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Mini Review

Helicobacter pylori: A Short Literature Review

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Abstract

Several years ago, it was thought that ulcers were caused by stress, smoking or lack of exercise and so on. In 1982, it was reported that the bacteria which was responsible for most of the stomach ulcers was *Helicobacter pylori* (*H. pylori*), a bacteria, which can enter the body and live in the digestive tract. Presence of *H. pylori* after several years can cause ulcers in the lining of the stomach or in the upper part of small intestine, which can lead to gastric cancer. It has been documented that infection with *H. pylori* effects almost two-thirds of the world's population.

However, it is now known that *H. pylori* doesn't affect everyone, but evidence links *H. pylori* infection with gastric diseases. *H. pylori* infection is a global infection in developing countries. It has been documented that the occurrence of *H. pylori* is higher in developing countries, because the bacterium is acquired at an early age compared to developed countries. Hence, it affects over 50% in developed countries, when compared with more than 80% in developing countries. This short review will summarize important facts from the scientific literature reported over several years, and will include, but not limited to gastric cancer, infection, eradication, treatment and resistance.

Keywords: *Helicobacter pylori (H. pylori); Stress; Smoking*

Introduction

H. pylori is a motile, curved and Gram negative bacillus [1]. The occurrence of infection is very much geographical, age, and ethnicity related. The occurrence of this disease was documented to be in greater numbers, in developing countries when compared to under developing countries, the region for this could be due to their finical situations [2]. The features displayed by *H. pylori* allows it's survived in very adversative conditions, such as high acidic environment in the stomach. Spreading of the infection occurs mainly through contaminated water and food [3]. Spreading of this bacterium has been shown in the saliva and dental plaque [4].

H. pylori infection is the main cause of continuing inflammation of the protective lining of the stomach. About 80% of the infected subjects develop a small cavity and the inflammation associated with changing of the gastric homeostasis with normal levels of gastric acid secretion. These patients may not develop intense problems. A low percentage of these patients may suffer from this gastric disease, where the gastrin level may be equal or greater than 99 - 125 pg/ml. With these high levels, often duodenal ulceration is associated. Some patients may also develop body inflammation and other gastric disease.

Helicobacter pylori infection

During the *H. pylori* infection, multiple strains could colonize the same host and heterogeneous genotypes raises to infection with one or multiple strains presenting different genotypes of resistance to strong antibiotic sch as clarithromycin. It became very clear that there is an association between *H. pylori* infection and gastric cancer risk [5]. It's noteworthy to say that not all the *H. pylori* infected patients developed gastric cancer, the exception was the patients the patients with duodenal ulcer were protected [6], it was noted that under some circumstances a change in the relationship between *H. pylori* infection and gastric cancer may have had taken place.

When looking at the factors that affect the infection, one should not rule out the age at which the infection took place, and geographies of the host, including the genetic, secretory capacity and the strain of the bacteria [7]. In 1998, it was noted that the cytotoxin-associated gene (*CagA*) and its equivalent protein were related with a greater risk of a diversity of gastric diseases [8]. Xiang Z., *et al.* documented different types strains of *H. pylori,* they are *a)* Type 1 - a highly infectious, b) Type 2 - an transitional strains; and c) Type 3 - low strength strain, this is of course, depend on the expression of the proteins in question [9]. Further role of *H. pylori* in infection will be outlined in the related topics below.

Helicobacter pylori gastric cancer

Gastric cancer remains one of the leading causes of cancer-related deaths worldwide [10]. *H. pylori* is known to reside in the human stomach and causes chronic inflammation of the gastric mucosa of the stomach, intestinal metaplasia, and gastric cancer. The behavior of *H. pylori* has been studied in mice and Mongolian gerbils [11]. Strong clinical indication has proposed that *H. pylori* is correlated with active long-lasting gastritis, peptic ulcers, atrophic gastritis, intestinal metaplasia, and malignant lymphoma or cancer. In order to prove that gastric cancer is related to *H. pylori* infection, many studied have been preformed to mimic human gastric cancer, however, the results were somewhat unsatisfactory [12]. A Mongolian gerbil model was used, which provided better results, which were closer to human condition. Smoking has been shown to be associated with many kinds of cancers occurring in humans [13].

A study from a Japanese group showed that smokers tend to have greater risk for gastric cancer than the rest of the population [14]. In this study it was also documented that the risk for the male Japanese smoker population much higher when compared to the female population [15]. The investigators studied the stromal cells from the androgen receptor and found that the gastric cancer in males was much higher when compared to the female and nonsmoking population.

From the same study it was documented that salt and salted foods would also affect the degree of gastric cancer acquired. Furthermore, Tajima., *et al.* [16] discovered that affection for salted foods including pickled vegetable and salted fishes, typical traditional Japanese foods, showed a significantly positive association with stomach cancer. Tests were conducted from the blood and urine (ecological studies) to see if there were any connection between the amount of salt measured in the urine, and from the number of patients died with stomach cancer. These results showed that there a was a very strong connection between the salt and gastric cancer, in men and in women all over the world [17].

Further research was carried out in *H. pylori* -infected gerbils. Where a low to high salt diet was introduced using *H. pylori* antibody concentration, serum gastrin levels, and inflammatory cell. It was found that the high salt diet increased the response to a stimulus specifically, and the amount of surface mucous cell mucin, which was a perfect environment for *H. pylori* foundation, however, reduced the amount of gland mucous cell mucin, preventing *H. pylori* infection by obstructing the bacterial cell wall component. Generally, the glandular stomach cancers are 15% with a normal diet, increasing by 33%, to 63% with extra 2.5% to 10% of salt in the diet, which indicated that depending on how much the salt is consumed, it will affect the infection accordingly. Hence, if the salt intake is decreased, this will definably reduce the stomach cancer.

H. pylori plays an important part in the initiation of gastric cancer formation, however, most of the cases have been found in the under-developed countries. Developing countries seems to have a higher case of gastric cancer, when compared with developed countries, such as Europe, Canada and USA.

Helicobacter pylori treatment

Concerning diagnosis, most of the invasive and noninvasive methods used for the diagnosis of *H. pylori* infection are long standing with efficient performance.

Endoscopy is the most valuable technique and seems to the most efficient way to diagnosis *H. pylori infection,* followed by the omics-based technique. All methods useful in the outline presentence and the occurrence of *H. pylori* in the population mentioned above.

Its obvious that despite several attempts, the *H. pylori* treatment has been somewhat difficult to cure [18]. One of the main ways to deal with this disease was to use vaccination, which now is not available. Thus, the normal now is, to treat *H. pylori* using an antibiotic therapy [19]. The initial success with the antibiotic therapy was great, it soon became intolerable for some patients, especially the triple eradication therapies, this is due to the resistance of the antibiotics. The common drugs used were clarithromycin, metronidazole, and levofloxacin to slow down or to temporarily stop the *H. pylori* infection [18,20].

Bismuth quadruple therapy (BQT) with relatively high side effects was also recommended by some physician, for the patient who had a penicillin allergy [20].

It's a well-known fact that resistance to amoxicillin is very low, and esomeprazole would exert a remarkable antimicrobial activity against *H. pylori*.

First-line of treatment for *H. pylori* eradication may be recommended as a dual therapy with high-dose of esomeprazole coupled with high-dose amoxicillin, which may be for a 10 day treat, which will generally eradicate *H. pylori* infection, but in some cases, it may take as long as 14 to 21 days. Amoxicillin/PPI dual therapy is and was the most popular drug to be used, dose given to a patient would depend on the age, weight and other factor and how frequent it was administrated [21,22]. In many clinical trials *H. pylori* eradication rate with BQT have been compared [23].

Around 2 grams of amoxicillin and esomeprazole has been prescribed once or twice per day has been as a gold standard to attain enough results of *H. pylori* eradication rate, when one compares with the other triple and quadruple therapy, this was concluded from several clinical trials [24].

Helicobacter pylori after treatment

During the 14 days of prescribed medicine for *H. pylori* eradication, the routine for the patient is quite challenging. it's very important that patients follow all the direction given by their physician, as failure to take at least 80% of the prescribed medicine will fail completely the *H. pylori* eradication, which of course, may leads to antibiotic-resistant. With these medicines, diarrhea is very common. Other antibiotic, such as Clarithromycin and metronidazole may cause taste problems. Furthermore, if metronidazole is prescribed for the treatment, it should be noted that alcohol should not be used during the treatment of *H. pylori* eradication, as there may be interaction, and the treatment may fail.

It is very important that when *H. pylori* is being treated, it should be noted that the infection may be linked with other long-term outcomes. *H. pylori* infection may be managed by using standard methods, such as a urea breath test, a biopsy-based or a fecal antigen test,

or an endoscopy performed. Most important that after the test are preformed a serious management of the disease is carried out. After the treatment of *H. pylori* infection, it is important to follow up with your physician.

Helicobacter pylori eradication

In 2013 another study in Japan started the *H. pylori* eradication therapy which should reduce the number of gastric cancer deaths. Since *H. pylori* eradication therapy is so complicated, in this study there was no change in the number of gastric cancers deaths. Infect, in this study, *H. pylori* eradication therapy predicted that by the year 2020, there will only be 30K deaths, but much to their surprise, by year 2017, the death toll had already reached 45K. Further attempts were made to analyses the problem of atrophic gastritis and intestinal metaplasia post *H. pylori* eradication therapy.

H. pylori -positive specimens were collected using endoscopic means, biopsies were taken. When analyzed, they found signs of a small, oval, pinhole-sized, or round pits after bacterial eradication, decreasing densities of fine, irregular vessels, which were not found in the specimens from patients with severe gastric atrophy and intestinal metaplasia [25]. Although, this is not always shown any histological improvements in gastric atrophy and intestinal metaplasia after the eradication of *H. pylori* [26]. Thus, there was a difference of opinion in studies carried out by several different researchers that eradication effectively improves gastric lesions in the antrum or corpus [27,28].

After the eradication of *H. pylori*, it was found that the number of neutrophils extremely decreased, when compared to the lower number of mononuclear cells present. It was noted that after the eradication the hyperplastic and hypertrophic enlargement of the surface foveolar epithelium in the gastric type was improved, but the intestinal type of metaplastic glands remained the same.

The eradication of *H. pylori* has been approved for both the prevention of metachronous cancer and cases of chronic atrophic gastritis [29]. After treatment of *H. pylori* infection, it was discovered that the preneoplastic gastric lesions and intestinal metaplasia were in a worst state then before the treatment [30,31].

Past and present studies have recognized that the successful eradication of *H. pylori* may reduce the occurrence of metachronous gastric cancer after the endoscopic resection of early lesions over a 3-year period [32-34]. In another study, it was also documented that [35] *H. pylori* eradication is only effective in a specific set of patients, who do not have intestinal metaplasia or dysplasia. It's been shown that when a patient under goes Endoscopic procedure, the gastric tumor area has a gastritis-like appearance rather than typical malignant characteristics [36].

A histopathological analysis of gastric dysplasia (as in the Western category [37], which is intramucosal adenocarcinomas according to the Japanese criteria [38] revealed significant and rapid alterations in tumor morphology and proliferative characteristics after the eradication of bacteria.

H. pylori eradication therapy represents a key clinical essential. Unfortunately, therapy against *H. pylori* has turned out to be more difficult over the years, principally due to the great decrease of standard eradication therapies efficacy.

The potential effects of *Helicobacter pylori* outside the stomach

There have been reports that *H. pylori* infection and Schöenlein-Henoch purpura may have a relationship after the eradication of the infection [39,40], as an improvement in skin lesions is seen.

It's well known that Rosacea is the most common dermatological disease which is connected to *H. pylori* infection. It is a lingering facial dermatitis that shows as erythema and cutaneous lesions with dilated red superficial capillaries, named telangiectasia.

H. pylori infection also affects nervous disorders, for example, stroke. Wang., *et al.* [41] published that continuing *H. pylori* infection and with *CagA*-positive strains present would be a very strong risk factors for ischemic stroke.

Alzheimer's disease (AD) is also recognized as one of the neurologic diseases linked to *H. pylori* infection, and it has been shown by many studies that *H. pylori* and dementia are also connected. Cognitive ability is another disease reported by Beydoun., *et al.* [42], which states that *H. pylori* infection affects the cognitive ability of an infected patient. In addition, it was reported that all these diseases may be eliminated after *H. pylori* eradication.

H. pylori infection was reported to be associated with Iron Deficiency Anemia (IDA) [43], however, not always and without a reason.

H. pylori infection has not been totally defined with cardiovascular diseases. However, Lai., *et al.* [44] in their article have shown that *H. pylori* infection may increases the risk of serious coronary artery disease.

Helicobacter pylori resistance

In *in vitro* conditions, *H. pylori* is sensitive to many antibiotics, however, only a few antibiotics can be used *in vivo* to treat infection. According to the Standard Guidelines, a low dose of clarithromycin-containing treatments is recommended at first, followed by a high dose of clarithromycin i.e. the quadruple treatment including bismuth. In case of unavailability of this therapy, non-bismuth (three antibiotics plus Proton pump inhibitors) quadruple therapy has been recommended as an alternative. Failure of treatment in *H. pylori* infections has become a serious concern.

The cause of treatment failure is many that can be grouped into microorganism-related factors, host-related factors and treatment-related factors. *H. pylori* resistance to antibiotic is widely recognized as the main reason for treatment failure [45,46]. Furthermore, antibiotic resistance should be considered as a dynamic idea, since its occurrence can change not only among diverse countries, but also between two different periods in the same area [46]. The rate of antibiotic resistance in *H. pylori* has been evaluated worldwide. Clarithromycin is the most potent antibiotic involved in the management of *H. pylori* infections, and its resistance to clarithromycin is important [46,47] and has been broadly studied. It was reported that the highest clarithromycin resistant area was North America and this study showed a slight increasing tendency of clarithromycin resistance of *H. pylori* in the world.

Metronidazole is also being used against *H. pylori* infections and is one of the few antibacterial agents that is effective in eradicated the microorganism. Study showed that resistance to metronidazole have remained significantly unchanging in Asian, European and North American countries but is increasing in African countries.

Amoxicillin is suggested for anti-*H. pylori* triple therapy in region where metronidazole resistance is high. The prevalence of amoxicillin resistance in Europe countries and North American is low from zero in certain area as Finland, Germany, Norway and Poland. The incidence of amoxicillin resistance in *H. pylori* seems to increase specially in Asia and South America.

Tetracycline is a bacteriostatic and broad-spectrum antimicrobial agent that is active against *H. pylori* and tetracycline is the most generally used antibiotic for treatment of *H. pylori* and other infectious diseases [48]. Tetracycline is extensively used in many countries, but resistance to this antibiotic has not become a great problem yet.

Resistance to levofloxacin is low worldwide. The prevalence rate was higher in Asia and South America as compared to Africa and Europe. Due to the dramatic increase in clarithromycin resistance, levofloxacin, and quinolone has been used as a substitute, however, the frequent use of quinolones for urinary tract infections has increased the incidence of *H. pylori* resistance in the world.

Since there is high *H. pylori* resistance to metronidazole in some region as China and South America, furazolidone has been used for *H. pylori* infections [49].

Conclusion

From our literature search, it was determined that the treatment for *H. pylori* infection requires a great deal of care, with the full attention of the physician and the patient, without this care the *H. pylori* eradication will fail. It is obvious that despite several attempts, the *H. pylori* treatment has been somewhat difficult to cure. One of the main ways to deal with this disease was to use vaccination, which now is not available. Thus, the normal now is, to treat *H. pylori* using an antibiotic therapy. Amoxicillin and esomeprazole have been very successful, however, there are some exceptions.

Triple and quadruple eradication therapies are being used. The common drugs used are clarithromycin, metronidazole, and levofloxacin to slow down or to temporarily stop the *H. pylori* infection. The initial success with the antibiotic therapy was great, it soon became intolerable for some patients, especially the triple eradication therapies, this is due to the resistance of the antibiotics. The use of Bismuth quadruple therapy with relatively high side effects was also recommended by some physician, for their patients who had a penicillin allergy.

Currently, a broad spectrum of diagnostic tests is available, most of them with high sensitivity and specificity. The 13C urea test remains the best noninvasive test for diagnosing *H. pylori* infection. The ELISA monoclonal fecal antigen test is also acceptable because of high sensitivity and specificity when 13C urea is not available. Endoscopic procedure is used to evaluate *H. pylori infection,* by providing information about inflammatory, atrophic and metaplastic lesions of the stomach. *H. pylori* causes an infectious disease and should be diagnosed and treated as infectious disease.

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Volume 7 Issue 2 February 2020