# Risk Factors,Diagnosis, and Management of Peptic ulcer Disease

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***Abstract:****For nearly 100 years, scientists and doctors thought that ulcers were caused by stress, spicy food, and alcohol. Treatment was bed rest and antacids, but in 1982 discovery of Helicobacter pylori confirmed its role in in gastric, duodenal ulcers and gastric cancer. Peptic ulcer disease (PUD) is the most common human ailment affecting nearly 50% of world population, with high mortality in gastric cancer. Gastric ulcer had male preponderance; duodenal ulcer was 10 times as common as in women. The causes of PUD include H.pylori infection, non- steroidal anti- inflammatory drugs (NSAIDs), pepsin, smoking, alcohol, bile-acids, steroids, stress and changes in gastric mucin consistency. Other causes include Bechetdisease, Zollinger_Ellisonsyndrome, Crohndisease, livercirrhosis, stomach cancer, coronary heart disease and inflammation of stomach lining or gall bladder. Frequent symptoms include epigastric pain, nausea, flatulence, bloating and heartburn. The currently recommended eradication regimens should have eradication rate of 90% or greater. Triple therapy is consist of PPI,a combination of two antimicrobials such as amoxicillin and clarithromycin.Quardrupletherapy:PPI(sandard dose twice daily)+metronidazole(500 mg 3 times daily)+ tetracycline(500 mg 3 times daily)+bismuth(dose depend on preparation) for 10 days.Prognosis of PUD is excellent if the underlying cause such as H.pylori infection or use of NSAIDs can be addressed.*
***Keywords:****Peptic ulcer disease (PUD),Riskfactors, Helicobacter pylori infection,NSAIDS,*

## I.    Introduction

Peptic ulcer disease (PUD) is one of the most common human ailments, affecting approximately 50% of the world population[1].PUD also known as peptic ulcer or stomach ulcer, is a break in the lining of the stomach, first part of the small intestine, or occasionally the lower esophagus[2].The life time for developing a peptic ulcer is approximately 10%[3].They resulted in 301,000 deaths in 2013 down from 327,000[4].In western countries the percentage of people with *Helicobacter pylori* infections roughly matches age(i.e.,20% at age 20,30% at age 30,80% at age 80).prevalence is higher in developing countries where it is estimated at about 70% of the population, whereas developed countries show a maximum of 40% ratio[5].In developing countries, where most children become infected by the age 10 of  .gastric cancer rates are very high[6].Researchers in Sabah, Malaysia confirmed a prevalence of 32.26 % *Helicobacter pylori* infection in 1156 subjects, in age groups 12 to 80 years[7].In the past duodenal ulcer was 10 times as common in men as in women and gastric ulcer had a male preponderance of 3:2,now the frequency is much less, largely because of *H.pylori* eradication incidence being more even[8].The sale of antacid drugs worldwide exceeds $5 billion, making ulcer disease a major burden to the public healthcare system[6,.In the UK mean initial in-hospital costs were £2458(SE=£216) per patient. Annual initial in-hospital costs of for all acute upper gastrointestinal bleeding(AUGIB)cases in the UK was estimated to be £155.5 million[9].Etiology of PUD include *H.pylori*infection,NSAIDS,pepsin,smoking,alcohol,bile-acids,steroids,stress,and changes in gastric mucin consistency(may be genetically determined)[10,11].Other causes include Behcetdisease,Zollinger-Ellison syndrome,Crohn disease and liver cirrhosis, and similar symptoms stomach cancer, coronary heart disease, and inflammation of the stomach lining or gallbladder[2].Symptoms of PUD are nonspecific and diagnosis is unreliable on history, frequent symptoms include, epigastric pain, nausea, flatulence and bloating, heartburn, a posterior ulcer may cause pain radiating to the back,symptoms are relieved by antacid[2].Diagnosis is mainly established based on the characteristic symptoms, endoscopies or barium contrast and tests for *H.pylori* infection[12].Prognosis of PUD is excellent if the underlying cause such as *H.pylori* infection or drugs can be addressed[13].The paper reviews the current literature, risk factors, diagnosis and  management of PUD.

## II.    Historical Perspective

The first description of a perforated peptic ulcer was in 1670 in Princess Henrietta of England[14].John Lykoudis,a general practitioner in Greece, treated patients for peptic ulcer disease with antibiotics, beginning in 1958,long before it was recognized that bacteria were a dominant cause for the disease[14].*Helicobacter pylori* was identified in 1982 by two Australian scientists Robin Warren and Barry J Marshal as a causative factor for

ulcers [15].In their original paper, Warren and Marshal contended that most gastric ulcers and gastritis were caused by colonization with this bacterium, not by stress or spicy food as had been assumed before[16].The *H.pylori* hypothesis was initially poorly received,[17] so in act of self-experimentation Marshall drank a Petri dish containing a culture of organisms extracted from a patient and five days later developed gastritis. His symptoms disappeared after two weeks, but he took antibiotics to kill the remaining bacteria at the urging of his wife, since halitosis is one of the symptoms to infection [18].In 2005,Barry Marshall and Robin Warren awarded the Nobel Prize in Physiology or Medicine for their discovery of bacterium *Helicobacter pylori* and its role in gastritis and peptic ulcer disease[19].In 1997,the Centers for Disease Control and Prevention, with other government agencies, academic institutions, and industry, launched a national education campaign to inform health care providers and consumers about link between *H.pylori* and ulcers. This campaign reinforced the news that ulcers are a curable infection and health can be greatly improved and money saved by disseminating information about *H.pylori*[20].

*H.pylori* has been isolated from persons in all parts of the world[21].Similar organisms have been isolated from primates, but other animal sources for H.pylori have not been identified, nor have reservoirs been found in food, soil, or water. It now appears that likely that humans are the major, if not sole, reservoir for *H.pylori*.Genetic loci with phylogeographic affinities indicate that *H.pylori* has been present un humans for at least 50,000 years, if not longer, the current geographic distribution of *H.pylori* alleles reflects ancient migration of human populations[22].These data support the notion that *H.pylori* is indigenous to humans and its relatives are to other mammals ,but they are disappearing as a result of modernization[23].

### III. Risk Factors

Common risk factors –causes for PUD and gastritis include infection with *H.pylori*,andNSAIDs.Less common risk factors include alcohol ,smoking, cocaine, severe illness, autoimmune problems, radiation therapy and Crohn disease among others[24].

**Helicobacter pylori** a major causative factor60% of gastritis and up to 50-75 % duodenal ulcers) is chronic inflammation due to*H.pylori* that colonizes the antralmucosa [25].The immune system is unable to clear the infection, despite the appearance of antibodies. Thus the bacterium can cause a chronic active gastritis (type B gastritis).Gastrin stimulates the production of gastric acid by parietalcells. In*H.pylori* colonization responses to increased gastrin, the increase in acid can contribute to the erosion of the mucosa and therefore ulcer formation [25].

*H.pylori* is able to survive and multiply in gastric environment, which is hostile to the growth of other bacteria [16]Numerous adaptations permit survival of *H.pylori* in the acidic milieu of the stomach[26].Although most organisms appear to be adherent to the mucosal epithelial cells and form adherence pedestal resembling those produced by enteropathogenic*Escherichia coli,* several important adhesins have been identified [27,28].Bacterial lipopolysaccharide usually has proinflammatoryactivities,but*H.pylori* lipopolysaccharide has remarkable little[29].*H. pylori*polysaccharide may express the type 11 Lewis$^x$,Lewis$^y$)neither, or both of these antigens[30],as well as type 1 antigens(Le$^a$,Le$^b$).This observation is significant because these antigens are present on gastric epithelial cells, and there is evidence that host Lewis phenotype selects for the particular Lewis expression of *the H.pylori* population[31].

*H.pylori* is highly associated with gastric ulcer disease. The pathogenic role of *H.pylori* in chronic active gastritis and its association between *H.pylori* and duodenal ulcer in 95 to 99% of patients is well established [32].All *H.pylori* spp. causes some degree of persistent inflammation in the mammalian stomach. Gastritis is found in virtually all infected humans, although the majority has no symptoms; only one in 10 develop ulcer disease. Gastric adenocarcinoma is 3 to 12 times more likely to develop in individuals infected with *H.pylori* [33].There a number of postulated mechanisms whereby *H.pylori* can cause injury to mucosa, urease can result in ammonia production and hemostatic factors and cytotoxins(e.g., protease, lipases and phospholipase A and vacuolatingcytotoxin) can cause injury[1].H.pylori is more likely to associated with the early or initial states of primary gastric lymphoma than advanced tumors;*H.pylori* can disappear during progression of gastric lymphoma[34].*H.pylori*-specific IgG antibody concentrations can be expected to fall significantly after successful antibacterial therapy[35].Asymptomatic and untreated patients continue to test IgG seropositive as long as *H.pylori* is present,even after histological resolution[36].Eradication of *H.pylori* is associated with significant reduction in duodenal ulcer recurrence[37],and is also useful in differentiating between *H.pylori* gastritis and gastric MALT lymphoma(mucosa-associated lymphoid tissue)[38].In *H.pylori* infected patients who develop gastric cancer, serum IgG against CagA is 94% sensitive and 93% specific, indicating that detection of antibodies to CagA is useful marker for diagnosis of duodenal and gastric cancer[39].

**NSAIDs**.Worldwide studies have confirmed that *H.pylori* infection was present in more than 90% of patients with duodenal ulcers and about 85 % of those with gastric ulcers, and they suggested that majority of the remaining ulcers were related to the use of nonsteroidal anti-inflammatory drugs(NSAIDS)[16,40,].The use of NSAIDS is the major cause of peptic ulcers, although the pathophysiological interaction between *H.pylori* infection and NSAIDS is still controversial[41].Surprisingly, a number of recent reports from around the world, especially from the United States and Australia suggest a relatively low prevalence of infection of *H.pylori* in duodenal and gastric ulcers, even when the users of NSAIDS ,are excluded[42].In the greater Rochester area, New York, only 61% of patients with non-NSAIDS induced duodenal as well as gastric ulcer showed the presence of *H.pylori*[43],but the situation is not the same outside the USA.In Europe, three studies from Scotland, Denmark, and Italy show a prevalence of *H.pylori*-negative ulcer 10-15 % which is lower than that observed in the US, but still higher than expected [44,45].NSAIDs interfere with mucosal defense in the stomach via direct toxic effects in addition to cyclooxygenase inhibition and depletion of endogenous prostaglandins[46].Among drugs diclofenac and aspirin are the most common commonly associated drugs[47].Aspirin increases the risk for gastric ulcer in patients of all ages, whereas non-aspirin,nonsteroidal use increases the gastric ulcers to varying degrees in patients over 55,depending on race and history of ulcer[48].The use ofNSAIDs increases the risk of peptic ulcer 3-anf 5 fold in *H.pylori* positive and *H.pylori* negative patients, respectively[49].The success of eradication therapy should always be confirmed, because of the risk of ulcer recurrence and bleeding in *H.pylori* infected patients who require anti-inflammatory treatments[50].

**Past gastric ulcer and family history** of ulcer disease, is an increased risk of recurrence with *H.pylori*infection [51].Family history of gastric ulcer disease is a risk factor [52] as there are some genetic predisposing to develop the disease, but there is no genetic relationship in developing *H.pylori*infection. Some research results suggest that there is a significant association between genetic polymorphism at the PGR-RFLP gene locus and gastric body ulcer [52].Genetic play an important role in ulcer pathogenesis. The concordance for peptic ulcer in identical twins is approximately 50%,and the lifetime prevalence of developing ulcer in first degree relatives of ulcer patients is about three-fold greater than in the general population. The inheritance of blood group 0 is associated with modest (1.3 fold) increase in duodenal ulcer [53].

**Stress and diet**.Stress due to serious health problems such as those requiring treatment in an intensive care unit is well described as a cause of peptic ulcers, which are termed stress ulcers [54].While chronic life stress was once believed to be the main cause of ulcers this is no longer the case. Itis, however, still occasionally believed to play a role [55].Dietary factors such as spice consumption, were hypothesized to cause ulcers until late in the 20$^{th}$ century, but have been shown to be of relatively minor importance [56].Caffeine and coffee, also commonly thought to cause or exacerbate ulcers, appear to have little effect [57].Skipping of meals allows gastric acid to directly act on surface mucosa of the stomach causing irritation which ultimately leads to gastric ulcers. Gastric ulcers cause abdominal pain which aggravate with meals [58].

**Smoking and alcohol**.Consumption of alcohol and smoking are risk factors. Chronic alcohol disturbs gastric mucosal barrier by inhibiting COX 1 receptor enzymes which reduce the production of cytoprotective prostaglandin.Cigarette smoking causes reduction of circulating epidermal growth factor and increase free radical production in gastric mucosa[59,60].Although some studies have found correlations between smoking and ulcer formation.Others have been more specific in exploring the risks involved and have found that smoking by itself may not be much of a risk factor unless associated with *H.pylori*infection [61,62].Researchers in Denmark in a series of 2416 subjects found that tobacco smoking and *H.pylori* infection are the main risk factors for PUD in Danish adults[63].Studies have found that alcohol consumption increases risk when associated with *H.pylori*infection, it does not seem to independently increase risk.Even coupled with *H.pylori*infection, the increase is modest in comparison to the primary risk factor[62,].Satarasinghe and colleagues in a series of 1500 patients found alcohol was a contributory factor in one third of gastrointestinal bleeding(IGIB)patients[64].

## IV.  Clinical Manifestations

Clinical manifestations include:[65].abdominal pain, classically epigastric strongly correlated to mealtimes, bloating and abdominal fullness,water brashnausea and vomiting, loss of appetite and weight loss, hematemesis(vomiting blood),melena(tarry, foul-smelling feces due to presence of oxidized hemoglobin),gastric or duodenal perforation, which leads to peritonitis. A history of heart burn, gastroesophagealreflux(GERD) and use of medications can raise the suspicion for peptic ulcer. In patients over 45 with more than two weeks of above symptoms, the odds for peptic ulceration are high enough to warrant rapid investigation by esophagogastrodudenoscopy(EGDS).Timing of the symptoms in relation to meal may differentiate between gastric and duodenal ulcers: A gastric ulcer would give epigastric pain during the meal, as gastric acid production in increased as food enters the stomach. Symptoms of duodenal ulcers would initially be relieved by

a meal, as the pyloric sphincter closes to concentrate the stomach contents, therefore acid is not reaching the duodenum .Duodenal ulcer pain would manifest mostly 2-3 hours after the meal, when the stomach begins to release digested food and acid into duodenum. Also symptoms of peptic ulcers may vary with the location of the ulcer and patient's age.[66].The pain caused by peptic ulcers can be felt anywhere from the navel up to the sternum.it may last few minutes to several hours and it may be worse the stomach is empty.Also,sometimes the pain may flare up at night and it can commonly be temporarily relieved by eating foods that buffer stomach acid or by taking antacid[67].However, peptic ulcer disease symptoms may be different for every sufferer[68].

**Other clinical presentations**include: **acute presentation**-natural,voluntary,or accidental *H.pylori* acquisition can cause acute upper gastrointestinal illness with nausea and upper abdominal pain[69],**chronic colonization** in most persons after acquisition *H.pylori* persists for years, if not for decades[67],**duodenal ulceration** in the absence of medication-associated ulceration,more than 90 % of patients with duodenal ulceration carry *H.pylori*,an occurrence that is significantly more common than in age-matched controls[70]

**Complications**.Frequentcomplications of PUD include:[71],gastrointestinal bleeding (GIB) is the most common. It occurs when the ulcer erodes one of the blood vessels, such as gastrointestinal artery,perforation or Valentino's syndrome(named after silent- film actor who experienced this pain before his death) often leads to catastrophic consequences if left untreated,perforation and penetration are when ulcer continues into adjacent organs such as the liver and pancreas[66],gastric outlet is the narrowing of pyloric canal by scarring and swelling of gastric antrum and duodenum due to pepticulcers. Patient often presents often with severe vomiting without bile,and cancer is included in the differential diagnosis (elucidated by biopsy),*Helicobacter pylori* as the etiological factor making it 3 to 6 times more likely to develop stomach cancer from ulcer [66].

## IV. Diagnosis

The diagnosis is mainly established based on the characteristic symptoms. Stomach pain is usually the first signal of a peptic ulcer. In some cases, doctors may treat ulcers without diagnosing them with specific tests and observe whether the symptoms resolve, thus indicating that their primary diagnosis was accurate [66].The demonstration of *H.pylori* colonization can be made either by invasively by endoscopy and biopsy or noninvasively by serologic analysis, breath test or fecal antigen detection [ 72].

## V. Management

*H.pylori* infection prevalence is higher in underdeveloped and developing countries and it is shown that the incidence has reduced with eradication therapy and improvement with sanitary conditions [73].A special diet is not indicated for patients with gastric ulcers. Better to avoid foods that may aggravate symptoms (fatty foods, spicy foods, coffee).The major goal of diet is to avoid extreme elevations of gastric acid secretion and the direct irritation of gastric mucosa[74].Smoking and alcohol intake are risk factors and both occurrence and prolongation of healing ulcers.Thus it is important to avoid alcohol and cigarette smoking[75].In a case of NSAID induced gastric ulcer disease or in patients with positive *H.pylori* test results,NSAIDs should be immediately discontinued. In a patient who must continue NSAIDs, one option is changing the drug to COX-2 selective inhibitor if possible. If same drug should be continued, PPI maintenance is recommended in preventing recurrences even after the eradication of *H.pylori* infection.tretment with prostaglandin analogue or a PPI is helpful in patients with bleeding ulcers and 6-8 weeks of treatment is needed for complete healing [76].Surgical care for perforated peptic ulcer should include emergency laparotomy in peritonitis, the surgery will include simple closure, truncal vagotomy and pyloroplasty and gastrectomy[77].Endoscopy balloon dilatation ,endoscopic incision have circumvented the use of surgery. Surgery is the gold standard for management of gastric outlet obstruction. Newer modalities like bio gradable stents also plays a role in the management [78].In gastric carcinoma surgery is the only curative treatment. Aim of surgery is to remove all grossly visible tissue and to obtain histologically tumor free surgical margins. Endoscopic (submucosal resection (EMER) or dissection (ESD), minimally invasive surgery,and open gastrectomy are the three major approaches in surgery [79].

## VI. Therapy

The treatment regimens that attain eradication rates of 90% or greater by per-protocol analysis and 80% or greater by intent-to-treat analysis are recommended for *H.pylori* infection[80].The regimens include: (a) Proton pump inhibitor(PPI) in standard dose + clarithromycin 500 mg + amoxicillin 1000 mg each given twice daily (b)PPI in standard dose + clarithromycin 500mg + metronidazole 400 mg ,each given twice daily(c)Ranitidine bismuth citrate(RBC) 400mg + clarithromycin 500 mg + amoxicillin 1000mg,each given twice daily (d)RBC 400 mg +clarithromycin 500 + metronidazole 400 mg, each given twice daily. Each of above regimen should be given for 7 days [81,82].

The national Institutes of Health Consensus Conference in 1994 concluded that ulcer disease was an infectious disease that could be cured by bacterial eradication [74.]Triple therapy is consistsof: a PPI,a combination of two antimicrobials such as amoxicillin and clarithromycin [83].

Quadruple Therapy: PPI(standard dose twice daily)+ metronidazole (500mg 3 times daily) + tetracycline(500 mg 3 times daily ) + bismuth(dose depends on preparation) for 10 days.

Sequential therapy:PPI(standard dose twice daily) + amoxicillin (I g twice daily ) for 5 days followed by PPI(standard dose twice daily ) + clarithromycin (500mg twice daily) + tindazole (500mg twice daily) for 5 daysLevofloxacin triple therapy:PPI (standard dose twice daily) + amoxicillin (Ig twice daily) +levofloxacine(500mg twice daily ) for 10 days.

Rifabutin triple therapy:PPI(standard dose twice daily) + amoxicillin (I g twice daily) +rifabutin (150-300 mg/day) for 10 days[83-85].

**Reinfection and treatment failure**.Reinfection after eradication is uncommon and appears to occur at rates as low as 1 % in developed countries [86].Following treatment failure with PPI-or RBC-based clarithromycin and amoxicillin combination, the same regimen may be repeated. Following one treatment failure with a regimen containing metronidazole, treatment may be repeated substituting amoxicillin for metronidazole [81,82].

**Therapy issues**: Therapeutic issues include:
a) The topical action of effective antibiotics is importantb) At increased gastric pH levels, the efficacy of many antibiotics is enhanced, which may help explain the higher rates of eradication of *H.pylori* when antimicrobials are combined with $H_2$ blockers or omeprazole.c) Compliance is important yet difficult because of high incidence of side effects with these regimens d) Acquisition of resistance during antibiotic therapy is a concern, especially with metronidazole, and may explain why some patients eradication of *H.pylori* fails with standard regimens.e)Reinfection after eradication is uncommon and appears to occur at a rate of 1-3 % annually[87,88.].

# VII.    Conclusion

*H.pylori* was associated with risk of gastric, duodenal ulcers and gastric cancer.NSAIDs increases the risk for gastric ulcer in patients. The success of eradication therapy should always be confirmed, because of the risk of ulcer recurrence and bleeding in *H.pylori*-infected patients who require NSAIDs treatment**.**

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