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TOPIC HIGHLIGHT

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Helicobacter pylori and autoimmune disease: Cause or bystander

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Abstract

Helicobacter pylori (*H. pylori*) is the main cause of chronic gastritis and a major risk factor for gastric cancer. This pathogen has also been considered a potential trigger of gastric autoimmunity, and in particular of autoimmune gastritis. However, a considerable number of reports have attempted to link *H. pylori* infection with the development of extra-gastrointestinal autoimmune disorders, affecting organs not immediately relevant to the stomach. This review discusses the current evidence in support or against the role of *H. pylori* as a potential trigger of autoimmune rheumatic and skin diseases, as well as organ specific autoimmune diseases. We discuss epidemiological, serological, immunological and experimental evidence associating this pathogen with autoimmune diseases. Although over one hundred autoimmune diseases have been investigated in relation to *H. pylori*, we discuss a select number of papers with a larger literature base, and include Sjögrens syndrome, rheumatoid arthritis, systemic lupus erythematosus, vasculitides, autoimmune skin conditions, idiopathic thrombocytopenic purpura, autoimmune thyroid disease, multiple sclerosis, neuromyelitis optica and autoimmune liver diseases. Specific mention is given to those studies reporting an association of anti-*H. pylori* antibodies with the presence of autoimmune disease-specific clinical parameters, as well as those failing to find such associations. We also provide helpful hints for future research.

Key words: Autoimmunity; *Helicobacter pylori*; Infection; Gastritis; Mimicry; Rheumatology

Core tip: Multiple infectious agents have been implicated in the development of autoimmune disease. *Helicobacter pylori* is one pathogen which has been linked with multiple autoimmune diseases. This review will critically discuss a select few studies which have a larger evidence base, both in terms of positive and negative findings.

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INTRODUCTION

Autoimmune diseases arise from the interaction of genetic susceptibility and environmental exposures[1-4]. Among environmental exposures, infectious triggers have been implicated and studied extensively[1,5]. Infectious agents include bacteria, viruses and parasites, and may also consist of those organisms which comprise the normal flora[5]. Several mechanisms by which infectious agents may cause autoimmune disease have been proposed[6,7]. These include molecular mimicry[8-10], epitope spreading, bystander effect[11,12], microbial super-antigens, immune complex formation[13], MHC class Ⅱ expression on non-immune cells[14], direct inflammatory damage[13], high levels of pro-inflammatory cytokines such as interferon (IFN)-γ[10], and T-regulatory/Th17 imbalance.

Among infectious agents implicated, *Helicobacter pylori* (*H. pylori*) has received particular attention, in that it has been implicated in both organ specific and non-organ specific autoimmune disease[15]. As gastric disease in relation to *H. pylori* has been discussed extensively in multiple reviews and studies[16-18], it will not be discussed in this review. Likewise, multiple other autoimmune conditions have been linked with *H. pylori*, with evidence bases of varying content. In fact, amongst the autoimmune or autoimmune related diseases listed by AARDA (American Autoimmune Related Diseases Association, http://www.aarda.org/), 95 have been studied sporadically or systematically in regard to their connection with *H. pylori*, while among the remaining 61 there are no studies (yet) in Pubmed (search up to 29 September 2013) (Tables 1 and 2). Therefore, this review will discuss selected autoimmune conditions, both organ specific and non-organ specific, which have an evidence base (positive or negative) in relation to *H. pylori* infection. Amongst the non-organ specific autoimmune disorders, we thoroughly discuss immune thrombocytopenic purpura (ITP) and autoimmune rheumatic diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjögren syndrome (SjS), systemic sclerosis (SSc). Amongst the organ specific diseases linked with *H. pylori*, autoimmune thyroid disease (AiTD), and multiple sclerosis (MS)/neuromyelitis optica (NMO) are discussed, as well as autoimmune liver diseases such as primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC) and autoimmune hepatitis (AIH). Although a wealth of literature is available for some conditions, we present selected papers that highlight the current findings, or lack thereof. It will become apparent that the evidence in support of *H. pylori* as a cause of some autoimmune conditions varies from one condition to the next.

POTENTIAL MECHANISMS OF *H. PYLORI*-INDUCED AUTOIMMUNITY

Several mechanisms of pathogen-induced autoimmunity have been described in studies of *H. pylori*-induced autoimmunity[19]. We briefly discuss some of these papers, starting with the study by Jackson and colleagues[20]. These investigators found that chronic *H. pylori* infection was associated with an increased risk of an elevated serum C-reactive protein, indicating an ongoing inflammatory state. This chronic inflammation may result in ongoing antigenic stimulation, and induces a systemic inflammatory response, and therefore extra-gastrointestinal disease[20]. However, such hypotheses are not accompanied by solid experimental data. We need to emphasize that this, as well as most other studies investigating the role of *H. pylori,* speculates rather than demonstrates a pathogenic role for this bacterium. Another study found that molecular mimicry of *H. pylori* antigens activated cross-reactive T cells in autoimmune gastritis[21]. *H. pylori* components (especially urease) have been shown to activate B cells to produce IgM rheumatoid factor, anti-ds-DNA, and anti-phospholipid choline antibodies[22]. The former studies belong to those few (compared to the great majority of the studies) that to some extent provide a mechanistic approach as to how the pathogen can inflict loss of immunological tolerance, which is an important component for the initiation of antigen-driven autoimmunity. Similar mechanisms have been proposed in relation to heat shock protein (hsp) 60[23]. Another piece of evidence which can support the major role of *H. pylori* in the development of autoimmune diseases (and not just in the induction of autoantibodies) stems from studies on animal models of autoimmune diseases. Infection of male C57BL/6 mice with *H. pylori* can induce a disease that resembles human PBC[24]. However, most animal models of autoimmune diseases do not rely on *H. pylori* infection for the induction of the disease or do not provide data to support that this pathogen is needed for disease development. Most of the mechanisms discussed in the literature remain as hypotheses that require more extensive investigation.

H. PYLORI AND AUTOIMMUNE RHEUMATIC DISORDERS

The pathogenetic evidence linking *H. pylori* with autoimmune rheumatic diseases varies amongst diseases. For example, while there are a reasonable number of studies investigating this topic in SjS, the data stemming from SLE are relatively few and inconsistent. There are several explanations that could account for the great variation in the number of the studies conducted amongst diseases. Some studies are rare and translational research is difficult to perform, as in for example the case of SSc. Other diseases do not have reliable animal models, and in these dis-

Table 1 Autoimmune diseases or autoimmune disease-related disorders which have been studied for their possible (direct or indirect) relation with *Helicobacter pylori* infection

	AID or AID-related disorders linked to *H. pylori*		AID or AID-related disorders linked to *H. pylori*
1	Alopecia areata	49	Juvenile diabetes (Type 1 diabetes)
2	Antiphospholipid syndrome	50	Kawasaki syndrome
3	Autoimmune angioedema	51	Leukocytoclastic vasculitis
4	Autoimmune hepatitis	52	Lichen planus
5	Autoimmune hyperlipidemia	53	Linear IgA disease
6	Autoimmune hemolytic anemia	54	Lupus (SLE)
7	Autoimmune myocarditis	55	Microscopic polyangiitis
8	Autoimmune oophoritis	56	Mixed connective tissue disease
9	Autoimmune pancreatitis	57	Mooren's ulcer
10	Autoimmune polyglandular syndromes	58	Multiple sclerosis
11	Autoimmune thrombocytopenic purpura	59	Myositis
12	Autoimmune thyroid disease	60	Narcolepsy
13	Autoimmune urticaria	61	Neuromyelitis optica (Devic's)
14	Axonal and neuronal neuropathies	62	Neutropenia
15	Behcet's disease	63	Ocular cicatricial pemphigoid
16	Bullous pemphigoid	64	Optic neuritis
17	Cardiomyopathy	65	Palindromic rheumatism
18	Celiac disease	66	Pars planitis (peripheral uveitis)
19	Chagas disease	67	Pemphigus
20	Chronic inflammatory demyelinating polyneuropathy	68	Peripheral neuropathy
21	Chronic recurrent multifocal osteomyelitis	69	Perivenous encephalomyelitis
22	Crohn's disease	70	Pernicious anemia
23	Cogans syndrome	71	Polyarteritis nodosa
24	Demyelinating neuropathies	72	Polymyalgia rheumatica
25	Dermatitis herpetiformis	73	Polymyositis
26	Dermatomyositis	74	Primary biliary cirrhosis
27	Devic's disease (neuromyelitis optica)	75	Primary sclerosing cholangitis
28	Eosinophilic esophagitis	76	Psoriasis
29	Eosinophilic fasciitis	77	(Idiopathic) pulmonary fibrosis
30	Erythema nodosum	78	Pyoderma gangrenosum
31	Experimental allergic encephalomyelitis	79	Raynaud's phenomenon
32	Fibromyalgia	80	Reactive Arthritis
33	Fibrosing alveolitis	81	Reiter's syndrome
34	Giant cell arteritis (temporal arteritis)	82	Relapsing polychondritis
35	Giant cell myocarditis	83	Rheumatoid arthritis
36	Glomerulonephritis	84	Sarcoidosis
37	Goodpasture's syndrome	85	Scleroderma (systemic sclerosis)
38	Graves' disease	86	Sjogren's syndrome
39	Guillain-Barre syndrome	87	Temporal arteritis/Giant cell arteritis
40	Hashimoto's thyroiditis	88	Thrombocytopenic purpura
41	Henoch-Schonlein purpura	89	Transverse myelitis
42	Hypogammaglobulinemia idiopathic thrombocytopenic purpura	90	Type 1 diabetes
43	IgA nephropathy	91	Ulcerative colitis
44	IgG4-related sclerosing disease	92	Undifferentiated connective tissue disease
45	Immunoregulatory lipoproteins	93	Uveitis
46	Inclusion body myositis	94	Vasculitis (other forms)
47	Interstitial cystitis	95	Vesiculobullous dermatosis
48	Juvenile arthritis		

The list includes diseases in alphabetic order as they have been deposited in the official website of AARDA (American Autoimmune Related Diseases Association) with minor revisions. Diseases with at least one study (Pubmed Search) investigating *Helicobacter pylori* (*H. pylori*) as a trigger have been included. AID: Autoimmune disease.

orders it has been almost impossible to assess the role of infectious agents in the induction of autoimmunity. Also, for some diseases the prevailing idea amongst researchers has been that *H. pylori* is not an attractive etiologic agent, and this has prevented more research in this topic over the years. Nevertheless, epidemiological, serological and clinical studies have been performed to some extent and are reviewed herein.

Sjögren's syndrome

SjS is an autoimmune condition characterized by lymphoid cell infiltration and destruction of exocrine glands[19]. As lacrimal and salivary glands are most affected, a link with *H. pylori* has been made given its prevalence in the oral cavity[19], which may be associated with anti-*H. pylori* antibodies[25].

Aragon *et al*[23] found that 79.4% of SjS patients had anti-*H. pylori* antibodies, and that 88.2% had anti-hsp60. This was significantly higher than other autoimmune controls (18.2% with anti-*H. pylori*; 27.3% with anti-hsp60), and healthy controls (48.8% anti-*H. pylori*; 37.2% anti-hsp60)[23]. El Miedany *et al*[26] failed to find statistically significant differences in the prevalence of anti-*H. pylori*

Table 2 Autoimmune diseases or autoimmune diseases-related disorders which have not been studied for their possible (direct or indirect) relation with *Helicobacter pylori* infection

	AID or AID-related disorders not linked to *H. pylori*
1	Acute Disseminated Encephalomyelitis
2	Acute necrotizing hemorrhagic leukoencephalitis
3	Addison's disease
4	Agammaglobulinemia
5	Amyloidosis
6	Ankylosing spondylitis
7	Anti-GBM/Anti-TBM nephritis
8	Autoimmune aplastic anemia
9	Autoimmune dysautonomia
10	Autoimmune immunodeficiency
11	Autoimmune inner ear disease
12	Autoimmune retinopathy
13	Balo disease
14	Castleman disease
15	Chronic fatigue syndrome
16	Churg-Strauss syndrome
17	Cicatricial pemphigoid/benign mucosal pemphigoid
18	Congenital heart block
19	Coxsackie myocarditis
20	CREST disease
21	Essential mixed cryoglobulinemia
22	Discoid lupus
23	Dressler's syndrome
24	Endometriosis
25	Evans syndrome
26	Granulomatosis with Polyangiitis (formerly called Wegener's Granulomatosis)
27	Hashimoto's encephalitis
28	Herpes gestationis
29	Juvenile myositis
30	Lambert-Eaton syndrome
31	Lichen sclerosus
32	Ligneous conjunctivitis
33	Lyme disease,
34	(Chronic) Meniere's disease
35	Mucha-Habermann disease
36	Myasthenia gravis
37	Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus
38	Paraneoplastic cerebellar degeneration
39	Paroxysmal nocturnal hemoglobinuria
40	Parry Romberg syndrome
41	Parsonage-Turner syndrome
42	POEMS syndrome
43	Postmyocardial infarction syndrome
44	Postpericardiotomy syndrome
45	Progesterone dermatitis
46	Psoriatic arthritis
47	Pure red cell aplasia
48	Reflex sympathetic dystrophy
49	Restless legs syndrome
50	Retroperitoneal fibrosis
51	Rheumatic fever
52	Schmidt syndrome
53	Scleritis
54	Sperm and testicular autoimmunity
55	Stiff person syndrome
56	Subacute bacterial endocarditis
57	Susac's syndrome
58	Sympathetic ophthalmia
59	Takayasu's arteritis
60	Tolosa-Hunt syndrome
61	Vitiligo

The list includes diseases in alphabetical order as they have been deposited in the official website of AARDA (American Autoimmune Related Diseases Association) with minor revisions. Diseases with at least one study (Pubmed Search) investigating *Helicobacter pylori* (*H. pylori*) as a trigger have been included. AID: Autoimmune disease.

antibodies between patients with primary and secondary SjS (80.6% *vs* 71% for IgG, and 47.2% *vs* 38.7% for IgA, respectively). However, anti-*H. pylori* antibodies were significantly less prevalent in patients with connective tissue disorders lacking sicca syndrome symptomatology (60.9% for IgG and 19.6% for IgM). The lowest prevalence of IgG and IgM anti-*H. pylori* antibodies was found in normal controls (56.3% for IgG and 12.5% for IgM, respectively)[26]. Similar results have been found in further studies[27], but contradictory data have been provided in others[28]. A study by the group of Theander[28] examined the prevalence of *H. pylori* in a Swedish cohort of 164 SjS patients, and found that 45% were seropositive for *H. pylori* infection, including 23% with anti-CagA antibodies. However, these rates were lower than those seen in a control group of orthopedic outpatients without autoimmune conditions, and similar to rates found among healthy individuals[28]. That group therefore concluded that *H. pylori* infection was not linked with SjS[28].

Some studies have attempted to link evidence of *H. pylori* infection with clinical features of SjS. For example, El Miedany *et al*[26] have found that there is a significant correlation between (IgG and IgM) anti-*H. pylori* antibody seropositivity and the presence of primary and secondary SjS, as well as various clinical parameters. Logistic regression analysis has revealed that the presence of IgG anti-*H. pylori* antibodies significantly correlates with age, disease duration and global score for disease status.

Another possible link between SjS and *H. pylori* may be found in mucosa-associated lymphoid tissue (MALT) lymphomas that may arise from chronic antigenic stimulation (*i.e.*, chronic infection and/or autoimmune disease). *H. pylori* was detected in gastric tissue from MALT, and interestingly, there is an increased incidence of MALT lymphomas and marginal zone B cell neoplasms in SjS[29]. It is possible that *H. pylori* eradication in SjS may result in decreased incidence of MALT, as is the case for gastric MALT lymphomas[30-32]. Further studies regarding the prevalence of *H. pylori* in SjS in different populations are currently needed, in addition to monitoring for *H. pylori* in at-risk individuals.

Rheumatoid arthritis

Sir James Paget was one of the very first to consider the possibility that what is now known as rheumatoid arthritis may indeed be caused by microbial infections. In 1853, Paget hypothesized that all diseases that manifest their symptoms symmetrically, such as "the deformities of chronic rheumatism", must be blood-borne and could be caused by a demonstrable virus. *H. pylori* has been considered one of the infectious agents linked to RA; however, the data do not support this. An increased incidence of peptic ulcer disease in RA patients is most likely related to the use of non-steroidal anti-inflammatory drugs[33]. Yamanishi *et al*[22] found increased IgM rheumatoid factor in B cells chronically stimulated with *H. pylori* urease. However, several studies demonstrated that there is a lower prevalence of *H. pylori* in RA patients, and other studies found the prevalence of *H. pylori* to be similar to that of the healthy controls[27,34,35]. After *H. pylori* eradication, no change in RA symptoms was reported by several studies[36-38], although improvement was noted in others[39,40]. Currently, the data are mixed regarding RA and *H. pylori*, and it appears that the link is weak.

Systemic lupus erythematosus

H. pylori prevalence has been studied in patients with SLE, but the results vary amongst reports. A recent study has failed to find significantly higher prevalence of anti-*H. pylori* antibodies in SLE patients compared to controls[41]. Of note, this study showed an increased prevalence of anti-*H. pylori* antibodies in patients with anti-phospholipid syndrome, giant cell arteritis, SSc and PBC[41]. Such findings have also been reported in the past. Kalabay *et al*[42] have studied the prevalence of anti-*H. pylori* antibodies in various autoimmune rheumatic diseases. These authors have found comparable prevalence of this pathogen in patients with SLE and healthy controls (57% *vs* 59%)[42]. The highest prevalence of anti-*H. pylori* antibodies was found in patients with undifferentiated connective tissue disorders (82%)[42]. Of interest, an early study reported a negative association between *H. pylori* seropositivity and the development of SLE in African-American women[43]. In particular, female African-American patients with SLE had a lower prevalence of *H. pylori* seropositivity compared to controls (38.1% *vs* 60.2%). That study also found that seronegative African-American females were more likely to develop SLE, and at an earlier age than their seropositive counterparts[43]. Thus, the mean age of onset for SLE was 34.4 years in the seropositive group and 28 years in the seronegative group. These data suggest that either the presence of the pathogen confers protection from SLE or that the same mechanisms that make individuals prone to *H. pylori* infection also promote the immune dysregulation which is necessary for SLE's induction in African-American females.

Much like RA, the role of *H. pylori* in SLE is also inconclusive. In an animal model, urease exposure induced anti-ssDNA antibody production[22]. However, low anti-*H. pylori* antibodies have been found in SLE patients, with levels comparable to healthy controls[27,43]. Overall, the evidence does not support a role for *H. pylori* in the development of SLE[44].

Systemic sclerosis

Dysregulation of innate and adaptive (humoral and cellular) immunity plays an important role in the induction of SSc[45-47]. The very low concordance rate for SSc in monozygotic twins has led investigators to consider that the pathogenesis of this disease rests more in the effect of environmental factors (including viruses and bacteria) rather than genetic influences[48].

In a Japanese cohort of SSc patients, IgG antibodies against *H. pylori* were found in 55.6% of the patients, a

prevalence significantly higher compared to that in the control group[49]. Another Japanese study found a similar prevalence of these antibodies (57.8%), and also a higher prevalence of reflux esophagitis amongst anti-*H. pylori* antibody-positive patients compared to anti-*H. pylori* antibody-negative patients[50]. Others have also noted an increased rate of *H. pylori* infection in patients with SSc compared to controls[15,23,51,52]. However, a significant number of studies has failed to find an increased prevalence of *H. pylori* seropositivity compared to control groups, further indicating the lack of conclusive data regarding the extent by which *H. pylori* confers susceptibility to SSc[53-56].

Of clinical relevance, early data have indicated that *H. pylori* eradication improves Raynaud's phenomenon in patients with SSc[57,58]. Another study has noted that skin involvement appears to be a predominant feature of *H. pylori*-infected SSc patients compared to their seronegative counterparts. No other clinical parameters, including the distribution of sex, age, disease duration, autoantibody profile, estimated pulmonary artery systolic pressure, hemoglobin, ESR, renal and liver function indices were different between *H. pylori*-infected or non-infected SSc patients[59]. On the other hand, SSc patients with Barrett's esophagus appear less likely to be *H. pylori*-positive compared to SSc patients without Barrett's esophagus (10% *vs* 42.5%). Such findings have underlined the potential protective role of *H. pylori* for the development of Barrett's esophagus[60]. In pathophysiological terms, the results of the data discussed so far could be interpreted as follows: (1) *H. pylori*-infected patients are more prone to develop SSc; (2) SSc patients are more susceptible to infection by *H. pylori*, probably due to the disturbed gastrointestinal motility which is a characteristic feature of SSc; and (3) after the development of SSc (probably caused by reasons other than H pylori), infection with the pathogen protects the affected patients from unwanted complications (such as Barrett's esophagus).

Danese *et al*[56] have tackled the topic from another corner. While they failed to find a difference in the prevalence of the pathogen between SSc patients and controls, they reported that 90% of the *H. pylori*-positive SSc patients were infected with the virulent CagA strain compared to just 37% of the non-CagA seropositive controls. Elevated levels of anti-hsp65 (but not of anti-hsp60) *H. pylori* antibodies have been found in SSc patients compared to controls[42].

Vasculitides

Data on the potential link between *H. pylori* and vasculitides are very limited. For example, we know very little about the role of this pathogen in granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis. A serological study has shown that anti-*H. pylori* antibodies are more prevalent in GPA compared to controls[61]. Such findings may be of biological significance as *H. pylori* has been considered a potential trigger of vascular inflammation. Thus, the SS1 strain of *H. pylori*-infected heterozygous low density-lipoprotein receptor (LDLR)+/- apoE apolipoprotein E (apoE)+/- mice develop autoimmune inflammation, platelet activation and atherosclerosis[62]. A role for the pathogen in atherosclerosis and vasculitis has been suggested but there is no general agreement on this issue[63]. A previous report was unable to identify significant differences in the rate of anti-*H. pylori* antibodies between patients with GPA and control diseases[64]. The study by Lidar *et al*[61] failed to find any association between anti-*H. pylori* antibody seropositivity in healthy controls and polyarteritis nodosa, microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis (EGPA), also known as Churg Strauss syndrome, and giant cell arteritis[61].

Another study reported disappearance of antiphospholipid syndrome after *H. pylori* eradication[65], but data are too limited on the issue to draw any conclusions.

IMMUNE-MEDIATED SKIN DISORDERS

H. pylori infection has been considered a potential inducer of several immune-mediated skin disorders. These disorders can be manifestations of systemic vasculitides (Behçet's disease) or may be related to skin disorders with presumed autoimmune origin (psoriasis, alopecia areata, lichen planus, *etc.*). Due to space constraints, this review will discuss the role of *H. pylori* in selected skin disorders including psoriasis, alopecia areata and Behçet's disease. Other skin disorders linked to *H. pylori* include, amongst others, atopic dermatitis, chronic or nodular prurigo, recurrent aphthous stomatitis, rosacea, chronic urticaria, lichen planus, and Sweet's syndrome, and are reviewed elsewhere[66]. We will also discuss the link between *H. pylori* and chronic urticaria, as a plethora of data have been obtained and the outcomes of these studies are extremely helpful for the understanding of the interactions between the pathogen and the host.

Psoriasis

Psoriasis affects 1%-3% of Caucasians. The etiology of the disease remains poorly understood, although immune-mediated mechanisms appear to play a significant role in the development of the disease, including exposure to particular pathogens.

To this end, several studies have investigated a possible link between *H. pylori* and psoriasis[67-74].

Anti-*H. pylori* antibodies have been reported to be more prevalent in psoriatic patients compared to controls. For example, Qayoom *et al*[72] have reported that 40% of psoriatic patients and only 10% of healthy controls (all without known upper gastrointestinal symptoms) had anti-*H. pylori* antibodies. However, other studies have failed to find any difference in the prevalence of *H. pylori*[70].

A large study from Turkey, investigating 300 psoriatic patients and 150 controls, has reported comparable prevalence of *H. pylori* infection in patients and controls.

However, the same study suggested that *H. pylori* status relates to clinical parameters[75], as it was able to show that patients lacking *H. pylori* had less severe psoriatic disease compared to the seropositive cases. Also, all patients with moderate or severe psoriasis were *H. pylori*-positive. Intriguingly, patients treated for both psoriasis (with acitretin) and for *H. pylori* (eradication therapy) showed more rapid improvement of the skin disease, compared to those treated with acitretin only. Notably, psoriasis was also improved in patients receiving only eradication treatment[75]. This study confirmed anecdotal reports or case studies showing that eradication therapy improves psoriasis[73,76].

Strains of *H. pylori* that express the cytotoxin-associated gene A (CagA) have been associated with a more virulent disease and are believed to play an important role in the clinical outcome of the infection. Several authors have considered that links between the pathogen and autoimmunity may differ in accordance to the virulence of the infecting strain. This has also been the case for *H. pylori* and psoriasis. To this end, Daudén *et al*[68] were unable to find any difference in terms of CagA seropositivity between psoriatic patients and patients with non-ulcer dysplasia (54.5% *vs* 68.1%, respectively).

Chronic urticaria

The pathogenic role of *H. pylori* infection has been extensively studied in chronic urticaria. Though this disease cannot be considered a typical autoimmune disease, it is of interest to discuss the findings provided so far, as these may help us understand the role of this pathogen in the development of immune-mediated pathologies. Investigations have not been limited to the prevalence of infection[66], but have been extended to include the role of eradication therapy in the clinical course of chronic urticaria[77-86]. Selected papers give us an insight into the extent by which the pathogen and its eradication influence the clinical outcome of the disease. For example, recurrence of urticaria following re-infection by *H. pylori* has been reported[87]. On the other hand, chronic urticaria has also been described upon administration of eradication therapy for *H. pylori* infection[79]. Nevertheless, some patients with chronic spontaneous urticaria are resistant to conventional doses of antihistamine medications. A subgroup of those (approximately 28%) receiving both eradication therapy and antihistamines show significant decrease of the Urticaria Activity Score and complete loss of their urticaria symptoms, suggesting that treatment for *H. pylori* makes these patients less resistant to antihistamines[77]. These findings are in agreement with other studies reporting an overall improvement of chronic urticaria following administration of eradication therapy for *H. pylori*[88-90]. Other studies have failed to find any relationship between eradication therapy and clinical phenotypes[91]. Of interest, a recent comprehensive review utilized the Grading of Recommendations Assessment, Development, and Evaluation approach to analyze and determine the quality of evidence for this proposed therapy. Their analysis has included 10 trials showing a benefit and 9 trials failing to report a benefit of *H. pylori* eradication therapy. This analysis reached the conclusion that the evidence provided so far that *H. pylori* eradication leads to improvement of chronic urticaria outcomes is weak and conflicting. Negative studies showing no benefit in the course of chronic urticaria also led to an overall very low grade of confidence. *H. pylori* virulent genotypes in the urticaria patients do not appear to affect the clinical course of the disease[92].

Behçet's disease

The role of *H. pylori* infection in Behçet's disease (BeD) remains controversial[93-95]. Most studies originate from Turkey, a country with a high incidence of BeD. Avci *et al*[95] have failed to find an association between *H. pylori* and BeD. Other studies published in the form of abstracts or in Turkish journals have published inconsistent results reporting comparable or higher prevalence rates of *H. pylori* infection in patients with BeD[93]. One study also from Turkey reported an increased seropositivity of *H. pylori* cytotoxin-associated gene-A in patients with BeD[96].

Improvement of BeD features in patients receiving eradication therapy has also been reported[95], and includes improvements in the cutaneous lesions, arthritis/arthralgia and oral or genital ulcers. The limited number of studies prevents safe conclusions as to the potential links.

Alopecia areata

AA is an immune-mediated disorder characterized by hair loss. The disease affects all ethnic groups, ages, and both sexes. Attempts to investigate the role of *H. pylori* in this disease have been very few and led to inconclusive results[97,98]. Seroprevalence rates of *H. pylori* infection in patients with AA are increased or not compared to controls[97,99]. Eradication of *H. pylori* in AA has also been proposed[100], but not studied extensively.

IMMUNE THROMBOCYTOPENIC PURPURA

ITP may occur by itself (idiopathically) or secondary to another condition, including autoimmune conditions (namely AiTD, SLE, anti-phospholipid syndrome). Although the prevalence of *H. pylori* in ITP patients has been found to be similar to controls[101], improvements in platelet counts following *H. pylori* eradication have been reported[102-107]. Suzuki *et al*[106] reported that the platelet response was more pronounced in those patients with the CagA-positive *H. pylori* strain. Interestingly, anti-CagA antibodies cross-react with peptides expressed on platelets of ITP patients[108]. These findings have led to the suggestion of eradication of *H. pylori* for the treatment of ITP[109]. Takahashi *et al*[110] reported that platelet-associated IgG declined after *H. pylori* eradication, as did

molecular mimicry with the CagA region. In that study, *H. pylori* was found in 75% (15 of 20 patients) of ITP patients of Japanese descent, and eradicated in 87% (13 of 15)[110]. Increased platelet count was observed in 54% (7 of 13) of patients within four months of eradication[110]. Over a dozen other studies have also indicated an improvement in platelet count following *H. pylori* eradication, and are well-reviewed by Hernando-Harder and colleagues[66]. Platelet eluates from 12 ITP patients recognized *H. pylori* CagA, although it should be noted that three of the 12 patients were seronegative for *H. pylori* infection[110]. Levels of anti-CagA antibodies declined in three patients following *H. pylori* eradication. This latter result suggested a role for cross-reactivity and molecular mimicry[110].

The role of molecular mimicry and cross reactivity between *H. pylori* components and self-peptides is not new, as antibodies against the H/K-ATPase in the gastric mucosa have been found to be generated *via* molecular mimicry with *H. pylori* in atrophic gastritis[111]. Molecular mimicry has been considered a mechanism that could explain other *H. pylori*-induced autoimmune phenomena, but very few studies have addressed this in an experimental way. The role of CagA strains is also under investigation in other conditions[112,113].

AUTOIMMUNE THYROID DISEASE

A larger amount of data links *H. pylori* infection with AiTD, and in particular with Graves' disease[114]. Bassi and colleagues[115] aimed to correlate the CagA strain of *H. pylori* with AiTD by investigating 112 consecutive patients at first diagnosis of AiTD. Those researchers tested for *H. pylori* in stool samples (to confirm ongoing infection), and CagA in serum samples. *H. pylori* and Graves' disease were associated (83.7% patients were *H. pylori* seropositive). No association was found with Hashimoto's thyroiditis[115]. Most patients (89.2%) seropositive for *H. pylori* were infected with the CagA strain[115]. This was in accordance with a previous study by the same group[116]. Negative findings in regard to Hashimoto's were reported in other studies[103,117], while some reported a positive association[114,118,119].

Cross-reactivity between bacterial and thyroid antigens has been proposed as a mechanism in *H. pylori*-induced AiTD[120]. Indeed, amino acid sequence similarities between CagA *H. pylori* and thyroid peroxidase have been reported[121], and one group described a reduction in thyroid autoantibodies following *H. pylori* eradication[122]. Larizza *et al*[123] suggests that *H. pylori* may induce or worsen Graves' disease in patients carrying HLA-DRB10301, and further suggested eradication in certain risk groups. These findings do suggest a possible causative link between the CagA strain of *H. pylori* and the development of Graves' disease, but deserve further research. It should be noted that AiTDs are often found concomitantly with other autoimmune conditions, and that the link between the pathogen and autoimmune thyroiditis may indeed reflect a potential contribution of *H. pylori* in the simultaneous induction of multiple autoimmune diseases in susceptible individuals[124]. The exact mechanisms by which exposure to a microbe elicit more than one autoimmune manifestations are not well defined but cross-reactive responses against a microbial mimic and several self-antigens have been documented[125-127], and may account for this. The reverse is also possible, whereby an autoepitope is cross-reactively targeted by several unrelated microbial mimics in a "multiple hit" scenario[128,129].

MULTIPLE SCLEROSIS AND NEUROMYELITIS OPTICA

H. pylori infection has been considered the likely trigger of various neurological disorders of the central nervous system including MS/NMO, Alzheimer's disease, Parkinson's disease, seizure disorders, cerebrovascular diseases, mild cognitive impairment, migraine and ophthalmic disorders, as reviewed elsewhere[130]. A large amount of data has been reported regarding *H. pylori* and MS/NMO. A recent study by Long *et al*[131] determined *H. pylori* infection status in a cohort of 2 NMO patients, 17 at high risk of NMO, 42 MS and 27 healthy controls. *H. pylori* antibodies were found in 90.4% NMO, 95.8% high-risk NMO, 73.8% MS, and 59.3% controls[131]. There was no statistically significant difference between the MS and control group ($P = 0.726$)[131]. Interestingly, 93% of patients with aquaporin-4 antibodies were also seropositive for *H. pylori*[131]. Yoshimura *et al*[132] analyzed 116 NMO patients for various antibodies to infectious agents, as well as for seropositivity for aquaporin-4 antibodies. They found that *H. pylori* infection was associated with anti-aquaporin-4 antibody positivity[132]. Similar findings were also reported in other studies[133-135].

Several studies found a lower prevalence of *H. pylori* amongst MS patients compared to controls. Mohebi and colleagues noted a lower prevalence of *H. pylori* in a cohort of MS patients[136], in a study which analyzed 163 MS patients and 150 controls for anti-*H. pylori* IgG and IgM. Seropositive *H. pylori* patients had a lower MS incidence and fewer neurological complications[136]. Wender also noted a lower anti-*H. pylori* prevalence in MS *vs* controls[137]. Li *et al*[138] evaluated 105 MS patients and 85 controls for antibodies against *H. pylori* in sera. The MS group was sub-divided into 52 opticospinal MS and 53 conventional MS. In the conventional MS group, 22.6% of patients were positive for anti-*H. pylori*, compared to 51.9% of opticospinal MS and 42.4% of controls[138]. These data suggest a potential link between NMO and *H. pylori*, although this does not appear to be the case in MS.

AUTOIMMUNE LIVER DISEASES

Some *Helicobacter* species, including *H. hepaticus*, *H. pul-*

lorum and *H. billis*, are more bile-tolerant compared to *H. pylori*, and can survive in very low concentrations in human bile[139]. This finding has prompted investigators to consider that *Helicobacter* species other than *H. pylori* are potential inducers of hepatocyte and biliary epithelia cell autoimmunity. Nevertheless, studies have addressed the role of *H. pylori* in autoimmune liver diseases, and provided interesting data.

The role of *H. pylori* has been studied mainly in PBC, an autoimmune cholestatic liver disease characterized by the immune-mediated destruction of small intrahepatic bile ducts. Some studies have also been conducted in PSC, another autoimmune cholestatic disease affecting the larger bile ducts. Studies on the role of this pathogen in the induction of AIH, an autoimmune liver disease affecting hepatocytes, are very limited.

Primary Biliary Cirrhosis

Tanaka *et al*[140] have failed to detect *H. pylori* in liver tissues from patients with PBC. Others have been able to detect *H. pylori* in PBC livers, although this was in a minority of samples tested[140].

Researchers have assessed the seroprevalence of *H. pylori* in PBC and identified significant differences amongst patients and controls[15]. For example, Shapira *et al*[41] reported anti-*H. pylori* antibodies in 54% of patients with PBC compared to 31% ($P < 0.01$) of patients with other conditions, while Tanaka *et al*[140] have failed to find any differences between patients and demographically-matched controls (51% *vs* 46%, respectively).

Our group has assessed the role of molecular mimicry between *H. pylori* and PBC-specific autoantigens and identified through database searches a significant amino acid sequence similarity between the major mitochondrial autoepitopic region from pyruvate dehydrogenase complex E2 subunit and urease beta of *H. pylori*[141]. However, we have failed to find any evidence of immunological cross-reactivity at the B-cell level[141]. We also tested the identified mimics as targets of CD4 T-cell responses, and we did not find any significant T-cell recognition[142]. In a subsequent study, we investigated the potential role of cross-reactive antibodies against *H. pylori* VacA antigen and human PDC-E2, but the results were also negative, clearly demonstrating that these two *H. pylori* antigens are unlikely candidates as cross-reactive targets in molecular mimicry mechanisms involved in PBC[143].

Primary Sclerosing Cholangitis

An early study in Scandinavian PSC patients indicated detectable *H. pylori* DNA in livers from patients with PSC and other liver diseases[140]. This has promoted a series of subsequent studies investigating the role of *Helicobacter* species in PSC and other autoimmune liver diseases. Krasinskas *et al*[144] detected *Helicobacter* DNA in 9 of 56 (16%) PSC patients by 16SrRNA PCR, including 7 (12.5% of the total), in whom there was evidence of *H. pylori* CagA by PCR. Recent PCR analyses have indicated that *H. pylori* or other *Helicobacter* species can be detected in up to 13% of liver tissue specimens from pediatric patients with autoimmune sclerosing cholangitis (an autoimmune form of PSC firstly noted in children) and AIH[145]. The same authors detected in the past *H. pylori* (but not other *Helicobacter* species) in liver tissues from PBC and adult PSC patients[140].

As PSC patients frequently suffer from ulcerative colitis, it has been hypothesized that alteration in the gut flora due to UC-related intestinal inflammation may promote gut translocation of *Helicobacter* to the liver. Gut translocation of pathogens appears an attractive mechanism for the induction of liver autoimmunity and there are some data in support of its validity[146,147].

The prevalence of anti-*H. pylori* antibodies does not differ between pediatric PSC patients (6.6%) and controls (4%-10% depending on the age)[145]. In fact, an increased prevalence of antibodies against non-gastric anti-*H. pylori* antibodies has been noted in patients with autoimmune liver diseases[148].

Autoimmune Hepatitis

The prevalence of anti-*H. pylori* antibodies does not appear to differ between patients with AIH (pediatric or adult) and controls[149-151]. Also, *H. pylori* DNA can be found in a minority of liver tissue samples from patients with AIH with no difference between patients and controls. Currently, there is insufficient evidence to link *H. pylori* with AIH.

UNMET CHALLENGES AND EXPERIMENTAL DOWNSIDES

The role of infectious agents in the development of autoimmune disease has been studied extensively. *H. pylori* is included among those organisms that have been investigated, although findings vary from one condition to the next. Large amounts of data suggest a plausible link with AiTD, NMO, ITP and psoriasis. Less evidence is present regarding RA, SLE, BeD, PBC, AIH and MS. There is inconclusive evidence regarding SjS, SSc, PSC and AA. Table 3 gives an overview of the major findings in support or against the implication of *H. pylori* in the development of these diseases.

Idiopathic diseases with an autoimmune component have been the focus of investigation in regard to the role of *H. pylori*. For example, an autoimmune form of idiopathic dysrhythmias has been linked specifically with CagA and VacA-positive *H. pylori* strains[152]. This indicated the potential of the pathogen to be linked with conditions now considered "idiopathic". Also, parasitic diseases such as the *Trypanosma cruzi*-induced Chagas disease need to be revisited, especially under recent developments showing not only that a proportion of these patients present with autoimmune features but also because such patients are also co-infected with *H. pylori* strains[153]. In addition, other conditions that are now considered to

Table 3 Evidence in support or against the role of *Helicobacter pylori* in autoimmune disease

Autoimmune condition	Evidence in support and/or against the role of *H. pylori*	Overall opinion
SjS	Support: Oral cavity populated with *H. pylori* Higher level of anti-*H. pylori* antibodies in SjS patients Increased incidence of mucosal associated lymphoid tissue and lymphomas in parotid and lacrimal glands of SjS patients Against: Low levels of anti-*H. pylori* antibodies in SjS patients compared to controls	Inconclusive
SSc	Support: Higher incidence of *H. pylori* antibodies in SSc patients than controls *H. pylori* eradication improves Raynaud's in SSc patients Possible protective role against Barrett's esophagus Higher level of CagA strain *H. pylori* infected patients Against: Low incidence of anti-*H. pylori* antibodies compared to controls	Inconclusive
RA	Support: Increased rheumatoid factor IgM from B cells chronically stimulated with *H. pylori* urease Against: Low prevalence of anti-*H. pylori* in RA patients Unchanged clinical course or symptomatology after *H. pylori* eradication	Unlikely
SLE	Support: *H. pylori* urease exposure induced anti-ssDNA antibody production in an animal model of SLE Against: Low levels of anti-*H. pylori* found among SLE patients, at levels comparable to controls Negative association between *H. pylori* seropositivity and the development of SLE in African-American women	Unlikely
ITP	Support: Improvement of platelet counts following *H. pylori* eradication (CagA type *H. pylori* in particular) Anti-CagA antibodies cross-react with peptides on platelets of ITP patient Platelet associated IgGs declined following *H. pylori* eradication Found in high prevalence in some ITP cohorts Platelet eluates from ITP patients recognize *H. pylori* CagA Against: Low levels of *H. pylori* found in ITP patients	Probable
AiTD	Support: Higher seropositivity and positive stool cultures for *H. pylori* in Graves' disease patients CagA strain predominant among Graves' disease patients Amino acid similarities between CagA and thyroid peroxidase Reduction in anti-thyroid antibodies following *H. pylori* eradication Against: Low levels of infection among Hashimoto's thyroiditis patients	Probable in Graves' disease Unlikely in Hashimoto's thyroiditis
MS and NMO	Support: High rate of *H. pylori* infection among NMO patients Correlation between *H. pylori* infection and presence of aquaporin-4 antibodies Against: *H. pylori* infection rates in MS patients similar to or lower than control groups	Probable in NMO Unlikely in MS
Psoriasis	Support: Higher levels of anti-*H. pylori* antibodies in patients Appears to be correlation between *H. pylori* infection and disease severity Clinical improvement following *H. pylori* eradication Against: No difference in anti-*H. pylori* levels compared to controls No difference of CagA seropositivity between patients and controls	Probable
Behçet's disease	Support: Higher infection prevalence in patients Some clinical improvement noted after eradication Against: No difference between patients and controls	Unlikely
Alopecia areata	Support: Higher infection prevalence Against: No difference in infection prevalence between patients and controls	Unlikely

PBC	Support: Higher prevalence of anti-*H. pylori* antibodies among PBC patients Amino acid similarities between pyruvate dehydrogenase E2 (PDC-E2) and urease beta of *H. pylori* Against: No differences of infection found between patients and controls No immunological cross reactivities at the B or CD4 T-cell level No crossreactivity between *H. pylori* VacA and PDC-E2	Unlikely
AIH	Support: No current evidence Against: No differences in anti-*H. pylori* antibodies between patients and controls No significant difference between *H. pylori* in liver tissues in patients compared to controls	Unlikely
PSC	Support: Detectable *H. pylori* DNA in PSC liver samples CagA in samples from PSC patients Concomitant ulcerative colitis may be related to *H. pylori* translocation from the gut to the liver Against: No difference in *H. pylori* prevalence among pediatric or adult PSC patients compared to controls No significant difference between *H. pylori* in liver tissues in patients compared to controls	Unlikely

Helicobacter pylori (*H. pylori*) has been implicated in the development of several autoimmune diseases. This table summarizes some of the evidence in support or against this hypothesis in various autoimmune diseases. Overall opinions reflect an inconclusive evidence base, those which are unlikely, and those which have a relatively strong or strong (probable) evidence base. SjS: Sjogren's syndrome; SSc: Systemic sclerosis; RA: Rheumatoid arthritis; SLE: Systemic lupus erythematosus; ITP: Immune thrombocytopenic purpura; AiTD: Autoimmune thyroid disease; MS: Multiple Sclerosis; NMO: Neuromyelitis optica; PBC: Primary biliary cirrhosis; AIH: Autoimmune hepatitis; PSC: Primary sclerosing cholangitis.

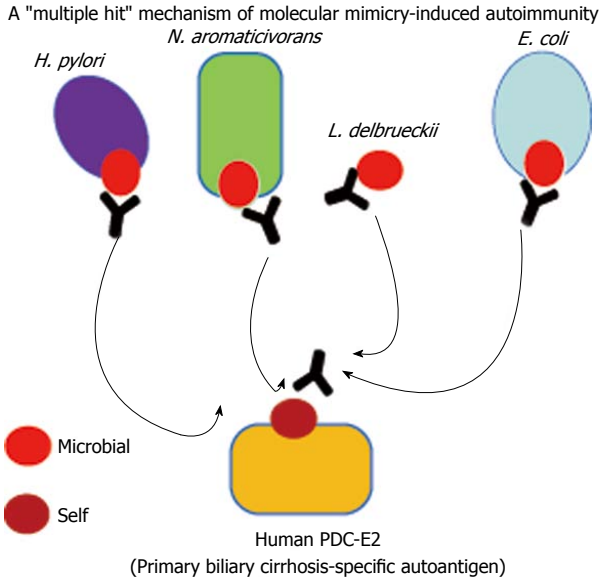

Figure 1 A "multiple hit" molecular mimicry mechanism involving microbial mimics originated from *Helicobacter pylori* and other microbes linked with primary biliary cirrhosis. The major autoepitope of primary biliary cirrhosis-specific anti-mitochondrial antibodies (PDC-E2, pyruvate dehydrogenase complex) shares amino acid similarities with 4 microbial mimics from *Helicobacter pylori* (*H. pylori*)[142], *N. aromaticivorans*[154], *L. delbrueckii*[155,156], and *E. coli*[140,157,158]. The working hypothesis is that exposure of susceptible individuals to infections caused by these microbial agents will initiate humoral and cellular immune responses against microbial epitopes (in our case, these will be those sharing similarity with the self-epitope). Antibodies or T-cells against the microbial mimics may then cross-react with the human autoepitope initiating an autoreactive immune response which could lead to the induction of cellular damage and the perpetuation of autoimmunity (and can cause autoimmune disease). Experimental data so far provided demonstrate the existence of cross-reactive responses between self and microbial peptides from *E. coli, N. amoraticivorans,* and *L. delbrueckii.* However, experimental testing has shown that the *H. pylori* mimic (from urease beta) is not a target of cross-reactive responses specifically present in primary biliary cirrhosis[159]. The prevailing notion is that the mimic from *H. pylori* does not share amino acid similarity to an extent that could initiate cross-reactive response. On the contrary, the other microbial mimics have sufficient homologies with the human autoepitope and can promote molecular mimicry-based immune responses against self.

be autoimmune (such as chronic fatigue syndrome) have not been evaluated for *H. pylori* involvement.

H. pylori is one of the very few infectious agents (along, for example, with Epstein-Barr virus) that have been considered a common denominator in more than 30 autoimmune disorders (Figure 1). Most research in this area has been limited to serological studies investigating two main topics: first, the prevalence of *H. pylori* in the disease under investigation *vs* the control groups; and second, the extent by which *H. pylori* eradication improves the symptomatology of the patients. However, both approaches suffer from conceptual and design constraints. For example, serological studies investigating the prevalence of anti-*H. pylori* antibodies in patients and controls have so far provided discrepancies. Demographic details which are known to affect *H. pylori* status must also be taken into account in cohort selection. This approach will help us to understand whether *H. pylori* infection predisposes to (or protects from) the development of specific autoimmune diseases. Also, the fact that the prevalence of *H. pylori* infection does not differ amongst diseases and control groups does not necessarily mean that this pathogen does not play an important role in the development of immune-mediated disease. Thus, several investigators have considered that it is not the infection per se but the ability of susceptible individuals to mount an immune response against hsps or other immunologically-important *H. pylori* antigens that plays a permissive role in the loss of immunological tolerance to self-antigens. A possibility also exists that the pathogen exerts its pathogenic effects in a "hit-a-run" scenario, (*i.e.*, long after the inflammation caused by the original infection). This could make it almost impossible to link the disease with the microbe in

biological material from individuals already suffering from the disease and its unwanted complications. Longitudinal studies enrolling patients at very early stages of the disease may help us to address this issue. For example, relevant autoantibodies may appear years before clinical manifestations of RA or SLE present. Researchers must also take into account reports indicating that infection with this pathogen may indeed confer protection rather than susceptibility to the development of autoimmunity.

Another topic which needs to be addressed is that the eradication of other autoimmune disease-relevant microbial agents is responsible for the improvement of symptoms of the patients receiving eradication therapy for *H. pylori*. In addition, *H. pylori* eradication may alter the microbiome status of the infected individuals, possibly promoting the persistence of potent infectious inducers of autoimmunity[5]. An immunosuppressive effect of medication may be another possibility. These hypotheses need to be addressed experimentally. Also, work on animal models of diseases and the role of infection with this pathogen are scarce. It is therefore apparent that the role of *H. pylori* in the development of autoimmune disease needs further research, as positive findings may indicate the need for eradication of the pathogen to alter the clinical course, or prevent autoimmune disease in those at risk.

In conclusion, *H. pylori* remains one of the most attractive candidate pathogens that could trigger autoimmunity. The ubiquitous nature of this pathogen may explain why it has been implicated in a large number of autoimmune conditions. There is no doubt that more basic work in immunological aspects of the microbial-host interactions is needed to address the pathogenic role of this multi-faceted pathogen.

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