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An overview: Current clinical guidelines for the evaluation, diagnosis, treatment, and management of dyspepsia ☆

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Dyspeptic symptoms are very common in the general population. Expert consensus has proposed to define dyspepsia as pain or discomfort centered in the upper abdomen. The more common causes of dyspepsia include peptic ulcer disease, gastritis, and gastroesophageal reflux disease.[4] At some point in life most individuals will experience some sort of transient epigastric pain. This paper will provide an overview of the current guidelines for the evaluation, diagnosis, treatment, and management of dyspepsia in a clinical setting.

Dyspeptic symptoms are very common in the general population, affecting an estimated 20% of persons in the United States.[1] While a good number of these individuals may never seek medical care, a significant proportion will eventually proceed to see their family physician. Several reports exist on the prevalence and impact of dyspepsia in the general population.[2,3] However, the results of these studies are strongly influenced by criteria used to define dyspepsia. Expert consensus has proposed to define dyspepsia as pain or discomfort centered in the upper abdomen. The more common causes of dyspepsia include peptic ulcer disease (PUD), gastritis, and gastroesophageal reflux disease (GERD).[4] However, it is not unusual for a complete investigation to fail to reveal significant organic findings, and the patient is then considered to have "functional dyspepsia."[5,6] The term "functional" is usually applied to disorders or syndromes where the body's normal activities in terms of the movement or sensitivity of the intestinal nerves, or the way in which the brain controls some of the gastrointestinal (GI) functions, are impaired. However, there are no structural abnormalities that can be seen by upper GI endoscopy or x-ray or by blood tests. Thus, it is identified by the characteristics of the symptoms and, less frequently, when considered necessary, limited tests.[5,6]

At some point in their lives most individuals will experience some sort of transient epigastric pain. As mentioned earlier, the

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causes of this pain can be attributed to a variety of etiologies, some of which may occur in conjunction with others. In a comprehensive assessment of the reporting of symptoms of functional GI disorders, 69% of the patients were found to have at least 1 of a number of different functional GI syndromes.[5-7] The Rome diagnostic criteria categorize the functional GI disorders and define symptom-based diagnostic criteria for each category.[5]

PUD

In the United States, PUD affects approximately 4.5 million people annually.[8] The prevalence of PUD has shifted from a predominance in males to similar occurrences in both males and females.[8] Lifetime prevalence is approximately 11%-14% in men and 8%-11% in women.[8] Age trends for ulcer occurrence reveal declining rates in younger men, particularly for duodenal ulcer, and increasing rates in older women.[8] PUD is most frequently associated with *Helicobacter pylori* infection, the use of acetylsalicylic acid (Aspirin), non-steroidal anti-inflammatory drug (NSAID) use, and cigarette smoking. Though the management of *H. pylori* infection has improved radically in recent years, prescribing of acetylsalicylic acid and NSAIDs, especially in older populations, has increased over the same period.[4,8,9]

Peptic ulcers are focal areas of deep erosion through the mucosa and, sometimes, submucosa. They commonly occur either in the stomach or duodenum. Excess gastric acid must be present for duodenal ulcers to form, whereas in gastric ulcers there is often normal or reduced gastric acid secretion.[4,8] *H. pylori* is causally related to serious disorders of the upper GI tract in adults and children. Over 50% of the world's population is infected with *H. pylori*, with the highest prevalence observed in developing countries.[9,10] Although some reports have shown that *H. pylori*-positive patients tend to have dyspepsia, the relationship between *H. pylori* and dyspepsia remains controversial.[11] Approximately only 1 in 6 individuals who are infected with *H. pylori* develop ulcers, and only a small (1%-2%) number of *H. pylori*-infected individuals develop gastric cancer.[4,10,12]

On physical examination, patients with ulcers may display epigastric tenderness (Table 1). Other possible associated findings on examination may include the following[4,8]:

1) A succussion splash. Sound produced by air and fluid in a distended stomach several hours following a meal because of gastric outlet obstruction.
2) Peritoneal signs such as rebound, rigidity, and guarding in the setting of a perforation.
3) Occult blood on rectal examination.

Table 1 Clinical manifestations of dyspepsia[4,8]

Peptic ulcer disease (PUD)	Duodenal ulcer disease
Epigastric pain (most common symptom)	Epigastric pain can be sharp, dull, burning, or penetrating
Gnawing or burning sensation	Hunger
Occurs 2-3 h after meals	Pain may radiate into the back
Relieved by food or antacids	About 20%-40% of patients describe bloating, belching, or symptoms suggestive of GERD
Patient awakens with pain at night	Ulcer-related pain generally occurs 2-3 h after meals and often awakens the patient at night. This pattern is believed to be the result of increased gastric acid secretion, which occurs after meals and during the late night and early morning hours when circadian stimulation of gastric acid secretion is the highest.
Pain may radiate into the back (consider penetration)	About 50%-80% of patients with duodenal ulcers experience nightly pain, as opposed to only 30%-40% of patients with gastric ulcers and 20%-40% of patients with nonulcer dyspepsia (NUD).
Nausea	Pain is often relieved by food, a finding often cited as being specific for a duodenal ulcer. However, this symptom is present in only 20%-60% of patients and is probably *not* specific for duodenal ulcers.
Vomiting	
Dyspepsia, including belching, bloating, distention, and fatty food intolerance	
Heartburn	
Chest discomfort	
Anorexia, weight loss	
Hematemesis or melena resulting from gastrointestinal bleeding	
Dyspeptic symptoms that might suggest PUD are *not* specific because only 20%-25% of patients with symptoms suggestive of peptic ulceration are found on investigation to have a peptic ulcer.	

In addition to lifestyle modifications, treatment goals, particularly in the acute setting, include the relief of discomfort and protection of the gastric mucosal barrier to promote healing. Eradication of *H. pylori* infection is a prolonged and complicated process requiring confirmation of the presence of the organism and eventual evidence of eradication. Cessation of the causative agent and antacids

Table 2 Treatment options

Drug class	Mechanism of action	Examples
Antacids: Aluminum-containing and magnesium-containing antacids can be helpful in relieving symptoms of gastritis by neutralizing gastric acids. These agents are inexpensive and safe.	They neutralize gastric acidity, resulting in an increase in stomach and duodenal bulb pH. Aluminum ions inhibit smooth muscle contraction, thus inhibiting gastric emptying. Magnesium and aluminum antacid mixtures are used to avoid bowel function changes.	Maalox, Mylanta
Proton pump inhibitors (PPIs): Proton pump inhibitors relieve pain and generally heal peptic ulcers more rapidly than H2 receptor antagonists. Drugs in this class are equally effective. Standard doses of PPIs inhibit more than 90% of 24-h acid secretion, compared to 50%-80% with H2-blockers. They all decrease serum concentrations of drugs that require gastric acidity for absorption, such as ketoconazole or itraconazole. Six drugs, as listed here, are now FDA approved in this category, and omeprazole, lansoprazole, and pantoprazole are now available in generic form. They are most effective when taken 30-60 min before the first meal of the day.	Decrease gastric acid secretion by inhibiting the parietal cell H^+/K^+ ATP pump. Used for up to 4 wk to treat and relieve symptoms of active duodenal ulcers. May be prescribed for up to 8 wk to treat all grades of erosive esophagitis. • *In addition, for short-term (4-8 wk) treatment and symptomatic relief of gastritis. As noted above, used for up to 4 wk to treat and relieve symptoms of active duodenal ulcers.	Dexiansoprazole (Dexilant): a dual delayed release (DDR) formulation; esomeprazole (Nexium): an S-isomer of omeprazole; lansoprazole (Prevacid); omeprazole (Prilosec), pantoprazole (Protonix),*rabeprazole (Aciphex),*and a rapid release form of omeprazole (Zegerid)
H2-receptor antagonists (H2RA): The 4 most common drugs in this class are all equally effective and are available over-the-counter in half prescription strength for heartburn treatment. Generally, none is as effective as PPIs.	Inhibits histamine at H2 receptors of the gastric parietal cells, resulting in reduced gastric acid secretion, gastric volume, and hydrogen ion concentrations.	Cimetidine (Tagamet), Famotidine (Pepcid), nizatidine (Axid), ranitidine (Zantac)
Gastrointestinal agents: Are effective in the treatment of peptic ulcers and in preventing relapse. Their mechanism of action is *not* clear. Multiple doses are required, and they are not as effective as the other therapeutic options.	Binds with positively charged proteins in exudates and forms a viscous adhesive substance that protects the GI lining against pepsin, peptic acid, and bile salts. Used for short-term management of ulcers.	Sucralfate (Carafate)
Prostaglandins: Can prevent peptic ulcers in patients taking NSAIDs and may be used with NSAIDs in patients at a high risk of complications.	A prostaglandin analog that protects the lining of the GI tract by replacing depleted prostaglandin E_1 in prostaglandin-inhibiting therapies.	Misoprostol (Cytotec) NOTE: Arthrotec also exists which contains diclofenac and misoprostol.

ATP = adenosine triphosphate; FDA = Food and Drug Administration.

may be sufficient outpatient therapy in mild cases. Most patients require an H2-receptor antagonist (H2RA) or a proton pump inhibitor (PPI), which has been shown to provide faster and more reliable healing than antacids.[4,13-17] Either an H2RA or a PPI can be used as a first-line agent. With continued symptoms, they may be used together. In refractory cases, sucralfate (Carafate) also may be indicated (Table 2). PPIs, generally, are more effective than H2RAs in reducing upper GI bleeds in patients taking NSAIDs, Aspirin, or clopidogrel (Plavix).[4,13-17] None of the anti-secretory agents has a significant effect in reducing bleeding risk in patients taking other anticoagulants.[4,13-17]

Gastritis

Gastritis technically refers to endoscopic or histological findings of inflammatory changes in the gastric mucosa; however, the term is often used clinically to refer to the symptoms of dyspepsia. Gastritis affects individuals of all age groups.[18-21] In general, no gender predilection exists.[18-21] The most common causes of gastritis are *H. pylori* bacterial infection, the incidence of which increases with age, and the use of NSAIDs and Aspirin.[18-21] Other medications that have been associated with gastritis include steroids, valproate (Depakote), and, more rarely, calcium

salts, potassium chloride, iron supplements, and antibiotics.[21]

Gastritis is typically divided into the following 2 subcategories: acute and chronic. Acute gastritis is a term covering a broad spectrum of entities that induce inflammatory changes in the gastric mucosa. The different etiologies share the same general clinical presentation. However, they differ in their unique histologic characteristics. The inflammation may involve the entire stomach or a region of the stomach. Acute gastritis can be broken down further into the following 2 subcategories: erosive (eg, superficial erosions, deep erosions, hemorrhagic erosions) and nonerosive (generally caused by *H. pylori*).[18-21] Chronic gastritis is a histopathologic entity characterized by chronic inflammation of the stomach mucosa. Gastritis can be classified based on the underlying etiologic agent (eg, *H. pylori*, bile reflux, NSAIDs, autoimmunity, allergic response) and the histopathologic pattern, which may suggest the etiologic agent and clinical course (eg, *H. pylori*-associated multifocal atrophic gastritis).[18-21]

Clinically, many people with gastritis may experience no symptoms at all.[18-21] However, upper central abdominal pain is the most common symptom; the pain may be dull, vague, burning, aching, gnawing, sore, or sharp. In addition, other signs and symptoms may include nausea, vomiting, belching (without pain relief), bloating, decreased appetite, and anorexia.

Treatment of gastritis depends on the specific cause. Acute gastritis caused by NSAIDs or alcohol may be relieved by stopping use of those substances. Chronic gastritis caused by *H. pylori* infection is treated by eradicating the bacteria. Most gastritis treatment plans also incorporate medications that treat stomach acid to reduce signs and symptoms one may be experiencing and promote healing in the stomach. Stomach acid irritates inflamed tissue in the stomach, causing pain and further inflammation. That is why, for most types of gastritis, treatment involves taking medications to reduce or neutralize stomach acid.[18-21]

Over-the-counter (OTC) antacids (eg, Maalox, Mylanta, and others) in liquid or tablet form are a common treatment for mild gastritis. Antacids neutralize stomach acid and can provide fast pain relief. When antacids do not provide enough relief, a physician may recommend an ***acid blocker***, such as cimetidine (Tagamet), famotidine (Pepcid), nizatidine (Axid), or ranitidine (Zantac), that helps reduce the amount of acid the stomach produces. ***PPIs*** reduce acid by blocking the action of tiny pumps within the acid-secreting cells of the stomach. This class of medications includes dexiansoprazole (Dexilant), esomeprazole (Nexium), lansoprazole (Prevacid), omeprazole (Prilosec), pantoprazole (Protonix), rabeprazole (Aciphex), and a rapid release form of omeprazole (Zegerid).[4,13-21]

Digestive problems can occur for many reasons, including lifestyle choices under one's control. In general, to keep the digestive system healthy, family physicians typically recommend the following:

1. **Practice good healthy eating habits.** Just as important as what one eats is the manner in which food is eaten. Eating moderate portions at regular times and relaxing while one eats are encouraged.
2. **Maintain a healthy weight.** Digestive problems can occur no matter what one weighs. However, heartburn, bloating, and constipation tend to be more common in people who are overweight. Maintaining a healthy weight can often help prevent or reduce these symptoms.
3. **Get plenty of regular exercise.** Aerobic exercise that increases breathing and heart rates also stimulates the activity of intestinal muscles, helping to move food waste through one's intestines more quickly. It is best to aim for at least 30 minutes of aerobic activity on most days of the week. The patient should check with their family physician before beginning an exercise program.
4. **Manage stress.** Stress increases stomach acid production and slows down digestion. Because stress is unavoidable for most people, the key is to learn how to handle it effectively—a task that is made easier by a nutritious diet, adequate rest, regular exercise, and healthy ways to relax. If one has trouble relaxing, consider taking up meditation or studying yoga or tai chi. According to the Mayo Clinic, "Yoga, as an example, brings together physical and mental disciplines to achieve peacefulness of body and mind, helping you relax and manage stress and anxiety."[22] These techniques can help focus one's mind, calm an individual's anxiety level, and reduce physical tension. In addition, therapeutic massage or osteopathic manipulative medicine (*mentioned later*) or both may loosen taut muscles, calm frazzled nerves, and treat any areas of somatic dysfunction.
5. **Smoking cessation and other healthy lifestyle modifications.**[23]

GERD

GERD, or *heartburn*, is a common condition that results from the reflux of gastric contents that subsequently leads to symptoms or esophageal complications or both. Approximately 7%-10% of individuals in the United States experience symptoms of GERD on a daily basis.[24,25] GERD occurs in all age groups, with an increasing prevalence in individuals older than 40 years.[24,25] Because many people control symptoms with OTC medications and without consulting their family physician, the actual number of individuals with GERD is probably higher.[24,25] GERD is as common in men as in women. However, the male-to-female incidence ratio for esophagitis is 2:1-3:1. The male-to-female incidence ratio for Barrett esophagus is 10:1.[24,25,27] Caucasian males are at a greater risk for Barrett esophagus and adenocarcinoma than other populations.[24,25,27]

The pathogenesis of GERD centers on the movement of gastric contents into the esophagus. This directly implies a failure of the antireflux mechanisms that function at the

gastroesophageal junction. The lower esophageal sphincter (LES) must have a normal length and pressure and a normal number of episodes of transient relaxation (relaxation in the absence of swallowing). The LES can be compromised by hiatal hernias, certain foods (eg, caffeine, chocolate, alcohol), or medications that decrease the pressure of the LES, and obesity because of increased abdominal pressure.[4,24,25]

Heartburn is most often felt as a retrosternal sensation of burning or discomfort that typically occurs after eating or when lying down or bending over. Common clinical manifestations of GERD may include regurgitation of gastric or esophageal contents or both into the pharynx and dysphagia.

Ambulatory pH monitoring is the gold standard for diagnosing GERD, but having a comprehensive list of possible differential diagnoses is very important when dealing with the possible etiology of GERD because a number of other disorders can present with epigastric pain.[4,24,25] GERD may also be asymptomatic, which could make the diagnosis more difficult. With GERD as a top choice on the list of differential diagnoses, the following (among other diagnoses) should also be considered: [4,24,25]

1. *H. Pylori* infection;
2. Asthma;
3. Cholecystitis;
4. Acute myocardial infarction; and
5. GERD complications (eg, peptic ulcers, Barrett esophagus, esophagitis, etc.)

The differential diagnoses above can be evaluated in a systematic process of laboratory tests and other studies. In previously undiagnosed patients, *H. Pylori* may be ruled out through a urease breath test, also known as the Campylobacter-like organism test, serology, blood antibody test, or biopsy via esophagogastroduodenoscopy.[4,24,25] These tests have a sensitivity of $>90\%$, making them a very useful tool for possibly ruling out an *H. Pylori* infection. In previously diagnosed patients, *H. Pylori* may be tested for and ruled out by performing a stool antigen test. Asthma is an atypical presentation associated with GERD and should be included in the differential diagnosis. Cholecystitis can be ruled out through an HIDA scan along with the classic symptoms and findings, such as right upper quadrant abdominal pain (a positive Murphy's sign on physical examination). Acute myocardial infarction can present with GERD along with other related GI symptoms and should be considered on the list of differential diagnoses. Radiologic studies and endoscopy are the main techniques in diagnosing GERD complications, and should be performed when appropriate symptoms are present.[4,24,25,28]

Treatment for GERD is entirely etiology dependent and should include healthy lifestyle modifications. Some things patients can do to help alleviate symptoms include the following: (1) elevating the head of the bed 6 inches at night, (2) decreasing and stopping smoking, (3) weight reduction, and (4) avoiding high acid foods and drinks.[4,24,25,29] As-needed *(or **PRN**)* pharmacotherapy such as antacids can offer quick relief of GERD associated symptoms and should be taken immediately after meals when symptoms occur. Some of the most popular ***antacids*** available OTC include milk of magnesia (MOM), Pepto-Bismol, Rolaids, and Tums. Antacids are cost effective and readily available, but patients should be made aware of possible drug interactions such as with tetracycline or fluoroquinolones.[4,13-17,24,25]

Patients who have moderate-to-severe symptoms with no erosive esophagitis may benefit from taking a daily prescription (Rx). One of the oldest treatments available is with ***H2RAs***, which, even today, are still considered the gold standard treatment.[4,13-17,24,25,27] This class of medications works by limiting both the baseline gastric acid and the stimulated secretion of acid. They include cimetidine (Tagamet), famotidine (Pepcid), nizatadine (Axid), and ranitidine (Zantac). These medications are usually very well tolerated, with the most common side effects being headache, diarrhea, and constipation. Cimetidine (Tagamet) has the most potential drug interactions, which should be checked if applicable.[4,13-17,24,25] H2RAs are usually given for ~8-12 weeks; if patients still experience symptoms, the dosage should be increased to the maximum effective dosage or switched to a PPI.[4,13-17,24,25]

As shown in Table 2, there are currently a number of ***PPIs*** that are available by prescription, several of which are now also available OTC in generic form: (1) dexiansoprazole (Dexilant), (2) esomeprazole (Nexium), (3) lansoprazole (Prevacid), (4) omeprazole (Prilosec), (5) pantoprazole (Protonix), (6) rabeprazole (Aciphex), and (7) a rapid release form of omeprazole (Zegerid). PPIs are generally very well tolerated, with the most common side effects being nausea, diarrhea, constipation, headache, and skin rash.[4,13-17,24,25] It should be noted that a combination therapy for patients with GERD is *not* recommended, and that a patient with erosive esophagitis diagnosed via endoscopy should receive a PPI due to the higher healing rates associated with this class of agents.[4,13-17,24,25,27]

Although there is no specific osteopathic manipulative medicine treatment for GERD and other related GI disorders, certain possible somatic dysfunctions that may be associated with the condition(s) can be treated. The osteopathic manipulative approach to a patient with GERD and other related GI disorders involves the sequential movement of lymph sequestered within the thoracic and abdominal regions, the normalization of the autonomics (decrease sympathetic expression), and improvement of the respiratory-circulatory mechanism as outlined by Zink. J. Gordon Zink, DO states that for "health", there must be good circulation of the body's fluids, and he believed that this is achieved by freedom of movement of the body's diaphragm (thoracic inlet and outlet). In addition, the use of therapeutic modalities to decrease sympathetic expression includes rib raising to inhibit the long fibers of the regional sympathetic chain ($T_{5\text{-}9}$), lymphatic drainage of the celiac

ganglion, and normalization of rib and mid-thoracic segmental somatic dysfunction. Therefore, screening and treating patients with GERD for dysfunctions with respect to the following areas or points, listed below, can be an important component of the diagnosis and treatment provided by the osteopathic physician.[30,31]

- Ribs
- Thoracic inlet
- Thoraco-abdominal diaphragm
- Chapman reflexes: exquisitely tender 2-5 mm sequestrations of lymphatic fluid that relate to specific visceral dysfunction (specifics described below).

Esophagus

– Anterior chest wall at bilateral parasternal spaces intercostally between ribs 2 and 3.
– Posteriorly between T2 and T3 bilaterally-halfway between the T2 and T3 spinous processes longitudinally, and within the transverse spinalis gutter of T2.

Stomach acidity

– Leftward and anteriorly between the costo-chondral junction of ribs 5 and 6.
– Posteriorly between T5 and T6 on the left side within the transverse spinalis gutter of T5 and T6.

Chapman reflexes can be treated by balancing the pelvic diaphragm to facilitate lymphatic flow and applying rotary pressure over the sequestered lymph at the sympathetically related site.

Along with continued healthy lifestyle modifications, maintenance therapy solely depends on the severity of the disease and should be treated accordingly. Patients with erosive esophagitis should be given the minimal effective dose to maintain remission because this disease has a high reoccurrence rate.[4,24,25,27] Surgery should only be considered as a last option when all medical or conservative therapies have failed or certain complications develop. [4,24,25] These complications, as mentioned earlier, can include Barrett esophagus and recurrent esophageal strictures. The surgery of choice is called the laparoscopic Nissen fundoplication procedure and has a cure rate of approximately 92%.[4,24,25] Overall prognosis with surgery is considered excellent. However, surgical morbidity and mortality are higher in patients who have complex medical problems in addition to gastroesophageal reflux.[4,24,25]

Summary

In conclusion, dyspeptic symptoms are very common in the general population. At some point in life most individuals will experience some sort of transient epigastric pain. This paper provides an overview of the more common causes of dyspepsia, which include PUD, gastritis, and GERD.[4] An increased awareness of the current clinical guidelines for the evaluation, diagnosis, treatment, and management of dyspepsia will provide family physicians with the tools necessary to provide better and the most-up-to date standards of care for their patients.

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