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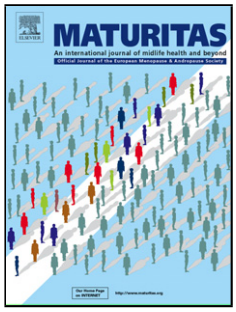

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Gout – an update of aetiology, genetics, co-morbidities and management

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Highlights

- Gout is a disease of urate crystal deposition that manifests primarily as inflammatory arthritis.
- Gout is not a disease that is present only during gouty flares: it is a chronic urate crystal deposition disease with flares being a symptomatic manifestation.
- Treating gout requires lowering serum urate levels to a predefined target to induce remission.
- Gout is associated with multiple co-morbidities that often complicate management and these co-morbidities should be identified and managed appropriately as part of the care of a patient with gout.
- The way allopurinol is initiated has changed, with lower doses used initially and slow uptitration, to improve safety and reduce associated flares.

Abstract

Gout is an increasingly common chronic disorder of urate crystal deposition that manifests as flares of acute inflammatory arthritis. Hyperuricaemia is a prerequisite and a fifth of both men and woman are hyperuricaemic. The prevalence of gout is much lower than the prevalence of hyperuricaemia for reasons that are not currently clear. Gout is more common in men than women prior to menopause due to the uricosuric effects of oestrogen, but after menopause the incidence of gout rises substantially in women. Co-morbidities are an important issue in gout, with cardiovascular disease, diabetes mellitus, obesity and chronic kidney disease all common in patients with gout. Environmental factors like diet affect the incidence of gout but there is little evidence to support an emphasis on diet in treating established gout. The diagnosis of gout is often made without the use of joint aspiration and validated diagnostic rules are available for both primary and secondary care as well as classification criteria for research use. The overarching principle of the management of gout with pharmacotherapy is the need to reduce serum urate levels to below a target of 0.30mmol/L or 0.36mmol/L depending on whether it is tophaceous or non-tophaceous respectively. The use of allopurinol has been researched extensively and newer strategies for safer effective dosing are now recommended. Newer agents have been introduced for the treatment of gout, including febuxostat and lesinurad. A number of important questions in the field are under current investigation.

Keywords: gout, uric acid, urate, hypertension, allopurinol, febuxostat, colchicine

1.0 Introduction

Gout is a chronic urate crystal deposition disease. As patients accumulate urate crystals over time their risk of clinically manifest gout increases. Gout is not a disease that is only present during gouty flares, it is a chronic urate crystal deposition disease with flares being a symptomatic manifestation. This distinction is important as it justifies the effort to lower serum urate (SU) in patients to prevent symptoms and joint damage.

The challenges in gout care centre on diagnosis and introduction of treatment as well as maintaining adherence to urate lowering therapy (ULT). This review aims to both highlight important points in gout and provide an update since the last review of this topic in *Maturitas* (1).

Major papers in the field since the last published manuscript were reviewed and included if they were felt to be important to the understanding of gout or its management. Papers that marked significant changes in understanding or management from anytime were included if they sought to change long held beliefs or practice that takes an extended time to disseminate throughout the medical and scientific community. Specifically, Medline [via Web of Science] was searched from 2014 - 2018 with the topic term ‘gout’ (15,198 results) and restricted by ‘highly sighted’ and ‘hot papers’ (73 results) which were then examined individually, initially by title and abstract review, then by full text review.

2.0 Aetiology

While gout has been considered by some in the past as a disease of excess and over-indulgence this view is increasingly being replaced by a more nuanced view (2). When gout is viewed as a chronic disease of urate crystal deposition then its cause can be related back to an imbalance between urate intake/production and excretion leading to urate accumulation and crystallisation in tissues. This creates the environment for innate immune system attack and the resultant acute inflammatory state and clinical manifestations.

2.1 Genetics

The vast majority of gout patients are under excreters of urinary urate compared to the normal population. Patients with gout have higher tubular reabsorption of urate (3, 4). This elevated reabsorption level is driven by genetic variation in urate transporters (5). The most significant genetic associations are *SLC2A9* (GLUT9) and *SLC22A12* (URAT1) with a large number of other genes, including numerous transporters, making smaller contributions. More recently discovered is the contribution of decreased function of the ABCG2 transporter in the gut contributing to hyperuricaemia (6). Genetic variation makes a substantial contribution to the variation seen in the prevalence of gout across different ethnic groups (7, 8).

Recent developments in gout genetics include the discovery of an association between reduced mitochondrial genetic copy number and gout (9). The nature of the link is currently unclear but may relate to innate immune system functioning. Multiple groups have also identified rare variants in genes encoding transporters such as *ABCG2*, *SLE22A1* and a gene encoding a member of the aldehyde dehydrogenase superfamily *ALDH16A1* associated with gout (10-12). The association with variants

in *ALDH16A1* is of note because the ALDH16A1 protein may interact with hypoxanthine-guanine phosphoribosyltransferase (HPRT1), a urate processing protein (13). HPRT1 deficiency causes Lesch-Nyhan Syndrome and urate accumulation (14). There has been a recent large Japanese genome wide association study (GWAS) which investigated genetic causes of hyperuricaemia. This study, along with others, helps define the non-European genetic associations with SU which are not as well investigated as European associations (15). The global gout genetics consortium has also planned a very large gout GWAS which will have power to detect a significant number of additional genetic associations. These recent discoveries are starting to build a more complex picture of the significant contribution that genetics makes to gout (16).

2.2 Environment Factors

The primary sources of urate are (1) dietary purines and foodstuffs that are converted into urate (eg. fructose), and (2) metabolism, from purine degradation (eg. cellular repair and replacement). Large epidemiological studies have demonstrated that intake of alcohol, sugar sweetened beverages and fructose, organ meat and seafood contribute to hyperuricaemia (17-19). However, it is worth noting that there is a lack of evidence from education and intervention trials that dietary limitation of these sources of urate makes a clinically meaningful impact on the management of established gout (20, 21). Patients may be able to achieve small reductions in SU with diet alone but these SU changes have not been shown to lead to sustained reductions in the frequency of gout flares. One illustrative trial provided dietary education twice to the intervention group and usual care to the control group and while there was improvement in knowledge and change in diet there was no change

is SU (20). A recent study examining the relative contributions of diet and genetics to SU levels in 17,000 participants found that consumption of 16 food items were associated with SU levels(2). Variation in consumption of these food items explained 3.3% of the SU variance whereas genetics explained 24% of SU variance. This combined simultaneous examination demonstrates how little diet contributes to SU variation.

Weight loss does lower SU substantially though (22). As an illustrative example of how weight loss can lower SU, a bariatric surgery study noted SU levels greater than 0.41mmol/L present in 83% of those with gout prior to surgery and 33% one year after operation (23). This is supported by the Mendelian randomisation evidence that fat mass directly increases SU (24, 25). These changes in SU are likely to translate into meaningful differences in clinical gout management (26).

There is extensive data about the impact of lifestyle and diet factors on the *incidence* of gout. A Health Professionals Follow-Up study cohort analysis over 26 years found that a diet with concordance with the Dietary Approaches to stop Hypertension (DASH) led to lower incident gout (27). This diet has higher fruits, nuts, legumes and vegetables and low-fat dairy products, and whole grains, and low intake of sodium, sweetened beverages, and red and processed meats did lead to lower incident gout. Bariatric surgery also makes a clinically meaningful difference to gout incidence with a large Swedish study of 1,982 obese patients and 1,999 obese controls finding an adjusted hazard ratio of 0.60 for gout incidence after surgery (28).

2.3 The transition from hyperuricaemia to gout

Only a proportion of patients with hyperuricaemia develop gout. Using the 2007 – 2008 United States National Health and Nutrition Examination Survey Choi and colleagues determined that the prevalence of gout was 5.9% and 2.0% in men and women respectively. However, the prevalence of hyperuricaemia was 21.2% and 21.6% in men and women respectively (29). Therefore only 28% of men and 9% of women in this cohort who are hyperuricaemic also had gout.

It is currently not clear what all the influences are that make a hyperuricaemic person develop gout, but the level of SU and the volume of urate crystals is potentially important. There is a strong relationship between level of SU and gout (30, 31). Imaging studies have demonstrated that the frequency and volume of urate crystals increases from the asymptomatic hyperuricaemic state to the clinically manifest gout state (32). Therefore, one explanation for the observed discrepancy between hyperuricaemia and gout would be that people who are hyperuricaemic are in the process of accumulating a crystal load that reaches a certain threshold to trigger gout. However, the discrepancy between those with raised SU and those with raised SU and gout is very large and variation in the functioning of the innate immune response to crystals may also potentially play a role. Supporting this theory is the finding from a study of weight loss after bariatric surgery where 20 participants went from a mean of 123 kg to a mean of 98kg. Significant reductions in white cell responses to monosodium urate crystals in respect to interleukin (IL)-1β, IL-8 and IL-6 were observed (33). This finding suggests that factors outside of the mere presence or volume of urate crystals play a role. In addition, two studies have found association between a critical component of the innate immune system and gout. The Toll-like receptor 4 variant rs2149356 has been found to be associated with

gout. However, the association was not found in all cohorts studied and needs further verification (34, 35). Finally, IgM antibodies that can bind monosodium urate crystals have been identified (36). These antibodies are able to promote urate crystallisation, so there is also potential involvement of the humoral immune system in the pathogenesis of gout.

Clinical studies of molecules that inhibit the innate immune response, for example canakinumab - a monoclonal IL-1 inhibitor, have already shown efficacy for treating and preventing gout flares (37). If further progress can be made in identifying the factors that turn a hyperuricaemic person into a patient with gout then this can provide fruitful opportunities to intervene to prevent this transition. The asymptomatic hyperuriciaemic person, with or without crystal deposition, has been included in a proposed staging system of gout, in part to “provide a rational basis for testing the potential role for screening of asymptomatic disease” (38).

3.0 Epidemiology

There is a steady increase in the prevalence of gout as men age with rates in elderly males well exceeding 10% in many cohorts (39, 40). Ethnicity also strongly influences gout prevalence with substantially higher prevalence rates of gout in groups like the New Zealand Maori, Pacific Islanders and Taiwanese. For example, in elderly New Zealand Maori the prevalence rate in males exceeds 40% (7). Gout prevalence in woman is much lower until the menopause due to oestrogen causing urate loss in the urine (41). It then rises substantially compared to pre-menopausal women but does not become as common as in elderly men, for example, the

prevalence in 80 year old New Zealand European women is around 7%, whereas in men it is around 17% (7).

4.0 Diagnosis

The majority of gout is diagnosed and managed in primary care. In this setting the diagnosis of gout is usually made on clinical grounds, considering the age, co-morbidities, symptoms, clinical signs and laboratory results. However, the gold standard of diagnosis is joint aspiration demonstrating monosodium urate crystals on microscopy. Due to practical issues the majority of patients do not have joint aspiration. This is often due to lack of skills, lack of a polarising light microscope or lack of time.

While clinical characteristics can be very helpful, they cannot be relied on exclusively. A study from the Netherlands examined 159 primary care patients presenting with acute 1st metatarsophalangeal (MTP) joint arthritis. It found a GP diagnosis of gout had a 0.99 sensitivity, 0.07 specificity, positive predictive value of 0.79 and negative predictive value of 0.75 (42). After 6 years of follow-up it was found that 77% had gout, 8% had another rheumatic disease and 15% had a transient unspecified monoarthritis. So 1st MTP arthritis is very likely to be gout, in around ¾ but in ¼ it is not. A diagnostic rule for the diagnosis of gout without an aspirate has been constructed and validated in both primary and secondary care, shown in Table 1 (43, 44). Classification criteria have also been constructed for research purposes, shown in Table 2. However, it is important to note these are designed for research use and not validated for clinical diagnostic use (45).

5.0 Co-morbidities

The co-morbidities of hypertension, chronic kidney disease (CKD), obesity and diabetes mellitus are common in gout patients (46, 47). CKD causes elevated SU. Many studies have demonstrated an association between gout and hypertension, diabetes and cardiovascular disease but there remains no convincing evidence that the presence of gout or raised SU contributes causally to these problems (48). Some animal evidence has found causal relationships between raised SU and disease, for example hypertension, but there remains a lack of consistent animal or human data to support this (49). There have also been interventional studies in humans with ULT with positive results, but the studies have been small and xanthine oxidase inhibitors also reduce systemic oxidative stress, so the exact mechanism by which the observed effects are occurring is unclear (50-52). Oxidative stress plays an important role in vascular endothelial dysfunction and reducing it through inhibiting the xanthine oxidase pathway has the potential to improve cardiovascular outcomes (53). In concert with this allopurinol initiation has been found to reduce death in a propensity score matched cohort study from the United Kingdom (54). Regardless of the causal nature of SU in co-morbidities the presence of them does mean that when gout is diagnosed then co-morbidities need to be considered and managed appropriately.

One of the major co-morbidities is CKD which presents challenges in the use of drugs to treat and prevent acute flares such as non-steroidal anti-inflammatories. CKD does also necessitate the slower up-titration of the urate lowering drug allopurinol. The Hande proposal to limit final allopurinol dose based on renal function has been replaced by the recommendation to start at an appropriate low dose and

cautiously up titrate the allopurinol dose until SU target has been met, see Table 3 (55, 56).

There have been recent proposals to group patients with gout based on their co-morbidities. Richette and colleagues used cluster analysis to identify five distinct clusters in a cohort of 2,763 French patients with gout (57). Cluster 1 had gout alone, cluster 2 had obesity, dyslipidaemia and hypertension, cluster 3 has 75% diabetes and dyslipidaemia, cluster 4 had pure dyslipidaemia and the cluster 5 had all those with heart disease, heart failure and renal failure. Roddy and colleagues have also identified co-morbidity clusters in gout patients (58). While these clusters have been observed, it remains to be seen how they relate to either pathophysiological processes or our approach to the clinical management of gout.

6.0 Management

6.1 Treatment principles

Guidelines suggest the commencement of urate lowering therapy when people with gout have more than one flare per year, see Table 4 (59). When treating gout with ULT it is important that the patient is aware that you are trying to deplete their body of urate crystal deposition. As such a long term, lifelong approach is required.

6.2 Patient Education

It is increasingly being recognised that patient education is an important part of gout management. If patients understand that gout is a chronic disease that requires long term therapy, then this may help with understanding the importance of adherence. A

British research group has shown that when education is used as part of a package of care then there is a high rate of reaching SU targets (92 - 95% at target at 12 months, and 95% at 24 months)(60, 61). There are some critical points about gout that it is important that patients understand and often education materials don't cover all of the important points (62). The first is that it is a chronic disease with flares, and not an episodic disease with attacks, the second is that it is often progressive, without treatment patients who experience a flare have a 63% chance of recurrence, in a mean of 3.5 years (63). So once started on ULT, the expectation is that this should continue lifelong to ensure gout flares don't recur.

6.3 Initiating urate lowering therapy

ULT is the core of effective gout management. The most common and recommended first line ULT is allopurinol (59, 64). The indications for initiating ULT are shown in Table 4. Historically it has been taught that ULT should not be commenced during an acute flare due to a perceived risk that the gout flare would be worsened. Two clinical trials including a total of 88 patients have now demonstrated that there is no difference in pain visual analogue scale outcome between anti-inflammatory treatment and combined anti-inflammatory and ULT treatment, see Figure 1 from the Taylor clinical trial (65, 66). This approach is also supported in the American College of Rheumatology guidelines (59). There is also evidence that patients who have ULT initiated during an acute gout flare are significantly more likely to reach their target serum urate earlier (67).

6.4 Treating serum urate to target

The effective treatment of gout revolves around the treatment of SU to target. The European League Against Rheumatism (EULAR) and the American College of Rheumatology's recommended SU target is less than 0.36mmol/L for non-tophaceous gout and less than 0.30mmol/L for tophaceous gout (59, 68). The British Society for rheumatology recommends a SU target of 0.30mmol/L for all patients with gout (69). These SU targets are, although different, all below the crystallisation point of urate at body temperature. The rationale for lower serum urate targets in those with tophaceous disease is that they have a higher crystal burden and the lower SU is the faster crystals will dissolve (70). Quality of care studies have shown that the minority of patients with gout are treated to target and therefore are unlikely to be free of symptoms (39).

6.4.1 Allopurinol

Allopurinol continues to be core therapy for urate lowering in gout. To reduce the risk of allopurinol hypersensitivity syndrome (AHS) it should be started at no more than 100mg per day and increased by 100mg every 2-5 weeks in those with renal function greater than 30mL/min. In those with renal function less than 30mL/min it is recommended to start at 50mg per day and increase slowly. Some authors recommend that a starting dose less than 100mg also be used in those in the 30 - 60mL/min renal function range (55). In those at higher risk of AHS then testing for the presence of the HLA-B*5801 allele is recommended (59). Patients with gout from Asian countries have a higher population prevalence of this allele compared to those of European descent, and those with renal impairment are also at increased risk (37). Universal screening for HLA-B*5801 is not recommended due to the low prevalence of the allele in European populations.

The treatment strategy of slowly up-titration of allopurinol to reach SUA target has been demonstrated to be safe and effective in a study from New Zealand (71-73). Although it needs to be noted that the prevalence AHS preclude definitive safety conclusions from clinical trials. The recommendations to take this approach are informed by a large case-control study that concluded that the relationship between renal function and allopurinol hypersensitivity was based on high starting doses of allopurinol, not on high maintenance doses (55). The mechanism relates to immune system tolerance to allopurinol (74).

6.4.2 Febuxostat

The introduction of febuxostat as a xanthine oxidase inhibitor for ULT was a significant step in gout therapeutics (75). At the time of registration it was noted that there were potentially concerning cardiovascular safety signals in the registration trials. As an example, in the APEX trial there were 11 cardiovascular events in the 670 febuxostat patients, 1 in the 268 allopurinol patients and 1 in the 134 placebo patients (76). Mandated safety trials were completed, and the US based trial has been published (CARES) with the European trial still pending (FAST, febuxostat versus allopurinol streamlined trial) and an additional Japanese trial in asymptomatic hyperuricaemia also ongoing ((FREED: febuxostat for cerebral and cardio-renovascular events prevention study) (64, 77, 78). The CARES study randomized 6,190 patients to allopurinol or febuxostat for a median of 32 months (79). The primary composite cardiovascular endpoint did not show a significant difference. However, death from any cause was increased in the febuxostat group with a hazard ratio of 1.22 (95% confidence interval (CI) 1.01 – 1.47) and there was also an

increase in cardiovascular death with a hazard ration of 1.34 (95% CI 1.03 – 1.73). The design of the trial does not allow conclusions relating to the absolute effect of febuxostat on risk of death, only the relative effect compared to allopurinol. The trial also had a high drop-out rate which may have introduced bias. The implications and possible explanations are discussed in this excellent review (64). These data now mean that consideration of this increase in death needs to be discussed with patients taking or contemplating taking ULT. As a result of these data it has now been recommended that febuxostat should not be used as first line ULT (64).

6.4.3 Probenecid

Probenecid is a uricosuric drug that promotes urate wasting in the urine. It should be avoided in those with kidney stones, or those with elevated urinary uric acid, namely fractional excretion of uric acid > 6% or urinary uric acid excretion > 700 mg/day/1.73 m^2 (80). The procedure for measuring spot fractional excretion of urate simply requires simultaneous collection of urine and plasma creatinine and urate, and then taking the product of the urinary creatinine and the plasma urate and dividing by the product of the plasma creatinine and the urinary urate (81). Probenecid is often used second line or as add on therapy to a xanthine oxidase inhibitor for ULT. It has historically been felt to not be effective in those with reduced renal function but recent case series data has suggested it is as effective in those with GFR < 50ml/min as it is in those with a GFR > 50mL/min (82).

6.4.4 Lesinurad

Lesinurad is a newly launched uricosuric agent. It is available in a 200mg daily dose. The dose of 400mg was also extensively tested in clinical trials but primarily due to

renal adverse events this was not registered in the United States (83). It is recommended that it be taken with a xanthine oxidase inhibitor to reduce the risk of renal adverse events. It is available in a combination tablet with 200mg lesinurad and 300mg allopurinol. It is currently unclear where it will sit in treatment algorithms. However, based on currently available information, in contrast to probenecid, lesinurad has fewer drug-drug interactions, but this position may change as it is used more widely in clinical practice.

6.5 Prophylaxis of acute flares while serum urate is being lowered

One of the challenges in managing gout is the successful introduction of urate lowering therapy. It is a well-recognised phenomenon that the introduction of SU lowering agents can cause gout to flare. This is thought to be due to ‘mobilisation’ of crystals, although the exact mechanism is not understood. All major guidelines recommend flare prophylaxis with colchicine or non-steroidal anti-inflammatory agents (68, 69, 84). Flares can extend for an extended period of time after SU target has been reached. Patients in the trial of nurse-led therapy had a mean of 1.5 gout flares even though 95% had been at or below their SU target for a year (61).

6.6 Asymptomatic hyperuricaemia

There is currently no indication for the treatment of asymptomatic hyperuricaemia and it is not recommended by any management guideline. By definition the patient does not have any symptoms of gout and the only abnormality is a raised SU on pathology testing. This does not represent a disease and there is no evidence that treatment in this group is either effective or safe. Although the level of SU is

correlated to the risk of developing gout, only around 20 – 25% of people with raised SU develop gout (29).

6.7 Patient Follow-Up

Once a patient with gout has reached their serum urate target it is not uncommon for them to continue to experience flares for extended periods. In the FOCUS study of febuxostat it was over 4 years before patients completely stopped experiencing flares (85). Other groups have found similar results (61, 63). The American College of Rheumatology has recommended that patients have a SU test every 6 months after target SU is achieved (59). This has been shown to be a cost-effective intervention based on assumptions regarding increases in medication adherence, and reductions in the cost of flare treatment (86).

7.0 Summary

There has been substantial progress in the strategies for the clinical management of gout, including a safer strategy for commencing allopurinol, a greater emphasis on prophylaxis of acute gout flares whilst commencing ULT and a strong focus on treating SU to target for effective gout management. This all demonstrates significant progress in managing this long neglected disease which has a huge impact on patients. There remains a number of important unanswered questions in the field, including what the optimal SUA target is and the safety of lowering SU very low (87-89). There are also proposals for different approaches to management, including the 'oncology' approach of induction therapy with rapid crystal depletion with intravenous uricase therapy and then maintenance therapy with oral agents. It remains to be seen whether these proposed approaches prove safe and effective.

Contributors

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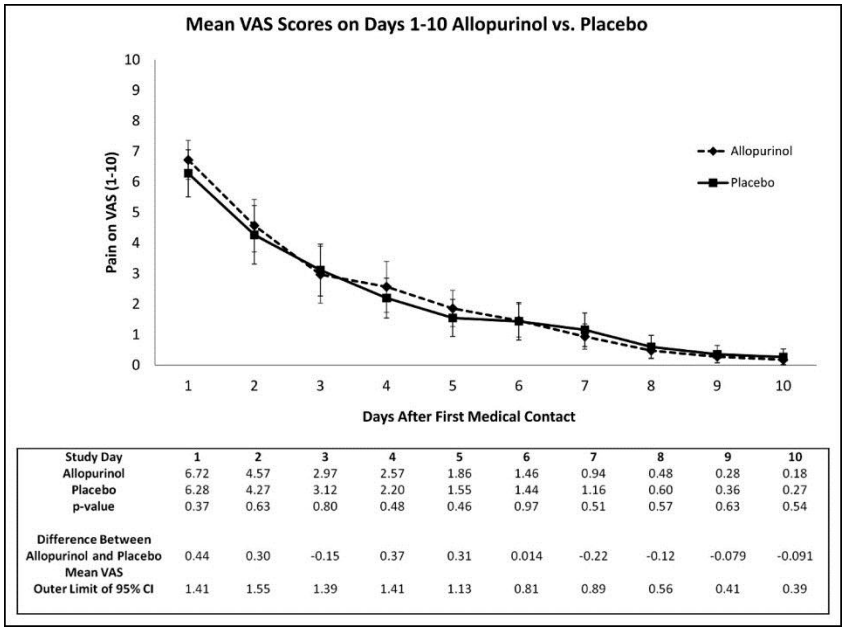
Figures

Fig 1



Study Day	1	2	3	4	5	6	7	8	9	10
Allopurinol	6.72	4.57	2.97	2.57	1.86	1.46	0.94	0.48	0.28	0.18
Placebo	6.28	4.27	3.12	2.20	1.55	1.44	1.16	0.60	0.36	0.27
p-value	0.37	0.63	0.80	0.48	0.46	0.97	0.51	0.57	0.63	0.54
Difference Between Allopurinol and Placebo Mean VAS	0.44	0.30	-0.15	0.37	0.31	0.014	-0.22	-0.12	-0.079	-0.091
Outer Limit of 95% CI	1.41	1.55	1.39	1.41	1.13	0.81	0.89	0.56	0.41	0.39

Table 1: Janssens/Kienhorst validated diagnostic rule for diagnosis of gout (1, 2)

Parameter	Score
Male Sex	2
Previous patient-reported arthritis attack	2
Onset within 1 day	0.5
Joint redness	1
MTPJ1 involvement	2.5
Hypertension or ≥1 cardiovascular diseases*	1.5
Serum uric acid level > 5.88 mg/dL / 0.35mmol/L	3.5

Score ≤ 4 = Very low likelihood of gout (95 - 97.2% non-gout); Score > 4 & < 8 = Diagnosis uncertain, obtain joint aspirate; Score ≥ 8 = High likelihood of gout (80 – 87% gout)

MTPJ1, first metatarsophalangeal joint
*Angina pectoris, myocardial infarction, heart failure, cerebrovascular accident, transient ischemic attack, or peripheral vascular disease

1. Janssens HJ, Fransen J, van de Lisdonk EH, van Riel PL, van Weel C, Janssen M. A diagnostic rule for acute gouty arthritis in primary care without joint fluid analysis. Arch Intern Med. 2010;170(13):1120-6.
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Table 2: ACR/EULAR 2015 Gout Classification Criteria (1)

Criteria	Category	Score

Pattern of joint/bursa involvement during symptomatic episode(s) ever	Ankle or midfoot (as part of monoarticular or oligoarticular episode without involvement of the first metatarsophalangeal joint)	1
	Involvement of the first metatarsophalangeal joint (as part of monoarticular or oligoarticular episode)	2
Characteristics of symptomatic episode(s) ever - Erythema overlying affected joint (patient- reported or physician-observed) - Can't bear touch or pressure to affected joint - Great difficulty with walking or inability to use affected joint	One characteristic	1
	Two characteristics	2
	Three characteristics	3
Time course of episode(s) ever: Presence (ever) of ≥2, irrespective of anti-inflammatory treatment: -Time to maximal pain <24 hours -Resolution of symptoms in ≤14 days -Complete resolution (to baseline level) between symptomatic episodes	One typical episode	1
	Recurrent typical episodes	2
Clinical evidence of tophus - Draining or chalk-like subcutaneous nodule under transparent skin, often with overlying vascularity, located in typical locations: joints, ears, olecranon bursae, finger pads, tendons (e.g., Achilles)	Present	4
Serum urate: Measured by uricase method. Ideally should be scored at a time when the patient was not receiving urate-lowering treatment and it was 4 weeks from the start of an episode (i.e., during intercritical period); if practicable, retest under those conditions. The highest value irrespective of timing should be scored	<4 mg/dl (<0.24 mmol/litre)	-4
	6–≤8 mg/dl (0.36–≤0.48 mmol/litre)	2
	8–≤10 mg/dl (0.48–≤0.60 mmol/litre)	3

	>10 mg/dl (0.60 mmol/litre)	4
Synovial fluid analysis of a symptomatic (ever) joint or bursa (should be assessed by a trained observer)	MSU negative	-2
Imaging evidence of urate deposition in symptomatic (ever) joint or bursa: ultrasound evidence of double-contour sign or DECT demonstrating urate deposition	Present (either modality)	4
Imaging evidence of gout-related joint damage: conventional radiography of the hands and/or feet demonstrates at least 1 erosion	Present	4

Entry criterion: At least 1 episode of swelling, pain, or tenderness in a peripheral joint or bursa. Sufficient criterion: Presence of MSU crystals in a symptomatic joint or bursa (i.e., in synovial fluid) or tophus. If Entry criteria met and sufficient criteria not met then can apply the above classification criteria. If the patient has a score ≥8 then they can be classified as having gout with a sensitivity of 92% and specificity of 89%.

ACR: American College of Rheumatology; EULAR European League Against Rheumatism; DECT Dual energy computed tomography

1. Neogi T, Jansen TL, Dalbeth N, Fransen J, Schumacher HR, Berendsen D, et al. 2015 Gout classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2015;74(10):1789-98.

Table 3: American College of Rheumatology Guidelines Recommended Allopurinol Up-titration regime(1)

	GFR > 30mL/min	GFR < 30mL/min
Starting dose	100mg	50mg
Up-titration dose	100mg	50mg
Up-titration interval	2 - 5 weeks	2 - 5 weeks

1. Khanna D, Fitzgerald JD, Khanna PP, Bae S, Singh MK, Neogi T, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res (Hoboken). 2012;64(10):1431-46.

Table 4 American College of Rheumatology indications for commencing urate lowering therapy (1)

1. CKD stage 2 or worse
2. Tophus or tophi by clinical examination or imaging study
3. Previous or current kidney stones
4. More than 1 gout flare per year

1. Khanna D, Fitzgerald JD, Khanna PP, Bae S, Singh MK, Neogi T, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res (Hoboken). 2012;64(10):1431-46.