U.PORTO

MESTRADO INTEGRADO EM MEDICINA

The Impact of Pediatric *Helicobacter pylori* Infection in Allergy and Immunity

Ema Rafaela dos Santos Campo

M

2025

The Impact of Pediatric *Helicobacter pylori* Infection in Allergy and Immunity

Ema Rafaela dos Santos Campo

up201905841@up.pt

Mestrado Integrado em Medicina

Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto

Orientadora:

Dra. Marta Daniela Brandão Lopes Tavares

Assistente Graduada de Pediatria, Unidade de Gastroenterologia Pediátrica do Centro Materno-Infantil do Norte Albino Aroso

Coorientadora:

Prof. Ermelinda Ramalho Santos Silva

Professora Convidada Associada do Instituto de Ciências Biomédicas Abel Salazar

Assistente Graduada de Pediatria, Unidade de Gastroenterologia Pediátrica do Centro Materno-Infantil do Norte Albino Aroso

Junho, 2025

Porto, Junho de 2025

Assinatura digital – Ema Rafaela dos Santos Campo

Assinado por: **Ema Rafaela dos Santos Campo**
Num. de Identificação: 14523082
Data: 2025.06.08 11:09:58 +0100

Assinatura digital – Doutora Marta Daniela Brandão Lopes Tavares

Assinado por: **Marta Daniela Brandão Lopes Tavares**
Num. de Identificação: 09912701
Data: 2025.06.08 10:55:40+01'00'

Assinatura digital – Professora Ermelinda Ramalho Santos Silva

Assinado por: Ermelinda Ramalho Santos Silva
Identificação: BI06531542
Data: 2025-06-07 às 20:48:51
Local: Porto

Dedicatória

Dedico este trabalho a todos os que me ensinaram que por vezes, quando tropeçamos nos nossos atacadores, é melhor parar e reatá-los, para seguirmos em frente.

Obrigada ao meu pai e à minha mãe pelo apoio inabalável e incondicional.

Obrigada à Carla e à Lúcia, por me terem acolhido e serem minhas irmãs, talvez não de sangue, mas em tudo o resto que verdadeiramente importa.

Obrigada ao Marco, que é a prova que os grandes amigos se podem formar numa milésima de segundo.

Obrigada à Xana, à Ana Rita, à Lara e à Inês por serem a prova que o mundo ainda tem belas almas, que por ele deambulam.

E por fim, obrigada ao Vader e ao Júnior, os meus companheiros de quatro patas, cuja companhia é um bálsamo para todos os males.

Resumo

Introdução: Há muito tempo que se coloca a hipótese de a infeção por Helicobacter *pylor*i (Hp) poder desempenhar um papel protetor contra algumas doenças alérgicas e imunes. O principal objetivo desta revisão sistemática é rever a literatura disponível para tentar encontrar um consenso nesta temática.

Métodos: Artigos publicados nos últimos dez anos, no que concerne a Hp, Asma, Doença Celíaca (CeD), Esofagite Eosinofílica (EoE), Alergia Alimentar (FA), Doença Inflamatória Intestinal (IBD) e outras doenças alérgicas, imunes e atópicas foram coletados de três bases de dados distintas, dos quais 27 foram incluídos. Estes artigos, foram sujeitos a uma análise de acordo com a ferramenta QUADAS-2 para determinar o risco de viés. A informação pertinente foi retirada de cada artigo para servir o propósito desta revisão.

Resultados: Dos 27 artigos, 12 eram de asma, 8 de CeD, 2 de EoE, 3 de FA, 5 de IBD e 5 sobre outras patologias. Para a asma averiguou-se uma tênue inclinação para uma relação inversa. Para IBD, os resultados estavam divididos de forma similar entre relação inversa e ausência de relação. Para as restantes patologias não se verificou uma tendência predominante.

Conclusão: A presente revisão apenas encontrou uma ligeira associação inversa entre infeção por Hp e Asma e resultados equitativamente repartidos entre ausência de relação e relação inversa. Para as restantes patologias analisadas, não se verificou uma tendência predominante, o que parece estar de acordo com a literatura atual.

Abstract

Introduction: It has long been hypothesized that Helicobacter *pylori* (Hp) infection might play a protective role on allergic and immune diseases. The main goal of this systematic review is to analyze the present literature and try to find a consensus on this relation.

Methods: Articles from the past ten years, regarding Hp and Asthma, Celiac Disease (CeD), Eosinophilic Esophagitis (EoE), Food Allergy (FA), Inflammatory Bowel Disease (IBD) and other diseases on the allergic, immune and atopic spectrum were retrieved from three separate databases, from which 27 were included. The 27 articles were submitted through QUADAS-2 analysis to determine the risk of bias. From each article the pertinent information was retrieved to fit the purpose of the review.

Results: From 27 articles included in the review, 12 were pertaining to asthma, 8 to CeD, 2 to EoE, 3 to FA, 5 to IBD and 5 to other miscellaneous conditions. For asthma, we noted a faint majority of articles found an inverse relation and for IBD there seemed to be a split result between inverse relation and no relation. Other conditions analyzed showed no clear trend.

Conclusion: This review only found a slight inverse relation between Hp infection and asthma, and split results between no relation and inverse relation in IBD. For the other analyzed conditions, no clear trend was observed, which seems to match the available literature, so far.

List of Abbreviations

AD – Atopic Dermatitis
AR – Allergic Rhinitis
BabA – Blood Group Antigen-Binding Adhesion
CagA – Cytotoxin Associated Gene A
CAI – Clinical Activity Index
CD – Crohn's Disease
CeD – Celiac Disease
CU – Chronic Urticaria
EoE – Eosinophilic Esophagitis
ESS – Endoscopic Severity Score
FA – Food Allergy
FC – Fecal Calprotectin
GATA-5 – GATA Binding Protein 5
Hp – *Helicobacter pylori*
HSP – Henoch Schönlein Purpura
IBD – Inflammatory Bowel Disease
IFN-γ – Interferon gamma
Ig – Immunoglobulin
IL-10 – Interleukin 10
IL-4 – Interleukin 4
IL-5 – Interleukin 5
miRNA – MicroRNA
NAP – Neutrophil Activating Protein
NARES – Nonallergic Rhinitis with Eosinophilia Syndrome
O.R. – Odds Ratio
PCDAI – Pediatric Crohn's Disease Activity Index
PUCAI – Pediatric Ulcerative Colitis Activity Index
Rc – Rhino conjunctivitis
SES-CD – Simple Endoscopic Score for Crohn's Disease
sIgG – Specific Immunoglobulin G
sIgG4 – Specific Immunoglobulin G4
SAT – Stool Antigen Test
TGT IgA– IgA Anti-Transglutaminase antibody
Th1 – T helper 1
Th17 – T helper 17
Th2 – T helper 2
Treg – Regulatory T cells
UBT – Urea Breath Test
UC – Ulcerative Colitis
UCEIS – Ulcerative Colitis Endoscopic Index of Severity
VacA – Vacuolating Toxin A
WA – Wheat Allergy

Contents

List of Tables

List of Figures

Introduction

*Helicobacter pylor*i (Hp) is a gram-negative bacterium, causative agent involved in most cases of chronic gastritis with an elevated prevalence worldwide and throughout most age brackets. Most cases are acquired during early childhood, evolving or not to symptomatic disease [1].

Overall prevalence of Hp infection is extremely high worldwide, which can attest to the different hygiene and sanitations regional levels, especially when considering the differences observed between underdeveloped and developed countries. In the latest trend of allergic and inflammatory diseases, the incidence has been rising in the last decades. In developed countries, prevalence as low as 3.4% (in Iceland) or 0.6% (in Norway) can be observed. However, this phenomenon cannot be reproduced to Asiatic countries such as Korea, Taiwan or China, where prevalence in the pediatric population seems to range from 14.8% to 25.8%, with a significant increase in prevalence with age [2]. Portuguese prevalence has been determined in previous publications, with reports as high as 66.2 % in adolescence [3]. Although much has been hypothesized as using this infection as an index for hygiene standards and socioeconomic status, alternative pathways of transmission, other than fecal-oral, must be considered, such as intra-familiar transmission, mainly from mother to child, but with a non-neglectable percentage of reported cases with father to child and between sibling transmission [3, 4].

In children, digestive manifestations of Hp infection may include recurrent abdominal pain and dyspeptic complaints, leading to chronic gastritis, peptic duodenitis and peptic ulcer disease. Some authors suggested that Hp infection can lead to growth impairment, short stature and diminished height and growth velocities. Whilst this concern has been raised multiple times, there is no consensual evidence. Even though Hp affects mainly the gastrointestinal tract, its impact can be multi-systemic, with recorded associations with diseases such as iron deficiency anemia, Henoch-Schönlein Purpura (HSP), obstructive sleep apnea syndrome and Type 1 Diabetes Mellitus. However, most associations are not causality evidence based and require additional studies and reviews for validation [2, 5].

The way Hp interacts with the host is much related to the gastric mucosa environment and the bacterium's virulence factors. Gastric mucosa has an acidic pH, but Hp infection and its ability to release urea and bicarbonate counteracts the natural mucosal environment, converting it into fertile ground for bacterial proliferation [6]. Of course, virulence factors such as cytotoxin associated gene A (CagA) and vacuolating toxin A (VacA) and other mucins and adhesins, like blood group antigen-binding adhesion (BabA), are also crucial to the survival and thriving of this pathogen. Also, it seems that epigenetic modulation factors such as GATA binding protein 5 (GATA-5) methylation, Trefoil-factor 1 and microRNA (miRNA) might be involved in the disease-host interaction [7]. It strikes as curious that Hp specimens removed from samples of peptic ulcers of pediatric patients showed higher adhesion to mucin, both in acidic and neutral conditions, which seemed to be attributed to a higher prevalence of BabA binding [7].

One of the main factors that makes pediatric Hp infection so peculiar is the innate changes over the immune system and its response, suffered throughout one's life. White cell lines, such as natural killer cells and neutrophils, suffer a decrease with age, being higher in newborns than in children, and so forth [8]. *Heuvel et al.* conducted a study that showed that in the first six months of life, the white cell count (monocytes, neutrophils, eosinophils, natural killer cells) decreases

until stability is reached. In contrast, B and T cells number increases in the first months of life, reaching stability between 3 and 6 years of age. In this same study, a subset of children that had Hp carrier status at six years old presented with higher populations of B memory cells, $CD272^+$ $IgA1^+$, TCRab1 and T-cell counts [8]. Such findings seem to suggest that the pediatric immune response to Hp infection is not only localized to the gastric mucosa but also with systemic repercussion. Pediatric immune response is linked to tolerance and the release of interleukin-10 (IL-10) and related cytokines, which evolves into a more invasive response in adults, potentially leading to an oncogenic pathway. Since CagA affects B cell apoptosis, this may be a maladaptive host response, influencing the aggressiveness of CagA positive strains infection [8, 9].

The evolving discussion around cancer concerns and potential benefits of Hp infection may influence global eradication strategies. According to the latest evidence, universal eradication in childhood is not recommended because of potential beneficial effects on the immune tolerance of this infection in pediatric setting, although this concept needs more support from evidence [10].

The present work aims to review the association between Hp and allergic and immune diseases. The hygiene hypothesis postulates that lesser exposure to environmental factors, such as diverse pathogens acquired in childhood, has led to an increase in prevalence of allergic diseases. Furthermore, Hp infection can lead to an immune T helper 1 (Th1) response, which can counteract the predominant T helper 2 (Th2) response, seen in allergic diseases [11]. Several studies have tried to confirm this association. Most of the published data reviewed the possible association of Hp infection to varying immune/allergic related conditions such as asthma, rhinitis and atopic dermatitis (AD) but also with celiac disease (CeD) and inflammatory bowel disease (IBD) or eosinophilic esophagitis (EoE), amongst others, with no apparent consensus. An early metanalysis showed a slight inverse relation between Hp infection and asthma but there are new and high-quality studies released in the recent years not always concordant with this first statement.

Therefore, the main goal of this systematic review is to analyze the available studies in the last decade that focus on the relation between pediatric Hp infection and the development of allergic and immune diseases. Speculation will be addressed on the impact this infection has on modulation of the Th2 immune response, even though Th1 response will be briefly addressed.

Methods

The following review followed the guidelines established by the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA), from 2020. Articles published from January 2014 to December 2024 written in English language were included, having been retrieved from the following databases: PubMed, Web of Science and SCOPUS. In March 2025, a new research was conducted, having included the new available articles retrieved from it. For supplemental information, manual research was conducted. The following terms were used in combination with Boolean operators: *Helicobacter pylori* AND Pediatrics AND (Allergy OR Asthma OR Eosinophilic Esophagitis OR Inflammatory Bowel Disease OR Dermatitis OR Food Allergy OR Allergic Rhinitis OR Epidemiology) NOT review.

Two researchers (EC and MT) conducted independent searches on the upper cited databases, where a predefined grid was used for data extraction. Disparities were analyzed by a third researcher (ESS).

The primary outcome defined was the correlation between Hp infection and the risk for allergic and immune diseases. We speculated, according to the outcome, the impact on Th1 immune response. The study retrieved the following variables: title, author, year, country, journal, type of study, number of participants, incidence and prevalence of immune and allergic diseases, and diagnosis and prevalence of Hp infection.

The inclusion criteria are as follows: prospective studies, retrospective studies, case-control studies, cohort studies; pediatric and adult populations; H. pylori infection diagnosis by urea breath test (UBT), stool antigen test (SAT), histology, or serology.

Exclusion criteria include: Hp infection diagnosis by urine, saliva, or methods outside the inclusion criteria; conference abstracts, expert cases, preclinical trials, case reports, narrative reviews, systematic reviews, meta-analyses; articles with high bias risk and low quality.

An overview of the selection process can be found in *Figure 1*.

The collected data was summarized in two tables: one for the article's innate qualities (*Table IA*) and another for the outcome of allergic and immune diseases (*Table IB*). The first table included title, author, year, journal, country, type of study, and number of participants. The second table included the number of participants, incidence and prevalence of immune and allergic diseases, presence of Hp infection and diagnostic methods, and other relevant details and conclusions from the articles.

Two researchers (EC and MT) independently evaluated quality assessment and risk of bias using the QUADAS-2 grid method. A third researcher (ESS) reviewed and analyzed any disparities in their evaluations.

Results

The first search was conducted on December 2024, on the following databases: PubMed, SCOPUS and Web of Science. A follow-up search was then conducted on March of 2025 to update the selection with recently published articles. From the first search, 446 records were identified, 270 from PubMed, 94 from SCOPUS and 82 from Web of Science. 96 duplicates were removed, first by EndNote’s automated tool and then manually. 350 records remained for the first screening that was conducted by title and abstract. On the first screening, 255 articles were excluded with a total of 95 articles identified for retrieval. All 95 full-text articles were successfully obtained and subsequently screened in their entirety. Out of these, 35 articles were excluded due to: 25 articles lacking relevant information for the review and 10 articles not meeting the inclusion criteria. Of the remaining 60 articles, 27 were selected for inclusion. An overview of the selection process can be found in *Figure 1*. The 27 articles selected for the review were analyzed using the QUADAS-2 tool to assess bias, quality, and applicability. Results are summarized in *Figure 2*.

General Overview of Included Studies

The articles selected were published from 2014 to 2025, and originate from various regions including Asia (China), Western Europe (Belgium, France, Greece, Italy, Netherlands, Norway, Portugal, Spain), Eastern Europe (Armenia, Croatia, Czech Republic, Lithuania, Serbia, Poland) Middle East (Iran, Israel, Palestine, Turkey), America (Colombia and North America) and Africa (Egypt). Among the selected studies 5 were observational, 5 were retrospective, 4 were prospective, 4 were case controls, 3 were cross-sectional, 3 were prospective case-controls, 2 were cohorts and 1 was an observational cross-sectional. Of the 27 articles reviewed, 12 were pertaining to asthma, 5 to IBD, 2 to EoE, 7 to CeD, 3 to food allergy (FA) and 5 to other allergic, atopic and immune diseases – HSP, AD, allergic rhinitis (AR) , chronic urticaria (CU), atopy and allergy. Hp diagnosis is described throughout the review and this information can be found summarized in *Tables IA* and *IB*.

Asthma

In regard to asthma, twelve articles were included for the review.

A study by Dore *et al*., published in 2014, included 64 children, and showed an overall prevalence of Hp infection of 14% (9/64), diagnosed by serology, and the overall prevalence of asthma was 17% (11/64). The prevalence of Hp infection was similar between asthmatic and non-asthmatic groups, at 9.1% and 15% respectively (p=0.6). Among those with Hp, 11% had asthma, compared to 18% in the Hp negative group. The study found no significant link between Hp infection and asthma or the risk of developing asthma (p=0.861) [12].

In an observational Iran based study, published in 2015 by Khamechian *et al.*, 300 children, with ages varying between 5 and 18 years old, were studied to assess the relation between Hp infection and asthma. The overall prevalence of Hp infection was 46% (138/300), and Hp diagnosis was serology based. Within the Hp positive group 5.8% were asthmatics (8/138). The overall prevalence of asthma was 12%, with 22% of asthmatics being Hp positive (8/36). The study found that there were significant differences between the prevalence of asthma in the Hp positive and Hp negative group, with 5.8% and 17.3%, respectively (p=0.002). Furthermore, it was found an inverse relation between Hp infection and asthma, even when variables such as gender, age and family history were taken into account – p values varying between 0.002 and 0.005, Odds Ratio (O.R.) values varying between 3.38 and 4.06 [13].

Hollander *et al.* published a cohort study in 2016, based in the Netherlands, that aimed to determine the relation between childhood Hp colonization and the development of asthma. In this study, the contribution of maternal Hp status was also evaluated. The study included 3797 children diagnosed with Hp infection by serology, with a mean age of 6.1 years old, and 2910 mothers, with a mean age of 31.1 years old. The overall prevalence of Hp infection in children was 8.7% (332/3797), from which 29% were CagA positive and 71% were CagA negative. Amongst mothers, the prevalence for Hp infection was 38% (1106/2910), from which 33% were CagA positive and 67% were CagA negative. The overall prevalence for asthma in children was 81% (3062/3797). This study reached the following conclusions: (1) the Hp colonization rate was higher in children with mothers who had Hp positivity (14.3%, $p<0.05$); (2) there was a higher prevalence of asthma in children with Hp positivity (9.5%, p=0.045) and (3) there was a linear relation between Hp colonization and the risk of developing asthma (O.R. 1.75), although this relation

could only be verified in the CagA negative subgroup (O.R. 2.11). No association was found in the CagA positive group (O.R. 0.94) [14].

In 2016, an Iranian cross-sectional study, conducted by Yousefichaijan *et al,* aimed to compare the difference in Hp serology between children with and without asthma. The study included 208 children, with varying ages from 5 to 12 years old; 104 children belonged to the control group and 104 children belonged to the cases group. Hp status was determined via serology. The overall prevalence for Hp positivity was 15% (31/208). In the asthmatic group 13% were Hp positive (13/104) and in the control group 17% were Hp positive (18/104). The overall prevalence of asthma in the study population was 50% (104/208). This study found no significant difference in Hp seropositivity between children with and without asthma (p=0.54). Furthermore, no significant difference in CagA serology was found between the control and cases group (p=0.23). However, it is to be noted that the duration of asthma was higher in the seropositive group than in the seronegative one (3.61 years *versus* 2.16 years, p=0.0001) [15].

In 2018, Fouda *et al*. published a cross-sectional study that aimed to determine the relation between Hp infection and childhood asthma. The study involved 180 children, 90 controls and 90 cases. Hp infection was diagnosed via serology. Hp infection prevalence was 35% overall (63/180), 26% in asthmatics (23/90), and 45% in controls (40/90), with a statistically significant difference (p=0.008). Asthma prevalence was 50% (90/180). The study found an inverse relationship between Hp seropositivity and asthma, with severe asthma cases having significantly lower Hp immunoglobulin (Ig) G antibody levels (p=0.042). Consistent with prior prevalence studies, a highly significant association was observed between Hp seropositivity and the crowding index (p=0.000) [16].

Molina-Infante published a multicenter prospective case-control study in 2018, that enrolled children from European countries and Colombia. The study included 808 participants, both children and adults, with ages ranging from 2 years to 83 years old. Although this particular study focused on the relation between Hp infection and EoE, it also breeches multiple other conditions, namely asthma. The diagnosis for Hp was made both through non-invasive methods, like UBT and SAT, but also through biopsies with histology. The overall prevalence of Hp infection in the study was 39% (312/808). Among those who tested positive for Hp, 34% had some form of atopic condition. The overall prevalence of asthma was 29% (236/808). In the group with asthma, 37% were positive for Hp. There was no significant difference in the prevalence of Hp infection between the non-asthmatic group (38%) and the asthmatic group (p=0.4). The study found no significant difference in Hp infection prevalence between asthmatics and non-asthmatics across all age groups, including children and adults (p values ranging from 0.1 to 0.4). Thus, it did not establish a link between Hp infection and asthma [17].

In 2019, a case-control study based in Greece analyzed the prevalence of Hp infection in asthmatic children, being that Hp infection was diagnosed based on serology and SAT. The study conducted by Tsigalou *et al*. included 81 children: 27 cases and 54 controls. The overall prevalence of asthma was 33% (27/81) and Hp infection was 23% (19/81). Among asthmatics, the prevalence of Hp infection was 11% (3/27), compared to 30% (16/54) in the control group. This difference was statistically significant and it also established an inverse association between Hp infection and asthma, with significance (p=0.026, O.R. 0.1) [18].

Elias *et al*. published in 2020 a case-control study, based in Israel, that aimed to assess the relation between Hp seropositivity and pepsinogen levels with the likelihood of childhood asthma. The overall prevalence of asthma was 32% (75/235). The overall prevalence of Hp seropositivity was 35% (83/235), with 25% prevalence in the cases group *versus* 40% in the controls, being that this difference was found to be statistically significant (p=0.03). Furthermore, within the cases, there were 7% who tested positive for CagA positive strands, which was found to be present in a significant lesser percentage than the controls with 19% (p=0.014). Children with serologic diagnosis of Hp and ratios of pepsinogen I/pepsinogen II lower than 6.78 were found to have 71% lesser chances of developing asthma (p=0.02). Therefore, the study concludes that there is an inverse association between asthma and Hp seropositivity, but only in regards to the CagA positive strains, with an O.R. of 0.3 (p_{CagA+}=0.026 *vs* p_{CagA-}=0.2) [19].

Melby *et al.* published in 2020 a cohort study, based in Norway, that aimed to assess the relation between Hp infection and the likelihood of childhood asthma. The study included 197 children diagnosed with Hp, via serology. The overall prevalence for Hp infection at 2 years of follow-up was of 6.1% (12/197), and at 10 years of follow-up the prevalence was 8.6% (17/197). The overall prevalence of asthma was 17% (32/197), and, within the asthmatic group, 6.2% were Hp positive (2/32). Of the 183 children who were Hp negative at 2 years, 11 became Hp positive by 10 years. Among the 2 borderline cases, 1 turned Hp positive. Of the original 12 Hp positive children, at 10 years of follow-up, only 5 remained positive at 10 years. Furthermore, when accounting the prevalence of asthma at 16 years of follow-up, the highest prevalence was verified amongst the group of children that exhibited Hp negative status 16.4% (30/183), with 0% (0/12) prevalence in children who initially had Hp positive status. Hence, the authors suggest that there is an inverse relation between Hp infection and the risk of developing asthma; however, this association was not statistically significant [20].

In 2022, Wang *et al*. published a cross-sectional study in Chinese children whose main goal was to assess the relation between Hp infection and asthma. The study included 2241 patients with a mean age of 8.67 years (4 to 18 years old). Hp infection was diagnosed via UBT. Hp infection had an overall prevalence of 13% (292/2241). Among the Hp positive group, 3.8% were asthmatic (11/292), compared to 7.2% in the Hp negative group (141/1949), which was a statistically significant difference (p<0.05). The overall prevalence of asthma was 6.8% (152/2241). Also of note was the fact that the Hp positive group and the Hp negative group had significant differences between family history of asthma and eosinophilic count, but other variables such as age, sex and BMI had no relevant differences. Overall, there was an inverse relation between Hp infection and asthma (p=0.028), that translated to multi-variable analyses, and the study finds that Hp infection might be an independent protecting factor against childhood asthma (O.R. ranging from 1.887 to 2.008) [21].

In a prospective Italian study, published in 2024 by Dore *et al.*, the authors aimed to study the relation between Hp infection and the risk of allergic disease. The study encompassed 492 children, aged between 7 and 37 months, and Hp diagnosis was obtained through serology. The overall prevalence of Hp infection was 11.8% (58/492). Within the Hp positive group, 6.9% were diagnosed with asthma (4/58). The total prevalence of asthma among the participants was 6.5% (32/492), accounting for 72.7% of the atopic and allergic diseases group. Notably, within the asthmatic group, 12% were Hp positive (4/32). The study concluded that asthma prevalence

among children with and without asthma was similar (6.9% *vs* 6.5%). Hp infection was more common in children living in rural areas (O.R. 3.8) and those with pets (O.R 1.8). Overall, there was no association found between Hp infection and the risk of developing asthma during childhood (p=0.374) [22].

In 2025, Hrizat *et al.* published a prospective case-control, filiated in Palestine and the USA, whose aim was to assess the relation between Hp infection and the risk of childhood asthma. The study included 143 children, with ages ranging between 6 and 15 years old, and the diagnosis of Hp was made through SAT. The overall prevalence of Hp infection was 45% (64/143); within the control group the prevalence of Hp was 51% (50/99) *versus* a prevalence of 32% (14/44) in the cases group. The overall prevalence of asthma was 31% (44/143). The study found no statistical difference between the age of onset of asthma and the presence of Hp infection, nor any correlation between Hp status and asthma severity. However, it did find an inverse relation between Hp infection and the likelihood of asthma, with an O.R. of 0.46 and a p value of 0.04 [23].

Celiac Disease

Eight articles on CeD were reviewed.

In 2015, Jozefczuk et al. [24] published a study from Poland on the frequency of Hp infection in children newly diagnosed with CeD. The study included 370 children (74 cases, 296 controls), whose Hp infection status was assessed by UBT. Hp infection prevalence was 13% overall, with 11% in the CeD group and 14% in the control group. CeD prevalence was 20%. Among those with Hp, CeD prevalence was 17%, similar to the 22% in the Hp-negative group. No significant relation between Hp infection and CeD was found (p=0.8742).

A 2016 case-control study, filiated in Poland, aimed to establish the relation between the presence and titers of rice and wheat specific immunoglobulin G (sIgG) and specific immunoglobulin G4 (sIgG4) in several conditions, namely wheat allergy (WA), Hp infection and CeD. Czaja-Bulsa's study [25] included 200 participants, where 50 participants were the control group, 50 participants had WA, 50 participants had CeD and 50 were representative of Hp infection (diagnosis was made through biopsy with histology). The main goal of the study was to assess the frequency and levels of wheat and rice sIgG and sIgG4 in all four upper mentioned groups. The study found Hp infection, WA, and CeD had a prevalence of 25% each (50/200). During active CeD phases, wheat and rice sIgG levels were higher when compared to remission phases, where these antibodies were negligible. In the control group, 66% had wheat sIgG, but no sIgG4 for rice nor wheat. During CeD flares, high levels of rice sIgG4 were observed. Similarly, in the Hp group 78% had high wheat sIgG and 76% had high sIgG4. Rice sIgG and sIgG4 were present at lower rates (56% and 12%). The study indicates that there is a higher prevalence of sIgG and sIgG4 in patients with CeD, WA, and Hp infection, showing a linear relationship. However, these antibodies are also present in the control group, albeit in smaller proportions, and do not appear to correlate with the severity of the disease. Therefore, while the linear relationship is noted, it should be noticed that the presence of these antibodies does not confirm a diagnosis of FA. Instead, it suggests that these specific gastric and intestinal conditions may lead to an increase in sIgG and sIgG4 levels.

A 2018 Turkish observational study by Tumgor [26] aimed to determine the frequency of peptic ulcers in celiac children and in non-celiac children. In this cohort of 74 children, where Hp diagnosis was obtained through biopsy with histology, Hp infection prevalence was 50% (37/74).

Among the CeD group, 14 out of 22 (64%) tested positive for Hp, while only 23 out of 52 (44%) in the non-CeD group were Hp positive. The overall CeD prevalence was 30% (22/74). Additionally, 37.8% of the Hp positive group were celiacs (14/37), compared to 21.6% (8/37) of the Hp negative group. The study concluded that there is a statistically significant ($p<0.001$) linear relationship between Hp infection and CeD, with most ulcers in celiac patients appearing to be associated with Hp infection.

Agin *et al.* [27] published a prospective study in 2019, regarding the prevalence of Hp infection in children with CeD and its impact on histopathological, clinical and laboratory findings. The studied population consisted of 1268 children, 256 celiac patients (age range between 1 and 18 years old) and 1012 controls. Hp infection was diagnosed via histology with biopsy and the overall prevalence was 23% (297/1268). Within the CeD group, 27% were Hp positive (27/256) and also 27% of the non-CeD population were Hp positive (270/1012). The overall prevalence of CeD was 20% (256/1268). This study found no significant difference between Hp prevalence in both the CeD and non-CeD groups. However, in the celiac patients, the Hp positive ones were more likely to present with diarrhea and abdominal distension ($p<0.005$).

In 2021, Bayrak *et al*. [28] published a case control study, based in Turkey, with 783 children. The study aimed to examine the association between Hp infection (obtained through biopsy with histology and rapid urease test) and celiac disease, particularly in patients with concurrent celiac disease and Type 1 Diabetes Mellitus. The overall prevalence of Hp infection was 43% (333/783). In the Hp positive group, 21% were celiacs (69/333) and 3.9% had both CeD and diabetes (13/333). The overall prevalence for CeD was 27% (215/783) and the prevalence for children with both CeD and diabetes was 8% (63/783). Within the CeD group, 32% were Hp positive (69/215) and, in the CeD and diabetes group, 21% (13/63) presented Hp positivity. The study reported an inverse relationship between CeD and Hp, with statistical significance ($p<0.01$). This difference can be observed between the control group and the CeD group (O.R. 1.43, $p<0.05$), and it extends to the comparison between the CeD and CeD plus diabetes group (O.R. 0.89, $p<0.05$).

In 2022, Akkelle *et al.* [29] published a prospective study in Turkey, investigating the link between positive celiac serology and Hp infection (diagnosed via biopsy with histology with rapid urease test). The study involved 155 children, finding an Hp infection prevalence of 22% (34/155), with 68% (23/34) being celiac. Overall, 77% (119/155) had CeD, and 19% (23/119) of them were Hp positive. No significant differences in IgA anti-transglutaminase antibody (TGT IgA) levels were found between patients with and without Hp infection. However, following Hp eradication therapy, a decrease in TGT IgA was observed, suggesting a potential link between Hp infection and TGT IgA levels due to neutrophilic activation extending into the gastrointestinal tract.

In 2024, Kotilea *et al.* published a multicentered retrospective study, involving 3890 participants from Europe and the Middle East [30]. The study assessed the incidental finding of Hp infection through upper gastrointestinal endoscopies for diagnosing CeD, IBD, and EoE. The prevalence of Hp infection was 9% (349/3890). Among patients with CeD, the prevalence was 45% (1733/3890), with 10% (173/1733) testing positive for Hp. The study also examined IBD and EoE, finding the highest Hp prevalence in the CeD group. The differences found between the groups were not statistically significant, indicating that the prevalence of Hp infection across diseases is similar. The study, which was based on a multicenter approach, revealed statistical differences according to geographical location, with higher incidences of Hp infection observed in the Middle East.

Eosinophilic Esophagitis

Two studies related to EoE were included in this review.

Molina-Infante published a study in 2018 that included 808 participants, divided equally into a control group and a study group, comprising individuals diagnosed with EoE through esophageal biopsies. Of the total population, 222 were females and 586 were males, with an age range spanning from 2 to 83 years. The primary objective of this research was to determine the prevalence of Hp infection among EoE patients and healthy subjects, and to assess differences in Hp prevalence across various age groups, atopic and non-atopic patients, as well as responders and non-responders to proton pump inhibitors. Hp infection status was determined by UBT, SAT or biopsy with histology. The overall prevalence of Hp infection was found to be 38% (312/808), with children exhibiting a higher prevalence than adults (45% *vs* 37%), a difference that reached statistical significance. The prevalence of Hp infection in the atopic population was lower compared to the non-atopic group (34% *vs* 42%), although this difference did not achieve statistical significance. Additionally, no significant difference was observed between the control group and the study group (42% *vs* 30%, p=0.3). While the main focus of the study was the relationship between Hp and EoE, other conditions such as asthma (236/808), FA (146/808), and AD (80/808) were also analyzed. However, no significant associations were found between these conditions and Hp infection. Ultimately, the study concluded that no significant association, whether inverse or linear, could be established between Hp infection and EoE (p=0.3) [17].

The 2024 study by Kotilea *et al.* [30] also found similar conclusions. This study included conditions such as IBD, CeD, and EoE. The overall prevalence of Hp infection, determined through histology, was 9% (349/3890). The prevalence in EoE was 7.6%, with no significant difference from other disease groups. Neither study showed a significant association between Hp and EoE [17, 30].

Food Allergy

Three studies on FA were reviewed.

Pedullà (2014), conducted a study to explore the role of specific Hp IgG in FA among children with AD. The study included 290 children, with an overall Hp infection prevalence of 11/290, while 30 tested positive for Hp serologies. IgE mediated FA was found in 65 out of 290, and non-IgE mediated FA was present in 23 participants. Among those with Hp infection (n=30), 4 had non-IgE mediated FA, 26 were controls, and none had both IgE mediated FA and confirmed Hp infection. A statistically significant difference was noted (p=0.032), showing an inverse association between Hp infection and FA [31].

The 2016 Czaja-Bulsa study, previously discussed in the Celiac Disease section, is relevant for WA. It found that 88 to 96% of subjects had wheat sIgG and sIgG4, and rice sIgG during diagnosis, treatment with diet, and tolerance periods. Rice sIgG4 appeared in only 46 to 50% of subjects. Wheat titters were consistently higher than rice titters, with statistical significance ($p<0.005$ and $p<0.001$). Notably, wheat sIgG4 levels stayed constant, except during dietary treatment, where they decreased. The study concluded that sIgG and sIgG4 do not correlate directly with WA's clinical state and are limited in diagnosing WA. These antibodies seem to increase due to other gastro-intestinal diseases rather than being a manifestation of FA [25].

The Molina-Infante study [16] aimed to assess the link between Hp infection and EoE. Patients with EoE are often prone to FA. Comparing two groups (EoE with FA and EoE without FA), Hp infection was found in 36% of the FA group and 39% of the non-FA group. In pediatric cases, Hp infection was 48% in the FA group and 43% in the non-FA group. These differences were not statistically significant (p=0.3 and p=0.1), indicating no established relation based on these results.

Inflammatory Bowel Disease

Five articles on IBD were included in this review.

In 2014, a retrospective study filiated in Greece aimed to study the prevalence of Hp positive and negative gastritis, in a population with and without IBD. The study conducted by Roka *et al*. [32] included 1368 children, from which 159 were cases and 1209 were controls. Hp was diagnosed through invasive testing (biopsy with histological assessment) and non-invasive testing (UBT). The overall prevalence of Hp infection was 14% (196/1368). Within the IBD population the prevalence of Hp infection was 3.8% (6/159), and in the non-IBD population the prevalence was as high as 16% (190/1209). The overall prevalence of IBD was 12% (159/1368). In the Hp positive population the prevalence of IBD was 3.1% (6/196) and in the Hp negative group the prevalence went as high as 13% (153/1172). In regards to age, the mean age in the IBD group was higher than in the non-IBD one ($p<0.001$). Overall, the study found an inverse association between having Hp positivity and the likelihood of having IBD, with statistical significance (p=0.006, O.R. 3.3).

In 2023, a study filiated in Turkey was published with the intention of studying the prevalence of Hp infection in children with IBD, as well as understanding it's distribution between ulcerative colitis (UC) and Crohn's disease (CD). This study included 50 children, with a mean age of 15.3 years old. The overall rate for Hp infection was 28%, with 14 infected patients, and Hp diagnosis was made through histology of gastric biopsies. From these, 10 belonged to the UC group and 3 to the CD group, 71% and 21%, respectively. From the 50 patients, 25 belonged to the UC group, from which 10 were positive for Hp and 15 were negative. 21 patients belonged to the CD group, with 3 being positive for Hp infection and 15 being negative. The study reported a higher prevalence of Hp infection within the UC group, and withdrew the conclusion that the relation that Hp presents with IBD varies accordingly to which subtype of disease was present, with a linear relation in regards to UC and an inverse relation in regards to CD [33].

In an already mentioned study, Kotilea [30] the relation between Hp infection and IBD was also approached. In this study, that included 3890 children, 1292 were diagnosed with IBD, making up 33% of the total study population. Hp infection was diagnosed via histology/biopsy. The overall prevalence of Hp infection was 9% (349 patients). From the total population of patients with IBD, only 8.5% were positive for Hp infection. Whilst some association was established in between regions, with a remarkably higher prevalence in the Middle East, no statistically significant difference incurred in between diseases, namely within IBD (p=0.735, O.R. 1.12).

Dilaghi *et al.* published in 2024 a prospective case-control study, with the collaboration of multiple Italian pediatric centers. The main aim of the study was to determine the prevalence of Hp infection in children recently diagnosed with IBD (76 patients) and non-IBD patients (148 patients). Furthermore, it aimed to assess the differences in clinical activity index (CAI) and endoscopic severity score (ESS) between IBD patients with and without Hp infection. Hp infection was diagnosed via biopsy and the overall prevalence was of (25/224), with 9.2% in the IBD group

(7/76) and 12% in the non-IBD group (18/148). The overall prevalence of IBD was 33.9% (76/224). From the 76 patients with IBD, 29 had the diagnosis of CD (38%) and 45 had UC (59%). 2 patients had unclassifiable IBD. The differences between the IBD and non-IBD group were not considered statistically significant (p=0.5065), hence no relation between Hp and IBD was established. In regards to CAI and ESS, a general improvement was found at follow-up, with statistical significance in the total study population ($p_{CAI\ UC}$=0.0004, $p_{CAI\ CD}$=0.0235, $p_{ESS\ UC}$=0.0001, $p_{ESS\ CD}$=0.0003). In the IBD group, some improvement was shown numerically, namely UC patients with a Pediatric Ulcerative colitis Activity Index (PUCAI) varying between 0 and 35 went from 2 to 4 patients at follow-up, and patients with an Ulcerative Colitis Endoscopic Index of Severity (UCEIS) score of 0 to 4 went from 3 to 4 patients. In the CD group, patients with a Pediatric Crohn's Disease Activity Index (PCDAI) varying between 0 and 40 remained 3, but no worsening was registered, and patients with a Simple Endoscopic Score for Crohn's Disease (SES-CD) score of 0 to 4 went from 0 to 3 patients. However, it is important to underline that these differences were not found to be statistically significant ($p_{CAI\ UC}$=0.4286, $p_{CAI\ CD}$=1.000, $p_{ESS\ UC}$ =1.000, $p_{ESS\ CD}$=1.000) [34].

Villaba-Davila published in 2025 a retrospective study that aimed to evaluate the impact that Hp infection has on fecal calprotectin (FC) levels. The study included 129 subjects, from which 37 were diagnosed with Hp infection (29%), via biopsy with histological analysis. FC levels were assessed in both Hp positive and Hp negative groups, finding much higher levels in the Hp positive group (241.2 μg/g *vs* 88.1 μg/g). This difference was found to be statistically significant, with p<0.001. Test subjects who presented with high levels of FC (generally >150 μg/g) were also more likely to undergo colonoscopies. It is to be noted that nine patients who were subjected to endoscopies were assessed via Sidney classification, that found a strong association between antral neutrophilic activity and FC levels (p=0.0013), suggesting that the raise registered was secondary to pro-inflammatory changes, inherent to Hp infection and not in relation to on-set of IBD. [35].

Miscellaneous

In total, seven articles were retrieved that delved into several conditions not previously mentioned, such as AD, AR, CU, HSP, and also general overviews on atopy and allergy.

In 2015, Akelma *et al.* [36] published a prospective study, based in Turkey, whose aim was to assess risk factors and response to Hp infection eradication treatment in children diagnosed with CU. The study comprised 67 participants, all diagnosed with CU. From the total population, 32 were children (age range from 3 to 15 years old) and 35 were adults (age range from 21 to 80 years old). Hp infection was diagnosed via SAT and the overall prevalence of Hp infection was 41.8%, with a prevalence of 31.2% in children (10/32) and 51.4% in adults (18/35), although this difference was not significant (p=0.09). There was, however, a statistically significant linear relation between age and prevalence of Hp infection, with older children registering higher rates than younger children (p<0.001). Numerically, we can observe that there was a linear relation between patients that underwent eradication therapy and the improvement of CU symptoms, with 100% of the children and 83.3% of adults reporting an improvement. However, this comparison does not have a statistical significance (p=0.172).

Whilst the main goal of the Molina-Infante study was to evaluate Hp infection and its relation to EoE, atopic conditions and rhino conjunctivitis (Rc) were also approached. As previously

mentioned, Hp status was determined using non-invasive methods (UBT or SAT) and invasive methods (histology with rapid urease test). The prevalence of Hp infection in the atopic group was of 34% *versus* 42% in the non-atopic group, which was considered a significant difference (p=0.01). The prevalence of Hp infection in the Rc group was 33% *versus* 41% in the non-Rc group, which was also considered a significant difference (p=0.01). Whilst these differences seem to suggest an inverse relation between Hp infection and atopy/allergic diseases, it is worth mentioning that this difference could only be attested when analyzing the population as a whole and could not be translated into other subgroups such as pediatric and adult participants [17].

A 2020 observational study, based in China, aimed to assess the possible association between infectious triggers and pediatric HSP. This study, published by Wang *et al.* [37], included 1200 children diagnosed with HSP, from which 672 were males and 528 were females, with an age range from 7 to 17 years old. Hp status was established by serology, and the overall prevalence of Hp infection was 5.92% (71/1200). The study found that Hp infected children were more likely to present with abdominal pain (63.38%), arthritis (49.3%) and renal involvement (22.54%); however, the Hp infected group didn't significantly differ from the other infections (p=0.27). In children that had HSP relapses (n=123), 7.23% presented with Hp infection, even if this had no difference with non-relapse group (p=0.75). Even though no significant relation was found between the presence of HSP and varying infectious agents, it showed a positive relation between improvement of remission rates and the institution of not only symptomatic treatment but also targeted treatment towards the infection (p<0.01).

In 2020, a cross-sectional observational study based in Turkey, published by Akiner *et al*., aimed to study the association between Hp colonization and the development of AR and nonallergic rhinitis with eosinophilia syndrome (NARES). The study was comprised by 349 patients (75 controls and 274 cases). Hp infection was determined through SAT, and the overall prevalence of Hp infection was 38% (134/349), with a remarkable difference in prevalence between cases and controls – 42% and 24%, respectively (p=0.02). The overall prevalence of AR and NARES was 79% (274/349). Within the study group, amongst the adults, mite allergy was present in 95 participants, pollen allergy in 29 participants, NARES in 114 participants and 11 subjects had both mite and pollen allergy. The prevalence of Hp was then assessed for each one of these conditions on both the study group and the control group, with higher prevalence in the study group and a significant difference in every single allergic condition, except in pollen allergy (p=0.27). Amongst the children, 23 had mite allergy, 4 had pollen allergy, 22 had NARES and 2 had both pollen and mite allergy. However, unlike the adult group, when the Hp infection rates were compared between the study group and the control group in each allergic disease presented, none were shown to have significant differences. Hence, the study found only a linear relation between Hp Infection and AR and NARES in the adult group [38].

In 2024, Dore *et al.* published a prospective study based in Italy, whose aim was to assess the relation between Hp infection and the risk of developing allergic diseases. This article has been already mentioned in the asthma subgroup of the results, but now we will focus on its findings regarding atopy. Hp status was determined via serology and the overall prevalence of Hp infection was 11.8% (58/492), and within the Hp positive group 5.2% had an allergic background. The overall prevalence of atopy was 8.9% (44/492) and within the atopic group 82% were Hp positive (36/44). Nevertheless, no significant difference was found in Hp prevalence in the atopic and non-

atopic group. (p=0.233). Hence, the article didn't establish a relation between Hp infection and the risk of developing atopy [22].

Discussion

General Considerations

This review examined various articles related to Hp infection and its possible association with different immune and allergic conditions. This topic is intricate and has generated significant discussion within the scientific community.

The first point of debate is the diagnostic definition of Hp. For epidemiological studies, serology has been widely used. However, serology serves more as a marker for previous exposure to Hp and not necessarily an indicator of current infection. Although the preferential diagnosis method is not consensual, the current ESPGHAN guidelines suggest that the best course of diagnosis is through gastric biopsies, with culture or molecular tests, and histopathology classification according to the Sydney system [10].

From the information supplied in *Table IB*, we can observe that the majority of studies did not, in fact, use this diagnostic method, with 44.4% using biopsies with histological evaluation, and 55.6% using other methods – with 37% making use of serologies and 18.5% making use of non-invasive tests, such as SAT or UBT. Some studies also applied more than one diagnosis method, combining invasive testing with noninvasive testing.

This multiple selection of diagnosis methods leads to a difference in prevalence numbers across studies based on serology and other biomarkers, compared to those that included children with endoscopic features of Hp infection and confirmative histology. Furthermore, the distinction between past exposure and the persistence *versus* transient nature of the infection remains a topic of discussion. This gains relevance when considering the risk of immune diseases associated with long term infections or allergic modulation by transient early-life exposure.

Our included studies were evenly distributed between prospective studies (4/27, 14.8%), observational studies and retrospective studies (5/27, 18.5% each), case control studies (4/27, 14.8%), cross-sectional studies (3/27, 11.1%) and prospective case controls (3/27, 11.1%). Two studies were cohorts (2/27, 7.4%), and one was an observational cross-sectional study (1/27, 3.7%). The elevated number of prospective studies with a natural lower risk of bias brings a high-quality selection to this review.

This systematic review aims to analyze published literature regarding immune diseases linked to Hp exposure. To provide a clearer understanding of findings, this discussion will be organized by specific conditions or diseases.

Asthma

Overall, 12 articles were included in the analysis. The primary origin of the study populations was the Middle East, with additional contributions from European, Asian and African countries. This is relevant due to the natural variations in Hp infection prevalence, that is notably higher in these regions. For instance, Çinar *et al*. reported a 49% positivity prevalence in his Turkish study [5].

Six out of 12 articles (50%) identified an inverse relationship between Hp infection and the risk of developing childhood asthma, five (41.7%) found no significant relationship and one (8.3%) article observed a linear relation between Hp infection and asthma.

An interesting phenomenon that warrants attention is the importance of determining whether the infection is caused by a CagA positive or negative strain. However, the findings are conflicting. Elias *et al*. noted an inverse relation only observed in CagA positive strands, Hollander *et al*. reported a linear relation specifically associated with CagA negative strains, and Yousefichaijan *et al.* presented evidence that the CagA status does not differ between asthmatics and non-asthmatics [14, 15, 19]. Future studies on this cytotoxin derived infection pattern may provide clarity on whether it represents a single Hp infection or a polymorphic behavior of the bacterium.

A 2017 review by Karakullukcu highlights the protective role of Hp infection against asthma, citing factors such as the hygiene hypothesis and immune response alterations. Asthma, being an allergic disease, expresses mainly a Th2 response, while Hp infection induces a Th1 response, which may explain why Hp immune response may diminish and mitigate asthma symptoms. In addition, T helper 17 (Th17) responses are also observed in some asthmatic patients. This specific subset of immune T cells exhibits a pro-inflammatory action, which is counterbalanced by regulatory T cells (Treg) that secrete inhibitory cytokines, such as IL-10. The relevance of this topic lies in the enduring impact that Hp acquired during childhood has on the immune system, with systemic upregulation of Treg and IL-10 pathway. The continued stimulation of Th1 and Treg responses may explain its inverse relationship with asthma [9, 39].

A review published in 2024 by Liu *et al.* compiled various studies that also indicated an inverse relationship between Hp and asthma, noting that CagA positive strains exhibited a particularly strong inverse relation. Liu proposed four main mechanisms to explain this relation: the hygiene hypothesis, alterations within the gut microbiota, the impact of tolerogenic dendritic cells, and the role of Th1/Th2 and Th17/Treg responses [40]. Chen *et al*. conducted a meta-analysis based on 18 studies, that further supports the evidence of an inverse association between asthma and Hp infection, confirming that CagA positive strains have a more pronounced association than CagA negative strains [11].

This review concludes that Hp infection has a slightly protective effect on asthma risk, as evidenced by 6 out of 12 articles. However, the impact of CagA remains unclear due to the limited and conflicting data from only three studies.

This conclusion seems do differ from previous studies, where a strong protective factor of Hp infection against asthma seemed to be highlighted, with some reviews putting the spotlight on the importance of CagA positive strains. Even so, our conclusions are reliable due to the high quality of the selected papers, not supporting the previously suggested inverse relations for Hp infection in general. Perhaps this will be useful in the future for the diagnostic determination of Cag species present in the infected patients' biopsies.

Celiac Disease

The review included 8 articles on CeD, with most originating from Turkey (6/8), and the rest from other European countries (2/8), one of them a multicenter study. Five studies (62.5%) found no or non-significant relations to CeD, one (12.5%) found an inverse relation, and two (25%) reported a

linear relation. Czaja-Bulsa's did not directly link increased specific immunoglobulins to CeD, but rather as byproduct of general inflammatory and immune changes in the gastrointestinal tract, offering limited relevance to CeD [25].

A 2021 systematic review by Amlashi *et al.* analyzed 26 studies (10 pediatric) on the relation between CeD and Hp infection, before the updated ESPGHAN's celiac disease guidelines. [41] No obligatory biopsy-based diagnostic test was present in all studies since genetic tests were also considered for diagnosis. They found a mild inverse relation [42], which contradicts our findings. It should be noted that our review included fewer articles (8 *vs* 26) and had a limited geographical diversity (mainly from Turkey) which could bias our results. Nevertheless, only 19.2% of Amlashi's articles were considered high quality and many didn't account for confounding factors, which might have played a significant role in the outcome [42]. Similarly, Kotilea *al*. found a diminished rate of Hp infection as an incidental finding in the workup of CeD but this doesn't cover the cases where currently celiac serology diagnosis is based [30].

Eosinophilic Esophagitis

In our review, two articles were included in relation to EoE. Both articles found no relation between EoE and Hp infection. In regards to provenience, both articles were multicenter studies that included mostly European countries, but also with some representation from the Middle East, which does contribute to diversity of the population. Even though the pool of articles selected is small, and this in itself might be a source of bias, it is relevant to compare our results to other published reviews and meta-analysis.

In a 2019 systematic review published by Shah *et al*. that included 11 articles, they found an inverse relation between Hp infection and EoE, reporting 37% lower chances of developing EoE after Hp exposure. Even when the data was analyzed in subgroups regarding pediatric *versus* adult studies, and areas with high *versus* low prevalence of Hp, the meta-analysis and regression studies showed that it was still possible to infer this same inverse relation [43]. More recently, Spinelli *et al.* conducted a meta-analysis, in 2025, with the same purpose as Shah. When analyzing the 19 included studies, they found a 46% lower chance of developing EoE after Hp exposure. This relation was also verified in other sub-analysis, namely in regards to geography and study type [44]. Even though our results differ from the ones presented in the previous reviews, it is to be noted that we included only two articles, and it might have limited our findings significantly.

Food Allergy

The review included three studies on FA: one from Poland, one from Italy, and a multicenter study mainly involving European countries. Among the studies, one (33.3%) found an inverse relation, one (33.3%) found no relation, and one (33.3%) found a linear relation. Czaja-Bulsa's article noted a linear relationship between specific immunoglobulin antibodies and Hp infection. However, it suggested that the observed increase in these markers, typically associated with FA, may be due to inflammatory changes mediated by Hp, and not necessarily indicating concurrent FA [25].

In an animal model conducted by Mai and Liang *et al.*, mice were conditioned into developing FA, more specifically peanut allergy, and later were administered spores containing *Helicobacter pillory* neutrophil activating protein (NAP). An increase in the IL-10 and interferon gamma (IFN-γ) levels, and a decrease in the interleukin 4 (IL-4) and interleukin 5 (IL-5 levels) were observed. This

study used IFN-γ/IL-4 or IFN-γ/IL-5 ratios as markers for Th1 or Th2 responses, with higher ratios in mice treated with the spores containing NAP, indicating a predominantly Th1 response. Therefore, NAP led to an immune switch from Th2 to Th1 response due to up-regulation of Tregs after FA challenge [45].

Our results exhibit considerable heterogeneity, likely due to the small sample size of the articles analyzed, which impedes the establishment of a definitive trend. In a review by Liu *et al.*, the role of Hp in protecting against FA is described as confounding and often contradictory: some meta-analyses indicate a protective effect, while others fail to reach any conclusion [40]. Liu further acknowledges that the current literature on this topic is limited, potentially contributing to the paucity of reports available for review.

Inflammatory Bowel Disease

Five articles on IBD were reviewed, with studies originating from Europe, Asia, America, and the Middle East. Only one study analyzed UC and CD separately, while the others examined unspecified IBD. Taskin's study should thus be counted twice [33]. Of the six studies, one (16.7%) found a positive link between UC and Hp infection, one (16.7%) found an inverse relation between IBD and Hp infection, one (16.7%) found an inverse relation between CD and Hp infection, and three (50%) found no relation. Our findings show a similar number of studies supporting diverse and conflicting associations, highlighting the need to compare these results with existing meta-analyses and systematic reviews.

The multifactorial nature of the disease and varied clinical symptoms make studying IBD and Hp infection challenging. Both conditions are Th1 driven, so the competitive immune response is unconvincing. Dysbiosis, a key risk factor for IBD, is also a natural consequence of the alkaline environment promoted by Hp infection, especially in long-term infections, since we know Hp infection can occur during early-life, and can lead to changes in the gastric and intestinal microbiome linked to gastric cancer. Investigating these microbiome changes could offer new insights into IBD, beyond just identifying the pathogen and its connection to the disease's complex clinical manifestations, especially in children [40, 46].

A systematic review and meta-analysis by Kong *et al.*, which included six articles, concluded that there is no relation between Hp and IBD. This finding was consistent for both UC and CD, aligning with most of our findings [47]. In a 2019 meta-analysis by Tepler *et al.*, which included three studies, it was found that CagA seropositivity was associated with a 69% lower chance of developing IBD and a 75% lower chance of developing CD, but no significant relation was found for UC [33, 48]. These results suggest that aggressive Hp CagA-producing species may alter immune tolerance and impact gut-level tolerance.

Rokkas *et al.* analyzed 33 articles on Hp and IBD, including UC and CD. They found a risk ratio of 0.62 for IBD, 0.38 for CD, and 0.53 for UC, confirming an inverse relationship between Hp infection and IBD. This correlation remained consistent even when analyzing each type of IBD separately. An analysis by study type was conducted to understand the heterogeneity, and the relationship was still evident [49]. Our results reflect the existing dichotomy in literature.

Miscellaneous

Various allergic/atopic diseases, including AR, non-allergic rhinitis, CU, and HSP, were covered in five articles from Europe, Asia, South America, and the Middle East. Due to the limited number of reports for each disease, we combined them into a single category and summarized the evidence.

The only article about CU observed a linear relationship between CU and eradication therapy. Though it provided numerical data without statistical significance, it noted that most patients experienced significant improvement in urticarial symptoms post-therapy, supporting this conclusion clinically if not statistically [36].

In regard to HSP, the article found no significant statistical relation between this entity and Hp infection or other infections. However, it notes that patients showed symptom improvement when treated for diagnosed infections in addition to standard therapy. This suggests that while Hp infection may not have a direct link to HSP, the underlying physiopathology might play a significant role, even if it is not fully understood [37].

One article each addressed allergy and atopy. Although an inverse relationship between allergy and Hp infection was noted (prevalence increased post-eradication), no significant link was found for atopic diseases. The review included one article each on AR, NARES, and Rc. AR and NARES showed a linear relationship with Hp infection in adults, while Rc displayed an inverse relationship observed across the entire study group [17, 22, 38].

These results appear dichotomous, likely due to the limited number of articles per disease. Liu *et al.* [40] notes in his review that the role of Hp infection in allergic diseases like AR is still uncertain, with some reports suggesting a protective role. However, due to the limited number of studies, these conclusions lack validity.

In a study published by Fan G. *et al.*, the association between Hp and allergic diseases genetic polymorphisms was investigated. The conclusions are as follow: (1) CagA, IgG and urea antibodies showed no statistical relation with allergic diseases; (2) there was a linear relation between allergic urticaria and CagA (O.R. 1.179); (3) the VacA antibody had a causal relation with allergic conjunctivitis; (4) other conditions such as allergic asthma, AD, and AR showed no direct relation with Hp infection, even though the VacA antibody had a causal relation with allergic conjunctivitis [50]. The results from the literature reflect our findings, showing conflicting evidence, no apparent consensus, and high variability in allergic and atopic diseases studies.

Conclusion

In summary, our findings are as follows: (1) for asthma, we identified several studies that indicate a protective role, consistent with existing literature and previous meta-analyses; (2) most articles that examined CeD found no relationship between this condition and Hp infection, despite contrasting with prior literature suggesting a protective role; (3) no association was observed between EoE and Hp infection in our review, which does not support existing literature; (4) regarding FA, no dominant trend emerged, with an equal number of studies reporting linear, inverse, and null relationships, which aligns with observations in other literature; (5) most articles on IBD showed a null relation, with some showing an inverse relation, consistent with existing

literature where the predominant finding is also an inverse association; (6) no clear trend was observed for other allergic, atopic, and immune diseases, aligning with current literature. This review found an inverse, protective relation between Hp infection and asthma, particularly in childhood, and to a lesser extent IBD.

This review has some limitations. In certain conditions, the limited number of selected articles restricted our ability to establish trends, but possibly diminished bias as the quality of the articles has been a major factor in this selection. Some articles did not primarily focus on the relationship between the chosen conditions and Hp infection, leading to a less detailed analysis. Additionally, we excluded articles that addressed related outcomes but focused on other topics like therapeutic approaches and prognosis, which did not align with the goals of this review.

Some barriers are also worth mentioning, namely the fact that it's hard obtaining permission to conduct an exclusively pediatric study and subject these patients to invasive diagnostic methods just for investigative purposes. Furthermore, guaranteeing a representative sample according to the geographical characteristics, prevalence and incidence of both the exposure and the outcome can be a demanding task. Also worthy of mention is the fact that the standard method criteria for diagnosis varies from country to country. Regional adherence to published guidelines is very low, implying that some individuals might be included or even excluded from the study, whilst they might be valid subjects.

Therefore, in future studies it would be pertinent to conduct a well-designed study, with a representative population according to the geographical area, whilst making sure that there is equality in diagnostic and inclusion criteria. It would also be important to compare the results with other geographical areas to understand the impact of Hp infection in diverse genetic background populations and their environmental influences, such as microbiome profiles, infectious exposure to other microorganisms other than Hp and long-term influence of Hp on gastric cancer. This could bring us a future guidance on the best treatment options and timely eradication of Hp.

References

1. Le Thi, T.G., et al., *Factors Associated With Decision to Treat or Not to Treat Helicobacter pylori Infection in Children: Data From the EuroPedHp Registry.* Helicobacter, 2024. **29**(5): p. e13134.
2. Kalach, N., P. Bontems, and J. Raymond, *Helicobacter pylori infection in children.* Helicobacter, 2017. **22**.
3. Lunet, N., et al., *Child day-care attendance and Helicobacter pylori infection in the Portuguese birth cohort Geração XXI.* Eur J Cancer Prev, 2014. **23**(3): p. 193-8.
4. Osaki, T., et al., *Analysis of intra-familial transmission of Helicobacter pylori in Japanese families.* J Med Microbiol, 2015. **64**(Pt 1): p. 67-73.
5. Sustmann, A., M. Okuda, and S. Koletzko, *Helicobacter pylori in children.* Helicobacter, 2016. **21**: p. 49-54.
6. Bugaytsova, J.A., et al., *Helicobacter pylori Adapts to Chronic Infection and Gastric Disease via pH-Responsive BabA-Mediated Adherence.* Cell Host Microbe, 2017. **21**(3): p. 376-389.
7. Mišak, Z., I. Hojsak, and M. Homan, *Review: Helicobacter pylori in pediatrics.* Helicobacter, 2019. **24 Suppl 1**: p. e12639.
8. van den Heuvel, D., et al., *Effects of nongenetic factors on immune cell dynamics in early childhood: The Generation R Study.* J Allergy Clin Immunol, 2017. **139**(6): p. 1923-1934.e17.
9. Yörgüç, E., et al., *Comparison of clinical outcomes and FOXP3, IL-17A responses in Helicobacter pylori infection in children versus adults.* Helicobacter, 2021. **26**(3): p. e12795.
10. Homan, M., et al., *Updated joint ESPGHAN/NASPGHAN guidelines for management of Helicobacter pylori infection in children and adolescents (2023).* Journal of Pediatric Gastroenterology and Nutrition, 2024. **79**(3): p. 758-785.
11. Chen, Y., X. Zhan, and D. Wang, *Association between Helicobacter pylori and risk of childhood asthma: a meta-analysis of 18 observational studies.* J Asthma, 2022. **59**(5): p. 890-900.
12. Dore, M.P., et al., *The association of childhood asthma and Helicobacter pylori infection in Sardinia.* Archives of Pediatric Infectious Diseases, 2014. **2**(3).
13. Khamechian, T., et al., *Evaluation of the Correlation Between Childhood Asthma and Helicobacter pylori in Kashan.* Jundishapur J Microbiol, 2015. **8**(6): p. e17842.
14. den Hollander, W.J., et al., *Helicobacter pylori in children with asthmatic conditions at school age, and their mothers.* Aliment Pharmacol Ther, 2016. **43**(8): p. 933-943.
15. Yousefichaijan, P., et al., *Helicobacter pylori seropositivity in children with asthma.* Archives of Pediatric Infectious Diseases, 2016. **4**(1).
16. Fouda, E.M., et al., *Helicobacter pylori seropositivity protects against childhood asthma and inversely correlates to its clinical and functional severity.* Allergol Immunopathol (Madr), 2018. **46**(1): p. 76-81.
17. Molina-Infante, J., et al., *Helicobacter pylori infection does not protect against eosinophilic esophagitis: results from a large multicenter case-control study.* Am J Gastroenterol, 2018. **113**(7): p. 972-979.
18. Tsigalou, C., et al., *Inverse association between Helicobacter pylori infection and childhood asthma in Greece: a case-control study.* Germs, 2019. **9**(4): p. 182-187.
19. Elias, N., et al., *Associations of Helicobacter pylori seropositivity and gastric inflammation with pediatric asthma.* Pediatric Pulmonology, 2020. **55**(9): p. 2236-2245.
20. Melby, K.K., et al., *Helicobacter pylori in early childhood and asthma in adolescence.* BMC Res Notes, 2020. **13**(1): p. 79.
21. Wang, D.H., et al., *Inverse association between Helicobacter pylori infection and childhood asthma in a physical examination population: a cross-sectional study in Chongqing, China.* Bmc Pediatrics, 2022. **22**(1).

22. Dore, M., et al., *Helicobacter pylori Infection Does Not Protect Against Allergic Diseases: Evidence From a Pediatric Cohort From Northern Sardinia, Italy.* Helicobacter, 2024. **29**(3).
23. Hrizat, A.S., et al., *Association of Helicobacter pylori Infection with Pediatric Asthma in Palestine.* Pediatr Gastroenterol Hepatol Nutr, 2025. **28**(1): p. 27-37.
24. Jozefczuk, J., et al., *Prevalence of Helicobacter pylori infection in pediatric celiac disease.* European Review for Medical and Pharmacological Sciences, 2015. **19**(11): p. 2031-2035.
25. Czaja-Bulsa, G., M. Bulsa, and A. Gębala, *Food IgG4 antibodies are elevated not only in children with wheat allergy but also in children with gastrointestinal diseases.* BMC Gastroenterol, 2016. **16**: p. 39.
26. Tumgor, G., et al., *Frequency of Celiac Disease in Children with Peptic Ulcers.* Dig Dis Sci, 2018. **63**(10): p. 2681-2686.
27. Agin, M., et al., *Prevalence of Helicobacter pylori in Turkish children with celiac disease and its effect on clinical, histopathological, and laboratory parameters.* Archives of Medical Science, 2019. **15**(6): p. 1475-1481.
28. Bayrak, N.A. and B. Volkan, *Helicobacter pylori Infection in Children with Concurrent Celiac Disease and Type 1 Diabetes Mellitus.* Dig Dis, 2021. **39**(5): p. 444-450.
29. Akkelle, B.S., et al., *Low Titer Tissue Transglutaminase Antibodies: A Link to Helicobacter pylori Infection?* Digestive Diseases, 2022. **40**(2): p. 168-174.
30. Kotilea, K., et al., *Helicobacter pylori infection found during upper endoscopy performed for the diagnosis of celiac, inflammatory bowel diseases, and eosinophilic esophagitis: A multicenter pediatric European study.* Helicobacter, 2024. **29**(3): p. e13092.
31. Pedullà, M., et al., *Helicobacter pylori immunization and atopic dermatitis in South Italian children.* United European Gastroenterology Journal, 2014. **2**(4): p. 263-267.
32. Roka, K., et al., *The prevalence of Helicobacter pylori gastritis in newly diagnosed children with inflammatory bowel disease.* Helicobacter, 2014. **19**(5): p. 400-5.
33. Taşkın, D.G., *Evaluation of the Presence of Helicobacter Pylori in Inflammatory Bowel Disease in Children.* Medical Journal of Bakirkoy, 2023. **19**(1): p. 93-96.
34. Dilaghi, E., et al., *Helicobacter Pylori infection in children with inflammatory bowel disease: a prospective multicenter study.* BMC Pediatr, 2024. **24**(1): p. 417.
35. Villalba-Davila, P., et al., *Helicobacter pylori infection is associated with significant elevations to fecal calprotectin, systemic inflammatory markers.* J Pediatr Gastroenterol Nutr, 2025.
36. Akelma, A.Z., et al., *A neglected cause for chronic spontaneous urticaria in children: Helicobacter pylori.* Allergol Immunopathol (Madr), 2015. **43**(3): p. 259-63.
37. Wang, J.J., et al., *Association of the infectious triggers with childhood Henoch-Schonlein purpura in Anhui province, China.* J Infect Public Health, 2020. **13**(1): p. 110-117.
38. Akiner, U., et al., *Helicobacter pylori in allergic and non-allergic rhinitis does play a protective or causative role?* Eur Arch Otorhinolaryngol, 2020. **277**(1): p. 141-145.
39. Karakullukcu, A., et al., *The protective role of Helicobacter pylori neutrophil-activating protein in childhood asthma.* Allergol Immunopathol (Madr), 2017. **45**(6): p. 521-527.
40. Liu, M., Y. Wang, and B. Du, *Update on the association between Helicobacter pylori infection and asthma in terms of microbiota and immunity.* Allergy Asthma Clin Immunol, 2024. **20**(1): p. 4.
41. Husby, S., et al., *European Society Paediatric Gastroenterology, Hepatology and Nutrition Guidelines for Diagnosing Coeliac Disease 2020.* J Pediatr Gastroenterol Nutr, 2020. **70**(1): p. 141-156.
42. Amlashi, F.I., et al., *A systematic review and meta-analysis for association of Helicobacter pylori colonization and celiac disease.* PLoS One, 2021. **16**(3): p. e0241156.
43. Shah, S.C., et al., *Association Between Helicobacter pylori Exposure and Decreased Odds of Eosinophilic Esophagitis-A Systematic Review and Meta-analysis.* Clin Gastroenterol Hepatol, 2019. **17**(11): p. 2185-2198.e3.

44. Spinelli, I., et al., *Meta-Analysis: Inverse Association Between Helicobacter pylori Infection and Eosinophilic Oesophagitis.* Alimentary Pharmacology and Therapeutics, 2025.
45. Mai, J., et al., *Oral administration of recombinant Bacillus subtilis spores expressing Helicobacter pylori neutrophil-activating protein suppresses peanut allergy via up-regulation of Tregs.* Clin Exp Allergy, 2019. **49**(12): p. 1605-1614.
46. Yu, Y., et al., *Helicobacter pylori infection and inflammatory bowel disease: a crosstalk between upper and lower digestive tract.* Cell Death Dis, 2018. **9**(10): p. 961.
47. Kong, G., et al., *The association between Helicobacter pylori infection and inflammatory bowel disease in children: A systematic review with meta-analysis.* Medicine (Baltimore), 2023. **102**(36): p. e34882.
48. Tepler, A., et al., *Systematic review with meta-analysis: association between Helicobacter pylori CagA seropositivity and odds of inflammatory bowel disease.* Aliment Pharmacol Ther, 2019. **50**(2): p. 121-131.
49. Rokkas, T., et al., *The association between Helicobacter pylori infection and inflammatory bowel disease based on meta-analysis.* United European Gastroenterol J, 2015. **3**(6): p. 539-50.
50. Fan, G.Z., et al., *Assessment of the bidirectional causal association between Helicobacter pylori infection and allergic diseases by mendelian randomization analysis.* Sci Rep, 2025. **15**(1): p. 5746.

Appendix

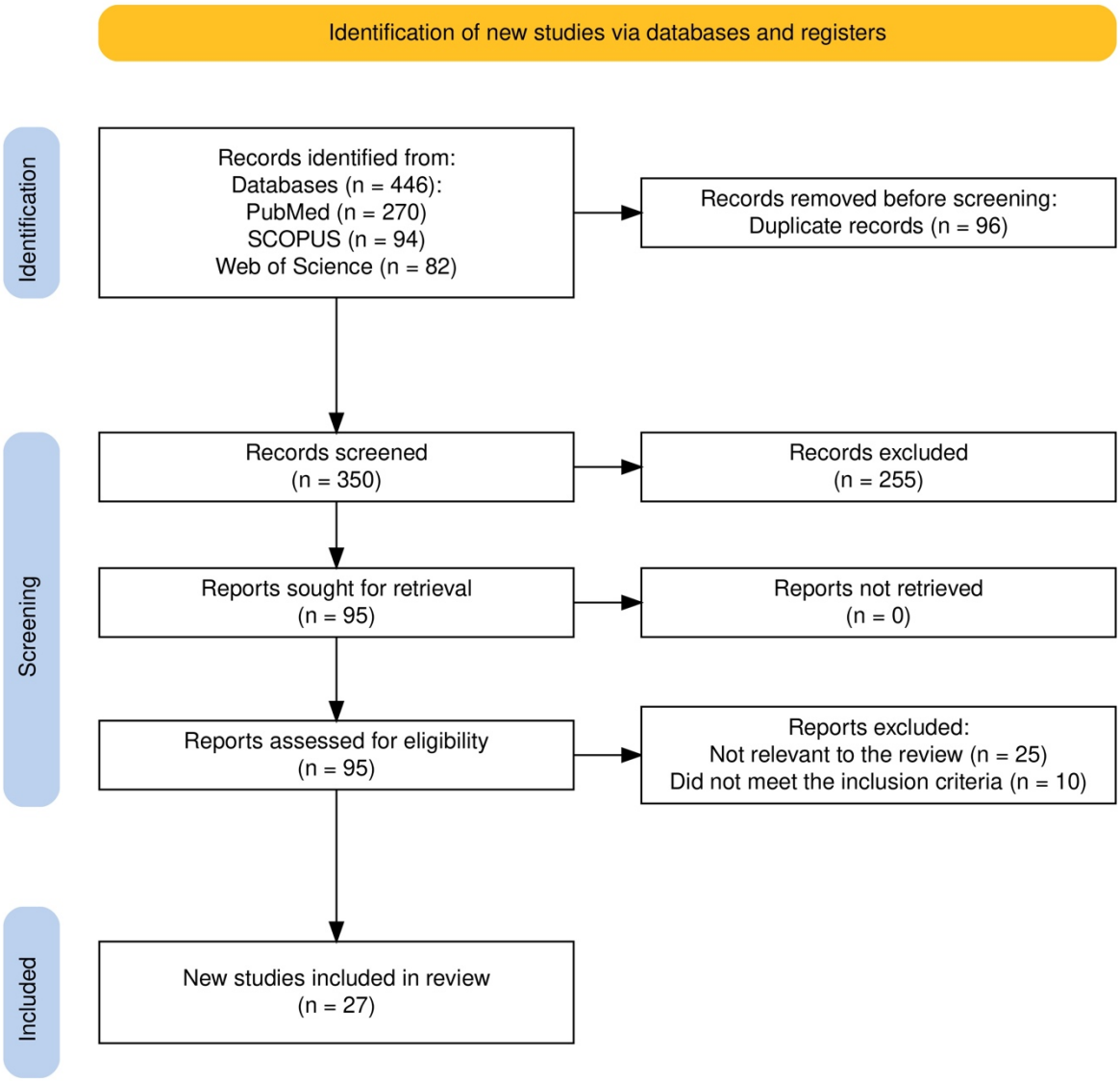

Figure 1

PRISMA flow diagram according to "PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only".

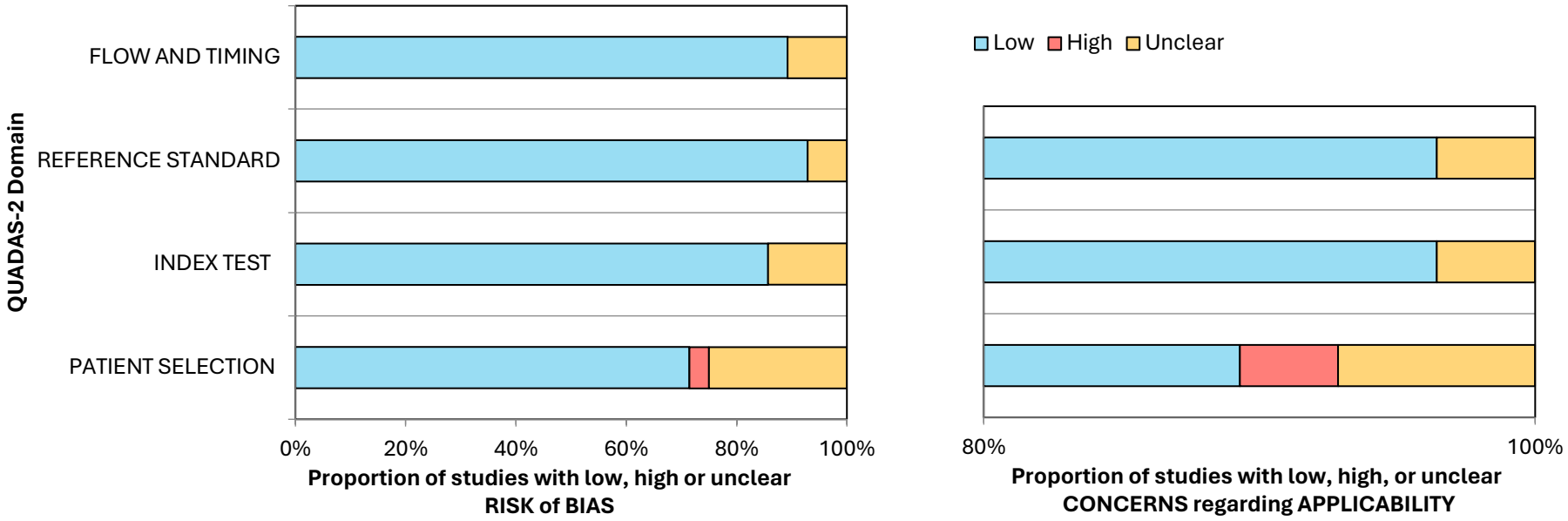

Figure 2

Summation of QUADAS-2 analysis of risk of bias and concerns regarding applicability – 28 articles were analyzed regarding the risk of bias: within patient selection 20 articles were identified as having low risk, 7 as unclear risk and 1 as high risk; within the index test 24 were low risk and 4 were unclear; within the reference standards 26 were low risk and 2 were unclear; within flow and timing 25 were low risk and 3 were unclear. Regarding applicability, within patient selection 25 articles were identified as having low risk, 2 as unclear risk and 1 as high risk; within the index test 27 were low risk and 1 was unclear; within the reference standards 27 were low risk and 1 was unclear. The one article identified as having high risk was excluded from the review.

Table IA

Summation of the included articles main characteristics, including title, author, publication year, country, study type, population, main characteristics of population, study objectives, prevalence/incidence of Hp infection, what allergic or immune diseases the study focus on, the incidence/prevalence of said disease and what relation the study assessed between Hp infection and the disease *[Continues with Table IB]*.

Title	Author	Publication Year	Journal	Country	Study Type	Population (n)	References
A neglected cause for chronic spontaneous urticaria in children: *Helicobacter pylori*	A. Z. Akelma, M. N. Cizmeci, E. Mete, N. Tufan and B. Bozkurt	2015	Allergology and Immunopathology (Madrid)	Turkey	Prospective	67	[36]
Association of *Helicobacter pylori* Infection with Pediatric Asthma in Palestine	A. S. Hrizat, A. A. Shahin, B. M. Mafarjeh, M. A. Atawneh, K. Gharaibeh, N. Rumman, et al.	2025	Pediatric Gastroenterology Hepatology and Nutrition	Palestine	Prospective, Case-Control	143	[23]
Association of the infectious triggers with childhood Henoch-Schönlein Purpura in Anhui province, China	J. J. Wang, Y. Xu, F. F. Liu, Y. Wu, S. Samadli, Y. F. Wu, et al.	2020	Journal of Infection and Public Health	China	Observational	1200	[37]
Associations of *Helicobacter pylori* seropositivity and gastric inflammation with pediatric asthma	N. Elias, E. Nasrallah, C. Khoury, B. Mansour, L. Abu Zuher, V. Asato, et al.	2020	Pediatric Pulmonology	Israel	Case-Control	235	[19]
Evaluation of the Correlation Between Childhood Asthma and *Helicobacter pylori* in Kashan	T. Khamechian, A. H. Movahedian, G. Ebrahimi Eskandari, M. Heidarzadeh Arani and A. Mohammadi	2015	Jundishapur Journal Microbiology	Iran	Observational	300	[13]
Evaluation of the Presence of *Helicobacter Pylori* in Inflammatory Bowel Disease in Children	Didem Gülcü Taşkın	2023	Medical Journal of Bakirkoy	Turkey	Retrospective	50	[33]
Food IgG4 antibodies are elevated not only in children with wheat allergy but also in children with gastrointestinal diseases	G. Czaja-Bulsa, M. Bulsa and A. Gębala	2016	BMC Gastroenterology	Poland	Case control	200	[25]
Frequency of Celiac Disease in Children with Peptic Ulcers	G. Tumgor, M. Agin, F. Doran and S. Cetiner	2018	Digestive Diseases and Sciences	Turkey	Observational	74	[26]
Helicobacter pylori immunization and atopic dermatitis in South Italian children	M. Pedulla, V. Fierro, E. Del Tufo, R. Alfano, M. Triassi and L. Perrone	2014	United European Gastroenterology Journal	Italy	Observational	290	[31]

Title	Author	Publication Year	Journal	Country	Study Type	Population (n)	References
Helicobacter pylori in allergic and non-allergic rhinitis does play a protective or causative role?	U. Akiner, H. Murat Yener, E. Deniz Gozen, S. Burcu Kuzu and Salih Canakcioglu	2020	European Archives of Oto-Rhino-Laryngology	Turkey	Cross-Sectional Observation	349	[38]
Helicobacter pylori in children with asthmatic conditions at school age, and their mothers	W. Hollander, A. Voort, I. Holster, J. Jongste, V. Jaddoe, A. Hofman, G. Perez-Perez, H. Moll, M. Blaser, L. Duijts and E. Kuipers	2016	Alimentation, Pharmacology and Therapy	Netherlands	Cohort	6707	[14]
Helicobacter pylori in early childhood and asthma in adolescence	K. Melby, K. Carlsen, G. Håland, H. Samdal and K. Carlsen	2020	BMC Research Notes	Norway	Cohort	197	[20]
Helicobacter pylori Infection Does Not Protect Against Allergic Diseases: Evidence From a Pediatric Cohort From Northern Sardinia, Italy	M. Dore, G. Meloni, I. Bassu and G. Pes	2024	Helicobacter	Italy	Prospective	492	[22]
Helicobacter Pylori Infection Does Not Protect Against Eosinophilic Esophagitis: Results From A Large Multicenter Case-Control Study	J. Molina-Infante, C. Gutierrez-Junquera, E. Savarino, R. Penagini, I. Modolell, O. Bartolo, A. García, A. Mauro, J. Alcedo, A. Perelló, C. Argente, N. Alcaide, A. Vegas, P. Barros-García, M. Pulgar, M. Perona, J. Gisbert and A. Lucendo	2018	The American Journal of Gastroenterology	Spain, Italy, France and Colombia	Prospective Case Control	808	[17]
Helicobacter pylori infection found during upper endoscopy performed for the diagnosis of celiac, inflammatory bowel diseases, and eosinophilic esophagitis: A multicenter pediatric European study	K. Kotilea, C. Romano, E. Miele, A. Kindermann, Y. Dolstra, Z. Misak, et al.	2024	Helicobacter	Belgium, France, Netherlands, Czech Republic, Croatia, Lithuania, Serbia, Portugal, Spain, Greece, Italy, Israel, Turkey and Armenia	Retrospective	3890	[30]
Helicobacter pylori Infection in Children with Concurrent Celiac Disease and Type 1 Diabetes Mellitus	N. Bayrak and B. Volkan	2021	Digestive Diseases	Turkey	Case-Control	783	[28]

Title	Author	Publication Year	Journal	Country	Study Type	Population (n)	References
Helicobacter Pylori infection in children with inflammatory bowel disease: a prospective multicenter study	E. Dilaghi, E. Felici, E. Lahner, E. Pilozzi, S. Furio, L. Lucchini, G. Quatrale, M. Piccirillo, P. Parisi, S. Curto, B. Annibale, A. Ferretti, M. Mennini, S. Persechino and G. Nardo	2024	BMC Pediatrics	Italy	Prospective Case-Control	224	[34]
Helicobacter pylori infection is associated with significant elevations to fecal calprotectin, systemic inflammatory markers	P. Villalba-Davila, S. Aronson, J. Lat, C. Charles, B. Schroeder, M. Pittman, V. Tang and Thomas Wallach	2025	Journal of Pediatric Gastroenterology and Nutrition	USA	Retrospective	129	[35]
Helicobacter pylori seropositivity in children with asthma	P. Yousefichaijan, G. Mosayebi, M. Sharafkhah, M. Kahbazi, P. Heydarbagi and M. Rafiei	2016	Archives of Pediatric Infectious Diseases	Iran	Cross-Sectional	208	[15]
Helicobacter pylori seropositivity protects against childhood asthma and inversely correlates to its clinical and functional severity	E. M. Fouda, T. B. Kamel, E. S. Nabih and A. A. Abdelazem	2018	Allergology and Immunopathology (Madrid)	Egypt	Cross-Sectional	180	[16]
Inverse association between *Helicobacter pylori* infection and childhood asthma in a physical examination population: a cross-sectional study in Chongqing, China	D. H. Wang, Y. X. Chen, Y. Ding and J. W. Tu	2022	Bmc Pediatrics	China	Cross-Sectional	2241	[21]
Inverse association between *Helicobacter pylori* infection and childhood asthma in Greece: a case-control study	C. Tsigalou, T. G. Konstantinidis, D. Cassimos, A. Karvelas, A. Grapsa, A. Tsalkidis, et al.	2019	Germs	Greece	Case-Control	81	[18]
Low Titer Tissue Transglutaminase Antibodies: A Link to *Helicobacter pylori* Infection?	B. S. Akkelle, O. K. Sengul, E. Tutar, B. Volkan, C. Celikel and D. Ertem	2022	Digestive Diseases	Turkey	Prospective	155	[29]
Prevalence of *Helicobacter pylori* in Turkish children with celiac disease and its effect on clinical, histopathological, and laboratory parameters	M. Agin, I. Batun, S. Ozdemir, F. Doran and G. Tumgor	2019	Archives of Medical Science	Turkey	Prospective	1268	[27]
Prevalence of *Helicobacter pylori* infection in pediatric celiac disease	J. Jozefczuk, B. Bancerz, M. Walkowiak, A. Glapa, J. Nowak, J. Piescikowska, et al.	2015	European Review for Medical and Pharmacological Sciences	Poland	Retrospective	370	[24]

Title	Author	Publication Year	Journal	Country	Study Type	Population (n)	References
The association of childhood asthma and *Helicobacter pylori* infection in Sardinia	M. P. Dore, M. Massidda, G. F. Meloni, S. Soro, G. M. Pes and D. Y. Graham	2014	Archives of Pediatric Infectious Diseases	Italy	Observational	64	[12]
The prevalence of *Helicobacter pylori* gastritis in newly diagnosed children with inflammatory bowel disease	K. Roka, A. Roubani, K. Stefanaki, I. Panayotou, E. Roma and G. Chouliaras	2014	Helicobacter	Greece	Retrospective	1368	[32]

Table IB

Summation of the included articles main characteristics, including title, author, publication year, country, study type, population, main characteristics of population, study objectives, diagnosis method for Hp infection, prevalence/incidence of Hp infection, what allergic or immune diseases the study focus on, the incidence/prevalence of said disease and what relation the study assessed between Hp infection and the disease *[Continuation of Table IA]; [yo: years old, HSP: Henoch-Schönlein Purpura, CU: Chronic Urticaria, WA: Wheat Allergy, CD: Chron's Disease, UC: Ulcerative Colitis, ET: Eradication Therapy, Hp: Helicobacter pylori, IBD: Inflammatory Bowel Disease, CeD: Celiac Disease, AD: Atopic Dermatitis, FA: Food Allergy, A: Asthma, CagA: Cytotoxin Associated Gene A, EoE: Eosinophilic Esophagitis, Rc: rhino conjunctivitis, PPI: Proton Pump Inhibitor, UGE: Upper Gastrointestinal Endoscopy, ESS: Endoscopic Severity Score, CAI: Clinical Activity Index, DMT1: Diabetes Mellitus Type 1, FU: Follow-up, FC: Fecal Calprotectin, TGT IgA: IgA anti-transglutaminase antibody, MA: mean age, +: with, -: without].*

Title	Population Characteristics	Outcome	Hp Diagnosis Method	Hp Infection Incidence/Prevalence	Disease	Disease Incidence/ Prevalence	Hp and Disease Relation	References
A neglected cause for chronic spontaneous urticaria in children: *Helicobacter pylori*	32 Children (3-15 yo) 35 Adults (21-80 yo)	Risk factors and treatment response to Hp infection in children with Chronic Urticaria	SAT	Children: 31.2% (10/32) Adults: 51.4% (18/35)	Chronic Urticaria	100% (67/67)	Clinical linear relation (eradication therapy improved CU symptoms)	[36]
Association of *Helicobacter pylori* Infection with Pediatric Asthma in Palestine	143 Children (6-15 yo)	Association between Hp infection and childhood asthma	SAT	45% (64/143) Control: 51% (50/99) Cases: 32% (14/44)	Asthma	31% (44/143)	Inverse relation (Hp+ children had lesser likelihood of asthma)	[23]
Association of the infectious triggers with childhood Henoch-Schönlein Purpura in Anhui province, China	672 Males 528 Females (7-17 yo)	Association of infectious triggers with childhood HSP	Serology	5.92% (71/1200)	Henoch-Schönlein Purpura	100% (1200/1200)	No relation found	[37]
Associations of *Helicobacter pylori* seropositivity and gastric inflammation with pediatric asthma	235 Children (4.8-17.3 yo)	Assessment of inverse relation between Hp infection and pepsinogen levels with pediatric asthma	Serology	35% (83/235) Controls: 40% Cases: 25%	Asthma	32% (75/235)	Inverse relation (O.R. 0.30)	[19]

Title	Population Characteristics	Outcome	Hp Diagnosis Method	Hp Infection Incidence/Prevalence	Disease	Disease Incidence/ Prevalence	Hp and Disease Relation	References
Evaluation of the Correlation Between Childhood Asthma and *Helicobacter pylori* in Kashan	300 People (5-18 yo)	Correlation between Hp and Asthma	Biopsy Histology	46% (138/300) Asthma+/Hp+: 5.8% (8/138) Asthma-/Hp+: 94.2% (130/138)	Asthma	12% (36/300) Hp+/Asthma +: 22% (8/36) Hp-/Asthma+: 78% (28/36)	Inverse Relation	[13]
Evaluation of the Presence of *Helicobacter Pylori* in Inflammatory Bowel Disease in Children	50 Children (MA: 15.3 yo) 22 Females 28 Males 45 Turkish 5 Non-Turkish	Prevalence of Hp infection in IBD patients and its distribution between CD and UC	Biopsy Histology	28% (14/50) UC+:71% (10/14) CD+:21% (3/14)	Inflammatory Bowel Disease (Chron's Disease and Ulcerative Colitis)	UC: 50% (25/50) Hp+: 10 Hp-: 15 CD: 42% (21/50) Hp+: 3 Hp-: 15	Linear relation with UC Inverse relation with CD	[33]
Food IgG4 antibodies are elevated not only in children with wheat allergy but also in children with gastrointestinal diseases	200 People 50 Wheat allergy 50 Celiacs disease 50 Hp 50 Controls	Frequency and titters of wheat and rice sIgG and sIgG4 in healthy children *vs* children with IgE-mediated WA, with CeD and Hp	Biopsy Histology	25% (50/200)	Celiac Disease and Wheat Allergy	CeD: 25% (50/200) WA: 25% (50/200)	Linear relation between Hp/Celiac Disease/ Wheat Allergy and IgG4 and IgG antibodies	[25]
Frequency of Celiac Disease in Children with Peptic Ulcers	74 People 36 Females 38 Males	Frequency of celiac disease in children with peptic ulcers and comparison with non-celiac peptic ulcers	Biopsy Histology	50% (37/74) Hp+/CeD+: 64% (14/22) Hp+/CeD-: 44% (23/52)	Celiac Disease	30% (22/74) CeD+/Hp+: 37.8% (14/37) CeD+/Hp-: 21.6% (8/37)	Linear relation	[26]

Title	Population Characteristics	Outcome	Hp Diagnosis Method	Hp Infection Incidence/Prevalence	Disease	Disease Incidence/ Prevalence	Hp and Disease Relation	References
Helicobacter pylori immunization and atopic dermatitis in South Italian children	290 Children (25-142 months old)	Association between specific Hp IgG production in both atopy and FA	Serology	3.8% (11/290) Hp+/AD+ and FA-: 4,5% (9/202) Hp+/AD+ and FA+ not IgE mediated: 8,7% (2/23) Hp+/ AD+ and FA+ IgE mediated: 0% (0/65)	Atopic Dermatitis and Food Allergy	AD: 100% (290/290) FA: 30% (88/290)	Inverse relation	[31]
Helicobacter pylori in allergic and non-allergic rhinitis does play a protective or causative role?	75 Controls 274 Cases (3-104 yo) 104 Females 170 Males	Association between Hp colonization and allergic rhinitis and NARES	SAT	38% (134/349) Cases: 42% (116/274) Controls: 24% (18/75)	Allergic Rhinitis and NARES	79% (274/349)	Linear relation	[38]
Helicobacter pylori in children with asthmatic conditions at school age, and their mothers	6707 People 3797 Children (MA: 6.1 yo) 2910 Mothers (MA: 31.1 yo)	Association between Hp colonization in children and risk of asthma Contribution of maternal Hp status to children status	Serology	Children: 8.7% (332/3797) CagA-: 71% (235/332) CagA+: 29% (97/332) Mothers: 38% (1106/2910) CagA-: 67% (741/1106) CagA+: 33% (365/1106)	Asthma	81% (3062/3797)	Linear relation between CagA negative strains and risk of asthma (O.R. 2.11)	[14]
Helicobacter pylori in early childhood and asthma in adolescence	197 Children	Relation between Hp infection and the risk of childhood asthma	Serology	At 2 years: 6.1% (12/197) At 10 years: 8.6% (17/197)	Asthma	17% (32/197) Hp+/A+: 6.2% (2/32) Hp-/A+: 93.8% (30/32)	Inverse relation, but not significant	[20]

Title	Population Characteristics	Outcome	Hp Diagnosis Method	Hp Infection Incidence/Prevalence	Disease	Disease Incidence/ Prevalence	Hp and Disease Relation	References
Helicobacter pylori Infection Does Not Protect Against Allergic Diseases: Evidence From a Pediatric Cohort From Northern Sardinia, Italy	492 Children (7-37 months old) 48.8% Females 51.2% Males	Relation between Hp infection and the risk of allergic diseases	Serology	11.8% (58/492) Allergy+/Hp+: 5.2% (3/58) A+/Hp+: 6.9% (4/58)	Asthma and Atopic Diseases	Atopic Disorders: 8.9% (44/492) Hp+/Atopy+: 82% (36/44) Hp-/Atopy+: 18% (8/44) Asthma: 72.7% (32/44) Hp+/A+: 12% (4/32) Hp-/A+: 88% (28/32)	No relation found	[22]
Helicobacter Pylori Infection Does Not Protect Against Eosinophilic Esophagitis: Results From A Large Multicenter Case-Control Study	808 People (2-83 yo) 586 Males 222 Females	Prevalence of Hp infection in a large cohort of pediatric and adult EoE patients *vs* symptomatic controls Differential Hp prevalence between children and adults, atopic and non-atopic and responders and non-responders to PPI therapy	UBT SAT Biopsy Histology	39% (312/808) Children: 45% (77/170) Adults: 37% (235/638) Atopic: 34% Non-Atopic: 42%	Eosinophilic Esophagitis and Atopic Diseases (Asthma, Food Allergy, Atopic Dermatitis, Rhino conjunctivitis)	EoE: 50% (404/808) Atopic Disorders: 51% (410/808) Asthma: 29% (236/808) Food allergy: 18% (146/808) Atopic dermatitis: 9.9% (80/808) Rc: 39% (317/808)	No relation found	[17]

Title	Population Characteristics	Outcome	Hp Diagnosis Method	Hp Infection Incidence/Prevalence	Disease	Disease Incidence/ Prevalence	Hp and Disease Relation	References
Helicobacter pylori infection found during upper endoscopy performed for the diagnosis of celiac, inflammatory bowel diseases, and eosinophilic esophagitis: A multicenter pediatric European study	3890 Children 1 Child IBD+ EoE+ CeD 2 Children IBD+EoE 5 Children CeD+EoE	Frequency of Hp infection during UGE performed for the diagnosis of CeD, IBD, and EoE Number of children who received eradication treatment and its indications	Biopsy Histology	9% (349/3890)	Celiac Disease, Inflammatory Bowel Disease and Eosinophilic Esophagitis	CeD: 45% (1733/3890) Hp+/CeD+: 10% (173/1733) IBD: 33% (1292/3890) Hp+/IBD+: 8.5% (110/1292) EoE: 22% (865/3890) Hp+/EoE+: 7.6% (66/865)	No relation found	[30]
Helicobacter pylori Infection in Children with Concurrent Celiac Disease and Type 1 Diabetes Mellitus	783 Children	Association between Hp and concomitant CeD+DMT1 in children	Biopsy Histology with rapid urease test	43% (333/783) Hp+/CeD+: 32% (69/215) Hp+/ CeD+DMT1+: 21% (13/63)	Celiac Disease and Celiac Disease with Type 1 Diabetes Mellitus	CeD: 27% (215/783) CeD+/Hp+: 21% (69/333) CeD+DMT1: 8.0% (63/783) CeD+DMT1/Hp+: 3.9% (13/333)	Inverse Relation	[28]
Helicobacter Pylori infection in children with inflammatory bowel disease: a prospective multicenter study	224 Children (1-17 yo) 76 Cases 148 Controls 106 Females 118 Males	Hp infection occurrence in newly diagnosed IBD pediatric-patients *vs* non-IBD patients Differential CAI and ESS between IBD-patients with and without Hp-infection, at baseline and 1-year-FU, after ET	Biopsy Histology	11% (25/224) Hp+/IBD+: 9.2% (7/76) Hp+/IBD-: 12% (18/148)	Inflammatory Bowel Disease (Crohn's Disease and Ulcerative Colitis)	CD: 38% (29/76) UC: 59% (45/76) Unclassified IBD: 2.6% (2/76)	No relation found	[34]

Title	Population Characteristics	Outcome	Hp Diagnosis Method	Hp Infection Incidence/Prevalence	Disease	Disease Incidence/ Prevalence	Hp and Disease Relation	References
Helicobacter pylori infection is associated with significant elevations to fecal calprotectin, systemic inflammatory markers	129 People	Impact of Hp infection on FC and downstream gastrointestinal care	Biopsy Histology	29% (37/129)	Fecal Calprotectin	FC in Hp+: 241.2 μg/g FC in Hp-: 88.1 μg/g	Linear relation (Sidney class. and FC, p=0.0013)	[35]
Helicobacter pylori seropositivity in children with asthma	208 Children (5-12yo) 104 Cases 104 Controls	Hp seropositivity in children with and without asthma	Serology	15% (31/208) Hp+/A+: 13% (13/104) Hp+/A-: 17% (18/104)	Asthma	50% (104/208)	No relation found (p=0.54)	[15]
Helicobacter pylori seropositivity protects against childhood asthma and inversely correlates to its clinical and functional severity	180 Children 90 Controls (2-18yo) 90 Cases (1-17yo) 52 Males 38 Females	Relationship between childhood asthma and Hp infection	Serology	Asthmatics: 26% (23/90) Controls: 45% (40/90)	Asthma	50% (90/180)	Inverse relation (p=0.008)	[16]
Inverse association between *Helicobacter pylori* infection and childhood asthma in a physical examination population: a cross-sectional study in Chongqing, China	2241 Children (MA 8.67 yo) 1240 Males 1001 Females	Relationship between Hp infection and pediatric asthma	UBT	13% (292/2241)	Asthma	6.8% (152/2241) A+/Hp+: 3.8% A+/Hp-: 7.2%	Inverse relation (p<0.05; O.R. 1.995)	[21]
Inverse association between *Helicobacter pylori* infection and childhood asthma in Greece: a case-control study	81 Children 54 Controls 27 Cases 18 Males 9 Females	Prevalence of Hp infection in asthmatic children	Serology SAT	23% (19/81) Hp+/A+: 11% (3/27) Hp+/A-: 30% (16/54)	Asthma	33% (27/81)	Inverse Relation (p=0.026; O.R. 0.1)	[18]
Low Titer Tissue Transglutaminase Antibodies: A Link to *Helicobacter pylori* Infection?	155 Children	Relation between positive celiac serology and concomitant Hp infection in children	Biopsy Histology with rapid urease test	22% (34/155) Hp+/CeD+: 19% (23/119) Hp+/CeD-: 31% (11/36)	Celiac Disease and TGT IgA	77% (119/155) CeD+/Hp+: 68% (23/34) CeD+/Hp-: 79% (96/121)	Positive association between Hp infection and TGT IgA levels	[29]

Title	Population Characteristics	Outcome	Hp Diagnosis Method	Hp Infection Incidence/Prevalence	Disease	Disease Incidence/ Prevalence	Hp and Disease Relation	References
Prevalence of *Helicobacter pylori* in Turkish children with celiac disease and its effect on clinical, histopathological, and laboratory parameters	1268 Children 256 Cases (1-18yo) 1012 Controls	Prevalence of Hp in children with CeD and its relationship with clinical, histopathological, and laboratory parameters	Biopsy Histology	23% (297/1268) Hp+/CeD+: 27% (27/256) Hp+/CeD-: 27% (270/1012)	Celiac Disease	20% (256/1268)	No relation found	[27]
Prevalence of *Helicobacter pylori* infection in pediatric celiac disease	370 Children 296 Controls 74 Cases (MA 6.5 yo) 33 Males 41 Females	Hp infection frequency in a group of pediatric CeD patients at diagnosis Comparison with age-matched healthy population	UBT	13% (48/370) Hp+/CeD+: 11% (8/74) Hp+/CeD-: 14% (40/296)	Celiac Disease	20% (74/370) CeD+/Hp+: 17% (8/48) CeD+/Hp-: 22% (70/322)	No relation found	[24]
The association of childhood asthma and *Helicobacter pylori* infection in Sardinia	64 Children 39 Males 24 Females	Relationship between Hp infection and childhood acquired asthma	Serology	14% (9/64) Hp+/A+: 9.1% (1/11) Hp+/A-: 15% (8/53)	Asthma	17% (11/64) A+/Hp+: 11% (1/9) A+/Hp-: 18% (10/55)	No relation found	[12]
The prevalence of *Helicobacter pylori* gastritis in newly diagnosed children with inflammatory bowel disease	1368 Children 159 Cases 1209 Controls	Prevalence of Hp+ and Hp- gastritis in newly diagnosed children with IBD *vs* without IBD	Biopsy Histology UBT	14% (196/1368) Hp+/IBD+: 3.8% (6/159) Hp+/IBD-: 16% (190/1209)	Inflammatory Bowel Disease	12% (159/1368) IBD+/Hp+: 3.1% (6/196) IBD+/Hp-: 13% (153/1172)	Inverse relation	[32]

INSTITUTO DE **CIÊNCIAS BIOMÉDICAS ABEL SALAZAR**