Gout

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Gout is a chronic disease of deposition of monosodium urate crystals, which form in the presence of increased urate concentrations. Although environmental factors contribute to hyperuricaemia, renal and gut excretion of urate is central to regulation of serum urate, and genetic factors are important. Activation of the NLRP3 inflammasome and release of interleukin 1β have key roles in initiation of acute gout flares. A "treat to target serum urate" approach is essential for effective gout management; long-term lowering of serum urate to less than 360 μmol/L leads to crystal dissolution and ultimately to suppression of flares. An allopurinol dose-escalation strategy is frequently effective for achieving treatment targets, and several new urate-lowering drugs are also available. Worldwide, rates of initiation and continuation of urate-lowering therapy are very low, and, consequently, achievement of serum urate targets is infrequent. Strategies to improve quality of gout care are needed.

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Introduction

Gout is a common and treatable form of inflammatory arthritis that affects almost 4% of adults in the USA.[1] The central pathological feature of gout is chronic deposition of monosodium urate crystals, which form in the presence of increased urate concentrations.[2] The clinical features of gout occur as a result of the inflammatory response to monosodium urate crystals, and treatment strategies that achieve crystal dissolution are central to effective gout management.[3] In the past decade, major progress has been made in understanding of the pathogenesis, impact, diagnostic approaches to, and treatment of this disorder. In this Seminar, we provide a summary of these advances with a focus on clinical management of gout.

Pathophysiology

Hyperuricaemia

The progression of gout can be defined by four pathophysiological stages: hyperuricaemia without evidence of monosodium urate crystal deposition or gout, crystal deposition without symptomatic gout, crystal deposition with acute gout flares, and advanced gout characterised by tophi, chronic gouty arthritis, and radiographic erosions.[4] Progression from one stage to the next is not inevitable.

Pathological hyperuricaemia has been defined as the serum urate concentration (408 μmol/L [6·8 mg/dL]) above which monosodium urate crystals form in vitro at physiological pH and temperature.[5] Hyperuricaemia can occur as a result of overproduction from hepatic metabolism and cell turnover, or renal underexcretion or extra-renal underexcretion, or both (figure 1).[6] Underexcretion is the dominant cause of hyperuricaemia in patients with gout.[7] Renal excretion accounts for around two-thirds of urate excretion; gut excretion accounts for the remainder.[8] Secretion and reabsorption coexist along the length of the proximal renal tubule, with roughly 10% of urate that is initially filtered eventually being excreted.[8] This process is controlled by a suite of apically and basolaterally expressed secretory and reabsorptive molecules, some of which are targets of urate-lowering drugs.[8] These molecules can be grouped into reabsorptive urate-anion exchangers (URAT1/SLC22A12, OAT4/SLC22A11, OAT10/SLC22A3), the reabsorptive GLUT9/SLC2A9 urate transporter, secretory anion-exchange transporters (OAT1, OAT2, OAT3) and sodium-phosphate transporter proteins (NPT1/SLC17A1 and NPT4/SLC17A3), and the ATP-driven secretory efflux pump MRP4/ABCC4. In the gut, the secretory transporter ABCG2 is important, with reduced functioning contributing to extra-renal underexcretion and causing a compensatory increase in urinary urate output.[6]

Monosodium urate crystal formation

Monosodium urate crystals form in some individuals with hyperuricaemia (figure 2). Factors controlling crystal formation are poorly understood, but those affecting urate solubility, such as temperature, pH, salt concentration, and cartilage matrix components, might contribute to the process.[11] In peripheral joints with lower tissue pH and temperature, monosodium urate crystallisation can occur at urate concentrations lower than 408 μmol/L—eg, at 35°C, in-vitro crystallisation occurs at 360 μmol/L.[5] Nucleation occurs when monosodium urate molecules have clustered and reached a critical stable mass and are no longer susceptible to dissolution within the solvent. Urate concentration is important, and factors in serum or synovial fluid affect the rate of formation, shape, and size of monosodium urate crystals.[12]

Search strategy and selection criteria

We searched the Cochrane Library and MEDLINE with the term "gout" for articles published in English between Aug 1, 2010, and Jan 31, 2016. We largely selected publications from the past 5 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Review articles and book chapters are cited to provide readers with more details and more references than this Seminar has room for. Our reference list was modified on the basis of comments from peer reviewers.

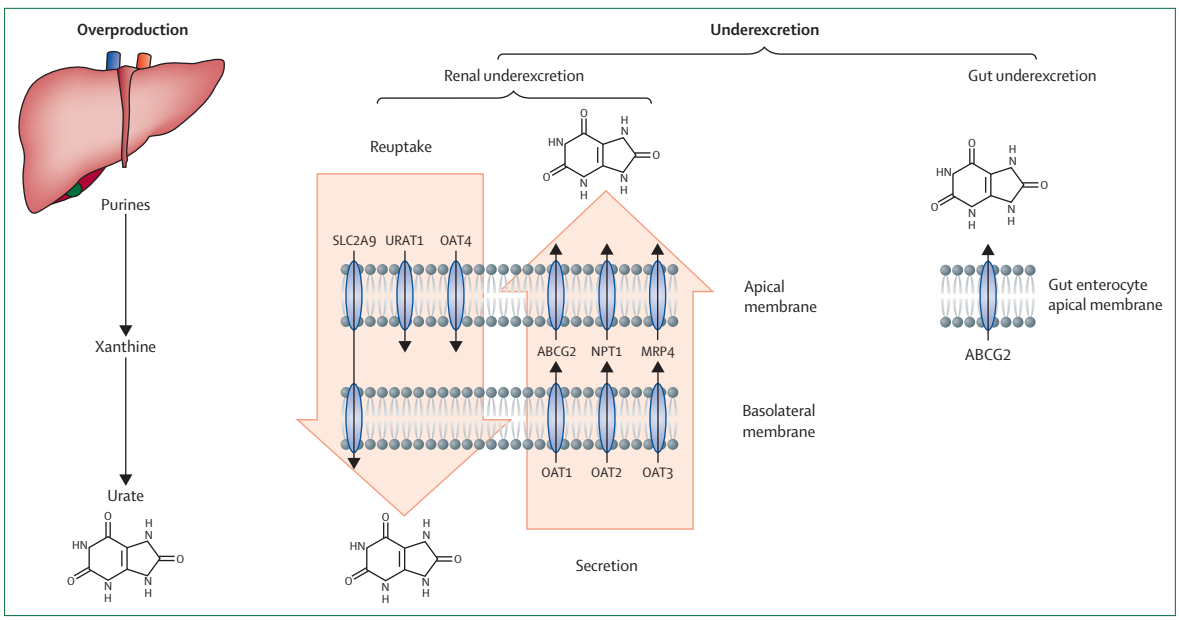

Figure 1: **Mechanisms of hyperuricaemia**
On the left, overproduction of urate through the purine degradation pathway is a minor contributor to serum urate concentrations. Underexcretion of urate is the dominant cause of hyperuricaemia in people with gout. In the centre, major components of the renal proximal tubule urate transportasome are clustered according to their role as reuptake transporters of urate from filtered urine or as secretory transporters. On the right, in the gut, variants in ABCG2 with reduced function block excretion and contribute to under-excretion.

Acute inflammatory response (flares)

Some people with intra-articular depositions of monosodium urate crystals develop an acute inflammatory response, manifesting as acute gout flares. This response is initiated when monosodium urate crystals interact with resident macrophages to form and activate the NLRP3 inflammasome (figure 2).[13] This process is promoted by microtubule-driven spatial co-localisation with mitochondria, involving α-tubulin acetylation.[14] Caspase 1, which is recruited by the activated inflammasome, processes pro-interleukin 1β into mature interleukin 1β.[13] In addition to monosodium urate crystals, another signal is needed for production of interleukin 1β (eg, long-chain free fatty acids).[15] The inflammatory response is amplified by activation of neutrophils and mast cells, leading to the release of a host of pro-inflammatory cytokines, chemokines, and other factors such as reactive oxygen species, prostaglandin E_2, and lysosomal enzymes.[16] In addition to the induction of anti-inflammatory cytokines and lipid mediators, the resolution phase of acute gouty inflammation is mediated by aggregated neutrophil extracellular trap structures.[17]

Advanced gout

In the absence of urate-lowering therapy, advanced gout typically occurs more than 10 years after initial presentation with an acute flare.[18] The tophus is the pathognomonic feature of advanced gout (figure 2). It is an organised chronic inflammatory granulomatous response to monosodium urate crystals that involves both innate and adaptive immune cells.[9] Pro-inflammatory cytokines such as interleukin 1β and tumour necrosis factor α and the anti-inflammatory transforming growth factor β1 are coexpressed in the tophus, suggesting a state of chronic monosodium urate-crystal-stimulated inflammation and attempted resolution.[9] Aggregated neutrophil extracellular traps might also have a role in tophus formation by organising monosodium urate crystals in a non-inflammatory state and developing the crystal core.[17] Infiltration of tophi into bone seems to be the dominant mechanism for bone erosion and joint damage in gout.[19]

Epidemiology

Incidence and prevalence

In UK and US studies, the incidence of gout varies from 0·30 per 1000 person-years in the 1970s, to 2·68 per 1000 person-years in the 2000s.[20] In western developed countries, contemporary prevalence of gout is 3–6% in men and 1–2% in women.[20] Prevalence steadily increases with age, but plateaus after 70 years of age.[20] Lower prevalences have been reported in developing countries—typically less than 1%.[20,21] Differences in health-care systems or case ascertainment might account for some of these differences. There are fewer incidence studies, although these findings reflect prevalence—ie, incidence seems two to six times higher in men than in women and plateaus after 70 years of age.[20] Some ethnic groups, such as the Taiwanese Aborigines and Māori and Pacific Islanders living in New Zealand have a prevalence more than two times greater than that of other ethnic groups.[20,22] The results of studies with consistent methods of case ascertainment seem to suggest that gout

prevalence is increasing. The US National Health and Nutrition Examination Survey showed a prevalence of 2·9% in 1988–1994, and 3·9% in 2007–08;[1] the UK Clinical Practice Research Database generated prevalence estimates of 1·4% in 1999, and 2·5% in 2012.[23,24]

Comorbid disorders

Comorbidities are common in patients with gout. According to the 2007–08 National Health and Nutrition Examination Survey data, 74% of participants with gout also had hypertension, 71% had stage 2 or greater chronic kidney disease, 53% were obese, 26% had diabetes, 14% had a history of myocardial infarction, and 10% had a history of stroke.[25] Furthermore, large prospective studies have shown that gout is associated with increased risk of death, primarily due to cardiovascular disease.[26] The cause–effect relation between comorbid disorders is difficult to assess because of the confounding inherent in observational epidemiology. Mendelian randomisation studies, in which genetic markers are used as unconfounded risk exposures, show that increased body-mass index is causally associated with increased urate, but that the reverse is not true.[27,28] Although mendelian randomisation studies show that serum urate concentrations are causally associated with gout,[29] no consistent evidence from these analyses shows a causal association between increased serum urate concentrations and coronary heart disease,[28–30] reduced kidney function,[31] hypertension,[28] or type 2 diabetes.[29,32] There is, however, some evidence that hyperuricaemia might causally contribute to worse outcomes in cardiovascular and kidney disease.[33–35]

Gout is associated with reduced risk of neurological disorders such as Parkinson's disease,[36] Alzheimer's disease,[37] and both vascular and non-vascular dementia.[38] Urate concentrations are inversely associated with Parkinson's disease.[39] Although the cause–effect relationship is yet to be established between urate and neurological disorders, these data might suggest that extracellular urate has neuroprotective or antioxidant properties.[40]

Non-genetic risk factors

Both non-genetic and inherited genetic risk factors can contribute to progression through the pathophysiological stages of gout. Hyperuricaemia is the central risk factor for development of gout,[41,42] and most risk factors identified for gout are also risk factors for increased urate concentrations (panel 1). Increasing age, male sex, and ethnic origin are key risk factors for hyperuricaemia and developing gout.[20]

Long-established dietary risk factors associated with increased urate concentrations and risk of developing gout are alcohol, red meat, and seafood.[43] Consumption of alcohol and red meat is associated with recurrent gout flares in case-control crossover studies.[44,45] More recently, consumption of sugar-sweetened beverages has been

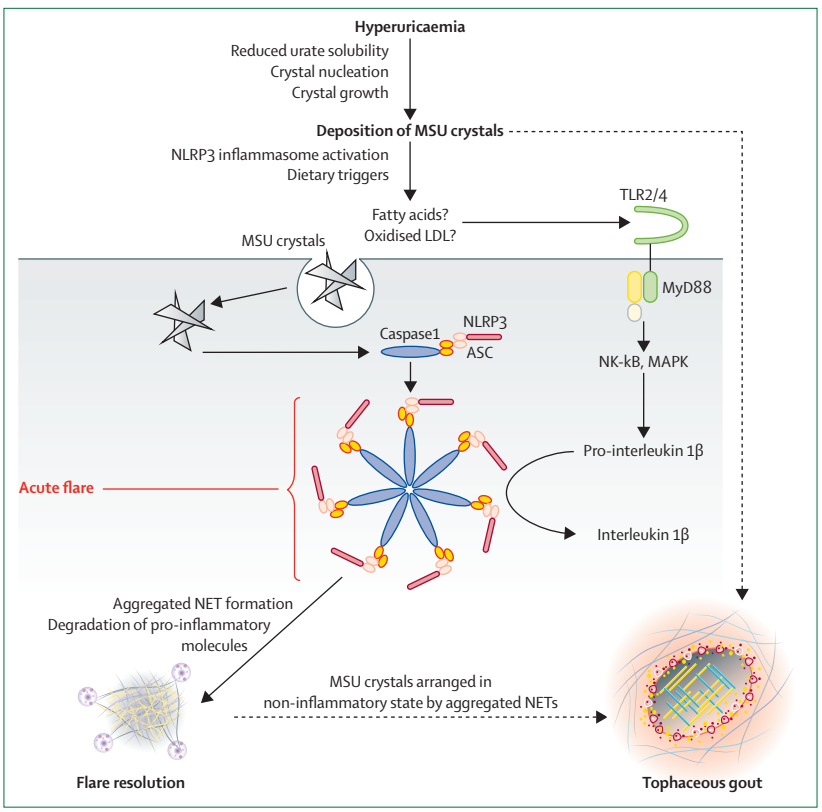

Figure 2: **Checkpoints in the progression from hyperuricaemia to the clinical manifestations of gout**
Factors controlling deposition of MSU crystals are not well understood. The acute flare results from production of mature interleukin 1β after activation of the NLRP3 inflammasome that occurs after ingestion of crystals by monocytes which in humans requires a second signal through TLRs. Flare resolution involves NETs, which bind MSU crystals (depicted in yellow). The NETs probably contribute to the formation of tophi. Images modified from Dalbeth et al,[9] and Czegley et al.[10] MSU=monosodium urate. LDL=low-density lipoprotein. ASC=apoptosis-associated speck-like protein containing a caspase recruitment domain. MAPK=mitogen-activated protein kinase. NET=neutrophil extracellular trap. TLR=toll-like receptor.

associated with increased urate concentrations and increased risk of gout.[46–49] Other less widely replicated links are the association between tomato consumption and increased urate concentrations, and between coffee and dairy consumption and reduced urate concentrations and risk of gout.[50–53] The pathogenetic mechanisms by which these foods affect the risk of gout are largely unclear, although ingestion of alcohol and fructose (a constituent sugar within sugar-sweetened beverages) rapidly increases serum urate by generation of urate through hepatic metabolism,[54,55] and increased lactic acid from alcohol consumption inhibits renal urate excretion[56] via trans-stimulation of URAT1.[57]

Serum urate concentrations and gout incidence increase after the menopause and are reduced by use of hormone replacement therapy.[58,59] Diuretic use is an important risk factor for hyperuricaemia and development of gout.[60] However, this association could be confounded by the comorbid association between gout and disorders that are the main indications for diuretic use, such as hypertension and heart disease.[61] Other comorbid disorders are also associated with the development of

***Panel 1*: Risk factors for development of gout**

Genetic*
- Male sex
- Ancestry
- *SLC2A9*
- *ABCG2*
- *SLC17A1*/*SLC17A3*
- *GCKR*

Drugs
- Diuretics
- Cyclosporin
- Tacrolimus
- Angiotensin-converting-enzyme inhibitors
- Non-losartan angiotensin II receptor blockers
- β blockers
- Pyrazinamide
- Ritonavir

Dietary
- Red meat
- Seafood
- Beer
- Spirits
- Sugar-sweetened beverages

Other
- Increasing age
- Menopause
- Chronic kidney disease
- Overweight, obesity, or weight gain
- Hypertension
- Hyperlipidaemia
- Hypertriglyceridaemia
- Congestive cardiac failure
- Obstructive sleep apnoea
- Anaemia
- Psoriasis
- Sickle cell anaemia
- Haematological malignancy
- Lead exposure

*Genes consistently associated with gout in various population groups are listed. All risk variants listed have odds ratios greater than 1·4.

gout: population-based prospective studies have established an association between risk of incident gout and chronic kidney disease,[62] and a dose-dependent relationship with increasing body-mass index.[63] Although type 2 diabetes is positively associated with prevalent gout, it is protective of incident gout; the uricosuric effects of glycosuria could explain this observation.[64]

Genetic risk factors

Gout is a complex disorder caused by the impact of environmental factors on a complement of inherited genetic risk variants. Genome-wide association studies (GWAS) survey common (>1–2%) genetic variations for associations with phenotypes. A GWAS involving more than 140 000 participants of European ancestry identified 28 genetic loci that affect serum urate concentations.[65] The two most prominent loci are those encoding urate transporters SLC2A9 and ABCG2, collectively explaining 3–4% of variance in serum urate; sex-specific effects (*SLC2A9* is stronger in women, and *ABCG2* in men) and harbouring of several genetic variants that control serum urate concentrations were noted. A second tier of loci is dominated by genes encoding urate transporters (*SLC22A11, SLC22A12, SLC17A1, SLC17A3*), with variations in the *GCKR* locus implicating glycolytic pathways. These loci emphasise the central role of kidney and gut urate handling in causing hyperuricaemia. The pathogenetic mechanisms controlled by a third tier of weaker effect (18 loci) are largely unclear, although network analysis has demonstrated an aggregate of genes involved in glucose metabolism. Collectively, the known 28 loci explain only 7% of variance in serum urate concentrations.[65] Predictably, most of the 28 loci that affect serum urate are associated with gout in several ancestral groups.[65–67]

GWAS with gout as an outcome are expected to identify loci controlling hyperuricaemia, formation of monosodium urate crystals, and inflammatory responses. However, few GWAS have been done, and those that have been done in patients with clinically-ascertained gout have been small (<3000 genome-wide typed participants); none has yet been done in Europeans.[68,69] The GWAS done in Chinese and Japanese samples identified several novel loci, although none contained genes with an obvious role in gouty inflammation.[68,69] Candidate gene studies have, however, provided evidence that genes involved in NLRP3 inflammasome activation and activity are causal in gout.[70,71] There are rare, clinically distinct forms of familial gout that are caused by defined mutations in genes involved in purine metabolism and renal urate handling.[72]

Clinical assessment and diagnosis

Presentation

Typically, gout presents for the first time as an acute episode of inflammation (flare) affecting the foot or ankle.[18] The first flare occurs after an asymptomatic period of hyperuricaemia. It is self-limiting during 1–2 weeks, with complete resolution in signs and symptoms of joint inflammation during the so-called intercritical period. If hyperuricaemia persists, recurrent flares can occur, which become increasingly frequent and prolonged and affect many joints (polyarticular flares), including joints of the upper limbs. When hyperuricaemia remains untreated, advanced gout with tophi or chronic gouty arthritis, or both, can develop in some individuals. Advanced gout is characterised by chronic joint pain, activity limitation, structural joint damage, and frequent flares.

Atypical presentations can occur, including early presentation of tophaceous disease without previous

flares.[73] Flares or tophi usually affect the peripheral joints, but can occur in atypical locations such as the eye, nose, spine, and viscera.[74]

Gout has an important effect on musculoskeletal function and health-related quality of life, particularly in patients with frequent flares and tophaceous disease.[75] Poorly controlled gout leads to absences from work, health-care use, and reduced social participation.[76] Comorbid disorders can further contribute to poor health-related quality of life in people with gout.[77]

Symptoms and signs

Gout flares present with symptoms of acute arthritis: pain, swelling, heat, redness, and difficulty moving the affected joint. A prodromal period of mild joint discomfort or tingling can be present before onset of severe pain that usually peaks within 24 h.[78] The maximum pain of a flare typically measures higher than 7 on a 0–10 scale, is throbbing or burning in nature, and is associated with extreme joint tenderness.[79] The most common site of involvement is the first metatarsophalangeal joint, although other sites in the foot and ankle are also commonly affected, which can cause difficulty with walking and other activities.[80] Flares often occur at night, with the patient waking from sleep with severe joint pain.[81] Triggers for flares include acute medical or surgical illness, dehydration, or dietary factors such as alcohol intake and purine-rich foods.[44,45,82] The patient might describe similar previous flares that have resolved entirely within 14 days.

Patients might describe subcutaneous nodules (tophi) in the hands, elbows, and feet. These lesions are typically pain free but can become acutely inflamed and, when severe, cause cosmetic concerns, difficulty finding suitable footwear, restriction of joint movement, and poor grip (if they are in the fingers).[83,84] There could be a history of discharging tophaceous (white, toothpaste-like) material from these nodules, or associated infection or ulceration.

Examination during a flare will show evidence of joint inflammation (synovitis), with pronounced tenderness, erythema, swelling, and warmth of the affected joint.[79] Bursitis or tendinitis can also occur. Features of systemic inflammation, including fever, might also be present, particularly in the presence of a polyarticular flare. As the flare resolves, skin peeling sometimes occurs over the affected joint. The tophus has the appearance of a "draining or chalk-like subcutaneous nodule under transparent skin, often with overlying vascularity".[85] Tophi most often occur over the first metatarsophalangeal joint, Achilles tendon, peroneal tendon, helix of the ear, olecranon bursa, and finger pad. Evidence of comorbid conditions, such as central obesity and hypertension, might be present on examination.

Diagnostic investigations

The gold standard for gout diagnosis is confirmation of monosodium urate crystals by polarising light microscopy of synovial fluid or tophaceous material. Crystals appear as negatively birefringent needle-shaped crystals, 1–20 µm in length (figure 3).[86] During an acute gout flare, synovial fluid appears yellow, cloudy, and non-viscous, with high numbers of white cells (sometimes >50 000 cells per mm³)—predominantly neutrophils. Although monosodium urate crystals are most often identified after aspiration of an acutely inflamed joint during a flare, these crystals are also frequently present in asymptomatic joints of hyperuricaemic patients with gout, particularly in joints that have been previously inflamed.[87]

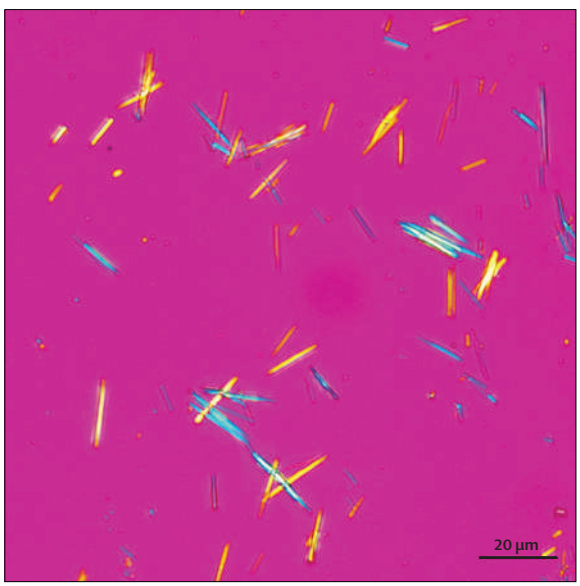

Figure 3: Monosodium urate crystals under polarising light microscopy

Serum urate testing is useful to assist with clinical diagnosis of gout in symptomatic individuals, but hyperuricaemia alone is not sufficient for diagnosis, because most people with hyperuricaemia do not have gout. Gout is unlikely in an individual with persistently low serum urate concentrations (less than 360 µmol/L).[79] Importantly, serum urate concentrations can fall into the normal range during an acute flare,[88] and if gout diagnosis is uncertain, serum urate should be retested after the flare has resolved.

Acute phase reactants, such as C-reactive protein, are usually increased during a flare—concentrations can be higher than 100 mg/L.[89] Neutrophil leucocytosis can also be present; however, these findings are non-specific and show the degree of systemic inflammation, rather than presence of gout. Laboratory tests contribute to assessment of comorbid disorders in patients with suspected or confirmed gout, including serum creatinine measurement for chronic kidney disease, lipid screening for dyslipidaemia, and HbA_{1c} or fasting glucose for type 2 diabetes.

Different imaging modalities are increasingly used to assist with the diagnosis of gout, particularly in situations when joint aspiration is not feasible. At the time of first presentation, radiographs are usually normal, except for

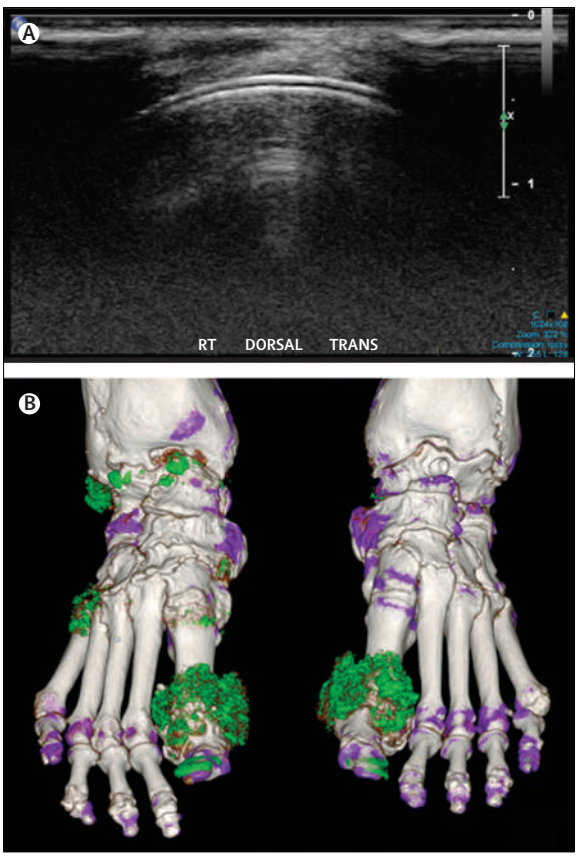

Figure 4: **Imaging features of monosodium urate crystal deposition**
The top image shows the double contour sign in the first metatarsophalangeal joint on ultrasonography (tranverse view of the dorsal surface of the joint), defined as hyperechoic enhancement over the surface of the hyaline cartilage. The bottom image shows a dual energy CT of a patient with tophaceous gout. Urate deposition (colour coded in green) can be seen at characteristic sites including the first metatarsophalangeal joint, midfoot, and ankle. Green signal at the nails of the big toes is an artifact commonly observed at this site.

	Odds ratio (95% CI)
Joint erythema	2·13 (1·06–4·29)
At least one episode involved difficulty walking	7·34 (1·17–46·06)
Time to maximum pain less than 24 h	1·32 (0·71–2·47)
Resolution by 2 weeks	3·58 (1·85–6·95)
Tophus	7·29 (2·42–21·99)
Involvement of first metatarsophalangeal joint at any time	2·30 (1·18–4·49)
Location of currently tender joints	2·82 (1·37–5·81) for first metatarsophalangeal joint; 2·28 (1·00–5·19) for other foot or ankle
Serum urate >360 µmol/L (6mg/dL)	3·35 (1·57–7·15)
Double contour sign on ultrasonography	7·23 (3·47–15·04)
Radiograph of erosion or cyst	2·49 (1·26–4·90)

These features were identified in a large international study of patients presenting to rheumatology clinics with possible gout and at least one swollen joint within 2 weeks of suspected tophus. Case definition of gout was identification of monosodium urate crystals by a certified observer. Reproduced with permission from Taylor et al, 2015.[79]

Table 1: **Key discriminating features of microscopically proven gout**

non-specific soft tissue swelling of the affected joint. Bone erosion on radiography is a feature of advanced gout and is characterised by a sclerotic rim and overhanging edge.[85] Ultrasonography might show features of monosodium urate crystal deposition, such as the double contour sign (hyperechoic enhancement over the surface of the hyaline cartilage; figure 4), which is thought to represent monosodium urate crystals overlying articular cartilage, tophi (hyperechoic inhomogeneous material surrounded by a small anechoic rim), and the snowstorm appearance of crystals within synovial fluid.[90,91] Dual energy CT is a method of CT imaging that, by analysing the difference in attenuation in a material exposed to two different x-ray spectrums, can identify and colour-code urate deposits in patients with gout (figure 4).[92] In a meta-analysis[93] of individuals presenting with joint swelling in which monosodium urate crystal confirmation was the gold standard, the double contour sign on ultrasonography had a pooled sensitivity of 0·83 and specificity of 0·76, and urate deposition on dual energy CT had sensitivity of 0·87 and specificity of 0·84. These imaging features are also present in around 25% of people with asymptomatic hyperuricaemia,[94,95] and whether such individuals are at higher risk of developing future symptomatic disease is unknown.

Differential diagnosis

Clinical diagnosis of gout requires synthesis of history, examination, laboratory, and, at times, imaging variables (table 1). The key differential diagnosis is septic arthritis (which can coexist with gout). Gram staining and culturing of synovial fluid is necessary to exclude septic arthritis. Other forms of inflammatory arthritis can mimic the clinical presentation of gout, including acute calcium pyrophosphate crystal arthritis, basic calcium phosphate crystal arthritis, psoriatic arthritis, and reactive arthritis.[79] Clinical assessment usually allows differentiation of gout from rheumatoid arthritis and osteoarthritis. A diagnostic rule has been developed to assist with diagnosis of gout in patients with monoarthritis in primary care;[96] this rule also works well in emergency departments and secondary care settings.[97,98]

Management of gout

Principles of management

Gout management includes rapid treatment of acute flares and effective long-term management (table 2).[3,99–101] The central strategy for long-term management is reduction of serum urate to a concentration that achieves dissolution of monosodium urate crystals. According to the 2012 American College of Rheumatology guidelines, urate-lowering therapy is indicated for those with recurrent gout flares (>1 flare a year), tophi, stage 2 or

worse chronic kidney disease, or kidney stones (table 2).[3] Urate-lowering therapy is not recommended for people with asymptomatic hyperuricaemia.[3] For people with gout commencing urate-lowering therapy, selection of a target serum urate concentration for the individual patient dependent on disease severity is important. The American College of Rheumatology guidelines recommend a target serum urate of less than 360 µmol/L (6 mg/dL) for all patients on urate-lowering therapy.[3] Prolonged lowering of serum urate concentrations to less than this cutoff leads to dissolution of monosodium urate crystals, suppression of flares, and regression of tophi.[102] A lower target of less than 300 µmol/L (5mg/dL) is recommended for patients with tophaceous or severe disease, as this concentration is associated with more rapid tophus regression.[103]

Traditionally, urate-lowering therapy has been commenced at least 2 weeks after an acute flare. However, two studies published in the past 5 years have shown that starting urate-lowering therapy during a gout flare does not prolong the flare, provided that the acute episode is adequately treated.[104,105] When indicated, urate-lowering therapy should be commenced and serum urate monitored frequently (eg, monthly), with dose titration until the chosen target urate concentration has been achieved. Once the target has been achieved, less frequent monitoring (eg, every 6 months) should continue to ensure that it is maintained.

Adherence to urate-lowering therapy is often poor (10–46% according to a 2014 systematic review).[106] Both patients and health-care practitioners frequently perceive that treatment is needed only for acute flares.[107] Patients' understanding of chronic deposition of monosodium urate crystals as the cause of gout and the rationale for long-term urate-lowering therapy is crucial to successful gout management.

Management of acute flares necessitates rapid and effective control of the inflammatory response to monosodium urate crystals, thereby reducing joint pain and swelling. Guidelines recommend a non-steroidal anti-inflammatory drug (NSAID), colchicine, or corticosteroids.[99–101] These drugs can be used alone or in combination for more severe flares. Topical application of ice to the affected joint reduces pain.[108] Patients' comorbidities and the potential for drug interactions should be considered carefully when selecting a drug. Therapy should be started as early as possible, and patients should have an action plan and supply of drugs to facilitate early treatment.

Gout flares can be precipitated by the introduction of intensive urate-lowering therapy and can continue to occur for many months after the target serum urate concentration has been achieved.[109] Careful education about this possibility and the use of anti-inflammatories to prevent flares in the early phase of urate-lowering therapy is crucial, because such flares frequently result in poor adherence.[99–101,107] Anti-inflammatory prophylaxis is recommended for at least 6 months from initiation of urate-lowering therapy.[101] Some patients with high serum urate concentrations might need prophylaxis for longer,[101] and the risks and benefits for the individual patient need to be considered.

	Recommendation
Indications for urate-lowering therapy	Established diagnosis of gout and either tophi (detected by physical examination or imaging), frequent acute gout flares (>1 per year), stage 2 chronic kidney disease or worse, or past urolithiasis
Target serum urate	<360 µmol/L (6 mg/dL) minimum; for severe or tophaceous disease, concentrations <300 µmol/L (5 mg/dL) might be necessary
Serum urate monitoring	Monthly until target serum urate achieved; 6 monthly thereafter to ensure maintenance of target
Drug treatment of acute flares	Non-steroidal anti-inflammatory drug, colchicine, or corticosteroid
Anti-inflammatory prophylaxis during initiation of urate-lowering therapy	Low dose colchicine or non-steroidal anti-inflammatory drug (third line: low dose corticosteroids) for at least 6 months, or until 3 months after achieving target serum urate if no tophi are present, or until 6 months after achieving target if tophi are present—whichever is greatest
Urate-lowering treatment options	Xanthine oxidase inhibitor (eg, allopurinol, febuxostat) are first line; uricosurics (eg, probenecid) are second line; uricases (eg, pegloticase) are third line if oral urate-lowering therapy is unsuccessful
Education	Patients should be educated about the rationale for long-term urate-lowering therapy and risk of flares during initiation of urate-lowering therapy, and be provided with an action plan for flare management and healthy lifestyle advice
Comorbidity screening	Type 2 diabetes, cardiovascular disease, hypertension, dyslipidaemia, chronic kidney disease, obesity, and obstructive sleep apnoea should be screened for

Based on the 2012 American College of Rheumatology gout management guidelines.[3,101]

Table 2: **Principles of gout management**

Lifestyle management, including weight loss and dietary modification, has been considered as a key component of gout management, although the evidence for benefit is scarce.[110,111] Weight loss has a weak urate-lowering effect;[112] bariatric surgery in patients with severe obesity could be more clinically significant.[113] Consumption of low fat dairy products has no significant effect on serum urate in patients with gout.[114] Supplemental vitamin C might lower serum urate concentrations in healthy people,[115] but in patients with gout its effect seems clinically ineffective.[116] Tart cherry concentrate has been suggested to lower serum urate and reduce flares but evidence is insufficient to support routine use.[117] Dietary modification is extremely difficult to maintain, and even with comprehensive dietary education, there is little effect on serum urate concentrations.[118] In view of the high prevalence of comorbidities, patients with gout should be screened for these disorders, which, if present, should be treated appropriately (table 2).[3,99,100]

Urate-lowering drugs

An increasing number of urate-lowering drugs are available. There are three main classes (table 3): drugs that inhibit urate production (xanthine oxidase inhibitors), such as allopurinol and febuxostat; drugs that normalise renal urate excretion (uricosurics), including probenecid, benzbromarone, and the newer URAT1 inhibitor lesinurad; and drugs that catalyse the

conversion of urate to the more water soluble and readily excretable allantoin (recombinant uricases), such as pegloticase and rasburicase.

A xanthine oxidase inhibitor, usually allopurinol, is given as first-line therapy.[3] Allopurinol is rapidly metabolised to its active metabolite, oxypurinol, which is cleared by the kidney. Although head-to-head studies have shown that febuxostat is more effective than allopurinol, these studies have all been of fixed-dose allopurinol (maximum dose 300 mg daily), and higher doses have not been compared with febuxostat in clinical trials.[119,120] This restriction in allopurinol doses is a result of concerns about allopurinol hypersensitivity syndrome with higher doses, particularly in patients with kidney impairment. However, several factors contribute to the syndrome, including higher starting doses,[121] the presence of HLA-B*5801,[122] kidney impairment,[123] and concomitant use of diuretics.[124] The risk factors, mechanisms, and ways to minimise the risk of allopurinol hypersensitivity syndrome have been more extensively reviewed elsewhere.[125] The syndrome typically occurs within the first 8 weeks of therapy.[123] The starting dose of allopurinol could be important and the maximum starting dose of allopurinol is recommended

	Allopurinol	Febuxostat	Probenecid	Benzbromarone	Pegloticase
Mechanism of action	Xanthine oxidase inhibitor: prevents urate production	Xanthine oxidase inhibitor: prevents urate production	Increases renal urate excretion	Increases renal urate excretion	Recombinant uricase: breaks down urate to water-soluble allantoin
Metabolism and excretion	Metabolised by aldehyde oxidase to oxypurinol, which is excreted predominantly by the kidneys	Hepatic: conjugation by uridine diphosphate-glucuronosyltransferase enzymes and oxidation to active metabolites by CYP1A2, CYP2C8, and CYP2C9; excreted via the kidneys	Oxidation of alkyl side chains and glucuronide conjugation; excreted via kidneys	Hepatic metabolism by CYP2C9 and CYP1A2; mainly excreted in bile and faeces, 6% excreted via kidneys	Renal excretion
Contraindications	Hypersensitivity to allopurinol	Use with caution in heart failure and ischaemic heart disease	Blood dyscrasias, uric acid kidney stones	Liver disease, porphyria; use with caution in patients with excess alcohol intake and history of kidney stones	Glucose-6-phosphate dehydrogenase deficiency (risk of haemolysis and methaemoglobinaemia); repeated infusion contraindicated if serum urate response is lost
Clinically important drug interactions	Azathioprine increases 6-mercaptopurine concentrations, resulting in myelosuppression; warfarin (increased anticoagulant effects); diuretics (possible increased risk of allopurinol hypersensitivity syndrome)	Azathioprine increases 6-mercaptopurine concentrations, resulting in myelosuppression	Aspirin; methotrexate (can increase methotrexate's toxic effects	Warfarin (increased anticoagulant effects); sulphonylureas—checkblood glucose Phenytoin Fluconazole—avoid combination Rifampicin—avoid combination	Other urate-lowering therapies can mask lack of response to pegloticase and thereby increase risk of infusion reaction; other PEGylated drugs
Dosing	50–900 mg daily (maximum of 800 mg approved by US FDA), which should be titrated to achieve target serum urate*	40–120 mg daily (maximum of 80 mg approved by US FDA), which should be titrated to achieve target serum urate	500–1000 mg twice a day	50–200 mg daily	8 mg intravenous infusion every 2 weeks
Important side-effects	Gout flares when initiating treatment, rash, allopurinol hypersensitivity syndrome	Gout flares when initiating treatment, abnormal liver function tests	Gout flares when initiating treatment, kidney uric acid stones	Gout flares when initiating treatment, hepatotoxic effects, kidney uric acid stones	Gout flares when initiating treatment, infusion reactions, immunogenic effects
Monitoring	Serum urate, renal and liver function	Serum urate, renal and liver function	Serum urate, renal function	Serum urate, liver function	Serum urate (loss of serum urate response precedes infusion reactions)
Special considerations	Dose escalation above renal based doses and above 300 mg daily to achieve target serum urate can be done with appropriate monitoring of renal and liver function and education about rash	Hypersensitivity might occur rarely in patients with prior allopurinol hypersensitivity	Advise about high fluid intake and consider urine alkalinisation to reduce risk of kidney stones	Advise about high fluid intake and consider urine alkalinisation to reduce risk of kidney stones	Should not be used with other urate-lowering therapies
Anti-inflammatory prophylaxis when commencing drug	Yes	Yes	Yes	Yes	Yes

CYP=cytochrome P450. PEG=polyethylene glycol. FDA=Food and Drug Administration. *Starting dose based on estimated glomerular filtration rate (eGFR): <30 mL/min per 1·73 m^2—1·5 mg/mL eGFR; 30–60 mL/min per 1·73 m^2—50 mg daily; >60 mL/min per 1·73 m^2—100 mg daily. Dose escalation monthly until target serum urate is achieved. Increase in increments of 100 mg monthly if estimated glomerular filtration rate >60 mL/min per 1·73 m^2 and 50 mg monthly if <60 mL/min per 1·73 m^2.

***Table 3*: Prescribing and monitoring of urate-lowering drugs**

to be no higher than 100 mg daily (reduced to 50 mg daily in those with moderate-to-severe chronic kidney disease).[3] There is increasing evidence that, in patients who tolerate allopurinol, the dose can be safely increased to more than 300 mg per day with a treat to target serum urate approach, even in patients with kidney impairment.[126] Although larger studies about the safety of this approach are underway, the American College of Rheumatoloy recommendations support the start low, go slow treat to target approach with allopurinol, with appropriate monitoring.[3]

Febuxostat is predominantly metabolised in the liver and therefore dose reduction is not necessary in patients with mild-to-moderate kidney impairment. In patients with severe kidney impairment (ie, estimated glomerular filtration rate <30 mL/min per 1·73 m^2), data are more limited. A study[127] of 70 patients with stage 3b–5 chronic kidney disease without gout showed that 10 mg febuxostat daily increasing to 60 mg daily over 12 weeks was safe and effective in achieving target serum urate in 70% of patients. Febuxostat is less cost-effective as first-line therapy compared with allopurinol.[128]

The uricosurics are second-line urate-lowering therapy for patients who do not reach target serum urate concentrations with a xanthine oxidase inhibitor.[3] Probenecid is the first-line uricosuric, and can be used as monotherapy or in combination with a xanthine oxidase inhibitor. Although the traditional belief is that probenecid is not effective in patients with estimated glomerular filtration rates of less than 50 mL/min per 1·72 m², the drug can have moderate urate-lowering effects in this group.[129] Benzbromarone is a more potent uricosuric that can be effective in patients with impaired kidney function although efficacy reduces when estimated glomerular filtration rates are less than 30 mL/min per 1·72 m². However, benzbromarone has been associated with hepatotoxic effects and is not widely available. Lesinurad is a URAT1 inhibitor approved in the last year that has additional urate-lowering effects when used in combination with xanthine oxidase inhibitors.[130,131] Close monitoring of kidney function is necessary in patients treated with lesinurad.

Pegloticase, which is given as an intravenous infusion every 2 weeks, is typically reserved for patients with severe, refractory gout in whom target serum urate concentrations are not achieved or who cannot tolerate oral urate-lowering therapy. Pegloticase results in a profound reduction in serum urate, with rapid improvements in musculoskeletal function, health-related quality of life, pain, and tophus burden.[132] Infusion reactions occur in as many as 40% of patients, and are preceded by loss of urate-lowering effect.[132,133] High titres of antibodies, typically against the polyethylene glycol portion of pegloticase, are found in around 40% of patients and are associated with loss of response and increased risk of infusion reactions.[134]

Treatment of acute flares

Although colchicine has been used for many years, it has been studied in only two randomised controlled trials for acute gout flares.[135,136] Low dose colchicine commenced within 12 h of a flare (1·2 mg immediately followed by 0·6 mg after 1 h) is as effective as high dose (1·2 mg immediately followed by 0·6 mg hourly for 6 h) and is associated with substantially fewer adverse effects, particularly gastrointestinal adverse effects.[136] Thus, low dose colchicine is the preferred option. The dose of colchicine should be further reduced in patients with kidney impairment and those receiving cytochrome P450 3A4 inhibitors (eg, diltiazem, verapamil, clarithromycin) or p-glycoprotein inhibitors (eg, ciclosporin).[137] Colchicine should also be used with caution in those with liver disease or taking statins.

NSAIDs are usually effective in acute flares, although might be contraindicated in patients with kidney impairment, cardiovascular disease, or a history of gastrointestinal disease. The selective cyclo-oxygenase 2 (COX2) inhibitors are as effective as traditional NSAIDs but are associated with fewer adverse effects, particularly gastrointestinal adverse effects.[138] In general, NSAIDs and selective COX2 inhibitors should be used at full dose for the shortest period.

For patients with several comorbidities, corticosteroids can be the most appropriate therapeutic option. When only one or two joints are involved, intra-articular corticosteroids can be effective. Oral prednisolone (35 mg daily) is as effective as 500 mg naproxen twice a day, with no noteworthy differences in adverse effects during 5 days of treatment.[139]

Adrenocorticotropic hormone acts via the melanocortin type 3 receptor to produce anti-inflammatory effects in gout.[140] In patients with several comorbidities who are admitted to hospital and in whom NSAIDs, colchicine, and corticosteroids are contraindicated, a single dose could be effective.[141] The interleukin 1 inhibitor canakinumab is safe and effective in acute gout flares,[142,143] and is approved by the European Medicines Authority for use in flares when other anti-inflammatory therapies are ineffective or contraindicated. The cost of this monoclonal antibody is substantially greater than that of other anti-inflammatory drugs used for acute gout flares.

Anti-inflammatory prophylaxis

0·5–0·6 mg colchicine once or twice a day is thought to be the first-line option for anti-inflammatory prophylaxis.[144,145] Although low-dose NSAIDs are frequently used and recommended as second-line agents for prophylaxis, there is a paucity of data. Low dose corticosteroids are reserved for patients with severe gout in whom colchicine and NSAIDs are contraindicated; no clinical trial data support this indication. Interleukin 1 inhibitors also effectively prevent acute gout flares during the initiation of urate-lowering therapy,[146,147] but are not currently approved for this indication.

***Panel 2*: Research questions in hyperuricaemia and gout**

- What are the molecular mechanisms of urate control identified by genome-wide association studies?
- In people with asymptomatic hyperuricaemia, does monosodium urate crystal deposition identified on ultrasound or dual energy CT increase the risk of developing symptomatic gout?
- Why do monosodium urate crystals form preferentially at certain sites?
- How do monosodium urate crystals deposit within the joint without inducing an acute flare?
- How do trigger foods precipitate an acute flare?
- Why do gout flares spontaneously resolve?
- Why do tophi form in some individuals?
- Do hyperuricaemia and gout causally contribute to comorbid disorders such as hypertension, chronic kidney disease, atherosclerosis, and metabolic syndrome?
- Should urate-lowering therapy be initiated earlier in the course of the disease (eg, in people with hyperuricaemia and asymptomatic deposits)?
- Does treatment of hyperuricaemia improve outcomes in comorbid disorders such as hypertension, chronic kidney disease, atherosclerosis, and metabolic syndrome?
- Is the serum urate target of 360 µmol/L low enough?
- Once people with gout have cleared monosodium urate crystals (ie, no flares or tophi), can a higher urate concentration be tolerated in the long term (using a remission induction–maintenance model of treatment)?
- Are there risks associated with very low serum urate concentrations?
- Can response be predicted to different urate-lowering therapies—eg, the chance of achieving target, risk of adverse effects?
- What is the role of complementary therapy in the management of gout?
- How can quality of care be improved for people with gout?

Controversies and uncertainties

Although the central cause of gout is well known and effective treatments are available, many uncertainties remain and understanding about pathogenesis is incomplete (panel 2). For example, why some individuals with hyperuricaemia develop monosodium urate crystal deposition and others do not is unknown. Why monosodium urate crystals preferentially deposit at specific sites and why deposited crystals can be present in the joint without clinically apparent inflammation is also unclear. The causal relations between hyperuricaemia and comorbid disorders such as hypertension, cardiovascular disease, and other features of metabolic syndrome are hotly debated.[148]

A further area of controversy is long-term urate-lowering therapy. At present, urate-lowering therapy is primarily recommended for patients with frequent flares or tophi.[3] The benefits of earlier initiation of urate-lowering therapy (including in individuals with hyperuricaemia and asymptomatic deposition of monosodium urate crystals) are unknown and will require careful analysis. Although the serum urate target of less than 360 µmol/L (6 mg/dL) is well established as the minimum required concentration for people with gout, whether lower targets are of benefit for all patients is unclear. Furthermore, the safety of long-term serum urate lowering to very low concentrations should be assessed carefully, particularly in view of the inverse association of serum urate and gout with neurological disorders such as Parkinson's disease.[36–39]

Despite the availability of effective urate-lowering therapies, globally gout management is poor, with very low rates of urate-lowering therapy initiation and continuation and achievement of serum urate targets.[149–151] Perhaps the most important question about gout management is how to improve long-term use of effective urate-lowering therapy. Optimum strategies that address both prescriber and patients' barriers remain an unmet need. Alternative models of care for people with gout, such as nursing-led or pharmacy-led approaches, show great promise to ensure understanding about the rationale for urate-lowering therapies, adequate dosing, and continuous supply.[152,153]

Conclusion

Despite major progress in the understanding of pathogenesis and therapeutic advances, the prevalence of gout is increasing and many patients have poorly controlled disease. Gout is a treatable disease and the strategy of long-term lowering of serum urate concentrations is highly effective in removing monosodium urate crystals. Implementation of this strategy necessitates focused attention to prevent the serious consequences of this disease.

Contributors

ND did the search of published work. All authors wrote the Seminar and approved the submitted version.

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