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A Primary Care Perspective on Gout

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Abstract: Gout causes patients' significant morbidity, work-related disability, loss of productivity, increased health care costs, and even all-cause hospital admissions. As a result, primary care providers must be armed with the knowledge to properly diagnose and manage gout. While many aspects of care remain the same, some key updates that primary care providers must consider when treating their patients with gout will be discussed. In this perspective we will highlight and discuss acceptable circumstances for empiric treatment, renewed emphasis on treat to target, access to commonly used medications, recommended first line agents, and the role of primary care physicians in gout flare prevention among other topics. These strategies will aid primary care physicians treat all but the most complex cases of gout.

Keywords: Acute gout flare, Gout, primary care provider, urate lowering therapy, xanthine oxidase inhibitors.

INTRODUCTION

Although not the most common disorder encountered in the ambulatory care setting, gout causes significant morbidity, work-related disability, loss of productivity, increased health care costs, and even all-cause hospital admissions in our patients. Primary care physicians are treating the vast majority of patients with gout in the United States (U.S.) [1]. With an eye towards promoting and maintaining health, generalists often find gout to be a disabling condition that frequently affects patients with multiple comorbidities. The introduction of the American College of Rheumatology's (ACR) Guidelines for the Management of Gout in 2012 brought increased clarity regarding first line treatment for acute gout as well as standards for long-term management and emphasizes treating-to-target even in the face of comorbidities such as chronic kidney disease (CKD). In this perspective, we will explore how primary care providers are actually using these guidelines and in what areas gout diagnosis, acute treatment, and long-term maintenance practices have changed since their publication.

EPIDEMIOLOGY

It has been well established that the prevalence of gout has been rising in the United States over the last five decades, more than doubling since 1960 [2 - 5]. National Health and Nutrition Examination Survey (NHANES) data from 2007-2008 show the overall prevalence of gout among U.S. adults was 3.9%, and sex and racial differences are seen with male, African-American, and Asian patients disproportionately affected (see Table 1 below) [1]. Its prevalence increases with age as well, reaching nearly 13% in patients 80 and older [4].

GOUT IN PRIMARY CARE

Data from the 2002 U.S. National Ambulatory Medical Care and National Hospital Ambulatory Medical Care Surveys showed that of the 973 million ambulatory care visits in the U.S., 3.9 million were for gout [1].

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More than two-thirds of these patients were evaluated and treated by primary care physicians, whereas only 1.2% were treated by rheumatologists [1]. Reflecting the general epidemiology of gout, the proportion of visits by men was higher (66%) than those by women (34%) [1]. Family practitioners and internists conducted the bulk of these visits but other medicine and non-medicine subspecialists also evaluated patients, and notably most did far more frequently than rheumatologists (see Table 2). This suggests that guidelines and best practices should be messaged most heavily outside the “expert” offices of rheumatologists [1].

Table 1. Prevalence of gout and number of affected adults in the US, NHANES 2007-2008* (Adapted from Zhu, Pandya, and Choi, 2011).

	Prevalence, % (95% CI)	No. of Affected US Adults, Million
Overall	3.9 (3.3, 4.4)	8.3
Sex		
Male	5.9 (4.7, 7.1)	6.1
Female	2.0 (1.5, 2.5)	2.2
Race/ethnicity		
White	4.0 (3.3, 4.8)	6.0
African American	5.0 (3.3, 6.6)	1.2
Mexican American	1.5 (1.0, 2.0)	0.3
Other	3.4 (1.2, 5.6)	0.8
Age category, years		
20-29	0.4 (0.0, 0.9)	0.2
30-39	1.3 (0.5, 2.0)	0.5
40-49	3.3 (1.8, 4.9)	1.5
50-59	3.7 (3.0, 4.4)	1.5
60-69	8.0 (5.8, 10.3)	2.0
70-79	9.3 (6.5, 12.0)	1.5
80+	12.6 (10.1, 15.1)	1.2

*The data were adjusted for clusters and strata of the complex sample design of the National Health and Nutrition Examination Survey (NHANES) 2007-2008, with incorporation of sample weights. CI = confidence interval.

Table 2. Distribution of visits to specialists among patients with a gout visit (none were seen by pediatricians, neurologists, or psychiatrists). (Adapted from Krishnan, Leinesch, and Kwoh, 2008).

Specialty	Visits for Non-Gout Reasons	Visits for Gout	Proportion of All Gout Visits to This Specialty, %	Overall Number of Visits
General/family practice	213,965,547	1,500,425	38.34	215,465,972
Internal medicine	155,488,884	1,203,310	30.75	156,692,194
Orthopedic surgery	38,018,169	9,710	0.25	38,027,879
Cardiovascular diseases	20,430,843	390,774	9.99	20,821,617
Dermatology	32,207,648	19,450	0.5	32,227,098
Rheumatology	3,437,744	46,019	1.18	3,483,763
Other specialties	103,586,205	388,049	8.74	100,490,491
Unknown/not available	83,103,414	235,656	6.02	83,339,070
Total	969,406,505	3,913,056	100	973,319,561

In a veteran population, patients with gout had similar mortality (2.6% vs 2.2%, $p = 0.23$) but significantly more annual primary care visits (3.5 vs 2.7, $p=0.001$) and all-cause admissions to the hospital (18.3% vs 15.1%, $p=0.01$) compared with veterans without gout [6]. Gout was also the primary indication for approximately 0.2% of all emergency department (ED) visits in 2008 [5]. In addition to factors previously identified for increased prevalence for gout (age and male sex), household income <\$39,000, private insurance, nonmetropolitan hospital location, and the location in the Southern U.S. were associated with an increased propensity for ED utilization in gout [5].

PRIMARY CARE AND RHEUMATOLOGY

In the U.S., one in three patients under the age of 65 is referred by his or her primary care physician to specialty care annually [7,8]. Elderly patients are referred at even higher rates, with some data suggesting that patients over the age of 65 receive an average of 2 referrals yearly [8,9]. Multiple studies have attempted to determine the appropriateness of specialty referrals, but there are no available data, which directly evaluate the chief indication for primary care physician referrals to rheumatology. In a limited practice model in which patient self-referral is prohibited, the majority of patients referred to rheumatology had vague or complicated conditions such as mixed connective tissue diseases or fibromyalgia and fewer had straightforward conditions such as osteoarthritis and gout [10].

A survey-based review of referrals from primary care physicians at two academic medical centers showed most referrals were motivated by the generalist's desire to obtain diagnostic or therapeutic advice; or to have the specialist perform a diagnostic or therapeutic procedure [11]. Other studies have shown that primary care providers report inadequate training and a lack of skills and confidence in performing joint exams and procedures, which may help explain these referral trends [12,13].

DIAGNOSIS

Establishing the definitive diagnosis of gout for patients is preferable as life-long urate lowering therapy (ULT) could be considered to prevent future bouts of acute gout as well as progression to chronic, recurrent and/or chronic tophaceous gout. The gold standard for diagnosis of acute gout is the visualization of monosodium urate crystals in fluid aspirated from the affected joint or bursa and the presence of such crystals is pathognomonic for gout [14,15]. The aspirated fluid should be examined under a polarized light microscope to look for negatively birefringent crystals. However, primary care physicians often examine the fluid under light microscopy if a polarized light microscope is not readily available to look for intracellular urate crystals.

Arthrocentesis and microscopic crystal analysis can also be useful in distinguishing other causes of inflammatory arthritis such as septic arthritis, trauma, and calcium pyrophosphate dihydrate deposition disease (pseudogout). There are limitations to diagnosing gout by arthrocentesis including supplies, time, and trained personnel. In these cases, primary care physicians uncomfortable with or unable to conduct arthrocentesis may consult orthopedics or rheumatology. Non-emergent referrals for gout diagnosis are reasonable since crystals can be visualized in fluid from a joint previously affected by gout (even if patients are on ULT) and hence a diagnosis of gout can be established by arthrocentesis during a quiescent period [16,17]. Similarly, fluid aspirated from tophi can diagnose gout with monosodium urate crystal visualization [18]. Although heralding more advanced disease, tophi are easy targets for a needle aspiration and primary care physicians take advantage.

A tentative diagnosis of gout is frequently made by clinical data in the event that arthrocentesis cannot be conducted or has not yet occurred. It should be noted that no validated diagnostic criteria for gout exist; a combination of clinical, laboratory, and imaging data, however, can support a working diagnosis of gout. Data primary care physicians often use include a classic history of an inflammatory, monoarticular arthritis with intercritical periods free of symptoms, onset of maximum symptoms within 24 hours, unilateral first metatarsophalangeal joint attack (podagra), presence of tophi, and hyperuricemia [14]. Baseline uric acid levels are not diagnostic or necessary as some patients will have normal uric acid levels even during acute attacks, and the majority of patients with hyperuricemia will never have a gout attack. Imaging studies including plain radiograph, MRI, ultrasound, and dual energy CT can aid in the presumptive diagnosis of gout, but these studies do not replace the gold standard of crystal visualization. Primary care physicians, however, rarely order these studies to diagnose or manage gout, especially in the era of high-value care. Most generalists favor the gold standard aspiration, either in their office or *via* referral to specialty care.

ACUTE MANAGEMENT

Traditionally, colchicine or high-dose non-steroidal anti-inflammatories (NSAIDs) were used as first line treatment for an acute gout flare. Now that colchicine is no longer available as a generic, it can be cost prohibitive for patients. If it is affordable, then most primary care providers follow the ACR guideline recommendations (*i.e.*, 1.2 mg PO for one dose, followed by 0.6 mg on hour later and then 0.6 mg 12 hours later) and continue it at 0.6 mg once or twice daily until the flare has resolved [19]. For patients who cannot afford or tolerate colchicine, using a high dose NSAID or oral steroid is considered reasonable if contraindications do not exist. There is no data showing higher efficacy with any one NSAID so the choice of NSAID, dosing, and frequency are based on preference, prior response, and/or tolerance. Generalists reserve the use of oral corticosteroids for patients who have gout refractory to the above treatment, cannot tolerate the above treatment, or who have CKD and cannot afford colchicine. In these cases, the ACR guidelines call for prednisone at 0.5 mg per kg for 5-10 days or 0.5 mg per kg for 2-5 days and then a taper over 7-10 days [19]. Practices vary depending on access to follow-up, with primary care physicians opting for the longer taper when prompt communication of response is not possible or if ULT is being initiated concurrently (discussed further below).

In patients with severe pain or a poly-articular attack, most primary care providers feel comfortable with a combination of colchicine with NSAIDs, unless contraindicated. If NSAIDs cannot be used, then many generalists will favor combining colchicine with oral steroids as the next best option. NSAIDs and oral steroids are not used together due to the increased risk of gastrointestinal bleeding. In patients who present with a mono-articular attack, intra-

articular steroids are a great option for providers who are comfortable with joint injections, especially if the patient has limited options for oral treatment. The dose of steroid varies but typically for a large joint such as a knee, generalists utilize methylprednisolone acetate 40-80 mg (or equivalent).

As always, a patient's prior response, tolerance, comorbidities, preferences, and other medications will influence which of the above options his or her primary care physician chooses. Each gout attack or routine visit should be used as an opportunity to reinforce important lifestyle modifications (further discussion below). It is also important to develop a self-management plan for patients to use in case of recurrence. This may help reduce the severity and duration of an attack at times when a patient cannot access acute care.

Primary care physicians are slowly adopting one of the more notable changes presented in the ACR guidelines that in patients in whom ULT is indicated, it can be safely started during an acute flare [19]. Anti-inflammatory prophylaxis should be continued while ULT is being initiated and titrated. This will be further discussed below.

MAINTENANCE

As gout is commonly encountered in ambulatory settings, primary care physicians should feel comfortable with both its acute and chronic management. Unfortunately, many of these patients have multiple comorbidities including CKD, heart failure, and diabetes mellitus that complicate management.

The ACR guidelines stress the importance of addressing diet and lifestyle as well as pharmacologic therapy to lower the serum urate level and decrease the frequency of future acute attacks. Studies have shown that proper diet and fitness can lower serum urate levels by 10-18% and help decrease frequency of acute attacks [20]. Primary care physicians are well suited for this task as dietary counseling is a routine part of care for patients with chronic medical conditions. Many of the lifestyle changes necessary to control gout are also useful in the treatment of other common chronic conditions including diabetes mellitus and cardiovascular disease. Counseling patients to avoid high purine (and often high cholesterol) foods such as liver, kidney, shellfish, and sardines is the focus. Generalists will also instruct patients to avoid high fructose corn syrup and alcohol (particularly beer) and encourage weight loss. Losing 10% of total body weight can decrease the risk of a recurrent gout attack by 30%, making a dramatic difference both in the treatment of gout and the treatment of many of the other co-morbid illnesses that complicate gout therapy [21]. For example, a similar amount of weight loss can decrease Hemoglobin A1c by about one point, or prevent the development of diabetes in patients with impaired glucose tolerance [22,23].

Despite focused efforts, dietary and lifestyle counseling are often insufficient in achieving targeted serum urate levels. Therefore, chronic management of gout and prevention of flares often requires pharmacologic ULT, namely a xanthine oxidase inhibitor (XOI) such as allopurinol or febuxostat. Most primary care providers are very comfortable with these medications. While formulary limitations play a role, generalists tend to use allopurinol initially. This is especially true in primary care centers located in underserved communities. In these settings the cost of medications is of particular importance, and the cost of febuxostat can be prohibitive. A recent article examining the cost-effectiveness of gout therapies noted that the cost of fixed-dose allopurinol and febuxostat was estimated at \$67 and \$2075 per year, respectively [24]. Clinical trials have demonstrated febuxostat 80 mg (maximum dose) to be more effective than allopurinol in doses less than or equal to 300 mg in lowering serum uric acid levels [24]. However, no trials have compared the two medications with escalating dosages of allopurinol. Given these limitations, it is reasonable to start with allopurinol especially when cost is an issue.

Two key recommendations out of the ACR guidelines that have most transformed gout management include starting maintenance therapy during an acute attack, and titrating allopurinol using a treat-to-target method. The recommendations call for using ULT prophylaxis and titrating therapy to achieve a serum uric acid level of <6 mg/dL in patients with two or more gout attacks per year, tophi on physical exam, CKD stages II-V, or a history of nephrolithiasis. Routine practice in primary care is to start patients on allopurinol 100 mg daily or 50 mg daily if there is evidence of CKD stage IV or higher. While the guidelines recommend titrating up therapy every two to five weeks, given the transportation and cost issues many patients face, it is typical practice to have them return for a serum uric acid level about a month after they start therapy and titrate as necessary until the level is <6 mg/dL. As physicians become more conscious of providing high value care to our patients, it will be interesting to see if any recommendations are made regarding the cost of such frequent monitoring. A substantial amount of evidence suggests that using allopurinol for monotherapy at doses of 300 mg or less failed to achieve the target serum urate level in about 50% of patients [20]. Allopurinol can be dosed up to 800 mg per day in patients with normal renal function, and should be

aggressively up-titrated to achieve uric acid goals as outlined above.

As noted above, pharmacologic ULT can be started at the time of an acute flare in those patients who would benefit from the therapy. Given the high frequency of acute gout attacks during the initiation of ULT, pharmacologic anti-inflammatory prophylaxis is indicated for all scenarios. As a first-line option, the ACR guidelines recommend oral colchicine 0.6 mg daily [19]. As mentioned, colchicine can be prohibitively expensive for many lower income and uninsured patients. A reasonable alternative would be low dose NSAID prophylaxis. As a last resort, generalists will turn to low-dose prednisone (<10 mg per day), if a patient has contraindications or intolerance to colchicine and NSAIDs. The ACR guidelines advise follow up evaluation of patients while on ULT for symptoms of gout. If no signs or symptoms of active gout are found, the recommendation is to continue prophylactic therapy for six months. However, if a patient is asymptomatic and has a urate level at target, we find that three months of prophylaxis is adequate [19]. This allows the generalist to balance prophylactic therapy with minimizing side effects and cost of additional medications.

As will be discussed in the next section, patients with gout and advanced CKD (stages IV-V) are challenging to manage, and involvement of nephrology and rheumatology services is frequently pursued.

REFRACTORY OR COMPLICATED GOUT

Despite clear guidelines, it is often particularly challenging to effectively manage gout with minimal side effects when chronic illnesses complicate the otherwise straight-forward management algorithm. Primary care physicians appropriately and safely treat many patients that suffer from gout while minimizing side effects and maximizing therapeutic efficacy. In general, primary care providers feel comfortable managing patients with concomitant diseases including diabetes mellitus, CKD, cardiovascular disease, and those with a history of gastrointestinal (GI) intolerance to NSAID medications.

There are times where specialty services are necessary. Primary care physicians consider specialty referral in patients who do not respond to usual care, even when it is modified to their particular needs. These include patients with persistent hyperuricemia and recurrent flares despite titration of conventional medications, or those who present with tophaceous gout, destructive joint changes, or nephro-lithiasis. Generalists almost certainly involve a specialist if immunogenic ULT, like peglitocase, is being considered.

Statistics show that generalists are most frequently treating gout and may actually be the best suited to do so. The focus on understanding the entire patient, and counseling on behavioral changes makes these providers quite adept at treating even the most complicated cases. Through regular prescribing habits, primary care physicians can help mitigate gout flares even when they are treating co-morbid illnesses and not the gout itself. For example, data suggest it may be better to choose losartan, an angiotensin receptor blocker (ARB), over an angiotensin converting enzyme inhibitor (ACE-I) for patients with gout and comorbid renal disease or heart failure [25]. While ACE-Is and ARBs are both effective for the latter two diseases, Losartan has uricosuric properties while ACE-Is do not [25]. This holistic approach to patient care is squarely in the wheelhouse of primary care providers as they care for patients with gout and other complicating disease processes.

Diabetes Mellitus

Patients with a diagnosis of diabetes certainly fall within the category of complicated cases. Often, these patients have co-morbid hypertension, CKD, and may be on medications that lead to gout exacerbations, like aspirin. When diabetes mellitus is the sole co-morbid illness, practitioners try to avoid the use of steroids. Regardless of route, steroids can cause elevation in serum glucose levels and make glucose control harder to attain [26]. General practitioners usually prefer to treat with an NSAID or colchicine therapy. If a strong contraindication exists to NSAIDs and colchicine, for example people 75 years of age or older, then steroids may be the best option. In this case, consider intra-articular instead of systemic steroid use. Primary care clinicians must provide anticipatory guidance about the effect that steroids will have on blood glucose during steroid therapy. Patients taking insulin therapy can be prescribed a simple sliding scale insulin plan to cover any hyperglycemic episodes while on steroid therapy. When patients take oral hypoglycemic medications it can be more challenging to pre-emptively increase their regimen. In these cases, frequent glucose monitoring is required. Patient's should call their provider if their blood glucose is consistently higher than 250, as their oral medications must be titrated at that time.

Chronic Kidney Disease

Managing acute and chronic gout in patients with CKD can be very challenging as there are contraindications for use of many mainstay therapies. Co-managing patients with gout and CKD likely represents the area where primary care providers feel the most uncomfortable with the ACR guidelines. NSAIDs, colchicine, and urate lowering medications (probenecid, allopurinol and perhaps feboxustat) use may be limited in the face of this chronic disease. During an acute attack, steroid use, either intra-articular or systemic, is likely the best course of action. Most generalists avoid prescribing NSAIDs altogether, instead using colchicine dosed appropriately for the patient's renal function.

CKD can also create an obstacle to appropriate prophylactic management as dosing and treatment options are more limited. While the new ACR treatment guidelines support using higher doses of allopurinol in patients with CKD, this is only advisable in patients that can be monitored closely for evidence of side effects. In these situations, daily doses of 300 mg daily or higher are acceptable, allowing for continued use of this medication as first line in gout prevention [20]. While the new guidelines support higher doses of allopurinol in this population, it is generally outside the comfort zone of primary care providers, especially with advanced CKD. Given the complexity and higher risk of side effects, general practitioners often opt for involvement of nephrology and rheumatology in patients with CKD IV-V. Another option for these patients is feboxustat. Metabolized by the liver, it could be considered as an alternative to allopurinol in patients with CKD, since it does not require dose adjustment until the CrCl falls below 30 mL per min. The ACR does not recommend feboxustat preferentially because of a lack of data about the use of this medication in advanced renal disease. As noted in the maintenance section a recent study found allopurinol to be more cost effective as prophylactic therapy. However, this study did not specifically consider renal disease as a possible scenario for feboxustat being more cost effective [24]. In patients with CKD, more frequent office visits and possible earlier referral might be considered when using allopurinol. It is possible that these costs might offset the lower price per tablet of allopurinol. Second line ULT with uricosuric agents, like probenecid, become less useful as renal disease worsens. While less toxic, uricosurics should not be used in patients with a CrCl of 50 mL per min or less, as they lack efficacy.

Cardiac Disease

Much like CKD, patients with co-morbid cardiac disease should be treated with any first line medication other than NSAIDs or cyclooxygenase-2 (COX-2) inhibitors. While first line gout therapies are equally efficacious, NSAIDs have a higher risk of deleterious cardiovascular events. This risk likely exists with any duration of therapy, and includes elevated blood pressure, risk of myocardial infarction (MI) and congestive heart failure (CHF) exacerbations [27]. In the latter, patients also have increased risk of renal failure with the addition of NSAID therapy. The pathophysiology of this risk is multifactorial. Poly-pharmacy plays a major role in this risk as patients are on many medications that effect renal blood flow and renal vascular function including diuretics, and ACE-Is and primary care physicians must be on alert for this [28]. It is not advisable to discontinue ACE-Is and diuretics in heart failure patients, so other medications that effect renal blood flow or may irritate the kidneys should be avoided completely. Hence, general practitioners typically use colchicine and steroids preferentially when treating gout in patients with cardiac disease.

NSAID-INDUCED GASTROINTESTINAL (GI) BLEEDING AND/OR ULCERS

While NSAIDs are both therapeutic and cost effective, they should be used with caution in patients that experience GI side effects. This intolerance runs the spectrum from abdominal pain to GI bleeding. The severity of the reaction should be considered when weighing therapeutic options in acute gout treatment. Primary care physicians have a lower threshold to treat patients with NSAIDs if the side effect experienced was abdominal pain. Since dyspepsia is not predictive of ulcer formation, these patients can likely be treated safely with NSAIDs and a Proton Pump Inhibitor or double dose Histamine-2 blocker to help symptomatically during their acute gout flare [29].

On the other hand, this class of medication should be avoided in those that have a history of ulcers, GI bleeding, are on oral anticoagulation therapy or are 75 years of age or older. The majority of primary care providers would consider the risk of NSAID-induced GI bleeding too high to warrant treatment when other therapies are available. Recurrent GI bleed or ulcer formation rates can be as high as 5% within six months of NSAID therapy, while the addition of NSAIDs to oral anticoagulation therapy increases the risk of a GI bleed by as much as six-fold [29].

SUMMARY

Primary care providers will encounter patients with gout in their practices and should feel empowered to treat this condition with some targeted assistance from subspecialists. Following the ACR Guidelines' focus on treating-to-target

uric acid levels, use of ULT, and acute management, generalists should remember to make a definitive diagnosis with joint aspiration at some point in their patient's care, and to always choose medication based on their patient's co-morbid illnesses and financial barriers. Lifestyle and behavioral changes can decrease symptoms, but there are situations where prophylactic therapy is required. In these instances, practitioners should waste no time in initiating ULT, and begin these medications even if the patient is experiencing an acute attack. Key to effective long-term prevention of gout flares is treating to a target uric acid level. With these key concepts in mind generalists can successfully manage the treatment of gout.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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