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UPDATE ON MANAGEMENT OF GOUT

- **Gout is a common inflammatory arthritis that is increasing in prevalence**
- **Gout is associated with comorbid conditions including cardiovascular disease, chronic kidney disease, diabetes mellitus and obesity**
- **The pharmacological management of gout includes treatment of the acute flare and long-term use of urate lowering therapy (ULT)**
- **Prophylaxis against acute flares during initiation of ULT is generally recommended**

INTRODUCTION

Gout is a common and treatable form of inflammatory arthritis that occurs due to the deposition of monosodium urate crystals in synovial fluid and other tissues.[1-6] Patients with gout experience recurrent acute arthritis ("acute gout flares"), subcutaneous tophi and chronic painful arthritis.[3-5] The worldwide incidence and prevalence of gout are increasing;[2,3] in Europe, the prevalence ranges from 0.9% to 2.5% depending on the country.[2] It is one of the commonest forms of inflammatory arthritis in those aged >65 years.[7] Gout is increasingly being recognised as a serious disease that causes functional disability, increased work absence and increased healthcare utilisation.[8-10] **Gout is associated with comorbidities including cardiovascular disease (CVD), chronic kidney disease (CKD), diabetes mellitus and obesity;** evidence also suggests that gout is a risk factor for mortality, in particular from cardiovascular causes.[1,27,8,11] This bulletin outlines the current management of gout.

PATHOPHYSIOLOGY

The central pathological feature of gout is chronic deposition of monosodium urate crystals in tissues, which occurs in the presence of hyperuricaemia.[1] Hyperuricaemia occurs due to the overproduction or underexcretion of urate; **underexcretion of urate is the dominant cause of hyperuricaemia in patients with gout.**[1,10] Gout progresses through four pathophysiological stages: 1) hyperuricaemia without evidence of monosodium urate crystal deposition or gout, 2) crystal deposition without symptomatic gout, 3) crystal deposition with acute gout flares and 4) advanced gout characterised by tophi, chronic gouty arthritis and radiographic erosions.[1] The factors controlling the formation of monosodium urate crystals are poorly understood; they typically form in relatively cooler parts of the body including the metatarsophalangeal joint of the big toe, the joints of the feet, knees, elbows and hand.[1] Infiltration of tophi into bone seems to be the dominant mechanism for bone erosion and joint damage in gout.[1]
Risk factors for hyperuricaemia and the development of gout are shown in Table 1.

Table 1: Risk factors for the development of gout[1]

Genetic	**Other**
• Male sex	• Increasing age
• Ancestry (e.g. Maoris in New Zealand)	• Menopause
• Genetic polymorphisms	• Chronic kidney disease
Drugs	• Overweight, obesity or weight gain
• Diuretics	• Hypertension
• Ciclosporin	• Hyperlipidaemia
• Tacrolimus	• Hypertriglyceridaemia
• Angiotensin-converting-enzyme inhibitors	• Congestive heart failure
• Angiotensin II receptor blockers (not losartan)	• Obstructive sleep apnoea
• Beta blockers	• Anaemia
• Pyrazinamide	• Psoriasis
• Ritonavir	• Sickle cell anaemia
Dietary	• Haematological malignancy
• Purine rich foods e.g. red meat, seafood	• Lead exposure
• Alcohol (beer/spirits)	
• Sugar-sweetened beverages	

Key risk factors for the development of gout include increasing age, male sex and the use of certain drugs (in particular diuretics).[1] Dietary risk factors include alcohol (particularly beer and spirits), red meat, seafood and consumption of sugar-sweetened beverages.[1,2,4,6] The menopause is associated with increased urate concentrations.[1] Genetic factors include rare X-linked inborn errors of metabolism and polymorphisms in several genes that are involved in renal urate transport.[6]
Gout is associated with reduced risk of neurological disorders such as Parkinson's disease and Alzheimer's disease; the cause-effect relationship is currently unknown.[1]

CLINICAL FEATURES

The clinical features of gout occur as a result of the inflammatory response to monosodium urate crystals in the joints/tissues.[1] Gout typically presents for the first time as an acute episode of inflammation (flare) affecting the foot or ankle, most commonly the first metatarsophalangeal joint; symptoms include throbbing/burning pain, swelling, heat, redness and difficulty moving the affected joint. Symptoms often occur at night waking the patient from sleep.[1]
Triggers for acute flares include certain drugs, dehydration, or dietary factors such as alcohol intake and

purine rich foods.[1] The flare typically occurs after an asymptomatic period of hyperuricaemia and usually results in complete resolution of symptoms within 1 to 2 weeks.[1] If hyperuricaemia persists, recurrent flares can occur which become increasingly frequent and prolonged, affecting many joints (polyarticular flares), including joints of the upper limbs.[1,12] **The presence of CVD, CKD and higher urate levels are associated with an increased risk of recurrence of flares.**[2]

Untreated hyperuricaemia can result in advanced gout with **tophi** (subcutaneous nodules) and/or **chronic gouty arthritis.**[1] Tophi most often occur over the first metatarsophalangeal joint, Achilles tendon, peroneal tendon, helix of the ear, olecranon bursa and finger pad; however they can also occur in atypical locations.[1] Tophi are typically pain free but they can become acutely inflamed and may become infected and ulcerated; when severe they cause cosmetic concerns, difficulty finding suitable footwear, restriction of joint movement and poor grip.[1] Atypical presentations of gout may occur including early presentation of tophaceous disease without previous flares.[1]

Diagnosis: The gold standard for the diagnosis of gout is the demonstration of urate crystals in synovial fluid from an affected joint or from a tophus,[1,13] however crystal evaluation is not performed routinely.[6] **The diagnosis of gout is usually made clinically;**[1,13] a typical presentation that is strongly suggestive of gout includes the rapid development of severe pain (within 24 hours), erythema, pronounced tenderness and swelling in a characteristic joint distribution.[1,6] Examination may also reveal features of systemic inflammation (e.g. fever), particularly in the presence of a polyarticular flare and evidence of comorbid conditions such as central obesity and hypertension.[1] **Serum urate testing** is useful to assist with clinical diagnosis of gout in symptomatic individuals, but **hyperuricaemia alone is not sufficient for the diagnosis of gout.**[1] Conversely, **serum urate concentrations may be in the normal range during an acute flare and should be retested after the flare has resolved.**[1,6] Other laboratory investigations to consider include C-reactive protein and neutrophils (which may be raised during an acute attack). Serum creatinine, lipids and fasting glucose may be useful in identifying comorbid conditions.[1] Plain x-rays are usually normal at the first presentation, apart from non-specific soft tissue swelling of the affected joint; bone erosion is a feature of advanced gout.[1] Other radiological investigations to consider include ultrasonography and dual energy CT, which might show features of monosodium urate crystals deposition. **Differential diagnoses** include inflammatory arthritic conditions (e.g. septic arthritis, rheumatoid arthritis and inflammatory episodes of osteoarthritis).[1,5] The general absence of fever, rash or other signs of systemic illness during an acute gout flare helps differentiate gout from septic arthritis, although joint aspiration is definitive.[14]

MANAGEMENT

The management of gout involves both non-pharmacological and pharmacological approaches.[4] There are a number of guidelines on the management of gout including the recently published EULAR (European League Against Rheumatism) guideline (2016).[2] The **major aims of managing gout are**: 1) to provide pain relief in the acute stage (flare) and 2) the initiation and monitoring of urate lowering therapy (ULT), which results in the dissolution of monosodium crystal deposits and the disappearance of gout features (including the tophi).[1-2,6,7,9] It is important to consider that the initiation of ULT may precipitate an acute flare up to 6 months after starting therapy.[1,7] **Patients should be advised to start treatment of acute flares as soon as possible**; they should have an action plan and supply of drugs to facilitate early treatment.[1,2,7]

In addition **patients with gout should be screened for associated comorbidities and risk factors including renal impairment, CVD, hyperlipidaemia, diabetes mellitus and obesity.**[1,2,15] The management of gout is often considered as sub-optimal; poorly treated gout is associated with recurrent hospital admission, disability and poor quality of life.[3,7,8,16,10]

NON-PHARMACOLOGICAL MANAGEMENT

Non-pharmacological management focuses on **patient education,** which is seen as a key aspect of gout management.[2] This includes advice on dietary modification (e.g. the avoidance of alcohol, prevention of dehydration, sugar-sweetened drinks and excessive intake of meat and seafood) and lifestyle changes, including weight loss and exercise,[1-4] even though the evidence of benefit of lifestyle modification is low.[1,2] Studies have found an inverse association between dairy intake and urate levels, in particular skimmed milk and low calorie yoghurt, therefore low-fat dairy products should be encouraged.[2] The US Arthritis Foundation website has dietary advice for patients with gout http://www.arthritis.org/about-arthritis/types/gout/articles/gout-foods.php.

Topical application of ice to the affected joint and resting the joint are also advised as treatment for an acute flare.[1,6] **Patients should also be educated about the need and importance of long-term ULT and informed of the risk of flares occurring during initiation of ULT**, which may impact on adherence.[1] Adherence to ULT is often poor; an Irish study found that approximately 46% of patients persisted with ULT after 6 months.[1,17] However, studies have shown that patient education increases adherence to ULT.[2]

PHARMACOLOGICAL MANAGEMENT

The pharmacological management of gout includes treatment of the acute flare, long-term use of ULT and prophylaxis against flares during initiation of ULT. The choice of drug depends on individual patient factors such as the severity of gout, comorbidities (e.g. renal impairment) and potential drug interactions.[1,2,6] Certain concomitant drugs may have urate-lowering effects including losartan, atorvastatin, fenofibrate and calcium channel blockers.[9] **Consideration should be given to the possibility of substituting existing medicines which may be risk factors for gout**; for example, consider substituting loop or thiazide diuretics with losartan or calcium channel blockers in hypertension.[2]

Treatment of acute flares

Acute flares of gout should be treated as early as possible in order to achieve rapid resolution of inflammation and pain.[1,2] Guidelines recommend non-steroidal anti-inflammatory drugs (NSAIDs), colchicine or corticosteroids as first-line for the treatment of acute flares.[1,4,9,18.19]

NSAIDs are generally recommended as first-line for acute flares, unless there are contraindications to their use.[4] NSAIDs are equally effective when given in optimum doses; they should be used for the shortest period (1 to 2 weeks).[1,18,19] NSAIDs may be contraindicated in patients with renal impairment, CVD or a history of gastrointestinal disease.[1,2] Concomitant use of a proton pump inhibitor may be required in patients at increased risk of gastrointestinal disease.[2,18] **Adverse effects** include dyspepsia, bleeding and renal impairment.[4]

Corticosteroids are also effective for acute flares and may be the most appropriate option for patients with contraindications to NSAIDs.[1] Evidence suggests that oral prednisolone (30-35 mg daily for 3 to 5 days) is equivalent to NSAIDs (e.g. naproxen and indomethacin) for treating flares.[2,4,20] Intra-articular injections of corticosteroids may also be considered for patients with monoarthritis of an easily accessible joint.[2] **Adverse effects** include dysphoria, mood disorders, immune suppression and fluid retention.[4]

Colchicine (available as a non licensed medicine in Ireland) is effective in an acute flare and may be used in patients when NSAIDs are contraindicated.[1,2,4,21] It is effective when given within 12 hours of flare onset. A loading dose of 1 mg colchicine followed by 0.5 mg after 1 hour is advised (however information sources may differ on the dose); after 12 hours, treatment can resume with a dose of 0.5mg every 8 hours to a maximum of 6 mg in 3 days.[2,21,22] Colchicine should be used with caution in patients with renal impairment and is contraindicated in patients with severe renal impairment.[21,22] Colchicine is a substrate for both CYP3A4 and P-glycoprotein, therefore there is a potential for drug interactions; it should not be given to patients receiving strong P-glycoprotein and/or CYP3A4 inhibitors (e.g. ciclosporin or clarithromycin).[2,21] **Adverse effects** include nausea, vomiting, abdominal pain, myopathy and blood disorders.[18,21]

Canakinumab (currently not marketed in Ireland) is a monoclonal antibody (an interleukin-1 inhibitor) which is effective in reducing pain in patients with flare.[1,2] It is approved for use in patients with frequent flares when other anti-inflammatory therapies are ineffective, contraindicated or not tolerated.[2,23] **Adverse effects** include dizziness and serious infections (e.g. pneumonia, bronchitis).[23]

Prophylaxis against acute flares is recommended for patients in conjunction with initiation of ULT (see next section); [2,19] guidelines recommend the use of low dose colchicine (0.5 mg twice daily) or low dose NSAIDs (e.g. naproxen 250mg twice daily) **for at least 6 months**.[1,2,9,7,19,22]

Urate-lowering therapy

Urate lowering therapy (ULT) is central to successful long-term gout management; withdrawal of therapy may result in recurrence of gout.[7] Recent studies report that <50% of patients with gout receive ULT and that when it is prescribed it is often at an insufficient dose.[2] The recent EULAR guidelines on the use of ULT are outlined in Table 2:

Table 2: EULAR clinical guidelines for the use of urate lowering therapy[2]

- ULT should be considered and discussed with every patient with a definite diagnosis of gout from the first presentation
- ULT is indicated for all patients with recurrent flares (≥2/year), tophi, urate nephropathy and/or renal stones
- ULT is recommended close to the time of first diagnosis in patients presenting at a young age (<40 years), or with a very high serum urate level (480 µmol/L) and/or comorbidities (renal impairment, hypertension, ischaemic heart disease, heart failure)

ULT-urate lowering therapy

ULT should be started at a low dose and then titrated upwards with regular monitoring (e.g. monthly), until the target serum urate level is reached. A level of 360 µmol/L is generally recommended, however a lower serum urate (300 µmol/L) is recommended for patients with severe gout (tophi, chronic arthropathy, frequent attacks).[1,2] The maintenance serum urate level is 360 µmol/L, which should be monitored every 6 months.[2]

There is controversy as to when ULT should be started following an acute flare. It is generally recommended to wait at least 2 weeks after an acute flare before commencing ULT.[2,14,24] However recent evidence suggests that starting ULT during a gout flare does not prolong the flare, provided that the acute episode is adequately treated, which is recommended in some sources.[1,8,25]

There are 3 main drug classes recommended as ULT; **xanthine oxidase inhibitors**, **uricosurics and uricases,** not all of which are authorised in Ireland.[1,7,12] Table 3 summarises the ULT that is currently authorised in Ireland.

Table 3: Urate lowering therapy currently authorised in Ireland for gout[1,4,7,10,12,13,25-29]

Drug (mode of action)	Dose*	Precautions with use include*	Adverse effects include*
Allopurinol (xanthine oxidase inhibitor)	100mg starting dose; slow dose titration (every 2-4 weeks) to achieve serum urate target (up to 900 mg daily) [Reduce starting dose in severe renal impairment]	Use with caution in patients with renal and hepatic impairment Regular monitoring of renal function and serum urate (every 6 months after target serum urate achieved) Potential for DDI including azathioprine, theophylline, warfarin, ampicillin/amoxicillin, ciclosporin, diuretics and ACEi	Rash, nausea, vomiting, gout flares, rarely allopurinol hypersensitivity (risk increases with higher starting dose, HLA-B*5801 allele, renal impairment and concomitant use of diuretics)
Febuxostat (xanthine oxidase inhibitor)	80 mg starting dose; ↑ dose (after 2-4 weeks) up to 120 mg daily to achieve target if necessary	Use with caution in patients with heart failure and ischaemic heart disease Monitoring of hepatic function prior to starting and during therapy Potential for DDI with mercaptopurine/ azathioprine	Rash, abdominal pain, diarrhoea, abnormal liver function, gout flares, rarely severe hypersensitivity reactions
Lesinurad** (uricosuric)	200 mg daily (administered at same time as xanthine oxidase inhibitor)	Due to ↑ renal events, renal function to be evaluated prior to initiation and monitored regularly Potential for DDI (CYP 3A inducer) including hormonal contraceptives	Headache, gastro-oesophageal reflux disease, renal failure

*-full prescribing information is available in the Summary of Product Characteristics, **- currently not marketed in Ireland
DDI – drug-drug interactions, ACEi – angiotensin converting enzyme inhibitor

Xanthine oxidase inhibitors which inhibit urate production, are recommended as first line treatment by all guidelines.[1,2,10]

Allopurinol is generally recommended as first line ULT in the majority of patients with normal renal function.[2,9,10] It is rapidly metabolised to its active metabolite oxypurinol, which is cleared by the kidney.[10] The starting dose is usually 100mg/day (see Table 3) with slow upward titration of the dose until the target serum urate is achieved.[1,2,10] **Higher starting doses may result in acute gout flare and increased risk of serious cutaneous adverse reactions.**[2] The starting dose may need to be adjusted in patients with severe renal disease (e.g. 100mg on alternate days).[10,26,29] The most commonly used allopurinol dose (300 mg/day) does not achieve the target urate level in up to 50% of patients with normal renal function, and doses of up to 900 mg/day may be required in divided doses.[2,6] Evidence suggests that allopurinol may be beneficial in patients with gout and with CVD, however further research is required in this area.[7] **Allopurinol hypersensitivity can present in different ways including maculopapular exanthema, hypersensitivity syndrome, Stevens-Johnson syndrome and toxic epidermal necrolysis;** [2,26] it usually occurs within the first 2 months of starting treatment.[9]

Febuxostat is recommended as first line if allopurinol is contraindicated and/or not tolerated.[1,2] It is predominantly metabolised in the liver and dose reduction is not necessary in patients with mild to moderate kidney impairment.[1,2,12] Doses of febuxostat at 80 and 120mg have been shown to be superior at lowering serum urate compared to allopurinol; however these studies compared feboxostat with allopurinol at fixed doses of 300 mg.[1,2,10,27] Cardiovascular events were the most common serious adverse events noted during treatment with febuxostat in clinical trials; there are currently several large prospective clinical trials examining the cardiovascular safety of allopurinol and febuxostat.[7,10,12] **There have also been reports of serious hypersensitivity reactions (including Stevens-Johnson syndrome) associated with febuxostat.**[12,27] Febuxostat is not recommended in patients concomitantly treated with mercaptopurine or azathioprine due to a potential drug-drug interaction.[1,12,27]

Uricosurics inhibit the renal tubular reabsorption of uric acid and are recommended as second line ULT, however they are not all currently authorised in Ireland.[1,2] ***Lesinurad*** which inhibits urate transporters in the proximal tubule of the kidney, is effective when used in combination with xanthine oxidase inhibitors.[10] It is authorised for use in combination with a xanthine oxidase inhibitor but is currently not marketed in Ireland.[1,30] Other uricosurics include ***probenecid*** and ***sulfinpyrazone,*** which are not authorised in Ireland.

Uricases convert uric acid to the more water soluble allantoin, which is readily excreted. ***Pegloticase*** given as an IV infusion, was withdrawn from the European market in July 2016 and was indicated for patients with severe refractory gout in whom target serum urate was not achieved or for those who could not tolerate xanthine oxidase inhibitors.[1,31]

MANAGEMENT OF GOUT: SUMMARY[2]

<table>
<tr><td colspan="2">Patient with first presentation of acute gout (flare)
(Exclude other conditions such as septic arthritis)</td></tr>
<tr><td>↓</td><td>↓</td></tr>
<tr><td>Non-pharmacological management
• Ice to the affected joint
• Education about the disease
• Individualised lifestyle advice
• Screen for current comorbidities and current medications</td><td>Pharmacological management: treat as early as possible with:
• NSAIDS* +/- PPI
or
• Colchicine* **
or
• Corticosteroids
• Combination therapy of above
• Consider canakinumab if above therapies not effective and/or contraindicated</td></tr>
<tr><td>↓</td><td>↓</td></tr>
<tr><td colspan="2"><u>Resolution of flare</u>
Educate patient to self-medicate (provide patient with management plan for future acute flares)
Consider initiation of urate lowering therapy together with flare prophylaxis</td></tr>
<tr><td>↓</td><td>↓</td></tr>
<tr><td colspan="2"><u>Initiation of ULT</u>
Decide on the serum urate target based on the severity of gout
360 or 300 µmol/L</td></tr>
<tr><td>↓</td><td>↓</td></tr>
<tr><td>Non-pharmacological management
• Education about the disease
• Individualised lifestyle advice
• Screen for current comorbidities
• If appropriate, stop diuretics and substitute with another medication
• Provide patient with management plan for acute flares
• Monitor for adverse effects to ULT</td><td>Pharmacological management
• Initiate ULT
o Allopurinol** (adapt dose to renal function)
▪ Slow dose titration until serum urate target achieved (monitor renal function monthly)
▪ Monitor serum urate every 6 months
o Febuxostat if allergic to allopurinol or target serum urate not achieved with allopurinol
▪ Monitor hepatic function
▪ Achieve target serum urate and continue treatment
▪ Monitor serum urate every 6 months
o Consider combined therapy with a uricosuric if target not achieved
• Prophylaxis against acute flare for 6 months
o NSAIDs* or colchicine* **</td></tr>
</table>

NSAIDs – non-steroidal anti-inflammatory drugs, PPI – proton pump inhibitors, ULT – urate lowering therapy
***avoid in severe renal failure, ** potential for drug-drug interactions**

List of references available on request. Date of preparation: January 2017

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