Treatment of gout flares

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INTRODUCTION

A gout flare is intensely painful and disabling. Typically, a gout flare affects a single joint, although flares affecting multiple joints can occur. Without therapy, a gout flare usually resolves completely within a few days to several weeks, particularly in early disease. However, symptoms improve faster with treatment [1].

Flares recur in the great majority of patients. With more frequent episodes, flares may be more severe and prolonged, and asymptomatic periods become shorter.

The management of gout flares will be reviewed here. The approach to asymptomatic hyperuricemia; the pathophysiology, clinical manifestations, and diagnosis of gout; and the prevention of recurrent gout after resolution of the gout flares are discussed separately:

- (See "Asymptomatic hyperuricemia".)
- (See "Pathophysiology of gout".)
- (See "Clinical manifestations and diagnosis of gout".)
- (See "Pharmacologic urate-lowering therapy and treatment of tophi in patients with gout".)

PRETREATMENT CONSIDERATIONS

Exclude alternate diagnoses — An alternative (or additional) cause of acute inflammatory arthritis (eg, infection) should be considered under the following circumstances:

- The current flare is atypical for the patient
- The diagnosis of gout has not been established
- The flare occurs in a patient at high risk for infection

In patients who require arthrocentesis and synovial fluid analysis to exclude infection, we avoid oral, parenteral, and intraarticular glucocorticoids until the synovial fluid white blood cell count and gram stain are available. However, these conditions would not preclude treatment with a nonsteroidal antiinflammatory drug (NSAID) or colchicine. The differential diagnosis and evaluation of gout is discussed separately. (See "Clinical manifestations and diagnosis of gout", section on 'Differential diagnosis of a gout flare'.)

Initiate therapy quickly — Once the diagnosis has been established and infection seems less likely, treatment should start as soon as possible after the patient perceives the beginning of a flare, preferably within hours of symptom onset. More rapid and complete resolution of symptoms occurs the earlier that treatment is introduced.

Continue or initiate chronic therapies for gout — During a gout flare, urate-lowering medication should be continued, without interruption. These medications may include allopurinol, febuxostat, probenecid, benzbromarone, or pegloticase. There is no benefit to temporary discontinuation of these medications. Moreover, subsequent reintroduction of urate-lowering therapies may precipitate another flare.

There is no contraindication to starting long-term urate-lowering therapies for gout during the treatment of a gout flare. The decision should be individualized depending on patient factors and a discussion about the indication for urate-lowering therapies should be initiated during the episode of the gout flare. (See "Pharmacologic urate-lowering therapy and treatment of tophi in patients with gout".)

INITIAL THERAPY

Selection of agent — Colchicine, nonsteroidal antiinflammatory drugs (NSAIDs), and systemic glucocorticoids are all effective treatment options and should be started as soon as possible after onset of the gout flare. Selection of an agent to treat an early flare will largely depend on the provider's familiarity with these agents and the patient's comorbidities (which may prevent the use of some of these drugs) (algorithm 1). Patient's familiarity, access, and prior successful use of a medication can also influence the initial choice.

However, glucocorticoids are increasingly favored by expert guideline panels as first-line therapy for gout flares [2-4].

We encourage patients to maintain a supply of gout flare medication at home to allow initiation of treatment at the first sign of flare.

Glucocorticoids

Intraarticular glucocorticoids — For patients with a gout flare affecting one or two joints, we suggest treatment with intraarticular glucocorticoids (eg, triamcinolone acetonide) if the practitioner has sufficient expertise to deliver this treatment in a timely manner. Such treatment avoids complications associated with systemic therapy.

We use a single injection of triamcinolone acetonide (40 mg for a large joint [eg, knee], 30 mg for a medium joint [eg, wrist, ankle, elbow], and 10 mg for a small joint). Methylprednisolone acetate may also be used (table 1).

If joint infection is suspected, synovial fluid culture should be used to exclude infection prior to treatment with intraarticular glucocorticoids. Septic arthritis and a gout flare can coexist; therefore, the possibility of septic arthritis should be considered, even in a patient with well-established gout.

In our experience, a single injection of intraarticular glucocorticoids is usually highly effective, and patients experience relief within 24 hours. However, published evidence supporting the use of intraarticular glucocorticoids is limited to small, open-label trials [5]. A 2013 systematic review noted that this practice has never been examined in a randomized study [6]. Evidence of effectiveness in other inflammatory arthritis, such as rheumatoid arthritis, also support its use in gout. Interarticular glucocorticoids should be avoided in patients with known or suspected septic arthritis. Other considerations, including complications and contraindications, are discussed separately:

- (See "Use of glucocorticoids in the treatment of rheumatoid arthritis", section on 'Intraarticular therapy'.)
- (See "Joint aspiration or injection in adults: Complications".)
- (See "Intraarticular and soft tissue injections: What agent(s) to inject and how frequently?".)

Oral glucocorticoids — For patients with a gout flare that affects multiple joints simultaneously or with monoarthritis when arthrocentesis is not feasible (eg, inaccessible joint,

lack of available expertise), treatment with prednisone 40 mg daily until the flare resolves is an option. Equivalent doses of prednisolone may also be used. Glucocorticoids may be administered through an intramuscular or intravenous route when oral administration is not feasible.

For most patients, we suggest tapering glucocorticoids over 7 to 10 days after the flare has resolved. For patients with a history of relapsing or refractory disease, we suggest extending the duration of the taper to 14 to 21 days.

Shorter glucocorticoid courses can be effective in many cases, mainly when the flare is treated within the first 48 to 72 hours since its onset. Glucocorticoid pack formulations are commonly used and can be effective in this setting. However, shorter glucocorticoid courses may increase the risk of rebound flares, particularly among patients with relapsing or refractory disease. Thus, the length of taper should be individualized and sometimes modified for any given patient.

Adverse effects associated with glucocorticoids are discussed separately. (See "Major adverse effects of systemic glucocorticoids".)

Several randomized trials comparing glucocorticoids with NSAIDs for gout flares demonstrate that glucocorticoids are at least as efficacious as NSAIDs and may be associated with fewer serious adverse outcomes [7-10].

Parenteral glucocorticoids — In patients who are unable to take medications orally and who are not candidates for intraarticular glucocorticoid injection, we generally suggest treatment with intravenous or intramuscular glucocorticoids:

- **Intravenous** – We suggest methylprednisolone 20 mg administered intravenously twice daily. When the flare begins to resolve, the dose may be tapered over the next 7 to 10 days. When feasible, the patient may be transitioned to oral glucocorticoids to complete the taper.

- **Intramuscular** – We suggest triamcinolone acetate 40 to 60 mg (or an equivalent dose of methylprednisolone), which can be repeated every 48 hours until the flare has resolved. Tapering doses are not necessary.

Few randomized trials have adequately evaluated the benefit of systemic parenteral glucocorticoids [10,11]; the published studies and the few randomized trials have significant limitations in quality and strength of evidence [12,13]. A network meta-analysis of randomized

trials found parenteral glucocorticoids appeared to have similar efficacy as other strategies used to treat gout flares [14].

We discourage the use of corticotropin (adrenocorticotropic hormone [ACTH]), although it has been reported to be efficacious for gout flare treatment. However, cost and availability considerations disfavor its use.

Colchicine

- **Indications and efficacy** – Colchicine has been used for centuries for the treatment of gout flares, but it has not been extensively studied in randomized trials [15,16]. However, the available studies imply that it is as effective as NSAIDs.

  In an open-label randomized trial of 399 patients with a gout flare, colchicine and naproxen were equally effective at pain reduction [17]. In another trial, more patients had a 50 percent reduction in pain at 24 hours with colchicine than those taking placebo (36 versus 16 percent) [16].

- **Contraindications** – Colchicine is contraindicated in the presence of any degree of kidney or hepatic impairment in patients receiving a P-gp inhibitor (table 2) or an agent that strongly reduces availability of the cytochrome P450 system component CYP3A4 (table 3) [18-20].

  We also avoid colchicine in patients with kidney or hepatic impairment if they have recently (eg, within the past 14 days) completed treatment with medications that inhibit CYP3A4 (table 3) and/or the P-glycoprotein (P-gp) efflux pump (table 2).

  Among patients with chronic kidney disease, drugs that inhibit CYP3A4 or P-glycoprotein may further reduce clearance of colchicine by interfering with colchicine metabolism. These agents include some commonly used antibiotics such as clarithromycin, azithromycin, and ketoconazole; antiretroviral drugs; and antihypertensive agents, including verapamil and diltiazem. Concurrent use of these medications with colchicine may thus increase the risk of myelosuppression, and fatal pancytopenia may ensue [21].

  Care should also be taken in combining use of colchicine with the wider array of less potent CYP3A4 inhibitors, including diltiazem, fluconazole, and grapefruit juice (table 3), and drugs with potential for additive side effects, such as myotoxicity, in combination with a statin or fibrate (eg, gemfibrozil).

  Guidance for dosing of colchicine in such patients is discussed below.

- **Administration and dosing** – We suggest an initial dose of 1.2 mg of oral colchicine. One hour later, another 0.6 mg should be administered for a total dose on the first day of therapy of 1.8 mg [16,18,20]. Subsequently, the colchicine dose should be reduced to 0.6 mg twice daily until 48 hours after resolution of the flare.

  Where 0.5 mg is the only available form, an initial dose of 1 mg may be used, followed by 0.5 mg one hour later for a total of 1.5 mg for the first day of therapy. Subsequently, the colchicine dose may be reduced to 0.5 mg twice daily until 48 hours after the resolution of the flare.

  In patients already receiving colchicine prophylaxis (0.6 or 0.5 mg once to twice daily) at the time of their flare, this regimen is used in place of the usual prophylactic dose, which may be resumed once the flare has been treated.

  When the gout flare fails to respond to three days of low-dose colchicine, an alternative antiinflammatory agent (eg, glucocorticoids, NSAIDs) should be added to the treatment regimen. (See 'Nonsteroidal antiinflammatory drugs (NSAIDs)' below.)

- **Precautions** – We discourage increasing colchicine beyond standard doses. In a randomized study of patients with a gout flare, colchicine 1.8 mg was found to be equally effective as high-dose colchicine (4.8 mg) at reducing pain by at least 50 percent in 24 hours (response rate 37.8 versus 32.7 percent) [16]. However, the high dose was associated with an increased risk of adverse events, including diarrhea and emesis.

  We do not administer colchicine intravenously, and we strongly advise against such use because of the risk of serious adverse effects, including death, which are associated with the intravenous administration of this drug. Due to this concern, in many countries, an intravenous form of colchicine is no longer available.

- **Modified dosing** – In patients with multiple factors that may potentially increase colchicine exposure beyond safe levels, we suggest using no more than 0.3 mg on day of flare. Subsequently, we suggest administering no more than 0.3 mg every three days until the flare has resolved. These particularly high-risk groups include:

  - Patients on colchicine prophylaxis within the past 14 days, with normal kidney and hepatic function, who have taken a strong CYP3A4 inhibitor (table 3) or a drug that inhibits P-gp (table 2) within the last 14 days [19].

  - Patients on colchicine prophylaxis within the past 14 days, with any kidney or hepatic impairment, who have taken a moderate CYP3A4 inhibitor (table 3) within the last 14

days.

- Patients regardless of recent colchicine use, with advanced kidney or hepatic impairment (creatinine clearance of <30 mL/minute or Child-Pugh class C cirrhosis or equivalent, respectively) who are not receiving any interacting medications. Patients with kidney or hepatic impairment who are receiving an interacting medication should not receive colchicine.

Additional factors that may affect dosing and further mandate a need for reduced dose and frequency of administration or avoidance of colchicine altogether include:

- Additional drug interactions beyond those recognized from drugs that are moderate or strong CYP3A4 (table 3) or P-gp (table 2) inhibitors (eg, additive myotoxicity with combined use of statin and colchicine). The drug interactions program available within UpToDate should be consulted for additional information.

- Advanced age. (See 'Older adults' below.)

- Chronic ill health and debility.

- Use of more than one medication that can interact with colchicine.

- Combinations of multiple factors, some of which alone may not be problematic but which in combination can increase risk of colchicine accumulation.

Dosing guidelines for colchicine have been proposed by one manufacturer for those patients with normal kidney and hepatic function who are receiving interacting agents or who have received them within 14 days, and guidelines for colchicine administration in patients with kidney or hepatic impairment who are not using an interacting medication have also been described [20]. However, formal guidelines for dose adjustment in patients with multiple interacting factors have not been established, and our approach, which is based upon our personal experience, may differ in some limited respects from the manufacturer's guidelines.

- **Toxicity** – All patients using colchicine should be advised about the potential for and management of adverse events on colchicine therapy. Patients who develop diarrhea, emesis, dysesthesias, or weakness should be instructed to stop therapy immediately. Close monitoring of pertinent organ function and clinical status may be required and should be individualized depending upon the patient’s clinical status.

Gastrointestinal symptoms (diarrhea and abdominal cramping, as well as abdominal pain, nausea, and vomiting) are the most common adverse reactions to colchicine administration [20]. Colchicine was reported to have more side effects than naproxen in a clinical trial, with higher frequencies of diarrhea and headaches [17].

Colchicine-induced neuromyopathy is a potential complication of chronic therapy, particularly in patients with a reduced creatinine clearance. It should be suspected in patients who complain of paresthesias, numbness, and/or weakness. Most cases occur in patients treated with daily low-dose colchicine for months to years. Complaints of weakness and functional decline while taking colchicine should prompt a careful neurologic examination, laboratory evaluation including a serum creatine kinase, and empirical drug discontinuation. (See "Drug-induced myopathies", section on 'Colchicine'.)

Severe colchicine toxicities may also occur, including cytopenias, rhabdomyolysis or myopathy, peripheral neuropathy, liver failure, or severe cutaneous eruption. Severe outcomes are rare among patients who receive a short course of colchicine for a gout flare [22].

Colchicine is a lipophilic alkaloid with a narrow therapeutic margin, and therefore toxicity can occur without markedly elevated doses. Caution should be taken to avoid unintended intoxication.

Patients receiving colchicine should have their medication regimen regularly analyzed for drug interactions, particularly when initiating and adjusting therapy; this may be done by use of the drug interactions program included with UpToDate.

Nonsteroidal antiinflammatory drugs (NSAIDs)

- **Indications and contraindications for NSAIDs** – We suggest NSAIDs for treatment of a gout flare in younger patients (less than 60 years old) with neither kidney nor cardiovascular comorbidities or active gastrointestinal disease for whom NSAID use is generally well tolerated.

  Aspirin is not used to treat gout flares, because low-dose salicylates induce kidney retention of uric acid [23-27]. However, low-dose aspirin used for cardiovascular prophylaxis should be continued during the treatment of a gout flare despite this effect [25,26]. Other important contraindications to NSAIDs are discussed separately.

- **Administration and choice of NSAID** – We suggest naproxen (500 mg twice daily) or indomethacin (50 mg three times daily). Other orally administered NSAIDs (and initial

doses) that may be used include ibuprofen (800 mg three times daily), diclofenac (50 mg two to three times daily), meloxicam (15 mg daily), and celecoxib (200 mg twice daily; alternatively, some experts treat with a single initial dose of 400 mg followed by 200 mg twice daily) (table 4) [28]. A number of trials have compared different NSAIDs with each other, without any apparent differences in efficacy [12,28-33]. For example, in one randomized trial, treatment with high doses of celecoxib (a single dose of 800 mg followed by 400 mg twice daily) was as effective as indomethacin (50 mg three times daily) [28].

NSAIDs are most effective when treatment is initiated within 48 hours of the onset of symptoms. The dose may be reduced after a significant decrease in symptoms has occurred, but the frequency of dosing should be maintained for several more days for optimal antiinflammatory effect.

NSAIDs may be discontinued a few days after clinical signs have completely resolved. Typically, the total duration of NSAID therapy for a gout flare is 7 to 10 days. Delayed therapy may make the flare less responsive and require a longer treatment course.

Nonselective NSAIDs of all types are inexpensive and readily available to patients at the onset of a flare (some without a prescription), and short courses are probably as effective and safe as other agents [12,17,29-33] for this indication [12,28,31-33]. Patients should not be treated concurrently with more than one NSAID and should be queried regarding their medications (including over-the-counter therapies) to avoid such unintended use. Combination NSAIDs with glucocorticoids should also be avoided where possible due to the risk of peptic ulcer disease.

- **Efficacy of NSAIDs** – In our experience, complete or nearly complete resolution of the pain and disability of a gout flare typically occurs within several days to one week.

  There are relatively few high-quality randomized trials of NSAIDs for gout flares [12,28,34,35]. A randomized open-label trial of 399 participants with gout flares compared naproxen 750 mg oral dose followed by 250 mg every eight hours for seven days with low-dose colchicine 0.5 mg three times daily for four days; at seven days, there was no difference in pain intensity, but naproxen caused fewer side effects [17].

  Several randomized trials comparing glucocorticoids with NSAID therapy for gout flare indicate similar benefit, although glucocorticoids may have fewer adverse effects, particularly in comparison with indomethacin [7-10].

Duration of therapy — Patients should be continued on oral or parenteral glucocorticoid treatment for the duration of the flare, although treatments may be tapered once a significant

reduction in symptoms is achieved.

For most patients, we suggest tapering glucocorticoids over 7 to 10 days. For patients with a history of relapsing or refractory disease, we suggest extending the duration of the taper to 14 to 21 days.

The duration of therapy for a gout flare may range from only a few days (eg, in a patient treated within hours of symptom onset) to several weeks (eg, in a patient with a severe or polyarticular flare or begun on treatment after four or five days of symptoms). Many patients require antiinflammatory treatment for no more than 7 to 10 days if begun on therapy within 12 to 36 hours of symptom onset.

NSAIDs may be discontinued a few days after clinical signs have completely resolved. Typically, the total duration of NSAID therapy for a gout flare is 7 to 10 days. Delayed therapy may make the flare less responsive, and require a longer treatment course.

SPECIAL CIRCUMSTANCES

Patients on anticoagulation — In patients on anticoagulants, we use one of the following approaches:

- When feasible, we suggest using colchicine, given its lack of effect on blood clotting. (See 'Colchicine' above.)
- When colchicine is contraindicated, oral glucocorticoids can be used (see 'Oral glucocorticoids' above). Caution and closer monitoring should be exercised if there is a history of peptic ulcer disease or gastrointestinal bleeding.
- When oral glucocorticoids are contraindicated, a highly experienced clinician can safely inject glucocorticoids into the joint of a patient on anticoagulation. Care is necessary to avoid a hemarthrosis, although in our experience, this complication is very rare. (See 'Intraarticular glucocorticoids' above and "Joint aspiration or injection in adults: Technique and indications", section on 'Approach to the patient on anticoagulants'.)
- When both colchicine and glucocorticoids are contraindicated, patients may be managed with celecoxib, which lacks the antiplatelet effect of the nonselective nonsteroidal antiinflammatory drugs (NSAIDs) but retains some potential for gastrointestinal toxicity. (See "Overview of COX-2 selective NSAIDs", section on 'Reduction in gastroduodenal toxicity' and "Overview of COX-2 selective NSAIDs", section on 'Lack of platelet inhibition and use during anticoagulation'.)

- When all standard therapies (ie, colchicine, glucocorticoids, NSAIDs) are contraindicated, patients may be managed with a short-acting interleukin 1 (IL-1) inhibitor such as anakinra. (See 'Resistant or refractory disease' below.)

Older adults — A systematic review suggested that all of the antiinflammatory agents discussed above are efficacious in older patients [36]. However, the use of these agents is complicated by the greater prevalence of comorbidities, including kidney dysfunction, which may preclude the use of NSAIDs or colchicine [37,38]. Some caveats regarding the choice of therapy in older adults include:

- **Colchicine** – Colchicine myopathy and peripheral neuropathy can be subtle in older adults, although brief courses (eg, less than a week) for gout flares should not be associated with these complications. In case of longer courses or frequent use, complaints of weakness and functional decline while taking colchicine should prompt a careful neurologic examination, laboratory evaluation including a serum creatine kinase, and empirical drug discontinuation.

- **NSAIDs** – Contraindications to the use of NSAIDs that are of particular concern in older adults include the presence of heart failure, kidney dysfunction, or gastrointestinal disease. (See 'Nonsteroidal antiinflammatory drugs (NSAIDs)' above.)

  In the absence of such contraindications, we still avoid the use of indomethacin in older adults because of the greater risk of adverse effects with this medication compared with other NSAIDs [39].

- **Glucocorticoids** – Brief courses of oral glucocorticoids are generally tolerated in patients in whom NSAIDs or colchicine may pose an increased risk. (See 'Oral glucocorticoids' above.)

General principles and special concerns in prescribing drugs in this population are discussed in more detail separately. (See "Drug prescribing for older adults".)

End-stage kidney disease and transplantation — We generally treat patients with advanced chronic kidney disease or end-stage kidney disease requiring maintenance dialysis with oral or intraarticular glucocorticoids. (See 'Oral glucocorticoids' above.)

When glucocorticoids are contraindicated, we modify treatment as follows:

- **Chronic hemodialysis** – In patients on chronic hemodialysis, NSAIDs may be used as an alternative to glucocorticoids, particularly in patients with milder gout flares in whom lower doses and shorter courses can be employed (see 'Nonsteroidal antiinflammatory

drugs (NSAIDs)' above). However, patients on hemodialysis may have an increased risk of gastrointestinal toxicity [40].

Colchicine is generally avoided in hemodialysis patients with gout flares because it is not removed by dialysis, and therefore these patients have a heightened risk of colchicine toxicity. (See 'Colchicine' above.)

- **Chronic kidney disease** – In patients with residual kidney function, including patients on peritoneal dialysis, NSAIDs should be avoided because of the risk of worsening kidney function; any use of NSAIDs in this setting should only be done in consultation with the patient's nephrologist. (See "NSAIDs: Acute kidney injury".)

- **Kidney transplant** – Gout flares in organ transplant recipients should only be managed by clinicians experienced with these clinical problems because of the complexities of management due to reduced uric acid excretion and because of the use of calcineurin inhibitors. Oral glucocorticoids are generally the preferred medication. Treatment in this setting is discussed in more detail separately. (See "Kidney transplantation in adults: Hyperuricemia and gout in kidney transplant recipients", section on 'Selection of initial antiinflammatory therapy'.)

Pregnancy and lactation — Gout flares are exceedingly uncommon during pregnancy and lactation, paralleling the low prevalence of hyperuricemia in women of childbearing age in most populations (see "Asymptomatic hyperuricemia", section on 'Epidemiology'). Thus, the occurrence of an acute inflammatory arthritis resembling gout during pregnancy or breastfeeding should direct attention to the exclusion of alternative diagnoses, such as septic arthritis. (See "Clinical manifestations and diagnosis of gout", section on 'Differential diagnosis'.)

Despite its rarity, gout flares during pregnancy and lactation have been reported among women with familial juvenile hyperuricemic nephropathy [41,42] (see "Autosomal dominant tubulointerstitial kidney disease", section on 'ADTKD due to UMOD pathogenic variants'), unspecified "kidney impairment," and gestational diabetes [43].

- **Pregnancy** – In pregnant women with a gout flare, we generally use oral glucocorticoid therapy (see 'Oral glucocorticoids' above). In a patient with recurrent flares during pregnancy or breastfeeding, we use daily low-dose glucocorticoids for prophylaxis, given the need to avoid both colchicine and NSAIDs.

  The use of NSAIDs is limited to the first 20 weeks of gestation, and short-term use of colchicine could be an option in pregnant women when glucocorticoids are contraindicated. (See 'Nonsteroidal antiinflammatory drugs (NSAIDs)' above.)

Potential contraindications to glucocorticoids in such patients include poorly controlled hypertension or diabetes, in addition to other usual concerns.

We also employ symptomatic treatment measures, such as icing.

- **Lactation** – In breastfeeding women, we use either glucocorticoids or NSAID therapy (see 'Oral glucocorticoids' above and 'Nonsteroidal antiinflammatory drugs (NSAIDs)' above) while continuing to avoid the use of colchicine.

Although antiinflammatory doses of an NSAID (eg, naproxen, ibuprofen, or indomethacin) have been effective in some pregnant patients with a gout flare, use of NSAIDs is limited to the first two trimesters of pregnancy because of concerns about NSAID-induced premature closure of the ductus arteriosus later in pregnancy. NSAID therapy should also be withheld during pregnancy in the presence of impaired kidney function. The use of NSAIDs during pregnancy and lactation is described in detail separately. (See "Safety of rheumatic disease medication use during pregnancy and lactation", section on 'NSAIDs'.)

Studies of colchicine in pregnant and breastfeeding patients with familial Mediterranean fever or pericardial diseases have not found increased adverse effects with its use [44,45]. However, there are reports of colchicine in breast milk and chromosomal damage associated with colchicine exposure [45-47].

RESISTANT OR REFRACTORY DISEASE

Reassess the diagnosis — In patients who fail to respond to therapy, we reevaluate the diagnosis and assess adherence. Arthrocentesis may be required to exclude other causes of a flare of acute inflammatory arthritis, including infection, if joint aspiration was not already performed during the gout flare.

Rebound flare — If the diagnosis and adherence are confirmed, we consider the possibility of a "rebound" gout flare, which may occur if glucocorticoids are tapered too quickly (eg, less than five days). If rebound flare seems likely, we increase glucocorticoids back to the last effective dose and then resume the taper over two to three weeks.

Partial response — In patients who have had gradual improvement in their symptoms, but have failed to return to their premorbid baseline, treatment may need to be extended for up to four weeks. This is more common among patients who started treatment several days after the start of the gout flare.

Resistant disease — In patients who fail to respond after three days of treatment with colchicine or nonsteroidal antiinflammatory drugs (NSAIDs), we would transition the patient to oral glucocorticoids. For patients who have persistent disease affecting only one or two joints, intraarticular glucocorticoids are an option, if this intervention is available locally.

Refractory disease — In patients who fail to respond to standard therapies, including systemic glucocorticoids, interleukin 1 (IL-1) blockade is an important option.

Interleukin 1 blockade — IL-1 is an important mediator of gouty inflammation and a therapeutic target in gout flares [48]. Thus, agents inhibiting IL-1 action are an effective treatment for gout flares (see "Pathophysiology of gout").

Anakinra — Anakinra (100 mg daily, administered subcutaneously daily until flare resolution) is the preferred IL-1 antagonist for use in a gout flare because of its short half-life. (See "Overview of biologic agents in the rheumatic diseases", section on 'IL-1 inhibition'.)

Randomized trials have demonstrated that anakinra is as effective as standard of care therapies for the treatment of gout flares, although there may be an increased risk of rebound flares.

- In a randomized trial of 88 patients with a crystal-proven gout flare, anakinra (100 mg daily for five consecutive days) was associated with similar short-term improvements in pain, tenderness, and swelling compared with standard of care therapies (eg, colchicine, oral glucocorticoids naproxen) [49].

- In another randomized trial of 165 patients with a gout flare who were not candidates for NSAID or colchicine therapy, anakinra in doses of 100 to 200 mg daily provided similar reductions in pain as a single 40 mg injection of intramuscular triamcinolone after 24 to 72 hours [50].

Canakinumab — Canakinumab has been approved in the European Union and the United States for treatment of patients who have at least three flares annually that cannot be managed with other treatment options [51,52]. Canakinumab is also effective for gout prophylaxis. (See "Pharmacologic urate-lowering therapy and treatment of tophi in patients with gout", section on 'Prophylaxis during initiation of urate-lowering therapy'.)

Two randomized trials comprising 456 patients with gout flare demonstrated that canakinumab 150 mg was associated with greater reductions in pain at 72 hours compared with intramuscular triamcinolone acetate [52].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Gout and other crystal disorders".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Gout (The Basics)")
- Beyond the Basics topics (see "Patient education: Gout (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Pretreatment considerations** – Early treatment of a gout flare leads to more rapid and complete resolution of the flare.

  However, gout and septic arthritis may present similarly. Glucocorticoids should be avoided until septic arthritis can be reasonably excluded. (See 'Pretreatment considerations' above.)

- **Treatment of gout flare** – For patients with a first or infrequent recurrent gout flare affecting one to two joints, we suggest intraarticular glucocorticoids if this treatment can be delivered in a timely manner (**Grade 2C**). When using intraarticular glucocorticoids, we use triamcinolone acetate (40 mg for a large joint; 20 mg for a medium joint). Such treatment is highly effective with a single dose and avoids complications associated with systemic therapy.

For all other patients (including when intraarticular glucocorticoids are not available), systemic nonsteroidal antiinflammatory drugs (NSAIDs), colchicine, or glucocorticoids are alternatives to intraarticular therapy. Patient factors, prior experience, and availability should guide the choice of therapy. (See 'Initial therapy' above.)

Guidance for dosing and administration include:

- **Glucocorticoids** – We use prednisone 40 mg daily until the flare resolves. Intravenous methylprednisolone 20 mg twice daily or intramuscular triamcinolone acetate 40 to 60 mg every two days are alternatives for patients who cannot take oral medications. Both should be continued until flare resolution.

- Colchicine – On the first day of therapy, 1.2 mg of oral colchicine is followed one hour later by 0.6 mg. On subsequent days, colchicine 0.6 mg twice daily should be administered until 48 hours following the flare. Colchicine is contraindicated in the presence of any degree of kidney or hepatic impairment in patients receiving a P-glycoprotein (P-gp) inhibitor (table 2) or an agent that strongly reduces availability of the cytochrome P450 system component CYP3A4.

  Colchicine most commonly causes gastrointestinal symptoms but also may be associated with neuropathy, cytopenia, myopathy, liver failure, and rash.

  Colchicine may need to be adjusted or avoided in patients with impaired liver or kidney function and in patients taking drugs that impact the cytochrome P450 system. (See 'Colchicine' above.)

- **NSAIDs** – We use naproxen 500 mg twice daily or indomethacin 50 mg three times daily until a few days after the flare has resolved. NSAIDs should be avoided in older patients and others who are at higher risk of the kidney, cardiovascular, and gastrointestinal side effects of NSAIDs (See 'Nonsteroidal antiinflammatory drugs (NSAIDs)' above.)

- **Special considerations**

  - **Patients on anticoagulation** – In patients taking anticoagulation, we use colchicine or oral glucocorticoids to avoid increasing the risk of bleeding that may occur with NSAIDs. An experienced provider may also be able to safely inject one or two joints with intraarticular glucocorticoids. (See 'Patients on anticoagulation' above.)

  - **Older adults** – For older adults, we typically use oral glucocorticoids to manage an acute flare. Older adults are often intolerant of both NSAIDs and colchicine. (See 'Older

adults' above.)

- **Patients with chronic kidney disease** – In patients with impaired kidney function, we use glucocorticoids and avoid colchicine and NSAIDs. In patients on chronic hemodialysis, NSAIDs may be used as an alternative to glucocorticoids. (See 'End-stage kidney disease and transplantation' above.)

- **Pregnant patients** – In women who are pregnant or breastfeeding, we suggest managing gout flares with glucocorticoids. NSAIDs should be avoided after 20 weeks of gestation but may be used beforehand or in women who are breastfeeding. (See 'Pregnancy and lactation' above.)

- **Resistant gout flares** – In patients who fail to respond to two or three days of treatment with NSAIDS or colchicine, we would initiate treatment with glucocorticoids. Intraarticular glucocorticoids may be appropriate in patients with only one or two affected joints. (See 'Oral glucocorticoids' above and 'Parenteral glucocorticoids' above.)

- **Refractory gout flares** – In patients who are refractory to standard therapies, options include interleukin 1 (IL-1) inhibition (ie, anakinra 100 mg subcutaneously daily until flare resolution) or one dose of canakinumab 150 mg subcutaneously. (See 'Interleukin 1 blockade' above.)

- **Prolonged therapy** – Patients who have had a partial response or experience a rebound flare after an initial response may need longer courses of therapy. This includes patients in whom treatment is delayed and patients who have persistent symptoms despite treatment. (See 'Resistant or refractory disease' above.)

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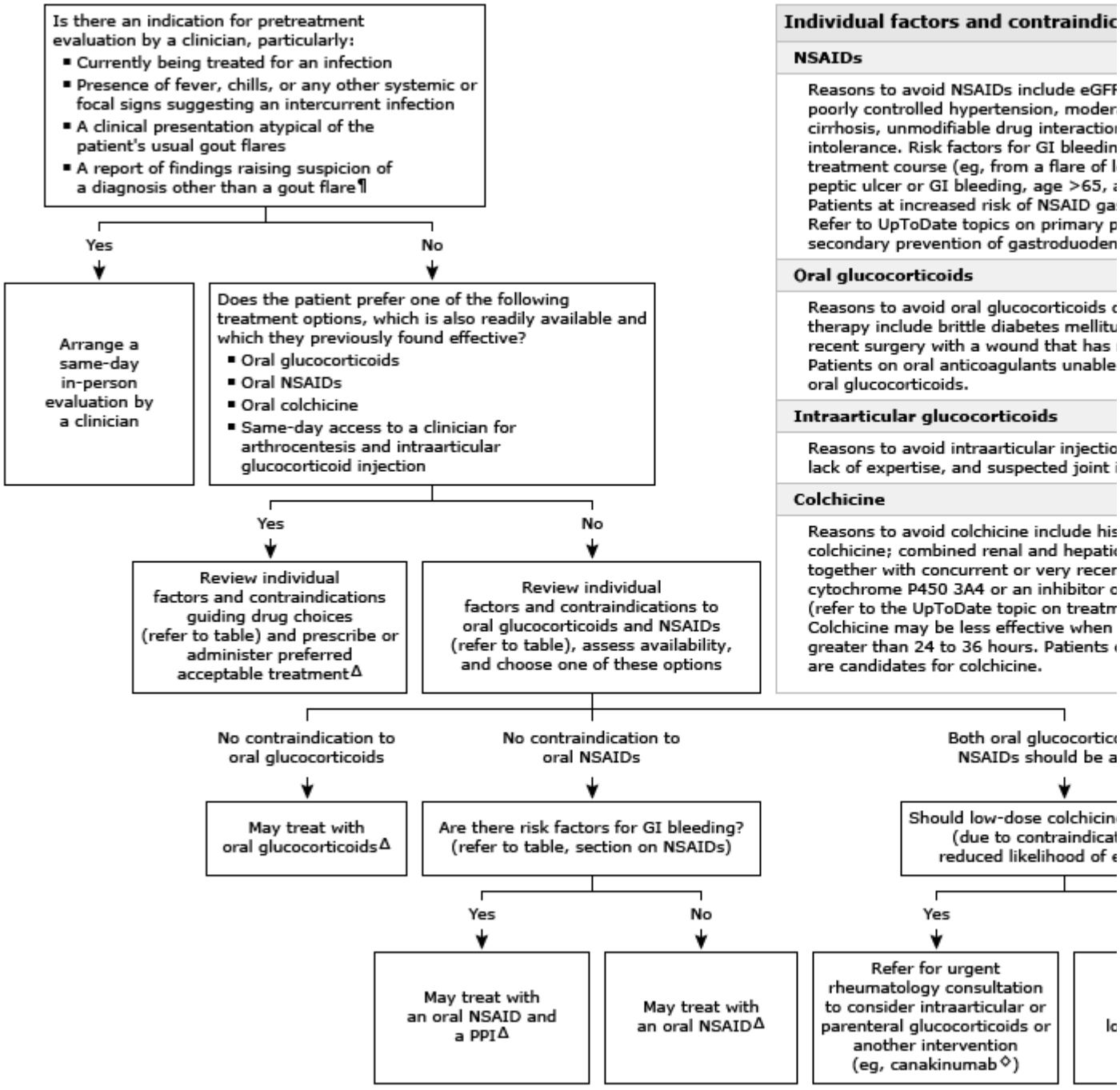
Topic 1666 Version 59.0

GRAPHICS

Initial management of gout flare for patients with known diagnosis of gout*



eGFR: estimated glomerular filtration rate; GI: gastrointestinal; NSAID: nonsteroidal antiinflammatory drug; PPI: proton pump inhibitor.

* This algorithm is applicable to nonpregnant adult gout patients who do not have an organ transplant.

¶ For additional information, refer to the UpToDate topic on the clinical manifestations and diagnosis of gout.

Δ For additional information, including specific dosing and treatment regimens, as well as other details, refer to the UpToDate topic on treatment of gout flares. In patients not already receiving long-term urate-lowering therapy who present with a flare, clinicians should discuss plans for such therapy. Ongoing urate-lowering therapy should be continued during treatment of the gout flare. For additional information, refer to the UpToDate topics on lifestyle modification and other strategies to reduce the risk of gout flares and progression of gout and on pharmacologic urate-lowering therapy and treatment of tophi in patients with gout.

◇ Canakinumab is reserved for use in patients who have frequent flares and in whom first-line therapies are ineffective, contraindicated, or not tolerated.

Graphic 121286 Version 3.0

Typical doses of long-acting (depot) intraarticular glucocorticoids for adults with musculoskeletal conditions

Depot glucocorticoid suspension	Dose according to joint size or extraarticular site			Average duration of action (days)	Available strengths
	Small*	Medium¶	Large△		
Methylprednisolone acetate	10 to 20 mg	40 to 60 mg	40 to 80 mg	7 to 84	20 mg/mL 40 mg/mL 80 mg/mL
Triamcinolone acetonide◇	8 to 10 mg	20 to 30 mg	20 to 40 mg	14	10 mg/mL 40 mg/mL 80 mg/mL

There is a lack of consensus on optimal dosing for joint injections. The dose ranges in this table are those often used by UpToDate contributors; a lower or higher dose may be used depending upon size of joint/body region, severity of inflammation, and amount of articular fluid present. UpToDate contributors usually dilute the glucocorticoid suspension with an equal volume of 1 or 2% lidocaine or other local anesthetic. Refer to topic on intraarticular and soft tissue injections.

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* Including metacarpophalangeal and proximal interphalangeal joints, tendon sheaths.

¶ Including wrist, ankle, and elbow.

△ Including knee, shoulder, and hip.

◇ An extended-release triamcinolone acetonide microsphere suspension (Zilretta) is also available for knee osteoarthritis pain as a 32 mg/mL preparation. It is not interchangeable with other triamcinolone acetonide suspensions and is costlier.

Courtesy of W Neal Roberts, Jr, MD and Derrick Todd, MD. Additional data from:

1. *Cole BJ, Schumacher HR Jr. Injectable corticosteroids in modern practice. J Am Acad Orthop Surg 2005; 13:37.*
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3. *Lexicomp Online. Copyright © 1978-2024 Lexicomp, Inc. All Rights Reserved.*

Graphic 115705 Version 6.0

Inhibitors and inducers of P-glycoprotein (P-gp) drug efflux pump (P-gp multidrug resistance transporter)

Inhibitors of P-gp		Inducers of P-gp
▪ Abrocitinib ▪ Adagrasib ▪ Amiodarone ▪ Azithromycin (systemic) ▪ Cannabidiol and cannabidiol-containing coformulations ▪ Capmatinib ▪ Carvedilol ▪ Clarithromycin ▪ Cobicistat and cobicistat-containing coformulations ▪ Cyclosporine (systemic) ▪ Daclatasvir ▪ Daridorexant ▪ Diosmin (a plant flavonoid sold as dietary supplement) ▪ Dronedarone ▪ Elagolix ▪ Elagolix-estradiol-norethindrone ▪ Eliglustat ▪ Elexacaftor-tezacaftor-ivacaftor ▪ Enzalutamide ▪ Erythromycin (systemic) ▪ Flibanserin ▪ Fostamatinib ▪ Glecaprevir-pibrentasvir ▪ Isavuconazole (isavuconazonium sulfate) ▪ Itraconazole ▪ Ivacaftor ▪ Ketoconazole (systemic)	▪ Lapatinib ▪ Ledipasvir ▪ Levoketoconazole ▪ Mifepristone[*] ▪ Neratinib ▪ Nirmatrelvir-ritonavir ▪ Ombitasvir-paritaprevir-ritonavir (Technivie)[¶] ▪ Osimertinib ▪ Pirtobrutinib ▪ Posaconazole ▪ Propafenone ▪ Quinidine ▪ Quinine ▪ Ranolazine ▪ Ritonavir and ritonavir-containing coformulations[¶] ▪ Rolapitant ▪ Selpercatinib ▪ Simeprevir ▪ Sotagliflozin ▪ Sotorasib[Δ] ▪ Tamoxifen[Δ] ▪ Tepotinib ▪ Tezacaftor-ivacaftor ▪ Ticagrelor[Δ] ▪ Tucatinib ▪ Velpatasvir ▪ Vemurafenib ▪ Verapamil ▪ Voclosporin	▪ Apalutamide ▪ Carbamazepine ▪ Fosphenytoin ▪ Green tea (*Camellia sinensis*) ▪ Lorlatinib ▪ Phenytoin ▪ Rifampin (rifampicin) ▪ St. John's wort

- Inhibitors of the P-gp drug efflux pump (also known as P-gp multidrug resistance transporter) listed above may **increase** serum concentrations of drugs that are substrates of P-gp, whereas inducers of P-gp drug efflux may **decrease** serum concentrations of substrates of P-gp.

- Examples of drugs that are substrates of P-gp efflux pump include: Apixaban, colchicine, cyclosporine, dabigatran, digoxin, edoxaban, rivaroxaban, and tacrolimus.
- The degree of effect on P-gp substrate serum concentration may be altered by dose and timing of orally administered P-gp inhibitor or inducer.
- These classifications are based upon US FDA guidance.[1,2] Other sources may use a different classification system resulting in some agents being classified differently.
- Specific drug interaction effects may be determined by using the Lexicomp drug interactions program included with UpToDate. Refer to UpToDate clinical topics on specific agents and conditions for further details.

P-gp: P-glycoprotein; US FDA: US Food and Drug Administration.

* Mifepristone is a significant inhibitor of P-gp when used chronically (eg, for hyperglycemia in patients with Cushing syndrome); not in single-dose use.

¶ The combination of ombitasvir-paritaprevir-ritonavir plus dasabuvir (Viekira Pak) is not a significant inhibitor of P-gp efflux pump.[3]

Δ Minor clinical effect or supportive data are limited to in vitro effects (ie, clinical effect is unknown).

References:

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2. *US Food & Drug Administration. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Available at: FDA.gov website.*
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Graphic 73326 Version 83.0

Cytochrome P450 3A (including 3A4) inhibitors and inducers

Strong inhibitors	Moderate inhibitors	Strong inducers	Moderate inducers
▪ Adagrasib ▪ Atazanavir ▪ Ceritinib ▪ Clarithromycin ▪ Cobicistat and cobicistat-containing coformulations ▪ Darunavir ▪ Idelalisib ▪ Indinavir ▪ Itraconazole ▪ Ketoconazole ▪ Levoketoconazole ▪ Lonafarnib ▪ Lopinavir ▪ Mifepristone[*] ▪ Nefazodone ▪ Nelfinavir ▪ Nirmatrelvir-ritonavir ▪ Ombitasvir-paritaprevir-ritonavir ▪ Ombitasvir-paritaprevir-ritonavir plus dasabuvir ▪ Posaconazole ▪ Ritonavir and ritonavir-containing coformulations ▪ Saquinavir ▪ Tucatinib ▪ Voriconazole	▪ Amiodarone[¶] ▪ Aprepitant ▪ Berotralstat ▪ Cimetidine[¶] ▪ Conivaptan ▪ Crizotinib ▪ Cyclosporine[¶] ▪ Diltiazem ▪ Duvelisib ▪ Dronedarone ▪ Erythromycin ▪ Fedratinib ▪ Fluconazole ▪ Fosamprenavir ▪ Fosaprepitant[¶] ▪ Fosnetupitant-palonosetron ▪ Grapefruit juice ▪ Imatinib ▪ Isavuconazole (isavuconazonium sulfate) ▪ Lefamulin ▪ Letermovir ▪ Netupitant ▪ Nilotinib ▪ Ribociclib ▪ Schisandra ▪ Verapamil	▪ Apalutamide ▪ Carbamazepine ▪ Encorafenib ▪ Enzalutamide ▪ Fosphenytoin ▪ Lumacaftor ▪ Lumacaftor-ivacaftor ▪ Mitotane ▪ Phenobarbital ▪ Phenytoin ▪ Primidone ▪ Rifampin (rifampicin)	▪ Bexarotene ▪ Bosentan ▪ Cenobamate ▪ Dabrafenib ▪ Dexamethasone[Δ] ▪ Dipyrone ▪ Efavirenz ▪ Elagolix, estradiol, and norethindrone therapy pack[◇] ▪ Eslicarbazepine ▪ Etravirine ▪ Lorlatinib ▪ Mitapivat ▪ Modafinil ▪ Nafcillin ▪ Pexidartinib ▪ Repotrectinib ▪ Rifabutin ▪ Rifapentine ▪ Sotorasib ▪ St. John's wort

- For drug interaction purposes, the inhibitors and inducers of CYP3A metabolism listed above can alter serum concentrations of drugs that are dependent upon the CYP3A subfamily of liver enzymes, including CYP3A4, for elimination or activation.
- These classifications are based upon US Food and Drug Administration (FDA) guidance.[1,2] Other sources may use a different classification system resulting in some agents being classified differently.

- Data are for systemic drug forms. Degree of inhibition or induction may be altered by dose, method, and timing of administration.
- Weak inhibitors and inducers are not listed in this table with exception of a few examples. Clinically significant interactions can occasionally occur due to weak inhibitors and inducers (eg, target drug is highly dependent on CYP3A4 metabolism and has a narrow therapeutic index). Accordingly, specific interactions should be checked using a drug interaction program such as the Lexicomp drug interactions program included within UpToDate.
- Refer to UpToDate topics on specific agents and indications for further details.

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* Mifepristone is a significant inhibitor of CYP3A4 when used chronically (eg, for hyperglycemia in patients with Cushing syndrome); not in single-dose use.

¶ Classified as a weak inhibitor of CYP3A4 according to FDA system.[1]

Δ Classified as a weak inducer of CYP3A4 according to FDA system.[1]

◇ The fixed-dose combination therapy pack taken in the approved regimen has moderate CYP3A4 induction effects. When elagolix is used as a single agent, it is a weak CYP3A4 inducer. Norethindrone and estradiol are not CYP3A4 inducers.

References:

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Graphic 76992 Version 98.0

Nonsteroidal antiinflammatory drugs (NSAIDs) and acetaminophen (paracetamol): Usual oral dosing for adults with pain or inflammation and selected characteristics

Drug	Usual analgesic dose (oral)	Maximum dose per day	Selected characteristics
Nonselective NSAIDs*			
Acetic acids			
Diclofenac¶	50 mg every 8 to 12 hours	150 mg For rheumatoid arthritis, labeling in United States permits up to 200 mg Approved maximum in Canada is 100 mg	▪ Dosing for free-acid preparation differs from doses listed here for sodium or potassium salts; refer to Lexicomp drug monograph
Etodolac	200 to 400 mg every 6 to 8 hours	1000 mg	▪ Relative COX-2 selectivity and minimal effect on platelet function at lower total daily dose of 600 to 800 mg
Indomethacin	25 to 50 mg every 8 to 12 hours	150 mg For rheumatologic conditions, labeling in United States permits up to 200 mg	▪ Used for treatment of acute gout and certain types of headache ▪ Potent inhibitory effects on kidney prostaglandin synthesis ▪ More frequently associated with CNS side effects (eg, headache, altered mental status) compared with other NSAIDs
Sulindac	150 to 200 mg every 12 hours	400 mg	▪ Rarely used ▪ More frequently associated with hepatic inflammation than other NSAIDs ▪ Metabolites implicated in the formation of renal calculi
Fenamates			

Meclofenamate (meclofenamic acid)	50 mg every 4 to 6 hours or 100 mg 3 times daily up to 6 days for dysmenorrhea	400 mg	▪ Used for treatment of dysmenorrhea ▪ Relatively higher incidence of GI side effects
Mefenamic acid	250 mg every 6 hours or 500 mg 3 times daily	1000 mg For dysmenorrhea, up to 1500 mg	▪ Used for treatment of dysmenorrhea; not indicated for treatment of chronic pain or inflammation ▪ Do not exceed 3 days (dysmenorrhea) to 7 days (acute pain) of use ▪ Less potent antiinflammatory effec
Nonacidic			
Nabumetone	1000 mg once to twice daily	2000 mg	▪ Relative COX-2 selectivity and minimal effect on platelet function at daily dose ≤1000 mg
Oxicams			
Meloxicam[Δ]	7.5 to 15 mg once daily (conventional tablet, oral suspension) 5 to 10 mg once daily (capsule)	15 mg (conventional tablet, oral suspension) 10 mg (capsule)	▪ Long duration of effect; relatively slow onset ▪ Relative COX-2 selectivity and minimal effect on platelet function at lower daily dose of 7.5 mg
Piroxicam	10 to 20 mg once daily	20 mg	▪ Long-acting alternative for treatment of chronic pain and inflammation poorly responsive to other NSAIDs ▪ Prescribing generally limited to specialists with experience in treatment of chronic pain and inflammation
Propionic acids			
Fenoprofen	200 mg every 4 to 6 hours or 400 to 600 mg every 6 to 8 hours	3200 mg	▪ More frequently associated with acute interstitial nephritis and nephrotic syndrome[1]

Flurbiprofen	50 mg every 6 hours or 100 mg every 8 to 12 hours	300 mg	
Ibuprofen[Δ]	400 mg every 4 to 6 hours or 600 to 800 mg every 6 to 8 hours	3200 mg (acute), 2400 mg (chronic)	▪ Shorter-acting alternative to naproxen; useful in patients withou cardiovascular risks
Ketoprofen	50 mg every 6 hours or 75 mg every 8 hours	300 mg	
Naproxen	Base: 250 to 500 mg every 12 hours or 250 mg every 6 to 8 hours	Base: 1250 mg (acute); 1000 mg (chronic); may increase to 1500 mg during a disease flare	▪ Often preferred by UpToDate for treatment of acute or chronic pain and inflammation in patients without relevant comorbidities or risks ▪ Higher dose (eg, 500 mg base twice daily) may have less cardiovascular toxicity than comparable doses of other NSAIDs;[2] refer to UpToDate topic review of cardiovascular effects of nonselective NSAIDs ▪ Naproxen sodium has a faster onse than naproxen base
	Naproxen sodium: 275 to 550 mg every 12 hours or 275 mg every 6 to 8 hours	Naproxen sodium: 1375 mg (acute); 1100 mg (chronic); may increase to 1650 mg during a disease flare	
Oxaprozin	1200 mg once daily	1200 mg or 1800 mg depending on body weight (refer to Lexicomp drug monograph)	▪ Prolonged half-life (41 to 55 hours); requires several days of treatment to reach full effect
Salicylate (acetylated)			
Aspirin	325 to 1000 mg every 4 to 6 hours	4000 mg	▪ Not commonly used for chronic pain and inflammation ▪ High daily doses have been used as antiinflammatory therapy; such use is limited by toxicity ▪ Irreversibly inhibits platelet functio ▪ Refer to appropriate UpToDate clinical topics and Lexicomp drug monograph for other uses
Salicylates (nonacetylated)			

Diflunisal	500 mg every 8 to 12 hours	1500 mg	▪ No significant effect on platelet function at usual doses ▪ Relatively lower GI bleeding risk than other nonselective NSAIDs at usual doses ▪ May be tolerated at lower daily doses by adults with AERD or pseudoallergic reactions (eg, asthma, rhinosinusitis); refer to UpToDate topic reviews of allergic and pseudoallergic reactions to NSAIDs
Magnesium salicylate	1160 mg every 6 hours	4640 mg	
Salsalate	1000 mg every 8 to 12 hours or 1500 mg every 12 hours	3000 mg	
COX-2 selective NSAIDs			
Celecoxib	200 mg daily or 100 mg every 12 hours	400 mg	▪ Less risk of GI toxicity relative to nonselective NSAIDs; benefit negated by low-dose aspirin, which may require concurrent gastroprotection ▪ No effect on platelet function ▪ Cardiovascular and kidney risks are dose-related and may be similar to nonselective NSAIDs ▪ May be tolerated by patients with AERD or pseudoallergic reactions (eg, asthma, rhinosinusitis) who cannot take other NSAIDs; refer to UpToDate topic reviews of allergic and pseudoallergic reactions to NSAIDs
Etoricoxib (not available in the United States)	30 to 60 mg once daily	60 mg (chronic pain and inflammation) 120 mg (acute pain for up to 8 days)	▪ May be associated with more frequent and severe dose-related cardiovascular effects (eg, hypertension) ▪ Other risks and benefits similar to celecoxib
Non-NSAID analgesic			
Acetaminophen (paracetamol)[Δ]	325 to 650 mg every 4 to 6 hours or 1000 mg every 6 hours up to 3	3000 mg 4000 mg in selected medically supervised patients	▪ Effective for noninflammatory pain; may decrease opioid requirements ▪ Doses ≤2000 mg per day do not appear to increase risk of serious G complications[3]

	times daily	Avoid or use a lower total daily dose (maximum 2000 mg) in older adults, patients at increased risk for hepatotoxicity (eg, regular alcohol use, malnourished), or patients with organ dysfunction	▪ Does not alter platelet function ▪ Can cause hepatotoxicity in chronic or acute overdose ▪ To avoid overdose, warn patients about acetaminophen content in combination prescription (eg, oxycodone-acetaminophen) and nonprescription (OTC) preparations

NSAIDs are useful for treatment of acute and chronic painful and inflammatory conditions and may reduce opioid requirements. The indications for use of NSAIDs in specific disorders, adverse effects, and toxicities are presented in the relevant UpToDate topics including reviews of NSAID-associated adverse cardiovascular effects, gastroduodenal toxicity, acute kidney injury, etc.

UpToDate contributors generally avoid use of NSAIDs, or use them with particular caution and at reduced doses, in older adults and patients (regardless of age) with existing or increased risk for cardiovascular, GI, or kidney disease. Concurrent gastroprotection (eg, a proton pump inhibitor) may be warranted. For information on gastroprotective strategies, including use of selective COX-2 inhibitors and other options, refer to the UpToDate topic reviews of COX-2 selective NSAIDs and NSAIDs (including aspirin) and primary prevention of gastroduodenal toxicity.

Short- to moderate-acting NSAIDs (eg, naproxen, ibuprofen) are preferred for most patients. Use the lowest effective dose for the shortest duration of time. For chronic inflammatory conditions, a trial of ≥2 weeks is advised to assess full efficacy. For patients who experience an inadequate response to an NSAID of 1 class, it is reasonable to substitute an NSAID of another class.

Dosing in this table is for immediate-release preparations in patients with normal organ (eg, kidney) function. For treatment of acute pain, a loading dose of some NSAIDs may be used; refer to Lexicomp drug monographs.

Drug interactions may be determined by use of the Lexicomp drug interactions program included within UpToDate.

AERD: aspirin-exacerbated respiratory disease; CNS: central nervous system; COX-2: cyclooxygenase, isoform 2; GI: gastrointestinal; OTC: over the counter.

* Nonselective NSAIDs reversibly inhibit platelet function, with some exceptions noted above.

¶ Also available as a topical agent.

Δ Also available for parenteral use.

References:

1. *Murray MD, Brater DC. Renal toxicity of the nonsteroidal anti-inflammatory drugs. Annu Rev Pharmacol Toxicol 1993; 33:435.*

2. *Bhala N, Emberson J, Merhi A, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomized trials. Lancet 2013; 382:769.*
3. *McCrae JC, Morrison EE, MacIntyer IM, et al. Long-term adverse effects of paracetamol – a review. Br J Clin Pharmacol 2018; 84:2218.*

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