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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]. Pangastitis 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 Maastricht 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 found such an association with either IR or MS^[70-72]. A meta-analysis 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.

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