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A Review Article in:

Peptic ulcer disease

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Abstract

Peptic ulcer disease (PUD) refers to acid peptic injury of the digestive tract, resulting in mucosal break reaching the sub mucosa. Peptic ulcers are usually located in the stomach or proximal duodenum, but they can also be found in the oesophagus or Meckel's diverticulum. *H. pylori* infection and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) are the predominant causes of peptic ulcer disease in the United States, accounting for 48 and 24 percent of cases, respectively. Typical symptoms of peptic ulcer disease include episodic gnawing or burning epigastric pain; pain occurring two to five hours after meals or on an empty stomach; and nocturnal pain relieved by food intake, antacids, or antisecretory agents. The pain of gastric ulcers increases 2 to 3 hours after a meal and may result in weight loss, whereas the pain of duodenal ulcers decreases with a meal and may result in weight gain. Any patient presenting with anemia, melena, hematemesis, or weight loss should be further investigated for complications of PUD, predominantly bleeding, perforation, or cancer. A physical exam may reveal epigastric abdominal tenderness and signs of anemia. Treatment always directed to the cause of ulcer. According to the latest WHO data published in 2018 Peptic Ulcer Disease Deaths in Iraq reached 147 or 0.09% of total deaths. The age adjusted Death Rate is 0.94 per 100,000 of population ranks Iraq #151 in the world, accordingly it is proposed in this study to review in details about PUD.

Introduction

The term peptic ulcer refers to acid peptic injury of the digestive tract, resulting in mucosal break reaching the submucosa. Peptic ulcers are usually located in the stomach or proximal duodenum, but they can also be found in the oesophagus or Meckel's diverticulum. In this article, the term

peptic ulcer disease refers to peptic ulcers located in the stomach or duodenum (1).

It was described by Lanas A, and Chan FK in 2017, that traditionally, a hypersecretory acidic environment together with dietary factors or stress were thought to cause most peptic ulcer diseases, but the discovery of *Helicobacter pylori* infection and the widespread use of nonsteroidal anti-inflammatory drugs (NSAIDs) in the second half of the 20th century have changed this perception (2). In 1997 , Kurata JH, Nogawa AN, mentioned that *H. pylori* infection and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) are the predominant causes of peptic ulcer disease in the United States, accounting for 48 and 24 percent of cases, respectively. A variety of other infections and comor-bidities are associated with a greater risk of peptic ulcer disease (e.g., cytomegalovirus, tuberculosis, Crohn's disease, hepatic cirrhosis, chronic renal failure, sarcoidosis, myeloproliferative disorder) (3). The same authors found that; critical illness, surgery, or hypovolemia leading to splanchnic hypoperfusion may result in gastroduo-denal erosions or ulcers (stress ulcers); these may be silent or manifest with bleeding or perforation. Smoking increases the risk of ulcer recurrence and slows healing.

Typical symptoms of peptic ulcer disease described by Ramakrishnan K, Salinas RC in 2007; to include episodic gnawing or burning epigastric pain; pain occurring two to five hours after meals or on an empty stomach; and nocturnal pain relieved by food intake, antacids, or antisecretory agents. Ramakrishnan K, Salinas RC in the same way obtained that the history of episodic or epigastric pain, relief of pain after food intake, and nighttime awakening because of pain with relief following food intake are the most specific findings for peptic ulcer and help rule in the diagnosis,

but less common features include indigestion, vomiting, loss of appetite, intolerance of fatty foods, heartburn, and a positive family history (4).

Aim of article

To review and discuss the etiology, epidemiology, clinical features and management of peptic ulcer.

Epidemiology

According to what was mentioned by Sonnenberg A. in 2013; the lifetime prevalence of peptic ulcer disease in the general population has been estimated to be about 5-10%, and incidence 0·1–0·3% per year, however, the prevalence and incidence of peptic ulcer disease is now probably lower than these estimates worldwide, especially in highincome countries, because epidemiological studies have shown a sharp decreasing trend in the incidence, rates of hospital admissions, and mortality associated with the disease in the past 20–30 years (5).

These decreasing numbers; according to what was discovered by Malmi H. et . al. in 2014, could be due to the introduction of new therapies, or they might be due to a cohort trend that cannot be fully explained by known causes (eg, *H pylori* infection and NSAID treatment). Many gastrointestinal diseases are characterised by rises and falls in prevalence, suggesting that an underlying birth-cohort trend might be present for peptic ulcer disease (6).

Etiology and risk factors

The major risk factors for PUD are attributed to H pylori infection and NSAID or ASA use. Causes of non-H- pylori non-NSAID ulcers are the use of antiplatelet agents, stress, Helicobacter heilmanii, cytomegalovirus infections, Behcet disease, Zollinger-Ellison syndrome, Crohn disease, and

cirrhosis with portal hypertension. Other risk factors include older age and ethnicity (7).

Table 1. Etiologic factors of PUD (25)

Common Causes	Infrequent Causes
- *Helicobacter Pylori* Infection - NSAIDs and ASA Treatment - Stress Ulcers	- Gastrinoma (Zollinger-Ellison syndrome) - Hyperplasia/hyperfunction of antral G cells - Systemic mastocytosis - Myeloproliferative Syndromes with basophilia - Viral infections (herpes simplex virus tipo I and cytomegalovirus) - Vascular insufficiency (cocaine) - Ischemia caused by stenosis of celiac artery - Radiation - Chemoembolization (via hepatic artery) - Crohn´s Disease - Type II amyloidosis - Neuhauser syndrome (tremor-nystagmus-ulcer) - Porphyria cutanea tarda - Other drugs (potassium chloride, biphosphonates, mycophenolate) - Idiopathic

Pathophysiology

The pathophysiology of the diseases declared by Huang JQ, et. al. in 2002, they said that; *H pylori* and the use of NSAIDs or aspirin are the main risk factors of both gastric and duodenal ulcers. However, only a few people with *H pylori* infection or taking NSAIDs or aspirin develop peptic ulcer disease, suggesting that individual susceptibility to bacterial virulence and drug toxicity is essential to the initiation of mucosal damage (8).

Malmi H. et al. in 2014 said that the interaction between bacterial and host factors determines the outcome of *H pylori* infection, and the ability

of *H pylori* strains to produce different proteins has been linked to their virulence and to the host immune response, and the organism produces urease to create an alkaline environment, which is essential for its survival in the stomach under the mucosal barrier. It also expresses adhesins such as blood group antigen adhesin (BabA) or outer inflammatory protein adhesin (OipA), which facilitate attachment of bacteria to gastric epithelium. A genome pathogenic island encodes the virulent factors CagA and PicB, which—together with other bacterial factors—are thought to interact strongly with host tissue and be linked to gastric mucosal inflammatory cell infiltration and gastric epithelial injury (9).

NSAIDs and aspirin are the other major risk factors linked to peptic ulcer disease and its complications. Compared with non-users, NSAID and aspirin use increase the risk of complications of peptic ulcer disease by four times in NSAID users, and by two times in aspirin users. As well as NSAID and aspirin use or *H pylori* infection, complications are largely driven by comorbidity and ageing. Concomitant use of NSAIDs or aspirin with selective serotonin-reuptake inhibitors, corticosteroids, aldosterone antagonists, or anticoagulants substantially increase the risk of upper gastrointestinal bleeding (10). The role of smoking and poor socioeconomic status is unclear (11).

Clinical features

In 2002, Malfertheiner P. et. al, the described that the predominant symptom of uncomplicated peptic ulcer is epigastric pain, which can be accompanied by other dyspeptic symptoms such as fullness, bloating, early satiety, and nausea. In patients with duodenal ulcer, epigastric pain occurs typically during the fasting state or even during the night and is usually relieved by food intake or acid-neutralising agents. Roughly a third of these

patients also have heartburn, mostly without erosive oesophagitis, and chronic ulcers can be asymptomatic (12).

In general , the absence of symptoms is seen in NSAID-induced ulcers, for which upper gastrointestinal bleeding or perforation might be the first clinical manifestation of the disease, anyway the most frequent and severe complication of peptic ulcers is bleeding, which is reported in 50–170 per 100 000, 0.05%-0.17% with the highest risk in people aged older than 60 years (13).

According to study done by Barkun A, and Leontiadis G.; in 2010; pain awakening the patient from sleep between 12 and 3 A.M. affects and one-third of gastric ulcer patients; therefore it is a key symptom of DUs. The authors added that however, it is also seen in one-third of patients with nonulcer dyspepsia. They also mentioned that substantial vomiting and weight loss suggest gastric outlet obstruction or gastric malignancy, and in a meta-analysis, 46% of patients had reflux symptoms, probably due to concomitant reflux disease including heartburn and acid regurgitation (14). Less common features of PUD are indigestion, belching, vomiting associated with gastric or pyloric stenosis, loss of appetite, intolerance of fatty foods, anemia caused by GI blood loss, and a positive family history. Weight loss precipitated by fear of food intake is also characteristic of gastric ulcers (15).

Diagnosis

Diagnosis of PUD requires history taking, physical examination, and invasive/non-invasive medical tests. A careful history should be obtained and noted for the presence of any complications. Patient reporting of epigastric abdominal pain, early satiety, and fullness following a meal raise suspicion of PUD. The pain of gastric ulcers increases 2 to 3 hours after a

meal and may result in weight loss, whereas the pain of duodenal ulcers decreases with a meal which can result in weight gain. Any patient presenting with anemia, melena, hematemesis, or weight loss should be further investigated for complications of PUD, predominantly bleeding, perforation, or cancer. A physical exam may reveal epigastric abdominal tenderness and signs of anemia (16).

If clinical symptoms suggest possible peptic ulcer disease and no alarm symptoms are noted, empiric treatment with anti-secretory therapy can be started. Furthermore, since *H. pylori* is a common cause of PUD, a test and treat strategy with a non-invasive test for *H. pylori* (stool antigen or urea breath test) is recommended in patients less than 55 years of age without alarm features, in geographic regions were gastric cancer is uncommon and the prevalence of *H. pylori* is greater than 20%. In older patients and those with alarm symptoms, endoscopy is recommended to establish a diagnosis. Alarm symptoms include GI bleeding, weight loss, early satiety, dysphagia or odynophagia, family history of upper GI malignancy, iron deficiency anemia or new upper GI symptoms in patients older than 55. Esophagogastroduodenoscopy (EGD) or upper endoscopy is the gold standard for the diagnosis of PUD. It is can be used to detect *H. pylori* with gastric biopsies and can also rule out malignancy (17).

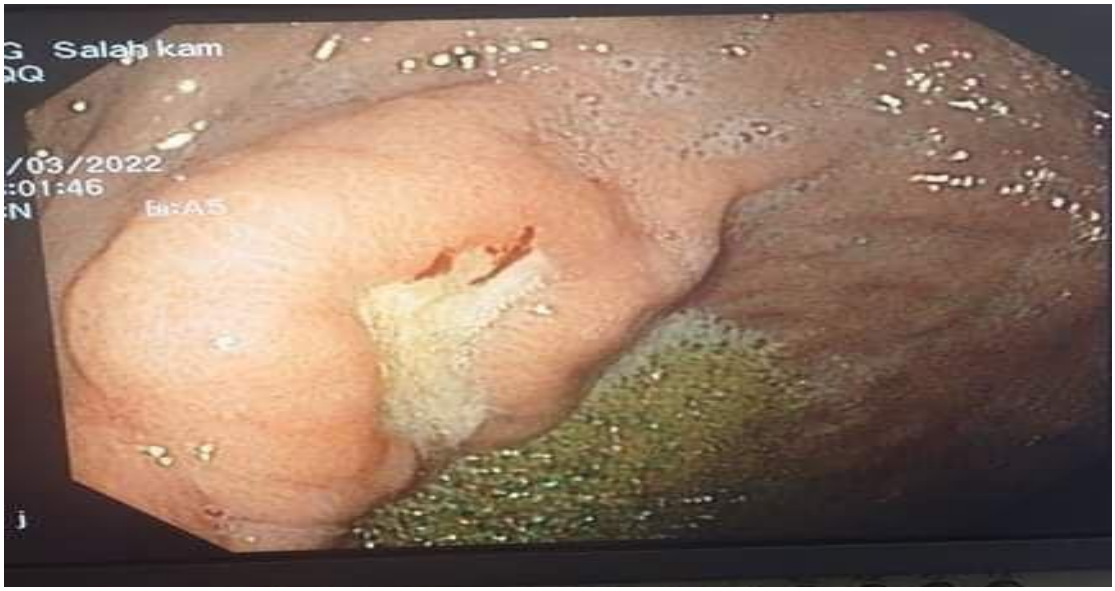

Figure 1. Peptic ulcer under OGD

Treatment

Treatment is usually directed at identifying the factors that lead to PUD. For *H. pylori*-associated PUD, eradication alone will lead to ulcer healing and prevent further mucosal injury. However, due to rising antibiotic resistance in *H. pylori*, treatment has become more difficult. First line therapy for *H. pylori* eradication includes a proton pump inhibitor (PPI), clarithromycin and amoxicillin or metronidazole (for penicillin-allergic patients) for seven to 14 days. PPIs work synergistically with antibiotics to eradicate *H. pylori*. Due to increasing antibiotic resistance, the efficacy of triple therapy has fallen below 70% in many countries (18).

As susceptibility testing is often not available in clinical practice, clarithromycin-based regimens should be avoided when local clarithromycin resistance rates are greater than 15%. Clarithromycin resistance rates are high (>20%) across the United States. When using clarithromycin-based triple therapy, eradication rates can be increased with use of high dose PPI and by extending the duration of treatment from seven to 14 days. For areas with high clarithromycin resistance, bismuth-

containing quadruple therapy with a PPI, bismuth, tetracycline and a nitroimidazole (metronidazole or tinidazole) for 14 days or PPI, clarithromycin, amoxicillin, and a nitroimidazole for 14 days is the preferred as first line treatment. There have been issues with the cost and availability of tetracycline and the data have been mixed on whether doxycycline can be substituted. The regimens discussed above yield eradication rates greater than 90% (19).

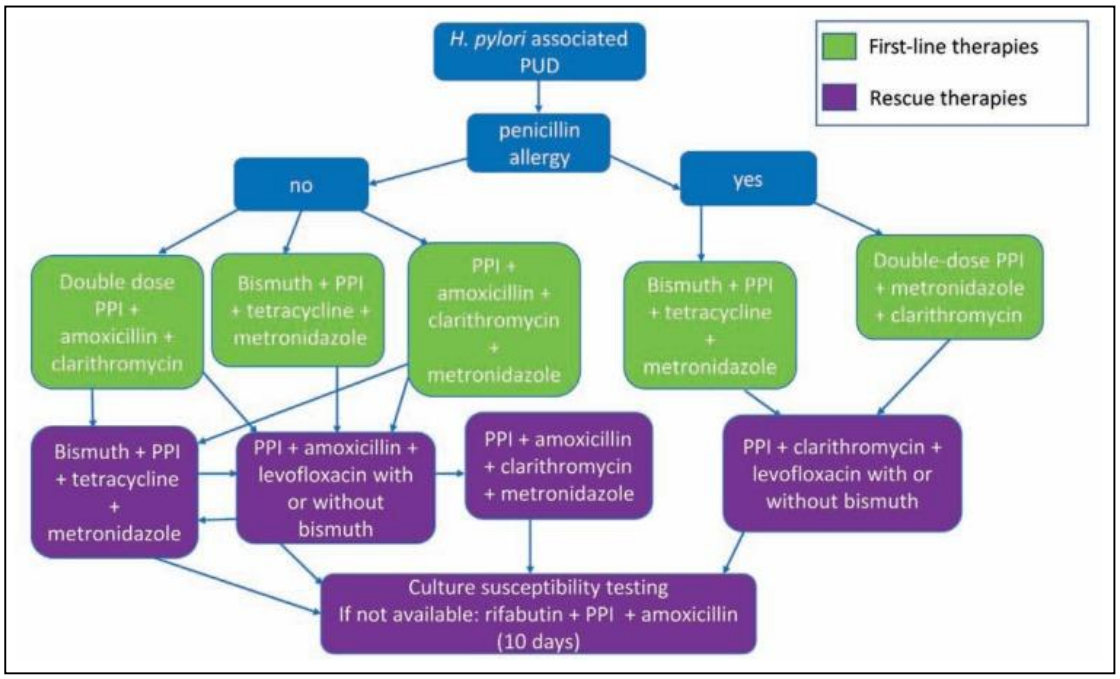

Figure 2. Treatment of Peptic ulcer caused by H. pylori

Bleeding peptic ulcers account for 40-60% of all causes of acute upper gastrointestinal bleeding. Timely endoscopic treatment and acid suppressive therapy are key for successful outcomes. Although surgery is the cornerstone for management of patients with uncontrolled or massive recurrent bleeding, radiological intervention has also gained importance in

recent years. Patients presenting with upper gastrointestinal bleeding should be assessed promptly and resuscitation should begin with crystalloid solutions (20).

Transfusion policy should be restrictive and aimed to maintain haemoglobin concentrations over 70 g/L, as this approach has been associated with reduced mortality (21).

Complications of peptic ulcer

Hemorrhage is the most frequent PUD complication and its incidence is increasing in comparison to perforation and stenosis. Peptic ulcers caused by *Helicobacter pylori* or nonsteroidal anti-inflammatory drugs (NSAIDs) can be very serious if they cause hemorrhage or perforate the stomach or duodenum. Up to 15% of people with ulcers experience some degree of bleeding, which can be life-threatening. Ulcers caused by NSAIDs are more likely to bleed than those caused by *H. pylori*. Populations at greatest risk are the elderly and those with other serious conditions, such as heart problems (22).

Perforation, that is the creation of a hole in the gastrointestinal wall, can cause the release of intestinal or stomach contents into the abdominal cavity. This can lead to acute peritonitis which causes intense pain in the abdominal area. Swelling and scarring caused by the presence of stomach ulcers can make the duodenum narrower, which may lead to gastric outlet obstruction. When this occurs, the person may experience severe vomiting and is likely to vomit blood too. Sometimes, complications can be triggered due to the spread of the ulcer to nearby organs. There have been cases where the ulcer has spread to the liver and pancreas (23).

When perforation is diagnosed promptly and treated expediently, outcomes are excellent – mortality rates range from 6 to 14%, and poor

outcomes have been associated with increasing age, major illness, and delay in diagnosis and management – advanced age (170) is associated with a higher mortality (approx. 41%) (24).

Conclusion

Peptic ulcer disease is relatively common health issue with heavy burden on the health authorities. It has serious complication and high morbidity and, if untreated, even significant mortality. The studies on the status of the disease in Iraq poor and need to be encouraged and continued.

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