The Year in Gout
2011-2012

Daria B. Crittenden, M.D., and Michael H. Pillinger, M.D.

Abstract

From an epidemiologic view, gout is an increasingly prevalent and increasingly pressing clinical problem. This fact, together with technical advances in biology, pharmacology, and imaging techniques, have led to a decade of increasingly rapid progress in our collective understanding of gout and hyperuricemia. Here we review some of the most important recent advances in gout over the past 12 to 18 months.

Our ability to understand and manage gout continues to advance. The past decade has seen progress in the basic biochemistry, cell biology, and pathophysiologic mechanisms of gout; a deeper epidemiologic insight into the populations that suffer from gout; technological advances in imaging of gout patients; and tremendous strides into new ways of thinking about managing gout. What has led to this miniature “Golden Age?” Mainly, a fortuitous conjunction of ability and need; in particular, the recognition that gout is major disease, with potentially serious implications, along with the astonishing technical advancements that allow us to ask new biological questions and to study old biological questions in newer and more discerning ways. In this review, we highlight some of the more interesting accomplishments in the gout field over the past 12 months, focusing on some of the studies that are most interesting or important and putting these developments in the context of the evolving landscape of gout research. Our method is selective, not encyclopedic. For clarity, we will divide the presentation according to methodologies or areas of interest; it must be recognized, however, that these subjects are interrelated, and advances in each particular area would have been unlikely without the collegiality and collaboration evident across the community of gout investigators.

Epidemiology: Disease Presence and Burden

Work by Hyon Choi and his colleagues over the past decade has shed light on gout prevalence and incidence, the importance of nutrition on hyperuricemia and the risk for gouty attack, the burden of alcohol use in hyperuricemia and gout, and the potential role of hyperuricemia in the development of comorbid conditions. An important recent contribution from this group was a study using the National Health and Nutrition Examination Survey (NHANES), a large survey conducted roughly every 10 years by the Centers for Disease Control.1 Using this survey, Choi and colleagues documented a prevalence of gout in 2007 to 2008 of approximately 3.9% in the United States, or approximately 12 million gout sufferers (more than double the number of patients with rheumatoid arthritis). Importantly, when compared with a prior NHANES study (1988 to 1994), the prevalence of gout could be seen to have increased by roughly 45%, continuing a trend seen in the decades from the 1970s to 1990s. Even larger increases were observed among populations at risk, including both males and the elderly. In the latter group (age > 80 years), the prevalence of gout was observed to increase from 5.9% in the earlier study to 12.6% in the latter, an increase of more than 100%. Clearly, gout has risen to the level of a common and highly prevalent disease.

There are several reasons why we should care about this rise in the burden of gout. Notably, gout is associated with
increased rates of morbidity (further discussed below) and mortality. Kuo and colleagues undertook a study of 6,631 patients over 5 years, including 53,048 patient-years of follow-up. They observed that gout patients experienced an increased rate of death compared with patients without gout; a difference that grew progressively as the study continued. By the end of 5 years, survival in the control group was still above 95%, whereas survival rates in the gout group had fallen to between 85% and 90%. This increased mortality rate was seen in both men and women, and appears to be accounted for by increased kidney, metabolic, and cardiovascular disease.

Gout is also an expensive disease, both in terms of medical costs and loss of workdays. In a recent study by Wu and colleagues, the cost of medical care for a patient with severe treatment failure gout (six or more attacks a year) was more than $25,000, compared with less than $5,000 for a patient without gout. The added costs included additional ER and clinic visits, hospitalizations, and the management of comorbid conditions. Regarding loss of productivity due to gout, Edwards and colleagues have recently conducted a prospective observational study addressing work loss attributed to gout in patients with chronic refractory gout. Among 81 patients less than 65 years of age, followed for 1 year, the median number of workdays lost to gout flares was between 30 and 60; there were also many lost days of social activities, and many days on which normal self-care activities were compromised.

**Advances in Basic Science**

The wheels of basic science turn slowly, but several reports in the past year clearly deserve notice. One important theme is the increasing recognition of the role of the macrophage in gout. Synovial macrophages may be the first cells to recognize urate crystals in situ and to initiate the inflammation of a gouty attack. However, new evidence suggests that macrophages may also participate in the resolution of gouty inflammation, helping to explain the long-appreciated fact that gout attacks, if left alone, will usually resolve spontaneously. In a 2012 study by Chen and colleagues, macrophages exposed to urate crystals were shown to produce not only IL-1β and TNF-α but also multiple anti-inflammatory molecules, including IL-10, TGF-β, IL-1Ra, and soluble TNF-α receptors.

Neutrophils also play an important role in gout, and studies in general neutrophil biology have experienced significant evolution in the past few years. Mitroulis and colleagues bring these two threads together with their discovery that monosodium urate crystals can lead to the activation of neutrophil extracellular traps, or NETS. NETS are filigree mesh works of chromatin that neutrophils have been shown to elicit under certain conditions of activation. These NETS can capture bacteria, but also may form extracellular frameworks for the assembly of proteases and other tissue destroying enzymes. Thus, NETS could contribute to gout-associated tissue damage.

Other studies in the past year have also examined mechanisms of gout-associated tissue damage. For example, the mechanisms through which tophi lead to bone erosion are not well understood. In a study by Chhana and colleagues, it has recently been demonstrated that tophi may promote increased osteoblast cell death and reduce the populations of osteoblasts surrounded the tophitic lesion. Thus, tophi may contribute to bone destruction, at least in part, by inactivating the mechanisms that would lead to bone healing once damage has taken place.

**Comorbidities of Gout and Hyperuricemia**

With gout prevalence on the rise, the comorbidities associated with gout pose an increasing health risk. While clinicians caring for patients with gout have long-appreciated the other diseases commonly seen in gout patients, recent studies have confirmed and quantified the extent of comorbidities in the gout population. In a study by Keenan and coworkers, the median number of comorbidities among gout patients cared for in a Veteran Affairs system was between three and four. The most common of these included hypertension (seen in > 90% of patients), hyperlipidemia (seen in > 60% of patients), diabetes and chronic kidney disease (each seen in > 50% of patients), and coronary artery disease (seen in > 45% of patients). More recently, Krishnan and colleagues demonstrated that gout patients may have as much as an 80% increased risk of congestive heart failure, a risk that appeared to increase over time.

Thus, the importance of heart failure as gout comorbidity may be underappreciated if patients with recent onset gout are considered. Moreover, Krishnan’s data suggest that gout patients with CHF have a higher relative risk of mortality than CHF patients without gout, even after adjusting for other known risk factors.

These studies were recently supported and extended in an NHANES study carried out and reported by Zhu and colleagues published this year. In this study of 5,707 participants in the 2007-2008 NHANES, 74% had HTN, 71% had CKD stage 2 or higher, 53% were obese, 26% had diabetes, 24% had nephrolithiasis, 14% had myocardial infarction, 11% had heart failure, and 10% had suffered a stroke; the prevalence of these comorbidities were also noted to increase with the degree of hyperuricemia, supporting the notion that serum urate is related to the presence of several gout comorbidities, either as a marker of disease or perhaps by itself exacerbating other diseases.

**Can Controlling Hyperuricemia or Gout Ameliorate Gout Comorbidities?**

The question of cause and effect between gout, hyperuricemia, and gout comorbidities has important clinical implications. Clearly, some of the comorbidities seen in gout patients are likely to contribute to the onset of gout itself. For example, renal insufficiency on any basis will
impair renal clearance of serum urate, causing hyperuricemia and raising the risk for gout. However, if any of the comorbidities associated with gout are—to any extent—a consequence rather than a cause of hyperuricemia or gout, then our decision-making regarding the pharmacological lowering of serum urate and control of gouty inflammation ought to include an assessment of the impact of such treatments not only on gout but on these accompanying comorbidities. In general, the data available are insufficient proof of such cause-and-effect relationships to allow incorporation into clinical practice. They do, however, reveal trends that suggest more study is strongly warranted.

One of the challenges in studying the role of urate and gout on comorbidities is the challenge of adjusting for multiple comorbidities. If a particular comorbidity represents a mechanism through which gout results in poor outcomes, statistical adjustments may obscure the relationship between gout and the diseases with which it is commonly seen. For example, consider the possibility that gout promotes CKD by worsening HTN; by adjusting for HTN, the causality between gout and CKD would be obscured. One approach to exploring causality in this setting is to ask whether lowering urate, or treating gout, reduces comorbid risk. A number of studies have recently begun to employ this approach. (However, it must be noted that to date these studies are either retrospective or small, and so their generalizability may be limited.) For example, Chen and Pan used a large dataset to show that the use of urate-lowering therapy is associated with significantly decreased cardiovascular and stroke mortality. In a similar vein, in a cross-sectional study, we have recently shown that the chronic use of colchicine may be associated with a decreased risk of myocardial infarctions in gout patients.

Several studies have attempted to address the impact of hyperuricemia, or the effects of urate-lowering, on renal function in both gout patients and patients without gout. In one study, Whelton and colleagues reorganized the data compiled in a 5-year febuxostat study into quartiles according to the degree of urate-lowering achieved (regardless of drug and dose). In this study, patients who achieved the most urate lowering experienced preservation of estimated glomerular filtration rate (eGFR), rather than the predicted physiologically-based renal deterioration over time. In contrast, those patients who experienced the least urate lowering experienced significant declines in eGFR (approximately 10 mL/min) (Fig. 1). In a 16-week, prospective study of patients with normal-range renal function and no gout, Kanbay and colleagues followed 30 control patients and 37 asymptomatic hyperuricemics, and treated an additional 30 asymptomatic hyperuricemics with 300 mg of allopurinol daily. In this study, the control patients started with higher eGFRs than either of the two hyperuricemia groups, whose mean eGFRs were similar. By the end of the study, both the control and the untreated hyperuricemic groups experienced no significant change in eGFR. In contrast, those patients treated with allopurinol experienced a significant increase in eGFR, bringing their renal function almost to the level of the control patients. An earlier study by Goicoechea and colleagues yielded similar results. These studies point to a potential beneficial effect of urate-lowering in the preservation or even improvement of renal function in hyperuricemic patients.

### Uric Acid and Osteoarthritis?

Recently, DeNoble and colleagues have suggested the possibility that uric acid may play a role in the development and progression of osteoarthritis (OA). This interesting hypothesis is predicated on two recent advances in the understanding of crystal biology over the past decade. First is the notion of uric acid as a danger signal. Danger signals are substances that are emitted by cells in extremis and drive antigen presentation to result in immunity (as opposed to the antigen causing immune tolerance). In a seminal observation, Rock and colleagues demonstrated that uric acid crystals are a danger signal produced by damaged cells and can activate immune responses.

The second advance was made by the late Jurg Tschopp and his group. Tschopp showed the ability of urate crystals to activate the inflammasome, a multimolecular complex responsible for the generation of IL-1β and IL-18. Interestingly enough, IL-1β is one of the cytokines most strongly associated with osteoarthritis. Could urate therefore play a role in OA? To assess this question, De Noble and colleagues studied the synovial fluid (SF) of 159 patients with OA but no gout. They found that: 1) SF urate levels correlated with levels of both IL-1β and IL-18; 2) SF IL-1β and
IL-18 levels correlated with OA severity; and 3) SF urate levels also correlated with OA severity. From these observations, the De Noble group proposed a model in which early osteoarthritis promotes cell death and local urate release, and micro-crystallization of urate induces IL-1ß/IL-18 production from viable chondrocytes, inducing additional inflammation and further OA propagation. This or other models suggesting an interaction between hyperuricemia and OA remain to be validated, but at least one study has suggested an association between crystal deposition and OA of the ankle. Intriguingly, Aran and colleagues have recently shown that daily colchicine reduces osteoarthritis symptoms in the knee. Taken together, these data are provocative and suggest that further research is warranted. If uric acid can be more definitively linked to the progression of OA, the presence or risk of OA may need to be taken into consideration when making decisions to lower serum urate pharmacologically.

**Dual Energy CT for Gout Assessment**

While our understanding of the basic science behind gouty inflammation and the interplay between gout and its comorbidities expands, technology has also advanced our ability to assess gout burden in individual patients. Dual energy CT (DECT) allows for identification of urate deposition in significantly more areas than physical exam and allows for automated volumetric assessment of total tophus volume load (Fig. 2). In a study by Choi and colleagues in 2009, DECT revealed 440 areas of urate deposition in 20 patients, compared to 111 areas of urate deposition determined by physical exam. DECT has more recently been shown to identify subclinical tophi in gout patients. Recent data suggests high sensitivity and specificity of DECT for diagnosing gout: 93% and 95% respectively in one study published in abstract form, and 78% and 93% in another study; in the latter study, the investigators speculated that longstanding urate lowering therapy may have resulted in a less impressive sensitivity. Inter- and intra-observer reproducibility in assessing tophus volume was excellent in the latter study. While this technology has not yet achieved a role in routine clinical care, it holds promise as a tool to help make diagnostic and perhaps treatment decisions in the future. MRI and ultrasound are also modalities of interest for gout imaging.

**Update on Treatment**

**Dietary Components**

It has long been appreciated that certain dietary components affect the risk of hyperuricemia and gout. The roles of dietary purines, and of alcoholic beverages, are well-established, and studies over the past decade have shed light additional light on the impact and mechanisms of these agents. More recently, dietary fructose has come to attention as a foodstuff that can raise serum urate, although some controversy remains. In contrast to purines, alcohol, and fructose, dairy has recently been suggested to have benefit in managing hyperuricemia. Epidemiologic studies suggest that patients who consume more dairy products have lower serum urates and lower risk for gouty attacks (independent of the effect of dairy consumption on the rest of the consumer’s diet), and at least two studies suggest that dairy consumption results in a rapid uricosuric effect. In an interesting animal study, Dalbeth and colleagues have shown that consumption of dairy product extracts may also have anti-inflammatory effects. With these observations in mind, Dalbeth recently conducted a prospective, proof-of-principle trial of dairy extracts as prophylaxis against acute gouty attacks. Gout patients daily received either lactose powder (control group), skim milk powder, or skim milk powder supplemented with GMP and G600, two milk sub-fractions that had previously been suggested to contain the most potent urate-lowering effect. As early as 1 month after initiation, and persisting until the end of the study (3 months), subjects in the skim milk/GMP/G600 group demonstrated significantly reduced numbers of gout attacks relative to the other groups. In contrast, the skim milk supplement alone showed little benefit. Collectively, these data suggest a benefit from dairy in the management of gout; whether they also suggest that dairy extract

**Figure 2** Dual energy CT image of a patient with tophaceous gout. This DECT image demonstrates tophaceous uric acid deposition, in green, in a patient with chronic refractory gout. The patient had previously undergone amputation of the great toe due to complications from a tophus. The purple color represents calcium deposition. (Color version of this figure available at www.nyuhjdbulletin.org.)
supplementation would be needed, rather than just dietary alterations, remains to be further clarified.

Pharmacotherapy
The last 5 years have seen the arrival of a handful of new agents for treating gout and advances in the use of some older agents as well. Among the older agents, colchicine has recently been found to work at a lower dose than used historically for acute gout, at 1.2 mg followed by 0.6 mgs 1 hour later, leading to FDA approval of the agent for the first time. Possibly the most important publication relating to colchicine this year, however, was the report by Terkelba and colleagues providing a dose-reduction algorithm for patients taking other drugs that are metabolized by the CYP450 3A4 and P-Glycoprotein systems, such as the commonly prescribed calcium channel blockers verapamil and diltiazem. This information should help make a generally safe drug (when used at appropriate doses) even safer.

The other potentially important advance in the field of gout inflammation has been the concept that agents capable of blocking interleukin-1β (IL-1β) activity may be effective in gout. The basis for this concept stems from the recognition that urate crystals activate the inflammasome; this observation places IL-18 at the center of the gouty response. Three biologic agents are available that bind and inactivate extracellular IL-18: anakinra, the IL-1β receptor antagonist developed for rheumatoid arthritis; rilonacept, or IL-1 Trap, consisting of two IL-1β receptors linked to an immunoglobulin Fc tail; and canakinumab, an anti-IL-1β antibody approved for childhood periodic fever syndromes.

In 2011-2012, several important studies regarding the latitude of gout inflammation have been published. Schlesinger and colleagues published the results of a dose-finding study comparing canakinumab against intramuscular triamcinolone for the treatment of acute gout, showing that canakinumab was equal to or superior triamcinolone at all doses tested. This observation places IL-18 at the center of the gouty response. Three biologic agents are available that bind and inactivate extracellular IL-18: anakinra, the IL-1β receptor antagonist developed for rheumatoid arthritis; rilonacept, or IL-1 Trap, consisting of two IL-1β receptors linked to an immunoglobulin Fc tail; and canakinumab, an anti-IL-1β antibody approved for childhood periodic fever syndromes.

In 2011-2012, several important studies regarding the latter two agents were published. Schlesinger and colleagues published the results of a dose-finding study comparing canakinumab against intramuscular triamcinolone for the treatment of acute gout, showing that canakinumab was equal to or superior triamcinolone at all doses tested. Subsequently, this observation was supported by two phase III trials of canakinumab 150 mg subcutaneously for treatment of acute flare in patients who could not take non-steroidal anti-inflammatory agents or colchicine, also evaluating time to next flare. In the weeks after treatment, the number of recurrent gout flares was much lower in the canakinumab vs. the triamcinolone group, consistent with the long half-life of canakinumab (approximately 26 days). Canakinumab has also been compared with colchicine, 0.5 mg daily, for the prevention of acute gout attacks during the initiation of urate lowering and found to be superior to colchicine for flare prevention during the 16-week active comparator phase of the study. Similar studies have demonstrated the potential benefit of rilonacept as a prophylactic agent. In two different trials, rilonacept 80 mg or 160 mg weekly was superior to placebo at suppressing gouty attacks in patients starting allopurinol. Of note, assessments of rilonacept vs. an active comparator (e.g., colchicine) have not yet been reported.

In the realm of urate-lowering therapy, the workhorse agent has long been the xanthine oxidase (XO) inhibitor allopurinol. Since 2009, febuxostat has represented an alternative XO inhibitor. Febuxostat has several theoretical advantages over allopurinol, including greater potency and specificity and a reduced reliance on renal excretion. As a non-competitive XO inhibitor, we may expect febuxostat to have an advantage over the competitive XO inhibitor allopurinol in settings of high levels of xanthine and hypoxanthine (i.e., among urate overproducers) since in that setting xanthine and hypoxanthine levels might have the potential to overwhelm the allopurinol but not febuxostat effect. However, whether these potential advantages outweigh febuxostat’s increased cost remains uncertain. A study by Singh and colleagues presented at this year’s American College of Rheumatology meeting, may shed some light. In a study of real-world use of the two agents, Singh and colleagues observed that a higher proportion of patients using febuxostat achieved a serum target level of either < 6.0 or < 7.0 mg/dL., although the relative advantage was modest. Further study is needed to clarify how to select between these two agents.

Another new agent for lowering serum urate levels is pegloticase, a recombinant mammalian uricase coated with polyethylene glycol strands to reduce immunogenicity (FDA approved in 2010). Although the pegloticase is highly effective at lowering serum urate, it loses efficacy in approximately half of patients that take it, and some patients may suffer severe allergic reactions. Recently published results of two phase III studies of the drug shed considerable light on this situation, and may help practitioners to better utilize the agent. These studies demonstrated that pegloticase is almost always highly effective in its initial usage, but that pegloticase patients rapidly diverge into two distinct groups. About half of the patients remain responders indefinitely. For the others, the drug rapidly loses activity, a condition related to the development of anti-pegloticase antibodies. This same group of patients is susceptible to severe infusion reactions. Accordingly, pegloticase use can be optimized by identifying those patients who cease to respond to pegloticase (detected by a rise in serum urate to greater than 6 mg/dL) and discontinuing use to prevent adverse outcomes. The remaining patients can utilize pegloticase indefinitely, maintaining low serum urate levels rarely seen with oral agents. Using this strategy, infusion reactions can be reduced by as much as 90%. Accordingly, the pegloticase package insert now recommends that serum urate should be assessed prior to every infusion, and that discontinuation should be considered if levels increase to above 6.0 mg/dL on two consecutive assessments.

Conclusion
Gout is an increasingly important disease in the United States and around the world, yet its complexity and clinical significance are frequently underestimated. Fortunately, our
understanding of the risk factors, biology, and treatment of gout is advancing steadily. With persistent focus, it is likely that our ability to prevent and treat gout and its related comorbidities will continue to improve as the decade advances.

**Disclosure Statement**

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**References**