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Intended Audience

This educational activity is intended for practicing internists and family physicians, as well as residents in training programs.

Learning Objectives

Upon completing this educational activity, participants will be able to:

- Assess the cardiovascular risks associated with cyclooxygenase-2 (COX-2) selective inhibitors and traditional nonsteroidal anti-inflammatory drugs (NSAIDs)
- Recognize NSAID-associated gastrointestinal (GI) pathologies and implement therapeutic strategies that prevent complications and heal injuries
- Distinguish pathologic gastroesophageal reflux disease (GERD) from physiologic gastroesophageal reflux (GER) in pediatric patients and design tailored evaluation and treatment plans.

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Updates on the management of upper gastrointestinal disorders in the primary care setting: NSAID-related gastropathies and pediatric reflux disease

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely used medications in the United States, owing to their analgesic, anti-inflammatory, and antipyretic properties.^{1,2} Aspirin, which is also an NSAID, is frequently used for cardiovascular (CV) prophylaxis. However, the use of “traditional” NSAIDs results in serious upper gastrointestinal (GI) adverse events in nearly one fourth of patients.³ Cyclooxygenase-2 (COX-2)-selective inhibitors are beneficial in alleviating GI adverse events, but with the possible trade-off of causing CV adverse events in at-risk patients. Hence, balancing the CV risks of COX-2 inhibitors with the higher GI risks of nonselective NSAIDs remains a major clinical challenge.

The management of gastroesophageal reflux disease (GERD) continues to garner significant attention among physicians who care for adults. However, there is an increasing awareness that this disorder may originate in childhood. Pediatric GERD is likely to share a similar pathophysiology with adult GERD. Early detection and treatment in children may yield better adult disease outcomes, improved quality of life, and a decreased overall health care burden.

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This review article examines important considerations pertaining to the management of some specific upper-GI disorders seen in the primary care setting, namely NSAID-associated gastropathies and pediatric reflux disease. Its content is derived from the proceedings of a satellite symposium that was held during the 2006 American Academy of Family Physicians' Scientific Assembly in Washington, D.C.

UPDATE ON THE MANAGEMENT OF GASTROINTESTINAL COMPLICATIONS IN NSAID USERS

NSAID-induced GI complications are attributed to their nonselective inhibition of both COX-1 and COX-2 enzymes and their suppression of mucosal prostaglandin synthesis, which impairs the ability of the gastroduodenal mucosa to adequately respond to injury.^{3,4} NSAID-related GI side effects are recognized as the most prevalent and serious type of drug-related toxicity in the United States.² Adverse peptic events include gastroduodenal ulcers, found at endoscopy in 15% to 30% of individuals taking NSAIDs regularly, and upper GI bleeding, which has an annual incidence as high as 1.5%.^{1,2} In addition, NSAIDs have been associated with a wide array of upper GI symptoms, including epigastric pain, dyspepsia, nausea, vomiting, eructation, and heartburn in up to 60% of users.

While prolonged use and higher doses of medication are significant risk factors, the greatest risk for NSAID-related GI complications exists within the first month after the initiation of therapy.⁵ The effect of aspirin, which causes serious GI adverse events on its own and yields incremental risk when used in combination with other NSAIDs, remains underappreciated by many clinicians.² Even low doses of aspirin are associated with GI bleeding, and lowering the dose (eg, 81 mg vs 325 mg daily) or altering the formulation (eg, buffering, enteric coating) of aspirin does little to reduce bleeding risk.⁶

One strategy for reducing NSAID-related GI complications consists of using COX-2 inhibitors instead of nonselective NSAIDs. Two landmark randomized controlled trials (RCTs), the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial and Celecoxib Long-term Arthritis Safety Study (CLASS), showed that COX-2 inhibitors significantly decreased the rates of symptomatic GI events and virtually eliminated the risk of perforation ulcers and GI bleeding in patients without risk factors.^{7,8} However, in light of the safety concerns that culminated with the withdrawal of both rofecoxib and valdecoxib, this strategy seems less valid, at least in at-risk patients. It is yet to be ascertained if celecoxib, the only COX-2 inhibitor still marketed in the United States, confers the same increased CV risk.⁹

In this context, many clinicians are switching patients treated for chronic pain (eg, musculoskeletal injuries, osteoarthritis, rheumatoid arthritis) back to nonselective NSAIDs. When the large number of individuals who self-medicate with over-the-counter NSAIDs or use aspirin as prophylaxis against CV conditions is added to these long-term NSAID users, the population at risk for NSAID-related GI complications is staggering. This is of particular concern in patients with well-documented GI risk factors (**TABLE 1, PAGE S3**).^{1,2} Indeed, it is estimated that as many as 300 people are hospitalized for and 30 die from NSAID-related GI adverse events every day in the United States, at an annual cost of over \$2 billion.¹⁰

■ CV risks associated with COX-2 inhibitors and NSAIDs

COX-2 inhibitors and some traditional NSAIDs have been associated with an increased incidence of hospitalization for congestive heart failure as well as an increased risk of elevated blood pressure and acute myocardial infarction (MI).^{11,12} Although the evidence is mixed regarding nonselective NSAIDs, the prothrombic effect of COX-2 inhibitors is clearly documented.¹³⁻¹⁵

Because the evidence of GI benefit from COX-2 inhibitors initially seemed to outweigh evidence of CV risk, the Food and Drug Administration (FDA) first pursued its policy of cautiously labeling celecoxib and rofecoxib in ways that reflected the outcomes of the CLASS and VIGOR studies.^{7,8} The VIGOR investigators found a higher rate of a composite CV end point (ie, nonfatal MI, stroke, and CV death) with rofecoxib 50 mg once daily compared with naproxen 500 mg twice daily (0.8% vs 0.4%; $P < .05$).⁷ These findings were mainly caused by a difference in the rate of MI (0.4% vs 0.1%; $P < .01$), and were met with concerns about whether these rates resulted from a cardioprotective effect of naproxen or a harmful effect of rofecoxib.

The release of the Adenomatous Polyp Prevention on Vioxx (APPROVe) study results in September 2004 dramatically shifted the burden of proof, leading to the immediate withdrawal of rofecoxib from markets worldwide.¹⁶ The investigators reported an overall increased risk of confirmed thrombotic events (ie, MI, stroke, unstable angina, transient ischemic attack, thrombosis, pulmonary embolism, and sudden CV death) with rofecoxib 25 mg daily compared with placebo (relative risk, 1.92; 95% confidence interval [CI], 1.19–3.11). These findings were confirmed by a meta-analysis of 18 RCTs involving 21,432 patients that revealed a significant increased risk of CV events with rofecoxib (relative risk, 2.24; 95% CI, 1.24–4.02).¹⁷

The effect of valdecoxib, the third COX-2 inhibitor approved for use in the United States by the FDA, and parecoxib, an intravenously administered prodrug of valdecoxib, on CV events was assessed in RCTs evaluating the combination of these medications in patients undergoing coronary artery bypass graft surgery. In particular, a landmark study showed that patients in the parecoxib/valdecoxib group experienced a significantly higher rate of CV or thromboembolic events compared with those in the placebo group (risk ratio, 3.7; 95% CI, 1.0–13.5).¹⁸ These findings eventually led to the withdrawal of these agents in April 2005, following a comprehensive review of their safety profiles by the FDA.

TABLE 1
*Major risk factors for upper
GI clinical events with NSAID use*

Risk Factor	Risk Increase
Prior upper GI clinical event	2.5- to 4-fold
Older age (>65 y)	2- to 3.5-fold
Anticoagulation (eg, warfarin)	3-fold
Corticosteroid therapy	2-fold
High-dose/multiple NSAIDs (eg, NSAID + low-dose aspirin)	2- to 4-fold (vs aspirin alone)

GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug
Adapted from Laine L. *Rev Gastroenterol Disord.* 2004;4(suppl 4):S33–S41.

Another landmark RCT, the Adenoma Prevention with Celecoxib (APC) trial, was interrupted by the National Cancer Institute after a mean follow-up of 33 months.¹⁹ The investigators reported a significantly higher incidence of MI, stroke or CV death with celecoxib compared with placebo (hazard ratio, 2.3 and 3.4 for celecoxib 200 mg and 400 mg daily, respectively; 95% CI, 0.9–5.5 and 1.4–7.8, respectively). These findings were confirmed by a meta-analysis of 4 RCTs involving 4422 patients, which revealed that celecoxib was associated with a 2.26-fold (95% CI, 1.00–5.10) increased risk of MI when compared with placebo alone.⁹ A secondary meta-analysis of 6 RCTs involving 12,780 patients showed a 1.88-fold (95% CI, 1.15–3.08) increased risk of MI when compared with all comparator treatment groups, including nonselective NSAIDs.⁹ A recent nested case-control study in a cohort of 486,378 subjects also showed that celecoxib was associated with a 1.56-fold (95% CI, 1.22–2.00) risk of acute MI compared with no NSAID use.¹¹

Whereas some epidemiologic studies demonstrated an increased CV risk associated with nonselective NSAIDs,^{20–23} others showed no increased risk or a decreased risk of nearly 15%.^{11,17,24–28} In particular, a meta-analysis of 11 observational studies suggested that naproxen might have a modest cardioprotective effect (relative risk, 0.86; 95% CI, 0.75–0.99).¹⁷ Conversely, diclofenac was associated with a significantly increased risk of acute MI (rate ratio, 1.37; 95% CI, 1.17–1.59).¹¹ As a result of these widely divergent

Consensus recommendations on the optimal use of COX-2 inhibitors and nonselective NSAIDs

The American Gastroenterological Association convened a panel gastroenterologists, rheumatologists, cardiologists, and internists to develop a comprehensive consensus statement based on the most robust clinical evidence available to date.¹ The recommendations of these experts are as follows:

1. Clinicians should carefully weigh the indications for nonsteroidal anti-inflammatory (NSAID) therapy against both GI and CV risk factors.
2. The decision to use a cyclooxygenase-2 (COX-2) inhibitor should be made on the basis of a risk/benefit analysis that balances CV risks and GI outcomes in individual patients:
 - a. For patients in whom the risk of life-threatening GI bleeding outweighs the risk of CV events, agents with lower GI risk are recommended, such as COX-2 inhibitors and certain nonselective NSAIDs (ie, diclofenac, etodolac, and ibuprofen).
 - b. For patients in whom the risk of CV events outweighs GI bleeding GI risk, COX-2 inhibitors should be ruled out.
 - c. In patients with established CV disease or those at high CV risk, low-dose aspirin is recommended.
3. The duration and dosage of prescribed regimens should be limited.
4. Patients should be asked about and told to avoid combination NSAID therapy, as many patients self-medicate with over-the-counter NSAIDs or use aspirin to mitigate CV risk without first consulting a physician.
5. Patients taking both nonselective NSAIDs and COX-2 inhibitors should be closely monitored for CV adverse events.
6. For NSAID users at high risk for GI complications, the following measures are strongly recommended:
 - a. Although most experts consider that both *Helicobacter pylori* infection and NSAID use are significant yet independent risk factors for peptic-ulcer disease (PUD), *H pylori* eradication may prove particularly beneficial in patients with a history of PUD or previous ulcer complications.²
 - b. Gastroprotection with a PPI should be instituted in patients at high GI risk, as NSAIDs plus PPIs are significantly safer than NSAIDs alone. COX-2-inhibitor therapy alone is similarly beneficial in reducing GI risks, but with the potential trade-off of increasing CV risks.

References

1. Wilcox CM, et al. *Clin Gastroenterol Hepatol*. 2006;4:1082–1089.
2. Huang JQ, et al. *Lancet*. 2002;359:14–22.

findings, the FDA released a memorandum requesting that all manufacturers of nonselective NSAIDs include a boxed warning regarding the potential CV risk in their labeling.²⁹

Finally, the most robust and comprehensive meta-analysis (138 RCTs involving 145,373 participants) published to date concluded that COX-2 inhibitors were associated with an overall 42% relative increase in the incidence of serious vascular events compared with placebo ($P=.003$), which was primarily attributed to an increased risk of MI (rate ratio, 1.86; 95% CI, 1.33–2.59).¹² Compared with placebo, the summary rate ratio for vascular events was 0.92 (95% CI, 0.67–1.26) for naproxen, 1.51 (95% CI, 0.96–2.37) for ibuprofen, and 1.63 (95% CI, 1.12–2.37) for diclofenac.

■ Prevention and healing of NSAID-associated GI symptoms and complications

Because prostaglandin depletion is a decisive mechanism for NSAID-related ulcer development, replacement therapy with misoprostol, a synthetic prostaglandin analog, reduces NSAID-associated GI toxicity.¹ Although misoprostol is approved by the FDA for the prevention of NSAID-induced ulcers and complications, compliance issues and significant dose-related side effects (eg, abdominal cramping, dyspepsia, diarrhea) substantially limit its clinical usefulness.

The alternative approach for reducing NSAID-associated GI toxicity and preventing peptic ulcers is gastric acid-suppression therapy. While histamine-

2-receptor antagonists (H₂RAs) are effective in healing NSAID-related ulcers when NSAIDs are discontinued, healing rates are significantly lower when NSAID therapy must be pursued. A RCT in patients treated with ranitidine 150 mg twice daily for confirmed NSAID-associated peptic ulcers yielded 8-week healing rates of 95% in patients with gastric ulcers who ceased taking NSAIDs versus 63% in those who remained on NSAID therapy ($P=.001$).³⁰ In patients with duodenal ulcers who stopped or continued taking NSAIDs, healing rates were 100% and 84% ($P=.006$), respectively.

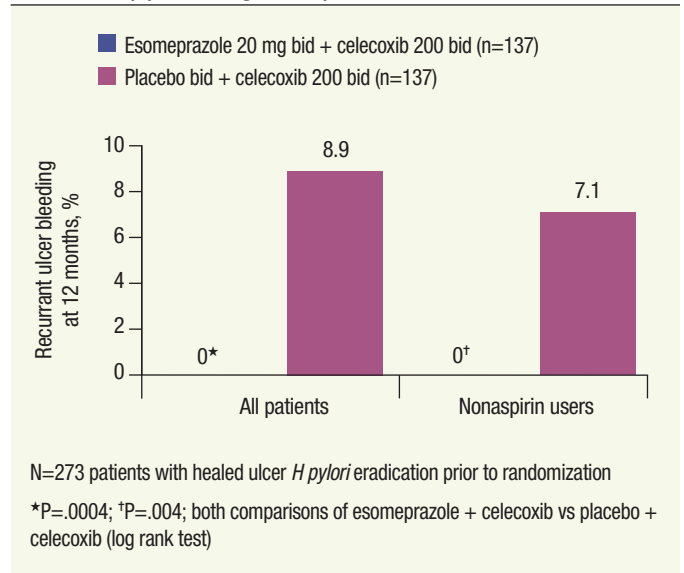
Proton-pump inhibitors (PPIs) have been proven to be significantly more effective than both misoprostol and H₂RAs in preventing NSAID-related ulcer recurrence and providing GI symptom control, thereby improving overall quality of life. This is largely because of their superior acid-suppression property and tolerability.^{31,32}

In a RCT by Graham et al, long-term NSAID users treated with lansoprazole 15 mg or lansoprazole 30 mg daily remained free from gastric ulcers significantly longer than those who received placebo ($P<.001$).³³ Patients on misoprostol remained free of ulcers significantly longer than those who received either lansoprazole 15 mg ($P=.01$) or 30 mg ($P=.04$). However, because of treatment-related adverse events that resulted in a significantly higher withdrawal rate, the investigators concluded that misoprostol had no practical advantage over lansoprazole.

Omeprazole 20 mg daily is significantly more effective than H₂RAs or placebo in decreasing NSAID-related symptoms (such as dyspepsia) and the associated reductions in quality of life.^{31,34} In patients with a history of ulcer bleeding, a recent RCT reported no significant difference in the rate of recurrent bleeding at 6 months across patient groups (4.9% with celecoxib vs 6.4% diclofenac and omeprazole).³⁵ Although the study was not powered to show equivalence, these findings suggest that both treatment strategies were similar in efficacy and that neither was sufficient to protect this high-risk group of patients. When follow-

FIGURE 1

Prevention of recurrent ulcer bleeding in H pylori-negative patients with arthritis



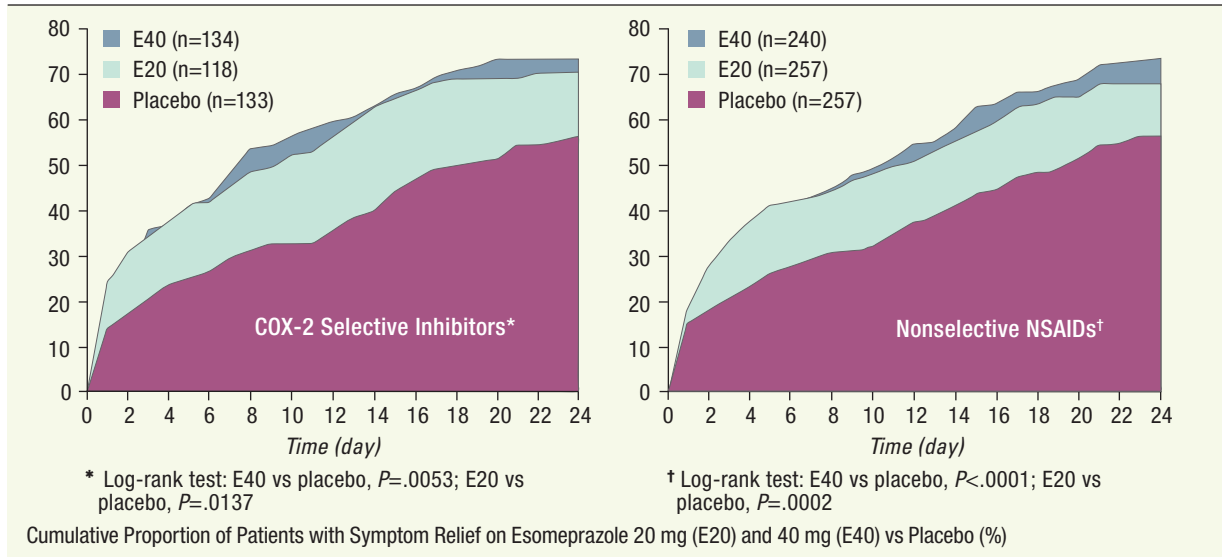
Adapted from Chan FK et al. *Gastroenterology*. 2006;130 (4 suppl 2):A-105. Abstract 732.

up endoscopies were performed among those with recurrent complications, ulcer rates were 19% and 26% in the celecoxib group and the diclofenac plus omeprazole group, respectively.³⁶ Based on these data, experts have suggested that these highest-risk patients should be treated concomitantly with a PPI and a COX-2 inhibitor to decrease the high rate of recurrent complications.^{1,2} This opinion was validated by the results of a recent RCT that found that treatment with esomeprazole plus celecoxib was significantly superior to celecoxib alone for the prevention of recurrent ulcer bleeding (FIGURE 1).³⁷

Among users of COX-2 inhibitors treated concomitantly with esomeprazole 20 mg or 40 mg, very few ulcers were observed (0.9% and 4.7% respectively) in a recent RCT, while those who received placebo experienced similar rates of ulcer recurrence (16.5%; $P\le.002$) as those taking nonselective NSAIDs.³⁸ In another recent RCT, the incidence of gastroduodenal ulcers at 6 months was significantly lower in aspirin users treated with esomeprazole 20 mg once daily (1.6%) than in those who received placebo (5.4%; $P=.0007$).³⁹ Two other RCTs reported that both esomeprazole

FIGURE 2

PPI therapy relieves upper GI symptoms associated with either COX-2-selective inhibitors or non selective NSAIDs



PPI = proton-pump inhibitors; GI = gastrointestinal; COX-2 = cyclooxygenase -2; NSAIDS = nonsteroidal anti-inflammatory drugs.
 Adapted from Hawkey C et al. *Am J Gastroenterol.* 2005;100:1028–1036.

20 mg and 40 mg were significantly superior to placebo in relieving upper GI symptoms in patients taking COX-2 inhibitors and in patients taking nonselective NSAIDs (FIGURE 2).⁴⁰ Similarly, resolution of aspirin-related upper GI symptoms was significantly higher with esomeprazole 20 mg once daily than with placebo for epigastric pain, burning and discomfort, as well as heartburn and bloating ($P<.05$ for all symptoms).³⁹

Potential adverse effects of long-term PPI and NSAID therapy

Although unsubstantiated by well-designed RCTs, some evidence suggests that long-term PPI use may interfere with calcium absorption. This would occur through induction of hypochlorhydria, which may reduce bone resorption through inhibition of osteoclastic vacuolar proton pumps and result in an increased risk of hip fracture in elderly patients. A recently published nested case-control study conducted in the United Kingdom (13,556 hip-fracture cases and 135,386 controls) revealed that the adjusted odds ratio for hip fracture associated with more than 1 year of PPI therapy was 1.44 (95% CI, 1.30–1.59).⁴¹

Some evidence has also pointed to an increased risk of community-acquired pneumonia and *Clostridium difficile* (*C difficile*)–associated disease with long-term PPI use. A case-control analysis involving 364,683 individuals revealed a higher incidence of pneumonia among those treated with PPIs (adjusted relative risk, 1.89; 95% CI, 1.36–2.62) compared with those who stopped using PPIs.⁴² Similarly, 2 other case-control analyses performed in the United Kingdom showed that the adjusted rate ratio of *C difficile*–associated disease in patients treated with PPIs was 2.9 (95% CI, 2.4–3.4). Interestingly, the long-term use of NSAIDs was also associated with an increased risk of *C difficile*–related disease (adjusted rate ratio, 1.3; 95% CI, 1.2–1.5).⁴³

Finally, prolonged gastric-acid suppression leads to hypergastrinemia, which promotes enterochromafin-like (ECL) cell hyperplasia of the oxyntic mucosa. A recently published study randomized 243 patients to either rabeprazole 10 mg or 20 mg or omeprazole 20 mg once daily for 5 years.⁴⁴ Although ECL hyperplasia occurred in a minority of patients and was associated with elevated serum gastrin concentrations, no ECL cell dysplasia or tumors were observed during the 5 years of PPI therapy.

UPDATE ON THE EVALUATION AND TREATMENT OF PEDIATRIC GERD

Gastroesophageal reflux (GER), defined as the physiologic passage of gastric contents into the esophagus or oropharynx, and gastroesophageal reflux disease (GERD), defined as the symptoms or pathologic complications resulting from GER, are common pediatric conditions seen in clinical practice.^{45,46} Although recurrent vomiting is reported in two thirds of infants by 4 months of age, regurgitation and vomiting usually resolves spontaneously by 1 year of age.^{45,47} Beyond infancy, up to one fourth of children and adolescents experience recurrent abdominal pain, whereas approximately 5% report heartburn or epigastric pain.^{46,47} Among children 6 months to 18 years of age that were hospitalized in the United States in 2001, GERD was singled out in 3.5% of discharge diagnoses.⁴⁸

Although not fully understood, the pathogenesis of GERD in children is comparable to that in adults.^{46,49} Transient relaxation of the lower esophageal sphincter (LES) is the most common cause of GERD in children.⁵¹ Impairment of esophageal peristalsis, which often results in delayed esophageal emptying, as well as decrease in LES resting tone without swallowing, hiatal hernia, gastric distention, and neurologic disorders have also been observed in children with GERD.⁴⁹⁻⁵¹ More disturbing is the recent observation in children of an increased incidence of GERD-related complications, including erosive esophagitis and Barrett's esophagus.⁴⁸ In adult patients, evidence has shown that the duration and frequency of GERD correlates with a significant increase in long-term complications.^{52,53} Although no longitudinal studies exist, the development of GERD during childhood is likely to lead to more severe disease manifestations that carry on into adulthood.^{46,54} A recent study reported that 63% of adult "refluxers" had at least 1 symptom of GERD during childhood compared with 35% of "nonrefluxers" ($P < .001$).⁵⁵

Clinical presentation and diagnosis of pediatric GERD

GERD manifests differently in children, especially those more than 10 years of age, than in adults who

TABLE 2

Age-specific signs and symptoms of pediatric GERD

Infants	Older Children/Adolescents
– Recurrent vomiting	– Early morning nausea
– Poor weight gain	– Abdominal pain and discomfort
– Generalized fussiness and irritability	– Substernal pain
– Failure to thrive	– Burning belching
– Apnea/choking episodes	– Heartburn
– Opisthotonic posturing (eg, arching)	– Dysphagia
– Feeding resistance	– Extra-esophageal symptoms: Apnea/bradycardia Wheezing/asthma Otitis media/sinusitis Hoarseness Chronic cough/sore throat Recurrent pneumonia Dental erosion

Adapted from Rudolph CD et al. *J Pediatr Gastroenterol Nutr.* 2001;32 (suppl 2):S1-S31; Gold BD. *Am J Med.* 2004;117 (suppl 5A):23S-29S.

frequently report the traditional symptoms of heartburn and regurgitation (**TABLE 2**).⁴⁵⁻⁴⁷ A comprehensive patient history and a thorough physical examination represent the cornerstone of the clinical diagnosis of GERD in primary care practice. Experts concur that in most infants with a history of recurrent vomiting and persistent irritability, and in most older children with heartburn, regurgitation, and epigastric pain, these signs and symptoms are adequate to reliably diagnose GERD, identify related complications, and initiate appropriate treatment.^{45,46,54} Expert guidelines suggest a trial of "time-limited" empiric medical therapy with a PPI, a widely used diagnostic test for GERD in adults,⁵⁶ to determine if GERD is causing specific symptoms.⁴⁵ Further diagnostic investigations, which may include referring the patient to a pediatric gastroenterologist, are warranted if empiric therapy and lifestyle modifications fail to yield any significant clinical benefit (**TABLE 3**).^{46,54}

Diagnostic testing may first consist of an upper GI series to diagnose surgically correctable anatomic abnormalities (eg, tracheoesophageal fistula, pyloric stenosis, achalasia, hiatal hernia, esophageal stricture)^{45,46} The highest estimates of sensitivity and specificity of the upper GI series for the definitive

TABLE 3

*Age-dependent modifications
in GERD management*

Infants	Older Children/Adolescents
– Thickened feedings	– Weight reduction if overweight
– Smaller, more frequent feedings	– Dietary modifications
– Antireflux positioning after feedings	– Smoking cessation
– Avoidance of passive tobacco smoke exposure	

Adapted from Rudolph CD et al. *J Pediatr Gastroenterol Nutr.* 2001;32 (suppl 2):S1-S31; Gold BD. *Am J Med.* 2004;117 (suppl 5A):23S-29S.

diagnosis of GERD in pediatric patients are 50%, as reported in the medical literature.⁴⁵ Other diagnostic tests include esophageal pH monitoring, which is a valid and reliable tool to determine the frequency and duration of acidic refluxate exposure.^{45,46} In children with alarm signs (eg, hematemesis, weight loss, occult bleeding in the stool), and those with symptoms not responsive to empiric therapy with or without lifestyle modifications, an upper GI endoscopy with biopsy can assess the presence and severity of erosive esophagitis, strictures, and Barrett’s esophagus, as well as exclude other GI disorders (eg, eosinophilic or infectious esophagitis, Crohn’s disease, herpes simplex).⁴⁵

■ **Treatment of pediatric GERD**

The treatment of GERD consists of a stepwise approach mainly based on the presence and severity of the child’s symptoms.^{45,46} The goals of therapy are to relieve reflux-related symptoms, heal esophagitis if present, maintain remission of symptoms, and prevent and manage complications. In children with mild symptoms, including those with regurgitation in the absence of pain or irritability, conservative dietary and behavioral changes may minimize the risk for GER and reduce the incidence of regurgitation.^{45,57} Lifestyle modifications in the management of GERD are age dependent (**TABLE 3**).^{45,46,54}

Pharmacologic intervention often proves necessary to relieve GERD symptoms and promote

the healing of the esophageal mucosa.⁴⁶ Prokinetic agents were widely used in the past in pediatric patients with GERD. However, cisapride was withdrawn from the market, owing to concerns about the potential for serious cardiac arrhythmias associated with this agent.^{45,46,54} The clinical utility of metoclopramide has been substantially diminished because of its potential to induce irreversible central nervous system side effects.^{45,46,54}

Robust evidence has shown that PPIs are significantly superior to H₂RAs, which have been associated with tachyphylaxis, in relieving reflux symptoms and healing erosive esophagitis, and they have become the mainstay of GERD therapy.^{45,56} In the United States, 3 PPIs are currently indicated for the treatment of GERD in pediatric populations: esomeprazole, lansoprazole, and omeprazole. Several landmark, multicenter pediatric studies have reported high rates of symptom relief and mucosal healing with these agents.^{58–60} Hassall et al treated 57 children 1 to 16 years of age with documented, severe erosive esophagitis refractory to other medication or surgery.⁵⁸ After 3 months of treatment with omeprazole 0.7 to 3.5 mg/kg/day, erosive esophagitis healed in 95% of patients, and reflux symptoms resolved in 93% of patients. Tolia et al treated 27 children 1 to 11 years of age with severe erosive esophagitis using lansoprazole 15 mg or 30 mg based on body weight, once or twice daily.⁵⁹ After 8 weeks of therapy, 78% of children displayed mucosal healing, and 100% of children were healed at 12 weeks. In addition, 70% of children experienced complete resolution or significant improvement of their GERD symptoms. Lastly, Tolia et al randomized 149 adolescents 12 to 17 years of age to either esomeprazole 20 mg or 40 mg once daily for 8 weeks.⁶⁰ Both dosages of esomeprazole significantly reduced the symptoms of heartburn, acid regurgitation, and epigastric pain from baseline.

Although the pharmacokinetic properties of PPIs in children are similar to those observed in adults, children often require wider and higher weight-related dose ranges (0.3 to 4.0 mg/kg/day) of PPIs for the reduction of symptoms and resolution of mucosal damage compared with adults, possibly due to

an age-related, enhanced metabolic capacity.^{46,54,61} In infants and young children, esomeprazole, lansoprazole, and omeprazole are best administered by emptying the enteric-coated granule contents of the capsules into soft foods, fruit drinks, or liquid dietary supplements.⁵⁴

Surgical intervention for GERD in children remains a controversial issue, owing to a scarcity of well-designed studies comparing the long-term outcomes of surgical versus pharmacological treatment.^{45,62} Indications for Nissen fundoplication are based on failed response to pharmacological therapy or recurrence of symptoms after weaning from pharmacological therapy.⁴⁵ The high rates of PPI efficacy for GERD compared with the risks inherent to surgery (up to 17% rate of complications) and the high failure rates reported in certain groups of children (up to 25% operative failure rate in medical nonresponders) have limited these indications in recent years.^{45,46,54} Children with life-threatening complications of GERD (eg, aspiration, apnea, peptic strictures with persistent reflux symptoms, Barrett's esophagus) or those with disabling side effects of pharmacological treatment are prime candidates for surgery.^{45,46} The experience of the surgeon and appropriate case selection (eg, children with regurgitation-predominant GERD, responders to pharmacological treatment) represent critical factors in optimizing surgical outcomes.⁴⁵

CONCLUSION

The management of NSAID-related gastropathies must be based on patients' risk for GI events and CV disease, as well as the efficacy and tolerability of both NSAID and gastroprotective cotherapy. Although COX-2 inhibitors reduce the risk for GI adverse events, recent safety concerns exclude their use in patients at risk for CV disease. In this context, the use of a nonselective NSAID under PPI protection appears to be the most clinically sound approach. In patients with high GI bleeding risk and low CV risk, however, the concomitant use of both

a PPI and a COX-2 inhibitor may decrease the high rate of recurrent GI complications.

Although the pathophysiology of GERD in children is similar to that in adults, children often present with gastroesophageal and extraesophageal symptoms distinct from classic heartburn. PPIs yield high rates of mucosal healing and symptom resolution in children, even in those who failed to respond to H₂RA therapy or surgery. These agents are safe and well tolerated, even at the higher milligram-per-kilogram doses required in pediatric patients due to their greater metabolic capacity.

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Updates on the management of upper gastrointestinal disorders in the primary care setting: NSAID-related gastropathies and pediatric reflux disease. EM07-001

CME POST-TEST

Select the single-letter response that best answers the question.

- There is some evidence that use of proton pump inhibitors may
 - Increase calcium absorption
 - Reduce the incidence of hip fracture
 - Be related to increased risk of community-acquired pneumonia and *Clostridium difficile*
 - Suppress enterochromaffin-like (ECL) tumors or dysplasia
- In what percent of users have NSAIDs been associated with a wide array of upper GI symptoms, including epigastric pain, dyspepsia, nausea, vomiting, eructation, and heartburn?
 - 30%
 - 40%
 - 0%
 - 60%
- GI risk factors include
 - Previous ulcer or ulcer complications
 - Use of multiple NSAIDs, including aspirin
 - Concomitant use of corticosteroids or anticoagulants
 - All of the above.
- In a recent randomized controlled trial (RCT), what percent of erosive esophagitis was healed in pediatric patients treated with omeprazole?
 - 70%
 - 78%
 - 93%
 - 95%
- The greatest risk for NSAID-related gastrointestinal complications exists:
 - Within the first 24 hours after initiation of therapy
 - Within the first month after initiation of therapy
 - With prolonged use
 - With higher doses.
- The most comprehensive meta-analysis to date (138 RCTs) concluded that COX-2 inhibitors were associated with what percent of increase in the incidence of serious vascular events?
 - No significant increase
 - 12%
 - 42%
 - 66%
- Cardiovascular and GI risk factors should be considered when recommending NSAID therapy.
 - True
 - False
- In another recent RCT, what percent of children treated with lansoprazole experienced complete resolution or significant improvement of their gastrointestinal reflux disease symptoms?
 - 70%
 - 78%
 - 93%
 - 95%
- The failure of surgery reported in children not responding to medical therapy is estimated to account for up to ___ of cases.
 - 12%
 - 17%
 - 25%
 - 29%
- The Adenomatous Polyp Prevention on Vioxx study reported
 - An overall increase in the incidence of myocardial infarction (MI) or stroke with rofecoxib versus NSAIDs
 - An overall increase in the incidence of MI or stroke with rofecoxib versus placebo
 - Equivalent increase risk with rofecoxib and naproxen at identical dosages
 - An overall decrease in thrombotic events with rofecoxib.

Credit application

Directions: Circle the letter in the Answer Section below that corresponds to the correct answer for each of the post-test questions. Fill in your name and address below, complete the evaluation form, and return the completed sheet to:

Rush University Medical Center or Fax to: (312) 942-2000
 Office of Continuing Medical Education Release date: March 2007
 Academic Facility 433 Expiration date: March 2008
 600 South Paulina Participant Information:
 Chicago, IL 60612

NAME / DEGREE	
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AFFILIATION	
MAILING ADDRESS / CITY / STATE / ZIP (Including name of business if work address)	
E-MAIL	
DAYTIME PHONE	
FAX	
SIGNATURE	DATE COMPLETED

Course Evaluation. You must complete this evaluation form as well as the self-administered test to receive credit. Circle one response to each of the following questions. (5 = Excellent; 4 = Very Good; 3 = Good; 2 = Fair; 1 = Poor)

	Excellent	Good	Poor
1. To what extent were the stated learning objectives of the activity achieved?			
a. Assess the cardiovascular risks associated with cyclo-oxygenase-2 (COX-2) selective inhibitors and traditional nonsteroidal anti-inflammatory drugs (NSAIDs).	5	4	3 2 1
b. Recognize NSAID-associated gastrointestinal (GI) pathologies and implement therapeutic strategies that prevent complications and heal injuries.	5	4	3 2 1
c. Distinguish pathological gastroesophageal reflux disease (GERD) from physiologic gastroesophageal reflux (GER) in pediatric patients and design tailored evaluation and treatment plans.	5	4	3 2 1
2. Accredited continuing medical education (CME) activities must be "free of commercial bias for or against any product. In this regard, how would you rate this activity?"	5	4	3 2 1
3. How well did the activity satisfy your reason for taking it?	5	4	3 2 1
4. In general, was the activity well organized and presented?	5	4	3 2 1
5. Do you anticipate that your participation in this CME activity will result in changes to the way in which you provide care for your patients?	5	4	3 2 1