# NSAIDs (including aspirin): Treatment and secondary prevention of gastroduodenal toxicity

**AUTHOR:** Mark Feldman, MD, MACP, AGAF, FACG
**SECTION EDITOR:** J Thomas Lamont, MD
**DEPUTY EDITOR:** Shilpa Grover, MD, MPH, AGAF

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: **Sep 2023.**
This topic last updated: **Jul 24, 2023.**

## INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, cause considerable morbidity and mortality related to gastric and duodenal mucosal toxicity, particularly by causing gastrointestinal (GI) bleeding [1]. NSAIDs are also important causes of GI bleeding in children [2].

This topic will review the treatment of gastroduodenal toxicity associated with NSAID therapy, and the secondary prevention of recurrent gastroduodenal toxicity associated with NSAID, low-dose aspirin, or both therapies. The pathogenesis, risk factors, manifestations and primary prevention of aspirin/NSAID-related gastroduodenal toxicity are discussed separately. (See "NSAIDs: Adverse effects on the distal small bowel and colon" and "NSAIDs (including aspirin): Pathogenesis and risk factors for gastroduodenal toxicity" and "NSAIDs (including aspirin): Primary prevention of gastroduodenal toxicity".)

## MANAGEMENT

**Discontinuation of aspirin/NSAIDs** — If a patient develops a gastric or duodenal ulcer while on an NSAID or low-dose aspirin, the NSAID or aspirin should be stopped if at all possible. If the patient has been taking low-dose aspirin for prophylaxis of cardiovascular disease, there is no consensus as to when to resume the aspirin. The indication for the low-dose aspirin should be

reviewed and the severity of the ulcer presentation considered. For most patients, the author recommends low-dose aspirin, if still indicated, be restarted approximately three to five days after initiating therapy with a proton pump inhibitor (PPI).

**Evaluation for and eradication of H. pylori** — As in all patients with peptic ulcers, the patient's *Helicobacter pylori* (*H. pylori*) status should also be assessed (if not done previously) [3]; if positive, appropriate therapy for *H. pylori* should be instituted [4]. However, the sensitivity of *H. pylori* testing in the setting of acute GI bleeding is significantly reduced. (See "Indications and diagnostic tests for Helicobacter pylori infection in adults", section on 'Patient undergoing upper endoscopy' and "Treatment regimens for Helicobacter pylori in adults".)

**Gastric acid suppression**

**Choice of therapy** — For patients who must remain on low-dose aspirin, NSAID therapy, or both, randomized trials have shown that ulcer healing occurs more rapidly with a PPI than an H2 receptor antagonist (H2RA), misoprostol, or sucralfate [5-11]. The table lists the available medications and their usual dose ( table 1). (See "Peptic ulcer disease: Treatment and secondary prevention".)

Multiple randomized trials comparing PPIs with an H2RA have demonstrated faster healing with the use of PPIs. While these trials were usually performed with ranitidine, an H2RA that has since been withdrawn due to unacceptable levels of N-nitrosodimethylamine (NMDA), the results are generalizable to other H2RAs due to their comparable efficacy [8,9,12]. In one illustrative trial, 541 patients who had ulcers or numerous (>10) erosions in either the stomach or duodenum and who required continuous treatment with NSAIDs were randomly assigned to treatment with omeprazole (20 or 40 mg orally daily) or ranitidine for four or eight weeks [8]. At eight weeks, endoscopic healing rates were higher with both doses of omeprazole as compared with ranitidine (80 and 79 versus 63 percent). (See "Antiulcer medications: Mechanism of action, pharmacology, and side effects", section on 'Adverse effects'.)

**Duration of treatment** — Treatment with a PPI is generally continued for four to eight weeks depending on the ulcer location, size, and severity of the initial clinical presentation. In general, we suggest PPI therapy (eg, omeprazole 20 to 40 mg daily or equivalent dose of an alternative PPI) for four to six weeks for ulcers <1 cm (especially for duodenal ulcers) and PPI therapy for six to eight weeks for ulcers ≥1 cm (especially for gastric ulcers) ( table 1).

Maintenance PPI therapy is indicated in patients who must remain on or resume low-dose aspirin or NSAIDs. The benefits of PPI maintenance therapy for secondary prevention of NSAID- or low-dose aspirin-associated ulcers considerably outweigh potential risks of long-term PPI

therapy [13]. (See "Proton pump inhibitors: Overview of use and adverse effects in the treatment of acid related disorders", section on 'Adverse effects'.)

**Endoscopic follow-up** — Endoscopic follow-up to assess ulcer healing is usually unnecessary for duodenal ulcers, but should be performed to assess healing of gastric ulcers if there had been any concern that malignancy had not been excluded at the initial endoscopy. (See "Peptic ulcer disease: Treatment and secondary prevention", section on 'Repeat upper endoscopy in selected patients'.)

## SECONDARY PREVENTION OF GASTRODUODENAL TOXICITY

Prevention of recurrent ulcer disease becomes critically important in patients with a history of gastroduodenal toxicity from NSAIDs, low-dose aspirin, or both therapies, and who require continued therapy. Only randomized secondary prevention trials using clinical ulcer disease as the outcome (rather than an endoscopic outcome) are discussed below.

**Assess the risks and benefits of continued asprin/NSAID use and risk of toxicity** — In patients on aspirin and NSAIDs, the indications for use, the availability of alternatives agents, and risk factors for bleeding should be considered when deciding on their use. Assessment of gastroduodenal toxicity risk is discussed in detail separately. (See "NSAIDs (including aspirin): Pathogenesis and risk factors for gastroduodenal toxicity", section on 'Assessment of gastroduodenal toxicity risk'.)

As an example, patients treated with low-dose aspirin have an increased risk of gastrointestinal (GI) bleeding, which must be weighed against a possible reduction in cardiovascular mortality [14]. The risk of recurrent bleeding in aspirin users may be higher in patients without a past or current *H. pylori* infection [15]. Risks of stopping low-dose aspirin were addressed in a randomized trial of 156 adults with cardiovascular or cerebrovascular disease who were being treated with low-dose aspirin and developed peptic ulcer bleeding. After control of bleeding with endoscopic therapy and use of a proton pump inhibitor (PPI), patients were assigned to continue taking aspirin (80 mg per day) or to stop the aspirin and switch to a placebo for eight weeks. Stopping aspirin therapy was associated with a nonsignificant decrease in the primary endpoint of recurrent ulcer bleeding within 30 days (5.4 percent versus 10.3 percent with continued aspirin therapy). Stopping aspirin was also associated with a significant increase in the secondary endpoint of overall mortality at eight weeks (12.3 versus 1.3 percent) [16]. (See "Aspirin for the secondary prevention of atherosclerotic cardiovascular disease", section on 'Efficacy' and "NSAIDs (including aspirin): Secondary prevention of gastroduodenal toxicity", section on 'Risk of stopping low-dose aspirin'.)

## Prevention strategies based on type and duration of exposure

**Patients on low-dose aspirin** — Patients who require low-dose aspirin for cardiovascular prophylaxis and have had a bleeding ulcer while taking low-dose aspirin should be treated with a PPI (rather than an H2-blocker), along with *H. pylori* eradication if they test positive for *H. pylori* [17]. There are no compelling data that suggest that any of the available PPIs are more effective than another. The table lists the available medications and their usual dose ( table 1). Randomized trials support the efficacy of PPI therapy in preventing recurrent bleeding in both *H. pylori* positive and negative patients with peptic ulcers receiving low-dose aspirin therapy [17-23]. In one illustrative trial, in which 123 patients with a history of peptic ulcer complications after using low-dose aspirin were assigned to lansoprazole daily or placebo, in addition to 100 mg of aspirin daily, for 12 months, recurrence of ulcer complications (bleeding, perforation, or obstruction) were significantly lower with concurrent PPI use (2 versus 15 percent) [19].

**Patients who require NSAIDs** — For patients who require an NSAID and are at high risk for recurrent GI toxicity or are on concomitant low-dose aspirin, selecting celecoxib (or another COX-2 selective agent, if available) plus a PPI can reduce recurrent bleeding ulcers. Long-term maintenance PPI therapy should be continued for risk reduction while on aspirin/NSAIDs [18]. Nevertheless, recurrent GI bleeding remains a concern in such patients. (See "NSAIDs (including aspirin): Pathogenesis and risk factors for gastroduodenal toxicity", section on 'Assessment of gastroduodenal toxicity risk'.)

Substituting a COX-2 inhibitor for the prior nonselective NSAID in patients with NSAID-related ulcer disease and ulcer complications should not be chosen over PPI maintenance therapy. This was demonstrated in a trial of 273 arthritis patients with NSAID-related bleeding ulcers [24]. Once the ulcers had healed, substituting celecoxib 200 mg twice daily plus esomeprazole (20 mg twice daily) for a year was significantly more effective in preventing recurrent bleeding ulcers than simply substituting celecoxib (plus placebo twice daily) for the NSAID that the patient had been taking previously [24]. Ulcer rebleeding rates after a median follow-up period of 13 months were 0 percent in the celecoxib/esomeprazole group and 8.9 percent in the celecoxib/placebo group.

In patients who require both an NSAID and low-dose aspirin and are at high risk of GI toxicity, a selective COX-2 inhibitor plus a PPI is preferred over a nonselective COX inhibitor plus a PPI as this can decrease the risk of ulcer bleeding. In a randomized trial, 514 patients with bleeding gastroduodenal ulcers related to NSAID and low-dose aspirin use were placed on celecoxib (COX-2 selective) plus esomeprazole or naproxen (COX nonselective) plus esomeprazole once the ulcer had healed [25]. Patients in both groups continued taking low-dose aspirin. Rates of recurrent ulcer bleeding over the ensuing 18 months were significantly lower in the celecoxib

group than in the naproxen group (5.6 versus 12.3 percent) [25]. (See "NSAIDs (including aspirin): Primary prevention of gastroduodenal toxicity".)

## 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: NSAID-related ulcer complications".)

## SUMMARY AND RECOMMENDATIONS

- **Management of gastroduodenal NSAID injury**
  - **Discontinue of** aspirin**/NSAID** – For patients who develop a symptomatic gastric or duodenal ulcer while on a nonsteroidal anti-inflammatory drug (NSAID) and/or low-dose aspirin, NSAIDs and/or aspirin should be discontinued.
  - **Acid suppression with PPI therapy** – For patients with gastroduodenal toxicity (ulcers or erosions), we recommend acid suppression therapy with a proton pump inhibitor (PPI) rather than an H2 receptor antagonist (**Grade 1B**). The duration of acid suppression therapy with a PPI is based on whether aspirin/NSAIDs can be discontinued. In general, we use PPI therapy (eg, omeprazole 20 to 40 mg daily or equivalent dose of an alternative PPI) for four to six weeks for ulcers <1 cm (especially for duodenal ulcers) and PPI therapy for six to eight weeks for ulcers ≥1 cm (especially for gastric ulcers). (See 'Management' above.)
  - **Test and treat *H. pylori*** – The patient's *H. pylori* status should also be assessed; if positive, appropriate therapy should be instituted. Eradication of *H. pylori* should be confirmed. (See "Treatment regimens for Helicobacter pylori in adults" and "Indications and diagnostic tests for Helicobacter pylori infection in adults", section on 'Patient undergoing upper endoscopy'.)
- **Secondary prevention in patients who resume** aspirin **and/or NSAIDs**
  - For patients with symptomatic gastroduodenal ulcers or multiple erosions who must continue NSAIDs or low-dose aspirin therapy, or both, we recommend treatment with a PPI ( table 1) (**Grade 1B**). We continue PPI therapy for as long as the NSAID and/or

aspirin is used. (See "NSAIDs (including aspirin): Secondary prevention of gastroduodenal toxicity", section on 'Secondary prevention of gastroduodenal toxicity'.)

- For patients who are at high risk for gastroduodenal toxicity on low-dose aspirin for cardiovascular prophylaxis, selecting celecoxib (or another COX-2 selective agent, if available) plus a PPI may be more effective than using a nonselective NSAID plus a PPI in reducing recurrent bleeding ulcers. Nevertheless, recurrent GI bleeding remains a concern in such patients. (See "NSAIDs (including aspirin): Secondary prevention of gastroduodenal toxicity", section on 'With continued NSAID therapy'.)



**REFERENCES**

1. Wallace JL. Nonsteroidal anti-inflammatory drugs and gastroenteropathy: the second hundred years. Gastroenterology 1997; 112:1000.
2. Cardile S, Martinelli M, Barabino A, et al. Italian survey on non-steroidal anti-inflammatory drugs and gastrointestinal bleeding in children. World J Gastroenterol 2016; 22:1877.
3. Sostres C, Carrera-Lasfuentes P, Benito R, et al. Peptic Ulcer Bleeding Risk. The Role of Helicobacter Pylori Infection in NSAID/Low-Dose Aspirin Users. Am J Gastroenterol 2015; 110:684.
4. Fallone CA, Chiba N, van Zanten SV, et al. The Toronto Consensus for the Treatment of Helicobacter pylori Infection in Adults. Gastroenterology 2016; 151:51.
5. Mo C, Sun G, Lu ML, et al. Proton pump inhibitors in prevention of low-dose aspirin-associated upper gastrointestinal injuries. World J Gastroenterol 2015; 21:5382.
6. Bhatt DL, Scheiman J, Abraham NS, et al. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. Circulation 2008; 118:1894.
7. Satoh K, Yoshino J, Akamatsu T, et al. Evidence-based clinical practice guidelines for peptic ulcer disease 2015. J Gastroenterol 2016; 51:177.
8. Yeomans ND, Tulassay Z, Juhász L, et al. A comparison of omeprazole with ranitidine for ulcers associated with nonsteroidal antiinflammatory drugs. Acid Suppression Trial: Ranitidine versus Omeprazole for NSAID-associated Ulcer Treatment (ASTRONAUT) Study Group. N Engl J Med 1998; 338:719.

9. Agrawal NM, Campbell DR, Safdi MA, et al. Superiority of lansoprazole vs ranitidine in healing nonsteroidal anti-inflammatory drug-associated gastric ulcers: results of a double-blind, randomized, multicenter study. NSAID-Associated Gastric Ulcer Study Group. Arch Intern Med 2000; 160:1455.
10. Hawkey CJ, Karrasch JA, Szczepañski L, et al. Omeprazole compared with misoprostol for ulcers associated with nonsteroidal antiinflammatory drugs. Omeprazole versus Misoprostol for NSAID-induced Ulcer Management (OMNIUM) Study Group. N Engl J Med 1998; 338:727.
11. Bianchi Porro G, Lazzaroni M, Manzionna G, Petrillo M. Omeprazole and sucralfate in the treatment of NSAID-induced gastric and duodenal ulcer. Aliment Pharmacol Ther 1998; 12:355.
12. Scally B, Emberson JR, Spata E, et al. Effects of gastroprotectant drugs for the prevention and treatment of peptic ulcer disease and its complications: a meta-analysis of randomised trials. Lancet Gastroenterol Hepatol 2018; 3:231.
13. Laine L, Nagar A. Long-Term PPI Use: Balancing Potential Harms and Documented Benefits. Am J Gastroenterol 2016; 111:913.
14. Fuster V, Sweeny JM. Aspirin: a historical and contemporary therapeutic overview. Circulation 2011; 123:768.
15. Chan FK, Ching JY, Suen BY, et al. Effects of Helicobacter pylori infection on long-term risk of peptic ulcer bleeding in low-dose aspirin users. Gastroenterology 2013; 144:528.
16. Sung JJ, Lau JY, Ching JY, et al. Continuation of low-dose aspirin therapy in peptic ulcer bleeding: a randomized trial. Ann Intern Med 2010; 152:1.
17. Ng FH, Wong SY, Lam KF, et al. Famotidine is inferior to pantoprazole in preventing recurrence of aspirin-related peptic ulcers or erosions. Gastroenterology 2010; 138:82.
18. Chan FK, Chung SC, Suen BY, et al. Preventing recurrent upper gastrointestinal bleeding in patients with Helicobacter pylori infection who are taking low-dose aspirin or naproxen. N Engl J Med 2001; 344:967.
19. Lai KC, Lam SK, Chu KM, et al. Lansoprazole for the prevention of recurrences of ulcer complications from long-term low-dose aspirin use. N Engl J Med 2002; 346:2033.
20. Chan FK, Ching JY, Hung LC, et al. Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding. N Engl J Med 2005; 352:238.
21. Lai KC, Chu KM, Hui WM, et al. Esomeprazole with aspirin versus clopidogrel for prevention of recurrent gastrointestinal ulcer complications. Clin Gastroenterol Hepatol 2006; 4:860.

22. Sugano K, Choi MG, Lin JT, et al. Multinational, double-blind, randomised, placebo-controlled, prospective study of esomeprazole in the prevention of recurrent peptic ulcer in low-dose acetylsalicylic acid users: the LAVENDER study. Gut 2014; 63:1061.
23. Iwakiri R, Higuchi K, Kato M, et al. Randomised clinical trial: prevention of recurrence of peptic ulcers by rabeprazole in patients taking low-dose aspirin. Aliment Pharmacol Ther 2014; 40:780.
24. Chan FK, Wong VW, Suen BY, et al. Combination of a cyclo-oxygenase-2 inhibitor and a proton-pump inhibitor for prevention of recurrent ulcer bleeding in patients at very high risk: a double-blind, randomised trial. Lancet 2007; 369:1621.
25. Chan FKL, Ching JYL, Tse YK, et al. Gastrointestinal safety of celecoxib versus naproxen in patients with cardiothrombotic diseases and arthritis after upper gastrointestinal bleeding (CONCERN): an industry-independent, double-blind, double-dummy, randomised trial. Lancet 2017; 389:2375.

Topic 14 Version 17.0

## GRAPHICS

### Recommendations for PPI doses in active therapy of uncomplicated gastroduodenal ulcers*

| Drug | Dose (adult) |
|---|---|
| Dexlansoprazole | 30 to 60 mg |
| Esomeprazole | 20 to 40 mg |
| Lansoprazole | 30 mg |
| Omeprazole | 20 to 40 mg |
| Pantoprazole | 40 mg |
| Rabeprazole | 20 mg |
| **All administered by mouth daily before breakfast** | |

PPI: proton pump inhibitor.

* As a general rule, active duodenal ulcers should be treated for four to six weeks and gastric ulcers for six to eight weeks.

---

*Adapted from: Wolfe MM, Sachs G. Acid suppression: Optimizing therapy for gastroduodenal ulcer healing, gastroesophageal reflux disease, and stress-related erosive syndrome. Gastroenterology 2000; 118:S9.*

---

Graphic 81079 Version 5.0

## Contributor Disclosures

**Mark Feldman, MD, MACP, AGAF, FACG** No relevant financial relationship(s) with ineligible companies to disclose. **J Thomas Lamont, MD** Equity Ownership/Stock Options: Allurion [Weight loss]. Consultant/Advisory Boards: Teledoc [Gastrointestinal diseases]. All of the relevant financial relationships listed have been mitigated. **Shilpa Grover, MD, MPH, AGAF** No relevant financial relationship(s) with ineligible companies to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy

→