Appendix 1 (as supplied by the authors): Outpatient evidence-based indications for proton pump inhibitor (PPI) initiation and chronic use

This supplemental appendix seeks to provide some of the evidence in support of the use of PPIs in specific conditions and point out areas where PPIs are frequently used without evidence of benefit. Tables A1 and A2 can be used as a helpful guide.

**Gastroesophageal Reflux Disease**

Gastroesophageal reflux disease affects 10-20% of Canadians (3.4-6.8 million individuals) and is a major reason for PPI use(1). The CADET-HR study, a Canadian randomized double-blind controlled trial comparing PPIs to H2-blocker therapy in patients with uninvestigated moderate-to-severe GERD without high-risk features from primary care centers, showed that an 8-week course of omeprazole was superior to ranitidine in providing heartburn relief (68.4% vs 51.6%. p=0.0009; Number Needed to Treat(NNT)=6)(2). A recent Cochrane review confirmed the superiority of PPIs over H2-RA for the empirical treatment of GERD (Risk Ratio=0.66, 95% CI 0.60-0.73) and endoscopy negative reflux disease (Risk Ratio=0.78, 95% CI 0.62-0.97) for heartburn remission and overall symptom improvement(3). The last Canadian guidelines on the management of GERD published in 2005 suggest single dose PPI for four to eight weeks in patients with frequent or severe symptoms, with up-titration to twice daily standard dose if severe symptoms persist(4). Similarly, if there is evidence of severe esophagitis (Grade C or D), twice daily standard dose of PPI is recommended. Endoscopy should be performed if there are alarming or atypical features and to detect Barrett’s esophagus. Long-term maintenance therapy should be given at the lowest dose and frequency that is sufficient to achieve optimal control of symptoms, including interruption of therapy after the initial four to eight week trial if symptoms have resolved and providing on-demand therapy as opposed to continuous therapy(4).

**Barrett’s Esophagus**

Barrett’s esophagus is characterized by the development of intestinal metaplasia which can ultimately progress to esophageal adenocarcinoma. This condition tends to occur in older patients with longstanding heartburn symptoms. The 2008 American College of Gastroenterology guidelines on Barrett’s esophagus mention that the goal of pharmacological therapy with acid suppressants is to control reflux symptoms(5). More recently, a meta-analysis including mainly case-control and cohort studies showed that proton pump inhibitors may protect against esophageal adenocarcinoma or any dysplasia (adjusted Odds Ratio=0.33; 95%CI 0.19-0.58) which lead some experts to recommend long-term proton pump inhibitor treatment in these patients(6). Unfortunately, this meta-analysis did not include 2 more recent large case-control studies that did not find an association between the use of proton pump inhibitors and a decrease in esophageal cancer rates(7, 8) and therefore the recommendation must be made cautiously.

**Uninvestigated Dyspepsia**

A meta-analysis from 2015 estimated that the prevalence of uninvestigated dyspepsia in Canada is around 25-30%(9). In 60% of cases, dyspepsia has no identifiable cause(10). The CADET-HN study, a Canadian randomized controlled trial comparing omeprazole, ranitidine, cisapride and placebo in patients with uninvestigated dyspepsia and negative *H. pylori* serology, showed that
omeprazole was superior to ranitidine in providing near-complete (NNT=7) and complete (NNT=8) resolution of symptoms after 4 weeks, but not at 6 months(11). The Canadian Dyspepsia Working Group recommend four to eight weeks of PPI for *H. pylori* negative dyspepsia and recommend long-term PPI over H2-blockers if warranted based on symptoms though the last recommendation is based on expert opinion with poor supportive evidence(12).

**Peptic Ulcer Disease**

The use of PPIs is also indicated in the acute and chronic management of peptic ulcer disease. Long-term management of patients with peptic ulcer disease depends on the underlying cause of the ulcer and whether high-risk features were seen on endoscopy. A randomized controlled trial compared an 8-week course of omeprazole to cimetidine in patients with high-risk endoscopic features after obtaining initial hemostasis and showed that omeprazole decreased rates of rebleeding compared to cimetidine at day 3 and 14 (4% vs 24%, p=0.004, NNT=5) but not hospital stay, rates of surgeries, and mortality(13). For patients with low-risk features on endoscopy, evidence is currently lacking to guide their management, but it is generally accepted to complete an 8-week course of PPI. Management of peptic ulcer disease caused by *H. pylori*, hypersecretory conditions, or drugs is summarized below. In patients with idiopathic ulcers (H Pylori negative, not drug-related, and no evidence of hypersecretory condition), the course of action is still unclear after an 8-week PPI treatment(14).

**H. pylori therapy**

Short course of proton pump inhibitors with antibiotics is recommended for the eradication of Helicobacter Pylori(15). The CADET-HP trial, a Canadian randomized controlled trial comparing a 7-day course of single dose omeprazole, clarithromycin and metronidazole to single dose omeprazole only in patients with moderate-to-severe dyspepsia and a positive urea breath test in primary care centers, showed that *H. pylori* eradication was superior to omeprazole single therapy at providing complete or near complete resolution of dyspepsia symptoms (50% vs 36%, p=0.02, NNT=7)(16). Furthermore, the 15-year follow-up of patients enrolled in the Shandong Intervention trial, a Chinese randomized controlled trial comparing a 2-week course of omeprazole and amoxicillin to placebo in *H. pylori*-positive patients, showed that *H. pylori* eradication lead to a decreased incidence of gastric cancer (3.0% vs 4.6%, p=0.032, NNT=63)(17). In patients with peptic ulcer disease caused by *H. pylori*, chronic PPI use is not warranted and should be stopped after successful eradication of *H. pylori* and treatment of underlying lesion seen on endoscopy as described above, if applicable, and no other competing indication is present.

**Non-steroidal anti-inflammatory (NSAID) related peptic ulcer disease**

The American College of Gastroenterology published guidelines in 2009 on the prevention of NSAID-related ulcer complications(18). In summary, all patients with a previous complicated peptic ulcer (ie bleeding, perforation, obstruction) or a combination of three risk factors (age > 65, high dose NSAIDs, a previous uncomplicated ulcer, concurrent use of aspirin or corticosteroids or anticoagulant) who take NSAIDs should receive long-term PPI, though the best option would be to avoid NSAIDs altogether. Patients with one or two risk factors (as described above) who take NSAIDs should receive long-term PPI. Lastly, patients with no risk...
factors who take NSAIDs regularly do not need gastroprotection, though it is recommended NSAIDs be used at the lowest effective dose for the shortest duration possible. Multiple randomized clinical trials have shown that in patients taking NSAIDs, PPI therapy leads to lower ulcer rate compared to H2-RA and placebo, including the ASTRONAUT trial which compared omeprazole to ranitidine in patients taking NSAIDs during a 6-month maintenance phase after documented healing of previous ulcers (5.2% vs 16.3%, NNT=9)(18, 19). In patients taking aspirin for primary prophylaxis, aspirin should be stopped.

**Hypersecretory conditions**

Chronic use of high-dose PPIs is appropriate in patients with known hypersecretory conditions, unless as in the case of Zollinger-Ellison, a gastrinoma is resected(20). Although most studies included only a small number of patients given it is a rare condition, prospective open-label trials of long-term PPI use showed normalization of erosive gastritis and duodenitis and general improvement in their symptoms, appetite and well-being(21).

Table A1: Evidence-based recommendations for Proton Pump Inhibitor (PPI) therapy

<table>
<thead>
<tr>
<th>Indications</th>
<th>Evidence-based recommendations for use</th>
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| Gastroesophageal Reflux Disease   | • For moderate-to-severe GERD§, an 8-week trial of PPI is superior to H2RA for heartburn relief and healing of erosive esophagitis (2, 3, 22).  
• For mild GERD#, an 8 week trial of PPI should be attempted after failure of lifestyle modification and H2RA (4).  
• In most cases, an attempt to reduce or stop the PPI should be made at least annually (23). |
| Uninvestigated, functional or non-ulcer dyspepsia | • Use of PPI in NUD remains controversial, but accepted (24-27).  
• Eight-week trial of PPI improves heartburn symptoms in patients with uninvestigated dyspepsia (11, 28). |
| Peptic Ulcer Disease              | • Pre-endoscopy IV PPI decreases higher risk stigmata on endoscopy and 72 hours of IV PPI reduces bleeding, surgery and mortality in ulcers with active bleeding, a non-bleeding visible vessel, or an adherent clot on endoscopy (29, 30).  
• Lower risk stigmata on endoscopy may receive oral PPI (31).  
• Eight weeks of once daily PPI decreases rate of re-bleeding compared to H2RA in patients with high-risk lesions. Stay in hospital, rate of surgeries, and mortality are not affected (13).  
• The PPI should be discontinued after an eight-week treatment if there are no other indications for ongoing use. |
| Helicobacter Pylori               | • The combination of high dose PPI and antibiotics up to 14 days is recommended for the eradication of Helicobacter pylori (15, 32, 33). |
| NSAID use | • Patients with prior upper gastrointestinal bleed or one other risk factor* should receive gastroprotection while on NSAID (34, 35).
• H2RA may be more cost-effective with NSAID use (36, 37).
• If patient develops NSAID-related PUD or bleeding, cessation of NSAID use should be considered (35). |
| Dual antiplatelet therapy | • Patients with a prior upper gastrointestinal bleed or one other risk factor* should receive gastroprotection (38).
• If patient develops DAPT-associated haemorrhage, the ongoing need for DAPT should be re-assessed. |
| Hypersecretory conditions | • Life-long use of PPIs is appropriate in patients with hypersecretory conditions (20, 21). PPIs may be stopped if a gastrinoma is resected. |
| Ulcer prevention after EVL | • Ten-day course of low dose PPI decreases the size of post-EVL ulcers and, may decrease the chance of bleeding after EVL (39). |
| ICU stress ulcer prophylaxis (high-risk patients) | • PPIs are currently accepted, but H2RA are more and may be associated with less ventilator-associated pneumonia, although this effect is not consistently seen (40, 41). |

*Age over 60, antithrombotic therapy, NSAID (including low-dose aspirin), corticosteroid or prior gastrointestinal event including peptic ulcer history or upper gastrointestinal bleeding.
Moderate-to-severe GERD: frequent, intense and long-lasting symptoms with an impact on patient quality of life or evidence of erosive esophagitis.
Mild GERD: infrequent heartburn episodes (less than 3 times per week).
UGIB=upper gastrointestinal bleed, PUD=peptic ulcer disease, NSAID=non-steroidal anti-inflammatory, DAPT=dual antiplatelet therapy, GERD=gastroesophageal reflux disease, ICU=intensive care unit, H2RA=H2 receptor antagonist, EVL=endoscopic variceal ligation, NUD=non-ulcer dyspepsia.
Table A2: Reasons for which the evidence suggests PPI use is likely not appropriate

<table>
<thead>
<tr>
<th>Non-evidence-based Indications</th>
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<tbody>
<tr>
<td><strong>Outpatient</strong></td>
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<tr>
<td>• NSAID therapy (including low-dose aspirin) without other risk factors.</td>
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<tr>
<td>• Remote history of peptic ulcer disease (35).</td>
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<tr>
<td>• Remote history of gastritis.</td>
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<tr>
<td>• Remote history of GERD.</td>
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<tr>
<td>• Chemoprevention in Barrett’s esophagus (5, 7, 8, 42).</td>
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<tr>
<td>• Uninvestigated anemia.</td>
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<tr>
<td>• Atypical chest pain.</td>
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<tr>
<td>• Hypertensive portal gastropathy (43)</td>
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<tr>
<td>• Long-term PPI use after elective EVL (44).</td>
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<tr>
<td><strong>Inpatient</strong></td>
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<tr>
<td>• Stress ulcer prophylaxis in the non-ICU setting (45).</td>
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<tr>
<td>• Acute esophageal variceal bleed (44).</td>
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NSAID=non-steroidal anti-inflammatory, GERD=Gastroesophageal reflux disease, PPI=proton pump inhibitor, EVL = esophageal variceal ligation, ICU=intensive care unit.
References:


