Recommendations in clinical practice guidelines on gout: systematic review and consistency analysis

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Abstract

Objective

To compare and analyse the recommendations from clinical practice guidelines (CPGs) on gout worldwide, examine the consistency across CPGs, and provide suggestions to develop and update gout guidelines.

Methods

We conducted systematic searches in MEDLINE, CBM, GIN, NICE, NGC, WHO, SIGN, DynaMed, UpToDate, and Best Practice databases, from their inception to August 2019 to identify and select CPGs related to gout. We used the search terms "gout", "hyperuricaemia" and "guideline". After two rounds of screening, we included the eligible CPGs of gout according to the pre-defined inclusion and exclusion criteria. Methodological quality of included guidelines was assessed with the AGREE-II instrument. The general characteristics of included guidelines and the recommendations were extracted, and the consistency of recommendations across guidelines was compared and analysed.

Results

A total of 15 gout guidelines including 359 recommendations were retrieved. The main topics covered by the recommendations were diagnosis, pharmacologic treatment of gout flares, pharmacologic urate-lowering therapy (ULT) of chronic gouty arthritis, lifestyle interventions, prophylaxis, and management of asymptomatic hyperuricaemia. The results of AGREE-II appraisal showed that only two guidelines achieved high scores (≥50%) in all six domains. There was substantial discrepancy between the guidelines in recommendations covering the value of computed tomography (CT) and x-rays for diagnosis, the use of corticosteroids as a first-line treatment for flare, the use of colchicine, indications for ULT, the use of febuxostat as first-line ULT, the administration of allopurinol, and the timing of ULT initiation.

Conclusion

A number of countries are devoting themselves to the development of gout guidelines, but the process of updating guidelines is slower than that suggested by the WHO. Methodological quality is not satisfactory in most guidelines, and recommendations between guidelines are not consistent.

Key words

guidelines, gout, recommendation, consistency analysis

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Received on May 26, 2019; accepted in revised form on November 4, 2019.

Funding: this work was supported by the National Key R&D program of China (2018YFC1705500).

Competing interests: none declared.

Introduction

Gout is one of the most common inflammatory arthropathies, with incidence increasing in the past decades (1). The prevalence of gout ranges from 0.9% to 3.9% across the countries (2-6). With the aging population and changes in lifestyle, the burden of gout also keeps increasing (7).

Clinical practice guidelines (CPGs) are statements that include recommendations intended to optimise patient care (8). Several organisations, such as the Evidence, Expertise, Exchange (3e) Initiative, American College of Rheumatology (ACR), European League Against Rheumatism (EULAR) and American College of Physicians (ACP), have developed guidelines for gout, but there may be substantial discordance among these guidelines. For example, big difference in the management of gout (especially recommendations of ULT) was identified between the ACP clinical practice guideline and all other international guidelines (including 2012 ACR, 2014 3e and 2016 EULAR) in the Gout, Hyperuricaemia and Crystal-Associated Disease Network (G-CAN) consensus statement (9). Consistent recommendations can promote the dissemination and popularisation of the guidelines, which is of great significance for clinical decision makers. However, inconsistent recommendations may puzzle the readers and cause a negative effect on the correct decision making of physicians. There are multiple reasons and complex rationale for the heterogeneity across guidelines (9). It is urgent to make a comparison in the guidelines based on the possibility of substantial discordance among recommendation of gout management. We therefore systematically analysed the recommendations from the CPGs on gout worldwide to identify and discuss the differences between CPGs and provide a reference for professional societies to develop and update their guidelines.

Materials and methods

Inclusion and exclusion criteria

We included clinical practice guidelines for diagnosis and treatment of gout published in Chinese or English in scientific journals. Former editions of the guidelines were excluded if a later version was available.

Search strategy

We searched MEDLINE, Chinese Biomedical Literature database (CBM), Guidelines International Network (GIN), National Institute for Health and Clinical Excellence (NICE), National Guideline Clearinghouse (NGC), World Health Organisation (WHO), Scottish Intercollegiate Guidelines Network (SIGN), DynaMed, UpToDate, and Best Practice databases. All searches of these databases and guideline websites were conducted from inception to August 2019. A manual search in Google Scholar was also performed to find relevant gout CPGs outside the databases. We used the keywords "gout", "hyperuricaemia", "guideline" in our search. The full search strategy is presented in Supplementary file 1.

Screening and extraction of literature

Two researchers (Y. Yu and D. Wang) independently screened first the titles and abstracts of all literature identified in the initial search, and then the full texts of the selected articles. Disagreements were resolved by face-to-face discussion, or in case of persistent disagreement, by consultation with a third researcher (Y. Chen). We used a pre-developed information extraction table to extract the general characteristics of included guidelines, the summary of recommendations and the evidence used. Recommendations were identified based on the summary table of recommendations, formatting (such as bullets, bolded text, and enumeration), headers (that include descriptors such as 'recommended') and presence of recommendation strength indicators.

Appraisal of methodological quality

The AGREE-II instrument (10) was used to assess the methodological quality of the included guidelines. AGREE-II instrument includes 23 key items grouped into 6 domains (scope and purpose, stakeholder involvement, rigor of development, clarify and presentation, applicability, and editorial independence). Each item uses a 7-point agreement scale from 1 (strongly disagree)

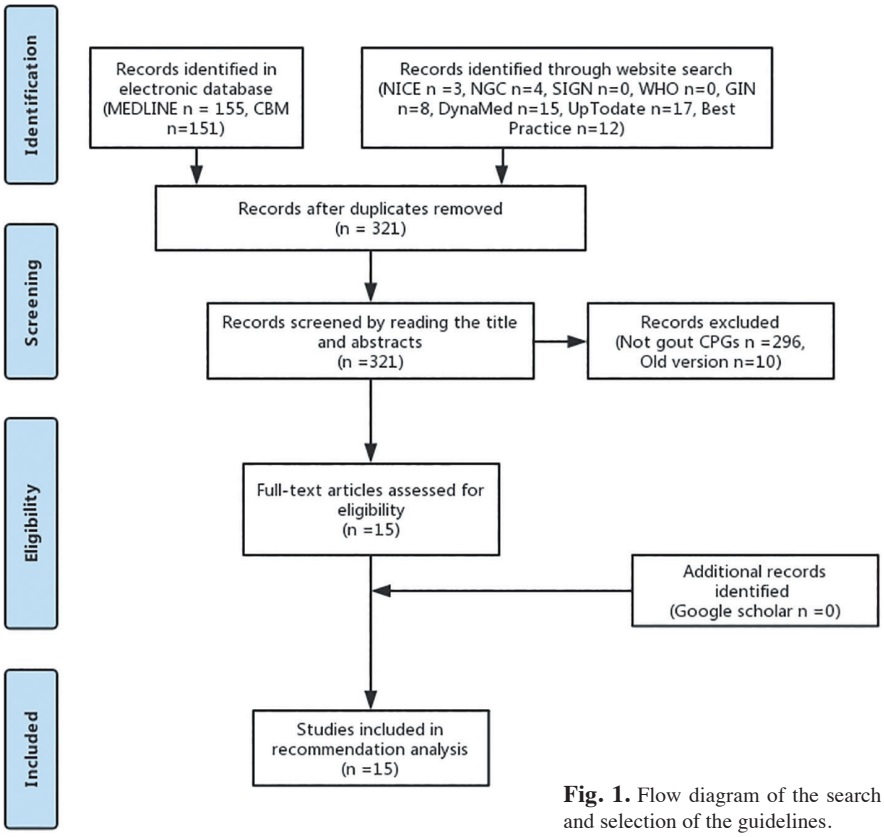

Fig. 1. Flow diagram of the search and selection of the guidelines.

to 7 (strongly agree). Two reviewers independently assessed each guideline. A final score of each domain for each guideline (standardised as a percentage) was calculated. Mean scores (SD) among guidelines was also calculated to assess the whole level of methodological quality. Each reviewer was trained to ensure the agreement of assessment between reviewers. Details of the assessment process were present in our another published article (11).

Analysis of the recommendations

The recommendations from different guidelines were categorised into domains according to topic, and analysed for consistency by two researchers. When comparing the recommendations across guidelines, we first reviewed the individual recommendations which were recognised by our criterion above. Each individual recommendation was always companied by a statement that described, for example, background information about the disease or condition to which the recommendation applies, the rationale for the recommendation, and information that amplifies how the recommendation might be carried out. In consideration of the case that some recommendations might be unspecific, we also further read such statements of each recommendation to extract implicit recommendations as a supplement. Finally, a comparison table of recommendations was formed based on both recommendations and their supplementary statements. Any disagreements between two researchers were resolved by discussion, if necessary, a third arbitrator will be consulted. Different from the classical systematic review of original studies, a meta-analysis was not applicable in this review of guidelines. We therefore must declare that a meta-analysis was not conducted in our analysis of the results.

Patient and public involvement

Not applicable.

Results

Basic information

• *Selection of gout CPGs*

Our search revealed 15 gout CPGs: one in Chinese and 14 in English (Fig. 1). The guidelines came from 12 countries or regions, and were published over a period of 10 years (2008-2018). Among the 15 guidelines, we identified 359 recommendations. The number of recommendations in each guideline ranged from 5 to 80 (mean: 24, median: 15). The detailed characteristics of the included guidelines are presented in Table I.

• *Content distribution of recommendations*

The contents of the recommendations covered mainly the following topics: diagnosis, pharmacologic treatment for gout flares, pharmacologic urate-lowering therapy (ULT) for chronic gouty arthritis, lifestyle interventions, prophylaxis, and management of asymptomatic hyperuricaemia (Suppl. file 2, Table S1). Also other topics, such as patients education, monitor for uric acid, drug discontinuation, uricosuric agents (other than probenecid and benzbromarone), other treatments of gout, and treatment of gout in general (without specifying the details), were included, and some recommendations were not directly related to management or diagnosis of gout.

• *Quality of guidelines*

The AGREE-II domain scores for each guideline are present in Table II. The mean domain score (range) for the domains among the 15 CPGs were: scope and purpose 71% (33%–100%; SD 20%); stakeholder involvement 41% (1%–67%; SD 21%); rigour of development 48% (20%–69%; SD 15%); clarity of presentation 81% (47%–100%; SD 14%); applicability 35% (10%–81%; SD 18%) and editorial independence 34% (0%–96%; SD 35%). Two (guideline 7 and 14) of the included guidelines showed a satisfying quality with a score of greater than 50% in all six AGREE-II domains. The guidelines received the highest scores in domains 4 (≥75% for 13 CPGs) and the lowest scores in domains 6 (≤25% for 9 CPGs). Those guidelines updated recently (2016-2018) were more often of higher AGREE-II scores.

Consistency of recommendations

• *Diagnosis of gout*

A total of eight guidelines gave recommendations on the diagnosis of gout (Table III). The recommendation on

Table I. Characteristics of included gout CPGs.

No.	Title	Region	Developer	Year	Count of recommendations
1	Clinical Practice Guidelines: Management of Gout (50)	Malaysia	Ministry of Health Malaysia	2008	23
2	Management of initial gout in adults (51)	USA	University of Texas	2009	15
3	Japanese Guidelines for the Management of hyperuricaemia and Gout: 2nd Edition (52)	Japan	Tokyo Women's Medical University	2011	22
4	Management of chronic gout in adults (53)	USA	University of Texas	2012	31
5	2012 American College of Rheumatology Guidelines for Management of Gout (54, 55)	USA	ACR, American College of Rheumatology	2012	80
6	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 (56)	International	3e (Evidence, Expertise, Exchange) Initiative/A panel of international rheumatologists	2013	10
7	Clinical practice guidelines for management of gout (57)	Spain	Spanish Society of Rheumatology - Medical Specialty Society	2013	69
8	Italian Society of Rheumatology recommendations for the management of gout (58)	Italy	SIR, The Italian Society of Rheumatology	2013	12
9	Portuguese recommendations for the diagnosis and management of gout (59)	Portugal	A panel of 78 international rheumatologists in 3e (Evidence, Expertise, Exchange) Initiative	2014	12
10	Australian and New Zealand recommendations for the diagnosis and management of gout: integrating systematic literature review and expert opinion in the 3e Initiative (60)	Australia and New Zealand	APLAR, Asia Pacific League of Associations for Rheumatology	2015	11
11	[2016 China gout clinical practice guideline] (61)	China	Chinese Rheumatology Association	2016	12
12	2016 updated EULAR evidence-based recommendations for the management & diagnosis of gout(29, 62)	Europe	EULAR, European League Against Rheumatism	2016/2018	22
13	Management of Acute and Recurrent Gout & Diagnosis of Acute Gout: A Clinical Practice Guideline From the American College of Physicians (63, 64)	USA	ACP, The American College of Physicians	2017	5
14	The British Society for Rheumatology Guideline for the Management of Gout (65)	UK	BSR, the British Society for Rheumatology	2017	21
15	Management of gout and hyperuricaemia: Multidisciplinary consensus in Taiwan (66)	Taiwan	Taiwan multidisciplinary working group	2018	14

diagnosis involved four aspects as followed: gold standard, classification criteria, clinical features and imaging. Identification of MSU crystals was recommended as the gold standard for diagnosis in all these guidelines with the exception of guideline 11. However, the value of other diagnosis methods varied. With regard to the gout classification criteria, the 2015 ACR-EULAR classification criterion was recommended in two guidelines (no. 11 and 15). Diagnosis with classical clinical features was recommended in five guidelines (no. 6, 9, 10, 12 and 13). With regard to the imaging techniques, ultrasound was recommended in five guidelines (no. 6, 7, 9, 11 and 12). The major discordances occurred in the recommendations for computed tomography (CT) and x-rays: it was not recommended to perform CT or x-rays for diagnosis of gout in guideline 7 while it was recommended in other five guidelines (CT: no. 6, 9 and 11; x-rays: no. 6, 10 and 12).

• *Pharmacologic treatment of gout flares*

Recommendations in all guidelines involved the pharmacologic treatment for gout flares, except in guideline 4. Most guidelines recommended non-steroidal anti-inflammatory drugs (NSAIDs), colchicine or corticosteroids. However, the recommendations of the treatment choices varied across the guidelines. According to guideline 12, all three medications were recommended as first-line options, without giving preference to any of them. Guideline 13 also recommended any of three anti-inflammatory medications, and highlighted that corticosteroids should be considered as first-line therapy in patients without contraindications. Guideline 8 recommended only NSAIDs and colchicine as first-line treatment. Guideline 2 recommended NSAIDs, colchicine and corticosteroids as the first-line, second-line and third-line drugs, respectively. Almost all guidelines recommended that pharmacologic treatment should be started as early as possible, but there were still differences in defining a specific time. Guidelines 2, 5 and 11 recommended that pharmacologic treatment should be started

Table II. Methodological quality of included guidelines according to the AGREE-II instrument.

No.	Domain scores (%)					
	Scope and purpose	Stakeholder involvement	Rigor of development	Clarify and presentation	Applicability	Editorial independence
1	94%	64%	21%	53%	17%	0%
2	94%	44%	39%	89%	33%	17%
3	58%	1%	20%	47%	17%	0%
4	100%	44%	45%	89%	38%	21%
5	53%	22%	45%	78%	46%	67%
6	69%	36%	49%	78%	38%	0%
7	92%	64%	64%	100%	52%	92%
8	69%	31%	47%	81%	19%	0%
9	64%	22%	47%	83%	33%	0%
10	78%	17%	41%	86%	29%	13%
11	75%	64%	64%	94%	10%	50%
12	39%	58%	69%	86%	35%	21%
13	83%	53%	64%	81%	48%	63%
14	67%	67%	63%	89%	81%	96%
15	33%	25%	35%	81%	23%	67%
Mean ± SD (%)	71±20%	41±21%	48±15%	81±14%	35±18%	34±35%

within 24 hours of the onset of a flare, while guideline 12 recommended starting within 12 hours. Almost all guidelines recommended the use of low-dose colchicine, but the strength of recommendation and the specific administration on dosage and usage were not consistent (Suppl. file 2, Table S2).

• *Pharmacologic urate-lowering therapy (ULT) of chronic gouty arthritis*

Recommendations of fourteen guidelines (all except guidelines 2) involved pharmacologic ULT of chronic gouty arthritis, including allopurinol, febuxostat, benzbromarone and probenecid (Suppl. file 2, Table S3). As for the indications of ULT, almost all guidelines involving this content recommended that the frequency of acute flares should be considered. Three guidelines (no. 1, 4, 11) recommended that ULT was necessary as long as the flare frequency was more than twice per year, whereas other four guidelines (no. 5, 12, 13 and 14) if the flare frequency was more than once per year. All guidelines mentioned tophi as an indication for initiating ULT, but there were differences in the strength of the recommendations (Suppl. file 2, Table S3). Other indications for ULT included renal stones, gouty arthropathy, radiographic changes of gout, and comorbidities such as chronic kidney disease (CKD) (Suppl. file 2, Table S3). It is worth noting that the latest three guidelines (no. 12, 13 and 14) recommended that the patient's opinion should be considered when deciding about starting ULT, and highlighted the importance of patients' education before the commencement of ULT. Besides, there was a great deal of debate on when to initiate ULT. Guideline 5 recommended that ULT can be initiated during an acute gout flare, provided that effective anti-inflammatory management has been instituted, while guidelines 1, 3 and 4 recommended that it should not be initiated until about 2 weeks after acute flare and guideline 14 advised that commencement of ULT was best delayed until inflammation has settled for the reason that ULT was better discussed when the patient was not in pain. As for the choice of drugs for ULT, four guidelines (no. 6, 9, 10, 12 and 14) recommended allopurinol to be the first-line option of ULT, while guidelines 4 and 5 recommend allopurinol or febuxostat. The administration of allopurinol, the most commonly used drug, was discussed in detail in most guidelines. Four guidelines (no. 4, 8, 11, 12 and 15) recommended to start with a dose of 100 mg/d; guideline 5 recommended a starting dose no greater than 100mg/d; guideline 3 recommended a starting dose of 50mg/d, guideline 14 recommended 50–100 mg/d and guideline 1 recommended 100-150 mg/d. The maximum dose of allopurinol also differed between the guidelines: guideline 14 recommended 900 mg/d, guidelines 4, 8 and 15 recommended 800 mg/d, and guideline 1 recommended an assessment by specialist when requiring higher doses. With respect to the target of treatment, guideline 13 actively recommends against "treat-to-target" (escalating urate-lowering therapy to reach a serum urate target) and favours a strategy of basing treatment intensity

Table III. Comparison of recommendations on the diagnosis of gout.

No.	Gold standard	Classification criteria	Classical clinical features	Imaging		
				ultrasound	CT	x-rays
6	Identification of MSU crystals	–	R	R	R	R
7	Identification of MSU crystals	–	–	R	NR	NR
9	Identification of MSU crystals	–	R	R	R	–
10	Identification of MSU crystals	–	R	–	–	R
11	-	2015 ACR-EULAR Gout Classification Criteria	–	R	R	–
12	Identification of MSU crystals	-	R	R	–	R
13	Identification of MSU crystals	–	R	–	–	–
15	Identification of MSU crystals	2015 ACR-EULAR Gout Classification Criteria	–	–	–	–

R: recommended; NR: not recommended; MSU: monosodium urate; EULAR: European League Against Rheumatism; ACR: American College of Rheumatology; CT: computed tomography. - : not involved or ambiguous recommendation (cannot be judged as recommended or not recommended).

Table IV. Comparison of recommendations on lifestyle interventions.

no.	Avoiding food high in purine	Avoiding excess alcohol	Weight control	Low-fructose diet	Intake of low-fat or non-fat dairy products
1	√ (B)	√ (B)	√ (C)	–	√ (B)
2	√ (A)	√ (A)	√ (B)	√ (A)	√ (A)
3	√ (B)	√ (B)	√ (B)	√ (B)	-
4	√ (B)	√ (B)	√ (A)	√ (B)	√ (B)
5	√	√	√	√	√
6	–	√ (B)	√ (B)	√ (B)	–
7	–	√ (D)	√ (D)	–	–
8	–	√	–	√	–
9	√ (D)	√ (D)	√ (D)	√ (D)	–
10	–	√ (D)	√ (D)	√ (D)	–
11	√ (1)	√ (1)	√ (1)	√ (1)	–
12	√	√	√	√	√
14	√	√	√	√	√
15	√ (B)	√ (B)	√ (B)	√ (B)	

"√" denotes that the guideline recommended the intervention, "-" denotes that the guideline did not mention it.
The figures or letters between brackets represented the strength of the recommendations, but the same figures or letters may not indicate a same strength of recommendations due to the use of inconsistent grading systems across guidelines.
Sources of the grading systems in each guideline: guideline 1, no name (modified version of the criteria used by the Catalonia Agency for Health Technology Assessment and Research (CAHTAR) Spain and modified from the Intercollegiate Guidelines Network (SIGN)); guidelines 2,4, U.S. Preventive Services Task Force [USPSTF] Ratings; guideline 3, no name (unclear source); guidelines 6,7,9,10,15, Oxford Centre for Evidence-based Medicine – Levels of Evidence; guideline 11, GRADE.

on minimising symptoms, in complete disagreement with the other guidelines which strongly recommend "treat-to-target". In the recommendations of serum urate target, most guidelines agreed that the serum urate target should be at least less than 6mg/dl for all patients, but with differing strengths of recommendations (Suppl. file 2, Table S3). In contrast, guideline 14 recommended a serum urate target of below 5mg/dl and level of <6mg/dL was the less stringent target.

• *Lifestyle interventions*

Most guidelines (except guideline 13) recommended lifestyle interventions, including avoiding food high in purine, avoiding excess alcohol, weight control, low-fructose diet, and the intake of low-fat or non-fat dairy products (Table IV). In most guidelines, there were no differences between the strengths of recommendations concerning different lifestyle interventions. However, the strength of recommendations of weight control in guidelines 1 and 2 was weaker than other lifestyle interventions, whereas in guideline 4 the opposite was true, even though guidelines 2 and 4 were developed by the same institution. The strength of recommendations on these lifestyle interventions between guideline 6, 15 and guidelines 7, 9, 10 were inconsistent in spite of using the same grading systems (Oxford Centre for Evidence-based Medicine – Levels of Evidence, using a four-step scale [A, B, C and D]): the former (published in 2013 and 2018, respectively) recommended them with B and the latter (published in 2013, 2014 and 2015, respectively) with D.

Discussion

Gout is a common and treatable form of inflammatory arthritis, and several countries and organisations have developed specific guidelines on gout. We identified 15 gout CPGs worldwide by our systematic search. We found that many of the CPGs on gout were developed by international organisations, or with international cooperation. Nevertheless, most guidelines were the first editions, showing a slow process for updating gout CPGs. Many guidelines were older than the maximum 'review-by' date (5 years) suggested by WHO (12), and some of the older guidelines should therefore be updated with the latest evidence to give optimal recommendations for diagnosis and treatment of gout. The contents of recommendations varied across guidelines, and most guidelines did not consider diagnosis or prophylaxis.

According to the results of AGREE-II appraisal, the methodological quality of the included guidelines varied, with only two guidelines having high scores in all six domains. Among the 15 included GPGs, the quality was optimal for "scope and purpose" and "clarity and presentation", but received the lowest scores for "applicability" and "editorial independence". High scores in "scope and purpose" and "clarity and presentation", showed that the guidelines in gout paid high attention to the reporting and presentation of guideline recommendation and guideline background, which was an important factor affecting the methodological quality of guidelines. As "rigor of development" ultimately affects the scientific basis of the recommendations made, it is always considered as the most important domain when assessing the quality of a guideline (13). However, the quality of "applicability" domain also plays a critical role in implementation of the guideline. Furthermore, "editorial independence" cannot be ignored as the recommendations may be biased by the influence of interest conflicts and supporting funds (67).

Recommendations on the diagnosis of gout varied across guidelines although a consensus of gold standard was reached in almost all guidelines. All guidelines (except for guideline 11) recommended identification of MSU as the gold standard. However, it often is difficult to use this method in primary care due to high requirement for skills and facilities. Thus, other alternatives for gout diagnosis were helpful. The modality and number of alternatives for diagnosis were various across guidelines. A clinical diagnosis of gout was widely recommended because both the sensitivities and specificities of clinical algorithms were greater than 80% for diagnosis as compared with the gold standard (14-20). With regard to the imaging technique for gout, all (including ultrasound, CT and x-rays) have their strengths and weaknesses. A good diagnostic performance of ultrasound has been determined in several studies (21-28), and it has the strengths of low cost,

widespread availability and absence of radiation exposure. Dual energy CT has the advantage of differentiating MSU crystal deposition from other tissues, but high costs limited its usage. Plain radiographic changes take several years to develop, so they may be helpful in supporting a diagnosis of gout in the later stages of the disease (29). However, evidence is still insufficient to support imaging as an independent diagnosis tool despite major advances have been made.

The consistency of recommendations on gout flares among the guidelines was in general low. There were wide differences in recommendations on how to choose the medication for gout flares. The main controversy was in the use of corticosteroids: the EULAR and ACP guidelines advised that corticosteroids should be considered as first-line therapy, while other guidelines did not recommend them. There is evidence showing that the impact of corticosteroids and NSAIDs is equivalent for various outcomes (30-35), and one study also found that NSAIDs were associated with more frequent adverse events (36). Furthermore, corticosteroids have lower costs and can be gained easier than colchicine. For these reasons, corticosteroids seemed to be a promising optimal medication for gout flares. Recommendations on dosage and usage of colchicine were less consistent among guidelines, but a low dosage of colchicine was recommended by most guidelines. A moderate-quality RCT (37) on the use of colchicine showed that lower doses of colchicine were as effective as higher doses for reducing pain and were associated with fewer adverse effects.

Recommendations on ULT also varied across guidelines. High frequency of flares as an indication to start ULT was mentioned by most guidelines, but there were differences in the threshold frequency. In most guidelines, high frequency of flares was recommended as an indication for ULT based on expert opinion without relevant high-quality evidence. A recent case-control study (38) however showed that disease duration and SUA were independent risk factors of acute flares to the patients with >2 acute flares of gout in the previous 12 months. This finding will hopefully help to solve the disagreements in future guidelines. Comorbidities began to be considered as indications for ULT with chronic kidney disease (CKD) already as early as 2007 version BSR guideline, but a systematic review (39) could not confirm whether treatments that lower urate had beneficial renal effects. The disagreement in recommendations on how to choose the urate-lowering drugs across guidelines mainly concerned the use of febuxostat: some guidelines recommended it as the first-line option of ULT, while some other guidelines disagreed. A 2014 Cochrane systematic review (40) found that patients on febuxostat were more likely to achieve target serum uric acid levels and had less total adverse events than patients on allopurinol at 24 to 52 weeks since treatment initiation, but after three years of use there seemed to be no difference. Febuxostat costs considerably more than allopurinol, so whether febuxostat should be taken as the first choice for ULT may need a more comprehensive review. We also found controversial recommendations on the dosage and usage of allopurinol in the different guidelines. Although all guidelines recommended that allopurinol should be started with a low dose and escalated to achieve a target serum urate, a disagreement across guidelines of recommendations on what the initial dose should be and whether there should be a maximum dose still existed. Results of one study (41) showed that a high starting dose might increase the risk of serious cutaneous adverse reactions, which gave evidence to start with low-dose allopurinol. Different guidelines had differing views on whether ULT can be initiated during an gout flare or whether a delay of two weeks is necessary. Most guidelines suggested the latter, because they thought that ULT started during an flare may prolong the flare or lead to rebound flares. Conversely, the 2012 ACR guideline gave a viewpoint that ULT could be initiated once effective anti-inflammatory control of the acute flare was established. Two small trials (42, 43) suggested that allopurinol initiation during an gout flare did not prolong the duration of flares nor worsen its severity as compared with delayed initiation, but the reliability of these results and their generalisability to more potent urate-lowering drugs may still need more trials to confirm. There was a significant controversy between the ACP guideline published recently and other guidelines in the question of "should patients be treated to lower serum urate levels below an agreed biochemical treatment target ("treat-to-target") or treated to reduction in symptoms ("treatment-to-avoid-symptoms")". However, we still cannot find relevant trials comparing a strategy of treatment based on attaining a specific urate level with treatment based on minimising symptoms at present.

Recommendations on lifestyle interventions were consistent across the guidelines, with only small differences in the strength of recommendation for weight control. A systematic review (44) found that greater body mass index increases the risk of gout. Weight control is beneficial for individual health, and we therefore agree with the strong recommendations for weight control. Moreover, regular physical activity might decrease the excess mortality associated with chronic hyperuricaemia (45), and consumption of coffee and cherries was found to be a protecting factor for gout (46-49). In consequence, a healthy lifestyle is essential for preventing and treating gout.

Inconsistency of recommendations across guidelines resulted from multiple potential reasons. First, the time span where the guidelines were developed is a major source of heterogeneity, for the reasons that the emergence of new evidence may overturn the old concept and the change of the historical background can lead to a different interpretation of the same literature. It is therefore acceptable to see differences among guidelines according to publication year. Second, different countries or areas consider the local preferences when developing guidelines. Third, lack or poor quality of evidence may lead to the recommendations being put forward based on expert opinion rather than evidence. Fourth, different grading systems may give different rank for the same evidence, then lead to form inconsistent recommendations. Poor

consistency across CPGs can confuse the guideline users, and we therefore advocate paying more attention to researching the controversies and updating guidelines timely to improve the consistency among CPGs.

These finding are thought to be significant in several way. For clinicians, the findings of our study can provide an objective guidance for selecting the appropriate recommendations, especially the rheumatologists, but even for those who are majoring in other fields, it can give them a reference to use specialised guidelines. For medical researchers, our study can present the current status of gout guidelines worldwide, giving them the opportunity to pay more attention to the existing gaps. Our study had many strengths. We conducted a systematic analysis of gout guidelines worldwide using the method of systematic review. We included the latest evidence and gave an objective review when we discussed the disagreement across guidelines. Finally, we put forward a large number of factors which may potentially cause the inconsistency among guidelines.

However, our study had several important limitations. First, we restricted our search to CPGs published in Chinese or English, and excluded the CPGs in other languages. The deficiency of these data can have an impact on our findings. Second, there is inherent subjectivity in the interpretation of recommendations. However, we attempted to mitigate this issue by an interdisciplinary cooperation. Third, we reviewed the guidelines with the method of AGREE-II which assesses how well a CPG development process is reported but not the specific clinical content of the CPG recommendations. Therefore, many other important aspects of guidelines were not rated.

In conclusion, developing CPGs on gout has received widespread attention during the past decade. There is a number of countries devoting to development of guidelines on gout, but the process of updating the guidelines is slower than that suggested by WHO. Quality of guidelines varied across included guidelines, with only two guidelines having high scores in all six domains. Guidelines on gout tended to lack consistency in recommendations, which is likely affected by multiple factors. As guidelines continue to be revised and updated, we are confident that the future guidelines will be developed with higher quality to form clear, unambiguous and consistent recommendations for diagnosis and treatment of gout.

Significance and innovations

- This is the first time to systematically analyse gout guidelines worldwide using the method of systematic review.
- We included the latest evidence and gave an objective review when we discussed the disagreement across guidelines.
- We found a large number of factors which may potentially cause the inconsistency among guidelines.

Acknowledgements

We thank Dr Xiaoqin Wang for her guidance on the design of search strategy, ensuring a systematic search of literature. We also thank Yuyu Wu, Lian Liu and Yajing Tong for their work on the translation of the recommendations.

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