Multinational evidence-based recommendations for the diagnosis and management of gout: integrating systematic literature review and expert opinion of a broad panel of rheumatologists in the 3e initiative

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ABSTRACT

We aimed to develop evidence-based multinational recommendations for the diagnosis and management of gout. Using a formal voting process, a panel of 78 international rheumatologists developed 10 key clinical questions pertinent to the diagnosis and management of gout. Each question was investigated with a systematic literature review. Medline, Embase, Cochrane CENTRAL and abstracts from 2010–2011 European League Against Rheumatism and American College of Rheumatology meetings were searched in each review. Relevant studies were independently reviewed by two individuals for data extraction and synthesis and risk of bias assessment. Using this evidence, rheumatologists from 14 countries (Europe, South America and Australasia) developed national recommendations. After rounds of discussion and voting, multinational recommendations were formulated. Each recommendation was graded according to the level of evidence. Agreement and potential impact on clinical practice were assessed. Combining evidence and clinical expertise, 10 recommendations were produced. One recommendation referred to the diagnosis of gout, two referred to cardiovascular and renal comorbidities, six focused on different aspects of the management of gout (including drug treatment and monitoring), and the last recommendation referred to the management of asymptomatic hyperuricaemia. The level of agreement with the recommendations ranged from 8.1 to 9.2 (mean 8.7) on a 1–10 scale, with 10 representing full agreement. Ten recommendations on the diagnosis and management of gout were established. They are evidence-based and supported by a large panel of rheumatologists from 14 countries, enhancing their utility in clinical practice.

INTRODUCTION

Gout is one of the most common inflammatory arthritis conditions, affecting up to 1–2% of men in Western countries[1] and causing morbidity, disability and poorer quality of life.[2] It is the consequence of deposition of monosodium urate (MSU) crystals in joints and other tissues, as a result of persistent hyperuricaemia. The aim of treatment is to reduce serum uric acid (SUA) levels, allowing MSU crystals to dissolve, leading to the elimination of acute episodes of inflammation, the disappearance of tophi, and, eventually, cure of the disease.[3] However, suboptimal management of the condition is still reported[4–6] despite the publication of a number of guidelines and recommendations,[7–11] the development of new therapeutic agents, and the introduction of target-directed management strategies.[12] Some evidence suggests that guidelines that are implemented improve quality of care and that interventions involving educational outreach may help the successful implementation and dissemination of guidelines.[13]

The 3e (Evidence, Expertise, Exchange) Initiative is a unique multinational collaboration aimed at promoting evidence-based practice in rheumatology by developing practical recommendations addressing relevant clinical problems.[14–16] Unlike most existing guidelines or recommendations developed by a limited panel of experts in the field, the 3e Initiative involves a large number of practising rheumatologists from around the world. Recommendations are made in response to the identification of the 10 most important clinical questions posed by the group, rather than the more all-purpose method of generating treatment recommendations. The objective was to develop evidence-based and practical recommendations for the diagnosis and management of gout with consensus from a large number of practising rheumatologists from many countries. In addition, through the dissemination of the results of systematic literature reviews (SLRs) to such a large number of rheumatologists, an understanding of the current extent of knowledge in this field was widely shared. This educational activity may increase the uptake of the guidelines.

METHODS

A total of 474 rheumatologists from 14 countries participated in the 2011 3e Initiative. Twelve scientific committees represented participating countries from Europe, South America and Australasia. The members of each of the national scientific committees formed a panel of experts who attended the multinational meetings. In addition, the bibliographic team comprised 10 multinational fellows (MA, ASRK, JM, RS, FS, MS, CvD, IvE, OV and MDW), six mentors (DA, CB, RB, LC, CJE and RBL) and the scientific chair (DMvdH). At the first international meeting, clinically relevant questions regarding gout diagnosis and management were spontaneously proposed, and 10 were selected via a modified Delphi voting process by the panel of 78 expert rheumatologists representing all 14 countries (table 1). The multinational fellows and supervising mentors then translated the questions into Population, Intervention, Comparator, Outcome (PICO) terms, agreed on the protocols, and undertook SLRs for each clinical question. A comprehensive search strategy was generated for each question aided by an experienced librarian (LF) (last date October 2011); where feasible, search terms were standardised (see online supplementary figures S1 and S2). Searches were conducted in Medline, Embase and the Cochrane Central Register of Controlled Trials (CENTRAL), and hand searches of the reference list of the selected articles and of abstracts presented at the 2010 and 2011 American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) scientific meetings were performed. Two independent reviewers screened the titles and abstracts of all citations identified by the searches, assessed potentially relevant articles in full text for inclusion according to predetermined criteria, and performed the data extraction of the selected studies (see online supplementary table S1). When discrepancies arose and no consensus could be reached, a mentor acted as arbiter. Included articles were restricted to those published in English or in a language in which at least one member of the bibliographic group was fluent (Dutch, French, German, Spanish). Standardised tools were used to assess the risk of bias of included studies (Cochrane Risk of Bias tool for intervention studies,[17] Hayden tool[18] for cohort studies, Newcastle-Ottawa Scale for case–control studies,[19] the Consensus-based stadards for the selection of health measurement instruments (COSMIN) checklist[20] for validation of measurement instruments, and the Cochrane Risk of Bias tool for diagnostic studies[21]). Where relevant, we considered outcomes proposed by OMERACT (Outcome Measures in Rheumatology Clinical Trials) to be used in the evaluation of interventions for acute and chronic gout.[22] We planned to pool relevant data from included studies provided that they were sufficiently homogeneous. This was predefined in each SLR protocol. Details and results of the SLR for each question will be published separately, but a summary of the supporting evidence is presented under each recommendation in the Results section. After presentation of the SLR results, each of the 12 national scientific committees produced recommendations leading from the 10 clinical questions. At the final international meeting, members of each of the scientific committees merged the national recommendations into 10 final multinational recommendations through a process of discussion and a modified Delphi vote with an electronic voting system (up to three rounds with prespecified cut-off points). The participating rheumatologists quantified their agreement with each recommendation on a 1–10 scale (fully disagree to fully agree), and the potential impact of each recommendation on their clinical practice on a multiple choice question (recommendation will change my practice/is in accordance with my practice/I don't want to apply this recommendation). The level of evidence for each recommendation was appraised and graded in accordance with the Oxford Centre for Evidence-based Medicine Levels of Evidence.[23] Where there was ambiguity regarding the appropriate grade or level of evidence, a lower grade or level was chosen.

RESULTS

The 10 final multinational recommendations are listed in table 2 with the levels of evidence and grades of recommendation; a summary of the supporting evidence and the expert opinion on each recommendation are presented below. The level of agreement by the rheumatologists with the recommendations ranged from 8.1 to 9.2 (mean 8.7) on a 1–10 point scale where 10 represents full agreement. For every recommendation, the proportion of rheumatologists voting 7 or more was over 80%. Many rheumatologists felt that the recommendations were in full accordance with their current practice (table 3). However, for two recommendations for which there was a lower accordance with current practice (comorbidity screen of renal function and cardiovascular risk factors, and achieve tight control of SUA in patients with tophi), there was a higher willingness to change current practice.

Table 1 Ten clinical questions of the Evidence, Expertise, Exchange (3e) Initiative

1	In which circumstances can a diagnosis of gout be made on clinical grounds with or without laboratory tests or imaging and when is the identification of crystals necessary?
2	In patients with hyperuricaemia and/or the diagnosis of gout, should we screen routinely for comorbidities and CV risk factors?
3	What is the role of glucocorticoids, colchicine, NSAIDs, anti-IL1 and paracetamol in the management of acute gout?
4	Which lifestyle changes (such as diet, alcohol intake, weight loss, smoking and/or exercise) are efficacious in the treatment/prevention of gout?
5	What is the efficacy, cost-efficacy and safety for ULT (allopurinol, but also febuxostat, peg-uricase, benzbromarone and probenecid) in the treatment of gout? Which sequence of ULT or combinations of should be recommended?
6	When introducing ULT, what is the best treatment to prevent an acute attack and for how long should it be continued? When is the optimum time to start ULT after an acute attack of gout?
7	How do common comorbidities (such as metabolic syndrome, CV, GI and renal disease) influence the choice of gout-specific drugs (such as colchicine, allopurinol and other ULT) in acute gout flare, chronic gout and in prophylaxis of acute flare?
8	What should be the treatment target and how should patients with gout be followed (with which measures (eg, patient-reported outcomes, clinical, biochemical and/or imaging))?
9	How should tophi be managed?
10	Can we prevent gouty arthritis, renal disease and CV events by lowering serum uric acid levels in patients with asymptomatic hyperuricaemia? If yes, what should be the target levels?

CV, cardiovascular; GI, gastrointestinal; IL, interleukin; NSAID, non-steroidal anti-inflammatory drug; ULT, urate-lowering therapy.

Table 2 Multinational recommendations on the diagnosis and management of gout

	Recommendation	Level of evidence	Grade of recommendation	Agreement, mean (SD)
1	Identification of MSU crystals should be performed for a definite diagnosis of gout; if not possible, a diagnosis of gout can be supported by classical clinical features* (such as podagra, tophi, rapid response to colchicine) and/or characteristic imaging findings**	*2b **2b	*D **B	8.8 (1.6)
2	In patients with gout and/or hyperuricaemia, renal function should be measured and assessment of cardiovascular risk factors is recommended	2c	C	8.4 (2.1)
3	Acute gout should be treated with low-dose colchicine* (up to 2 mg daily), NSAIDs** and/or glucocorticoids (intra-articular***, oral**** or intramuscular*****) depending on comorbidities and risk of adverse effects	*1b– **1a– ***4 ****1a– *****1a–	*D **D ***D ****D *****D	8.9 (1.7)
4	Patients should be advised a healthy lifestyle including reducing excess body weight, performing regular exercise, smoking cessation, avoiding excess alcohol and sugar sweetened drinks	5	D	8.5 (1.7)
5	Allopurinol should be the first line urate-lowering therapy*; alternatives to consider next include uricosurics** (eg, benzbromarone, probenecid) or febuxostat***; uricase as monotherapy should only be considered in patients with severe gout in whom all other forms of therapy have failed or are contraindicated****. Urate-lowering therapy (except uricase) should be started in a low dose and escalated to achieve a target serum urate*****	*2b **2b ***2b ****2b *****5	*C **C ***C ****C *****D	9.1 (1.3)
6	When introducing urate-lowering therapy, patient education on the risk and management of flare is essential*; prophylaxis should be considered using colchicine (up to 1.2 mg daily)**, or if contraindicated or not tolerated NSAIDs*** or low dose glucocorticoids**** may be used. The duration of prophylaxis depends on individual patient factors	*5 **1b ***5 ****5	*D **B ***D ****D	8.1 (2.1)
7	In patients with mild-moderate renal impairment, allopurinol may be used with close monitoring for adverse events, starting at a low daily dose (50–100 mg) up-titrated to achieve usual target of serum uric acid*; febuxostat** and benzbromarone*** are alternative drugs that can be used without dose adjustment	*4 **2b ***4	*D **B ***D	8.5 (1.7)
8	The treatment target is serum urate below 0.36 mmol/L (6 mg/dL), and the eventual absence of gout attacks and resolution of tophi*; monitoring should include serum urate level, frequency of gout attacks and tophi size**	*2b **1b	*C **B	9.0 (1.8)
9	Tophi should be treated medically by achieving a sustained reduction in serum uric acid, preferably below 0.30 mmol/L (5 mg/dL); surgery is only indicated in selected cases (eg, nerve compression, mechanical impingement or infection)	2b	B	9.2 (1.4)
10	Pharmacological treatment of asymptomatic hyperuricaemia is not recommended to prevent gouty arthritis, renal disease or CV events	2b	D	8.6 (2.5)

CV, cardiovascular; MSU, monosodium urate; NSAID, non-steroidal anti-inflammatory drug.
Level of evidence and grade of recommendation were according to the Oxford Centre for Evidence-based Medicine levels of evidence.[21] Agreement relates to the entire statement and was voted on a scale from 1 to 10 (fully disagree to fully agree) by the 70 rheumatologists attending the 3e multinational closing meeting (Brussels, 22–23 June 2012). These attendees were members of the national scientific committees from the 14 countries involved in 3e.

Recommendation 1: diagnosis

Four studies used MSU crystal identification as the reference standard to evaluate the diagnostic performance of over 60 individual clinical, laboratory and imaging findings.[24–27] Most clinical, laboratory and x-ray features—including podagra and hyperuricaemia—show a low diagnostic utility as stand-alone findings with the exception of response to colchicine therapy and the presence of tophi. Advanced imaging techniques, such as ultrasound (US) and dual-energy CT, performed better.

Experts showed a strong consensus that identification of MSU crystals—in a joint fluid sample or in a tophi aspirate—is required for a definite diagnosis of gout. Since life-long urate-lowering therapy (ULT) is commonly prescribed after diagnosis, this procedure should be routinely undertaken. However, as this might prove difficult in some settings, it was felt that clinical or imaging findings could support a diagnosis. The presence of hyperuricaemia on its own is insufficient to establish a diagnosis of gout. Response of acute arthritis to colchicine could support a clinical diagnosis of gout, but was felt unhelpful in differentiating types of crystal arthritis (eg, gout and acute calcium pyrophosphate arthritis). Availability, cost and the need for trained personnel and specific equipment may limit the use of advanced imaging techniques in routine clinical practice.

Recommendation 2: comorbidity screening

The focus was on those comorbidities that could be both screened for and treated. An increased incidence of end-stage renal disease was found in patients with hyperuricaemia,[28] but gout was not an independent predictor for this disease.[29] However, a fourfold increase in mortality due to kidney disease has been reported in patients with gout compared with non-gouty patients.[30] We identified evidence that hyperuricaemia may increase the risk of developing diabetes or hypertension[31 32]; however, no prospective studies were identified that investigated the risk of these conditions in people with gout. The available data showed that hyperuricaemia does not increase the risk of developing coronary heart disease (CHD)[31–36] or stroke.[37–39] On the other hand, there was evidence to suggest that people with gout have an increased risk of developing CHD[40–43] and slightly increased risk of CHD-related mortality.[44]

Experts agreed to highlight the need to screen for renal disease on the basis of the strong evidence of association and the implications for gout therapy. Experts also agreed that hyperuricaemia and gout should be considered red flags for metabolic syndrome and cardiovascular diseases.

Table 3 Impact of the recommendations on the practice of rheumatologists of the Evidence, Expertise, Exchange (3e) Initiative

Recommendation (number and topic)	The recommendation will change my practice, %	The recommendation is in full accordance with my practice, %	I do not want to apply this recommendation in my practice, %
1. Diagnosis	7.5	88.7	3.8
2. Comorbidity screening	27.4	60.8	11.8
3. Acute gout	7.5	88.7	3.8
4. Lifestyle	18.5	77.8	3.7
5. Urate-lowering therapy	18.9	79.2	1.9
6. Flare prophylaxis	13.2	69.8	17.0
7. Effect of comorbidities on drug choices	17.0	81.1	1.9
8. Monitoring	16.7	79.6	3.7
9. Tophi	31.5	64.8	3.7
10. Asymptomatic hyperuricaemia	9.8	80.4	9.8

Recommendation 3: acute gout

Twenty-six trials were included on treatment of acute gout flares (21 evaluated non-steroidal anti-inflammatory drugs (NSAIDs),[45] five glucocorticoids,[46] two colchicine, and one canakinumab[47]). The available evidence showed that low-dose colchicine (total dose 1.8 mg in 24 h) was more effective than placebo[48 49] and as effective as high-dose colchicine (total dose 4.8 mg), but lower doses of colchicine had a significantly better safety profile.[49] There was no high-quality evidence comparing NSAIDs with placebo[50] and no NSAID (conventional or selective COX-2 inhibitor) has proven superior to another.[51–67] Three trials concluded that systemic glucocorticoids were as effective as NSAIDs, with a similar safety profile.[68–70] Despite a comprehensive search strategy, no trials assessing intra-articular glucocorticoids or paracetamol in the treatment of acute gout flares were identified.

There was consensus that NSAIDs, colchicine and glucocorticoids (given as intra-articular, oral or intramuscular therapy) are all effective in the treatment of acute gout flares and that there was insufficient evidence to prioritise them. Individual treatment decisions should be based on consideration of an individual's characteristics and each drug's safety profile. Paracetamol, although not recommended as the primary therapy, can be useful as an adjunct analgesic.

Recommendation 4: lifestyle

There is no evidence to support the idea that intervening in lifestyle factors translates into improved outcomes in patients with gout. Despite a comprehensive search strategy,[71 72] only one study assessing the efficacy of lifestyle interventions in the treatment of chronic gout was identified.[73] The use of skimmed milk powder enriched with two dairy fractions (glycomacropeptide and G600 fat extract) did not result in a reduction in frequency of acute gout flares when compared with standard skimmed milk or lactose powder.[73]

Current understanding of the lifestyle factors associated with gout is largely derived from large, cross-sectional, epidemiological studies. Given the lack of evidence supporting lifestyle interventions in the treatment of gout per se, experts recommend general healthy lifestyle habits such as would be advisable for all individuals. Regarding alcohol consumption, experts agreed that there should be more emphasis on discouraging beer and spirits over wine intake. Together with general lifestyle advice, education about the need for compliance with lifelong ULT was deemed essential.

Recommendation 5: ULT

Over 40 studies were included in the evaluation of the efficacy, cost-efficacy and safety of ULT. There is high-quality evidence that allopurinol,[74] febuxostat (40–240 mg daily)[74 75] and pegloticase (8 mg intravenously every 2 or 4 weeks)[76] are more effective than placebo in lowering SUA levels in patients with gout. One study showed that benzbromarone was effective in patients who failed to reach target uric acid on allopurinol.[77] Febuxostat (80–240 mg daily) was more effective than potentially suboptimal doses of allopurinol (300 mg in patients with normal renal function, 100–200 mg if renal insufficiency) in lowering SUA, with a similar overall safety profile.[74 78 79] Step-up therapy with allopurinol (300–600 mg) or benzbromarone (100–200 mg) are both effective in lowering SUA levels.[80] Pegloticase, although highly efficacious, is associated with an increase in acute gout flares, infusion reactions and increased withdrawals due to adverse events compared with placebo.[76] Available evidence for cost-efficacy was at a high risk of bias[81 82] or outdated.[83] No studies addressed the sequence of ULT.

There was a strong consensus that allopurinol constitutes first-line ULT after consideration of its safety, efficacy and cost. Low starting doses can optimise safety and minimise the risk of acute flares; doses should be gradually increased until target SUA levels are achieved (see recommendation 8). Uricosurics—where available—and low to medium doses of febuxostat (40–120 mg) are alternatives in the presence of intolerance or non-responsiveness to allopurinol. Uricase should only be considered in selected patients without other therapeutic options. Pegloticase should not be combined with other ULT, as this may mask the increase in SUA levels warning of an increased risk of infusion reactions and anaphylaxis.

Recommendation 6: flare prophylaxis

Four studies addressing flare prophylaxis when ULT is initiated were identified. In two randomised controlled trials, the use of colchicine (0.6–1.5 mg daily) for the initial 3–6 months after the start of ULT resulted in a reduction in the number of patients who developed acute gout attacks and a reduction in the severity of these flares compared with placebo.[84 85] Despite an increase in diarrhoea in one study,[84] overall adverse effects and withdrawals were similar between the colchicine and placebo groups. No evidence on the use of NSAIDs or glucocorticoids as prophylaxis was retrieved.

Experts considered that the need for acute gout flare prophylaxis when initiating ULT should be considered on an individual

basis. Optimal duration is currently unclear and should be decided after assessing factors such as flare frequency, gout duration and the presence and size of tophi. There was no consensus on when ULT should be started after an acute attack. However, the majority felt that low initial doses of ULT, with slow dose increases, is an integral part of flare prevention, supporting the motto 'start low, go slow'.

Recommendation 7: effect of comorbidities on drug choice

Two studies, of low to moderate quality, showed that gradual dose escalation of allopurinol in patients with renal impairment resulted in a higher proportion of patients obtaining target SUA levels without a parallel increase in serious toxicity,[86 87] when compared with the commonly used and more conservative dosing guidelines.[88] Allopurinol has been compared with other ULTs in populations with renal impairment of mostly mild or moderate levels (creatinine clearance >30 mL/min). Both febuxostat (80 mg/day)[74 79] and unadjusted benzbromarone (100–200 mg/day)[89] resulted in a higher proportion of patients achieving target SUA compared with renal function-adjusted allopurinol (100–300 mg/day), with a similar safety profile. The combination of allopurinol and benzbromarone allowed a reduction in SUA levels except in cases of severe renal dysfunction.[90]

Recommendation 8: monitoring

The target for the treatment of any disease is either cure or control. Both of these goals may be abstract concepts and can be difficult to measure. Often a surrogate marker associated with the cure or control is used; in gout, this surrogate marker is SUA.[8 9 11 91–93] The association of SUA with other potential outcomes[22] was systematically reviewed. Six studies linked the reduction of SUA levels with a decreased rate of acute attacks,[94–99] two studies with tophus regression,[100 101] and three studies with crystal disappearance—either through US[102] or synovial fluid microscopy.[103 104] The quality of these studies was low to moderate. The most commonly used SUA cut-off point in studies was 0.36 mmol/L (6.0 mg/dL), but there is some evidence that lower SUA levels could lead to a higher speed of tophi reduction and a longer time to recurrence of acute attacks after treatment withdrawal.[94 100] Numerous tools have been used for monitoring the different outcome domains in patients with gout, including biological markers, clinical features, patient-reported outcomes or imaging. The physical component of the SF-36 questionnaire,[105 106] the Health Assessment Questionnaire,[105 107] and tophus measurement by caliper[108] or US[109] have shown adequate clinimetric properties.

Experts considered that monitoring should include at least SUA levels, the frequency of gouty attacks, and tophi size, but recommended no specific tool. They agreed that the target should be an SUA level below 0.36 mmol/L, but recommended even lower cut-off points if tophi are present (see recommendation 9).

Recommendation 9: tophi

After a comprehensive search strategy,[110] only four prospective studies assessing pharmacological agents for patients with tophaceous gout were identified: two randomised controlled trials with pegloticase,[76] an open extension study with febuxostat,[111] and a case series of patients with tophaceous gout on different ULTs.[100] A sustained reduction in SUA led to tophi reduction and in some cases resolution, independently of which ULT was used. The only evidence for the use of surgery to treat tophi came from case reports and case series.

Experts agreed that a lower SUA level (0.3 mmol/L) should be a treatment target for patients with tophaceous gout, as the evidence suggested that lower SUA levels increase the speed of tophi reduction. Surgery should only be considered in selected cases (eg, nerve compression, mechanical impingement or infection).

Recommendation 10: asymptomatic hyperuricaemia

Defining asymptomatic hyperuricaemia was controversial; the agreed definition excluded patients with a background of arthritis or tophi, but allowed the inclusion of patients with pre-existing renal or cardiovascular disease. After an extensive search, only three studies[112–114] were retrieved. Patients with asymptomatic hyperuricaemia and normal renal function[112 113] or chronic kidney disease[114] at baseline were allocated to receive allopurinol or no treatment over a 3–12 month period; no significant differences were noted in glomerular filtration rate, serum creatinine or proteinuria between the two groups. No studies dealing with prevention of gout or cardiovascular disease met the inclusion criteria.

Although there was an absence of evidence supporting the use of ULT for asymptomatic hyperuricaemia, experts agreed that lifestyle advice on diet, weight loss or exercise would apply to patients with asymptomatic hyperuricaemia, especially after considering the increased risks stated in recommendation 2.

DISCUSSION

The 3e Initiative developed 10 recommendations for the diagnosis and management of gout. These address questions relevant to the clinical setting, are informed by the currently available evidence, and are endorsed by a large international panel of rheumatologists.

Even though gout is a potentially curable disease, its management is far from optimal[5] in both primary care and rheumatology clinics. The quality of care provided to gout patients needs to improve. Guidelines that are implemented improve quality of care,[115] and educational outreach has an effect on implementation[14]; therefore, we may suppose that multinational evidence-based recommendations developed in a way in which education—in both gout and evidence-based medicine[116]—and dissemination are final aims can contribute towards this goal.

Two sets of recommendations have recently been published: the first by an American group (with a USA perspective)[11] and the second on behalf of the ACR.[9 10] The first group's approach differed from ours, accepting the 2006 EULAR recommendations[7 8] as a basis and reappraising the evidence published in the past 6 years (2005–2011). The ACR recommendations—produced following the RAND/University of California at Los Angeles (UCLA) methodology—centred on the treatment and prophylaxis of acute gout flares and the appropriate use of ULT in gout, excluding issues on gout diagnosis or asymptomatic hyperuricaemia. The recommendations are similar in some areas, but methodological differences between the 3e Initiative and the ACR guidelines—including the exclusion of benzbromarone (unavailable in the USA) and cost and cost-effectiveness appraisals—have given rise to differences in drug therapy hierarchies.

The 3e recommendations have been developed through an established process with a number of strengths. First, the formal voting process of a broad international panel representing several continents resulted in the development of 10 relevant clinical questions. Second, the available evidence was appraised and summarised following a rigorous approach, which was then combined with the experience of numerous rheumatologists. Last, the high level of agreement with the final recommendations and the multinational participation increases their utility

and will hopefully facilitate their dissemination and implementation worldwide. Most participating rheumatologists either follow the recommendations or are willing to change their practice according to them, suggesting a solid potential impact of this set of recommendations.

A number of limitations of these recommendations must, however, be taken into account. Other specialties (eg, nephrology, primary care), health professionals and patients have not participated in the development of these recommendations. It is therefore unclear how applicable or relevant they are in non-rheumatological settings. Also, many recommendations are complex, including several statements with different degrees of evidence. However, experts voted on their global agreement with the entire recommendation. Finally, variability in agreement of some recommendations suggests a certain degree of dispersion; however, it must be noted that the proportion of attending rheumatologists voting 7 or over for each recommendation was over 80%, suggesting a significant degree of support for these recommendations.

In summary, 10 multinational recommendations for the diagnosis and management of patients with gout in daily clinical practice have been developed, integrating SLR and expert opinion, with the aim of improving patient care.

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