



# Therapeutic Options

## FOCUS ON GOUT

Gout, one of the most common rheumatic diseases of adulthood, has an estimated prevalence of approximately 3.9 per cent.<sup>1,2</sup> While the prototypical presentation is acute, excruciatingly painful inflammation of the first metatarsophalangeal joint, gout can manifest as a spectrum of clinical and pathologic features related to an excess body burden of uric acid.<sup>1,3,4</sup> The debilitating symptoms are associated with functional impairment and a detrimental impact on quality of life.<sup>5,6</sup> Unfortunately, evidence indicates that only a minority of patients with gout receive adequate advice and treatment, leading to suboptimal outcomes.<sup>7</sup>

### ETIOLOGY & PATHOPHYSIOLOGY

The primary symptoms of gout result from the deposition of monosodium urate (MSU) crystals into articular or periarticular tissues.<sup>1,3</sup> These crystals trigger a cascade reaction that involves complement activation and release of

several proinflammatory cytokines, culminating in acute but self-limited neutrophilic inflammation.<sup>5,8</sup>

### RISK FACTORS

Hyperuricemia, defined variably as a serum uric acid level greater than 400  $\mu\text{mol/L}$  or 420  $\mu\text{mol/L}$ , is the most important risk factor for gout.<sup>1,3,9</sup> Increased serum urate levels can be related to uric acid overproduction and high dietary intake of purines (which are metabolized to uric acid); however, hyperuricemia is a result of underexcretion of uric acid by the kidneys in the vast majority of instances.<sup>4,8,9</sup>

Other notable risk factors for gout and hyperuricemia are listed in Box 1.

### SIGNS & SYMPTOMS

Typically, gout presents initially as acute episodic arthritis affecting one or more joints.<sup>1,6</sup> Associated pain is often excruciating.<sup>8</sup> Although the big toe has been cited as the most

common joint afflicted, various small and large joints may be involved.<sup>6,10</sup>

The rapid development of severe pain, swelling, and tenderness that reach maximum intensity within 6–12 hours is characteristic of acute monoarticular gout attacks of the lower extremities.<sup>11</sup> Overlying erythema is usually present.<sup>11</sup> Bouts are generally self-limited; however, the pain of an acute attack may last a week or more without treatment.<sup>3,8,10</sup> Untreated or poorly treated gout often leads to further acute attacks, as well as progressive joint and tissue damage.<sup>9</sup>

Chronic tophaceous gout can develop after years of acute intermittent gout.<sup>3</sup> Tophi, which are nodular masses of uric acid crystals, can form in any joints or soft tissues, but most commonly affect the finger tips and hands.<sup>3,10</sup> Chronic tophaceous gout is associated with joint deformity, limited motion, and chronic pain.<sup>10</sup>

Extra-articularly, gout can

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lead to urolithiasis and chronic interstitial nephropathy.<sup>1</sup>

## PHARMACOTHERAPY

The main goals of gout therapy are to manage acute flares (this includes treating pain as quickly as possible), prevent future flares, and slow or reverse joint and soft tissue damage (e.g., eliminate tophi).<sup>8,9</sup> In addition, identifying and controlling associated diseases (see Box 1) should be a priority.<sup>8,9</sup>

### Treatment of Acute Attacks

Managing the pain and inflammation of acute gout attacks is typically accomplished with nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, and/or corticosteroids.<sup>3,9</sup> Recent guidelines from the American College of Rheumatology (ACR) recommend that monotherapy with one of these agents is appropriate first-line treatment for attacks of mild/moderate severity,<sup>\*</sup> particularly those involving one or a few small joints, or one or two large joints.<sup>†</sup> Among other factors, the choice of a single agent should be based on patient and physician preference, prior response to therapy, and presence of comorbidities.<sup>6,11</sup>

For acute attacks characterized by severe pain,<sup>‡</sup> the ACR guidelines recommend that combination therapy is an appropriate option, especially in instances of polyarticular gout or cases involving more than one large joint.<sup>6</sup> Specific combinations proposed include full therapeutic doses<sup>§</sup> of colchicine + NSAID; oral corticosteroid + colchicine; and intra-articular corticosteroid + any another recommended modality (see Table 1).<sup>6</sup>

Combination therapy is also deemed appropriate for patients not responding adequately<sup>\*\*</sup> to initial pharmacologic monotherapy.<sup>6</sup> Alternatively, patients with an inadequate response to initial monotherapy could be switched

to a different single agent.<sup>6</sup>

Therapy should be initiated at the onset of an attack<sup>††</sup> and should be continued until attack resolution, which typically takes 1–2 weeks.<sup>9</sup> To facilitate prompt treatment, providing patients with instruction (and a prescription, where necessary) to start medication at the earliest sign of an acute attack (e.g., “pill in the pocket” approach<sup>12</sup>) has been advocated.<sup>6</sup>

Dosing guidelines and other pertinent information about anti-inflammatory medications used commonly for acute gout are presented in Table 1.

### Prevention of Recurrent Attacks

Pharmacologic prevention of recurrent attacks of gout generally comprises both urate-lowering therapy (ULT) and anti-inflammatory prophylaxis, as discussed below. Dosing guidelines and comments regarding preventive medications for gout are summarized in Table 2.

#### Urate-lowering therapy

Long-term serum urate lowering has been cited as the cornerstone of effective gout management.<sup>2</sup> The aim of ULT is to reduce uric acid levels below the saturation point at which MSU crystals form.<sup>2,11</sup> The goals of therapy are to prevent acute flares, as well as the development of tophi and chronic gouty arthropathy, and also to promote tophi dissolution.<sup>11</sup> The primary target to accomplish these goals is a serum uric acid level <360 μmol/L, although levels <300 μmol/L may be necessary for disease control in certain patients (e.g., those with tophi).<sup>1,11</sup>

There is some lack of consensus regarding indications for ULT. According to the ACR guidelines, ULT is indicated for any patient with an established diagnosis of gout and:

- tophi (or a single tophus);
- ≥2 acute gout attacks per year;
- stage 2 (or worse) chronic kidney disease<sup>‡‡</sup>; or

#### Box 1 – Some risk factors for gout/hyperuricemia<sup>1,3,8,9</sup>

- Hypertension
- Type 2 diabetes mellitus
- Metabolic syndrome
- Obesity/increased BMI<sup>a</sup>
- Chronic kidney disease
- Hyperlipidemia
- Cardiovascular disease
- Myeloproliferative/lymphoproliferative disorders
- Use of certain medications (e.g., thiazide and loop diuretics, low-dose acetylsalicylic acid, cyclosporine, tacrolimus, niacin, cytotoxic agents)
- High alcohol consumption (particularly beer)
- High dietary intake of meat (especially organ meat, wild game, turkey), seafood, fructose-sweetened beverages
- Male gender<sup>b</sup>
- Advanced age

BMI = body mass index

- a. Compared with a man with a BMI of 21–22.9 kg/m<sup>2</sup>, the relative risk of gout is doubled for a man with a BMI of 25–29.9 kg/m<sup>2</sup> and tripled for a man with a BMI ≥35 kg/m<sup>2</sup>.<sup>9</sup>
- b. Approximately 75% of affected individuals are men.<sup>9</sup>

- a history of urolithiasis.<sup>1</sup>

Historically, practitioners have been advised that ULT should not be initiated during an acute gout attack due to the risk of aggravating or prolonging the attack,<sup>9</sup> and such advice is included in recently published guidelines from the European League Against Rheumatism (EULAR).<sup>11</sup> However, the ACR guidelines suggest that ULT can be initiated during a flare, provided that effective anti-inflammatory therapy has been instituted.<sup>1</sup> Importantly, patients should be instructed to continue ULT without interruption during acute attacks of gout.<sup>4,6</sup> Generally, ULT is considered lifelong, although some

\* Defined by a rating ≤6 out of 10 on a visual analog pain scale (0–10).<sup>6</sup>

† Defined as ankles, knees, wrists, elbows, hips, and shoulders.<sup>6</sup>

‡ Defined by a rating ≥7 out of 10 on a visual analog pain scale (0–10).<sup>6</sup>

§ Or, where appropriate, full doses of 1 agent and prophylactic doses of the other.<sup>6</sup>

\*\* There is no uniform definition as to what constitutes an inadequate response to initial therapy in acute gout; however, a proposed definition is <20% improvement in pain score within 24 hours or <50% improvement in pain score ≥24 hours after initiating pharmacologic therapy.<sup>6</sup>

†† The ACR guidelines<sup>6</sup> recommend that pharmacologic therapy ideally be initiated within 24 hours of onset of an acute gout attack.

‡‡ See <http://www.kidney.ca/page.aspx?pid=320> for a description of chronic kidney disease stages.

Table 1 – Some medications for acute gout<sup>6,8,9,11-16</sup>

Therapeutic Option	Suggested Dosing <sup>a</sup>	Comments <sup>b</sup>
NSAIDs, <sup>c</sup> oral <sup>d</sup>	Indomethacin 50 mg tid; <sup>e</sup> Naproxen 750 mg once, then 250 mg tid or 500 mg bid <sup>e</sup>	<ul style="list-style-type: none"> <li>No specific NSAID is recommended preferentially over others; all are believed to be equally effective when used in maximum doses</li> <li>Indomethacin and sulindac are Health Canada-approved for the treatment of acute attacks of gouty arthritis; naproxen is also approved for gout in the US</li> <li>Suppositories may be used if oral route is inadvisable</li> <li>Coadministration of a PPI or misoprostol is advised for patients at increased risk of GI toxicity (ulcers, bleeds, perforation)</li> <li>Concomitant use with systemic corticosteroids leads to synergistic GI toxicity</li> </ul>
Colchicine	1.2 mg once, then 0.6 mg one hour later <sup>f,g</sup>	<ul style="list-style-type: none"> <li>Should be initiated as soon after symptom onset as possible (within 36 hours at the latest)</li> <li>If subsequent gout flares require therapy within 14 days of the acute dosing regimen, an NSAID or corticosteroid is recommended; acute colchicine dosing can be repeated if &gt;14 days have elapsed</li> </ul>
Corticosteroids, oral	Prednisone 0.5 mg/kg/day <sup>h</sup>	<ul style="list-style-type: none"> <li>Generally recommended in preference to other routes of corticosteroid administration</li> <li>A particularly appropriate primary treatment strategy in patients with moderate-to-severe CKD according to some experts</li> <li>Concomitant use with NSAIDs leads to synergistic GI toxicity</li> </ul>
Corticosteroids, parenteral	Methylprednisolone sodium succinate 0.5–2 mg/kg IM/IV single dose <sup>i</sup>	<ul style="list-style-type: none"> <li>Useful when oral corticosteroids are desirable but cannot be used</li> <li>Concomitant use with NSAIDs leads to synergistic GI toxicity</li> </ul>
Corticosteroids, intra-articular	Single dose, dependent on size of joint <sup>i</sup>	<ul style="list-style-type: none"> <li>Recommended as an option when 1 or 2 large joints are affected</li> <li>May be used in combination with oral corticosteroids, NSAIDs, or colchicine</li> </ul>

*bid = twice daily; CKD = chronic kidney disease; GI = gastrointestinal; IM = intramuscular; IV = intravenous; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton pump inhibitor; tid = three times daily*

- Where options exist within a class, drug choices listed are representative examples of the class. Dosages listed do not take comorbidities into consideration and may require adjustment; refer to product monographs for details.
- It is notable that comments do not focus on safety aspects of the treatment options, including monitoring; however, online guidelines<sup>1,6,11</sup> and other sources<sup>3,5,15</sup> provide a more detailed discussion of this subject matter (see References, below, for URLs).
- In carefully selected patients with contraindications or intolerance to traditional NSAIDs, the ACR guidelines list celecoxib as an option for acute gout, keeping in mind that the risk/benefit ratio for the high-dose regimen studied (800 mg once, followed by 400 mg on day 1, then 400 mg twice daily for a week) is not yet clear.<sup>6</sup>
- The ACR guidelines offer no direction on the use of parenteral or topical NSAIDs for acute gout.<sup>6</sup>
- In patients with multiple comorbidities or hepatic/renal impairment, the ACR guidelines offer the option of tapering the dose (as opposed to continuing at full dose until attack resolution), but do not provide detailed guidance on doing so.<sup>6</sup>
- This regimen can be followed (after 12 hours) by prophylactic dosing at 0.6 mg once or twice daily (unless dose adjustment is required) until the gout attack resolves.<sup>6</sup>
- This regimen was shown to be equivalent in efficacy to, but much better tolerated than, a high-dose colchicine regimen (4.8 mg over 7 hours) when administered within 12 hours of symptom onset.<sup>8</sup>
- The ACR guidelines provide 2 options for duration of therapy: (1) continue recommended dose for 5–10 days, then stop; or (2) continue recommended dose for 2–5 days, then taper for 7–10 days, and then stop.<sup>6</sup>
- Doses can be repeated.<sup>6</sup>
- For example, triamcinolone hexacetonide 2–6 mg for small joints or 10–20 mg for large joints.<sup>14</sup>

experts suggest that patients who make major lifestyle changes could eventually discontinue treatment.<sup>4</sup>

The ACR and EULAR guidelines list the xanthine oxidase inhibitors allopurinol and febuxostat<sup>§§</sup> both as first-line alternatives for ULT.<sup>1,11</sup> If either is contraindicated or not tolerated, the guidelines list probenecid (a uricosuric agent) as an alternative.<sup>1,11</sup> If target urate levels cannot be achieved with an appropriately titrated dose of allopurinol or febuxostat, a uricosuric agent may be added.<sup>1,11</sup>

**Anti-inflammatory prophylaxis**

Since ULT initiation may be associated

with an increase in acute attacks of gout early in therapy,<sup>\*\*\*</sup> concurrent prophylaxis with an anti-inflammatory agent is recommended.<sup>1,4,6</sup> First-line options include colchicine or low-dose NSAIDs.<sup>6</sup> Low-dose oral prednisone or prednisolone may be considered in patients who cannot use, or are refractory to, first-line alternatives.<sup>6</sup>

While the ACR guidelines<sup>6</sup> indicate that anti-inflammatory prophylaxis may be initiated at the same time as (or just prior to) ULT, the EULAR guidelines<sup>11</sup> advise such prophylaxis be started at least two weeks prior to ULT. Discrepancies also exist in the recommended duration of anti-

inflammatory prophylaxis. The ACR guidelines recommend prophylaxis be continued as long as there is any clinical evidence of continuing gout disease activity<sup>†††</sup> and/or the serum urate target has not yet been achieved.<sup>1,6</sup> Specifically, the guidelines recommend a duration of at least six months, and longer if warranted<sup>††††</sup>.<sup>1,6</sup> In contrast, the EULAR guidelines imply prophylaxis need only be continued for 6–12 months, regardless of signs/symptoms or urate levels.<sup>11</sup>

**NONPHARMACOLOGIC INTERVENTIONS**

A full discussion regarding nonpharmacological interventions

§§ It is notable that cost was not considered in the ACR guideline development process; allopurinol has been favoured by another analysis that considered cost,<sup>4</sup> and also by some experts.<sup>17</sup>

\*\*\* It is hypothesized that flares are caused by mobilization of MSU crystals, which results from a rapid and substantial change in urate concentration.<sup>6,9</sup>

††† For example, acute flares in the past 3 months, presence of palpable tophus/tophi, or chronic tophaceous gouty arthropathy (with chronic synovitis) in the past 3 months.<sup>6</sup>

†††† For 3 months after achieving target serum urate levels in those without tophi on physical exam, and for 6 months after achieving target serum urate levels in those with tophi on physical exam.<sup>6</sup>

## Continuing Education – Therapeutic Options Focus on Gout

for gout is beyond the scope of this review. However, detailed recommendations about diet and lifestyle

are provided in the ACR guidelines<sup>1</sup> (see References, below, for URL). During acute attacks, affected

joints should be rested for 1–2 days.<sup>3</sup> Topical ice may be used as needed to supplement pharmacologic treatments.<sup>6</sup>

**Table 2 – Some preventive medications for gout<sup>1,4,6,11,13,14,16</sup>**

Therapeutic Option	Suggested Dosing <sup>a</sup>	Comments <sup>b</sup>
<b>Urate-lowering therapy<sup>c,d</sup></b>		
Allopurinol	Start at ≤100 mg <sup>e</sup> daily; titrate upwards by 100 mg/day q2–5wks to achieve target SUA level; maximum dose is 800 mg/day	<ul style="list-style-type: none"> <li>Dosage may be increased above 300 mg/day, even in those with CKD, as long as there is appropriate patient education and monitoring for toxicity (e.g., pruritus, rash, elevated hepatic transaminases)</li> <li>HLA-B*5801 testing should be considered prior to therapy in select patient subpopulations at elevated risk for AHS</li> <li>Substitution with febuxostat is an appropriate option if first-line allopurinol is not tolerated or does not achieve SUA target</li> </ul>
Febuxostat	80 mg daily <sup>f</sup>	<ul style="list-style-type: none"> <li>Substitution with allopurinol is an appropriate option if first-line febuxostat is not tolerated or does not achieve SUA target</li> </ul>
Probenecid <sup>g</sup>	Start at 500 mg daily; titrate upwards by 500 mg/day q4wks to achieve target SUA level; maximum dose is 3 g/day	<ul style="list-style-type: none"> <li>First-line alternative to a xanthine oxidase inhibitor for ULT monotherapy in patients with normal renal function (not effective in the presence of significant renal insufficiency [e.g., CrCl &lt;50 mL/min])</li> <li>Measure urinary uric acid prior to therapy to rule out uric acid overproduction (uricosurics are contraindicated in this setting)</li> <li>Liberal fluid intake (e.g., ~2 L/day) and alkalinizing the urine<sup>h</sup> during the first few days of therapy can help prevent urolithiasis</li> </ul>
<b>Anti-inflammatory prophylaxis</b>		
NSAIDs, oral	Naproxen 250 mg bid	<ul style="list-style-type: none"> <li>Use concomitant gastroprotective therapy (e.g., PPI, misoprostol) where indicated</li> </ul>
Colchicine	0.6 mg daily or bid	<ul style="list-style-type: none"> <li>May be used in the presence of CKD with appropriate dose reduction and monitoring</li> </ul>
Corticosteroids, oral	Prednisone ≤10 mg/day	<ul style="list-style-type: none"> <li>Reserved for patients with intolerance or contraindication or refractoriness to both colchicine and NSAIDs</li> </ul>
<p>AHS = allopurinol hypersensitivity syndrome; CKD = chronic kidney disease; CrCl = creatinine clearance; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton pump inhibitor; SUA = serum uric acid; ULT = urate-lowering therapy</p> <p>a. Where options exist within a class, drug choices listed are representative examples of the class. Dosages listed do not take comorbidities into consideration and may require adjustment; refer to product monographs for details.</p> <p>b. It is notable that comments do not focus on safety aspects of the treatment options, including monitoring; however, online guidelines<sup>1,6,11</sup> and other sources<sup>3,5,15</sup> provide a more detailed discussion of this subject matter (see References, below, for URLs).</p> <p>c. In addition to ULT, the ACR guidelines suggest considering the potential elimination of non-essential urate-elevating medications<sup>1</sup> (see Box 1 for examples).</p> <p>d. Monitor serum urate regularly (e.g., every 2–5 weeks) during ULT titration; continue to monitor once target level is achieved (e.g., every 6 months).<sup>1</sup></p> <p>e. Starting dose should be 50 mg daily in patients with chronic kidney disease stage IV or worse.<sup>1</sup></p> <p>f. In other jurisdictions where lower and higher tablet strengths are available, starting doses of 40 mg daily are recommended, with titration to 80 mg or 120 mg daily if target urate levels are not achieved.<sup>1,17</sup></p> <p>g. Fenofibrate, losartan, vitamin C, and moderate- to high-dose acetylsalicylic acid also have uricosuric properties, although evidence to support their use in gout is limited and they are not commonly used for this purpose.<sup>4</sup> Still, the ACR guidelines<sup>1</sup> note that fenofibrate and losartan can be components of a comprehensive ULT strategy and either may be used (as an alternative to probenecid) in combination with a xanthine oxidase inhibitor.</p> <p>h. May be accomplished with sodium bicarbonate (3–7.5 g/day) or potassium citrate (7.5 g/day).<sup>5</sup></p>		

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