REVIEW PAPER

Helicobacter Pylori and non-Malignant Haematological Disorders in Adults

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ABSTRACT

Background: Helicobacter pylori infects half of world's population causing local tissue damage in gastric mucosa. The implication in a variety of extraintestinal disorders is less clear and the available studies often lead to conflicting results.
Aim: This article will review the implication of Helicobacter pylori in the development of non-malignant haematological disorders in adults. Epidemiological data, possible pathogenetic mechanisms and the role of eradication therapy are analyzed.
Methodology: Relevant articles published in English during the last two decades were found through PubMed and SCOPUS.
Results: Significant advances have been made in understanding the pathophysiology of Helicobacter pylori-induced haematological disorders. The investigation of persistently thrombocytopenic and anaemic patients in absence of other causative factors should include Helicobacter pylori assays. Half of infected thrombocytopenic patients respond to eradication, whereas the outcomes are less clear in anaemic disorders. Bacterial strains and genetic factors seem to influence the outcome of bacterium eradication. The implication of Helicobacter pylori in atherosclerosis remains controversial and it is attributed either to inflammation process or to direct alteration in haemostatic factors.
Conclusion: Large randomized studies are needed to determine the subpopulation at risk of developing Helicobacter pylori-related haematological disorders. In this case prompt screening and eradication treatment could be of major importance.

Keywords: anaemia, Helicobacter pylori, iron deficiency, thrombocytopenia, thrombosis

Introduction

Helicobacter pylori (HP) is a common pathogen, infecting approximately 50% of world's population (Ali & Whitehead, 2008). The prevalence in developed countries is 25-40% and is almost 100% in developing ones (Windsor et al, 2005). Bacteria have been isolated from feces, saliva; and dental plaques, suggesting a fecal-oral route of transmission (Ndip, 2003). The infection is usually acquired at the age of 10 and persists lifelong without antibiotic treatment (Sherman, 2004). Anti-HP IgG antibodies increase with age. They have been found in 40% of those aged 1-14 years and in up to 60% of 18-24 year-old Mexicans; and 100% of 60-69 year-old Turkeys (Kikuchi & Dore, 2005).

HP is a gram-negative spiral shaped bacterium colonizing the human gastric mucosa. High humidity, microaerophilic environment; and incubation temperature of 37°C are essential factors for its growth (Winn et al, 2006). Some virulence factors such as urease and flagella are present in all strains and participate in pathogenesis and colonization of gastric mucosa (Anderson, 2007). There are two different phenotypes based on the presence of vacuolating toxin (VacA) and cytotoxin-associated gene (CagA). The proteins of outer membrane facilitate the adhesion and colonization (Wang et al, 2012). An interaction between bacterial factors and host signal transduction pathway mediates cell transformation, cell proliferation, invasion, apoptosis; and angiogenesis (Zhang et al, 1998). The infection provokes an inflammatory process via cytokines. The neutrophil-activating protein (NapA) can shift antigen-specific T-cell response from Th2 to Th1 phenotype, which is characterized by high levels of cytokines, such as interferon-γ and tumor necrosis factor α (TNFα) (Takahashi et al, 2004).

HP can readily be detected at endoscopy by histology, cultures; or urease test. Non-invasive tests include the 13C-urea breath test (UBT) and stool antigen with sensitivity and specificity 90-95% (Logan & Walker, 2001). Proton pump inhibitors (PPIs) should be stopped at least 2 weeks before UBT and stool antigen test to prevent false negative results. Serology assays have low cost but are not specific of active infection (Logan & Walker, 2001).

The association between HP active chronic gastritis and peptic ulceration is well established. Nowadays, there is an increasing number of studies suggesting HP implication in haematological disorders, such as idiopathic thrombocytopenic purpura (ITP), iron deficiency anaemia (IDA); and arterial thrombosis. Eradication treatment often seems to be an essential element in the management of the above disorders. The recommended regime consists of a full dose PPIs, with either amoxicillin 1g and clarithromycin 500mg; or metronidazole 400mg and clarithromycin 250mg, all given twice daily for 7-14 days. Eradication is effective in 80-85% of cases on triple therapy using either antibiotic combination (Malfertheiner et al, 2007).

The aim of this article is to review the available data about HP implication in non-malignant haematological disorders in adults. Initially, clinical studies and review articles published in English over the last two decades were found through PubMed and SCOPUS, using combinations of the following keywords: anaemia, Helicobacter pylori, iron deficiency, thrombocytopenia; and thrombosis. The bibliography of retrieved literature is assessed for additional reports of clinical trials.

HP and idiopathic thrombocytopenic purpura

ITP is characterized by low platelet count, caused by autoantibodies against platelets. Persistent thrombocytopenia for more than 6 months defines the chronic form of the disease. The Maastricht III consensus states that HP infection should be sought for and treated in patients with ITP (Malfertheiner et al, 2007). In 2010, the international consensus included UBT or stool antigen test in basic work-up for patients with suspected ITP regardless the geographical region (Provan et al, 2010).

The host immunity can be altered by HP infection with the development of autoreactive clonal antibodies, increased phagocytic activity; and reduced expression of the inhibitory Fcγ receptors IIB on monocytes (Yamanishi et al, 2006; Asahi et al, 2008). Anti-CagA antibodies can cross-react with platelet glycoproteins, causing platelet destruction (Takahashi et al, 2004). Lewis antigens, expressed by some HP strains, can be absorbed by the platelets and serve as targets for anti-Lewis antibodies (Gerhard et al, 2002). Yeh et al. showed increase of P selectin in infected patients, leading to platelet aggregation and subsequent thrombocytopenia (Yeh et al, 2010). Some HP strains bind von Willebrand factor (vWF) and induce glycoprotein (GP) Iβ-FcRIIα-dependent platelet aggregation in the presence of anti-HP antibodies (Byrne et al, 2003). There are limited data regarding the implication of major histocompatibility complex class II. Infected ITP patients showed significantly higher frequencies of HLA–DRB1*11, *14 and –DQB1*03 and lower frequency of –DRB1*03. Moreover, HLA–DQB1*03 pattern is associated with a higher probability for platelet response after eradication (table 1) (Veneri et al, 2005).

Table 1. Biological pathways
1. IMMUNE THROMBOCYTOPENIC PURPURA
1a. Immune response
Cross react anti-Cytotoxic-associated gene A antibodies against platelets' glycoproteins (Takahashi et al, 2004; Yamanishi et al, 2006; Asahi et al, 2008; Arnold & Stasi, 2008)
Anti-Lewis antibodies (Gerhard et al, 2002)
1b.Increased platelet aggregation
Increased P-selectin expression (Yeh et al, 2010)
Interactions with von Willebrand Factor and glycoprotein Ib/IX (Byrne et al, 2003)
1c.Genetic factors
HLA–DRB1*11, *14 and –DQB1*03 (Veneri et al, 2005; Fujimura et al, 2005)
2. IRON DEFICIENCY ANAEMIA
2a. Blood loss
Gastric mucosa lesions (chronic gastritis, ulceration) (Zhang et al, 1998; Kim et al, 2013)
2b.Impaired iron homeostasis
Reduced divalent metal ion transporter 1 expression (Zhang et al, 2010)
Increased lactoferrin levels (Choe et al, 2003; Hershko, Lahad & Kereth, 2005; Wang et al, 2012)
Hypochlorhydria (Zhang et al, 1998; Kim et al, 2013)
Increased hepcidin expression (Schwarz et al, 2012)
2c. Red cell deformation
Increased adhesion to type A red cells (Nakao et al, 2011)
3. ARTERIAL THROMBOSIS
3a. Inflammatory response
Interactions between bacterial lyposacharides and endothelial Toll-like receptors (Liao, 1996)
Cross-react anti-Cytotoxic-associated gene A antibodies against endothelial cells (Franceschi et al, 2002; Pietroiusti et al, 2002; Markus et al, 2002; Ikeda et al, 2013)
3b. Alterations on coagulation factors
Increased homocysteine levels (Markle, 1997; Sealy-Jefferson et al, 2013)
Increased prothrombin fragments 1+2 (Consolazio et al, 2004; Lee et al, 2004)
3c. Platelet aggregation
Increased P-selectin expression (Yeh et al, 2010)
Interactions with von Willebrand Factor and glycoprotein Ib/IX (Byrne et al, 2003)

A study of 207 HP-positive ITP patients showed that 55% of those had persisting platelet response 12 months after eradication (Fujimura et al, 2005). In a randomized controlled trial with 25 HP-positive patients, the platelet response was 46% and 0% in eradication and non-eradication group respectively (Suzuki et al, 2005). In a systematic review, including 696 patients, the complete response rate was 42.7% and overall response 50.3% after eradication (Stasi et al, 2009). High response rates have been seen in Japanese and Italian studies, where the HP prevalence is above 50% (Arnold et al, 2009). In contrast, studies from North America and Australia have showed inferior outcomes with no sustainable platelet response after eradication

(Arnold et al, 2009; Jarque et al, 2001; Michel et al, 2004). Thus, Jarque et al. showed a low platelet response rate (13%) following eradication treatment in 56 adults with chronic ITP (Jarque et al, 2001). Similarly, Michel et al. observed no platelet recovery, despite bacterium eradication in 14 ITP cases (Michel et al, 2004). In a small Malaysian series, 10 of 50 ITP patients had eradication treatment with overall response 30% and all responders relapsed after 6 months (Gan et al, 2013). The above discrepancies could be attributed to variability of bacterial strains depending on geographical factors (Takahashi et al, 2004).

Eradication is not efficient for uninfected thrombocytopenic patients. Asahi et al. showed that 62% of HP-positive patients achieved platelet response, whereas none of uninfected cases after antibiotic treatment (Asahi et al, 2006). The response was accompanied by significant decrease in anti-GPIIβ/IIIα antibody-producing B cells in HP-positive responders (p value< 0.0001), but not in HP-negative patients. Similarly, in an evidence-based review, platelet response was observed in 65 of 131 infected patients (49.6%) and none of 44 uninfected patients (Arnold & Stasi, 2008). A metanalysis of 11 studies (8 from Japan) showed that the odds of obtaining a platelet response following bacterium treatment were increased by 14.5 times [95% CI 4.2-83.0] in HP-positive compared to HP-negative thrombocytopenic patients (51.2% versus 8.8%) (Arnold et al, 2009).

Favorable predictors of platelet response include shorter ITP duration, platelet count more than 30×10^9/L, HLA-DQB1* 03 haplotype; and CagA positivity. Patients from Japan, Italy, and Colombia, where the bacterium prevalence in general population is higher, are more likely to respond. Age, sex; and previous therapies were not useful markers to predict response (Veneri et al, 2005; Fujimura et al, 2005; Stasi et al, 2009; Veneri et al, 2011).

HP and anaemia

Based on the Maastricht III consensus report, HP infection should be sought for and treated in patients with unexplained IDA (Malfertheiner et al, 2007). HP-related IDA is defined by absence of gastrointestinal symptoms, negative endoscopy for bleeding mucosa lesions, sufficient iron intake, resistance to iron supplementation; and response to eradication treatment (Wang et al, 2012).

The pathophysiology of impaired iron metabolism is not fully understood in HP infected subjects (table 1). Prominent pathogenetic pathways include occult blood loss secondary to chronic gastritis; and decreased iron absorption due to either atrophy-associated hypochlorhydria or reduced ascorbic acid (Zhang et al, 2010; Kim et al, 2013). Divalent metal ion transporter 1 (DMT1) mediates iron transport into enterocytes where iron is stored as ferritin. HP can affect DMT1 expression and cause duodenal disease which may increase the slough of enterocytes (Ford et al, 2004; Zhang et al, 2010). A recent study showed significantly upregulated gastric hepcidin expression which was normalized after HP eradication (Schwarz et al, 2012). Lactoferrin increases in gastric mucosa via neutrophils and captures iron from transferring. Bacteria pick up the iron for their growth through membrane receptors (Hershko, Lahad & Kereth, 2005). Co-cultivated erythrocytes with HP for 4 hours showed significant iron loss contrary to high iron concentration in bacteria (Wang et al, 2012). Choe et al. reported a decrease in tissue lactoferrin and increase in haemoglobin after bacterium eradication (Choe et al, 2003). A series of 1,406 non-cancer patients, who examined for serum anti-HP IgG antibodies, showed that HP infection was more frequent in patients with blood group type A. The bacterium probably has different binding capacities for the host erythrocytes and it can readily bind to type A cells, causing significant membrane deformation (Nakao et al, 2011).

A metanalysis of 19 observational and six intervention studies showed an increased risk for IDA [odds ratio (OR) 2.8; 95% CI 1.9-4.2] and iron deficiency (OR 1.38; 95% CI 1.16-1.65) among infected patients (Muhsen & Cohen, 2008). Similarly, a metanalysis of 15,183 patients from 20 studies showed a correlation between HP and IDA (OR 2.22; 95% CI 1.52-3.24) (Qu et al, 2010). In a study of 84 HP eradicated patients, IDA was more frequent in men (80%) and postmenopausal women (71.4%) (Mónzon et al, 2013). In a series of 1,060 cases, serum iron was lower in seropositive males, but there were no significant differences in serum ferritin in either males or females between seropositive and

seronegative subjects (Collett et al, 1999). In contrast, a study of 45 HP-positive and 16 HP-negative patients showed no significant differences in haemoglobin, haematocrit, serum iron; and ferritin between the two groups (Doğan et al, 2012).

A metanalysis of 8 randomized controlled trials, involving 800 patients, showed that eradication treatment accelerated the improvement of ferritin [mean difference (MD) 7.74mcg/L; 95% CI 4.61-10.88; p value< 0.00001] after 1 and 2 months, but did not improve the haemoglobin in the overall analysis (MD 3.80g/L; 95% CI, –4.50-12.2; p value= 0.37) (Zhang et al, 2010). The subgroup analysis revealed an improvement of ferritin levels in Asian studies (MD 9.63mcg/L; 95% CI 5.22-14.03; p value< 0.0001) in contrast to American ones, a fact that can be attributed to differences of HP strains among countries (Zhang et al, 2010). Recently, the effect of eradication on IDA was assessed in 84 previously iron-dependent and/ or iron-refractory patients. Recovery was observed in 32 patients (38.1%; 95% CI 28.4-48.8) 6 months post eradication and there was no relapse after a mean follow-up of 21±2 months (Mónzon et al, 2013).

The effect of HP infection on vitamin B12 and folate level has not been elucidated so far. HP gastritis could lead to destruction of parietal cells and to subsequent impaired production of intrinsic factor which is essential for vitamin B12 absorption. HP infection was detected in 77 of 138 patients (55.7%) with pernicious anaemia and antibiotic treatment improved serum vitamin B12 in 40% of those (Kaptan et al, 2000). Inversely, Sarari et al. showed that 67.4% of HP-infected patients had vitamin B12 deficiency (Sarari et al, 2008). Rasool et al. in a study of 132 patients showed that the HP presence did not have any impact on vitamin B12 and folate levels (Rasool et al, 2012).

HP and arterial thrombosis

The association between HP and arterial events is a matter of debate. In a recent study of 1,621 subjects, anti-HP IgG antibodies predicted the stroke incident in Mexican-Americans (OR 1.58; 95% CI 1.09-2.28) (Sealy-Jefferson et al, 2013). In 4 other case-control studies, seropositivity was associated with increased risk of atherothrombotic and/or microangiopathic stroke (Markus & Medall, 1998; Heuschmann et al, 2001; Grau et al, 2001; Ponzetto et al, 2002). In contrast, a prospective case-control study showed no significant association between HP-IgG positivity and risk of myocardial infarction and stroke (Ikeda et al, 2013). Bacterial DNA has been found in atherosclerotic plaques, but without any successful isolation of viable microorganisms (Ameriso et al, 2001; Latsios et al, 2004).

There are some biologically plausible pathways by which HP can affect the incidence of vascular events (table 1). Lipopolysacharides on the outer membrane of HP can bind to Toll-like receptors of endothelial cells, monocytes; and macrophages, which results to endothelium damage and the initiation of atherosclerosis (Liao, 1996). Inflammation process alters the coagulation through the release of pro-inflammatory cytokines in gastric mucosa. Anti-CagA antibodies cross-react with vascular wall antigens and seroprevalence against CagA stains has been found increased in large-vessel stroke (Franceschi et al, 2002; Pietroiusti et al, 2002). A case-control study, involving 80 stroke patients and 320 blood donors, showed that CagA positivity tended to be associated with myocardial infarction in middle-aged Japanese (OR 1.72; 95% CI 0.91-3.26; p value= 0.10) (Ikeda et al, 2013). However, in a series of 183 normal individuals, there was no significant association between HP seropositivity, CagA strain and increased intima-media thickness of common carotid artery after controlling other cardiovascular risk factors (Markus et al, 2002).

Impaired folate and vitamin B12 absorption could result in decreased activity of methionine synthase and increased serum homocysteine. Homocysteine is toxic to endothelium and a risk factor for atherosclerosis (Markle, 1997). However, a recent study of 132 patients with functional dyspepsia showed that HP infection had no impact on vitamin B12, folate; and homocysteine levels (Rasool et al, 2012).

Platelet aggregation can trigger the development of thrombotic thrombocytopenic purpura in infected patients (Byrne et al, 2003; Yeh et al, 2010). Byrne et al. showed that HP strain 60190 induces platelet aggregation through interactions between HP, anti-HP antibodies and platelet receptor FcγRIIA as well as vWF and its receptor GPIb/IX. The platelet aggregation through the direct binding between vWF and HP was

inhibited by anti-vWF antibodies, aspirin; and GPIIβ/IIIα antagonists (Byrne et al, 2003).

The eradication reduces systemic cytokines, attenuates the lumen reduction of coronary artery in patients undergoing angioplasty; and eliminates the number of coronary events (Kowalski, 2001; Elizalde et al, 2004). A statistically significant decrease in C-reactive protein (CRP) and improvement in overall survival has also been reported after combined treatment for HP (Stone et al, 2002). In HP-positive patients with gastritis, prothrombin fragments 1+2 and TNFα showed significant decrease at 2 months (p value= 0.03 and p value= 0.02, respectively) and reached the levels of uninfected patients and controls six months after eradication (Consolazio et al, 2004). In a study of 94 patients who underwent angioplasty, both acute inflammatory markers and coagulation parameters such as, white cells, CRP, fibrinogen, homocysteine, prothrombin time, activated partial thromboplastin time, plasminogen activator inhibitor-1; and tissue plasminogen activator, were not significantly different between infected and uninfected subjects, indicating that HP cannot be an independent risk factor for coronary heart disease (Lee et al, 2004).

Discussion

H. pylori infection is one of the most common infections worldwide, infecting approximately 50% of world's population. Infection persists lifelong without any treatment. Nowadays, the detection of bacterium does not rely on endoscopic investigation of gastrointestinal tract since reliable non-invansive methods such as UBT and stool antigen testing are available. Over the last years, the number of studies evaluating the spectrum of non-gastrointestinal manifestations of HP infection has increased. However, many of those refer either to small series of patients or to individual cases leading to conflicting and debated results due to absence of significant statistical power.

Significant advances have been made in understanding the role of HP in the pathophysiology of ITP. Several haematology associations, including American Society of Hematology, suggest HP detection as a part of the basic work-up in patient with suspected ITP. According to the Maastricht III consensus conference, HP eradication has been suggested for infected ITP patients. Approximately half of adults obtain platelet count recovery after eradication. However, the available data show a geographical discrepancy of platelet response to eradication treatment with less sustained response rates in America and Australia. Possibly, HP strain and genetic factors may influence the therapeutic outcome. Large randomized studies are needed to elucidate the HP implication in ITP and to determine the subpopulation where HP screening and eradication treatment is beneficial.

Conflicting data have been reported as regards the relationship between HP and IDA. According to the Maastricht III consensus unexplained IDA is the second extraintestinal entity for which HP testing is needed. In some studies eradication treatment seems to improve the absorption of oral ferrous and improve the parameters of iron metabolism. The lack of reproductivity of those results highlights the need of well structured studies evaluating the role of HP in pathogenesis of IDA in absence of other causative factors. Despite the micronutrient deficiencies observed in infected subjects, the aetiological role of HP in vitamin B12 and folate deficiency is not clear so far.

HP has been found in a number of atherosclerotic lesions and has been associated with inflammatory cell response. Despite the well known implication of inflammation in the development of thrombotic events, the studies have failed to provide convincing evidences of a causative relation between HP infection and vascular disease. Further research may help to establish the pro-inflammatory role of H. pylori in atherosclerosis, altering possibly the assessment of thrombotic risk and the thromboprophylactic modality.

References

Ali M. & Whitehead M. (2008) Clearance of chronic psoriasis after eradication therapy for Helicobacter pylori infection. Journal of the European Academy of Dermatology Venereology 22:753-754.

Ameriso S., Fridman E., Leiguarda R. & Sevlever G. (2001) Detection of Helicobacter pylori in human carotid atherosclerotic plaques. Stroke 32:385–391.

Andersen L. Colonization and infection by Helicobacter pylori in humans. (2007) Helicobacter 12:12-15.

Arnold D. & Stasi R. (2008) Does Helicobacter pylori eradication therapy result in a platelet count

improvement in adults with immune thrombocytopenic purpura regardless of Helicobacter pylori infection? Hematology American Society Hematology Education Program 2008:31-32.

Arnold D., Bernotas A., Nazi I., Stasi R., Kuwana M., Kelton J. & Crowther M. (2009) Platelet count response to H. pylori treatment in patients with immune thrombocytopenic purpura with and without H. pylori infection: a systematic review. Haematologica 94:850-856.

Asahi A., Kuwana M., Suzuki H., Hibi T., Kawakami Y. & Ikeda Y. (2006) Effects of a Helicobacter pylori eradication regimen on anti-platelet autoantibody response in infected and uninfected patients with idiopathic thrombocytopenic purpura. Haematologica 9:1436–1437.

Asahi A., Nishimoto T., Okazaki Y., Suzuki H., Masaoka T., Kawakami Y., Ikeda Y. & Kuwana M. (2008) Helicobacter pylori eradication shifts monocyte Fc gamma receptor balance toward inhibitory Fc gamma RIIB in immune thrombocytopenic purpura patients. The Journal of Clinical Investigation 118:2939–2949.

Byrne MF., Kerrigan SW., Corcoran PA., Atherton JC., Murray FE., Fitzgerald DJ. & Cox DM. (2003) Helicobacter pylori binds von Willebrand factor and interacts with GPIb to induce platelet aggregation. Gastroenterology 124:1846-1854.

Choe YH., Oh YJ., Lee NG., Imoto I., Adachi Y., Toyoda N. & Gabazza EC. (2003) Lactoferrin sequestration and its contribution to iron-deficiency anemia in Helicobacter pylori-infected gastric mucosa. Journal of Gastroenterology and Hepatology 18:980–985.

Collett JA., Burt MJ., Frampton CM., Yeo KH., Chapman TM., Buttimore RC., Cook HB. & Chapman BA. (1999) Seroprevalence of Helicobacter pylori in the adult population of Christchurch: risk factors and relationship to dyspeptic symptoms and iron studies. New Zealand Medical Journal 112:292–295.

Consolazio A., Borgia MC., Ferro D., Iacopini F., Paoluzi OA., Crispino P., Nardi F., Rivera M. & Paoluzi P. (2004) Increased thrombin generation and circulating levels of tumour necrosis factor-a in patients with chronic Helicobacter pylori-positive gastritis. Alimentary Pharmacology and Therapeutics 20:289–294.

Doğan Y., Erkan T., Önal Z., Usta M., Doğusoy G., Çokuğras FC. & Kutlu T. (2012) Lactoferrin levels in the gastric tissue of helicobacter pylori-positive and -negative patients and its effect on anemia. Mediators of Inflammation 2012:214581.

Elizalde JI., Pérez-Pujol S., Heras M., Sionis A., Casanovas N., Martorell T., Lozano M., González J., Escolar G., Sanz G. & Piqué JM.. (2004) Effects of Helicobacter pylori eradication on platelet activation and disease recurrence in patients with acute coronary syndromes. Helicobacter 9:681-689.

Ford AC., Delaney BC., Forman D. & Moayyedi P. (2004) Eradication therapy in Helicobacter pylori positive peptic ulcer disease: systematic review and economic analysis. American Journal of Gastroenterology 99:1833-1855.

Franceschi F., Sepulveda AR., Gasbarrini A., Pola P., Silveri NG., Gasbarrini G., Graham DY. & Genta RM. (2002) Cross-reactivity of anti-CagA antibodies with vascular wall antigens: possible pathogenic link between Helicobacter pylori infection and atherosclerosis. Circulation 106:430–434.

Fujimura K., Kuwana M., Kurata Y., Imamura M., Harada H., Sakamaki H., Teramura M., Koda K., Nomura S., Sugihara S., Shimomura T., Fujimoto TT., Oyashiki K. & Ikeda Y. Is eradication therapy useful as the first line of treatment in Helicobacter pylori-positive idiopathic thrombocytopenic purpura? Analysis of 207 eradicated chronic ITP cases in Japan. International Journal of Hematology 81:162–168.

Gan GG., Norfaizal AL., Bee PC., Chin EFM., Habibah AH. & Goh KL. (2005) Helicobacter pylori infection in chronic immune thrombocytopenic purpura patients in Malaysia. (2013) Medical Journal of Malaysia 68:231-233.

Gerhard M., Rad R., Prinz C. & Naumann M. (2002) Pathogenesis of Helicobacter pylori infection. Helicobacter 7:17-23.

Grau AJ., Buggle F., Lichy C., Brandt T., Becher H. & Rudi J. (2001) Helicobacter pylori infection as an independent risk factor for cerebral ischemia of atherothrombotic origin. Journal of Neurological Sciences 186:1–5.

Hershko C., Lahad A. & Kereth D. (2005) Gastropathic sideropenia. Best Practice and Research Clinical Haematology 18:363–380.

Heuschmann PU., Neureiter D., Gesslein M., Craiovan B., Maass M., Faller G., Beck G., Neundoerfer B. & Kolominsky-Rabas PL. (2001) Association between infection with Helicobacter pylori and Chlamydia pneumoniae and risk of ischemic stroke subtypes: results from a population-based case control study. Stroke 32:2253–2258.

Ikeda A., Iso H., Sasazuki S., Inoue M. & Tsugane S.; JPHC Study Group. (2013) The combination of Helicobacter pylori- and cytotoxin-associated gene-A seropositivity in relation to the risk of myocardial infarction in middle-aged Japanese: The Japan Public Health Center-based study. Atherosclerosis 230:67-72.

Jarque I., Andreu R., Llopis I., De la Rubia J., Gomis F., Senent L., Jimenez C., Martín G., Martínez JA., Sanz GF., Ponce J. & Sanz MA. (2001) Absence of platelet response after eradication of Helicobacter pylori infection in patients with

chronic idiopathic thrombocytopenic purpura. British Journal of Haematology 115:1002–1003.

Kaptan K., Beyan C., Ural AU., Cetin T., Avcu F., Gülşen M., Finci R. & Yalçín A. (2000) Helicobacter pylori: is it a novel causative agent in vitamin B12 deficiency? Archives of Internal Medicine 160:1349-1353.

Kikuchi S. & Dore MP. (2005) Epidemiology of Helicobacter pylori infection. Helicobacter 10:1-4.

Kim HK., Jang EC., Yeom JO., Kim SY., Cho Y., Kim SS., Chae HS. & Cho YS. (2013) Serum prohepcidin levels are lower in patients with atrophic gastritis. Gastroenterology Research and Practice 2013:201810

Kowalski M. (2001) Helicobacter pylori (H. pylori) infection in coronary artery disease: influence of H. pylori eradication on coronary artery lumen after percutaneous transluminal coronary angioplasty. The detection of H. pylori specific DNA in human coronary atherosclerotic plaque. Journal of Physiology and Pharmacology 52:3–31.

Latsios G., Saetta A., Michalopoulos NV., Agapitos E. & Patsouris E. (2004) Detection of cytomegalovirus, Helicobacter pylori and Chlamydia pneumoniae DNA in carotid atherosclerotic plaques by the polymerase chain reaction. Acta Cardiologica 59:652–657.

Lee SY., Kim DK., Son HJ., Lee JH., Kim YH., Kim JJ., Paik SW. & Rhee JC. (2004) The impact of Helicobacter pylori infection on coronary heart disease in Korean population. The Korean Journal of Gastroenterology 44:193-198.

Liao W. (1996) Endotoxin: Possible roles in initiation and development of atherosclerosis. The Journal of Laboratory and Clinical Medicine 128:452-460.

Logan RP. & Walker MM. (2001) ABC of the upper gastrointestinal tract: Epidemiology and diagnosis of Helicobacter pylori infection. British Medical Journal 323:920-922.

Malfertheiner P., Megraud F., O' Morain C., Bazzoli F., El-Omar E., Graham D., Hunt R., Rokkas T., Vakil N., Kuipers EJ. (2007) Current concepts in the management of Helicobacter pylori infection: the Maastricht III consensus report. Gut 56:772-781.

Markle HV. (1997) Coronary artery disease associated with Helicobacter pylori infection is at least partially due to inadequate folate status. Medical Hypotheses 49:289–292.

Markus HS. & Mendall MA. (1998) Helicobacter pylori infection: a risk factor for ischaemic cerebrovascular disease and carotid atheroma. Journal of Neurology Neurosurgery and Psychiatry 64:104-107.

Markus HS., Risley P., Mendall MA., Steinmetz H. & Sitzer M. Helicobacter pylori infection, the cytotoxin gene A strain, and carotid artery intima-media thickness. Journal of Cardiovascular Risk 9:1–6.

Michel M., Cooper N., Jean C., Frissora C. & Bussel JB. (2002) Does Helicobater pylori initiate or perpetuate immune thrombocytopenic purpura? (2004) Blood 103:890–896.

Monzón H., Forné M., Esteve M., Rosinach M., Loras C., Espinós JC., Viver JM., Salas A. & Fernández-Bañares F. (2013) Helicobacter pylori infection as a cause of iron deficiency anaemia of unknown origin. World Journal of Gastroenterology 19:4166-4171.

Muhsen K. & Cohen D. (2008) Helicobacter pylori infection and iron stores: a systematic review and meta-analysis. Helicobacter 13:323-340.

Nakao M., Matsuo K., Ito H., Shitara K., Hosona S., Watanabe M., Ito S., Sawaki A., Iida S., Sato S., Yatabe Y., Yamao K., Ueda R., Tajima K., Hamajima N. & Tanaka H. (2011) ABO genotype and the risk of gastric cancer, atrophic gastritis, and Helicobacter pylori infection. Cancer Epidemiology, Biomarkers and Prevention 20:1665–1672.

Ndip RN., MacKay WG., Farthing MJ. & Weaver LT. (2003) Culturing Helicobacter pylori from clinical specimens: review of microbiologic methods. Journal of Pediatric Gastroenterology and Nutrition 36:616-622.

Pietroiusti A., Diomedi M., Silvestrini M., Cupini LM., Luzzi I., Gomez-Miguel MJ., Bergamaschi A., Magrini A., Carrabs T., Vellini M. & Galante A. (2002) Cytotoxin-associated gene-A-positive Helicobacter pylori strains are associated with atherosclerotic stroke. Circulation 106:580–584.

Ponzetto A., Marchet A., Pellicano R., Lovera N., Chianale G., Nobili M., Rizzetto M. & Cerrato P. (2002) Association of Helicobacter pylori infection with ischemic stroke of non-cardiac origin: the BAT.MA.N. Project study. Hepatogastroenterology 49:631–634.

Provan D., Stasi R., Newland AC, Blanchette VS., Bolton-Maggs P., Bussel JB., Chong BH., Cines DB., Gernsheimer TB., Godeau B., Grainger J., Greer I., Hunt BJ., Imbach PA., Lyons G., McMillan R., Rodeghiero F., Sanz MA., Tarantino M., Watson S., Young J. & Kuter DJ. (2010) International consensus report on the investigation and management of primary immune thrombocytopenia. Blood 115:168-186.

Qu XH, Huang XL, Xiong P, Zhu CY., Huang YL., Lu LG., Sun X., Rong L., Zhong L., Sun DY., Lin H., Cai MC., Chen ZW., Hu B., Wu LM., Jiang YB. & Yan WL. (2010) Does Helicobacter pylori infection play a role in iron deficiency anemia? A metaanalysis. World Journal of Gastroenterology 16:886–896.

Rasool S., Abid S., Iqbal MP., Mehboobali N., Haider G. & Jafri W. (2012) Relationship between vitamin B12, folate and homocysteine levels and HP infection in patients with functional dyspepsia:

A cross-section study. BMC Research Notes 5:206.

Sarari AS., Farraj MA., Hamoudi W. & Essawi TA. (2008) Helicobacter pylori, a causative agent of vitamin B12 deficiency. Journal of Infection in Developing Countries 2:346-349.

Schwarz P, Kübler JA, Strnad P, Müller K., Barth TF., Gerloff A., Feick P., Peyssonnaux C., Vaulont S., Adler G. & Kulaksiz H. (2012) Hepcidin is localised in gastric parietal cells, regulates acid secretion and is induced by Helicobacter pylori infection. Gut 61:193–201.

Sealy-Jefferson S., Gillespie BW., Aiello AE., Haan MN., Morgenstern LB. & Lisabeth LD. (2013) Antibody levels to persistent pathogens and incident stroke in Mexican Americans. PLoS ONE 8:e65959.

Sherman PM. (2004) Appropriate strategies for testing and treating Helicobacter pylori in children: when and how? American Journal of Medicine 117:S30-S35.

Stasi R., Sarpatwari A., Segal JB., Osborn J., Evangelista ML., Cooper N., Provan D., Newland A., Amadori S. & Bussel JB. (2009) Effects of eradication of Helicobacter pylori infection in patients with immune thrombocytopenic purpura: a systematic review. Blood 113:1231-1240.

Stone AF., Mendal MA., Kaski JC., Edger TM., Risley P., Poloniecki J., Camm AJ. & Northfield TC. (2002) Effect of treatment for Chlamydia pneumoniae and Helicobacter pylori on markers of inflammation and cardiac events in patients with acute coronary syndromes: South Thames Trial of Antibiotics in Myocardial Infarction and Unstable Angina (STAMINA). Circulation 106:1219–1223.

Suzuki T., Matsushima M., Masui A., Watanabe K., Takagi A., Ogawa Y., Shirai T. & Mine T. (2005) Effect of Helicobacter pylori eradication in patients with chronic idiopathic thrombocytopenic purpura: a randomized controlled trial. American Journal of Gastroenterology 100:1265–1270.

Takahashi T, Yujiri T, Shinohara K, Inoue Y., Sato Y., Fujii Y., Okubo M., Zaitsu Y., Ariyoshi K., Nakamura Y., Nawata R., Oka Y., Shirai M. & Tanizawa Y. (2004) Molecular mimicry by Helicobacter pylori CagA protein may be involved in the pathogenesis of H. pylori-associated chronic idiopathic thrombocytopenic purpura. British Journal of Haematology 124:91-96.

Takahashi T., Yujiri T. & Tanizawa Y. (2004) Helicobacter pylori and chronic ITP: the discrepancy in the clinical responses to eradication therapy might be due to differences in the bacterial strains. Blood 104:594.

123:1924-1930

Veneri D., De Matteis G., Solero P., Federici F., Zanuso C., Guizzardi E., Arena S., Gaio M., Pontiero P., Ricetti MM. & Franchini M. (2005) Analysis of B- and T-cell clonality and HLA class II alleles in patients with idiopathic thrombocytopenic purpura: correlation with Helicobacter pylori infection and response to eradication treatment. Platelets 16:307-311.

Veneri D., Bonani A., Franchini A., Fedrizzi A. & Pizzolo G. (2011) Idiopathic thrombocytopenia and Helicobacter pylori infection: platelet count increase and early eradication therapy. Blood Transfusion 9:340-342.

Wang Z., Zhang L., Guo Z., Liu L., Ji J., Zhang J., Chen X., Liu B., Zhang J., Ding Q., Wang X., Zhao W., Zhu Z.& Yu Y. (2012) A unique feature of iron loss via close adhesion of Helicobacter pylori to host erythrocytes. PLoS ONE 7:e50314.

Windsor HM., Abioye-Kuteyi EA., Lebor JM., Morrow SM., Bulsara MK. & Marshall BJ. (2005) Prevalence of Helicobacter pylori in indigenous Western Australians: Comparison between urban and remote rural populations. Medical Journal of Australia 182:210-213.

Winn Jr W., Allen S. & Janda W (2006) Koneman's Color Atlas and Textbook of Diagnostic Microbiology. Lippincot Williams and Wilkins, Philadelphia, USA.

Yamanishi S., Iizumi T., Watanabe E., Shimizu M., Kamiya S., Nagata K., Kumagai Y., Fukunaga Y. & Takahashi H. (2006) Implications for induction of autoimmunity via activation of B-1 cells by Helicobacter pylori urease. Infection and Immunity 74:248–256.

Yeh JJ., Tsai S., Wu DC., Wu JY., Liu TC. & Chen A. (2010) P-selectin–dependent platelet aggregation and apoptosis may explain the decrease in platelet count during Helicobacter pylori infection. Blood 115:4247-4253.

Zhang QB., Etolhi G., Dawodu JB., Husain A., Gemmell CG. & Russell RI. (1998) Relationship between mucosal levels of interleukin 8 and toxinogenicity of Helicobacter pylori. Inflammopharmacology 6:109-117.

Zhang ZW., Patchett SE., Perrett D., Katelaris PH., Domizio P.& Farthing MJ. (1998) The relation between gastric vitamin C concentrations, mucosal histology, and CagA seropositivity in the human stomach. Gut 43:322–326.

Zhang ZF., Yang N,. Zhao G., Zhu L., Zhu Y. & Wang LX. (2010) Effect of Helicobacter pylori eradication on iron deficiency. Chinese Medical Journal