Diagnosis and Treatment of Gout and Pseudogout for Everyday Practice

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KEYWORDS

- Crystalline arthropathy • Gout • Arthritis • Pseudogout
- Calcium pyrophosphate deposition disease • Monoarthritis • Polyarthritis
- Urate-lowering therapy

KEY POINTS

- The clinical recognition and differentiation of gout and pseudogout from other causes of inflammatory arthritis is key in rendering appropriate and timely treatment.
- Nonsteroidal antiinflammatory drugs, colchicine, and corticosteroids can control acute gout symptoms; allopurinol and febuxostat are the first-line urate-lowering therapies to definitively treat gout.
- Medication noncompliance is the most common reason for "treatment-resistant" gout.
- Aside from treatment of acute arthritis in pseudogout, there is no proven therapy to prevent recurrence or result in long-term remission.

INTRODUCTION

The crystalline arthropathies, gout and pseudogout, are often successfully managed by the primary care provider. It is essential that primary care clinicians understand the underlying pathophysiology of these diseases, differentiate them from other forms of inflammatory arthritis, know the guidelines for treatment and monitoring, and understand indications for referral to a rheumatologist. A basic knowledge of more advanced medications used in these diseases is important, especially the potential side effects and medication interactions. In this article we present gout and pseudogout from diagnosis to treatment for everyday practice.

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GOUT

Gout incidence is increasing—doubling between the 1970s and 1990s.[1] Hyperuricemia, regardless of the etiology, is the primary cause of this disease. Needle-shaped monosodium urate (MSU) crystals deposit and precipitate within the synovium, ultimately triggering an intense inflammatory response through activation of the innate immune system.

PATHOPHYSIOLOGY

Pathophysiology of Hyperuricemia

Uric acid is a byproduct of purine metabolism. Purines are required for DNA, RNA, adenosine triphosphate, diphosphate, and monophosphate, cyclic adenosine monophosphate, and many other integral molecules. Hyperuricemia results from urate overproduction, underexcretion through the renal tubules, or a combination thereof.

During purine metabolism, uric acid is synthesized via multiple intermediaries, including hypoxanthine and guanine, which converge at the common substrate xanthine (**Fig. 1**). The enzyme xanthine oxidase (XO) then converts xanthine into uric acid. In humans, purine metabolism ends with uric acid. In almost all animals except humans and primates, the enzyme uricase converts uric acid into allantoic acid, a soluble compound that can be degraded into urea and excreted. In addition to de novo synthesis, the purine salvage pathway works through hypoxanthine guanine phosphoribosyl transferase and is responsible for resynthesizing the purines inosine 5'-monophosphate and guanosine monophosphate from hypoxanthine and guanine. The loss of hypoxanthine guanine phosphoribosyl transferase activity results in hyperuricemia. Once serum urate reaches a certain threshold, urate crystals are deposited in synovium. Secondary causes of urate overproduction include increased cell turnover causing increased purine generation (**Box 1**).

Hyperuricemia may also occur as a result of decreased uric acid excretion. Approximately 65% of uric acid is excreted through the renal system.[2] The gastrointestinal tract also excretes uric acid and in chronic kidney disease, may increase its excretion.[3] In the kidneys, uric acid secretion and resorption occur across the proximal tubule epithelium. Important transporters for excretion of uric acid include URAT1, GLUT9, OAT4, and others[4] (**Fig. 2**). URAT1, on the apical tubule surface, transfers tubule lumen urate into the cytosolic environment of the epithelial cell and is the target for some urate lowering therapies. Renal insufficiency and metabolic acidosis, regardless of the cause, promote urate underexcretion, and involve a complex process beginning with a decrease in filtered volume past the glomerulus. Drugs that may promote hyperuricemia include thiazide and loop diuretics and salicylates.

Pathophysiology of Acute and Chronic Gouty Arthritis

Under the appropriate conditions, MSU crystals can activate the NLRP3 inflammasome, a multiprotein cytosolic complex that activates caspase-1.[5] The caspase-1 enzyme cleaves pro-interleukin (IL)-1β to the active IL-1β protein, which is central to the subsequent acute inflammatory response. MSU crystals also induce many other inflammatory cytokines and chemokines, including complement activation. Large amounts of neutrophils are recruited to the joint during an acute gout attack and play a crucial role in the intense inflammation in gout. Neutrophils also release serine proteases that further activate IL-1β, contributing to a positive inflammatory feedback loop.[6]

The tophus is the cardinal feature of chronic gout. A granuloma-like response results in large collections of MSU crystals and inflammatory cells. The tophus produces a persistent inflammatory response in adjacent bone along with reduced osteoblast