



## REVIEW

# Does gastric atrophy exist in children?

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## Abstract

Several clinical reports confirmed that gastric atrophy is a pathology not only limited to adult patients. In pediatrics, it is most often described in association with a *H pylori* infection but this bacteria does not seem to be the only etiological factor of this preneoplastic state in children. The frequency of gastric atrophy and intestinal metaplasia in children are unknown because they are not systematically sought during upper gastrointestinal endoscopy. The lack of specific histological classification of children's gastropathies makes their diagnosis difficult for pathologists. Based on our knowledge to date, we think that it is necessary to describe, in detail, the natural course of this lesion during childhood. A close and prolonged clinical and endoscopic follow-up is important for children with gastric atrophy.

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**Key words:** Gastric atrophy; Gastritis; *H pylori*; Intestinal metaplasia; Gastric cancer; Children

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## INTRODUCTION

The discovery of *H pylori* in adult patients by Warren and Marshall<sup>[1]</sup> was a major event in modern gastroenterology, rewarded with the Nobel Prize in 2005, and strongly stimulated paediatric studies focused on gastroduodenal pathology. The presence of this microorganism in children's stomachs was described several years after it was found in adults. In fact, up to that time, gastric biopsy had never been a priority for paediatricians because of the

low frequency of gastroduodenal pathologies in children and the non existence of gastric cancer at this age of life. On the contrary, gastric atrophy is systematically sought for in adult stomach biopsies because of cancer pathology. Its histological diagnosis is based on the updated Sydney System<sup>[2]</sup>. During the last few years, several publications reported the presence of this preneoplastic state in children and the search for *H pylori* during endoscopy contributed to the improved knowledge of histological lesions of gastric mucosa in pediatrics. However, uncertainty persists regarding histological criteria of chronic gastritis in children, its long term course, its relationship with intestinal metaplasia in adults<sup>[3,4]</sup> as well as the responsibility of other etiological agents other than *H pylori*.

## GASTRIC ATROPHY IN PEDIATRICS

Several clinical reports confirmed that gastric atrophy is a pathology not only limited to adult patients<sup>[5-9]</sup>. However, because of the non-systematic search during pediatric gastroscopy for this histological state considered as preneoplastic in adults<sup>[3,4,10,11]</sup>, its prevalence is not well evaluated in pediatrics, varying from 0 to 72% according to different studies (Table 1). Moreover, published clinical data refer mainly to *H pylori*-infected children and therefore, the prevalence of gastric atrophy due to other etiologies is unknown at this time. Finally, the reported prevalence of gastric atrophy and intestinal metaplasia (IM) in pediatric studies includes all histological grades, whereas in the majority of adults' studies only medium and severe grades are considered; this could be a possible source of overestimation.

A recent Turkish study reported prevalence of 72% of gastric atrophy in a small series of 18 *H pylori*-infected patients<sup>[6]</sup>. This study was performed in a country with a very high *H pylori* prevalence ranging from 43.9% to 53% and a relatively high age of the recruited patients (median age of 12.2 years) which incites one to think that such a severe mucosal alteration could be related to a prolonged disease duration, in predisposed individuals<sup>[6,16]</sup>, as it has been suggested in adults<sup>[17,18]</sup>. However, a selection bias cannot be excluded because another Turkish group, which examined gastric biopsies of 175 *H pylori* positive children, found only five cases of gastric atrophy and/or IM corresponding to a lower prevalence of 2.8%<sup>[8]</sup>. Authors of studies carried out in other countries, who focused on *H pylori*-positive children, reported gastric atrophy in a very limited number of cases varying from 0 to 4%<sup>[13,14,19,20]</sup>.

Gastric atrophy of young children was only described in five cases<sup>[5,7]</sup>; two were one year-old infants and two others were two year-old patients. Those observations do

Table 1 Studies concerning atrophic gastritis in children

Authors	Updated Sydney system	Total of included patients	Average age of included patients (yr)	Hp+ (n)	Prevalence of gastric atrophy (and/or IM) <sup>1</sup> (%)	Average age of patients with GA (yr)	Number of patients < 10 yr with GA
-Whitney <sup>[5]</sup> 2000 USA	Yes	42	11	42	19% Hp+ ( <sup>1</sup> 0%)	11	4
-Kolho <sup>[12]</sup> 2000 Finland	Not reported	71	9	71	0% ( <sup>1</sup> 0%)	Not reported	0
-Cohen <sup>[13]</sup> 2000 Argentina	Yes	15	11	15	0% ( <sup>1</sup> 0%)	Not reported	0
-Campbell <sup>[14]</sup> 2001 Gambia	Yes	37	2	21	0% (0%)	Not reported	0
-Ozturk <sup>[6]</sup> 2003 Turkey	Yes	27	12	18	72% Hp+ and 11% Hp- ( <sup>1</sup> 78% all Hp+)	Not reported	Not reported
-Guarner <sup>[7]</sup> 2003 USA	Yes	64	Hp+=9 Hp-=9	19	63% Hp+ and 22% Hp- ( <sup>1</sup> 21% all Hp+)	8 (Hp+)	6
-Usta <sup>[8]</sup> 2004 Turkey	Yes	175	12	175	2% Hp+ ( <sup>1</sup> 2%)	12	1
-Levine <sup>[9]</sup> 2004 Israel	Not reported	95	14	55	1% 1Hp- (0 Hp+) ( <sup>1</sup> 0%)	14	0
-Kato <sup>[15]</sup> 2006 Japan	Yes	196	11	131	- antral GA : 52% Hp+/11% Hp- (5% Hp+/5% Hp-) - fundic GA : 35% Hp+/8% Hp- (0% Hp+/4% Hp-)	Not reported	Not reported

<sup>1</sup>IM: Intestinal metaplasia. Hp: *H pylori*

not call into question the hypothesis of Correa *et al*<sup>[4]</sup> about the progressive, stepwise installation of precancerous lesions but they incite one to think that individual susceptibility to those premalignant lesions probably exists. In fact, it is probable that genetic and environmental factors do not only participate in the pathogenesis of gastric atrophy in adults<sup>[21]</sup> but also in children. This was shown in the study by Campbell *et al*<sup>[14]</sup>, which was carried out within the West African population where the infection rate with *H pylori* is one of the highest in the world (70% to 90%), yet did not describe any cases of gastric atrophy. This phenomenon was called “the African enigma”. To our knowledge, there is no pediatric study, comparing by using the same methodology, the prevalence of gastric atrophy in a population according to its geographic/genetic origins or environmental factors.

Cases of intestinal metaplasia in stomach, which is also considered as a precancerous lesion in adults<sup>[3,4,10,11]</sup>, were more rarely reported in pediatric patients<sup>[6,8,15]</sup> (Table 1). According to some authors, intestinal metaplasia is never associated to *H pylori* infection<sup>[5,13,14,19]</sup>, whereas others point out its frequency to be lower than 5% among infected patients<sup>[8,15,20,22]</sup>. In contrast with this very low rate, Guarner *et al*<sup>[7]</sup> reported a prevalence of 21% which brings one to think that an obvious relationship exists between *H pylori* gastritis and intestinal metaplasia.

## ARE SPECIFIC HISTOLOGICAL CRITERIA FOR PAEDIATRIC ATROPHIC GASTRITIS AVAILABLE?

Up until now, no specific histological classification of children's gastropathies has been validated<sup>[23]</sup>. By extension with adult gastropathies, in clinical practice, the Updated Sydney System is widely used<sup>[2]</sup>. Its main

purpose is to allow for pathologists to establish a severity classification by visual comparison between the sampling and the published diagrams by Dixon *et al*<sup>[2]</sup>. This essential publication defines gastric atrophy as glandular loss of mucosa which is replaced either by fibrous tissue or by intestinal metaplastic cells. However, the interposition of inflammatory cells between the stomach's glandular cells may inappropriately orientate the pathologist to the diagnosis of atrophy, where one is not present. Sampling interpretation is observer-dependent and this was emphasized by several studies<sup>[13,24,25]</sup>. Without strict validated criteria, the severity assessment of gastric atrophy remains subjective and not easily reproducible<sup>[26]</sup>.

The authors of the same study recommend to perform five gastric biopsies in adults (2 antral, 2 corporeal and one from the angulus) for histological analysis but no consensus is available about the optimal number of biopsies needed in children. Clinical practices in this domain are very heterogeneous, which may be responsible for the underestimation of the prevalence of atrophic gastritis in children. To this end, Bedoya *et al*<sup>[26]</sup> performed only two gastric biopsies in the diagnosis of 175 cases of *H pylori* gastritis, whereas Guarner *et al*<sup>[7]</sup> as well as Derambure-Wizla *et al*<sup>[27]</sup> carried out 3 or 4 biopsies for series of 64 and 436 children, respectively. In light of these studies and the Dixon's recommendations<sup>[2]</sup>, it is probable that the multiplication of gastric biopsies is an essential factor for a positive diagnosis and severity assessment of gastric atrophy in children.

Regarding intestinal metaplasia with a patchy distribution throughout the gastric mucosa<sup>[27]</sup>, the situation is similar and it may be easily missed if not enough gastric biopsies are taken. In contrast to gastric atrophy, metaplastic epithelium is easily detected by the pathologist, owing to the very characteristic goblet cells<sup>[2]</sup>.

However, endoscopy for younger children cannot be

as frequently performed as in adult patients. Less invasive procedures for detecting histological modifications of gastric mucosa could be valuable in the clinical practice. In adult patients, it has been shown that gastric atrophy was responsible for loss of production of hydrochloric acid, decreased serum levels of pepsinogen I and increased gastrin serum levels<sup>[28]</sup>. Probably, hypergastrinemia could be a valuable marker for gastric atrophy in pediatrics, in order to select patients for further investigation by gastroscopy<sup>[29]</sup>. It was also hypothesized that low levels of gastric acid secretion were a factor in the development of gastric atrophy in adults<sup>[30]</sup> but no evidence for this hypothesis was published regarding pediatric patients. Due to the low prevalence of gastric atrophy during childhood, it would be difficult to validate these potential screening tests for children.

## ARE THERE SPECIFIC FEATURES FOR CHILDREN'S GASTRIC ATROPHY?

Even though reported frequencies of gastric atrophy and intestinal metaplasia in children are extremely variable depending on authors (Table 1), they are definitely lower than those in adults<sup>[31-35]</sup>, thus some authors do not confirm their existence<sup>[22,36,37]</sup>. It seems that in the series where the median age is higher, the prevalence of gastric atrophy is also increased. It is plausible that the duration of *H. pylori* infection in childhood may explain this phenomenon<sup>[38]</sup>.

No specific clinical symptoms are noted in adults and children. In most pediatric cases, its diagnosis is established in relationship with upper gastrointestinal symptoms<sup>[39]</sup>, but the prevalence of asymptomatic cases is unknown.

The main histological differences between atrophic gastritis of children and adults seem to be related to the characteristics of inflammatory response accompanying mucosal atrophy. In most series comparing children and adults, the degree of gastric mucosa colonisation by *H. pylori* seems to be significantly more important in children. However, the severity of the inflammatory response remains controversial depending on the authors' findings. Whitney *et al*<sup>[5]</sup> reported a higher gastritis activity in adults compared to children, whereas Meining *et al*<sup>[22]</sup> concluded that gastric inflammation is very severe in the pediatric age group. The absence of standards to measure inflammation could explain those differences. This highlights the importance of generalising the use of the Updated Sydney Classification for the assessment of gastric inflammation (not used by Meining). Finally, the study by Campbell *et al*<sup>[14]</sup> carried out in Western Africa, using the Updated Sydney System, confirms some of the conclusions by Whitney: severity of gastric inflammation is more important in adults than in children, while differences in the degree of mucosal colonization by *H. pylori*, between children and adults, was not found.

## IS *H. PYLORI* THE ONLY RESPONSIBLE AGENT FOR GASTRIC ATROPHY IN CHILDREN?

The role of *H. pylori* as a main etiological agent in atrophic gastritis is indisputable. However, several observations of

**Table 2 Studies reporting observations of atrophic gastritis in children without *H. pylori* infection**

Authors	Total of cases		atrophic gastritis	Clinical symptoms (average age)
	Hp+ (n)	Hp- (n)	Hp- (n)	
- Ozturk <sup>[11]</sup> 2003 Turkey	18	9	1 mild	Chronic abdominal pain (12 yr)
- Guarner <sup>[12]</sup> 2003 USA	19	45	10	Upper chronic digestive symptoms (9 yr)
- Levine <sup>[14]</sup> 2004 Israel	55	40	1	Gastro-esophageal reflux, epigastric pain, collagenous gastritis

Hp: *H. pylori*.

gastric atrophy in children without infection are reported<sup>[6,7,9]</sup> and Table 2). It seems logical to suspect the existence of other etiological factors responsible for gastric atrophy. In adults, Kuipers *et al* reported that patients receiving omeprazole for long periods of time presented with a higher risk to develop gastric atrophy, yet in their series, all patients were *H. pylori*-positive<sup>[40,41]</sup>. Those data were not confirmed in more recent studies<sup>[42-44]</sup> and to date, proton pump inhibitors (PPI) are not considered as responsible for gastric atrophy in adults. To our knowledge, no cases of gastric atrophy attributable to PPI in pediatrics have been reported.

The hypothesis of an autoimmune disorder responsible for the appearance of antigastric antibodies was confirmed in adults. The frequency of those antibodies in patients with gastric atrophy may be as high as 50%<sup>[45,46]</sup>. It has been reported that in some cases of severe gastric atrophy in adults, previously infected by *H. pylori*, any infection stigmata may disappear when anti-gastric-parietal cell antibodies appear<sup>[47,48]</sup>. The authors of those observations suggested that anti-gastric-parietal cells antibodies could be a biological marker for the severity of gastric atrophy. In contrast, very few pediatric data are available. The only clinical situation where anti-gastric-parietal cell antibodies were discovered was type I diabetes with a frequency of 6% but no cases of atrophic gastritis have been reported<sup>[49-51]</sup>. Celiac disease is another cause of chronic gastritis with positive findings of anti-gastric-parietal cell antibodies in 10% of cases in adults<sup>[52]</sup>, but similarly, no pediatric data are available. The study by Kolho *et al*<sup>[12]</sup> included sixty children with celiac disease but no cases of anti-gastric-parietal cell antibodies have been pointed out. Nevertheless, several anecdotic cases of autoimmune thyroiditis and juvenile hypothyroidism, some of which with achlorhydria and gastric antibodies have been reported<sup>[53]</sup>.

## LONG TERM COURSE OF GASTRIC ATROPHY IN CHILDREN

The long term course of gastric atrophy in children is unknown. To our knowledge, no longitudinal study of this course, through to adulthood, has been published.



In adults, Correa *et al* suggested that chronic gastritis, gastric atrophy, intestinal metaplasia, dysplasia and gastric cancer develop stepwise over decades, in predisposed individuals infected by *H pylori*<sup>[2,3]</sup>. However, observations of atrophic gastritis have been reported in very young children (Table 1), including the presence of intestinal metaplasia in pediatric patients. Therefore, the chronological sequence of appearance of those lesions is not respected in all the cases. The association of intestinal metaplasia with *H pylori* infection is variable and it is impossible to prove that intestinal metaplasia is preceded by gastric atrophy in all cases. The risk of cancer in adults grows proportionately with the histological progression of metaplasia (evaluated from I: mild to III: according Dixon *et al*<sup>[54]</sup>). Gastric cancer is exceptional in pediatric population and only one case has been reported, involving a 15 years old boy who was not infected by *H pylori*<sup>[55]</sup>.

It is actually well established that only 1% of *H pylori*-positive patients will develop gastric cancer<sup>[56]</sup>, whereas infection starts almost all the time during childhood<sup>[57-60]</sup>. The rarity of intestinal metaplasia and gastric cancer in the pediatric age group could probably be explained by the long time period necessary for those complications to appear as well as the absence of other cumulative factors for gastric cancer, during childhood.

Probably insufficient ingestion of vitamin C could contribute to the development of *H pylori* infection in children<sup>[61]</sup> and in adults<sup>[62-64]</sup> but its role in the genesis of gastric precancerous lesions is not clearly established<sup>[63,65]</sup>. Moreover, the question of the spontaneous reversibility of gastric atrophy after *H pylori* eradication is frequently discussed.

It seems difficult or even impossible, because of evident ethical barriers, to investigate whether the eradication of *H pylori* during childhood would decrease the risk of gastric cancer during adulthood<sup>[66]</sup>.

## CONCLUSION

Gastric atrophy exists in children and it is sometimes found in very young children. It is necessary to describe, in detail, the natural course of this lesion during childhood. A close and prolonged clinical and endoscopic follow-up is necessary for children with gastric atrophy. The efficiency of preventive strategy<sup>[66]</sup> or screening of *H pylori* infection in evaluating the risk of gastric atrophy and cancer in adult age should be evaluated. Finally, it is necessary to identify, by means of multicentric studies, the other circumstances (excluding *H pylori*) predisposing to gastric atrophy and its evolutionary potential over decades.

## REFERENCES

- 1 Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet* 1984; **1**: 1311-1315
- 2 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
- 3 Correa P, Haenszel W, Cuello C, Zavala D, Fontham E, Zarama G, Tannenbaum S, Collazos T, Ruiz B. Gastric precancerous process in a high risk population: cross-sectional studies. *Cancer Res* 1990; **50**: 4731-4736
- 4 Correa P, Haenszel W, Cuello C, Zavala D, Fontham E, Zarama G, Tannenbaum S, Collazos T, Ruiz B. Gastric precancerous process in a high risk population: cohort follow-up. *Cancer Res* 1990; **50**: 4737-4740
- 5 Whitney AE, Guarner J, Hutwagner L, Gold BD. Helicobacter pylori gastritis in children and adults: comparative histopathologic study. *Ann Diagn Pathol* 2000; **4**: 279-285
- 6 Öztürk Y, Büyükgebiz B, Arslan N, Ozer E. Antral glandular atrophy and intestinal metaplasia in children with Helicobacter pylori infection. *J Pediatr Gastroenterol Nutr* 2003; **37**: 96-97; author reply 97-98
- 7 Guarner J, Bartlett J, Whistler T, Pierce-Smith D, Owens M, Kreh R, Czinn S, Gold BD. Can pre-neoplastic lesions be detected in gastric biopsies of children with Helicobacter pylori infection? *J Pediatr Gastroenterol Nutr* 2003; **37**: 309-314
- 8 Usta Y, Saltk-Temizel IN, Ozen H. Gastric atrophy and intestinal metaplasia in Helicobacter pylori infection. *J Pediatr Gastroenterol Nutr* 2004; **38**: 548
- 9 Levine A, Milo T, Broide E, Wine E, Dalal I, Boaz M, Avni Y, Shirin H. Influence of Helicobacter pylori eradication on gastroesophageal reflux symptoms and epigastric pain in children and adolescents. *Pediatrics* 2004; **113**: 54-58
- 10 Muñoz N, Kato I, Peraza S, Lopez G, Carrillo E, Ramirez H, Vivas J, Castro D, Sanchez V, Andrade O, Buiatti E, Oliver W. Prevalence of precancerous lesions of the stomach in Venezuela. *Cancer Epidemiol Biomarkers Prev* 1996; **5**: 41-46
- 11 Guarner J, Mohar A, Parsonnet J, Halperin D. The association of Helicobacter pylori with gastric cancer and preneoplastic gastric lesions in Chiapas, Mexico. *Cancer* 1993; **71**: 297-301
- 12 Kolho KL, Jusufovic J, Miettinen A, Savilahti E, Rautelin H. Parietal cell antibodies and Helicobacter pylori in children. *J Pediatr Gastroenterol Nutr* 2000; **30**: 265-268
- 13 Cohen MC, Cueto Rúa E, Balcarce N, Donatone J, Drut R. Assessment of the Sydney System in Helicobacter pylori-associated gastritis in children. *Acta Gastroenterol Latinoam* 2000; **30**: 35-40
- 14 Campbell DI, Warren BF, Thomas JE, Figura N, Telford JL, Sullivan PB. The African enigma: low prevalence of gastric atrophy, high prevalence of chronic inflammation in West African adults and children. *Helicobacter* 2001; **6**: 263-267
- 15 Kato S, Nakajima S, Nishino Y, Ozawa K, Minoura T, Konno M, Maisawa S, Toyoda S, Yoshimura N, Vaid A, Genta RM. Association between gastric atrophy and Helicobacter pylori infection in Japanese children: a retrospective multicenter study. *Dig Dis Sci* 2006; **51**: 99-104
- 16 Cohen MC, Rúa EC, Balcarce N, Drut R. Sulfolomucins in Helicobacter pylori-associated chronic gastritis in children: is this incipient intestinal metaplasia? *J Pediatr Gastroenterol Nutr* 2000; **31**: 63-67
- 17 Villako K, Kekki M, Maaroos HI, Sipponen P, Uibo R, Tammur R, Tamm A. Chronic gastritis: progression of inflammation and atrophy in a six-year endoscopic follow-up of a random sample of 142 Estonian urban subjects. *Scand J Gastroenterol Suppl* 1991; **186**: 135-141
- 18 Kuipers EJ, Uytendin AM, Peña AS, Roosendaal R, Pals G, Nelis GF, Festen HP, Meuwissen SG. Long-term sequelae of Helicobacter pylori gastritis. *Lancet* 1995; **345**: 1525-1528
- 19 Guiraldes E, Peña A, Duarte I, Triviño X, Schultz M, Larraín F, Espinosa MN, Harris P. Nature and extent of gastric lesions in symptomatic Chilean children with Helicobacter pylori-associated gastritis. *Acta Paediatr* 2002; **91**: 39-44
- 20 Bazzola C, Boldorini R, Guidali P. Mild infiltration in childhood Helicobacter pylori gastritis: a morphometric and morphologic analysis. *Gut* 2002; **51** Suppl 2: A82
- 21 Machado JC, Figueiredo C, Canedo P, Pharoah P, Carvalho R, Nabais S, Castro Alves C, Campos ML, Van Doorn LJ, Caldas C, Seruca R, Carneiro F, Sobrinho-Simões M. A proinflammatory genetic profile increases the risk for chronic atrophic gastritis and gastric carcinoma. *Gastroenterology* 2003; **125**: 364-371
- 22 Meining A, Behrens R, Lehn N, Bayerdörffer E, Stolte M. Different expression of Helicobacter pylori gastritis in children: evidence for a specific pediatric disease? *Helicobacter*

- 1996; **1**: 92-97
- 23 **Dohil R**, Hassall E, Jevon G, Dimmick J. Gastritis and gastropathy of childhood. *J Pediatr Gastroenterol Nutr* 1999; **29**: 378-394
- 24 **Guarner J**, Herrera-Goepfert R, Mohar A, Sanchez L, Halperin D, Ley C, Parsonnet J. Interobserver variability in application of the revised Sydney classification for gastritis. *Hum Pathol* 1999; **30**: 1431-1434
- 25 **el-Zimaity HM**, Graham DY, al-Assi MT, Malaty H, Karttunen TJ, Graham DP, Huberman RM, Genta RM. Interobserver variation in the histopathological assessment of Helicobacter pylori gastritis. *Hum Pathol* 1996; **27**: 35-41
- 26 **Bedoya A**, Garay J, Sanzón F, Bravo LE, Correa H, Craver R, Fonham E, Du JX, Correa P. Histopathology of gastritis in Helicobacter pylori-infected children from populations at high and low gastric cancer risk. *Hum Pathol* 2003; **34**: 206-213
- 27 **Wizla-Derambure N**, Michaud L, Ategbro S, Vincent P, Ganga-Zandzou S, Turck D, Gottrand F. Familial and community environmental risk factors for Helicobacter pylori infection in children and adolescents. *J Pediatr Gastroenterol Nutr* 2001; **33**: 58-63
- 28 **Kekki M**, Samloff IM, Varis K, Ihamaäki T. Serum pepsinogen I and serum gastrin in the screening of severe atrophic corpus gastritis. *Scand J Gastroenterol Suppl* 1991; **186**: 109-116
- 29 **Segni M**, Borrelli O, Pucarelli I, Delle Fave G, Pasquino AM, Annibale B. Early manifestations of gastric autoimmunity in patients with juvenile autoimmune thyroid diseases. *J Clin Endocrinol Metab* 2004; **89**: 4944-4948
- 30 **Sipponen P**, Kekki M, Seppälä K, Siurala M. The relationships between chronic gastritis and gastric acid secretion. *Aliment Pharmacol Ther* 1996; **10** Suppl 1: 103-118
- 31 **Chen XY**, van Der Hulst RW, Shi Y, Xiao SD, Tytgat GN, Ten Kate FJ. Comparison of precancerous conditions: atrophy and intestinal metaplasia in Helicobacter pylori gastritis among Chinese and Dutch patients. *J Clin Pathol* 2001; **54**: 367-370
- 32 **Eidt S**, Stolte M. Prevalence of intestinal metaplasia in Helicobacter pylori gastritis. *Scand J Gastroenterol* 1994; **29**: 607-610
- 33 **Correa P**, Cuello C, Duque E, Burbano LC, Garcia FT, Bolanos O, Brown C, Haenszel W. Gastric cancer in Colombia. III. Natural history of precursor lesions. *J Natl Cancer Inst* 1976; **57**: 1027-1035
- 34 **Zaitoun AM**. Histological study of chronic gastritis from the United Arab Emirates using the Sydney system of classification. *J Clin Pathol* 1994; **47**: 810-815
- 35 **Hu PJ**, Li YY, Lin HL, Zhou SM, Du G, Chen MH, Mitchell HM, Hazell SL. Gastric atrophy and regional variation in upper gastrointestinal disease. *Am J Gastroenterol* 1995; **90**: 1102-1106
- 36 **Ashorn M**. What are the specific features of Helicobacter pylori gastritis in children? *Ann Med* 1995; **27**: 617-620
- 37 **Czinn SJ**, Glassman MS. Helicobacter pylori in infants and children. *Adv Pediatr Infect Dis* 1996; **11**: 389-401
- 38 **Kuipers EJ**, Klinkenberg-Knol EC, Vandenbroucke-Grauls CM, Appelmek BJ, Schenk BE, Meuwissen SG. Role of Helicobacter pylori in the pathogenesis of atrophic gastritis. *Scand J Gastroenterol Suppl* 1997; **223**: 28-34
- 39 **Kalach N**, Mention K, Guimber D, Michaud L, Spyckerelle C, Gottrand F. Helicobacter pylori infection is not associated with specific symptoms in nonulcer-dyspeptic children. *Pediatrics* 2005; **115**: 17-21
- 40 **Kuipers EJ**, Uytterlinde AM, Peña AS, Hazenberg HJ, Bloemena E, Lindeman J, Klinkenberg-Knol EC, Meuwissen SG. Increase of Helicobacter pylori-associated corpus gastritis during acid suppressive therapy: implications for long-term safety. *Am J Gastroenterol* 1995; **90**: 1401-1406
- 41 **Kuipers EJ**, Lundell L, Klinkenberg-Knol EC, Havu N, Festen HP, Liedman B, Lamers CB, Jansen JB, Dalenback J, Snel P, Nelis GF, Meuwissen SG. Atrophic gastritis and Helicobacter pylori infection in patients with reflux esophagitis treated with omeprazole or fundoplication. *N Engl J Med* 1996; **334**: 1018-1022
- 42 **Lundell L**, Havu N, Andersson A. Gastritis development and acid suppression therapy revisited. Results of a randomised clinical study with long-term follow-up (abstract). *Gastroenterology* 1997; **112**: A28
- 43 **Lamberts R**, Brunner G, Solcia E. Effects of very long (up to 10 years) proton pump blockade on human gastric mucosa. *Digestion* 2001; **64**: 205-213
- 44 **Klinkenberg-Knol EC**, Nelis F, Dent J, Snel P, Mitchell B, Prichard P, Lloyd D, Havu N, Frame MH, Romàn J, Walan A. Long-term omeprazole treatment in resistant gastroesophageal reflux disease: efficacy, safety, and influence on gastric mucosa. *Gastroenterology* 2000; **118**: 661-669
- 45 **Negrini R**, Lisato L, Zanella I, Cavazzini L, Gullini S, Villanacci V, Poiesi C, Albertini A, Ghielmi S. Helicobacter pylori infection induces antibodies cross-reacting with human gastric mucosa. *Gastroenterology* 1991; **101**: 437-445
- 46 **Faller G**, Steininger H, Eck M, Hensen J, Hann EG, Kirchner T. Antigastric autoantibodies in Helicobacter pylori gastritis: prevalence, in-situ binding sites and clues for clinical relevance. *Virchows Arch* 1996; **427**: 483-486
- 47 **Oksanen A**, Sipponen P, Karttunen R, Miettinen A, Veijola L, Sarna S, Rautelin H. Atrophic gastritis and Helicobacter pylori infection in outpatients referred for gastroscopy. *Gut* 2000; **46**: 460-463
- 48 **Ito M**, Haruma K, Kaya S, Kamada T, Kim S, Sasaki A, Sumii M, Tanaka S, Yoshihara M, Chayama K. Role of anti-parietal cell antibody in Helicobacter pylori-associated atrophic gastritis: evaluation in a country of high prevalence of atrophic gastritis. *Scand J Gastroenterol* 2002; **37**: 287-293
- 49 **Kokkonen J**. Parietal cell antibodies and gastric secretion in children with diabetes mellitus. *Acta Paediatr Scand* 1980; **69**: 485-489
- 50 **Petäys T**, Miettinen A. Autoantibodies (AAb) in the sera of Finnish children with IDDM. *Acta Endocrinol* 1991; **124** Suppl 3: 28
- 51 **Barrio R**, Roldán MB, Alonso M, Cantón R, Camarero C. Helicobacter pylori infection with parietal cell antibodies in children and adolescents with insulin dependent diabetes mellitus. *J Pediatr Endocrinol Metab* 1997; **10**: 511-516
- 52 **Volta U**, De Franceschi L, Molinaro N, Tetta C, Bianchi FB. Organ-specific autoantibodies in coeliac disease: do they represent an epiphenomenon or the expression of associated autoimmune disorders? *Ital J Gastroenterol Hepatol* 1997; **29**: 18-21
- 53 **Kuitunen P**, Mäenpää J, Krohn K, Visakorpi JK. Gastrointestinal findings in autoimmune thyroiditis and non-goitrous juvenile hypothyroidism in children. *Scand J Gastroenterol* 1971; **6**: 336-341
- 54 **Filipe MI**, Muñoz N, Matko I, Kato I, Pompe-Kirn V, Jutersek A, Teuchmann S, Benz M, Prijon T. Intestinal metaplasia types and the risk of gastric cancer: a cohort study in Slovenia. *Int J Cancer* 1994; **57**: 324-329
- 55 **Aichbichler BW**, Eherer AJ, Petritsch W, Hinterleitner TA, Krejs GJ. Gastric adenocarcinoma mimicking achalasia in a 15-year-old patient: a case report and review of the literature. *J Pediatr Gastroenterol Nutr* 2001; **32**: 103-106
- 56 **Kuipers EJ**. Review article: Relationship between Helicobacter pylori, atrophic gastritis and gastric cancer. *Aliment Pharmacol Ther* 1998; **12** Suppl 1: 25-36
- 57 **Banatvala N**, Mayo K, Megraud F, Jennings R, Deeks JJ, Feldman RA. The cohort effect and Helicobacter pylori. *J Infect Dis* 1993; **168**: 219-221
- 58 **Cullen DJ**, Collins BJ, Christiansen KJ, Epis J, Warren JR, Surveyor I, Cullen KJ. When is Helicobacter pylori infection acquired? *Gut* 1993; **34**: 1681-1682
- 59 **Mitchell HM**, Li YY, Hu PJ, Liu Q, Chen M, Du GG, Wang ZJ, Lee A, Hazell SL. Epidemiology of Helicobacter pylori in southern China: identification of early childhood as the critical period for acquisition. *J Infect Dis* 1992; **166**: 149-153
- 60 **Rowland M**, Daly L, Vaughan M, Higgins A, Bourke B, Drumm B. Age-specific incidence of Helicobacter pylori. *Gastroenterology* 2006; **130**: 65-72; quiz 211
- 61 **Baysoy G**, Ertem D, Ademoğlu E, Kotiloglu E, Keskin S,

- Pehlivanoglu E. Gastric histopathology, iron status and iron deficiency anemia in children with *Helicobacter pylori* infection. *J Pediatr Gastroenterol Nutr* 2004; **38**: 146-151
- 62 **Kim DS**, Lee MS, Kim YS, Kim DH, Bae JM, Shin MH, Ahn YO. Effect modification by vitamin C on the relation between gastric cancer and *Helicobacter pylori*. *Eur J Epidemiol* 2005; **20**: 67-71
- 63 **Rood JC**, Ruiz B, Fontham ET, Malcom GT, Hunter FM, Sobhan M, Johnson WD, Correa P. *Helicobacter pylori*-associated gastritis and the ascorbic acid concentration in gastric juice. *Nutr Cancer* 1994; **22**: 65-72
- 64 **Jarosz M**, Dzieniszewski J, Dabrowska-Ufniaz E, Wartanowicz M, Ziemiński S, Reed PI. Effects of high dose vitamin C treatment on *Helicobacter pylori* infection and total vitamin C concentration in gastric juice. *Eur J Cancer Prev* 1998; **7**: 449-454
- 65 **Burr ML**, Samloff IM, Bates CJ, Holliday RM. Atrophic gastritis and vitamin C status in two towns with different stomach cancer death-rates. *Br J Cancer* 1987; **56**: 163-167
- 66 **Imrie C**, Rowland M, Bourke B, Drumm B. Is *Helicobacter pylori* infection in childhood a risk factor for gastric cancer? *Pediatrics* 2001; **107**: 373-380

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