Hyperuricemia & Gout
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Commentaries

Medication Trials In an Imperfect World: Gout and Parkinson’s Disease

This issue of Medicine & Health, Rhode Island is the perfect venue to discuss a new, potentially useful treatment for slowing progression of Parkinson’s disease (PD), because it is based on increasing uric acid levels, hence putting people at risk for gout and possibly cardiovascular disease. It forces us to focus on several important clinical issues, including iatrogenesis, and how does one, both practically and ethically, recruit for a study that may cause significant complications in return for which the subject is rewarded with a clap on the back and an enhanced feeling of altruism but nothing else?

The basic facts are straightforward. A few large studies of PD, performed for a variety of different reasons, have included, for safety purposes, uric acid levels. Analyses have shown, without conflict, that PD patients with higher uric acid levels progress more slowly than PD patients with lower levels. Studies comparing people with PD to those without PD have consistently shown that PD patients have lower uric acid levels. Uric acid is one of the body’s strongest antioxidants, and PD has been thought to result from excess oxidation within neurons. Thus elevated uric acid levels may be beneficial for people with PD. And although diet plays a role in uric acid levels, and diet may be altered in PD, experts believe that the differences in uric acid levels found in PD vs. controls cannot be explained by diet alone. These observations led to the idea of increasing uric acid serum levels to determine if this will slow PD progression. It must always be kept in mind that when one sees associations between potential cause and effect, that the connection, while robust, may not be what it seems. The connection between alcohol and lung cancer is strong, but is mediated via cigarettes, for example. Decreasing alcohol alone will not decrease lung cancer.

The first step required to study a new drug to determine if it will slow disease progression is to perform a safety study, to prove to the Food and Drug Administration (FDA), which regulates testing of experimental medications, that this drug is safe to test in PD. Of course, this requires testing the drug in PD patients, but the structure of the study is quite different for a safety study than it is for an efficacy trial. For the goal of the preliminary study is to demonstrate that the drug is safe, not that it is therapeutically effective. The rationale for this is that safety studies require far fewer subjects, and generally are much shorter in duration so that fewer people are put at risk should the drug ultimately be shown to be unsafe.

It is not easy to recruit for a study when the goal is safety, not efficacy. Most patients do not want a placebo; they want to feel better. Many of our efficacy studies promise the subjects that they will be able to take the experimental medicine once the placebo phase has ended on an open label basis. This is considered “fair” although it is an oddity of our testing system since the efficacy study is performed exactly to find out if the drug is, in fact, effective; so how, without knowing the results of the study, can we justify giving it to patients? In a safety study, we don’t even have any data, other than experimental, to indicate that the drug will be effective. In the case of a drug intended to slow disease progression, one doesn’t even feel better while taking the drug. Furthermore, in this particular study, we are even requiring a lumbar puncture to determine how well the study drug is altering urate levels within the cerebrospinal fluid, and, presumably, the brain.

Would I enroll in this study if given the chance? I like to think so. I’m not sure if I should be running a trial that I wouldn’t participate in as a subject. My own reservations have to do with the long-term safety of the drug. Will the FDA allow a drug that may induce gout and all its complications to be prescribed for people with PD? Will people with PD be willing to take a drug that may cause gout? At the initial meeting of site investigators, I asked the group who had made the observations about urate levels and PD, and who had designed this trial, if any of them had ever had a kidney stone. No one in the room had besides myself. Having had a few I can vouch for each one being memorably painful. Would I take a medication that might precipitate such a thing? Maybe, if it really slowed PD down a lot. What about cardiovascular disease? I’ve got that too. How keen am I to further increase my risk?

Most patients don’t have a history of kidney stones, and if they did, they would not be urate stones, and the connection between cardiovascular disease and urate levels is no more solid than that between urate and PD.

So the final decision rests, as it should, on clinical equipoise. Should we, or shouldn’t we? We simply have insufficient data to make a decision. When this happens, and the stakes are high, it is time for a study to answer the question. Unfortunately for those in the early studies, safety comes first. The later subjects have the benefit of helping determine if the drug actually works.

If there were medals for altruism, those who volunteer for safety studies should get the gold ones. They truly reap no substantive gain.

– JOSEPH H. FRIEDMAN, MD

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A 59 year-old British physician, in 1683, describes an attack of articular pain in his patient: “The victim goes to bed and sleeps in good health. About two o’clock in the morning he is awakened by a severe pain in the great toe, more rarely in the heel, ankle or instep. The pain is like that of a dislocation and yet the parts feel as though cold water were poured over them. Then follows chills and shiver and a little fever. The pain, at first moderate, becomes more intense. After a time this comes to full height accommodating itself to the bones and ligaments of the tarsus and metatarsus. Now it is a violent stretching and tearing of the ligaments — now it is a gnawing pain and now a pressure and tightening. So exquisite and lively meanwhile is the feeling of the part affected, that it cannot bear the weight of the bedclothes nor the jar of a person walking in the room.”

Truly an authentic description of an age-old disorder called gout. The physician was Thomas Sydenham (1624 – 1689) and the patient was himself. When physicians describe diseases in their patients, the descriptions tend to be starkly objective and coldly impersonal with little of the patient’s inner reactions to the ailment. But when the physician is both victim and portrayer of the disease, the narration inevitably takes on dimension, greater accuracy and more benevolence.

Gout was well known to the ancient Egyptians; and despite the passage of millennia, some of their mummified remains still contain toes with the characteristic anatomic changes of gout. The Classical-era Greeks were also familiar with this unique form of arthritis, calling the disorder podagra.

This much was known about the predilection, pathology and prognosis of gout by the late 17th Century, the dawn of scientific inquiry: It was a disease selectively but not exclusively of affluent society with a typical onset in late adult life. Men, to the exclusion of eunuchs, were its prime victims. Women became vulnerable to gout, but only beyond the menopause. Gout seemed to choose its victims from amongst those who ate in excess of food, wine and debauchery. John Milton, Isaac Newton, Samuel Johnson and even that champion of the proletariat, Karl Marx.

Sydenham concluded: “Gout, unlike any other disease, kills more rich men than poor, more wise men than simple. Great kings, emperors, generals, admirals have all died of gout.” He might have added: “And countless commoners.”

— Stanley M. Aronson, MD

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Stanley M. Aronson, MD, has no financial interests to disclose.

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Introduction: Hyperuricemia and Gout

Bernard Zimmermann, MD

The pathophysiology of gout is well understood, and effective treatments for acute gout and hyperuricemia leading to gout are widely available. Nonetheless, many patients suffer from severe tophaceous gouty arthritis, adverse effects of medications for gout, and inadequate treatment of hyperuricemia. The incidence of gout is rising in both men and women. The diagnosis and treatment of gout are challenging in patients with arthritis, renal and hepatic diseases. Acute gout is usually not difficult to treat, but evidence to guide therapeutic decisions for gout patients with complex medical problems is woefully lacking. Fortunately, new medications for treatment of gout and hyperuricemia are becoming available, and exciting new research is increasing our understanding of the role of hyperuricemia in the pathogenesis of hypertension and cardiovascular disease.

In this issue of Medicine and Health/ Rhode Island we discuss the epidemiology of gout in women, and review new data regarding the importance of hyperuricemia as a marker and perhaps a causative agent involved in the pathogenesis of the metabolic syndrome. We review the risks and benefits of various treatment options for acute gout and discuss the potential utility of febuxostat, the first new drug approved for treatment of hyperuricemia in 40 years. In addition, we describe ongoing studies of rasburicase and pegloticase which may offer dramatic improvement for patients with severe tophaceous gout.

We hope to share the excitement in the rheumatology community that has been generated by the potential of new therapies and advances in our understanding of gout and hyperuricemia, and to improve the care of all patients with gout.

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The author has no financial interests to disclose.

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WHAT IS HYPERURICEMIA?

Uric acid is an oxidation product of purine metabolism, which in primates (including humans) is largely eliminated by the kidney and the gut. Most non-primate mammals express uricase, an enzyme that converts serum uric acid into allantoin, which is easily excreted by the kidneys. Non-primate mammals thus usually have low serum uric acid (SUA) levels (below 2 mg/dl), while primates have the potential to develop hyperuricemia, because they lack uricase. In humans, renal under excretion of uric acid is the cause of 90% of hyperuricemia, while 10% is due to overproduction of uric acid. Uric acid is more toxic to tissues than other purine metabolites such as xanthine, hypoxanthine and allantoin.

Hyperuricemia is defined as a serum urate level greater than 6.0 mg/dl in women, and 7.0 mg/dl in men. Above this concentration, urate is supersaturated in body fluids, and is prone to crystallization and subsequent tissue deposition. The rising prevalence of hyperuricemia over the last several decades can be attributed to several factors. Westernization of diets and widespread use of high-fructose syrup may play a role in increasing SUA levels. Other factors that might be involved include increased lifespan and more common use of certain medications, including diuretics and cyclosporine. The prevalence of asymptomatic hyperuricemia in US is estimated to be 5-8% among adult Caucasian men and it is even more common in some ethnic groups, such as Filipinos and Polynesians.

While a few studies have noted a potential beneficial antioxidative effect of uric acid and even suggested a neuroprotective role, most studies link hyperuricemia with such co-morbidities as hypertension, renal disease, metabolic syndrome and cardiovascular disease (CVD).

HYPERURICEMIA AND GOUT

The most well known medical manifestation of hyperuricemia is gout. Gout is caused by deposition of uric acid crystals in and around the joints and has 4 stages: asymptomatic hyperuricemia, acute gout, intercritical gout, and chronic tophaceous gout. The duration of each stage varies significantly among individuals. (Table 1)

Fewer than one-third of individuals with asymptomatic hyperuricemia will develop gouty arthritis. The risk of developing gout increases with age and the degree of hyperuricemia. In the Normative Aging Study, the 5-year cumulative incidence of gout among those with a uric acid level between 7.0 and 8.0 mg/dl was 3%, compared to 22% in those with a uric acid level of 9.0 mg/dl. (Figure 1)

Acute gouty arthritis occurs when uric acid crystals interact with synovial phagocytes, which in turn activate neutrophils and initiate an inflammatory cascade. Urate crystals that serve as a trigger for an acute attack may derive from preformed synovial deposits or precipitate in the joint de novo. Clinically, acute gout presents with rapid onset of a painful, erythematous and swollen joint that may be accompanied by fever. Inflammation of the first metatarsophalangeal joint (also known as podagra), is the most characteristic presentation but other joints are often involved.

Intercritical gout is the name given to the asymptomatic interval between acute attacks. In early gout, intercritical periods may last for years, but with progression of the disease the time between attacks tends to lessen.

Chronic tophaceous gout is characterized by the development of tophi in and around the joints, which can cause destructive arthritis. (Figure 2) Tophi are commonly found in the soft tissues, including tendons, pinnae and subcutaneous fat. Tophi have been reported in such unusual locations as heart valves, spinal cord, sclera, breast and even Cushing's striae.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Duration</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic hyperuricemia</td>
<td>&gt;10-15 years</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Acute gout</td>
<td>1-2 weeks</td>
<td>Sudden onset of acute mono- or oligoarthritis (e.g., podagra)</td>
</tr>
<tr>
<td>Intercritical gout</td>
<td>From weeks to years</td>
<td>Asymptomatic intervals between acute attacks</td>
</tr>
<tr>
<td>Chronic tophaceous gout</td>
<td>10 or more years after the first episode of acute gout</td>
<td>Development of tophi in and around the joints and soft tissues</td>
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</tbody>
</table>

Figure 1. Cumulative Incidence of Gouty Arthritis by Prior Serum Urate Levels. The numbers refer to the number of examination intervals for each group. Reprinted from American Journal of Medicine, 1987 March 82(3); Campion EW, Glynn RJ, DeLabry LO. Asymptomatic hyperuricemia. Risks and consequences in the Normative Aging Study. Pages: 421-6 Copyright 2009, with permission from Elsevier.
HYPERURICEMIA AND HYPERTENSION

Numerous studies have demonstrated an association between hyperuricemia and hypertension, and recent evidence even suggests there may be a causal relationship. This evidence was first noted in animal studies: in Sprague-Dawley rats, hyperuricemia can be induced by feeding with an uricase inhibitor. Mildly increased SUA is associated with development of hypertension in the rats within 3 weeks. The development of hypertension in the rats can be prevented by co-treatment with a uric acid lowering therapy such as allopurinol or a uricosuric agent.3

Upon pathologic evaluation, the hyperuricemic rats have lower levels of nitric oxide in the renal endothelium, suggesting increased renal vasoconstriction and activation of the renin-angiotensin system, leading to ischemic tissue damage. Uric acid crystal deposition is not seen in the kidneys of the hypertensive rats.

In humans, a prospective study involving more than two thousand patients demonstrated that an increased SUA level predicts development of future hypertension independent of age, alcohol use or renal function.4

Further evidence of the association between hyperuricemia and hypertension comes from pediatric literature: 90% of adolescents with newly diagnosed hypertension are found to have hyperuricemia.5 In a double-blind placebo-controlled study involving 30 adolescents with hyperuricemia and hypertension, allopurinol therapy normalized blood pressure in 86% of patients compared to 3% of patients in a placebo group.6 This suggests not only an early role of uric acid in the pathogenesis of primary hypertension, but also the possibility that early treatment of hyperuricemia may prevent the development of hypertension. Clearly, more clinical trials are needed to explore these issues.

HYPERURICEMIA AND RENAL DISEASE

Before uric acid lowering therapy was available, hyperuricemia was thought to be a cause of chronic kidney disease because of their frequent coexistence. However, in the late 1970s the results of several epidemiologic studies made a direct causal relationship between elevated uric acid and renal impairment questionable.7 It is clear that chronic kidney disease is associated with hyperuricemia. However, it is not clear whether renal impairment is due to a direct nephrotoxic effect of uric acid, or due to the conditions that are caused by hyperuricemia (e.g., hypertension).

Most of the recent evidence for a direct pathogenic effect of hyperuricemia on the kidneys comes from animal studies, as noted above. In humans, epidemiologic studies demonstrate that hyperuricemia is associated with decline in kidney function.8 It has also been shown that allopurinol might slow this decline. In one prospective study patients with asymptomatic hyperuricemia treated with 300 mg of allopurinol showed significant improvement in glomerular filtration rate (GFR) after 3 months of the therapy.9 Siu et al. reported that among the patients with chronic kidney disease treated with allopurinol, 16% progressed to end stage renal disease, compared to 46% in the control group.10

URIC ACID AND METABOLIC SYNDROME

Metabolic syndrome is defined as a group of modifiable risk factors that are associated with an increased risk for CVD, type 2 diabetes mellitus, and mortality from CVD. The factors that define metabolic syndrome include systolic hypertension, hypertriglyceridemia, central obesity, and impaired glucose tolerance. Hyperuricemia has been shown to be significantly more common in patients with metabolic syndrome than the normal population.11 In a recent population-based study all metabolic syndrome components correlated with elevated SUA level, with waist circumference being the strongest.11

It has been generally thought that hyperuricemia was a result of hyperinsulinemia in those with metabolic syndrome, as insulin decreases the renal excretion of uric acid. However, animal studies showed that the opposite scenario might be the case. Nakagawa et al. showed in fructose-fed rats with hyperuricemia, that treatment with allopurinol or benz bromarone (a uricosuric agent) prevented development of features of metabolic syndrome including hyperinsulinemia, systolic hypertension, hypertriglyceridemia, and weight gain.1

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Epidemiologic evidence shows that there may be a connection between the rise of the use of high-fructose corn syrup, the increasing prevalence of metabolic syndrome, and the rapid increase in worldwide hyperuricemia.

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Figure 2. Severe tophaceous gout in the hands. Photograph by Harald A. Hall, MD
It has been suggested that uric acid may cause metabolic syndrome by promoting a state of insulin resistance. It is well known that insulin stimulates glucose intake in skeletal muscle via increased blood flow to these tissues through a nicotinic oxide-dependent pathway. Uric acid decreases levels of nitric oxide and arterial dilatation and blocks the action of insulin, resulting in increased insulin resistance and hyperinsulinemia.

One of the most interesting recent findings in hyperuricemia and gout concerns high-fructose corn syrup. Epidemiologic evidence shows that there may be a connection between the rise of the use of high-fructose corn syrup, the increasing prevalence of metabolic syndrome, and the rapid increase in worldwide hyperuricemia. Unlike glucose or other sugars, fructose rapidly increases uric acid production in humans and its consumption is associated with an increased incidence of gout. Animal studies have shown that when glucose and fructose-fed rats are compared, only fructose-fed animals developed metabolic syndrome as well as hyperuricemia. Several large population-based studies have confirmed the correlation between increased fructose intake and hyperuricemia and metabolic syndrome in humans.

**HYPERURICEMIA AND CARDIOVASCULAR DISEASE (CVD)**

Hyperuricemia is frequently associated with CVD. However, conflicting data have caused controversy whether hyperuricemia is an independent risk factor for CVD or simply an indicator for co-morbidities that are frequently seen in patients with CVD (e.g., hypertension, insulin resistance). Analysis of data from the Framingham Heart study showed no association between hyperuricemia and cardiovascular outcomes. On the other hand, a study based on data from the first National Health and Nutrition Examination Survey (NHANES-I) did find an independent relationship between hyperuricemia and CVD, but only in women. A meta-analysis of 21 prospective cohort studies by Baker et al. suggested a moderate and independent association between SUA and CVD in patients at high risk for CVD. As for individuals with low risk for CVD, that correlation was not found to be consistent (only 4 out of 6 studies demonstrated an independent link). It should be mentioned, however, that the studies of healthy individuals in which correlation between hyperuricemia and cardiovascular mortality was not found tended to have a low number of events per person-years.

Hyperuricemia has also been associated with peripheral vascular disease and all cause mortality. Baker et al. found that elevated level of SUA, independent of other co-morbidities, predicted worse outcomes after an acute stroke over 2 years. The association was so strong that it was suggested that in-house SUA level should be considered as a useful prognostic indicator in patients hospitalized for acute stroke.

New data from the Chinese Cohort Study involving 93,393 participants (about half male, half female) demonstrated that hyperuricemia was an independent risk factor of mortality from all causes, total CVD and ischemic stroke. This correlation was more significant in women than men. This study also found a linear relationship between SUA and all-cause and CVD mortality. In conclusion, hyperuricemia is clearly an important risk factor for not only for developing gout but also for other co-morbidities which are associated with cardiovascular and all-cause mortality. More clinical trials are needed to determine whether the treatment of asymptomatic hyperuricemia may reduce the incidence of severity of hypertension, cardiovascular and renal disease and related co-morbidity conditions.

**REFERENCES**


**DISCLOSURE OF FINANCIAL INTERESTS**

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Risk factors for the development of acute gout include hyperuricemia, increased age, and a family history of gout. Consumption of alcohol and purine-rich foods and medications such as thiazide diuretics, loop diuretics, and cyclosporine contribute to the development of hyperuricemia. Hypertension, diabetes, obesity, and chronic renal failure are often associated with gout. When gout is suspected, aspiration of the affected joint should be performed to confirm the presence of intracellular negatively birefringent needle-shaped crystals by compensated polarized light microscopy. However, in some situations this is not practical. The most recent European League Against Rheumatism report proposes ten key recommendations for the diagnosis of gout:1

1. The rapid onset of severe pain and swelling (especially with overlying erythema) within 6 to 12 hours is highly suggestive of crystal inflammation. However, this is not specific for gout.
2. Classic podagra, involvement of the first metatarsophalangeal joint, has a high sensitivity and specificity, but is not definitive without crystal identification.
3. Definitive diagnosis is made by demonstration of monosodium urate (MSU) crystals in synovial fluid or tophus.
4. Synovial fluid from undiagnosed inflammatory arthritis should be routinely examined for the presence of monosodium urate crystals.
5. Identification of MSU crystals may be possible in intercritical periods (between attacks).
6. If septic arthritis is suspected, gram stain and culture of synovial fluid should be performed even if MSU crystals are present.
7. Serum uric acid levels alone cannot confirm or exclude gout, as patients with hyperuricemia may not develop gout, and uric acid may be normal during acute attacks.
8. In selected patients (those with a personal or family history of onset of gout before age 25, or patients with renal calculi), determination of renal uric acid excretion is useful for evaluation and management.
9. Radiographs are not helpful in confirming the diagnosis of early or acute gout, although they may be useful for differential diagnosis and may show characteristic changes in chronic gout.
10. Risk factors for gout and associated comorbidities should be assessed, including features of the metabolic syndrome (obesity, hyperglycemia, hyperlipidemia, and hypertension).

The differential diagnosis for symptoms suggesting an acute gout attack includes acute pseudogout, septic arthritis, inflammatory arthritis, cellulitis, and trauma. Because these diagnoses may have similar presentations, it is important to establish a correct diagnosis, as the treatment implications are significant. For example, pseudogout, caused by calcium pyrophosphate crystals, should not be treated with urate-lowering therapy; and septic arthritis demands immediate attention with antibiotics and joint drainage.

A definitive diagnosis of acute gout is made by detection of monosodium urate crystals in the synovial fluid of an inflamed joint.

MEDICAL TREATMENT FOR ACUTE GOUT

Colchicine

Colchicine has been used both in the acute setting and in the management of chronic gout. It exerts anti-inflammatory effects through several mechanisms. Colchicine binds to tubulin causing anti-proliferative effects by arresting cell growth. It also inhibits phagocytic and cytokine secretory functions of leukocytes. Chemotactic responses of neutrophils to leukotriene B4, IL-8, and other cytokines are disrupted. At high concentrations, colchicine has recently been shown to inhibit urate crystal-induced activation of NALP3 inflammasome. This protein complex cleaves caspase-1 which then activates interleukin-1β, a pro-inflammatory cytokine felt to be central in the pathogenesis of gout.

The optimal dosing of colchicine for treatment of acute gout remains controversial. In the only published randomized, placebo-controlled study of colchicine therapy, patients in the treatment group received oral colchicine 1 mg then 0.5 mg every 2 hours until a complete response or until side effects developed.1 Of the 22 patients in the treatment group, 73% achieved greater than a 50% reduction in pain within 48 hours. However, gastrointestinal toxicity (diarrhea and/or vomiting) developed in 55% of the patients before the reduction in pain was achieved, and all patients experienced these adverse side effects at some point during the study. A randomized, controlled multicenter trial, presented in abstract form, compared high-dose colchicine (1.2 mg, then 0.6 mg hourly for six hours) versus low-dose colchicine (1.2 mg, then 0.6 mg in one hour) and showed equivalent efficacy and less gastrointestinal toxicity with the lower dose regimen.4 Recently, the European League Against Rheumatism issued consensus guidelines in favor of lower doses of colchicine to avoid unacceptable side effects while maintaining efficacy.5 They recommend a maximum of three tablets of 0.5 mg in the first 24 hours.

Overdose or chronic administration of colchicine may result in side effects including granulocytopenia, aplastic anemia, and reversible myopathic and neuropathic toxicity.6 Patients with abnormal renal function are at increased risk for developing neuromuscular toxicity by accumulation of toxic plasma levels of colchicine. This condition typically presents with proximal muscle weakness and elevated CPK, which can mimic polymyositis. Symptoms of colchicine myopathy resolve within three to four weeks after discontinuing the medication. Colchicine is contraindicated in patients on hemodialysis and should be used

Table 1. Half-Life of Various NSAIDs.12

<table>
<thead>
<tr>
<th>Short Half-Life (&lt;6 hours)</th>
<th>Long Half-Life (&gt;6 hours)</th>
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<tbody>
<tr>
<td>Ibuprofen (2 hours)</td>
<td>Nabumetone (24 hours)</td>
</tr>
<tr>
<td>Diclofenac (1-2 hours)</td>
<td>Naproxen (14 hours)</td>
</tr>
<tr>
<td>Indomethacin (2.5 hours)</td>
<td>Etodolac (7 hours)</td>
</tr>
<tr>
<td>Ketoprofen (2 hours)</td>
<td>Sulindac (13 hours)</td>
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</table>
with caution in patients with renal insufficiency or hepatobiliary dysfunction. Drug interactions have been reported with cyclosporine, statins, and macrolides.

The FDA recently withdrew its approval for the use of intravenous colchicine. The most common side effect associated with IV colchicine is local extravasation of the drug which can lead to painful inflammation and necrosis of surrounding tissue. Increased risk of systemic side effects such as renal and hepatic toxicity, bone marrow suppression, and congestive heart failure have also been reported with IV colchicine. Fifty reports of adverse events, including 23 deaths, were submitted to the FDA through June 2007. Three of these deaths were attributed to an IV colchicine compounding error.

### Non-steroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs are commonly used for treatment of acute gout. The anti-inflammatory effects of these medications occur mainly through inhibition of the cyclo-oxygenase enzyme which prevents the transformation of arachidonic acid to prostaglandins, particularly prostaglandin E2. Other NSAID mechanisms include inhibition of lipoxygenase with reduced generation of leukotriene B4 and inhibition of neutrophil activation and aggregation.

Early administration and appropriate dosage of NSAIDs are more important in achieving a therapeutic response than the particular NSAID used. However, NSAIDs with short half-lives (less than six hours) reach steady-state levels more quickly than NSAIDs with long half-lives (more than six hours) and may be preferred in managing acute gout. (Table 1)

Regardless of which NSAID is administered, large initial doses are recommended (indomethacin 150-200 mg/day; naproxen 1000 mg/day, diclofenac 150 mg/day). Duration of treatment is generally 4-8 days which minimizes potential adverse side effects. Patients should be treated until symptoms resolve and then gradually tapered.

Traditional NSAIDs inhibit both COX-1 and COX-2, with their main anti-inflammatory effects being via inhibition of COX-2 and most adverse effects by inhibition of COX-1. While both selective and non-selective NSAIDs inhibit COX-2 equally, the selective COX-2 inhibitors spare inhibition of COX-1 therefore reducing gastrointestinal toxicity. Etoricoxib, a selective COX-2 inhibitor, was shown to be as efficacious as indomethacin for treatment of acute gout with fewer gastrointestinal side effects. This medication is not FDA-approved for use in the United States because of potential cardiovascular side effects. Celecoxib is the only approved selective COX-2 inhibitor available in the US; however, no trials of its use in gout have been published.

### The FDA recently withdrew its approval for the use of intravenous colchicine

Relative contraindications to the use of NSAIDs include severe heart failure, peptic ulcer disease, gastrointestinal hemorrhage, aspirin-induced or NSAID-induced asthma and renal impairment. There is an increased risk of bleeding when NSAIDs are used concomitantly with warfarin.

### Corticosteroids

#### Systemic corticosteroids

Systemic corticosteroids may be used for treating acute gout when NSAIDs and colchicine are contraindicated. Corticosteroids exert their anti-inflammatory effect by inhibition of pro-inflammatory cytokines (IL-1, IL-6, IL-8, and TNF-α) and upregulation of genes for lipocortin and vasocortin, which have anti-inflammatory effects by inhibiting phospholipase A2.

A Cochrane review evaluated the efficacy and safety of systemic corticosteroids for the treatment of acute gout. Only three studies involving a total of 74 patients were found that met the search criteria. In the first study, intramuscular injections of triamcinolone were compared to oral indomethacin. Intramuscular triamcinolone was compared to IM injections of ACTH in the second study. Oral prednisolone was compared to IM diclofenac combined with oral indomethacin in the third study. The results of these three studies show no clinically relevant differences between systemic corticosteroids and comparator drugs. No significant adverse side effects attributable to corticosteroids were found. This review concluded that systemic steroids are a safe and effective treatment for acute gout, but more studies are needed.

One randomized, controlled trial published after the Cochrane review tested the equivalence of prednisolone and naproxen for treatment of monoarticular gout. One-hundred and twenty primary care patients with confirmed gout were randomly assigned to receive either prednisolone (35 mg daily) or naproxen (500 mg twice daily) for five days. The primary outcome was pain. After 90 hours, the reduction in pain score was similar for both groups. Adverse effects were also comparable between both groups. This study suggests that corticosteroids are as effective as and as safe as NSAIDs in the acute setting.

Corticosteroids should be used with caution in patients with poorly controlled diabetes mellitus, hypertension, congestive heart failure, advanced coronary artery disease or severe infection. When using prednisone most practitioners start at a dose of 20–40 mg per day and gradually taper and discontinue the drug over 10-14 days.

### Intraarticular corticosteroids

Intraarticular corticosteroids have a role in the treatment of mono- or oligoarticular gout. The absence of joint infection should be confirmed before injection of corticosteroid. The dose of steroid varies based on the size of the joint involved. (Table 2) Some potential (but rare) side effects of intraarticular corticosteroids include skin atrophy and septic arthritis. Systemic absorption does occur, but the clinical impact of this effect is mild and short-lived.

### ACTH

Synthetic adrenocorticotropic hormone (ACTH) is another steroid preparation that has been useful in the acute set-

<table>
<thead>
<tr>
<th>Joint</th>
<th>Intra-articular corticosteroid dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee</td>
<td>40 mg triamcinolone</td>
</tr>
<tr>
<td>Ankle</td>
<td>30 mg triamcinolone</td>
</tr>
<tr>
<td>Wrist</td>
<td>30 mg triamcinolone</td>
</tr>
<tr>
<td>Elbow</td>
<td>30 mg triamcinolone</td>
</tr>
<tr>
<td>Metacarpophalangeal joints</td>
<td>10 mg triamcinolone</td>
</tr>
<tr>
<td>Proximal interphalangeal joints</td>
<td>10 mg triamcinolone</td>
</tr>
</tbody>
</table>
tong; however, it is not universally available. It is administered by intramuscular or intravenous injection of 40-80 IU. ACTH induces glucocorticoid release from the adrenal cortex. Drawbacks include rebound attacks, mild hypokalemia, worsening of glycemic control, and fluid retention. Other features that render this a less attractive option are cost, inconvenience of parenteral administration, and dependence on the sensitivity of the adrenal cortex.

**Anakinra**

The inhibition of IL-1 has been investigated as a novel therapeutic option for the treatment of acute gout. Monosodium urate crystals activate toll-like receptors and the NALP3 "inflammasome complex" to release IL-1β from monocytes and synovial mononuclear cells. So et al conducted a pilot study in which 10 patients with gout who were unable to tolerate conventional anti-inflammatory medication were given anakinra, an IL-1 inhibitor, daily at a dose of 100 mg subcutaneously for three days. All 10 patients had a rapid response and no adverse side effects were noted. While these preliminary data are promising, these findings need to be confirmed in a larger, controlled study.

**Common Pitfalls in the Management of Acute Gout**

Patients taking uric acid lowering agents (allopurinol, febuxostat, or probenecid) should continue these medications during an acute attack. There are no data to suggest that a flare is exacerbated by continuing anti-hyperuricemics. An acute attack may, however, be precipitated during initiation or dose adjustment of urate lowering therapy if the patient is not also taking a prophylactic medication (colchicine or NSAIDs). This occurs as a result of fluctuations in serum uric acid levels that may trigger an acute attack.

In one study, a retrospective chart review was performed to assess the treatment of acute gout in hospitalized patients. Only 25% of patients diagnosed with acute gout had arthrocentesis performed for crystal analysis, despite this being the gold standard. Combination anti-inflammatory agents (prednisone with colchicine, NSAIDs with colchicine, and steroid with NSAIDs) were used in over 50% of patients. There is a paucity of evidence to support such treatment, and this practice increases the risk of combined side effects.

Over 80% of patients given colchicine or NSAIDs had renal failure. Renal failure increases the time needed for clearance of colchicine, thereby increasing the risk of toxic side effects. NSAIDs should be avoided in patients in this setting given their potential for further renal toxicity.

Other pitfalls in management include delays in treatment, insufficient doses of medications, and premature termination of treatment. An appropriate dose of anti-inflammatory medication (NSAIDs, colchicine, or corticosteroids) should be given at the first onset of symptoms. Treatment should be continued until symptoms have resolved and then tapered for at least 2-3 days until all signs of inflammation are absent.

**Summary**

A definitive diagnosis of acute gout is made by detection of monosodium urate crystals in the synovial fluid of an inflamed joint. However, when this is not feasible a clinical diagnosis can sometimes be made with reasonable accuracy. The mainstays of acute gout management are colchicine, NSAIDs, and systemic or intra-articular corticosteroids. NSAIDs are preferable to colchicine because of their more favorable side effect profile. Successful treatment occurs with the prompt initiation of high dose short half-life NSAIDs. Since many patients with gout have comorbidities that preclude the use of NSAIDs or colchicine, systemic corticosteroids are commonly used to treat acute gouty arthritis. Intra-articular injections are appropriate in the setting of mono- or oligoarticular involvement. Adequate duration of anti-inflammatory therapy and careful patient education are essential elements of successful therapy for acute gout. Evaluation and management of hyperuricemia should be undertaken when all symptoms of acute gout are resolved and the patient is stable on daily prophylaxis with NSAIDs or colchicine.

**References**

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Despite a sound understanding of the synthetic and metabolic pathways that control serum uric acid levels, clinicians have been limited to a few urate lowering agents and one urate synthesis inhibitor since the development of allopurinol in 1956.\(^1\) Febuxostat (Uloric) became the second urate synthesis inhibitor when the Food and Drug Administration (FDA) approved it in early 2009. The role of febuxostat in the management of hyperuricemia and gout remains to be fully determined. This review will discuss the traditional agents used for the lowering of serum uric acid and address the potential benefits febuxostat may offer in clinical practice.

**Sources of Serum Urate**

Serum uric acid accumulates from the metabolism of purine nucleic acids which are derived either from cellular breakdown or directly from foods rich in purines such as red meats, beer, shellfish, and yeast extracts.\(^2\) Catabolism of purines is mediated through a cascade of well regulated enzymes that includes phosphoribosyl pyrophosphate synthetase (PRPS), hypoxanthine-guanine phosphoribosyltransferase (HRPT), and xanthine oxidase (XO).\(^3\) (Figure 1) A deficiency in HRPT or PRPS over-activity results in hyperuricemic syndromes like Lesch-Nyhan and Kelley-Seegmiller, with resultant gouty arthropathy in some patients. Unlike other animal species, humans and other primates do not express uricase, the enzyme which converts uric acid into the more soluble allantoin for excretion. Uric acid is therefore the end product in human purine catabolism and is ultimately excreted in urine and also, to a lesser proportion, in the stool. Drugs that inhibit xanthine oxidase and uricosuric agents that increase renal uric acid excretion are the cornerstone of therapy for hyperuricemia.

**Asymptomatic Hyperuricemia**

Uric acid exceeds its solubility in extracellular spaces such as the joint or soft tissue at a concentration of 6.8 mg/dL. Uric acid precipitates as monosodium urate (MSU) crystals in these compartments but for varying reasons, does not always cause an inflammatory response. The risk of having symptomatic hyperuricemia is related to the degree of serum urate elevation. In an early study, Campion et al. demonstrated that in patients with serum urate levels less than 7.0 mg/dL, the annual incidence of gouty arthritis was only 0.1% as compared to 4.9% in patients with serum rate greater than 9.0 mg/dL.\(^4\) However, after five years of follow-up even patients with serum urate greater than 9.0 mg/dL only had a cumulative incidence of gouty arthritis of 22%, demonstrating that a large proportion of patients with increased serum uric acid remain unaffected by gout. While the extent of hyperuricemia is correlated with a higher risk for gouty arthritis, hyperuricemia for any individual can persist for years without symptoms. Therefore, empiric treatment of asymptomatic hyperuricemia is not advised.

**Indications for Treatment of Hyperuricemia**

Pharmacologic reduction of hyperuricemia is generally required in patients with symptomatic disease. Most commonly, urate lowering agents are indicated for patients with more than one episode of acute gouty arthritis, all patients with tophaceous gout and chronic gouty arthritis, and patients with uric acid renal stones. Other situations that require the use of allopurinol include hyperuricemia associated with known inherited disorders like the Lesch-Nyhan and Kelley-Seegmiller syndromes, or more frequently as prophylaxis before cytolytic therapy for cancer.

**Treating Hyperuricemia: Dietary Approach and Adjunctive Therapy**

Approximately 60% of patients who have experienced acute gout arthritis experience a repeat attack within one year, based on historical data.\(^7\) Prospective data to guide physicians are lacking, but it may be beneficial to attempt lifestyle and dietary modification rather than to commit to lifelong therapy in patients with a single attack of gout. If this fails, antihyperuricemic therapy will be necessary.

Patients should be educated on dietary and lifestyle modifications that can reduce serum urate levels. These patients should attempt to reduce purine-rich foods such as red or organ meats and shellfish, and they should avoid alcohol intake, especially beer. Weight loss and...
exercise have been also been shown to have a positive impact on urate reduction.\textsuperscript{6} From the clinician’s standpoint, loop diuretics or thiazide diuretics should be avoided when possible. Agents with mild uricosuric effects like losartan may be considered instead for patients with hypertension. Likewise, fenofibrate may be preferred for select patients with hypercholesterolemia and gout.

**WEIGHING THE DECISION TO TREAT HYPERURICEMIA**

The decision to initiate and commit to treatment with a long term serum urate lowering agent is not an easy one for patients. In a retrospective study of 9,482 patients prescribed allopurinol for gout, only 65.9\% filled their initial prescription; of these, 18\% were fully compliant with the treatment regimen recommended by their primary providers.\textsuperscript{7} It is often difficult for clinicians to convince patients of the need to continue these medications during clinically quiescent periods, especially given the high medical costs incurred by patients with multiple medical conditions.\textsuperscript{8}

Measurements of urine uric acid levels are no longer routinely performed during the workup of gout. Twenty-four hour urine uric acid and creatinine measurements continue to be useful in patients who are younger than 25 years old, those with strong family history of early onset gout, or patients with nephrolithiasis.\textsuperscript{9} If urine uric acid is greater than 800mg per day, the patient is likely an over-producer of purines where hemolytic syndrome or lymphoproliferative disorders might be considered. If the patient has a uric acid clearance of less than 6ml per minute, then renal excretory defects such as Barter’s or Gitelman’s disease or lead nephropathy may be possible.\textsuperscript{9} The urinary excretion of uric acid should be measured if uricosuric therapy is being considered, as these drugs will increase the possibility of renal stone formation in patients with high uric acid excretion.

The treatment of acute gout is discussed elsewhere in this journal. It is important to note that during the “intercritical” period, when the patient is tapering off higher doses of non-steroidal anti-inflammatory drugs (NSAIDs) or oral prednisone, colchicine at 0.6 mg twice daily has been shown to be useful for preventing recurrent flares. Colchicine or NSAID prophylaxis should be given during the initiation of anti-hyperuricemic therapy and continued until the patient has been free of acute attacks for a prolonged period of time.

**URICOSURIC AGENTS**

Uricosuric agents are employed less frequently than allopurinol primarily because of the need for three times daily dosing and the requirement for measuring 24-hour urinary uric acid before beginning therapy. Uricosurics continue to be useful in patients with allopurinol intolerance or hypersensitivity or in patients with known defects in renal excretion of uric acid.

Probenecid is the primary uricosuric agent available in the United States. It blocks the renal proximal tubule exchanger URAT1, which reabsorbs uric acid. A study of forty patients with uncomplicated chronic gout receiving probenecid, or sulfipyrazone versus allopurinol found the similar recurrence rates of acute gouty attacks, although serum urate level was lower in the allopurinol group. Other smaller trials suggest that uricosuric agents are just as efficacious as allopurinol in chronic gout patients without renal impairment.\textsuperscript{8}

Table 1. Suggested Dosing of Allopurinol. Treatment should be initiated on a dose of allopurinol adjusted according to renal function. Then the dose of allopurinol should be titrated until serum uric acid is less than 6.0 mg/dL.

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>Initial Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD</td>
<td>50mg Q Day (Administer after HD)</td>
</tr>
<tr>
<td>0</td>
<td>50mg Q 3 Days</td>
</tr>
<tr>
<td>1-10</td>
<td>50mg Q 2 Days</td>
</tr>
<tr>
<td>11-20</td>
<td>50mg Q Day</td>
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<tr>
<td>21-40</td>
<td>50mg Q Day</td>
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<td>41-60</td>
<td>100mg Q Day</td>
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<tr>
<td>61-80</td>
<td>100mg Q Day</td>
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<tr>
<td>81-100</td>
<td>100mg Q Day</td>
</tr>
<tr>
<td>101-120</td>
<td>100mg Q Day</td>
</tr>
<tr>
<td>&gt; 120-140</td>
<td>300mg Q Day</td>
</tr>
</tbody>
</table>

CrCl: creatinine clearance; HD: hemodialysis.

Initial dosing of probenecid is recommended to start at 0.5 grams per day to minimize flares, and then titrated to a typical dose of 0.5 grams twice a day to three times a day to a maximum dose of 3 grams per day. The contraindications for uricosurics are patients who have any history of nephrolithiasis, patients with low urine output, or patients with reduced renal excretion (GFR less than 60ml per minute). Significant drug interactions include the elevation of penicillin, salicylate, dapsone, heparin or zidovudine serum concentration by inhibition of renal tubular excretion.\textsuperscript{5}

**XANTHINE OXIDASE INHIBITORS**

**Allopurinol**

Allopurinol and its metabolite, oxypurinol, competitively block xanthine oxidase conversion of hypoxanthine to xanthine and xanthine to uric acid. It is very effective in lowering serum urate levels and reducing tophus size as shown in a study of sixty-three patients who received allopurinol with or without concurrent bezbromarone, a uricosuric used in Europe and Asia.\textsuperscript{10}

Allopurinol is generally well tolerated, with mild gastrointestinal intolerance being the most common side effect experienced. **Allopurinol hypersensitiv-**
ity syndrome (AHS) may occur during the first three months of therapy. It is estimated to occur in 0.1% of patients and has a mortality rate of as high as 26%. Signs and symptoms of AHS include severe exfoliative dermatitis progressing to toxic epidermal necrolysis, stomatitis, peripheral eosinophilia, leukocytosis, fever, hepatitis, and acute renal insufficiency. There exists no specific treatment for AHS other than discontinuation of allopurinol and supportive care, with the role of systemic steroids unsubstantiated. Patients who develop an allergic reaction to allopurinol can be treated using an allopurinol desensitization protocol. Desensitization, however, should be attempted only in patients with mild to moderate reactions to allopurinol ranging from maculopapular rash, mild fever to peripheral eosinophilia without any liver or renal impairment.

Initial allopurinol dose should be based on the patient’s GFR. A suggested starting dose according to creatinine clearance is provided in Table 1. The starting dose, however, is often inadequate to reduce serum urate to target levels. In a study of 250 patients in New Zealand who were prescribed a fixed allopurinol dose based on renal dosing calculator, only 19% of the study cohort reached a target serum urate level of less than 6.0 mg/dL. Uric acid levels should be monitored at six to eight weeks intervals, and allopurinol increased until the serum uric acid is less than 6.0 mg/dL.

**Febuxostat**

Febuxostat is a non-purine inhibitor of xanthine oxidase. Because it is dissimilar from the structure of purines, it does not interfere with purine and pyrimidine metabolism. Furthermore, it is degraded by glucuronide formation and oxidation in the liver, with half of all febuxostat and its active metabolites excreted in the stool, with the other half in the urine. Unlike allopurinol, febuxostat does not require renal dose adjustment. The major reservation is its use in patients with underlying liver disease, current alcohol use, or history of alcohol abuse, but short term use of febuxostat 80mg daily for seven days was demonstrated to be safe in 8 patients with Child-Pugh A liver disease and 8 patients with Child-Pugh B disease.

In the first phase III randomized double-blind 52-week multicenter trial of 762 patients with gout with serum urate levels greater than 8.0 mg/dL (FACT trial), febuxostat 80mg daily or febuxostat 120mg daily was compared with allopurinol 300mg daily. The study population was composed primarily of Caucasian men with a mean age of 51 years. Patients with a creatinine greater than 1.5mg/dL, any history of alcohol abuse, or current alcohol use of more than fourteen drinks a week were excluded from the study. The authors found that a higher proportion of patients in the two febuxostat groups (53% & 62%) achieved serum urate levels of less than 6.0mg/dL than patients in allopurinol controls (21%). Patients receiving febuxostat also experienced a larger decrease in tophus size compared to patients on allopurinol. An important criticism is that patients given allopurinol were not allowing dose increases during the study. This arbitrary distinction underestimates the true efficacy of allopurinol in clinical practice.

Adverse events were minor across all groups. Self limited reactions like diarrhea, headache, joint discomfort, and mild elevations in transaminase levels occurred in similar frequency in all groups. However, it was noted that significantly more patients in the febuxostat groups dropped out of the study and experienced more acute gout flares. An unexpected finding was four deaths in the febuxostat cohorts, as opposed to none in the allopurinol arm. The cause of death appeared unrelated to febuxostat and ranged from congestive heart failure, metastatic colon cancer complications, cardiac arrest, and anti-coagulation related diathesis.

To address some of the concerns raised in the FACT trial, a 28-week, phase III randomized-double-blind placebo controlled trial was completed in 2008 (APEX trial). The same investigators studied 1,072 gout patients with serum urate greater than 8.0mg/dL. This study included patients with creatinine between 1.5 mg/dL to 2.0mg/dL. The demographics of the study population were similar to the FACT trial, composed predominantly of Caucasian men. The authors looked at five study cohorts: patients either received febuxostat 80mg daily, 120mg daily, 240mg daily, allopurinol dosed according to serum creatinine levels, or placebo. Similar to the FACT trial, the APEX trial found that febuxostat reached the primary endpoint of serum urate less than 6.0 mg/dL in higher proportion by the end of the study: 36% of patients on febuxostat 80mg; 52% of patients on febuxostat 120mg; 66% of patients on febuxostat 240mg; 10% of patients on allopurinol; 0% of patients on placebo. Similar results were seen in patients with renal impairments. They were unable to demonstrate a decrease in tophus size or number due to the short length of the study. The occurrence of minor and serious adverse reactions requiring hospitalization was similar across study group. Liver enzyme dysfunction was higher in patients receiving either febuxostat or allopurinol compared to placebo controls (19%-25% versus 15%). Unlike the FACT trial, no deaths were reported during the study.

Though the authors had intended to study febuxostat in patients with impaired renal function, only 40 patients recruited had creatinine between 1.5mg/dL to 2.0mg/dL. Additionally, patients with more impaired renal functions were excluded from this study, as in the FACT trial. Published data on febuxostat use patients with renal impairment or hepatic impairment continue to be lacking and will require ongoing post-market surveillance.

**Conclusion**

Management of hyperuricemia in the setting of recurrent or tophaceous gout has traditionally relied on the use of allopurinol. Uricosuric agents have proven utility but are beneficial in a limited number of situations. Febuxostat as described here and synthetic uricase as described elsewhere in this journal are much welcomed additions to the rheumatologist’s armamentarium. Experience with these agents is limited and their cost-effectiveness remains unstudied. Therefore, allopurinol will remain the first line agent for uric acid lowering therapy. In patients with clinical factors that preclude the use of probenecid and in those who had experienced allopurinol hypersensitivity, febuxostat may prove to be a valuable alternative.
REFERENCES


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Gout has long been associated with old men with red faces who imbibe heavy alcohol and eat rich meats. Because of this, it was dubbed “the disease of Kings.” These misconceptions persist, and many people continue to believe that gout is a condition that is self-inflicted by overindulgence, occurs only in men, with symptoms confined to the foot.

**WOMEN GET GOUT TOO**

Gout is not rare in women. Although women comprise approximately 5% of all gout patients, the incidence has risen. According to Arromdee, et al, the incidence of gout in men and women has doubled over the past 20 years. Because it is principally a disease seen in men, gout is often misdiagnosed in women, and/or the diagnosis is often delayed.

In this article we will discuss some of the epidemiological, clinical and treatment aspects that distinguish female from male gout patients.

Women are older than men at the time of diagnosis of gout. In several studies, the mean age at diagnosis of gout was 7-12 years greater in women than in men. In patients older than 60 years with newly diagnosed gout, approximately half will be women. The incidence of females with gout peaks at age 80 years and older.

One important difference between women and men with gout is the change in urate levels that occurs in women after menopause. Serum urate concentrations in men average about 1mg/dl higher than those in adult women until after menopause, at which time the serum levels of uric acid in women approach or equal those in men. In 2008, Hak and Choi reviewed data from the Third National Health and Nutrition Examination Survey, and published their findings on menopause, postmenopausal hormone use, and serum uric acid levels in women. They concluded that menopause was associated with higher serum uric acid levels, and that postmenopausal hormone replacement was associated with lower serum uric acid levels, suggesting that estrogen plays a key role in protecting women from hyperuricemia and gout.

Pui et al found further evidence of the role of estrogens in regulating serum uric acid: they found early onset hyperuricemia and gout following hormone treatment given for the purpose of female to male gender reassignment. Estrogen may enhance renal uric acid excretion. During gender assignment, testosterone treatment likely dampens the effect of estrogen, and causes increased serum urate concentrations by reducing renal excretion of uric acid. It was also suggested that sex hormones may also influence the expression of acute gout through effects on the inflammatory response to monosodium urate crystals.

Another important risk factor for gout in women is the use of diuretics. Both loop and thiazide diuretics increase serum uric acid. Meyers, et al., analyzing 92 women with gout, found that 78% of them were receiving diuretic treatment. Although many of the women who were taking diuretics were postmenopausal, diuretic use appears to be an independent risk factor. Yu, et al found that 18% of premenopausal women had “diuretic-induced acute gouty arthritis.” In a case report Hayem et al. showed that diuretic abuse for the purpose of weight loss was implicated in three premenopausal women with tophaceous gout. Another case report described a 32-year-old woman with anorexia nervosa who developed tophaceous gout. This case was also attributed to diuretic abuse, as she had been taking furosemide to lose weight since age 18.

Several studies have shown an increased incidence of renal insufficiency in women with gout. Renal insufficiency can reduce the serum uric acid excretion, thereby increasing risk for hyperuricemia and gout. Puig, et al. found that more than 50% of women with gout had renal insufficiency, whereas approximately 11% of men with gout had renal insufficiency. This report described four of five premenopausal women with gout, none of whom were taking diuretics. Also, Yu’s study noted some form of renal disease in 85% of premenopausal women with gout. Many of the reports that showed higher prevalence of renal insufficiency in gouty women also showed a higher prevalence of hypertension and diuretic use.

A widely observed association in female gout is the presence of pre-existing joint disease, in particular, osteoarthritis (OA). (Figure 1) Lally, et al. found pre-existing joint disease in 70% of women and in only 37% of men. This paper described 6 women with tophi and/or acute gouty arthritis in association with Heberden’s or Bouchard’s nodes. Similarly, Puig et al. reported 76% of women with gout had OA compared to 40% of men. The latter study also found a relationship between nodal OA and monosodium urate crystal deposition in women with gout and nodal disease in the hands. The presentation of acute or subacute gout in the fingers of a woman with nodal OA may contribute to a delayed or in-

**Table 1. Differences between Women and Men with Gout**

<table>
<thead>
<tr>
<th></th>
<th>Women Older (50s-60s)</th>
<th>Men Younger (40s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal insufficiency</td>
<td>More (~28%)</td>
<td>Less (~16%)</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>Less</td>
<td>More</td>
</tr>
<tr>
<td>Family history</td>
<td>More (~50%)</td>
<td>Less (~25%)</td>
</tr>
<tr>
<td>Pre-existing joint disease</td>
<td>More (~30%)</td>
<td>Less (~13%)</td>
</tr>
<tr>
<td>Obesity</td>
<td>Less</td>
<td>More</td>
</tr>
<tr>
<td>Diuretic use</td>
<td>More (~30%)</td>
<td>Less (~13%)</td>
</tr>
</tbody>
</table>
correct diagnosis.

Although environmental factors influence gouty arthritis, hereditary factors also play a role. Studies demonstrate an increased prevalence of gout in relatives of patients with gout. Serum uric acid levels are controlled by multiple genes in both genders. However, this seems to be more strongly associated with women. In one example, Yu found a higher familial influence in premenopausal gout patients, citing a positive family history of gout in 59% of premenopausal patients, versus 34% in postmenopausal ones.9

There also seems to be a relationship between serum glucose levels and uric acid levels. In the Third National Health and Nutrition Examination Survey, Choi and Ford observed that individuals with moderately elevated hemoglobin A1c levels (6.0-6.9), may be at higher risk of hyperuricemia and gout, particularly in women, however, higher HbA1c levels were associated with a lower risk of these conditions, particularly in men.13 This observation corresponds to Chou’s report in 2001, which states that hyperuricemia in women was correlated with older age, higher fasting serum insulin levels, plasma glucose and hyperinsulinemia.14 It is suggested that there is a uricosuric effect of glycosuria, which occurs when the blood glucose level is greater than 10 mmol/l.

Several articles on risk factors for hyperuricemia and gout note the association of obesity and alcohol consumption; however, these associations are not as strong in women as they are in men. Puig reported the incidence of obesity seen in his gout population was approximately 10% less in women, compared with the men in the study. And, in the comparison between women and men with gouty arthritis in Lally’s study, that less than 9% of the women had associated alcoholism, compared to 45% of men.2,5

**Clinical Manifestations**

The articular findings of gout are similar in men and women. Podagra is commonly the initial manifestation of gout in both genders. However, during the course of the disease, women tend to have more upper extremity joint involvement, and the onset of the gout attack is more often insidious in women. In some studies, women were more often afflicted with polyarticular gout. In fact, in an analysis of 92 women with gout by Meyers, et al, 70% of women presented with pauciarticular or polyarticular disease, and only 24% of those patients gave a history of preceding acute monoarticular attacks.6 In some studies, women were shown to have higher incidence of tophi at presentation. Lally’s study, however, did not find a significant difference between tophi in men versus women at presentation.2

According to the data reported by Puig, et al, the mean serum uric acid levels in women (541µmol/L) with gout has been shown to be significantly higher than those seen in men (476µmol/L). This finding was supported by several other studies, including the studies by Lally and Meyers.2,6 Puig also noted a lower mean urinary uric acid excretion in women with gout. This finding was independent of age, renal insufficiency, alcoholism or previous diuretic use.5

The diagnosis of gout should especially be considered in postmenopausal women, who have associated co-morbidities, women who are taking diuretics, women who have a positive family history, or women who present with an atypical pattern of inflammatory arthritis. Special attention should be given to women with nodal OA in order that coexisting gouty arthritis not be overlooked.

**Treatment Considerations**

Once the diagnosis of gout is made, treatment is basically the same in men and women. Recommendations are aimed at decreasing the modifiable risk factors, i.e., avoid alcohol, discontinue diuretics if possible, maintain normal serum glucose levels and blood pressure, maintain ideal body weight and consume a diet low in red meat, fructose, and shell fish.

The use of medications is often required for treatment of acute gout and maintenance of normal serum uric acid. The most commonly recommended therapies for acute gout include nonsteroidal anti-inflammatory drugs (NSAIDs), such as indomethacin or naproxyn, intra-articular corticosteroid injections, oral colchicine, and oral corticosteroids. Uricosuric drugs such as probenecid, and the xanthine oxidase inhibitors allopurinol, and the newly FDA approved drug febuxostat are indicated for the control of hyperuricemia in gouty patients. The proper use of these medications is discussed elsewhere in this journal.

Premenopausal women who are pregnant, or plan to become pregnant require special consideration. Colchicine and allopurinol are both classified as category C. Both enter the breast milk, and should be used with caution. NSAIDs are category C/D. They also enter the breast milk, and use is not recommended in females who are or may become pregnant. Sufficient data on febuxostat is not available for use in pregnant or lactating women, therefore, avoidance is recommended in that group. For acute flares of gout in pregnant or lactating women, prednisone may be the best option for treatment.
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REFERENCES


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Treatment options for gout are well established and reasonably effective. They include anti-inflammatory agents such as non-steroidal anti-inflammatory drugs (NSAIDS), glucocorticoids and colchicine and urate-lowering therapies such as allopurinol and probenecid. However, despite the availability of effective urate-lowering therapy, there remains a subset of patients with gout who, despite aggressive therapy, have intractable disease, manifest as recurrent gout flares, chronic arthritis and progressive tophaceous deposits. These patients are referred to as having “refractory gout” or “treatment failure gout” (TFG). The term “treatment failure gout” includes five ways by which patients may develop poorly controlled disease. These pertain mainly to the use of urate-lowering therapy and include delayed prescribing, inadequate dosage, intolerance, noncompliance and inadequate response in spite of generally acceptable dosages. (Table 1) The new xanthine oxidase inhibitor febuxostat (Uloric) has not been studied in TFG, but may ultimately prove useful for this indication. Febuxostat is discussed elsewhere in this journal.

Regardless of the pathway, all patients with treatment failure gout are unable to reduce and maintain serum urate below the therapeutic target of 6 mg/dl. An estimated 100,000 to 300,000 of the nearly 3 million cases of gout in the US are not adequately managed with current therapies. Additionally, many patients with gout have significant and multiple co-morbidities that preclude the use of those therapies.

Allopurinol, the most common treatment used to lower serum urate levels, is generally regarded as safe and effective. It lowers serum urate by inhibiting the purine nucleotide pathway enzyme xanthine oxidase. However, about 20% of patients receiving allopurinol report side effects and about 5% discontinue the medication due to intolerance. Allopurinol may also be contraindicated because of potential adverse drug interaction with azathioprine. Moreover, the presence of kidney disease may preclude adequate dosing because allopurinol-related toxicity is increased in the presence of significant renal impairment. Even though severe toxicity is rare, inadequate dosing of allopurinol to achieve target serum urate level <6.0 mg/dl is common. Noncompliance is another common problem with allopurinol: in one study patients in a managed care cohort were non-compliant with allopurinol about 44% of the time.

Probencid is the only uricosuric agent available in the United States. However, its use has declined due to important interactions with several other medications such as heparin, furosemide, aspirin and NSAIDS. Dosing is also a problem since probenecid is optimally administered twice or thrice daily, making full compliance difficult. There is also risk of central nervous system toxicity manifesting as seizures and respiratory arrest at higher doses. Most importantly, probenecid loses all of its uricosuric activity when the glomerular filtration rate falls below 50 ml/minute, a common situation in patients with gout.

Febuxostat is a more potent uricosuric agent than probenecid. It is effective even in patients with moderate renal failure. However, it is potentially hepatotoxic, with reports of fatal hepatitis, and is not commercially available in the United States.

Additionally, the use of uricosuric agents requires that patients maintain adequate hydration because the risk of nephrolithiasis is increased in poorly hydrated patients, particularly individuals with cardiovascular disease or those receiving diuretic agents.

Patients with TFG experience significant joint pain and swelling, impaired functional status, chronic pain and reduced quality of life. In a recent study to assess the quality of life and disability in a group of subjects with TFG, the authors found that severe gout is associated with poor health related quality of life (HRQOL) and disability, especially for patients who experience more gout flares and have greater number of joints involved.

Accordingly there is a need for improved therapies that will allow treatment for this population by controlling the consequences of hyperuricemia. Fortunately, several newer agents developed or being developed will be useful for patients with TFG. We will review pharmacologic therapy and also address the role of surgery in patients with TFG.

Rasburicase

“Urate oxidase” or “uricase” is a hepatic enzyme that catalyses the enzymatic oxidation of uric acid to allantoin, a more soluble and easily excreted end product of purine metabolism. Humans and higher primates experienced the mutational loss of the enzyme uricase during the process of evolution. The absence of a functional urate oxidase gene predisposes humans to hyperuricemia and gout.

In contrast to allopurinol, which prevents the production of uric acid, uricase is capable of reducing existing urate stores such as found in gouty joints and tophi. Thus treatment with uricase has potential as a powerful therapy for the management of severe tophaceous gout.

Two types of uricase, rasburicase and pegloticase, have been studied for the treatment of gout.

Rasburicase

A purified fungal (Aspergillus flavus) uricase has been used for many years in Europe to prevent urate nephropathy during chemotherapy for hematologic
malignancies. A recombinant *Aspergillus flavus* uricase, known as rasburicase, became available in the US in 2002 and has been approved by the Food and Drug Administration (FDA) for use in patients for the prevention of tumor lysis syndrome after chemotherapy. For this indication, the recommended dosage is 0.20 mg/kg per day for 5-7 days administered intravenously (IV). It has been demonstrated to be superior to allopurinol in the control of serum urate in a randomized trial of pediatric and adult patients at risk for tumor lysis syndrome. Although the FDA has not approved rasburicase for the management of gout, a number of case reports and small series have described its use in patients with severe tophaceous gout.

A 56-year-old woman with chronic renal insufficiency and severe recurrent gouty arthritis who had an allopurinol hypersensitivity reaction was treated successfully with 10 IV infusions of rasburicase over 16 months. Rasburicase treatment was well tolerated without allergic side effects, but she did have gout flares during the first three infusions. After the sixth infusion, the patient had dramatic regression of hand synovitis, resolution of gouty tophi and restoration of functional capacity to both hands. Her renal function remained stable.

Another case was reported of a 33-year-old renal transplant patient with recurrent gouty attacks and an allergy to allopurinol. She had also had surgery for recurrent tophi. She was begun on rasburicase infusions at a dose of 0.15 mg/kg IV monthly. Rasburicase therapy was well tolerated and produced no adverse effects other than occasional gout flares which resolved with a decrease in the dose. During the 3 years of treatment the patient experienced resolution of gout attacks; the size of tophi decreased substantially and her functional status improved.

In a retrospective study of 10 patients, the short term safety and efficacy of rasburicase 0.2 mg/kg in monthly vs. daily dosing schedules was compared in patients with renal failure and tophaceous gout, not adequately treated by allopurinol. The 5 patients receiving a daily infusion for 5 days had rapid but not sustained reduction in serum urate concentration and did not have any reduction in tophus size. Fifty percent of the patients in the group receiving monthly infusions for 6 months had reduction in tophus size. Serum urate was dramatically decreased with maximal decline at 7 days. Eight of ten patients experienced gout flares that were treated with colchicine and NSAIDs. Two patients also had hypersensitivity reactions to the medication.

Rasburicase has a short half-life (18 hours) requiring repeated injections. It is known to be antigenic. This raises the concern for hypersensitivity and decreased efficacy with repeated administration. Studies have demonstrated that time to detection of antibodies ranges from 1-6 weeks after administration and that the presence of antibodies is not associated with severe side effects. One of the byproducts of urate breakdown by uricase is hydrogen peroxide. Therefore G6PD deficiency contraindicates treatment with rasburicase because of risk of hemolysis. Other side effects include fever, respiratory distress, sepsis, neutropenia and mucositis.

Although the results from these reports appear promising, data regarding optimal dosing and interval between infusions are lacking due to the absence of larger clinical studies of rasburicase in gout.

PEGLOTICASE

Pegloticase is a genetically engineered, recombinant polyethylene glycol (PEG)-conjugated mammalian uricase. A pegylated form of uricase has been formulated with the potential for reduced immunogenicity and a longer half-life. Pegloticase has been studied extensively to evaluate both efficacy and safety in treatment failure gout. It is undergoing clinical trials in human subjects.

The results of two phase I clinical trials involving subcutaneous and IV infusions of PEG-conjugated uricase (pegloticase) demonstrated that this agent rapidly lowered and maintained serum urate levels at <6.0 mg/dl for a 2-3 week period. The bioavailability, efficacy and tolerability of IV pegloticase were greater than that of subcutaneous pegloticase.

In a phase II trial, 41 patients were randomized to undergo 12 weeks of treatment with IV pegloticase at 4 or 8 mg every 2 weeks for six doses, and 8 or 12 mg every 4 weeks for three doses. Serum uricase activity, serum urate and anti pegloticase antibodies were measured. Pegloticase was effective in rapidly reducing and maintaining serum urate levels at <6mg/dl in most patients in whom conventional therapy had been unsuccessful. The most effective dose was 8 mg every 2 weeks. The most common side effects were gout flares, which were mild to moderate in severity.

The results of phase III clinical trials were presented in abstract form at the American College of Rheumatology meeting in 2008. Two hundred twelve patients with TFG were treated with IV pegloticase or placebo in replicate 6 month randomized, double blind studies. Subjects were randomized to pegloticase 8 mg q2week, 8mg q4week or placebo. The primary endpoint was plasma uric acid concentration <6mg/dl and the secondary endpoints were reduction in tophus size, gout flare incidence, swollen joints, tender joints, quality of life by SF-36 and disability by HAQ-DI and safety. Complete resolution of ≥1 tophus occurred in 21/52 q2week, 11/52 q4week and 2/29 placebo subjects. SF-36 physical component summary score and HAQ-DI for physical functioning improved significantly in both groups.

Gout flares and infusion reactions were the most common adverse events. Infusion reactions were the most common reason for withdrawal. The study concluded that 40% of patients treated with pegloticase achieved primary endpoint.

### Table 1. Mechanisms of Treatment Failure Gout

1. Physician failure to diagnose and treat gout
2. Inadequate dosing of urate-lowering therapy
3. Allergy or intolerance to urate-lowering therapy
4. Inadequate response to adequate dosing of urate-lowering therapy
5. Lack of compliance with prescribed therapy
**Surgical Therapy for Gout**

The use of surgical intervention for gout dates back to the time of Hippocrates, when relief from severe pain was provided by burning the painful tophus with crude flax. Before the introduction of effective urate lowering therapy in the management of gout, surgery was frequently used for cosmetic reasons or for removal of large deposits of sodium urate.18

Tophi are characteristically deposited in articular and periarticular structures, and have a predilection for avascular structures. Nerves, blood vessels and muscles are not usually involved. Straub et al condensed and reclassified the earlier indications of Linton and Talbot for surgery in gout into four main categories: 1) functional: excision to permit wearing of shoes and clothing, restoration of motion, and stabilization of joints; 2) symptomatic: control of drainage and infection, reduction of pain and decompression of nerves; 3) cosmetic restoration and 4) metabolic: decrease of total body urate.19

The role of surgery for gout is now generally limited to the complications of tophaceous disease which include infection, nerve compression due to mass effect of the tophus, joint deformity and intractable pain. Tophaceous gout may compress peripheral nerves, the cauda equina or the spinal cord in which case prompt surgical intervention is needed to prevent permanent neurological impairment.

In a retrospective analysis of 45 patients who underwent surgery for gouty tophi, sepsis control in infected or ulcerated tophi was the main indication for surgery (51%), followed by mechanical problems caused by foot, elbow and hand tophi (27%). Four percent of patients underwent tophus surgery mainly for pain control.20

Recurrence of tophi is unpredictable. In the series of Straub, 36 procedures were performed and tophi recurred in only 3 cases. However, few clinical trials address the long term efficacy of surgery in the management of tophaceous disease.

It is universally recommended that before surgery is considered for the treatment of gout, optimal urate-lowering medical therapy should be employed to reduce the size of tophi.
A 84-year old woman with left-sided pansinusitis had a large mass in the left nasal cavity which was removed with endoscopic surgery. Histologically, the tumor demonstrated highly abnormal malignant cells with increased mitotic activity without necrosis. Immunohistochemically, malignant cells express Pan-Melanoma Marker and S-100 protein. All others, including organ-specific markers are not expressed.

Fortunately, primary malignant mucosal melanoma of the head and neck is rare. Approximately 1% of all melanomas are mucosal melanomas, and ~55% of them involve mucous membranes of head and neck.1

In sinonasal melanoma, ~57% patients present with symptoms of obstruction, followed by epistaxis (52%). In the late stages of disease, rhinorrhea, epiphora, proptosis, facial pain, and swelling may occur.

Once mucosal melanoma is discovered, the main goal is to gain local control at the primary site. If local control is achieved, patients have a better survival and a decreased chance of developing distant metastasis.2

Drug regimens for treating mucosal melanoma are still in the trial phase.

Gene therapy is also a possible treatment modality.

Mucosal melanoma is a rare disease that even with aggressive resection and treatment still has a poor 5-year survival.

REFERENCES:

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Mark Andreozzi, DO, is an otolaryngologist, Cranston, Rhode Island.

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Use of Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers and Lipid-lowering Therapies among Rhode Islanders with Diabetes Enrolled in Medicare Part D Plans in 2006 and 2007

Stephen Kogut, PhD, MBA, RPh, Aisling Caffrey, PhD, and Lynn Pezzullo, RPh

WITH THE INTRODUCTION OF MEDICARE PART D IN 2006, MEDICARE Quality Improvement Organizations (QIOs) were directed to collaborate with Medicare Part D prescription drug plan providers to improve the safety, efficiency and effectiveness of prescription drug use.1 Quality Partners of Rhode Island, the Medicare-contracted QIO for Rhode Island, initiated an effort to improve the quality of medication use among that state’s Medicare beneficiaries with diabetes mellitus. Selecting diabetes presented a logical starting point, because epidemiologic studies have described the under-use of medications.2-7 Additionally, patients with diabetes can be identified from pharmacy claims data with an acceptable level of specificity.

This initiative sought to increase the use of lipid-lowering and angiotensin-directed drug therapies (i.e. angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs)), from the perspective of both prescribing and patient adherence. When this study was initiated, the American Diabetes Association (ADA) recommended that all senior patients with diabetes be treated with statin therapy to achieve cholesterol reduction, regardless of baseline LDL level.3 The ADA also recommended that ACEI/ARB therapy be prescribed for patients having both diabetes and hypertension, a group which comprised “the majority of people with diabetes”.4 The ADA noted that “ACE inhibitors have been shown to improve cardiovascular outcomes in high–cardiovascular risk patients with or without hypertension.”

Quality Partners collaborated with the University of Rhode Island College of Pharmacy, provider groups, and several Medicare Part D drug plans in the state. The initiative included academic detailing by a clinical pharmacist, presentations at physician group meetings, dissemination of educational materials, and targeted letters presenting physician-level prescribing rates for ACEI/ARB and lipid-lowering therapies. The audience learned the utilization rates of ACEI/ARB and lipid-lowering therapies among Part D plan enrollees having diabetes, and the significant differences in the rates of use of these therapies among sub-groups. This report presents that data.

METHODS

We conducted cross-sectional analyses of dispensings of ACEI/ARB and lipid-lowering drugs for two 6-month periods: January 1 - June 30th, 2006; and January 1 - June 30th, 2007. Pharmacy data were provided by several but not all Medicare Part D prescription drug plans operating in Rhode Island during 2006 and 2007. The pharmacy data included patient age and gender; a prescriber identifier (DEA number); the drug name and quantity, and the date of dispensing. For 2007, information describing gender was missing for approximately one-third of patients and was imputed based on the percentage of patients in the population for which gender was documented.

Among patients receiving medications for diabetes, we determined the percentage of patients who were dispensed an ACEI/ARB and a lipid-lowering drug therapy at least once during a 6-month period. Lipid-lowering therapies included both statin and non-statin medications.

We classified age as 50-64 years, 65-74 years, or 75 years of age or older. We hypothesized that medication utilization would be higher among patients with coronary artery disease, and we used the proxy of receiving a prescription for a nitrate-containing product to identify this comorbidity. We also sought to determine if ACEI/ARB and lipid-lowering therapy utilization rates were higher among patients receiving care from one of the physician group practices that were participating in this initiative,
and thus compared rates of use among patients receiving prescriptions from physicians affiliated with these groups versus patients receiving prescriptions from physicians not affiliated with these groups. ACEI/ARB and lipid-lowering therapy rates were assessed among patients receiving at least one dispensing for any medication from an endocrinologist as compared to patients who did not receive prescriptions from an endocrinologist.

Within-group comparisons for each year were conducted, and reported here as the frequency and percent of use of ACEI/ARB and lipid-lowering medications. For these analyses we assessed the statistical significance of group differences using the chi-square test.

RESULTS

Part D pharmacy data were provided for nearly 38,000 Medicare beneficiaries, representing approximately 40% of the population of beneficiaries enrolled in Medicare drug plans in Rhode Island during 2006 and 2007. For 2006, we identified 5,009 patients who received medications for diabetes; in 2007, 7,331 such patients.

Table 1 presents descriptive statistics for the patients. Most were older: roughly 12% were younger than 65 years. Approximately 9% of patients received dispensings for nitrate-containing medications. Slightly more than half of patients (56%) received medications from a practitioner affiliated with one of the collaborating group practices. Roughly 15% of patients received medication from an endocrinologist.

Table 2 presents overall rates of use of ACEI/ARB and lipid-lowering therapies for the two periods. For the analysis using 2006 data, 69% of beneficiaries received at least one dispensing for an ACEI or ARB medication, and 63% of patients received at least one dispensing for a lipid-lowering drug. In the following year, 70% of patients received at least one dispensing for an ACEI or ARB medication, and 65% received at least one dispensing for a lipid-lowering drug. The increased utilization of lipid-lowering therapy observed between 2006 and 2007 was statistically significant (p<0.05).

Table 3 presents the patient characteristics identified in Table 1 by ACEI/ARB and lipid-lowering therapy utilization for the 2007 period. Statistically significant differences (p<0.05) were found for nearly all comparisons. Both the youngest and oldest patient groups were found to be less likely to receive these drug therapies, compared with patients in the 65-74 age category. Women received these drug therapies more frequently than men (74% versus 70% for ACEI/ARB therapy; 70% versus 63% for lipid therapies), as did patients who also received dispensings for nitrate-containing products (75% versus 69% for ACEI/ARB therapy; 77% versus 64% for lipid therapies). Patients receiving prescriptions from physicians affiliated with one of the group practice collaborators more frequently received an ACEI/ARB or lipid-lowering therapy (72% versus 68% for ACEI/ARB therapy; 68% versus 62% for lipid-lowering therapies, p<0.05 for both comparisons). Patients who received prescription dispensings from an endocrinologist received both ACEI/ARB and lipid-lowering therapies more frequently, yet only the latter was a statistically significant difference (p<0.05).

DISCUSSION

Our study reveals that a majority of the Medicare beneficiaries with diabetes identified in this analysis were receiving lipid-lowering and ACEI/ARB therapies. But a substantial percentage of patients with diabetes did not receive these therapies.

These results suggest higher ACEI/ARB and lipid-lowering therapy utilization rates in Rhode Island than those reported nationally and in other locales. For example, using data from the 2003 Medicare Current Beneficiary Survey, Tjia and Briesacher reported ACEI/ARB and statin rates of use among seniors with diabetes to be less than 50%. In another study using data from the National Ambulatory Medical Care Survey, Segars and Lea found that fewer than one in four visits made by diabetic patients included mention of the prescribing of a statin medication. In another study of more than 30,000 diabetic Medicare patients in Pennsylvania, Winkelmayer et al reported rates of use of ACEI/ARB therapy to be approximately 50%.

### Table 1. Patient and Provider Characteristics among a Sample of Diabetic Medicare Part D Plan Enrollees in Rhode Island, 2006 and 2007

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>N = 5,009</td>
<td>N = 7,331</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-64</td>
<td>621 (12.4)</td>
<td>916 (12.5)</td>
</tr>
<tr>
<td>65-74</td>
<td>2,080 (41.5)</td>
<td>3,108 (42.4)</td>
</tr>
<tr>
<td>75+</td>
<td>2,308 (46.1)</td>
<td>3,307 (45.1)</td>
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<tr>
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<td></td>
</tr>
<tr>
<td>Female</td>
<td>2,989 (59.7)</td>
<td>4,390 (59.9)</td>
</tr>
<tr>
<td>Male</td>
<td>2,020 (40.3)</td>
<td>2,940 (40.1)</td>
</tr>
<tr>
<td>Coronary artery disease (receiving nitrates)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>461 (9.2)</td>
<td>635 (8.7)</td>
</tr>
<tr>
<td>No</td>
<td>4,548 (90.8)</td>
<td>6,696 (91.3)</td>
</tr>
<tr>
<td>Physician affiliation</td>
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</tr>
<tr>
<td>Group practice collaborator</td>
<td>2,795 (55.8)</td>
<td>4,083 (55.7)</td>
</tr>
<tr>
<td>Other</td>
<td>2,214 (44.2)</td>
<td>3,248 (44.3)</td>
</tr>
<tr>
<td>Endocrinologist care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>708 (14.1)</td>
<td>1,071 (14.6)</td>
</tr>
<tr>
<td>No</td>
<td>4,301 (85.9)</td>
<td>6,260 (85.4)</td>
</tr>
</tbody>
</table>

### Table 2. Use of ACEI/ARB and Lipid-lowering Medications among a Sample of Diabetic Medicare Part D Plan Enrollees in Rhode Island, 2006 and 2007

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td></td>
<td>N = 5,009</td>
<td>N = 7,331</td>
</tr>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>3,478 (69.4)</td>
<td>5,123 (69.9)</td>
</tr>
<tr>
<td>Lipid therapy</td>
<td>3,165 (63.2)</td>
<td>4,796 (65.4)</td>
</tr>
</tbody>
</table>

Abbreviation: ACEI/ARB = angiotensin-converting enzyme inhibitors and angiotensin receptor blockers
Caution should be applied in comparing our results with other research, given differing data sources, populations, and methodologies. Yet it is evident that in our study, ACEI/ARB and lipid-lowering medications were frequently prescribed among diabetic Medicare beneficiaries, and at higher rates than reported elsewhere.

Patients in the 65-74 year old age group received both medication classes more frequently than those in the younger and older age categories. Perhaps this indicates a greater prevalence of severe illness among the oldest patients, such as advanced renal disease and other conditions where lipid management was a lesser priority. Yet the less frequent utilization of lipid-lowering medications among the oldest patients perhaps reflects a lack of clinical aggressiveness that may not be justified.9 The lower frequency of use of these medications among younger patients is also of concern. Physicians may be less inclined to prescribe these medications among younger, healthier diabetic patients. Perhaps this results from younger patients’ poorer adherence in refilling medications. Regardless of the cause, our analyses point out that younger diabetic patients received these medications less frequently.

To determine if these medications were more likely to be received among patients having coronary disease, we used a proxy of receiving nitrate-containing prescriptions to identify such patients. While this method is a poorly sensitive means for identifying patients with coronary disease, we believed it to be sufficiently specific, and would provide some evidence of known-groups validity. The results revealed that patients receiving prescriptions for nitrate-containing medications also more frequently received ACEI/ARB and lipid-lowering medications. Among users of nitrate-containing products, approximately 1 in 4 did not receive a dispensing for a lipid-lowering medication during the study timeframe.

This project entailed collaboration with local physician group practices. We sought to determine if ACEI/ARB and lipid-lowering drug utilization rates were higher among physicians affiliated with these practices, compared with overall rates among physicians not affiliated with these practices. We found that rates of use of these medications were higher for patients receiving prescriptions from physicians affiliated with one of the collaborating group practices.

As a final sub-group analysis, we determined if rates of medication use were higher when a patient was receiving care from an endocrinologist. Indeed, patients receiving medications from an endocrinologist more frequently filled prescriptions for ACEI/ARB and lipid-lowering therapies, with a substantial and statistically significant difference in the use of lipid-lowering therapies (72% versus 64%, p<0.05). While one may theorize that patients receiving care from an endocrinologist may have been further along the continuum of disease, we note that statin therapy is recommended for most senior patients with diabetes.10, 11

Several factors may explain why the utilization rates for these medications are less than 100%. First, the pharmacy claims data used for this analysis identified dispensed prescriptions only. It is likely that many patients were prescribed these medications yet did not refill them, because patient adherence to chronic medication therapies is poor.12, 13 For this reason we applied a liberal threshold in classifying patients as using these therapies, giving credit even if a patient received just one prescription dispensing during the 6-month measurement period.

A second explanation for the lower calculated rates of use of these medications pertains to our inability to identify and exclude patients having a contraindication to these drug therapies. However, for both lipid-lowering and ACEI/ARB medications, many types of contraindications to one class of drugs would not preclude the use of a medication from a different class. For example, ARB medications would be an acceptable alternative for most patients that experienced a bothersome cough from an ACEI. Similarly, because some patients are poorly tolerant of statin medications, we also included non-statin lipid-lowering medications such as fibrates and bile acid resins in our analysis. We do not mean to imply that these other classes of lipid-lowering medications are acceptable and evidence-based alternatives to statin therapy, but rather may have been a necessary second-line option.

Third, patients may have received medications as samples, or bought these medications for cash through discount programs (e.g. $4 generics). The data provided by the Part D drug plans would not have captured this data. Yet the patients in this study were identified as having diabetes based on their receipt of prescription medication dispensings for hypoglycemic medications under Part D, indicating that patients were utilizing their Part D benefit at least to purchase some drugs.

### Table 3. Use of ACEI/ARB and Lipid-lowering Medications According to Patient and Provider Characteristics, January 1 – June 30, 2007 (N = 7,331)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ACEI/ARB n(%)</th>
<th>Lipid therapy n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall percentage:</td>
<td>5,123 (69.9)</td>
<td>4,796 (65.4)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-64</td>
<td>611 (66.7)</td>
<td>591 (64.5)</td>
</tr>
<tr>
<td>65-74</td>
<td>2,280 (73.4)</td>
<td>2,190 (70.5)</td>
</tr>
<tr>
<td>75 +</td>
<td>2,232 (67.5)</td>
<td>2,015 (60.9)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>3,236 (73.7)</td>
<td>3,090 (70.4)</td>
</tr>
<tr>
<td>Male</td>
<td>2,063 (70.2)</td>
<td>1,840 (62.6)</td>
</tr>
<tr>
<td>Coronary artery disease (receiving nitrates)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>473 (74.5)</td>
<td>488 (76.9)</td>
</tr>
<tr>
<td>No</td>
<td>4,650 (69.4)</td>
<td>4,308 (64.3)</td>
</tr>
<tr>
<td>Physician affiliation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group practice collaborator</td>
<td>2,930 (71.8)</td>
<td>2,769 (67.8)</td>
</tr>
<tr>
<td>Other</td>
<td>2,193 (67.5)</td>
<td>2,027 (62.4)</td>
</tr>
<tr>
<td>Endocrinologist care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>770 (71.9)</td>
<td>774 (72.3)</td>
</tr>
<tr>
<td>No</td>
<td>4,353 (69.5)</td>
<td>4,022 (64.3)</td>
</tr>
</tbody>
</table>

Abbreviation: ACEI/ARB = angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

p < 0.05 for all comparisons except by endocrinologist care among patients receiving ACEI/ARB therapy
Fourth, to mitigate the potential effect of being in the Part D coverage gap (i.e. the “donut hole”), we analyzed pharmacy claims data from the first 6 months of the year, before most patients would have fallen into that gap.

**Conclusion**

This report describes rates of use of two clinically important drug therapies for patients having diabetes mellitus. While a majority of patients were receiving these medications, approximately 30% of patients did not fill prescriptions for an ACEI/ARB therapy, while 35% of patients did not receive a dispensing for a lipid-lowering medication. We note that this may reflect either failure to prescribe, or the failure of patient persistence in refilling medication. We cannot ascertain which cause may have contributed the most to our findings.

Patients received these medications more frequently if they were age 65-74 years (compared with younger and older groups), and also if they were female. Patients dispensed medications prescribed by a physician affiliated with one of the collaborating provider groups more frequently received these therapies. Lipid-lowering medications were more frequently utilized by patients under the care of an endocrinologist.

We hope these findings may help identify patients who should be receiving these therapies.

**References**


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Asymptomatic Versus Symptomatic Urinary Tract Infections
In Long-Term-Care-Facility Residents

Porpon Rotjanapan, MD, and David Dosa, MD, MPH

You are in your office seeing patients when a nurse calls from the nursing home to report the urinalysis results of Mrs. X. Mrs. X, 75 years-old, with mild Alzheimer’s dementia, was admitted to the facility for rehabilitation and low back pain control after two falls. Her medical history also includes hypertension, hyperlipidemia, chronic obstructive pulmonary disease (COPD), osteoporosis, and two new vertebral compression fractures. Yesterday the nursing staff noticed foul smelling urine and contacted your covering physician for an order to obtain a clean catch urine. Currently, Mrs. X is afebrile, without any specific complaints. She takes oxycodone and acetaminophen for pain control, donepezil for her Alzheimer’s, a bisphosphonate for her osteoporosis, and an albuterol inhaler for her COPD. She has no medication allergies. The urinalysis reveals 20-30 WBC/ml, 5-10 RBC/ml, and numerous bacteria. A urine culture has been sent but results are unavailable. The nurse asks whether you would like to start antibiotics.

Urinary tract infections (UTIs) are the most common bacterial infection in older populations, both in the community and in the nursing home (NH). UTIs are the most common reason for antimicrobial prescriptions in NHs, and are responsible for the initiation of 20-60% of systemic antimicrobial courses in long-term care residents. Fifty percent of female and 40% of male residents have been reported to have a UTI at one time or another. Nursing home residents are at particular risk for UTIs. Risk factors for infection in this population include immobility, which leads to incomplete bladder emptying; poor hygiene, which favors bacterial growth; incontinence; and age-associated physiological changes, such as a decline in the effectiveness of immune function, loss of estrogen effect on genitourinary mucosa, and changes in colonizing flora.

Despite the high prevalence of UTIs in the NH, most patients are clinically asymptomatic. Numerous organizations (e.g., the American Medical Director’s Association, The Infectious Disease Society of America) have advocated against the treatment of asymptomatic bacteriuria for a number of reasons. First, the presence of asymptomatic bacteriuria in the older patient - including the diabetic - does not predict future UTI or mortality. Furthermore, treatment of asymptomatic bacteriuria does not prevent recolonization or reduce the risk of developing symptomatic UTI. On the other hand, unnecessary treatment of asymptomatic UTIs has been correlated with increased resistance in colonizing bacteria.

Are there criteria that I can use to determine if my patient has asymptomatic or symptomatic bacteriuria?

The Department of Health and Human Services and the Centers for Medicare and Medicaid Services issue yearly guidelines for NHs that state that only residents meeting the McGeer Criteria should be treated for UTI. Urine culture results are not required by these criteria to make a decision on empirical coverage. The McGeer criteria for NH residents without an indwelling catheter state that 3 of the following criteria must be met to identify a UTI: (1) a temperature of 38 C (100.4 F) or higher; (2) new or increased burning sensation on urination, frequency of urination, or urgency of urination; (3) new flank or suprapubic pain or tenderness; (4) change in character of urine; and (5) worsening of mental or functional status. Other guidelines for UTIs proposed by Loeb et al. can also be useful as minimum criteria necessary for empirical antibiotic therapy. For nursing home residents without an indwelling catheter, the Loeb criteria recommend empirical coverage in the setting of: acute dysuria alone or fever (a temperature of greater than 37.9 C (100 F) or an increase of 1.5 C (2.4 F) above baseline temperature) plus at least 1 of the following symptoms: new or worsening urgency or frequency of urination, suprapubic pain, gross hematuria, costovertebral angle tenderness, or urinary incontinence.

You decide not to start antimicrobial therapy for Mrs. X, since her clinical presentation does not meet either the McGeer or Loeb criteria. Three months later, Mrs. X develops dysuria and a fever to 101. Examination reveals tachycardia and suprapubic tenderness. Her urinalysis reveals 30 WBC/ml, 3-5 RBC/ml, 1+ squamous epithelial cells. Given her overt symptoms, you decide to start empirical antibiotics pending results from a urine culture. Your patient has no known drug allergies. Which antibiotic is the best option?

Empirical Treatment for Symptomatic UTIs

The treatment of a lower tract UTI can usually be managed in the NH. Choices for empiric regimens should always be made with the knowledge of the individual nursing home’s antibiogram and resistance pattern, and resistance patterns of the usual colonizing flora. In most nursing homes, the medical director leads the infection control team and assembles an antibiogram for distribution to other clinicians practicing there. If one is not available, there are several general recommendations.
In the setting of an acute uncomplicated bacterial cystitis in an otherwise healthy adult nonpregnant woman, current recommendations suggest that a 3-day course of a recommended antibiotic is as effective as the same antimicrobial given for a longer duration.  

**Trimethoprim-Sulfamethoxazole (TMP-SMZ)** for 3 days is generally considered first-line therapy in non-sulfa allergic patients. Other antibiotics that have been shown to be as equally effective as TMP-SMZ for empiric therapy include: Trimethoprim alone, and renally excreted members of the fluoroquinolone family (e.g., ofloxacin, ciprofloxacin, levofloxacin). Although empirical therapy with a quinolone or other broad-spectrum antimicrobial may be appropriate in selected clinical presentations, the universal application of empirical therapy with a given agent should be discouraged, given the developing resistance to these drugs and the overall expense related to prescribing these medications compared with less costly alternatives.  

Other drugs to consider empirically include Nitrofurantoin and fosfomycin, both of which may become more useful in the future as resistance to TMP-SMZ and trimethoprim alone increases. Nevertheless, nitrofurantoin should not be prescribed for patients with a creatinine clearance < 60 ml/min. Oral amoxicillin-clavulanate may be used as an alternate agent, and is especially useful when a patient has a polymicrobial infection with both susceptible gram-negative rods and *Enterococcus* spp. Finally, several oral second-and third-generation cephalosporins, such as cefuroxime axetil, cefixime, cefditoren, and cefpodoxime, may be used as alternate therapies in the management of UTI when patients cannot tolerate first-line therapies or have organisms with resistance to first-line agents.  

There are many antibiotics that should be avoided for empiric therapy. For example, when given for 3 days, B-lactam penicillins and cephalosporins as a group are less effective than the previously described drugs. Amoxicillin and ampicillin should not be used empirically because many community-acquired and nursing home-acquired strains of *Escherichia coli* produce B-lactamase, which renders these agents inactive. Additionally, numerous studies over the years have shown that B-lactam antibiotics, such as penicillins and cephalosporins are not as efficacious in curing cystitis or eradicating uropathogens from their perineal reservoirs.  

When an oral agent cannot be used, IM ceftriaxone, cefotaxime, or another injectable cephalosporin is appropriate. The duration of treatment for older women with uncomplicated cystitis can be 3 days. Seven to 10 days of treatment should be prescribed for:  

- Women with more than 1 week of symptoms prior to diagnosis  
- Women with structural or functional abnormalities of the urinary tract  
- Infection caused by *S saprophyticus*  
- Men

**Double strength TMP-SMZ is started on Mrs. X. At 48 hours, she feels much better and final urine culture report reveals E coli that is sensitive to TMP-SMZ, ciprofloxacin, levofloxacin, amoxicillin-clavulanic acid, nitrofurantoin, and ceftriaxone. You opt not to change her previous antibiotics. After the three-day course of TMZ-SMZ, Mrs X’s family raises a concern as to whether she should repeat urine tests to confirm success of treatment.**

Routine follow-up, including urine culture, is generally unnecessary after treatment for cystitis, unless symptoms do not abate.  

A review of Mrs. X’s medical records reveals that this is her 3rd UTI in 6 months. The nurse asks you if you would like to consider prophylactic antibiotics to prevent future infections.  

Prophylaxis should not be initiated until the eradication of active infection is confirmed by a negative urine culture at least one to two weeks after treatment is discontinued. Continuous prophylaxis, typically with medication taken once daily at bedtime, is an option for women who have had two or more symptomatic infections during one 6-month period or three or more such infections over a 12-month period. Acceptable choices for prophylaxis include single strength TMP-SMZ ½ tablet a night or three times weekly; Trimethoprim 100 mg nightly; or Nitrofurantoin macrocrystals 50-100 mg nightly.  

The TMP-SMZ prophylaxis is initiated after a negative urine culture at two weeks confirms sterile urine.  

**Summary of recommendations:**  

1. Only patients meeting the McGeer or Loeb criteria should be treated for UTI based on currently accepted guidelines.  
2. Screening for and treatment of asymptomatic bacteriuria is not recommended for diabetic women, elderly, institutionalized patients, and catheterized patients while the catheter remains in situ.  
3. Most patients with consistent symptoms and a positive dipstick test can be treated without the need to obtain a urine culture unless any of the factors associated with an upper tract or complicated infection is present.  
4. Cultures are warranted to identify usual or resistant organisms in women whose symptoms either do not abate or recur within two to four weeks after the completion of treatment.  
5. Prophylaxis might be warranted for two or more symptomatic infections during one 6-month period or three or more such infections over a 12-month period.  

**References**

The vagus nerve, sometimes called the pneumogastric nerve, is the tenth of twelve paired nerves emanating from the primate brain stem and are collectively called the cranial nerves. It is the longest and most complex of the cranial nerves. It emerges from the medulla oblongata, and, via the diaphragm, the abdomen. The vagus nerve has been a sturdy mainstay within textbooks on neuroanatomy for centuries. No medical student could possibly consider promotion to the clinical years without knowing the distribution and sensory/motor responsibilities of this important cranial nerve. And now, with the increasing employ- ment of the vagus nerve stimulator (VNS) as a therapeutic adjunct, the nerve has assumed even greater practical importance. The word, wander, however, is purely Germanic (through various north Teutonic permutations including Old English) with not a trace of Latin or Greek. The word, vandal, derives from it; and through a reverse linguistic migration then turns up in Latin as Vandalus, the name that the Romans bestowed upon the pagan Germanic tribes that ravaged Spain and Gaul particularly during the Fifth Century.

The vagus nerve has been a sturdy mainstay within textbooks on neuroanatomy for centuries. No medical student could possibly consider promotion to the clinical years without knowing the distribution and sensory/motor responsibilities of this important cranial nerve. And now, with the increasing employment of the vagus nerve stimulator (VNS) as a therapeutic adjunct, the nerve has assumed even greater practical importance.

– STANLEY M. ARONSON, MD
Diabetes is the seventh leading cause of death in the United States. People with diabetes have twice the risk of death of people without diabetes of the same age, and complications from the disease can diminish the quality of life. However, people with diabetes can take steps to control the disease and minimize the risks of complications. Rhode Island tracks several Healthy People 2010 goals (HP2010) goals for diabetes. The RI Diabetes Prevention and Control Program is preparing to lead the Statewide Diabetes Health System (SDHS) in strategic planning for the next five years. Prevalence estimates and progress towards clinical preventive services and mortality goals are presented here.

**METHODS**

RI Behavioral Risk Factor Surveillance System (RI BRFSS) data were used to obtain prevalence estimates, track clinical preventive services and obtain denominator data for mortality rates. Methodology of the BRFSS is described elsewhere. In order to increase the statistical reliability of the estimates three years of data (2006, 2007 and 2008) were combined for prevalence estimates among subgroups.

RI mortality data were obtained using the Office of Vital Records of the Rhode Island Department of Health death certificate data. Diabetes (ICD-10 E10-E14) was coded if it was mentioned on the death certificate as either the underlying or a contributing cause of death. A cardiovascular death had cardiovascular disease (ICD 10 I00-I78) listed as the underlying cause and diabetes as any other listed cause. Denominators were obtained from the 2007 US census population estimates. Census denominators were adjusted to produce estimates of the number of diabetics through weighting with three-year age-, race-, and sex-specific average prevalence rates for diabetes from the RI BRFSS.

Prevalence and death rates were age-adjusted to the 2000 United States Standard Population using age groups 0-44, 45-64 and 65+ for general population estimates and age groups 18-44, 45-64 and 65+ for diabetic population estimates. To allow comparisons between groups age-adjusted estimates are reported.

US age-adjusted estimates for clinical preventive services were downloaded from the Centers for Disease Prevention and Control (CDC) Division of Diabetes Translation’s Diabetes Data and Trends webpage. US age-adjusted estimates for diabetes related mortality were downloaded using CDC’s WONDER system.

**RESULTS**

The increase in diabetes among adults in RI closely resembled the nation’s trend. In 2007, an estimated 7.2% of Rhode Island adults aged 18 years or older had diagnosed diabetes compared to 8.0% of United States adults. The proportion of adults in RI with diabetes rose to 11% when the approximately 30,000 adults with diabetes but who were undiagnosed were included with the known 60,000 cases.

Older adults had a high prevalence of diagnosed diabetes compared to younger adults (3% age 18-44, 9% age 45-64 and 17% age 65+). Men had a higher prevalence compared to women (8.1% compared to 6.5%). In Rhode Island the prevalence of diagnosed diabetes was highest among Black, non-Hispanic adults (15.7%) and Hispanic adults (11.3%) compared to White non-Hispanic adults (6.7%) and adults of other or multiracial identity (6.9%). People who preferred to speak Spanish had a higher prevalence (14.4%) compared to those whose preferred language was English (7.1%).

| Table 1: Prevalence of diagnosed diabetes among civilian, non-institutionalized adults age 18+ |
|-----------------------------------------|------------------|------------------|
| Population Group | Age-adjusted prevalence estimate | 95% Confidence Interval |
| All | 7.2 | 6.8, 7.7 |
| **Age Group** | | |
| 18-44 | 2.6 | 2.0, 3.2 |
| 45-64 | 9.2 | 8.3, 10.1 |
| 65+ | 16.9 | 15.7, 18.3 |
| **Sex** | | |
| Male | 8.1 | 7.3, 8.9 |
| Female | 6.5 | 5.9, 7.0 |
| **Race/Ethnicity** | | |
| White, Non-Hispanic | 6.7 | 6.2, 7.2 |
| Black, Non-Hispanic | 15.7 | 11.7, 19.7 |
| Hispanic | 11.3 | 8.7, 13.9 |
| Other/multi-racial | 6.9 | 4.5, 9.3 |
| **Preferred Language** | | |
| English | 7.1 | 6.6, 7.6 |
| Spanish | 14.4 | 10.5, 18.3 |
| **Income** | | |
| Less than $25,000 | 11.4 | 9.9, 13.0 |
| $25,000 - $74,999 | 7.3 | 6.5, 8.1 |
| $75,000+ | 5.2 | 4.4, 6.0 |
| **Education** | | |
| Less than High School | 11.9 | 9.9, 14.0 |
| High School Graduate | 7.5 | 6.6, 8.5 |
| At least Some College | 6.4 | 5.8, 7.0 |
| **Insurance Status** | | |
| Medicare | 16.2 | 12.0, 20.5 |
| Private | 6.6 | 5.9, 7.2 |
| Fee for Service Medicaid | 16.4 | 11.4, 21.5 |
| Uninsured | 4.4 | 1.5, 7.3 |
| Rite Care | 8.9 | 0.0, 19.9 |
| Other | 9.4 | 7.3, 11.4 |
Nationally, low income populations have a diabetes prevalence of up to two times higher compared to wealthy populations. In RI, 11.4% of those with an income less than $25,000, 7.3% of those with an income between $25,000 and $75,000, and 6.9% of those with an income greater than $75,000 had diagnosed diabetes. A similar trend was seen in education: those without a high school education had the highest prevalence of diagnosed diabetes (11.9%) compared to high school graduates (7.5%) or people who had attended college (6.4%). In addition, prevalence of diabetes differed by insurance status. The highest prevalence was among those with Medicare (16.2%) and Fee-for-Service-Medicaid (16.4%) compared to those with RIte Care (8.9%), private insurance (6.6%), other insurance (9.4%), or the uninsured (4.4%). It should be noted, however, that those without insurance were less likely to be screened for diabetes (only 40% screened in the past three years compared to greater than 57% for all other groups).

### Table 2: Healthy People 2010 Diabetes Goals for RI adults age 18+

<table>
<thead>
<tr>
<th>Clinical Preventive Services Goal</th>
<th>HP 2010 Goal</th>
<th>2007 US (Age-Adjusted)</th>
<th>2007 RI (Age-Adjusted)</th>
<th>2007 RI (Age-Adjusted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At Least 2 A1c Tests in Past Year</td>
<td>50%</td>
<td>69.8%</td>
<td>73.1 (67.7, 78.6)</td>
<td>73.1 (66.3, 80.0)</td>
</tr>
<tr>
<td>Annual Dilated Eye Exam</td>
<td>75%</td>
<td>66.3%</td>
<td>81.8 (77.6, 86.0)</td>
<td>78.7 (73.1, 84.3)</td>
</tr>
<tr>
<td>Annual Foot Exam</td>
<td>75%</td>
<td>69.4%</td>
<td>74.9 (70.0, 79.9)</td>
<td>75.1 (68.9, 81.4)</td>
</tr>
<tr>
<td>Attended Diabetes Outpatient Education Ever</td>
<td>60%</td>
<td>57.7%</td>
<td>46.8 (41.0, 52.5)</td>
<td>45.5 (38.3, 52.7)</td>
</tr>
<tr>
<td>Ever had Pneumococcal Vaccine</td>
<td>60% (18-64)</td>
<td>38.9%</td>
<td>59.0 (53.3, 64.7)</td>
<td>47.7 (40.8, 54.6)</td>
</tr>
<tr>
<td>Annual Influenza Vaccine</td>
<td>60% (18-64)</td>
<td>51.3%</td>
<td>69.4 (64.0, 74.7)</td>
<td>62.3 (55.4, 69.3)</td>
</tr>
<tr>
<td>Mortality Goal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduce diabetes-related deaths among people with diabetes</td>
<td>78 per 10,000 adults with diabetes</td>
<td>62 (15.0, 16.0)</td>
<td>78.9 (75.1, 82.7)</td>
<td></td>
</tr>
<tr>
<td>Reduce deaths from cardiovascular disease in people with diabetes</td>
<td>30.9 deaths per 10,000 adults with diabetes</td>
<td>20.2 (55.6, 61.8)</td>
<td>29.0 (26.8, 31.1)</td>
<td></td>
</tr>
<tr>
<td>Reduce the diabetes death rate.</td>
<td>4.5 deaths per 10,000 population.</td>
<td>7.4 (8.5, 9.1)</td>
<td>7.8 (7.5, 8.2)</td>
<td></td>
</tr>
</tbody>
</table>

### Healthy People 2010 Goals

RI met or exceeded the HP2010 goals for adults with diabetes having at least two A1C test in the past year, having an annual dilated eye exam, and for having an annual foot exam. In addition, while RI has not yet met the HP2010 goal for having ever had a pneumococcal vaccine or having had an annual influenza vaccine, RI was substantially higher than the national averages for these clinical preventive services (and for the age group 45-64 RI has met the HP2010 goal for annual influenza vaccine). Only in ever having attended diabetes outpatient education has RI not surpassed the national average or met the HP2010 goal.

RI reduced diabetes-related deaths from 86.3 in 1999 to 78.9 per 10,000 people with diabetes in 2007. This met the HP2010 goal but was higher than the national rate. Cardiovascular disease is a major cause of death among persons with diabetes. Adults with diabetes have heart disease rates about two to four times higher than adults without heart disease. RI reduced deaths due to cardiovascular disease among persons with diabetes from 50.5 in 1999 to 29.0 per 10,000 people with diabetes in 2007. This exceeded the HP2010 goal but was higher than the national rate. Perhaps due to the increasing prevalence of diabetes, diabetes-related deaths among the general population rose from 6.4 in 1999 to 7.8 per 10,000 general population, failing to meet the HP2010 goal and remaining higher than the US average.

### Discussion

While RI met or exceeded five HP2010 goals, more work remains for the SDHS, to reduce the prevalence of diabetes and meet patients’ needs for clinical preventive services.

### Acknowledgement

We thank Kathy Taylor from the Center for Health Data and Analysis for providing death certificate data.

### References

Anyone experienced in performance measurement and improvement has felt the frustration of maintaining high performance levels. Complex systems that we frequently rely on in hospitals are subject to breakdown through distracting forces such as changing priorities, staff turnover without adequate training, shortcutting due to excessive workload, etc. These systems that are codified as policies, procedures and processes seem subject to unforgiving degradation. This predictable deterioration can be referred to as “relapsing mediocrity.” How can one maintain high levels of performance?

**IMPLEMENTATION ISSUES**

It is a basic tenet that processes and procedures should be simple and unambiguous in design. Complexity begets errors through the possibilities of poor handoffs, misapplication, etc. Secondly, complex processes are high maintenance systems that require more resources to keep them functioning at the top level. Managers often do not recognize, or overlook, this second reality. Resources for the ongoing orientation of new employees, refresher training for existing staff, performance measurement of sufficient frequency to be meaningful, periodic feedback reports at both the group and individual level, and, if necessary, revision and retraining must be anticipated in order to avoid relapse (deterioration of performance). A myriad of once-touted creative initiatives that have fallen to mediocre levels because of lost leadership or shifted resource priority can be cited. While organizations can, with fanfare, implement data-based “best practices,” it can be difficult to sustain those initiatives.

The evidence is that reimbursement concerns have long had a higher priority than the quality of care, including patient safety. Concern for the accuracy of financial data in the hospital information system has exceeded the concern for accurate clinical data at the individual provider level. The funds to purchase software and consulting for fiscal services have exceeded those available for risk management and quality management. Quality managers’ failure to maintain many of the past improvements in performance has not helped to forward the argument for resources. Staffing levels of the typical medical staff office and quality management and risk management programs are usually very small compared to the expectations demanded by even the basic requirements of the Joint Commission. The reason seems related to the focus on short term “return-on-investment” priority in resource allocation. Organizations may be reluctant to implement or sustain improved care practices unless they can project a financial benefit. Clinical outcomes have only recently become a consideration in this decision-making process. There are and will be increasing financial consequences of quality problems that will work to shift this balance.

**HOLDING THE LEVEL OF PERFORMANCE**

What can be done now?

Most important is the establishment of genuine organizational support. If there is not commitment and advocacy within senior management that includes willingness to create the proper organizational structure, develop and enforce the necessary policies and procedures and provide adequate resources, it will not be possible to sustain and improve the level of performance within the organization. “Proper organizational structure” is an organizational chart that groups the departments that are key to execution of the collection, performance monitoring, training for performance improvement, performance measurement, quality, risk management/patient safety, physician credentialing and profiling and all related reporting into one administrative division. The “necessary” policies and procedures must be writ-

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**Prevention of Relapsing Mediocrity:**

**How to Maintain Performance Improvement in Hospitals**

*John S. Coldiron, MD, MPH*

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The authors have no financial interests to disclose.
ten to ensure coordinated, uninterrupted flow of information and data that enables accurate monitoring, measurement and reporting, and unambiguous delineation of accountability for performance of each function. “Adequate resources,” at a minimum, means sufficient software and programming to relieve the staff of the mountains of paperwork involved in aggregating data from dissimilar and non-communicating databases to produce non-standardized, individualized reports to countless committees, managers and other publics. It also means providing funds for a dedicated position with Staff responsibility for oversight of the key aspects of performance measurement and improvement within the organization. This position should be viewed as similar to an internal auditor but with an expert level of familiarity with the tools of quality improvement and quality management. The authority to hold any group or individual at any level within the organization accountable for compliance with the established Performance Improvement Plan should be granted. Accountability and reporting should be to a top manager and/or the top Quality oversight body.

The next most important activity is the provision of feedback, formatted to be useful to the target audience. This usually requires multiple revisions to reach a report that conveys the intended information to a large majority of the users. This is the reason for the data collection and analysis and performance measurement. Without the feedback of results, the collection and analysis activities are wasted.

**OTHER CONSIDERATIONS**

As one confronts new issues requiring improvement, the process designed is likely to include new work for someone. It may be a simple item for documentation. But, how long will it really take? How inconvenient is it within the existing workflow of the provider? Is it truly “simple” to do or is it going to place additional stress on individuals who already struggle to meet all the demands placed on their time? Will this “last straw” force a decision to trade one task for another or as a last resort, since documentation is audited, to supply false documentation? Don’t forget the relationship between workload and performance as one approaches capacity for added duties. It may require a work analysis prior to process implementation.

Prudent direct observation of how a process is actually being performed is often dropped from consideration since it can embarrass the observer and is perceived to demean the observed. None-the-less, this is an important function within the performance management program. Familiar examples are anonymous observation of hand-washing and use of a disclosing compound to measure housekeeping effectiveness. Some activities, such as pre-operative protocols to prevent wrong site surgery, are too important to leave any doubt as to whether there is 100% compliance. Documentation is not the same as witnessing it happen.

Don’t forget the characteristics of memory that should influence planning for training and retraining. The simple rule is, the amount learned depends on the time spent learning.4 This, of course, is impacted by the quality of the teaching provided and how well accelerated learning techniques can be applied. Also to be incorporated in the planning is the reality that there is a rapid loss of material that has been learned. The frequency of retraining is modified by the complexity of the process design, the critical rating of the process or procedure, and the frequency the task is performed.

**CONCLUSION**

No professional wishes to affiliate with an institution that is not committed to achieving and maintaining a high level of performance. Mediocre performance demeans the provider and inevitably results in patient harm and wasted resources. Prevention of relapse in performance levels requires planning, persistence and a reward structure that promotes performance advances. Inattention will result in frustration and rework that competes with new initiatives. The energy devoted to maintaining improvement levels should be valued as equally satisfying and beneficial to patients as efforts given to new improvement projects. It requires both to produce a high level of performance throughout the institution.

**REFERENCES**


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The author has no financial interests to disclose.

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FIFTY YEARS AGO - NOVEMBER 1959

Captain George Calvy, MC, NSN, Commanding Officer, the Naval Medical Field Research Lab, Camp Lejeune, presented the following talk at the Interim Meeting of the Rhode Island Medical Society, September 1959: “Staphylococcal Pulmonary Infections.” He reflected on his personal experience in a large hospital, seeing more than 40 cases of antibiotic-resistant staphylococcal pneumonia, “principally due to a hospital acquired strain, diagnosed and treated over 20 years.” Seven members of his staff were infected. He found that adding ristocetin to the medications was effective.

Joseph S. Kars, MD, Kenneth B. Nanian, MD, Lester L. Vargard, MD, and Frank Merlino, MD, all from Rhode Island Hospital, discussed six cases in “Combined Left Ventricular and Suprasternal Percutaneous Puncture in Assessment of Mitral and Aortic Valve Disease.”

Seebert J. Goldowsky, MD, in “The Hospital at Portsmouth Grove,” recounted the history of this Civil War Hospital (called Lovell General) at Portsmouth Grove Avenue on Aquidneck Island. In July 1862 two reporters noted: “The stern realities of war are now brought to our own doors.” Ships brought 1724 sick and wounded patients, casualties from the Army of the Potomac, who had been evacuated from the hospital at Yorktown, PA. A reporter noted that 1800 citizens, including physicians, greeted the patients. At the time the Medical Director at Yorktown was Dr. Francis L. Wheaton, son of Dr. Levi Wheaton (Brown Medical School 1826).

An Editorial, “Quackery on Television,” railed against the “outpouring of tawdry and misleading advertising by the patent medicine industry…There are products for ‘tired blood,’ to quench burning fires in the stomach and to still the hammers that pound and the lightning that flashes inside the cranium. Diagrams show drugs that go ‘round and round and come out here…” The Editorial contrasted the surge of misleading advertising with the industry’s efforts to stop rigged quiz shows.

TWENTY-FIVE YEARS AGO – NOVEMBER 1984

Sarah C. Aronson, Kemi Nakabashi, Michael Siegel, William Q. Sturner, MD, and Stanley M. Aronson, MD, in “Traffic Fatalities in Rhode Island: Part IV. The Pedestrian Victim,” recounted results from a statistical analysis of the 173 pedestrian deaths recorded by the Medical Examiner’s Office 1977-1982 (22.6% of the registered 766 traffic fatalities). Pedestrian fatalities occurred more frequently on weekends, especially Saturdays. Victims had blood alcohol levels at ≥ .06 gm per cent in one-third of the cases. Most fatalities happened after dark.

A.A. Savastano, MD, Chair, Rhode Island Board of Medical Review (established 1976 by the General Assembly) described the make-up: 9 members appointed by the Governor “for not more than 2 consecutive 3-year terms.” The nine comprised 5 physicians, 1 hospital administrator, 2 public sector members, and the Department of Health Director ex officio.

As of 1982, the board had heard 73 allegations (24 related to insurance company repeals, 16 to JUA malpractice cases, 15 to allegations of unprofessional conduct).

John DiOrio, MD, in “Short-Course Antibiotic Prophylaxis in First-Trimester Abortion,” noted: “Complications were acceptably low and consistent with previous studies.” The study followed 478 patients at a local outpatient ambulatory facility from October 1982 to January 1983. A study group received 500 mg tetracycline at the time of the procedure, 500 mg 6 hours later. A standard group received 250 mg at the onset, then 250 mg every 6 hours for 4 days.
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