suggest celiac disease. Pancreatic and liver chemistries are obtained for possible pancreaticobiliary causes. Ultrasound, CT, or MRI is performed if abnormalities are found. Gastric emptying testing is considered to exclude gastroparesis for dyspeptic symptoms that resemble postprandial distress when drug therapy fails and in some GERD patients, especially if surgical intervention is an option. Breath testing after carbohydrate ingestion detects lactase deficiency, intolerance to other carbohydrates, or small-intestinal bacterial overgrowth.

TREATMENT INDIGESTION

GENERAL PRINCIPLES

For mild indigestion, reassurance that a careful evaluation revealed no serious organic disease may be the only intervention needed. Drugs that cause gastroesophageal reflux or dyspepsia should be stopped, if possible. Patients with GERD should limit ethanol, caffeine, chocolate, and tobacco use due to their effects on the LES. Other measures in GERD include ingesting a low-fat diet, avoiding snacks before bedtime, and elevating the head of the bed. Patients with functional dyspepsia also may be advised to reduce intake of fat, spicy foods, caffeine, and alcohol.

Specific therapies for organic disease should be offered when possible. Surgery is appropriate for biliary colic, whereas diet changes are indicated for lactase deficiency or celiac disease. Peptic ulcers may be cured by specific medical regimens. However, because most indigestion is caused by GERD or functional dyspepsia, medications that reduce gastric acid, modulate motility, or blunt gastric sensitivity are used.

ACID-SUPPRESSING OR -NEUTRALIZING MEDICATIONS

Drugs that reduce or neutralize gastric acid are often prescribed for GERD. Histamine H_2 antagonists like cimetidine, ranitidine, famotidine, and nizatidine are useful in mild to moderate GERD. For severe symptoms or for many cases of erosive or ulcerative esophagitis, PPIs such as omeprazole, lansoprazole, rabeprazole, pantoprazole, esomeprazole, or dexlansoprazole are needed. These drugs inhibit gastric H^+, K^+-ATPase and are more potent than H_2 antagonists. Up to one-third of GERD patients do not respond to standard PPI doses; one-third of these patients have nonacidic reflux, whereas 10% have persistent acid-related disease. Furthermore, heartburn typically responds better to PPI therapy than regurgitation or atypical GERD symptoms. Some individuals respond to doubling of the PPI dose or adding an H_2 antagonist at bedtime. Infrequent complications of long-term PPI therapy include infection, diarrhea (from *Clostridium difficile* infection or microscopic colitis), small-intestinal bacterial overgrowth, nutrient deficiency (vitamin B_{12}, iron, calcium), hypomagnesemia, bone demineralization, interstitial nephritis, and impaired medication absorption (e.g., clopidogrel). Many patients started on a PPI can be stepped down to an H_2 antagonist or be switched to an on-demand schedule.

Acid-suppressing drugs are also effective in selected patients with functional dyspepsia. A meta-analysis of eight controlled trials calculated a risk ratio of 0.86, with a 95% confidence interval of 0.78–0.95, favoring PPI therapy over placebo. H_2 antagonists also reportedly improve symptoms in functional dyspepsia; however, findings of trials of this drug class likely are influenced by inclusion of large numbers of GERD patients.

Antacids are useful for short-term control of mild GERD but have less benefit in severe cases unless given at high doses that cause side effects (diarrhea and constipation with magnesium- and aluminum-containing agents, respectively). Alginic acid combined with antacids forms a floating barrier to reflux in patients with upright symptoms. Sucralfate, a salt of aluminum hydroxide and sucrose octasulfate that buffers acid and binds pepsin and bile salts, shows efficacy in GERD similar to H_2 antagonists.

HELICOBACTER PYLORI ERADICATION

H. pylori eradication is definitively indicated only for peptic ulcer and mucosa-associated lymphoid tissue gastric lymphoma. The utility of eradication therapy in functional dyspepsia is limited, although some cases (particularly with the epigastric pain syndrome subtype) relate to this infection. A meta-analysis of 18 controlled trials calculated a relative risk reduction of 10%, with a 95% confidence interval of 6–14%, favoring *H. pylori* eradication over placebo. Most drug combinations **(Chaps. 188 and 348)** include 10–14 days of a PPI or bismuth subsalicylate in concert with two antibiotics. *H. pylori* infection is associated with reduced prevalence of GERD, especially in the elderly. However, eradication of the infection does not worsen GERD symptoms. No consensus recommendations regarding *H. pylori* eradication in GERD patients have been offered.

AGENTS THAT MODIFY GASTROINTESTINAL MOTOR ACTIVITY

Prokinetics like metoclopramide, erythromycin, and domperidone have limited utility in GERD. The γ-aminobutyric acid B (GABA-B) agonist baclofen reduces esophageal exposure to acid and nonacidic fluids by reducing TLESRs by 40%; this drug is proposed for refractory acid and nonacid reflux. Several studies have promoted the efficacy of motor-stimulating drugs in functional dyspepsia, but publication bias and small sample sizes raise questions about reported benefits of these agents. Some clinicians suggest that patients with the postprandial distress subtype may respond preferentially to prokinetic drugs. The 5-HT_1 agonist buspirone may improve some functional dyspepsia symptoms by enhancing meal-induced gastric accommodation. Acotiamide promotes gastric emptying and augments accommodation by enhancing gastric acetylcholine release via muscarinic receptor antagonism and acetylcholinesterase inhibition. This agent is approved for functional dyspepsia in Japan and is in testing elsewhere.

OTHER OPTIONS

Antireflux surgery (fundoplication) to increase LES pressure may be offered to GERD patients who are young and require lifelong therapy, have typical heartburn and regurgitation, are responsive to PPIs, and show evidence of acid reflux on pH monitoring. Surgery also is effective for some cases of nonacidic reflux. Individuals who respond less well to fundoplication include those with atypical symptoms or who have esophageal body motor disturbances. Dysphagia, gas-bloat syndrome, and gastroparesis are long-term complications of these procedures; ~60% develop recurrent GERD symptoms over time. The utility and safety of endoscopic therapies (radiofrequency ablation, transoral incisionless fundoplication) to enhance gastroesophageal barrier function have unproved durable benefits for refractory GERD.

Some patients with functional heartburn and functional dyspepsia refractory to standard therapies may respond to antidepressants in tricyclic and selective serotonin reuptake inhibitor classes, although studies are limited. Their mechanism of action may involve blunting of visceral pain processing in the brain. Gas and bloating are among the most troubling symptoms in some patients with indigestion and can be difficult to treat. Dietary exclusion of gas-producing foods such as legumes and use of simethicone or activated charcoal provide benefits in some cases. Low FODMAP (fermentable oligosaccharide, disaccharide, monosaccharide, and polyol) diets and therapies to modify gut flora (nonabsorbable antibiotics, probiotics) reduce gaseous symptoms in some IBS patients. The utility of low-FODMAP diets, antibiotics, and probiotics in functional dyspepsia is unproven. Herbal remedies such as STW 5 (Iberogast, a mixture of nine herbal agents) are useful in some dyspeptic patients. Psychological treatments (e.g., behavioral therapy, psychotherapy, hypnotherapy) may be offered for refractory functional dyspepsia, but no convincing data confirm their efficacy.