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ROLE OF HELIOCOBACTER PYLORI INFECTION IN PEPTIC ULCER DISEASE

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ABSTRACT

The discovery of*Helicobacter pylori*in 1982 confirmed its role in the gastric ulcer disease.With medical advances and introduction of new antimicrobial agents with extended spectrum against *H.pylori*,the high mortality rate associated with the organism in gastric cancer continues. Gastric acid hypersecretion is still considered to be a necessary factor; it is not a sufficient etiological factor. Extensive scientific research shows that two major etiological factors involved in PUD are infection with *H.pylori* and ingestion of non-inflammatory drugs (NSAIDs).Diet and genetic are important factors Persons with serological evidence of carrying *cag*-positive strains are at high risk of developing both PUD and gastric carcinoma Diagnosis of *H.pylori* infection both by invasively by endoscopy and biopsy or noninvasively by serologic analysis, and breath test.Common therapies include proton pump inhibitor, such as omeprazole and lansoprazole, and are used as parts of triple, quadruple, and sequential therapies.

KEYWORDS: Helicobacter Pylori, Peptic Ulcer Disease, Nsaids

INTRODUCTION

Helicobacter pylori (formerly known as campylobacter pylori)was first isolated from humans in 1982 [1].H.pylori commonly found in the human stomach, when, asthe single dominant species; essentially all persons colonized with H.pylori have a cellular infiltrate in the lamina propria of the gastric antrum and fundus [2].Of special significance is that H.pylori is present in most persons with “idiopathic” peptic ulcer disease(PUD). The presence of H.pylori increases peptic ulcer disease and gastric cancer [3,4],but decreases the risk of esophageal reflux and its consequences, and may protect against childhood asthma and related disorders [5,6] H.pylori has been isolated from persons from all parts of the world, it now appears likely that, humans are the major, if not sole, reservoir for H.pylori [7,8].The high prevalence and incidence of colonization among persons in settings where sanitary conditions are suboptimal, including institutions for the mentally retarded and orphanages, and in developing countries do not reflect modern standards, suggesting the fecal oral transmission occurs [8].On occasion, transmission occurs from person to person via improperly cleaned endoscopes [9].The prevalence of *H.pylori*colonization is chiefly related to age and geographic location .Males and females have essentially equal rates of colonization ,with slight male predominance.[10].The incidence of *H.pylori* has been progressively declining in the United States and other developed countries [11].The first description of a perforated peptic ulcer was in 1670 in Princess Henrietta of England[12].Peptic ulcers are present in around 4% of the population. About 10% of people develop ulcer at some point in their life[13,14].They resulted in 301,000 deaths in 2013 down from 327,000 deaths in 1990[15].The paper reviews the current literature, and role *of H .pylori* in peptic ulcer disease.

PATHOGENESIS

H.pylori is able to survive and multiply in gastric environment, which is hostile to the growth of other bacteria [16].When intraluminal acidity diminishes as a result of gastric atrophy ,*H.pylori* is no longer able to colonize, possibly because of competing organisms. Outstanding *H.pylori* characteristics that permit gastric colonization include microerophilism for survival within mucus gel, spiral shape and flagella for motility within the viscous layer and urease activity, which generate ammonium ions that buffer gastric acidity [17].*H.pylori* overlies only gastric –type not intestinal-type, epithelial cells. Affected gastric !epithelial cells may be in the gastric antrum or fundus or may be ectopic in the duodenum or in the esophagus [18,2].In contrast,*H.pylori* does not colonize intestinal epithelium, even present in the stomach [2].The gastric tissue underneath *H.pylori* colonization virtually always has a cellularinfiltrate. The lamina propria most commonly contains mononuclear cells, including lymphocytes, monocytes, and plasma cells. Neutrophils and, to a lesser extend eosinophils may be present in the lamina propria and epithelium. Epithelial glands have a more complex architecture and less mucus than when *H.pylori* is absent[2].In children, a follicular lymphoid pattern is common. The presence of *H.pylori* induces these changes and the bacterium is not just a secondary colonizer- cells responses may have systemic regulatory functions [19].

The mechanism of tissue injury are not clearly established, and both bacterial and host factors may be determinants of outcome [20].*H.pylori* does not appear invadetissue, except as an incidental finding. Thus, the lesions are likely to reflect a response to extracellular products or to contact from organism.Ammonia, produced by urease and by deaminases,may potentiate neutrophil-induced mucosal injury [21].Both the *CagA* and *VacA* proteins are important signaling molecules elaborated by *H.pylori*,and host mount antibody responses to both [22,23].Strains from patients with ulcers or stomach cancer more commonly express CagA compared with controls. Urease may be shed by *H.pylori* cells, has been observed in affected tissues, and is a chemoattractant and activator of host phagocytic cells [3,23].

The presence of *H.pylori* overlying the gastric mucosa activates epithelial cells to produce proinflammayory cytokines [24],and activaltes mononuclear and polymorphonuclear cells to produce cytokines,superoxide,tumor necrosis factor-α,and other proinflammatory molecules [25].Because *H.pylori* persist in the stomach for many decades, these proinflammatory activities must be down regulated to permit this universally stable colonization [26].*H.pylori*positive persons have different T-cell populations in the gastric mucosa,with increased numbers of T-reg and T_H17 cells [19].These may be down regulating the local inflammatory responses but also may have systemic consequences [27].

Humans are polymorphic in the genetic loci involved in regulating proinflammatory cytokine production.Proinflammatory alleles regulating interleukins-1βand interleukin-10 affect risk of gastric cancer in *H.pylori* positive persons [28].Virtually all patients with duodenal ulceration are colonized by strains possessing *cag*A (thus *cag* pathogenicity island)[29].Thus *cag*A,the first gene described to not be conserved *among H.pylori*strains, is highly associated with both peptic ulcer disease and gastric cancer [30].In East Asia, most *H.pylori*strains are *cag*A [27].

Persons colonized with *H.pylori* have different gastric secretory physiology than do those who are not colonized. On average, colonized persons have higher gastric levels, which are reduced by eradication of the organism [31].The mechanism for increased gastrin production appears to be related to low gastric somatostatin levels[32],which may reflect cytokine production in the colonized antrum[33].Increased gastrin may contribute to the increase in parietal cell mass observed in many patients with duodenal ulceration. In contrast,*H.pylori*products may indirectly affect parietal cells [34],

which may diminish acid production. That*H.pylori* involves gastric tissues concerned with both acid production(fundus) and its regulation(antrum) may in part be responsible for the multiplicity of potential outcomes of its colonization[21].Differences among colonized hosts in cell- mediated immunity and cytokine responses to *H.pylori* are other possible determinants of outcome variability[35].Findings similar to those observed in humans develop in nonhuman primates colonized with *H.pylori*[36].The development of experimental *H.pylori* infections in conventional rodents and inhuman volunteers[37],has allowed new avenues for exploring host –microbe interaction[38].

ROLE OF NSAIDS IN PUD

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)[39,40].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, NewYork, 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].

CONTRIBUTORY FACTORS IN PUD

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 as stress ulcers[46].

Dietary factors such as spicy consumption, were hypothesized to cause ulcers until late 20th century, but have been shown to be of relatively minor importance [47].Caffeine and coffee ,also commonly thought to cause or exacerbate ulcers, appear to have little effect[48].Similarly,while studies have found that alcohol consumption increases risk when associated with *H.pylori*infection, it does not seem to independently increase risk. Even when coupled with *H.pylori*infection, the increase is modest in comparison to the primary risk factor[49].

Smoking.Although some studies have found correlation between smoking and ulcer formation [50].Other has been more specific in exploring the risks involved and has found that smoking by itself may not be much of a risk factor unless associated with *H.pylori* infection[49].Gastrinomas(Zollinger Ellison syndrome),rare gastrin-secreting tumors, also cause multiple and difficult to-heal ulcers[2].

CLINICAL SYMPTOMS

Acute Presentation

Natural,voluntary, oraccidental *H.pylori* acquisition may cause an acute upper gastrointestinal illness with nausea and upper abdominal pain [51].Vomiting, burping, and fever may be present. Symptoms last from 3 to 14 days, with most illnesses persisting less than 1 week. A diagnosis of foodpoisoning may be made in persons seeking medical attention. For many individuals, the acquisition of *H.pylori* is clinically silent [51].One adult volunteer who ingested *H.pylori* seemed to

have had an acute self-limiting infection [51].

Chronic Colonization

In most persons after acquisition *H.pylori* persists for years, if not for decades [51].Not every exposure to *H.pylori* leads to persistent colonization, either due to lack adaptation to the particular host or to coincident or proximate use of antibiotic [52].the acute *H.pylori*-induced upper gastrointestinal symptoms do not return in most persons; most with persistent *H.pylori* colonization are asymptomatic. However, studies of patients with nonulcer dyspepsia indicate that *H.pylori* may be slightly more common in cases than in age-matched models, and that *H.pylori* colonization may be one of the causes of this common but poorly defined heterogeneous group of disorders [53].Supporting this hypothesis are the results of some studies indicating that some patients with nonulcer dyspepsia who are colonized with *H.pylori* show better responses to antimicrobial therapy than to placebo, an effect not seen in patients with nonulcer dyspepsia who do not have *H.pylori* colonization [54,55].

Peptic Ulcer Disease

Gastric ulceration. A smaller -50% to 80% proportion of patients with benign gastric ulcer than with duodenal ulceration are colonized by *H.pylori*.The major reason is that a much higher proportion of gastric are due to NSAIDs or aspirin use, When such use is excluded most the remaining patients with benign gastric ulcer are colonized with *H.pylori*,which significantly more common than age-matched controls [56].The results of treatment of gastric ulceration with antimicrobial agents parallel the results of treatment of duodenal ulceration, changing its natural history [57].

Dudenal 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 [58,59].Conversely, duodenal ulceration in the absence of aspirin or NSAIDs use or Zollinger-Ellison syndrome is usually associated with *H.pylori* colonization..*H.pylori* may colonize the duodenum but only overlies metaplastic islands of gastric –type epithelium(gastric metaplasia) [2].The occurrence of *H.pylori* colonization gastric metaplasia is highly associated with active duodinitis,a precursor lesion to ulceration, and the presence of *H.pylori* in the duodenum is associated with a markedly increased risk of duodenal ulceration [60,61] Previous *H.pylori* colonization is associated with three to four fold increased risk of development of either gastric or duodenal ulceration and the risk of *cagA*$^{+}$ strains [58,3].In total a significant body of evidence association *H.pylori*colonization with idiopathic duodenal ulceration has accumulated. A causative role of *H.pylori* in ulcer disease is unproven; none of the experimental human studies have shown progression to ulceration and why peptic ulcer has a remitting and relapsing course in the face of persistent colonization has never been resolved [62].

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 [63].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 [27].

THERAPY

The most commonly used therapies include proton pump inhibitor, such as omeprazole and lansoprazole, and used as parts of triple, quadruple and sequential [64-66]therapies:

Proton pump inhibitor (PPI) triple Therapy: PPI(standard dose twice daily) + amoxicillin (I g daily) + clarithromycin (500mg twice daily) for 7 to 10 days.

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 days

Levofloxacin 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.

CONCLUSIONS

In PUD *H.pylori* infection and history of NSAIDs are important factors. Persons with serological evidence of *H.pylori* virulence factors cagA,vacA and newly discovered *dupaA* are at increased risk of developing PUD.A successful eradication of *H.pylori* is the main goal.

REFERENCES

1. **Marshal BJ**.History of the discovery of *Campylobacter pylori.In BlaserMJ.ed.Campylobacter pylori in Gastritis and Peptic Ulcer Disease.New York:IgakuSchoin*,1989;7-23.
2. **Tham KT,Peek RM,Atherton JC**,*et al.Helicobacter pylori* genotypes,host factors,and gastric mucosal histopathology in peptic ulcer disease.*Hum Pathol*.2001;**32**:264-73.
3. **Nomura AMY,Perez-Paerez GI,Lee J,***et al.*Relationship between *H.pylori*cag Astatus and risk of peptic ulcer disease. *Am J Epidemiol.*2002;**155:**1054-59.
4. **Blaser MJ.**The changing relationship of *Helicobacter pylori* and humans :implications for health and disease.*J Infect Dis.*1999;**179**:1523-30.
5. **Helicobacter and Cancer Collaborative Group.**Gastric cancer and *Helicobacter pylori*: a combined analysis of twelve case-control studies nested within prospective cohorts.*Gut.*2001;**49**:347-53.
6. **Chen Y,Blaser MJ.**Inverse associations of *Helicobacter pylori* with asthma and allergy.*Arch Intern Med*.2007;**167**:821-27.
7. **Taylor DN,Blaser MJ.**The epidemiology of *Helicobacter pylori* infections. *Epidemiol Rev*.1991;**13**:42-59.
8. **Falush D, Writh T,Linz B,*et al.***Traces of human migration in *Helicobacter pylori*

populations.*Science*.2003;**299**:1582-85.

9. **Graham Dy,Alpert IC,Smith JI,***et al***.**Iatrogentic *Campylobacter pylori* infection is a cause of epidemic achlorhydria.*Am J Gastroenterol*.1988;**83**:974-80.
10. **Perez –**Perez GI,Bodhidatta I.Wongsrichanalai J,*et al*.Seroprevalence of Helicobacter pylori infections in Thailand.*J Infect Dis*.1990;**161**:1237-41.
11. **Personnet J.**The incidence of *Helicobacter pylori*infection. *Aliment Pharmacol Ther*.1995;**9**: 45-51.
12. **Milosavljevic T,Kostic-Milosavlijev M,Jovanovic IKM**.Complications of peptic ulcer disease.*Digestive diseases(BaselSwistzerland)*.2011**;29**(5):491-3.
13. **Njm WI.**Peptic ulcer disease.*Primary care*.2011;**38**(3):383-94,vii.
14. Snowden FM.Emerging and reemerging diseases:a historical persepective.*Immunol Rev*.2008;**225**(1):9-26.
15. **GBD** 2013 Mortality and causes of death,Collaborators(17 December 2014) Global, reginol,and national age-sex specific all-cause and cause –specific mortality for 240 causes of death,1990-2013:a systematic analysis for the Global Burden Disease Study 2013.*Lancet*.doi:10.1016/S0140-6736(14)61682-2.
16. **Webb GF,Blaser MJ**.Dynamics of bacterial phenotype selection in a colonized host. ProcNatlAcadSci USA.2002;**99**: 3135-40.
17. **Scott DR**.**Werks D,Hong C**,*et al*.The role of internal urease in acid resistance of *Helicobacter pylori*.*Gastroenterol*.1998;**114**:58-70.
18. **Morris A,Maher K,Thomsen L,***et al*.Distribution of *Campylobacter pylori* in the lumen stomach obtained at post-mortem,*Scan J Gastroenterol*.1988;**23**:257-64.
19. **Lundgren A,Stromberg E,Sjoling A,***et al***.**Mucosal FOXP3-expressing CD4+CD25 high regulatory T cells in *Helicobacter pylori*-infected patients. *Infect Immun*. 2005; **73**:523-31.
20. **Letley DP,Rhead JL,Twells RJ,***et al***.**Determinants of non-toxicity in the gastric pathogen *Helicobacter pylori*.J Biol Chem.2003;278:26734-26741.
21. **Suzuki M,Miura S,Suematsu M,***et al***.***Helicobacter pylori* associated ammonia production enhances neutrophil dependent gastric mucosal cell injury. *Am JPhysiol*. 1992;**263**:G719-G725.
22. **Yamazaki S,Yamakawa A,Yoshiuki I,***et al*.The CagA protein of *Helicobacter pylori* is trans-located inti epithelial cells and binds to SHP-2 in human gastric mucosa.*J Infect Dis*.2003;**187**:334-7.
23. **Cover TC,Cao P,Murthy UK,***et al*.Serum neutralizing anti-body response to the vacuolatingcytotoxin of *Helicobacter pylori*.*J Clin Invest*.1992;**90**:913-18.
24. **Sharma SA,Tummuru MKR,Miller GG,***et al*.Interleukin-8 response of gastric epithelial cell lines to *Helicobacter pylori* stimulation in vitro .*Infec Immun*. 1995 :**63**:1681-87.
25. **Mai UEH,Perez-Perez GI,Whl LM**,*et al*. Soluble surface proteins from *Helicobacter pylori* activate monocytes/macrophages by lipopolysaccharide-independent mechanism.*J Clin Invest*.1991;**87**:894-900.

26. **Goodwin CS,Armstrong JA,Chilvers T,***et al.*Transfer of *Campylobacter pylori* and *Campylobacter mustelaeto Helicobacter* gene nov. as *Helicobacter mustelae* comb.nov.,respectively.*Int J sys Bacteriol*.1989;**39**:397-405.
27. **Blaser MJ.***Helicobacter pylori* and other gastric *Helicobacter* species.*In Mandell,Douglas and Bennett's Principles and Practice of Infectious Diseases*,7th Ed.Mandell GL,Bennett JE, JE,Dolin R(editors).Churchill Livingstone Elsevier, 2010. 2803-2813.
28. **EI-0mar EM,Carrington M,Chow WH**,*et al*.Interleukin-1 polymorphisms associated with increased risk of gastric cancer.*Nature*.2002;404:398-402.
29. **Blaser MJ,Crabtree JE**,Cag A and the outcome of the *Helicobacter pylori* infection. *Am J Clin Pathol*.1996;**106**:565-67.
30. **Nomura AMY,Lee J,Stemmeran G,***et al.Helicobacter pylori* cag A serosensitivity and gastric carcinoma in a Japanese American population.*J Infect Dis*. 2002; **186**:1138-44.
31. **Smith JTL,Pounder RF,Nwoklo CU,***et al.*Inapproprriate hypergasterinemia in asymptomatic healthy subjects with *Helicobacter pylori.Gut*.1990;**31**:522-525.
32. **Moss SF,Legon S,Bishop AE,***et al***.**Effect of *Helicobacter pylori* on gastric somastatin in duodenal ulcer disease.*Lancet*.1992;**340**:930-32.
33. **Blaser MJ.**Hypotheses on the pathogenesis and natural history of *Helicobacter pylori*-induced inflammation.*Gastroenterol*.1992;**102**:720-27.
34. **Cave DR,Vargas M**.Effect of a *Campylobacter pylori* protein on acid secretion by parietal cells.*Lancet*.1989;**2**:187-89.
35. **Kartunen R**.Blood lymphocyte proliferation,cytokine secretion and appearance of Tcells with activation surface markers in-cultures with *Helicobacter pylori*:comparison of the responses of subjects with and without antibodies to *H.pylori.Clin ExpImmunol*.1991;**83**:396-400.
36. **Hazel SL,Eischberg JW,Lee DR,***et al.*Selection of chimpanzee over the baboon as a model for*Helicobacter pylori* infection.*Gasteroenterol*.1992;**103**:848-54.
37. **Aebischer T,Bumann D,Epple HJ,***et al.*Correlation of T cell response and bacterial clearance in human volunteers challenged with *Helicobacter pylori* revealed by randomized controlled vaccination withTy21a-based Salmonella vaccines .*Gut* .2008; **57**:1065-70.
38. **Marchetti M,Arico B,Burroni D,***et al.*Development of a mouse model of *Helicobacter pylori* infection that mimics human disease.*Science*.1995;**267**:1655-58.
39. **Marshal BJ,Warren JR.**Curved bacilli in the stomach of patients with gastritis and peptic ulceration.*Lancet*.1984;**16**:1311-15.
40. **Kuipers Ej,Thijs JC,Festen HP.**The prevalence of *Helicobacter pylori* in peptic ulcer disease.*Phamacol Ther*.1995;**9**:59-69.

41. **Chan Fk,Leung WK.**Peptic ulcer disease.*Lancet*.2002;**360**:933-41.

42. **Quan C,Talley NJ.**Management of peptic ulcer disease not related to *Helicobacter pylori* or NSAIDS. *J Gastroenterol*.2002;**97**:2850-61.

43. **Jyotheeswar S,Shah AN,Jin H0,***et al***.**Prevalence of *Helicobacter pylori* in peptic ulcer patients in greater Rochester,NY:is empirical triple therapy is justified ?.*J Gastroenterol*. 1998;**93**:574-8.

44. **Meucci G,Di Battista R,Abbiati C,***et al*.Prevalence and risk factors of Helicobacter pylori negative peptic ulcer:a multicenter study.*Clin Gastroenterol*.2002;**31**:42-7.

45. **McColl Ke,el-Nujumi AM,Jittajallu RS**,*et al*.A study of the pathogenesis of *Helicobacter pylori* negative chronic duodenal ulceration.*Gut*.1993;**34:**762-8.

46. **Steinberg KP**.Stress- related mucosal disease in the critically ill patient: risk factors and strategies to prevent stress-related bleeding in intensive care unit. Critical care *med*.2002;**20**(6 Suppl):S362-4.

47. **National** Digestive Diseases Information Clearinghouse(http://digestive.niddk,nihgov.ddiseases/pubs/hoylori.For 100 years, scientists and doctors thought that ulcers were caused by stress, spicy food, and alcohol. Treatment involved bed rest and bland diet. Later researchers added stomach acid to the list of causes and began treating ulcers with antacids.

48. **Ryan Harshman M,Aldoori W.**How diet and lifestyle affect duodenal ulcers.Review of evidence..*Cand famil Physi Med de famille candadien*.2004**;50**:727-32.

49. **Salih B,M Fatih Abasiyanik,Nizammettin B,***et al***.***H pylori* infection and other risk factors associated with peptic ulcers in Turkish patients:A retrospective study. *World JGastroenterol*.2007**;13**(23):3245-8.

50. **Kato IA, MY,Nomura,Grant N**.A prospective study of gastric and duodenal; ulcer and its relationship to smoking, alcohol, and diet. *Am J Epideimol*.1992;**135**(5):521-30.

51. **Harford WV,Bernett C,Lee F,***et al*.Acute gastritis with hypochlorhydra: report of 35 cases with long term follow up.Gut.2000,**47**:467-72.

52. **Kang J,Blaser MJ.**Bacterial populations as perfect gases: genomic integrity and diversification tensions in *Helicobacter pylori*.*Nat Rev Microbiol*.2006;**4**:826-36.

53. Shallcross TM,Rathbone BJ,Heatley RV.*Campylobacter pylori* and non-ulcer dyspepsia.In:Rathbone RJ,Heatley RV,eds.*Campylobacter pylori and Gastrodudenal Diseases.*Oxford:Blackwell;1989;155-66.

54. **McColl K,MurrayJ, EL-0mar E**,*et al*.Symptomatic benefit from eradicating *Helicobacter pylori* infection in patients with non-ulcer dyspepsia.*N Engl JMed*.1998; 339:1869-74.

55. **Kang JY,Tay HH, Wee A**,*et al*. Effect of colloidal bismuth sub citrate on symptoms and gastric histology in non-ulcer dyspepsia: a double blind placebo controlled study.*Gut*.1990**;31**:476-80.

56. **Blaser MJ,Perez-Perez GI,Lindenbaum J,***et al*.Association of infection due to *Helicobacter pylori* with specific upper gastrointestinal pathology.*Rev InfectDis*.1991;13 (Suppl):S704-S708.

57. **Sung JJ,Chung Sc,Ling TK,***et al.*Antibacterial treatment of gastric ulcers associatedwith *Helicobacter pylori.N Engl J Med.*1995;**332**:139-42.

58. **Nomura A,Stemmerman GN,Chyou PH,***et al***.***Helicobacter pylori* infection and the risk for duodenal and gastric ulceration.*Am Intern Med*.1994;**120**:977-81.

59. **NIH Consensus conference.***Helicobacter pylori* in peptic ulcer disease. *JAMA.* 1994;**120**:977-81

60. **Wyatt JI,Rathbone BJ,Dixon MF**,*et al.Campylobacter pyloridis* and acid-induced gastric metaplasia in the pathogenesis of duodenitis.*J Clin Path*.1987**;40:**841-48.

61. **Carrick J,Lee A,Hazel S,***et al.Campylobacter pylori* duodenal ulcer and gastric metaplasia:possible role of functional hetero-tropic tissue in ulcer genesis.*Gut.* 1989;**30**:790-97.

62. **Blaser MJ.***Helicobacter* are indigenous to the human stomach: duodenal ulceration is due to changes in gastric microecology in the modern era.*Gut.*1998;**43:**721-27.

63. **PepticUlcer(**http://www.merckmanuals.com/home/digestive_disorders/peptic_disorders/peptic_ulcer.html).Home *Health Handbook for patients & Caregivers.Merck Manuals.*October 2006

64. **Vakil N,Vaira D**.Sequential therapy for *Helicobacter pylori*:time to consider making the switch?*JAMA*.2008;300:1346-47.

65. **Millar MR,Pike J**.Bacterial activity of antimicrobial agents against slowly growing *Helicobacter pylori.Antimicrob Agent Chemother*.1992;**36**:185-87.

66. **Graham** DY,Lew GM,Malaty HM,*et al***.**Factors influencing the eradication of *Helicobacter pylori* with triple therapy.*Gastroenterology.*1992;**102**:4930-96.