

## **The Approach to Dyspepsia and Associated Conditions in Family Medicine**

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### **I. Introduction**

Dyspepsia is marked by vague, uncharacteristic, subjective symptoms that manifest in the form of pain or a discomfort in the upper abdomen. ROMA III criteria have been used commonly to define dyspepsia. The presence of one or more of symptoms such as epigastric pain, epigastric burning, postprandial fullness and early satiation leads to the diagnosis of dyspepsia on the condition that the symptom starts six months before the diagnosis and lasts at least for the past three months. Epigastric pain is defined as unpleasant pain in the epigastric region with no obvious explanation. Epigastric burning is burning sensation with no obvious explanation. Postprandial fullness refers to the discomfort caused by the sensation that food persists for a long time in the stomach. Early satiation refers to the condition characterized by feeling full right after starting to eat – regardless of the amount of food – and not being able to finish the meal (1). Dyspepsia constitutes about one twentieth of patients consulting a family physician, and about 1% of these patients are transferred to higher healthcare services for endoscopic evaluation (2). Approximately 40% of patients with dyspeptic complaints present to primary healthcare centers (3). Family physicians employed in family healthcare centers play a major role in the initial evaluation of patients, and contribute to the optimization of healthcare services (4). It is of particular importance for family physicians to listen to and comprehend a patient's complaints thoroughly and arrive at a correct diagnosis. Dyspepsia is an easily diagnosed condition when there is an effective communication between physician and patient; however, in cases where the communication between physician and patient is inadequate, the patient is subject to continuous tests in secondary and then tertiary healthcare centers – a situation that is likely to cause a vicious cycle with loss of time, effort and money (5). There is a need to carry out endoscopy when alarm symptoms of dyspepsia are present. The alarm symptoms include being aged over 45, recent onset of symptoms, presence of upper gastrointestinal system (GIS) malignancy in the family, progressive weight loss, leukocytosis, anemia, rectal bleeding, sleep disorder at night due to dyspeptic complaints, odynophagia, persistent and recurrent vomiting and fever (6).

**Types of Dyspepsia and Underlying Causes:** There are two forms of dyspepsia, i.e. organic dyspepsia and functional dyspepsia. In organic dyspepsia, peptic ulcer – a GIS disease – plays an important role in differential diagnosis. In peptic ulcer, pain that wakes patients up at night is one of the main reasons for consulting a physician, and the use of non-steroidal anti-inflammatory drugs (NSAIDs) is a significant factor in etiology. Gastroesophageal reflux disease (GERD), another common GIS condition marked by main symptoms such as retrosternal burning and regurgitation, plays a role in the development of dyspepsia (7). As gastric or esophageal cancers and pancreatic or biliary tract disorders may also cause pain in the epigastric region or around the middle, their symptoms may be confused with dyspeptic symptoms. Another cause of dyspepsia is diabetes mellitus (DM) – a systemic disease. Given that postprandial fullness, early satiation, nausea and vomiting are among the symptoms of DM, special attention should be paid in diagnosis. Other systemic diseases, including collagen vascular diseases, thyroid gland disorders, ischemic heart diseases, adrenal insufficiency, and metabolic disorders such as hyperthyroid and hyperkalemia are also likely to cause dyspeptic complaints. Helicobacter Pylori infections, as well, cause duodenal and gastric ulcer and hence dyspeptic complaints. Among medications, particularly NSAIDs and corticosteroids induce chronic mucosal irritation, which may finally cause dyspeptic complaints. Among food types, especially spicy foods, alcohol, tomato, fatty foods and coffee may provoke dyspeptic complaints. Functional dyspepsia, a persistent and recurrent condition in which the causes of dyspeptic complaints cannot be detected through tests, is the most commonly encountered form of dyspepsia. The ROMA III criteria defined for functional dyspepsia are: 1) the presence of at least one of postprandial fullness, early satiation, epigastric pain and epigastric burning that starts six months prior to diagnosis and lasts at least for the past three months, and 2) lack of a structural disorder that explains these symptoms. Functional dyspepsia is divided into two, i.e. epigastric pain syndrome (EPS) and postprandial distress syndrome (PDS). EPS refers to the condition where the patient suffers from periodic pain or burning in the epigastric region at least once a week and is not relieved by defecation or passage of flatus. PDS refers to the condition where the patient feels full after meal and early satiation before finishing a regular meal at least several times per week (1).

**Clinical Approach to Dyspepsia:** A careful anamnesis is of particular importance in the diagnosis of dyspepsia. Among the indicators considered in diagnosis are presence of GERD, drugs used by the patient, whether the patient received H. pylori eradication treatment due to similar complaints and presence of alarm symptoms. If alarm symptoms are present, the patient is advised to undergo endoscopy or radiological examination. If alarm symptoms are not present but the patient suffers from postprandial fullness, early satiation, epigastric pain, epigastric burning or nausea, then empiric therapy is administered considering that the patient is likely to have dyspepsia. If endoscopic results are normal and H. pylori is negative in a patient with dyspeptic complaints, then the patient is considered to have functional dyspepsia. H. pylori is sought in patients for whom endoscopy is not required. Eradication treatment is performed if H. pylori is positive. In the event that dyspeptic complaints still persist six months after the administration of eradication treatment, the patient is diagnosed with functional dyspepsia (6).

### **Gastroesophageal Reflux Disease (GERD)**

GERD refers to all symptoms and complications that appear after abnormal reflux of gastric content into the esophagus. This is a physiological condition that happens 8-10 times per day particularly after the meal. However, if it has caused damage in the distal esophagus mucosa or manifestation of certain symptoms, it is no longer gastroesophageal reflux but is gastroesophageal reflux disease. There are some mechanisms that prevent or minimize the damage caused by reflux. These are anti-reflux barrier, lower esophagus sphincter, cardiac notch, crus of diaphragm, peristaltic movements that shorten the length of mucosal contact and ensure the cleaning of esophagus, and esophageal mucosal resistance. Any pathology in one of these mechanisms or impairment of the balance between defense mechanisms and aggressive mechanisms is likely to cause the development of GERD (8, 9). In studies conducted in Europe and the United States, the rate of GERD prevalence is up to 20%. It is reported that these patients suffer from regurgitation or retrosternal burning symptoms at least once per week. A study, conducted with 2203 patients in Turkey to find out the GERD prevalence among patients admitted to primary healthcare centers, has shown that 33.9% of patients were diagnosed with GERD (10). A detailed anamnesis is highly valuable in GERD diagnosis. A thorough anamnesis and physical examination may enable physicians to diagnose GERD. The most common symptoms are regurgitation of sour liquid in one hour after a meal, heartburn and acid regurgitation. According to the Montreal classification, GERD is classified into either esophageal syndromes or extraesophageal syndromes. Esophageal symptomatic syndromes are typical reflux syndrome and reflux chest pain syndrome, and esophageal syndromes that cause damage are reflux esophagitis, reflux stricture, Barrett's esophagus and adenocarcinoma. Extraesophageal syndromes that are proved to be associated with GERD are reflux cough, reflux laryngitis, reflux asthma and reflux dental erosions, and that are considered to be associated with GERD are sinusitis, pharyngitis, pulmonary fibrosis and recurrent otitis media (11).

### **Tests used in the evaluation of GERD diagnosis and complications:**

**Tests for reflux:** Intraesophageal pH monitoring test, intraesophageal pH and impedance monitoring test, ambulatory bilirubin monitoring test, scintigraphy, barium-based esophageal imaging.

**Tests performed to evaluate the symptoms:** Empiric proton pump inhibitor test, intraesophageal pH monitoring test, acid perfusion test (Bernstein), endoscopy, endoscopic biopsy, barium-based esophageal imaging.

**Tests performed to evaluate the damage in esophagus:** Endoscopy, endoscopic biopsy, barium-based esophageal imaging.

**Pathogenesis tests:** Esophageal manometry, gastric analysis, scintigraphy (12, 13).

**Atypical symptoms and alarm symptoms associated with GERD:** Atypical symptoms of GERD include asthma, chest pain, chronic cough, tooth enamel erosion, heartburn and regurgitation (symptom onset after the age of 45), recurrent laryngitis, persistent sore throat, sensation of a lump in the throat and subglottic stenosis. Alarm symptoms and findings of GERD comprise dysphagia, early satiation, gastrointestinal bleeding, iron deficiency anemia, odynophagia, vomiting and weight loss (14).

**Treatment of GERD:** The aim of treatment is keeping symptoms under control, healing esophagitis, preventing possible complications, and ensuring sustainable recovery. While antacid treatment is effective in non-severe cases, it may be required to suppress acid secretion in more severe cases. Changing the style of life is of particular importance in GERD treatment given that it is a recurring condition. It is also important to avoid alcohol consumption and smoking, to use a high loft pillow, not to eat before bed, to avoid acidic, spicy and fatty food, and to lose weight (if the patient is obese). Obesity has been an increasing problem across the world, and changing the style of life not only helps to prevent obesity but also reduces the development of GERD, which is a disease associated with obesity (15, 16). Antacids alone are useful in non-severe cases. However, they are effective only when taken at frequent intervals and high doses. H2 receptor blockers may also be used in non-severe cases to suppress acid secretion and to treat GERD. H2 receptor blockers are generally prescribed

to be used twice per day. However, in long-term use, their effect may reduce as patients are likely to develop tolerance. In GERD cases of medium or higher severity, physicians prefer proton pump inhibitors (PPIs). PPIs are taken 30-45 minutes before the meal once a day. Recovery is achieved in over 85% of patients after the use of PPIs for 8-10 weeks. Prokinetics reduce the development of reflux by increasing the pressure of lower esophageal sphincter and shortening the period of gastric emptying, but has limited place in GERD treatment. It should be noted that the disease recurs in patients after they stop taking medications. That is why additional treatment is required in most patients. H<sub>2</sub> receptor blockers and mostly PPIs are preferred in additional treatment. In GERD treatment, it is important that patients do not stop medications abruptly. Patients are required to come off gradually by reducing the dose of medications over a period of 6-8 weeks. Surgery is advised when at least one of severe esophagitis, hemorrhagic esophagitis or symptoms related to the respiratory system is present in patients that do not respond to medical treatment. Surgical treatment includes laparoscopic Nissen fundoplication. Physicians must take time before deciding to perform surgery. They need to consider and evaluate carefully a patients' clinical findings, age, response to medications and other health problems (17).

**H. pylori and Its Eradication:** *Helicobacter pylori* (*H. pylori*), colonized in the gastric mucosa of about half of the world population, is associated with gastritis, peptic ulcer, gastric cancer and some other systemic diseases. *H. pylori* infection starts at an early age and continues during whole life unless treated. People generally become infected with *H. pylori* through food and water subject to fecal contamination, which manifests itself with dyspeptic symptoms including discomfort and pain in the upper abdomen and feeling of full after eating, loss of appetite, nausea, vomiting and feces in dark color (18). Tests used for the diagnosis of *H. pylori* are divided into two categories, i.e. non-invasive and invasive tests. Non-invasive tests include urea breath test, fecal antigen test and *H. pylori* serology. Invasive tests are upper gastrointestinal system endoscopy, urease test, histopathology, culture and PCR.

**Urea breath test:** This is a reliable test used for diagnosing the presence of *H. pylori*. Urea breath test is the most sensitive and specific test performed to evaluate response to treatment (19). In this test, a patient's swallow urea is labelled by either C13 or C14. Urea is broken down by urease enzyme produced by *H. pylori* and turns into carbon dioxide (CO<sub>2</sub>). The carbon dioxide is excreted after passing first to blood circulation and then to respiratory system. If there is urease activity in the stomach, the amount of labeled carbon excreted in the breath is greater than the basal amount, and this means that *H. pylori* is present. The sensitivity of urea breath test is approximately 90%. However, the use of antibiotics and H<sub>2</sub> receptor blockers before the test procedure may cause misleading negative results. This is a costly test.

**Fecal antigen test:** Polyclonal and monoclonal antibodies are used to detect the presence of *H. pylori* in feces. The sensitivity of this test is approximately 90%. However, the use of PPIs and bismuth preparations may cause misleading negative results. Therefore, patients are required to stop these medications two weeks prior to the test.

**H. pylori serology:** *H. pylori* serology is generally used to detect the frequency of *H. pylori* infection in the community. The results are not affected by the use of PPIs and antibiotics. The test is sensitive up to 90%, but it is not a practical one. Among invasive tests, culture is the most reliable diagnostic tool in principle with a sensitivity rate of up to 95%. A clinician determines characteristics of the bacterium with the help of culture and decides on the type of antibiotic that patient needs to use (20).

**Treatment of H. Pylori Infection:** Triple therapy (PPI + Amoxicillin + Clarithromycin or metronidazole) is the most frequently used treatment in primary healthcare services. A seven-day therapy is the standard one; however, a 14-day therapy is also advised. Adding bismuth to triple therapy increases the chance of *H. pylori* eradication by 10%. If a patient is allergic to amoxicillin, metronidazole is used instead. The sequential therapy starts with the use of PPI and amoxicillin in doses of 2x1 per day for five days, and continues with the use of PPI, clarithromycin and metronidazole for five days. The sequential therapy is superior to seven-day therapy, and has the same effect as the 14-day therapy. Quadruple therapy is divided into two categories – with bismuth and without bismuth. In therapy without bismuth, metronidazole is added to triple therapy. Therapy with bismuth includes PPI, bismuth, metronidazole and tetracycline. This is more effective in patients that have antibiotic resistance. It is found that PPI, levofloxacin and amoxicillin therapy is more effective than quadruple therapy in patients with antibiotic-resistant *H. pylori* infection. Patient adherence to treatment is of utmost importance in all treatment protocols. If dyspeptic symptoms continue after the treatment, tests must be repeated. Tests are repeated 4-6 months after the treatment. Consultation with gastroenterology specialists may be required in secondary healthcare services. The purpose of eradication procedures is to eradicate the microorganism and prevent possible complications. The triple therapy is preferred commonly; however, physicians are required to consider other treatment protocols as well (18). Taking high dose of PPIs (4x1) and 500 mg amoxicillin for 14 days results in 100% eradication in cases where other treatment protocols have not eradicated *H. pylori*. While the eradication rate is about 50% in a 7- or 10-day therapy, the rate increases up to

95% after a 14-day therapy. Regardless of the treatment regime, 14-day therapy is the new standard for *H. pylori* eradication (21).

Consequently, it is important for family physicians to keep up with the most up-to-date and multidisciplinary approaches and develop an effective relationship with patients in order to have successful results in the diagnosis, treatment and eradication of dyspepsia and associated conditions – a very common cause of presenting to family healthcare centers (22). As the gastrointestinal problems are one of the most important causes of emergency admittances so that clinicians should be aware of appropriate treatment options (23). Given the increasing antibiotic resistance to *H. pylori* and other infections, avoiding unnecessary use of antibiotics is of particular significance for individual and public health as well as national economics.

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