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BRIEF ARTICLE

Autoimmune thyroid diseases and *Helicobacter pylori*: The correlation is present only in Graves's disease

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Abstract

AIM: To investigate the correlation between autoimmune thyroid diseases (ATDs) and the prevalence of Cag-A positive strains of *Helicobacter pylori* (*H. pylori*) in stool samples.

METHODS: Authors investigated 112 consecutive Caucasian patients (48 females and 4 males with Graves' disease and 54 females and 6 males with Hashimoto's thyroiditis HT), at their first diagnosis of ATDs. Authors tested for *H. pylori* in stool samples using an amplified enzyme immunoassay and Cag-A in serum samples using an enzyme-linked immunoassay method (ELISA). The results were analyzed using the two-sided Fisher's exact test and the respective odds ratio (OR) was calculated.

RESULTS: A marked correlation was found between the presence of *H. pylori* ($P \leqslant 0.0001$, OR 6.3) and, in particular, Cag-A positive strains ($P \leqslant 0.005$, OR 5.3) in Graves' disease, but not in Hashimoto's thyroiditis, where authors found only a correlation with Cag-A strains ($P \leqslant 0.005$, OR 8.73) but not when *H. pylori* was present.

CONCLUSION: The marked correlation between *H. pylori* and Cag-A, found in ATDs, could be dependent on the different expression of adhesion molecules in the gastric mucosa.

Key words: Autoimmunity; Cag-A; Graves' disease; Hashimoto's thyroiditis; *Helicobacter pylori*; Hyperthyroidism; Hypothyroidism

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INTRODUCTION

Autoimmune thyroid diseases (ATDs) are represented, essentially, by Hashimoto's thyroiditis (HT) and its variants (postpartum and sporadic thyroiditis), Graves' disease (GD) and atrophic thyroiditis[1]. A typical marker of HT and GD is the presence of autoantibodies against thyroglobulin (TgAbs), thyroperoxidase (TPOAbs) and thyrotropin receptor (TRAbs)[2]. Both genetic and environmental factors are involved in the pathogenesis of ATDs. Some bacteria and viruses are suspected of being able to mimic the antigenic profile on the thyroid

cell membrane, and play an important role in the onset of autoimmune diseases[3-6]. *Helicobacter pylori* (*H. pylori*) infection is found worldwide and has an incidence of up to 50% in the population of developed countries[7]. A cohort effect has been demonstrated for such infection, and a higher prevalence rate is found in the elderly and in males[8]. *H. pylori* is a gram-negative, motile bacterium, which typically colonizes and infects the gastric mucosa; the most virulent strains can usually be identified by the presence of the cytotoxin-associated gene A (Cag-A) antigen[9]. Therefore, the microorganism is responsible for gastric diseases such as gastritis, gastric/duodenal ulcers and carcinomas.

Several studies[10-12] have shown a positive correlation between the presence of *H. pylori* and HT, although others did not find such an association[13,14]. Moreover, we recently demonstrated a noteworthy correlation between *H. pylori* infection and GD, independent of hormonal status[15].

The aim of this study was to investigate the prevalence of *H. pylori* in ATDs and, in particular, HT, to help clarify the controversial results observed in previous studies. We detected the presence of *H. pylori* in fresh stool samples from our patients using an enzyme immunoassay method, and Cag-A positivity using a serological test.

MATERIALS AND METHODS

ATDs patients

We studied 112 consecutive Caucasian patients (48 females and 4 males with GD and 54 females and 6 males with HT), at their first diagnosis of ATDs, enrolled over a period of 18 mo (from October 2008 to March 2010). The mean age (± SD) of the ATDs patients was 49.7 ± 6.6 years (48.8 ± 3.9 years for GD patients and 50.2 ± 9.7 years for HT patients). The study inclusion criteria were previously reported[15]. Briefly, these criteria included the absence of other diseases, a negative anamnesis for antimicrobial drugs use for at least three months and the absence of dyspeptic symptoms (epigastric pain, nausea, heartburn) or gastric diseases. The study was approved by the ethical committee of our institution and informed consent was obtained from each patient.

GD diagnosis was defined by hormonal hyperthyroidism [suppressed thyrotrophin (TSH), elevated FT3 and FT4], diffuse and high iodine capture on thyroid scintigraphy, and positive titers of TPOAbs, TgAbs and TRAbs. To eliminate possible bias between subclinical and frank primary hypothyroidism, HT diagnosis was defined by a cut-off value higher than 35 mU/mL TSH, low FT3 and FT4 values, positive titers of TPOAbs and TgAbs and hypoechogenicity pattern on echography (Table 1).

Controls

The control population was composed of 100 body mass index-, socio-economic- and inclusion criteria class-matched individuals (90 females and 10 males, mean age 49.0 ± 4.5 years, Table 1). All of these subjects showed normal TSH, FT3 and FT4 values with absent titers of TPOAbs, TgAbs and TRAbs.

Table 1 Clinical characteristics of the investigated groups

Group	*n*	Sex female/male	Age (yr) (mean ± SD)	Smokers yes/no	Ophthalmopathy yes/no
Control	100	90/10	49.0 ± 4.5	44/56	-
GD	52	48/4	48.8 ± 3.9	21/31	34/18
HT	60	54/6	50.2 ± 9.7	26/34	0/60
ATDs	112	102/10	49.2 ± 6.9	47/65	34/112

No significant statistical differences in sex and age were present among the different groups. ATDs: Autoimmune thyroid diseases; HT: Hashimoto's thyroiditis; GD: Graves' disease.

Study of the presence of H. pylori in stool samples

The tests were performed by laboratory technicians blinded to the subject's diagnosis. Fresh stool samples were obtained and tested using an amplified enzyme immunoassay for the detection of *H. pylori* antigens (Amplified IDEIA *H. pylori* StAR, Oxoid, United Kingdom). This test is highly specific for *H. pylori* antigens (sensitivity 95%, specificity 95%), with no cross-reactivity with other microorganisms. An absorbance value > 0.150 using a dual wavelength (450/620 to 650 nanometers) was considered positive for the presence of *H. pylori*.

Detection of Cag-A antibodies

Fresh serum samples were tested with the enzyme-linked immunoassay method (ELISA, Radim, Pomezia, Italy, sensitivity 93.7%, specificity 100%). Anti-Cag-A immunoglobulin-G values greater than 15 units/mL were regarded as Cag-A positive.

Statistical analysis

The relationship between the different studied groups, in terms of *H. pylori* and Cag-A positivity, was investigated with the two-sided Fisher's exact test and calculation of the respective odds ratio (OR, with 95% confidence interval, using the approximation of Woolf, Instat 3.06, Graphstat Software Inc., San Diego, CA, United States). $P \leqslant 0.05$ was considered significant.

RESULTS

Detection of H. pylori in fresh stool samples

Of 112 ATDs patients, 43/52 (82%) in the GD group and 28/60 (46%) in the HT group were positive for *H. pylori* infection, *vs* 43 [43.0%, $P \leqslant 0.0001$, OR 6.3 (2.7-14.3) *vs* the GD group, not significant *vs* the HT group] of 100 controls (Table 2).

Immunoassay testing on the stool samples confirmed that the observed *H. pylori* positivity was dependent on ongoing *H. pylori* presence in the gastric mucosa and not on past infection. Furthermore, no correlation was found between the presence of *H. pylori* and smoking habit in the two groups of ATDs patients (data not shown).

Table 2 The HP- and CagA-positivity in patients in the different study groups

Group	*n*	HP-	HP+	CagA+	CagA-	Overall CagA+
Control	100	57	43	21	22	21/100
GD total	52	9	43[c]	36[b]	7	36[c]/52
HT total	60	32	28[1]	25[b]	3	25[a]/60
ATDs total	112	41	71[2]	61[c]	10	61[c]/112

[a]$P \leqslant 0.05$ *vs* control, [b]$P \leqslant 0.005$, [c]$P \leqslant 0.0001$. [1]Not significant; [2]Not calculated.

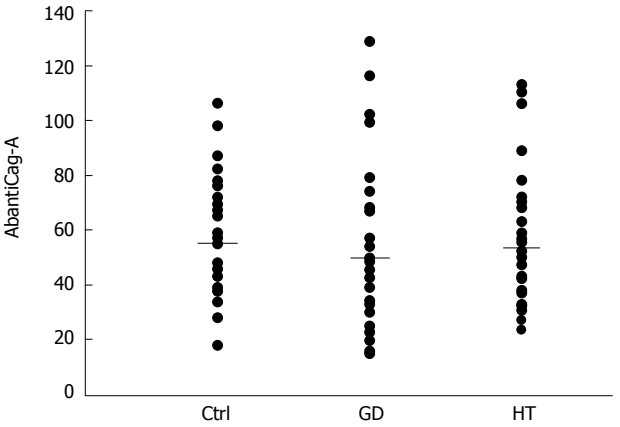

Figure 1 The AbantiCag-A levels are shown for the investigated groups. The bars show the different means. No significant difference was found among the different groups. GD: Graves' disease; HT: Hashimoto's thyroiditis.

Cag-A positivity in the serum of H. pylori-positive patients

Thirty-six (83.7%) of 43 *H. pylori*-positive GD patients and 25/28 (89.2%) *H. pylori*-positive HT patients were positive for Cag-A antigens *vs* 21/43 [48.8%, $P \leqslant 0.005$, OR 5.3 (1.9-14.7) *vs* the GD group and $P \leqslant 0.005$, OR 8.73 (2.7-33.0) *vs* the HT group] of infected controls. Again, considering the overall prevalence of infection by Cag-A-positive *H. pylori* in the studied groups of ATDs patients, the results were statistically significant, [61 of 112 or 54.4% *vs* the controls, 21 of 100 subjects or 21%, $P \leqslant 0.0001$ OR 4.5 (2.4-8.2), Table 2].

Cag-A antibody levels, expressed in mU/mL [control 56 ± 24.3 (mean ± SD), GD 50.3 ± 28.6, HT 54.1 ± 22.6], were similar among the three groups of investigated subjects (Figure 1) and did not correlate with the respective titers of TgAbs, TPOAbs or TRAbs (data not shown).

DISCUSSION

H. pylori infection is found world wide and affects up to 50% of the population of developed countries, such as Italy, and the most virulent strains are identified by the presence of Cag-A antigens[9]. Recently, a significant correlation was shown between the Cag-A carrier *H. pylori* strains and GD, independent of the hormonal status of the investigated patients[15]. Moreover, other studies have investigated the association between such microorganisms and HT, however, the results are controversial. Some investigations point to a noteworthy correlation[10,11,12], others do not[13,14]. The use of different techniques to assess *H. pylori* infection could explain these conflicting conclusions. For instance, serological detection of *H. pylori* antibodies can not discriminate between past and ongoing infection. Conversely, the ^{13}C-urea breath test and immunoassay test on fresh stool samples can only detect ongoing *H. pylori* infection, therefore these tests are currently considered the preferred not-invasive methods of investigation[7]. Moreover, the presence of similar antigenic sites for Cag-A and TPO could cause false positive results in the Abs titers against *H. pylori*, leading to a bias in group selection of the enrolled patients[16]. In addition, the different grade of thyroid function in HT patients, such as subclinical or frank hypothyroidism, could be a misleading factor.

Our results, using a stool antigen test, confirmed that a correlation was present between *H. pylori* and hyperthyroid GD patients, but this correlation was not seen in hypothyroid HT patients.

In accordance with the guidelines[7], we did not perform further invasive exams, such as gastroscopy, in consideration of the age (usually under 45 years old in the investigated patients) and the absence of digestive symptoms in *H. pylori*-positive patients.

Several factors could be considered to explain the different results regarding *H. pylori* prevalence in GD and HT. Usually, the onset and/or progression of ATDs are dependent on different autoimmune mechanisms. Cellular autoimmunity with the TH1 profile of CD4 + T helper precursor cells is predominant in HT, whereas humoral autoimmunity (production of TRAbs or TSH-receptor blocking antibodies) with the TH2 profile is prevalent in GD and atrophic thyroiditis[17]. These different activated profiles in ATDs induce the expression of different panels of cytokines, such as interleukin (IL)-4, IL-5, IL-6 and IL-10 in GD and IL-2, interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α) in HT[17]. Also, the opposite thyroid function, i.e., hyperthyroidism in GD *vs* hypothyroidism in HT, could be another factor leading to the controversial results on *H. pylori* prevalence in GD and HT patients.

In our study, both GD and HT show a comparable elevated prevalence of Cag-A positive strains in *H. pylori*-positive patients, in agreement with previous observations in TH patients[11].

The involved factors could operate through a common pathway, such as the glycoconjugates-mediated adhesion of *H. pylori* to the gastric mucosa, which represents a crucial step in the establishment of successful infection. *H. pylori* glycan receptors include fucosylated ABO blood group antigens[18,19] and glycans with charged groups, such as sialic acid[20]or sulfate[21], and neolacto core chains[22] Two different *H. pylori* adhesins have been characterized on the basis of their interactions with the receptors: the

blood group antigen-binding adhesin (BabA) is specific for H type-1 and Lewis b antigens, admitting terminal blood groups A and B glycan determinants, whereas the sialic acid binding adhesin (SabA) recognizes the Sialyl-Lewis a and Sialyl-Lewis x antigens[20,23].

In particular, the potential effect of the suggested factors, such as hyperthyroidism or the production of cytokines induced by humoral immunity, could modify the profile of the adhesion molecules expressed on the gastric mucosa, increasing *H. pylori* binding in GD and selecting the Cag-A positive strains in ATDs.

Regarding the pathogenetic role of HP in the onset of ATDs, it has been postulated that viral and bacterial infections could play a noteworthy role. Usually, elevated levels of antibodies against some bacteria have been found in GD patients[4-6] and, conversely, an antigen structure, such as TSH-binding protein, is described in many gram-positive and gram-negative bacteria[24]. Moreover, Cag-A positive *H. pylori* strains show some nucleotide sequence similarity to TPO sequence[25]. A positive linear regression between *H. pylori*-Abs titers and microsomal autoantibodies[9] and a significant reduction in these antibodies after *H. pylori* eradication have been demonstrated[26]. Therefore, cross-reactivity of the antibodies produced against thyroid antigen structures during *H. pylori* infections could potentially induce a biological effect[27], in a similar way to that of *H. pylori* which triggers the onset of autoantibodies against the H^+K^+-ATPase in the gastric autoimmunity[28-29]. Moreover, the increased prevalence of *H. pylori* in GD, on first diagnosis, and the observation that, usually, *H. pylori* infection starts during childhood[30], suggest that the bacterium could be present before the onset of the autoimmune disease. Larizza *et al*[31] proposed that *H. pylori* infection can induce and/or worsen the course of GD in susceptible young patients, carrying the human leukocyte DRB1*0301 antigen. The authors also suggested that *H. pylori* eradication could prevent GD in these "at high risk" children.

Conversely, hyperthyroid GD patients could just be more susceptible to *H. pylori* infection, and the presence of the microorganism could represent an epiphenomenon, not involved in the onset of the autoimmune disease.

In conclusion, we report an increased *H. pylori* prevalence only in hyperthyroid GD patients, but not in hypothyroid HT patients, although the strains involved in both GD and HT are, prevalently, carriers of Cag-A antigens. These results suggest the execution of screening for *H. pylori* in ATDs patients, taking into account either the presence of virulent strains in autoimmune diseases and the increased *H. pylori* prevalence in GD. Therefore, a possible role of *H. pylori* infection might be postulated for GD, but further studies are needed to confirm such a hypothesis.

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COMMENTS

Background

Autoimmune thyroid diseases (ATDs) are represented, essentially, by Hashimoto's thyroiditis (HT) and its variants (postpartum and sporadic thyroiditis) and Graves' disease (GD). *Helicobacter pylori* (*H. pylori*) infection is found worldwide with an incidence of up to 50% in the population of developed countries and a possible correlation has been suggested between the bacterium and ATDs.

Research frontiers

A wide range of diseases are correlated with the presence of *H. pylori* and a possible pathogenetic role is suspected.

Innovations and breakthroughs

A noteworthy correlation between *H. pylori* and GD, but not with HT, has been demonstrated. In contrast, the prevalence of Cag-A expression was increased in both ATDs.

Applications

Screening for *H. pylori* in ATDs patients is suggested, taking into account either the presence of virulent strains in autoimmune diseases and the increased *H. pylori* prevalence in GD.

Peer review

The manuscript is well written and the methods are adequate. The results justify the conclusions drawn.

REFERENCES

1 **Pearce EN**, Farwell AP, Braverman LE. Thyroiditis. *N Engl J Med* 2003; **348**: 2646-2655
2 **Delemarre FG**, Simons PJ, Drexhage HA. Histomorphological aspects of the development of thyroid autoimmune diseases: consequences for our understanding of endocrine ophthalmopathy. *Thyroid* 1996; **6**: 369-377
3 **Rapoport B**, McLachlan SM. Thyroid autoimmunity. *J Clin Invest* 2001; **108**: 1253-1259
4 **Valtonen VV,** Ruutu P, Varis K, Ranki M, Malkamaki M, Makela P. Serological evidence for the role of bacterial infections in the pathogenesis of thyroid diseases. *Acta Med Scand* 1986; **219**: 105-111
5 **Joasoo A,** Robertson P, Murray IPC. Viral antibodies and thyrotoxicosis. *Lancet* 1975; **2**: 125-131
6 **Tomer Y**, Davies TF. Infection, thyroid disease, and autoimmunity. *Endocr Rev* 1993; **14**: 107-120
7 **Malfertheiner P**, Megraud F, O'Morain C, Bazzoli F, El-Omar E, Graham D, Hunt R, Rokkas T, Vakil N, Kuipers EJ. Current concepts in the management of Helicobacter pylori infection: the Maastricht III Consensus Report. *Gut* 2007; **56**: 772-781
8 **Ponzetto A**, Pellicano R, Morgando A, Cirillo D, Marchiaro G, Curti F, Rizzetto M. Seroprevalence of Helicobacter pylori infection among blood donors in Torino, Italy. *Minerva Gastroenterol Dietol* 2001; **47**: 3-7
9 **Atherton JC**. H. pylori virulence factors. *Br Med Bull* 1998; **54**: 105-120
10 **de Luis DA**, Varela C, de La Calle H, Cantón R, de Argila CM, San Roman AL, Boixeda D. Helicobacter pylori infection is markedly increased in patients with autoimmune atrophic thyroiditis. *J Clin Gastroenterol* 1998; **26**: 259-263
11 **Figura N**, Di Cairano G, Lorè F, Guarino E, Gragnoli A, Cataldo D, Giannace R, Vaira D, Bianciardi L, Kristodhullu S, Lenzi C, Torricelli V, Orlandini G, Gennari C. The infection by Helicobacter pylori strains expressing CagA is highly prevalent in women with autoimmune thyroid disorders. *J Physiol Pharmacol* 1999; **50**: 817-826
12 **Papamichael KX**, Papaioannou G, Karga H, Roussos A, Mantzaris GJ. Helicobacter pylori infection and endocrine disorders: is there a link? *World J Gastroenterol* 2009; **15**: 2701-2707
13 **Tomasi PA**, Dore MP, Fanciulli G, Sanciu F, Realdi G, Deli-

tala G. Is there anything to the reported association between Helicobacter pylori infection and autoimmune thyroiditis? *Dig Dis Sci* 2005; **50**: 385-388
14 **Franceschi F**, Satta MA, Mentella MC, Penland R, Candelli M, Grillo RL, Leo D, Fini L, Nista EC, Cazzato IA, Lupascu A, Pola P, Pontecorvi A, Gasbarrini G, Genta RM, Gasbarrini A. Helicobacter pylori infection in patients with Hashimoto's thyroiditis. *Helicobacter* 2004; **9**: 369
15 **Bassi V**, Santinelli C, Iengo A, Romano C. Identification of a correlation between Helicobacter pylori infection and Graves' disease. *Helicobacter* 2010; **15**: 558-562
16 **Johansen HK**, Nørgaard A, Andersen LP, Jensen P, Nielsen H, Høiby N. Cross-reactive antigens shared by Pseudomonas aeruginosa, Helicobacter pylori, Campylobacter jejuni, and Haemophilus influenzae may cause false-positive titers of antibody to H. pylori. *Clin Diagn Lab Immunol* 1995; **2**: 149-155
17 **Roura-Mir C**, Catálfamo M, Sospedra M, Alcalde L, Pujol-Borrell R, Jaraquemada D. Single-cell analysis of intrathyroidal lymphocytes shows differential cytokine expression in Hashimoto's and Graves' disease. *Eur J Immunol* 1997; **27**: 3290-3302
18 **Aspholm-Hurtig M**, Dailide G, Lahmann M, Kalia A, Ilver D, Roche N, Vikström S, Sjöström R, Lindén S, Bäckström A, Lundberg C, Arnqvist A, Mahdavi J, Nilsson UJ, Velapatiño B, Gilman RH, Gerhard M, Alarcon T, López-Brea M, Nakazawa T, Fox JG, Correa P, Dominguez-Bello MG, Perez-Perez GI, Blaser MJ, Normark S, Carlstedt I, Oscarson S, Teneberg S, Berg DE, Borén T. Functional adaptation of BabA, the H. pylori ABO blood group antigen binding adhesin. *Science* 2004; **305**: 519-522
19 **Borén T**, Falk P, Roth KA, Larson G, Normark S. Attachment of Helicobacter pylori to human gastric epithelium mediated by blood group antigens. *Science* 1993; **262**: 1892-1895
20 **Mahdavi J**, Sondén B, Hurtig M, Olfat FO, Forsberg L, Roche N, Angstrom J, Larsson T, Teneberg S, Karlsson KA, Altraja S, Wadström T, Kersulyte D, Berg DE, Dubois A, Petersson C, Magnusson KE, Norberg T, Lindh F, Lundskog BB, Arnqvist A, Hammarström L, Borén T. Helicobacter pylori SabAadhesin in persistent infection and chronic inflammation. *Science* 2002; **297**: 573-578
21 **Guzman-Murillo MA**, Ruiz-Bustos E, Ho B, Ascencio F. Involvement of the heparansulphate-binding proteins of Helicobacter pylori in its adherence to HeLa S3 and Kato III cell lines. *J Med Microbiol* 2001; **50**: 320-329
22 **Miller-Podraza H**, Weikkolainen K, Larsson T, Linde P, Helin J, Natunen J, Karlsson KA. Helicobacter pylori binding to new glycans based on N-acetyllactosamine. *Glycobiology* 2009; **19**: 399-407
23 **Ilver D**, Arnqvist A, Ogren J, Frick IM, Kersulyte D, Incecik ET, Berg DE, Covacci A, Engstrand L, Borén T. Helicobacter pylori adhesin binding fucosylatedhisto-blood group antigens revealed by retagging. *Science* 1998; **279**: 373-377
24 **Byfield PG,** Davies SC, Copping S, Barclay FE, Borriello SP. Thyrotrophin (TSH)-binding proteins in bacteria and their creoss reaction with autoantibodies against the human TSH receptor. *J Endocrinol* 1989: **121**:571-577
25 **Tomb JF**, White O, Kerlavage AR, Clayton RA, Sutton GG, Fleischmann RD, Ketchum KA, Klenk HP, Gill S, Dougherty BA, Nelson K, Quackenbush J, Zhou L, Kirkness EF, Peterson S, Loftus B, Richardson D, Dodson R, Khalak HG, Glodek A, McKenney K, Fitzegerald LM, Lee N, Adams MD, Hickey EK, Berg DE, Gocayne JD, Utterback TR, Peterson JD, Kelley JM, Cotton MD, Weidman JM, Fujii C, Bowman C, Watthey L, Wallin E, Hayes WS, Borodovsky M, Karp PD, Smith HO, Fraser CM, Venter JC. The complete genome sequence of the gastric pathogen Helicobacter pylori. *Nature* 1997; **388**: 539-547
26 **Bertalot G**, Montresor G, Tampieri M, Spasiano A, Pedroni M, Milanesi B, Favret M, Manca N, Negrini R. Decrease in thyroid autoantibodies after eradication of Helicobacter pylori infection. *Clin Endocrinol* (*Oxf*) 2004; **61**: 650-652
27 **Ko GH**, Park HB, Shin MK, Park CK, Lee JH, Youn HS, Cho MJ, Lee WK, Rhee KH. Monoclonal antibodies against Helicobacter pylori cross-react with human tissue. *Helicobacter* 1997; **2**: 210-215
28 **D'Elios MM**, Appelmelk BJ, Amedei A, Bergman MP, Del Prete G. Gastric autoimmunity: the role of Helicobacter pylori and molecular mimicry. *Trends Mol Med* 2004; **10**: 316-323
29 **Bergman MP**, D'Elios MM. Cytotoxic T cells in H. pylori-related gastric autoimmunity and gastric lymphoma. *J Biomed Biotechnol* 2010; **2010**: 104918
30 **Nabwera HM,** Nguyen-van-Tam JS, Logan RFA. Prevalence of Helicobacter pylori infection in Kenyan schoolchildren aged 3–15 years and risk factors for infection. *Eur J Gastroenterol Hepatol* 2000; **12**: 483-487
31 **Larizza D**, Calcaterra V, Martinetti M, Negrini R, De Silvestri A, Cisternino M, Iannone AM, Solcia E. Helicobacter pylori infection and autoimmune thyroid disease in young patients: the disadvantage of carrying the human leukocyte antigen-DRB1*0301 allele. *J Clin Endocrinol Metab* 2006; **91**: 176-179

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