Helicobacter pylori: A Major Causative Organism for Peptic Ulcer and its Eradication

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Abstract

Peptic ulcer is one of the most common diseases in the third world countries. This review illustrates the understanding of the pathogenesis of peptic ulcer. The theories and concepts regarding the onset of peptic ulcer have changed by the discovery of Helicobacter pylori. The discovery of H pylori, which proved that it plays a major role in causing ulcer. It has also been reported that H pylori has a tendency to cause non-ulcer dyspepsia and gastric carcinoma. The unique features of H pylori play an important role in the diagnosis of this infection and the establishment of diagnostic procedures for its eradication. The ideal treatment for the peptic ulcer is to focus on the relief of the pain, healing of ulcer and delay in its reoccurrence. These treatments are targeted on the cytotoxic factors and also on the enhancement of the activity of cytoprotective factors.

Key Words: H pylori, peptic ulcer, cytotoxic, antibiotics.

INTRODUCTION

Few centuries ago, peptic ulcer was considered a major cause of mortality and morbidity in many countries. With the discovery of the Helicobacter pylori by Marshall and Warren in 1982, they found that it occurs in the patients who are suffering from chronic gastritis and gastric ulcers. It was than believed that no organism is associated with these two diseases. The pathophysiology of peptic ulcer is associated with an imbalance between mucosal protective (cytoprotective) and mucosal aggressive (cytotoxic) factors that are present in the stomach. The major aggressive factor was believed to be gastric acid but then it was revealed that it is also due to the peptic enzymes activity in stomach. This cytotoxic mechanism consists of acid (HCl), pepsin (enzyme), medications that include NSAIDs (aspirin etc), bile acids and infection caused by H pylori. Cytoprotective mechanism includes mucous layer, local bicarbonate secretion, mucin, prostaglandins and mucosal blood flow and the disease is caused due to alterations in the cytoprotective mechanism.

Ulcers is defined as a deep wound that is penetrating throughout the lining of the gastrointestinal tract mucosal muscularis and mucosa. Peptic ulcer is also known as Peptic Ulcer diseases (PUD). It is believed that many factors play a vital role in the pathogenesis of peptic ulcer including smoking, alcoholism, spicy food intake, drugs, torpid activities and various infections that are caused by bacteria. In the past it was strongly believed that peptic ulcer is caused due to the stress and spicy food but later it was suggested that these two are only aggravating factors. The major cause of peptic ulcer is considered to be due to bacterial infection and also the reaction to some medicines.

Historical Background

The spiral bacteria was discovered in animals and later in human a century ago. In first half of the last century there was an awareness of the gastric urease activity present in animals and not of bacterial origin. In this century the postmortem studies confirmed the presence of gastric bacteria, but without convincing histopathologic changes. The studies carried out on fresh surgical specimen showed that there is a high prevalence of gastric bacteria in necrotic tissues that were surrounding a lesion. After this investigation it was concluded that the gastric bacteria were a secondary pestilence.

In 1970s with the discovery of fiberoptic endoscopy it was found that gastric mucosal biopsies from the patients with gastroduodenal pathology show the presence of spiral shape gram-negative bacteria which
was associated with acute inflammation. This organism was located on the surface of the gastric epithelium beneath the mucous layer of gastric cavity and the bacterium was phagocytized by neutrophils. This suggested an association between the presence of H pylori and chronic gastritis. Marshall later confirmed the Koch postulate on the role of H pylori, in antral gastritis during a self administration experiment which was repeated by many other researchers.

**Virulence OF H pylori**

Helicobacter pylori was originally classified as a species of Campylobacter pylori but there were many dissimilarities which included morphological and biochemical characteristics. These dissimilarities lead to the reclassification of the bacterium into Helicobacter pylori. This spiral shape gram negative bacterium display a number of specialties which not only permit it to live in a clashing environment of gastric cavity and thus cause injury to the gastric tissues. Strong peristaltic activity in gastric cavity does not allow any organism to have prolonged stasis. Routine secretion of hydrochloric acid (HCl) in stomach, to maintain pH in the range of 1 to 2 is a strong hindrance to potential pathogen. It has unique features which help it to overcome these difficulties. Due to these properties it has a widespread prevalence that varies with the ethnicity and age, in western countries it is about 20-40% in the adults and in third world countries it is about 60-80%.

Motility: It possess 4 to 6 unipolar sheathed flagella with bulbous tip which help in the motility of organism that can penetrate in viscous solutions like mucous layer. It has been confirmed that motility contributes to the virulence of the organism. Highly motile organism are 100% infective as compared to the nonmotile, which contribute only 17% to infect the animals.

Adhesion: It has a selective affinity toward gastric epithelium; its polysaccharide glycocalyx is capable of fusing with the gastric epithelial polysaccharide to form an adherence pedestal. The bacterium rarely penetrates into the gastric mucosa except in the setting of acquired immunodeficiency syndrome. It has been reported that this bacteria colonizes in heterotopic mucosa of gastric cavity in the proximal oesophagus, rectum and Meckel's diverticulum. Demonstration of H pylori colonization of gastric metaplasia in the duodenal bulb has been associated with duodentitis. The common condition that was thought to be correlated with acid exposure is gastric metaplasia of duodenal bulb.

**Urease and Other Enzymes:**

The survival of the bacterium in acidic medium is due to the powerful urease activity. As this enzyme is surface bound that breaks urea into ammonia and turns acidic pH to relatively alkaline. This permits the existence of H pylori at low pH (1.5) in the presence of considerable amount of urea. It also performs other function that is to hydrolyze urea into carbon dioxide (CO₂), which is the requirement of heterotrophic bacteria. Catalase present in these bacteria helps against the damaging effect of oxygen metabolites i.e. H₂O₂ (Hydrogen peroxide). This effect is very useful to avoid the destruction caused by neutrophils.

It appears to be resistant against the high concentration of H₂O₂ and also produces lipases, phospholipases and proteases, they have capability to destroy mucus layer of gastric cavity.

Toxins: Different pathogens produce different types of cytotoxins which gives the property of virulence to these pathogens. These pathogens include E. coli, Shigella species, Clostridium difficile, enterohemorrhagic and Campylobacter jejuni. H pylori contain two different types of toxins. First is cytolethal toxin that is produced in more than one half of the clinical isolates and second is vacuolating cytotoxin that is produced less than one half of the clinical isolates. The second type of toxins are present in 67% of the H pylori that were isolated from the patients that are diagnosed with peptic ulcer, and around 30% of this toxin is present in the patients which were labeled as gastritis.
H pylori and Peptic Ulcer

It has been found that 100% patients suffering from ulcers have the infection related to the H pylori. About 50% of the H pylori strains release cytotoxins, which in results cause gastritis and ulcer. These cytotoxins cause inflammation which along with other phospholipases and proteases attacks mucosal membrane and damage it. They also compromise with the gastrointestinal barrier and allow the back diffusion of the hydrogen ions that cause more severe injury. There is some evidence that the causing agent of this infection also reduces the amount of ascorbic acid in gastric juices, it has been found that the level of ascorbic acid in infected patients were only about 25% compared to that of healthy individuals. Eradication of this infection in result increases a considerable amount in gastric juice ascorbate and if this concentration is further decreased it result in peptic ulcer and gastric cancer.

DIAGNOSIS of H pylori INFECTIONS

There are many methods which are used to identify whether the infection is related to the H pylori or not. These methods are different in some aspects i.e. invasive or non-invasive, simple or difficult, cheap or expensive, and the choice depends on the nature of the infection.

Invasive Method

Culture:

In this biopsy specimen is taken during endoscopy and homogenized and the homogenate is then kept on specific agar plates at high temperature. This method is considered as a gold standard for the determination of this type of infections.

Histology:

Histological examination of tissue samples helps in the detection of the bacterial infection along with the estimation of tissue damage. In the case of gastric infection haematoxylin and eosin (H&E) stain is used but it is not conclusive. The sensitivity of Wright-Giemsa and Brown-Hopps stains is 100% conclusive.

CLO Test:

This test is carried out for the identification of infection caused by Campylobacter like organism. Tissue specimen at the time of endoscopy and biopsy is taken off which is then placed in a test solution containing urea, pH indicator and a bacteriostatic agent. The presence of urease results in the hydrolysis of urea into alkaline ammonia along with a pH change and the change in colour (usually from yellow to red).

Non-Invasive Method

Breathing Testing:

This is a non-invasive diagnostic procedure that is a specific indicator for the detection of H pylori infections. In this procedure the patient to ingested urea, with labelled with $^{13}$C and $^{14}$C standard meal. Presence of urease results in the production of carbon dioxide which is then absorbed in blood and exhaled out from breath.

Antibody Measurements:

Detection of antibodies against H pylori circulates in blood or found in saliva. It has excellent sensitivity and specificity (> 95%). This technique is simple and comparable with invasive methods. These methods give results quickly and do not give any false impression for the patients, who have taken antibiotics, bismuth compounds and omeprazole.

ERADICATION OF H pylori

The pervasive and repetitive nature of peptic ulcer requires long term management which in result requires long term management and make it expensive. Osler was the first to treat H pylori infections by bismuth subnitrate lozenges. Single drug therapy is not a successive approach for the eradication of these infections. For this reason combination therapy is used in which H$_2$-receptor antagonist (cimetidine, famotidine and ranitidine), proton pump inhibitors (PPI) (Lansoprazole and omeprazole), cytoprotective agents (scurfate) and antibiotics (clarythromycin, amoxicillin and metronidazole) are used.
**H₂-Receptor Antagonist:**
This class of drugs is used to arrest the action of histamine on the parietal cell of stomach that results in decreased acid production. These drugs are used in dyspepsia (indigestion), peptic ulcer, gastroesophageal reflux diseases (GERD) ⁶⁶. Proton Pump Inhibitors: These drugs are used for the reduction of gastric acid secretion and are considered as the most sold drugs in the world ⁶⁷. These are inhibitors of H⁺/K⁺ Atpase pump and powerful inhibitors of gastric acid secretions. They are responsible for the release of hydrogen ion in the lumen of gastric glands and stomach ⁶⁸.

**Cytoprotective Agents:**
Cytoprotective agents are used for the peptic ulcer, GERD and stress ulcers ⁶⁹. These drugs (e.g. sucralfate) are basically a complex of sucrose octasulfate and polyaluminum hydroxide that forms a sticky gel that adheres to injured mucosa at pH values less than 4. It also forms a viscous layer on the surface of the duodenum and stomach and protects it from further damage ⁷⁰. Recent advances also prove that sucralfate also increases the production of prostaglandin E₂ and gastric mucosa ⁷¹, ⁷².

**Anticholinergic Agents:**
These drugs (e.g. atropine etc) were used in the past for the management of peptic ulcer and the infection caused by H pylori but is ineffective as like a single therapy which produces no significant effect on the treatment. These agents reduce the basal acid secretion and reduce the acid secretion which is produced in response to pentagastric, histmain, insulin or food. These drugs along with antacid reduce the acid secretion for a longer period of time as compared to other drugs ⁷³.

**Antibiotics:**
These along with other drugs are used for the eradication of H pylori. Clarithromycin and amoxicillin are the drugs which are commonly used for the eradication of the infection, because the H pylori is highly sensitive to these drugs, other drugs that are used for this infection include metonidazol, tetracycline and ciprofloxacin ⁷⁴.

**THERAPY**
H pylori causing peptic ulcer cannot be treated by single drug therapy. For this reason the treatment is focused on the combination therapy which includes the above mentioned drugs. There are two types of combination therapy treatment which are discuss as follows;
First-Line Treatment: This includes triple therapy which is the gold standard for the treatment and many regimens are given in the guidelines for the treatment of peptic ulcer ⁷⁵-⁷⁷. Eradication rate for the first-line treatment must be above 90 %, as per the protocol analysis (PP) and 80 % as per the intention to treat analysis (ITT) ⁷⁶. The drugs which are included in first-line therapy are given in Table 1.
Second-Line Treatment: Individuals which are not responding to first-line treatment are shifted to second-line treatment which includes four drugs therapy and is termed as quadruple therapy. This is the best choice of regimen for those who are resistant to first-line therapy ⁷⁶. Drugs which are included in the second-line therapy are given in Table 1.
Table 1. Therapy regimes for the treatment of H pylori infections

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<tr>
<th>First-Line Treatment</th>
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<tr>
<td>1</td>
<td>PPI standard dose + amoxicillin 1 gram + clarithromycin 500 mg, all twice daily for 7 days (up to 14 days)</td>
</tr>
<tr>
<td>2</td>
<td>PPI standard dose + metronidazole 400 mg + clarithromycin 500 mg, all twice daily for 7 days, (up to 14 days) (for patient allergic to penicillin)</td>
</tr>
<tr>
<td>3</td>
<td>PPI standard dose + amoxicillin 1 gram + metronidazole 400 mg, all twice daily for 7 days, (up to 14 days) (for patients allergic to clarithromycin, or cost concern)</td>
</tr>
<tr>
<td>4</td>
<td>PPI standard dose twice daily + bismuth 240 mg twice daily + metronidazole 400 mg three times daily + tetracycline 500 mg four times daily for 7 days (up to 14 days) (for patient allergic to penicillin)</td>
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<th>Second-Line Treatment</th>
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<tr>
<td>1</td>
<td>PPI standard dose twice daily + bismuth 240 mg twice daily + metronidazole 400 mg three times daily + tetracycline 500 mg four times daily for 7 days (up to 14 days)</td>
</tr>
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**PPI standard dose:** Omeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg, rabeprazole

20 mg, esomeprazole 20 mg

**CONCLUSION**

The present review deals with the occurrence and cure of peptic ulcer in human and the role of H pylori in the prevalence of the disease. The various caused of the peptic ulcer have been outlined. The biological characteristics, enzymatic activity and eradication of H pylori have been discussed. Various diagnostic tests for the H pylori infections have been discussed. A table on the therapy regimens first-line and second-line for the treatment of H pylori infections has been included.

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