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Current Concepts in Diagnosis and Management of Peptic Ulcer

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ABSTRACT

Peptic ulcer disease had a tremendous effect on morbidity and mortality until the last decades of the 20th century, when epidemiological trends started to point to an impressive fall in its incidence. Two important developments are associated with the decrease in rates of peptic ulcer disease: the discovery of effective and potent acid suppressants and of *Helicobacter pylori*. With the discovery of *H. pylori* infection, the causes, pathogenesis, and treatment of peptic ulcer disease have been rewritten. The inhibition of gastric acid secretion is a key therapeutic target for the ulcer diseases (viz., peptic, duodenal ulcers or that through H. pylori infection), gastro esophageal reflux disease (GERD), Zollinger–Ellison syndrome (Z-E), and gastritis. Currently this is achieved by blocking the acid secretary effect of histamine (HA) through the use of H2-receptor antagonists or the irreversible H+/K+-ATPase inhibitors, popularly referred to as proton pump inhibitors (PPIs). The incidence of ulcer diseases shows global variation and their treatment should be designed to alleviate the symptoms.

Key words: Peptic ulcer, *Helicobacter pylori*, Zollinger–Ellison syndrome

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INTRODUCTION

Peptic ulcer disease embraces both gastric and duodenal ulcers and has been a major threat to the world's population over the past two centuries, with a high morbidity and substantial mortality. Epidemiological data for this disease and its complications have shown striking geographical variations in incidence and prevalence. Development of ulcer disease and death from it has been associated with the birth of urbanization and was interpreted as a birth-cohort event with the peak of disease in those born during the late 19th century.[1, 2] The fall of the acid dogma in peptic ulcer disease, which had found its undisputed acceptance during and after the introduction of histamine H2-receptor antagonists, led to the present therapeutic principle. Maintenance acid suppressive therapy for duodenal ulcer, which followed decades of dominance of surgical interventions (subtotal gastric resections, several forms of vagotomy), was replaced with a short-term antibiotic regimen targeting eradication of *H pylori* infection .[3, 4] The management of ulcer disease and its complications remains a clinical challenge. Additionally, non-steroidal anti-inflammatory drugs (NSAIDs) and low-dose aspirin are an increasingly important cause of ulcers and their complications even in *H pylori*-negative patients.[5, 6] Other rare causes of ulcer disease in the absence of *H pylori*, NSAIDs, and aspirin also exist. The inhibition of gastric acid secretion is a key therapeutic target for the ulcer diseases (viz., peptic, duodenal ulcers or that through H. pylori infection), gastro esophageal reflux disease (GERD), Zollinger–Ellison syndrome (Z-E), and gastritis. Currently this is achieved by blocking the acid secretary effect of histamine (HA) through the use of H2-receptor antagonists or the irreversible H+/K+-ATPase inhibitors, popularly referred to as proton pump inhibitors (PPIs). The incidence of ulcer diseases shows global variation and their treatment should be designed to alleviate the symptoms, while keeping the risk of adverse effects to minimum. In western countries duodenal ulcers are more common, where as in eastern countries gastric ulcers predominate. These differences are attributed to factors like diet and genetic make up.[7] The discovery of the gastric acid was the first step to understand the role of the stomach in digestion and the diseases associated with hyper secretion of acid.[8, 9]

Mechanism of Gastric Acid Secretion: [10, 11]

Stomach is a primary site of digestion. Presence of food stimulates release of acids and enzymes in stomach. The chemo- and mechano sensitive receptors present in stomach are triggered by presence of food to produce specific responses. The acid secreting parietal cell is the principal cell in gastric glands. The physiological regulation of acid secretion by the parietal cells is thus

an important factor behind the rationale of use of various agents to reduce gastric acidity. Three major pathways activating parietal acid secretion include: neuronal stimulation via the vagus nerve, paracrine stimulation by local release of histamine from enterochromaffin-like (ECL) cells, and endocrine stimulation via gastrin released from antral G cells. In neuronal pathway, acetylcholine (Ach) released by vagal nerve directly stimulates gastric acid secretion through muscarinic M3 receptors located on the basolateral membrane of parietal cells. The CNS is considered to be the chief contributor for initiating gastric acid secretion in response to the anticipation of food. Ach indirectly stimulates release of histamine from enterochromaffin-like (ECL) cells in the fundus and gastrin from the G cells in the gastric antrum. ECL cells, the sole source of gastric histamine involved in acid secretion, are present in close proximity to parietal cells. Histamine released from ECL cells activates parietal cells in paracrine fashion by binding to H2 receptors. Gastrin is primarily present in antral G cells. Release of gastrin is under regulation of central neural activation, local distension, and chemical composition of gastric content. Gastrin stimulates parietal cells by binding with gastrin receptors. Gastrin also exerts its action in an indirect manner by causing the release of histamine from ECL cells. Binding to respective G-protein coupled receptors by Ach, gastrin, and histamine results in activation of second-messenger systems. Vagal stimulation and the action of gastrin (from duodenal and antral G cells) stimulate release of histamine from paracrine-ECL cells or mast cells. Increased levels of both intracellular Ca2+ by gastrin/Ach and cyclic AMP by histamine finally cause acid secretion. The final step in acid secretion is mediated by H+/K+-ATPase, also called as gastric proton pump. Activation of either the cAMP or $Ca2^{+}$-dependent pathway or both causes stimulation of H+/K+-ATPase on parietal cells. H+,K+-ATPase, like Na+,K+ ATPase, with which it has 60%amino acid homology ,is a member of P-type ion-transporting ATPase ,which also include the Ca++-ATPase. Inhibition of the H+,K+ATPase totally blocks gastric acid secretion .Drugs such as omeprazole substituted benzimidazole, are accumulated in acid spaces and are activated at low pH. Then they bind irreversibly to sulfhydryl groups of the H+, K+ ATPase, inactivating it. These pump inhibitors are the most potent of the different types of acid secretory inhibitors and are effective agents in the treatment of peptic ulcer, even those caused by gastrinoma (Zollinger –Ellison syndrome).

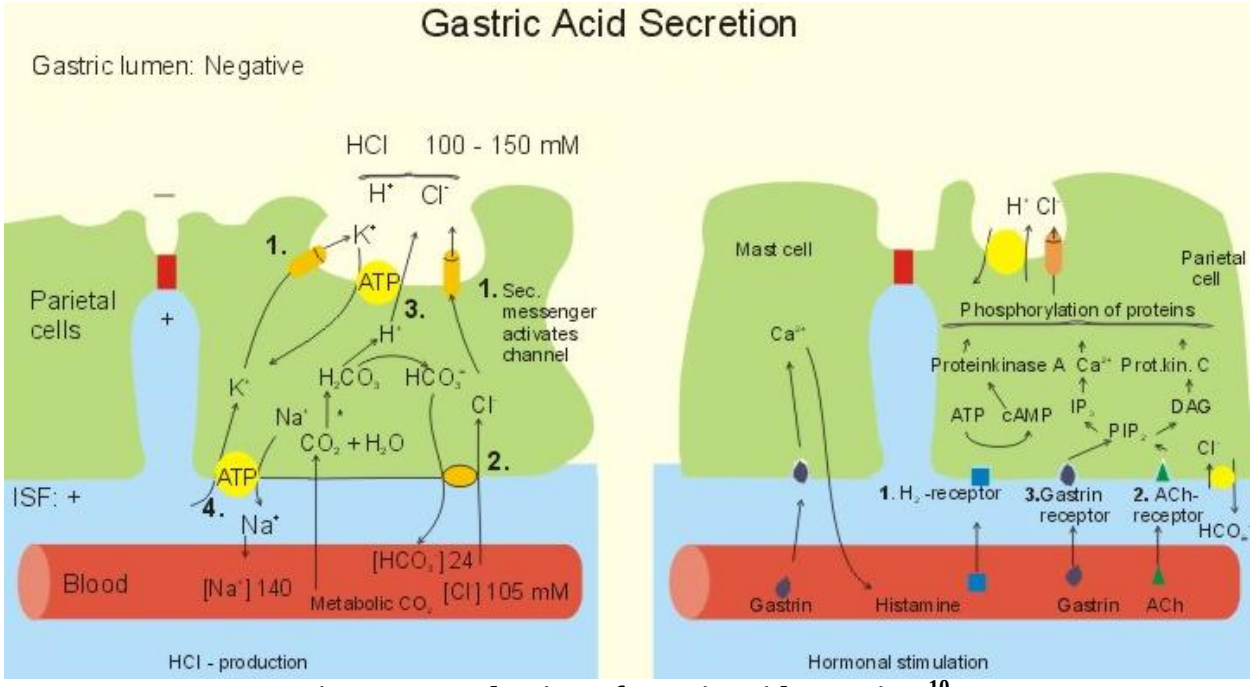

Figure 1: Mechanism of gastric acid secretion.[10]

Pathogenesis of peptic ulcer:

The complex and multifactorial pathogenesis of peptic ulcer has been studied over several decades, and results from an imbalance of aggressive gastric luminal factors acid and pepsin and defensive mucosal barrier function. Several environmental and host factors contribute to ulcer formation by increasing gastric acid secretion or weakening the mucosal barrier.[12,13,14] Among environmental factors, smoking, excessive alcohol use, and drug use are most often quoted but none of them, apart from NSAID use, were identified as an individual ulcerogenic agent. Emotional stress and psychosocial factors are frequently identified as important contributors to ulcer pathogenesis. [15-17] although stress cannot be neglected as a contributing factor, convincing evidence for it being the sole cause of duodenal ulcer is scarce. The definition of stress ulcer should be restricted to bleeding ulcers in the context of severe organic illness, such as cerebral trauma, burning, and sepsis with multi organ failure in intensive care units.[18,19]

CAUSES OF PEPTIC ULCERS:

***Helicobacter pylori* (*H. pylori*) infection**

Helicobacter pylori were discovered in 1984.[20] and are considered to be the most frequent bacterial infection worldwide. The pathology that is associated with *H. pylori* infection may vary from no symptoms to ulcer disease, gastric cancer and MALT-lymphoma .[21]The bacterium *Helicobacter pylori* are a ubiquitous Gram-negative bacterium that infects the stomach of more than half of the world's population. *H. pylori* interaction with genetic and environmental factors

and diet jointly influence the risk of developing human disorders. The combination of host genetic factors, bacterial virulence factors, and environmental and lifestyle factors, determine the severity of gastric damage and the clinical outcome of *H. pylori* infection. Persistent inflammatory gastritis is a typical morphological feature of all *H. pylori* infections.[22, 23] Epidemiologic studies demonstrate a major etiological role for *H. pylori* in several gastroduodenal diseases, including gastritis, gastric ulcer, duodenal ulcer, gastroesophageal reflux disease (GERD) and gastric mucosa-associated lymphoma [24]. Colonization of the gastric mucosa by *H. pylori* results in the development of chronic gastritis in virtually all infected individuals, but only in a subset of patients does chronic gastritis progress to complications such as ulcer diseases and/or extra-gastric disorders. The clinical outcome of disease is dependent on many variables, including *H. pylori* genotype, innate host physiology, genetic predisposition, and environmental factors. The acquisition of the bacterium usually occurs during childhood, with up to 90% of children becoming infected by 10 years of age. However, clinical disease appears many years later resulting in severe degenerative conditions only in advanced age in a small percentage of infected subjects. Chronic infection of the stomach by *H. pylori* may be associated with either decreased or increased acid secretion, depending on the severity and distribution of gastritis. The complexity of the acid-producing machinery in the stomach may contribute to the individual variability of the response in patients with *H. pylori* infection. The mechanism by which *H. pylori* inhibits acid secretion is multifactorial and includes: (1) direct inhibition of parietal cell functions by a bacterial product (e.g., vacuolating cytotoxin, lipopolysaccharide, or acid-inhibitory factor)[25] , and (2) indirect inhibition of parietal cell function as a result of changes in cytokines as well as hormonal, paracrine, and neural regulatory mechanisms.[26]Gastric ulcer patients may exhibit normal, increased, or decreased basal and stimulated acid production. This suggests that altered gastric mucosal defense may be the primary culprit and may explain the propensity for non steroidal anti-inflammatory drug (NSAID)-induced ulcers to occur in the stomach. The effects of *H. pylori* infection on gastric acid secretion is exerted through multiple mechanisms including release of inhibitory cytokines, production of fatty acids inhibiting H+/K+–ATPase, impairment of the feedback between gastrin and acid secretion, induction of damage to gastric-body mucosa, and ammonia production[27.] Gastric ulcers have been classified according to their location and concomitant association with duodenal ulcers. Type I ulcers occur in the gastric body and are generally characterized by low acid secretion, particularly at night. Type II ulcers occur in the antrum and are characterized by low, normal, or high acid secretion.

Type III ulcers occur within 3 cm of the pylorus, are accompanied by duodenal ulcer, and are characterized by high acid output.

Type IV ulcers occur in the gastric cardia and are characterized by low acid secretion[28]. The pattern of colonization and distribution of gastritis is strongly correlated with the clinical manifestation. Antral predominant gastritis shows a strong correlation with the development of duodenal ulcers, whereas patients with corpus predominant gastritis are known to have a higher risk for developing gastric ulcers, gastric atrophy, intestinal metaplasia, and finally gastric adenocarcinoma[29] .In *H. pylori*-infected patients, the lifetime risk for developing peptic ulcer disease ranges from 3 to 25%. Eradication of *H. pylori* dramatically reduces the relapse of *H. pylori*-related peptic ulcers and leads to long-term remission of peptic ulcer disease[30]. *H. pylori* eradication heals active gastritis and dramatically reduces the incidence and/or recurrence of peptic ulcer. The aims of *H. pylori* eradication therapy are either to reverse the inflamed mucosa to a normal state or to prevent further progression of advanced chronic changes (atrophic gastritis, intestinal metaplasia). *H. pylori* eradication should be attempted before the onset of pre-neoplastic lesions.[31, 32]

Non steroidal anti inflammatory drugs (NSAIDS)

The use of non-steroidal anti-inflammatory drugs(NSAIDs)is associated with the occurrence of de novo adverse digestive events, including gastric mucosal erosions, ulcers, bleeding and perforation, as well as an increased risk of severe complications from pre-existing chronic ulcers.[33] The NSAIDs were shown to damage the stomach mainly by suppression of gastric prostaglandin synthesis.[34]The discovery of two isoforms of Cyclo-Oxygenase (COX), COX-1 and COX-2, sparked an enormous drive by the pharmaceutical industry to develop COX-2-selective NSAIDs as gastric-sparing anti-inflammatory analgesics. Now, good evidence exists that selective inhibition of COX-2 reduces but does not eliminate risk of gastroduodenal ulcers and their complications.[35] Work in animals has shown that neutrophil adherence to gastric microcirculation plays a crucial part in initiation of NSAID injury. Neutrophil adherence damages the mucosa by liberating oxygen free radicals, releasing proteases, and obstructing capillary blood flow. Inhibition of neutrophil adherence alleviates NSAID induced damage in animal models. Attention has focused on the role of nitric oxide (NO) and hydrogen sulphide (H2S), in maintenance of gastric mucosal integrity. NO and H2S increase mucosal blood flow, stimulate mucus secretion, and inhibit neutrophil adherence.[36] NO-releasing and H2S-releasing derivatives of NSAIDs induce much less gastric damage than do their parent drugs.[37] Unlike animal ulcer models, however, NSAID gastropathy in man is characterized by an absence of

inflammatory cells unless *H pylori* infection is present. Whether neutrophils initiate NSAID injury in man is unknown. Acid suppression has been the mainstay of management of NSAID-associated ulcer disease. Gastric acid probably exacerbates NSAID injury by converting superficial mucosal lesions to produce deeper injury, [38] interfering with platelet aggregation, [39] and impairing ulcer healing.[40] Patients taking NSAIDs have about a four-fold increase in risk of ulcer complications such as bleeding compared with non-users. Several risk factors have been identified in these patients, such as history of ulcer or ulcer complications, old age, comorbidities, use of high-dose NSAIDs, concomitant use of corticosteroids, aspirin, or anticoagulants, and *H pylori* infection.[41-44] A history of ulcer complications is the most important predictor of future ulcer complications associated with NSAID use.[42] How past history increases risk is unclear. Indirect evidence exists that ulcers tend to recur at previous sites, [45, 46] suggesting that local factors determining mucosal defense might play an important part in ulcerogenesis. Contrary to general belief, use of corticosteroids is not ulcerogenic.[47] However, both corticosteroids and anticoagulants substantially increase risk of ulcer bleeding when used concomitantly with NSAIDS.[42,47,48] Anticoagulants probably provoke bleeding from ulcers induced by NSAIDs in addition to causing generalized mucosal bleeding.

Lifestyle related factors

Cigarette smoking not only causes ulcer formation, but also increases the risk of ulcer complications such as ulcer bleeding, stomach obstruction and perforation. Cigarette smoking is also a leading cause of ulcer medication treatment failure. Smoking reduces the LES pressure and then promotes the reflux of gastric content into the esophagus. Moreover it may diminish salivary base secretion and thus impair acid esophageal clearance.[49] several studies have shown that smoking delays ulcer healing and promotes ulcer relapse[50] .Alcoholic beverages, such as beer and wine, have been observed to potently stimulate gastric acid secretion in rats, dogs, and humans. There are several reports examining the mechanisms of gastric acid stimulation resulting from such beverages. Since both beer and wine stimulate gastrin release , an increased level of gastrin is postulated to be involved in the mechanism of stimulated gastric acid secretion.[51] Fatty foods delay gastric emptying, which could also predispose to the disease.[52] Certain foods such as chocolate, peppermints, onions and garlic, and both decaffeinated and regular coffee should be avoided, as should drugs such as theophylline, α-adrenergic blockers, β-antagonists, anticholinergic, dopamine, nitrates, meperidine, diazepam, morphine, and calcium – channel blockers[53].

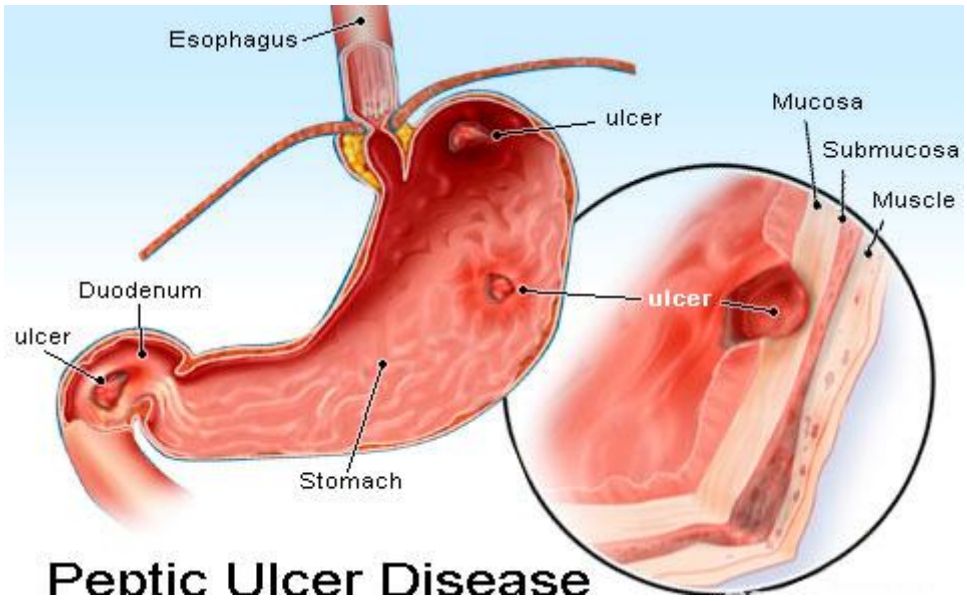

Figure 2: Different forms of peptic ulcer disease

Duodenal ulcer:

Duodenal ulcers (DU) and benign gastric ulcers are grouped together as peptic ulcers. These are defects in the gastrointestinal mucosa that extend through the sub mucosa into the muscle layer. DU presents with a dull ache in the epigastrium which is relieved by food or antacids. Often this pain is accompanied by a constellation of symptoms known as 'dyspepsia'. Dyspepsia involves symptoms of nausea, vomiting, anorexia, fullness and bloating in addition to pain and abdominal discomfort. The cause of this pain is not clear. It is not directly related to intra duodenal acidity, but is rapidly relieved by antacids[54]. Duodenal ulcer has been associated with a number of medical conditions, including chronic renal failure, hyperparathyroidism, liver cirrhosis, cardiovascular disease and chronic respiratory disease. At the beginning of this century it was commonly believed that the presumed association between stress and physical illness was mediated by factors in the pre morbid personality. It was believed that personality traits determined the nature and strength of emotional responses, which then caused the physical disease. Thus, early research groups looked at the personality characteristics of patients suffering from a duodenal ulcer[55].

Gastric ulcer (gu):

Perforation remains a frequent and a lethal surgical complication despite the availability of effective medical treatment for peptic ulcer. Gastric perforation though less common, is associated with greater morbidity and mortality compared to duodenal ulcer. Information on gastric perforations is limited and the recommendations for its management are not clear. The clinical profile, etiopathogenesis and the surgical options for gastric perforation are different

from duodenal perforation.[56] Gastric ulcers are more common in Asia than DU.[57] Gastric ulcers have been classified into Type -I, occurring along the lesser curvature, Type -II, with concurrent or historical DU, Type –III, prepyloric and Type –IV, cardiac.[58] Defective mucosal defense is implicated as a pathogenic factor. Concomitant stress and NSAID therapy are more often present .Type- I and Type –IV are associated with increased risk of malignancies . Still the majority of gastric ulcers are associated with *H. pylori* infection, although result of eradication therapy is less successful. [59]

Zollinger–ellison (z-e) syndrome:

Since Zollinger and ellison[60] first described the association of severe gastric acid hyper secretion and peptic ulcer disease with a non β-cell islet tumor, treatment for the entity of Zollinger-Ellison syndrome (ZES) has continued to evolve. Surgical therapy initially consisted of total gastrectomy to remove the target organ from high gastrin levels. In this disease, a non β- cell tumor of the pancreatic islets may produce gastrin in a quantity sufficient to stimulate the secretion of gastric acid to life-threatening levels. This can lead to severe gastroduodenal ulcerations and other consequences of the uncontrolled hyerchlorhydria. The therapy is aimed at reducing gastric acid secretion. During the last two decades highly potent pharmacologic agents have been developed that have eliminated the need for acid-reduction procedures. Symptoms of acid hyper secretion can now be controlled in virtually all patients with ZES with the use of H^+-K^+- adenosine triphosphatase pump inhibitors (omeprazole, lansoprazole) or high-dose histamine H2-receptor antagonists. [61]

Stress–related ulcers:

Stress-related mucosal damage—an acute erosive gastritis—occurs in many critically ill patients. Several factors have a role in the pathogenesis of SRMD, including gastric acid secretion, mucosal ischemia (as a result of splanchnic hypo perfusion), and reflux of upper intestinal contents into the stomach. [62, 63] Gastric hypo perfusion leads to an imbalance between oxygen supply and demand that may induce mucosal damage. Moreover, reperfusion after prolonged hypo perfusion may itself result in non occlusive mesenteric ischemia and mucosal damage. As a result of ischemia, there is also a reduced ability to neutralize hydrogen ions, which can contribute to cell death and ulceration. In stress ulceration, homeostasis of the gastric mucosa is disrupted as are the cellular defense mechanisms that normally protect against a highly acidic gastric milieu. [64]

Dyspepsia:

Dyspepsia, defined as pain or discomfort centered in the upper part of the abdomen is a very common complaint, even among healthy individuals in the background population[65]. Potential underlying causes include peptic ulcer disease, gastro-esophageal reflux disease, functional dyspepsia and gastric cancer. Drugs are also frequently implicated as a possible cause in new onset dyspeptic symptoms and few drugs are free of the suspicion of causing abdominal complaints. Gastrointestinal (GI) symptoms such as nausea, anorexia, abdominal pain and dyspepsia make up between one-tenth and one-third of reported adverse reactions but they are all so common, both in the background population and among patients, that they are all too easily attributed to the illness rather than to the drug. Dyspepsia is often defined as any symptom thought by the physician to originate from the GI tract, and may thus embrace a variety of symptoms such as nausea, early satiety, vomiting, epigastric pain, heartburn and even bloating. Others reserve the term dyspepsia for epigastric pain or discomfort. Many reports of dyspepsia as an adverse effect of drug use do not define the term. At least in part as a consequence of this terminological confusion, epidemiological studies have produced differing estimates of the incidence and prevalence of dyspepsia, and of its association with potential risk factors, such as drug use. [66]

DIAGNOSIS OF PEPTIC ULCER

Gastro intestinal endoscopy

The extent of mucosal injury can be assessed at endoscopy. Endoscopy also evaluates any complication of the disease, such as stricture or Barrett's esophagus, and is recommended if patients have alarm features with reflux symptoms, such as weight loss or progressive dysphagia. Ultra thin endoscopes have been developed, which can be passed either orally or transnasally. These instruments are accurate and well tolerated by the patients without the need for sedation[67]. Magnification endoscopy has been evaluated to assess whether patients with non erosive reflux disease have subtle changes in the esophageal mucosa that could help in diagnosis. Small changes such as white or red mucosa or edema, however is not reliably identified [68].One of the major advances in endoscopy in recent years are the development of video telemetry capsules that is small enough to be swallowed [69]. There were initial difficulties with this approach but accuracy seems to be improving [70.]

Invasive (endoscopic) tests for Helicobacter pylori

Patients with ulcers should be tested for Helicobacter pylori. Biopsy-based tests are most convenient if the ulcer is diagnosed at upper gastrointestinal endoscopy. Biopsy-based tests are

unreliable if the patient has had proton pump inhibitors within two weeks or antibiotics or bismuth within four weeks and testing should be deferred.

Biopsy urease test

The rapid urease test is an indirect test for Helicobacter pylori. It is based on the ability of the bacteria to break down urea to ammonia, resulting in a rise in pH and a colour change in a pH indicator. It is the most widely used endoscopic biopsy-based test. Some tests become positive very quickly, allowing treatment before the patient leaves the Endoscopy Department. Negative tests must be read again at 24 hours to confirm there is no low-level infection. Biopsy urease tests have a specificity of about 95% and a sensitivity of >90%, but tests may be false-negative if there is bleeding in the upper gastrointestinal tract.[71]

COMPLICATIONS OF PEPTIC ULCER:

Patients with ulcers generally function quite comfortably. Some ulcers probably heal even without medications. Therefore, the major problems resulting from ulcers are related to ulcer complications. Complications include ulcer bleeding, ulcer perforation, and gastric obstruction.

Gastrointestinal hemorrhage

Peptic ulceration is the commonest cause of acute haemorrhage of the upper gastrointestinal tract, which may present with haematemesis, melaena or both. It is particularly common in NSAID users, in whom it is sometimes preceded by no or minimal dyspeptic symptoms. Management involves adequate resuscitation followed by urgent endoscopy. This makes the diagnosis and also allows interventions to halt bleeding or reduce rebleeding. Rebleeding still reoccurs in 10-20 % of endoscopically treated patients. Whether repeat endoscopy or surgery is appropriate at this stage is unclear although salvage surgery after a second rebleeding episode has a high mortality .[58] Many endoscopic interventions are used, including epinephrine injection, coagulation with a heater probe, and clipping; a combination of methods is most effective. Endoscopic therapy reduces rebleeding and the need for surgery. High-dose proton pump inhibitors (i.v.) after endoscopy are used in addition to endoscopic therapy.

Perforation

Perforation occurs more commonly in chronic duodenal ulcers than in chronic gastric ulcers. Perforation has decreased in men since 1950 s, but increase in women and elderly.[72] Smoking and NSAIDS appears to be co-morbid factors. The relationship between perforation and period of stress social conflict is well recognized. This may account for the still high frequency of perforation in developing countries, where delays in presentation & high mortality are

common.[73] Ulcer perforation leads to the leakage of gastric contents into the abdominal (peritoneal) cavity, resulting in acute peritonitis (infection of the abdominal cavity). These patients report a sudden onset of extreme abdominal pain, which is worsened by any type of motion. Abdominal muscles become rigid and board-like. Urgent surgery is usually required. Diagnosis is usually not difficult with board like rigidity and free intra peritoneal air. CT scan is particularly sensitive.[74] Non-operative management may be undertaken successfully for very ill patients, although if gastrografin series shows continued leak surgery should not be delayed. The standard procedures are an omental patch for DU and excisional/resectional biopsy and closure for GU.[58]

Obstruction

Patients with gastric obstruction often report increasing abdominal pain, vomiting of undigested or partially digested food, diminished appetite, and weight loss. The obstruction usually occurs at or near the pyloric canal. The pyloric canal is a naturally narrow part of the stomach as it joins the upper part of the small intestine called the duodenum. Upper endoscopy is useful in establishing the diagnosis and excluding gastric cancer as the cause of the obstruction. In some patients, gastric obstruction can be relieved with tube suction of the stomach contents for 72 hours, along with intravenous anti-ulcer medications, such cimetidine and ranitidine. Patients with persistent obstruction require surgery. *H.pylori* eradication therapy is indicated early on in positive patients as resolution has been reported.[75] Cases which do not resolve on nasogastric suction and intravenous therapy have usually been treated with various types of vagotomy and drainage procedure .[76]

CONCLUSION:

Although the origin of parietal cells has yet to be elucidated, it appears that parietal cells function to secrete highly concentrated gastric acid following ingestion of food or alcoholic beverages to permit digestion of food and/or prevention of pathogenic disease. It is well known that excessive, or even normal, acid secretion is problematic for maintenance of the normal integrity of the upper gastrointestinal tract, resulting in acid-related peptic disease. Currently available H2R antagonists and acid pump inhibitors represent powerful and reliable pharmacotherapy for the treatment of acid-related peptic disease with few side effects. Peptic ulcers caused by H. pylori can be treated by combination of antibiotics and anti-secretory medications. However, complex drug regimen and associated side effects may limit usefulness. Launch of omeprazole in 1988 introduced a conceptually new approach of inhibition of proton pump in the management of

acid-related disorders. PPIs proved to be superior to any of the previously used drugs including H2-antagonists.

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