Abstract

*Helicobacter pylori* is a gastric pathogen that colonizes approximately 50% (over 3 billion) of the world's population, mainly in the developing countries. Infection with *H. pylori* leads to a chronic inflammatory condition called severe chronic atrophic gastritis (SCAG) and significantly increases the risk of developing duodenal and gastric ulcer disease and gastric cancer. Infection with *H. pylori* is the strongest known risk factor for gastric cancer. Gastric cancer ranks fourth in incidence and second in mortality among all cancers worldwide. People with SCAG have an increased risk of gastric adenomas in both the upper and lower parts of the stomach.

Although *H. pylori* affects a large percentage of the population, only a small percentage of carriers develop this malignancy. Recent investigations have begun to identify the factors that lead to these complications. Such clinical diversities are caused by variations of *H. pylori* pathogenicity, host susceptibility, environmental factors, and interactions of these factors. The exact mechanisms underlying how *H. pylori* triggers or causes gastric cancer remain elusive.

Key words: *Helicobacter pylori*; *Helicobacter pylori* infection; Severe chronic atrophic gastritis (SCAG); Gastric cancer.

1. Introduction

The human gastric pathogen *Helicobacter pylori* (Hp) infection plays a crucial role in gastric cancer pathogenesis (You *et al.*, 2000; Peek and Blaser, 2002; IARC Monogr Eval Carcinog Risks Hum., 1994). It is the major cause of chronic gastritis, peptic ulcers, and gastric malignancies, including gastric non-cardia adenocarcinoma and mucosal-associated lymphoid tissue (MALT) lymphoma (Peek and Crabtree, 2006). It accounts for up to two thirds of gastric cancer cases (Parkin, 2006). The estimated incidence in 2008 was 989 600, and the majority of new cases occurred in developing countries (American Cancer Society, 2011). The incidence of gastric cancer has declined dramatically in most countries over the past 70 years. It remains the fourth most common cancer and the second most frequent cause of cancer-related deaths (Hohenberger and Gretschel, 2003; Parkin, 2004; Parkin *et al.*, 2002), accounting for 10.4% of cancer deaths worldwide (Brenner *et al.*, 2009) with high incidence in definite area (China, Eastern Europe, and Japan) (Bruckner *et al.*, 2003). Reasons for reductions in overall gastric cancer incidence and mortality have not been fully elucidated, but changes in lifestyle/environmental factors and improved health care could be possible factors. These include decreased intake of salted and preserved foods due to use of fridges, increased consumption of fruits and vegetables, reduced chronic Hp infection owing to better hygiene and medication, mass screening measures to detect precancerous lesions in some regions such as Japan, and decreased smoking in developed countries (Bertuccio *et al.*, 2009; Jemal *et al.*, 2010).

Persistent inflammation caused by Hp infection induces hypochlorhydria and chronic atrophic gastritis of the body-fundus, which are two early precursors of gastric cancer development (Testino *et al.*, 2004) as shown below (Israel and Peek, 2001) (Fig. 1). However, although the prevalence of Hp infection ranges from 40 to 80% in humans, only a small proportion (probably < 3%) of infected patients develops gastric cancer (Peek and Blaser, 2002). Genetic variation in genes encoding cytokines and their receptors, which determine the intensity of the inflammatory response to the bacteria, may contribute to individual differences in severity of outcome of Hp infection and progression of gastric lesions (Gonzalez *et al.*, 2002). It infects the gastric mucosa leading to an acute followed by chronic inflammatory response, accompanied by the production of several proinflammatory cytokines. These cytokines enhance the immune response and inhibit gastric acid secretion. Consequently, an excessive production of gastrin and free radicals ultimately lead to neoplastic transformation of the gastric mucosa (Matthews and Butler, 2005). Individual differences in the intensity of the inflammatory response may contribute to gastric mucosa transformation (Gonzalez *et al.*, 2002).

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**Figure 1:** Relationship of Hp-induced gastric inflammation with variable disease outcomes. (Adapted from Israel and Peek, 2001)
Certain cytokine gene polymorphisms have been associated with the occurrence of gastric cancer, with the most consistent results referring to the increased gastric cancer risk associated to IL1B-511, IL1RN variable number tandem repeat (VNTR), and TNFA-308, despite the heterogeneous findings across previous meta-analyses (Camargo et al., 2006; Gorouhi et al., 2008; Kamangar et al., 2006; Loh et al., 2009; Vincenzi et al., 2008; Wang et al., 2007; Zhang et al., 2008). Different risk estimates have been described according to the histologic type of the tumor, with stronger associations for the intestinal type (Camargo et al., 2006; Gorouhi et al., 2008; Kamangar et al., 2006; Wang et al., 2007). These tumors are the most frequent (Lauren and Nevalainen, 1993) and are preceded by a set of sequential precancerous lesions (Correa et al., 1975), from which intestinal metaplasia is much more frequent than dysplasia (Uemura et al., 2001) and more strongly associated with gastric cancer than gastric atrophy. Addressing the potential associations between the cytokine gene polymorphisms and gastric precancerous lesions may contribute to the understanding of some of the previous heterogeneous findings from studies having gastric cancer as the outcome. Here, we review the recent advances in our understanding of the association of H. pylori infection and the risk of gastric cancer.

2. Diversity of H. pylori and Variations in their Genome

2.1 H. pylori Populations

There are three types of bacterial population structure: clonal, panmictic and endemic (Achtman, 2004). If intra-species or inter-species recombination is rare, the genetic diversity of a bacterial species predominantly comes from evolution of the ancestry. This species has a clonal population structure. In a species with high frequency of recombination, introduction of foreign gene fragments into the genome occurs frequently in the evolution history. As foreign genes have a different evolution history, the evolution speed of individual genes is different. In this case, the species possesses a panmictic structure. For a bacterial species with a panmictic structure, a temporal clonal structure may occur if it rapidly spread among naive hosts. In this situation, a bacterial species has an endemic structure.

2.2 Genomic Variations

Hp shows great inter-strain variation in genetic content (Suerbaum and Achtman, 1999). None of the individual strains is identical as demonstrated by multiple fingerprinting methods (Akopyanz et al., 1992; Han et al., 2003). Sequence divergence is the main cause of this variation. Hp diversity researches on the human population sampling from Asia, Africa, and South America demonstrated that H. pylori coevolution has been for about 58,000 years (Linz et al., 2007; Yamaoka et al., 2002; Falush et al., 2003; Devi et al., 2007). This bacterium is natural competence cell and developed a specified Type IV Secretion System (T4SS), the comB-system, to integrate exogenous DNA into its genome through genetic recombination (Hofreuter et al., 2003; Hofreuter et al., 1998). Human stomach has low bacterial diversity on the level of species but is rich in genetic variants in subpopulations of Hp. The maintenance of high diversification makes this bacterium to cope with particular challenges in individual hosts (Kang and Blaser, 2006).

2.3 Cytotoxin-associated Gene A (CagA)

At the phenotypic level, strains can be characterized into two types: those that contain a gene associated with cytotoxin expression, the so called CagA (cytotoxin-associated gene A) gene, and those that do not (Telford et al., 1994; Xiang et al., 1995). CagA positive Hp, which comprise some 50%-60% of United States isolates, cause more extensive inflammation of the gastric mucosa than CagA negative strains (Crabtree et al., 1995; Cover et al., 1995; Crabtree et al., 1991; Peek et al., 1995; Blaser, 1995). CagA positive (strains carrying the cag PAI) infections are also more likely to progress to atrophic gastritis than CagA negative infections (Kuipers et al., 1995). Furthermore, a nested case-control study among Japanese-American men suggested that CagA antibodies are more common in infected persons with gastric malignancy than in infected persons without such malignancy (Blaser et al., 1995). Whereas this finding was not statistically significant, the two-fold increase in CagA positive Hp among intestinal type cancers appeared unlikely to be due to chance alone.

2.4 H. pylori Strains, CagA and Genomic Size

A number of strains have been sequenced to date (Alm et al., 1999; Tomb et al., 1997; Baltrus et al., 2009; Clancy et al., 2012; Lehours et al., 2011). Of these, the origin and other information of 30 strains are publicly available. These include 14 strains from hpEastAsia (7 from hspEasia and 7 from hspAmerind subpopulations, respectively), 10 from hpEurope, 5 from hpAfrica1 and 1 from hpAfrica2 (Schott et al., 2011; Kawai et al., 2011; Avasthi et al., 2011; Kersulyte et al., 2010). All, except for strain B38 from hpEurope, possess CagA and the Cag pathogenicity island (cag PAI). The genomic size of CagA-positive Hp ranges from approximately 1.55 mbp to 1.71 mbp with an average of 1.61 mbp. For CagA-negative strains, their genome is generally smaller because of the lack of the Cag pathogenicity island of about 40 kbp. The average genomic sizes of CagA-positive Hp strains from different populations have been reported (Devi et al., 2010; Thiberge et al., 2010; Farnbacher et al., 2010; Dong et al., 2009; McClain et al., 2009; Oh et al., 2006; Dong et al., 2012). The average genomic size of strains from hpEurope is approximately 1.65 mbp, which is significantly larger than that from hpEastAsia (1.60 mbp, P < 0.05) or hpAfrica1 (1.60 mbp).

The cag PAI is a 40-kb DNA fragment which contains 27 to 31 genes flanked by 31-bp direct repeats (Censini et al., 1996). It encodes CagA, the major virulence determinant of Hp and components of a type IV secretion system (Covacci et al., 1993; Kutter et al., 2008). The latter translocates CagA into host cells (Odenbreit et al., 2000). Once inside the host cells, CagA binds to a number of host cell proteins disrupting intracellular signaling systems via tyrosine phosphorylation-dependent or -independent pathways (Murata-Kamiya, 2011). This causes elongation and loss of polarity of host cells, promoting proliferation and inflammation. The presence of the cag PAI in Hp is associated with increased risk of severe gastritis, atrophic gastritis, and distal gastric cancer compared with strains that lack the cag island (Israel et al., 2001; Miehlke et al., 2000; Plummer et al., 2000).
A marked difference lies between hpEurope and hpEast- Asia in the prevalence of strains possessing the cag PAI. Approximately 60% to 70% of Western Hp strains express CagA (Miehlke et al., 2000; Owen et al., 2001), indicating the presence of the cag PAI.

Nine Hp genome sequences are available from public databases to date: 26695 (accession number: AE000511) (Tomb et al., 1997), J99 (AE001439.1) (Alm et al., 1999), P12 (EMBL:CP001217, EMBL:CP001218 for plasmid) (Fischer et al., 2010), HPAG1 (CP0000241, CP0000242 for plasmid) (Oh et al., 2006), or G27 (CP001173,CP001174 from plasmid) (Baltrus et al., 2009), Shi470 (CP001072) (Devi et al., 2006), B38 (FM991728) (Thiberge et al., 2010), 51(CP000012) and 52 (CP001680). These nine genomes represent the genetic information of isolates from patients with various diseases (from gastritis to cancer) from different geographic regions (Alm et al., 1999). Several articles on the comparisons of Hp genomes have been published (Alm et al., 1999; Tomb et al., 1997; Baltrus et al., 2009; Clancy et al., 2012; Lehours et al., 2011; Schott et al., 2011; Kawai et al., 2011; Avasthi et al., 2011; Kersulyte et al., 2010; Devi et al., 2010; Thiberge et al., 2010; Farnbacher et al., 2010; Dong et al., 2009; McClain et al., 2009; Oh et al., 2006; Devi et al., 2006; Lara-Ramirez et al., 2011).

3. Risk of Gastric Cancer Associated with H. pylori Infection

3.1 Prevalence of Hp Infection

Hp is present in the stomach of more than half of the world population. Its infection has an association with the occurrence of gastrointestinal diseases, including gastric inflammation, peptic ulcer, gastric mucosa-associated lymphoid-tissue (MALT) lymphoma and gastric cancer. It is a key strategy to prevent and treat these diseases by eradicating Hp (Hohenberger and Gretschel, 2003). In the MALT-lymphoma patients, approximately 50% of cases were diagnosed with gastrointestinal non-Hodgkin's lymphoma; most are linked to Hp infection. In the early stages of low-grade MALT lymphoma, 60-80% can be cured by Hp eradication (Wotherspoon et al., 1993; Chen et al., 2005; Statthis et al., 2009). It has been implicated in the pathogenesis of several gastrointestinal, systemic or hematological diseases (Papagiannakis et al., 2013). Gastric cancer occurs in only a minority of infected individuals, however. Such clinical diversities are caused by variations of Hp pathogenicity, host susceptibility, environmental factors, and interactions of these factors. Based on compelling epidemiological evidences, the International Agency for Research on Cancer, World Health Organization (IARC/WHO) concluded in 1994 that Hp had a causal linkage to gastric carcinogenesis and is a definite carcinogen in humans (Sugiyama, 2004).

3.2 Risk Factors of Hp Infection

Hp infection is the most common infectious disease in the world (Pounder and Ng, 1995). The prevalence of Hp ranges from less than 10% to over 80% in children (Jafar et al., 2013) and nearly 50% of the world's population is estimated to be infected (Achtman, 2004). The risk factors for Hp infection include socioeconomic status, household crowding, ethnicity, migration from high prevalence regions, and infection status of family members.

4. Diagnostic Tests and Treatment Strategies

Diagnostic tests for Hp are generally divided into two categories: invasive and noninvasive. Invasive tests comprise the histological examination of gastric specimens. Noninvasive tests are based on peripheral samples such as blood, breath, stools, urine, and saliva, in order to detect antibodies, bacterial antigens, or urease activity. The choice of a specific test always depends on local experience and clinical settings, but usually a combination of two methods is often recommended since, for example, the detection of Hp-specific antibodies does not ultimately reflect a current infection (Bauer and Meyer, 2011).

Treatment of infection relies on a combination of antimicrobial agents and antisecretory agents, the elevation of the gastric pH by antisecretory agents being required for the bactericidal effect of the antimicrobial agents. Alternatively, although the mechanism of action is not yet clear, phytomedicines and probiotics have been used to improve eradication of Hp. The effect of antimicrobial agents and antisecretory agents depends not only on their pharmacological activities, but also on their pharmacokinetic properties. Many antimicrobial agents, including amoxicillin, clarithromycin, levofloxacin, metronidazole, tetracycline, rifabutin, and bismuth-containing compounds, have been used for Hp therapy, while the main antisecretory agents used are proton pump inhibitors (PPIs) (Yang et al., 2014).

Although Hp is sensitive to a wide range of antibiotics in vitro, they all fail when applied as monotherapy in vivo. Therefore, a combined therapeutic strategy is used, usually including two antibiotics (clarithromycin, combined with amoxicillin or metronidazole) and either a bismuth compound or a proton pump inhibitor (PPI). Rarely, quadruple therapies are used in which the bismuth compound and PPI are used in combination with two antibiotics. The use of these drugs has resulted in effective therapies, with eradication rates over 80%. During the past several years, however, resistant bacteria have been detected constantly (Kist, 2007; Wueppenhorst et al., 2009), leading to the search for alternative drugs and treatment strategies.

In the past decade, much effort has been devoted to the development of vaccination strategies. Based on the successful elimination of Helicobacter felis after mucosal immunization of mice with urease (Salzinger et al., 1998), the focus of much research has been the induction of a humoral or Th2-driven immune response. To date, however, effective vaccination has only been observed in animal models and no human vaccine trial has been successful (Aebischer et al., 2008). The failure to replicate the success of the vaccine in humans may be due to differences in Hp-specific immune responses or anatomical differences of the stomach. For instance, one of the main surface bacterial virulence factors, cagPAI, is usually switched off in mice.

Vaccines and antibiotics are not the only ways to prevent and cure Hp infection or Hp-associated disease. Hp-positive individuals infected with helminthes have standard levels of Hp colonization rates and gastritis patterns, but they develop significantly less Hp-associated disease (Du et al., 2006; Elshal et al., 2004). These are intriguing observations.
that might result in low-dose administration of immunomodulating agents to Hp-positive patients, which have the same consequences as enteric helminth infections.

Another approach is the application of probiotics. There is convincing evidence that Hp is killed by Lactobacilli both in vitro and to a limited extent in vivo (Lorca et al., 2001; Midolo et al., 1995; Sakamoto et al., 2001). Furthermore, Lactobacilli show a positive impact on some Hp therapy-related side effects, and recent studies suggest that Lactobacilli supplements could be effective in increasing eradication rates (Zou et al., 2009).

5. Environmental, Genetic Factors and Gastric Cancer

Among the environmental and lifestyle factors, tobacco use is reported as the most risky factor (Gonzalez et al., 2003). It causes to develop gastritis ulcers, intestinal metaplasia and finally, gastric cancer. There is strong evidence supporting tobacco use aggravates Hp infection in most cases. Many researchers reported the connection of high salt intake with gastric cancer development. The in vitro studies revealed the virulence of Hp bacteria on oncogenicity with increased concentration of salt in the medium. This is due to the increased expression of oncogenic protein (CagA). Studies on 36 cagA-positive Hp strains from Colombian patients established considerable heterogeneity in salt-regulated CagA expression (Loh et al., 2012).

Many Hp-associated diseases including peptic ulcer, gastric cancer, and MALT lymphoma only develop decades after infection (Fig. 2), their medical burden is tremendous. Gastric cancer is one of the most common forms of cancer; with approximately 700,000 to 900,000 new cases diagnosed every year, and the second leading cause of cancer-related deaths worldwide (Parkin et al., 2002). Survival rates are very low, ranging from 15% if diagnosed during later stages of the disease to 65% if diagnosed early. Incidence rates vary widely geographically, and, in general, more males than females are affected (50% lower incidence). Although high-risk areas in Japan, China, Eastern Europe, and certain Latin America countries still remain (WHO, 2009), incidence rates worldwide have been declining for several decades (Bertuccio et al., 2009).

Gastric adenocarcinomas are mainly divided into two histologically distinct forms, diffuse-type gastric adenocarcinoma, and intestinal-type adenocarcinoma (Lauren classification) each exhibiting different epidemiological and pathophysiological features (Lauren, 1965). Diffuse-type gastric adenocarcinoma is found predominantly in younger people, with no gender bias. It consists of individually infiltrating neoplastic cells that do not form glandular structures and are not associated with intestinal metaplasia (Polk and Peek, 2010). The more prevalent form of gastric adenocarcinoma is called intestinal-type adenocarcinoma, which usually occurs in elderly people, predominates inmen, and progresses through a well-defined chain of histological events, typically starting with a transition from normal mucosa to chronic gastritis, followed by atrophic gastritis and intestinal metaplasia which finally ends in dysplasia and adenocarcinoma (Correa, 1992). Hp significantly increases the risk of developing both cancer types. We focus here mainly on the association between Hp and intestinal-type adenocarcinoma as the mechanisms of disease progression are better characterized as compared to diffuse-type gastric adenocarcinoma. Gastric cancers are also classified by their localization within the stomach: the most important distinction being between cardia (the proximal part of the stomach) and noncardia. Hp is the strongest risk factor for the development of non-cardia (distal) gastric cancer.

![Figure 2: Time line of disease progression in Hp-infected persons. All infected individuals develop a superficial gastritis within the first weeks of infection, followed by a chronic active gastritis which develops after months or years. After decades, patients can develop antral gastritis or pangastritis, depending on the localization of the infection. The antral inflammation can lead to gastric metaplasia, which supports the growth of duodenal ulcer. The latter can lead to atrophy and intestinal metaplasia, two prerequisites for the development of gastric cancer or gastric ulcer. In contrast, constant chronic active gastritis can lead to the growth of MALT lymphomas. (Adapted from Telford et al., 1997).](image-url)
6. Host Genetic Factors

Host genetic factors, as polymorphisms in inflammatory and immune response genes, are mainly related to the recognition of the bacteria by the immune system and the variation in the level of cytokine response (Garza-González et al., 2005). Among host factors, several inflammatory proteins including cytokines, growth factors, and chemokines have been known to control immune response against Hp infection (Achyt et al., 2007; Trejo-de la et al., 2008). Therefore, many studies have focused on the analyses of polymorphisms in genes associated with the inflammatory response in the gastric mucosa and risk for malignancy (Rad et al., 2009; Kumar et al., 2009; Melo Barbosa et al., 2009; Partida-Rodríguez et al., 2010). Extensive epidemiology studies have shown that Hp infection is a major risk factor for gastric cancer and its precursor lesions (Eslick et al., 1999). The risk of developing gastric cancer is estimated to increase 2 to 6 times in patients with Hp infection, as determined by retrospective case-control and prospective epidemiology studies (Covacci et al., 1993). Among individuals infected with Hp, a small percentage develops gastric cancer by a process influenced by bacterial virulence.

7. Hp Virulence Factor

The most widely studied Hp virulence factor is the Caga antigen, a 96- to 138-kDa protein (Arents et al., 2001). The Caga gene, found on a genomic region called the cag pathogenicity island (PAI), is considered as a marker for enhanced virulence. Moreover, individuals infected with Caga-positive Hp strains have a higher risk of developing peptic ulcers and gastric cancer compared to those harboring Caga-negative Hp strains (Arents et al., 2001).

The role of Hp infection on gastric cancer is yet to be confirmed but two related mechanisms by which Hp could promote cancer are under investigation. One mechanism involves the enhanced production of free radicals near Hp and an increased rate of host cell mutation. The other proposed mechanism has been called a “perigenetic pathway” and involves enhancement of the transformed host cell phenotype by means of alterations in cell proteins, such as adhesion proteins. Hp has been proposed to induce inflammation and locally high levels of TNF-a and/or interleukin 6 (IL-6). According to the proposed perigenetic mechanism, inflammation-associated signaling molecules, such as TNF-a, can alter gastric epithelial cell adhesion and lead to the dispersion and migration of mutated epithelial cells without the need for additional mutations in tumor suppressor genes, such as genes that code for cell adhesion proteins (Tsuji et al., 2003; Suganuma et al., 2008).

The entire mechanism underlying tumorigenesis and metastasis of gastric cancer is not yet known. The involvement of signal transducer and activator of transcription 3 (STAT3) in GA is reported by Wang et al. (Wang et al., 2013). The STAT3 can be activated by tyrosine phosphorylation in response to growth factors and cytokines ([IL]-6). Interleukin-6 and its signaling component STAT3 play essential roles in the process of inflammation and abnormal immunity as well as carcinogenesis (Bowman et al., 2000; Hodge et al., 2005; Huang, 2007). Under certain abnormal conditions, STAT3 continues, to trigger oncogene transcription (Kim et al., 2009; Yu and Jove, 2004). This leads to the progression of GA with metastasis.

8. Conclusion

Hp infection contributes to the development of diverse gastric and extragastric diseases which are both important public health burdens which could be largely eliminated by Hp eradication. Gastric cancer develops in persons infected with Hp but not in uninfected persons. Those with histologic findings of severe gastric atrophy, corpus-predominant gastritis, or intestinal metaplasia are at increased risk. Persons with Hp infection and nonulcer dyspepsia, gastric ulcers, or gastric hyperplastic polyps are also at risk, but those with duodenal ulcers are not (Uemura et al., 2001). Undoubtedly, future studies must be undertaken to clarify further the role of Hp in the four gastrointestinal disorders discussed in this systematic overview, especially gastric cancer. The infection is necessary but not sufficient for the development of gastric adenocarcinoma. Its eradication would eliminate a major worldwide cause of cancer death, therefore there is much interest in identifying how, if, and when this can be accomplished. There are several mechanisms by which Hp contributes to the development of gastric cancer. Gastric adenocarcinoma is one of many cancers associated with inflammation, which is induced by Hp infection, yet the bacteria also cause genetic and epigenetic changes that lead to genetic instability in gastric epithelial cells. Hp eradication reduces both. However, many factors must be considered in determining whether treating this bacterial infection will prevent cancer or only reduce its risk-these must be considered in designing reliable and effective eradication therapies (Graham, 2015).

Despite of intensive investigation, the mechanisms of Hp-induced gastric cancer remain poorly understood, the stem cell hypothesis hold the promise to elucidate the origin/initiation of gastric cancer. Furthermore, important questions such as (a) variations in disease susceptibility in different populations, (b) gastric cancer progression in relation to Hp virulence genes polymorphism, and (c) the correlation of stem cell with different types of gastric cancer are all waiting for further clarification.

Hp infection triggers inflammation, interactions of bacteria with host cell in local microenvironment also affect gastric stem/progenitor cells and their differentiation, this may potentiate oncogenic transformation. Therefore, focus on Hp-induced molecular pathogenesis and the impact of microenvironment in gastric stem or progenitor cells will be crucial to identify the molecular targets in tumor initiation and the origin of gastric cancer; investigation of which will also provide insights to uncover the carcinogenic mechanisms and options for cancer intervention and prevention (Ding and Zheng, 2012).

Furthermore, Hp infection has been proposed to provide some benefits, such as reducing the risks of obesity or childhood asthma, although there are no convincing data to support the benefits of Hp infections (Graham, 2015).
References


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