Peptic Ulcer Disease in Nigeria

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ABSTRACT

Peptic ulcer disease is due to the circumscribed, complete loss of gut epithelium in parts of the digestive tract exposed to hydrochloric acid and pepsin secretion. It can be acute or chronic and occurs as a result of an imbalance between the defensive and aggressive forces at play in the mucosal lining of the stomach, combined with superimposed environmental or immunological injury. NSAIDs contribute to peptic ulcer formation by undermining a vital part of the mucosal defensive forces. The greatest impact of the understanding of the role of H. pylori in PUD has been the ability to obtain a cure and prevent recurrence of what was once a recurrent disease. The true prevalence rate of PUD in the Nigerian populace is not certain although over three decades ago Nigeria was listed as an area of high PUD prevalence[8] with perforation being the most frequent indication for surgery. More recent studies begin to show similar prevalence rates for DU and GU in both southern and northern Nigeria[12-14] and this is attributed to improved diagnostic facilities[12].

INTRODUCTION

Peptic ulcer is defined as a circumscribed, complete loss of gut epithelium in those parts of the digestive tract exposed to hydrochloric acid and pepsin secretion. It is **acute** if it lies superficial to the *muscularis mucosae* but **chronic** if it penetrates beyond it[1]. An ulcer is described as active during a recurrence or when it is causing symptoms. The principal areas affected by peptic ulcer include the lower oesophagus, stomach and the first part of the duodenum. In rare circumstances, peptic ulcer may be found in colonic (Meckel's) diverticulum with functioning gastric glands, sites in the small intestine brought close to the stomach by surgical anastomosis or in the jejunum in cases of Zollinger-Ellison syndrome (ZES). Peptic ulcer disease (PUD) encompasses gastric and duodenal ulcers as well as the erosive/ulcerative forms of gastro-oesophageal reflux disease (GORD).

Aetiopathogenetic Mechanisms[2, 3]

PUD tends to occur as a result of an imbalance between the defensive and aggressive forces at play in the mucosal lining of the stomach, combined with superimposed environmental or immunological injury. The normal mucosal defensive forces include mucus-bicarbonate barrier, rich mucosal blood flow sustaining mucosal integrity, epithelial tight junctions, epithelial renewal/regeneration and prostaglandins. These cytoprotective factors are undermined by ischaemia, shock, delayed gastric emptying or duodeno-gastric bile reflux thereby making the gastric mucosa vulnerable to the damaging action of the aggressive forces, namely, hydrochloric acid and pepsin. In particular, bile causes gastric mucosal injury with back diffusion of H^+ ions and inflammation. On the other hand, an ulcer may also result if there is excessive acid-pepsin secretion even in the presence of normal defensive forces as in ZES.

Non-steroidal anti-inflammatory drugs (NSAID), such as acetyl salicylate, inhibit the activity of cyclo-oxygenase thereby reducing the tissue levels of prostaglandins and thromboxanes. NSAID, therefore, contribute to peptic ulcer formation by undermining a vital part of the mucosal defensive forces.

Cigarette smoking not only delays the healing of duodenal ulcer (DU) and gastric ulcer (GU) but also causes ulcer relapse. The postulated mechanisms include inhibition of pancreatic and duodenal bicarbonate secretion and inhibition of prostaglandin synthesis in the gastric mucosa.

Peptic ulceration is also known to occur following stress. Acute diffuse mucosal lesions tend to occur in sepsis, shock, liver failure, trauma, surgery, extensive burns (Curling's ulcer), uraemia, brain injury (Cushing's ulcer), acute respiratory insufficiency and advanced carcinomatosis. The mechanism is uncertain but may include acid and pepsin hypersecretion, mucosal ischaemia with disruption of barrier to H^+ ions and mucus deficiency.

Infection with *Helicobacter pylori* has been found in 70 – 80% of gastric ulcer (GU) patients and in 90% of those with duodenal ulcer (DU). The organism was first linked to chronic type B gastritis in 1983 and since then it has been associated with mucosa-associated lymphoid tissue (MALT), malignant gastric B-cell lymphoma, gastric carcinoma in addition to GU and DU. Patients infected with *H. pylori* are 3 to 6 times more likely to develop intestinal-type adenocarcinoma of the

gastric antrum and body than non-infected persons. Eradication of the organism is usually followed by ulcer healing and reduced ulcer relapse rate.

Clinical Features and Complications

The history, almost in all cases, is that of abdominal pain, usually epigastric in location. This symptom together with discomfort or fullness or nausea (especially when related to meals) constitutes what is known as dyspepsia, which is a rather common feature of most gastroduodenal disorders with a poor predictive value for either DU or GU. The epigastric pain may be described as a burning, gnawing or aching sensation frequently relieved by antacids or food. Pain that awakens the patient from sleep at night (between midnight and 3.00 A. M.) is the most discriminating symptom with two-thirds of DU patients describing this complaint[5]. In some GU and pyloric channel ulcer patients, epigastric pain or discomfort may actually be precipitated by food and nausea and weight loss tend to occur in them more often. An appreciable number of patients may present with a complication without antecedent symptoms.

The most frequent finding on physical examination is epigastric tenderness and sometimes no physical sign is elicited. Evidence of ulcer complication may also be found during physical examination. Tachycardia and orthostasis suggest dehydration secondary to vomiting or active gastrointestinal blood loss. Anaemia is usually seen in patients with chronic blood loss. A severely tender, board-like abdomen suggests perforation while the presence of a succession splash indicates retained fluid in the stomach, a feature of gastric outlet obstruction. The list of gastroduodenal and non-gastroduodenal disorders that can mimic GU or DU is quite extensive. Some of the disease processes that may present with "ulcerlike" symptoms include proximal gastrointestinal tumours, GORD, vascular disease, pancreatico-biliary disease and gastroduodenal Crohn's disease.

Haemorrhage is the most common complication of PUD and usually presents with melaena (black tarry stools), haematemesis ("coffee grounds" or frank red blood) and very rarely, haematochezia. Other symptoms include weakness, orthostasis, syncope, thirst and sweating. Bleeding occurs more often in patients over 60 years of age and is likely due to the increased use of Non steroidal anti-inflammatory drugs [NSAIDs] in this group.

The second most common ulcer-related complication is free perforation. An anterior DU is mainly responsible for this and usually presents as an acute abdomen.

An ulcer may penetrate the gastric or duodenal wall and enter a contiguous space (e.g. lesser sac) or organ (e.g. pancreas or liver or gall bladder). This leads to localized peritonitis as adhesions prevent leakage into the free peritoneal space. Pancreatic penetration occurs mostly with posterior DU and presents with intense and persistent pain (due to localized pancreatitis) that is referred to the back. Cholecysto-duodenal and gastro-colic fistulas associated with DU and GU respectively, have also been described.

Gastric outlet obstruction (GOO) is another notable complication of PUD. GOO is said to be functional if it is due to an acute exacerbation of a chronic DU leading to inflammatory oedema and/or spasm in the peri-pyloric region. This form of GOO is temporary as the condition is reversible with drug treatment. Another form of GOO is a fixed, mechanical obstruction caused by scarring in the peri-pyloric area. The latter form of GOO can only be relieved by endoscopic (balloon dilatation) or surgical intervention. GOO presents with recurrent large volume vomiting, persistent bloating, early satiety, loss of appetite, weight loss, dehydration and alkalosis.

Ulcer recurrence can be problematic. One-year relapse rate for DU and GU without anti-*H pylori* therapy is 60% but less than 10% with anti-*H pylori* therapy[6]. Causes of recurrence include poor drug compliance, fake drug syndrome, unsuccessful *H pylori* eradication, ingestion of NSAID, cigarette smoking and, rarely, a gastrinoma (Zollinger-Ellison syndrome).

Methods of Diagnosis of PUD[4, 6]

- Occult blood in stool. Positive occult blood in the stool of a patient with dyspepsia should arouse suspicion for the presence of peptic ulcer or gastric malignancy.
- Barium studies especially double-contrast barium x-ray. Chronic DU with scarring will often give typical features of the duodenal cap on barium meal. Radiological contrast study will help in the confirmation of diagnosis of GOO and pancreatic penetration.
- An upright or lateral decubitus abdominal x-ray. This will show free air under the diaphragm or in the peritoneal cavity in cases of ulcer perforation.
- Upper gastrointestinal (UGI) endoscopy with multiple biopsies. Currently, this is the most favoured and popular mode of diagnosing PUD. It is superior to radiological studies as

lesions can be directly visualized including superficial mucosal lesions and biopsies taken for histology.

- Investigation for *H. pylori* infection. Diagnosis of *H. pylori* infection can be by invasive or non-invasive tests. The invasive tests are UGI endoscopy with gastric biopsy samples subjected to microscopy, histology, culture or urease tests. The urease test is relatively simple and rapid. The test kit contains urea, which is hydrolysed by urease enzyme [produced by the organism] with the release of ammonia. The latter compound raises the pH and alters the colour of the indicator. The non-invasive tests include serology, urea breath test (UBT) and faecal antigen test (FAT). The UBT procedure requires the subject to fast and ingest a solution of urea labelled with carbon-13. In the presence of *H. pylori*, the radio-labelled urea is rapidly hydrolysed by the urease enzyme and the $^{13}CO_2$ liberated is absorbed in to the blood and excreted in the breath. The amount of radioactive carbon dioxide in the breath is measured by spectrometry.

Treatment of PUD

The goals of treating PUD are to provide symptom relief, promote ulcer healing and ultimately prevent ulcer recurrence and complications. To achieve these goals a variety of anti-ulcer drugs are available. However, the greatest impact of the understanding of the role of *H pylori* in PUD has been the ability to obtain a cure and prevent recurrence of what was once a recurrent disease.

- Anti-ulcer drugs include:
- **Antacids**. These are weak bases that react with gastric acid to form salt and water. Their anti-ulcer effect is exerted by reducing gastric acidity and pepsin activity. They also stimulate prostaglandin production and bind to unidentified injurious substances. They are mainly used for symptomatic relief of indigestion or dyspepsia. Examples are aluminium and magnesium hydroxide or trisilicate. The dose of antacid for ulcer healing is 200 – 300mls per day for 4 to 8 weeks.
- **Histamine (H_2) Receptor Antagonists [H_2RA]**. The drugs that belong to this group bind to the parietal cell H_2 receptor producing a decrease in both meal and gastrin-mediated gastric acid secretion through the reduction of the intra-cellular concentration of cyclic AMP. Examples include Cimetidine (400mg bid or 800mg nocte), Ranitidine (150mg bid or 300mg nocte), Famotidine (20mg bid or 40mg nocte) and Nizatidine (150mg bid or 300mg nocte). The usual duration of therapy is 4 to 8 weeks.
- **Anti-Muscarinic Drugs**. The only example of this group for use in PUD is pirenzepine. It specifically blocks the M_1 receptor, the type of muscarinic receptor found on the gastric parietal cell. The dose is 50mg bid or tds for 4 to 6 weeks.
- **Proton Pump Inhibitors [PPI]**. These drugs are substituted benzimidazoles that act by suppressing gastric acid secretion through the inhibition of the H^+ - K^+ ATPase enzyme (i.e. Proton Pump). The latter pump is the final common path for gastric acid secretion and for this reason the PPI are highly potent inhibitors of gastric acid secretion. Examples are Omeprazole (20mg daily), Lanzoprazole (30mg daily), Pantoprazole (40mg daily), Rabeprazole (20mg daily) and Esomeprazole (20 or 40mg daily).
- **Cytoprotective Agents**. These include prostaglandin analogues such as Misoprostol, PG E_1 analogue, sucralfate and colloidal bismuth compounds. Misoprostol inhibits acid secretion and enhances the secretion of mucus and bicarbonate. It is particularly useful for patients at high risk for NSAID-induced ulcer and the dose is 200µg qid for 4 – 8 weeks. The drug must never be used in pregnant women because of its powerful abortifacient properties. Sucralfate acts by polymerization and selective binding to necrotic tissue in the ulcer base thereby forming a protective gel over the ulcer. The dose is 1g qid or 2g bid for 4 – 6 weeks. Sucralfate is suitable for pregnant women with PUD and for patients with GORD. Colloidal bismuth acts like sucralfate but in addition, inhibits pepsin, stimulates mucus production, increases PG synthesis and has an intrinsic anti-*H pylori* activity. Examples are Bismuth subcitrate and Bismuth subsalicylate. The dose is usually 120mg qds for 4 – 6 weeks.
- ***H pylori* Eradication Therapy**.[7] Most *H pylori* eradication therapeutic regimens currently in use combine an anti-secretory agent with two antibiotics (Triple Therapy). The anti-secretory agent is either a H_2RA or a PPI and the two antibiotics are selected from a growing list of antimicrobials. A quadruple therapy consisting of an anti-secretory agent, a bismuth compound and two antibiotics is also available in case of failure of triple therapy (see Table 1). The currently recommended duration of therapy for both regimens is 10 to 14 days.

Stage of Treatment	Component Drugs
First Line (Triple)	Bismuth + Tetracycline + Metronidazole
	Bismuth + Amoxicillin + Metronidazole
	Ranitidine bismuth citrate (RBC) + Clarithromycin + Amoxicillin
	RBC + Clarithromycin + Metronidazole
	*PPI + Clarithromycin + Amoxicillin
	*PPI + Clarithromycin + Metronidazole
	*PPI + Levofloxacin + Azithromycin
	*PPI + Levofloxacin + Amoxicillin
	*PPI + Furazolidine + Metronidazole
	*PPI + Amoxicillin + Rifabutin
Second Line (Quadruple)	#H_2RA + Bismuth + Tetracycline + Metronidazole
	*PPI + Bismuth + Tetracycline + Metronidazole
	*PPI + Bismuth + Amoxicillin + Metronidazole
	*PPI + Bismuth + Amoxicillin + Furazolidine
	*PPI + Bismuth + Metronidazole + Furazolidine

**Proton Pump Inhibitor #Histamine$_2$Receptor Antagonist*

Table 1: Helicobacter Pylori Eradication Regimens (Duration of Therapy = 10 – 14 days)

PUD in Nigeria

As far back as more than three decades ago Nigeria was listed as an area of high PUD prevalence[8]. At that time DU was regarded to be more common in southern Nigeria than in the northern parts of the country[9]. Mabogunje *et al*[10] reported a sizeable number of patients operated for GU at Zaria with perforation being the most frequent indication for surgery. The lower prevalence of DU in northern Nigeria was also reported by Holcombe,[11] though he claimed that GU was rare in Africans. However, more recent studies are beginning to show similar prevalence rates for DU and GU in both southern and northern Nigeria[12-14]. This present trend has been attributed to improved diagnostic facilities[12].

The true prevalence rate of PUD in the Nigerian populace is not certain but an autopsy study at Ibadan obtained a prevalence rate of 5% and PUD was the cause of death in 1.5% of all the autopsy cases[15]. In that study, UGI bleeding was the most common cause of death followed by perforation and factors that contributed to mortality were non-compliance with treatment and delayed presentation. Lawal *et al*[16] working in Ile-Ife obtained a mortality rate of 20% from PUD perforation and this was also attributed mainly to late presentation. The most common complication of PUD found in Benin City was gastric outlet obstruction (GOO) followed by perforation and bleeding in that order[17]. Similar findings were reported from Calabar[18]. GOO was also the most common surgical presentation among the PUD patients seen at Ibadan[19].

With the advent of *H. pylori* eradication therapy in PUD there have been some noticeable changes in the presentation and course of this condition. Perforation and GOO rates have declined with *H. pylori* eradication therapy[20]. Yearly presentations of PUD patients for surgery have been declining and the need for surgical intervention has also greatly reduced due to H_2RA and PPI-based *H. pylori* eradication[17, 19].

Nigerian PUD patients are generally young, most of them in their mid-thirties to early forties and the male to female ratio ranges from 1.3 – 3.5:1.0. DU is the most common endoscopic finding among Nigerian dyspeptic patients and the prevalence of GU ranges from 0 to 6.4%[12-14, 21-22]. *H pylori* prevalence rates among dyspeptic patients ranged between 73% and 77.5% with DU and non-ulcer dyspepsia (NUD) patients having similar infection rates of 76 – 80%[21, 22].

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