Helicobacter pylori and its hematological effect
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Background
Helicobacter pylori causes several gastric, intestinal, and extraintestinal manifestations. It also causes persistent infection and can cause serious various hematological effects.

Aims
To investigate the hematological effect of H. pylori infection.

Patients and methods
This is a cohort study that included 50 adult (age range: 18–75 years) patients infected with H. pylori and 50 adult patients who presented with symptoms suggestive of gastritis. All patients underwent upper endoscopy, and biopsies were taken. Moreover, the patients underwent complete blood count, iron studies, hepatitis C virus antibodies, vitamin B12 level, and bone marrow aspirate.

Result
The results showed that hemoglobin level, serum iron level, vitamin B12 levels, and platelets count were much lower in patients infected with H. pylori than the control group.

Conclusion
H. pylori causes iron-deficiency anemia, vitamin B12 deficiency, and thrombocytopenia, and treatment of H. pylori causes much improvement in these parameters.

Keywords: Helicobacter pylori, iron-deficiency anemia, iron deficiency, thrombocytopenia, vitamin B12

Introduction
Helicobacter pylori is one of the most common infection in humans. It causes several gastric, intestinal, and extragastric manifestations. H. pylori causes chronic gastritis, peptic ulcer, gastric mucosa-associated lymphoid tissue lymphoma, and gastric adenocarcinoma [1]. It also causes more than 50 extragastric manifestations, including cardiac, dermal, endocrinial, gynecological, obstetrical, pneumatology, neurological, ophthalmological, and hematological ones [2].

Our study is only concerned with hematological manifestations, including iron-deficiency anemia, vitamin B12 deficiency, and immune thrombocytopenia.

Iron-deficiency anemia
Iron deficiency is a serious medical problem whether associated with anemia or not. It occurs mostly in a chronic process with a slow onset, in which the iron imbalance may take several years to establish and manifest clinically [3].

The mechanism by which H. pylori causes iron-deficiency anemia is not well understood. Studies show that serum hepcidin is elevated in patients infected with H. pylori, and these levels are normalized after eradication of the infection, allowing the iron to be absorbed by the enterocytes and released from macrophages of the reticuloendothelial system, where they are confined [4].

Other explanation of iron imbalance in patients infected with H. pylori is chronic blood loss which occurs owing to chronic gastritis, which may be so severe up to causing erosive gastritis, especially in patients with active bleeding peptic ulcers and in patients who chronically ingest NSAID including aspirin [5].

Furthermore, highly virulent strains such as H. pylori with the cytotoxin-associated gene A (CagA) related to gastric tumor and the vacuolating cytotoxin A (VacA) related to gastric ulceration, act through molecular mimicry mechanisms to produce or magnify iron deficiency in patients compared with patients infected with other less virulent strains [6].

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Other explanation may be the interaction between VacA and Cag-pathogenicity island (PAI), as there are two types of H. pylori strains, type I or type II, that depend on the presence or not of both the Cag-PAI and the VacA, respectively.

H. pylori strains that have PAI are found to be more virulent than those that do not. A new study revealed that CagA inhibits VacA-induced apoptosis by preventing pinocytotic uptake of VacA, resulting in a decrease in vacuole formation within the host cell [7], so H. pylori uses CagA and VacA to take iron from mucosal epithelial cells. Moreover, CagA increases transferrin uptake from the basolateral surface, giving it to the apical surface to be released into the lumen, whereas VacA increases transferrin-receptor uptake from the surface and transfers it to the sites of bacterial attachment, causing decrease in serum iron level [8].

Treatment of H. pylori infection in cases of unexplained iron-deficiency anemia leads to improvement of ferrokinetic parameters [6,9].

Vitamin B12 deficiency
Vitamin B12, also called cobalamin, is a water-soluble vitamin that has a key role in the normal functioning of the brain and nervous system via the synthesis of myelin, and the formation of red blood cells. It is involved in the metabolism of every cell of the human body, especially affecting DNA synthesis, fatty acid, and amino acid metabolism [10].

Vitamin B12 deficiency is very common, and there are serious health problems owing to inability of the body cells to synthesize it, and it needs to be externally supplemented. Its incidence varies from 20 to 60% in developing countries and up to 20% in developed countries [11].

Mechanisms by which H. pylori causes vitamin B12 deficiency are not fully clarified.

Persistent infections by H. pylori cause chronic gastritis that may proceed to atrophic gastritis and achlorhydria, leading to intrinsic factor deficiency. The lack of intrinsic factor reduces the absorption and transport of vitamin B12 from the diet. This leads to vitamin B12 deficiency over long periods and depletion of its reservoir over many years [12].

Thrombocytopenia
It is an autoimmune disease characterized by isolated thrombocytopenia (peripheral blood platelet counts <100×10^9/l) in the absence of other causes or disorders. Immune thrombocytopenia (ITP) is a diagnosis of exclusion, and it is necessary to exclude causal diseases such as systemic lupus erythematosus and HIV or acquired immunodeficiency syndrome before diagnosis [13].

H. pylori infection leads to production of autoantibodies by B-lymphocytes, which leads to overactivation of innate and acquired immunity to the number of the circulating platelets count by decreasing the levels of the inhibitory receptor FcγRIIB in monocytes, leading to increased monocyte function with nonspecific phagocytosis and autoreactivity with B and T lymphocytes [14].

Amino acid sequences of virulence factors (VacA and CagA) and urease B are present in H. pylori infection and are the major antigens associated with autoimmune response against platelets. The homology of these antigens with platelet surface glycoproteins including glycoprotein IIIa and other platelet antigens associated with antibodies anti-CagA shows the importance of H. pylori infection in ITP [15].

Patients and methods
Our study was done on 50 patients and 50 controls, who were recruited from Outpatient Clinics and Inpatients of Gastroenterology Unit of Internal Medicine Department of Assiut University Hospitals. All patient had signed a written consent of their agreement to perform upper endoscopy and biopsy were taken and lab tests were performed and their agreement to involve their results in the research for publication.

Inclusion criteria
All of them complained of symptoms suggestive of gastritis whether acute (within 2 weeks) or chronic (3 or more months) and were diagnosed at endoscopy to have H. pylori infection by biopsy.

Patients aged more than 18 years old of both sexes (44 of them were males and 56 of them were females) were included.

Exclusion criteria
Patients with malignant diseases or gastric malignancy, other causes of thrombocytopenia such as systemic lupus erythematos and HIV and/or acquired immunodeficiency syndrome, other causes of anemias with or without blood loss, and hepatitis C virus (HCV) infection were excluded.
Data collection

Sample size
A total of 100 patients were presented with symptoms suggesting of gastritis, and they were grouped as follows: group A included 50 patients with positive *H. pylori* biopsy result and group B included 50 patients with negative *H. pylori* biopsy result.

The two groups were subjected to assessment of age, sex, associate diseases, and family history of the same illness or others. Detailed history about gastric symptoms and duration of the disease was taken. Full clinical examination was done. Laboratory investigations included complete blood count with reticulocyte count, upper endoscopy, diagnostic biopsy, serum iron, total iron binding capacity and serum ferritin, vitamin B<sub>12</sub>, folic acid level if indicated, and bone marrow aspirate if indicated.

Statistical analysis
Statistical analysis and tabulation were done using statistical package for the social science (SPSS for Windows). The following statistical tests were used:

1. Descriptive statistics: frequencies, percentages, means, and SDs.
2. Tests of significance: $\chi^2$ test.
3. Statistically significant differences were considered when $P$ value was less than or equal to 0.05%.

Result
A total of 100 patients were enrolled in the study, with 44 males and 56 females. Overall, 42 patients were between 18 and 29 years, 22 patients were 30 and 49 years, 35 patients were between 50 and 70 years, and one patient was 75 years old.

Our study showed no difference in incidence regarding age. In control, mean±SD was 48.12±13.1 years, and cases, it was 49.50±13.6 years, as shown in Fig. 1.

Regarding sex, our study showed no sex predilection for *H. pylori* infection. The prevalence of male in control was 40% compared with 48% in cases, and female prevalence in control was 60% to 52% in cases, as shown in Fig. 2.

There was no statistically significant relation between smoking (cigarettes) and presence of *H. pylori* infection, as 32% of the patients were cigarette smokers with *H. pylori* infection versus 42% nonsmokers, as shown in Fig. 3.

Our study showed no ulcer detection in control (*H. pylori* negative), whereas in cases (*H. pylori* positive), there was 62% detection of ulcer and 38% detection of gastric inflammation. So, iron-deficiency anemia may be secondary to chronic blood loss in patients with *H. pylori* infection and may be owing to *H. pylori* itself (as ulcers were nonactive at the time of the research, as it was under treatment), as shown in Figs 1 and 4.
Our study showed there was no difference in white blood cell (WBC) (cells×10³/μl) in control, with mean ±SD of 5.61±0.3, and in cases, with 6.86±0.4. The current study showed slight decrease in hemoglobin (Hb) (g/dl) level in cases versus control, as in control mean±SD was 12.89±1.2 and in cases was 10.35±1.6. In control, mean±SD mean corpuscular volume (MCV) was 84.43±3.3 and in cases was 82.98±10.6. There is no difference between mean corpuscular hemoglobin (MCH) between control (mean±SD: 29.24±1.1) and cases (28.09±4.2).

In our study, there was a statistically significant correlation between cases and control in the number of platelet count (plt×10³/μl), as there was an increase in control (mean±SD: 335.90±14.2) versus cases (236.76±17.1), as shown in Figs 2 and 5.

In the current study, there was a statistically significant correlation between \textit{H. pylori} infection and various parameters of iron loss, as such serum iron (μg/dl), vitamin B₁₂ (μg/dl), folic acid (ng/ml), and total iron binding capacity (TIBC).

Regarding comparative analysis, our study showed there was a significant decrease in serum iron level and a significant increase in TIBC. In cases, serum iron (mean±SD) was 35.10±9.2 and TIBC was 523.48±48.7, as shown in Figs 3 and 6.

Our study showed there was a significant decrease in vitamin B₁₂ level (mcg/dl) and folic acid (ng/ml) in cases (mean±SD 135.31±7.3 and 135.31±7.3, respectively), as shown in Figs 4 and 7.

Regarding bone marrow aspirate, our study showed there was a significant difference between control and cases. There were 80% of cases with abnormal finding in bone marrow aspirate in the form of decrease number of platelets versus 20% normal findings, as shown in Figs 5 and 8.

HCV infection was excluded from thrombocytopenic patient.

10 patients were diagnosed to have HCV positive antibodies, none of them had thrombocytopenia in CBC.

As shown in Table 1, there was no statistical correlation between combined conditions as diabetes mellitus (DM) ($P=0.685$), hypertension ($P=0.673$), and family history ($P=0.041$) and increased incidence of \textit{H. pylori} in cases versus controls, and regarding comorbidity and family history, our study showed there was no difference in incidence of having DM in control 40% and in cases 44%.

Regarding hypertension, our study showed there was no difference in the incidence of having hypertension between controls (32%) and cases (36%).

Regarding family history of \textit{H. pylori} infection, our study showed there was a significant increase in
incidence in cases (42%) versus in controls (28%), as shown in Table 1.

Our study showed there were significant factors influencing Helicobacter infection, as shown in Table 2:

(1) There was no significance difference in relation to age or sex to H. pylori infection between control and cases, as regarding age, the unadjusted odds ratio was 1.01 and \(P\) value was 0.603, and regarding sex, the unadjusted odds ratio was 0.72 and \(P\) value was 0.421.

(2) Regarding WBC, there was a 23 times increasing incidence of H. pylori infection with each 1000 cell/dl increase in number of WBC, as the unadjusted odds ratio was 1.23 and \(P\) value was 0.020.

(3) As regard Hb, there was a 74 times decreasing incidence of H. pylori infection with each increase in Hb level by 1 mg, as the unadjusted odds ratio was 0.26 and \(P\) value was 0.001.

(4) Regarding platelet count, there was a two times decreasing incidence of H. pylori infection with an increase of platelets number by 1000, as the unadjusted odds ratio was 0.98 and \(P\) value was 0.001.

(5) Regarding family history, there was 86 times increased risk of H. pylori infection with a positive family history, as the unadjusted odds ratio was 0.98 and \(P\) value was 0.001.

There were significant factors influencing Helicobacter infection in this study in multivariate logistic regression analysis, as shown in Tables 3 and 4:
Figure 5

Mean platelet count differences between cases and control.

Figure 6

Mean total iron and TIBC level differences between cases and controls.

Figure 7

Mean vitamin B₁₂ and folic acid level differences between cases and controls.
Regarding sex, there was an 11 times increased risk of getting *H. pylori* infection in males more than females, as adjusted odds ratio was 11.20 and *P* value was 0.004.

Regarding Hb level, there was an 85 times decreased incidence of getting infection by *H. pylori*, with each increase of Hb level by 1 g/dl as adjusted odds ratio was 0.15 and *P* value was less than 0.001.

Regarding family history, there was a 98 times increasing risk of getting infected with *H. pylori* in patients with positive family history, as adjusted odds ratio was 2.06 and *P* value was 0.012.

**Discussion**

Our study showed no significant correlation between age and occurrence of hematological problems with *H. pylori* infection, which differs from Schwarz *et al.* [16].
and Bruce and Maaros [17] who found that H. pylori infection is usually acquired during childhood (2–6), which was more prevalent in male (29.4%) than females (14.9%) and more with older age, as described by Xu et al. [18]. This differs from a study done by de Martel C and Parsonnet [19] which showed that H. pylori infection in children occurred with the same rates in males and females.

Our study showed that there was no statistically significant relation between cigarette smoking and presence of H. pylori infection. There were 32% cigarette smokers with H. pylori infection versus 42% nonsmokers with H. pylori infection.

Our study showed there was no difference in WBC, as in control group (mean±SD) was 5.61±0.3 and in cases was 6.86±0.4. This nondifference could be owing to the presence of inflammation in the study control group as well as most control population of our study, who were complaining of inflammation at time of diagnosis, which may narrow the difference in WBCs count between control and cases. This differed from Linz et al. [20] and Kodaman et al. [21] who described that infected cases had significantly elevated WBC counts compared with noninfected ones, which showed elevated total WBC counts, neutrophil counts, and monocyte counts. This could explain the exaggerated systemic inflammatory response in cases with H. pylori infection. This is in disagreement with Gupta et al. [22] who found that H. pylori infection causes autoimmune neutopenia, Papadaki et al. [23,24].

The current study showed slight decrease in Hb level in cases versus control. In control, mean±SD was 12.89±1.2, and in cases was 10.35±1.6. There was a statistically significant correlation between H. pylori infection and various parameters of iron loss such as serum iron and TIBC (iron-deficiency anemia). This is in concordance with Xu et al. [18], Gheibi et al. [25], DeLoughery [26], Mubarak et al. [27], Queiroz et al. [28], Xia et al. [29], and Senkovich et al. [30], who found that the prevalence of iron–deficiency anemia in the H. pylori+ group was significantly higher than in the H. pylori− group.

The pathogenic mechanisms by which H. pylori might contribute to anemia in asymptomatic people are not well understood and may be owing to several explanations such as owing to a chronic idiopathic iron deficiency represented by autoimmune atrophic gastritis, which had been shown to be responsible for refractory iron–deficiency anemia in more than 20% of patients with no evidence of gastrointestinal blood loss.

Such a disease was considered a possible outcome of a long-lasting H. pylori infection. Infected patients, in fact, had circulating antibodies to the H⁺,K⁺-ATPase of the gastric parietal cells. Hershko and Ronson [31] and others such as Queiroz et al. [28] and Rad et al. [32] referred this to owing to blood loss from asymptomatic gastric erosions, impaired absorption of iron owing to increased gastric pH, reduced vitamin B₁₂ levels owing to atrophic gastritis, and parietal cell loss.

Other mechanisms such as chronic gastrointestinal blood loss were a well-known cause of iron deficiency anemia, and there was gastric ulceration without gastrointestinal blood loss in a high proportion of the H. pylori-infected patients. In addition, we detected increased gastric pH and parietal cell loss in H. pylori-infected animals. Therefore, both blood loss from gastric ulceration and H. pylori-induced hypochlorhydria (with the resulting impaired iron absorption) probably contributed to the development of anemia [26,33].

Another possibility was that the H. pylori bacterial sequestration of free iron affects iron transporter molecules, thereby inhibiting free iron absorption and causing food cobalamin malabsorption. In addition, H. pylori gastric colonization required continuous supplementation of nutrients essential for bacterial growth and could use the host’s own iron stores. Severe anemia was related to H. pylori infection in one case report on school-age children, which recommends screening for H. pylori infection and appropriate treatment for severe iron–deficiency anemia [34,27].

Our study showed there was a significant decrease in vitamin B₁₂ level in cases infected with H. pylori. This is in agreement with Vannella et al. [35], Andrés et al. [36], Saito et al. [37], and Kaptan et al. [38]. This might be owing to the presence of antibodies against intrinsic factor and parietal cells and H⁺/K⁺ ATPase autoantibodies, which were closely linked to classical autoimmune gastritis and were also significant indicators for mucosa atrophy in chronic H. pylori gastritis. H. pylori infection could cause malabsorption of different micronutrients among which included the vitamin B₁₂.

Likewise, H. pylori eradication in vitamin B₁₂ deficiency patients was followed by increasing of serum levels of vitamin B₁₂ and decreased serum levels of homocysteine. Moreover, it was known that there was an association of H. pylori with stomach cancer, and it was already widely recognized by the
scientific community that pernicious anemia was closely related to the development of stomach cancer [39]. This association was recently verified by Vannella et al. [35] after a systematic review and meta-analysis showed that the relative risk to develop gastric cancer in patients with pernicious anemia was elevated at 6.8.

The current study showed there was a significant relationship between *H. pylori* infection and thrombocytopenia, which is in agreement with the study published by Department of Biological Engineering, Massachusetts Institute of Technology (2014), and a systematic review by Sato et al. [40] of 25 studies (1555 adult patients), all of which included at least 15 patients, which found that platelet counts in patients with ITP tended to increase after *H. pylori* eradication. The possible role of *H. pylori* infection in the development of ITP was a subject of extensive investigation. Systematic reviews of past literature showed an overall platelet response in more than 50% of the patients successfully treated for the infection and increased response rates in countries with a high prevalence of *H. pylori* infection in background populations, that is, in patients with less severe degrees of thrombocytopenia and in those with shorter disease duration [41,14]. As far as the putative mechanisms that may account for such an association were concerned, an Italian group suggested that infection by *H. pylori* strains expressing CagA could play a role in chronic ITP cases, which evoked host systemic immune response that produced autoantibodies that cross-reacted with the host platelet [42,43].

Although a definitive mechanism by which *H. pylori* may induce thrombocytopenia remained elusive, proposed pathways include molecular mimicry of CagA by host autoantibodies against platelet surface glycoproteins, as well as perturbations in the phagocytic activity of monocytes. Traditional treatments of ITP had been largely empirical, involving the use of immunosuppressive agents and immunoglobulin therapy. However, based on the findings of clinical reports emerging over the past 20 years, health organizations around the world increasingly suggested the detection and eradication of *H. pylori* as a treatment for ITP. Elucidating the exact molecular mechanisms of platelet activation in *H. pylori*-positive ITP patients, while considering biogeographical differences in response rates, could offer insight into how best to use clinical *H. pylori* eradication to treat ITP [44]. In a multicenter randomized controlled trial performed in Thailand’s children with ITP showed that eradication of *H. pylori* led to an increase in platelet counts in patients with ITP [45]. However, some studies had reported that there was no significant improvement of platelet counts after eradication of *H. pylori* infection in patients with ITP [46,47].

However, another study showed that there was a positive relationship between *H. pylori* infection and thrombocytosis as infected gerbils had significantly higher platelet count than uninfected ones [48]. These findings indicated that *H. pylori* colonization of the infected stomach leads to not only a gastric mucosal inflammatory response but also a systemic one.

Our study showed there was no relationship between hypertension and *H. pylori* infection. This was in disagreement with a study by Xu et al. [18], which showed that patients with hypertension demonstrated improvement of platelet counts after eradication of *H. pylori* infection.

Our study showed there was no significant relationship between *H. pylori* and having DM. This was in agreement with Ciortescu et al. [49] and Krause et al. [50] who did not find any correlation between *H. pylori* infection and glycemic status in both type 1 and 2 DM. On the contrary, Gunji et al. [51] performed a study examining the association between *H. pylori* infection and insulin resistance, and results showed that *H. pylori* infection significantly and independently contributed to promoting insulin resistance.

Another study by Wang et al. [52] conducted on type 2 DM patients showed that *H. pylori* infection had a significant effect on the daily blood glucose level and blood glucose fluctuation in those patients. Eshraghian et al. [53] performed a study and showed that *H. pylori* infection was associated with higher fasting serum insulin levels.

Our study showed that there was a statistically significant relationship between *H. pylori* infection and positive family history. This was in agreement with Eyermann et al. [54] who showed that having an infected parent especially an infected mother increased the risk of *H. pylori* infection apart from interfamilial spread.

**Conclusion and recommendations**

In conclusion, the recognition of hematologic diseases associated with *H. pylori* infection and their inclusion as indications for study and eradication in the international consensus and management guides on *H. pylori* infection, represent a deep change in the management paradigm of these diseases and a great
breakthrough for humanity. Many benefits can be brought by eradication of the infection, especially those related to gastric cancer, peptic acid disease, and many hematological disorders.

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References
1 Sánchez Delgado J, García-Iglesias P, Titó L, Puigd I, Planellaf M, Gené E, et al. Update on the management of Helicobacter pylori infection. Gastroenterol Hepatol 2014; 41:272–280.
2 Stolte M, Bayerdorffer E, Morgner A, Alpen B, Wündisch T, Thiede C, Neubauer A. Helicobacter and gastric MAL T lymphoma. Gut 2002; 50 (Suppl 3):III19–III24.
3 Goodnough LT, Nemeth E, Greer JP, Arter DA, Glader B, List AF, et al. Wintrobe’s clinical hematology. 13th ed. Philadelphia, PA: Lippincott Williams & Wilkins 2013. 617–642
4 Ge R, Sun X. Iron trafficking system in Helicobacter pylori. Biometals 2012; 25:247–258.
5 Pentti Sipponen a and Heidi-Ingrid Maaroos. Chronic gastritis. Scandinavian Journal of Gastroenterology. 2015; 50:657–667. PMID: PMC4673514, PMID: 25901896
6 Campuzano-Mayra G. Hematologic manifestations of Helicobacter pylori infection. World J Gastroenterol 2014; 20:12818–12838.
7 Akada JK, Aoki H, Torigoe Y, Kitagawa T, Kurazono H, Hoshida H, et al. Helicobacter pylori CagA inhibits endocytosis of cytotoxin VacA in host cells. Dis Model Mech 2010; 3:605–617.
8 Bridge DR, Merrell DS. Polymorphism in the Helicobacter pylori CagA and VacA toxins and disease. Gut Microbes 2013; 4:101–117.
9 Mwaly SN, Afana WM. Hematological parameters, serum iron and vitamin B12 levels in hospitalized Palestinian adult patients infected with Helicobacter pylori. Helimat Trans fus Cell Ther 2018; 40:160–165.
10 Dali-Youcef N, Andrés E. An update on cobalamin deficiency in adults. QJM 2009; 102:17–28.
11 British Committee for Standards in Haematology General Haematology 11
12 Franchini M, Cruciani M, Mengoli C, Pizzolo G, Veneri D. Effect of Helicobacter pylori pylori and autoimmune neutropenia. Clin Lab Haematol 2002; 24:183–185.
13 Kodaman N, Prazos A, Schneider BG, Piazuelo MB, Mera R, Sobota RS, et al. Human and Helicobacter pylori coevolution shapes the risk of gastric disease. Proc Natl Acad Sci U S A 2014; 111:1455–1460.
14 Gupta V, Edan AJ, Mills MJ. Helicobacter pylori and autoimmune neutropenia. Clin Lab Haematol 2002; 24:183–185.
15 Papadaki HA, Pontikoglou C, Stavroulaki E, Minadakis G, Eliopoulos DA, Pyrovolaki K, et al. High prevalence of Helicobacter pylori infection and monoclonal gammopathy of undetermined significance in patients with chronic idiopathic neutropenia. Ann Hematol 2005; 84:317–320.
16 DeLoughery TG. Microcytic anemia. N Engl J Med 2014; 371:1324–1331.
17 Mubarak N, Gasim GI, Khalafalla KE, Ali NI, Adam I. Helicobacter pylori, anemia, iron deficiency and thrombocytopenia among pregnant women at Khartoum, Sudan. Trans R Soc Trop Med Hyg 2014; 108:380–384.
18 Queiroz DM, Rocha AM, Crabtree JE. Unintended consequences of Helicobacter pylori infection in children in developing countries. Gut Microbes 2013; 4:494–504.
19 Xia W, Zhang X, Wang J, Sun C, Wu L. Survey of anaemia and Helicobacter pylori pylori infection in adolescent girls in Suhua, China and enhancement of iron intervention effects by H. pylori eradication. Br J Nutr 2012; 108:357–362.
20 Senkovitch O, Ceaser S, McGee DJ, Testerman TL. Unique host iron utilization mechanisms of Helicobacter pylori revealed with iron-deficient chemically defined media. Infect Immun 2010; 78:1841–1849.
21 Hershko C, Ronson A. Iron deficiency, Helicobacter pylori infection and gastritis. Acta Haematol 2009; 122:97–102.
22 Rad R, Schmid RM, Prinz C. Helicobacter pylori, iron deficiency, and gastric autoimmunity. Blood 2006; 107:4969–4970.
23 Wians FH, Urban JE, Ketter JH, Kroft SH. Discriminating between iron deficiency anemia and anemia of chronic disease using traditional indices of iron status vs transferrin receptor concentration. Am J Clin Pathol 2001; 115:112–118.
24 Rockey DC, Cello JP. Evaluation of the gastrointestinal-tract in patients with iron-deficiency anemia. N Engl J Med 1993; 329:1691–1695.
25 Vannella L, Lahner E, Osborn J, Annibale B. Systematic review: gastric cancer incidence in pernicious anemia. Aliment Pharmacol Ther 2013; 37:375–382.
26 Andrès E, Loukili NH, Noel E, Kaltenbach G, Abdelgheni MB, Perrin AE, et al. Vitamin B12 (cobalamin) deficiency in elderly patients. CMAJ 2004; 171:251–259.
27 Salto M, Mori A, Irie T, Tanaka M, Morikoa M. Helicobacter pylori pylori infection is not associated with pernicious anemia in Japan. Rinsho Ketsueki 2008; 49:1569–1571.
28 Kaplan K, Beyan C, Ural AU, Cetin T, Avcu F, Gülßen M, et al. Helicobacter pylori pylori is it a novel causative agent in Vitamin B12 deficiency? Arch Intern Med 2000; 160:1349–1353.
29 Payne RW. Pernicious anaemia and gastric cancer in England and Wales. Br Med J 1961; 1:1807–1809.
30 Sato R, Murakami K, Ohtomo T, Watanabe K, Kodama M, Fujioka T. Development of corpus atrophic gastritis may be associated with Helicobacter pylori pylori-related idiopathic thrombocytopenic purpura. J Gastroenterol 2011; 46:991–997.
31 Pellicano R, Franceschi F, Saracco G, Fagonese S, Roccacina D, Gasbarrini A. Helicobacters and extragastrointestinal diseases. Helicobacter 2009; 14(Suppl 1):58–68.
32 Scandellari R, Allemand E, Vettore S, Plebani M, Randi ML, Fabris F. Platelet response to Helicobacter pylori pylori eradication therapy in adult chronic idiopathic thrombocytopenic purpura seems to be related to the presence of anti-cytotoxin-associated gene A antibodies. Blood Coagul Fibrinolysis 2009; 20:108–113.
33 Takahashi T, Yujiri T, Shinohara K, Inoue Y, Sato Y, Fujii Y, et al. Molecular mimicry by Helicobacter pylori CagA protein may be involved in the pathogenesis of H. pylori-associated chronic idiopathic thrombocytopenic purpura. Br J Haematol 2004; 124:91–96.
34 Frydman GH, Davis N, Beck PL, James G. Helicobacter pylori pylori eradication in patients with immune thrombocytopenic purpura: a review and the role of biogeography. Helicobacter 2015; 20:239–251.
45 Noonavath RN, Lakshmi CP, Dutta TK, Kate V. *Helicobacter pylori* eradication in patients with chronic immune thrombocytopenic purpura. World J Gastroenterol 2014; 20:6918–6923.

46 Michel M, Cooper N, Jean C, Frissora C, Bussel JB. Does *Helicobacter pylori* initiate or perpetuate immune thrombocytopenic purpura? Blood 2004; 103:890–896.

47 Ahn ER, Tiede MP, Jy W, Bidot CJ, Fontana V, Ahn YS. Platelet activation in *Helicobacter pylori*-associated idiopathic thrombocytopenic purpura: eradication reduces platelet activation but seldom improves platelet counts. Acta Haematol 2006; 116:19–24.

48 Gong Y, Wei W, Jingwei L, Nannan D, Yuan Y. *Helicobacter pylori* infection status correlates with serum parameter levels responding to multi-organ functions. Dig Dis Sci 2015; 60:1748–1754.

49 Ciortescu I, Sturli C, Stan M, Graur M, Stanciu C. Prevalence of *Helicobacter pylori* infection in patients with diabetes mellitus. Rev Med Chir Soc Med Nat Iasi 2009; 113:1048–1055.

50 Krause I, Anaya JM, Fraser A, Barzilai O, Ram M, Abad V, et al. Anti-infectious antibodies and autoimmune-associated autoantibodies in patients with type I diabetes mellitus and their close family members. Ann N Y Acad Sci 2009; 1173:633–639.

51 Gunji T, Matsuhashi N, Sato H, Fujibayashi K, Okumura M, Sasabe N, et al. *Helicobacter pylori* infection is significantly associated with metabolic syndrome in the Japanese population. Am J Gastroenterol 2008; 103:3005–3010.

52 Wang SZ, Shi YN, Zhao J, Wang ZD. Effects of *Helicobacter pylori* on blood glucose fluctuation in type 2 diabetic patients. Zhonghua Yi Xue Za Zhi 2009; 89:958–961.

53 Eshraghian A, Hashemi SA, Hamidian Jahromi A, Eshraghian H, Masoompour SM, Darvapanah MA, et al. *Helicobacter pylori* infection as a risk factor for insulin resistance. Dig Dis Sci 2009; 54:1966–1970.

54 Eyermann M, Rothenbacher D, Brenner H. Acquisition of *Helicobacter pylori* infection in early childhood: independent contributions of infected mothers, fathers, and siblings. Am J Gastroenterol 2009; 104:182–911.