World Journal of Gastroenterology

ORIGINAL ARTICLE

Retrospective Study

Helicobacter pylori infection in patients with selective immunoglobulin E deficiency

Eli Magen, Menachem Schlesinger, Itzhak Ben-Zion, Daniel Vardy

Eli Magen, Menachem Schlesinger, Itzhak Ben-Zion, Daniel Vardy, Leumit Health Services, Ashdod 77456, Israel

Eli Magen, Allergy and Clinical Immunology Unit, Barzilai University Medical Center, Ashkelon 78278, Israel

Daniel Vardy, Ben-Gurion University of Negev, Beer-Sheva 8410501, Israel

Correspondence to: Eli Magen, MD, Allergy and Clinical Immunology Unit, Barzilai University Medical Center, 2 Hahistadrout St, Ashkelon 78278, Israel. allergologycom@gmail.com
Telephone: +972-8-6745710
Fax: +972-8-6745712

Abstract

AIM: To investigate the prevalence and clinical characteristics of *Helicobacter pylori* (*H. pylori*)-infected dyspeptic patients with selective immunoglobulin E deficiency (IgEd).

METHODS: All individuals who underwent serum total immunoglobulin E (IgE) measurement at the Leumit Healthcare Services (Israel) in 2012 were identified in an electronic database search ($n = 18487$). From these, selected case group subjects were ≥ 12 years of age and had serum total IgE < 2 kIU/L ($n = 158$). The control group was selected from a random sampling of the remaining subjects ≥ 12 years of age to obtain a case-control ratio of 1:20 ($n = 3160$). Dyspeptic diseases, diagnosed no more than 5 years before serum total IgE testing, were identified and retrieved from the electronic database using specific International Classification of Diseases diagnostic codes. Results of C^{13}-urea breath tests were used to identify subjects infected with *H. pylori*. Categorical variables between case and control subjects were analyzed using Fisher's exact tests, whereas continuous variables were analyzed using χ^2 tests.

RESULTS: Dyspepsia was present in 27.2% (43/158) of case subjects and 22.7% (718/3160) of controls. Of these, significantly more case subjects (32/43, 74.4%) than controls (223/718, 31.1%) were positive for *H. pylori* ($P < 0.01$). Esophagogastroduodenoscopy was performed in 19 case and 94 control subjects, revealing that gastritis was more prevalent in IgEd case subjects than in controls (57.9% *vs* 29.8%, $P < 0.05$). Furthermore, a significantly greater proportion of case subjects presented with peptic duodenal ulcers (63.2% *vs* 15.9%, $P < 0.01$). Histopathologic examination showed marked chronic inflammation, lymphoid follicle formation and prominent germinal centers, with polymorphonuclear cell infiltration of gastric glands, that was similar in case and control biopsy tissues. Finally, IgEd case subjects that underwent esophagogastroduodenoscopy were more likely to exhibit treatment-refractory *H. pylori* infections that require second-line triple antibiotic therapy (47.4% *vs* 11.7%, $P < 0.01$).

CONCLUSION: IgEd is associated with higher rates of

H. pylori-associated gastritis and peptic duodenal ulcers.

Core tip: A deficiency in levels of immunoglobulin E (IgEd) has been associated with chronic inflammatory diseases, immune dysregulation, oncologic diseases, and chronic infections. This retrospective case-control study evaluated the clinical characteristics of *Helicobacter pylori* (*H. pylori*)-related dyspeptic syndrome in patients with IgEd. Analyses revealed a higher prevalence of *H. pylori* infection in dyspeptic patients with IgEd. Furthermore, gastritis and peptic ulcer disease were more prevalent in subjects with IgEd compared with gender- and age-matched *H. pylori*-infected dyspeptic patients with normal or high serum IgE levels. Finally, patients with IgEd were more likely to present treatment-refractory *H. pylori* infections.

INTRODUCTION

Immunoglobulin E (IgE) elicits effects that are both pathologic, as manifested in allergic disease, and beneficial, as expressed in the body's defense against parasitic infections, particularly by helminths[1]. IgE concentrations in normal human sera are between 10 and 400 ng/mL, with a half-life of 2 to 2.5 d [2,3]. A significant decrease in these levels, to < 2 kIU/L (equivalent to 4.8 ng/mL), is defined as selective IgE deficiency (IgEd) in the case where other immunoglobulin levels are normal, or mixed IgEd if they are diminished[4]. However, this distinction is mainly a laboratory finding, as most of the affected individuals are asymptomatic[5].

An association between IgEd and chronic inflammatory diseases of both the upper and lower respiratory tracts has been investigated[6,7], though its association to immunodeficiency remains controversial[8-11]. We recently investigated clinical and laboratory characteristics of patients with IgEd and found that adults with an undetectable serum total IgE level had immune dysregulation and autoimmunity with high prevalences of chronic infections, and autoimmune and oncologic diseases[8]. A case of persistent *Helicobacter pylori* (*H. pylori*) infection with anti-IgE biologic therapy (with omalizumab) was reported by Zandman *et al*[12] who suggested that IgE

may influence the inflammatory response to infection. *H. pylori* infection has increasingly been inversely associated with allergic diseases[13,14], and suppression of the infection improves allergic symptoms[15,16]. The primary aim of the present study was therefore to investigate the prevalence and clinical characteristics of *H. pylori*-infected patients with IgEd who presented with dyspeptic symptoms at the primary care setting.

MATERIALS AND METHODS

Data source

This retrospective, matched, case-control study was based on data from the Leumit Healthcare Services (Israel) Database. The database includes information on over 720000 insured people in Israel, including records of visits to clinics, laboratory test results classified by the International Classification of Diseases (ICD-9-CM), and demographic data. To maintain patient privacy, the data were extracted using unique patient identifiers. This study was approved by the committee of the Barzilai Medical Center and the Leumit Healthcare Services Institutional Review Committee.

Subjects

The database was searched for all subjects $\geq$ 12 years of age that had undergone serum total IgE measurements and C^{13}-urea breath tests (C^{13}-UBT) in 2012 for any reason. Subjects identified with serum total IgE of < 2 kIU/L were included in the case group. The control group was comprised of a random sample from the remaining subjects (serum total IgE $\geq$ 2 kIU/L) with a case-control ratio of 1:20. The randomization was performed using Epi Info 6 software (available from the Centers for Disease Control and Prevention; www.cdc.gov) using simple random sampling. Dyspeptic diseases were identified using specific ICD-9-CM diagnostic codes and had been diagnosed by board-certified family physicians and gastroenterologists no more than 5 years prior to serum total IgE testing. Dyspepsia was diagnosed as a syndrome consisting of pain or discomfort centered in the upper abdomen (epigastric pain), including burning, fullness, discomfort, nausea, vomiting and belching.

Criteria for exclusion from the study included: common variable immunodeficiency, chronic system corticosteroid therapy, selective IgA deficiency, ataxia telangiectasia and human immunodeficiency virus/acquired immunodeficiency syndrome. Subjects were also excluded if they had received any form of immunosuppressive therapy during the four weeks before measurement of serum total IgE. Furthermore, subjects with alarm symptoms (weight loss, anemia, hematemesis, melena, abdominal tumor, use of non-steroidal anti-inflammatory drugs) were excluded from the study.

Ig measurements

Serum samples were analyzed for total IgE levels using

Table 1 Clinical and laboratory characteristics of the subjects *n* (%)			
Characteristic	Cases (*n* = 158)	Controls (*n* = 3160)	*P* value
Female	113 (71.5)	2147 (67.9)	0.38
Age, yr	44.3 ± 20.4	43.1 ± 22.5	0.51
Body mass index, kg/m^2	26.2 ± 3.5	26.5 ± 3.4	0.29
Total IgE, kIU/L	0.3 ± 0.2	109.1 ± 77.6	< 0.01
WBC, *n*/mm^3	7.1 ± 3.4	6.8 ± 3.1	0.23
Lymphocytes, *n*/mm^3	2.4 ± 1.3	2.3 ± 1.1	0.26
Eosinophils, *n*/mm^3	0.31 ± 0.14	0.32 ± 0.11	0.27
Basophils, *n*/mm^3	0.15 ± 0.11	0.16 ± 0.09	0.18
Platelets, *n* × 10^8/mm^3	259 ± 124	267 ± 129	0.44
Dyspepsia	43 (27.2)	718 (22.7)	0.47
H. pylori-positive dyspepsia[1]	32 (74.4)	223 (31.1)	< 0.01

[1]Percentage reflects the proportion of dyspeptic subjects. WBC: White blood cell; IgE: Immunoglobulin E; *H. pylori*: *Helicobacter pylori*.

an immunometric assay on an Immulite 2000 system (Siemens, Munich, Bavaria, Germany). In all cases of serum total IgE < 2 kIU/L, other serum Igs (IgM, IgA, IgG, IgG1, IgG2, IgG3, IgG4) were routinely measured by nephelometry (BN II System; Dade Behring, Deerfield, IL, United States) to exclude humoral immunodeficiency.

Assessment of H. pylori infection
Trained nurses in regional laboratories performed the C^{13}-UBT for *H. pylori* (*Helicobacter* Test INFAI; INFAI GmbH, Köln, Germany) and the samples were analyzed by a mass spectrometer (AP 2003; Analytical Precision, Edinburgh, United Kingdom) in the central laboratory of Leumit Health Services in Israel. Proton pump inhibitors, H$_2$ antagonists, and antibiotics were not permitted for 15 d prior to the C^{13}-UBT. The patients were given 75 mg urea labeled with C^{13} in 200 mL of orange juice, and breath samples were collected before C^{13} intake (T0) and 30 min later (T30). The cutoff C^{12}/C^{13} at T30/T0 was 3.5 according to the manufacturer's instructions and previous methods[17].

H. pylori infection was also evaluated in biopsy samples by rapid urease tests (*H. pylori* ONE kit; GI Supply, Camp Hill, PA, United States) and histological examination. Multiple gastric biopsies (two from the antrum, two from the body, and additional specimens from any lesions visible by endoscopy, if needed) were taken and stained with hematoxylin and eosin[18].

Esophagogastroduodenoscopy
Esophagogastroduodenoscopy (EGD) procedures were performed by experienced board-certified gastroenterologists using a video-esophago-gastro-duodenoscope (Evis Smartage Gastro GIF V70 Serial; Olympus, Shinjuku, Tokyo, Japan). Procedures were video-recorded and representative findings documented on high-resolution images.

H. pylori eradication regimens
H. pylori eradication was comprised of a 14-d treatment with 1 g amoxicillin, 500 mg clarithromycin, and 20 mg omeprazole, *bid*, *H. pylori* eradication was confirmed by a second ^{13}C-UBT eight wk following the end of the treatment. Subjects with *H. pylori* infections resistant to first-line triple therapy received a 10-d second-line therapy consisting of 40 mg pantoprazole *bid* along with 750 mg levofloxacin and 100 mg doxycycline, once per day.

Statistical analyses
Statistical analyses were performed using Statistica 6 (StatSoft Inc., Tulsa, OK, United States). Categorical variables were analyzed using a Fisher's exact test, whereas continuous variables were analyzed using a χ^2 test. All values are expressed as mean ± SD. Two-tailed *P* values less than 0.05 were considered as significant.

RESULTS

Demographic and laboratory characteristics of cases and controls
A total of 18487 subjects, 4-69 years of age, were identified as having received a serum total IgE test between January 1 and December 31, 2012, primarily for allergy-related symptoms. Total serum IgE values ranged from 2 to 2000 kIU/L, and 158 case subjects ≥ 12-year-old with serum total IgE < 2 kIU/L were identified. The corresponding control group therefore consisted of 3160 subjects with serum total IgE ≥ 2 kIU/L. With the exception of serum total IgE levels, there were no differences between the cases and controls with regard to demographic and laboratory characteristics (Table 1). Although there was no difference in the percentage of subjects with dyspepsia (27.2% *vs* 22.7% for cases and controls, respectively), a significantly larger proportion of dyspeptic case subjects were *H. pylori*-positive (74.4% *vs* 31.1%, *P* < 0.01).

EGD results
EGD was performed on 59.4% (19/32) and 42.2% (94/223) of the *H. pylori*-positive dyspeptic cases and control subjects, respectively (Table 2). A significantly larger proportion of case subjects experienced gastritis (*P* < 0.05), which was evident particularly for multifocal atrophic gastritis. In addition, a larger proportion of case subjects presented with duodenal ulcers (63.2% *vs* 15.9%, *P* < 0.01). Moreover, more case subjects that underwent EGD exhibited treatment-refractory *H. pylori* infections compared to controls (47.4% *vs* 11.7%, *P* < 0.01). Second-line therapy successfully eradicated *H. pylori* in these subjects.

The pathologic findings from biopsied gastric tissues were similar in case and control subjects. Histopathologic analyses showed marked chronic inflammation, lymphoid follicle formation and prominent germinal centers, with

Characteristic	Cases	Controls	*P* value
	(*n* = 19)	(*n* = 94)	
Female	11 (57.9)	49 (52.1)	0.81
Age, yr	43.9 ± 10.2	42.5 ± 9.7	0.49
Gastritis	11 (57.9)	28 (29.8)	0.03
Antral predominant gastritis	7 (36.8)	21 (22.3)	0.24
Body predominant gastritis	1 (5.3)	5 (5.3)	1.00
Multifocal atrophic gastritis	3 (15.8)	2 (2.1)	0.03
Duodenal ulcer	12 (63.2)	15 (15.9)	< 0.01
Gastric ulcer	1 (5.3)	1 (1.1)	0.31
Treatment-refractory *H. pylori* infection	9 (47.4)	11 (11.7)	< 0.01

H. pylori: Helicobacter pylori.

polymorphonuclear cell infiltration of gastric glands.

DISCUSSION

The results of this study show a higher prevalence of *H. pylori* infection in dyspeptic patients with IgEd. It is widely recognized that *H. pylori* infection produces strong local and systemic antibody production and cell-mediated immunity, infiltrating the gastric mucosa with inflammatory lymphocytes, macrophages, neutrophils, plasma cells, and eosinophils[19,20]. Although the role of humoral immunity on bacterial colonization and the inflammatory response is poorly understood, it may provide some protection against *H. pylori* infection[21].

H. pylori directly binds to mast cells, which produce pro-inflammatory cytokines and which migrate and accumulate in the gastric mucosa[22,23]. Specific antibodies are known to impair and eliminate *H. pylori* and gastric inflammation[24], and several lines of evidence indicate that IgE may be one such antibody. For example, IgE-positive plasma cells show significant growth in gastritis patients positive for *H. pylori*[25], and *H. pylori*-induced gastritis is accompanied by an increase in IgE production[26]. These antibodies can continuously activate mast cells in mucosal tissue[27], and subnormal IgE levels impair the normal response of mast cells to antigens, causing Th1-related immunopathology[28]. Specific IgE antibodies further induce receptor-specific upregulation and stabilization that is essential for establishing long-lasting mast cell memory[29]. Therefore, failure of mast cells to function as immune guards at early stages of infection may play an important role in mediating susceptibility to *H. pylori* in patients with IgEd.

Another important finding of this study is that IgEd subjects had a higher prevalence of gastritis and peptic ulcer disease (PUD). By affecting basophils and mast cells, IgE plays an important role in T-cell activation[30]. Whereas uncomplicated chronic gastritis is associated with a mixed Th1/Th2 response, PUD is associated with Th1 polarization of gastric cell responses in *H. pylori*-infected patients[31]. Several studies indicate that Th1 polarization of the *H. pylori*-specific T-cell response is associated with more severe disease[32,33]. The "African enigma" is a phenomenon where despite the high prevalence of *H. pylori* infection in Africa, PUD and gastric cancer are uncommon[34]. A possible explanation is that the endemic parasitic burden causes Th2 responses to predominate, which, together with a high serum total IgE, protects *H. pylori*-infected patients from developing PUD. An increase in T-regulatory cells in infected individuals contributes to asymptomatic persistent infection, whereas subjects with inadequate T-regulatory responses develop gastroduodenal pathology[35]. We recently found that IgEd is characterized by impaired immunologic tolerance with high rates of organ-specific and systemic autoimmune diseases[8]. Perhaps the high rates of gastritis and PUD in the patients with IgEd and persistent *H. pylori* infection demonstrate an underlying inappropriate "tolerance" to the infection.

Some limitations of the study should be acknowledged. First, this was a retrospective study, which is vulnerable to information bias from inaccurate clinical records and missing data. Second, there are no studies of *H. pylori* bacterial virulence factors in IgEd or any experimental work to explain how IgEd facilitates the development of *H. pylori*-associated gastroduodenal disease. Third, as no *H. pylori* culturing for *in vitro* antibiotic sensitivity was performed following the treatment failures, we cannot determine whether IgEd is associated with infection by antibiotic-resistant *H. pylori* or with a failure to clear the *H. pylori* infection. Last, it is unclear whether IgEd patients are more susceptible to *H. pylori* infection or gastritis. Unfortunately, it was not possible to identify the rate of *H. pylori* infection in the study groups.

In summary, the results demonstrate that patients with IgEd are more prone to gastritis and PUD, as well as treatment-refractory *H. pylori* infection. However, further experimental studies are needed to assess the role of IgE in the pathogenesis of *H. pylori* infection.

COMMENTS

Background
A deficiency in levels of immunoglobulin E (IgE) has been associated with chronic inflammatory diseases, immune dysregulation, oncologic diseases, and chronic infections. A recent case involving IgE immunosuppression was associated with chronic *Helicobacter pylori (H. pylori)* infection. However, there are no published epidemiologic studies regarding the prevalence and clinical features of *H. pylori* infection in IgE deficiency (IgEd).

Research frontiers
Recent studies have indicated that IgEd is associated with immune-related diseases; however, the association has not been investigated in great detail, and there are no identified mechanisms for the role of IgE in immune regulation.

Innovations and breakthroughs
The results of this study demonstrate that subjects with IgEd have a significantly higher prevalence of *H. pylori* infection, gastritis and peptic ulcer disease. Furthermore, treatment-refractory *H. pylori* infections were more common in IgEd subjects.

Applications
The results of this study suggest that IgE may play an important role in a host's immune response to *H. pylori* infection.

Terminology
Dyspepsia is a syndrome consisting of pain or discomfort centered in the upper

abdomen described as a burning or fullness, which is accompanied by nausea, vomiting, and belching. *H. pylori* is a gram-negative bacterium found in the stomach that is linked to the development of gastritis, gastric ulcers, duodenal ulcers and gastric cancer.

Peer review

The topic of this study is very interesting, involving the evaluation of the immunologic association between a rare disease of IgEd and *H. pylori* infection. The authors found more cases of *H. pylori*-positive gastritis in patients with IgEd. The *H. pylori* eradication rate for legacy triple therapy was statistically inferior in the IgEd group compared to the control, but second-line levofloxacin-based triple therapy was equally effective for these subjects. This information is of interest for clinicians treating patients with IgEd.

REFERENCES

1   **Sutton BJ**, Gould HJ. The human IgE network. *Nature* 1993; **366**: 421-428 [PMID: 8247150 DOI: 10.1038/366421a0]

2   **Frazer JK**, Capra JD. Immunoglobulins: Structure and function. In: Paul WE, ed. Fundamental Immunology. 4th ed. Philadelphia: Lippincott-Raven Publishers, 1999: 60

3   **Ishizaka K**, Ishizaka T. Identification of gamma-E-antibodies as a carrier of reaginic activity. *J Immunol* 1967; **99**: 1187-1198 [PMID: 4168663]

4   **Pate MB**, Smith JK, Chi DS, Krishnaswamy G. Regulation and dysregulation of immunoglobulin E: a molecular and clinical perspective. *Clin Mol Allergy* 2010; **8**: 3 [PMID: 20178634 DOI: 10.1186/1476-7961-8-3]

5   **Smith JK**, Krishnaswamy GH, Dykes R, Reynolds S, Berk SL. Clinical manifestations of IgE hypogammaglobulinemia. *Ann Allergy Asthma Immunol* 1997; **78**: 313-318 [PMID: 9087159 DOI: 10.1016/S1081-1206(10)63188-2]

6   **Cain WA**, Ammann AJ, Hong R, Ishizaka K, Good RA. IgE deficiency associated with chronic sinopulmonary infection. *J Clin Invest* 1969; **48**: 12a

7   **Famuyiwa F**, Rubinstein I. Chronic sinopulmonary inflammatory diseases in adults with undetectable serum IgE in inner-city Chicago: a preliminary observation. *Lung* 2012; **190**: 291-294 [PMID: 22310879 DOI: 10.1007/s00408-012-9375-y]

8   **Magen E**, Schlesinger M, David M, Ben-Zion I, Vardy D. Selective IgE deficiency, immune dysregulation, and autoimmunity. *Allergy Asthma Proc* 2014; **35**: e27-e33 [PMID: 24717782 DOI: 10.2500/aap.2014.35.3734]

9   **Polmar SH**, Waldmann TA, Balestra ST, Jost MC, Terry WD. Immunoglobulin E in immunologic deficiency diseases. I. Relation of IgE and IgA to respiratory tract disease in isolated IgE deficiency, IgA deficiency, and ataxia telangiectasia. *J Clin Invest* 1972; **51**: 326-330 [PMID: 5009116]

10 **Levin TA**, Ownby DR, Smith PH, Peterson EL, Williams LK, Ford J, Young P, Johnson CC. Relationship between extremely low total serum IgE levels and rhinosinusitis. *Ann Allergy Asthma Immunol* 2006; **97**: 650-652 [PMID: 17165274 DOI: 10.1016/S1081-1206(10)61095-2]

11 **Levy Y**, Nakum A, Segal N, Monselise Y, Danon YL. The association of selective IgA deficiency and IgE hypogammaglobulinemia. *Allergy* 2005; **60**: 836-838 [PMID: 15876317 DOI: 10.1111/j.1398-9995.2005.00799.x]

12 **Zandman D**, Hahn W, Moss S. A Case of Persistent Helicobacter pylori infection occurring with anti-IgE immunosuppression. *ACG Case Rep J* 2013; **1**: 16-18

13 **Chen Y**, Blaser MJ. Helicobacter pylori colonization is inversely associated with childhood asthma. *J Infect Dis* 2008; **198**: 553-560 [PMID: 18598192 DOI: 10.1086/590158]

14 **Blaser MJ**, Chen Y, Reibman J. Does Helicobacter pylori protect against asthma and allergy? *Gut* 2008; **57**: 561-567 [PMID: 18194986 DOI: 10.1136/gut.2007.133462]

15 **Shiotani A**, Okada K, Yanaoka K, Itoh H, Nishioka S, Sakurane M, Matsunaka M. Beneficial effect of Helicobacter pylori eradication in dermatologic diseases. *Helicobacter* 2001; **6**: 60-65 [PMID: 11328367 DOI: 10.1046/j.1523-5378.2001.00009.x]

16 **Magen E**, Mishal J, Schlesinger M, Scharf S. Eradication of Helicobacter pylori infection equally improves chronic urticaria with positive and negative autologous serum skin test. *Helicobacter* 2007; **12**: 567-571 [PMID: 17760727 DOI: 10.1111/j.1523-5378.2007.00522.x]

17 **Gal E**, Abuksis G, Fraser G, Koren R, Shmueli C, Yahav Y, Niv Y. 13C-urea breath test to validate eradication of Helicobacter pylori in an Israeli population. *Isr Med Assoc J* 2003; **5**: 98-100 [PMID: 12674657]

18 **Dixon MF**, Genta RM, Yardley JH, Correa P. Classification and grading of gastritis. The updated Sydney System. International Workshop on the Histopathology of Gastritis, Houston 1994. *Am J Surg Pathol* 1996; **20**: 1161-1181 [PMID: 8827022 DOI: 10.1097/00000478-199610000-00001]

19 **Del Giudice G**, Covacci A, Telford JL, Montecucco C, Rappuoli R. The design of vaccines against Helicobacter pylori and their development. *Annu Rev Immunol* 2001; **19**: 523-563 [PMID: 11244046 DOI: 10.1146/annurev.immunol.19.1.523]

20 **Akhiani AA**, Lycke N. T cell involvement in experimental Helicobacter pylori specific protective immunity. *Recent Res Dev Immunol* 2002; **4**: 259-272

21 **Brandtzaeg P**, Bjerke K, Kett K, Kvale D, Rognum TO, Scott H, Sollid LM, Valnes K. Production and secretion of immunoglobulins in the gastrointestinal tract. *Ann Allergy* 1987; **59**: 21-39 [PMID: 3318585]

22 **Montemurro P**, Nishioka H, Dundon WG, de Bernard M, Del Giudice G, Rappuoli R, Montecucco C. The neutrophil-activating protein (HP-NAP) of Helicobacter pylori is a potent stimulant of mast cells. *Eur J Immunol* 2002; **32**: 671-676 [PMID: 11857341 DOI: 10.1002/1521-4141(200203)32:3<671::AID-IMMU671>3.3.CO;2-X]

23 **Supajatura V**, Ushio H, Wada A, Yahiro K, Okumura K, Ogawa H, Hirayama T, Ra C. Cutting edge: VacA, a vacuolating cytotoxin of Helicobacter pylori, directly activates mast cells for migration and production of proinflammatory cytokines. *J Immunol* 2002; **168**: 2603-2607 [PMID: 11884423 DOI: 10.4049/jimmunol.168.6.2603]

24 **Akhiani AA**, Schön K, Franzén LE, Pappo J, Lycke N. Helicobacter pylori-specific antibodies impair the development of gastritis, facilitate bacterial colonization, and counteract resistance against infection. *J Immunol* 2004; **172**: 5024-5033 [PMID: 15067084 DOI: 10.4049/jimmunol.172.8.5024]

25 **Berczi L**, Sebestyén A, Fekete B, Tamássy K, Kopper L. IgE-containing cells in gastric mucosa with and without Helicobacter pylori infection. *Pathol Res Pract* 2000; **196**: 831-834 [PMID: 11156324 DOI: 10.1016/S0344-0338(00)80083-7]

26 **Liutu M**, Kalimo K, Kalimo H, Uksila J, Leino R. Mast cells and IgE-containing cells in gastric mucosa of Helicobacter pylori infected and non-infected patients with chronic urticaria. *J Eur Acad Dermatol Venereol* 2004; **18**: 69-72 [PMID: 14678535 DOI: 10.1111/j.1468-3083.2004.00701.x]

27 **Zhang N**, Holtappels G, Gevaert P, Patou J, Dhaliwal B, Gould H, Bachert C. Mucosal tissue polyclonal IgE is functional in response to allergen and SEB. *Allergy* 2011; **66**: 141-148 [PMID: 20659077 DOI: 10.1111/j.1398-9995.2010.02448.x]

28 **Kawakami T**, Kitaura J. Mast cell survival and activation by IgE in the absence of antigen: a consideration of the biologic mechanisms and relevance. *J Immunol* 2005; **175**: 4167-4173 [PMID: 16177053 DOI: 10.4049/jimmunol.175.7.4167]

29 **Turner H**, Kinet JP. Signalling through the high-affinity IgE receptor Fc epsilonRI. *Nature* 1999; **402**: B24-B30 [PMID: 10586892 DOI: 10.1038/35037021]

30 **Kimura T**, Hisano M, Inoue Y, Adachi M. Tyrosine phosphorylation of the linker for activator of T cells in mast cells by stimulation with the high affinity IgE receptor. *Immunol Lett* 2001; **75**: 123-129 [PMID: 11137136]

31 **D'Elios MM**, Manghetti M, Almerigogna F, Amedei A, Costa F, Burroni D, Baldari CT, Romagnani S, Telford JL, Del Prete G. Different cytokine profile and antigen-specificity repertoire in Helicobacter pylori-specific T cell clones from the antrum of chronic gastritis patients with

or without peptic ulcer. *Eur J Immunol* 1997; **27**: 1751-1755 [PMID: 9247587 DOI: 10.1002/eji.1830270723]

32   **de Jonge R**, Kuipers EJ, Langeveld SC, Loffeld RJ, Stoof J, van Vliet AH, Kusters JG. The Helicobacter pylori plasticity region locus jhp0947-jhp0949 is associated with duodenal ulcer disease and interleukin-12 production in monocyte cells. *FEMS Immunol Med Microbiol* 2004; **41**: 161-167 [PMID: 15145461 DOI: 10.1016/j.femsim.2004.03.003]

33   **Wen S**, Velin D, Felley CP, Du L, Michetti P, Pan-Hammarström Q. Expression of Helicobacter pylori virulence factors and associated expression profiles of inflammatory genes in the human gastric mucosa. *Infect Immun* 2007; **75**: 5118-5126 [PMID: 17709414 DOI: 10.1128/IAI.00334-07]

34   **Holcombe C**. Helicobacter pylori: the African enigma. *Gut* 1992; **33**: 429-431 [PMID: 1582581 DOI: 10.1136/gut.33.4.429]

35   **Robinson K**, Kenefeck R, Pidgeon EL, Shakib S, Patel S, Polson RJ, Zaitoun AM, Atherton JC. Helicobacter pylori-induced peptic ulcer disease is associated with inadequate regulatory T cell responses. *Gut* 2008; **57**: 1375-1385 [PMID: 18467372 DOI: 10.1136/gut.2007.137539]

Baishideng®