Inverse correlation between allergy markers and *Helicobacter pylori* infection in children is associated with elevated levels of TGF-β

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Objectives **We evaluated allergy/hypersensitivity clinical markers and their correlation with *Helicobactor pylori* infection in children and adults to analyze how early acquisition of *H. pylori* could modulate allergic disorder expression.**

Patients and methods ***H. pylori*** **presence was assessed by the rapid urease test and histology of antrum biopsies in 165 patients. Skin tests, serum IgE, and two clinical allergy questionnaires were performed. Allergy severity was operationally defined using a combined score. Findings were correlated with *H. pylori* status and cytotoxin-associated gene A presence in pediatric and adult patients. Transforming growth factor β (TGF-β) levels were measured by an enzyme-linked immunosorbent assay in serum and gastric biopsies of *H. pylori* (+) patients.**

Results ***H. pylori*** **(–) children had more positive skin tests to a higher number of antigens than *H. pylori* (+) children ($P<0.05$). Operationally defined allergy inversely correlates with *H. pylori* infection in children, but not in adults. The percentage of *H. pylori* infection was lower in children with severe allergy (32.3%) compared with children with mild allergy (43.4%) or no allergy (64.3%) ($P<0.05$). Colonization with virulent strains (cytotoxin-associated gene A+) showed a nonsignificant inverse correlation with severity of allergies in pediatric patients. *H. pylori*-infected children, but not adults, without allergy markers showed increased levels of TGF-β compared with allergic children both in serum and gastric mucosa ($P<0.05$).**

Conclusion **There was a strong inverse correlation between allergy markers and *H. pylori* infection in pediatric patients associated with elevated levels of TGF-β locally and systemically. *H. pylori*-associated chronic gastritis might downregulate clinical allergy expression. *Eur J Gastroenterol Hepatol* 23:656–663 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

An increase in allergy prevalence has been reported in Western developed countries [1,2]. Although asthma and other allergic disorders are most commonly reported in developed countries, it is becoming increasingly common in developing countries, such as Latin America and Africa [3]. Several models have been proposed to explain this phenomenon. The hygiene hypothesis points to a decline in basal stimulation of the immune system due to decreased exposure to microorganisms in cleaner environments associated with increasing socioeconomical development [4,5]. In contrast, the disappearing microbiota hypothesis suggests that cleaner environments, decrease in breast-feeding, increase in cesarean sections, and general change of lifestyles affect the progression of bacterial colonization in a particular host are responsible for the increase of allergies [6]. Both theories account for a lack of proper formation or maturation of a highly complex mucosal immune system that must learn to differentiate proper and safe antigens from that of dangerous and foreign antigens.

Helicobacter pylori is a Gram-negative bacterium that colonizes gastric epithelium and has been associated with the development of peptic ulcer and gastric cancer, although most carriers develop no symptoms [7]. *H. pylori* meets several assumptions of both theories mainly because it colonizes its host in early childhood and the infection can last for a lifetime. This bacterium has been described to colonize human stomachs for thousands of years and its presence has been described even in pre-Columbian mummies [8]. Such a long-lasting relationship allows us to consider it as a part of the indigenous microbiota. In addition, *H. pylori* is also able to induce a local immune response that is unsuccessful in eradicating the bacteria and is characterized by polymorphonuclear and

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mononuclear infiltrations of gastric tissue. *H. pylori* elicits an infiltration of CD8 + and CD4 + T cells characterized by the secretion of interferon γ (IFN-γ), characteristic of a T helper type 1 (Th)-1 response, [9–11]. A simultaneous T regulatory (Treg) response has also been described in the gastric mucosa of patients infected by *H. pylori* [12–14].

In view of the impact of *H. pylori* on gastroduodenal and extragastric diseases [15], and the local as well as the systemic immune responses associated with *H. pylori*, and considering that a differential immune response in the gastric mucosa of infected children and adults has been described by our group and other investigators [14], we evaluated the relationship between allergy/hypersensitivity markers and *H. pylori* infection in a developing population with a high rate of infection in different age group settings. We hypothesized a negative relationship between allergy markers and *H. pylori* infection.

Patients and methods

Patients

One hundred and sixty-five consecutive individuals with abdominal symptoms were enrolled in this institutional review board-approved study. Criteria for patient inclusion included symptoms suggestive of peptic disease such as hematemesis, nocturnal or burning abdominal pain, chronic vomiting associated with feedings, and suspicion of peptic ulcer relapse. Patients with a history of functional recurrent abdominal pain plus a first-degree relative with an endoscopically proven diagnosis of peptic ulcer disease were also considered as eligible patients. Exclusion criteria included hemodynamically unstable patients and recent antibiotic therapy, antacid, H_2 blocker, proton-pump inhibitors, and bismuth compound or NSAID usage during the previous 4 weeks. A detailed clinical history was obtained from each patient or their parents. Signed informed consent forms by the patients or their parents/legal guardian were obtained.

Endoscopy and assessment of *Helicobactor pylori* infection

Endoscopic procedures were performed in the facilities of the Hospital Clínico of the Pontificia Universidad Católica de Chile and in the Dr Sótero del Rio Hospital. Each individual underwent serum collection at the moment of the venous puncture for sedation. Endoscopic findings were recorded in a separate report form. Serum samples were stored at −70°C and then analyzed for antibodies to whole *H. pylori* (IgG) and cytotoxin-associated gene A [CagA (IgA)] by an enzyme-linked immunosorbent assay (Orgenics, Israel). Cut-off values were determined specifically for this study population for IgG [16]. For CagA–IgA serology, we considered a patient positive if CagA titers were above the mean plus 2 standard deviations of all *H. pylori*-negative patients. An individual was considered to be colonized by *H. pylori* when the IgG anti-*H. pylori* antibodies and either the rapid urease test (Pronto Dry, Ecifarma, Chile) or histological staining of *H. pylori* were positive or when both endoscopy-based techniques were positive.

Evaluation of gastric histopathology

Serial sections of formalin-fixed paraffin-embedded gastric tissue of each patient were stained with hematoxylin and eosin stain and examined for the presence of *H. pylori* and associated pathology by two pathologists in a blinded fashion. Bacteria were identified as *H. pylori* on the basis of size, spiral morphology, and tissue location. In addition, each biopsy specimen was assessed for the presence of polymorphonuclear cell infiltration, mononuclear cell infiltration, lymphoid follicles, atrophy, and intestinal metaplasia according to the Sydney grading system [17].

Allergy/hypersensitivity evaluation

IgE-dependent allergy/hypersensitivity was evaluated through a combination of skin test (ST), serum IgE level, and two clinical questionnaires. An aliquot of the serum collected at the moment of the endoscopy was analyzed for total serum IgE (Immulite-DPC, Los Angeles, California, USA) and the result is expressed in International Units/milliliter. Cut-off levels according to age were used for positivity criteria [18]. Clinical questionnaires and ST were scheduled 1–2 weeks after the endoscopy. Before the ST, type 1 antihistamines, chlorpromazine and derivates and type 2 antihistamines and steroids were discontinued. The ST was performed according to the standard procedure (Laboratories CBF LETI, Spain) [19,20]. Forty standardized allergen extracts, diluent (negative control), and histamine (positive control) were inoculated in the forearm of each patient; 24 respiratory/cutaneous allergen extracts such as several fungi, animal dander, insect antigens, common dust allergens, and pollens and 16 alimentary antigens such as peanuts and tree nuts, egg, milk, seafood, wheat, soy, and fruits were used. The skin reaction was measured 15 min later after the test. A response of at least 3 mm more than diluent control performed at the same time was considered as a positive response, as proof of the presence of cutaneous allergen specific IgE.

Two clinical validated clinical allergy questionnaires (AQ) were administered to the patients or the parents in the children's group the same day of the ST-performing procedure. The first questionnaire was the International Study of Asthma and Allergies in Childhood (ISAAC) focused on personal and family history of respiratory, cutaneous, or food allergy [21]. The second questionnaire was an open questionnaire with regard to the personal and familial medical history of allergy. Both questionnaires were self-administrated instruments; no limit of time was requested. The responsible father or mother answered the questionnaire in a room available for clinical

interviews and one of the investigators (E.T.) was available all the time to answer questions.

Allergy/hypersensitivity definitions

Operational, not clinical-oriented, definitions of allergy/hypersensitivity severity were constructed for this study using a combined score of all measured variables. Non-allergy/nonhypersensitivity was defined when a patient had negative STs with none or only one of secondary tests (IgE or AQ) positive. Mild allergy/hypersensitivity was defined when a patient had negative STs and positive IgE and AQ or positive ST for one to six allergens plus either a positive serum IgE or a positive AQ. Finally, severe allergy/hypersensitivity was considered when a patient had a positive ST for seven or more allergens, regardless of whether they have positive IgE or AQ.

Cytokine levels determination

Gastric tissue levels of transforming growth factor β (TGF-β), interleukin-5 (IL-5), and IFN-γ were determined in biopsies. Biopsies were homogenized with a tissue homogenizer (OMNI Th international, Gainesville, Virginia, USA) separately in 500 µl of normal saline. Supernatants were obtained by centrifugation in a mini Eppendorf centrifuge (Hamburg, Germany) (12 000 g for 5 min at 4°C). Total protein content was measured using the modified bicinchoninic acid method (Pierce, Rockford, Illinois, USA), and the concentration in biopsy homogenates was expressed as milligram/milliliter. Cytokine concentration in gastric tissue and serum samples was measured by enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, Minnesota, USA), as recommended by the manufacturer using recombinant human cytokines as positive controls for the development of standard curves. The final cytokine concentrations in biopsy homogenates were expressed in microgram of cytokine/milligram of total protein for TGF-β and picogram of cytokine/milligram of total protein for IL-5 and IFN-γ. Final cytokine concentrations in serum samples were expressed as microgram of cytokine/milliliter.

Statistical analysis

Comparisons between groups were made using Student's *t*-test for continuous parametric data and with the Mann–Whitney test for continuous nonparametric data. Categorical data were analyzed using a χ^2 test and Fisher's exact test. In addition, multiple regression model analysis was carried out using *H. pylori*-infection parameters and different cytokine serum or tissue levels as predictor variables for allergy intensity as the main outcome. Statistical significance was defined as a *P* value of less than 0.05.

Results

Patients and *Helicobacter pylori* status

The study included 165 individuals, 98 children and 67 adults with similar sex distribution. Children (42.9%) and adult (52.2%) patients were infected by *H. pylori*, respectively, showing an increase in the prevalence of the infection with age. The mean age was similar between infected and noninfected patients in each age group. As expected, patients infected by *H. pylori*, regardless of their age, showed a significant increase in the presence of histological gastritis and mononuclear and polymorphonuclear cell infiltrations than noninfected patients. Macroscopically, duodenal ulcers (DU) predominated in *H. pylori*-infected children and adults compared with noninfected patients ($P < 0.05$). Infected children, but not adults, showed a significant presence of gastric nodularity than their noninfected counterparts. In this nonepidemiologic study, the high proportion of children with peptic ulcer and nodularity compared with adults mainly reflects the higher threshold for endoscopy indication in children in this population. Children (23.8%) and adult (17.1%) patients infected by *H. pylori* were CagA positive according to the cut-off value described in the 'Materials and methods' section. CagA titers were significantly increased in infected patients (30.9 + 52.4 UA/ml and 15.9 + 30.2 UA/ml in infected children and adults, respectively) (Table 1).

Allergy/hypersensitivity markers and *Helicobacter pylori* status

We next analyzed the relationship between selected allergy/hypersensitivity markers and the presence of *H. pylori* infection in children and in adults. We found that *H. pylori*-negative children, but not adults, had more percentage of positive ST (91.1%) compared with *H. pylori*-positive children (71.4%) ($P < 0.05$). Similarly, the mean number of respiratory/cutaneous allergens detected in the ST of *H. pylori*-negative children (87.5%), but not in adults, was significantly higher than the mean number of allergens detected in the ST of *H. pylori*-positive children (66.7%) (Table 2). The frequency of recognition for antigen groups was similar for noninfected and *H. pylori*-infected children. Only one nonfood antigen, that is animal dander, was significantly more recognized in noninfected children (Fig. 1a).

In addition, pediatric patients with positive total serum IgE and clinical questionnaires were less infected by *H. pylori*, although this difference does not reach significance (Table 2). When we analyzed the same selected allergy/hypersensitivity markers in adults, we did not find any differences in the percentage of positive ST, in the mean number of respiratory/cutaneous allergens detected in the ST, or in the frequency of recognition of antigen groups between *H. pylori*-negative and *H. pylori*-positive adults (Table 2, Fig. 1b).

Table 1 Characteristics of the study population by *H. pylori* status

	Children		Adults	
	H. pylori (−)	*H. pylori* (+)	*H. pylori* (−)	*H. pylori* (+)
Number (%)	56 (57.1)	42 (42.9)	32 (47.8)	35 (52.2)
Age (years)				
Mean ± SD	11 ± 3.1	12.6 ± 2.7	44.3 ± 16	42 ± 12.4
Sex [*N* (%)]				
Male	20 (35.7)	23 (54.8)	7 (21.9)	15 (43)
Female	36 (64.3)	19 (45.2)	25 (78.1)	20 (57)
Endoscopy findings [*N* (%)]				
Esophagitis	5 (8.9)	7 (16.7)	7 (21.9)	10 (28.6)
Gastric ulcer (antrum)	1 (1.8)	3 (7.1)	0 (0)	2 (5.7)
Gastric ulcer (corpus)	0 (0)	0 (0)	0 (0)	0 (0)
Gastric nodularity	3 (5.4)	24 (57.1)*	2 (6.3)	4 (11.4)
Duodenal ulcer	1 (1.8)	7 (16.7)*	0 (0)	2 (5.7)
Duodenal nodularity	0 (0)	3 (7.1)	0 (0)	0 (0)
Histology findings [*N* (%)]				
Gastritis				
Present	18 (32.7)	41 (97.6)*	16 (50)	33 (91.4)*
Mononuclear cell infiltration				
Mild	7 (16.3)	39 (92.9)*	10 (40)	32 (91.4)*
Moderate	0 (0)	2 (4.8)	0 (0)	1 (2.9)
Polymorphonuclear cell infiltration				
Mild	3 (5.5)	22 (52.4)*	7 (21.9)	19 (54.3)*
Moderate	1. (1.8)	9 (21.4)	2 (6.2)	11 (31.4)
Severe	0 (0)	1 (2.4)	0 (0)	0 (0)
CagA antibodies				
CagA, number of positive [*N* (%)]	1 (1.8)	10 (23.8)*	1 (3.1)	6 (17.1)*
CagA serum titer (mean ± SD)	2.4 ± 8.7	30.9 ± 52.4*	8.7 ± 15	15.9 ± 30.2

SD, standard deviation.
*$P<0.05$, χ^2 test between patients with different *Helicobacter pylori* (*H. pylori*) status per age group.

Table 2 Allergy/hypersensitivity markers and *H. pylori* status

	Children		Adults	
	H. pylori (−)	*H. pylori* (+)	*H. pylori* (−)	*H. pylori* (+)
Allergy markers [*N* (%)]				
IgE				
Number of positive individuals	23 (41.1)	15 (35.7)	8 (25)	14 (40)
Level (mean ± SD)	141 ± 200	157 ± 332	161 ± 337	100 ± 111
Skin test (total)				
Number of positive individuals	51 (91.1)*	30 (71.4)	23 (71.9)	29 (82.9)
Mean number of antigens	4.6 ± 3.7	3.9 ± 5.2	4.9 ± 5.4	5.9 ± 6.3
Skin test (respiratory/cutaneous)				
Number of positive individuals	49 (87.5)*	28 (66.7)	22 (68.8)	28 (80)
Mean number of antigens	3.9 ± 3.3†	3 ± 3.9	4.3 ± 4.8	4.5 ± 5.2
Questionnaires [*N* (%)]				
Number of positive individuals to both AQ	40 (40.8)	33 (33.7)	23 (71.8)	19 (54.3)

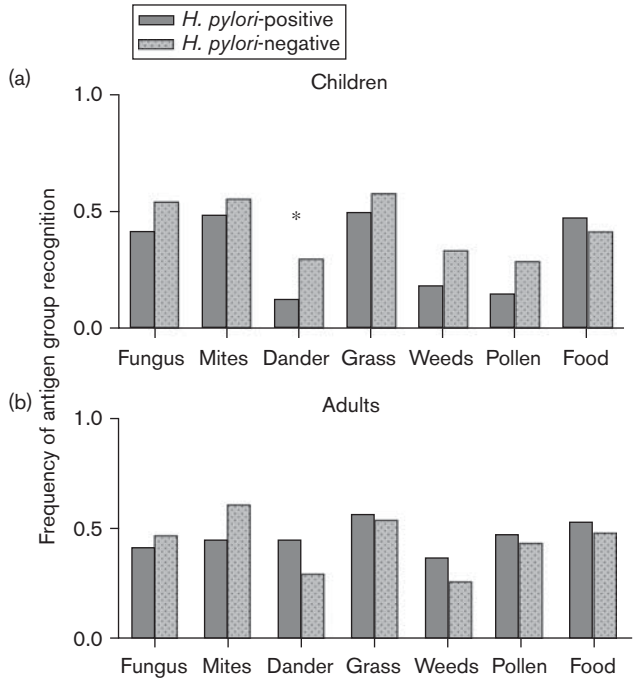
AQ, allergy questionnaires.
*$P<0.05$, χ^2 test between patients with different *Helicobacter pylori* (*H. pylori*) status per age group.
†$P<0.05$, Kruskal–Wallis test between patients with different *H. pylori* status per age group.

Patients with DU had less positive ST than the other groups for all antigens ($P = 0.04$) and particularly for cutaneous/respiratory antigens ($P = 0.04$). We did not find a relation between lymphonodular hyperplasia and allergy markers (data not shown).

Allergy/hypersensitivity intensity and *Helicobacter pylori* status

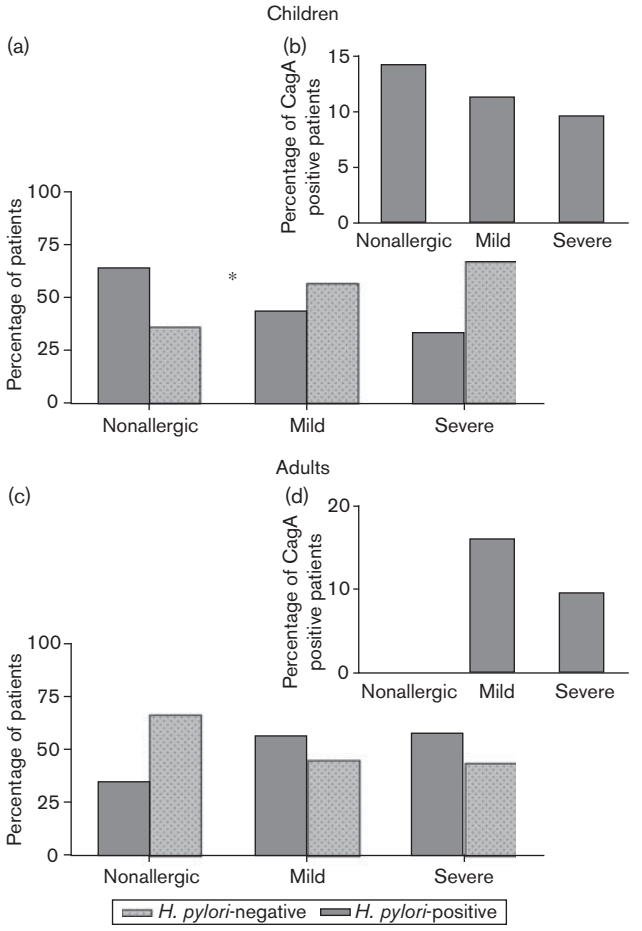
For comparative purpose, we defined the severity of the allergy/hypersensitivity reaction on the basis of a combined score of the individual parameters measured as defined in the 'Materials and methods' section. We found that the severity of allergy/hypersensitivity reaction was inversely correlated with *H. pylori* status in children. The percentage of *H. pylori* infection is lower in children with severe allergy (32.3%) compared with children with mild allergy (43.4%) or no allergy (64.3%) ($P < 0.05$) (Fig. 2a). However, none of these differences were observed in the adult patients (Fig. 2c). We also analyzed whether the presence of more virulent strains, measured by the presence of CagA antibodies, would also correlate inversely with the presence of allergies. Although not significant, CagA positivity tends to decrease, whereas severity of allergy/hypersensitivity increases in the children's group (Fig. 2b). This trend does not appear in adult patients (Fig. 2d).

Fig. 1



Frequency of recognition of skin test antigens by patients infected by *Helicobacter pylori* (*H. pylori*). (a and b) *H. pylori*-infected and noninfected patients show similar pattern of skin test antigen group recognition with regard to the age status of the patients, with the exception of dander in *H. pylori*-infected children (*$P<0.05$).

Fig. 2



Allergy/hypersensitivity intensity and *Helicobacter pylori* (*H. pylori*) status. Percentage of infected children and adults (a and c) according to the intensity of allergy/hypersensitivity as defined in the 'Materials and methods' section, (b and d) and percentage of positive CagA patients according to the intensity of allergy/hypersensitivity in children and adults (insets) (*$P<0.05$).

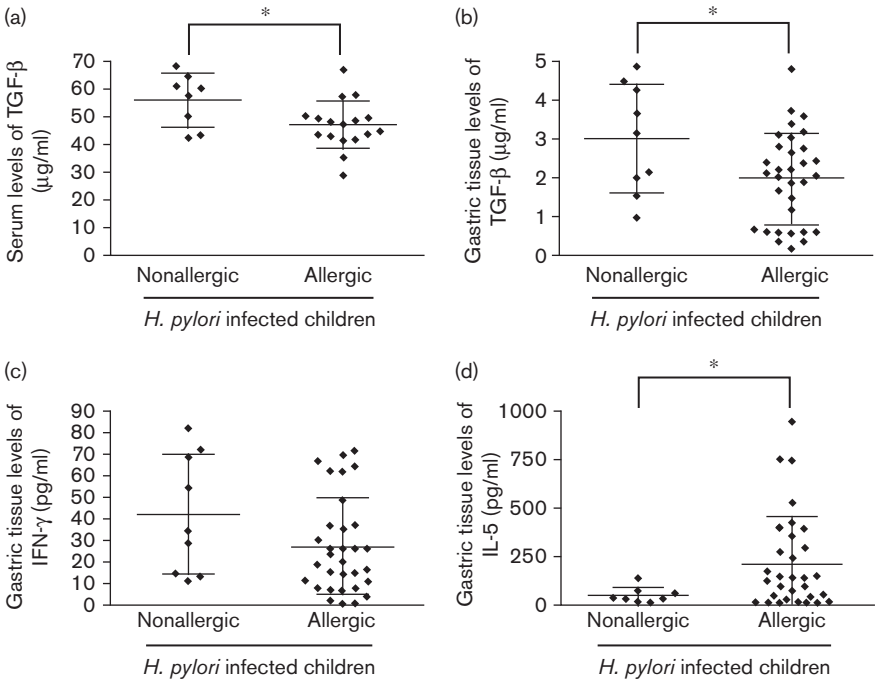
Cytokine levels in *Helicobacter pylori*-positive patients with or without allergy markers

H. pylori-infected children without allergy markers (allergy defined operationally as described in the 'Materials and methods' section) showed increased levels of TGF-β compared with children with allergy markers, both systemically [serum (microgram/milliliter)] and locally [antrum (microgram/milligram of tissue)] (Fig. 3a and b). In addition to TGF-β analysis, we also measured Th1 and Th2 signature cytokines IFN-γ and IL-5, respectively, in gastric mucosa of *H. pylori*-positive patients. We found that infected children with allergy markers show a significant increase of IL-5 mucosal levels and a nonsignificant decrease of IFN-γ levels than infected children without allergy (Fig. 3c and d). The differences of cytokine levels both in serum and gastric mucosa observed in *H. pylori*-infected children with regard to allergic status occurred neither in serum nor in gastric mucosa of *H. pylori*-infected adults with or without allergy markers (data not shown). Owing to the striking differences between TGF-β levels in phenotypically allergic children, we further analyzed, in this age group, the relationship between serum levels of this regulatory cytokine and the presence of *H. pylori* infection by multiple regression analysis to explain the differences in intensity of allergy response in pediatric patients (Table 3). The best possible model showed an inverse relationship between the presence of the infection ($P = 0.06$) and the serum levels of TGF-β ($P = 0.05$) with the intensity of the allergy with a significance of 0.043 for the model.

Discussion

This study shows that *H. pylori*-infected children, compared with noninfected children, showed less presence of allergy/hypersensitivity markers. Although we could only find significant differences when considering ST, children with high amounts of total serum IgE and positive clinical questionnaires are also less infected by *H. pylori*. The lack of significance in these two markers might be explained by the fact that there is a wide overlap in total serum IgE between atopic and nonatopic population, which leads to less discriminatory power as an allergy test, and because AQ may be affected by patients'/parents' subjectivity. Regardless of this fact, we described

Fig. 3



Cytokine levels in *Helicobacter pylori* (*H. pylori*)-positive patients with or without allergy markers. Transforming growth factor β (TGF-β) levels in gastric mucosa (microgram/milligram of tissue) (a) and serum samples (microgram/milliliter) (b) of *H. pylori*-infected children with and without allergy/hypersensitivity. Interferon γ (IFN-γ) (c) and interleukin-5 (IL-5) (d) levels in gastric mucosa (picogram/milligram of tissue) of *H. pylori*-infected children with and without allergy/hypersensitivity (*$P < 0.05$).

Table 3 Multiple regression for allergy intensity in children

Predictor	Estimate (B)	Standard error	*P* value	Model *P* value
Constant	3.118	0.475	0.0000	0.0437
Serum levels of TGF-β	−0.018	0.009	0.05	
Helicobacter pylori infection status	−0.394	0.208	0.06	

TGF-β, transforming growth factor β.

a consistent inverse relationship between allergy markers and a significant increase in severity of allergy, defined operationally by a combined score that considers all of the measured variables such as an increased number of responsive ST, higher titers of total serum IgE and AQ, with *H. pylori* infection. This inverse association is only evident in children, but not in adults, suggesting a role for *H. pylori* infection in modulating allergy/hypersensitivity conditions mainly in childhood, as previously suggested by other investigators [22–24]. This study evaluated *H. pylori* infection in children with markers of allergy (IgE sensitization), a previous step in the 'allergic march'. We did not evaluate *H. pylori* infection in children with clinical phenotypes of allergic diseases; it is likely that our findings would be overexpressed in children with overt clinical allergic manifestations such as allergic asthma, atopic dermatitis, etc. We have to consider that this study was conducted in patients with peptic disease symptoms. The selection bias ('digestive' symptomatic patients) may underscore the strength of the association found. More symptomatic patients (i.e. DU) have less positive ST that nonulcer and noninfected patients. *H. pylori* modulation of allergy disorders and the observed protective relationship may be more profound for asymptomatic *H. pylori*-infected populations.

One of the proposed mechanisms by which *H. pylori* is able to dampen allergic responses includes a phenomenon called bystander suppression [5], which relies on the capability of Treg cells to suppress immune responses distinct from responses against the antigen they originated from. *H. pylori* is able to induce not only a CD4 + Th1 immune response but also a simultaneous Treg response [13]. This response would account for the settlement of the bacteria in the stomach in a chronic manner, diminishing the ability of immune response in achieving bacterial clearance. These induced regulatory cells would be able to diminish not only the Th1 response generated by the bacteria itself but also the Th2 response generated by concomitant allergic conditions [14,25].

Previously, we have described that *H. pylori*-infected children develop an immune response to this bacteria, mainly characterized by the expression of regulatory cytokines such as IL-10 and TGF-β and infiltration of Foxp3 + cells, which are not present in the gastric mucosa of *H. pylori*-infected adults [14]. If Tregs are in part responsible for the decrease in allergy severity in *H. pylori*-infected children, a differential regulatory response to *H. pylori* in different age group settings would account for the differences in these two age groups.

In this study, we show that *H. pylori*-infected children, the ones that are defined as allergic, have lower levels of circulating TGF-β, a reliable marker of a Treg response, in serum and in gastric mucosa tissue. In contrast, adults have the same levels of TGF-β when they are infected by *H. pylori*, regardless of the presence of concomitant allergy markers, contributing to the idea that Tregs, and in particular, TGF-β may participate in the inverse relationship between *H. pylori* infection and the clinical expression of allergy markers in children, but not in adults.

In our study population, approximately 20% of patients infected by *H. pylori* were infected with CagA-positive strains and differences in clinical outcomes were not due to colonization with virulent strains (data not shown). Several other investigators have described an inverse association of allergy with infection with CagA-positive strains [22,26]. In our study, CagA titers were similar in infected patients, regardless the presence or absence of allergy markers and the severity of allergy/hypersensitivity, although in children colonization with CagA-positive strains shows a trend toward a decrease with increasing intensity of allergy. This inverse trend is particular to children and does not occur in adults. Robinson *et al*. [13] reported an increase in Treg responses in CagA-positive patients that would account for the inverse relationship between CagA-positive colonizing *H. pylori* and atopy. In our population setting, we failed to find a significant relationship between infection with CagA-positive strains and increased levels of TGF-β, which would account for the lack of significant difference with regard to the presence of CagA-positive strains and the expression of allergy markers. Historically, in our particular population, a developing country, we have not been able to find any correlation between the infection with CagA-positive strains and the development of peptic ulcers or gastric cancer, all clinical outcomes of *H. pylori* infection that have shown a strong correlation with the presence of CagA-positive strains in other populations [26–28].

In conclusion, our results suggest that *H. pylori* infection itself, with or without the expression of canonical virulence factors such as CagA, might regulate the course of hypersensitivity conditions in pediatric patients. Our findings also raise the possibility that massive *H. pylori* eradication in asymptomatic population may promote the clinical expression of an underlying atopic disease. Therefore, *H. pylori*-associated chronic superficial gastritis and its immune T cell response could serve to blunt the characteristic Th2-mediated allergic inflammatory response in those genetically predisposed children.

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Conflicts of interest: none declared.

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