Indian Health Service  
National Pharmacy and Therapeutics Committee  
Formulary Brief: GERD & Peptic Ulcers  
-May 2018-

Background:  
Treatment options for Gastroesophageal Reflux Disease (GERD) and Peptic Ulcer Disease (PUD) include lifestyle modifications, antacids, alginates, sucralfate, histamine-2 receptor antagonists (H2RAs), proton pump inhibitors (PPIs), misoprostol, and, for exceptional cases, metoclopramide, baclofen, and surgery. Among these, the IHS National Core Formulary (NCF) currently lists “any PPI” and ranitidine for use. The National Pharmacy & Therapeutics Committee last reviewed this topic in February 2014. Ultimately, there were no modifications made to the NCF following the clinical review and pharmacoeconomic analyses.

Discussion:  
For PUD, PPIs are the most effective acid suppression for healing¹ and prevention of bleeding complications². Every treatment regimen in every guideline includes PPIs³⁴. For ulcer prevention, PPIs and misoprostol may be equally effective and both are recommended by guidelines¹⁵. Unfortunately, misoprostol requires frequent dosing, often causes GI side effects, and is indicated as an abortifacient, limiting its widespread use for ulcer prevention⁶.

For GERD, PPIs are superior for both erosive esophagitis⁷ and symptoms of non-erosive esophagitis⁸. RCT data demonstrate superiority for prevention of recurrent esophagitis after healing⁹, and observational data suggest that PPIs are most effective for preventing progression of Barrett’s to cancer¹⁰.

For pediatrics, RCT data is lacking, but several case series report that PPIs healed severe esophagitis that had been unresponsive to H2RA therapy¹¹. For pregnancy, RCT data is also lacking, except for a sucralfate study demonstrating safety and effectiveness. Here also, however, safety of H2RAs and PPIs has been established and their use is widespread¹².

Prokinetics, among which metoclopramide is the only widely available option, are inferior for almost every indication¹³. Usefulness is further diminished by its common and serious side effects, such as dystonia and tardive dyskinesia in 1% of patients, earning it a black box warning¹⁴. Alginates have only been studied in brief, low-quality studies¹⁵, but may be reasonable alternatives to antacids.

Network meta-analyses of PPIs and H2RAs have failed to find significant differences between PPIs and between H2RAs, for either effectiveness or tolerability, when comparable doses are used¹⁶-¹⁸. Of note, associations with PPI therapy include stroke, dementia, allergies/asthma, pneumonia, enteric infections, Clostridium difficile, small bowel bacterial overgrowth, fundic gland polyps, subacute cutaneous lupus erythematosus, acute interstitial nephritis, chronic kidney disease, deficiencies of iron/B12/magnesium, hip fractures, rhabdomyolysis, and myocardial infarction (MI). These associations have been found through case reports, epidemiologic studies, and secondary analyses of RCTs¹⁹.

The association with MI provides an instructive example. A meta-analysis of RCTs found a statistically significant association—but only for omeprazole, and only for PPI use >8 weeks. Authors point out that there may be nothing unique about omeprazole, as the preponderance of data on use for >8 weeks comes from omeprazole trials²⁰. Critics point out that, for these trials, MI was not a pre-specified endpoint, in contrast to the COGENT trial, in which cardiac events were a primary endpoint.

The COGENT trial compared omeprazole + clopidogrel versus clopidogrel alone for 3761 adults who needed aspirin + clopidogrel for ≥12 months (most with recent acute coronary syndrome [ACS] or stent). Omeprazole did not increase the combined endpoint of ACS, stroke, death, or coronary revascularization²¹. The FDA response points out that there were “…too few events to draw any conclusions but certainly not reassuring as to the absence of an effect of omeprazole.”²². The FDA product labeling continues to warn against concomitant administration of clopidogrel and omeprazole or esomeprazole, but expert opinion remains divided.
The guidelines deal with this uncertainty over complications in a broadly similar way, recommending use of the lowest dose for the shortest time, periodically re-evaluating to consider dose reduction, switching to PRN dosing, or discontinuing. Deprescribing is not recommended for those with erosive esophagitis, peptic stricture, Barrett’s, or high-risk NSAID use. The American Gastroenterology Association guidelines recommend against supplementing with vitamin B12, calcium, or magnesium or routinely monitoring bone mineral density, serum creatinine, magnesium, or B12, but this is only expert opinion.

A Cochrane review attempted to compare deprescribing regimens, but identified only six trials that met their quality criteria: five trials of switching to on-demand PPI and one trial of abrupt discontinuation. They found no quality RCTs for intermittent therapy, step-down to H2RAs, on-demand H2RAs, or tapering regimens. Included patients had non-erosive reflux disease, with their symptoms controlled by PPIs for at least 4 weeks. After step-down to on-demand therapy, only 16% had their symptoms relapse compared with 9% relapse in the group that stayed on continuous PPIs (RR 1.71, 95% CI 1.31 to 2.21).

Findings:
While PPIs have proven superior effectiveness for almost every indication, they are associated with several adverse outcomes. Proving causation, of course, is much more difficult and guidelines counsel for common sense deprescribing as indicated. They do not guide PPI selection, however, as they have equivalent effectiveness and tolerability at comparable doses.

Conclusions:
For the treatment of GERD and PUD, the NPTC recommends:
- Any PPI. Leaving the class open allows sites to adjust for local insurance coverage and availability and to accommodate for prescribers concerned about MIs and omeprazole with clopidogrel.
- Ranitidine. While essentially equivalent to famotidine at comparable doses, ranitidine has essentially become the universal choice in IHS. The NPTC continues to support this consistency.

If you have any questions regarding this document, please contact the NPTC at [6]. For more information about the NPTC, please visit the NPTC website.

References:
6. Feldman M. NSAIDs (including aspirin): Primary prevention of gastroduodenal toxicity. UpToDate, Waltham, MA. (Accessed April 29, 2018.).
11. Winter HS, Gastroesophageal reflux in infants. In: UpToDate, Post TD (Ed), UpToDate, Waltham, MA. (Accessed April 29, 2018.).
14. Camilleri M. Treatment of gastroparesis. In: UpToDate, Post TD (Ed), UpToDate, Waltham, MA. (Accessed on April 21, 2018.).
17. Li M-J, Li Q, Sun M, Liu L-Q. Comparative effectiveness and acceptability of the FDA-licensed proton pump inhibitors for erosive esophagitis. Medicine (Baltimore) [Internet]. 2017 Sep 29 [cited 2018 May 23];96(39).
18. Iq S, Chung M, Moorthy D. Comparative Effectiveness of Management Strategies for Gastroesophageal Reflux Disease: Update [Internet]: Agency for Healthcare Research and Quality (US); 2011 Sep. [Comparative Effectiveness Reviews, No. 29.] Results.