Acta Biomed 2018; Vol. 89, Supplement 8: 65-71 DOI: 10.23750/abm.v89i8-S.7893

Review

How and when investigating and treating *Helicobacter pylori* infection in children

Marco Manfredi[1], Federica Gaiani[2], Stefano Kayali[2], Barbara Bizzarri[2], Silvia Iuliano[2], Roberta Minelli[2], Gioacchino Leandro[3]; Francesco Di Mario[2], Gian Luigi de'Angelis[2]

[1] Azienda USL di Reggio Emilia-IRCCS, Maternal and Child Department, Pediatric Unit, Sant'Anna Hospital, Castelnovo ne' Monti, Reggio Emilia, Italy; [2] Gastroenterology and Endoscopy Unit, Department of Medicine and Surgery, University of Parma, Parma, Italy; [3] National Institute of Gastroenterology "S. De Bellis" Research Hospital, Castellana Grotte, Italy

Summary. For thousands of years humans have lived in symbiosis with *Helicobacter pylori*. This infection is acquired mainly during childhood and, despite it represents one of the most common infections in humans, only a minority of infected people may develop health issues and life-threatening diseases. For diagnosing *Helicobacter pylori* infection in children we can use, at first, non-invasive diagnostic tests, if clinical pattern and/or history are of suspicion. Then, invasive tests i.e. gastroscopy are necessary to confirm the infection. As antibiotics are not widely available in children affected by *Helicobacter pylori* infection, they should be chosen based on individual antibiotic susceptibility testing obtained by gastric biopsy specimens or the local antibiotic resistance pattern, in empirical treatment is chosen. Test and treat strategy in children should be avoided. In this brief review we summarize how and in which children the infection should be investigate and which the most appropriate eradication treatment should be chosen. (www.actabiomedica.it)

Key words: *Helicobacter pylori*, children, antimicrobial susceptibility testing, antibiotic resistance, esophagogastroduodenoscopy

Introduction

Helicobacter pylori (*H. pylori*) has been belonging to humans at least for 58,000 years (1). The Italian ice mummy, called 'Otzi', which dates to 5,200 years ago, was affected too (2). Therefore, many authors have started considering *H. pylori* as a commensal organism and only an opportunistic pathogen (3). Anyway analyzing the gastric microbiota, when *H. pylori* is present, it tends to dominate the microbial gastric community and patients have lower bacterial richness and diversity compared to healthy people (4).

The prevalence of *H. pylori* infection is higher in non-industrialized countries, but it varies around the world and depends on numerous factors such as age, ethnicity, geographical and socioeconomic status, bacterial virulence, host characteristics and environmental factors (mainly hygienic conditions). The highest infection rates belong to South Korea (50.8%), Shanghai (71.7%) and South Africa (66.1%), while the lowest are in the USA (7.5%) and Australia (15.5%). The higher prevalence rate in children is in Ethiopia (48% in children aged 2-4 years), in Nigeria (82% in children aged 5-9 years) and in Mexico (43% in children aged 5-9 years); while Canadian children have a prevalence of 7.1% (in 5-18 years children). In Europe the most infected children come from Bulgaria (61.7%) and the least infected from the Netherlands (1.2%) (5).

H. pylori infection is predominantly acquired in early childhood and person-to-person contact within the same household appears to be a key route for the transmission, mainly the mother-child dyad. Siblings and grandparents too, specially grandmothers, can be a potential origin of the spreading (6, 7).

After the colonization of the gastric mucosa, *H. pylori* can cause chronic gastritis (usually asymptomatic, particularly in children), peptic ulcer, gastric mucosa-associated lymphoid tissue lymphoma, and gastric adenocarcinoma (8). Furthermore *H. pylori* was classified by WHO as a carcinogenic of first class; this means it has ascertained carcinogenicity in humans (9). Anyway, luckily, the carcinogenic development is quite rare in developed countries while adult or elderly people especially in low-income countries can be at high risk (10).

For these reasons, although many authors around the world have been trying to define and optimize the strategy against *H. pylori* infection in children, there is still not a uniformity of diagnostic and therapeutic approach in pediatrics.

When should we investigate the *H. pylori* infection in children?

H. pylori infection typically remains undetected at the onset because of its lack of specific symptoms (11). Since its discovery, many gastrointestinal and extra-gastrointestinal symptoms have been associated to *H. pylori* infection in children. Hence many children have been often treated simply by a 'test and treat strategy' with the purpose to avoid or reduce the future risk of development of severe complications. Most infected people have no significant symptoms and remain symptoms-free throughout life (12).

Approximately 10-20% of *H. pylori* infected people may develop gastric or duodenal ulcers, gastric atrophy, intestinal metaplasia, dysplasia, lymphoma, or gastric adenocarcinoma depending on virulence features of the bacteria, host characteristics and environmental factors (5).

We do not have pathognomonic symptoms of *H. pylori* infection in children, but recurrent abdominal pain (RAP), perhaps, has been representing the main symptom for which doctors investigate *H. pylori* infection in pediatric age. A recent study in Iran showed that children with RAP had higher *H. pylori* infection rate than controls, although the difference was not statistically significant (13) and a study by Sykora *et al* showed a positive correlation between *H. pylori* infection and functional abdominal pain disorders fulfilling the Rome III criteria (14). On the contrary, *H. pylori* infection was identified only in 52% of cases in Brazilian children investigated for chronic non-ulcer dyspepsia (15).

H. pylori infection can be also associated to several extra-gastrointestinal symptoms, mainly acute idiopathic thrombocytopenic purpura, iron-deficiency anemia, B12 deficiency and allergic diseases (5) and, although some studies suggest an association between *H. pylori* infection and short stature (16), its role on failure to thrive remains controversial (10, 17).

How to investigate

The last ESPGAHN/NASPGHAN guidelines recommend diagnosing *H. pylori* infection in children only when symptoms, which can usually vary among vomiting, persistent/recurrent abdominal pain and gastrointestinal bleeding, can justify esophagogastroduodenoscopy with histological examinations because it is important to determine the underlying cause of the symptoms and not solely focus on the presence of *H. pylori* infection (17).

Despite this, many non-invasive diagnostic exams are available and well validated even in children.

Serological testing is the most widely available non-invasive method for diagnosing *H. pylori* infection. Moreover serology is the only test that is not affected by local changes in the stomach mainly due to drug therapy (proton-pump-inhibitors (PPIs), antibiotics, Non-Steroidal-Anti-Inflammatory-Drugs (NSAIDs)) that could lead to false-negative results in other tests as Urea Breath Test and stool antigen test. Furthermore serological testing is rapid, cheap, and may help in screening populations or in confirming the presence of *H. pylori* infection in case of equivocal results of the other diagnostic methods. Nevertheless, it cannot be used to distinguish between ongoing or past infections neither to monitor the progress of antimicrobial therapy, nor the eradication. The sensitivity ranges from 76% to 84% and specificity from 79% to 90% (18).

H. pylori ***stool antigen test*** using monoclonal antibodies detects the antigen of the bacterium and not the

antibodies and it is able to diagnose an ongoing infection. Low cost, easy use and sample collection at home have increasingly widespread the use of this method. It has a good sensitivity (about 94.6%) and specificity (about 98.4%), only modestly lower than Urea Breath test (18).

Urea Breath Test (UBT) is a widely available test with high sensitivity and specificity (from 90% to 100%) for diagnosing *H. pylori* infection. Moreover, its non-invasiveness, the simplicity of execution and safety make it elective in the suspicion of infection in adulthood, childhood, and in pregnancy. However, the specificity of UBT decreases in young children (< 6 year old) because it requires active cooperation of the patient to avoid false negative results.

Both stool antigen and UBT must be performed at least 4-6 weeks after either PPIs or antibiotics or NASIDs therapy (18).

Another non-invasive approach is the detection of IgG ***antibodies*** anti-*H. pylori* in ***urine*** samples. This might represent a good alternative to blood-based antibody tests and has the major benefit that it can be easily applied in the doctor's office. Being a test based on antibodies title, it presents the same limits as the serological test.

The detection of *H. pylori* in saliva and dental plaque are not still standardized (19).

Molecular methods applied to gastric biopsy specimens have provided a valuable alternative for detecting antibiotic resistance. Among them, polymerase chain reaction (PCR) and fluorescence *in situ* hybridization (FISH) are the most preeminent ones. Although they are still unusual methods in clinical practice, they are gathering the medical community confidence (20).

There is no single test that can be considered as the gold standard for the diagnosis of *H. pylori* infection. The appropriate test for any specific situation will be influenced by the clinical circumstances, the pretest probability of infection, as well as the availability and costs of the individual diagnostic tests. Non-invasive tests are the most usual methods for routine *H. pylori* detection, but they fail to provide complementary information on the location of *H. pylori* in the stomach, on the histopathological lesions underlying the presence of the bacteria and on the antimicrobial profile of the infecting strain. Because of these limitations, it is generally assumed that invasive tests by upper gastrointestinal endoscopy provide a more complete diagnosis. Culture from gastric biopsies should be performed from 2 different locations (i.e. antrum and body) and put in the same jar, for increasing the sensitivity of antimicrobial susceptibility testing (17).

Who to treat

According to the main international guidelines, the primary indications for treating *H. pylori* infection in children are peptic ulcer disease and first-degree familiarity of patients with gastric cancer. Although the eradication is always recommended specially to avoid long-term complications, in children with RAP or functional abdominal pain the risk of not obtaining the complete resolution of symptoms after eradication or the absence of absolute certainty in achieving eradication should always be critically discussed with parents before starting therapy. For these reasons it is essential to perform upper gastrointestinal endoscopy not to misdiagnosis other possible underlying causes.

Furthermore, *H. pylori* eradication seems related to an increase of gastroesophageal reflux disease and allergic diseases. Iron deficiency anemia and idiopathic thrombocytopenic purpura represent the only extra-intestinal diseases where the cause-effect relationship with *H. pylori* infection was demonstrated (17.)

How to treat

A "test and treat strategy" is no longer recommended in children (17).

Although many efforts have been made in obtaining eradication, several difficulties remain to be overcome. For many years the standard triple therapy (PPIs + amoxicillin + clarithromycin or metronidazole) has been the first-line therapy recommended by the international guidelines for the eradication of *H. pylori* infection. During the last years, the widespread use/abuse of antibiotics, particularly for respiratory tract infections, has led to the emergence of increasing resistance of *H. pylori* infection to common antibiotics, mainly to clarithromycin. A recent study showed an evident

increase of clarithromycin resistance, though with no statistical significance, while metronidazole resistance has been reducing in children in our geographical area during the last 13 years. Furthermore, ampicillin resistance has been confirmed to be very rare (21).

Unlike more common pathogens, which can usually be managed with a wide variety of treatments, *H. pylori* is only sensitive to a few drugs. Moreover, the widespread use (and, sometimes, abuse) of antibiotics in children to treat common infections has led to a reduction in antibiotics efficacy against this bacterium. The situation is exacerbated by the fact that *H. pylori* itself generates pharmacological resistances that differ depending on the geographic area and compromise successive second and third-line therapies (22).

For achieving a successful eradication rate three strategic points should be considered:

a) The eradication rate by geographic area.

b) The systematic use of susceptibility testing.

c) Treatment compliance higher than 90% (23).

H. pylori antibiotic resistance varies among countries and among areas within the same country. It depends on the frequency of the antibiotics used for treating other infections, especially those of the respiratory system (5, 21).

The more recent pediatric international guidelines recommend setting up the eradication therapy based on susceptibility testing. Moreover, before starting an eradication therapy, doctors should emphasize the importance of a strict adherence to therapy (17).

Treatment choices if antibiotic susceptibility testing is available

Standard triple therapy (amoxicillin + clarithromycin or metronidazole) or sequential therapy are good options (Table 1). All drugs are administered twice a day. In case of failure, bismuth-quadruple therapy (when bismuth is available), concomitant therapy, triple therapy or sequential therapy with high dosage amoxicillin can be chosen as second choices. Triple therapy with amoxicillin at high dosage (75 mg/kg/day) can increase the eradication rate associating between clarithromycin or metronidazole the one that had not been used previously in the first-line choice (17). Even sequential therapy with high dosage of amoxicillin, if standard triple therapy was used as first-line, may represent a good second-choice, as we can benefit of the amoxicillin increase associated with the ability of sequential regimen to overcome antibiotic resistance (table 2) (24, 25).

Therapeutic options in empirical treatment

Standard triple therapy for 10-14 days or sequential therapy for 10 days are equivalent as first-line therapy, remembering that the use of clarithromycin is recommended if its resistance does not exceed 15% in the considered geographic area (see Table 3). All drugs are administered twice a day. (17) Then, in case of failure, the second-line therapy should be chosen based on antibiotic susceptibility testing.

Table 1: First-line therapy if antimicrobial susceptibility is available (PPIs proton pump inhibitors, CLA: clarithromycin, MET: metronidazole). All drugs are administered two times a day

Standard Triple Therapy with CLA susceptibility	PPIs 1-2 mg/kg/day amoxicillin 50 mg/kg/day clarithromycin 20 mg/kg/day	10-14 days
Standard Triple Therapy with CLA resistance and MET susceptibility	PPIs 1-2 mg/kg/day amoxicillin 50 mg/kg/day metronidazole 20 mg/kg/day	10-14 days
Sequential Therapy	PPIs 1-2 mg/kg/day amoxicillin 50 mg/kg/day metronidazole 20 mg/kg/day	5 days
	+	
	PPIs 1-2 mg/kg/day clarithromycin 20 mg/kg/day tinidazole 20 mg/kg/day	5 days

Table 2. Second-line therapy by using high dose of amoxicillin in empirical treatment (PPIs proton pump inhibitors, CLA: clarithromycin, MET: metronidazole). All drugs are administered two times a day

Standard Triple Therapy if MET susceptibility and CLA used previously	PPIs 1-2 mg/kg/day amoxicillin 75 mg/kg/day metronidazole 20 mg/kg/day	10-14 days
Sequential Therapy if Standard Triple Therapy used previously	PPIs 1-2 mg/kg/day amoxicillin 75 mg/kg/day metronidazole 20 mg/kg/day +	5 days
	PPIs 1-2 mg/kg/day clarithromycin 20 mg/kg/day tinidazole 20 mg/kg/day	5 days

Table 3. First-line therapy in empirical treatment based on local CLA resistance rate (PPIs proton pump inhibitors; CLA: clarithromycin). All drugs are administered two times a day

Standard Triple Therapy if local CLA resistance rate <15%	PPIs 1-2 mg/kg/day amoxicillin 50 mg/kg/day clarithromycin 20 mg/kg/day	10-14 days
Standard Triple Therapy if local CLA resistance rate > 15%	PPIs 1-2 mg/kg/day amoxicillin 50 mg/kg/day metronidazole 20 mg/kg/day	10-14 days
Sequential Therapy	PPIs 1-2 mg/kg/day amoxicillin 50 mg/kg/day metronidazole 20 mg/kg/day +	5 days
	PPIs 1-2 mg/kg/day clarithromycin 20 mg/kg/day tinidazole 20 mg/kg/day	5 days

Otherwise, sequential therapy may be an option even in children with clarithromycin and metronidazole resistance with a good eradication rate, as showed in a recent study (24). Standard triple therapy or sequential therapy with amoxicillin at high dosage (75 mg/kg/day) is another valid alternative in case of antimicrobial resistance or in second-line treatment (table 2).

Eradication monitoring

The success of eradication therapy should be monitored 4 to 8 weeks after the end of antibiotic therapy and 2 weeks after stopping PPIs or 4 weeks after stopping antibiotics and NSAIDs by using either fecal antigen or UBT.

Probiotic use seems to be beneficial in *H. pylori* eradication in children (23). A mixture of probiotics can also be useful in improving side effects due to antibiotics in adult-affected patients. (26).

However, further studies are needed to identify the optimal dose and probiotic combination.

Discussion

H. pylori infection in children often has *pauci*-or asymptomatic clinic presentation.

The recent pediatric international guidelines recommend investigating *H. pylori* only by using upper gastrointestinal endoscopy because it is important to determine the cause underlying symptoms and not

merely focus on *H. pylori* infection. Researchers stress the concept that "test and treat strategy" should no longer be recommended in children. During esophagogastroduodenoscopy, additional biopsy specimens for rapid urease test and culture with susceptibility testing are recommended, but if *H. pylori* infection is an incidental finding during endoscopy, eradication therapy may be considered following careful discussion with parents (17).

In children with iron deficiency anemia and idiopathic thrombocytopenic purpura, *H. pylori* infection should be investigated and if positive, it should be treated after other causes have been excluded. Eradication therapy in persistent or functional abdominal pain is not expected to systematically improve symptoms in children (17).

Because the best results of *H. pylori* eradication are obtained after the first treatment, subsequent therapies using the same antibiotics should be avoided. The effectiveness of the eradication treatments depends on the sensitivity of *H. pylori* strains, the duration of the therapy and patients' compliance. Nowadays, it is essential to tailor eradication therapy based on the antibiotic susceptibility of *H. pylori* strains specific for the considered geographic area.

Hence, clarithromycin should not be used in empirical treatment of *H. pylori* infection in children if its local resistance rate is higher than 15%. Otherwise its use should be limited only to children with known antimicrobial susceptibility (21).

Treatment failure increases the percentage of second-line and third-line therapies, raising the costs of treatments and the number of patients who undergoing numerous antibiotic treatments. So, while choosing between two therapies, it is illogical and unethical to advise using the one with the lower eradication rate as the initial therapy. Considering the restrict choice of antibiotic in children affected by *H. pylori* infection, sequential therapy could be a good treatment option even in case of antimicrobial resistance (24). Equally, increasing the dose of amoxicillin could represent a good alternative option in presence of antibiotic resistance.

Therefore, the best eradication therapy of *H. pylori* infection should be based on individual antimicrobial susceptibility. With regards to this, molecular methods from biopsies (real-time PCR and FISH) have become one of the most promising techniques, even preferable to culture by gastric specimens (20).

Alternatively, if antimicrobial susceptibility tests are not available, empirical therapy based on local antibiotic resistance still remains the best therapeutic option (27).

Finally, since all antibiotic therapies generate unpleasant (but usually not serious) side effects, we believe that the combination with probiotics helps the patient withstand therapy which may easily result in unpleasant ailments (especially of the gastrointestinal tract) (26).

References

1. Linz B, Balloux F, Moodley Y, et al. An African origin for the intimate association between humans and *Helicobacter pylori*. Nature 2007; 445: 915-918.
2. Megraud F, Lehours P, Vale FF. The history of *Helicobacter pylori*: from phylogeography to paleomicrobiology. Clin Microbiol Infect 2016; 22: 922-927.
3. Li J, Perez-Perez GI. *Helicobacter pylori* the latent human pathogen or an ancestral commensal organism. Front Microbiol 2018; 3; 9: 609. doi: 10.3389/fmicb.2018.00609.
4. Llorca L, Perezs-Perez GI, Urruzuno P, et al. Characterization of the gastric microbiota in a pediatric population according to *Helicobacter pylori* status. Pediatr Infect Dis J 2017; 36: 173-178.
5. Iwanczak BM, Buchner AM, Iwanczak F. Clinical differences of *Helicobacter pylori* infection in children. Adv Clin Exp Med 2017; 26: 1131-1136.
6. Urita Y, Watanabe T, Kawagoe N, et al. Role of infected grandmothers in transmission of *Helicobacter pylori* to children in a Japanese rural town. J Paediatr Child Health 2013, 49: 394-398.
7. Manfredi M, Iuliano S, Gismondi P, et al. *Helicobacter pylori* infection: we should always verify the intrafamilial transmission. Biol Med (Aligarth) 2016; 9.1. DOI: 10.4172/0974-8369.1000366.
8. Hsu PI, Yamaoka Y, Goh KL, et al. *Helicobacter pylori* infection. Biomed res Int 2015; 2015: 278308. doi: 10.1155/2015/278308.
9. Schistosomes, liver fllukes and *Helicoobacter pylori*: IARC Working Group on the Evaluation of Carcinogenic Risks to Humans; Lyon, 7-14 June 1994. IARC Monogr Eval Carcinog Risks Hum 1994; 61: 1-241.
10. Sierra MS, Hastings EV, Goodman KJ. What do we know about benefits of *H. pylori* treatment in childhood? Gut Microbes 2013; 4: 549-67.
11. Torres J, Pérez-Pérez GI, Goodman KJ, et al. A compre-

hensive review of the natural history of *Helicobacter pylori* infection in children. Arch Med Res 2000; 31: 431-69. PMID: 11179581; http://dx.doi.org/10.1016/S0188-4409(00)00099-0.
12. Laszewicz W, Iwanczak F, Iwanczak B, Task Force of the polish Society of Gastroenterology. Seroprevalence of *Helicobacter pylori* infection in Polish children and adults depending on socioeconomic status and living conditions. Adv Med Sci 2014; 59: 147-150.
13. Alimohammadi H, Fouladi N, Salehzadeh F, et al. Childhood recurrent abdominal pain and *Helicobacter pylori* infection, Islamic Republic of Iran. East Mediterr Health J 2017; 22: 860-864.
14. Sykora J, Huml M, Siala K, et al. Pediatric Rome III criteria-related abdominal pain is associated with *Helicobacter pylori* and not with Calprotectin. J Pediatr Gastroenterol Nutr 2016; 63: 417-422.
15. Correa Silva RG, Machado NC, Carvalho MA, Rodrigues MA. *Helicobacter pylori* infection is high in paediatric non-ulcer dyspepsia but not associated with specific gastrointestinal symptoms. Acta Paediatr 2016; 105: e228-e231.
16. Goodman KJ, Correa P, Mera R, et al. Effect of *Helicobacter pylori* infection on growth velocity of school-age Andean children. Epidemiology 2011; 22: 118-126. doi: 10.1097/EDE.0b013e3181fe7e31.
17. Jones NL, Koletzko S, Goodman K, et al. Joint ESPGHAN/NASPGHAN Guidelines for the management of *Helicobacter pylori* in Children and Adolescents (Update 2016). J Pediatr gastroenterol Nutr 2017; 64: 991-1003.
18. Aloe R, Bonaguri C, de'Angelis GL, Fornaroli F, et al. Non-Invasive Methods - Common techniques: serological, stool antigen, and Urea Breath Tests. In "*Helicobacter pylori*: Detection Methods, Diseases and Health Implications", Marco Manfredi and Gian Luigi de'Angelis eds, NOVA Publishers, 2013, Chapter 1, pag. 5-18.
19. Horemans T, Boulet G, Delputte LM, Cos P. Non-Invasive Methods - Unusual techniques: Stool and Dental Plaque PCR, Urinary antibodies. In "*Helicobacter pylori*: Detection Methods, Diseases and Health Implications", Marco Manfredi and Gian Luigi de'Angelis eds, NOVA Publishers, 2013, Chapter 2, pag. 19-38.
20. Almeida C, Azevedo NF, Joao Vieira M. Invasive Methods - Unusual techniqes - Identification of H. pylori from biopsies: culture, PCR and FISH. In "*Helicobacter pylori*: Detection Methods, Diseases and Health Implications", Marco Manfredi and Gian Luigi de'Angelis eds, NOVA Publishers, 2013, Chapter 4, pag.69-81.
21. Manfredi M, Gismondi P, Maffini V, et al. Primary Antimicrobial Susceptibility Changes in Children with *Helicobacter pylori* Infection over 13 Years in Northern Italy. Gastr Res Pract 2015; Article ID 717349, 5 pages. http://dx.doi.org/10.1155/2015/717349.
22. Manfredi M, de'Angelis GL. Eradication of *Helicobacter pylori*: in search of a better therapy. Clin Microbial 2013, 1:1. http://dx.doi.org/10.4172/cmo.1000e101.
23. Kalach N, Bontems P, Raymond J. *Helicobacter pylori* infection in children. Helicobacter 2017; 22 (Suppl. 1): e12414. https://doi.org/10.1111/hel.12414.
24. Gaiani F, Manfredi M, Iuliano S, et al. Can Sequential Therapy Overcome Antimicrobial Resistance in Children with *Helicobacter pylori* Infection? Biomed J Sci &Tech Res 2018; 4(5). doi:10.26717/BJSTR.2018.04.001111.
25. Tong JL, Ran ZH, Shen J, Xiao SD. Sequential therapy vs. standard triple therapies for *Helicobacter pylori* infection: a meta-analysis. J Clin Pharm Ther 2009; 34: 41–53.
26. Manfredi M, Bizzarri B, Sacchero RI, et al. *Helicobacter pylori* Infection in Clinical Practice: Probiotics and a Combination of Probiotics + Lactoferrin Improve Compliance, But Not Eradication, in Sequential Therapy. Helicobacter 2012; 17: 254-263. doi: 10.1111/j.1523-5378.2012.00944.x
27. Manfredi M, Bizzarri B, Manzali, et al. Which treatment in *Helicobacter pylori* infection? Clin Exp Pharmacol 2013, 3:4 http://dx.doi.org/10.4172/2161-1459.1000139

Correspondence:
Marco Manfredi MD, PhD, Chief of Pediatrics,
Azienda USL of Reggio Emilia-IRCCS,
Maternal and Child Department, Pediatric Unit,
Sant'Anna Hospital, Via Roma, 2
42035 Castelnovo ne'Monti, Reggio Emilia, Italy
E-mail: marco.manfredi@ausl.re.it