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Guidelines

The British Society for Rheumatology Guideline for the Management of Gout

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Scope and purpose

Background to the disease

Gout is the most common cause of inflammatory arthritis worldwide. In UK general practice, the overall prevalence has increased from 1.4% in 1999 to 2.49% in 2012 [1], despite the availability of effective and potentially curative urate-lowering drugs for >50 years and evidence-based British and European management guidelines for nearly a decade [2, 3].

Clinical manifestations of gout resulting from monosodium urate crystal deposition include tophi, chronic arthritis, urolithiasis and renal disease as well as recurrent acute arthritis, bursitis and cellulitis. Gouty arthritis and tophi are associated with chronic disability, impairment of health-related quality of life [4–7], increased use of healthcare resources and reduced productivity [8]. Gout is also frequently associated with co-morbidities such as obesity, dyslipidaemia, diabetes mellitus, chronic renal insufficiency, hypertension, cardiovascular disease, hypothyroidism, anaemia, psoriasis, chronic pulmonary diseases, depression and OA [1] as well as with an increase in all-cause mortality (adjusted hazard ratio 1.13, 95% CI: 1.08, 1.18) and urogenital malignancy [1, 9].

Sustained hyperuricaemia is the single most important risk factor for the development of gout. Hyperuricaemia occurs secondarily to reduced fractional clearance of uric acid in > 90% of patients with gout [10]. Age, male gender, menopausal status in females, impairment of

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renal function, hypertension and the co-morbidities that comprise the metabolic syndrome are all risk factors for incident gout associated with decreased excretion of uric acid, as are the use of diuretic and many anti-hypertensive drugs, ciclosporin, low-dose aspirin, alcohol consumption and lead exposure. Tophi and chronic arthritis [11], alcohol consumption [12] and recent use of diuretic drugs [13] are important risk factors for recurring flares.

Genome-wide association studies have identified a number of genes coding for urate anion transporters expressed in the proximal renal tubular epithelium, but these account for <5% of the variation in serum urate [14]. Serum urate levels are influenced by dietary intake and synthesis as well as by renal excretion. Diets high in red meat or seafood, and increased consumption of beer, spirits and fructose- or sugar-sweetened soft drinks are established risk factors for developing gout [15–17]. Single gene disorders associated with urate overproduction, hyperuricaemia and accelerated purine synthesis *de novo* (such as glycogen storage diseases and Lesch–Nyhan syndrome) are very rare causes of primary gout. Diseases (such as lympho- and myeloproliferative disorders and severe exfoliative psoriasis) and drugs (such as cytotoxics, vitamin B12 and ethanol) associated with increased cellular turnover and destruction can lead to secondary hyperuricaemia and gout [18].

The identification of monosodium urate crystals in joint and tissue samples remains the gold standard for the diagnosis of gout. Although identification of urate deposits by dual-energy CT [19] and US [20] are being used increasingly as an aid to the diagnosis of gout in research and hospital practice, joint aspiration or imaging to confirm crystal presence is rarely undertaken in primary care settings where the majority of patients with gout are managed. For diagnosis in clinical practice, clinical scores, without imaging or synovial fluid analysis, have been proposed [21] that include consideration of the patient's history and co-morbidities.

Need for revised management guideline

The British Society for Rheumatology/British Health Professionals in Rheumatology (BSR/BHPR) guideline for the management of gout was published in 2007 [2]. There are four broad reasons why a revised and updated guideline is now required. First, new pharmaceutical treatment options have become available and the evidence base for the efficacy and safety of available drugs has expanded. Second, the incidence, prevalence and severity of gout have increased [1] despite the availability of safe, effective and potentially curative therapy. Third, research studies and audits have consistently shown that fewer than 50% of patients with gout seen in general practice receive urate-lowering therapy (ULT) [22–25] and that many patients with gout being treated with ULT in both primary [1, 26] and secondary care [27, 28] do not achieve reductions of serum uric acid (sUA) levels to the target level recommended in the BSR/BHPR (300 μmol/l) or EULAR (360 μmol/l) guidelines. Finally, as evidence has accumulated that the provision of information to patients with gout is suboptimal [29] and qualitative studies have begun to define a range of patient and provider barriers to effective care [30–32], preliminary data are emerging that demonstrate that these barriers can be overcome, and outcomes improved, with better provision of information and a package of care based on guideline recommendations [33].

Other guidelines available

Recently published guidelines include the 2012 ACR Guidelines for the Management of Gout [34, 35] and the 2013 evidence-based recommendations for the diagnosis and management of gout by a multinational panel of rheumatologists participating in the 3e initiative [36]. Other national and regional guidelines include the US Agency for Healthcare Research and Quality's 2014 guidelines for Diagnosis of Gout and Management of Gout [37, 38], and the Australian and New Zealand [39] and Portuguese [40] recommendations for the diagnosis and management of gout that arose from the 3e initiative [36]. Updated EULAR recommendations for the management of gout were published in 2016.

Objective

This guideline aims to offer revised and updated, concise, patient-focused, evidence-based, expert recommendations for the management of gout in the UK.

Target audience

The guideline has been developed to provide assistance to doctors and allied health professionals who treat and manage patients with gout in primary care and hospital practice. The guideline should also provide a helpful resource for patients and those responsible for commissioning care for patients with gout in the National Health Service (NHS).

Areas that the guideline does not cover

Evidence-based recommendations for the diagnosis and investigation of gout are not included in this guideline. Some recommendations for the diagnosis of gout are addressed in the recent 3e recommendations for the diagnosis and management of gout [36] and EULAR recommendations for the diagnosis of gout [3] are in the process of being updated [41].

Stakeholder involvement

The guideline has been developed by a Multidisciplinary Working Group of rheumatologists (M.H., M.D., K.J., G.N., E.R.), general practitioners (G.D., C.M.), secondary care physicians with specialist experience in general internal medicine, clinical pharmacology (T.M.), and nephrology (S.C.), allied health professionals (A.C., W.J.), lay patients (H.F., A.P.), and an epidemiologist with expertise in evidence-based medicine (W.Z.), on behalf of the BSR/BHPR Standards, Audit and Guidelines Working Group. The draft guideline was presented and discussed in open session by a multidisciplinary audience at the annual scientific meetings of the BSR in 2014 and 2016. The consensus recommendations were developed without any input

from, or consultation with, any pharmaceutical company and potential conflicts of interest of all members of the working group have been fully declared. This guideline has been reviewed and endorsed by the Royal College of General Practitioners.

Rigour of development

Scope of the guideline and strategy for guideline development

The scope of the revised guideline and the key clinical management questions that needed to be addressed were agreed by consensus at an initial face-to-face meeting of the guideline working group after detailed review of the published guideline and results of a systematic literature review. Seventeen clinical management questions (Table 1) were subsequently subjected to additional focused systematic literature searches after transposition into 20 questions in Population, Comparator, Outcome, Time format [42].

Systematic literature search

Systematic literature searches were undertaken by M.H. using MEDLINE 1946 to present, EMBASE 1974 to present, PubMed from inception to present, the Cochrane Controlled Trials Register from inception to present and the ISI Web of Science and AMED databases 1985 to present. An initial literature search in March/April 2012 was updated in June 2015 (see Supplementary table S1, available at *Rheumatology online*, for search strategy).

Inclusion criteria

Articles included were systematic reviews, randomized controlled trials (RCTs), uncontrolled trials, observational studies including cohort, case–control and cross-sectional studies, or those where economic evaluation was made.

Exclusion criteria

Editorials, commentaries, conference abstracts and non-evidence-based narrative/personal reviews were excluded. Studies of hyperuricaemia were included only if they related to the management of gout.

Delphi exercise to generate consensus recommendations

Concise consensus recommendations for the management of gout were developed. Members of the guideline working group were asked to generate a comprehensive list of propositions for the management of gout based on available research evidence and their own clinical expertise after reviewing the published recommendations and the results of the systematic literature reviews. Following elimination of closely similar and overlapping recommendations, a preliminary list of 51 proposed recommendations included 13 for the management of acute gout, 15 relating to education, diet and lifestyle modification, and 23 for the management of recurrent, inter-critical and chronic gout. Consensus for 30 revised draft recommendations was reached after three rounds of a Delphi exercise conducted by email in which propositions with $>60\%$ of votes were accepted, those with $<20\%$ rejected and those attracting between 20 and 60% of votes reconsidered after amalgamations and minor rewording. The draft recommendations were presented for discussion and feedback at the annual scientific meeting of the BSR in 2014. Final consensus on the most appropriate wording for 21 recommendations was agreed at a second face-to-face meeting of the guideline working group after further minor amalgamations and discussion

Table 1 Principal clinical questions considered

1. In patients with acute gout, does the use of ice packs reduce pain?
2. In patients with acute gout, what medication should be used to manage acute attacks?
3. For patients on diuretic therapy presenting with acute gout, should diuretic therapy be discontinued?
4. What are the potential patient and healthcare professional barriers to management of patients with gout?
5. Is patient education effective for patients with gout and, if so, in what format?
6. Is dietary advice effective in the management of patients with gout?
7. In patients with gout and renal failure, should the dose of allopurinol be adjusted?
8. Should patients with gout be screened for co-morbidities?
9. In patients with hyperuricaemia or gout, when should urate-lowering therapy be commenced?
10. In patients with gout, should allopurinol be used as first-line urate-lowering therapy?
11. In patients with gout, should febuxostat be used as an alternative urate-lowering therapy to allopurinol and, if so, in what situations?
12. In patients with gout, should other medications such as benzbromarone, sulfinpyrazone and probenecid be used?
13. In patients initiating urate-lowering therapy, for how long should prophylactic colchicine be continued?
14. In patients initiating urate-lowering therapy, should canakinumab and rilonacept be used to prevent gout attacks?
15. In patients with hyperuricaemia, gout and hypertension, should an angiotensin II blocker rather than an angiotensin-converting enzyme blocker be used?
16. In patients with gout and hyperlipidaemia, should fenofibrate be used as an adjunctive urate-lowering agent?
17. In patients with debilitating chronic tophaceous gout refractory to oral urate- lowering drugs, or in whom these drugs are contraindicated, should pegloticase be used?

of the draft recommendations and the feedback from members of the BSR.

Level of evidence

The level of evidence (LoE) in support of each recommendation was determined (1a: meta-analysis of RCTs; 1b: at least one RCT; IIa: at least one well-designed controlled study without randomization; IIb: at least one well-designed quasi-experimental study; III: at least one non-experimental descriptive study, for example, comparative, correlation or case–control study; IV: expert committee reports, opinions and/or experience of respected authorities) [43]. Where a superior LoE was found, for example, a systematic review for a particular intervention, preceding studies regarding that intervention were not further analysed.

Strength of recommendation

The strength of recommendation (SOR) for each treatment recommendation by members of the guideline development group was graded anonymously on a 0–100 mm visual analogue scale by those present at the final face-to-face meeting and by the others via email.

The SOR for each management recommendation was based on the opinions of the guideline working group after considering the research evidence for efficacy, safety and cost-effectiveness of each treatment proposed, and the personal expertise of each member of the group [44]. This included considerations such as the experts' experience and perception of patient tolerance, acceptability and adherence to the treatment in question, as well as their expert knowledge of any logistic issues involved in the administration of the recommended treatment. A simplified algorithm (Fig. 1) illustrates the suggested care pathway.

Recommendations

Recommendations for management of acute attacks

(i) Educate patients to understand that attacks should be treated as soon as an attack occurs and ensure that patients are aware of the importance of continuing any established ULT during an attack. LoE: IV; SOR: 90% (range 81–100%).

Rationale

The SOR for educating patients to understand the importance of treating acute attacks of gout as early as possible is largely based on common sense, patient experience and expert opinion because of the severity of pain experienced by patients with acute gout. Reduction of pain within 24 h following treatment with an NSAID [45] and with colchicine [46] has, however, been demonstrated in two small placebo-controlled RCTs. The recommendation to continue treatment with urate-lowering drugs during acute gout flares is based on a widespread consensus of expert opinion [2, 34, 47], and qualitative studies that suggest that many patients are unaware of the need to do so [30, 31].

(ii) Affected joints should be rested, elevated and exposed in a cool environment. Bed-cages and ice-packs can be effective adjuncts to management. LoE: Ib (ice-packs), IV (other); SOR: 89% (range 54–100%).

Rationale

The recommendation to rest acutely affected joints is based on widespread patient experience and expert opinion. While there is evidence that urate crystal-induced experimental arthritis in dogs is aggravated by movement and ameliorated by rest [48], there have been no RCTs of rest undertaken in patients with gout. The recommendation for using ice is supported by a Cochrane systematic review of a single small RCT (n = 19) in which topical ice was added to prednisolone and colchicine [49]. In this trial, greater pain reduction (−3.3 cm, 95% CI: −5.84 to −0.82 on 10 visual analogue scale) was observed with adjunctive use of ice packs without additional adverse events. Ice packs may be used as safe adjuncts to pharmacological treatment for acute gout, or when drugs are contraindicated because of multiple active co-morbidities.

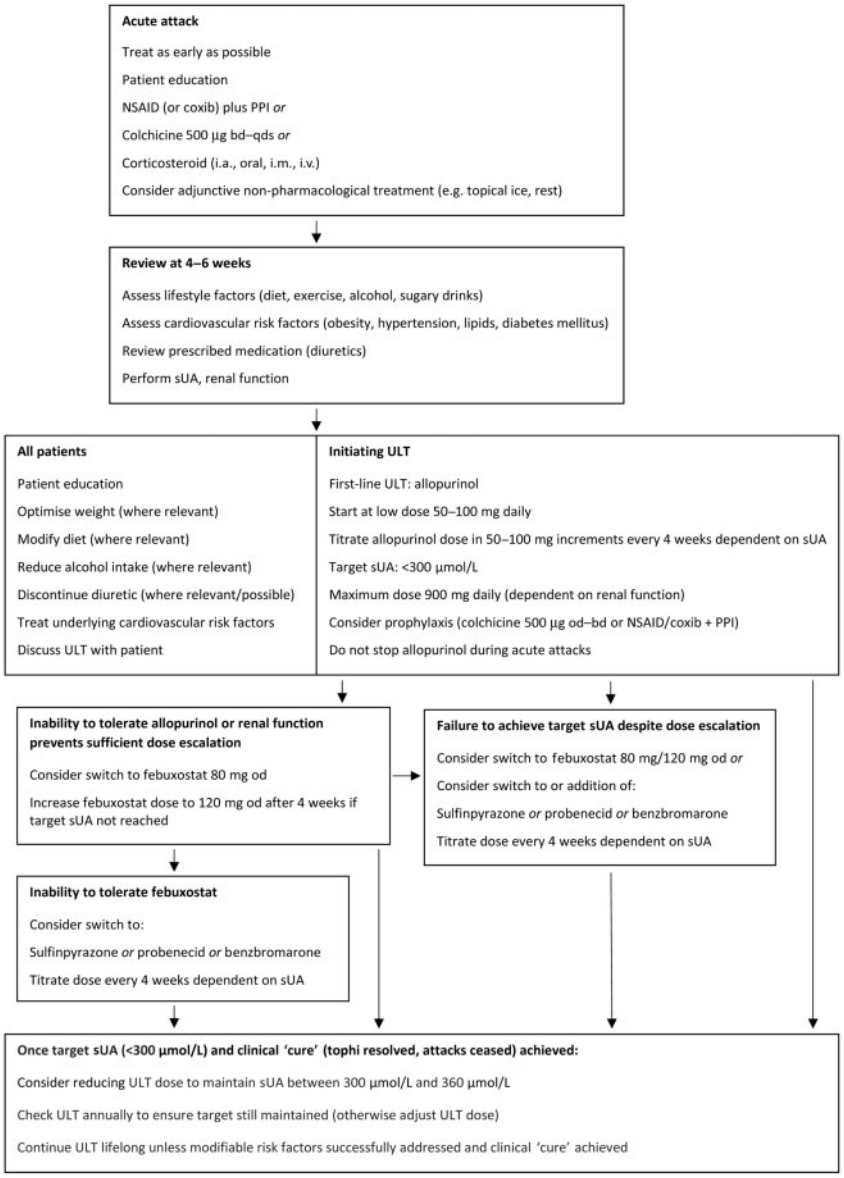
(iii) An NSAID at maximum dose or colchicine in doses of 500 μg bd-qds is the drug of choice when there are no contraindications. Choice of first-line agent will depend on patient preference, renal function and co-morbidities. Patients on NSAIDs or cyclooxygenase-2 inhibitors (coxibs) should be co-prescribed a gastro-protective agent. LoE: Ia; SOR: 95% (range 80−100%).

Rationale

Khanna *et al.* [50] recently published a systematic review that included 30 papers examining the management of acute gout. Although NSAIDs are used more often than colchicine in general practice [24], evidence that either is consistently more effective is lacking, so that choice should be determined by individual patient's preference as well as by renal function and co-morbidities.

The efficacy of NSAIDs is supported by a single placebo-controlled RCT of tenoxicam 40 mg daily [45]. Most RCTs have been head-to-head comparisons with no single agent having greater efficacy. There is, however, widespread expert consensus that, where there is no contraindication to do so, NSAIDs should be prescribed at high dose when treating patients with acute gout because of the severity of the pain and inflammation [2, 3, 35]. NSAIDs are, however, frequently contraindicated in patients with renal insufficiency, peptic ulceration or a history of previous upper gastrointestinal haemorrhage or perforation. Selective cyclooxygenase-2 inhibitors such as etoricoxib have equal efficacy and better gastrointestinal tolerability than non-selective NSAIDs [51], but there are ongoing uncertainties about their relative cardiovascular and renal toxicity with chronic administration [52].

Fig. 1 Algorithm for the management of gout



coxib: cyclooxygenase-2 inhibitor; PPI: proton pump inhibitor; sUA: serum uric acid; ULT: urate-lowering therapy.

Co-prescription of gastro-protection is recommended for patients treated with NSAIDs in accordance with National Institute for Health and Care Excellence (NICE) clinical guidelines [53].

For colchicine, Khanna *et al*. [46, 54] found two placebo-controlled RCTs demonstrating statistical reduction in pain at 24 and 48 h. Terkeltaub's study demonstrated that a low-dose colchicine regimen (1.2 mg followed by 600 μg after 1 h) was equally effective, and was associated with much less nausea, vomiting and diarrhoea, as a high-dose regimen of 4.8 mg over 6 h. A Cochrane review of the same two RCTs [55] also concluded that there was low quality evidence for the efficacy of low-dose colchicine and for no additional efficacy with high doses, which were significantly more likely to be associated with adverse effects (risk ratio (RR) = 3.00, 95% CI: 1.98, 4.54). In the absence of further trial evidence for the efficacy and safety of this proposed regimen, the BSR working group recommends treating acute gout with colchicine in doses of 500 μg bd–qds when there are no contraindications to doing so. The maximum dose of 500 μg qds is, however, often limited by gastrointestinal side effects, most frequently diarrhoea. Colchicine is contraindicated in patients with estimated glomerular filtration rate (eGFR) <10 ml/min/1.73 m^2 and doses should be reduced in patients with eGFR 10–50 ml/min/1.73 m^2 and in the elderly

[56]. Colchicine should also only be used with caution and at low doses in patients taking drugs that are potent inhibitors of cytochrome P450 3A4 (e.g. cimetidine, clarithromycin, erythromycin, fluoxetine, ketoconazole, protease inhibitors, tolbutamide) or p-glycoprotein (e.g. clarithromycin, ciclosporin, erythromycin) [57]. Caution is also required when using colchicine in patients receiving statins, particularly in those with renal impairment, as there are case reports of myopathy and rhabdomyolysis following combined use of colchicine and statins [58–60].

(iv) Joint aspiration and injection of a corticosteroid are highly effective in acute monoarticular gout and may be the treatment of choice in patients with acute illness and co-morbidity. A short course of oral corticosteroid or a single injection of an intramuscular corticosteroid is an alternative in patients who are unable to tolerate NSAIDs or colchicine and in whom intra-articular injection is not feasible. Such systemic therapy is also appropriate for oligo- or polyarticular attacks of gout. LoE: Ib (oral), III (intraarticular, intramuscular), IV (oligo/polyarticular attacks); SOE: 94% (range 83–100%).

Rationale

A Cochrane review in 2013 [61] found no RCTs of intra-articular steroid use for the management of acute gout. However, small observational studies, expert opinion and clinical experience suggest that intra-articular and intramuscular steroid injections can be very effective treatments for acute gouty arthritis [62–64].

A Cochrane review of systemic corticosteroids [65] for acute gout included one randomized double-blind equivalence trial that showed that 5-day courses of naproxen 500 mg twice daily and prednisolone 35 mg daily had equal efficacy [66].

(v) In patients with acute gout where response to monotherapy is insufficient, combinations of treatment can be used. LoE: IV; SOR: 80% (28–100%).

Rationale

This recommendation is supported only by expert opinion [67]. A survey in 2006 [68] found that the most commonly used combination agents are NSAIDs with either intra-articular corticosteroids, or oral steroids or colchicine.

(vi) IL-1 inhibitors may be considered in patients who have previously not responded adequately to standard treatment of acute gout (although not approved by NICE). LoE: Ib (canakinumab, rilonacept), III (anakinra); SOR: 61% (range 8–100%).

Rationale

Anakinra, canakinumab and rilonacept are three IL-1 inhibitors that have been investigated to some extent for the management of acute gout [69–74]. In an RCT, the mAb anti-human IL-1β antibody canakinumab (150 mg by subcutaneous injection) showed good efficacy in reducing pain and swelling when compared with 40 mg intramuscular triamcinolone acetonide [69, 70]. Canakinumab is licensed for use in Europe by the European Medicines Agency (EMA) but not in the USA by the Food and Drug Administration (FDA) because of uncertainty about its risk/benefit ratio. There are currently no published RCTs for the use of anakinra, an IL-1 receptor antagonist, in patients with gout. However, an open label study using 100 mg s.c. on three consecutive days demonstrated pain relief in patients with gout who could not tolerate or had failed conventional treatment [72] and a retrospective review of its use off-label in 26 patients suggested that it could be an effective and safe alternative treatment for acute gouty arthritis in medically complex hospitalized patients who fail or cannot undergo more conventional therapy [73].

These findings and ongoing uncertainty concerning the efficacy and safety of IL-1 inhibitors are reflected in a recent Cochrane review [74]. None of anakinra, canakinumab and rilonacept is approved by NICE for use in the treatment of acute gout. Prescribers in the UK should be aware of the potential need to obtain approval for an individual funding request before these drugs are used.

Recommendations for modification of lifestyle and risk factors

(i) If diuretic drugs are being used to treat hypertension rather than heart failure, an alternative antihypertensive agent can be considered as long as blood pressure is controlled. LoE: IV; SOR: 91% (range 85–100%).

Rationale

Thiazide and loop diuretics are used for a number of indications including the management of hypertension, heart failure and other causes of fluid overload. Whilst diuretics have been found to be associated with an increased risk of gout with a rate ratio of 11.8 (95% CI: 5.2, 27.0) [75], blood pressure control may require a number of agents and often includes a diuretic [76]. A systematic review published in 2012 [77] attempted to assess the risk, but as the number of studies was small, it concluded that there was insufficient evidence to recommend the discontinuation of diuretics across all indications in patients with gout. A recent population-based case–control study using the General Practice Research Database demonstrated that while the use of thiazide and loop diuretics was associated with the development of incident gout, the use of potassium-sparing diuretics was not [78].

(ii) All patients with gout should be given verbal and written information about the following: the causes and consequences of gout and hyperuricaemia; how to manage acute attacks; lifestyle advice about diet, alcohol consumption and obesity; and the rationale, aims and use of ULT to target urate levels. Management should be individualized and take into account co-morbidities and concurrent medications. Illness perceptions and potential

barriers to care should be discussed. LoE: IIb; SOR: 96% (range 83–100%).

Rationale

There is growing evidence regarding the importance of education in gout. An observational, proof of concept study [33] has demonstrated how education and individualized lifestyle advice along with ULT can achieve therapeutic targets. In this study of 106 participants, 92% achieved the therapeutic target, adherence at 1 year was excellent, and there were improvements in pain and other patient-centred outcomes.

Qualitative studies [30] suggest that an inadequate understanding of the causes and consequences of gout, belief that it is only a man's disease, and a stereotypical view of gout as being entirely self-inflicted through lifestyle abuse are important barriers to care. This may result in gout sufferers being hesitant in seeking medical advice and adhering to pharmacological treatments that are not well explained. Other studies have shown that such negative views about gout and its treatment are associated with lower adherence to ULT and suboptimal control of disease [32, 79, 80]. Patients who do not, or cannot, adhere to prescribed ULT are more likely to experience more gout attacks more frequently and in more joints. Such factors, as well as co-morbid disease, have been found to be associated with poorer health-related quality of life [6]. While patients are frequently interested in details of the influence of dietary constituents, they commonly also have important concerns relating to drug safety and drug interactions that are seldom adequately discussed [31].

(iii) In overweight patients, dietary modification to achieve a gradual reduction in body weight and subsequent maintenance should be encouraged. Diet and exercise should be discussed with all patients with gout, and a well-balanced diet low in fat and added sugars, and high in vegetables and fibre should be encouraged: sugar-sweetened soft drinks containing fructose should be avoided; excessive intake of alcoholic drinks and high-purine foods should be avoided; inclusion of skimmed milk and/or low fat yoghurt, soy beans and vegetable sources of protein, and cherries in the diet should be encouraged. LoE: I (vitamin C and skimmed milk), III (others); SOR: 92% (range 80–100%).

Rationale

A recent systematic review of predominantly observational studies [81] identified a number of modifiable dietary factors that were associated with gout. Excessive consumption of meat, seafood, alcoholic drinks (especially beer and spirits), sugar-sweetened soft drinks and fructose-containing foods are all significant risk factors for incident gout. Episodic excessive alcohol consumption, regardless of type of alcohol-containing beverage, is also associated with an increased risk of recurrent gout attacks [82]. Low-fat dairy intake, folate intake, coffee consumption and diets high in dietary fibre appear to be associated with a reduced risk of incident gout as well as a reduction in risk of recurrent gout flares in some, but not all, cases [83]. Fruit consumption has been found beneficial and this may be related to consumption of vitamin C (see recommendation VIII for the optimal use of urate-lowering therapies).

The urate-lowering effect of cherry was previously reported in healthy women [84]. A case-crossover study conducted in 633 subjects with gout [85] found that consumption of cherry and cherry extract was associated with a statistically significant 35% lower risk of gout attacks when compared with no cherry intake. When cherry intake was combined with allopurinol use, the risk of gout attacks was 75% lower than during periods without either exposure (odds ratio (OR) = 0.25, 95% CI: 0.15, 0.42).

A Cochrane systematic review of the efficacy and safety of dietary supplements in patients with gout found only two RCTs, one for skimmed milk powder (SMP) enriched with glycomacropeptides (n = 120) and the other for vitamin C (n = 40) [86]. Pain from self-reported flares was marginally less in those receiving enriched, compared with unenriched, SMP (mean difference −1.03, 95% CI: −1.96 to −0.10), but enriched SMP was no better in reducing the mean number of acute attacks or the sUA. Vitamin C (500 mg/day for 8 weeks) reduced the sUA (−0.014 mmol/l) much less than allopurinol (−0.118 mmol/l) in patients with gout, and also less than the mean reduction of 0.02 mmol/l reported in the meta-analysis of 13 RCTs of vitamin C administration in patients with hyperuricaemia who did not have gout [87]. Vitamin C supplementation in this modest dose does not appear to have a clinically significant uricosuric effect in patients with gout [87]. It is certainly insufficient for use as monotherapy and a trial suggested that its efficacy as a urate-lowering agent, even when used as an adjunct to standard ULT with allopurinol, was minimal [88].

(iv) Patients with gout and a history of urolithiasis should be encouraged to drink >2 l of water daily and avoid dehydration. Alkalinization of the urine with potassium citrate (60 mEq/day) should be considered in recurrent stone formers. LoE: IV; SOR: 57% (range 17–100%).

Rationale

While there are no published trials of prevention of urolithiasis in patients with gout and recurrent stone formation, there have been two recent systematic reviews and meta-analyses of RCTs of medical management of recurrent urolithiasis in all adults [89, 90]. There is moderate strength evidence from relatively poor quality RCTs for risk reduction with increased fluid intake (RR = 0.45, 95% CI: 0.24, 0.84) and further reduction of risk with additional therapy with citrates (RR = 0.25, 95% CI: 0.14, 0.44).

(v) Cardiovascular risk factors and co-morbid conditions such as cigarette smoking, hypertension, diabetes mellitus, dyslipidaemia, obesity and renal disease should be screened for in all patients with gout, reviewed at least annually and managed appropriately. LoE: III; SOR: 90% (range 77–100%).

Rationale

Co-morbidities associated with gout are well recognized [81, 91, 92]. The need to manage these co-morbidities is also recognized but at present no prescriptive guidance exists. An RCT found that allopurinol slows the progression of renal disease in patients with chronic kidney disease (CKD) and hyperuricaemia [93]. The importance of screening for co-morbidities is highlighted by a recent population-based study that has demonstrated gout to be an independent risk factor for mortality from coronary heart disease and renal disease [94].

Recommendations for optimal use of urate-lowering therapies

(i) The option of ULT should be explained to patients when the diagnosis is confirmed and they are being given information about gout. Patients should be fully involved in the decision as to when to commence ULT. The importance of taking ULT regularly and continually to prevent the return of gout attacks should be explained. Patients should be supported during the process of lowering their serum uric acid levels as it can cause an increase in gout flares during this time. LoE: Ib; SOR: 94% (range 82–100%).

Rationale

Reasons for full patient involvement have been discussed earlier in this guideline and are supported by preliminary evidence from a proof of concept study [33]. Poor patient understanding of the need for ULT is not confined to the UK and has been documented in a large population-based observational study in the USA [80], in a survey conducted in South China [95] and in a focus group qualitative study in New Zealand Maoris [96].

(ii) Urate-lowering therapy should be discussed and offered to all patients who have a diagnosis of gout. ULT should particularly be advised in patients with the following: recurring attacks ($\geqslant 2$ attacks in 12 months); tophi; chronic gouty arthritis; joint damage; renal impairment (eGFR < 60 ml/min); a history of urolithiasis; diuretic therapy use; primary gout starting at a young age. LoE: Ia (attacks, tophi, chronic gouty arthritis, joint damage, renal impairment), III (urolithiasis), IV (diuretics, young age). SOR: 95% (range 82–100%).

Rationale

Research evidence supporting the treatment gout with ULT has increased considerably in the last decade. Treatment of patients with recurring attacks, tophi and chronic gouty arthritis is supported by three systematic reviews and meta-analyses [97–99]. However, the recommendation to consider treatment with ULT in all patients with gout is only based on expert opinion and increasing imaging evidence that gout is a chronic crystal deposition disease even at the time of the first attack [100]. For patients known to have other pre-existing risk factors or co-morbidities when presenting with the first episode of gout, such consideration is particularly pertinent. The length of time between the first and subsequent episode of gout can vary considerably between individuals, but typically is < 2 years. Over time, the inter-critical periods shorten and as good practice in patient education, it is worth having the discussion about treatment early in the course of the disease, always bearing in mind that this potentially curable condition can have a significant impact on patient quality of life if left untreated [5, 6]. It is not recommended that asymptomatic hyperuricaemia is treated. However, the wisdom of the recommendation that commencement of ULT should at least be considered after the first attack of gout is supported by observational data from the UK Clinical Practice Research Datalink that showed that less than half the patients with gout eligible for ULT were offered treatment [23].

Earlier recommendations to offer treatment with ULT only to gout patients with recurring acute attacks were supported by a health economic study in a Canadian healthcare setting that showed that only 62% of patients with gout had a second attack within 1 year and that treatment with ULT only became cost-effective (cost saving) in patients suffering more than three attacks per year [101]. This study, however, does not take into account the ongoing silent deposition of crystals and the significant pain experienced by patients with each attack. Clinical experience and epidemiological studies [102, 103] also show that the risk of gout attacks rises sharply when the serum urate is very high (>500 μmol/l). However, the decision as to when to start ULT in any individual will also be influenced by the patient's co-morbidities, any potential contraindications, intolerance or drug interactions, as well as by consideration of the overall balance of risks and benefits and the patient's wishes.

A large population-based study has demonstrated that gout is an independent risk factor for mortality and specifically for death due to coronary heart disease and renal disease [94]. Gout is a risk factor for the development of end-stage renal failure [104] and hyperuricaemia is an independent risk factor for renal impairment [105]. There is now evidence from RCTs that allopurinol slows progression in hyperuricaemic patients with CKD [93, 106] and a recently published systematic review supports the concept that treating gout with ULT improves renal function [55].

Treatment of patients with gout and urolithiasis with ULT is supported by observational studies [107], while the recommendation to consider ULT in patients taking diuretic drugs is supported by three cohort studies and four case–control studies that demonstrated higher risks

of gouty arthritis in users compared with non-users of diuretics [77].

The recommendation to treat patients with primary gout at an early age with ULT is largely based on expert opinion. A number of rare monogenic disorders associated with inborn errors of purine metabolism [108, 109], glycogen storage diseases [110] or uromodulin mutations associated with decreased fractional urate excretion [111] can result in the development of gout at an early age. A retrospective study of patients seen by rheumatologists in Taiwan suggested that the age at which gout presents was falling [112] and heritability accounts for 35% of gout risk in men and 17% in women in Taiwan [1]. Common dysfunctional variants in the ABC G2 urate transporter may be important causes of early onset gout in Japanese males [113] and in Han Chinese [114] but evidence from twin studies in the USA suggests that while genetic factors have an important influence on serum urate levels and hyperuricaemia, lifestyle and environmental factors are more important risk factors for primary gout, outside the context of the rare single gene disorders [115].

(iii) Commencement of ULT is best delayed until inflammation has settled as ULT is better discussed when the patient is not in pain. LoE: IV; SOR: 94% (range 87–100%).

Rationale

Although a small RCT has shown that commencement of allopurinol during an acute attack was not associated with a significant increase in daily pain, recurrent flares or inflammatory markers [116], the working group thought that postponing detailed discussion of long term ULT until a time when the patient was no longer in pain would allow the information to be better absorbed. However, in patients in whom attacks are so frequent to make this difficult, the findings of this trial support initiation of ULT before inflammation has resolved.

(iv) The initial aim of ULT is to reduce and maintain the sUA at or below a target level of 300 μmol/l to prevent further urate crystal formation and to dissolve away existing crystals. The lower the sUA the greater the velocity of crystal elimination. After some years of successful treatment, when tophi have resolved and the patient remains free of symptoms, the dose of ULT can be adjusted to maintain the sUA at or below a less stringent target of 360 μmol/l to avoid further crystal deposition and the possibility of adverse effects that may be associated with a very low sUA. LoE: III (sUA target <300 μmol/l), IV (subsequent dose adjustment to sUA <360 μmol/l); SOR: 97% (range 90–100%).

Rationale

The target sUA of <300 μmol/l recommended in the previous BSR/BHPR guideline [2] remains the recommended target to prevent crystal formation and recurrent flares [117]. Evidence that greater velocity of crystal elimination is associated with a lower sUA is derived from observational data [118, 119]. The recommendation for ULT dose reduction to the less stringent target of sUA below 360 μmol/l once the patient is stable to avoid further crystal deposition and the possibility of adverse effects that may be associated with a very low sUA is based on expert opinion, a reasoned proposal for such a two-stage approach [119] and caution in the light of studies that have shown a possible association between low sUA levels and progression of neurodegenerative disorders such as Parkinson's disease [120], dementia [121], Huntingdon's disease [122] and amyotrophic lateral sclerosis [123]. One study showed an increased risk of incident Parkinson's disease in men with sUA <300 μmol/l compared with those with sUA 300–500 μmol/l [124].

(v) Allopurinol is the recommended first-line ULT to consider. It should be started at a low dose (50–100 mg daily) and the dose then increased in 100 mg increments approximately every 4 weeks until the sUA target has been achieved (maximum dose 900 mg). In patients with renal impairment, smaller increments (50 mg) should be used and the maximum dose will be lower, but target urate levels should be the same. LoE: Ib (dose escalation), III (dose adjustment for renal function). SOR: 97% (range 88–100%).

Rationale

Research evidence for the efficacy and safety of allopurinol has been studied in a recent systematic review [125]. Eleven trials involving a total of 4531 patients compared allopurinol in various doses with placebo (two trials); febuxostat (four trials); benzbromarone (two trials); colchicine (one trial); probenecid (one trial); continuous *vs* intermittent allopurinol (one trial); and different doses of allopurinol (one trial). In double blind RCTs, allopurinol given in a fixed dose of 300 mg daily was more effective than placebo [126] but less effective than febuxostat 80 mg or 120 mg daily [126, 127]. However, these trials, and observational studies of gout being treated in UK general practice [33], have shown that many patients do not achieve reductions of sUA to target levels recommended by the BSR (300 μmol/l) [2] or EULAR (360 μmol/l) [3] when treated with allopurinol in doses of 300 mg or less daily. Recent data from the Nottingham proof of concept study [33] and from the Febuxostat versus Allopurinol Streamlined Trial (FAST) [128] have confirmed that gradual up-titration of allopurinol is effective in lowering sUA to target levels and generally well tolerated. The median dose of allopurinol found to be required to achieve the less stringent therapeutic sUA target of ⩽360 μmol/l in >90% of the Nottingham patients was 400 mg/day. While we await direct comparison between allopurinol and febuxostat (and other ULTs) using recommended, best practice, up-titration regimens rather than fixed doses, allopurinol should remain the first option. The recommendation that allopurinol should be the first-line ULT

to consider is further supported by health economic studies [129, 130].

Although well tolerated by the majority of patients, allopurinol is rarely (~0.1–0.4%) associated with potentially life-threatening severe, cutaneous adverse reactions (SCAR) including toxic epidermal necrolysis, hypersensitivity drug reactions with rash, eosinophilia and systemic symptoms (DRESS) or Stevens–Johnson syndrome with vasculitis, liver and renal toxicity [131]. Allopurinol should not be used in people carrying the variant allele HLA-B*5801 [132] as the risk of SCAR during treatment with allopurinol is greatly increased (OR = 73) [133]. Screening patients of Korean, Han Chinese and Thai descent for HLA-B*5801 before considering ULT with allopurinol has been recommended [35] because of the high frequency (6–12%) of this allele in these ethnic groups compared with <2% in Caucasian populations.

Based on reports of a relationship between the use of full dose allopurinol and the development of allopurinol hypersensitivity in patients with renal impairment, previous recommendations were to dose allopurinol according to creatinine clearance (CrCl) [134]. Unfortunately subsequent observational studies showed that dose adjustment according to CrCl seldom resulted in adequate reduction of sUA in patients with gout and renal insufficiency [135], and a case–control study showed no evidence of a reduction in frequency of allopurinol hypersensitivity in patients dosed according to CrCl [136]. More recently, studies by Stamp *et al.* [137] have suggested that lowering the starting dose of allopurinol appropriate to the level of renal function (Table 2) reduces the risk of allopurinol hypersensitivity, and that subsequent gradual increase in the dose above the dose based on CrCl resulted in reduction of sUA to target levels in most patients without any increase in toxicity [138].

(vi) Febuxostat can be used as an alternative second-line xanthine oxidase inhibitor for patients in whom allopurinol is not tolerated or whose renal impairment prevents allopurinol dose escalation sufficient to achieve the therapeutic target. Start with a dose of 80 mg daily and, if necessary, increase after 4 weeks to 120 mg daily, to achieve therapeutic target. LoE: Ia; SOR: 90% (range 63–100%).

Table 2 Starting regime of allopurinol according to glomerular filtration rate

Estimated GFR ml/min/1.73 m^2	Allopurinol starting dose
<5	50 mg/week
5–15	50 mg twice weekly
16–30	50 mg every 2 days
31–45	50 mg/day
46–60	50 mg and 100 mg on alternate days
61–90	100 mg/day
91–130	150 mg/day
>130	200 mg/day

From Stamp LK *et al.* Starting dose is a risk factor for allopurinol hypersensitivity syndrome: a proposed safe starting dose of allopurinol. *Arthritis Rheumatol* 2012;64:2529–36. Copyright © 2012 by John Wiley & Sons, Inc. Reprinted by permission of John Wiley & Sons, Inc. GFR: glomerular filtration rate.

Rationale

Systematic reviews and meta-analyses [97, 99] of RCTs [126, 127, 139], among other RCTs, have demonstrated the efficacy of febuxostat in reducing sUA levels, and reducing the risk of gout flares. When compared with a fixed dose of 300 mg of allopurinol, febuxostat (80 mg and 120 mg/day) was more effective in reducing the sUA to <360 mmol/l (RR = 1.56; 95% CI: 1.22, 2.00) but not the risk of gout flares (RR = 1.16; 95% CI: 1.03, 1.30) [97]. There was heterogeneity in the dosages of febuxostat and allopurinol used, the length of time patients had had gout, the length of follow-up, and whether prophylaxis was used.

Febuxostat is generally well tolerated and can be used in doses of 80 mg or 120 mg daily in elderly patients [140] and others with mild to moderate renal impairment (GFR >30 ml/min/1.73 m^2). There are currently insufficient data available on its use in patients with more severe CKD. Severe cutaneous hypersensitivity reactions to febuxostat [141–144] are very unusual but the risk of SCAR or DRESS with febuxostat in patients with previous allopurinol hypersensitivity has still to be established. Treatment with febuxostat in patients with ischaemic heart disease or congestive cardiac failure is currently not recommended [143, 144] but large scale RCTs are currently in progress in Europe [128] and North America [145] to establish and compare the cardiovascular safety of febuxostat and allopurinol in patients with gout, high cardiovascular risk and co-morbidities.

Health economic studies have shown that febuxostat is cost-effective as a second-line ULT [129, 130]. In the UK, NICE have recommended the use of febuxostat only when allopurinol is contraindicated or not tolerated [144] while the Scottish Medicines Consortium (SMC) accepts febuxostat as a suitable second-line ULT when treatment with allopurinol is inadequate, not tolerated, or contraindicated [146].

(vii) Uricosuric agents can be used in patients who are resistant to, or intolerant of, xanthine oxidase inhibitors. The preferred drugs are sulfinpyrazone (200–800 mg/day) or probenecid (500–2000 mg/day) in patients with normal or mildly impaired renal function, or benzbromarone (50–200 mg/day) in patients with mild to moderate renal insufficiency. LoE: Ia; SOR: 92% (range 82–100%).

Rationale

Uricosuric drugs were the first agents to be used for ULT >60 years ago [147]. Their efficacy and safety for ULT is supported by a recent systematic review and meta-

analysis [148] of two RCTs comparing benzbromarone with allopurinol, two RCTs comparing benzbromarone with probenecid and one non-randomized case–control trial comparing probenecid with allopurinol, and a cohort study examining probenecid [149], but there have been no placebo-controlled RCTs of the three drugs that are currently approved for use as ULT in patients with gout in Europe (sulfinpyrazone 200–800 mg od, probenecid 250–500 mg qds, benzbromarone 50–200 mg od). In an RCT of patients who did not tolerate allopurinol 300 mg/day well or achieve target sUA, benzbromarone 200 mg/day was found to be more effective and better tolerated than probenecid 2 g/day [150], and benzbromarone 200 mg daily was approximately equipotent with allopurinol 600 mg/day in lowering sUA to target in another RCT [151]. All uricosurics are contraindicated or need to be used with great caution in patients with urolithiasis or severe renal impairment. Clinical experience indicates that sulfinpyrazone and probenecid have limited efficacy in patients with mild or moderate renal insufficiency (GFR $<$ 60 ml/min) but benzbromarone has been shown to maintain uricosuric efficacy when the GFR is as low as 20 ml/min [152]. Probenecid and benzbromarone are only available for the treatment of patients with gout in the UK on a named patient basis, and patients requiring these unlicensed drugs should be under the care of a rheumatologist. The use of benzbromarone was restricted in Europe following rare reports of severe hepatotoxicity, mainly from Asian countries. Patients treated with benzbromarone should have liver function tests monitored but the risk of serious hepatotoxicity in patients receiving the benzbromarone in Europe is estimated as approximately 1 in 17 000 [153].

(viii) Losartan and fenofibrate should not be used as a primary ULT but where treatment for hypertension or dyslipidaemia, respectively, is required, they may be considered as they have a weak uricosuric effect. Vitamin C supplements (500–1500 mg daily) also have a weak uricosuric effect. LoE: III; SOR: 89% (range 63–100%).

Rationale

Unlike ACE inhibitors, beta blockers and other angiotensin II receptor blockers used for treating hypertension, losartan 50 mg od has been shown to have mild uricosuric effects in patients with gout [154], and the use of losartan was associated with a significantly reduced risk of incident gout (RR = 0.81, 95% CI: 0.70, 0.94) in a large community-based UK case–control study using data from The Health Improvement Network [155].

The lipid-lowering agent fenofibrate has been shown to be uricosuric [156] and to have a modest additional urate-lowering effect in gout patients being treated with allopurinol [157, 158]. Losartan (50 mg od) and fenofibrate (300 mg od) were both found to have some additional urate-lowering efficacy when administered to gout patients receiving ULT with allopurinol or benzbromarone in one small study [159].

A meta-analysis of 13 RCTs found that sUA can be lowered by vitamin C supplementation in patients without gout and that sUA reductions were greater in trials administering vitamin C $>$500 mg/day [87]. A single RCT in patients with gout showed that vitamin C (500 mg/day for 8 weeks) reduced the sUA ($-$0.014 mmol/l) much less than allopurinol ($-$0.118 mmol/l) [88]. Vitamin C supplements in this modest dose only have a very weak uricosuric effect in people with gout, which is insufficient for it to be used as substitute monotherapy for allopurinol or other licensed ULT. Moreover, the study of Stamp suggests that in this dosage it is also unlikely to be a clinically useful adjunct to standard ULT with allopurinol [88]. No studies have been undertaken to assess whether vitamin C supplementation is effective in reducing the incidence of recurrent gout attacks.

(ix) A uricosuric agent can be used in combination with a xanthine oxidase inhibitor in patients who do not achieve a therapeutic serum urate target with optimal doses of monotherapy. LoE: III; SOR: 88% (range 71$-$100%).

Rationale

Enhancement of uric acid excretion and reduction of sUA in patients with tophaceous gout by combined treatment with sulfinpyrazone and allopurinol was first demonstrated nearly 50 years ago [160]. Observational studies by Perez-Ruiz and colleagues have shown that the velocity of tophus volume reduction in patients with chronic tophaceous gout could be accelerated with more profound reduction of sUA by combined treatment with allopurinol and benzbromarone [118]. They subsequently demonstrated that even gout patients that are primary overproducers of urate, with apparently increased urine uric acid excretion, also have evidence of defective fractional urate clearance [161] and may therefore respond to addition of a uricosuric drug if their sUA is not reduced to target levels with a xanthine oxidase inhibitor alone. More recent observational studies have also shown that combined treatment with allopurinol and benzbromarone was more effective in lowering sUA than either agent alone [162]. A recent single case report has demonstrated effective lowering of sUA in a patient with gout and chronic renal failure with addition of a combination of allopurinol and febuxostat to benzbromarone when combination of a single xanthine oxidase inhibitor with benzbromarone was ineffective [163]. Most recently phase III trials of a new selective uric acid reabsorption inhibitor, lesinurad, have shown it to be effective in doses of 200 mg od and 400 mg od in lowering the sUA to target levels in combination with allopurinol in patients with gout that have not responded adequately to allopurinol $\geqslant$300 mg daily ($\geqslant$200 mg in moderate renal impairment) [164]. Its use for this indication has recently been given FDA and EMA approval and marketing authorization.

(x) Colchicine 500 μg bd or od should be considered as prophylaxis against acute attacks resulting from initiation or up-titration of any ULT and continued

for up to 6 months. In patients who cannot tolerate colchicine, a low-dose NSAID or coxib, with gastroprotection, can be used as an alternative providing there are no contraindications. LoE: Ib; SOR: 86% (range 29–100%).

Rationale

Prophylaxis against acute flares in patients initiating ULT has been the subject of two recent systematic reviews [125, 165]. There is more evidence from RCTs to support the use of colchicine, than for NSAIDs, for flare prophylaxis. In a 6-month placebo-controlled RCT in patients with gout receiving probenecid for ULT, the flare rate was reduced from 6 to 2.3 flares per annum in patients receiving colchicine 500 μg daily [166]. In another 6-month placebo-controlled RCT in patients initiating allopurinol at a dose of 100 mg od followed by up-titration in 100 mg increments, flares occurred in 33% of patients given colchicine 500 μg bd for flare prophylaxis compared with 77% of those treated with placebo [167]. An investigator-initiated reanalysis of gout flare data from the three phase III trials of febuxostat found that flare prophylaxis for up to 6 months with colchicine 600 μg od or naproxen 250 mg bd, during the initiation of ULT with febuxostat or allopurinol, appeared to provide greater benefit than flare prophylaxis for 8 weeks, with no increase in adverse events [168]. There is little other research evidence to help determine the optimal duration of prophylaxis. A systematic review [125] identified a single RCT comparing three treatment groups given colchicine 1000 μg daily for 3–6, 7–9 and 10–12 months [169]. By 12 months, recurrent acute gout was reported by 54%, 28% and 23%, respectively. Adverse events did not differ between the three groups. However, the risk of bias was high.

Long-term prophylaxis with colchicine or NSAIDs in patients with gout always demands a careful consideration of the overall benefit to risk balance in individual patients, and especially in those with co-morbidities and potential for drug interactions. When using Cox-2 selective or non-selective NSAIDs, the risks of upper GI bleeds and cardiovascular risk should be considered, and gastro-protection with a proton pump inhibitor is recommended. Although usually well tolerated, possible side effects of long-term colchicine include diarrhoea, nausea/vomiting, marrow suppression, myopathy and rhabdomyolysis.

The use of flare prophylaxis is particularly important when ULT is initiated with febuxostat, as the lowest available starting dose in the UK (80 mg) lowers the serum acid level to a greater degree than the starting dose of allopurinol (100 mg), and the risk of precipitating a gout flare is consequently greater [97].

There is no research evidence to support the use of corticosteroids for flare prophylaxis.

IL-1 inhibitors have also been investigated for use for flare prophylaxis [69, 169–172] but none are currently approved for this indication by the EMA or FDA and it is likely that the costs of these biologics will preclude their use for this indication in patients with gout in the UK NHS. In a phase II trial of various doses of canakinumab and colchicine 500 μg od in over 400 patients initiating treatment with allopurinol, the mean number of flares per patient after 4 months was less in the canakinumab-treated patients at all doses >50 mg but there was no evidence of a dose response and there were more infections in the canakinumab-treated patients (18%) than in those given colchicine prophylaxis (12%) [169].

Management points in special groups

Patients with renal insufficiency

CKD and nephrolithiasis are very common in patients with gout. A recent systematic review and meta-analysis of epidemiological and observational studies suggested that the overall prevalence of CKD (stage 3 or greater; GFR < 60 ml/min/1.73 m^2) in patients with gout was 24% compared with 8.5% in the non-gouty population, and the prevalence of self-reported nephrolithiasis was 14% [173]. This presents physicians with important challenges in managing patients with gout, and management of gout in patients with renal impairment has been the subject of two recent systematic reviews and a guideline from the US National Kidney Foundation [174, 175].

For the management of acute gout, the dose of oral colchicine should be reduced in patients with eGFR 10–50 ml/min/1.73 m^2 but is contraindicated in patients with more severe renal impairment (GFR < 10 ml/min/1.73 m^2). High-dose NSAIDs should not be used even in patients with moderate renal impairment [176, 177]. Although the efficacy of corticosteroids in those with CKD has not been evaluated in RCTs [174], clinical experience suggests that they can be effective and safe for managing acute gout in patients with severe renal impairment or in other patients in whom colchicine and NSAIDs cannot be used. Intra-articular triamcinolone hexacetonide (40 mg for large joints, 10–20 mg for smaller joints) is often recommended if only one or two joints are inflamed, or a 7–14-day course of oral prednisolone (30–40 mg tapering to nothing), if multiple joints are involved or if arthrocentesis is not possible.

Guidelines for the use of allopurinol, febuxostat and uricosuric drugs in patients with renal impairment have been discussed following recommendations V, VI and VII for the optimal use of urate-lowering therapies.

Flare prophylaxis with colchicine or NSAIDs in patients with gout and renal insufficiency initiating ULT needs to be undertaken with great caution as the risks of colchicine toxicity, especially myopathy, are increased in patients with renal impairment [178] and NSAIDs can cause acute kidney injury and further impair renal function in patients with CKD [179]. Prophylaxis with low-dosage colchicine, adjusted for renal function, is believed to be a safer option than low-dose NSAIDs [174, 175]. Based on pharmacokinetic data in patients with CKD [180], it is suggested that there is no need for reduction in colchicine dosage (500 μg od or bd) for flare prophylaxis in patients with mild renal insufficiency (eGFR >60 ml/min/1.73 m^2) but the dose should be limited to 500 μg od in those with an eGFR of 30–60 ml/min/1.73 m^2 and to 500 μg

every 2–3 days with eGFR 10–30 ml/min/1.73 m^2 [181] and avoided altogether if eGFR <10 ml/min/1.73 m^2. Although it is usually recommended that NSAIDs should be avoided in all patients with renal impairment, a recent systematic review and meta-analysis of observational studies found no evidence of accelerated CKD progression in patients with moderate to severe renal impairment treated with low-dose NSAIDs (OR: 0.96; 95% CI: 0.86, 1.07) [176].

Severe refractory tophaceous gout

Patients with severe symptomatic tophaceous gout in whom hyperuricaemia cannot be controlled with standard ULTs alone, or in combination, should be referred to a rheumatologist. Pegloticase, a polyethylene glycol modified mammalian uricase, can be effective in such patients [182, 183], although not approved by NICE. The drug is administered by i.v. infusion (8 mg in 250 ml normal saline over 2 h) every 2 weeks by physicians with experience and facilities for dealing with infusion reactions, and patients should be pre-treated with antihistamines and steroids to reduce the risk of infusion reactions, in addition to low-dose colchicine or NSAIDs for flare prophylaxis. Despite heavy pegylation, pegloticase is immunogenic. sUA should be measured before each infusion, and treatment discontinued if the sUA is >360 μmol/l as transient responders (about 50%) appear to be at increased risk for infusion reactions and anaphylaxis. Pegloticase is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency because of the risk of haemolysis, and extra caution is required in patients with congestive heart failure. Pegloticase has FDA approval and EMA marketing authorization in Europe but has not been approved by NICE or the SMC because of concerns about toxicity and cost. Rasburicase, a recombinant *Aspergillus flavus* uricase that is licensed for the treatment and prophylaxis of tumour lysis syndrome, but not for gout, has also been used successfully in some patients with severe refractory gout [184] despite its greater potential immunogenicity. Prescribers in the UK should be aware of the potential need to obtain approval for an individual funding request before these drugs should be used.

In pregnancy

Apart from patients with familial juvenile hyperuricaemic nephropathy [185], gout is very uncommon in pre-menopausal women and in pregnancy [186] and so data are sparse. Conservative measures including ice are safe for managing acute attacks. NSAIDs can be used in the mid-trimester [187]. Steroids are generally safe to use in pregnancy [188] and the recommendations for lifestyle modifications including the dietary changes discussed previously are also safe.

The safety data for colchicine during pregnancy are largely derived from studies of its use in FMF [189] although there are also some reports of chromosomal damage. High concentrations of colchicine can be found in breast milk and so colchicine is best avoided when breast feeding.

Allopurinol and febuxostat have not been adequately tested during pregnancy. Probenecid was used extensively in the past during antibiotic treatment of infections in pregnant women without any reported fetal toxicity.

Applicability and utility

Statement of potential organizational barriers to introduction

Despite the increasing prevalence of gout and the availability of effective and potentially curative ULT for >50 years, its management remains poor with only 40% of patients with gout ever receiving ULT [1]. Inadequate provision of information to patients [29] has been identified as one of the key barriers [30–32] to effective management of gout. There is preliminary evidence that patient adherence to ULT and lowering of sUA to target levels can be achieved with better provision of information and a package of care based on guideline recommendations [33]. Effective provision of information and monitoring of treatment to achieve target sUA levels requires regular ongoing clinical review. However, anecdotal reports suggest that some secondary care organizations prohibit follow-up of patients with gout, insisting on discharge with a treatment plan to primary care where treatment is known to be suboptimal. Furthermore, although ~20% of people presenting with their first attack will have a second episode within 12 months [190], patients often do not consult for subsequent attacks, so practitioners may not be aware of recurrent attack frequency and the need for ULT, highlighting the case for discussing ULT early in the course of disease.

Potential cost implications for implementation of the guideline

Although there are few cost-effectiveness studies in gout, the guideline takes these into account. The guideline recommends as the first-line ULT allopurinol, which is inexpensive and likely to be tolerated and effective in the vast majority of patients with gout. The cost-effectiveness of febuxostat as a second-line ULT has been established and our guidance for its use concords with its NICE and SMC approval [129, 130, 144, 146]. The guideline does include recommendations for unlicensed or non-NICE-approved use of pegloticase and IL-1 inhibitors although the need to use these drugs is likely to be rare and individual clinicians are advised to consider local arrangements for funding individual funding requests if using these drugs.

Summary of changes in the revised recommendations

This guideline contains several important changes from the 2007 BSR/BHPR guideline [2]. The importance of patient education and provision of information about gout and its treatment are strongly emphasized in the updated guideline (recommendation I for the management of acute attacks, recommendations II and III for the modification of

lifestyle and risk factors and recommendation I, II and III for the optimal use of urate-lowering therapies). It is now recommended that an NSAID or colchicine are both drugs of choice for acute gout when there are no contraindications and that the choice of first-line agent should be determined by renal function, co-morbidities and patient preference (recommendation III for the management of acute attacks). Combinations of NSAIDs with corticosteroids or colchicine can be used for acute attacks where response to monotherapy is insufficient (recommendation V for the management of acute attacks), and IL-1 inhibitors may be considered in patients who have not responded adequately to standard treatment (recommendation VI for the management of acute attacks).

The revised guideline emphasizes that all patients with gout should be screened for cardiovascular risk factors and co-morbid conditions such as cigarette smoking, hypertension, diabetes mellitus, dyslipidaemia, obesity and renal disease at least annually and treated appropriately (recommendation V for the modification of lifestyle and risk factors). It is now recommended that that the option of ULT should be explained and offered to all patients with gout as part of their education about the condition and that patients are fully involved in the decision as to when to commence ULT (recommendations I and II for the optimal use of urate-lowering therapies). Although the revised guideline still recommends reduction of sUA with ULT to a target of 300 μmol/l, ULT dose adjustment to the less stringent sUA target of 360 μmol/l is now recommended after some years of successful ULT when tophi have resolved and the patient remains symptom free (recommendation IV for the optimal use of urate-lowering therapies). It is now recommended that in patients with renal impairment the maintenance dose of allopurinol need not be strictly limited according to the creatinine clearance. The starting dose should, however, be low and then carefully increased with smaller increments (50 mg) until the target sUA of 300 μmol/l is reached (recommendation V for the optimal use of urate-lowering therapies). Febuxostat can be used as an alternative second-line xanthine oxidase inhibitor for patients in whom allopurinol is not tolerated or whose renal impairment prevents allopurinol dose escalation sufficient to achieve the therapeutic target (recommendation VI for the optimal use of urate-lowering therapies). For patients with severe symptomatic tophaceous gout in whom hyperuricaemia cannot be controlled with standard ULTs alone, or in combination, treatment with pegloticase can be considered by physicians with experience and facilities for dealing with infusion reactions.

An audit tool is available on the website of the British Society for Rheumatology. Questions for audit and recommendations for future clinical research can be found Supplementary Table S2, available at *Rheumatology online* and in the audit tool.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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