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Review

Gout: state of the art after a decade of developments

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Abstract

This review article summarizes the relevant English literature on gout from 2010 through April 2017. It emphasizes that the current epidemiology of gout indicates a rising prevalence worldwide, not only in Western countries but also in Southeast Asia, in close relationship with the obesity and metabolic syndrome epidemics. New pathogenic mechanisms of chronic hyperuricaemia focus on the gut (microbiota, ABCG2 expression) after the kidney. Cardiovascular and renal comorbidities are the key points to consider in terms of management. New imaging tools are available, including US with key features and dual-energy CT rendering it able to reveal deposits of urate crystals. These deposits are now included in new diagnostic and classification criteria. Overall, half of the patients with gout are readily treated with allopurinol, the recommended xanthine oxidase inhibitor (XOI), with prophylaxis for flares with low-dose daily colchicine. The main management issues are related to patient adherence, because gout patients have the lowest rate of medication possession ratio at 1 year, but they also include clinical inertia by physicians, meaning XOI dosage is not titrated according to regular serum uric acid level measurements for targeting serum uric acid levels for uncomplicated (6.0 mg/dl) and complicated gout, or the British Society for Rheumatology recommended target (5.0 mg/dl). Difficult-to-treat gout encompasses polyarticular flares, and mostly patients with comorbidities, renal or heart failure, leading to contraindications or side effects of standard-of-care drugs (colchicine, NSAIDs, oral steroids) for flares; and tophaceous and/or destructive arthropathies, leading to switching between XOIs (febuxostat) or to combining XOI and uricosurics.

Key words: gout, hyperuricaemia, tophus, management, clinical inertia, allopurinol, febuxostat, uricosurics, chronic kidney disease, metabolic syndrome, cardiovascular diseases

Rheumatology key messages

- Gout is the most frequent recurrent arthritis in men presenting with classical hallmarks of inflammation.
- Gout, a deposit disease of urate microcrystals within and around joints, is related to chronic hyperuricaemia.
- Gout is effectively managed with longstanding urate-lowering drugs, with pre-defined targets, avoiding clinical inertia.

Introduction

Gout has long remained a frequent yet neglected disease. However, since the discovery of the nucleotide-binding, leucine-rich repeat, and pyrin-domain-containing 3 (NLRP3) inflammasome as activating the pivotal cytokine IL-1β [1] 10 years ago, the concomitant marketing of febuxostat, and the decision by the Food and Drugs Administration (FDA) to secure the market of colchicine, many studies have contributed to an increased knowledge of different aspects of this old disease. These events prompted the first large-scale clinical trials in gout and a re-examination of how gout is and should be managed. Gathering an overview of the 'State of the Art' of gout is essential for providing an understanding of the disease, the advances made and the unmet medical needs. Significant extensive reviews covering recent advances on gout have been published every 5 years [2, 3]. The aim of this review is now to provide a critical overview of the data published on gout over the past 10 years and the research agenda for every aspect of gout.

Epidemiology

Current data allow both a larger and more extensive picture of global and regional epidemiology of gout, with recent

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updates [4, 5] (Fig. 1). One of the most difficult challenges when attempting to validate gout prevalence data is to determine how the diagnosis of gout was confirmed in the various surveys. The variety of diagnostic tools used explains the discrepancy in gout epidemiology data and limits its usefulness. An international collaborative initiative tested simple survey definitions and obtained the best results for 'self-report of gout or urate-lowering therapy (ULT) use' [6]. Epidemiological surveys using this definition remain imprecise (82% sensitivity, 72% specificity) and tend to overestimate gout prevalence. Performance was better with an 11-item questionnaire developed in France for telephone surveys that was able to accurately classify 90% of people interviewed; external validation is needed in other populations [7].

In Europe, recent epidemiological studies showed an increased gout prevalence in both males and females in the UK, rising from 1.52 in 1997 to 2.49% in 2012 [8]. In Northern Europe, in Sweden, gout could impair between 0.5 and 1.8% of adults, depending on the criteria used [9]. In Southern Europe, the prevalence of gout is 0.9% in continental France [7, 10]. Similarly, the prevalence of gout is 0.9% in Italy, with a north–south gradient possibly related to diet pattern [11].

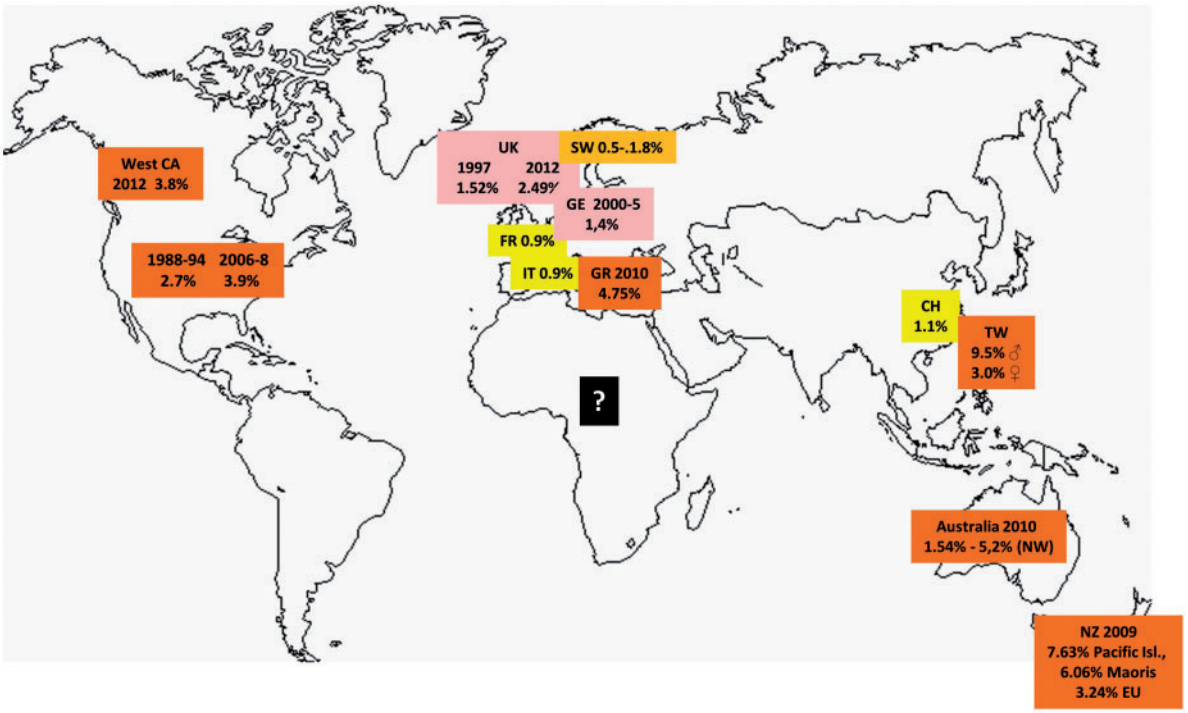
In North America, US surveys have shown regular progression over time, from 2.7% in the National Health and Nutrition Examination Survey (NHANES)-III study (1988–94) up to 3.9% in the NHANES 2006–08 study [12], which translates into 8.3 million US adults. Recently, in British Columbia, Canada, the 2012 prevalence of gout was 3.8% among the overall population, with a 2.9/1000 person-years incidence. Both gout prevalence and incidence increased substantially over the study period. This burden additionally increased according to age category, affecting >8% of people aged 60–69 years in 2012 [13].

More dramatic rises have been observed in Asia, including in China and Thailand, where gout was very low 20–30 years ago [14]. South Korea is also largely involved, with 495 998 newly diagnosed patients in the 2 years between 1 January 2007 and 31 December 2008 [15]. In Taiwan, 1 in 16 people have gout [16], one of the highest prevalences worldwide; regions with the highest prevalence and incidence are the eastern coastal counties and offshore islands, where indigenous people are clustered. Pacific Islanders, including New Zealand Maoris, are also prone to developing severe gout related to genetic disorders (see 'Genetics' section), leading to enhanced uric acid (UA) intestinal absorption and reduced renal excretion. Moreover, in all countries, diet and behavioural changes (such as higher protein and calorie intake, beverages sweetened with high fructose corn syrup, purine intake in beer, lower physical activity) appear to enhance expression of the genetic susceptibility (genetics-environment interactions).

Comorbid disorders

Comorbid disorders, particularly chronic kidney disease (CKD) and metabolic syndrome, have an increasing

Fig. 1 Current prevalence of gout worldwide



CA: Canada; UK: United Kingdom; FR: France; IT: Italy; SW: Sweden; GE: Germany; GR: Greece; CH: China; TW: Taiwan; NZ: New Zealand.

place in the management of gout patients. Whereas the extent of hyperuricaemia being itself a cardiovascular (CV) risk factor is still debated, gout now clearly is, and it is of note that it has been associated with higher CV mortality [17–20]. In particular, the association of several CV risk factors is common and even considered to be part of the gout phenotype [21]. Screening for other CV risk factors is therefore recommended by both the ACR and EULAR at the time of gout diagnosis and throughout the follow-up [22, 23]. Peripheral vascular disease is more prevalent in the gout population, particularly in women in a large cohort study [20]. In large databases, obesity is linked both to incident gout and to risk of recurrent flares [24, 25].

The relationship between gout and renal impairment is also well established. Data from 5085 German CKD patients yielded a 24.3% overall prevalence of gout, and an increased prevalence, rising from 16.0% with an estimated glomerular filtration rate (eGFR) $\geqslant$60 ml/min/1.73 m^2 to 35.6% with eGFR $<$30 ml/min/1.73m^2 [26]. Conversely, CKD is misdiagnosed when considering gout management by primary care physicians (PCPs) and private practice rheumatologists [27, 28]. eGFR formulas should be systematically used when managing gout patients, since the absolute serum creatinine (sCr) value is inaccurate. Perez-Ruiz *et al.* [29] performed a cohort study showing that measuring sCr alone underestimates the proportion of patients with renal impairment. Most drugs used in gout require dose adjustment and are contraindicated in patients with severe CKD, particularly colchicine and uricosurics for instance. Indeed, reducing serum uric acid (SUA) with current xanthine oxidase inhibitors (XOIs) might improve eGFR [30].

Recent data suggest a higher rate of associated depressive disorders among gout patients, particularly those with active and untreated disease [31, 32]. Two published US and UK studies suggest an association between gout and atrial fibrillation [33, 34]. On the contrary, there may be a decreased risk of neurodegenerative disorders among the gout population [35, 36].

To date, it is still unclear whether ULTs have an impact on the outcome of such comorbidities, particularly on CV disease. Yet, data from cohort studies suggest an effect of allopurinol on all-cause mortality and CV mortality [37, 38]. Results are conflicting regarding CV events only [37, 39].

Genetics

The genetics of hyperuricaemia has been largely studied over the last decade. Recent reviews are provided for the reader [40, 41]. Genome-wide association studies for SUA have identified 28 loci influencing serum urate levels [42]. The largest genetic effects on SUA result from genes encoding transporters (so-called urate transportosomes) that excrete UA via the kidney and/or gut. Urate transporter 1 (URAT-1) is the renal transporter coded by *SCL22A12*, and ABCG2, a urate transporter expressed in both gut and kidney [43]. Other genetic effects depend upon glycolysis genes. There are interactions between genes and environmental factors affecting serum urate (diuretics, beer, spirits and sugar-sweetened beverages). Genome-wide association studies using well-defined phenotype cases to identify loci controlling progression from hyperuricaemia to chronic urate deposits and inflammatory gout are ongoing and results are still pending.

Pathophysiology

Causes of hyperuricaemia

The chemical definition of hyperuricaemia is 6.8 mg/dl (416 μmol/l), which corresponds to the solubility threshold of urate at a bodily pH of 7.4 and a temperature of 37°C [44]. It has long been known that the urate solubility threshold can be influenced by temperature, pH and sodium concentration [44, 45]. In physiological conditions, MSU crystals can form when SUA levels are as low as 6.0 mg/dl (360 μmol/l), and this value of SUA is generally accepted as the lower limit of hyperuricaemia [46]. Hyperuricaemia can be caused by excessive purine intake, endogenous overproduction (rare) or mainly by renal (70%) and digestive (30%) underexcretion. These various factors are summarized in Fig. 2.

URAT-1 is considered to be a key urate transporter at the proximal renal tubule; diuretics such as furosemide or thiazides enhance its activity and increase UA reabsorption; conversely, old and new uricosurics inhibit this transporter. Recently, deficiency of the ABCG2 transporter, present both in the renal epithelial cell apical membrane and in the gut, was found to affect SUA levels through the reduction of classically neglected gut urate excretion [47]. Microbiote dysbiosis should also be considered and has not yet revealed its importance [48].

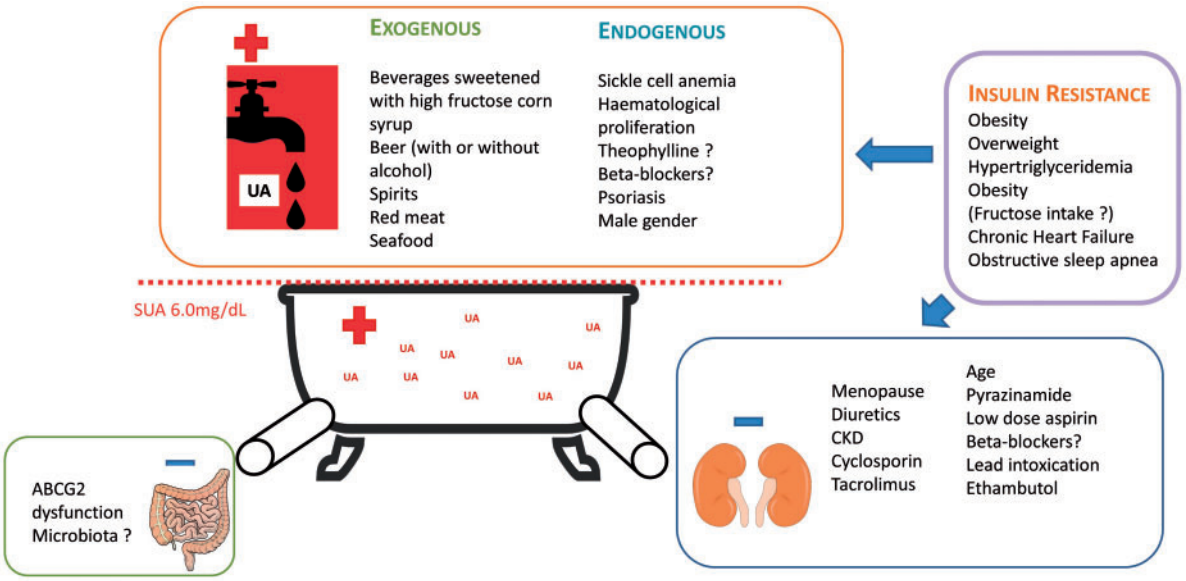
Crystal formation

MSU crystal formation is governed by a variety of factors explaining that hyperuricaemia alone is insufficient to generate urate crystallization. Once SUA levels reach the solubility threshold, the second step of crystallization is nucleation which is basically the clustering of the dispersed molecules. This nucleus is the starting point of a more rapid crystal growth [49]. It is being suggested that exposed collagenous and non-collagenous fibres could guide crystal organization and account for the relationship between gout and OA [50, 51].

Cellular mechanisms of gout flare

The discovery of the NLRP3 inflammasome [1] was seminal in our understanding of intracellular mechanisms implicated in gout flare. Activation of the inflammasome requires an interaction between MSU crystals and macrophages. In *in vitro* studies and in animal models, MSU crystals alone do not induce inflammatory reactions but require additional co-factors [52, 53]. Particularly, free fatty acids are able to engage Toll-like receptor 2 and provide the necessary co-signal to induce IL-1β processing [52, 53]. Complement components and immunoglobulins have been identified on the MSU crystal surface, and their pathways seem determinant in both phagocytosis of microcrystals and

Fig. 2 Current pathogenesis of chronic hyperuricaemia—schematic representation



UA: uric acid; SUA: serum uric acid level.

inflammatory response triggering [54]. Sodium overload induced by internalization of MSU crystals could also trigger the activation of NRLP3 inflammasomes through an induced decrease in the intracellular potassium content [55]. Activated inflammasome activates caspase 1, which splits pro-IL-1β to produce mature IL-1β. In return, secreted IL-1β binds IL-1 receptor, leading to activation of nuclear factor-κB [56]. This inflammatory cascade also leads to the production of various inflammatory cytokines, chemotactic factors, lysosomal enzymes, eicosanoids and reactive oxygen species, and particularly involves mast cells, monocytes–macrophages and neutrophils [54, 56–59]. As a paradigm, resolution of inflammation is an active and timely process leading to restoration of tissue homeostasis. Several self-limiting mechanisms for gout flare have been evoked, including switch from monocytes to proinflammatory M1 macrophages, followed by a second switch towards anti-inflammatory M2 macrophages. TGFβ-1 and IL-10 have been identified as central anti-inflammatory cytokines [60, 61]. The regulatory role of AMP-activated protein kinase, a master regulatory component of metabolism and inflammation, was recently explored on the inflammasome, and notably explained a new mechanism of action of colchicine in gout flare [62]. More recently, a biphasic role for neutrophils has been highlighted, because when the neutrophil concentration is high, NETosis allows the trapping of crystals in SF and the degradation of inflammatory factors [63].

Stages and clinical presentation

Nicola Dalbeth and Lisa Stamp [3] have proposed a new clinical staging system depicting gout as a crystal deposition and chronic disease [64]. Asymptomatic hyperuricaemia might not be part of the disease, since among subjects with hyperuricaemia, only 10–15% will develop a clinical inflammatory response to crystals. Silent MSU crystal deposition might be the next step, since US can easily detect MSU crystal deposition in up to 42% of subjects with asymptomatic hyperuricaemia, based on the double-contour (DC) sign at the cartilage surface, and tophi [65]. This observation allows redefining of the diagnosis as asymptomatic gout—of importance in patients with CKD, for instance. The ultimate stage is related to gout flares, and further MSU crystal deposition leading to s.c. and palpable, but also occult, tophi.

Other classifications focus on advanced gout, including arthropathy, large numbers of tophi, but also on refractory gout among patients with a severe MSU crystal load and high SUA levels that are difficult to reduce in spite of available oral ULTs [66]. Finally, difficult-to-treat (DTT) gout encompasses patients with severe comorbidities, mostly CKD 4 or 5, and contraindications to all anti-inflammatory drugs used for flare, and/or ULTs: diabetes for steroids, CKD, chronic heart failure (CHF) and recent myocardial infarction for NSAIDs, and severe skin reactions to allopurinol and/or febuxostat, as examples [66].

Diagnosis

The gold standard for the diagnosis of gout is the identification of MSU crystals in the SF or in a suspected clinically palpable tophus. This can be done using light microscopy (or even better, polarized microscopy), preferably with double compensation. Any joint can be tapped, including the first MTP joint, and SF kept at 4°C until further processing [67], allowing SF examination with a 14-day delay without harming crystal identification.

Since MSU identification is often unavailable in primary care, composite classification and diagnostic criteria have

been developed [68–70]. From the oldest '1977 American Rheumatism Association preliminary criteria for the classification of the acute arthritis of primary gout' through to the recently published 2015 ACR/EULAR gout classification criteria, the same signs and symptoms have been weighed differently to obtain the best possible sensitivity and specificity [71, 72] (Table 1). These classification criteria are designed to include homogeneous populations in gout studies, but may be considered not sufficiently convenient for clinical practice. An easy-to-use clinical diagnostic rule was developed by Dutch PCPs for primary care management [69], with recent validation [70]; it is available as an app ('Gout calculator') for smartphones. Combining clinical features to increase the probability of a correct diagnosis of gout is essential, because 25% of patients presenting with 'acute arthritis' of the first MTP joint do not have gout [73]. More recently, the new 2015 ACR/EULAR classification criteria integrated definite imaging features together with the clinical characteristics of gout attack [72].

Imaging techniques

Conventional radiographs

It has long been known that plain radiographs are of little use for diagnosis of early acute gout, because a normal aspect or non-specific soft tissue swelling or effusions [74]. With time, specific features appear, such as margin bone erosions, joint-space narrowing, soft-tissue and intra-osseous tophi that tend to calcify with time, pencilling-in deformities of the shafts, and finally ankyloses and subluxations [74–76]. A gouty erosion is defined by the 2015 ACR/EULAR criteria as ''a cortical break with sclerotic margin and overhanging edge'. Gouty erosions have some significant weight in establishing the diagnosis of chronic gout arthritis [72]. Radiographic damage assessment using a gout-modified Sharp/van der Heidje scoring method, inspired by RA experience, has been established to reliably represent joint damage in gout, and can be proposed as an outcome measure [77]. A prospective cohort study of 290 gout patients showed that the main factors associated with progression of joint damage over 3 years were the development of s.c. tophi and the severity of baseline joint damage [78].

CT and MRI

Conventional CT can contribute to the assessment of structural damage [79] and has been used to evaluate potential benefits of zoledronic acid on bone erosion (negative study) [80]. Older studies have shown that CT can disclose lesions containing round and oval opacities, with a mean density of ~160 Hounsfield units; in late tophi, secondary calcified deposits are displayed [81]. MRI can be useful for examining early cartilage modifications or synovitis [82], and a gout scoring system has been proposed [83], but to date, MRI has not found its full usefulness in this context.

Only recently, imaging techniques developed for the diagnosis and assessment of other diseases have been used to objectively detect urate crystal deposition [84].

Table 1 Symptoms and respective weights according to classification or diagnostic criteria

Features	ACR/EULAR 2015 [75]	2010 'Nijmegen score' [72]	1977 ACR[74]
Localization of flare			
Ankle or midfoot joint	12.5	0	16.7
First MTP joint	25	31.2	16.7
Clinical features of flare			
Erythema of the joint	12.5	12.5	16.7
Cannot bear light touch or pressure to affected joints	12.5	0	0
Inability to walk or use the affected joint	12.5	0	0
Time course of episodes: time to maximal pain <24 h; flare resolution <15 days; complete resolution between two episodes (2/3 characteristics)			
One typical episode	12.5	N/A	16.7
Recurrent typical episodes	25	25	16.7
Clinical tophus	50	0	16.7
Hyperuricaemia			
6–8 mg/dl	25	43.7	0 or 16.7
8–10 mg/dl	37.5	43.7	16.7
⩾10 mg/dl	50	43.7	16.7
Imaging			
Radiographic erosion	50	0	16.7
US double-contour sign	50	0	0
DECT demonstrating urate deposition	50	0	0
Negative features			
MSU negative SF analysis	−25	0	0
SUA <4 mg/dl	−50	0	0

Values given as percentages. MTP: metatarsophalangeal; US: ultrasonography; DECT: dual energy CT; MSU: monosodium urate crystals; SUA: serum uric acid level.

Two methods, US and dual-energy CT (DECT), are very important approaches.

Ultrasonography

US is well recognized as a useful method in the diagnosis of gout, and a general consensus has been reached for defining specific elementary gout lesions [85–89]. Three different features are considered as characteristic signs of gout: a DC sign, aggregates and unapparent tophi. A DC sign is related to MSU crystal deposits at the cartilage surface, as confirmed by arthroscopy, but has the lowest agreement value [90]. Recently, OMERACT definitions for gouty lesions have been published [90]. US is also reliably able to identify bone erosions and both intra-articular and intra-tendinous microcrystal hyperechoic aggregates (HAGs) [86].

The kinetics of these US features has been studied in a cross-sectional study of 100 patients, suggesting that aggregates appear first, followed by the DC sign, erosions and finally tophi [91]. A prospective controlled study of 133 patients comparing gout patients with healthy subjects, or patients affected by other non-crystal rheumatic diseases, suggested that bilateral US assessment of one joint, three articular cartilages and two tendons is sufficient for the diagnosis of gout. The assessment of the radiocarpal joint for HAGs, the patellar tendon and the triceps tendon for HAGs, and three articular cartilages (i.e. first metatarsal, talus and second metacarpal/femoral) for DC sign showed the best balance between sensitivity and specificity (84.6 and 83.3%, respectively) [87]. Other target joints have been suggested, such as the trochlea of the knee and the Achilles tendons [85, 92]. Sensitivity was, however, found lower in another prospective study including 109 patients with suspected crystal arthritis with relatively short disease duration (almost half of these patients presented with their first flare) [89].

Data are also emerging concerning the usefulness of US for monitoring treatment efficacy, demonstrating regression of US signs at 6 months of treatment in responders, with an excellent correlation between the resolution of US signs and SUA levels [93, 94]. US is therefore being considered as an outcome measure in gout, but needs further standardization [95]. Overall, US has good sensitivity and specificity in diagnosing gout. Sensitivity depends on disease duration, joint site and disease severity [85]. Although individuals with asymptomatic hyperuricaemia lack US features of inflammation or structural joint changes, they demonstrate a similar frequency of the DC sign as gout patients, but they do not present with tophi [96].

DECT

DECT, a technique using two X-ray beams with different energies (80 and 140 KV), has had a recent development in its use in gout. The dual-energy configuration allows a distinction between chemical entities, because each compound has a unique signature [97]. In gout patients, DECT can distinguish between urate and calcium deposits, allowing the demonstration of urate deposits both in joints and soft tissues, particularly the frequent deposition in tendons and ligaments [97, 98]. Its contribution to the diagnosis of gout is established in difficult cases [99–101]. A diagnostic study of 40 patients with crystal-proven non-tophaceous gout compared with 41 patients with other rheumatic diseases yielded 90% sensitivity and 83% specificity, confirming results from another prospective study [102, 103]. A site-by-site analysis correlated urate deposits observed by DECT and radiographic joint damage in 92 patients [104]. Sensitivity depends on the number of joints (especially in the upper limbs) included in the scanning protocol. Visualizing urate deposits is not exclusive for gout patients, as asymptomatic hyperuricaemia patients can also have MSU deposits but seemingly to a lesser extent, suggesting a potential threshold of deposits before clinical gout occurs [105]. Similar detection rates were observed with DECT of the lower limbs compared with US in a systematic survey of 40 patients with gout, but DECT yielded a higher detection rate in the upper limbs, 42.3 *vs* 19.2.%, respectively [106]. Of note, the volume of a tophus corresponds to sum of the core (demonstrated by DECT) and the cellular crown (demonstrated by US). Some tophi may be missed by DECT if the volume of the MSU core is below the detection threshold [107]. A quantitative DECT scoring system for measuring MSU deposition in gout patients has been recently developed and is the first attempt to standardize DECT observations in gout [108]. However, limited longitudinal data is available on the outcome of urate deposits under ULT. A follow-up study of 10 patients treated with pegloticase has shown significant regression in tophus size, visualized by DECT scan [109, 110].

Recently, DECT showed that in tophaceous gout, MSU crystal deposition is present within the joint, on bone surface and within bone erosion, but it is not observed within bone in the absence of a cortical break. These data support the concept that MSU crystals deposit outside bone and contribute to bone erosion [111].

Comparisons between performance levels of DECT and US for the diagnosis of gout have provided evidence that DECT is superior, particularly with recent devices, but its use is limited by its low availability and the radiation risk (which can be reduced by focusing on the extremities) [106, 112, 113].

Management

Treatment of acute flares

Uncomplicated gout

The treatment of gout flares has long remained empirical due to a lack of well-conducted studies, but the gap has been partially bridged over the last decade. These studies have provided data that have enabled international societies to produce more solid guidelines [23, 114, 115]. However, the implementation of such detailed guidelines in general practice is still in the future.

Full doses of NSAIDs, namely naproxen 500 mg BID (twice a day) for 5 days, or indomethacin 50 mg TID (three times a day) for 2 days followed by 25 mg TID for 3 days, exhibited efficacy similar to prednisolone 35 and

30 mg QD (once a day), respectively [116, 117]. Within the NSAID class, several double-blind randomized controlled trials (RCTs) and open-labelled RCTs support a similar efficacy of Cox-2 selective NSAIDs (used at high doses only) compared with non-selective NSAIDs with a potentially better tolerance profile, bearing in mind that gout patients have many CV comorbidities limiting the use of coxibs [118–121]. Several registries or studies have shown that naproxen was the NSAID with the lowest CV risk. Naproxen is not associated with an increased risk of re-infarction or sudden death in patients with recent myocardial infarction [122]. These results indicate that naproxen should be the preferred drug if NSAID treatment cannot be avoided. Other NSAIDs are associated with increased CV risk [123]. The very recently published PRECISION trial, however, questions prior findings and provides reassuring data on celecoxib *vs* naproxen and ibuprofen [124].

Anecdotally, retrospective data of 181 patients suggested significant efficacy of a 1 mg i.m. injection of adrenocorticotropic hormone (ACTH) [125], though it may be less efficient at lower doses than systemic steroids, as shown in a very small prospective study [126].

The first clinical trial on colchicine had proved that colchicine is effective in part, but high doses showed its poor tolerance [127]. Terkeltaub *et al* provided reliable proof that low doses of colchicine (1.8 mg on the first day) were as effective as high doses (4.8 mg) and were better tolerated. Significant superiority of both colchicine arms over the placebo arm confirmed the efficacy of colchicine [128]. The earlier the start on colchicine after first symptoms, the better the effect, suggesting that patients should have colchicine at hand (in nightstand, bag or pocket). This demonstration of colchicine's efficacy at low doses justified its first-line position in the 2012 ACR guidelines for treating gout flares, together with NSAIDs and systemic steroids [114]. Doses recommended by the ACR are 1.2 mg, followed an hour later by 0.6 mg and 0.6–1.2 mg daily after that. Updated EULAR recommendations suggest that 1.5 mg on the first day of treatment may be sufficient [23]. Colchicine has not yet been compared with other historical treatments of flares. Results from a recent RCT comparing low-dose colchicine with naproxen are awaited (NCT01994226).

Difficult-to-treat gout

This group of gout patients encompasses polyarticular flares, and patients with comorbidities, mostly CKD or CHF, leading to contraindications or side effects of standard-of-care (SOC) drugs (colchicine, NSAIDs, oral steroids).

Polyarticular gout flare. ACR guidelines consider initial combination therapy of NSAIDs/colchicine or colchicine/CSs in case of severe polyarticular flare, or after insufficient pain decrease after 24 h monotherapy [114]. For monoarticular attacks, intra-articular steroid injections can be used after ruling out sepsis. Deciding which drug to choose for treating such a flare should be guided perhaps even more importantly by safety issues for each drug. Keenan *et al.* extracted data from medical records of 575 US veterans to assess potential contraindications of gout flare drugs [129]. Overall, 50% to almost 100% of patients presented with comorbidities that required at least precautions in prescribing SOC drugs. More interestingly, 20–45% of patients had strong contraindications to any one of these drugs.

Special attention should also be given to co-administered drugs. CSs have limited drug interactions, but it is well known that caution is needed when using NSAIDs with anti-hypertensive and anti-thrombotic drugs [130]. Terkeltaub *et al.* summarized seven individual studies of colchicine drug–drug interactions with other cytochrome P450 3A4 inhibitors [131]. Significant increase of colchicine concentrations and exposure was observed with co-administration of ciclosporin A, ritonavir, ketoconazole, macrolide antibiotics and calcium channel blockers. Co-prescription of statins could also increase muscular toxicity of both drugs, as reported in case reports [132, 133]. Daily use of these SOC drugs is therefore not so easy, and a cohort study showed a notable colchicine misuse for gout flares, particularly in CKD and elderly patients [28].

Patients with CKD and other severe comorbidities. CSs and ACTH. Since NSAIDs should not be used in patients with CKD or CV comorbidities, alternative drugs include CSs and IL-1 blockers. Several RCTs have shown that prednisone 30–35 mg QDfor 3–5 days represents an alternative choice to full dose NSAIDs [116, 117]. Such steroid treatment even for a short time could be deleterious with diabetes. Long-term use of steroids obtained without a prescription, as is seen in some countries (Mexico, Vietnam) as a symptomatic treatment for flares, can lead to severe tophaceous gout and secondary Cushing syndrome when patients do not receive appropriate ULT. Such DTT gout patients will benefit from IL-1 inhibitors.

IL-1 inhibitors. IL-1β is considered as the pivotal cytokine in MSU crystal-induced inflammation. Therefore targeting IL-1β in acute gout was considered to be a promising approach, especially for DTT patients, namely those refractory or intolerant to the above-mentioned SOC treatments [134]. Three therapeutic approaches have been developed.

Anakinra. Historically, anakinra, the soluble IL-1 receptor antagonist, was found in a bench-to-bedside approach to be effective in treating these DTT patients [115]. Only retrospective data from 92 DTT gout patients are available from 5 case series and 10 additional patients from an open-labelled pilot study [135–140]. After three consecutive s.c. daily injections of 100 mg anakinra, treatment efficacy was rapid in most cases (within 24 h, overall 80% responders) and the tolerance profile was satisfying, although some infectious events were noted. An ongoing RCT is comparing 100 mg s.c. anakinra for 5 days *vs* i.m. 120 mg DepoMedrol® for acute flares in DTT patients, namely with CKD3 or worse (NCT02578394). A larger RCT was launched recently to compare two different

doses of anakinra (100 and 200 mg) for 5 days with i.m. triamcinolone acetonide (NCT03002974).

Canakinumab. Canakinumab, a fully human anti-IL-1β neutralizing mAb, was compared with i.m. 40 mg triamcinolone acetonide in a single-blind study [141]. Almost twice the number of patients achieved no or mild pain 24 h after the s.c. injection of 150 mg canakinumab, compared with the triamcinolone group. The β-RELIEVED-I and -II trials confirmed this efficacy, though results were less impressive as the primary end point showed that the pooled mean pain visual analogue scale at 72 h was 10.7 mm (6.0, 15.4) lower in the canakinumab group (with similar results since 24 h), which is above the 13% difference of improvement considered clinically significant often used in gout studies [116, 117, 142]. Canakinumab is now approved by the FDA and the EMEA but its high price limits its use.

Rilonacept. Rilonacept is a fully human recombinant decoy receptor that binds both IL-1α and -β [143]. Despite studies for flare prophylaxis, only one RCT is available in treating gout flares [144]. Results were negative *vs* full daily dose indomethacin, and rilonacept is not licensed in this indication.

Urate-lowering therapies

Since gout is a chronic deposition disease with body MSU crystal burden as evidenced by clinical examination, US and even DECT, the goal for treatment is to significantly reduce the SUA level below the solubility threshold allowing crystal dissolution. A SUA level below 6.0 mg/dl is widely considered as the target [46, 145]. The updated 2017 British Society for Rheumatology (BSR) recommendations are even focusing on 5.0 mg/dl as a primary target, followed by the 6.0 mg/dl target after sustained debulking by any ULT [115]. Such a low SUA level is also associated with more rapid size reduction of tophi. The lower the faster [146]. Therefore, ULT is the KEY treatment. Of importance, sustained reduced SUA levels allowed MSU crystals to clear up and ultimately flares to stop.

Current available ULTs should control hyperuricaemia and gout in most uncomplicated cases, especially in PCP practices. However, for decades, globally, there has been no significant improvement in the rates of patients receiving ULTs, of patients achieving the SUA target, and patients within the maintenance rate for 1 year or more. Overall 20–40% of gout patients are treated with ULTs, with <30% with 6.0 mg/dl SUA level as a target [147].

This may be due to clinical inertia (an overarching concept for explaining insufficient management of chronic diseases) [148]. This concept, first described in diabetes mellitus in the 1990s, underlines delay in adjusting or modifying treatment in spite of unstable biomarkers, namely delay in the switch to insulin when HbA1c is not controlled by three oral anti-diabetic drugs [149]. Herein allopurinol dosage, as the first-line ULT, is prescribed at a low mean dosage (i.e. insufficient to reduce SUA level below the target). As one example out of many, two recent studies from France have not shown any significant changes in the mean daily dose or the percentage of patients at the target between 2008 and 2014 [150, 151].

Allopurinol dosage has been coined to be 'limited' to 300 mg daily for unfair reasons, since in all countries this cheap drug can be titrated up to 800 or 900 mg daily, according to national regulations. Clearly, there is an anxiety related to skin toxicity, as shown below, in patients with CKD and high initial dosing. 'Start low go slow' in titrating allopurinol is a safe procedure.

To avoid clinical inertia, general principles can be proposed in keeping with the management of other conditions such as diabetes and RA: treat to target; tight control, namely regular monitoring of the SUA level up to target; start low and go slow; annual SUA and eGFR measurements. These easy-to-handle recommendations can be summed up as quality indicators (Table 2).

Indeed, available ULTs are efficient, but are neither optimally administered nor monitored. This has been clearly evidenced by Doherty's group in Nottingham, revealing the role of the rheumatologist first (to explain and negotiate ULT, and colchicine where appropriate as prophylaxis), and the role of research nurses to follow [to monitor ULT titration (face to face or by phone call)]. In this pilot study, after 1 year 92% of the 106 participants had achieved the therapeutic target (SUA ⩽ 360 μmol/l, 6.0 mg/dl); 85% had an SUA level <300 μmol/l, 5.0 mg/dl [152]. Allopurinol was the most commonly used ULT, requiring a median dose of 400 mg daily to achieve the target. Remarkably, the persistence and adherence to ULT in primary care 5 years after this initial 1-year nurse-led treatment of gout was recently reported [153]. Questionnaires were filled by 75 out of 106 patients, yielding 5-year persistence on ULT of 90.7%; moreover, 85.3% of responders self-reported taking ULT ⩾6 days/week. Of the 65 patients who attended the study visit, the mean SUA level was 292 μmol/l. Following this pilot study, a 2-year RCT comparing nurse-led treatment *vs* usual management by PCPs has been completed and is currently under analysis (NCT01477346).

Approved ULTs: XOIs, allopurinol and febuxostat

All the major Societies have proposed indications for starting ULT according to age of onset, previous flares, CKD and features of severe gout (Fig. 3; Supplementary Table S2, available at *Rheumatology* online).

Allopurinol

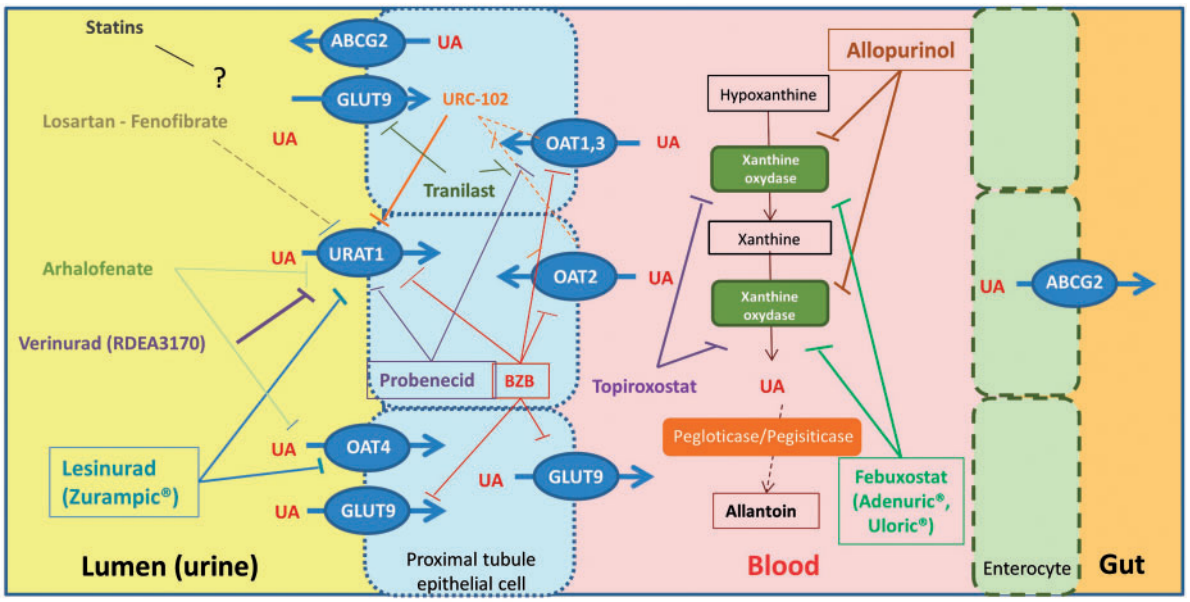
Although allopurinol is the first-line ULT in gout, as MTX is in RA, data of its efficacy predominantly relies on results from trials of other drugs in which allopurinol was the comparative arm. A recent large cohort study of 1732 patients receiving allopurinol for at least 6 months showed that 54.1% receiving a daily dose of >300 mg reached the SUA level of < 6.0 mg/dl [154]. The main concern around allopurinol use is tolerance and particularly the risk of allopurinol hypersensitivity syndrome (AHS), Stevens–Johnson syndrome, toxic epidermal necrolysis and DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome within the first 3 months and marked by poor

Table 2 A set of six key indicators for gout management[a]

Key indicator	Significance
Treat to target: GO to 6.0	Reduce SUA level below 6.0, or even 5.0 mg/dl[b]
Start low, go slow	Start allopurinol at 100 mg daily, increase by (50 or) 100 mg every month (for convenience) since there is no reason to drop SUA level abruptly
'Chi va piano va sano'	The start low and go slow reduces flares and contributes to avoid skin rashes or DRESS
Tight control	Increase allopurinol steadily up to optimal dosage to achieve SUA target
Avoid clinical inertia	Do not hesitate/do not fear to increase allopurinol dosage and switch to febuxostat or/and add uricosurics where appropriate. Treat to target always and always up to tophi resolution
Monitor regularly	Check SUA level and eGFR every 6 months when target is achieved. Use for patient adherence

[a]For rheumatologists, please note that some, if not all, of these concepts are those implemented in RA management. [b]According to ACR and EULAR, 6.0 mg/dl is the SUA target (whereas 5.0 mg/dl is the new 2017 BSR target) for all patients starting treatment. SUA: serum urate level; DRESS: drug reaction with eosinophilia and systemic symptoms; eGFR: estimated glomerular filtration rate; BSR: British Society for Rheumatology.

Fig. 3 Schematic mechanisms of action of current and future urate-lowering drugs



UA: uric acid; BZB: benzbromarone; ABCG2: ATP binding cassette subfamily G member 2; URAT1 or SLC22A12: urate transporter 1 or solute carrier family 22 member 12; OAT: organic cation transporter; GLUT9 or SLC2A9: solute carrier family 2 member 9.

outcome [22, 154]. This risk is notably higher in patients of Asian and African origins, with CKD, initial high doses of allopurinol and the presence of the HLAB58: 01 allele, especially in Asia [155–158]. Skin reactions are reduced by a starting-low, going-slow process. The initial allopurinol dosage should be 100 mg daily (or 50 mg/day for the elderly), with progressive titration up to achieve the SUA target, as coined by 2012 ACR, 2016 EULAR and even 2017 BSR recommendations [22, 23]. In addition, from a retrospective case–control study of gouty patients who developed AHS, it has been shown that starting allopurinol at a dose of 1.5 mg/U of eGFR may be associated with a reduced risk of AHS [159]. In patients who tolerate allopurinol, the dose can be gradually increased to achieve the target SUA level. New dosing rules should be designed according to new eGFR formulas. A recent RCT including 183 participants, carried out by Stamp *et al.* [160], compared creatinine clearance–based doses of allopurinol and a dose escalation strategy regardless of renal impairment. At month 12, 32% of patients receiving creatinine

clearance–based doses and 69% of patients in the dose-escalation group had an SUA level of <6 mg/dl. There was no signal regarding adverse events.

Febuxostat

The efficacy of febuxostat was demonstrated *vs* allopurinol in large RCTs, but some patients experienced serious adverse CV effects in the febuxostat groups [161, 162]. The concerns raised about febuxostat's CV safety were explored in the CONFIRMS trial, which provided reassuring data at 6 months with similar events in the allopurinol and febuxostat groups [163]. Precautions with patients with CHF and coronary heart disease are still effective in many countries. The question of the comparative efficacy of allopurinol and febuxostat has been raised since the early developments of the latter [164]. Face-to-face comparisons have been performed, but allopurinol treatment was never correctly optimized or appropriately prescribed, as is the case in real life, as shown in a USA managed care cohort [165]. The allopurinol–control groups usually received a maximum dosage of 300 mg daily, even when kidney function allowed higher doses [161–163, 166, 167]. These studies suggest that 300 mg allopurinol has similar urate-lowering potency to 40 mg febuxostat in the USA population. However, it is now well recognized that only about half of the patients reach the SUA objective at the dose of 300 mg [22].

The cost effectiveness data of allopurinol and febuxostat are somewhat conflicting, although the allopurinol–febuxostat sequential therapy seems satisfying [168, 169]. Given these data, contrary to the 2012 ACR guidelines that equally placed allopurinol and febuxostat as first-line ULTs, EULAR now recommends first use of allopurinol for economic reasons [22, 23]. In the UK, The National Institute for Health and Care Excellence (NICE) guidance is the following: ''Febuxostat, within its marketing authorization, is recommended as an option for the management of chronic hyperuricaemia in gout only for people who are intolerant to allopurinol or for whom allopurinol is contraindicated. Febuxostat had not been shown to be clinically or cost effective compared with the more appropriate comparator of allopurinol up-titrated in accordance with established best clinical practice.'' However, febuxostat would be helpful in patients with CKD, not only CKD 3 but also, as shown in several open retrospective studies, in CKD 4 and 5, or even in renal transplants (off label) [170, 171]. Since febuxostat's licence will end soon, the choice will not depend upon cost after generic drugs become available. There is a need for 40 mg febuxostat tablets, allowing titration.

Uricosurics

Uricosurics are for the time being placed down the line in the treatment sequence, both by American and European guidelines [22, 23]. They are of interest since they target the renal tubule pathogenic dysfunction (URAT1). Both probenecid and benzbromarone are proposed as monotherapy or in combination with XOIs [172]. Benzbromarone is more potent than probenecid [173]. Although probenecid has a poor general tolerance profile and requires two daily intakes, benzbromarone use was impaired by very rare cases of serious hepatotoxicity, explaining its withdrawal in some countries [174, 175], in spite of lobbying by rheumatologists [176].

Lesinurad, a novel selective UA reabsorption inhibitor directed toward URAT1, recently obtained FDA and EMEA approvals. Results from the phase II trial including inadequate responders to allopurinol demonstrated significant response rates (SUA <6.0 mg/dl) at 4 weeks for all dosages [177]. The study raised concerns about increased sCr, particularly in the high dosage (400 mg/QD) group. Phase III trials have demonstrated efficacy in combination with allopurinol. In a 12-month, randomized, phase III trial, European gout patients on allopurinol ⩾300 mg (⩾200 mg in moderate renal impairment) who had an SUA level ⩾6.5 mg/dl (⩾387 μmol/l) at screening and two or more gout flares in the prior year, were enrolled in a 12-month trial. Lesinurad at 200 and 400 mg doses, added to allopurinol, significantly increased proportions of patients achieving the SUA target *vs* allopurinol-alone therapy by month 6 (55.4, 66.5 and 23.3%, respectively, $P < 0.0001$ both lesinurad + allopurinol groups) [178]. Similar results were achieved in the USA trial [179]. At the recommended 200 mg dose, the drug was associated with usually reversible increased incidence of sCr elevations and adverse reactions related to renal function, according to the label information. The boxed warning has been addressed by the FDA and the EMEA for post-marketing CV and renal safety monitoring. A fixed dose of allopurinol 200 mg/lesinurad 300 mg was approved by the FDA in August 2017.

Pegloticase

Pegloticase is a mammalian recombinant uricase with a very potent urate-lowering effect in RCTs, but a very low tolerance profile (numerous infusion-related reactions) [180, 181]. This potent drug for the treatment of refractory gout is currently unavailable apart from in the USA. The safety issue is related to drug-induced neutralizing antibodies in 50% of patients, and drug infusion reactions and loss of efficacy. Sustained low SUA levels are achieved (<1.0 mg/dl), but recent reviews and a cohort study are reassuring for any risk of neurodegenerative disorders [182].

Flare prophylaxis with ULT initiation

Determining the time when ULTs should be introduced after a flare is still a matter of debate and is entirely dependent on flare prophylaxis. Since SUA levels vary during gout flares [183], and since slowly reducing SUA levels with ULTs is less likely to provoke flares [152], ULTs are traditionally introduced 2–4 weeks after a flare. However, on the basis of a first RCT, the ACR recommended in 2012 the introduction of ULTs during the flare [7]. This relatively small-sized trial (51 patients) proposed an unusual double prophylaxis of flares with a full dose of both indomethacin (150 mg daily) and colchicine (1.2 mg daily), far from the SOC of a low-dose colchicine prophylaxis [22]. This design explained the absence of prolonged or recurrent flares over the 30 days of follow-up, despite the high initial

dose of allopurinol (starting dose of 300 mg!). A second RCT found similar results, and the longer duration of the flare in the allopurinol group was not statistically significant [184]. However, in this very small-sized study (14 patients in the allopurinol group), treatment of the flare was not standardized. None of these studies are sufficiently robust to end this debate, and further RCTs are required

Both ACR and EULAR guidelines agree on a 6-month flare prophylaxis after ULT initiation [114]. Prolonged prophylaxis is recommended by experts in tophaceous gout. Low-dose colchicine (0.5 or 0.6 mg once or twice daily) should be favoured. With a lower level of evidence and with inherent risks of prolonged use, low-dose NSAIDs or CSs below 10 mg daily can be used [114]. Other prophylactic strategies have been explored [185], and particularly anti-IL-1 drugs can be useful in case of contraindications for SOC drugs [186, 187].

Pipeline drugs

New drugs are in the pipeline at various stages of development (Fig. 4 supplementary Table S1, available at *Rheumatology* online).

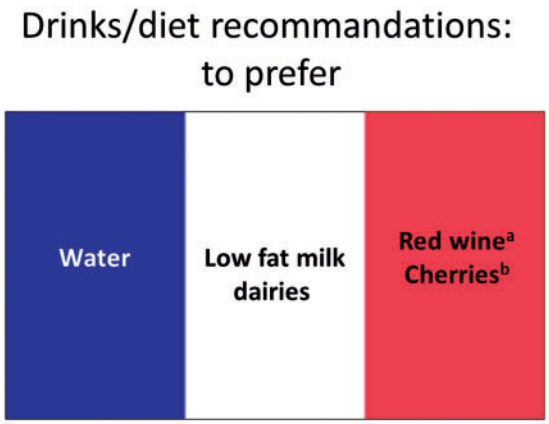
Diet and life-style changes

Over the last decade, high-concentration fructose beverages, fruit juices, have been identified to be a risk factor for hyperuricaemia, gout and even diabetes [188–190]. The increased risk occurs for exposure as low as one unit (can of soda) per day. A genes – beverage sweetened with high fructose interaction is clearly identified, with a specific role for glucose transporter [191] and ABCG2 at the gut level [192].

Conversely, regular heavy beer intake, including non-alcoholic beer, is associated with hyperuricaemia and gout, given the high-concentration guanine content. Similarly, spirits, through various mechanisms, will increase SUA levels and should be avoided. Risk for wine has not been identified for hyperuricaemia or gout; indeed, one unit of wine or any alcohol provides 90–100 calories. Keep in mind that chronic alcohol intake can lead to addiction. In gout patients, diet recommendations are quite easy to abide by and will help limit specific intakes and reduce weight [193], another index associated with hyperuricaemia and gout (Fig. 4).

Regarding comorbidities, losartan and amlodipine (with uricosuric effect) should be preferred as hypertension drugs. Diuretics being a cause of secondary hyperuricaemia and gout, especially in elderly women, should be discontinued where appropriate, except in CHF or severe CKD. Statins and fenofibrate have also shown hypouricaemic effect in cohort studies of non-gout patients and are the drugs of choice in treating dyslipidaemia [194, 195].

Fig. 4 Drinks modifications (easy to read)



Water (blue) in quantity will allow patients to reduce their risk of flares; low fat milk (white) or dairy products are associated with uricosuric effects; [a]wine (red), in modest amounts, is not associated with hyperuricaemia or gout. By contrast, spirits and beer, including alcohol-free beer, is clearly linked with hyperuricaemia and gout. [b]Cherries might have anti-inflammatory effects.

Conclusion

Although gout has for a long time been thought of as a self-inflicted and embarrassing condition, as shown in a recent overview of popular newspapers performed by Duyck *et al.* [196], researchers seem to have embraced this cause. Appropriate gout management is readily achieved with current medications, but further efforts are needed to reach full implementation in routine practice and to clearly define the role of new therapies.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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