CHAPTER 13

MUSCULOSKELETAL CONDITIONS

13.1 ARTHRITIS, RHEUMATOID (RA)

M05.80-89/M05.90-99/M06.00-09/M06.80-09/M06.90-99/M08.30-39/M08.40-49/ M08.80-89/M08.90-99

DESCRIPTION

A chronic, inflammatory, systemic condition with a fluctuating course. It may affect many organs, but the joints are predominantly affected. Characteristic joint manifestations are:

» Swelling or fluid, affecting at least three joint areas simultaneously.
» Pain.
» Limited movement with morning stiffness >1 hour, which improves with activity. This helps distinguish osteoarthritis from rheumatoid arthritis.
» Destruction and deformity of affected joints.
» The small joints of the fingers and hands, with the exception of the distal interphalangeal joints, are usually involved, although any joint can be involved.
» Arthritis is typically symmetrical.

GENERAL MEASURES

Manage by co-ordinated multidisciplinary care.
The primary objective is to improve and maintain functional status.
Early use of non-drug measures, especially nursing, physiotherapy and occupational therapy, is essential.
Acute flare-ups: rest affected joints and consider the use of day and/or night splints.
Obtain a baseline complete blood count, serum creatinine, alanine aminotransferase (ALT), and erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) in all patients.
Obtain X-rays of the hands and wrists, as well as both forefeet to include the metatarsophalangeal joints as a baseline for evaluating change in the joints during treatment.

MEDICINE TREATMENT

All patients with suspected RA should be seen by a specialist. Evaluate all patients with suspected RA for disease-modifying anti-rheumatic drug (DMARD):

- Methotrexate (preferred initial therapy)
- Chloroquine sulphate
- Sulfasalazine

Monitoring response to DMARDs:

» Assess response to DMARD therapy by monitoring the number of swollen and tender joints, restricted to 28 joints (shoulders, elbows, wrists, 5 metacarpophalangeal joints, 5 proximal interphalangeal joints and knees bilaterally) together with ESR or CRP.

» If there is poor response to one DMARD, after 3 months, add another DMARD. *LoE:II*[i]

» Patients on DMARDs must be monitored regularly for toxicity, as outlined below:

- Methotrexate, oral, 7.5 mg once per week. Specialist consultation.
  - Increase dose gradually to a maximum of 25 mg per week.
  - Monitor: ALT and FBC before and 12 weekly during treatment.

AND

- Folic acid, oral, 5 mg per week at least 24 hours after the methotrexate dose.

LoE:II[ii]

AND/OR

- Chloroquine sulphate, oral, 150 mg (as base) daily for 5 days of each week.
  - Do ophthalmic examination at baseline within the first year of treatment and annually thereafter, to monitor for ocular damage.

AND/OR

- Sulfasalazine, oral, 500 mg 12 hourly with meals.
  - Gradually increase over one month from 500 mg to 1 g 12 hourly.
  - FBC and ALT monthly for first 3 months then every 3–6 months.

LoE:III[iii]

Oral corticosteroids

Systemic corticosteroids are effective at relieving symptoms in RA and have been shown to modify the course of the disease, but long-term use is discouraged because this is associated with considerable toxicity, notably osteoporosis, which is very common in patients with RA.

Indications:

» As bridging therapy while waiting for DMARDs to take effect.

» Acute disease flares.

» Severe extra-articular manifestations, e.g. scleritis.

- Corticosteroids (intermediate-acting) e.g.:
- Prednisone, oral, 40 mg daily for 2 weeks.
  - Thereafter gradually reduce the dose to ≤7.5 mg daily. (Refer to Appendix II for an example of a dose reduction regimen).
  - Discontinue at 3–6 months.
  - If disease flares after stopping corticosteroids DMARD therapy should be optimised. *LoE:II*[iv]

Patients requiring corticosteroids for longer than 3 months should be educated to take in enough calcium in their diet.

For pain:

- Paracetamol, oral, 500 mg to 1 g, 4 to 6 hourly as required (to a maximum of 4 g in 24 hours).
  - Maximum dose: 15 mg/kg/dose.

NSAIDs

NSAIDs are used for symptomatic relief in patients with active inflammation and pain. They have no long-term disease modifying effects.
NSAID dose should be reduced and then stopped once the DMARDs have taken effect.
Reduce NSAID doses in the elderly.
NSAIDs are relatively contra-indicated in patients with significantly impaired renal function, i.e. eGFR <60 mL/minute.

CAUTION
Concomitant use of more than one oral NSAID has no additional clinical benefit and only increases toxicity.
Use of all NSAIDs is associated with increased risks of gastrointestinal bleeding, renal dysfunction, and cardiovascular events (stroke and myocardial infarction).
NSAIDs should be used judiciously at the lowest effective dose for the shortest duration. Explore and manage exacerbating factors for pain. See Section 26.1: Chronic pain.
Do not use NSAID in pregnancy or while breastfeeding.

- NSAID, e.g.:
- Ibuprofen, oral, 400 mg 8 hourly with meals. *LoE:I[v]*

An extra **night-time** dose of an NSAID may be added in some patients with severe nocturnal pain/morning stiffness.

Note: When an additional night-time dose is added to the patient's regimen, the risk of NSAID toxicity increases. A reduction in the daytime dose of NSAIDs is recommended as the night-time dose will often exceed the recommended total daily NSAID dose.
If a reduction in daytime dose causes increased pain, then the use of the night-time dose must be for the shortest period possible.

In high-risk patients: >65 years of age; history of peptic ulcer disease; on concomitant warfarin, aspirin, or corticosteroids:

ADD *LoE:II[vi]*

- PPI, e.g.:
- Lansoprazole, oral, 30 mg daily while on an NSAID.

Adjunct for pain control:

- Amitriptyline, oral, 10–25 mg at night.

- Titrate dose according to response.
- Initial dose in the elderly: 10 mg at night.
- Maximum dose: 75 mg at night.
- Use with caution in patients with angle closure glaucoma, prostatic hypertrophy and the elderly.

Intra-articular corticosteroids
Consider only in cases where a few joints are very actively inflamed.
To be prescribed by a specialist.
Not more than 2–3 injections per year per joint are recommended.
- Intra-articular corticosteroid, e.g.:
- Methylprednisolone acetate, 20–80 mg depending on joint size.

LoE:III[vii]

REFERRAL
» At initial diagnosis.
» Disease activity cannot be controlled with the measures as mentioned.
» Compression neuropathy.
» For joint replacement.

Urgent
» Rupture of tendons.
» Scleritis.
» Unstable upper cervical spine.
» Vasculitis.
» Cricoarytenoid joint involvement with hoarseness and inspiratory stridor.

13.2 ARTHRITIS, SEPTIC AND OSTEOMYELITIS, ACUTE
M00.90-99/M86.10-19

DESCRIPTION
Septic arthritis is typically an acute infective condition involving one or more joints. The joint is hot, swollen, very painful on movement, and with restricted movements.
Acute osteomyelitis typically involves the long bones or the vertebrae.
Signs of systemic infection are usually present. The infection is usually bloodborne, but may follow trauma. The course may be acute or protracted. The commonest causative organism is *Staphylococcus aureus*. *N. gonorrhoeae* is an important cause of septic arthritis.
Note: Acute gout and haemophiliacs with bleeding into joints may mimic septic arthritis.

GENERAL MEASURES
Baseline X-ray.
Rest and immobilisation.

Septic arthritis: Drainage is important. Discuss with a specialist.

MEDICINE TREATMENT

Empiric antibiotic therapy

Therapy is directed against *S. aureus* unless there is evidence of urethritis or PID, in which case gonococcal infection should be covered.

It is crucial to obtain cultures of blood, joint or aspirate of osteomyelitis focus before administering antibiotics.

- Cefazolin, IV, 2 g 8 hourly for 4 weeks. *LoE:II*[viii]

After 2 weeks of IV therapy, a change to oral therapy may be considered in patients with a good clinical response:

- Flucloxacillin, oral, 1 g 6 hourly to complete the 4 weeks' treatment.

Severe penicillin allergy: (Z88.0)

- Clindamycin, IV, 600 mg 8 hourly.

After 2 weeks of IV therapy, a change to oral therapy may be considered in patients with a good clinical response:

- Clindamycin, oral, 450mg 8 hourly to complete the 4 weeks' treatment.

LoE:III[ix]

For gonococcal arthritis A54.4+ + (M01.30-39*)

- Ceftriaxone, IV, 1 g daily for 1 week.

AND

- Azithromycin, oral, 1 g, as a single dose. *LoE:III*[x]

Severe penicillin allergy: (Z88.0)

Refer.

Analgesia

- NSAID, e.g.:
- Ibuprofen, oral, 400 mg 8 hourly with meals. *LoE:I*[xi]

AND/OR

- Paracetamol, oral, 500 mg to 1 g, 4 to 6 hourly as required (to a maximum of 4 g in 24 hours).
  - Maximum dose: 15 mg/kg/dose.

REFERRAL

» Acute osteomyelitis/ septic arthritis for early drainage by specialist surgeon.
» If pyrexia persists despite adequate antibiotic therapy, a sub-periosteal abscess must be sought and drained by a specialist surgeon.
» Chronic osteomyelitis.
» Pathological fractures.

13.3 OSTEOARTHRITIS

M13.00-19/M16.0-9/M17.0-9/M18.0-9/M19.00-09/M19.80-99

DESCRIPTION

A disorder typically affecting weight-bearing joints and the hand (distal and

proximal interphalangeals, and first metacarpophalangeal joints).
Signs and symptoms include:
» Pain on effort, relieved by rest.
» Morning stiffness, lasting < 30 minutes.
» Limited movement.
» Joint swelling (effusions and/or osteophytes).

GENERAL MEASURES

Weight reduction.
Exercise: postural and non-weight bearing. Quadriceps strengthening for knee involvement.
Support and alleviate weight bearing of affected joints, i.e. walking stick.
Physiotherapy and/or occupational therapy.

MEDICINE TREATMENT

When only pain relief is required:

- Paracetamol, oral, 500 mg to 1 g, 4 to 6 hourly as required (to a maximum of 4 g in 24 hours).
  - Maximum dose: 15 mg/kg/dose.

If ineffective:

ADD

- NSAID, e.g.:
- Ibuprofen, oral, 400 mg 8 hourly with meals. *LoE:I*[xii]

As many of these patients, particularly the elderly, have concomitant medical conditions such as cardiovascular, gastrointestinal disease or renal function impairment, NSAIDs must be used with caution.

Patients on aspirin for cardiovascular risk reduction should take this agent 30 minutes before the 1st dose of NSAID in the morning, as taking aspirin and NSAID at the same time may reduce aspirin's efficacy. *LoE:III*[xiii]

In high-risk patients: >65 years of age; history of peptic ulcer disease; or on concomitant warfarin, aspirin or corticosteroids:

ADD *LoE:II*[xiv]

- PPI, e.g.:
- Lansoprazole, oral, 30 mg daily.

CAUTION

Use of all NSAIDs is associated with increased risks of gastrointestinal bleeding, renal dysfunction, and cardiovascular events (stroke and myocardial infarction).
NSAIDs should be used judiciously at the lowest effective dose for the shortest duration. Explore and manage exacerbating factors for pain. See Section 26.1: Chronic pain.
Do not use NSAID in pregnancy or while breastfeeding.

If ineffective:
Adjunct for pain control:
- Amitriptyline, oral, 10–25 mg at night.
  - Titrate dose according to response.
  - Initial dose in the elderly: 10 mg at night.
  - Maximum dose: 75 mg at night.

Intra-articular corticosteroids
Consider in cases where a joint is actively inflamed.
To be prescribed and administered by a specialist only.
Not more than 2–3 injections per year per joint are recommended.
- Intra-articular corticosteroid, e.g.:
- Methylprednisolone acetate, 20–80 mg depending on joint size.

LoE:III[xv]

REFERRAL
» For consideration for joint replacement.
» Intractable pain.
» Neurogenic compression.

13.4 GOUT
M10.90-99

DESCRIPTION
A metabolic disease in which uric acid crystal deposition occurs in joints and other tissues.
Gout is managed in the following three stages:
i) Treating the acute attacks;
ii) Prevention of acute flares;
iii) Lowering excessive uric acid to prevent flares and tissue deposition of urate crystals.

LoE:III[xvi]

Acute gout:
Joint involvement is characterised by recurrent attacks of acute arthritis, which usually affects one joint, and is accompanied by extreme pain and tenderness, swelling, redness, and local heat.
» The inflammation may extend beyond the joint.
» In many patients the first metatarsophalangeal joint is initially involved.
» The instep, ankle, heel, and knee are also commonly involved.
» Bursae (such as the olecranon) may be involved.

Chronic gout:
Gout with one or more of the following:
» uric acid deposits in and around joints, bursae and cartilages of the extremities (tophi)
» initial involvement of the first metatarsophalangeal joint in most patients
» involvement of the instep, ankle, heel and knee

» involvement of bursae (such as the olecranon)
» significant periarticular inflammation
» bone destruction
» prolongation of attacks, often with reduction in pain severity
» incomplete resolution between attacks

GENERAL MEASURES

Acute gout:
Rest and immobilisation.

Chronic gout:
Lifestyle modification, including high fluid intake.
Avoid alcohol intake.
If possible, avoid diuretics, or use the lowest dose possible.

MEDICINE TREATMENT

ACUTE GOUT:

Initiate treatment as early as possible in an acute attack:

- NSAID, e.g.:
- Ibuprofen, oral, 400 mg 8 hourly with meals. *LoE:I*[xvii]

In high-risk patients: > 65 years of age; history of peptic ulcer disease; on concomitant warfarin, aspirin, or corticosteroids:

ADD *LoE:II*[xviii]

- PPI, e.g.:
- Lansoprazole, oral, 30 mg daily while on an NSAID.

If NSAIDS are contraindicated, e.g. warfarin therapy and renal dysfunction:

- Corticosteroids (intermediate-acting) e.g.:
- Prednisone, oral, 40 mg daily for 5 days.

CHRONIC GOUT:

If possible, avoid known precipitants and medicines that increase uric acid, including:
» low dose aspirin,
» ethambutol,
» pyrazinamide, and
» thiazide and loop diuretics.

If diagnosis uncertain, joint aspiration with microscopy for crystal analysis is recommended.
Investigate for and treat secondary causes (e.g. haematological malignancies) where clinically indicated.
Measure serum creatinine and urate.
Serum urate may be normal during acute attacks.

Urate lowering therapy
Urate lowering therapy is recommended in the following circumstances:

» >2 acute attacks per year
» chronic tophaceous gout
» urate renal stones
» urate nephropathy

When the acute attack has settled, i.e. usually after 2 weeks:

- Allopurinol, oral, 100 mg daily.
  - Increase monthly by 100 mg according to serum urate levels.
  - Titrate dose to reduce serum urate to <0.35 mmol/L.
  - Allopurinol dosage is dependent on severity of disease and serum urate concentration. Doses in excess of 300 mg should be administered in divided doses. *LoE:III*[xix]
  - Maximum dose: 900 mg per day.
  - Elderly: start with 50 mg daily.
  - Renal impairment: Adjust dose according to renal function.
    - eGFR 30–60 mL/minute: start with 50 mg daily.
    - eGFR <10 mL/minute: consult a specialist. *LoE:III*[xx]

Caution in prescribing allopurinol to patients with renal impairment as they have an increased risk of a hypersensitivity reaction. Immediate cessation of allopurinol if rash or fever occurs.

LoE:III[xxi]

Prophylaxis to prevent breakthrough gout attacks:

An increase incidence of gout flares is associated with initiation of urate lowering therapy. Thus, colchicine or NSAIDs is recommended as anti-inflammatory prophylaxis when initiating allopurinol.

Anti-inflammatory prophylaxis should be discontinued at **6 months** provided gout symptoms have resolved**.**

- NSAID, e.g.: *LoE:I*[xxii]
- Ibuprofen, oral, 400 mg 8 hourly with meals.
  - Monitor renal function, as clinically indicated.

OR

Colchicine, oral, 0.5 mg 12 hourly for 6 months. *LoE:III*[xxiii]

- eGFR < 50 mL/minute: consult a specialist

CAUTION

Concomitant use of more than one oral NSAID has no additional clinical benefit and only increases toxicity.

Use of all NSAIDs is associated with increased risks of gastrointestinal bleeding, renal dysfunction, and cardiovascular events (stroke and myocardial infarction).

NSAIDs should be used judiciously at the lowest effective dose for the shortest duration. Explore and manage exacerbating factors for pain. See Section 26.1: Chronic pain.

Do not use NSAID in pregnancy or while breastfeeding.

In high-risk patients: i.e. patients > 65 years of age, or with a history of peptic ulcer disease, or on concomitant warfarin, aspirin or corticosteroids:

ADD *LoE:II*[xxiv]

- PPI, e.g.:
- Lansoprazole, oral, 30 mg daily.

Do not stop urate lowering drugs during an acute attack.

REFERRAL

» No response to treatment despite adequate adherence.
» Suspected secondary gout.
» Non-resolving tophaceous gout.

13.5 SERONEGATIVE SPONDYLARTHRITIS

M45.X0-X9/M47.9099

DESCRIPTION

A group of diseases in which the rheumatoid factor is usually negative and the spine is often involved. These disorders have certain similar clinical features and occur predominantly in individuals with HLA-B27 antigen. The rheumatological manifestations in these disorders are variable, typically including asymmetrical lower-limb arthritis, sacro-iliitis, spinal inflammation (spondylitis), and enthesitis (e.g., Achilles tendonitis). The spondyloarthritides include ankylosing spondylitis, reactive arthritis, psoriatic arthropathy, and arthritis associated with inflammatory bowel disease. Extra-articular manifestations occur, especially uveitis, in about one third of patients.

GENERAL MEASURES

Physiotherapy to prevent spine deformity.

MEDICINE TREATMENT

Initiate treatment with NSAIDs.

- NSAID, e.g.:
- Ibuprofen, oral, 400 mg 8 hourly with meals. *LoE:I*[xxv]

In high-risk patients: i.e. patients > 65 years of age, or with a history of peptic ulcer disease, or on concomitant warfarin, aspirin or corticosteroids:

ADD *LoE:II*[xxvi]

- PPI, e.g.:
- Lansoprazole, oral, 30 mg daily.

REFERRAL

» Uveitis, to an ophthalmologist.
» Psoriasis, to dermatologist and rheumatologist

» Arthritis refractory to NSAIDs, to a rheumatologist.
» Deformity at diagnosis, to a rheumatologist.

13.5.1 ARTHRITIS, REACTIVE

M02.30-39

DESCRIPTION

A spondylarthritis often preceded by enteric or urogenital infections 1–4 weeks before the arthritis and occurring predominantly in individuals with HLA-B27 antigen.
It is a clinical diagnosis with no laboratory test or radiographic findings.
It occurs more commonly in HIV infection.
It is usually self-limiting.

MEDICINE TREATMENT

- NSAID, e.g.:
- Ibuprofen, oral, 400 mg 8 hourly with meals. *LoE:I*[xxvii]

In high-risk patients: i.e. patients > 65 years of age, or with a history of peptic ulcer disease, or on concomitant warfarin, aspirin or corticosteroids:

ADD *LoE:II*[xxviii]

- PPI, e.g.:
- Lansoprazole, oral, 30 mg daily.

If urethritis is present, treatment may prevent further episodes of arthritis:

- Ceftriaxone, IM, 250 mg as a single dose.
  - For ceftriaxone IM injection: Dissolve ceftriaxone 250 mg in 0.9 mL lidocaine 1% without epinephrine (adrenaline).

AND

- Azithromycin, oral, 1 g, as a single dose.

LoE:II[xxix]

13.6 SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

M32.9

These patients need to be managed by a specialist.

GENERAL MEASURES

Education regarding the disease and complications.
Avoid cigarette smoking as it is a trigger for lupus.
Sun protective barrier creams are often indicated.
Regularly monitor urine for blood and protein.
Provide advice regarding family planning as pregnancy may cause a lupus flare.

MEDICINE TREATMENT

MILD DISEASE

For pain:

- Paracetamol, oral, 500 mg to 1 g, 4 to 6 hourly as required (to a maximum of 4 g in 24 hours).
  - Maximum dose: 15 mg/kg/dose.

AND/OR

- NSAID, e.g.:
- Ibuprofen, oral, 400 mg 8 hourly with meals. *LoE:I*[xxx]

In high-risk patients: i.e. patients > 65 years of age, or with a history of peptic ulcer disease, or on concomitant warfarin, aspirin or corticosteroids:

ADD *LoE:II*[xxi]

- PPI, e.g.:
- Lansoprazole, oral, 30 mg daily.

To suppress disease activity

- Chloroquine sulphate, oral, 150 mg (as base) daily for 5 days of each week.
  - Do ophthalmic examination at baseline within the first year of treatment and annually, to monitor for ocular damage.

LoE:I[xxii]

Corticosteroids

Initiate therapy in patients with life threatening manifestations and organ involvement.

- Corticosteroids (intermediate-acting) e.g.:
- Prednisone, oral, 2 mg/kg daily, initial dose.
  - Taper to the lowest maintenance dose after a response has been obtained. Refer to Appendix II for an example of a dose reduction regimen.
  - Usual maintenance dose: 10 mg daily.

Patients requiring corticosteroids for >3 months (long-term) should be managed for secondary prevention of osteoporotic fractures. See Section 8.12: Osteoporosis.

Additional immunosuppressive therapy

Is often required for life-threatening disease, particularly kidney and CNS involvement. These medicines should be initiated by a specialist and regular FBC monitoring should be done.

- Azathioprine, oral, 1 mg/kg daily, titrated to a maximum of 3 mg/kg daily.

OR *LoE:III*

Cyclophosphamide, oral, 100 mg daily, titrated to a maximum of 200 mg daily (or 1–3 mg/kg daily).

LoE:III

RAYNAUD'S PHENOMENON I73.0

- Amlodipine, oral, 5 mg daily.

LoE:II[xxxiii]

ANTIPHOSPHOLIPID ANTIBODY SYNDROME

- Aspirin, oral, 150 mg daily.

Patients with previous thrombo-embolic episodes should receive lifelong warfarin (target INR 3 to 4).

LoE:III

Hormonal therapy in women

The use of oral contraceptives is controversial.
Until there is clarity it is advisable to use either progesterone-only, or low dose oestrogens, or non-hormonal methods.

REFERRAL

» All patients to a specialist for initial assessment.
» Lupus flare.
» Nephritis for renal biopsy.
» Persistent haematological derangements i.e. thrombocytopaenia.
» Neurological manifestations of lupus.

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PPI (high risk patients on chronic NSAID therapy): Serrano P, Lanas A, Arroyo MT, Ferreira IJ. Risk of upper gastrointestinal bleeding in patients taking low-dose aspirin for the prevention of cardiovascular diseases. Aliment PharmacolTher. 2002 Nov;16(11):1945-53. http://www.ncbi.nlm.nih.gov/pubmed/12390104

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PPI (high risk patients on chronic NSAID therapy): Scarpignato C, Gatta L, Zullo A, Blandizzi C; SIF-AIGO-FIMMG Group; Italian Society of Pharmacology, the Italian Association of Hospital Gastroenterologists, and the Italian Federation of General Practitioners. Effective and safe proton pump inhibitor therapy in acid-related diseases - A position paper addressing benefits and potential harms of acid suppression. BMC Med. 2016 Nov 9;14(1):179. https://www.ncbi.nlm.nih.gov/pubmed/27825371

[xxix] Ceftriaxone, IM: National Department of Health STI Guidelines, 2014 and PHC STGs and EML, 2014. http://www.health.gov.za

Lidocaine 1% with epinephrine (adrenaline): National Department of Health STI Guidelines, 2014 and PHC STGs and EML, 2014. http://www.health.gov.za

Azithromycin: National Department of Health STI Guidelines, 2014 and PHC STGs and EML, 2014. http://www.health.gov.za

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NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Van Walsem A, Pandhi S, Nixon RM, Guyot P, Karabis A, Moore RA. Relative benefit-risk comparing diclofenac to other traditional non-steroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors in patients with osteoarthritis or rheumatoid arthritis: a network meta-analysis. Arthritis Research & Therapy 2015;17:66. https://www.ncbi.nlm.nih.gov/pubmed/25879879

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NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Coxib and traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet 2013; 382: 769–79. https://www.ncbi.nlm.nih.gov/pubmed/23726390

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. BMJ 2011;342:c7086. https://www.ncbi.nlm.nih.gov/pubmed/21224324

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Ong CKS, Lirk P, Tan Ch, Seymour RA. An evidence-based update on nonsteroidal anti-inflammatory drugs. Clinical Medicine and Research 2007; 5(1):19-34. https://www.ncbi.nlm.nih.gov/pubmed/17456832

NSAIDs as a therapeutic class (diclofenac, naproxen, ibuprofen): Stam WB, Jansen JP, Taylor SD. Efficacy of etoricoxib, lumiracoxib, non-selective NSAIDs, and acetaminophen in osteoarthritis: a mixed treatment comparison. The Open Rheumatology Journal 2012; 6:6-20. https://www.ncbi.nlm.nih.gov/pubmed/22582102

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PPI (high risk patients on chronic NSAID therapy): Narum S, Westergren T, Klemp M. Corticosteroids and risk of gastrointestinal bleeding: a systematic review and meta-analysis. BMJ Open. 2014 May15;4(5):e004587. https://www.ncbi.nlm.nih.gov/pubmed/24833682

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SOUTH AFRICAN ADULT HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 13: MUSCULOSKELETAL CONDITIONS
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2017 -2019)

Medicine amendment recommendations, with supporting evidence and rationale are listed below. Kindly review the medicine amendments in the context of the dental and oral conditions chapter.

SECTION	MEDICINE	ADDED/DELETED/AMENDED
13.1 Arthritis, rheumatoid (RA)	DMARDs, oral	Directions for use amended
	Sulfasalazine, oral	Directions for use amended
	NSAIDs, oral	Caution amended and example of class retained as ibuprofen
	PPI, oral	Evidence updated for PPI prophylaxis in patients on concomitant NSAID with corticosteroids
13.2 Arthritis, septic and osteomyelitis, acute	Cloxacillin, IV	Deleted
	Cefazolin, IV	Added
- *Gonococcal arthritis*	Ceftriaxone, IV	Retained
	Azithromycin, oral	Added
13.3 Osteo-arthritis	Tramadol, oral	Not added
	NSAIDs, oral	Caution amended and example of class amended from ibuprofen to diclofenac
	PPI, oral	Evidence updated for PPI prophylaxis in patients on concomitant NSAID with corticosteroids
	Amitriptyline, oral	Retained as adjunctive therapy
13.4 Gout		
- *Acute gout*	Colchicine, oral	Not added
	NSAIDs, oral	Example of class retained as ibuprofen
- *Chronic gout*	Allopurinol, oral	Dose, directions for use and caution amended
- *Prophylaxis to prevent breakthrough gout attacks*	Colchicine, oral	Duration of therapy amended and dose-adjustment for renal impairment added
	NSAIDs, oral	Caution amended and example of class retained as ibuprofen
	PPI, oral	Evidence updated for PPI prophylaxis in patients on concomitant NSAID with corticosteroids
13.5 Seronegative spondylarthritis	NSAIDs, oral	Example of class retained as ibuprofen
13.5.1 Arthritis, reactive	NSAIDs, oral	Example of class retained as ibuprofen
13.6 Systemic lupus erythematosus (SLE)	NSAIDs, oral	Example of class retained as ibuprofen

13.1 ARTHRITIS, RHEUMATOID (RA); 13.3 OSTEO-ARTHRITIS; 13.4 GOUT; 13.5 SERONEGATIVE SPONDYLARTHRITIS; 13.5.1 ARTHRITIS, REACTIVE *and* 13.6 SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

NSAIDs, oral: *example of class retained as ibuprofen*

NEMLC had recommended that NSAIDs be recommended as a class (i.e. diclofenac, naproxen and ibuprofen) and be advertised as a class in the tablet tender, accordingly. The contract had been awarded to the supplier(s) of ibuprofen, and as this is the only agent that is accessible through public pharmaceutical tender, the example of class of NSAIDs throughout the STGs and EML is listed as ibuprofen, oral, 400 mg 8 hourly. However, diclofenac, naproxen and ibuprofen listed as options in the NSAID group in the therapeutic interchange database for Adult Hospital Level STGs and EML, 2019.

Refer to the medicine review, NSAIDs for arthritis (January 2018) for detailed information.

NSAIDs for Arthritis_AdultsRevie

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation

Following this report on the efficacy and safety of traditional(t)NSAIDs, the Adult Hospital Level Committee recommended that diclofenac 150mg be considered for patients. There does not seem to be an NSAID that completely relinquishes a cardiovascular side effect profile. NSAID use should be instituted with great caution in those at risk of cardiovascular events. On review of the risk benefit profiles of various NSAIDs, therapeutic alternatives that may be considered include naproxen and ibuprofen.

Rationale: This medicine review included numerous systematic reviews and meta-analyses of RCTs which assessed the efficacy and safety of tNSAIDs and coxibs.Diclofenac 150mg daily does appear to be the most efficacious tNSAID, however its cardiovascular risks are similar to the coxibs as presented by the Coxib and tNSAID trialists' collaboration[1]. The recently published network meta-analysis by Van Walsem et al[2] mitigates these risks and highlights a similar cardiovascular risk profile to ibuprofen and an improved GI safety profile (as compared to ibuprofen). Ibuprofen at high doses (2400mg daily) has been shown to have a comparable efficacy to diclofenac 150mg daily, however it was also shown to increase major coronary events (the Coxib and tNSAID trialists' collaboration) and stroke (Trelle et al[3]). Ibuprofen also had an increased rate of non-fatal MI as compared to naproxen in the PRECISION trial. Naproxen does appear to lack efficacy when compared to other tNSAIDs (The Oxford League Table[4] and Stam et al[5]). Naproxen does have the more favourable cardiovascular profile, as highlighted in the studies by Trelle et al and the Coxib and tNSAID trialists' collaboration, however these findings were diminished by an FDA advisory committee meeting[6] and by the Coxib and tNSAID trialists' collaboration themselves. Finally, the tNSAIDs meloxicam and piroxicam have not had adequate assessment of their cardiovascular safety profiles and cannot be successfully compared to diclofenac, ibuprofen, and naproxen.

Conclusion:

Evidence from this review supports the increased risk of cardiovascular and gastrointestinal adverse events associated with use of all the tNSAIDs diclofenac, ibuprofen and naproxen. If clinically indicated, the choice of NSAID should be based on the individual risk profile of the patient. Risks for developing cardiovascular and/or gastrointestinal adverse events could be minimised by using the lowest tolerated dose for the shortest possible duration of treatment time. Diclofenac 150mg, as appearing to be more efficacious with a similar cardiovascular and improved gastrointestinal safety profile compared to ibuprofen, is recommended. Therapeutic alternatives of ibuprofen and naproxen could be considered.

Level of Evidence: I Systematic review and meta-analyses, RCTs, Expert opinion

[1] Coxib and traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet 2013; 382: 769–79.

[2] Van Walsem A, Pandhi S, Nixon RM, Guyot P, Karabis A, Moore RA. Relative benefit-risk comparing diclofenac to other traditional non-steroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors in patients with osteoarthritis or rheumatoid arthritis: a network meta-analysis. Arthritis Research & Therapy 2015;17:66.

[3] Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. BMJ 2011;342:c7086.

[4] Ong CKS, Lirk P, Tan Ch, Seymour RA. An evidence-based update on nonsteroidal anti-inflammatory drugs. Clinical Medicine and Research 2007; 5(1):19-34.

[5] Stam WB, Jansen JP, Taylor SD. Efficacy of etoricoxib, lumiracoxib, non-selective NSAIDs, and acetaminophen in osteoarthritis: a mixed treatment comparison. The Open Rheumatology Journal 2012; 6:6-20.

[6] Bello AE, Holt RJ. Cardiovascular risk with non-steroidal anti-inflammatory drugs: clinical implications. Drug Saf. 2014 Nov;37(11):897-902. https://www.ncbi.nlm.nih.gov/pubmed/25079141

Medicines in the NSAID therapeutic group:

Medicine	Comparative daily dose[7]
Diclofenac, oral	75-150 mg
Naproxen, oral	1000-2000 mg
Ibuprofen, oral	600-1200 mg

13.1 ARTHRITIS, RHEUMATOID (RA)

DMARDs, oral: *directions for use amended*
RE: Statement "If there is poor response to one DMARD, after 3 months, add another".

Aligned with ACR[8] and EULAR[9] RA guidelines – the primary evidence was a pooled analysis of patient data from pivotal RCTs and the conclusion of this study was that "The 3-month time point is a critical decision point. Not achieving minor responses at 3 months makes reaching of the treatment target at 6 months highly unlikely, while reaching major responses is highly predictive of reaching the treatment target".[10]
Recommendation: For optimal dosing of DMARDs to achieve a therapeutic target, DMARDs to be given for at least 3 months before therapy escalation or switching.
Rationale: Data from pooled analysis of RCTs shows that "not achieving minor responses at 3 months makes reaching of the treatment target at 6 months highly unlikely".
Level of Evidence: II Evidence extrapolated from RCTs, Guidelines

Sulfasalazine, oral: *directions for use amended*
Aligned with the SAMF, 2016 that recommends administration with meals.
Level of Evidence: III Guidelines

NSAIDs, oral: *caution amended*
The following was editorially amended for correctness and clarity purposes, from:

~~Concomitant use of more than one oral NSAID has no additional clinical benefit and only increases toxicity.~~
~~Chronic use of all NSAIDs is associated with increased risks of gastrointestinal bleeding, renal failure, and cardiovascular events (stroke and myocardial infarction).~~

To:

Concomitant use of more than one oral NSAID has no additional clinical benefit and only increases toxicity.
Use of all NSAIDs is associated with increased risks of gastrointestinal bleeding, renal failure, and cardiovascular events (stroke and myocardial infarction).
NSAIDs should be used judiciously at the lowest effective dose for the shortest duration. Explore and manage exacerbating factors for pain. See section 26.1: Chronic pain.
Do not use NSAID in pregnancy and breastfeeding.

Aligned with SAMF, 2016.
Level of Evidence: III Guidelines

NSAIDs, oral: *retained as an example of class* (see above)

[7] SAMF, 2016.
[8] Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol. 2016 Jan;68(1):1-26. https://www.ncbi.nlm.nih.gov/pubmed/26545940
[9] Smolen JS, Landewé R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis. 2017 Jun;76(6):960-977. https://www.ncbi.nlm.nih.gov/pubmed/28264816
[10] Aletaha D, Alasti F, Smolen JS. Optimisation of a treat-to-target approach in rheumatoid arthritis: strategies for the 3-month time point. Ann Rheum Dis 2016;75:1479–85. https://www.ncbi.nlm.nih.gov/pubmed/26420577

PPI, oral: *evidence updated for PPI prophylaxis in patients on concomitant NSAID with corticosteroids*

Meta-analysis by Narum et al (2014)[11] showed an associated risk of corticosteroid monotherapy and gastrointestinal events in hospitalised patients only (OR 1.42, 95% CI 1.22 to 1.66); whilst for patients in ambulatory care, the increased risk was not statistically significant. However, subgroup analysis of documented concomitant NSAID use showed an increased risk (OR 1.30, 95% CI 0.81 to 2.07). Of note, is that the definition of gastrointestinal events varied between trials and RCTs were heterogeneous.

Systematic review[12] (that included the meta-analysis above) suggests that gastrointestinal risk of corticosteroid monotherapy is marginal and that PPI co-therapy should not routinely be indicated in patients taking corticosteroids unless they have a history of peptic ulcer disease or are taking NSAIDs.
Level of Evidence: II Systematic review and meta-analysis of RCTs of low to moderate quality

13.2 ARTHRITIS, SEPTIC AND OSTEOMYELITIS, ACUTE

Cloxacillin, IV: *deleted*
Cefazolin, IV: *added*
Staph aureus resistance to oxacillin has recently been reported in two Provinces, with 9% MRSA detected in community acquired pneumonia.[13]
NEMLC approved circular: Due to continuous supply challenges with Cloxacillin, IV, NEMLC[14] had approved a circular recommending cefazolin, IV in place of cloxacillin, IV for a number of indications based on the systematic review of cohort studies by Loubet et al[15].
Recommendation: Cloxacillin, IV be replaced with cefazolin, IV (that has cover against MSSA and streptococci).
Rationale: Aligned with Guidelines[16] and retrospective cohort study showed that cloxacillin was comparable to cefazolin with regards to mortality at 90 days in ICU (HR 0.58; 95% CI 0.31 to 1.08)[17].
Level of Evidence: II Retrospective cohort study, Susceptibility study, Guidelines

Gonococcal arthritis
Ceftriaxone, IV: *retained*
Azithromycin, oral: *added*
Aligned with CDC and WHO Guidelines.

Dual therapy recommended for gonococcal infections – parenteral ceftriaxone with a single dose of oral azithromycin – to reduce the emergence of resistance.
Level of Evidence: III Guidelines[18]

[11] Narum S, Westergren T, Klemp M. Corticosteroids and risk of gastrointestinal bleeding: a systematic review and meta-analysis. BMJ Open. 2014 May15;4(5):e004587. https://www.ncbi.nlm.nih.gov/pubmed/24833682
[12] Scarpignato C, Gatta L, Zullo A, Blandizzi C; SIF-AIGO-FIMMG Group; Italian Society of Pharmacology, the Italian Association of Hospital Gastroenterologists, and the Italian Federation of General Practitioners. Effective and safe proton pump inhibitor therapy in acid-related diseases - A position paper addressing benefits and potential harms of acid suppression. BMC Med. 2016 Nov 9;14(1):179. https://www.ncbi.nlm.nih.gov/pubmed/27825371
[13] Perovic O, Singh-Moodley A, Govender NP, Kularatne R, Whitelaw A, Chibabhai V, Naicker P, Mbelle N, Lekalakala R, Quan V, Samuel C, Van Schalkwyk E; for GERMS-SA. A small proportion of community-associated methicillin-resistant Staphylococcus aureus bacteraemia, compared to healthcare-associated cases, in two South African provinces. Eur J Clin Microbiol Infect Dis. 2017 Dec;36(12):2519-2532. https://www.ncbi.nlm.nih.gov/pubmed/28849285
[14] Minutes of the NEMLC meeting of 2 November 2017.
[15] Loubet P, Burdet C, Vindrios W, Grall N, Wolff M, Yazdanpanah Y, AndremontA, Duval X, Lescure FX. Cefazolin versus anti-staphylococcal penicillins for treatment of methicillin-susceptible Staphylococcus aureus bacteraemia: a narrative review. ClinMicrobiol Infect. 2017 Jul 8.pii: S1198-743X(17)30358-0.https://www.ncbi.nlm.nih.gov/pubmed/28698037
[16] Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, Hirschmann JV, Kaplan SL, Montoya JG, Wade JC; Infectious Diseases Society of America. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014 Jul 15;59(2):e10-52. https://www.ncbi.nlm.nih.gov/pubmed/24973422
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[18] Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015 Jun 5;64(RR-03):1-137. Erratum in: MMWR Recomm Rep. 2015 Aug 28;64(33):924. https://www.ncbi.nlm.nih.gov/pubmed/26042815

NICD have reported that azithromycin resistant Neisseria Gonnorhoea (MIC > 1mcg/ml) has not been detected in gonococcal isolates at sentinel surveillance sites. It is noted that there are no established interpretive criteria/breakpoints for azithromycin susceptibility and no clear correlation between MIC and treatment success; however, an isolate with azithromtycin MIC >1 mcg/ml likely to have resistance determinants.

13.3 OSTEOARTHRITIS

Tramadol, oral: *not added*

Tramadol was not recommended for inclusion to the NEMLC-approved PHC EML for management of osteoarthritis in patients with co-morbid renal impairment or cardiovascular complications.

Rationale: There is limited evidence for use of opioids in arthritic patients with co-morbid renal impairment or cardiovascular complications. And, a Cochrane review of RCTs of ostero-arthritic patients suggests that the risk outweighs the benefit of opioids.

Level of Evidence: I Systematic review[19]

However, external comments received from commentators including South African Rheumatology Association of South Africa to reconsider including tramadol and amitriptyline to the Adult Hospital Level EML for management of osteoarthritic pain.

Background: Previously, the NEMLC recommended deletion of tramadol and amitryptiline for the management of osteoarthritis, aligned with NEMLC-approved PHC STGs and EML, 2018. The rationale was that there is limited evidence for use of opioids in arthritic patients with co-morbid renal impairment or cardiovascular complications. And, a Cochrane review of RCTs of ostero-arthritic patients suggests that the risk outweighs the benefit of opioids[20]. For adjunctive amitryptiline therapy there is limited evidence for recommending combination therapy for inflammatory arthritis, and some evidence of benefit in fibromyalgia, but no evidence of benefit of amitriptyline in osteoarthritis[21]. Subsequently, the evidence was re-reviewed for due diligence.

Limited evidence shows that tramadol alone or in combination with paracetamol showed no important clinically meaningful benefit in reducing pain or improving physical function when compared to placebo. However, there were slightly more safety concerns; and risk-benefit assessment does not warrant use of tramadol for osteoarthritis.

Level of Evidence: II Systematic review of low to moderate quality RCTs

- *Guidelines:* American College of Rheumatology 2012[22] Guidelines and NICE Guidelines, 2014[23] recommends opioids (e.g. tramadol), where there has been no/inadequate response to paracetamol and NSAIDs. Risk-benefit assessment is required especially amongst the elderly.
- *Safety:* Concerns regarding the safety of tramadol as indicated in a recent Cochrane review[24] of

[19] da Costa BR, Nüesch E, Kasteler R, Husni E, Welch V, Rutjes AW, Jüni P. Oral or transdermal opioids for osteoarthritis of the knee or hip. Cochrane Database Syst Rev. 2014 Sep 17;(9):CD003115. https://www.ncbi.nlm.nih.gov/pubmed/25229835

[20] da Costa BR, Nüesch E, Kasteler R, Husni E, Welch V, Rutjes AW, Jüni P. Oral or transdermal opioids for osteoarthritis of the knee or hip. Cochrane Database Syst Rev. 2014 Sep 17;(9):CD003115. https://www.ncbi.nlm.nih.gov/pubmed/25229835

[21] Ramiro S, Radner H, van der Heijde D, van Tubergen A, Buchbinder R, Aletaha D, Landewé RB. Combination therapy for pain management in inflammatory arthritis (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, other spondyloarthritis). Cochrane Database Syst Rev. 2011 Oct 5;(10):CD008886. https://www.ncbi.nlm.nih.gov/pubmed/21975788

[22] Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, Towheed T, Welch V, Wells G, Tugwell P; American College of Rheumatology. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken). 2012 Apr;64(4):465-74. https://www.ncbi.nlm.nih.gov/pubmed/22563589

[23] NICE. Osteoarthritis: care and management Clinical Guidelines, 2014. https://www.nice.org.uk/guidance/cg177

[24] Toupin April K, Bisaillon J, Welch V, Maxwell LJ, Jüni P, Rutjes AW, Husni ME, Vincent J, El Hindi T, Wells GA, Tugwell P. Tramadol for osteoarthritis. Cochrane Database Syst Rev. 2019 May 27;5:CD005522. https://www.ncbi.nlm.nih.gov/pubmed/31132298

low to moderate quality RCTs (downgraded due to risk of bias), noting that most RCTs were industry funded:

- *Pain reduction* (assessed using visual analogue scale (VAS): no important clinically meaningful benefit shown)
  - Tramadol vs placebo: 4% absolute improvement, 95% CI 3% to 5%; NNTB[25] 13, 95% CI 10 to 18; (8 RCTs, n=3972)
  - Tramadol + acetaminophen (paracetamol) vs placebo: 4% absolute improvement, 95% CI 2% to 6%; NNTB 13, 95% CI 9 to 21; (2 RCTs, n=614).
- *Physical function* (assessed using Western Ontario and McMaster Universities Arthritis Index (WOMAC)):
  - Tramadol vs placebo: 50.3 vs 54.3 = 4% absolute improvement, 95% CI 2% to 6%; (5 RCTs n=2550)
  - Tramadol + acetaminophen (paracetamol) vs placebo: 4% absolute improvement, 95% CI 2% to 7% (2 RCTs, n=614).
- *Adverse events* (most frequent adverse events were nausea, dizziness and tiredness).
  - Tramadol vs placebo: RR 1.34, 95% CI 1.24 to 1.46 (i.e. 17% increase, 95% CI 12% to 23%)
  - Tramadol + acetaminophen (paracetamol) vs placebo: RR 1.91, 95% CI 1.32 to 2.76 (i.e. 22% increase, 95% CI 8% to 41%)
- *Withdrawal due to adverse events*
  - Tramadol + acetaminophen vs placebo: RR 2.78, 95% CI 1.50 to 5.16; corresponding to 8% absolute improvement, 95% CI 2% to 19% (2 RCTs, n=614).
- *Serious adverse events (SAEs):*
  - Tramadol vs placebo: 110/2459 vs 22/1153; RR 1.78, 95% CI 1.11 to 2.84 (7 RCTs, n=3612), which corresponded to 1% more SAEs (95% CI 0% to 4%).

Amitriptyline, oral: *retained*

Despite the NEMLC-approved PHC recommendation to delete amitriptyline, oral for osteoarthritis from the PHC EML, amitriptyline, oral was retained as adjunctive therapy for pain control in the management of osteoarthritis, for secondary level of care.

NEMLC REPORT FOR PRIMARY HEALTHCARE, CHAPTER14: MUSCULOSKELETAL CONDITIONS, 12 APRIL 2018

NEMLC Recommendation: At the meeting of the 2 November 2017, NEMLC recommended that the PHC Committee review the evidence for efficacy of amitriptyline in osteoarthritis.

Amitriptyline, oral: *deleted*

The PHC Committee conducted a search of Pubmed, and the Cochrane library, and could find no studies that assessed amitriptyline in osteoarthritis. The PHC Committee recommended that amitriptyline, oral be deleted from the PHC EML as add-on neuromodulator for osteoarthritis.

Rationale: Limited evidence for recommending combination therapy for inflammatory arthritis, and some evidence of benefit in fibromyalgia, but no evidence of benefit of amitriptyline in osteoarthritis.

Level of Evidence: II Systematic review of low quality studies[26]

Added as adjunctive therapy for pain control in the management of osteoarthritis, for secondary level of care as this is currently considered standard of care and there is uncertainty as to whether amitriptyline is ***not*** efficacious. Of note is that a Cochrane review[27] is currently underway to

[25] "*NNTB corresponded to the number of participants that needed to be treated to see one participant improve. Improvement defined as reaching a minimal clinically important difference (MCID) of 20% on the given scale. NNTB calculated using the Wells calculator (from the CMSG Editorial office: https://musculoskeletal.cochrane.org/)*".

[26] Ramiro S, Radner H, van der Heijde D, van Tubergen A, Buchbinder R, Aletaha D, Landewé RB. Combination therapy for pain management in inflammatory arthritis (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, other spondyloarthritis). Cochrane Database Syst Rev. 2011 Oct 5;(10):CD008886. https://www.ncbi.nlm.nih.gov/pubmed/21975788

[27] Lyttle JR, Urquhart DM, Cicuttini FM, Wluka AE. Antidepressants for osteoarthritis. Cochrane Database of Systematic Reviews 2016, Issue 4. Art. No.: CD012157. DOI: 10.1002/14651858.CD012157.

determine the safety and efficacy of antidepressants for osteoarthritis.

- Van den Driest et al, 2017[28]: Systematic review of RCTs to determine the effectiveness of amitryptiline in reducing musculoskeletal pain and improving functionality. Limited number of RCTs retrieved that only analysed rheumatoid arthritis, lower back pain and arm pain due to repetitive use; which were heterogenous. Authors concluded that amitriptyline may be effective, but further research is needed to establish efficaciousness and specific indication(s) for amitryptilline.

Level of Evidence: II Systematic review of low quality RCTs

NSAIDs, oral: *caution box added and example of class retained as ibuprofen* (see above)
Caution aligned with section 13.1 Arthritis, rheumatoid (RA).

PPI, oral: *evidence updated for PPI prophylaxis in patients on concomitant NSAID with corticosteroids* (see above).

13.4 GOUT

Description
The layout of the chapter amended to provide an overview for the management of gout delineating between management for i) acute, ii) chronic, ii) prophylactic and breakthrough episodes of gout[29].

Medicine Treatment
i) Acute Gout
Colchicine, oral: *not added*
NSAIDs, oral: *retained*
Prednisone, oral: *retained*
A number of external comments were received for colchicine to manage acute gout. Previous recommendation of not recommending colchicine, oral for acute gout attacks was upheld as no new evidence was submitted and despite Cochrane review[30] of low-quality evidence suggesting that low-dose colchicine is likely to be an effective treatment for acute gout; as colchicine is potentially toxic and the Adult Hospital Level Committee was of the opinion that harm outweighs the benefit. An updated medicine review was developed, to determine if there is new evidence for colchicine in the management of acute gout episodes. Refer to the medicine review summary for detailed information:

Colchicine for AcuteGout_ AdultsR

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation: Colchicine not be added to the EML for management of acute gout.
Rationale: There is no new evidence. Cochrane review[31] showed that low-quality evidence suggests that low-dose colchicine is likely to be an effective treatment for acute gout. However, colchicine is potentially toxic and the Adult Hospital Level Committee was of the opinion that harm outweighs the benefit.
Level of Evidence: I Systematic review, Expert opinion

[28] van den Driest JJ, Bierma-Zeinstra SMA, Bindels PJE, Schiphof D. Amitriptyline for musculoskeletal complaints: a systematic review. Fam Pract. 2017 Apr 1;34(2):138-146.
[29] Dalbeth N, Reid S, Stamp LK, Arroll B. Making the right thing the easy thing to do: strategies to improve outcomes in gout. Lancet Rheumatology. October 01, 2019. 1:2:PE122-E131. DOI:https://doi.org/10.1016/S2665-9913(19)30004-9
[30] van Echteld I, Wechalekar MD, Schlesinger N, Buchbinder R, Aletaha D. Colchicine for acute gout. Cochrane Database Syst Rev. 2014 Aug 15;8:CD006190. https://www.ncbi.nlm.nih.gov/pubmed/25123076
[31] van Echteld I, Wechalekar MD, Schlesinger N, Buchbinder R, Aletaha D. Colchicine for acute gout. Cochrane Database Syst Rev. 2014 Aug 15;8:CD006190. https://www.ncbi.nlm.nih.gov/pubmed/25123076

ii) Chronic gout

Allopurinol, oral: *dose, directions for use and caution amended*

- *Dose:* Allopurinol dosage is dependent on severity of disease and urate serum concentration. Of note – doses in excess of 300 mg should be administered in divided doses (maximum dose 900 mg per day).
  Level of Evidence: III Guidelines[32]

- *Dose-adjustment in renal impairment:* As renal impairment is not a contra-indication for allopurinol, guidance was provided for dose adjustment in renal impairment. Evidence[33] [34] suggests that allopurinol may slow the progression of kidney disease.
  Level of Evidence: III Disease oriented RCTs, Guidelines[35]

The directions for use of allopurinol updated from:

~~Allopurinol, oral, 100 mg daily.~~
- ~~Increase monthly by 100 mg according to urate blood levels and eGFR.~~
- ~~Titrate dose to reduce serum urate to < 0.35 mmol/L.~~
- ~~Most patients will be controlled with a dose of 300 mg daily.~~
- ~~Elderly and patients with renal impairment (eGFR between 30–60 mL/minute): start with50 mg daily.~~

To:

- Allopurinol, oral, 100 mg daily.
  - Increase monthly by 100 mg according to urate blood levels and eGFR.
  - Titrate dose to reduce serum urate to < 0.35 mmol/L, to a maximum of 900 mg per day in divided doses.
  - Elderly: start with 50 mg daily.
  - Renal impairment: Adjust dose according to renal function.
    - eGFR 10–50 mL/minute: start with 50 mg daily.
    - eGFR <10 mL/minute: consult a specialist

- *Caution:* Caution box amended, also noting the caution in prescribing allopurinol to patients with comorbid renal impairment due to increased risk of hypersensitivity reaction. Allopurinol should be stopped immediately if rash or fever occurs.

~~Allopurinol is contra-indicated in patients with eGFR < 30 mL/minute.~~
Caution in prescribing allopurinol to patients with comorbid renal impairment as increased risk of hypersensitivity reaction. Immediate cessation of allopurinol if rash or fever occurs.

Level of Evidence: III Observational study[36]

iii) Prophylaxis to prevent breakthrough gout attacks:

The following guidance was added to the STG, aligned with American College of Rheumatology (ACR) guidelines[37], noting that an update of the NICE Guidelines is expected by 2022.

An increase incidence of gout flares is associated with initiation of urate lowering therapy. Thus, colchicine or NSAIDs is recommended when/prior to initiating allopurinol.
Evaluate gout symptoms whilst on allopurinol. If gout signs and symptoms still present, continue anti-inflammatory prophylaxis. However, if no symptoms are present continue colchicine for 6 months.

Level of Evidence: III Guidelines

[32] SAMF 2016
[33] Siu YP, Leung KT, Tong MK, Kwan TH. Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. Am J Kidney Dis. 2006;47(1):51–59. https://www.ncbi.nlm.nih.gov/pubmed/16377385
[34] Goicoechea M, de Vinuesa SG, Verdalles U, Ruiz-Caro C, Ampuero J, Rincón A, Arroyo D, Luño J. Effect of allopurinol in chronic kidney disease progression and cardiovascular risk. Clin J Am Soc Nephrol. 2010 Aug;5(8):1388-93. https://www.ncbi.nlm.nih.gov/pubmed/20538833
[35] SAMF, 2016
[36] Yang CY, Chen CH, Deng ST, Huang CS, Lin YJ, Chen YJ, Wu CY, Hung SI, Chung WH. Allopurinol Use and Risk of Fatal Hypersensitivity Reactions: A Nationwide Population-Based Study in Taiwan. JAMA Intern Med. 2015 Sep;175(9):1550-7. https://www.ncbi.nlm.nih.gov/pubmed/26193384
[37] Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol. 2016 Jan;68(1):1-26. https://www.ncbi.nlm.nih.gov/pubmed/26545940

Colchicine, oral: *duration of therapy amended and dose-adjustment for renal impairment added*

- *Duration of therapy:* Colchicine recommended for 6 months for the prevention of breakthrough gout attacks, aligned with American College of Rheumatology Guidelines[38] and primary evidence cited in these guidelines - a review of 3 Phase III RCTs[39] that showed that "flare rates increased dramatically (up to 40%) at the end of 8 weeks of prophylaxis and then declined gradually, whereas flare rates were consistently low (range, 3%–5%) at the end of 6 months of prophylaxis". Similarly, the American College of Physician Guidelines[40] mentions that "*high-strength evidence suggests that prophylaxis with either colchicine or NSAIDs reduces the risk for acute gout attacks in patients initiating urate-lowering therapy; the optimal duration of such prophylactic therapy is unknown, but moderate strength evidence suggests that it should be longer than 8 weeks".* NICE Guidelines for management of gout are also under review and expected date of finalisation was 2022.

- *Dose-adjustment in renal impairment:* Dose adjustment for colchicine in renal impairment was added to the STG as follows:

  - Colchicine, oral, 0.5 mg 12 hourly for 6 months.
    - eGFR <50 mL/minute: consult a specialist.

NSAIDs, oral: *caution box amended and example of class retained as ibuprofen (see above)*

PPI, oral: *evidence updated for PPI prophylaxis in patients on concomitant NSAID with corticosteroids* (see above).

13.5 SERONEGATIVE SPONDYLARTHRITIS

NSAIDs, oral: *example of class retained as ibuprofen* (see above)

13.5.1 ARTHRITIS, REACTIVE

NSAIDs, oral: *example of class retained as ibuprofen* (see above)

13.6 SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

NSAIDs, oral: *example of class retained as ibuprofen* (see above)

Report prepared by TD Leong: Secretariat to the Adult Hospital Level Committee (2017-2020)
- ***Note:*** *Information was sourced from NEMLC ratified minutes and NEMLC-approved documents.*

[38] Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol. 2016 Jan;68(1):1-26. https://www.ncbi.nlm.nih.gov/pubmed/26545940
[39] Wortmann RL, Macdonald PA, Hunt B, Jackson RL. Effect of prophylaxis on gout flares after the initiation of urate-lowering therapy: analysis of data from three phase III trials. Clin Ther. 2010 Dec;32(14):2386-97. https://www.ncbi.nlm.nih.gov/pubmed/21353107
[40] Shekelle PG, Newberry SJ, FitzGerald JD, Motala A, O'Hanlon CE, Tariq A, Okunogbe A, Han D, Shanman R. Management of Gout: A Systematic Review in Support of an American College of Physicians Clinical Practice Guideline. Ann Intern Med. 2017 Jan 3;166(1):37-51. https://www.ncbi.nlm.nih.gov/pubmed/27802478