

WJG 20th Anniversary Special Issues (6): *Helicobacter pylori***Extraintestinal manifestations of *Helicobacter pylori*: A concise review**

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Abstract

Helicobacter pylori (*H. pylori*) infection has been clearly linked to peptic ulcer disease and some gastrointestinal malignancies. Increasing evidence demonstrates possible associations to disease states in other organ systems, known as the extraintestinal manifestations of *H. pylori*. Different conditions associated with *H. pylori* infection include those from hematologic, cardiopulmonary, metabolic, neurologic, and dermatologic systems. The aim of this article is to provide a concise review of the evidence that supports or refutes the associations of *H. pylori* and its proposed extraintestinal manifestations. Based on data from the literature, PUD, mucosal associated lymphoid tumors lymphoma, and gastric adenocarcinoma has well-established links. Current evidence most supports extraintestinal manifestations with *H. pylori* in immune thrombocytopenic purpura, iron deficiency anemia, urticaria, Parkinson's, migraines and rosacea; however, there is still plausible link with other diseases that requires further research.

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Key words: Migraine; Iron deficiency; Urticaria; Rosa-

cea; Immune thrombocytopenic purpura

Core tip: *Helicobacter pylori* (*H. pylori*) is the most common chronic infection in humans and has been associated with a variety of extraintestinal manifestations. While evidence exists for associations, the strongest correlation for *H. pylori* infection is for iron deficiency anemia and immune thrombocytopenic purpura. Symptom improvement noted in urticaria and rosacea with eradication therapy. Possible association with stroke, coronary artery disease, Parkinson's and Alzheimers.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) has been associated with the formation of peptic ulcers as well as other complications of gastrointestinal malignancies, namely adenocarcinoma and mucosal associated lymphoid tumors (MALT). However, since its discovery, *H. pylori* have been associated with other disorders outside of the gastrointestinal (GI) tract including diseases in hematologic, cardiopulmonary, metabolic, neurologic, and dermatologic systems. The evidence for the so called extraintestinal manifestations of *H. pylori* infection will be discussed in the following sections.

HEMATOLOGIC MANIFESTATIONS**Iron deficiency anemia**

Iron deficiency is the most common nutritional deficiency and cause of anemia^[1]. Iron deficiency anemia (IDA)

occurs in 2%-5% of adults in the developed world, with gastrointestinal tract blood loss being the most common cause^[2]. Additionally, IDA is seen in 5%-12% of otherwise healthy premenopausal women^[3], related to menstrual blood loss and increased iron needs during pregnancy^[4].

Eighty percent of dietary iron in Western countries requires an acidic intragastric pH to be reduced to ferrous form for absorption^[5]. This reaction is promoted by ascorbic acid, which is secreted from plasma into gastric juice. Ascorbic acid is considered the most potent enhancer of iron absorption^[6].

The link between *H. pylori* and IDA is well supported in the literature. The first case report was published in 1991 by Blecker *et al*^[7] who described a 13 year old girl with IDA related to *H. pylori*-positive chronic active gastritis. Hemoglobin levels normalized with eradication of *H. pylori* without iron supplementation^[7]. Later reports described similar cases in adults^[8-10]. A recent meta-analysis of thoroughly designed observational epidemiologic studies revealed an increased risk of IDA in *H. pylori* infected patients (OR = 2.8, 95%CI: 1.9-4.2)^[11].

Valiyaveetil *et al*^[12] conducted a randomized controlled trial with 52 anemic adult patients undergoing upper GI endoscopy; findings were suggestive of *H. pylori* eradication improving iron status. Malik *et al*^[13] recently showed that administration of iron in patients with IDA of pregnancy and *H. pylori* infection is less effective in comparison with when patients are cured of *H. pylori* infection. Four meta-analyses of randomized control trials have supported this association and also suggested a role of *H. pylori* in iron absorption^[14-17].

H. pylori cause IDA by several mechanisms. There is increased iron loss due to active hemorrhage caused by gastritis, peptic ulcer disease or gastric cancer^[18]. Pangastritis leads to leading to decreased gastric acid^[19] as well as ascorbic acid secretion^[20]. There is also evidence of enhanced iron uptake by *H. pylori*^[11]. Recently, Boyanova^[21] reviewed the role of *H. pylori* in iron acquisition. *H. pylori* possesses proteins involved in iron transport and storage but exact molecular mechanisms of iron acquisition remain unclear. *H. pylori* strains possessing virulence factors cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA) have been studied with interest. CagA models have been shown, *in vitro* and *in vivo*, to increase internalization of transferrin. Both CagA and VacA have been shown to participate in iron acquisition and colonization without damaging host tissue, thus promoting chronicity.

In summary, *H. pylori* infection has been well studied in relation to IDA. This is supported clinically by current guidelines such as the British Society of Gastroenterology who recommends *H. pylori* eradication in patients with recurrent IDA and a normal colonoscopy and esophagogastroduodenoscopy^[22]. Additionally, the recent Mastricht IV guidelines suggest eradication in all patients with unexplained IDA^[23].

Immune thrombocytopenic purpura

Immune thrombocytopenic purpura (ITP) is defined as an autoimmune disorder characterized by immunologic destruction of otherwise normal platelets^[24]. *H. pylori* infection is a well known cause of secondary ITP. The prevalence of *H. pylori* infection in patients with ITP is higher than age and gender matched healthy individuals^[18]. There is, however, no evidence to suggest these patients have a more severe form of ITP^[25].

Gasbarrini *et al*^[26] first reported an association in 1998 when a significant increase in platelet count was noted in ITP patients following *H. pylori* eradication. This effect was confirmed in several subsequent reports and summarized in a systematic review of 24 observational studies and 1 control study involving 1555 patients. Stasi *et al*^[27] found that 50% of adults has sustained platelet response after eradication of *H. pylori*, notably in those with mild ITP. A systematic review of 11 controlled studies documented a platelet count response in 51% of *H. pylori* infected patients versus an 8.8% platelet count increase in *H. pylori* negative controls^[28], further strengthening the causal association.

The long-term prognosis of *H. pylori* related ITP has been studied and appears to be excellent. In an 8 year follow-up study after successful eradication, no recurrence was seen^[29].

There is no proven mechanism regarding the role of *H. pylori* infection in the pathogenesis of ITP. Several proposed mechanisms have been studied. The induction of platelet aggregation *via* von Willebrand factor by certain strains of *H. pylori* has been documented^[30]. Molecular mimicry involving antibodies against *H. pylori* CagA protein and platelet antigens have also been implicated^[31]. Additionally, an activated monocyte/macrophage phenotype has been proposed to contribute to the anti-platelet pathogenesis^[32].

In summary, studies thus far support the detection and eradication of *H. pylori* in ITP. The current American Society of Hematology guidelines have suggested eradication therapy is indicated in patients who are found to have *H. pylori* infection^[24].

CARDIOPULMONARY MANIFESTATIONS

Coronary artery disease

Known risk factors for coronary artery disease (CAD) such as diabetes, hypertension, dyslipidemia, obesity and smoking contribute to atherosclerosis^[33]. Chronic inflammation is also a risk factor for atherosclerosis^[34]. Inflammation arising from chronic infections including *H. pylori* have been studied, however its role in CAD is conflicting.

In a case-control study, Mendall *et al*^[35] first reported an association (OR = 2.15, *P* = 0.03) between CAD and *H. pylori* in 1994. This was supported by subsequent studies and in patients with angiographically confirmed CAD^[36]. Eradication of *H. pylori* was shown to attenuate reduction in artery lumen after angiography^[37], suggesting a benefit to treatment. Rogha *et al*^[38] identified *H. pylori*

infection to be an independent risk factor for CAD in an Iranian population. Additionally, there is evidence linking *H. pylori* to both early^[39] and advanced atherosclerosis, specifically CagA strains^[40,41].

On the contrary, there is also evidence that does not support such an association. Danesh *et al*^[42] conducted a meta-analysis of 18 epidemiological studies including 10000 patients and did not find an association. A recent study from Padmavati *et al*^[43] did not find an association between CAD and *H. pylori* in an Indian population. Lastly, no association was found between *H. pylori* infection or chronic atrophic gastritis and major cardiovascular events in a recent German based study^[44].

There are several different proposed mechanisms linking *H. pylori* to CAD. *H. pylori* was found in substantial numbers in carotid atherosclerotic plaques, thus proposed to be a direct pathogen of the vessel wall^[45]. Tamer *et al*^[46] suggested that *H. pylori* may cause atherogenesis through low-grade persistent inflammatory stimulation. An up-regulation of serum levels of hsCRP has also been reported^[47]. Molecular mimicry between CagA antigen and atherosclerotic plaque peptides is another possible pathogenic link^[48]. Finally, there is evidence of modification of lipid metabolism^[49], with recent evidence of increased total cholesterol and low-density lipoprotein-cholesterol (LDL-C) in infected patients^[50].

In conclusion, there is controversial evidence linking CAD and *H. pylori* infection. The mechanisms proposed are plausible however not conclusive. No adequate interventional studies exist that demonstrate a lower incidence of CAD as a result of *H. pylori* treatment.

Asthma

There has been an increased prevalence of asthma and other atopic disorders over several decades^[51]. The hygiene hypothesis states that exposure to certain infectious agents may protect against the development of allergic diseases^[52]. In support of this, a negative association between *H. pylori* infection and asthma development has been observed. Studies with both children^[53,54] and adult subjects^[53] have reported a lower prevalence of *H. pylori* infection in asthmatic patients. The most supported pathogenic mechanism of this protective effect is the ability of *H. pylori* to stimulate the T-helper type 1 (Th1) immune response^[55]. This promotes persistent infection but confers protection against asthma.

Conversely, other studies have reported neutral and even positive associations between infection and asthma^[56,57]. Recent meta-analyses have been performed in order to clarify these controversial findings. Wang *et al*^[58] reviewed 19 studies and found a weak inverse association between asthma and *H. pylori* infection. Similarly, Zhou *et al*^[59] found a significantly lower rate of *H. pylori* infection in asthmatics in a review of 14 studies.

At this point, this inverse relationship is fairly well supported in the literature, especially in childhood asthma. However, studies with larger sample sizes are needed in order to clarify this association. In addition, studies

looking at eradication of *H. pylori* and subsequent asthma symptoms may be helpful.

METABOLIC MANIFESTATIONS

Metabolic syndrome and insulin resistance

Metabolic syndrome (MS) includes several risk factors for cardiovascular disease and type 2 diabetes, such as hyperglycemia, dyslipidemia, obesity and hypertension^[60]. Insulin resistance (IR) is a key pathogenic factor in MS^[61]. The role of *H. pylori* infection in the pathogenesis of MS and IR has been studied but remains controversial.

Epidemiological studies have supported a link between MS, IR and *H. pylori* infection^[62-65]. Hypothesized pathophysiological mechanisms include activation of pro-inflammatory and vasoactive substances^[66], production of reactive oxygen species^[66] and altered ghrelin^[67] and leptin levels^[68]. Given this supportive link, it has been proposed that treatment of *H. pylori* infection could prevent coronary artery disease and MS^[69]. A systematic review of 9 studies by Polyzos *et al*^[66] suggested a trend toward a positive association of *H. pylori* infection and IR. It was highlighted however, that there was substantial heterogeneity amongst the studies reviewed.

In contrast, other studies have not find such an association with either IR or MS^[70-72]. A meta-analyses of 18 studies involving 10000 patients found no strong correlation between *H. pylori* infection and serum concentrations of total cholesterol and triglycerides^[42]. Naja *et al*^[73] studied the association between *H. pylori* infection and both IR and MS in a Lebanese population. They found no association for either and concluded that eradication therapy of *H. pylori* to prevent IR and MS was not warranted. Furthermore, Lu *et al*^[74] did not find a change in fasting blood sugar or lipids after the eradication of *H. pylori* in a prospective study including 48 patients.

The evidence available at this time remains contradictory. Great interest rests in the possible association of *H. pylori* infection with IR and MS, as it would identify a potentially treatable risk factor for the development of cardiovascular disease.

Type 2 diabetes mellitus

It has been well documented that markers of low-grade inflammation are associated with type 2 diabetes (T2D)^[75-77]. Chronic infections with various pathogens have been hypothesized to contribute to this inflammatory state. Initial studies, using cross-sectional analyses, did not support this association^[78-80]. Specifically, infection with Chlamydia pneumonia, *H. pylori*, cytomegalovirus, herpes simplex virus and/or hepatitis A was not found to be associated with insulin resistance or diabetes^[79,80].

In contrast, support for this association has also been published^[81]. A meta-analysis of 41 observational studies involving 14080 patients found a high prevalence of *H. pylori* infection in patients with diabetes, especially type 2^[82]. Interestingly, a recent prospective study of 768 Latino patients followed over 10 years, found *H. pylori* sero-

positivity to be associated with a greater rate of incident diabetes^[83].

H. pylori has also been linked to microalbuminuria, which is a strong predictor of the development of diabetic nephropathy^[84]. Chung *et al*^[85] conducted a cross-sectional study of 2716 Korean patients and found that *H. pylori* seropositivity was independently associated with microalbuminuria.

At this time, larger prospective studies are needed in this field to clarify recent findings. If *H. pylori* is in fact an etiological factor for diabetes, more aggressive eradication therapy may be warranted to prevent the devastating outcomes of poor glycemic control. Further studies incorporating eradication therapy and subsequent glycemic control may shed more information.

NEUROLOGIC MANIFESTATIONS

Ischemic stroke

Ischemic stroke accounts for approximately 50% of all types of stroke. Inflammatory parameters and chronic infections have been considered to modify stroke risk^[86]. *H. pylori* infection has been considered an independent risk factor, however the results are controversial.

Whincup *et al*^[87] first reported an association in 1996, however the relationship was considerably weakened after adjustment for several major risk factors. Markus *et al*^[88] reported an association, particularly in stroke due to small artery occlusion. Conversely, Ashtari *et al*^[89] did not show an association between seropositivity and in a case-control study. Ridker *et al*^[90] did not find *H. pylori* serology useful to predict the occurrence of cardiovascular events.

Higher prevalence of CagA strain in ischemic stroke has been demonstrated^[91,92]. This has been further supported by association with greater intima-media thickness and worse National Institute of Health Stroke Scale score^[93].

A recent meta-analysis by Wang *et al*^[94] including 13 studies and 4041 Chinese patients found a significant association, especially non-cardioembolic stroke. Interestingly, they reported that a positive anti-CagA IgG was more effective for prediction than anti-*H. pylori* IgG or (13)C-urea breath test.

Several mechanisms have been proposed. There is evidence of direct bacterial invasion into the atherosclerotic plaque^[45], which has also been a plausible link to CAD. CagA strains have been reported to affect carotid plaque instability^[95]. Interestingly, slow coronary flow and endothelial disturbance has been linked to *H. pylori* infection^[96].

At present, the link between *H. pylori* and ischemic stroke is debated however evidence does exist with respect to plausible mechanisms.

Parkinson's disease

Before the discovery of *H. pylori*, an excess of peptic ulcers was observed in patients with Parkinson's disease^[97]. Altschuler^[98] first suggested a possible causal link in 1996. It is now proposed that neuronal damage in Parkinson's

disease may be a response to chronic *H. pylori* infection^[25].

In a randomized double blind controlled study, Bjarnason *et al*^[99] found that eradication of *H. pylori* changed the course of disease. Pierantozzi *et al*^[100] found that successful eradication of *H. pylori* improved the pharmacokinetic and clinical response to L-dopa by increasing L-dopa absorption. This may be due to resolution of active gastroduodenitis caused by *H. pylori*. Finally, neurologic deterioration was noted in patients when *H. pylori* eradication failed^[101]. Persistence of serum CagA antibodies appears to be predictive for Parkinson's disease and is associated with a poor prognosis^[102].

In summary, there is evidence of disease modification and not cure with treatment of *H. pylori*. The mechanisms proposed include *H. pylori* triggering mitochondrial damage^[103] and autoimmunity^[104].

Alzheimer's disease

Infections have been proposed as risk factor for cognitive impairment, dementia and Alzheimer's disease (AD)^[105]. *H. pylori* is one of the infections proposed, along with herpes simplex virus, picornavirus, Borna virus, Chlamydia pneumonia, spirochete infections^[105].

Kountouras *et al*^[106] reported a significantly higher prevalence of *H. pylori* infection in a Greek population with AD. This was supported by a higher prevalence of anti-*H. pylori* IgG in the cerebrospinal fluid of patients with AD^[107]. After a 2 year follow-up, cognitive and functional status parameters improved in patients where *H. pylori* was successfully eradicated^[108].

Several mechanisms in the pathogenesis have been studied. Platelets are a source of beta amyloid and *H. pylori* infection has been proposed to promote platelet and platelet-leukocyte aggregation^[109]. Cross reactivity between endothelial and *H. pylori* antigens has been studied. Reactive oxygen metabolites and circulating lipid peroxides that have also been involved in pathophysiology of *H. pylori* and AD^[110]. Finally, animal studies have suggested a role for *H. pylori* influencing the apoptotic process that may be an important form of cell death in neurodegenerative diseases^[111].

Therefore, a few trials has demonstrated improvement in symptoms in those with successful treatment of *H. pylori*; however, more studies are needed to clarify this association.

Migraine headaches

Migraines are a common neurologic disorder characterized by recurrent episodes of severe headache and associated symptoms such as light/sound sensitivity. Up to a quarter of patients suffer accompanying migraine auras^[112], a neurologic phenomenon that includes sensory and motor disturbances.

Contemporary theories of migraine pathophysiology point towards a primary neuronal dysfunction, rather than the traditional model of vasoconstriction and vasodilatation^[113,114]. Although the exact etiology is still unknown, genetic and environmental factors have

been associated with chronic migraines^[115]. Among them, chronic infections including *H. pylori* has been implicated particularly in those with migraines without aura^[116].

Among patients with migraines, different studies have shown increased prevalence of *H. pylori* infection. A case-control study from Greece observed a significantly greater prevalence of *H. pylori* infection in migraine patients; however, methodology for diagnosis was different among cases and controls (urea breath test *vs* histology) which may not represent a direct comparison^[117]. Another study found greater prevalence of migraine in *H. pylori* infected patients, as determined by positive urea breath test^[118]. Similarly, using serologies, *H. pylori* IgG positivity was found to be higher in those with migraines compared to matched controls^[119].

Furthermore, several studies demonstrate that following eradication of *H. pylori*, a significant proportion of migraine patients report no further headaches or reduction in severity of symptoms^[118-120]. Gasbarrini *et al*^[118] have found complete resolution of headaches in 17% of patients which remaining patients reporting clinical improvement in those following *H. pylori* eradication. Following confirmation of eradication using stool antigen testing, another study found significant improvement in severity of clinical migraine attacks in 84% of patients^[120]. Similarly, among Chinese hepatitis B cirrhotic patients with migraines, eradication of *H. pylori* lead to resolution or decrease in severity of headache symptoms^[121].

In contrast, several studies have not shown a significant increase in *H. pylori* infection in those with migraines. An early Italian case-control study compared the *H. pylori* infection rate using serology and urea breath test and did not find a significant difference in infection prevalence among migraine sufferers and matched controls^[122]. Two studies of migraines in children also did not find a significant increase in *H. pylori* infection by breath testing^[123] or by biopsy specimens^[124].

In summary, *H. pylori* may be associated with the severity of migraine attacks as multiple studies have shown improvement in symptoms following eradication; however, the association in terms of prevalence has conflicting data. More studies are required to further establish a firm link, particularly larger epidemiologic studies as well as double blind randomized trials.

DERMATOLOGIC MANIFESTATIONS

Chronic spontaneous urticaria

Chronic spontaneous urticarial (CSU) is defined as spontaneous occurrence of wheal and/or angioedema lasting for longer than 6 wk^[125]. CSU affects up to 1% of the general population^[126,127]. The etiology remains undetermined in 80%-90% of patients, which is termed chronic idiopathic urticarial (CIU). However, up to 30% of affected patients are found to have functional autoantibodies^[128].

An association between *H. pylori* and CSU has been reported but remains controversial. Fukuda *et al*^[129] found that amongst a group of *H. pylori* positive patients with

CSU, a significant improvement was noted in those who received eradication therapy. This was supported by a systemic review of 10 studies by Federman *et al*^[130]. Conversely, Daudén *et al*^[131] failed to show an association in a Spanish based 25 patient case-control study. Moreira *et al*^[132] also failed to show an association. However, they did find that those with clinical remission of CSU had greater 13 carbon urea breath test titers, suggesting a role for the amount of colonization by *H. pylori* in the pathogenesis of CSU. A recent prospective trial by Chiu *et al*^[133] was supportive of an overall association between *H. pylori* and CSU. Interestingly, no significant association was found with virulent genotypes of *H. pylori* (CagA, VacA) in the remission of CSU after eradication^[133].

The possible mechanisms of cutaneous pathology are not clearly elucidated. Increased gastric mucosal permeability^[134] resulting in greater exposure to alimentary antigens^[135] has been proposed. The role of immunomodulation with identification of immunoglobulin-binding antigenic structures to *H. pylori* has also been described^[136].

In summary, the studies are controversial however the most recent study in the field is supportive. Genotypes and virulent strains of *H. pylori* do not appear to be important in association. The mechanisms of pathogenesis are not entirely clear and remain to be further investigated.

Rosacea

Rosacea is chronic dermatologic condition characterized by persistent central facial erythema with presence of telangiectasia in the classic erythematotelangiectatic subtype. Other subtypes are also recognized including acne-like lesions in the papulopustular rosacea, irregularly thickened skin (usually affecting the nose) in the phymatous rosacea, and associated eye symptoms in ocular rosacea^[137].

From epidemiologic studies, those of Northern European and Celtic origins appear to be at highest risk of rosacea^[138]. It is estimated that the prevalence of rosacea is 1%-10% in fair-skinned populations^[138]. Generally, adults over the age of 30 are affected and occurs more often in females^[139,140].

The pathophysiology of rosacea is incompletely understood; however, it is thought that inflammation plays a crucial role in its pathogenesis. Inflammatory mediators from an altered innate immune response leading to generation of reactive oxygen species (ROS) such as nitric oxide appear to be part of the mechanisms of disease^[140], as studies have demonstrated higher levels of ROS in patients with rosacea^[141,142]. Treated rosacea is associated with less ROS^[141].

Studies suggest a linkage between *H. pylori* and rosacea due increased seroprevalence of the organism in patients with rosacea^[143,144]. A possible pathologic correlation stems from the observation that *H. pylori* induces oxidative stress in gastric epithelial cells in part due to production of ROS^[145,146].

Many studies since have reported conflicting results to the degree of correlation between *H. pylori* and rosa-

Table 1 Summary of the extraintestinal manifestation of *Helicobacter pylori* infection

Organ systems	Manifestations	Comments
Hematologic	Iron deficiency anemia	Well supported. Eradication may reverse deficiency
	Immune thrombocytopenic purpura	Higher prevalence of ITP in those with <i>H. pylori</i> infection and improvement in platelet count after eradication
Cardiopulmonary	Coronary artery disease	Inconclusive evidence to draw definitive link between infection and CAD
	Asthma	<i>H. pylori</i> associated with lower incidence of asthma, particularly pediatric populations
Metabolic	Metabolic syndrome	Contradictory evidence fails to establish causal link between infection and metabolic syndrome
	Diabetes mellitus type II	Conflicting evidence on prevalence of <i>H. pylori</i> and DM
Neurologic	Ischemic stroke	Possible weak positive association. Studies conflicting with regards to increase stroke risk and infection
	Parkinson's disease	Improvement in symptoms noted in patients with successful eradication of <i>H. pylori</i>
	Alzheimer's disease	Limited data suggests improved symptoms with eradication of <i>H. pylori</i>
	Migraines	Multiple studies show improvement in headaches following eradication of <i>H. pylori</i>
Dermatologic	Chronic spontaneous urticaria	Studies generally supportive of association. Eradication shown to improve CSU symptoms
	Rosacea	Conflicts in prevalence data but eradication appears to reduce skin disease severity
Miscellaneous	Fibromyalgia	Present data is conflicting with regards to prevalence of <i>H. pylori</i> and fibromyalgia

H. pylori: *Helicobacter pylori*; ITP: Immune thrombocytopenic purpura; CAD: Coronary artery disease; CSU: Chronic spontaneous urticarial.

cea^[147]. While some studies have shown increased prevalence of *H. pylori* in rosacea, some studies did not^[148,149]. More recent studies demonstrate significant improvement of in severity of rosacea in *H. pylori* positive patients who received eradication therapy^[150-152].

Rosacea as an extraintestinal manifestation of *H. pylori* requires further research; however, despite conflicting prevalence data, eradication therapy in those with both rosacea and *H. pylori* appears to be beneficial in reducing severity of skin disease.

MISCELLANEOUS MANIFESTATIONS

Fibromyalgia

Fibromyalgia (FM) is a common pain disorder characterized by chronic myalgias and arthralgias without clinical evidence of tissue inflammation. The etiology of the pain remains unknown; however, current pathophysiologic studies have focused on the role of altered central nervous system pain processing^[153,154]. One such mechanism proposed is cytokine mediated, which may induce activation of spinal cord glia and dorsal horn neurons resulting in central sensitization of pain.

The role of infections has been implicated in pathogenesis of FM and temporal associations have been found with hepatitis C, human immunodeficiency virus, and Lyme disease^[155].

H. pylori infection appears to be in association with FM. An Egyptian case-control study found significantly higher *H. pylori* IgG serological prevalence in females with FM compared to controls^[156]. In addition, among FM patients, those with positive serology have worse symptoms as measured by the Fibromyalgia Impact Questionnaire^[156]. A similar Turkish case-control also found a significant increase in serologic prevalence in females with FM compared to control^[157]; however, no difference was observed in severity of symptoms between *H. pylori* serologic status.

In contrast, an early case-control found no difference in serologic prevalence between fibromyalgia patients and age matched controls^[158].

Because of the conflicting results with regards to serological evidence of *H. pylori* infection, more studies are required before a definitive link between FM can be established. Furthermore, if a link is present, future studies with eradication of *H. pylori* and subsequent symptom assessment may serve to strengthen the association.

CONCLUSION

In conclusion, *H. pylori* has been linked to the pathogenesis of multiple extraintestinal disease states. Table 1 provides a quick summary. Numerous studies exist examining the hematologic, cardiopulmonary, metabolic, neurologic, and dermatologic manifestations of *H. pylori*. The association of *H. pylori* with ITP and IDA are the best supported at this time. There appears to be improvement in some neurologic and dermatologic conditions with eradication therapy. Although evidence exists, further studies are needed to clarify the role of *H. pylori* in many disease states reviewed in the present article.

REFERENCES

- 1 Lee R, Foerster J, Lukens J, Paraskevas F, Greer JP, Rodgers GM. Wintrobe's Clinical hematology, Vol. 1 and 2. Philadelphia: Williams & Wilkins, 1998
- 2 Monzón H, Forné M, Esteve M, Rosinach M, Loras C, Espinós JC, Viver JM, Salas A, Fernández-Bañares F. Helicobacter pylori infection as a cause of iron deficiency anaemia of unknown origin. *World J Gastroenterol* 2013; **19**: 4166-4171 [PMID: 23864779 DOI: 10.3748/wjg.v19.i26.4166]
- 3 Looker AC, Dallman PR, Carroll MD, Gunter EW, Johnson CL. Prevalence of iron deficiency in the United States. *JAMA* 1997; **277**: 973-976 [PMID: 9091669 DOI: 10.1001/jama.1997.03540360041028]
- 4 Coad J, Conlon C. Iron deficiency in women: assessment, causes and consequences. *Curr Opin Clin Nutr Metab Care*

- 2011; **14**: 625-634 [PMID: 21934611 DOI: 10.1097/MCO.0b013e32834be6fd]
- 5 **Brittenham GM.** Disorders of iron metabolism: Iron deficiency and overload. In: Hoffman R, BenZ EJ, Shattil SJ, Furie B, Cohen HJ, Silberstein LE, editors. *Haematology: Basic Principles and Practice*. New York: Churchill Livingstone, 1995: 492
 - 6 **Conrad ME, Umbreit JN, Moore EG.** Iron absorption and transport. *Am J Med Sci* 1999; **318**: 213-229 [PMID: 10522550 DOI: 10.1097/00000441-199910000-00002]
 - 7 **Blecker U, Renders F, Lanciers S, Vandenplas Y.** Syncopes leading to the diagnosis of a *Helicobacter pylori* positive chronic active haemorrhagic gastritis. *Eur J Pediatr* 1991; **150**: 560-561 [PMID: 1954961 DOI: 10.1007/BF02072207]
 - 8 **Annibale B, Marignani M, Monarca B, Antonelli G, Marcheggiano A, Martino G, Mandelli F, Caprilli R, Delle Fave G.** Reversal of iron deficiency anemia after *Helicobacter pylori* eradication in patients with asymptomatic gastritis. *Ann Intern Med* 1999; **131**: 668-672 [PMID: 10577329 DOI: 10.7326/0003-4819-131-9-199911020-00006]
 - 9 **Sugiyama T, Tsuchida M, Yokota K, Shimodan M, Asaka M.** Improvement of long-standing iron-deficiency anemia in adults after eradication of *Helicobacter pylori* infection. *Intern Med* 2002; **41**: 491-494 [PMID: 12135186 DOI: 10.2169/internalmedicine.41.491]
 - 10 **Yoshimura M, Hirai M, Tanaka N, Kasahara Y, Hosokawa O.** Remission of severe anemia persisting for over 20 years after eradication of *Helicobacter pylori* in cases of Ménétrier's disease and atrophic gastritis: *Helicobacter pylori* as a pathogenic factor in iron-deficiency anemia. *Intern Med* 2003; **42**: 971-977 [PMID: 14606710 DOI: 10.2169/internalmedicine.42.971]
 - 11 **Muhsen K, Cohen D.** *Helicobacter pylori* infection and iron stores: a systematic review and meta-analysis. *Helicobacter* 2008; **13**: 323-340 [PMID: 19250507 DOI: 10.1111/j.1523-5378.2008.00617.x]
 - 12 **Valiyaveetil AN, Hamide A, Bobby Z, Krishnan R.** Effect of anti-*Helicobacter pylori* therapy on outcome of iron-deficiency anemia: a randomized, controlled study. *Indian J Gastroenterol* 2005; **24**: 155-157 [PMID: 16204902]
 - 13 **Malik R, Guleria K, Kaur I, Sikka M, Radhakrishnan G.** Effect of *Helicobacter pylori* eradication therapy in iron deficiency anaemia of pregnancy - a pilot study. *Indian J Med Res* 2011; **134**: 224-231 [PMID: 21911976]
 - 14 **Yuan W, Li Yumin D, Yang L.** Iron deficiency anemia in *Helicobacter pylori* infection: meta-analysis of randomized controlled trials. *Scand J Gastroenterol* 2010; **45**: 665-676 [PMID: 20201716 DOI: 10.3109/00365521003663670]
 - 15 **Zhang ZF, Yang N, Zhao G, Zhu L, Zhu Y, Wang LX.** Effect of *Helicobacter pylori* eradication on iron deficiency. *Chin Med J (Engl)* 2010; **123**: 1924-1930 [PMID: 20819579]
 - 16 **Huang X, Qu X, Yan W, Huang Y, Cai M, Hu B, Wu L, Lin H, Chen Z, Zhu C, Lu L, Sun X, Rong L, Jiang Y, Sun D, Zhong L, Xiong P.** Iron deficiency anaemia can be improved after eradication of *Helicobacter pylori*. *Postgrad Med J* 2010; **86**: 272-278 [PMID: 20448223 DOI: 10.1136/pgmj.2009.089987]
 - 17 **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.** Does *Helicobacter pylori* infection play a role in iron deficiency anemia? A meta-analysis. *World J Gastroenterol* 2010; **16**: 886-896 [PMID: 20143469]
 - 18 **Papagiannakis P, Michalopoulos C, Papalexi F, Dalampoura D, Diamantidis MD.** The role of *Helicobacter pylori* infection in hematological disorders. *Eur J Intern Med* 2013; **24**: 685-690 [PMID: 23523153 DOI: 10.1016/j.ejim.2013.02.011]
 - 19 **Dickey W.** Iron deficiency, gastric atrophy and *Helicobacter pylori*. *Dig Liver Dis* 2002; **34**: 313-315 [PMID: 12118945 DOI: 10.1016/S1590-8658(02)80121-9]
 - 20 **Annibale B, Capurso G, Lahner E, Passi S, Ricci R, Maggio F, Delle Fave G.** Concomitant alterations in intragastric pH and ascorbic acid concentration in patients with *Helicobacter pylori* gastritis and associated iron deficiency anaemia. *Gut* 2003; **52**: 496-501 [PMID: 12631657 DOI: 10.1136/gut.52.4.496]
 - 21 **Boyanova L.** Role of *Helicobacter pylori* virulence factors for iron acquisition from gastric epithelial cells of the host and impact on bacterial colonization. *Future Microbiol* 2011; **6**: 843-846 [PMID: 21861616 DOI: 10.2217/fmb.11.75]
 - 22 **Goddard AF, James MW, McIntyre AS, Scott BB.** Guidelines for the management of iron deficiency anaemia. *Gut* 2011; **60**: 1309-1316 [PMID: 21561874 DOI: 10.1136/gut.2010.228874]
 - 23 **Malfertheiner P, Megraud F, O'Morain CA, Atherton J, Axon AT, Bazzoli F, Gensini GF, Gisbert JP, Graham DY, Rokkas T, El-Omar EM, Kuipers EJ.** Management of *Helicobacter pylori* infection--the Maastricht IV/ Florence Consensus Report. *Gut* 2012; **61**: 646-664 [PMID: 22491499 DOI: 10.1136/gutjnl-2012-302084]
 - 24 **Neunert C, Lim W, Crowther M, Cohen A, Solberg L, Crowther MA.** The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood* 2011; **117**: 4190-4207 [PMID: 21325604 DOI: 10.1182/blood-2010-08-302984]
 - 25 **Tan HJ, Goh KL.** Extragastrintestinal manifestations of *Helicobacter pylori* infection: facts or myth? A critical review. *J Dig Dis* 2012; **13**: 342-349 [PMID: 22713083 DOI: 10.1111/j.1751-2980.2012.00599.x]
 - 26 **Gasbarrini A, Franceschi F, Tartaglione R, Landolfi R, Pola P, Gasbarrini G.** Regression of autoimmune thrombocytopenia after eradication of *Helicobacter pylori*. *Lancet* 1998; **352**: 878 [PMID: 9742983 DOI: 10.1016/S0140-6736(05)60004-9]
 - 27 **Stasi R, Sarpatwari A, Segal JB, Osborn J, Evangelista ML, Cooper N, Provan D, Newland A, Amadori S, Bussel JB.** Effects of eradication of *Helicobacter pylori* infection in patients with immune thrombocytopenic purpura: a systematic review. *Blood* 2009; **113**: 1231-1240 [PMID: 18945961 DOI: 10.1182/blood-2008-07-167155]
 - 28 **Arnold DM, Bernotas A, Nazi I, Stasi R, Kuwana M, Liu Y, Kelton JG, Crowther MA.** Platelet count response to *H. pylori* treatment in patients with immune thrombocytopenic purpura with and without *H. pylori* infection: a systematic review. *Haematologica* 2009; **94**: 850-856 [PMID: 19483158 DOI: 10.3324/haematol.2008.005348]
 - 29 **Kikuchi T, Kobayashi T, Yamashita T, Ohashi K, Sakamaki H, Akiyama H.** Eight-year follow-up of patients with immune thrombocytopenic purpura related to *H. pylori* infection. *Platelets* 2011; **22**: 61-64 [PMID: 20942598 DOI: 10.3109/09537104.2010.515272]
 - 30 **Byrne MF, Kerrigan SW, Corcoran PA, Atherton JC, Murray FE, Fitzgerald DJ, Cox DM.** *Helicobacter pylori* binds von Willebrand factor and interacts with GPIb to induce platelet aggregation. *Gastroenterology* 2003; **124**: 1846-1854 [PMID: 12806618 DOI: 10.1016/S0016-5085(03)00397-4]
 - 31 **Takahashi T, Yujiri T, Shinohara K, Inoue Y, Sato Y, Fujii Y, Okubo M, Zaitzu Y, Ariyoshi K, Nakamura Y, Nawata R, Oka Y, Shirai M, Tanizawa Y.** 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 [PMID: 14675413 DOI: 10.1046/j.1365-2141.2003.04735.x]
 - 32 **Asahi A, Nishimoto T, Okazaki Y, Suzuki H, Masaoka T, Kawakami Y, Ikeda Y, Kuwana M.** *Helicobacter pylori* eradication shifts monocyte Fcγ receptor balance toward inhibitory FcγRIIB in immune thrombocytopenic purpura patients. *J Clin Invest* 2008; **118**: 2939-2949 [PMID: 18654664]
 - 33 **Onat A, Sari I, Hergenç G, Yazici M, Uyarel H, Can G, Sansoy V.** Predictors of abdominal obesity and high susceptibility of cardiometabolic risk to its increments among Turkish

- women: a prospective population-based study. *Metabolism* 2007; **56**: 348-356 [PMID: 17292723]
- 34 **Lobo RA.** Inflammation, coronary artery disease, and hormones. *Menopause* 2008; **15**: 1036-1038 [PMID: 18779754 DOI: 10.1097/gme.0b013e318184c45a]
- 35 **Mendall MA,** Goggin PM, Molineaux N, Levy J, Toosy T, Strachan D, Camm AJ, Northfield TC. Relation of Helicobacter pylori infection and coronary heart disease. *Br Heart J* 1994; **71**: 437-439 [PMID: 8011406 DOI: 10.1136/hrt.71.5.437]
- 36 **Pieniazek P,** Karczewska E, Duda A, Tracz W, Pasowicz M, Konturek SJ. Association of Helicobacter pylori infection with coronary heart disease. *J Physiol Pharmacol* 1999; **50**: 743-751 [PMID: 10695556]
- 37 **Kowalski M,** Konturek PC, Pieniazek P, Karczewska E, Kluczka A, Grove R, Kranig W, Nasserri R, Thale J, Hahn EG, Konturek SJ. Prevalence of Helicobacter pylori infection in coronary artery disease and effect of its eradication on coronary lumen reduction after percutaneous coronary angioplasty. *Dig Liver Dis* 2001; **33**: 222-229 [PMID: 11407666 DOI: 10.1016/S1590-8658(01)80711-8]
- 38 **Rogha M,** Nikvarz M, Pourmoghaddas Z, Shirmeshan K, Dadkhah D, Pourmoghaddas M. Is helicobacter pylori infection a risk factor for coronary heart disease? *ARYA Atheroscler* 2012; **8**: 5-8 [PMID: 23056092]
- 39 **Park MJ,** Choi SH, Kim D, Kang SJ, Chung SJ, Choi SY, Yoon DH, Lim SH, Kim YS, Yim JY, Kim JS, Jung HC. Association between Helicobacter pylori Seropositivity and the Coronary Artery Calcium Score in a Screening Population. *Gut Liver* 2011; **5**: 321-327 [PMID: 21927661 DOI: 10.5009/gnl.2011.5.3.321]
- 40 **Huang B,** Chen Y, Xie Q, Lin G, Wu Y, Feng Y, Li J, Zhuo Y, Zhang P. CagA-positive Helicobacter pylori strains enhanced coronary atherosclerosis by increasing serum OxLDL and HsCRP in patients with coronary heart disease. *Dig Dis Sci* 2011; **56**: 109-114 [PMID: 20503072 DOI: 10.1007/s10620-010-1274-6]
- 41 **Niccoli G,** Franceschi F, Cosentino N, Giupponi B, De Marco G, Merra G, Conte M, Montone RA, Ferrante G, Bacà M, Gasbarrini A, Silveri NG, Crea F. Coronary atherosclerotic burden in patients with infection by CagA-positive strains of Helicobacter pylori. *Coron Artery Dis* 2010; **21**: 217-221 [PMID: 20389238 DOI: 10.1097/MCA.0b013e3283399f36]
- 42 **Danesh J,** Peto R. Risk factors for coronary heart disease and infection with Helicobacter pylori: meta-analysis of 18 studies. *BMJ* 1998; **316**: 1130-1132 [PMID: 9552950 DOI: 10.1136/bmj.316.7138.1130]
- 43 **Padmavati S,** Gupta U, Agarwal HK. Chronic infections & coronary artery disease with special reference to Chlamydia pneumoniae. *Indian J Med Res* 2012; **135**: 228-232 [PMID: 22446866]
- 44 **Schöttker B,** Adamu MA, Weck MN, Müller H, Brenner H. Helicobacter pylori infection, chronic atrophic gastritis and major cardiovascular events: a population-based cohort study. *Atherosclerosis* 2012; **220**: 569-574 [PMID: 22189198 DOI: 10.1016/j.atherosclerosis.2011.11.029]
- 45 **Ameriso SF,** Fridman EA, Leiguarda RC, Sevlever GE. Detection of Helicobacter pylori in human carotid atherosclerotic plaques. *Stroke* 2001; **32**: 385-391 [PMID: 11157171 DOI: 10.1161/01.STR.32.2.385]
- 46 **Tamer GS,** Tengiz I, Ercan E, Duman C, Alioglu E, Turk UO. Helicobacter pylori seropositivity in patients with acute coronary syndromes. *Dig Dis Sci* 2009; **54**: 1253-1256 [PMID: 18770033 DOI: 10.1007/s10620-008-0482-9]
- 47 **Oshima T,** Ozono R, Yano Y, Oishi Y, Teragawa H, Higashi Y, Yoshizumi M, Kambe M. Association of Helicobacter pylori infection with systemic inflammation and endothelial dysfunction in healthy male subjects. *J Am Coll Cardiol* 2005; **45**: 1219-1222 [PMID: 15837252 DOI: 10.1016/j.jacc.2005.01.019]
- 48 **Franceschi F,** Sepulveda AR, Gasbarrini A, Pola P, Silveri NG, Gasbarrini G, Graham DY, Genta RM. Cross-reactivity of anti-CagA antibodies with vascular wall antigens: possible pathogenic link between Helicobacter pylori infection and atherosclerosis. *Circulation* 2002; **106**: 430-434 [PMID: 12135941 DOI: 10.1161/01.CIR.0000024100.90140.19]
- 49 **Chimienti G,** Russo F, Lamanuzzi BL, Nardulli M, Messa C, Di Leo A, Correale M, Giannuzzi V, Pepe G. Helicobacter pylori is associated with modified lipid profile: impact on Lipoprotein(a). *Clin Biochem* 2003; **36**: 359-365 [PMID: 12849867 DOI: 10.1016/S0009-9120(03)00063-8]
- 50 **Kucukazman M,** Yavuz B, Sacikara M, Asilturk Z, Ata N, Ertugrul DT, Yalcin AA, Yenigun EC, Kizilca G, Okten H, Akin KO, Nazligil Y. The relationship between updated Sydney System score and LDL cholesterol levels in patients infected with Helicobacter pylori. *Dig Dis Sci* 2009; **54**: 604-607 [PMID: 18649137 DOI: 10.1007/s10620-008-0391-y]
- 51 **McCune A,** Lane A, Murray L, Harvey I, Nair P, Donovan J, Harvey R. Reduced risk of atopic disorders in adults with Helicobacter pylori infection. *Eur J Gastroenterol Hepatol* 2003; **15**: 637-640 [PMID: 12840675 DOI: 10.1097/00042737-200306000-00010]
- 52 **Strachan DP.** Family size, infection and atopy: the first decade of the "hygiene hypothesis". *Thorax* 2000; **55** Suppl 1: S2-10 [PMID: 10943631]
- 53 **Chen Y,** Blaser MJ. Helicobacter pylori colonization is inversely associated with childhood asthma. *J Infect Dis* 2008; **198**: 553-560 [PMID: 18598192 DOI: 10.1086/590158]
- 54 **Corrado G,** Luzzi I, Pacchiarotti C, Lucarelli S, Frediani T, Cavaliere M, Rea P, Cardi E. Helicobacter pylori seropositivity in children with atopic dermatitis as sole manifestation of food allergy. *Pediatr Allergy Immunol* 2000; **11**: 101-105 [PMID: 10893012 DOI: 10.1034/j.1399-3038.2000.00028.x]
- 55 **Oertli M,** Müller A. Helicobacter pylori targets dendritic cells to induce immune tolerance, promote persistence and confer protection against allergic asthma. *Gut Microbes* 2012; **3**: 566-571 [PMID: 22895083 DOI: 10.4161/gmic.21750]
- 56 **Annagür A,** Kendirli SG, Yilmaz M, Altintas DU, Inal A. Is there any relationship between asthma and asthma attack in children and atypical bacterial infections; Chlamydia pneumoniae, Mycoplasma pneumoniae and Helicobacter pylori. *J Trop Pediatr* 2007; **53**: 313-318 [PMID: 17535826 DOI: 10.1093/tropej/fmm040]
- 57 **Holster IL,** Vila AM, Caudri D, den Hoed CM, Perez-Perez GL, Blaser MJ, de Jongste JC, Kuipers EJ. The impact of Helicobacter pylori on atopic disorders in childhood. *Helicobacter* 2012; **17**: 232-237 [PMID: 22515362 DOI: 10.1111/j.1523-5378.2012.00934.x]
- 58 **Wang Q,** Yu C, Sun Y. The association between asthma and Helicobacter pylori: a meta-analysis. *Helicobacter* 2013; **18**: 41-53 [PMID: 23067334 DOI: 10.1111/hel.12012]
- 59 **Zhou X,** Wu J, Zhang G. Association between Helicobacter pylori and asthma: a meta-analysis. *Eur J Gastroenterol Hepatol* 2013; **25**: 460-468 [PMID: 23242126]
- 60 **Grundt SM,** Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC, Spertus JA, Costa F. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 2005; **112**: 2735-2752 [PMID: 16157765 DOI: 10.1161/CIRCULATIONAHA.105.169404]
- 61 **Polyzos SA,** Kountouras J, Zavos C, Deretzi G. The association between Helicobacter pylori infection and insulin resistance: a systematic review. *Helicobacter* 2011; **16**: 79-88 [PMID: 21435084 DOI: 10.1111/j.1523-5378.2011.00822.x]
- 62 **Gunji T,** Matsuhashi N, Sato H, Fujibayashi K, Okumura M, Sasabe N, Urabe A. Helicobacter pylori infection is significantly associated with metabolic syndrome in the Japanese population. *Am J Gastroenterol* 2008; **103**: 3005-3010 [PMID: 19086952 DOI: 10.1111/j.1572-0241.2008.02151.x]
- 63 **Gunji T,** Matsuhashi N, Sato H, Fujibayashi K, Okumura M,

- Sasabe N, Urabe A. Helicobacter pylori infection significantly increases insulin resistance in the asymptomatic Japanese population. *Helicobacter* 2009; **14**: 144-150 [PMID: 19751440 DOI: 10.1111/j.1523-5378.2009.00705.x]
- 64 **Aydemir S**, Bayraktaroglu T, Sert M, Sokmen C, Atmaca H, Mungan G, Gun BD, Borazan A, Ustundag Y. The effect of Helicobacter pylori on insulin resistance. *Dig Dis Sci* 2005; **50**: 2090-2093 [PMID: 16240220 DOI: 10.1007/s10620-005-3012-z]
- 65 **Eshraghian A**, Hashemi SA, Hamidian Jahromi A, Eshraghian H, Masoompour SM, Davarpanah MA, Eshraghian K, Taghavi SA. Helicobacter pylori infection as a risk factor for insulin resistance. *Dig Dis Sci* 2009; **54**: 1966-1970 [PMID: 19009348 DOI: 10.1007/s10620-008-0557-7]
- 66 **Polyzos SA**, Kountouras J, Zavos C. Nonalcoholic fatty liver disease: the pathogenetic roles of insulin resistance and adipocytokines. *Curr Mol Med* 2009; **9**: 299-314 [PMID: 19355912 DOI: 10.2174/156652409787847191]
- 67 **Osawa H**, Nakazato M, Date Y, Kita H, Ohnishi H, Ueno H, Shiya T, Satoh K, Ishino Y, Sugano K. Impaired production of gastric ghrelin in chronic gastritis associated with Helicobacter pylori. *J Clin Endocrinol Metab* 2005; **90**: 10-16 [PMID: 15483107 DOI: 10.1210/jc.2004-1330]
- 68 **Roper J**, Francois F, Shue PL, Mourad MS, Pei Z, Olivares de Perez AZ, Perez-Perez GI, Tseng CH, Blaser MJ. Leptin and ghrelin in relation to Helicobacter pylori status in adult males. *J Clin Endocrinol Metab* 2008; **93**: 2350-2357 [PMID: 18397989 DOI: 10.1210/jc.2007-2057]
- 69 **Gen R**, Demir M, Ataseven H. Effect of Helicobacter pylori eradication on insulin resistance, serum lipids and low-grade inflammation. *South Med J* 2010; **103**: 190-196 [PMID: 20134372 DOI: 10.1097/SMJ.0b013e3181cf373f]
- 70 **Christodoulou DK**, Milionis HJ, Pappa P, Katsanos KH, Sigounas D, Florentin M, Elisaf M, Tsianos EV. Association of Helicobacter pylori infection with cardiovascular disease—is it just a myth? *Eur J Intern Med* 2011; **22**: 191-194 [PMID: 21402252 DOI: 10.1016/j.ejim.2010.11.010]
- 71 **Dore MP**, Bilotta M, Malaty HM, Pacifico A, Maioli M, Graham DY, Realdi G. Diabetes mellitus and Helicobacter pylori infection. *Nutrition* 2000; **16**: 407-410 [PMID: 10869894 DOI: 10.1016/S0899-9007(00)00267-7]
- 72 **Gillum RF**. Infection with Helicobacter pylori, coronary heart disease, cardiovascular risk factors, and systemic inflammation: the Third National Health and Nutrition Examination Survey. *J Natl Med Assoc* 2004; **96**: 1470-1476 [PMID: 15586651]
- 73 **Naja F**, Nasreddine L, Hwalla N, Moghames P, Shoaib H, Fatfat M, Sibai A, Gali-Muhtasib H. Association of *H. pylori* infection with insulin resistance and metabolic syndrome among Lebanese adults. *Helicobacter* 2012; **17**: 444-451 [PMID: 23066847 DOI: 10.1111/j.1523-5378.2012.00970.x]
- 74 **Lu YH**, Yen HW, Lin TH, Huang CH, Lee KT, Wang WM, Wu DC, Voon WC, Lai WT, Sheu SH. Changes of coronary risk factors after eradication of Helicobacter pylori infection. *Kaohsiung J Med Sci* 2002; **18**: 266-272 [PMID: 12355926]
- 75 **Hu FB**, Meigs JB, Li TY, Rifai N, Manson JE. Inflammatory markers and risk of developing type 2 diabetes in women. *Diabetes* 2004; **53**: 693-700 [PMID: 14988254 DOI: 10.2337/diabetes.53.3.693]
- 76 **Pradhan AD**, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA* 2001; **286**: 327-334 [PMID: 11466099 DOI: 10.1001/jama.286.3.327]
- 77 **Rutter MK**, Meigs JB, Sullivan LM, D'Agostino RB, Wilson PW. C-reactive protein, the metabolic syndrome, and prediction of cardiovascular events in the Framingham Offspring Study. *Circulation* 2004; **110**: 380-385 [PMID: 15262834 DOI: 10.1161/01.CIR.0000136581.59584.0E]
- 78 **Fernández-Real JM**, López-Bermejo A, Vendrell J, Ferri MJ, Recasens M, Ricart W. Burden of infection and insulin resistance in healthy middle-aged men. *Diabetes Care* 2006; **29**: 1058-1064 [PMID: 16644637 DOI: 10.2337/dc05-2068]
- 79 **Howard BV**, Best L, Comuzzie A, Ebbesson SO, Epstein SE, Fabsitz RR, Howard WJ, Silverman A, Wang H, Zhu J, Umans J. C-Reactive protein, insulin resistance, and metabolic syndrome in a population with a high burden of subclinical infection: insights from the Genetics of Coronary Artery Disease in Alaska Natives (GOCADAN) study. *Diabetes Care* 2008; **31**: 2312-2314 [PMID: 18796618 DOI: 10.2337/dc08-0815]
- 80 **Lutsey PL**, Pankow JS, Bertoni AG, Szklo M, Folsom AR. Serological evidence of infections and Type 2 diabetes: the MultiEthnic Study of Atherosclerosis. *Diabet Med* 2009; **26**: 149-152 [PMID: 19236617 DOI: 10.1111/j.1464-5491.2008.02632.x]
- 81 **So WY**, Tong PC, Ko GT, Ma RC, Ozaki R, Kong AP, Yang X, Ho CS, Lam CC, Chan JC. Low plasma adiponectin level, white blood cell count and Helicobacter pylori titre independently predict abnormal pancreatic beta-cell function. *Diabetes Res Clin Pract* 2009; **86**: 89-95 [PMID: 19747747 DOI: 10.1016/j.diabres.2009.08.010]
- 82 **Zhou X**, Zhang C, Wu J, Zhang G. Association between Helicobacter pylori infection and diabetes mellitus: a meta-analysis of observational studies. *Diabetes Res Clin Pract* 2013; **99**: 200-208 [PMID: 23395214 DOI: 10.1016/j.diabres.2012.11.012]
- 83 **Jeon CY**, Haan MN, Cheng C, Clayton ER, Mayeda ER, Miller JW, Aiello AE. Helicobacter pylori infection is associated with an increased rate of diabetes. *Diabetes Care* 2012; **35**: 520-525 [PMID: 22279028 DOI: 10.2337/dc11-1043]
- 84 **Mogensen CE**, Chachati A, Christensen CK, Close CF, Deckert T, Hommel E, Kastrup J, Lefebvre P, Mathiesen ER, Feldt-Rasmussen B. Microalbuminuria: an early marker of renal involvement in diabetes. *Uremia Invest* 1985; **9**: 85-95 [PMID: 3915933]
- 85 **Chung GE**, Heo NJ, Park MJ, Chung SJ, Kang HY, Kang SJ. Helicobacter pylori seropositivity in diabetic patients is associated with microalbuminuria. *World J Gastroenterol* 2013; **19**: 97-102 [PMID: 23326169 DOI: 10.3748/wjg.v19.i1.97]
- 86 **Yang X**, Gao Y, Zhao X, Tang Y, Su Y. Chronic Helicobacter pylori infection and ischemic stroke subtypes. *Neurol Res* 2011; **33**: 467-472 [PMID: 21669114 DOI: 10.1179/016164111X13007856083963]
- 87 **Whincup PH**, Mendall MA, Perry IJ, Strachan DP, Walker M. Prospective relations between Helicobacter pylori infection, coronary heart disease, and stroke in middle aged men. *Heart* 1996; **75**: 568-572 [PMID: 8697158 DOI: 10.1136/hrt.75.6.568]
- 88 **Markus HS**, Mendall MA. Helicobacter pylori infection: a risk factor for ischaemic cerebrovascular disease and carotid atheroma. *J Neurol Neurosurg Psychiatry* 1998; **64**: 104-107 [PMID: 9436737 DOI: 10.1136/jnnp.64.1.104]
- 89 **Ashtari F**, Shayegannejad V, Saberi A, Rabiee E. Relationship between Helicobacter pylori immunoglobulin G antibody and thrombotic ischemic stroke. *Acta Med Iran* 2008; **46**: 303-306
- 90 **Ridker PM**, Hennekens CH, Buring JE, Kundsin R, Shih J. Baseline IgG antibody titers to Chlamydia pneumoniae, Helicobacter pylori, herpes simplex virus, and cytomegalovirus and the risk for cardiovascular disease in women. *Ann Intern Med* 1999; **131**: 573-577 [PMID: 10523217 DOI: 10.7326/0003-4819-131-8-199910190-00004]
- 91 **Pietroiuisti A**, Diomedes M, Silvestrini M, Cupini LM, Luzzi I, Gomez-Miguel MJ, Bergamaschi A, Magrini A, Carrabs T, Vellini M, Galante A. Cytotoxin-associated gene-A--positive Helicobacter pylori strains are associated with atherosclerotic stroke. *Circulation* 2002; **106**: 580-584 [PMID: 12147540 DOI: 10.1161/01.CIR.0000023894.10871.2F]
- 92 **De Bastiani R**, Gabrielli M, Ubaldi E, Benedetto E, Sanna G, Cottone C, Candelli M, Zocco MA, Saulnier N, Santoliquido A, Papaleo P, Gasbarrini G, Gasbarrini A. High prevalence

- of Cag-A positive *H. pylori* strains in ischemic stroke: a primary care multicenter study. *Helicobacter* 2008; **13**: 274-277 [PMID: 18665936 DOI: 10.1111/j.1523-5378.2008.00610.x]
- 93 **Strauss EJ**, Tejwani NC, Preston CF, Egol KA. The posterior Monteggia lesion with associated ulnohumeral instability. *J Bone Joint Surg Br* 2006; **88**: 84-89 [PMID: 16365126 DOI: 10.1212/01.WNL.0000138025.82419.80]
- 94 **Wang ZW**, Li Y, Huang LY, Guan QK, Xu da W, Zhou WK, Zhang XZ. Helicobacter pylori infection contributes to high risk of ischemic stroke: evidence from a meta-analysis. *J Neurol* 2012; **259**: 2527-2537 [PMID: 22688569]
- 95 **Gabrielli M**, Santoliquido A, Cremonini F, Cicconi V, Candelli M, Serricchio M, Tondi P, Pola R, Gasbarrini G, Pola P, Gasbarrini A. CagA-positive cytotoxic *H. pylori* strains as a link between plaque instability and atherosclerotic stroke. *Eur Heart J* 2004; **25**: 64-68 [PMID: 14683744 DOI: 10.1016/j.ehj.2003.10.004]
- 96 **Evrengul H**, Tanriverdi H, Kuru O, Enli Y, Yuksel D, Kilic A, Kaftan A, Kirac S, Kilic M. Elevated homocysteine levels in patients with slow coronary flow: relationship with Helicobacter pylori infection. *Helicobacter* 2007; **12**: 298-305 [PMID: 17669101]
- 97 **Strang RR**. The Association of Gastro-Duodenal Ulceration and Parkinson's Disease. *Med J Aust* 1965; **1**: 842-843 [PMID: 14313339]
- 98 **Altschuler E**. Gastric Helicobacter pylori infection as a cause of idiopathic Parkinson disease and non-arteric anterior optic ischemic neuropathy. *Med Hypotheses* 1996; **47**: 413-414 [PMID: 8951807 DOI: 10.1016/S0306-9877(96)90223-6]
- 99 **Bjarnason IT**, Charlett A, Dobbs RJ, Dobbs SM, Ibrahim MA, Kerwin RW, Mahler RF, Oxlade NL, Peterson DW, Plant JM, Price AB, Weller C. Role of chronic infection and inflammation in the gastrointestinal tract in the etiology and pathogenesis of idiopathic parkinsonism. Part 2: response of facets of clinical idiopathic parkinsonism to Helicobacter pylori eradication. A randomized, double-blind, placebo-controlled efficacy study. *Helicobacter* 2005; **10**: 276-287 [PMID: 16104943 DOI: 10.1111/j.1523-5378.2005.00330.x]
- 100 **Pierantozzi M**, Pietroiusti A, Brusa L, Galati S, Stefani A, Lunardi G, Fedele E, Sancesario G, Bernardi G, Bergamaschi A, Magrini A, Stanzione P, Galante A. Helicobacter pylori eradication and l-dopa absorption in patients with PD and motor fluctuations. *Neurology* 2006; **66**: 1824-1829 [PMID: 16801644 DOI: 10.1212/01.wnl.0000221672.01272.ba]
- 101 **Dobbs SM**, Dobbs RJ, Weller C, Charlett A, Bjarnason IT, Lawson AJ, Letley D, Harbin L, Price AB, Ibrahim MA, Oxlade NL, Bowthorpe J, Leckstroem D, Smee C, Plant JM, Peterson DW. Differential effect of Helicobacter pylori eradication on time-trends in brady/hypokinesia and rigidity in idiopathic parkinsonism. *Helicobacter* 2010; **15**: 279-294 [PMID: 20633189 DOI: 10.1111/j.1523-5378.2010.00768.x]
- 102 **Weller C**, Charlett A, Oxlade NL, Dobbs SM, Dobbs RJ, Peterson DW, Bjarnason IT. Role of chronic infection and inflammation in the gastrointestinal tract in the etiology and pathogenesis of idiopathic parkinsonism. Part 3: predicted probability and gradients of severity of idiopathic parkinsonism based on *H. pylori* antibody profile. *Helicobacter* 2005; **10**: 288-297 [PMID: 16104944 DOI: 10.1111/j.1523-5378.2005.00329.x]
- 103 **Dobbs RJ**, Dobbs SM, Weller C, Charlett A, Bjarnason IT, Curry A, Ellis DS, Ibrahim MA, McCrossan MV, O'Donohue J, Owen RJ, Oxlade NL, Price AB, Sanderson JD, Sudhanva M, Williams J. Helicobacter hypothesis for idiopathic parkinsonism: before and beyond. *Helicobacter* 2008; **13**: 309-322 [PMID: 19250506 DOI: 10.1111/j.1523-5378.2008.00622.x]
- 104 **Hunot S**, Hirsch EC. Neuroinflammatory processes in Parkinson's disease. *Ann Neurol* 2003; **53** Suppl 3: S49-58; discussion S58-60 [PMID: 12666098 DOI: 10.1002/ana.10481]
- 105 **Honjo K**, van Reekum R, Verhoeff NP. Alzheimer's disease and infection: do infectious agents contribute to progression of Alzheimer's disease? *Alzheimers Dement* 2009; **5**: 348-360 [PMID: 19560105 DOI: 10.1016/j.jalz.2008.12.001]
- 106 **Kountouras J**, Tsolaki M, Gavalas E, Boziki M, Zavos C, Karatzoglou P, Chatzopoulos D, Venizelos I. Relationship between Helicobacter pylori infection and Alzheimer disease. *Neurology* 2006; **66**: 938-940 [PMID: 16567719 DOI: 10.1212/01.wnl.0000203644.68059.5f]
- 107 **Kountouras J**, Boziki M, Gavalas E, Zavos C, Deretzi G, Grigoriadis N, Tsolaki M, Chatzopoulos D, Katsinelos P, Tzilves D, Zabouri A, Michailidou I. Increased cerebrospinal fluid Helicobacter pylori antibody in Alzheimer's disease. *Int J Neurosci* 2009; **119**: 765-777 [PMID: 19326283 DOI: 10.1080/00207450902782083]
- 108 **Kountouras J**, Boziki M, Gavalas E, Zavos C, Grigoriadis N, Deretzi G, Tzilves D, Katsinelos P, Tsolaki M, Chatzopoulos D, Venizelos I. Eradication of Helicobacter pylori may be beneficial in the management of Alzheimer's disease. *J Neurol* 2009; **256**: 758-767 [PMID: 19240960 DOI: 10.1007/s00415-009-5011-z]
- 109 **Kountouras J**, Mylopoulos N, Chatzopoulos D, Zavos C, Boura P, Konstas AG, Venizelos J. Eradication of Helicobacter pylori may be beneficial in the management of chronic open-angle glaucoma. *Arch Intern Med* 2002; **162**: 1237-1244 [PMID: 12038941 DOI: 10.1001/archinte.162.11.1237]
- 110 **Malaguarnera M**, Bella R, Alagona G, Ferri R, Carnemolla A, Pennisi G. Helicobacter pylori and Alzheimer's disease: a possible link. *Eur J Intern Med* 2004; **15**: 381-386 [PMID: 15522573 DOI: 10.1016/j.ejim.2004.05.008]
- 111 **Hallam DM**, Capps NL, Travelstead AL, Brewer GJ, Marroun LE. Evidence for an interferon-related inflammatory reaction in the trisomy 16 mouse brain leading to caspase-1-mediated neuronal apoptosis. *J Neuroimmunol* 2000; **110**: 66-75 [PMID: 11024535 DOI: 10.1016/S0165-5728(00)00289-7]
- 112 **Charles A**. The evolution of a migraine attack - a review of recent evidence. *Headache* 2013; **53**: 413-419 [PMID: 23278169 DOI: 10.1111/head.12026]
- 113 **Cutrer FM**. Pathophysiology of migraine. *Semin Neurol* 2006; **26**: 171-180 [PMID: 16628527 DOI: 10.1055/s-2006-939917]
- 114 **Charles A**. Vasodilation out of the picture as a cause of migraine headache. *Lancet Neurol* 2013; **12**: 419-420 [PMID: 23578774 DOI: 10.1016/S1474-4422(13)70051-6]
- 115 **Deleu D**, Hanssens Y, Worthing EA. Symptomatic and prophylactic treatment of migraine: a critical reappraisal. *Clin Neuropharmacol* 1998; **21**: 267-279 [PMID: 9789706]
- 116 **Gervil M**, Ulrich V, Kaprio J, Olesen J, Russell MB. The relative role of genetic and environmental factors in migraine without aura. *Neurology* 1999; **53**: 995-999 [PMID: 10496258]
- 117 **Yiannopoulou KG**, Efthymiou A, Karydakis K, Arhiman-dritis A, Bovaretos N, Tzivras M. Helicobacter pylori infection as an environmental risk factor for migraine without aura. *J Headache Pain* 2007; **8**: 329-333 [PMID: 18071631 DOI: 10.1007/s10194-007-0422-7]
- 118 **Gasbarrini A**, De Luca A, Fiore G, Franceschi F, Ojetti V V, Torre ES, Di Campli C, Candelli M, Pola R, Serricchio M, Tondi P, Gasbarrini G, Pola P, Giacobuzzo M. Primary Headache and Helicobacter Pylori. *Int J Angiol* 1998; **7**: 310-312 [PMID: 9716793 DOI: 10.1007/s005479900121]
- 119 **Hong L**, Zhao Y, Han Y, Guo W, Wang J, Li X, Han Y, Fan D. Reversal of migraine symptoms by Helicobacter pylori eradication therapy in patients with hepatitis-B-related liver cirrhosis. *Helicobacter* 2007; **12**: 306-308 [PMID: 17669102 DOI: 10.1111/j.1523-5378.2007.00512.x]
- 120 **Tunca A**, Türkay C, Tekin O, Kargili A, Erbayrak M. Is Helicobacter pylori infection a risk factor for migraine? A case-control study. *Acta Neurol Belg* 2004; **104**: 161-164 [PMID: 15742606]
- 121 **Hosseinzadeh M**, Khosravi A, Saki K, Ranjbar R. Evaluation of Helicobacter pylori infection in patients with common migraine headache. *Arch Med Sci* 2011; **7**: 844-849 [PMID: 22291830 DOI: 10.5114/aoms.2011.25560]

- 122 **Pinnessi L**, Savi L, Pellicano R, Rainero I, Valfrè W, Gentile S, Cossotto D, Rizzetto M, Ponzetto A. Chronic Helicobacter pylori infection and migraine: a case-control study. *Headache* 2000; **40**: 836-839 [PMID: 11135029 DOI: 10.1046/j.1526-4610.2000.00151.x]
- 123 **Caselli M**, Chiamenti CM, Soriani S, Fanaro S. Migraine in children and Helicobacter pylori. *Am J Gastroenterol* 1999; **94**: 1116-1118 [PMID: 10201507 DOI: 10.1111/j.1572-0241.1999.1116a.x]
- 124 **Mavromichalis I**, Zaramboukas T, Giala MM. Migraine of gastrointestinal origin. *Eur J Pediatr* 1995; **154**: 406-410 [PMID: 7641777 DOI: 10.1007/BF02072116]
- 125 **Haberl H**. Net land-atmosphere flows of biogenic carbon related to bioenergy: towards an understanding of systemic feedbacks. *Glob Change Biol Bioenergy* 2013; **5**: 351-357 [PMID: 23956793 DOI: 10.1155/2013/436727.]
- 126 **Ring J**. Allergy in Practice. Berlin, Germany: Springer, 2005
- 127 **Zuberbier T**, Asero R, Bindslev-Jensen C, Walter Canonica G, Church MK, Giménez-Arnau A, Grattan CE, Kapp A, Merk HF, Rogala B, Saini S, Sánchez-Borges M, Schmid-Grendelmeier P, Schünemann H, Staubach P, Vena GA, Wedi B, Maurer M. EAACI/GA(2)LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria. *Allergy* 2009; **64**: 1417-1426 [PMID: 19772512 DOI: 10.1111/j.1398-9995.2009.02179.x]
- 128 **Nichols KM**, Cook-Bolden FE. Allergic skin disease: major highlights and recent advances. *Med Clin North Am* 2009; **93**: 1211-1224 [PMID: 19932327 DOI: 10.1016/j.mcna.2009.08.004]
- 129 **Fukuda S**, Shimoyama T, Umegaki N, Mikami T, Nakano H, Munakata A. Effect of Helicobacter pylori eradication in the treatment of Japanese patients with chronic idiopathic urticaria. *J Gastroenterol* 2004; **39**: 827-830 [PMID: 15565400 DOI: 10.1007/s00535-004-1397-7]
- 130 **Federman DG**, Kirsner RS, Moriarty JP, Concato J. The effect of antibiotic therapy for patients infected with Helicobacter pylori who have chronic urticaria. *J Am Acad Dermatol* 2003; **49**: 861-864 [PMID: 14576665 DOI: 10.1016/S0190-9622(03)00846-6]
- 131 **Daudén E**, Jiménez-Alonso I, García-Díez A. Helicobacter pylori and idiopathic chronic urticaria. *Int J Dermatol* 2000; **39**: 446-452 [PMID: 10944090 DOI: 10.1046/j.1365-4362.2000.00995.x]
- 132 **Moreira A**, Rodrigues J, Delgado L, Fonseca J, Vaz M. Is Helicobacter pylori infection associated with chronic idiopathic urticaria? *Allergol Immunopathol (Madr)* 2003; **31**: 209-214 [PMID: 12890412 DOI: 10.1016/S0301-0546(03)79180-0]
- 133 **Chiu YC**, Tai WC, Chuah SK, Hsu PI, Wu DC, Wu KL, Huang CC, Ho JC, Ring J, Chen WC. The Clinical Correlations of Helicobacter pylori Virulence Factors and Chronic Spontaneous Urticaria. *Gastroenterol Res Pract* 2013; **2013**: 436727 [PMID: 23956739 DOI: 10.1155/2013/436727]
- 134 **Goodgame RW**, Malaty HM, el-Zimaity HM, Graham DY. Decrease in gastric permeability to sucrose following cure of Helicobacter pylori infection. *Helicobacter* 1997; **2**: 44-47 [PMID: 9432322 DOI: 10.1111/j.1523-5378.1997.tb00057.x]
- 135 **Wedi B**, Kapp A. Helicobacter pylori infection in skin diseases: a critical appraisal. *Am J Clin Dermatol* 2002; **3**: 273-282 [PMID: 12010072 DOI: 10.2165/00128071-200203040-00005]
- 136 **Bakos N**, Fekete B, Prohászka Z, Füst G, Kalabay L. High prevalence of IgG and IgA antibodies to 19-kDa Helicobacter pylori-associated lipoprotein in chronic urticaria. *Allergy* 2003; **58**: 663-667 [PMID: 12823128 DOI: 10.1034/j.1398-9995.2003.00200.x]
- 137 **Powell FC**. Clinical practice. Rosacea. *N Engl J Med* 2005; **352**: 793-803 [PMID: 15728812 DOI: 10.1056/NEJMc042829]
- 138 **Elewski BE**, Draeos Z, Dréno B, Jansen T, Layton A, Picardo M. Rosacea - global diversity and optimized outcome: proposed international consensus from the Rosacea International Expert Group. *J Eur Acad Dermatol Venereol* 2011; **25**: 188-200 [PMID: 20586834 DOI: 10.1111/j.1468-3083.2010.03751.x]
- 139 **Abram K**, Silm H, Maaros HI, Oona M. Risk factors associated with rosacea. *J Eur Acad Dermatol Venereol* 2010; **24**: 565-571 [PMID: 19874433 DOI: 10.1111/j.1468-3083.2009.03472.x]
- 140 **Yamasaki K**, Gallo RL. The molecular pathology of rosacea. *J Dermatol Sci* 2009; **55**: 77-81 [PMID: 19481425 DOI: 10.1016/j.jdermsci.2009.04.007]
- 141 **Bakar O**, Demirçay Z, Yuksel M, Haklar G, Sanisoglu Y. The effect of azithromycin on reactive oxygen species in rosacea. *Clin Exp Dermatol* 2007; **32**: 197-200 [PMID: 17244346 DOI: 10.1111/j.1365-2230.2006.02322.x]
- 142 **Peus D**, Vasa RA, Beyerle A, Meves A, Krautmacher C, Pittelkow MR. UVB activates ERK1/2 and p38 signaling pathways via reactive oxygen species in cultured keratinocytes. *J Invest Dermatol* 1999; **112**: 751-756 [PMID: 10233767 DOI: 10.1046/j.1523-1747.1999.00584.x]
- 143 **Rebora A**, Drago F, Picciotto A. Helicobacter pylori in patients with rosacea. *Am J Gastroenterol* 1994; **89**: 1603-1604 [PMID: 8079962]
- 144 **Gürer MA**, Erel A, Erbaş D, Çağlar K, Atahan C. The seroprevalence of Helicobacter pylori and nitric oxide in acne rosacea. *Int J Dermatol* 2002; **41**: 768-770 [PMID: 12452999 DOI: 10.1046/j.1365-4362.2002.01452.x]
- 145 **Bagchi D**, Bhattacharya G, Stohs SJ. Production of reactive oxygen species by gastric cells in association with Helicobacter pylori. *Free Radic Res* 1996; **24**: 439-450 [PMID: 8804987 DOI: 10.3109/10715769609088043]
- 146 **Mashimo M**, Nishikawa M, Higuchi K, Hirose M, Wei Q, Haque A, Sasaki E, Shiba M, Tominaga K, Watanabe T, Fujiwara Y, Arakawa T, Inoue M. Production of reactive oxygen species in peripheral blood is increased in individuals with Helicobacter pylori infection and decreased after its eradication. *Helicobacter* 2006; **11**: 266-271 [PMID: 16882330 DOI: 10.1111/j.1523-5378.2006.00410.x]
- 147 **Lazaridou E**, Giannopoulou C, Fotiadou C, Vakirlis E, Trigoni A, Ioannides D. The potential role of microorganisms in the development of rosacea. *J Dtsch Dermatol Ges* 2011; **9**: 21-25 [PMID: 21059171 DOI: 10.1111/j.1610-0387.2010.07513.x]
- 148 **Sharma VK**, Lynn A, Kaminski M, Vasudeva R, Howden CW. A study of the prevalence of Helicobacter pylori infection and other markers of upper gastrointestinal tract disease in patients with rosacea. *Am J Gastroenterol* 1998; **93**: 220-222 [PMID: 9468246 DOI: 10.1111/j.1572-0241.1998.00220.x]
- 149 **Schneider M**, Skinner RBJ, Rosenberg EW. Serological determination of Helicobacter pylori in rosacea patients and in controls. *Clin Res* 1992; **40**: 831A
- 150 **Szlachcic A**. The link between Helicobacter pylori infection and rosacea. *J Eur Acad Dermatol Venereol* 2002; **16**: 328-333 [PMID: 12224687 DOI: 10.1046/j.1468-3083.2002.00497.x]
- 151 **Utaş S**, Ozbakir O, Turasan A, Utaş C. Helicobacter pylori eradication treatment reduces the severity of rosacea. *J Am Acad Dermatol* 1999; **40**: 433-435 [PMID: 10071314]
- 152 **Son SW**, Kim IH, Oh CH, Kim JG. The response of rosacea to eradication of Helicobacter pylori. *Br J Dermatol* 1999; **140**: 984-985 [PMID: 10354058 DOI: 10.1046/j.1365-2133.1999.02852.x]
- 153 **Schmidt-Wilcke T**, Clauw DJ. Fibromyalgia: from pathophysiology to therapy. *Nat Rev Rheumatol* 2011; **7**: 518-527 [PMID: 21769128]
- 154 **Dadabhoy D**, Crofford LJ, Spaeth M, Russell IJ, Clauw DJ. Biology and therapy of fibromyalgia. Evidence-based biomarkers for fibromyalgia syndrome. *Arthritis Res Ther* 2008; **10**: 211 [PMID: 18768089 DOI: 10.1186/ar2443]
- 155 **Buskila D**, Atzeni F, Sarzi-Puttini P. Etiology of fibromyalgia: the possible role of infection and vaccination. *Autoimmun Rev* 2008; **8**: 41-43 [PMID: 18706528 DOI: 10.1016/j.jejr.2013.01.004]
- 156 **Olama SM**, El-Arman M. Helicobacter pylori in Egyptian patients with fibromyalgia syndrome. *Egyptian Rheumatolo-*

gast 2013; **35**: 167-173

- 157 **Akkaya N**, Akkaya S, Polat Y, Turk M, Turk T, Turhal E, Sahin F. Helicobacter pylori seropositivity in fibromyalgia syndrome. *Clin Rheumatol* 2011; **30**: 43-49 [PMID: 21120564]

DOI: 10.1007/s10067-010-1618-9]

- 158 **Malt EA**, Olafsson S, Ursin H. Fibromyalgia A manifestation of Helicobacter pylori infection? *Scand J Rheumatol* 2004; **33**: 131 [DOI: 10.1080/03009740410006826-1468]

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