Prevention of Gastric Cancer by *Helicobacter Pylori* Eradication: A Review

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Summary

Stomach is the organ of gastro intestinal tract. Stomach cancer has many of its symptoms e.g. Abdominal pain, uneasiness, nausea and vomiting, weight loss, fatigue and weakness. *Helicobacter pylori* bacterium is present when there is stomach problem. *Helicobacter pylori* eradication is done as prevention of gastric cancer.

Introduction

Stomach is the organ of gastro intestinal tract. [1,2] The food we eat goes to stomach through esophagus. An unusual growth of cells is called cancer. When this unusual and uncontrolled growth occurs in stomach is called stomach cancer. It is malignant epithelium growth. It can inhabit anywhere in stomach. Stomach cancer has many of its symptoms e.g. abdominal pain, uneasiness, nausea and vomiting, weight loss, fatigue and weakness. As there are sign and of symptoms of stomach cancer there must be its causes like carcinogens, mutation in genetic factors, dietary risks e.g. pickled vegetables, nitrates, nitrites and some micro-organisms e.g. *Helicobacter pylori* bacterium. There are many tests for the diagnosis of stomach cancer e.g. Gastroscopic examinations, upper GIT series and computed tomography. There are many stages of stomach cancer. The major factor which is responsible for the stomach cancer is bacterium *Helicobacter pylori*. The bacterium which lives in different sites of stomach is gram negative type. It is helix shaped micro-organism. It has its ideal home in the mucous layer of stomach. It has flagellum because of them it enters into the stomach layers and underlying cells. For the diagnosis of infection of *H. pylori* physician take a small piece of stomach cells and by histopathological investigations we diagnose the infection of *H. pylori*. Iga type anti helicobacter antibody response for protective function, so, human immunity combat with infestion of helicobacter pylori. Clinical trials have done. Gastric cancer and helicobacter pylori show the bug and host environment. *Helicobacter pylori* eradication is done as prevention of gastric cancer. Therapies are done for this purpose; many drugs are used for this eradication e-g Bismuth and metronidazole. Prevention of stomach cancer may be done by the annihilation of helicobacter pylori.

Gastric cancer

Gastric cancer also known as stomach cancer, can originate in anywhere or in anywhere of the stomach and possibly will extend throughout the stomach and to other organs and the whole stomach and organs come in contact with cancerous cells and spread completely; specially the esophagus,(a tube like structure of GIT) lungs, lymph nodes, and the liver. Gastric cancer is habitually asymptomatic(it means having disease but not symptoms of it) or causative agent for only imprecise sign and symptoms in its early development stages.[3] With the passage of time symptoms of cancer appear, the cancer has frequently reached an sophisticated level of cancer , this is the main reason for its poor prognosis, (Prognosis means a guess of the possibility of revitalization or endurance from a ailment).

SIGN AND SYMPTOMS

In its early developing stage the sign and symptoms are Indigestion or a burning sensation [4,5] (heartburn), heartburn is also known as pyrosis or acid indigastion is a burning sensation in the chest, just behind the sternum, Loss of appetite, particullarly for meat. In late stage the symptoms are Abdominal pain or discomfort, in the upper abdomen Nausea [6] (a situation of discomfort and unease in the upper part of the stomach and with a feeling of vomiting) and vomiting,Diarrhea [7] (it is a situation in which 3 or more loose or liquid bowl movements per day occur) or constipation, after meal the stomach bloating, weight will reduce, fatigue and weakness, Bleeding either in stool or in vomiting. Than this causes anemia Dysphagia; this character leads to a cancer or tumor in stomach extending toward oesophagus. These symptoms if a person have may be cahracterized of having stomach cancer. This is prescribed by oncologist or surgeon. [8]

CAUSES

Contamination by Helicobacter pylori(bacterium) is predicted to be the causative agent for many of stomach cancer while autoimmune atrophic gastritis it means swelling of stomach layer mucosa, changing of stomach epithelium and many hereditary characters are ralated with the enlarged risk levels. The clinical medical reference the Merck Manual lists that diet have no important role in the production of gastric cancer. Nevertheless, the American Cancer Society states the following dietary danger level, and defensive character , for gastric cancer: "smoked foods, salted fish and meat, and pickled vegetables (considered to enhance the risk levelof gastric cancer.) Nitrates and nitrites are substances commonly found in meats treated with salts. They can be converted by certain bacteria, such as H pylori, into compounds that have been found to cause stomach cancer in animals. On the other hand, eating fresh fruits and vegetables that contain antioxidant vitamins (such as A and C) appears to lower the risk of stomach cancer." A December 2009 article in American Journal of Clinical Nutrition found a statistically significant inverse correlation between higher adherence to a Mediterranean Dietary Pattern and stomach cancer. H. pylori is the main risk factor in 65–80% of gastric cancers, but in only 2% of such infections. Tobacco smoking also causes the stomach cancer. Gastric cancer is more in male than female. For every three males, one female get affected by stomach cancer. Women are protected due to the harmone estrogen against this gastric cancer. HDGC (hereditary diffuse gastric cencer) is also identified.[10]

HISTOPATHOLOGY

Stomach cancer is a malignant tumor of epithelium, the stomach mucosa have glandular epithelium from which it originate. Gastric malignancies are overpoweringly cancers of epithelium (90%). The classification of cancer of stomach epithelium done histologically, based on Lauren classification; Intestinal type and Diffuse type.

Intestinal type

Adenocarcinoma tumor cells describe irregular tubular structures, harboring pluristratification, multiple lumens, and reduced stroma. Often, it associates intestinal metaplasia in neighboring mucosa.

Diffuse type

Adenocarcinoma [11] (mucinous, colloid, linitis plastica, leather-bottle stomach) Tumor cells are discohesive and secrete mucus which is delivered in the interstitium producing large pools of mucus/colloid (optically "empty" spaces). It is poorly differentiated. If the mucus remains inside the tumor cell, it pushes the nucleus at the purpled- "signet-ring cell". Around 5% of gastric carcinomas are lymphomas (MALTomas, or MALT lymphoma). Carcinoid and stromal tumors may also occur.

STAGING

If histopathology test is positive and cancerous cells are present in the given sample of tissues, then found the level of cancer how much it is developed. Doctor diagnoses the stage of cancer. There are many tests which are used to investigate that the where the cancer has spread or it is restricted to one position.

The surgery is done to complete the staging. The lymph nodes and the other samples of tissues are removed by a surgeon from different sites of stomach and to the pathologist for examination.

The medically divided stomach cancer stages are:

Stage 0 The cancer is restricted to internal layering or lining of stomach.

Stage I. Dissemination occurs to the more internal layers of stomach, to the second and third lining. (Stage 1A) penetration to second layer closely placed lymph nodes (Stage 1B).

Stage II. Dissemination into the third lining or layer and to the far away lymph nodes.

Stage III. Dissemination occur in third lining and the lymph nodes present at more distances,

Stage IV. Cancer has extended to in close proximity tissues and more remote lymph nodes, or has metastasized to other organs. Another system is used for the staging of cancer called TMN staging system.

DIAGNOSIS

The three parameters which are involved in the diagnosis of gastric cancer 1, medical history, 2 performance of physical investigation, 3 laboratory investigations. A mass or tumor which can be feel with fingers when surgeon press that tumor. These are the tests which can diagnose the malignancy.

Fecal occult blood test in this test blood is seen with the help of microscope which conclude that stomach cancer is present.

Complete blood count (CBC) This test is used to count the erythrocytes, leucocytes and thrombocytes.
In an upper GI series, in this test the liquid barium is drink by patient and x-rays are taken. In double-contrast barium swallow, air is blown into the esophagus and stomach to help the liquid coat the wall of the organs more wholly.

MICROBIOLOGY
The bacterium named as *Helicobacter pylori* is that type of bacterium that does not give crystal violet dye when gram staining technique is done. It means it is a gram negative micro-organism.[12, 13] It is a type of micro-organism that requires little quantity of oxygen it means it is microaerophilic bacteria. It can make its home anywhere in stomach. This bacterium is specially concerned with the constant swelling of stomach layers and associated with the stomach and duodenal ulcers. More than 80% people are get contaminated with this bacteria have the disease but they have no symptoms it means they are asymptomatic. Originally the bacterium was recognized as Campylobacter pyloridis. To correct the Latin grammar error it was renamed as C. pylori. In 1989 it positioned in its own genus known as helicobacter due to evidence produced by 16S rRNA gene sequencing is done. This name is a derivative of ancient Greek word that mean spiral or coil. It has a valve known as pyloric valve this is a spherical opening leading toward the duodenum from stomach due to this it is called as pylori the Greek ancient word that means gatekeeper. Helicobacter pylori anchorage in the upper GIT tract. Its contamination spreading largely in under developed countries while its infection is decreasing in European countries. It disseminate in the mucosal lining of stomach.[14, 15]
H. pylori is a helix-shaped (classified as a curved rod, not spirochete) Gram-negative bacterium, [16] about 3 micrometers long with a diameter of about 0.5 micrometers. It is microaerophilic; [17] that is, it requires oxygen, but at lower concentration than is found in the atmosphere. It contains a hydrogenase which can be used to obtain energy by oxidizing molecular hydrogen (H_2) that is produced by intestinal bacteria. It produces oxidase, catalase, and urease. It is capable of forming biofilms and can convert from spiral to a possibly viable but nonculturable coccoid form, both likely to favor its survival and be factors in the epidemiology of the bacterium. The coccoid form can adhere to gastric epithelial cells *in vitro*.
H. pylorus possesses five major outer membrane protein (OMP) families. The largest family includes known and putative adhesins. The other four families include porins, iron transporters, flagellum-associated proteins and proteins of unknown function. Like other typical Gram-negative bacteria, the outer membrane of H. pylori consists of phospholipids and lipopolysaccharide (LPS). The O antigen of LPS may be fucosylated and mimic Lewis blood group antigens found on the gastric epithelium. The outer membrane also contains cholesterol glucosides, which are found in few other bacteria. *H. pylori* has 4-6 lophotrichous flagella; all gastric and entero-hepatic *Helicobacter* species are highly motile due to flagella. The characteristic sheathed flagellar filaments of *Helicobacter* are composed of two copolymerized flagellins, FlaA and FlaB.[28] Its infection causes stomach cancer. [18]

H. pylori senses the pH gradient within the mucus layer by chemotaxis and swims away from the acidic contents of the lumen towards the more neutral pH environment of the epithelial cell surface. *H. pylori* is also found on the inner surface of the stomach epithelial cells and occasionally inside epithelial cells. It produces adhesins which bind to membrane-associated lipids and carbohydrates and help it adhere to epithelial cells. For example, the adhesin Baja binds to the Lewis b antigen displayed on the surface of stomach epithelial cells. H. pylori produce large amounts of the enzyme urease, molecules of which are localized inside and outside of the bacterium. Urease breaks down urea (which is normally secreted into the stomach) to carbon dioxide and ammonia. The ammonia is converted to ammonium by taking a proton (H^+) from water, which leaves only a hydroxyl ion. Hydroxyl ions then react with carbon dioxide, producing bicarbonate which neutralizes gastric acid. The survival of *H. pylori* in the acidic stomach is dependent on urease. The ammonia produced is toxic to the epithelial.

PATHOPHYSIOLOGY

To colonize the stomach, H. pylori must survive the acidic pH of the lumen and burrow into the mucus to reach its niche, close to the stomach's epithelial cell layer. The bacterium has flagella and moves through the stomach lumen and drills into the mucoid lining of the stomach. Many bacteria can be found deep in the mucus, which is continuously secreted by Goblet cells and removed on the lumenal side. To avoid beincells, and, along with the other products of H. pylori—including proteases, vacuolating cytotoxin A (VacA), and certain phospholipases—damages those cells. The full genetic code of *H. pylori* is now known. About 60% of H. pylori isolates possess a cytotoxin-associated gene (CagA), and CagA-positive strains are more strongly associated with intestinal type gastric cancer.

Correlation of Helicobacter pylori and gastric carcinoma

Though the incidence of gastric carcinogenesis has decreased markedly in the western world it remains one of the common malignancies in many parts of the globe. The role of H. pylori in gastric carcinogenesis is a subject of increasing interest. Reports regarding relationship of H. pylori infection to gastric carcinogenesis are conflicting. Some epidemiological data point to this association although several unresolved issues still cast doubts on the real weight of the association. These issues are that male to female ratio of gastric cancer range from 1.5-4:1 in all studies but prevalence of H. pylori is same in both sexes; the prevalence of H. pylori is as high as 90% in several developing countries whereas frequency of gastric cancer is very low. Atrophic gastritis and intestinal metaplasia are well-accepted pre-cancerous conditions for gastric cancers. 80% of gastric cancers are related to *H. pylori* gastritis. *H. pylori* is not necessarily important for the development of gastric malignancy in atrophic gastritis although *H. pylori* is the key phenomenon in the triggering of gastritis related processes and the subsequent carcinogenic events. In our study younger patients of less than 45 years had the prevalence of 75% as compared to 63% in older patients though it was not statistically significant. This falls in concordance with the observation of others that younger patients with H. pylori are at higher risk for developing gastric cancer. *H. pylori* infection was present in 66% of our cases against 74% in the control group. Many authors have documented a higher overall *H. pylori* positively rate. The highest rates are from Shibata in Japan with value up to 90%.

H. pylori have been associated with location of the tumor as tumor of the body and antrum has been associated with *H. pylori* while cardiac tumors are unrelated. The site distribution of gastric cancer was different in our study. Antral lesions comprised 66% of the study group with cardiac and body cancers at 16% and 18% respectively. Shibata found maximum incidence of gastric cancer in body (52%) followed by antrum and cardiac at 38% and 10% respectively. The prevalence of *H. pylori* in our study was 50% in cardiac, 66.6% in body and 69.7% in antrum though there was no statistically significant difference between the various locations. Shibata found the positively to be 60-80%, 69-96.2% and 78.9-84.2% in the three sites respectively. Though our findings are somewhat different in respect to maximum incidence, they corroborate the hypothesis of Huang et al that *H. pylori* infection is more associated with non-cardiac gastric cancer when compared to lesions near cardiac. Gastric carcinoma, by far is one of the leading killers.

Infection with *H. pylori* is strongly associated with an increased risk of gastric carcinoma. However, most persons infected with H. pylori will never have gastric carcinoma. Therefore, other factors that increase the risk of gastric carcinoma among persons infected with *H. pylori* need to be identified [19] [20] [21].

These gastric irritants can add fuel to the fire by contributing to the formation of an ulcer, or by exacerbating an existing one.

Alcohol, *H. pylori* is more common in smokers, Non steroidal anti-inflammatory drugs (NSAIDs), (aspirin, ibuprofen, and naproxen sodium), Corticosteroids (hydrocortisone, cortisone, prednisone, etc.), Caffeine, Acid and pepsin, H. pylori was more prevalent in people who had dyspepsia, Radiation therapy, burns, and physical injury, stomach acid production is actually increased after drinking milk, and does not relieve stomach ulcers[22][23].

DRUGS USED TO ERADICATE H PYLORI INFECTION

Proton-Pump Inhibitors (PPIs)
Bismuth
Metronidazole
Clarithromycin
Amoxicillin
Tetracycline

What conditions are associated with *H. pylori* infection?

Strong evidence demonstrates that *H. pylori* is a causal factor in gastritis and duodenal ulcer and to a lesser extent gastric ulcer. Moderate epidemiologic evidence supports a relation between H. pylori and gastric adenocarcinoma and lymphoma [24, 25].

Eradication of *H. pylori*

A specific treatment has been developed for the eradication of this bacterium. It consists of two different antibiotic medicines - Clarithromycin, and amoxicillin - and another medication that reduces the production of acid in the stomach – a proton pump inhibitor, or PPI. Examples of commonly used PPIs are pantoprazole (Somac) and rabeprazole (Pariet). [26][27].

HELICOBACTER PYLORI ERADICATION

Once *H. pylori* is detected in patients with a peptic ulcer, the normal procedure is to eradicate it and allow the ulcer to heal.The patients have peptic ulcers or having stomach cancer is advised for the eradication of *Helicobacter pylori*.[29] The patients having reflux oesophagitis (lower esophagus sphincter does not close properly and food leak back or reflux to esophagus), and are taking non steroidal anti inflammatory drugs (NSAIDs) have no obvious proposal for the annihilation of H. pylori. A test and treat strategy which is as effective as endoscopy is used the patients under 55 having uncomplicated dyspepsia. The patients which are above 55years having uncomplicated dyspepsia a non invasive H. pylori test and treat strategy may be as suitable as endoscopy for preliminary examinations management. H. pylori eradication is done when there is functional dyspepsia (pain in stomach, discomfort, uneasiness near the ribs in the upper belly) it means in functional dyspepsia it is consider as option. There are three problems during this therapy 1. Compliance; drug regime results should be balanced the treatment failure from non compliance with a complex treatment regime failure. Treatment will fail if the patients miss one or two doses in week treatment regime. The second problem 2 is side effect side may effect the compliance though they are not very severe, but in some cases they are very adverse that treatment has to stop. Some common side effects may include nausea, diarrhoea, allergic drug reaction and candidiasis. The 3rd effect is drug resistance; the patients are enduring antibiotics resistance e-g metronidazole and clarithromycin, but still the drugs are effective and used in treatment. When there is need of eradication a correct way of eradication therapy is used a breath test is also followed to detect the presence of Hp. The patients with acid suppression (discontinue) priority to the test is given; otherwise result will be false due to acid suppression rather than eradication therapy. We use dual therapy instead of triple therapies. Triple therapies are also done. Clarithromycin and metronidazole confrontation is recognized by laboratory investigation that is related with compact annihilation of H. pylori. One week schedule does not enhance the annihilation speed then two week of triple therapy. At the annihilation schedule is make which is as follow:

- For all seven days amoxicillin 500mg tds+ Omeprazole 20mg bd+ metronidazole 400mg tds
- For all seven days clarithromycin 500mg bd+ amoxicillin 1g bd+ Omeprazole 20mg bd
- For all seven days Omeprazole 20mg bd+ Omeprazole 20mg bd + metronidazole 400mg bd.

Conclusion

Helicobacter pylori is causative agent for the development of stomach cancer but the eradication of this bacterium does not cure the stomach cancer. Once H. pylori is detected in patients with a peptic ulcer, the normal procedure is to eradicate it and allow the ulcer to heal.Sop, the patients have peptic ulcers or having stomach cancer is advised for the eradication of helicobacter pylori (Hp).

So, if we eradicate the infection of helicobacter pylori it does not cure the stomach cancer.

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