Helicobacter Pylori and Iron Deficiency Anemia in Children: Case Series and Review of Literature

Francesca Penagini[*,1], Dario Dilillo[1], Matteo Torcoletti[2], Silvia Mauri[2], Paolo Fociani[3] and Gian Vincenzo Zuccotti[1]

[1]*Department of Paediatrics, Ospedale dei Bambini V. Buzzi, University of Milan, Italy*

[2]*Department of Paediatrics, Luigi Sacco Hospital, University of Milan, Italy*

[3]*Department of Pathology, Luigi Sacco Hospital, University of Milan, Italy*

Abstract: *Helicobacter pylori (H. pylori)* infection has been described as a possible cause of refractory iron deficiency anemia (IDA) in children. Nevertheless, the relationship between *H. pylori* infection and IDA in children remains an area of controversy due to the contrasting data in literature. We report a case series of two children who presented with IDA refractory to iron treatment, which reversed only after eradication of *H. pylori* infection, supporting the causal role of this bacterium in pathogenesis of IDA. In both cases *H. pylori* presented a high antimicrobial resistance, raising the issue on the importance of considering geographical susceptibility of *H. pylori* strains when starting empirical treatment and the importance of performing antimicrobial susceptibility testings, in particular if standard empirical therapy fails. The present review gives a complete overview of the literature regarding the relationship between *H. pylori* and IDA in children, explains the possible pathogenetic mechanisms involved in *H. pylori*-related IDA and addresses the issue of the high antimicrobial resistance often encountered in *H. pylori* infection in children.

Keywords: *Helicobacter pylori*, iron deficiency anemia, gastritis, children.

INTRODUCTION

Helicobacter pylori (*H. pylori*) is a Gram-negative microaerophilic bacterium that colonizes the human gastric mucosa and which is usually acquired during the first years of life by oral ingestion. The colonization doesn't necessarily lead to pathology, as several factors are involved in the etiopathogenesis of disease such as bacterial genotype, host immune response and host genetics [1]. Even though *H. pylori* related gastro-duodenal lesions are considered a disease of adulthood with a tendency to occur decades after acquisition of the infection, *H. pylori* positive gastritis and peptic ulcers may also occur, even if rarely, in children and adolescents [2]. The epidemiology of *H. pylori* infection in children presents a geographic distribution with higher prevalence in developing countries. In northern or western Europe and in north America, the prevalence of *H. pylori* infection is low, around 10 % [3, 4]. On the contrary, in low-income countries such as Mexico, south America, Africa and Asia the infection is very frequent and almost endemic [5]. Clinical symptoms of *H. pylori* infection in children may be of variable severity, ranging from asymptomatic infection to acute abdominal pain and gastrointestinal hemorrhage if peptic ulcer occurs. Several case reports and clinical trials have shown an association between iron deficiency anemia (IDA) and *H. pylori* infection [6-8] and several possible mechanisms to explain this association have been described [9, 10]. In first instance, a decreased gastric acidity caused by gastric inflammation in *H. pylori* gastritis may impair oral iron solubility and absorption. Secondly, *H. pylori* may cause iron deficiency by competing with host for available food iron. In fact, iron is an essential growth factor for *H. pylori* [9]. As last mechanism involved in the development of IDA, *H. pylori* gastritis may be associated with occult gastrointestinal bleeding as a result of diffuse hemorrhages, erosions and ulcerations [10]. Nevertheless, some recent randomized controlled clinical trials (RCT) conducted in pediatric patients have not been able to confirm the association between *H. pylori* infection and IDA [11-15]. In consideration of the contrasting data in literature, the relationship between *H. pylori* infection and IDA in children still remains controversial. We report a case series of two children with *H. pylori*-related IDA, in whom IDA reversed only after eradication of the bacterium.

CASE REPORT 1

A 10-year-old Chilean boy presented to our Pediatric Department for clinical evaluation after adoption from an Italian family. Very little was known about his biological family and past medical history. The only data available from his medical records was that in his native country, when he was 5 years of age, he was found to have severe anemia (Hemoglobin (Hb) 3 g/dL). Unfortunately, the clinical symptoms and the

*Address correspondence to this author at the Department of Paediatrics, Ospedale dei Bambini V. Buzzi, University of Milan, Italy;
Tel: 00393335651596; E-mail: frapenagini@tiscali.it

E-ISSN: 2311-8687/14

reason that lead him to have blood tests done were not described in the child's medical documentation. In Chile investigations for anemia ruled out celiac disease, hemolysis, gastrointestinal occult bleeding, intestinal parasitosis and hematological malignancies. The presence of Meckel's diverticulum, which can be responsible for painless rectal bleeding leading to anemia was also ruled out by a Meckel's scan which was negative. To rule out a gastrointestinal cause of IDA the child underwent esophagogastroduodenoscopy (EGDS) which showed signs of chronic gastritis of antral mucosa, but it is not known whether investigations for *H. pylori* were performed. Hence, anemia was attributed to chronic malnutrition and the boy was started on oral iron treatment. Subsequently, the child moved to Italy in February 2012 and we met him one month later, in March 2012. The child was looking well. Physical examination was normal except for cutaneous pallor and a II/VI heart murmur. His weight was 30 kg (25^{th} c.le), his height was 134 cm (25^{th} c.le), BMI was 16.7 (25^{th}-50^{th} c.le). Blood pressure was normal according to gender and age. Blood tests showed a severe IDA. His hematological parameters were: Hb 5.6 g/dL, mean corpuscular volume (MCV) 65.6 fL, mean corpuscular hemoglobin (MCH) 18 pg. Iron stores were: serum iron 13 µg /dL, transferrin 3.60 g/L, transferrin saturation 2.6%, and ferritin 1 µg /L. Nutritional assessment including dietary recall revealed an adequate dietary intake of iron according to the child's nutritional requirements. Celiac disease, intestinal parasitosis and the presence of fecal occult blood were ruled out. Causes of hemolytic anemia such as hemoglobinopathies and glucose-6-phosphate dehydrogenase deficiency were excluded. Serology for Hepatitis B and C, HIV and syphilis were negative. Abdominal ultrasound was normal. A blood transfusion was administered with transient increase of hemoglobin levels to 7.4 g/dL, subsequently a course of intravenous iron therapy was given for 5 days. EGDS showed features of micronodular antral gastritis and duodenitis. Histology of antral and fundus mucosa biopsies revealed the presence of *H. pylori* and atrophy of antral mucosa (Figure **1**). Standard triple therapy with oral amoxicillin (50 mg/kg/day), clarithromycin (20 mg/kg/day) and omeprazole (1 mg/kg/day) was undertaken for 2 weeks. At the same time he was started on oral iron, folic acid and vitamin B12 supplementation, which were continued until *H. pylori* was eradicated. Full blood count (FBC) 10 days post-treatment showed an increase of Hb to 10.3 g/dL. Six weeks post-treatment a non-invasive test to detect the presence of *H. pylori* infection was performed, the 13-Carbon urea breath test (UBT), which came back positive and repeat blood tests showed recurrence of IDA: Hb 8.9 g/dL, MCV 71 fL, serum iron 17 µg/dL, transferrin 4.06 g/L, transferrin saturation 3 %, and ferritin 4 µg /L. A second course of eradication treatment with oral amoxicillin (50 mg/kg/day), metronidazole (20 mg/kg/day) and omeprazole (1 mg/kg/day) was done for 2 weeks. Again, the UBT one month post-treatment was still positive. Sequential therapy was initiated with oral amoxicillin (50 mg/kg/day) and omeprazole (1 mg/kg/day) for 5 days followed by metronidazole (20 mg/kg/day), clarithromycin (20 mg/kg/day) and omeprazole (1 mg/kg/day) for other 5 days. Also this treatment failed, hence a triple therapy was started with oral amoxicillin (50 mg/kg/day), levofloxacin (15 mg/kg/day) and omeprazole (1 mg/kg/day) for 14 days. Finally *H. pylori* was eradicated and 4 months later the child's hematologic parameters showed significant improvement with normal levels of hemoglobin and iron status within limits for age (Hb 12.2 g/dL, MCV 72 fl, MCH 21.6 pg, serum iron 61 µg/dL, transferrin 4.40 g/L, transferrin saturation 3 % and ferritin 7.5 µg /L). During the clinical follow-up the child was well with normal growth parameters and stable hemoglobin levels.

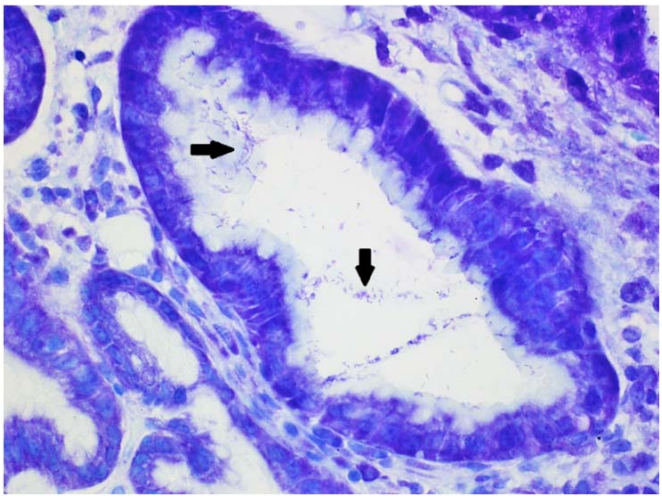

Figure 1: Patient 1: a 10-year-old boy with severe iron deficiency anemia and *Helicobacter pylori* positive micronodular antral gastritis and duodenitis. In the figure: antral mucosa with presence of *Helicobacter pylori* (black arrows). Giemsa. OM x 60.

CASE REPORT 2

A 16-month-old boy was admitted to our Pediatric Department for acute viral gastroenteritis. The boy was born in Italy at 37+6 weeks of gestation from South American parents. Neonatal period was uncomplicated. The child was exclusively breastfed until 6 months of age and thrived well on the 50^{th} centile for weight.

Feeding issues presented upon weaning leading to food refusal and continuation of breast feeding until we met him at 16 months of age. Upon admission the child looked well, was not pale or jaundiced. His weight was 11.770 kg (50th c.le). Laboratory tests revealed severe IDA (Hb 6.3 g/dl, MCV 55.3 fl, MCH 15 pg, serum iron 21 µg/dL, transferrin 3, 80 g/L, transferrin saturation 3,5 %, ferritin 6 µg/dL). Investigations for IDA including celiac serology, fecal occult blood test, urinalysis, peripheral blood smear, hemoglobin electrophoresis and work up for hemolytic anemia all came back negative. The IDA was attributed to poor dietary intake of iron. Hence, iron supplementation was administered initially by intravenous infusion and once the viral gastroenteritis had resolved, was continued orally for a total of 4 weeks. At 3 weeks post iron treatment blood tests showed only a mild improvement in Hb levels and iron status: Hb 7.6 g/dl, MCV 62.2 fl, MCH 18 pg, serum iron 35 µg/dL, transferrin 3,5 g/L, transferrin saturation 2,80 %, ferritin 21 µg/dL. Fecal antigen test for *H. pylori* was performed and was found to be positive. EGDS showed normal esophageal, gastric and duodenal mucosa. Histologic evaluation of biopsies revealed signs of chronic follicular gastritis in gastric antrum and fundus with positivity for *H. pylori* infection (Figure **2**). The patient required two courses of antibiotic treatment before eradicating the bacterium.

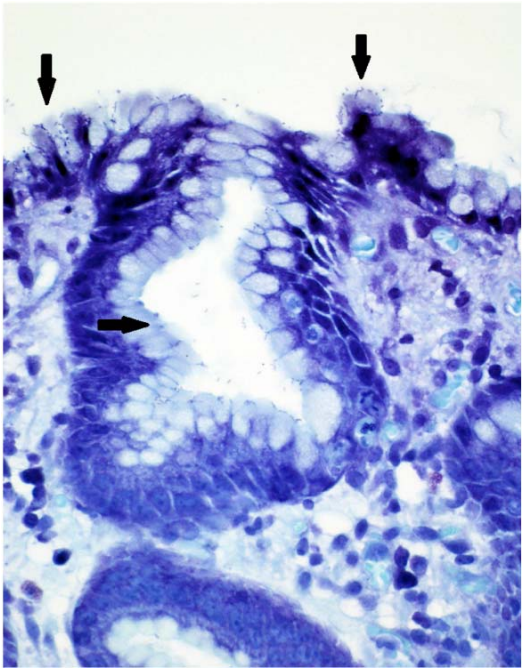

Figure 2: Patient 2: a 16-month-old boy with severe iron deficiency anemia and chronic follicular gastritis in gastric antrum and fundus with positivity for *H. pylori* infection. In the figure: mucosa of gastric fundus with presence of *Helicobacter pylori* (black arrows). Giemsa. OM x 60.

In fact, the child was initially treated with amoxicillin (50 mg/kg/day), clarithromycin (20 mg/kg/day) and esomeprazole (1 mg/kg/day) for two weeks. Four weeks post-treatment UBT was still positive for *H. pylori.* Subsequently, a second antibiotic course was done with amoxicillin (50 mg/kg/day), metronidazole (20 mg/kg/day) and esomeprazole (1 mg/kg/day) for other 2 weeks with successful eradication of *H. pylori*, as demonstrated by negativity of UBT test four weeks post-treatment. Iron supplementation was continued throughout the antibiotic courses. Blood tests post *H. pylori* eradication showed reversal of IDA with the following hematologic parameters: Hb 10.9 g/dl, MCV 72 fl, MCH 24 pg serum iron 40 µg/dL, transferrin 4,8 g/L, transferrin saturation 5 %, ferritin 77 µg/dL. The child is currently thriving well and presents stable hematologic parameters.

DISCUSSION AND REVIEW OF LITERATURE

Iron deficiency anemia (IDA) is a common finding in pediatric population. In children, among the different causes of reduced iron availability, the most common include poor intake, malabsorption and/or chronic losses of oral iron. Nevertheless, *H. pylori* infection may have a potential role in etiology of IDA as a consequence of the pathogenetic mechanisms described above. With regards to evidence provided by literature, since the 1990's, several case reports and case series of *H. pylori* related IDA have been described in children and adolescents, as summarized in Table **1** [16-22]. Besides from case series, some RCTs have focused on the relationship between *H. pylori* and IDA, producing controversial results. Among the studies that support a causal role between *H. pylori* infection and IDA [7-8, 23-24], Choe *et al.* [7] conducted a double-blind, placebo-controlled trial in 25 *H. pylori* positive subjects aged 10-17 years with IDA. Hemoglobin levels increased significantly in the group of subjects who received *H. pylori* eradication treatment together with oral iron treatment compared to subjects who received oral iron therapy alone. The same group of Authors confirmed this finding by conducting a large population survey (n= 995) on female Korean adolescents with *H. pylori* positivity and IDA. In fact, also in this study IDA reversed after combined treatment for eradication and iron supplementation on comparison with iron therapy alone [23]. Table **2** summarizes the main clinical trials that have demonstrated a causal relationship between *H. pylori* infection and IDA in children. Nevertheless, there are intervention trials that have not shown a causal relationship between *H. pylori* infection and IDA in

pediatric population [11, 12]. For example, Gessner *et al.* [11] conducted a study on 219 children living in Alaska who were iron deficient (ID) and *H. pylori* positive. The prevalence of ID at 14 months after treatment initiation was not reduced in the subjects who received the eradication treatment compared to the group who received iron supplementation alone. In the same group of subjects, a slight reduction of ID was noticed only on long-term follow-up, after more than 14 months from *H. pylori* eradication [12]. Another study conducted by Sarker *et al.* [13] did not show a beneficial effect of *H. pylori* eradication on improvement of iron status and prevalence of anemia. In fact, Authors enrolled 200 *H. pylori* positive children aged 2-5 years with either IDA or ID and randomized them to receive either a treatment with an *H. pylori* eradication regime together with iron supplementation, *H. pylori* therapy alone, iron supplementation alone, or placebo for 2 weeks. The study also included a negative control group represented by 60 *H. pylori* negative children with IDA who received iron treatment. No significant differences were observed between groups in terms of improvement of IDA or ID. Furthermore, a randomized controlled trial conducted in USA showed no changes in iron stores following *H. pylori* eradication in *H. pylori* positive children [14]. Table **3** summarizes the main clinical trials that have not confirmed a causal relationship between *H. pylori* infection and IDA or ID in pediatric patients.

Table 1: Case Series Reporting a Reversal of IDA after *H. pylori* Eradication

Case series reporting reversal of IDA after *H. pylori* eradication	
Reference	**Number of children/age**
Dufour *et al.* 1993 [16]	7-year-old child
Carnicier *et al.* 1997 [17]	11- year-old child
Barabino *et al.* 1999 [19]	4 Children aged 4-13 years
Konno *et al.* 2000 [20]	6 Adolescents aged 13-15 years
Ashorn *et al.* 2001 [21]	7 children 7-15 years
Santalha *et al.* 2013 [22]	12-year-old adolescent

In our case series IDA was refractory to iron treatment alone since hematological parameters did not improve on iron treatment until *H. pylori* was eradicated, supporting a causal role of the bacterium in pathogenesis of IDA. In addition, in both case reports *H. pylori* showed a high antimicrobial resistance particularly in case report 1 where three courses of antibiotic treatment with clarithromycin failed. The only regime that managed to eradicate the infection was the one based on levofloxacin and amoxicillin. This clinical observation is consistent with scientific data on the

Table 2: Main Clinical Trials Supporting the Causal Role of *H. pylori* Infection in Etiopathogenesis of IDA

Main clinical trials supporting the causal role of *H. pylori* infection in etiopathogenesis of IDA			
Reference	**Number of *H. pylori* + children/adolescents with IDA**	**Age range**	**Findings**
Choe *et al.* 1999 [7]	25	10-17 years	Increase of Hb levels after *H.pylori* eradication + iron treatment vs iron treatment alone.
Choe *et al.* 2000 [23]	13	15-17 years	Increase in Hb and ferritin levels after *H. pylori* eradication.
Kurekci *et al.* 2005 [8]	140	6-16 years	Reversal of IDA after *H. pylori* eradication without iron supplementation.
Fagan *et al.* 2009 [12]	219	6-11 years	Modest reduction of ID and IDA prevalence at long term follow-up (>14 months) after *H. pylori* eradication.

Table 3: Main Clinical Trials that have Not Shown an Association between *H. pylori* Eradication and Improvement of IDA

Main clinical trials that have not shown an association between *H. pylori* eradication and IDA			
Reference	**Number of children**	**Age range**	**Findings**
Gessner *et al.* 2006 [11]	219	6-11 years	No improvement of ID or IDA after 14 months of successful eradication of *H. pylori* infection.
Sarker *et al.* 2008 [13]	200	2-5 years	Similar cure rates of ID or IDA in *H. pylori*+ group compared to *H. pylori*– group.
Cardenas *et al.* 2011 [15]	110	3-10 years	No improvement of iron status after *H. pylori* eradication.

pattern of *H.pylori* antimicrobial susceptibility. In fact, in European countries clarithromycin resistance is fairly high, approximately around 24% and represents the first cause of treatment failure in both adults and children. The occurrence of this phenomenon could be secondary to the wide spread use of this antibiotic for respiratory tract infections [25-28]. In developing countries, while the resistance rate to clarithromycin is similar to the one observed in European countries, occurring approximately around 19.5% of cases, the resistance rate of *H. pylori* to metronidazole is fairly high. In fact, it is estimated to be around 40.2% in both pediatric and adult population, probably due to the wide spread use this antibiotic for treatment of parasitic and gynecologic infections in these countries [29-33]. With regards to amoxicillin, even though it is commonly used in pediatric practice in both developed and developing countries, the resistance rate of *H. pylori* to this antibiotic is very low, ranging from 0% to 2%, making it a good option in eradication therapy [34, 35].

In conclusion, the present case series adds knowledge to the literature, mainly with regards to two aspects. In first instance, it adds further evidence on the causal role of *H. pylori* in development of IDA in children, reminding general pediatricians to search for *H. pylori* particularly in case of iron refractory IDA. In fact, also in our case reports, IDA was refractory to iron treatment, and reversed only after *H. pylori* eradication. Nevertheless, the causal relationship between *H. pylori* infection and IDA in children still remains an area of controversy and further placebo-controlled clinical trials would be useful to add more robust evidence. Secondly, the present case series raise the issue about *H. pylori* antimicrobial resistance. Both case reports highlight the importance of considering the geographical susceptibility of *H. pylori* strains before starting empirical treatment and of performing susceptibility testings, particularly when standard triple therapy fails. Antimicrobial choice should be guided according to the resistance pattern for optimization of treatment.

CONFLICT OF INTERESTS

Authors declare that they have no competing interests.

ABBREVIATIONS

BMI = Body mass index

EGDS = Esophagogastroduodenoscopy

FBC = Full blood count

H. pylori = Helicobacter pylori

Hb = Hemoglobin

IDA = Iron deficiency anemia

MCV = Mean corpuscular volume

MCH = Mean corpuscular hemoglobin

UBT = Urea breath test

REFERENCES

[1] Homan M, Hojsak I, Kolacek S. Helicobacter pylori in pediatrics. Helicobacter 2012; 17: 43-8. http://dx.doi.org/10.1111/j.1523-5378.2012.00982.x

[2] Kalach N, Bontems P, Koletzko S, Mourad- Baars P, Shcherbakov P, Celinska- Cedro D, *et al.* Frequency and risk factors of gastric and duodenal ulcers or erosions in children: a prospective 1-month European multicenter study. Eur J Gastroenterol Hepatol 2010; 22: 1174-81. http://dx.doi.org/10.1097/MEG.0b013e32833d36de

[3] Rowland M, Daly L, Vaughan M, Higgins A, Bourke B, Drumm B. Age-specific incidence of Helicobacter pylori. Gastroenterology 2006; 130: 65-72. http://dx.doi.org/10.1053/j.gastro.2005.11.004

[4] Goodman KJ, O' Rourke K, Day RS, Wang C, Nurgalieva Z, Phillips CV, *et al.* Dynamics of Helicobacter pylori infection in a US-Mexico cohort during the first two years of life. Int J Epidemiol 2005; 34: 1348-55. http://dx.doi.org/10.1093/ije/dyi152

[5] Azevedo NF, Huntington J, Goodman KJ. The epidemiology of Helicobacter pylori and public health implications. Helicobacter 2009; 14: 1-7. http://dx.doi.org/10.1111/j.1523-5378.2009.00703.x

[6] Koletzko SI, Jones NL, Goodman KJ, Gold B, Rowland M, Cadranel S, *et al.* Evidence-based guidelines from ESPGHAN and NASPGHAN for Helicobacter pylori infection in children. J Pediatr Gastroenterol Nutr 2011; 53: 230-43.

[7] Choe YH, Kim SK, Son BK, Lee DH, Hong YC, Pai SH. Randomized placebo-controlled trial of Helicobacter pylori eradication for iron-deficiency anemia in preadolescent children and adolescents. Helicobacter 1999; 4: 135-9. http://dx.doi.org/10.1046/j.1523-5378.1999.98066.x

[8] Kurekci AE, Atay AA, Sarici SU, Yesilkaya E, Senses Z, Okutan V, *et al.* Is there a relationship between childhood Helicobacter pylori infection and iron deficiency anemia? J Trop Pediatr 2005; 51: 166-9. http://dx.doi.org/10.1093/tropej/fmi015

[9] Perez-Perez GI and Israel DA. Role of iron in Helicobacter pylori: its influence in outer membrane protein expression and in pathogenicity. Eur J Gastr Hepatol 2000; 12: 1263-65. http://dx.doi.org/10.1097/00042737-200012120-00001

[10] Yip R, Limburg PJ, Ahlquist DA, Carpenter HA, O'Neill A, Kruse D, *et al.* Pervasive occult bleeding in an Alaska native population with prevalent iron deficiency. Role of Helicobacter pylori gastritis. JAMA 1997; 277: 1135-9. http://dx.doi.org/10.1001/jama.1997.03540380049030

[11] Gessner BD, Baggett HC, Muth PT, Dunaway E, Gold BD, Feng Z, *et al.* A controlled, household-randomized, open-label trial of the effect that treatment of Helicobacter pylori infection has on iron deficiency in children in rural Alaska. J Infect Dis 2006; 193: 537-46. http://dx.doi.org/10.1086/499604

[12] Fagan RP, Dunaway CE, Bruden DL, Parkinson AJ, Gessner BD. Controlled, Household-Randomized, Open-Label Trial of Effect of Treatment of Helicobacter pylori Infection on Iron Deficiency among Children in Rural Alaska: Results at 40

months. J Infect Dis 2009; 199: 652-60.
http://dx.doi.org/10.1086/596659

[13] Sarker SA, Mahmud H, Davidsson L, Alam NH, Ahmed T, Alam N, *et al.* Causal relationship of Helicobacter pylori with iron-deficiency anemia or failure of iron supplementation in children. Gastroenterology 2008; 135: 1534-42.
http://dx.doi.org/10.1053/j.gastro.2008.07.030

[14] Afifi RA, Ali DK, Shaheen IA. A localized case-control study of extra-gastric manifestations of Helicobacter pylori infection in children. Indian J Pediatr 2011; 78: 418-22.
http://dx.doi.org/10.1007/s12098-010-0308-6

[15] Cardenas VM, Prieto-Jimenez CA, Mulla ZD, Rivera JO, Dominguez DC, Graham DY, *et al.* Helicobacter pylori eradication and change in markers of iron stores among non-iron-deficient children in El Paso, Texas: an etiologic intervention study. J Pediatr Gatroenterol Nutr 2011; 52: 326-32.
http://dx.doi.org/10.1097/MPG.0b013e3182054123

[16] Dufour C, Brisigotti M, Fabretti G, Luxardo P, Mori PG, Barabino. A Helicobacter pylori gastric infection and sideropenic refractory anemia. J Pediatr Gatroenterol Nutr 1993; 17: 225-7.
http://dx.doi.org/10.1097/00005176-199308000-00018

[17] Carnicier J, Badia R, Argemì J. Helicobacter pylori gastritis and sideropenic refractory anemia. J Pediatr Gatroenterol Nutr 1997; 25: 441.
http://dx.doi.org/10.1097/00005176-199710000-00017

[18] Marignani M, Angeletti S, Bordi C, Malagnino F, Mancino C, Delle Fave G, *et al.* Reversal of long-standing iron deficiency anemia after eradication of Helicobacter pylori infection. Scand J Gastroenterol 1997; 32: 617-22.
http://dx.doi.org/10.3109/00365529709025109

[19] Barabino A, Dufour C, Marino CE, Claudiani F, De Alessandri A. Unexplained refractory anemia associated with Helicobacter pylori gastric infection in children: further clinical evidence. J Pediatr Gatroenterol Nutr 1999; 28: 116-9.
http://dx.doi.org/10.1097/00005176-199901000-00027

[20] Konno M, Muraoka S, Takahashi M, Imai T. Iron deficiency anemia associated with Helicobacter pylori gastritis. J Pediatr Gatroenterol Nutr 2000; 31: 52-6.
http://dx.doi.org/10.1097/00005176-200007000-00012

[21] Ashorn M, Ruuska T, Makipernaa. A Helicobacter pylori and iron deficiency anaemia in children. Scand J Gastroenterol 2001; 36: 701-5.
http://dx.doi.org/10.1080/003655201300191950

[22] Santalha MF, Costa E, Miguel N, Vizcaino R, Barbot J, Pereira F Iron deficiency anemia due to lymphocytic Gastritis with Helicobacter pylori infection in childhood: case report. J Pediatr Hematol Oncol 2013; 35: 321-2.
http://dx.doi.org/10.1097/MPH.0b013e318286d129

[23] Choe YH, Lee JE, Kim SK. Effect of Helicobacter pylori eradication on sideropenic refractory anemia in adolescent girls with Helicobacter pylori infection. Acta Pediatr 2000; 89: 154-7.
http://dx.doi.org/10.1111/j.1651-2227.2000.tb01208.x

[24] Choe JH, Kwon YS, Jung MK, Kang SK, Hwang TS, Hong YC. Helicobacter pylori-associated iron deficiency anemia in adolescent female athletes. J Pediatr 2001; 139: 100-4.
http://dx.doi.org/10.1067/mpd.2001.114700

[25] Mégraud F, Occhialini A, Doermann HP. Resistance of Helicobacter pylori to macrolides and nitroimidazole compounds. The current situation. J Physiol Pharmacol 1997; 48: 25-38.

[26] Kalach N, Benhamou PH, Campeotto F, Bergeret M, Dupont C, Raymond J. Clarithromycin resistance and eradication of Helicobacter pylori in children. Antimicrobial Agents Chemother 2001; 45: 2134-5.
http://dx.doi.org/10.1128/AAC.45.7.2134-2135.2001

[27] Mégraud F. H. pylori antibiotic resistance: prevalence, importance, and advances in testing. Gut 2004; 53: 1374-84.
http://dx.doi.org/10.1136/gut.2003.022111

[28] Koletzko S, Richy F, Bontems P, Crone J, Kalach N, Monteiro ML, *et al.* Prospective multicentre study on antibiotic resistance of Helicobacter pylori strains obtained from children living in Europe. Gut 2006; 55: 1711-6.
http://dx.doi.org/10.1136/gut.2006.091272

[29] Ogata SK, Oritz Godoy AP, da Silva Patricio FR, Kawakami E. High Helicobacter pylori resistance to metronidazole and clarithromycin in Brazilian children and adolescents. J Pediatr Gastroenterol Nutr 2013; 56: 645-8.
http://dx.doi.org/10.1097/MPG.0b013e31828b3669

[30] Prazeres Magalhaes P, De Magalhaes Queiroz DM, Campos Barbosa DV, Aguir Rocha G, Nogueira Mendes E, Santos A, *et al.* Helicobacter pylori primary resistance to metronidazole and clarithromycin in Brazil. Antimicrobial Agents Chemother 2002; 46: 2021-3.
http://dx.doi.org/10.1128/AAC.46.6.2021-2023.2002

[31] Godoy AP, Ribeiro ML, Benvengo YH, Vitiello L, Miranda Mde C, Mendonca S, *et al.* Analysis of antimicrobial susceptibility and virulence factors in Helicobacter pylori clinical isolates. BMC Gastroenterology 2003; 3: 20.
http://dx.doi.org/10.1186/1471-230X-3-20

[32] Cuadrado-Lavin A, Salcines-Caviedes JR, Carrascosa MF, Mellado P, Monteagudo I, Llorca J, *et al.* Antimicrobial susceptibility of Helicobacter pylori to six antibiotics currently used in Spain. J Antimicrob Chemother 2012; 67: 170-3.
http://dx.doi.org/10.1093/jac/dkr410

[33] Miendje Deyi VY, Bontems P, Vanderplas J, De Koster E, Ntounda R, Van den Borre C, *et al.* Multicentre survey of routine determinations of resistance of Helicobacter pylori to antimicrobials over last 20 years (1990-2009) in Belgium. J Clin Microbiol 2011; 49: 2200-9.
http://dx.doi.org/10.1128/JCM.02642-10

[34] Mégraud F, Lehours P. Helicobacter pylori detection and antimicrobial susceptibility testing. Clin Microbiol Reviews 2007; 20: 280-332.
http://dx.doi.org/10.1128/CMR.00033-06

[35] Rerksuppaphol S, Hardikar W, Midolo PD, Ward P. Antimicrobial resistance in Helicobacter pylori isolates in children. J Pediatr Child Health 2003; 39: 332-5.
http://dx.doi.org/10.1046/j.1440-1754.2003.00153.x

Received on 28-11-2014 Accepted on 03-12-2014 Published on 31-12-2014

DOI: http://dx.doi.org/10.12974/2311-8687.2014.02.02.3