

Aspirin therapy in aspirin-exacerbated respiratory disease: A risk–benefit analysis for the practicing allergist

Troy W. Baker, D.O., and James M. Quinn, M.D.

ABSTRACT

This study was designed to investigate the risks associated with aspirin (ASA) therapy that is used in high doses for the treatment of ASA-exacerbated respiratory disease (AERD) and to review therapeutic strategies for the prevention of nonsteroidal anti-inflammatory drug (NSAID)–induced side effects. A PubMed search was performed using the key words “aspirin” and “adverse effects.” Additional citations were generated by surveying the reference lists of the pulled articles. More than 120 articles were reviewed and references were selected based on their relevance to the subject matter. Prevalence rates of ASA hypersensitivity in the general population have been reported to be 0.6–2.5%. Asthmatic patients have higher rates of ASA hypersensitivity. The allergy/immunology specialty is unique in the use of prolonged high-dose ASA therapy for the treatment of AERD. ASA use is associated with an increased risk for the development of serious gastrointestinal (GI) events including GI bleeding, ulcers, and perforation. Established risk factors for GI ulcer development include advanced age, history of ulcer or GI bleed, concomitant use of corticosteroids or anticoagulants, high-dose ASA/NSAID therapy, and possibly concomitant Helicobacter pylori infection. Effective strategies to prevent GI complications include initiation of a proton pump inhibitor (PPI), misoprostol, or double dose H₂-receptor antagonists (H₂RAs) at the start of ASA therapy. Allergist/immunologists are involved in treatment decisions regarding high-dose ASA use in AERD. The primary risk of using ASA therapy is the development of GI complications. Cotherapy with a PPI, misoprostol, or double dose H₂RAs can reduce GI complications associated with high-dose ASA therapy.

(Allergy Asthma Proc 32:335–340, 2011; doi: 10.2500/aap.2011.32.3457)

Aspirin (ASA) is a valuable agent in the treatment of ASA-exacerbated respiratory disease (AERD) and in the primary and secondary prevention of a wide variety of other disorders such as cardiovascular disease (CVD) and cerebrovascular disease. Primary prevention trials for cardiovascular events over the last 25 years typically use lower doses of ASA ranging from 75 to 325 mg daily.¹ Low-dose ASA is commonly defined as doses ranging from 75 to 325 mg daily.² With advances in antirheumatic and pain relief pharmacology, high-dose ASA is rarely used as a chronic therapy outside the specialty of allergy/immunology.

In concert with existing AERD literature, a recent review recommended a starting dose of ASA for treatment in AERD patients after desensitization be 650 mg twice a day for the first 6 months (if tolerated) and then decreased to 325 mg twice daily.³ Excellent review articles on the topic of AERD are available to help the practicing allergist select appropriate patients, understand the benefits of high-dose

ASA therapy, and select a desensitization protocol.^{3–5} However, there is a limited discussion in primary allergy/immunology journals discussing the side effects and risks associated with the use of chronic, high-dose ASA therapy.

The primary focus of this article is to aid the practicing allergy/immunology specialist in the process of risk–benefit analysis and communication when considering chronic high-dose ASA therapy and to aid in selecting patients who may benefit from risk-modifying approaches and therapies. Allergists must consider each patient individually to minimize harm and optimize the health benefits of this drug. This requires clinicians to carefully consider the following questions: What are the side effects of high-dose ASA? Which patients are at greatest risk of complications? And, how can I minimize the unwanted side effects? Because data specific to high-dose ASA is sometimes limited, the answers to these questions require the analysis of studies using both high-dose ASA and other nonsteroidal anti-inflammatory drugs (NSAIDs) with similar pharmacologic properties.

Today, the prevalence of ASA hypersensitivity varies depending on which population is studied and the diagnostic methodology. Prevalence rates of ASA hypersensitivity in the general population have been reported to be 0.6–2.5%.^{6–9} People with asthma have even higher rates of ASA hypersensitivity and rates have been reported in questionnaire surveys in Fin-

From Wilford Hall Medical Center, U.S. Air Force, Lackland Air Force Base, Texas
The authors have no conflicts to declare pertaining to this article

The views expressed in this article are the private views of the authors and are not to be construed as reflecting the views of the Department of the Air Force, the Department of Defense, or the United States government

Address correspondence and reprint requests to Troy W. Baker, D.O., 59th MDG/SG05A, 2200 Bergquist Drive, Suite 1, Lackland AFB, TX 78236

E-mail address: troy.baker@us.af.mil

Copyright © 2011, OceanSide Publications, Inc., U.S.A.

land, Australia, and Poland as 8.8, 11, and 4.3%, respectively.⁷⁻⁹

THERAPEUTIC USES OF ASA

Randomized controlled trials (RCTs) have consistently shown that ASA reduces the risk of CVD events in adults without a history of CVD and lowers the incidence of myocardial infarctions in men and ischemic strokes in women.¹ ASA therapy is also an effective modality for treatment of AERD in patients' refractory to conventional methods. The use of ASA has been shown to significantly reduce the activity of respiratory disease by improving sense of smell, reducing purulent sinus infections, decreasing the need of further polyp surgeries, and lowering the frequency of systemic corticosteroid prescriptions.¹⁰⁻¹²

MECHANISM OF ACTION

Prostanoids (prostaglandins [PGs]) are generated from fatty acid metabolism (arachidonic acid) produced *via* the cyclooxygenase (COX) pathway. COX exists in at least two distinct forms: COX-1, the constitutive isoform, and COX-2, the inducible isoform. Activation of the two known COX isoforms catalyze the first committed step in the biosynthesis of PGs (*i.e.*, PGE₂, PGI₂, and PGF₂), thromboxane A₂ (TXA₂), and other eicosanoids.¹³ PGE₂ and PGI₂ (prostacyclin) produced by COX-1 have cytoprotective properties on the gastrointestinal (GI) mucosa. This is accomplished by PGE₂ and PGI₂ reducing the quantity of gastric acid secretion by parietal cells in the stomach, increasing mucosal blood flow, and promoting the release of viscous mucus. TXA₂ is formed by platelets and is a potent platelet aggregating agent.¹⁴ Thus, COX-1 inhibition can result in side effects such as gastroduodenal ulceration and bleeding by inhibiting PGs and TXA₂. COX-2 expression is induced by inflammatory stimuli and cytokines from many different sources, including macrophages and synovial cells.¹⁵ Generally, the anti-inflammatory properties of NSAIDs are mediated through the inhibition of COX-2, whereas the unwanted side effects occur *via* COX-1 inhibition.¹⁵⁻¹⁷ Selective COX-2 inhibitors thus minimize gastric complications and bleeding by the sparing effects of PGE₂, PGI₂, and TXA₂, which are generated *via* COX-1.

RISK FACTORS FOR GI COMPLICATIONS OF ASA

Studies have reported as many as 58–81% of patients with serious GI complications from NSAIDs do not report any preceding side effects.^{18,19} Armstrong *et al.* investigated 235 consecutive patients who either died as a result of, or required emergency surgery for, bleeding or perforation of a peptic ulcer over a 36-month period. They found that >58% of patients using

NSAIDs did not report any history of dyspepsia before developing an acute life-threatening complication secondary to a peptic ulcer.¹⁸

Several well-designed studies have helped identify those patients who are most likely to develop NSAID-induced GI complications. The main risk factors generally include age >65 years, concomitant use of prednisone, previous NSAID-induced GI side effects, history of a prior GI hospitalization, and the use of higher NSAID doses.²⁰⁻²² *Helicobacter pylori* infections have also been associated with GI disease including chronic gastritis, peptic ulcer disease, and gastric malignancy.^{23,24}

The risk of NSAID-induced complications is also substantially higher in patients immediately after initiation of treatment.^{21,22,25} Lanas *et al.* reported the odds ratio (OR) for GI bleeding in subjects taking ASA (at any dose) for ≤1 month, compared with subjects taking ASA (at any dose) for >1 month was 8.9 (95% CI, 6.6–14.5) and 2.8 (95% CI, 1.6–4.0), respectively.²⁵

Laine and colleagues in a prospective, double-blind outcome trial evaluated significant risk factors for upper GI events comparing the COX-2 selective inhibitor, rofecoxib, and the nonselective NSAID, naproxen, in 8076 patients with rheumatoid arthritis. The primary end point in this study was clinical upper GI events (*i.e.*, bleeding, perforation, obstruction, and symptomatic ulcers). Significant risk factors (in the naproxen arm) for upper GI events with a relative risk (RR) of >3 included age of ≥75 years and prior history of any upper GI events. Ages 65–74 years were found to have a RR of >2. Factors with a RR of ≥1.59–1.99 included baseline steroid use, no baseline NSAID use (for 30 day before baseline), history of GI symptoms, and baseline use of low-dose H₂-receptor antagonist (H₂RA).²¹

SPECTRUM OF ASA INJURY

ASA use today is typically directed toward primary and secondary prevention of cardiovascular and cerebrovascular events. Randomized, double-blind, placebo-controlled (RDBPC) studies have shown that even the lowest doses of ASA (30 and 50 mg daily) significantly increase the risk for GI bleeding.^{26,27} An extensive meta-analysis that included 14 RCTs with >57,000 patients on low-dose ASA (75–325 mg daily) for prevention of CVD revealed a RR of 2.07 (95% CI, 1.61–2.66) and 1.65 (95% CI, 1.06–5.99) versus placebo for significant GI and intracranial bleeding, respectively. Overall, the authors found the absolute increase in major bleeding viewed as number needed to harm would require treatment of 769 patients (95% CI, 500–1250) with low-dose ASA to prevent one additional major bleeding episode annually.²⁸

Derry and Loke performed a meta-analysis of almost 66,000 participants, including 24 RCTs (12 RCTs with

high-dose ASA ranging from 900 to 1500 mg daily), on long-term ASA therapy. They noted that GI hemorrhage occurred in 2.47% of patients taking ASA compared with 1.42% taking placebo (OR, 1.68; 95% CI, 1.51–1.88). The number needed to harm was 106 (82–140) based on an average of 28 months of therapy. Interestingly, meta-regression analysis did not show a relation between GI hemorrhage and ASA dose.²⁹

These studies emphasize that although serious GI side effects with ASA therapy are well established, they are infrequent. The early and more common ASA-induced GI mucosal injury is superficial and self-limited bleeding. Systemic reviews and meta-analyses provide useful summaries of RCTs that can help the clinician gain important information on the risk and benefits of ASA use. However, limitations in the clinical value of these reviews must be considered. First, most current systemic reviews and meta-analyses studies may be limited because they commonly evaluate the effects of low-dose ASA (75–325 mg daily) while allergists frequently use higher doses of ASA (650–1300 mg daily) in the treatment of AERD. Also, meta-analysis and systemic reviews often include short-term ASA studies, which may not be of sufficient duration to find infrequent, but serious events. Finally, it has been less common to report absolute incidences and numbers needed to harm as measures of risk that clinicians may find more useful in risk–benefit analysis and risk communication.

TOLERABILITY OF ASA IN AERD PATIENTS

Clinical efficacy is vital in determining the optimal starting dosage of ASA. Equally important is the patient's ability to tolerate the medication. The principal complaint among AERD patients receiving long-term ASA is dyspepsia. Fortunately, most patients tolerate high-dose ASA therapy after desensitization.

Lee *et al.* studied 137 patients who had undergone successful ASA desensitization and randomized them into two groups, 650 mg twice daily and 325 mg twice daily. Both groups increased, maintained, or decreased their ASA dosage based on their symptom control and continued that dosage for the remainder of the year. Of the 137 patients, 32 (23%) discontinued or experienced adverse reactions. Reasons for stopping ASA or lowering the ASA dose included dyspepsia, 12/32 (38%); bleeding/ecchymosis, 4/32 (13%); asthma complications, 4/32 (13%); hives/angioedema, 4/32 (13%); tinnitus/myalgias, 2/32 (6%); and other considerations (*i.e.*, unknown, jailed, or pregnancy), 6/32 (19%). Most of the patients were able to be followed up at 1 year after initiating ASA therapy. Overall, a total of 22/137 (16%) patients discontinued daily ASA, dyspepsia (experienced in 9% of total patients) being the most common reason.³⁰

Berges-Gimeno *et al.* desensitized 172 AERD patients and initiated ASA, 650 mg, twice daily. ASA doses were gradually reduced after 1 year if the patient's clinical course was satisfactory or sooner for those participants who experienced gastritis or bruising. The authors found 24 (14%) of 172 patients discontinued ASA treatment because of known side effects within the 1st year of initiating therapy: 14 with pain caused by gastritis, 2 with gastric bleeding resulting in hematemesis, 6 with hives, and 2 with bleeding from the nose and an ear. The overwhelming reason for discontinuation of ASA treatment was gastritis in 16 (66%) of 24 patients. The authors recommended that physicians treating patients with AERD who develop gastric pain during treatment reduce the ASA dose and also add a proton pump inhibitor (PPI) or misoprostol.¹⁰

In an earlier study, Stevenson and colleagues reported that 9/75 (12%) patients who initially were desensitized and started on 650 mg of ASA twice daily discontinued ASA therapy because of gastritis. Two of these patients experienced bleeding from gastritis.¹¹

In a final study, Rozsasi and colleagues investigated if lower doses of ASA are efficacious in reducing nasal/pulmonary symptoms when reduced to either 100- or 300-mg total daily dosing. The authors found that all patients (7/7) receiving the 100 mg of ASA daily dosing had recurrent nasal polyps at 1-year follow-up. However, none of the 7 patients in the 300-mg daily ASA arm showed recurrent nasal polyps in endoscopic examination. As a result of the first evaluation in these 14 patients, subsequent patients were only enrolled to receive 300-mg daily ASA for treatment. The authors reported that 39 patients who had taken ASA for >1 year were available for follow-up (median follow-up, 2.3 years; range, 1–4.5 years). Of those participants, 4/39 (10%) patients receiving 300-mg daily ASA had discontinued therapy after 1.5 years secondary to GI intolerance, 2/39 (5%) secondary to lack of improvement of pulmonary function, and 1 patient (2.5%) omitted ASA for >1 week and was reluctant to restart. The main limitation of this study was the small sample size and the open study design.¹²

STRATEGIES TO PREVENT MUCOSAL DAMAGE

Proton Pump Inhibitors

Several valuable pharmaceutical agents can help optimize mucosal protection and should strongly be considered when starting high-dose ASA therapy. Among those are PPIs. PPIs are the most potent inhibitors of gastric acid secretion available for clinical use.³¹ PPIs work to block gastric acid secretion by irreversibly inhibiting the proton pump (H^+/K^+ ATPase) function. PPIs significantly reduce the risk of both endoscopic duodenal and gastric ulcers compared with placebo in

prophylaxis trials for patients on NSAIDs.^{32–34} A recent large RDBPC study evaluated PPI protection in adults ≥ 60 years of age who were taking daily prophylactic ASA (dose, 75–325 mg). Yeomans *et al.* found that 5% (27/498) of participants given placebo for 26 weeks developed endoscopic gastric and/or duodenal ulcers compared with 1.6% (8/493) of patients who were treated with 20-mg once-daily esomeprazole. Kaplan-Meier life-table corresponding estimates for the development of an ulcer over 6 months were estimated to be 6.2% in the placebo group versus 1.8% in the esomeprazole group ($p = 0.0007$), which equated to a relative reduction of an ulcer by 71% when taking esomeprazole.³² Overall, PPIs are regarded as one of the safest classes of drugs in clinical use.³⁵

Misoprostol

Misoprostol, a synthetic analog of PGE₁, was the first agent approved for prevention of NSAID-induced ulceration. The use of misoprostol offers significant prevention and treatment of ulcer formation, erosions, and symptoms associated with NSAIDs in RDBPC studies.^{34,36–38} In one large RDBPC investigation, 4404 participants (mean age, 68 years) were treated with 200 μ g of misoprostol four times daily. Those treated with misoprostol were 40% less likely to develop serious upper GI complications (OR, 0.598; CI, 0.364–0.982; $p = 0.049$). Unfortunately, poor tolerability is a major limitation of the use of misoprostol. Overall, 27% of patients taking misoprostol reported GI side effects including diarrhea, nausea, abdominal pain, and flatulence.³⁶ Of note, one RDBPC study demonstrated that misoprostol, 200 μ g, three times daily was found to be equally effective at preventing both gastric and duodenal ulcers as misoprostol, 200 μ g, four times daily with significantly less side effects.³⁸

H₂ Receptor Antagonists

H₂RAs provide gastric protection by increasing the intragastric pH by decreasing hydrogen ion secretion. A recent systematic review found that among RDBPC studies only double-dose H₂RAs (*i.e.*, famotidine, 40 mg, twice daily) were effective at reducing the risk of developing both duodenal and gastric ulcers. Doubling the dose of H₂RAs when compared with placebo reduces the risk of duodenal (RR, 0.26; 95% CI, 0.11–0.65) and gastric ulcers (RR, 0.44; 95% CI, 0.26–0.74), whereas standard-dose H₂RAs are generally only effective at reducing the risk of duodenal ulcers (RR, 0.24; 95% CI, 0.1–0.57).³⁹

Sucralfate

Sucralfate is an antiulcer drug that has been shown to increase the release of endogenous PGs from the gastric mucosa.⁴⁰ It has been suggested that sucralfate

Table 1 Risk factors and prevention strategies for NSAID-associated gastroduodenal ulcers

Established risk factors
Advanced age (substantial risk after age 65 yr)
History of ulcer or GI bleed
Concomitant use of corticosteroids or anticoagulants
Concomitant use of other NSAIDs
High-dose NSAID therapy
Serious systemic disorders
Possible risk factors
Concomitant infection with <i>Helicobacter pylori</i>
Prevention strategies
Proton pump inhibitor
Misoprostol, 200 μ g, four times daily*
Double-dose H ₂ -receptor antagonists#

*Misoprostol, 200 μ g, three times daily has been shown to be as effective as four-times daily dosing in the prevention of gastric and duodenal ulcers.¹⁸

#Famotidine, 40 mg, twice daily.³⁹

GI = gastrointestinal; NSAIDs = nonsteroidal anti-inflammatory drugs.

may be helpful in the prevention of NSAID-induced ulcers because of its ability to reduce mucosal damage from various irritants including NSAIDs and ethanol.⁴¹ However, RCTs have not been able to show a significant benefit in patients receiving NSAID therapy for the prevention of gastric or duodenal ulceration.^{41,42}

Enteric or Buffered ASA

ASA covered with a combination of cellulose, silicon, or other inactive ingredients (enteric coating) have been designed to resist ASA disintegration in the stomach and delay dissolution until it reaches the more neutral duodenal environment. Buffering agents (*i.e.*, calcium carbonate, magnesium oxide, and magnesium carbonate) have been designed to lower the hydrogen ion concentration, increase the solubility of ASA within the GI tract, and, ultimately, decrease the contact time between ASA particles and the GI mucosa.⁴³ Studies have shown a modest benefit with enteric-coated ASA for gastric mucosal protection but no benefit with buffered ASA in RCTs.^{44,45}

APPROACH FOR THE PREVENTION OF NSAID-RELATED COMPLICATIONS

Several well-established risk factors need to be taken into consideration when evaluating a patient's risk of developing NSAID-associated gastroduodenal ulcers (see Table 1). The Practice Parameters Committee of the American College of Gastroenterology recently published new guidelines on preventing NSAID-related ulcer complications.⁴⁶ The report stratified pa-

tients arbitrarily into three categories: low (no risk factors), moderate (one to two risk factors), or high risk (history of a previously complicated ulcer or more than two risk factors). The expert consensus opinion recommended that patients at moderate risk (aged >65 years, high-dose NSAID therapy, previous history of an uncomplicated ulcer, or concurrent use of ASA or corticosteroids or anticoagulants) should be treated by a COX-2 inhibitor alone or an NSAID plus misoprostol or a PPI.⁴⁶

Brown *et al.* evaluated four cost-effective strategies, *viz.*, NSAIDs plus an H₂RA, NSAIDs plus a PPI, NSAIDs plus misoprostol, and COX-2 selective NSAIDs, for the prevention of NSAID-induced GI toxicity. This study showed that the optimal strategy depends on the "willingness to pay" with NSAIDs plus an H₂RA or misoprostol being the least costly strategies.⁴⁷

CONCLUSION

The main concern regarding ASA use is the clear potential for development of serious GI events. Currently, American College of Gastroenterology guidelines recommend cotherapy with PPIs or misoprostol for primary prevention of NSAID-induced GI toxicity for patients on high-dose NSAID therapy.⁴⁶ Patients with AERD on ASA therapy may require corticosteroid bursts to treat asthma exacerbations or nasal polyposis, which further places them at increased risk for bleeding complications. Low-dose ASA is defined as doses ranging from 75 to 325 mg daily.² Rozsasi and colleagues showed promising data that low-dose ASA (300 mg) daily may be a viable therapeutic option in treating AERD patients.¹²

As more allergists embark on treating AERD with high-dose ASA, risk communication including assessing, determining, and minimizing unwanted side effects of ASA will be a critical role of the allergist/immunologist. We have presented substantial data to help assess the risk of ASA therapy and determine possible prevention strategies (see Table 1). Ongoing research regarding the role of ASA in AERD will be helpful to define and clarify the magnitude of benefit, dosing, and duration of ASA and end points of therapy.

REFERENCES

1. Wolff T, Miller T, and Ko S. Aspirin for the primary prevention of cardiovascular events: An update of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 150:405–410, 2009.
2. Laine L. Review article: Gastrointestinal bleeding with low-dose aspirin—What's the risk? *Aliment Pharmacol Ther* 24:897–908, 2006.
3. Hope AP, Woessner KA, Simon RA, et al. Rational approach to aspirin dosing during oral challenges and desensitization of patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol* 123:406–410, 2009.
4. Stevenson DD. Aspirin sensitivity and desensitization for asthma and sinusitis. *Curr Allergy Asthma Rep* 9:155–163, 2009.
5. Stevenson DD, and Simon RA. Selection of patients for aspirin desensitization treatment. *J Allergy Clin Immunol* 118:801–804, 2006.
6. Gomes E, Cardoso MF, Praça F, et al. Self-reported drug allergy in a general adult Portuguese population. *Clin Exp Allergy* 34:1597–1601, 2004.
7. Hedman J, Kaprio J, Poussa T, et al. Prevalence of asthma, aspirin intolerance, nasal polyposis and chronic obstructive pulmonary disease in a population-based study. *Int J Epidemiol* 28:717–722, 1999.
8. Vally H, Taylor ML, and Thompson PJ. The prevalence of aspirin intolerant asthma (AIA) in Australian asthmatic patients. *Thorax* 57:569–574, 2002.
9. Kasper L, Sladek K, Duplaga M, et al. Prevalence of asthma with aspirin hypersensitivity in the adult population of Poland. *Allergy* 58:1064–1066, 2003.
10. Berges-Gimeno MP, Simon RA, and Stevenson DD. Long-term treatment with aspirin desensitization in asthmatic patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol* 111:180–186, 2003.
11. Stevenson DD, Hankammer MA, Mathison DA, et al. Aspirin desensitization treatment of aspirin-sensitive patients with rhinosinusitis-asthma: Long-term outcomes. *J Allergy Clin Immunol* 98:751–758, 1996.
12. Rozsasi A, Polzehl D, Deutsche T, et al. Long-term treatment with aspirin desensitization: A prospective clinical trial comparing 100 and 300 mg aspirin daily. *Allergy* 63:1228–1234, 2008.
13. Rao P, and Knaus EE. Evolution of nonsteroidal anti-inflammatory drugs (NSAIDs): Cyclooxygenase (COX) inhibition and beyond. *J Pharm Pharm Sci* 11:81s–110s, 2008.
14. Whittle BJ, and Moncada S. Pharmacological interactions between prostacyclin and thromboxanes. *Br Med Bull* 39:232–238, 1983.
15. Needleman P, and Isakson PC. The discovery and function of COX-2. *J Rheumatol Suppl* 49:6–8, 1997.
16. Wolfe MM, Lichtenstein DR, and Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *N Engl J Med* 340:1888–1899, 1999.
17. Vane JR, and Botting RM. The mechanism of aspirin. *Thromb Res* 110:255–588, 2003.
18. Armstrong CP, and Blower AL. Non-steroidal anti-inflammatory drugs and life threatening complications of peptic ulceration. *Gut* 28:527–532, 1987.
19. Singh G, Ramey DR, Morfeld D, et al. Gastrointestinal tract complications of nonsteroidal anti-inflammatory drug treatment in rheumatoid arthritis. A prospective observational cohort study. *Arch Intern Med* 156:1530–1536, 1996.
20. Fries JF, Williams CA, Bloch DA, et al. Nonsteroidal anti-inflammatory drug-associated gastropathy: Incidence and risk factor models. *Am J Med* 91:213–222, 1991.
21. Laine L, Bombardier C, Hawkey CJ, et al. Stratifying the risk of NSAID-related upper gastrointestinal clinical events: Results of a double-blind outcomes study in patients with rheumatoid arthritis. *Gastroenterology* 123:1006–1012, 2002.
22. Griffin MR, Piper JM, Daugherty JR, et al. Nonsteroidal anti-inflammatory drug use and increased risk for peptic ulcer disease in elderly persons. *Ann Intern Med* 114:257–263, 1991.
23. Chey WD, and Wong BC. American College of Gastroenterology guideline on the management of *Helicobacter pylori* infection. *Am J Gastroenterol* 102:1808–1825, 2007.
24. Chan FKL, Chung SCS, 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* 344:967–973, 2001.
25. Lanas A, Bajador E, Serrano P, et al. Nitrovasodilators, low-dose aspirin, other nonsteroidal antiinflammatory drugs, and the risk of upper gastrointestinal bleeding. *N Engl J Med* 343:834–839, 2000.
 26. The Dutch TIA Trial Study Group. A comparison of two doses of aspirin (30 mg vs. 283 mg a day) in patients after a transient ischemic attack or minor ischemic stroke. *N Engl J Med* 325:1261–1266, 1991.
 27. Diener HC, Cunha L, Forbes C, et al. European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci* 143:1–13, 1996.
 28. McQuaid KR, and Laine L. Systematic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials. *Am J Med* 119:624–638, 2006.
 29. Derry S, and Loke YK. Risk of gastrointestinal haemorrhage with long term use of aspirin: Meta-analysis. *BMJ* 11:1183–1187, 2000.
 30. Lee JY, Simon RA, and Stevenson DD. Selection of aspirin dosages for aspirin desensitization treatment in patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol* 119:157–164, 2007.
 31. Scarpignato C, Pelosini I, and Di Mario F. Acid suppression therapy: Where do we go from here? *Dig Dis* 24:11–46, 2006.
 32. Yeomans N, Angel L, Joachim L, et al. Efficacy of esomeprazole (20 mg once daily) for reducing the risk of gastroduodenal ulcers associated with continuous use of low-dose aspirin. *Am J Gastroenterol* 103:2465–2473, 2008.
 33. Bianchi Porro G, Lazzaroni M, Imbesi V, et al. Efficacy of pantoprazole in the prevention of peptic ulcers, induced by non-steroidal anti-inflammatory drugs: A prospective, placebo-controlled, double-blind, parallel-group study. *Dig Liver Dis* 32:201–208, 2000.
 34. Graham DY, Agrawal NM, Campbell DR, et al. Ulcer prevention in long-term users of nonsteroidal anti-inflammatory drugs: Results of a double-blind, randomized, multicenter, active- and placebo-controlled study of misoprostol vs lansoprazole. *Arch Intern Med* 162:169–175, 2002.
 35. Labenz J, Petersen KU, Rösch W, et al. A summary of Food and Drug Administration-reported adverse events and drug interactions occurring during therapy with omeprazole, lansoprazole and pantoprazole. *Aliment Pharmacol Ther* 17:1015–1019, 2003.
 36. Silverstein FE, Graham DY, Senior JR, et al. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 123:241–249, 1995.
 37. Hawkey CJ, Karrasch JA, Szczepanski L, et al. Omeprazole compared with misoprostol for ulcers associated with non-steroidal antiinflammatory drugs. *N Engl J Med* 338:727–734, 1998.
 38. Raskin JB, White RH, Jaszewski R, et al. Misoprostol and ranitidine in the prevention of NSAID-induced ulcers: A prospective, double-blind, multicenter study. *Am J Gastroenterol* 91:223–227, 1996.
 39. Rostom A, Dube C, Wells GA, et al. Prevention of NSAID-induced gastroduodenal ulcers. *Cochrane Database Syst Rev* 4:CD002296, 2002.
 40. Ligumsky M, Karmeli F, and Rachmilewitz D. Sucralfate protection against gastrointestinal damage: Possible role of prostanooids. *Isr J Med Sci* 22:801–806, 1986.
 41. Agrawal NM, Roth S, Graham DY, et al. Misoprostol compared with sucralfate in the prevention of nonsteroidal anti-inflammatory drug-induced gastric ulcer. A randomized, controlled trial. *Ann Intern Med* 115:195–200, 1991.
 42. Lanza F, Peace K, Gustitus L, et al. A blinded endoscopic comparative study of misoprostol versus sucralfate and placebo in the prevention of aspirin-induced gastric and duodenal ulceration. *Am J Gastroenterol* 83:143–146, 1988.
 43. Kelly JP, Kaufman DW, Jurgelon JM, et al. Risk of aspirin-associated major upper-gastrointestinal bleeding with enteric-coated or buffered product. *Lancet* 348:1413–1416, 1996.
 44. Lanza FL. Endoscopic evaluation of the effects of aspirin, buffered aspirin, and enteric-coated aspirin on gastric and duodenal mucosa. *N Engl J Med* 303:136–138, 1980.
 45. Petroski D. Endoscopic comparison of three aspirin preparations and placebo. *Clin Ther* 15:314–320, 1993.
 46. Lanza FL, Francis KLC, and Eamonn MMQ. Guidelines for prevention of NSAID-related ulcer complications. *Am J Gastroenterol* 104:728–738, 2009.
 47. Brown TJ, Hooper L, Elliott RA, et al. A comparison of the cost-effectiveness of five strategies for the prevention of non-steroidal anti-inflammatory drug-induced gastrointestinal toxicity: A systematic review with economic modeling. *Health Technol Assess* 10:1–183, 2006. □

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.