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Review Article

ROLE OF HELICOBACTER PYLORI IN PEPTIC ULCER: AN OVERVIEW

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Abstract

Abstract

Helicobacter pylori colonizes and grows in human gastric epithelial tissue and mucus. Its presence is associated with gastritis and there is substantial evidence that it causes peptic and duodenal ulcers and chronic gastritis. Since 1994, H. pylori has been classified as carcinogenic to humans. Helicobacter pylorus infection is one of the most common bacterial infections world wide.Nearly 50% of the world's population is affected. Though the prevalence of this infection appears to be decreasing in many parts of the world, H. pylori remains an important factor linked to the development of peptic ulcer disease, gastric malignancy and dyspeptic symptoms.4 Majority of H. pylori infected persons remain asymptomatic. Approximately 10- 15% of the infected persons develop associated illnesses, 1 to 10% developing peptic ulcer disease, 0.1 to 3% developing gastric cancer and less than 0.01% developing gastric mucosaassociated lymphoid tissue (MALT) lymphoma.

Key Words: Helicobacter pylori, Peptic ulcer

INTRODUCTION-

H. pylori is a type of bacteria a germ that may cause infection. H. pylori infection is common, particularly in developing countries, and often begins in childhood. Symptoms usually don't occur until adulthood, although most people never have any symptoms.[1] the current consensus is that H. pylori screening and eradication therapy are recommended for preventing the development of gastric cancer.[2]

Ulcer disease results from an imbalance between aggressive factors and the ability of the gastro-duodenal mucosal to protect and heal itself. Acid and pepsin secreted by the stomach are key 'aggressive elements' and are generally required for ulcers to develop. Helicobacter pylori and NSAIDs are the principal causes of impaired mucosal resistance and are the main cause of peptic ulcers. Other causes of peptic ulcer include pathologic hypersecretory states (e.g., Zollinger-Ellision syndrome, mast cell disease) and other infections (herpes simplex) but they are rare and will not be considered further here.[3] This increase has been attributed to the increased use of non-steroidal anti-inflammatory drugs (NSAIDs) and low-dose aspirin.[4,5]

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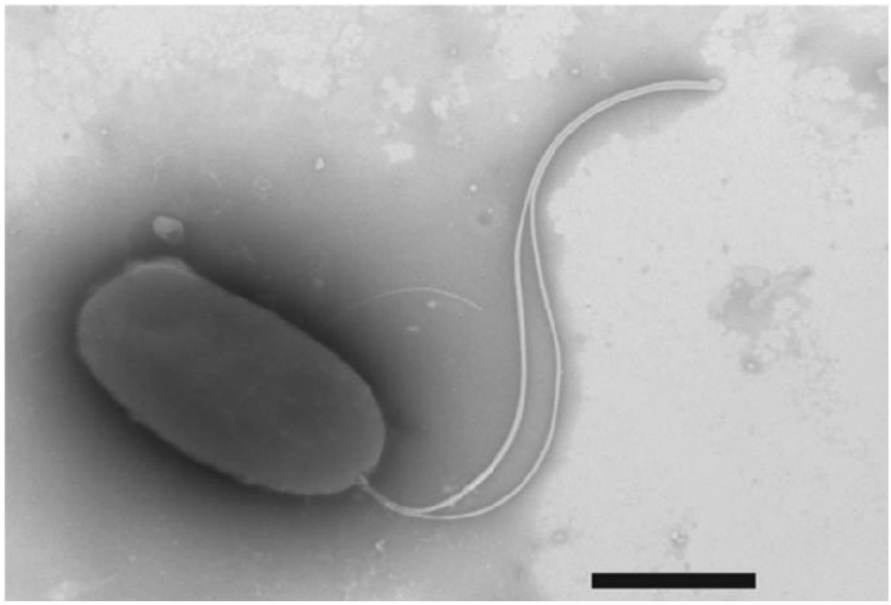

Fig1. Electron Micrograph of H. Pylori with Multiple Flagella (Negative Staining).

A better understanding of the mechanisms by which NSAIDs damage the stomach has led to the development of potent antiulcer agents and, recently, highly selective cyclo-oxygenase (COX)-2 inhibitors. Although there is evidence from large-scale clinical trials that these agents that reduce the gastrointestinal toxicity of NSAIDs, whether these findings will translate in to clinical benefits is unclear.[6] However, whether H. Pylori infection modifies the risk of ulcer in patients taking NSAIDs has generated many conflicting data.[7]

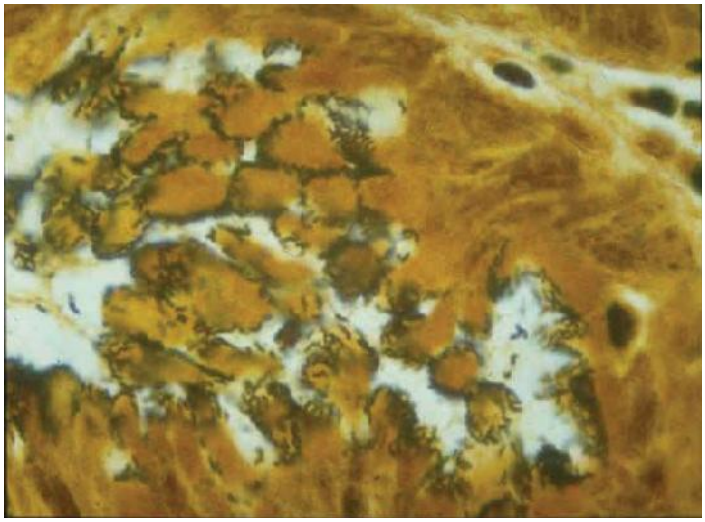

Fig2. A hematoxylin and eosin stained section of a stomach biopsy showing the presence of bacteria on the surface of cells.

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I. What Is It?

Gastritis is an inflammation of the stomach lining. The lining of the stomach often looks red, irritated and swollen, and it may have raw areas that can bleed.

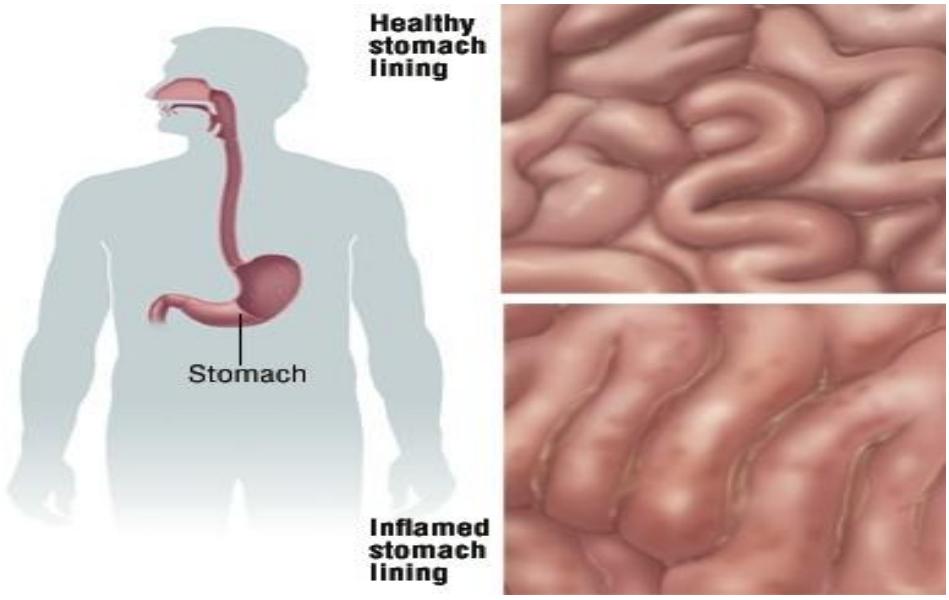

Fig3.Inflammation of the Stomach

Many different illnesses and irritants — acting either alone or in combination — can trigger the inflammation of gastritis. Some of the most common triggers include:

Infection with Helicobacter pylori (H. pylori) bacteria — In addition to causing gastritis, H. pylori infections have been linked to the development peptic ulcer disease, open sores inside the stomach or part of the small intestine. However, many people have H. pylori in their stomach and have no symptoms.

Viral infections — Brief bouts of gastritis are common during short-term viral infections.

Irritants — Chemical and environmental irritants can damage the stomach lining and cause gastritis. Common irritants include alcohol; cigarette smoke; aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (Advil, Motrin and others) and naproxen (Aleve, Naprosyn and others).

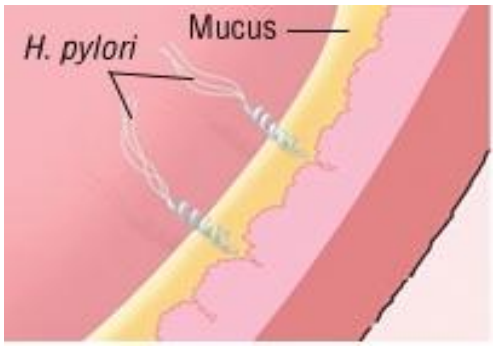

Fig4.H pylori invade and damage protective mucus layer

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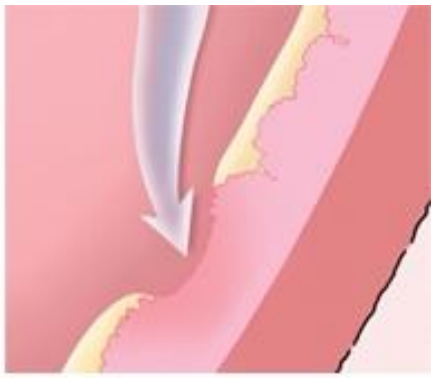

Fig 5.Stomach acid passes through weakened mucus layer causing an ulcer

What causes peptic ulcers?

A bacterium called Helicobacter pylori (H. pylori) is a major cause of peptic ulcers. Nonsteroidal anti-infl ammatory drugs (NSAIDs), such as aspirin and ibuprofen, are another common cause. Rarely, cancerous or noncancerous tumors in the stomach, duodenum, or pancreas cause ulcers. Peptic ulcers are not caused by stress or eating spicy food, but both can make ulcer symptoms worse. Smoking and drinking alcohol also can worsen ulcers and prevent healing.

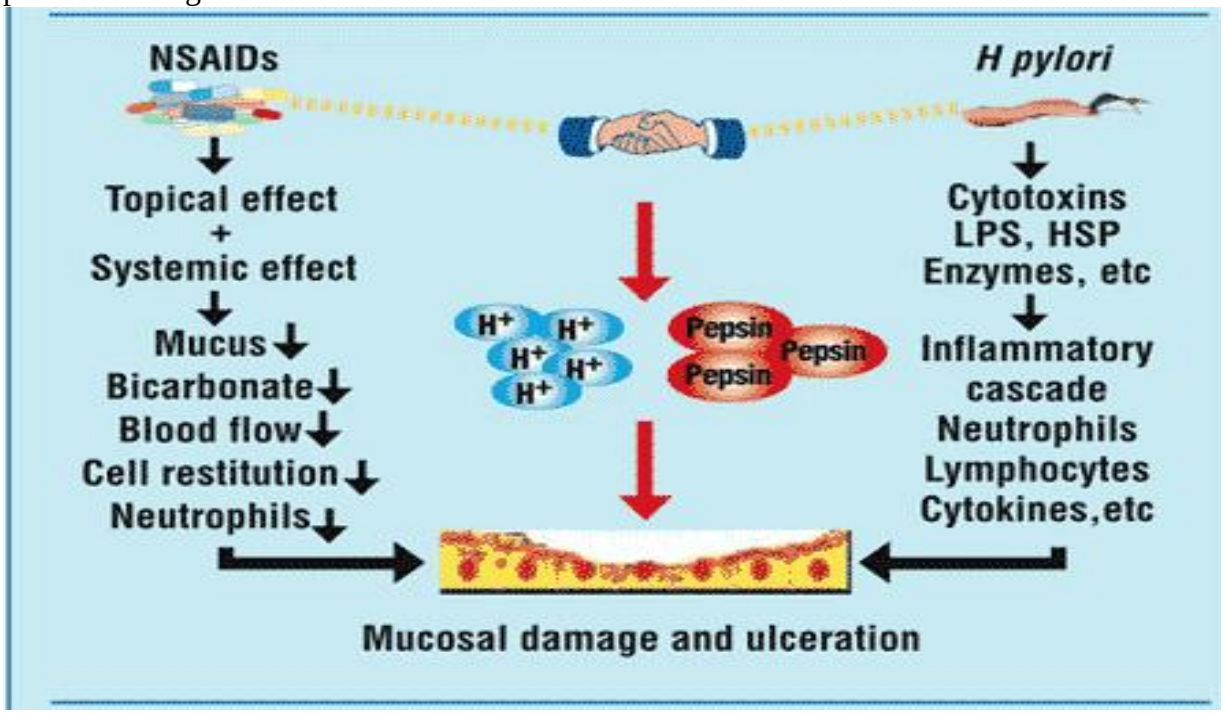

Fig6.Hpylori and Nsaid :Additive on Synergistic on Gastric Mucoal Damage

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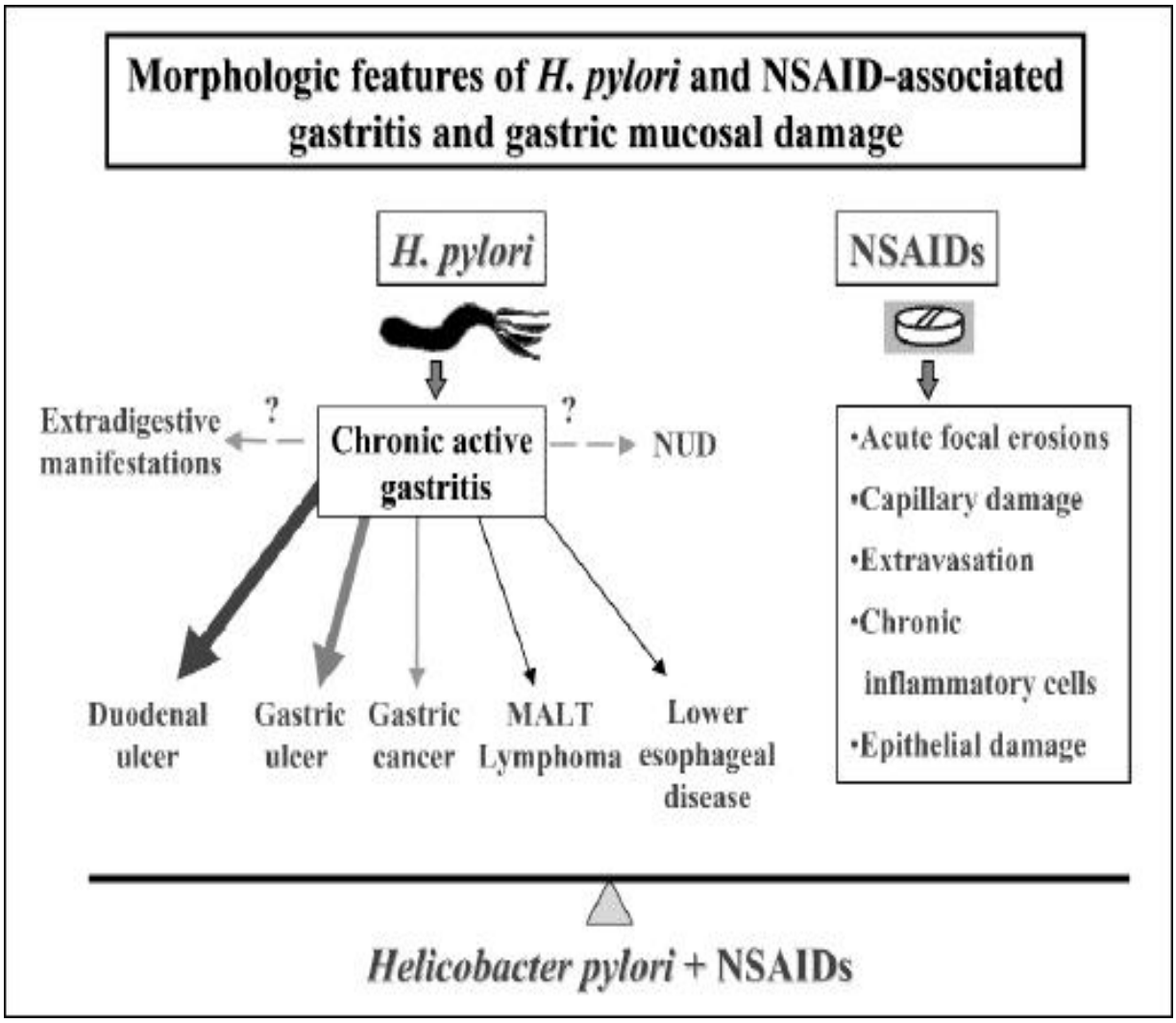

Fig 7. Morphological Features of H.Pylori And Nsaid Associated Gastric And Gastric Mucosal Damage

Mechanism of NSAID related ulcer formation

Colonizing gastric mucosa. ASA attracts polymorphonuclear (PMN) cells and triggers production of reactive oxygen species (ROS) while inhibiting of the COX enzyme-derived prostaglandins (PGE2 and PGI2). H.pyloriacts as a "Troyan horse" adhering to the surface epithelial cell compartment and injecting cytotoxins andammonia responsible for the aquisition of the bacteria in acidic envinroment of the stomach and triggers the activation ofneutrophils and inflammatory response mediated by proinflammatory cytokines (IL-8, TNF-alpha and IL-1ß).

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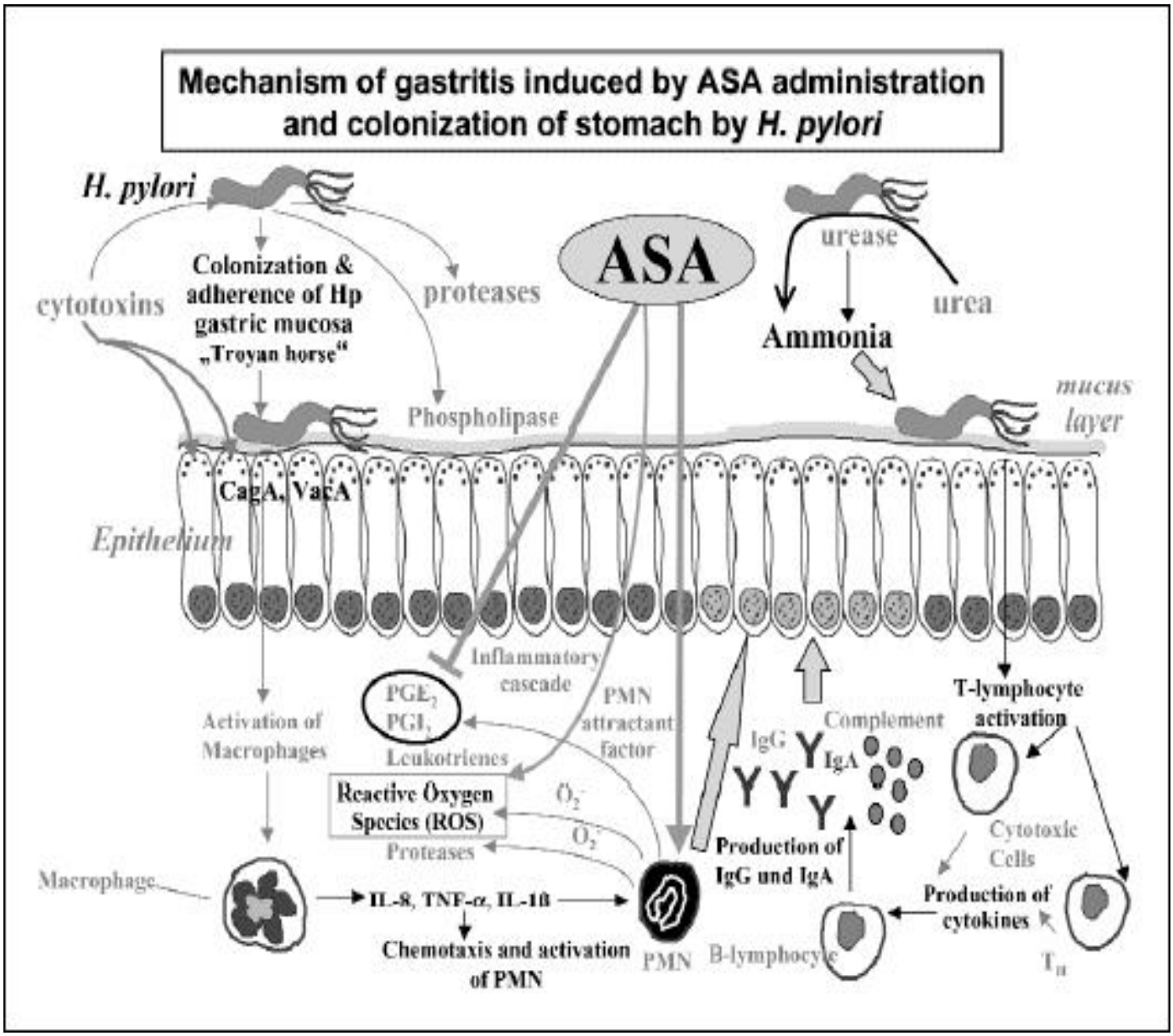

Fig8.Mechanism of Acute And Chronic Damage Induced By Nsaids Such Asaspirin (ASA) and H.Pylori

How is H. pylori spread?

Researchers are not certain how H. pylori is transmitted, although they think it may be spread through contaminated food or water. People may pick up the bacterium from food that has not been washed well or cooked properly or from drinking water that has come from an unclean source. Other research is exploring how infection spreads from an infected person to an uninfected person. Studies suggest that having contact with the stool or vomit of an infected person can spread H. pylori infection. And H. pylori has been found in the saliva of some infected people, which means infection could be spread through direct contact with saliva.

- **What are the symptoms of a peptic ulcer?**
- Abdominal discomfort is the most common symptom of both duodenal and gastric ulcers. Felt anywhere between the navel and the breastbone, this discomfort usually

- is a dull or burning pain
- occurs when the stomach is empty— between meals or during the night
- may be briefly relieved by eating food, in the case of duodenal ulcers, or by taking antacids, in both types of peptic ulcers
- lasts for minutes to hours
- comes and goes for several days or weeks
- Other symptoms of a peptic ulcer may include
- weight loss
- poor appetite
- bloating
- burping
- nausea
- vomiting

Some people experience only mild symptoms or none at all.

Emergency Symptoms

A person who has any of the following symptoms should call a doctor right away:

- sharp, sudden, persistent, and severe stomach pain
- bloody or black stools
- bloody vomit or vomit that looks like coffee grounds
- These “alarm” symptoms could be signs of a serious problem, such as
- bleeding—when acid or the peptic ulcer breaks a blood vessel
- perforation—when the peptic ulcer burrows completely through the stomach o duodenal wall
- obstruction—when the peptic ulcer blocks the path of food trying to leave the stomach

Pathophysiology

Patho-physiology of peptic ulcers

Up to 70% of gastric ulcers are associated with H. Pylori infection. Three types of gastric ulcers have been described. Type I ulcers occur in the body of the stomach and are not related to other gastro-duodenal disease. Type II ulcers also occur in the body of the stomach and are associated with a duodenal ulcer scar or active ulcer. Type III ulcers occur in the immediate pre-pyloric area. Type II and III ulcers are associated with higher levels of gastric acid secretion as seen in patients with duodenal ulcers, but type I ulcers tend to be associated with normal or low levels of gastric acid secretion. Role of H. Pylori in these different types of gastric ulcer is not known. Gastric acid secretion may not be the most important factor in the development of gastric ulcers as gastric ulcers have been seen in the presence of achlorhydria.[8] It has also been observed that basal and stimulated gastric acid secretion is within normal limits in groups of patients with gastric ulcers.

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Patho-physiology of duodenal ulcers

The mechanism by which Helicobacter pylori predisposes to duodenal ulcer is unclear. The pathogenesis of duodenal ulcer appears to be multi-factorial, involving an imbalance between "damaging" (e.g. acid, pepsin) and "protecting" (e.g. mucus, mucosal barrier, bicarbonate production, blood flow, cellular regeneration) factors.[9] The bacterium seems to affect different aspects of gastric and intestinal mucosal physiology that may contribute to development of ulcer disease. Disturbances in gastric acid secretion, gastric metaplasia, host inflammatory and immune response and down-regulation of various mucosal defence factors may contribute to ulcer formation. Various bacterial, host and environmental factors may also have a role in the pathogenesis of duodenal ulcer.

Disturbances in gastric acid secretion

Gastric acid secretion is elevated in patients with duodenal ulcers.[10,11] Helicobacter pylori infection can alter acid secretion in both directions. Acid secretion decreases temporarily during acute infection and may dwindle later if H. Pylori causes gastric atrophy.[12] In patients with duodenal ulcers, H. Pylori produces inflammation of non-acid secreting antral region of the stomach, whereas the more proximal acid-secreting fundic mucosa is relatively spared.[13]This may explain the increased gastric acid secretion in patients with duodenal ulcers. When compared to H. Pylori negative subjects, patients with duodenal ulcers have elevated basal acid output, peak acid output, fasting and meal-stimulated gastrin concentrations.[14]

H. Pylori infection is thought to change the physiological control of acid secretion. H. Pylori infection has been found to decrease the local expression of the inhibitory peptide somatostatin and to increase the release of the acid-stimulating hormone, gastrin. Hypergastrinemia, in addition to decreased inhibitory somatostatin, may be responsible for the increased gastric acid secretion. Hypergastrinemia may result from a decrease in the inhibitory peptide somatostatin.[15] Bacterial factors that inhibit somatostatin release have not been recognised, although TNF-alpha induced by H. Pylori infection may play a role in inhibiting somatostatin release.[16] In patients with H. Pylori infected duodenal ulcers, there is an exaggerate response to stimulation by gastrin. This may be due to increased parietal cell mass in patients with duodenal ulcers (Duodenal ulcer patients have approximately twice the normal parietal cell mass). [17] But it is unclear whether or not this is due to H. Pylori infection. Increased parietal cell mass may be due to trophic effects of hypergastrinemia over time or it may be related to host factors.[18]

Gastric metaplasia

Elevated gastric acid secretion increases the duodenal acid load, which damages the duodenal mucosa, causing ulceration and gastric metaplasia. Gastric metaplasia occurs in the duodenum in response to acidic PH (when PH is less than 2.5).[19]Metaplastic gastric epithelium allows H. Pylori to colonise the duodenal mucosa, where it produces an acute inflammatory response. Colonization of these areas of gastric metaplasia by H. Pylori may significantly increase the risk of ulceration.[20]However, gastric metaplasia is found in most, but not all patients with duodenal ulcers.[21-23] Gastric metaplasia can also be commonly found in the duodenum of healthy persons.[22-24]Therefore, the role of gastric metaplasia in the pathogenesis of duodenal ulcer disease is unclear. [25]

PATHOGENESIS OF H. PYLORI INFECTION

Although chronic gastritis will develop in nearly all individuals who are persistently colonized with H. pylori, 80% to 90% will never experience symptoms or develop clinical disease.2 It has not been clearly established as to how the presence of H. pylori leads to

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gastric and duodenal ulcers, but disruption of gastric and duodenal mucosal integrity seems to involve a complex interaction between the host and pathogen.[26, 27]

H. pylori infection elevates levels of gastrin, a gastrointestinal regulatory peptide that plays a key role in the physiologic regulation of gastric acid secretion.[28] H. pylori's effects on gastrin and acid are likely mediated through somatostatin, a peptide produced by antral D cells. Somatostatin, which serves as the ''brake'' for gastrin secretion, seems to be up-regulated or downregulated as a result of the severity and distribution of H. pylori-associated inflammation.[29] Eradication of the bacterium causes gastrin levels to return to normal. An acute H. pylori infection can cause transient hypochlorhydria,whereas persistent infection often leads to elevated secretion of acid, which predisposes patients to duodenal ulcers. Low acid secretion might predispose patients to gastric ulcer and, in some cases, lead to gastric carcinoma. The effects of H. pylori infection on gastric physiology are complex. The presence of H. pylori induces a chronic, active inflammation in the mucosa via the release of chemokines and cytokines (such as interleukin- 8, tumor necrosis factor-α, and interleukin-1β).[30]This immune response is usually unable to eradicate the organism and instead leads to persistent gastric mucosal damage as neutrophils, lymphocytes, and plasma cells are recruited to perpetuate the inflammatory state. The organism adheres to the gastric epithelium, which disrupts membrane integrity and induces host cells to elease cytotoxins, toxic proteins, platelet activating factor, and lipopolysaccharides that all further damage the gastric mucosa.[31,32]

H. pylori-related disease:

H. pylori infection causes the majority of duodenal (90-95%) and gastric ulcers (60-70%).The life time risk for developing a peptic ulcer among those with H. pylori infection is in the range of 1 in 6. H. Pylori infection is typically acquired in childhood and clinical disease only occurs after a long latent period during which progressive gastroduodenal damage occurs. H.pylori infection elicits an inflammatory response characterized by infiltration of both acute and chronic inflammatory cells, which tend to impair mucosal integrity. Until the discovery of H.pylori, therapy was directed toward improving mucosal resistance and reducing the aggressive factors of acid and pepsin. These approaches were effective in enhancing ulcer healing but did not eliminate the disease hence the sayings 'once an ulcer, always an ulcer' and 'no acid, no ulcer'. H. Pylori eradication is associated with ulcer healing, healing of the mucosal inflammation and restitution of the normal control mechanism regulating gastric acid secretion.

H. pylori eradication:

Anti-H.pylori therapy consists of the antibiotics often with antisecretory drugs. Triple therapy is a legacy therapy consisting of a proton pump inhibitor (PPI) and two antibiotics (combination of amoxicillin, clarithromycin or metronidazole). Cure rates with 7-10 days therapy are far below the expected cure rates of greater than 95% for other infectious diseases typically falling in the range of 60-80%.The most successful therapy is a 4-drugcombination (quadruple therapy) that consist of a PPI plus bismuth, a high dose of metronidazole and tetracycline (e.g., 500 mg of each three times daily) for 14 days. In areas with a high prevalence of clarithromycin resistant H.pylori, this combination is the preferred regimen.[33]

Diagnostic Methods to Confirm H.pylori Eradication:

H.pylori eradication was defined as a negative ^{13}c- urea breath test (with citric acid and 100 mg of urea, as previously reported)[34] preferred 8 weeks after completion of eradication treatment. The ^{13}c-urea breath test was carried out by operators unaware of therapy and patients' H.pylori status.[35, 36]

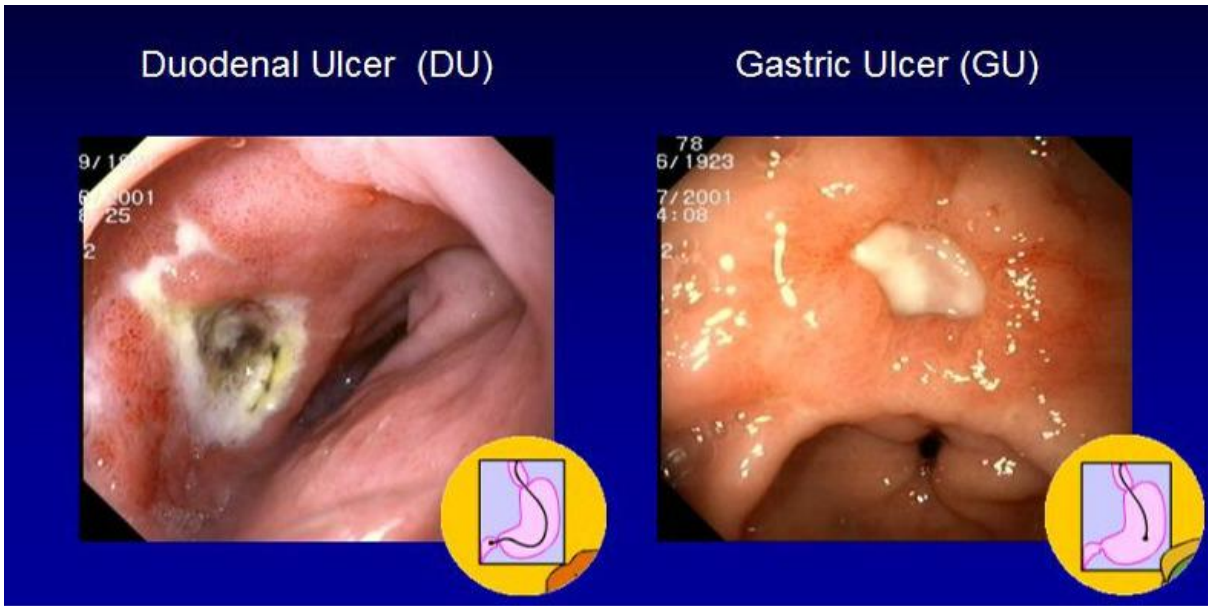

Fig 4.structure of duodenal ulcer and gastric ulcer

Mechanisms and targets to improve eradication rates:

One approach has been the sequential administration of drugs.[37-39]The underlying concept is to start with drugs that are rarely associated with resistance. This will markedly reduce the bacterial load, making the presence of a pre-existing small population of resistant organism less likely. The third or third and fourth drugs are then added to kill the remaining organisms. The reported sequential treatment regimen consists of a PPI plus amoxicillin for 5 days followed by a PPI plus clarithromycin (250 or 500 mg) and tinidazole (500 mg) for an additional 5 days. Head-to-head comparisons have shown superiority to the conventional triple therapy with the PPI and two antibiotics administered concomitantly. However all four drugs have been given as a 5-day concomitant therapy with excellent results making it unclear whether the proposed mechanism of improved results with sequential therapy is responsible for its improved effectiveness.[40, 41]

H.pylori and MALT Lymphoma:

Subsequent Maastricht II, important new data have been published which have strengthened

MALT LYMPHOMA

Evidence exists that, in addition to being associated with gastric cancer, H. pylori is also associated with the development of MALT lymphoma, the most common gastric and possibly gastrointestinal lymphoma. Gastric MALT lymphoma is a B-cell lymphoma but presumably results from chronic T-cell antigenic stimulation. It is far less prevalent than gastric adenocarcinoma, but its incidence parallels the rate of H. pylori infection in different countries. Lymphoid follicles are present in at least 30% of people with chronic, long-term H. pylori infection,3 and while benign, these follicles are assumed to be progenitors of MALT lymphoma. MALT lymphomas tend to progress very slowly and might manifest for a period of years as gastric ulcers that fail to completely heal, with symptoms ranging from dyspepsia to vomiting and gastrointestinal bleeding.3 Diagnosis requires specialized immunohistologic staining of tissue to confirm that lymphoid cells are monoclonal, malignant, and of B-cell origin. Tumor staging is best done with endoscopic ultrasound. An association between chronic H. pylori infection and gastric MALT lymphoma was recognized in the early 1990s, and a number of studies have confirmed this pathogenic link. Accordingly, testing and

treating for H. pylori infection has become an important part of tumor management. If the MALT lymphoma is at stage 1 (localized), eradication of H. pylori is now considered the accepted initial therapy. Results indicate that H. pylori eradication can lead to a complete remission in approximately 80% of cases of low-grade MALT lymphoma and can sometimes even lead to remission in cases of high-grade lymphoma, as well as lymphomas of the duodenum, small intestine, rectum, and salivary glands. However, H. pylori eradication as sole therapy for MALT lymphoma remains experimental, so it is recommended that other proven therapies be considered in addition to eradication especially for more advanced tumors.[42, 43, 44]

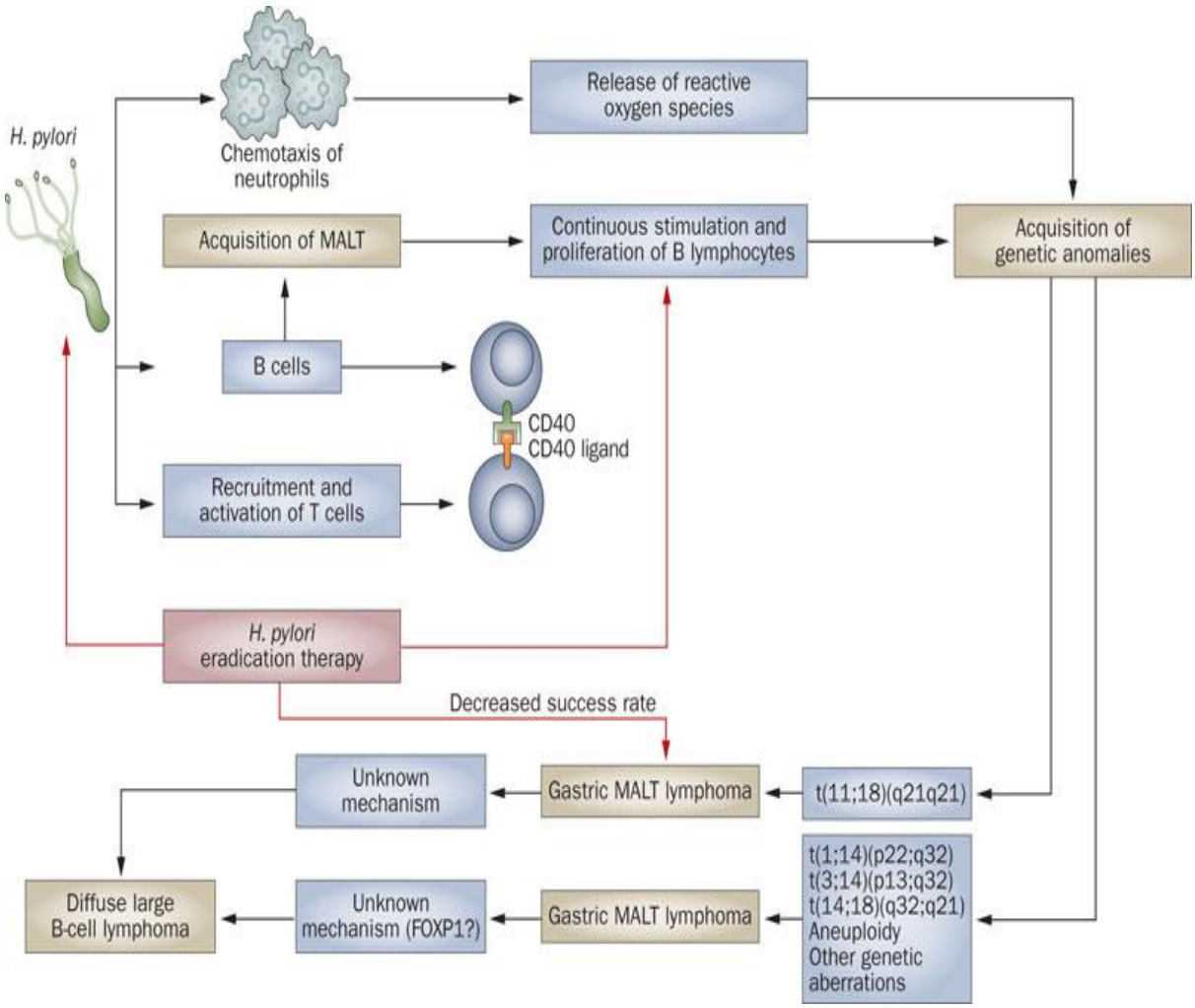

Fig 5. Hypothetical Model of Gastric MALT Lymphoma Pathogenesis

Detection and identification of H. pylori

Several tests are available to detect H. pylori. In an infected individual's stomach, H. pylori is the only organism that expresses urease: thus H. pylori can be detected indirectly by identifying urease in a biopsy specimen. Foods and faeces are not routinely tested for H. pylori. When they are tested, isolation and detection of the pathogen can be obscured by many factors (described below), leading to false negative results. Furthermore, the incubation

time of the infection might be too long to allow a connection to be made between the source of infection and
apparent clinical disease.[45,46]

Can antacids or milk help a peptic ulcer heal?

An antacid may make the ulcer pain go away temporarily, but it will not kill H. pylori. People being treated for an H. pylori ulcer should check with their doctor before taking antacids. Some of the antibiotics used to kill H. pylori may not work as well if combined with an antacid.

People used to believe drinking milk helped peptic ulcers heal. But doctors know now that while milk may make an ulcer feel better briefly, it also increases stomach acid, which can make ulcers worse. Patients should talk with their doctor about drinking milk while an ulcer is healing.

Can H. pylori infection be prevented?

No one knows for sure how H. pylori spreads, so prevention is difficult. Researchers are trying to develop a vaccine to prevent—and even cure—H. pylori infection. To help prevent infection, doctors advise people to

- wash their hands with soap and water after using the bathroom and before eating
- eat food that has been washed well and cooked properly
- drink water from a clean, safe source

Diagnostic procedures

Several factors, including the need for endoscopy, pretest probability of infection, local availability, and an understanding of the performance characteristics of the individual tests, influence choice of evaluation for an individual patient. Most diagnostic methods used for detecting H. pylori are negatively affected by drugs that suppress the bacterial population. Antibiotics and bismuth should not be used for 4 weeks before a test based on H. pylori urease production, such as rapid urease tests (RUT) performed at endoscopy and UBTs. Proton pump inhibitors should be stopped for at least 1 week before performing a diagnostic test. The diagnostic accuracy of UBT is >95%. These are accurate, practical and readily available tests, and are the mainstay of H. pylori diagnostics if the patient does not require an endoscopy.[47, 48, 49]

After reviewing your symptoms, the doctor will ask you about your lifestyle. Specifically, the doctor will want to know:

- The amount of alcohol you drink
- Medications you are taking, in particular aspirin or NSAIDs
- Whether you have tried over-the-counter antacids or other medicines to treat your symptoms and whether these helped
- Your doctor will examine you, paying special attention to your abdomen. He or she may do a digital rectal examination to obtain a small smear of feces or rectal fluids to be checked for the presence of blood.

Based on your medical history, symptoms and physical examination, your doctor will decide if you should try medical treatment first to see if symptoms improve or if you need further testing. You may need blood tests or a breath test to determine whether you have an H. pylori infection. In some cases, your doctor may want to inspect your stomach lining directly with a procedure called gastroscopy, in which a flexible, lighted instrument is passed into

your stomach. During the procedure, your doctor can take a biopsy, a small tissue sample to be examined in the laboratory

Common side effects
PPIs- Headache and diarrhoea

Clarithromycin -Gastrointestinal (GI) upset, diarrhoea, and altered taste
Amoxicillin GI upset, diarrhoea, and headache

Metronidazole -Tends to be dose related, a metallic taste, dyspepsia, a disulfiram-like reaction with alcohol consumption
Tetracycline -GI upset photosensitivity

Bismuth subcitrate -Darkening of the tongue and stool, nausea, and GI upset

Furazolidone -Nausea, vomiting, headache, and malaise in up to a third of patients. Less frequently hypersensitivity, hypotension, a disulfiram-like reaction with alcohol consumption, and mild reversible haemolytic anaemia.

Rifabutin -Red discoloration of urine while using the drug. Rash, diarrhoea, nausea, vomiting, dyspepsia. Small but serious risk of myelotoxicity and ocular toxicity. Can select for resistance among mycobacteria.

Points to Remember

- A peptic ulcer is a sore in the lining of the stomach or duodenum.
- Most peptic ulcers are caused by H. pylori. Use of NSAIDs—such as aspirin and ibuprofen—is another common cause.
- Neither stress nor spicy food causes ulcers. Smoking or drinking alcohol, however, each can worsen ulcers and prevent their healing.

The abdominal discomfort of peptic ulcers

- feels like a dull or burning pain occurs when the stomach is empty—between meals or during the night may be briefl y relieved by eating food, in the case of duodenal ulcers, or by taking antacids, in both types of peptic ulcers lasts for minutes to hours

Comes and goes for several days or weeks

- A combination of antibiotics and acid-reducing medicines is the most effective treatment for H. pylori-induced peptic ulcers.
- Testing after treatment is needed to be sure the H. pylori infection is gone.
- To help prevent an H. pylori infection, people should wash their hands after using the bathroom and before eating eat properly prepared food drink water from a clean, safe source.

Hope through Research

While H. pylori infection is becoming less common in developed countries, some strains of the bacteria have become resistant to antibiotics that are used to destroy it. Researchers have identifi ed and continue to study new antibiotic combinations that can kill these types of H. pylori.

Other promising research may help identify treatments that kill the H. pylori bacteria with fewer medicines in less time use different antibiotic combinations in back-to-back treatment better protect the stomach lining when eliminating H. pylori.

Researchers also are studying

- characteristics of H. pylori bacteria
- traits of people who develop H. pylori ulcers
- transmission of H. pylori infection
- vaccines to prevent and cure H. pylori infection

Participants in clinical trials can play a more active role in their own health care, gain access to new research treatments before they are widely available, and help others by contributing to medical research. For information about current studies.

Conclusions

Knowledge about the reservoirs and modes of transmission could help to explain the high prevalence rates found for H. pylori. Most studies have been crosssectional and have focused on the prevalence of and risk factors for H. pylori infection. Prevalence is high in developing countries (90%), whereas in industrialized countries the figure is lower (50%) and is decreasing. Childhood is the critical period for infection, and transmission most probably occurs from person to person. The iatrogenic route certainly exists, but is considered relatively unimportant. Much debate surrounds the oral–oral and faecal–oral routes, which are probably more significant.

H. pylorus continues to be one of the most common bacterial infections and much remains unknown about its pathogenesis and relationship to disorders of the gastrointestinal tract. On the basis of the extensive data, the general consensus is to treat H. pylori infection in patients with PUD and MALT lymphoma, with some recommending eradication treatment with those with precancerous changes in the gastric mucosa. However, the data relating to treatment of H. pylori in those with functional dyspepsia are more ambiguous. H. pylori's role in GERD is also less clear and the evidence for treating infection in the setting of GERD is not strong. Owing to the wide genetic diversity of H. pylori isolates and infected hosts, it has been difficult to define the host and microbial factors that determine the ultimate clinical outcome of H. pylori infection. A large body of information concerning genetic and virulence factors is available, but the relationships are not yet sufficiently defined to guide clinicians in making treatment decisions Antimicrobial resistance to agents commonly used to treat H. pylori remains a significant problem.72 Developing strategies for preventing H. pylori infection, as well as novel and alternative therapeutic regimens, will be important for future clinical practice.

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