REVIEW ARTICLE

Article received on November 26, 2015 and accepted for publishing on January 21, 2016.

Management of Helicobacter pylori infection – new insights

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Abstract: *Introduction: Our objective is to review current international guidelines for Helicobacter Pylori treatment and our department`s experience in this field.*

Materials and methods: Helicobacter pylori is a Gram-negative, microaerophilic bacterium that can be found mainly in the gastric mucus or on the inner surface of the gastric epithelium, infecting up to 50% of the population. Colonization with this bacterium is not a disease in itself, but can cause chronic gastritis, peptic ulcer, gastric cancer and MALToma. Because of this, infection with H. pylori continues to be a major healthcare burden, especially in less-developed countries.

A multitude of non-invasive tests are available for the diagnosis of Helicobacter pylori infection (blood antibody, stool antigen or urea breath test), but the most reliable method of diagnosis is histological examination from two sites after endoscopic biopsy, combined with either a microbial culture or rapid urease test.

Treatment of Helicobacter pylori infection is becoming a challenge, as eradication following standard triple therapy is decreasing worldwide due to increased bacterial resistance against antibiotics, which has led to the development of newer therapies such as the sequential treatment in which a PPI and amoxicillin is given for 5 days followed by a PPI, clarithromycin and metronidazole for another 5 days, or the quadruple therapy based on a PPI, bismuth subcitrate, metronidazole and tetracycline for 10 days.

Results and conclusion: H. pylori infection remains one of the most challenging infectious diseases, causing high morbidity and mortality, mainly because none of the actual antibiotic therapies can provide successful eradication.

Keywords: Helicobacter pylori, ulcer, adenocarcinoma, antibiotics, PPI

INTRODUCTION

Helicobacter pylori (Hp) is a helix shaped, Gram-negative, microaerophilic bacterium that can be found mainly in the gastric mucus or on the inner surface of the gastric epithelium[1]. Hp infection is the most common chronic infection in humans, but colonization with this bacterium is not a disease in itself. Although most infected individuals remain asymptomatic for life, Hp is responsible for a number of pathological manifestations including chronic gastritis, gastric or duodenal ulcer, adenocarcinoma

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of the stomach or gastric mucosa–associated lymphoid tissue (MALT) lymphoma[2].

THE DISCOVERY OF HELICOBACTER PYLORI

The Helicobacter pylori bacterium was discovered by two Australian researchers by the name of Barry Marshall and Robin Warren, who also deciphered its role in gastritis and peptic ulcer disease (PUD)[3]. Their discovery was published in 1982, at a time when it was a long-standing belief that stress and lifestyle factors were the major causes of PUD. The scientific community of the time met their findings with skepticism and a lot of criticism, refusing to belief that any life-form can survive in the acid medium of the stomach. This is why it took a very long time and effort for their discovery to become widely accepted[4].

Marshall`s 1985 “self-help” experiment rebutted the “stress and life-factors” dogma. He first underwent gastric biopsy to show the absence of the bacterium, then, to the horror of his assistant, ingested a turbid, foul-tasting solution of Hp. Soon he developed a number of symptoms including nausea and vomiting and an endoscopy with biopsy was performed, which revealed signs of gastritis and the presence of Helicobacter Pylori[3].

EPIDEMIOLOGY

Transmission of Hp is believed to be by gastro-oral or fecal-oral routes as the bacterium can be cultured from vomitus or diarrhea stools. Therefore, the overall prevalence of infection can be influenced by lack of proper sanitation and basic hygiene, of safe drinking water, as well as overcrowding, making it a public-health issue in developing countries[1].

One of the most important risk factors is childhood socioeconomic status, meaning that infection is acquired at an early age, especially in developing countries. It is common for spontaneous clearance to occur during early childhood, but the chance of reinfection is greater in developing countries compared to developed ones – where it is estimated to occur in less than 0.5% of cases per year[5].

Due to these factors, prevalence of infection can reach up to 80 % by the age of 20-30 in developing areas, whereas in developed countries prevalence is less than 20 % in individuals younger than 30 years, but can reach up to 40-50 % in those 60 of age or older[2].

PATHOPHYSIOLOGY

Clinical outcome of Hp infection is dependent on sophisticated interactions between the bacterial, host and environmental factors. In order to promote chronic infection, H. pylori first has to survive in the harsh acidic environment of the gastric medium[6]. One of the most important bacterium survival technique is the “acid acclimation mechanism” that adjusts periplasmic pH by regulating activity of urease. Another factor on which successful colonizationof the gastric epithelium depends is bacterial motility provided by the presence of 4 to 6 functional unipolar flagella. Recent studies show that peptidoglycan-degrading enzymes are necesary for the proper assembly ofthese flagella[7]. After colonization, adherence to gastric epithelial cells is necessary and this is done thanks to a variety of outer membrane proteins (OMPs), several of which can serve as adhesins, the most important being BabA and SabA. H. pylori employs genetic diversification to adapt to the host immune response and promote persistent infection[8].

This pathogen possesses various virulence factors known to be significant in the induction of disease during infection. One of the most studied effector molecule is cytotoxin-associated gene A (CagA) which is injected into the host cell upon contact via the cag pathogenicity island (cagPAI)-encoded typeIV secretion system. Once intracellular, CagA localizes on the inner surface of the celular membrane and is subjected to a tyrosine-phosphorylation process by Src family kinases. The phosphorylated CagA subsequently induces a signaling cascade, causing proinflammatory responses in epithelial cells[9]. While the literature is contradictory, some studies, including those of Kang et al. and Papadakos et al., sugest that inflamation is induced via the nuclear factor (NF)-kB signaling pathway and subsequent interleukin (IL)-8 secretion[7]. Taking this into

consideration, and also the fact that CagA translocation and phosphorylation are mediated by cholesterol-rich microdomains of the plasma membrane, Lin et al. found that methylantcinate B, a triterpenoid extracted from the Antrodia camphorata mushroom, attenuates CagA translocation and phosphorylation and inhibits CagA functions, including NF-kB pathway activation and IL-8 secretion; but further in vitro research is needed to assess the possibility of a new, antibiotic-free regimen[9].

DIAGNOSIS

The diagnostic procedure of Hp infection can be difficult due to the fact that up to 80-85% of infected individuals are asymptomatic, while the rest develop a series of non-specific symptoms, such as nausea, vomiting, abdominal pain, heartburn, halitosis or diarrhea[1]. This is why specific indications for testing were stipulated. These include active or documented history of peptic-ulcer disease, early-stage gastric MALToma, early gastric cancer, or uninvestigated dyspepsia in high prevalence areas[4]. Testing for the primary prevention of gastric cancer can be performed in individuals with high risk, such as those with family history of gastric cancer, or first-generation immigrants from a region with high-incidence for this malignancy. Some physicians recommend testing prior to starting long-term non steroidal anti-inflammatory drugs or proton pump inhibitors (PPI)[10].

There is also clear evidence that Hp can be involved in the pathogenesis of some extra digestive diseases, with a clear indication to test for infection in individuals with unexplained iron-deficiency anaemia, idiopathic thrombocytopenic purpura (ITP) and vitamin B12 deficiency[11]. Other studies have tried to find a link between Hp infection and some cardiovascular, lung, hepatobiliary or neurological disorders, but failed to produce an unequivocal causative association thus far[12].

Several methods are currently available for detecting Hp infection. Unfortunately, there is no gold-standard diagnostic test due to the fact that every method has it`s limitations and disadvantages [13] (as seen in table 1).

Table 1: Diagnostic tests for Helicobacter pylori infection [14]

Endoscopic Testing	Advantages	Disadvantages
A) Histology	Excellent sensitivity and specificity	Expensive. Requires infrastructure and trained personnel
B) Rapid urease testing	Inexpensive. Provides rapid results. Excellent specificity and very good sensitivity.	Posttreatment sensitivity significantly reduced
C) Culture	Excellent specificity. Allows antibiotic sensitivities determination	Expensive. Difficult to perform. Not widely available.
D) Polymerase chain reaction (PCR)	Excellent sensitivity and specificity. Allows antibiotic sensitivities determination	Not standardized across laboratories. Not widely available
Nonendoscopic Testing	**Advantages**	**Disadvantages**
A) Antibody testing (quantitative and/or qualitative)	Inexpensive. Widely available Very good NPV	PPV dependent upon background Hp prevalence. Not recommended after Hp therapy
B) Urea breath tests (^{13}C and/or ^{14}C)	Identifies active Hp infection. Excellent PPV and NPV regardless of Hp prevalence. Useful before and after Hp therapy	Reimbursement and availability remain inconsistent
C) Fecal antigen test	Identifies active Hp infection. Excellent NPV and PPV, regardless of Hp prevalence. Useful before and after Hp therapy	Polyclonal test less well validated compared to the UBT in posttreatment settings. Monoclonal test appears reliable before and after Hp therapy.

The sensitivity of all tests (endoscopic and nonendoscopic) that identify active Hpi infection is reduced by the recent use of PPIs, bismuth, or antibiotics
PPI = proton pump inhibitor; NPV = negative predictive value; PPV = positive predictive value; UBT = urea breath test.

Table 2: Possible reasons for Helicobacter pylori treatment failure.

1	resistance acquired by mutations
2	the low gastric pH limits antibiotic efficacy
3	antibiotic concentration can be insufficient if there is a high bacterial load
4	existence of sanctuaries to which antibiotics do not diffuse
5	existence of viable bacteria in dormant forms not accessible to antibiotics
6	impaired host mucosal immunity
7	risk of re-infection
8	lack of patient compliance (due to adverse effects or poor understanding of complex antibiotic regimen)

TREATMENT

Historically, various combinations of antibiotics have been used to eradicate the infection, however, no optimal treatment has yet been defined, as there is not a single drug regimen that can eradicate it. There are many factors that have increasingly compromised the effectiveness of most commonly used therapies (as seen in table 2)[1].

These factors have reduced the eradication rates to unacceptable levels (< 80% in some geographic areas). As a response, new treatment strategies have been studied and recently been validated to replace the standard ones[15].

Eradication therapies should be guided ideally by individual susceptibility testing. As this is not cost-effective, local antibiotic resistance patterns should dictate the regimen. Another factor that influences the treatment strategy is drug availability in different countries[16]. These regimens can be divided into first-line treatment and second-line or rescue treatment and are summarized in table 3[1].

Table 3: Treatment regimens for Helicobacter pylori infection

First-line therapies		
Regimen name	*General characteristics*	*Duration*
"Standard triple treatment"	simultaneous PPI + clarithromycin + amoxicillin (each twice daily)	7 days
10 or 14 days triple	simultaneous PPI + clarithromycin + amoxicillin (each twice daily)	10 or 14 days
Sequential therapy	5 or 7 days simultaneous PPI + amoxicillin, followed by 5 or 7 days simultaneous PPI + clarithromycin + 5-nitroimidazole (each twice daily)	10 or 14 days
Quadruple therapy	Simultaneous PPI (twice daily) + bismuth subsalicylate, metronidazole and tetracycline (each 4 times daily)	10 or 14 days
Second-line and rescue therapies		
Regimen name	*General characteristics*	*Duration*
Concomitant therapy	Simultaneous PPI + 3 antibiotics (often amoxicillin, clarithromycin, and 5-nitroimidazole) (each twice daily)	7, 10 or 14 days
Levofloxacin therapies	Levofloxacin will replace clarithromycin in triple, sequential or concomitant regimens	7, 10, 14 days
Hybrid therapy	7 days simultaneous PPI + amoxicillin, followed by 7 days simultaneous PPI + amoxicillin + clarithromycin + 5-nitroimidazole (each twice daily)	14 days
Rifabutin triple therapy	PPI + amoxicillin + rifabutin (each twice daily)	14 days

PPIs are mandatory compounds in every regimen and are administered twice daily at standard doses: omeprazole 20 mg, esomeprazole 40 mg, lanso-prazole 30 mg or pantoprazole 40 mg (with studies showing higher eradication rates for the more potent second-generation PPIs – namely esomeprazole). Standard antibiotic dosages are used in all treatment regimens: amoxicillin 1 g, clarithromycin 500 mg,

metronidazole 500 mg, tinidazole 500 mg, bismuth subsalicylate 524 mg or bismuth subcitrate 420 mg, tetracycline 500 mg, levofloxacin 500 mg, and rifabutin 300 mg[17].

A recently published meta-analysis by Li et al. has compared many of the available regimens for efficacy and tolerance. In terms of efficacy, the standard triple therapy was outranked by all other regimens, with the best eradication rates for the sequential therapy amongst first-line treatments and for the concomitant therapy amongst rescue treatments. The same study has shown that increased treatment duration improves eradication rates, but at the same time enhances the likelihood of adverse effects, lowering patient compliance – almost all rescue regimens were poorly ranked in terms of tolerance[18]. Because of the fact that none of these regimens is ideal, eradication should always be assessed, preferably using a non-invasive test (eg: urea breath test or stool antigen test). Confirmation of eradication can also provide an early image on the pattern of antibiotic resistance in a specific population[15].

All this effort in treating Hp infection is justified by the many benefits of eradication for patience with PUD, but also some malignant conditions. For example a cured individual has better ulcer remission rates for both gastric and duodenal ulcer and does not need maintenance acid suppression therapy after eradication and ulcer healing[10]. It is also more cost-effective and superior compared to maintenance acid suppressive therapy in preventing duodenal ulcer[1]. As for malignant pathologies, early stage low-grade MALT lymphoma can be cured by Hp eradication up to 80% of cases and there is also the possibility of regression or decrease in progression of precancerous gastric lesions (atrophic gastritis and intestinal metaplasia) after eradication[15].

Other studies have shown inverse associations between Hp infection and the prevalence of certain diseases. A recent study published by Rubenstein et al. confirmed prior studies that showed a strong negative association between Hp infection (particularly the cagA strain) and erosive esophagitis, Barrett's esophagus or adenocarcinoma of the esophagus. However, contrary to the prevalent hypothesis explaining this association, they were unable to detect a negative association between Hp infection and gastroesophageal reflux disease symptoms[19]. Lebwohl et al. found a strong inverse relationship between Hp presence and celiac disease (CD), but failed to establish the mechanism by which Hp might be protective against CD[20]. Other studies have postulated that Hp is protective against some extradigestive conditions, especialy asthma and other allergic pathologies in children[21].

THE ROLE OF PROBIOTICS IN HP MANAGEMENT

Probiotics are defined by the World Health Organization (WHO) as "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host". Most commonly used in clinical practice are lactic-acid-producing micro-organisms (Lactobacillus spp. or Bifidobacterium spp.). Lactic acid produced by these probiotics can have a direct antimicrobial effect by lowering the pH, but can also inhibit the Hp urease. There is also increasing evidence in animal models that some strains of probiotics can inhibit H. pylori growth by competing with different adhesion sites in the gastric mucosae. Another mechanism being stipulated is that some probiotics can increase the expression of the MUC2 and MUC3 genes, which can subsequently lead to an increase of mucus thickness in both antrum and corpus after long-term probiotic intake.

Many studies have been conducted in this field and by analyzing some of them Enzo et al. have reached the conclusion that the use of probiotics as an adjuvant to PPI–antibiotic treatment could improve eradication rates, but the main benefit of this association is the prevention of side-effects, leading to better patient compliance[22].

FUTURE THERAPIES

Efforts to develop a vaccine against H. pylori began in early 1990`s with initial attempts to promote a localized mucosal immune response in the stomach via oral vaccines. Recently, an intramuscularly trivalent vaccine (recombinant Cag-A, Vac-A, and neutrophil-activating protein) was developed, but

failed to induce immunity, despite the fact that these antigens were recognized by the host's humoral and cellular immune systems. Although considerable progress has been made in understanding the innate and adaptive immune response against Hp infection, it is still uncertain how to promote the development of host immunity with the final goal of creating a successful vaccine[23].

DISCUSSIONS AND CONCLUSIONS

Despite the constant progress made in the management of Helicobacter pylori infection, it is still considered a major public health issue due to it`s high prevalence (especially in developing countries) and various conditions that can arise from it (even though 80-85% of infected individuals are asymptomatic). The main reasons for treatment failure is resistance acquired by mutations and lack of patient compliance and recent studies are showing that the standard triple therapy is out-performed in effectiveness by most other treatments. Probiotic adjuvant therapy appears to have a clear effect in reducing side effects, but insufficient data exists to conclude that their use improves eradication rates. Knowing that there is no "gold-standard" in Hp eradication therapy and falling short of the individual susceptibility testing goal, the regimen should be dictated by local antibiotic resistance patterns.

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