

## Difficult-to-manage Gout

a report by

**N Lawrence Edwards, MD**

*Professor and Program Director, Medicine Residency Training Program, and Vice Chairman for Housestaff Education, Department of Medicine, University of Florida*

Gout is one of the most common and 'curable' forms of arthritis. However, despite a relatively clear understanding of its pathogenesis, acceptable diagnostic criteria, and decades of experience with urate-lowering therapies (ULTs), gout remains one of the most poorly managed conditions by both primary care physicians and arthritis specialists.<sup>1</sup> Since gout is due to urate crystal deposition, the goal of ULT is 'cure' through the prevention of further crystal formation and the dissolution of existing crystals by maintaining serum uric acid levels below the saturation point for crystal formation (<360µmol/l or <6mg/dl).<sup>2</sup>

The incidence and prevalence of gout has been steadily increasing over the past 40 years. From the mid-1960s to the mid-1990s, the prevalence of gout in most westernized countries increased by 200–300%, and gout is now the most common inflammatory arthritis in men.<sup>3</sup> Mikuls et al. used the UK General Practice Research Database and determined an overall population prevalence in the UK of 1.4%.<sup>4</sup> A population-based study in New Zealand demonstrated the prevalence of gout to be 4.7% in subjects over 15 years of age.<sup>5</sup> There are many potential explanations for this proliferation of gout, including:

- a rise in beer consumption;<sup>6</sup>
- more common usage of thiazide diuretics in the treatment of hypertension<sup>7</sup> and mini-dose aspirin for cardiovascular prophylaxis;<sup>8</sup>
- the alarming obesity epidemic;<sup>9</sup> and
- the general aging of the baby-boomer population, with the greatest increase in prevalence coming in the group over the age of 65 years.<sup>4</sup>

### Barriers to Gout Management

One of the barriers to optimal management of gout is our inability to diagnose early gout with assurity. The universally agreed upon 'gold standard' of diagnosis is the examination of synovial fluid for the presence of monosodium urate crystals using compensated polarized microscopy. In reality, this gold standard is uncommonly used by rheumatologists and rarely used by the primary care physicians who manage the vast majority

of gout patients. The still non-validated preliminary criteria for diagnosing gouty arthritis issued by the American Rheumatism Association (ARA) in 1977<sup>10</sup> are used in clinical trials but rarely in practice. In 2006, the European League Against Rheumatism (EULAR) produced guidelines for the diagnosis of gout.<sup>11</sup> This has certainly renewed interest in gout, but the utility of these new guidelines is still unproven. The importance of misdiagnosis is underscored by several publications where the majority of patients experiencing life-threatening or fatal complications of allopurinol were, in fact, on this drug for no clear reason.<sup>12</sup>

An even more important barrier to the management of gout is the limited number of drugs currently available to lower serum uric acid. In the US, there are only two medications approved for this purpose: allopurinol and probenecid. Allopurinol is by far the more popular of these two agents and is the choice for ULT more than 95% of the time. Although allopurinol is generally a well-tolerated drug, it may induce unacceptable toxicities and, for this reason, adequate dosing with this drug is not achieved in the majority of patients taking it.<sup>13</sup> Concerns about potential hypersensitivity and renal toxicities led to widely accepted guidelines for adjusting the dose of allopurinol based on creatinine clearance.<sup>12</sup> Recent studies have shown that by adhering to these guidelines we are both undertreating our patients<sup>14,15</sup> and not reducing the risk of allopurinol toxicity.<sup>15</sup>

Concerns about toxicity have also dampened enthusiasm for the use of probenecid. This drug was originally developed for its ability to interfere with the renal excretion of other drugs—specifically, penicillin. There is a long list of other commonly used drugs that are influenced by probenecid, including heparin, furosemide, aspirin, and other non-steroidal anti-inflammatory drugs (NSAIDs). Dosing is also a problem when using probenecid as a life-long therapy for lowering uric acid levels. Unlike allopurinol, which can and should be given once daily, probenecid requires multiple dosings daily. Although it is marketed as a twice-daily drug, its optimal effectiveness occurs when given in three or four doses daily.<sup>16</sup> Finally, probenecid loses virtually all of its uricosuric activity in patients with glomerular filtration rates (GFRs) under 50ml/min—a level not uncommon in patients with advanced gout.

Rheumatologists have always viewed gout as a minor disease within the spectrum of rheumatic conditions. For this reason, the burden of caring for gout sufferers has shifted to internists and general practitioners. A generally poor understanding of diagnostic and treatment guidelines by all levels of the medical profession has resulted in a disease that, while potentially 'curable,' is frequently misdiagnosed and undertreated.<sup>1</sup>

N Lawrence Edwards, MD, is Professor of Medicine in the Division of Clinical Immunology, Department of Medicine, at the University of Florida, a position he has held since 1995. He also serves as Program Director of the Medicine Residency Training Program and Vice Chairman for Housestaff Education in the Department of Medicine at the University of Florida. Previously, Dr Edwards served as Clinical Chief in the Division of Rheumatology and Clinical Immunology. Prior to his appointment at the University of Florida, he was an Assistant Professor of Internal Medicine in the Division of Rheumatology at the University of Michigan Medical School, Ann Arbor, Michigan. Dr Edwards received his MD from the University of Miami in 1973.

### The Impact of Gout

Despite the historically comedic view of gout, it is a very painful and frequently disabling disease. The vision most people have of gout sufferers is that of a corpulent, overindulgent man with his painful foot resting on a pillow. The reality is that gout is a complex disease that affects adult men and older women of all socioeconomic classes. It is a disease that progresses over years and decades from intermittent, excruciatingly painful arthritis involving one or several joints to a chronic disabling form of arthritis involving almost any joint in the body and greatly influencing quality of life.

In men, the first gouty attacks usually occur between the fourth and sixth decades of life. In women, age at onset is higher and varies with several factors, the most important of which is age at menopause.<sup>17</sup> In the early stages of gout, the painful attacks are immobilizing but self-limited, with attacks lasting for four to seven days. The frequency of the early attacks varies greatly, but the mean interval between the first and second attack is approximately 11 months.<sup>17</sup> Over time, the intervals between attacks shorten to the point at which the patient may be having attacks every two to three months, and the attacks may last for seven to 10 days. During this stage of gout, when the patient is experiencing episodes of painful arthritis interspersed with periods of no musculoskeletal problems, the underlying process of uric acid accumulation around the body continues at a slow but unrelenting pace. During this first phase of gout, the patient's employability is at risk because of the unpredictability of the attacks.

However, the real health and socioeconomic impact of gout is felt in its advanced or chronic stage, in which there are no pain-free intervals between attacks. Attacks continue to occur, but the intervening periods are marked by steadily escalating pain and disability. During this phase, subcutaneous collections of monosodium urate crystals known as tophi begin to appear, often around joints. Like the chronic destructive arthritis with which they are frequently associated, tophi may lead to physical disability and pain in their own right.<sup>17</sup>

Nearly half of all gout patients have either American College of Rheumatology (ACR) Class II or Class III disability.<sup>18</sup> This means that they not only have difficulty participating in recreation and other quality-of-life activities, but some will also have difficulty with even basic activities of daily living. The presence of tophi is associated with musculoskeletal disability with a relative risk of 4.3.<sup>18</sup> Gout also has an enormous economic burden, with work absenteeism and hospitalization costs being major factors. The difference in the cost of health benefits for a US employee with gout versus an employee without gout was calculated to be \$3,166/year in 2005.<sup>19</sup>

### 'Difficult-to-manage' Gout

The greatest impediments to current management of gout are our heavy reliance on allopurinol as the main mechanism of urate lowering on the one hand, and on the other hand our unwillingness to use the full dose range of allopurinol to achieve optimal control. An example of this general underutilization of our current antigout therapies is the report recently published by Roddy et al. from Nottingham, UK.<sup>20</sup> Questionnaires were sent to all patients in two large clinical practices, and those with episodes suggestive of gout were interviewed directly. The results showed alarming

underutilization of current resources. Despite the severely painful nature of gout, 12% of patients determined to have gout never sought medical consultation. Only 30% of subjects with symptomatic hyperuricemia had ever been started on allopurinol or other ULTs. No patient was prescribed more than 300mg daily of allopurinol. At this dose, multiple studies have shown that the success rate in achieving a target serum uric acid level of <6.0mg/dl (<360µmol/l) is between 21 and 47%.<sup>13,20-22</sup>

The term 'difficult-to-manage' gout usually implies one of several scenarios. It might refer to a patient with very advanced gout in whom acute and chronic symptoms and multiple tophi make any therapeutic progress seem entirely too slow. Another interpretation might be a patient with gout who has been started on allopurinol but still has symptoms of gout. The underlying problem with this patient is that the dose of allopurinol has not been adequately escalated and that prophylactic anti-inflammatory medication is not being maintained. Additionally, poor patient compliance, resulting in undertreatment and thus difficult management, is a scenario we will have very poor success in overcoming. The real challenge for physicians with regard to difficult-to-manage gout is when this implies that all therapeutic options seem to be exhausted, the patient is still symptomatic, and we are unsure what we can do that will improve matters.

There are many factors that limit allopurinol's effectiveness other than the creatinine clearance-adjusted dose schedule discussed above. Skin manifestations occur in 2–3.5% of patients started on the drug; this warrants treatment discontinuation even though these rashes will rarely progress into a severe, potentially life-threatening hypersensitivity reaction to allopurinol.<sup>23</sup> Other, less common, side effects of allopurinol include gastrointestinal disturbances (abdominal pain, nausea, and diarrhea) and hepatic (centrilobular necrosis or granulomatous hepatitis) and neurological (delayed peripheral neuropathy and Guillain-Barre syndrome) symptoms.<sup>23-25</sup> Myelotoxicity is a very rare complication of allopurinol use unless the patient has significant liver or kidney disease or is being treated with the chemotherapeutic agents azathioprine, 6-mercaptopurine, or cyclophosphamide.<sup>26</sup> True refractoriness to allopurinol is rare, but adverse events necessitating the discontinuation of therapy with this drug may occur in as many as 20% of drug starts.<sup>27</sup>

A number of drug interactions can also limit the use of allopurinol. Concurrent use with ampicillin or amoxicillin will increase the chances of cutaneous rash by three- to four-fold.<sup>28</sup> Allopurinol also reduces the hepatic metabolism of multiple drugs, including warfarin, phenytoin, theophylline, and the antiviral drug vidarabine.<sup>23</sup>

If a patient is not a candidate for allopurinol, he or she qualifies as a difficult-to-manage gout patient because the alternative drug, probenecid, is a 'difficult-to-manage' drug. Its primary limitations are that it is ineffective in subjects with a GFR below 50 and in patients with urinary excretion of uric acid greater than 800mg/day on a normal diet, who would be at great risk for precipitating kidney stones. Other limitations of probenecid mentioned earlier include the requirement for two to three doses per day, which will greatly influence compliance over years of therapy, and the numerous drug interactions associated with probenecid.

When allopurinol and probenecid are no longer therapeutic options for the treatment of a person with gouty arthritis, we are truly faced with the problem of difficult-to-manage gout. Difficult—but not impossible. There are numerous mechanisms of risk reduction and urate lowering that rely on neither allopurinol nor probenecid. While many of these approaches should optimally be tried in the early stages of gout—and possibly even before starting ULT—once the option of using allopurinol and probenecid has been lost, greater attention and focus should be given to risk reduction and lifestyle modification. Generally, these approaches—singly or together—will reduce serum uric acid levels by only 1–3mg/dl. This may not be enough to make the patient normouricemic, but it may be enough to reduce symptoms and slow down the destructive process of uric acid accumulation.

Obesity is directly associated with hyperuricemia, and gout and weight reduction can substantially lower serum uric acid levels and the risk of gout.<sup>29</sup> While a physician's recommendation of weight loss to a patient is famously ineffective in most circumstances, patients with painful gout and no other therapeutic options may be much more motivated than the general population. Specific dietary recommendations to eliminate beer and foods known to raise uric acid levels may also be taken more seriously when other options have disappeared. Adding dietary supplements such as 500–1,000mg of vitamin C daily will have a modest effect on lowering uric acid, but will not add any toxicity to the patient.

Finally, looking at the entire list of other medications taken by a patient with difficult-to-manage gout may reveal some opportunities for replacing urate-retaining drugs, such as hydrochlorothiazide (HCTZ), with drugs that promote uric acid excretion, such as losartan. There are numerous examples of such exchanges. For instance, most NSAIDs cause

uric acid retention. Diclofenac and sulindac, on the other hand, have mild uricosuric effects.

### Conclusion

There are many obstacles to improving our rather dismal efforts to control gout and hyperuricemia. The two greatest problems are:

- the lack of understanding and acceptance of treatment guidelines by the medical profession; and
- the very restricted list of agents available to us for lowering serum uric acid levels.

The treatment targets of lowering serum uric acid to less than 6.0mg/dl in most people with gout and to 4.0–5.0mg/dl in gouty patients with tophi have been discussed for decades, but have only recently been promoted as 'hard targets' in a similar way to low-density lipoprotein (LDL), glycosylated hemoglobin (HbA<sub>1c</sub>), and blood pressure measurements. It is possible that as these targets gain recognition and acceptance the number of difficult-to-manage gout cases will diminish.

Similarly, as physicians treating gout begin to appreciate that they are not constrained by a 300mg/day 'ceiling' of allopurinol dosing, but that doses of 400mg up to 600 or 800mg daily may be necessary to achieve the therapeutic targets, we will see less and less of the undertreated segment of what have traditionally been considered as difficult-to-manage gout patients.

Finally, for those patients with true difficult-to-manage gout, in whom existing therapeutic options have been exhausted, there is clearly a need for new therapeutic approaches. ■

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