

Peptic Ulcer Disease – the impact of Helicobacter pylori on management in the developing world

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1.0 Introduction

Peptic Ulcer Disease (PUD), non-malignant duodenal and gastric ulcers, is an important disease entity, responsible for considerable morbidity and mortality. Our understanding of the etiology and pathogenesis and our approach to treatment have undergone remarkable changes in the last 30 years. Up to the early 1980s, PUD was seen as a disease of excessive gastric acid production and its treatment primarily surgical. The

surgical preoccupations of that time were to develop criteria for low morbidity surgical procedures with adequate cure rates. The recognition that PUD was associated with *Helicobacter pylori* infection caused a sea change in the approach to this disease. Concurrently, very powerful drugs to lower gastric acid secretion and heal ulcers have been developed. A number of very good reviews document the consequences of these developments from a developed world perspective. (1-6) This Review will summarize these and focus on the impact they have had on the diagnosis and treatment of PUD in the developing world.

2.0 History

Many of the great names in the history of Western surgery, from Bilroth to Heinecke and von Mikulicz to Dragstedt are associated with the treatment of PUD. (7) The development of subtotal gastrectomy, which had a high cure rate but, unfortunately, many deleterious side effects, was followed by a search for less radical procedures: vagotomy and antrectomy, vagotomy and pyloroplasty and highly selective vagotomy.(8) These procedures result in progressively higher relapse rates, but are associated with a decreasing disturbance in gastric physiology and side effects. The development of Histamine-2 receptor antagonists (H2RAs) during the 70s and then proton pump inhibitors (PPIs) in the late 80s raised further questions as to the role of surgery for this disease.

At the same time the epidemiology of PUD disease was changing dramatically in Europe and North America during the 20th century. Deaths from PUD had risen discordantly in both sexes in the latter part of the 19th century. Duodenal ulcer became extremely common, affecting up to 10% of males. Then in the 1950s incidence and mortality rates began to fall. In a landmark paper in 1962 (reproduced with commentaries in 2001) Susser and Stein (9) interpreted this data as showing a birth-cohort phenomenon. This is an explanation of subsequent morbidity on the basis of a common environmental factor, related to era of birth. This was the period when excessive gastric acid production, mediated through various genetic and environmental factors, was deemed to be the main cause of PUD.

It was only 20 years later that the discovery by Marshall and Warren (10) of an “unidentified bacilli in the stomach” of PUD patients ushered in the new era. Since that time this bacterium, *Helicobacter pylori*, has not only been established as the major cause of PUD, but also, as humanity’s most ubiquitous chronic bacterial pathogen, it evidences extremely complex ethno-geographic variations in epidemiology and pathogenicity. In the developed world, mortality from PUD has generally continued to decline (data from Asia show a lag, perhaps reflecting delayed development (11)) in association with falling infection rates as well as better diagnostic and therapeutic efforts. The same cannot be said for the rest of the globe.

3.0 *Helicobacter pylori*

The last 20 years of study have uncovered the complicated relationship between humans and this organism, in terms of transmission, physiologic consequences of infection and subsequent disease states. (12) A particularly thorough review of the pathophysiology of *H. pylori* infection has recently been published. (13) While the majority of infected persons remain asymptomatic, 10-15% will develop PUD (3-10x increased risk), 1% will

develop non-cardia gastric cancer (3-5x increased risk), and an even fewer (less than 1%) the rare mucosal associated lymphoid tissue (MALT) lymphoma.(14) This data derives from studies in the developed world. There are also unresolved associations with non-ulcer dyspepsia, GERD and a host of non gastrointestinal diseases.(15)

3.1 Epidemiology

Prevalence of H.pylori infection is strongly correlated with socio-economic conditions, associated with low levels of education and income, household crowding, etc. (16) Familial clustering of infection occurs. Transmission occurs via the oral route, by saliva, vomitus, fecal contamination or tainted water supplies, usually early in childhood.

Unless eradicated by antibiotics, infection usually persists life-long.

In the developing world 80% of the population shows evidence of infection, compared to only 35-40% in the industrialized world. (17) The prevalence of infection is even smaller in younger cohorts in the developed world. In Japanese children it is now less than 5%. In developed countries, seropositivity is low in childhood and rises slowly with age at approximately 0.5%/yr, while in the developing world the infection is acquired in early childhood with prevalence of 70% by the age of 5.

Interestingly, in the developed world, as the prevalence of H. pylori has fallen, so too has the percentage of duodenal ulcers associated with infection. In Africa, however infection is present in the majority of the population and 90% of duodenal ulcers are H. pylori positive. (18) There is a marked geographical distribution of DU in sub-Saharan Africa with increased prevalence in the Nile/Congo watersheds, coastal West Africa and urban areas. Gastric ulcer is also much less common in Africa than in the developed world and there is also a relatively low risk of gastric cancer which accounts for about 2% of all GI cancers.

3.11 The African Enigma

Some authorities have claimed that the high prevalence of H. pylori infection in countries with a low prevalence of gastric cancer represents “the African enigma”. (19)

They have used this apparent disassociation to question the H. pylori/ulcer paradigm. (20) However a number of studies have shown that, despite certain geographic differences, PUD, in sub-Saharan Africa, is almost always associated with H. pylori infection. (21-23) A recent literature review of endoscopic studies concludes that there is no “African enigma”. (24) In fact any differences in the clinical consequences of H. pylori infection may represent differences in immune and pathogenic processes.

3.2 Bacteriology/Pathogenesis

H. pylori is a microaerophilic, gram negative, spiral bacterium with flagellae and a potent producer of urease. It is through the production of bicarbonate, by metabolizing the urea in gastric fluid, that the organism is able to survive in the low pH environment of the stomach. There it colonizes the gastric epithelial cells passing into the extra-cellular, mucous layer with its more pH-neutral conditions. (13) There infection induces a host response which results in mucosal damage and a chronic active gastritis. This occurs initially in the non-acid secreting areas of the stomach in the antrum. (25) (**see pictures 1- 4**)

Depending on various environmental, bacterial and host characteristics, two major forms of colonization occur which determine the possible resulting disease states. In persons with antral predominant gastritis, acid production is maintained or increased and duodenal ulcers are the major pathologic consequence. In persons with pangastritis, the

inflammation of corpus, acid secreting, parietal cells consequent to colonization results in reduced acid production through an atrophic gastritis. This may then proceed to intestinal metaplasia and malignancy. Gastric ulcer and cancer are the two main disease states resulting from pangastritis. The different pathologic consequences of differential sites of colonization explain the apparent paradox of PUD and gastric cancer, diseases with very different pathologies, both being associated with *H. pylori* infection.

The ethno- geographic differences in PUD between the West and Asia, Japan and China, are well known. The first gastric ulcer was recognized 2000 years ago in the Western Han Dynasty. (11) Gastric cancer which is quite common has an inverse relationship with duodenal ulcer rates. Cyclical trends exist. Sex-ratios show wide divergence. Duodenal/Gastric ulcer ratios vary from 32:1 in India to 19:1 in Africa (1975 data) to 1:2 in Japan.

Bacterial adherence to the gastric epithelial cells is mediated through a number of adherence factors some of which bind to Lewis B blood group antigens. Two main bacterial virulence factors have been identified: a vacuolating toxin (*vacA*) and a cytotoxin (*cagA*).

The *cagA* toxin is associated with stimulation of interleukin IL-8 expression and increased inflammation.(26) The inflammatory response is mediated through neutrophils, followed by T and B lymphocytes, plasma cells and macrophages. There is a strong infiltration of CD4+ and activation of helper cells. Infection induces a vigorous humoral antibody response. Despite these immunologic responses spontaneous eradication of the infection is unusual. The role by which *H. pylori* evades host immune response is gradually becoming clear. (27) In fact the pathologic consequences depend on a combination of host and bacterial factors. (28) Genetic polymorphism in the host, favoring pro-inflammatory factors like interleukin IL-1, the most potent inhibitor of gastric acid secretion, increases the risk of gastric cancer.

An interesting and relevant expression of the impact of the host immune response relates to coincident infection with HIV. An initial study in 2001 by Fernando in an impoverished urban area with high (35%) HIV prevalence suggested discordance between HIV and *H. pylori* infection. (29) Subsequent studies have shown that HIV positive and negative patients seem to have an equal prevalence of *H. pylori* infection. (30-33) However, it appears that with decreasing CD4 counts the prevalence of *H. pylori* infection decreases. Helper cells appear to be involved. (26)

McColl gives a good review of gastric acid physiology and the complex effects of *H.pylori* infection. (34) In *H. pylori* positive patients with duodenal ulcer serum gastrin and the acid response to gastrin releasing peptide is increased as compared to uninfected patients. This may be mediated through damage to antral delta cells which normally secrete somatostatin, a potent inhibitor of gastrin release.(35) Gastrin is the main stimulus to acid production in the parietal cells. These features occur in patients with non-atrophic antrum predominant gastritis and are eliminated by eradication of the *H. pylori*. Conversely, in patients with atrophic pangastritis, acid secretion is reduced. This may be an effect of stimulation of interleukin 1-B, a potent acid inhibitor, in the body of the stomach or the consequence of antral atrophy with decreased gastrin release. (36)

It also appears that acid secretion may limit the colonization of the body by *H. pylori*. Evidence for this comes from the different consequences of proton pump inhibitor (PPI) treatment in *H. pylori* positive and negative patients. (37) *H. pylori* positive patients

treated with PPIs often show a redistribution of infection into the body of the stomach with the development of marked corpus gastritis. This suggests inhibition of colonization of the corpus by acid production. Furthermore PPIs have a more dramatic effect of raising intragastric pH in *H. pylori* positive as compared to negative patients. Reduction, in acid secretion by PPIs, facilitates *H. pylori* growth of the body, which then further lowers acid secretion. High acid secretion in *H. pylori* positive DU patients often results in gastric metaplasia of the duodenum itself with subsequent bacterial colonization and direct mucosal damage. (38;39) The high duodenal acid load is also felt to wash out bile salts which inhibit *H. pylori* growth. (40)

While duodenal ulcer pathogenesis is fairly well understood, the development of gastric ulcers is less clear. Gastric ulcer patients tend to have more pangastritis and the ulcers tend to develop at the junction between corpus and antral mucosa. The complex balance between protective and ulcerogenic phenomena, between bacterial and host responses, is impacted by environmental factors such as stress, smoking, alcohol, NSAIDs, etc. (41) The molecular basis of ulcer healing is also being understood. (42)

3.3 Diagnosis

A number of different methods for diagnosing *H. pylori* have been developed. (43) Active infection must be distinguished from mere serologic positivity. Invasive tests, such as histology, culture biopsy, which is one of the gold standards and rapid urease test require endoscopy. (13) Noninvasive tests, such as urea breath test, the other gold standard may be expensive. An inexpensive fecal stool antigen test may have applicability in the developing world. (44) Local costs and expertise play a role in which test should be used.

Endoscopy has surpassed upper GI series as the initial diagnostic procedure for presumed PUD. Its role in patients with dyspeptic symptoms, as compared to *H. pylori* testing and treatment alone is the subject of protocols. (45) Patients, older than 55, with recent onset or anyone with alarm symptoms, should be gastroscopied. (see Alarm symptoms) Haemoglobin and stools for OB should be checked.

3.4 Disease States

While our focus is on PUD (see 4.0), it is prudent to briefly review some clinical aspects of the relationship between *H. pylori* and various disease states.

3.41 Gastric Cancer (see pictures 5-6)

The relationship between non cardia gastric cancer and *H.pylori* infection is now clearly established and there is some evidence that eradicating *H. pylori* will lower the risk of gastric cancer. (46) There are however widely divergent prevalence and locations for gastric cancers in different societies over time. (47) In the West the 20th century has shown a marked drop in gastric body cancers, particularly amongst white males, with a resulting increased proportion of cardiac cancers. This can be correlated with falling *H. pylori* prevalence which predates the *H. pylori* era. In developed countries in Asia this decline has occurred more recently since 1970 and gastric cancer prevalence remains high. This is anticipated to drop. There is 2 fold increase risk of subsequent gastric cancer in patients who have had gastric resection for PUD. (48)

3.42 MALT Lymphoma (see picture 7)

Normally gastric mucosa does not contain lymphatic tissue and MALT (mucosal associated lymphatic tissue) is always associated with *H. pylori* infection. Because of the rarity of the former, the relationship between *H.pylori* infection and the subsequent

MALT lymphoma is unclear. However approximately 1% of H. pylori positive persons will develop MALT lymphomas in the developed world. Moreover 60-80% of lymphomas confined to the stomach will respond to eradication therapy alone; although some of these will recur. (13) The association of MALT lymphomas and HIV is recognized. (49) Furthermore these tumours may be more common in HIV infected children. (50) HAART and eradication therapy for H. pylori infection may be adequate therapy. (51)

3.43 Non-ulcer dyspepsia

The relationship between H. pylori and dyspepsia has been extensively investigated. (52) While definitions vary, dyspepsia usually denotes upper gastrointestinal discomfort meaning pain, fullness, bloating, early satiety and nausea. It is often associated with eating. Patients with predominant reflux symptoms should be excluded from this definition. Studies from the developed world show the prevalence of dyspepsia to be from 25-40%. There are a number of issues concerning the relationship of this symptom complex to organic disease. Moayeddi found that neither clinical impression nor computer models could distinguish functional from organic dyspepsia. (53) The consensus is that patients over 55 with new onset dyspepsia alone should undergo gastroscopy.

The remainder can undergo H. pylori testing with a “test and treat” approach. This may be more effective than treatment with PPIs alone. (54;55) The Maastricht consensus recommended non-invasive testing for H. pylori in all patients with dyspepsia under 45 and treating all positives with eradication therapy. (45) This was found to be more cost effective than endoscopy.(56) Some authorities recommend endoscopy as the first line of investigation. (57) A rigorous approach to gastrointestinal symptoms has been published. (58) Not surprisingly dyspeptic patients in the developing world have a high rate of organic disease. (59;60) H. pylori infection rates are high and the prevalence of gastric cancer in both of these studies was not low. There is no significant difference in response to eradication therapy between patients with PUD and non ulcer dyspepsia. (61)

3.44 GERD

The relationship between H. pylori and gastro-esophageal reflux disease is complex. There appears to be an inverse relationship between GERD prevalence and H. pylori infection. (62;63) Eradication of H. pylori in GERD patients is indicated before starting long term PPI therapy in order to prevent gastric atrophy. Possible positive effects of H. pylori infection have led some to question the value of universal eradication. (35;37)

4.0 Forms of Peptic Ulcer Disease

4.1 DU (see pictures 8-9)

Despite regional variation, duodenal ulcer DU remains the most common manifestation of peptic ulcer disease and the one most commonly associated with H. pylori infection. In the 1980s, in the West, 90% of duodenal ulcers were H. pylori positive and these responded to eradication regimes (see 5.1) with high cure rates. For various reasons the prevalence of H. pylori in duodenal ulcers has fallen recently with a higher percentage of NSAID induced ulcers (see 4.4). Other factors play a role. High dietary fibre appears to lower the risk of DU as well as Vitamin A intake.(64) Alcohol and smoking both increase the risk. Complications of duodenal ulcer: bleeding and perforation have not really decreased in recent years.

4.2 GU (see picture 10)

Gastric ulcers GU are more common in Asia than DU. (11) In the West this relationship is reversed. Women and the elderly are more likely affected. (65) GUs have been classified into Type I, occurring along the lesser curve, Type II, with concurrent or historical DU, Type III, prepyloric, and Type IV, cardiac. (66) GU are also more likely associated with reduced gastric acid secretion and pangastritis. Defective mucosal defence is implicated as a pathogenic factor. Concomitant stress (67) and NSAID therapy (see 4.4) are more often present. Type I and IV are associated with increased risk of malignancy. Still the majority of GUs are associated with *H. pylori* infection, although results of eradication therapy is less successful.

4.3 ZE syndrome

The Zollinger-Ellison syndrome (ZES) is a clinical syndrome of severe peptic ulcer disease and diarrhea associated with gastric acid hypersecretion secondary to a gastrin producing neuroendocrine tumor. (68) Gastrinomas occur in both familial (MEN-1) and sporadic forms. In ZES/MEN-1 patients the majority of tumors are found in the duodenum. The role of surgery in these patients is unclear because of the necessity for pancreaticoduodenectomy, the inability to identify aggressive tumors and the relatively good long-term survival with current medical therapy with proton pump inhibitors PPI and somatostatin analogues. (69) Patients with sporadic tumors without distant metastases are however candidates for surgical resection. New localization techniques have improved the results. (70)

4.4 NSAIDS

It has long been recognized that aspirin and other non-steroidal anti-inflammatory agents NSAIDs, which inhibit prostaglandin formation, can cause peptic ulcer disease, particularly gastric ulcers. (71;72) The extremely widespread use of these agents in the West, for a variety of medical conditions, has increased the significance of these complications. *H. pylori* infection and NSAID use are independent and synergistic risk factors for uncomplicated and bleeding peptic ulcer. (73) The substitution of these agents by COX-2 inhibitors has not had much influence on peptic ulcer complications. Misoprostol, PPIs and double dose histamine 2 receptor antagonists (H2RAs) are effective in preventing NSAID related PUD. (74;75) Misoprostol 800ug/day appears to be the most effective, but causes more diarrhea. These findings led to the Maastricht consensus to recommend prior testing and treating for *H. pylori* in patients for whom NSAID therapy is planned. (45;76)

4.5 Neither *H. pylori* nor NSAID

The percentage of non-*H. pylori* and non-NSAID PUD is also increasing at least in the West. (77;78) Inability to detect actual *H. pylori* infection needs to be assessed carefully. Recent or current use of antibiotics, PPIs or bismuth agents may cause errors. In non-*H. pylori*, non-NSAID ulcers the Zollinger-Ellison syndrome needs to be excluded. Other infections such as CMV may be important in HIV positive patients. Crohn's disease may give rise to gastroduodenal ulceration which mimics PUD. Idiopathic ulcers are best treated with PPIs. (79)

4.6 Children

While *H. pylori* is usually contracted in childhood in the developing world, PUD is uncommon in this age group. (80;81) PUD has a broader etiologic base in children and *H. pylori* negative ulcers are more common. (82)

5.0 Management of Peptic Ulcer Disease

5.1 Eradication Therapy for *H. pylori*

The ability of eradication of *H. pylori*, to not alone induce ulcer healing, but also to prevent its recurrence, have been two of the most convincing indications of its central role in the pathophysiology of PUD. Combinations of multiple antibiotics and acid reducing agents, usually PPIs, have been the mainstay of these regimes. Cure rates of greater than 80% (intent to treat) are possible. (83;84) The Maastricht Consensus organizes its indications for eradication therapy into two levels. (45) (Box 1) One of the main regimes is clarithromycin 500mg BID, amoxicillin 1 gm BID and a PPI (omeprazole 20mg BID or 40mgOD) for 7-14 days. This regime has been tested in a multicentre trial in Asia and Africa with eradication rate of 80% (intention to treat) and 94% ulcer healing rate. (85) Metronidazole 500mg BID may be substituted for patients with penicillin allergy. Bismuth subsalicylate 525 mg QID, metronidazole 250mg QID, tetracycline 500mgQID with a PPI for 14 days is a lower cost alternative. An H2RA such as ranitidine may be used for 4 weeks. (Box 2) For gastric ulcers the PPI is continued for a total of 1 month. Antibiotic monotherapy should not be used because of the risk of developing resistance. Gisbert showed that PPIs are all equivalent and more effective than H2RAs for *H. pylori* eradication. (86) These eradication regimes have been proven more effective than antisecretory drugs alone for healing of duodenal ulcers.(87) For preventing recurrence they are equivalent to long term maintenance therapy. Eradication regimes are equivalent to ulcer healing drugs for gastric ulcers and superior to no treatment for preventing recurrence. A study for the Cochrane Database confirms this. (88) Proof of eradication should be obtained in cases of PUD, MALT lymphoma, atrophic gastritis and early gastric cancer. (89) Failure of these first line treatments is usually due to antibiotic resistance or poor compliance. Metronidazole resistance is higher in the developing world (20-30%) and can be partially overcome by increasing the dosage. Whereas the optimal retreatment strategy has not been developed, repeat triple therapy with changing one of the antibiotics is recommended. Using the bismuth regimes might be appropriate. (89) The re-infection is considered to be very low in the developed world. However in the Chile, with a higher prevalence of *H. pylori* in the overall population the re-infection has been shown to be 13% after 3 years. (90)

5.11 Vaccines

Because of the numerous clinical conditions associated with *H. pylori* infection, including gastric cancer, and despite its falling prevalence in the developed world, vaccination has been considered as a means of preventing infection. While 10 years of vaccination would be sufficient to lower prevalence in the developed world, continuous vaccination would be required in the developing world. (91) However, the ability of the organism to evade spontaneous eradication, despite a significant host immune response, is an impediment to the development of an effective vaccine. (14) Mast cells appear to be important in bacterial clearance.

5.3 Medical Therapy

All patients who have been diagnosed with PUD should be advised to stop smoking, avoid alcohol and NSAIDs, including aspirin. If *H. pylori* infection is documented, one of the above regimes should be instituted. If negative, an empiric trial of eradication therapy may be tried or acid suppression therapy with H2RAs or PPIs.(6) Sucralfate or

misoprostol may also be used. Therapy should be continued for 3 months, if a precipitating cause was identified, and long term maintenance therapy should be considered in all patients with an ulcer complication, in elderly patients on NSAIDs, in smokers or those with a history of bleeding or recurrent ulcer, for whom re-ulceration carries a high mortality. (6)

Eswaran and Roy give a good review of the different agents available and their pharmacology. (92) H₂ receptor antagonists such as ranitidine bind to the histamine 2 receptor on the parietal cell and inhibit basal and meal-stimulated acid secretion. (93) Proton pump inhibitors like omeprazole irreversibly bind to the H⁺K⁺ATPase pump. (94) At mealtime PPIs can affect 60-70% of pumps. Therefore, intragastric pH control is best when the PPI is given in the morning with a meal. (95) The parietal cells synthesize new pumps in 72 hours. New agents with different site of action are being investigated. (96) Considerable interest exists over traditional practices (97) and natural ulcer remedies. (98)

5.4 Surgical Therapy

Surgery may still be considered the mainstay for complicated PUD: long history or failed medical therapy, gastric outlet obstruction, suspicion of malignancy or complication such as perforation or bleeding. (99) The search has been for effective operations with few side effects or long term sequelae. (100) The advent of H. pylori therapy has radically altered the role of surgery particularly the frequency of its necessity. New technologies also have impacted on the role of surgery. Endoscopic approaches to bleeding have obviated the need for some surgeries. Laparoscopic procedures have been proposed as an alternative to most open procedures. (101) At the moment, there is no consensus concerning specific procedures, which requires individualization for each patient and operative indication. (102) Specific options will be discussed with each complication (see 6.1-6.4). The long term prognosis of patients subjected to gastric resection for PUD in the past is of interest. (103) Symptomatic enterogastric reflux, bile gastritis, metabolic disturbances, dumping syndrome and risk of gastric stump cancers are all important considerations.

6.0 Complications

One has the impression that peptic ulcer complications are more common in the developing world. Perforation and obstruction both are frequent reasons for operation. In reports from Ethiopia (104) and Nigeria (105) obstruction was the most common complication; while in a report from Kenya (106) perforations accounted for 56% of cases.

6.1 Non-healing or recurrent ulcers

The definition of a non-healing ulcer is failure to heal, after appropriate treatment, in two months for DU or three months for GU. It must be said that these are rare, especially in the developing world. A diagnostic dilemma in these cases has been observed. (107) H. pylori persistence or re-infection needs to be ruled out, as does ZE syndrome. Other aggravating factors - NSAIDs, smoking, alcohol – need to be eliminated if possible. If the ulcer recurs, one option is long term PPI therapy. If there is failure to heal on these, surgery becomes indicated. In GUs, particularly Type I, the standard procedure has been the Bilroth I gastrectomy with excision of the ulcer. (108) Pre/peri-operative biopsies should be performed to make sure the ulcer is not malignant and a larger resection not

required. For DUs, the modern options have been some form of vagotomy, truncal vagotomy with drainage or highly selective vagotomy (parietal cell vagotomy) versus vagotomy and antrectomy. (109) The latter procedure has an improved cure rate with increased side effects. Recurrence of ulcer after surgery has long been a problem, often requiring more aggressive surgery. (110)

6.2 Perforation

In the industrialized world, perforation has decreased in men since the 1950s, but increased in women and the elderly. (111) Smoking and NSAIDs appear to be co-morbid factors. The relationship between perforation and periods of stress and social conflict is well recognized. This may account for the still high frequency of perforation in developing countries, where delays in presentation and high mortality are common. (112-114) Patients without previous PUD history often form the majority of cases. The clinical sequence of shock from chemical peritonitis to that of bacterial peritonitis is well established. The mortality depends more on the condition of the patient and adequacy of intensive care facilities than the operative procedure itself. (115) Diagnosis is usually not difficult with board like rigidity and free intra-peritoneal air. CT scan is particularly sensitive. (116) Non-operative management may be undertaken successfully for very ill patients, although if gastrograffin series shows continued leak, surgery should not be delayed. (99) The standard procedures are an omental patch for DU and excisional/resectional biopsy and closure for GU(66), although definitive surgery for patients with a history of chronic PUD performed well in trials before H. pylori therapy. Laparoscopic procedures using suture, patch or fibrin sealant have shown equivalent results to open approaches.(117;118) Even though H. pylori infection is less common in perforated PUD, it is recommended that patients begin eradication therapy in the post-operative period. (119)

6.3 Obstruction

Chronic peptic ulcers in the pyloric region or duodenum may cause scarring which results in gastric outlet obstruction. Vomiting and weight loss are the physiologic results with the succussion splash being the classic physical sign. Hypokalemic metabolic alkalosis is found in blood chemistry. Obstruction is the commonest PUD complication in some areas of Nigeria. (105;120;121) H. pylori eradication therapy is indicated early on in positive patients as resolution has been reported. (122) Cases which do not resolve on nasogastric suction and intravenous therapy have usually been treated with various types of vagotomy and drainage procedure.(66;115) Endoscopic dilatation may be a useful modality.

6.4 Bleeding (see picture 11)

Upper gastrointestinal hemorrhage is an important and potentially life-threatening problem. PUD remains the single commonest cause of upper gastrointestinal hemorrhage in the USA. (123) Mortality rates are between 7-10% and are higher after rebleeding. While 80% of patients will stop bleeding spontaneously, hemodynamic instability, repeated hematemesis or hematochezia, or failure of the gastric aspirate to clear with lavage, are all signs of severe ongoing hemorrhage. Age and comorbidity are poor prognostic signs. Endoscopic appearance of the ulcer is critical. Ulcers greater than 1-2 cm, with active bleeding or visible vessel have the greatest risk of rebleeding. After initial resuscitation, endoscopy should be undertaken for diagnosis, staging and possible endoscopic therapy. (124) To ensure adequate visualization, the stomach needs to be

emptied of blood and clots. Endoscopic therapy, injection with epinephrine (1/100,000), coagulation with heater probe or laser, is indicated for active bleeding or non-bleeding visible vessel. (125) There is evidence that such treatment decreases rebleeding episodes and the need for surgery. Injection is the easier modality, but there is some evidence that combination treatment is more effective. The issue of whether clots should be disturbed is not completely resolved. It seems worthwhile to irrigate the clot briefly to see if high risk bleeding lesions are uncovered.

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. The standard surgical procedure has been suture ligation of the bleeding site, truncal vagotomy and pyloroplasty. (66) Four quadrant suturing of the gastroduodenal artery, if involved, should be carried out. Whether, in the era of H. pylori eradication therapy, simple suture is adequate surgical therapy is unclear. What is clear is that both aggressive anti-secretory treatment with PPIs and antibiotics to eliminate H. pylori, decrease the rebleeding episodes and need for surgery, although perhaps not mortality rates. (126) PPIs are more effective than H2RAs. Furthermore H.pylori eradication therapy is more effective than anti-secretory therapy alone in preventing rebleeding. (127)

7.0 Recommendations

- 1. Invasive (culture biopsy or rapid urease test) and non invasive (stool antigen and/or urea breath test) should be available for diagnosis of H. pylori infection.**
- 2. Upper GI endoscopy should be available for diagnosis of PUD and injection therapy available for therapy of upper GI hemorrhage.**
- 3. Symptomatic patients should be tested off all anti-secretory medication, antibiotics and bismuth.**
- 4. Patients under 45 with dyspeptic symptoms who are positive for H. pylori should undergo eradication therapy.**
- 5. Patients with alarm symptoms should undergo gastroscopy and gastric and possibly duodenal biopsy for H. pylori.**
- 6. All patients with both complicated and uncomplicated PUD should have H. pylori testing and treatment if positive.**
- 7. Triple therapy of 7 days with a PPI, clarithromycin and amoxicillin should be first line eradication therapy in Africa due to increased resistance to metronidazole. Quadruple therapy with bismuth, metronidazole, tetracycline, PPI for 14 days or ranitidine for 28 days may be substituted if cost is a factor.**
- 8. H. pylori status should be assessed non-invasively 1 month post therapy.**
- 9. Persistently positive patients should receive supervised second line therapy.**
- 10. Patients with PUD should stop NSAIDS and be encouraged to avoid alcohol and smoking.**
- 11. Long term anti-secretory maintenance therapy should not be necessary for uncomplicated H. pylori PUD.**
- 12. Perforated PUD should be treated with vigorous resuscitation and broad spectrum antibiotics and anti-secretory therapy, followed by simple surgery to control the leak.**

13. Gastric outlet obstruction should be treated with nasogastric suction, intravenous therapy, antisecretory therapy, endoscopy for diagnosis and H. pylori testing. Patients with non resolution of the obstruction after 1 week should undergo either balloon dilatation or vagotomy and some form of drainage procedure.
14. Bleeding peptic ulcers require vigorous resuscitation, antisecretory therapy with PPIs and endoscopy for diagnosis, prognostic indicators and possible endoscopic therapy. Visible clots should be irrigated to assess underlying vessels. With active bleeding or visible vessel, a trial of endoscopic therapy with injection of epinephrine, heat probe or both is appropriate. Rebleeding patients should undergo prompt surgery with ligation of bleeding vessel and vagotomy if stable. H. pylori should be eradicated if found.

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Pictures 1-11

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