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Change gout: how to deal with this 'silently-developing killer' in everyday clinical practice

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Abstract

Despite being regarded as an easily-treatable disease, gout diagnosis and management can be challenging. We discuss here current issues in gout management and propose some potential solutions. Gout diagnosis should be reached as early as possible and often requires specific tests, such as synovial fluid analysis or imaging techniques that are not available in most centers, leaving health care professionals to rely only on clinical presentations and their experience. In addition, gout management requires the evaluation of multiple aspects, such as monitoring of serum uric acid (sUA) level (which should be reduced to <6 mg/dL) to ensure adherence and efficacy of treatment, evaluation of patient's risk profile and comorbidities, and continuous assessments to manage clinical manifestations. An important premise in gout management is non-pharmacological interventions; however, pharmacological urate-lowering therapy is crucial for an optimal control of the disease. Available options include xanthine-oxidase inhibitors (XOI), targeting uric acid overproduction, and uricosuric agents which target the predominant cause of hyperuricemia (underexcretion). Among these, lesinurad is the novel uricosuric agent to be used in combination with XOI in patients with gout not adequately controlled with XOI alone, which can further contribute to the control of hyperuricemia in gout. Multidisciplinary management is crucial for the diagnosis and treatment of gout in order to ensure treatment continuity and improve management. We therefore advise that educational activities for General Practitioners and specialists should be implemented to help raise awareness on gout diagnosis, monitoring and treatment.

Keywords: gout/pathology, gout/drug therapy, gout/diagnosis, hyperuricemia, Xanthine Oxidase/antagonists & inhibitors, uricosuric agents

Introduction

Gout represents the most frequent cause of inflammatory arthropathy in adults. This condition is often regarded as an ancient disease and its current worldwide prevalence ranges from 0.5 to 4.0%, while its incidence has increased up to 40% in Western countries over the last years [1-3].
Hyperuricemia is the causative factor for the development of gout, which results from crystallization, aggregation and deposition of monosodium urate (MSU) crystals that silently accumulate in joints and soft tissues [4,5]. Therefore, hyperuricemia can be considered the 'most noisy' signal of silently-developing gout, as well as a marker of several other clinical conditions [6]. Several risk factors contribute to the increased occurrence of hyperuricemia, including alcohol use, diet rich in high purine food and sugar-sweetened beverages [7,8], obesity, metabolic syndrome, renal disease and diuretic use [9].
Gout can be diagnosed with confidence on clinical grounds when the presentation is typical (i.e. sudden onset of severe pain with associated redness, swelling and tenderness to touch, affecting the first metatarsophalangeal joint (MTPJ), in the presence of hyperuricemia) as supported by the EULAR recommendations for diagnosis and recently proposed classification criteria [10,11]. On the other hand, gout may be difficult to diagnose because symptoms may be episodic and/or the disease can present with atypical features; the common belief that gout may only develop as podagra is also a frequent cause of misdiagnosis. Moreover, gout may mimic other conditions, becoming a diagnostic challenge for clinicians, especially in elderly patients [12]. Furthermore, although hyperuricemia is a prerequisite for gout, serum uric acid (sUA) levels may remain in normal range during acute attacks, with limited diagnostic utility [13]. Therefore, the actual prevalence of gout is likely higher than what is reported in epidemiological studies [13].
At present, the importance of a correct diagnosis and optimal management of gout is underestimated by many health care professionals due to a low interest and suboptimal knowledge of the disease [1,4,14]. Moreover, gout diagnosis often requires specific equipment (synovial fluid analysis or ultrasonography) which are not available in most centers [15]. This opinion paper provides an overview of current issues in gout management and proposes some potential solutions, according to the experience of a multidisciplinary group of Italian Experts. In particular, the potential role of lesinurad – a novel selective uric acid reabsorption inhibitor recently introduced in the pharmacological armamentarium of gout – is discussed.

Methodology
The group included six Experts belonging to different areas (Rheumatology, Cardiology, Nephrology, General Practice), identified according to their experience in the field by the project leaders (CS and WG). The Experts assembled in three meetings and they were free to discuss the topics of the manuscript under the guidance of an independent professional facilitator.

Gout: clinical features, causes, and associated comorbidities

Gout is an inflammatory arthritis with progressively-increased severity. Hyperuricemia may lead to subclinical urate deposition - that may continue for prolonged periods of time - in joints, tendons, soft tissues and internal organs, especially kidneys.
Ultrasound scan examination of long-term asymptomatic hyperuricemic patients (30–50%) discloses frequent MSU crystal deposits, leading to the identification of a subset of patients with asymptomatic MSU deposition [16].
This important finding could lead to revise the temporal classification of hyperuricemia and gout by introducing a phase of "asymptomatic MSU deposits" [17,18], which would take place before the gout clinical manifestations, as shown in Figure 1. Such asymptomatic deposits appear to form years before the first occurrence of flares, which seem to be triggered by mobilization of preformed crystals from deposits [16], following spontaneously or after stressful events. This mobilization leads to shedding of crystals and consequent inflammation with marked release of pro-inflammatory cytokines causing acute attacks, or flares, characterized by excruciating pain [1].

However, if not adequately controlled and reversed crystal deposition can lead to more frequent and longer attacks, and polyarticular involvement [1]. Between flares, the patient can remain asymptomatic. These time intervals are defined as “intercritical” periods; they can last for many years and may be erroneously considered to be free from any underlying pathogenic process - such as inflammation or tissue damage - therefore not requiring any therapeutic intervention [13]. However, during these time intervals, MSU crystals continue to deposit [19,20] and therefore the inflammatory status remains, although of lower severity. It is thus crucial to treat the patient even during intercritical periods [14]. Indeed, if not treated appropriately, gout develops into a condition called chronic tophaceous gout, characterized by the involvement of more joints and by the presence of clinical evident tophi, deposits of MSU crystals which can cause joints destruction with irreversible bone erosion, chronic pain, and serious impairment of joint function and general clinical condition [1]. Classically, tophi may present as periarticular and subcutaneous firm nodules particularly around the olecron process, knee joint, volar aspects of forearm, Achilles tendon and helix of the ear. Sometimes, tophi break through the skin and appear as white or yellowish-white, chalky nodules. However, it is important to note that intra-articular tophi can be present also at an early stage of the disease, and that the formation of multiple tophaceous depositions does not always lead to articular destruction, chronic pain and bone erosion.

Biochemistry and physiology of uric acid

Knowledge of the basic biochemistry and physiology of UA is a key prerequisite for understanding gout management and treatment. Uric acid is the end product of purines metabolism. About one-third of the human daily purine load is from diet, while two-thirds is generated endogenously [21]. It is produced by the enzyme xanthine-oxidase; approximately one third of UA elimination occurs in the gastrointestinal tract, while the remainder, that represents the majority [4,22] is excreted by the kidneys, where the balance between re-absorption to the plasma and excretion is regulated by multiple renal transporters, located primarily in the proximal renal tubules, the most important being the UA transporter (URAT-1) [1,23]. Elevated serum UA (sUA) is defined as a concentration >6.8 mg/dl (>0.40 mmol/L). Of note, minimal variations of local environment (e.g. changes in pH) facilitate its crystallization and deposit. Therefore, it is now preferred to consider 6 mg/dL (0.36 mmol/L) as target concentration [1]. Hyperuricemia results mostly from the inefficient renal excretion of UA, from the overproduction of urate and often from a combination of the two [1]. Interestingly, the elevation of UA often occurs prior to the development of other conditions such as hypertension or metabolic syndrome, suggesting the involvement of UA also in their development [24]. Moreover, it has been recently suggested that UA could help trigger innate and adaptive immune response. In more details, MSU crystals stimulate both inflammasome-dependent and independent pathways to generate the proinflammatory cytokine IL-1, which in turn promotes both local and systemic inflammation and contributes to the development of other comorbidities [25]. The presence of elevated sUA should therefore be considered a red flag for a number of other conditions, and not only of gout. Close monitoring and adherence to treatment are therefore crucial also during intercritical periods.

sUA and comorbidities associated with gout

Overall, some evidence collected in experimental and epidemiological studies supports the association between increased sUA and gout with the development of cardiovascular (CV), renal and metabolic disease [24,26-28,29-33]. Indeed, increased UA can induce vascular and tissue damage through multiple pathophysiologic mechanisms, such as endothelial dysfunction and oxidative stress, vasoconstriction and stimulation of renin angiotensin system. These processes act at the kidney level, within arterioles and tubular cells, as well as at the systemic vasculature and tissue level causing hypertension, atherosclerosis and myocardial dysfunction [24,34]. Yet, the association between increased sUA and CV events has been recently challenged by a study using a Mendelian randomization approach [35]. Further prospective evidence is required to investigate this issue [36].

Impact of hyperuricemia and gout on the healthcare burden and quality of life

Due to the above-mentioned findings, gout has a major short- and long-term impact on quality of life (QoL) and individual productivity [1].
Indeed, a pooled analysis of five studies showed that gout patients, and especially elderly subjects, incur substantially greater direct and indirect costs as compared with gout-free individuals; direct costs are directly associated with increased severity of disease [37]. In a large retrospective Italian analysis (N=112,170), the risk of hospitalization related to gout and/or nephrolithiasis was higher in patients with gout, with increased risk in those with higher sUA levels; a similar trend was reported for hospitalization due to chronic kidney disease and CV disease. This led to progressively increased costs of hospitalization per patient [from € 1,515 for sUA <6 mg/dL to € 3,096 for sUA >8 mg/dL (0.48 mmol/L)] [38].
With respect to QoL, an Italian observational study showed that, after adjustment for potential sociodemographic and general-health confounders, gout-specific variables significantly impacted on health-related (HR) QoL [17]. These variables included polyarticular involvement [Odds Ratio (OR) 3.82; 95% Confidence Interval (CI) 1.63, 8.95] and recent attacks (OR 2.20; 95% CI 1.27, 3.81).
Collectively, these data provide evidence for an association between gout and gout-related features with HRQoL, thus further supporting the need to improve management of this condition.

Management of gout: a patient's (and physician's) journey

Gout is a long journey for the patient, as well as for the treating physicians. We comment here on how to manage the different stages of this journey.

From acute attack to diagnosis
Common factors triggering first clinical manifestations of gout (i.e. gout flares) include acute illness, infections, contrast media injections, acidosis, rapid rise and fall in sUA (e.g. due to trauma, surgery, psoriasis flare-ups, chemotherapy) [39,40]. In addition, an acute attack may be also triggered by an excessive consumption of purine-rich food and alcohol [41].
It is important that physicians, including General practitioners (GPs), identify the risk profile of potential gouty patients, even in absence of clinical manifestation (i.e. acute attack) and monitor their sUA levels, with the aim to establish early therapy when necessary [13].
The differential diagnosis of acute gout is usually infectious arthritis, psoriatic arthritis or other crystal-induced arthropathies, particularly pseudogout. It is important to underline that all these diseases may coexist with gout. In the primary care setting, the diagnosis of gout can be made on the basis of clinical presentation mainly, with assessment of the presence of risk factors and of a triggering event. Other features would point to the need for additional diagnostic tests, including more gradual onset, less clinically evident inflammation, involvement of joints other than the first MTP joint.
Then, in case of doubtful diagnosis and resistance to first-line treatment, the patient should be referred to the rheumatologist, with all his/her clinical information, for the confirmation of diagnosis. The definitive diagnosis of gout can be performed by aspiration of a joint or tophus and the subsequent identification of needle-shaped MSU, that should be associated with clinical and/or US/imaging confirmation [42].

What to do once diagnosis is established?
Once gout is established, proper screening for associated comorbidities and CV risk factors is highly recommended [14].
First, the gouty subject should receive proper information by the treating physicians, including explanations on mechanisms of disease, life-style and treatment, with the aim to make him active part of the management process. Notably, patients must be educated to proper adherence to therapy, which represents a key contributor to treatment success, also during the intercritical phases of disease. At the same time, monitoring of the patient should be planned, to evaluate the efficacy of treatment, identify and manage adverse events, and further promote adherence. Notably, tailored assessment of comorbidities should be planned by the rheumatologist and the GP, to help formulate a personalized, comprehensive management plan. To this end, the National Health System may predispose dedicated clinical pathways.

Management of the gouty patient: current issues and how to address them

Treatment of gout is possible and frequently considered as easy. Indeed, crystal formation is reversible, and therefore this condition can be controlled by reducing sUA levels below the limits of solubility and up to the safety threshold of 6 mg/dL [4,14].

However, gout is also the worst managed joint disease, partly because it is often underestimated by both patients and physicians [1,13]. Patients frequently present poor adherence to gout treatment, especially during intercritical phases [4]. Moreover, it has been shown that even physicians have a very poor adherence to current management recommendations, and only 25-30% of them appropriately monitor the levels of sUA [43-45]. Improved adherence to guidelines by clinicians represents the first step towards improved management of gout in clinical practice. We also believe that educational activities, also during formal graduate and post-graduate training, will be useful in raising awareness on gout and associated comorbidities, as well as prompting a close monitoring and treatment of this condition. Last, multidisciplinary management by different specialists is also crucial for the diagnosis and treatment of gout.

Treatment of gout is based on both non-pharmacological and pharmacological interventions [14]. EULAR 2016 guidelines state that every person with gout should receive advice regarding lifestyle. However, the task force recognized that lifestyle and dietary modification has little effect on urate concentrations and that the level of evidence to support the effect of lifestyle modification on sUA levels is low, being this principle mainly based on expert opinion [14]. Indeed, recent data from the Third National Health and Nutrition Examination Survey, conducted in US on 14,809 participants between 1988 and 1994, showed how minimal is the impact of diet modification [46-50].

With respect to pharmacological management, according to EULAR 2016 guidelines urate lowering therapy (ULT) should be considered from the first presentation of gout (the first acute attack), as well as recommended in the presence of recurrent acute attacks, tophi, gouty arthropathy and/or kidney stones and maintained over time. This is because the first acute attack occurs after years of hyperuricemia and so as not to expose patients to a further load of crystals [14,42]. The definition of gout itself may influence the prescription of ULT as to whether it should only be considered in the presence of symptoms or also in patients with asymptomatic deposition. However, given that a critical amount of MSU crystal deposits may be needed for the development of clinical manifestations, a gout condition defined as “asymptomatic MSU deposits” has been recently proposed; however, because of the lack of follow-up studies, the benefit of lowering uricemia in patients with asymptomatic deposits remains unknown [16].

To manage acute attacks, the same EULAR guidelines suggest anti-inflammatory therapies, namely colchicine, nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids [14].

In any case, the ultimate aim is to reduce sUA levels below 6 mg/dL, or, in case of severe and or tophaceous disease, 5 mg/dL (0.30 mmol/L). Xanthine-oxidase inhibitors (XOI) are recommended as ULTs. The XOIs (allopurinol as first line of therapy and febuxostat as second line of therapy) are “uricostatic agents”, since they inhibit the production of UA [14]. Clinical trials have shown that, despite high adherence, around 40-50% of patients with gout does not reach the target levels of sUA with allopurinol alone, even at the higher dosages [51-54]. Educational efforts can contribute to increase the number of patients reaching this therapeutic goal [55]. If the sUA target cannot be reached by an appropriate dose of allopurinol, allopurinol should be switched to febuxostat or an uricosuric agent, or combined with an uricosuric drug. As a second-line therapy for gout, febuxostat is a recognized option, which does not require dose-adjustments in patients with mildly- or moderately- impaired renal function [56]. Of note, most patients with gout present a combination of impaired excretion of sUA in addition to enhanced production [42,57]. In patients who do not reach the target sUA concentration with XOI alone, using drug combinations targeting the two etiologies of the disease may more effectively reduce the concentration of sUA to ≤6 mg/dL [4].

With respect to safety, it has been reported that XOI might be associated with some tolerability issues, especially in case of high doses or in patients with chronic kidney disease [1]. XOI treatment, when administered without prophylaxis, may induce higher rates of attacks, leading to withdrawal and self-medication of attacks. Importantly, most patients with gout are on multiple medications, therefore raising some potential concerns in terms of pharmacological interactions [58].

Given the above, uricosuric agents characterized by a mechanism of action complementary to XOI mechanism and targeting impaired excretion (the most frequent alteration underlying gout) may be a

suitable option in clinical practice. These molecules act on the renal tubules by inhibiting the action of transporters like the uric acid transporter 1 (URAT1) and the organic anion transporter 4 (OAT4) [57]. Different uricosuric agents, including probenecid and benzbromarone, proved to be effective in the treatment of gout. However, availability of these drugs varies considerably from country to country due to the risk of pharmacological interactions (probenecid) and liver toxicity (benzbromarone) [57,59].
Research conducted in recent years has focused on the development of new therapeutic options with the same mechanism of action of previous uricosuric agents, but with increased selectivity and a better safety profile [1]. In this line, based on the most recent data on emerging uricosuric agents, the EULAR 2016 guidelines recommend a combination therapy with a XOI and an uricosuric agent in gouty patients who do not achieve sUA target with XOI monotherapy [14]. This combination is based on a dual mechanism for sUA lowering—increase in UA excretion and reduction in urate production [60].

Lesinurad as a new therapeutic tool

Lesinurad (Zurampic®) is an oral selective inhibitor of URAT1 and OAT4 renal transporters, which increases renal UA excretion and lowers sUA levels by inhibiting UA reabsorption. Compared with other uricosuric agents, lesinurad exhibits minimal drug–drug interactions and side effects [61].
Lesinurad 200 mg once daily is indicated in combination with a XOI to treat hyperuricemia in adults with gout who have not achieved target sUA levels with a XOI alone [62]. This molecule presents negligible interactions with other drugs used in gout treatment [63].
As of today, lesinurad is the only uricosuric drug to have undergone a complete clinical development programme (Phase I-III). Approval was based on the results of 3 pivotal Phase III trials which evaluated this molecule in combination with allopurinol in adults with gout inadequately responsive to allopurinol (CLEAR 1 and 2), or in combination with febuxostat in adults with tophaceous gout (CRYSTAL). All three trials had a core study period of 12 months plus an extension of a further 12 months, and overall showed a significantly higher proportion of patients reaching target sUA levels and a more evident reduction of sUA concentration when lesinurad was added to the XOI, as compared with XOI monotherapy [60,64,65].
Notably, the efficacy of lesinurad in combination with both allopurinol and febuxostat vs monotherapy was also evident considering lower sUA target levels [<5.0 mg/dl (<0.30 mmol/L) and <4.0 mg/dl (<0.24 mmol/L)] [60,64,65].
Over a longer term, the clinical benefits of lesinurad 200 mg/day plus XOIs were progressively more evident: indeed, over the 24 months of core plus extension studies the proportion of subjects with complete resolution of at least one target tophus continued to increase and the proportion of patients with gout flares requiring treatment also decreased across all treatment groups [62]. Overall, lesinurad treatment was well-tolerated, with a safety profile similar to XOI monotherapy.
The combination of lesinurad to XOI therapy does represent a new tool for the management of gout in patients not adequately controlled with XOI monotherapy. Indeed, due to its mechanism of action, which targets UA underexcretion, the most frequently impaired pathophysiological basis of the onset of gout, lesinurad may allow enhanced efficacy than XOI alone, avoiding the need of increasing allopurinol doses. Moreover, lesinurad can become part of tailored regimens (e.g., induction with increasing doses of allopurinol, followed by maintenance therapy with lesinurad plus allopurinol).
Potentially, lesinurad can be a promising option for the long-term maintenance therapy, as a prophylactic therapy in patients at risk (e.g., those with mild renal insufficiency, and subjects on diuretic or ASA therapy), or in hyperuricemic subjects with subclinical gout. However, the use of lesinurad in these settings require confirmation in dedicated trials. Moreover, educational activities for physicians – including GPs – appear crucial to increase the awareness of clinicians on lesinurad and gout itself. Dedicated software and registries may also be useful to identify patients who may benefit from lesinurad in the primary care setting, with the aim to include them into dedicated management programs.

Conclusions

Although gout should be regarded as the most easily treatable inflammatory arthritis, it is often very poorly managed in clinical practice. Increased involvement of patients, institution of a tailored management pathway, as well as of prompt and continued treatment – relying also on new therapeutic opportunities - are crucial for the management of gout.
Based on our experience, we elaborated 'a Decalogue' for the management of gout in clinical practice (Table 1). We hope it could contribute to stimulate further educational efforts to GPs and other specialists involved in the management of gout, which can increase the awareness about this condition and help patients during their long journey with gout.

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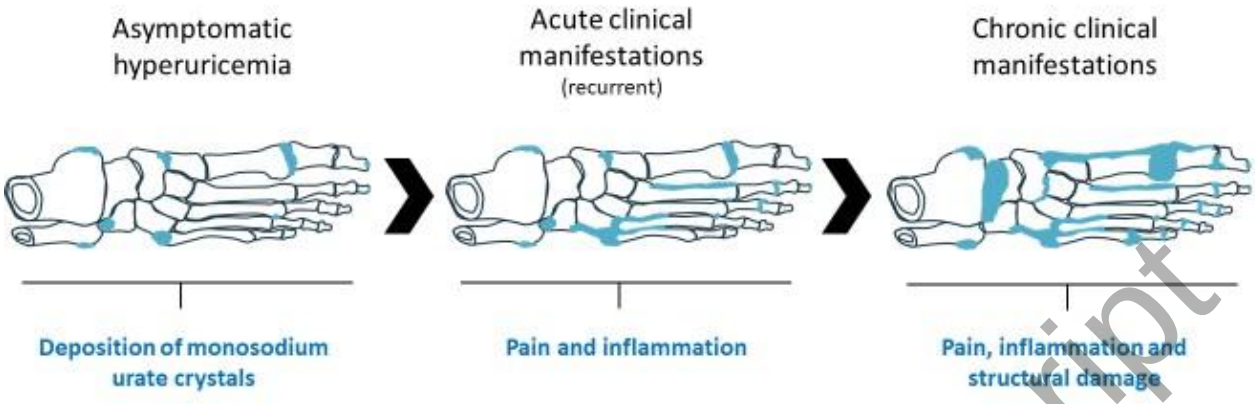
Figure Legends
Figure 1. Stages in gout development



TABLES

Table 1. The 'Decalogue' in the management of gout.

Rule
1. Know the disease, its associated complications, its management and your responsibilities
2. Remember that gout can be cured
3. Treat flares in the prodromic phase
4. Monitor sUA levels periodically
5. Identify all potential complications of gout early
6. Identify all potential complications of therapy early
7. Maintain a correct lifestyle
8. Don't stop treatment unless strictly advised
9. Don't add other treatments/nutritional integrators without the suggestion of the rheumatologist
10. Respect all recommendations of your expert coach