PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #377
MANAGEMENT OF REFRACTORY GASTROESOPHAGEAL REFLUX DISEASE
Adam Greenfield, PharmD, Tara Cook, MD, Jennifer Pruskowski, PharmD

Background Refractory gastroesophageal reflux disease (rGERD) can be characterized as symptomatic reflux or esophagitis despite an adequate trial of twice daily proton pump inhibitor (PPI) therapy (1). Patients with rGERD might describe their symptoms as heartburn, poorly localized chest pain, or acid reflux. Non-verbal patients (e.g. patients obtunded from the dying process) may be at risk of untreated GERD. This *Fast Fact* reviews treatment options for rGERD in patients with life-limiting illness.

Etiologies Mechanisms that contribute to rGERD in palliative care populations are varied and include both gastrointestinal and non-gastrointestinal processes such as: increased esophageal acid exposure (i.e. secondary to gastric carcinoid tumors); opioid-induced gastroparesis/delayed emptying; and/or peristaltic deficiency associated with cirrhotic ascites; malignancy-induced bowel obstructions; and transient lower esophageal sphincter relaxation (TLESR) (1,2). Clinicians should consider rGERD in the differential diagnosis of non-verbal patients who appear to be imminently dying and are uncomfortable, especially if they have a history of GERD, cancer, and/or cirrhosis.

Symptom Management When possible, therapeutic management of rGERD should target the underlying etiology (e.g. triple therapy for helicobacter pylori). However, in palliative care patients, clinicians must factor in prognosis, the amount of symptom distress, and the clinical situation to determine the extent of diagnostic work-up (e.g. endoscopy) and specialized consultation that is appropriate. For many palliative care patients, empiric treatment of rGERD is pursued.

Traditional Acid Suppressing Agents
Adding a ***nocturnal histamine-2 receptor antagonist (H_2RA)*** such as ranitidine for at least one month while on concurrent PPI therapy has been associated with improvements in night-time reflux symptoms, GERD-associated sleep disturbance, and overall GERD symptom management in up to 74% of patients; only 13% discontinued nocturnal H_2RA due to tolerance issues (3). Coadministration of H_2RAs and PPIs is felt to be safe (4), although some experts suggest separating evening PPI and bedtime H_2RA doses for optimal effect. Solutions containing ***sodium alginate*** (i.e. Gaviscon®) have reliably decreased the severity and frequency of heartburn, especially when used post-prandially, with few side effects (5,6). Likewise, ***sucralfate*** in two-to-four daily doses may improve rGERD as well as mucosal healing for erosive disease (7). However, none of these agents have been well-studied in the seriously ill.

More Targeted Strategies to Palliate rGERD
- ***Baclofen*** reduces regurgitation events and TLSER via gamma-aminobutyric acid activity (8). Although literature is scarce in palliative care patients, decreased duodenal reflux and improvement in symptom severity was observed in a small prospective study (n=16) of patients with heartburn lasting > 3 months (8). Baclofen crosses the blood brain barrier and is known to cause significant adverse CNS effects like drowsiness, confusion, and seizures (see *Fast Fact* #340). Dose ranges of 10-30 mg/day, divided into twice-daily or three-times-daily doses, are most commonly used, but up to 60 mg/day has been described (8). It should not be titrated more often than every three days (8).
- ***Metoclopramide*** is a prokinetic agent that may improve rGERD symptoms and nausea in patients with delayed esophageal peristalsis, delayed gastric emptying (gastroparesis), and partial bowel obstruction at oral or parenteral doses of 10 mg three to four times a day. It is not recommended nor effective for patients who do not have evidence of gastroparesis or a partial bowel obstruction (9). It has been associated with adverse effects such as tardive dyskinesia and dystonia, especially if used for longer than 12 weeks (9).
- ***Antidepressants*** Selective serotonin reuptake inhibitors and trazodone have been shown to reduce GERD symptoms in symptomatic patients with normal endoscopies (10-12). Citalopram and fluoxetine have both been shown to be effective in placebo-controlled randomized trials (10,11) and

even showed superiority to omeprazole in controlling heartburn symptoms in one comparison trial in patients with concomitant depression (11). Evidence for trazodone has been limited to the symptomatic relief of chest pain in patients with esophageal contraction abnormalities (12).

Other Considerations

- *Lifestyle interventions:* Although, tobacco use, and alcohol consumption may reduce lower esophageal sphincter pressure, cessation of these agents has not been clearly shown to lead to improvements in GERD symptoms (13). Some experts recommend head of bed elevation and avoidance of a late-night evening meal (within 2-3 hours of bedtime) to mitigate rGERD, although the degree to which these interventions help is not clearly established (14).
- Botulinum toxin injection (see *Fast Fact* #324) can help patients with achalasia, which is a gastric motility disorder characterized by lower esophageal sphincter (LES) non-relaxation (15). Without confirmed LES non-relaxation, its use could increase LES relaxation and thereby worsen rGERD symptoms, however. Major side effects include anaphylaxis, voice disorders, and pharyngitis.
- CYP2C19 genotype status can contribute to pharmacokinetic variability of the effectiveness of PPIs, but genotypic testing in palliative care patients is not routinely performed. The clinical utility of switching appropriately dosed PPIs in patients without genotypic testing is not well described.
- Long-term PPI use, generally greater than eight weeks, without substantial clinical benefit is not generally recommended. Long-term PPI use has been linked to increased risk of bone fracture, clostridium difficile infections, hypomagnesemia, and vitamin B12 deficiency (16).

Cost: The average wholesale price of PPIs (e.g. omeprazole) is double that of H_2RAs (e.g. ranitidine) at $0.72/tablet versus $0.34/capsule. Both classes of medications are available over-the-counter (OTC). Prescription pricing may be nearly 3 times that of OTC. The cost of baclofen, metoclopramide, and trazodone are $0.50/tablet, $0.13/tablet, and $0.44/tablet, respectively. SSRIs and botulinum toxin injection are costlier: $2.42/tablet and $721.20/100 unit injection, respectively.

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Authors' Affiliations: University of Maryland Medical Center, Baltimore, MD; University of Pittsburgh Medical Center; Pittsburgh PA
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