Failure of *H. pylori* eradication with triple therapy in a compliant patient is usually due to infection with a resistant organism. Quadruple therapy (Table 348-4), where clarithromycin is substituted for metronidazole (or vice versa), should be the next step. The combination of pantoprazole, amoxicillin, and rifabutin for 10 days has also been used successfully (86% cure rate) in patients infected with resistant strains. Additional regimens considered for second-line therapy include levofloxacin-based triple therapy (levofloxacin, amoxicillin, PPI) for 10 days and furazolidone-based triple therapy (furazolidone, amoxicillin, PPI) for 14 days. Unfortunately, there is no universally accepted treatment regimen recommended for patients who have failed two courses of antibiotics. If eradication is still not achieved in a compliant patient, then culture and sensitivity of the organism should be considered. Additional factors that may lower eradication rates include the patient's country of origin (higher in Northeast Asia than other parts of Asia or Europe) and cigarette smoking. In addition, meta-analysis suggests that even the most effective regimens (quadruple therapy including PPI, bismuth, tetracycline, and metronidazole and triple therapy including PPI, clarithromycin, and amoxicillin) may have suboptimal eradication rates (<80%), thus demonstrating the need for the development of more efficacious treatments.

In view of the observation that 15–25% of patients treated with first-line therapy may still remain infected with the organism, new approaches to treatment have been explored. One promising approach is sequential therapy. Regimens examined consist of 5 days of amoxicillin and a PPI, followed by an additional 5 days of PPI plus tinidazole and clarithromycin or levofloxacin. One promising regimen that has the benefit of being shorter in duration, easier to take, and less expensive is 5 days of concomitant therapy (PPI twice daily, amoxicillin 1 g twice daily, levofloxacin 500 mg twice daily, and tinidazole 500 mg twice daily). Initial studies have demonstrated eradication rates of >90% with good patient tolerance. Confirmation of these findings and applicability of this approach in the United States are needed, although some experts are recommending abandoning clarithromycin-based triple therapy in the United States for the concomitant therapy or the alternative sequential therapies highlighted above.

Innovative non–antibiotic-mediated approaches have been explored in an effort to improve eradication rates of *H. pylori*. Pretreatment of patients with *N*-acetylcysteine as a mucolytic agent to destroy the *H. pylori* biofilm and therefore impair antibiotic resistance has been examined, but more studies are needed to confirm the applicability of this approach. In vitro studies suggest that certain probiotics like *Lactobacillus* or its metabolites can inhibit *H. pylori*. Administration of probiotics has been attempted in several clinical studies in an effort to maximize antibiotic-mediated eradication with varying results. Overall, it appears that the use of certain probiotics, such as *Lactobacillus* spp., *Saccharomyces* spp., *Bifidobacterium* spp., and *Bacillus clausii*, did not alter eradication rates but importantly decreased antibiotic-associated side effects including nausea, dysgeusia, diarrhea, and abdominal discomfort/pain, resulting in enhanced tolerability of *H. pylori* therapies. Additional studies are needed to confirm the potential benefits of probiotics in this setting.

Reinfection after successful eradication of *H. pylori* is rare in the United States (<1% per year). If recurrent infection occurs within the first 6 months after completing therapy, the most likely explanation is recrudescence as opposed to reinfection.

THERAPY OF NSAID-RELATED GASTRIC OR DUODENAL INJURY

Medical intervention for NSAID-related mucosal injury includes treatment of an active ulcer and primary prevention of future injury. Recommendations for the treatment and primary prevention of NSAID-related mucosal injury are listed in **Table 348-5**. Ideally, the injurious agent should be stopped as the first step in the therapy of an active NSAID-induced ulcer. If that is possible, then treatment with one of the acid inhibitory agents (H_2 blockers, PPIs) is indicated. Cessation of NSAIDs is not always possible because of the patient's severe underlying disease. Only PPIs can heal GUs or DUs, independent of whether NSAIDs are discontinued.

TABLE 348-5 RECOMMENDATIONS FOR TREATMENT OF NSAID-RELATED MUCOSAL INJURY

Clinical Setting	Recommendation
Active ulcer	
NSAID discontinued	H_2 receptor antagonist or PPI
NSAID continued	PPI
Prophylactic therapy	Misoprostol
	PPI
	Selective COX-2 inhibitor
H. pylori infection	Eradication if active ulcer present or there is a past history of peptic ulcer disease

Abbreviations: COX-2, isoenzyme of cyclooxygenase; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor.

The approach to primary prevention has included avoiding the agent, using the lowest possible dose of the agent, using NSAIDs that are theoretically less injurious, using newer topical NSAID preparations, and/or using concomitant medical therapy to prevent NSAID-induced injury. Several nonselective NSAIDs that are associated with a lower likelihood of GI toxicity include diclofenac, aceclofenac, and ibuprofen, although the beneficial effect may be eliminated if higher dosages of the agents are used. Primary prevention of NSAID-induced ulceration can be accomplished by misoprostol (200 μg qid) or a PPI. High-dose H_2 blockers (famotidine, 40 mg bid) have also shown some promise in preventing endoscopically documented ulcers, although PPIs are superior. The highly selective COX-2 inhibitors, celecoxib and rofecoxib, are 100 times more selective inhibitors of COX-2 than standard NSAIDs, leading to gastric or duodenal mucosal injury that is comparable to placebo; their utilization led to an increase in cardiovascular events and withdrawal from the market. Additional caution was engendered when the CLASS study demonstrated that the advantage of celecoxib in preventing GI complications was offset when low-dose aspirin was used simultaneously. Therefore, gastric protection therapy is required in individuals taking COX-2 inhibitors and aspirin prophylaxis. Finally, much of the work demonstrating the benefit of COX-2 inhibitors and PPIs on GI injury has been performed in individuals of average risk; it is unclear if the same level of benefit will be achieved in high-risk patients. For example, concomitant use of warfarin and a COX-2 inhibitor was associated with rates of GI bleeding similar to those observed in patients taking nonselective NSAIDs. A combination of factors, including withdrawal of the majority of COX-2 inhibitors from the market, the observation that low-dose aspirin appears to diminish the beneficial effect of COX-2 selective inhibitors, and the growing use of aspirin for prophylaxis of cardiovascular events, have significantly altered the approach to gastric protective therapy during the use of NSAIDs. A set of guidelines for the approach to the use of NSAIDs was published by the American College of Gastroenterology and is shown in **Table 348-6**. Individuals who are not at risk for cardiovascular events, do not use aspirin, and are without risk for GI complications can receive nonselective NSAIDs without gastric protection. In those without cardiovascular risk factors but with a high potential risk (prior GI bleeding or multiple GI risk factors) for NSAID-induced GI toxicity, cautious use of a selective COX-2 inhibitor and co-therapy with misoprostol or high-dose PPI are recommended. Individuals at moderate GI risk without cardiac risk factors can be treated with a COX-2 inhibitor alone or with a nonselective NSAID with misoprostol or a PPI. Individuals with cardiovascular risk factors, who require low-dose aspirin and have low potential for NSAID-induced toxicity, should be considered for a non-NSAID agent or use of a traditional NSAID in combination with gastric protection, if warranted. Finally, individuals with cardiovascular and GI risks who require aspirin must be considered for non-NSAID therapy, but if that is not an option, then gastric protection with any type of NSAID must be considered. Any patient, regardless