osteoporosis. GCs are a major risk factor for osteoporosis.[80,86-91] RA is an added risk factor, particularly in postmenopausal women. GCs directly inhibit osteoblastic bone formation and indirectly increase bone resorption through increased parathormone secretion as a result of impaired intestinal calcium absorption and renal calcium wasting. Although there is variable individual sensitivity to the bone toxic effects of GCs, doses of prednisone of 7.5 mg daily or more tend to be associated with bone loss. Trabecular bone (spine) is lost more rapidly than cortical bone. Since 50% of the loss occurs in the first 6 - 12 months, prophylactic therapy should be started early. Treatment consists of elemental calcium 1 g daily and calciferol (vitamin D) 50 000 units weekly. Ideally, bone densitometry should be performed before initiating long-term GC therapy. In patients with a T-score of –1.5 or less compared with the young normal mean, antiresorptive therapy in the form of hormone replacement therapy and/or bisphosphonates should be considered. Where densitometry is not available and there are significant risk factors, prophylactic therapy should be considered.[92]

Refer also to the '**Osteoporosis Guidelines**'.[92]

16.4 Surgery

Surgical management of patients with RA should be viewed as part of the continuum of their treatment. Early consultation with an orthopaedic surgeon for evaluation and management planning is necessary.

The aims of surgery are:

- relief of pain
- preservation or restoration of function
- prevention or correction of deformities
- cosmetic improvement.

Surgical management varies depending on the ACR anatomic stage of joint destruction.[93]

In stage I and II joint disease resistant to medical treatment, synovectomy may prevent joint degeneration and deformity. Synovectomy may be done chemically or surgically (either arthroscopically or by open surgery).

In stage III and IV disease, joint replacement arthroplasty is often indicated for management of pain, deformity, instability or loss of function. Timely arthroplasty substantially improves functional and quality of life outcomes in these patients. Conversely, delayed surgery may only relieve pain but not improve function. Arthrodesis is an option in certain joints.

Persistent tenosynovitis may result in tendon rupture and consequent loss of function. Tenosynovectomy usually prevents this complication.

Active rheumatoid disease is not a contraindication to surgery, although an acute flare-up should preferably be controlled before surgery.

16.4.1 Anaesthesia

Anaesthesia in the patient with RA can be extremely hazardous.

- Stiffness of the temporomandibular and laryngeal joints may render endotracheal intubation difficult or impossible. Advanced intubation techniques may be necessary to establish a secure airway.
- Atlantoaxial subluxation or atlantoaxial impaction may be present, even in patients without symptoms. Special attention, including assessment of the cervical spine, is therefore necessary to prevent neurological complications.

In patients with RA, anaesthesia is safest in a specialist environment.

16.5 Refractory RA

Management of patients with refractory RA is one of the major challenges in modern rheumatology. For practical purposes, patients may be considered as having refractory RA when they have failed to respond to conventional DMARDs such as CQ, SSZ and MTX, either singly or in combination. The first option is to increase the dose above the standard dosage regimen. Another option is to combine DMARDs. In late disease, cyclosporine improves a suboptimal clinical response to MTX[94] and the triple combination of MTX, sulphasalazine and chloroquine[95] appears more effective than the individual components. GCs are often added in refractory disease and are used in several different ways, including low daily dose or high-dose (bridging) therapies.[96] For localised refractory disease, intra-articular corticosteroids or radiochemicals may be useful. The biological agents (TNF antagonists) are useful in these patients. The use of target-oriented therapies (such as monoclonal antibodies), for induction as part of combination therapy, as chronic monotherapy, or as a kind of bridging therapy, will need to be further defined in the future, but current evidence suggests that long-term therapy is needed. Other experimental therapeutic modalities that may prove useful include gene therapy,[97] stem cell transplantation[98] and oral tolerance induction.[99]

17. Women's health issues

17.1 Fertility

RA has no adverse effect on fertility. Reproductive processes are normal in patients with RA and the usual investigations would be necessary to ascertain the cause for infertility. Apart from the immunosuppressive drugs used in RA, DMARDs have no adverse effect on fertility. There are some reports of anovulatory cycles associated with certain NSAIDs. Contraceptive use in females may protect against the development of RA, but this is controversial.[100]

17.2 Pregnancy

RA tends to improve during pregnancy and there is therefore a reduced need for drug therapy during the gestational period. GCs in low dose are generally safe in pregnancy and may be needed to control symptoms. The NSAIDs may be used in the second trimester but they should be discontinued in the third trimester to prevent premature closure of the ductus arteriosus. The DMARDs should always be discontinued when pregnancy is planned, in order to avoid potential teratogenicity. Patients using MTX should be advised to avoid attempts at conception for 3 - 6 months after stopping therapy.[101]

17.3 Lactation

Many of the drugs used to treat RA are excreted in breast-milk, and the DMARDs should be deferred until breast-feeding has stopped, while NSAID should be used with caution.

17.4 Menopause

RA may start in the menopausal period and many patients with onset in adult life will reach the menopause. Osteoporosis is an important complication of RA.[102-103] Special caution is needed to prevent osteoporosis when a CS is used in conjunction with DMARD and NSAID therapy in the postmenopausal patient.

18. Disclaimer

This national clinical guideline is for reference and education only and is not intended to be a substitute for the advice of the appropriate health care professional or for independent assessment and judgement. SAMA relies on the source of the national clinical guideline to provide updates and to notify us if the guideline protocol becomes outdated. SAMA accepts no responsibility or liability arising from any information contained in or any error in or omission from the protocol or from the use of any information contained in it.

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Annexure A: Methodology

This project was initiated by SAMA. On the recommendation of the South African Rheumatism and Arthritis Association (SARAA), Professor G M Mody was mandated with the task of developing the guidelines and invited the following to contribute to the process: R Asherson, D Bouwer, S Brighton, B Cassim, D Gotlieb, A A Kalla, O L Meyers, A Stanwix and M Tikly.

The draft for the Rheumatoid Arthritis: Clinical Guideline 2003 was drawn up by A A Kalla, A Stanwix, D Gotlieb, R Asherson and G M Mody.

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On 3 and 4 December 1999, a nationally representative arthritis consensus meeting was held in Gauteng. Participants were invited as representatives of professional government and consumer groups with an interest in the arthritis field. Each organisation so invited, nominated its own representatives. All participants received a copy of a draft guideline developed previously together with the relevant references before the meeting. A neutral chairperson chaired the meeting. The purpose of the meeting was to consider the content of the draft guideline and to either endorse or amend the document. The proceedings were audio-recorded and transcribed for future reference.

The endorsement document was revised according to the proceedings of the national consensus meeting and was circulated to all participants and many other interested persons.

Amendments to this endorsement draft were made where there was sufficient need as indicated by the comments received. The document as revised was submitted to the SAMA Guideline Committee for endorsement according to the set criteria. Once endorsed, the guideline was sent for publication to the *South African Medical Journal*.

The grants were made in accordance with the SAMA code of sponsorship, which precludes attempts by sponsors to influence, unethically, the content of the guideline. All funds were paid directly into SAMA's accounts and all disbursements were made from that fund.

Annexure B: Consensus Group for Arthritis Guidelines

South African Medical Association: F J Milne (Chairperson); Arthritis Foundation: O L Meyers; Representatives of the Authoring Group (SARAA): A A Kalla, D Gotlieb, G Mody, S Brighton, O L Meyers; DENOSA: G Brown; Department of Health: Directorate Pharmacy (EDL): J Ludick, Directorate Chronic Disease: C Kotzenberg; National Osteoporosis Foundation: C Schnitzler; National Pathology Group: P Cole; Pain Management Society of SA and SAMA Nominee: P Dessein; Radiological Society of SA: P du Plessis; SAMA: Centre for Quality Care: V Pinkney-Atkinson; SAMA Nominee: D Kastanos; SA Academy of Family Practice: S Namane; SA Association of Occupational Therapists: T Pistorius; SA Orthopaedic Association: N J G Maritz; SA Society of Physiotherapy: H Gardener; Society for General and Family Practitioners: J Fourie; **Observer delegates:** MSD: M Combrink, B Crouse, S Nkalashe, B Prinsloo; Searle: M Doveton, G Hirsch, G Muir, L Wiggil; Medscheme: H Seftel.

The contact details for the Arthritis Foundation are:

Arthritis Foundation Head Office
PO Box 6775
Roggebaai
Cape Town
8012

Tel. (021)425-4738, 425-2344

Fax (021) 421-7330

e-mail info@arthritis.org.za
web page www.arthritis.org.za