Consensus for the management of *Helicobacter pylori* infection in children : still searching for a paradigm

S. Cadranel, P. Bontems and J. Snyder*

Dept. of Gastroenterology-Hepatology, Queen Fabiola Children's Hospital, Université Libre de Bruxelles ; * Dept. of Pediatrics, Gastroenterology, Hepatology and Nutrition, University of California, San Francisco.

Introduction

Short afer its recognition by Marshall and Warren (1) as a pathogen in the stomach of adults, *Helicobacter pylori* (H. pylori) was also "discovered" in children, simultaneously by Hill (2), Cadranel (3) and Czinn (4). Many reports agree upon the early acquisition of H. pylori infection in infancy or childhood, even in industrialised countries where H. pylori-related peptic ulcers are less frequent in children than in adults.

Epidemiology

The incidence of *H. pylori* infection in childhood varies geographically (see table I) and is much higher in the developing (more than 50%) than in the developed countries (less than 20% below the age of 20). Low socio-economic conditions (5,6), nutritional factors (7), living in crowded conditions, family clustering and sharing beds between siblings (8) are proven determinant factors that influence the prevalence of the infection which is more frequent among institutionalized children (9). Non treated H. pylori infection has a life-long course although spontaneous eradications have been observed but this phenomenon is probably rare since only few cases have been described (10).

Table I. — **Prevalence of *H. pylori* infection**

Authors (year)	Countries	Age range (y)	Prevalence (%)
Sullivan 1990 (46)	Gambia	below 5	46
Oliveira 1994 (47)	Brasil	at 2 at 18	16,5 64,3
Kontiainen 1994 (48)	Finland	below 6 6 to 15	0 6
Patel 1994 (49)	Scotland		11
Blecker 1995 (20)	Belgium	2 to 8 8 to 14	5,4 13,4
Goodman 1997 (50)	Colombia	2 to 9	69
Rodrigo-Saez 1997 (51)	Spain	below 10 10 to 20	13,6 25,4
Kehrt 1997 (52)	Nicaragua	0,1 to 5	77,2
Pelser 1997 (53)	South Africa	0,2 to 2 2 to5 5 to 10 10 to 15	13,5 48,5 67,3 84,2

Immune responses

Bacterial factors (11), increased or decreased acid secretion secondary to alteration in gastrin release (12,13) induced mucosa (14) and humoral immune responses and autoimmunity (15,16) are directly implicated in the pathogenesis of the gastro-duodenal damage and the host immune and inflammatory response is emerging as an important element in the pathogenesis of these gastric diseases (17). Moreover, factors released by immune cells might regulate acid secretion (13,18).

Peptic ulcer disease is uncommon in children as well as mucosal atrophy whereas, on the contrary, nodularity of the antrum is a typical feature of the infection in children (3). The reason why the mucosal damages are different is not yet elucidated : the more commonly proposed explanation is that the duration of the infection is much shorter although it is well known in adults that ulcers can relapse only a few months after unsuccessful treatment eradication or re-infection by *H. pylori.* There is no evidence that bacterial virulence factors are different in children compared to adults and, most probably, children are infected with their parent's strains. We know that the systemic serological response is often weak and can be absent in children. In our series, less than 70% of children below 8 years have detectable antibodies against *H. pylori* (see table II).

Table II. — **diagnostic accuracy of serology (Cobas Core-Roche) in 330 children (median age 10.4 years-range 0,5-17,8) investigated for HP infection contemporaneously of histo logical and microbiological analysis of gastric biopsies**

Age < 8 y	sensitivity (%) specificity (%)	66,7 98,4
Age > 8 y	sensitivity (%) specificity (%)	86,2 85,4

This could reflect an immaturity of the immune system or a difference in *H. pylori* antigen recognition in childhood and might have some importance in the understanding of the pathogenesis of *H. pylori* infection and also in view of a vaccine strategy.

Symptomatology

In children, histologically proven gastritis can be completely asymptomatic but can also be responsible for recurrent abdominal pain (RAP), most often epigastric, bouts of nausea and vomiting, belching, dyspepsia, halitosis and also growth retardation or weight loss. In the absence of large placebo-controlled randomised double-blind studies in paediatrics, the exact role of *H. pylori* in non-ulcer-dyspepsia remains most controversed (19-22).

The methodology used in the majority of paediatric studies is weak and the diagnosis is often based only on serological data, often unreliable because non validated in childhood and in infants.

The Role of H. pylori in Recurent Abdominal Pain

Several questions should be considered in order to understand the role of *H. pylori.*

What pain are we evaluating ?

To date, investigators of the role of *H. pylori* in abdominal pain have not used a consistent definition of pain (22,23). Many pediatric investigators have evaluated children with recurrent abdominal pain but some have chosen to assess dyspepsia, which is the current standard for studies in adults (24). The most widely accepted definition of "recurrent abdominal pain" (RAP) was described by Apley (25), in 1957 : at least 3 episodes of abdominal pain severe enough to interfere with normal activities during a 3 month period. This definition somewhat outdated is often confounded with symptoms of "non-ulcer dyspepsia" as used in the adult.

A consensus on the use of a standardised definition would improve the ability to make comparisons across studies although the choice for pediatrics may not be the same as for adults exposed to high risk co-factors like tobacco and alcohol.

What is the prevalence of *H. pylori* in children with dyspepsia or RAP ?

Study	Cohort RAP and controls	N	DX	Hp+	RAP	a-SX HP+
Vander Meer 1992 (26)	GI clinic Netherlands	121	serology	9	9%	5%
Mc Callon 1995 (27)	Day surgery Ireland	439	serology	127	30%	29%
Chong 1995 (28)	GI clinic Indianapolis	456	serology	63	17%*	10%
Hardikar 1996 (29)	RAP clip/ day surgery Australia	196	serology	16	5%	14%

DX = method of diagnosis ; a-SX = asymptomatic ; * $p < 0.05$.

In addition, several studies of endoscopic evaluation of children with abdominal pain have shown a low positive predictive value for *H. pylori* infections and pain (20,21,30-32). Taken together, these data indicate that the organism is found about as often in adults and in children with and without abdominal complaints and does not appear to cause a specific symptom complex (24). Also, no consistent abnormalities of gastric emptying or gastrointestinal motility have been proven to be associated with *H. pylori* infection which could help explain an association with abdominal pain (33).

What is the effect of treatment on *H. pylori* in patients with dyspepsia or RAP ?

The best way to evaluate the role of *H. pylori* in dyspepsia and abdominal pain is to perform randomised, placebo-controlled, double-blinded studies in patients with these complaints. Unfortunately, there are as yet no such studies in children (22). In adults, studies showing a positive effect of therapy and those showing no effect are about equal in number 33. No conclusive answers can be reached based on these data, primarily because of methodological deficiencies (22,24). The identification of treatment subgroups of those with dyspepsia or abdominal pain has not yet proved useful as there is often substantial overlap in symptoms (34).

However, *H. pylori* virulence factors may help identify those who would benefit from therapy. For example, infections with *H. pylori* strains expressing vacuolating cytotoxin (vacA) are more often associated with peptic ulcer disease than those negative for vacA (35). Similarly, the presence of the high-molecular weight immunodominant antigen (CagA) is more often associated with peptic ulcer disease and gastric carcinoma than CagA negativity (35). Unfortunately, no virulence factor or factors have yet been identified which have a high enough sensitivity or specificity to guide management decisions (33).

What methodology is required to determine whether treatment of *H. pylori* will improve symptoms of dyspepsia or RAP ?

Optimal studies should utilize (24-36) :

- a consistent definition of disease
- a well-defined patient population (ideally, as broad-based as possible)
- consistent inclusion and exclusion criteria (evaluation for ulcers and
- exclusion of patients with daily use of NSAIDs or evidence for irritable bowel syndrome
- evidence for the effectiveness of therapy, including eradication of *H. pylori*
- a randomized, double-blind, placebo-controlled methodology
- validated outcome measures
- follow-up of at least one year using non-invasive tests (^{13}C-urea breath test).

Is there a potential harm in treating patients with *H. pylori* and dyspepsia or RAP ?

Although the data are conflicting on the effectiveness of treating patients with *H. pylori* and dyspepsia or

abdominal pain, many patients do receive therapy. The following factors should be considered before embarking on testing and treating (24,36,37) :

- testing for *H. pylori* is only recommended if treatment is planned
- ideally, patients should receive treatment as part of a protocol to evaluate the efficacy
- the potential problems with therapy must be considered : no current therapy is 100% successful. Increasing bacterial resistance is a real concern. A high placebo response rate exists for treatment of dyspepsia and abdominal pain. Patient compliance has often been poor. A fairly high rate of side effects is often reported. Therapy involving proton pump inhibitors and the newer antibiotics is expensive. Eradication of *H. pylori* may be associated with increased rates of GE reflux. Fewer than 20% of all infected persons will develop any clinical consequences (37). It is possible that there may be a "neutral" or "good" *H. pylori* as well as the "bad" and "very bad" strains associated with ulcers and gastric cancer. Other factors like nutrition may also play a role in the development of the disease.

H. pylori is associated with the development of atrophic gastritis and gastric cancer but these diseases occur in only a small number of those infected and there are no data on the impact of universal treatment of *H. pylori* on the development of atrophic gastritis and gastric cancer.

Diagnosis

Invasive or non-invasive techniques are used for the diagnosis of *H. pylori* infection. Invasive methods rely on the detection of the bacterium on biopsies taken endocopically in the antrum and fundic region of the patient's stomach. In case of children, the endoscopy is somewhat more uneasy to perform and should be achieved using only the appropriate miniaturised endposcopes which means also that the size of the biopsies is reduced and this peculiarity must be taken into account : t has some (but little) influence in determining the presence of the germ using the rapid urease test or through histological study on stained (Giemsa) biopsies but two biopsies are advisable in order to get a reliable answer for the cultivation of *Helicobacter pylori*. This needs the use of a microaerophilic medium, sometimes for as long as one week (38). However the extra cost of this delay is counterbalanced by the possibility of testing the sensitivity of the H. pylori strain to antibiotics and consequently guiding the choice and improving their efficacy (39-40).

There are two non-invasive techniques : serology and labeled urea breath test. Serology, based on the detection of host's anti-*Helicobacter pylori* antibodies using an ELISA technique with purified antigens, has been extensively utilised in epidemiological studies mainly because of its relatively low cost. However serology is not very helpful to evaluate the efficacy of an eradication treatment because the decrease of the antibodies titers is too slow. Furthermore it is not optimal (table II) because of a frequent weaker antibody response in children (sometimes absent in "non responder" infants).

The labelled urea breath test (UBT) is based on the in situ activity of the bacterium's urease which, although present in other bacteria, is secreted in large amounts only by *Helicobacter pylori*. Although the ^{14}C isotope has a very weak radioactivity, the ^{13}C stable isotope is preferred in children. The test has been validated in the adult population and we have standardised and simplified it in a large paediatric population (41). Although the UBT has proven to be a far more reliable test than serology in children, because of its high (current ?) price, it is not used for epidemiological studies and suits only for the detection of symptomatic patients and evaluation of eradication treatment.

Treatment

The main and unquestionable reason for treating *Helicobacter pylori* infection is the prevention of relapsing ulcers since the improvement of symptoms linked to the gastritis is probably multifactorial. However, the possibility of developing malignant transformations is another important reason for treating infected subjects and improving preventive measures either by elimination of the contamination reservoirs or by interruption of contamination mechanisms or by the use of the proper and much awaited vaccine.

Eradication of H. pylori is much more difficult than it appears from the germ's in vitro high sensitivity to many antibiotics and treatment failures are frequent for several reasons including an insufficient patient's compliance. Monotherapy with only one antibiotic has clearly proved to be inefficient and two, three and sometimes four drugs have to be prescribed (42). In adult patients, hundreds of papers on the efficacy of combinations of several anti-microbial agents have been published, which is a potent indirect proof that the ideal formula remains to be found. The most used anti-microbial agents are the betalactamines (amoxicillin), nitroimidazoles (metronidazole and tinidazole), colloidal bismuth sub-citrate, macrolides (clarithromycin, azithromycine and roxythromycin) and tetracycline. The activity of these drugs is potentialised by the association of antagonists of H2 receptors or by proton pump inhibitors (PPI). Because of the unfrequency of peptic ulcers in children and also because of their unadapted pharmacological presentation of these drugs for paediatric use, PPI are seldom used and, consequently, there are no reliable data to support such combinations of PPI with one or two antibiotics in children.

In a comprehensive review of the literature (43), 23 studies (six published as abstracts) report the efficacy

of 21 different combinations : eradication rates with five different tritherapy schemes vary between 67% and 95%. In our historic series based on the results of the antibiogram, we used a bi-therapy consisting in amoxicillin 50 mg/kg/day (in three doses) and metronidazole 20 mg/kg/day (in two doses) during 8 to 12 days ; in case of imidazole-resistance, clarithromycin 25 mg/kg/day (in two doses) replaced metronidazole. The general eradication rate was 69% with an important difference between girls (84%) and boys (50%). We believe that compliance in teenagers is quite low in boys compared to girls. Although this combination achieves lower eradication rates than those reported in the adult, its low cost and good tolerance allows to consider it as an acceptable choice as long as other combinations including IPP have not yet been fully validated in children.

In Europe in 1991, 7 to 49% H. pylori are imidazoles-resistant strains (44) and macrolides have been replacing imidazole derivates in the therapeutic schemes. The frequency of macrolide-resistant strains is increasing in our population (45) : between January 1989 and December 1996, *Helicobacter pylori*-gastritis was detected in 316 out of 1494 children and adolescents by means of a rapid urease test, a histological study of the antral and fundic mucosa as well as a culture of the biopsies and an antibiogram is available for 300 of them. There was no resistance to amoxicillin nor to bismuth salts. The increasing resistance of *Helicobacter pylori* strains to nitroimidazole and macrolides (table III) makes the antibiogram, whenever possible, a valuable and cost-efficient tool for the guidance of the best eradication therapeutic scheme.

Table III. — **Antibiotic-resistant *Helicobacter pylori* strains**

	Resistant	strains	Imidazoles	Macrolides	Imidaz. +Macrol.
1989	3/19	16%	3	0	0
1990	5/24	21	5	0	0
1991	6/37	16	2	3	1
1992	14/48	29	11	2	1
1993	6/34	18	4	2	0
1994	8/34	24	4	3	1
1995	19/47	40	10	7	2
1996	20/57	35	11	9	0
Total	81/300	27	50	26	5

Conclusion

The role of *H. pylori* as pathogen is well documented. Whereas ulcers are rarely observed in childhood, Helicobacterpylori is responsible for a peculiar type of micro nodular antritis (named after its endoscopic aspect). Recurrent abdominal pain, a typical paediatric syndrome equivalent to adult's non-ulcer dyspepsia, can be one of the many presentations of *Helicobacter pylori* infection although RAP can be due to many other causes. Further randomised placebo-controlled studies are needed in order to decide whether the relationship between *Helicobacter pylori* infection and RAP, very controversed, is a causative or fortuitous. The detection of *Helicobacter pylori* infection using non-invasive methods, such as ^{13}C UBT, is particularly helpful in children, especially because of the lack of sufficient sensitivity of serology. However, like in any other infectious disease, isolation and identification of the micro-organism in endoscopical biopsies remains advisable in order to visualise and evaluate accurately the mucosal lesions (and also cultivate *Helicobacter pylori* strains) through an initial endoscopy. The incidence of *Helicobacter pylori* infection in childhood is low in Belgium. Collection of data concerning symptoms, clinical presentation and laboratory data is recommended. Ideal treatment has not yet been standardised in children and some triple therapy combinations, effective in adults, can prove disappointing in children and further controlled studies in large populations are needed altogether with studies about the possible association with diarrhoeal diseases, mainly in developing areas of the world.

References

1. MARSHALL B.J., WARREN J.R. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet*, 1984, **i** : 1311-5.
2. HILL R., PEARMAN J., WORTHY P., CARUSO V., GOODMAN S., BLINCOVE E. *Campylobacter pyloridis* in children. *Lancet*, 1986, **i** : 387.
3. CADRANEL S., GOOSSENS H., DE BOECK M., MALENGREAU A., RODESCH P., BUTZLER J.P. *Campylobacter pyloridis* in children. *Lancet*, 1986, **i** : 735-736.
4. CZINN S.J., DAHMS B.B., JACOBS G.H., KALLEN B., ROTHSTEIN F.C. *Campylobacter*-like organisms in association with symptomatic gastritis in children. *J. Pediatr.*, 1986, **109** : 80-83.
5. FIEDOREK S.C., MALATY H.M., EVANS D.L., HUMPHREY C.L., CASTEL H.B., EVANS D.J., GRAHAM D.Y. Factors influencing the epidemiology of *H. pylori* infection in children. *Pediatrics*, 1991, **88** : 578-82.
6. MALATY H.M., GRAHAM D.Y. Importance of childhood socioeconomic status on the current prevalence of *Helicobacter pylori* infection. *Gut*, 1994, **35** : 742-745.
7. CLEMENS J., ALBERT M.J., RAO M., HUDA S., QADRI F., VAN LOON F.P., PRADHAN B., NAFICY A., BANIK A. Sociodemographic, hygienic and nutritional correlates of *Helicobacter pylori* infection of young Bangladeshi children. *Aliment. Pharmacol. Ther.*, 1996, **10** : 1015-9.
8. MC CALLION W.A., MURRAY L.J., BAILIE A.G., DALZELL A.M., O'REILLY D.P., BAMFORD K.B. *Helicobacter pylori* infection in children : relation with current household living conditions. *Gut*, 1996, **39** : 18-21.
9. LEWINDON P.J., LAU D., CHAN A., TSE P., SULLIVAN P.B. *Helicobacter pylori* in an institution for disabled children in Hong Kong. *Dev. Med. Child Neurol.*, 1997, **39** : 682-5.
10. GRANSTRÖM M., TINDBERG Y., BLENNOW M. Seroepidemiology of *Helicobacter pylori* infection in a cohort of children monitored from 6 months to 11 years of age. *J. Clin. Microbiol.*, 1997, **35** : 468-70.
11. LEE A. The nature of *Helicobacter pylori. Scand. J. Gastroenterol.*, 1996, **31** : 5-8.
12. EL-OMAR E.M., PENMAN I.D., ARDILL J.E., CHITTAJALLU R.S., HOWIE C., MCCOLL K.E. *Helicobacter pylori* infection and abnormalities of acid secretion in patients with duodenal ulcer disease. *Gastroenterology*, 1995, **109** : 681-691.
13. MCCOLL K., EL-OMAR E.M. *Helicobacter pylori* and disturbance of gastric function associated with duodenal ulcer disease and gastric cancer. *Scand. J. Gastroenterol.*, 1996, **215** (suppl.) : 32-7.
14. WEISS S.J. Tissue destruction by neutrophils. *N. Engl. J. Med.*, 1989, **320** : 365-76.

15. NEGRINI R., SAVIO A., POIESI C., APPELMELK B., BUFFOLI F., PATERLINI A., CESARI P., GRAFFEO M., VAIRA D., FRANZIN G. Antigenic mimicry between *Helicobacter pylori* and gastric mucosa in the pathogenesis of body atrophic gastritis. *Gastroenterology*, 1996, **111** : 655-665.
16. APPELMELK B., SIMOONS-SMIT I., NEGRINI R., MORAN A.P., ASPINALL G.O., FORTE J.G. *et al.* Potential role of molecular mimicry between *Helicobacter pylori* lipopolysaccharide and host Lewis blood group antigens in autoimmunity. *Infect. Immun.*, 1996, **64** : 2031-40.
17. ERNST P.B., CROWE S.E., REYES V.E. How does *Helicobacter pylori* cause mucosal damage ? The inflammatory response. *Gastroenterology*, 1997, **113** : S35-42.
18. MEZEY E., PALKOVITS M. Localization of targets for anti-ulcer drugs in cells of the immune system. *Science*, 1992, **258** : 1662-5.
19. LAMIREAU T., RIGOT A., MEGRAUD F. and DE MASCAREL A. Gastrite à *Helicobacter pylori* chez l'enfant. *Arch. Pédiatr.*, 1995, **2** : 310-6.
20. BLECKER U., HAUSER B., LANCIERS S. *et al.* Symptomatology of *Helicobacter pylori* infection in children. *Acta Paediatr.*, 1996, **85** : 1156-8.
21. OZTURK H., SENOCAK M.E., UZUNALIMOGLU B. *et al. Helicobacter pylori* infection in symptomatic and asymptomatic children : a prospective clinical study. *Eur J. Pediatr. Surg.*, 1996, **6** : 265-9.
22. MAC ARTHUR C., SAUNDERS N., FELDMAN W. *Helicobacter pylori*, gastro-duodenal disease and recurrent abdominal pain in children. *JAMA*, 1995, **273** : 729-34.
23. VAN ZANTEN S., SHERMAN P. A systematic overview of *Helicobacter pylori* infection as the cause of gastritis, duodenal ulcer, gastric cancer and non-ulcer dyspepsia : applying eight diagnostic criteria in establishing causation. *Canadian Med. Ass. Journal*, 1994, **150** : 177-85.
24. TALLEY N.J. A critique of therapeutic trials in *Helicobacer pylori* positive functional dyspepsia. *Gastroenterology*, 1994, **106** : 1174-83.
25. APLEY J., NAISH N. Recurrent abdominal pains : a field survey of 1000 school children. *Arch. Dis. Child*, 1957, **33** : 165-70.
26. VAN DER MEER S., FORGET P.P., LOFFELD R.J., STOBBE-RINGH E., KUJTEN R.H., ARENDS J.W. The prevalence of *Helicobacter pylori* serum antibodies in children with recurrent abdominal pain. *Eur J. Pediatr.*, 1992, **152** : 799-801.
27. MC CALLON W.A., BAILIE A.G., ARDILL J.E.S., POTTS S.R., BOSTON V.E. *Helicobacter pylori*, hyper gastrinemia and recurrent abdominal pain in children. *J. Pediatr. Surg*, 1995, **30** : 427-9.
28. CHONG S.K.F., LOU Q., ASNICAR M.T., ZIMMERMAN S.E. *Helicobacter pylori* infection in abdominal pain in childhood : comparison of diagnostic tests and therapy. *Pediartrics*, 1995, **96** : 211-5.
29. HARDIKAR W., FEEKERY C., SMITH A., OBERKLAI F., GRIMWOD K. *Helicobacter pylori* and recurrent abdominal pain in children. *J. Pediatr. Gastroenterol. Nutr.*, 1996, **22** : 148-52.
30. SNYDER J.D., HARDY S.C., THORNE G.M., HIRSCH B.Z., ANTONIOLI D.A. Primary antral gastritis in young American children : low prevalence of *Helicobacter pylori* infections. *Dig. Dis. Sci.*, 1994, **39** : 1859-63.
31. GORMALLY S.M., PRAKASH N., DURMIN M.T., DALY L.E., CLYNE M., KIERCE B.M., DRUMM B. Association of symptoms with *Helicobacter pylori* in children. *J. Pediatr.*, 1995, **126** : 753-56.
32. REIFEN R., RASOOLY I., DRUMM B., MURPHY K., SHERMAN P. *Helicobacter pylori* infection in children : is there a specific symptomatology ? *Dig. Dis. Sci.*, 1994, **39** : 1488-92.
33. VELDHUYZEN VAN ZANTEN S.J.O. The role of *Helicobacter pylori* infection in non-ulcer dyspepsia. *Aliment. Pharmacol. Ther.*, 1997, **11** (suppl. 1) : 63-8.
34. TALLEY N.J., WEAVER A.L., TESMER D.L., ZINSMEISTER A.R. Lack of discriminant value of dyspepsia subgroups in patients referred for upper endoscopy. *Gastroenterology*, 1993, **105** : 1378-86.
35. COVER T.L., BLASER M.J. *Helicobacter pylori* infection, a paradigm for chronic mucosal inflammation : Pathogenesis and implications for eradication and prevention. *Adv. Internal. Med.*, 1996, **41** : 85-117.
36. VELDHUZEN VAN ZANTEN S.J.O., CLEARY C., TALLEY N.J. Drug treatment of functional dyspepsia : A systematic analysis of trial methodology with recommendations for design of future trials. *Am. J. Gastroenterol.*, 1996, **91** : 660-73.
37. BLASER M.J. *Helicobacter pylori* eradication and its implications for the future. *Aliment. Pharmacol. Ther.*, 1997, **11** (suppl. 1) : 103-7.
38. LABENZ J., BORSCH G. Highly significant change of the clinical course of relapsing and complicated peptic ulcer disease after cure of *Helicobacter pylori* infection. *Am. J. Gastroenterol.*, 1994, **89** : 1785-8.
39. DELTENRE M., GLUPCZINSKI Y., DEPREZ C. *et al.* The reliability of urease test, histology and culture in the diagnosis of *Campylobacter pylori* infection. *Scand. J. Gastroenterol.*, 1989, **160** (suppl.) : 19-24.
40. GLUPCZYNSKI Y., LABBE M., HANSEN W. *et al.* Evaluation of the E test for quantitative antimicrobial susceptibility testing of *H. pylori*. *J. Clin. Microbiol.*, 1991, **29** : 2072-2075.
41. CADRANEL S., CORVAGLIA L., BONTEMS P. *et al.* Detection of *Helicobacter pylori* infection by a non invasive method : standardisation of the 13C-urea breath test in children. *J. Pediatr. Gastroenterol. Nutr.*, 1996, **22** : 432.
42. TYTGAT G.N.J. Current indications for *Helicobacter pylori* eradication therapy. *Scand. J. Gastroenterol.*, 1996, **31** (suppl. 215) : 70-73.
43. CADRANEL S. Etudes de l'efficacité des médicaments de l'infection à *Helicobacter pylori* chez l'enfant. *In* : PONS G., DUPONT C. (eds). Les médicaments du reflux gastro-oesophagien et de l'infection à *Helicobacter pylori* chez l'enfant. Springer-Verlag, Paris, 1996, 179-91.
44. GLUPCZYNSKI Y. Results of a multicentre European survey in 1991 of metronidazole resistance in *Helicobacter pylori*. *Eur J. Clin. Microbiol. Infect. Dis.*, 1992, **11** : 777-81.
45. DE OLIVEIRA ANDRADE D., BONTEMS P., CORVAGLIA L., CADRANEL S. Increasing resistance of *H. pylori* to antibiotics : usefulness of culture and antibiograms. *J. Pediatr. Gastroent. Nutr.*, 1996, **22** : 431.
46. SULLIVAN P.B., THOMAS J.E., WIGHT D.G.D. *et al. Helicobacter pylori* in Gambian children with chronic diarrhoea and malnutrition. *Arch. Dis. Child.*, 1990, **65** : 189-191.
47. OLIVEIRA A.M.R., QUEIROZ D.M.M., ROCHA G.A. *et al.* Seroprevalence of *H. pylori* infection in children of low socio economic level in Belo Horizonte, Brasil. *Am. J. Gastroenterol.*, 1994, **89** : 2101-2204.
48. KONTIAINEN S., SEPPALA I., MIETTINEN A., *et al.* Antibodies against some bacterial antigens in children. *Acta Paediatr.*, 1994, **83** : 1137-1142.
49. PATEL P., MENDALL M.A., KHULUSI S. *et al. Helicobacter pylori* infection in childhood : risk factors and effect on growth. *BMJ*, 1994, **309** : 1119-1123.
50. GOODMAN K.J., CORREA P., TENGANA A.U.X. H.J., DFELANY J.P., COLLAZOS T. Nutritional factors and *H. pylori* infection in Colombian children. *J. Pediatr. Gastroenterol. Nutr.*, 1997, **25** : 507-15.
51. RODRIGO SAEZ L., RIESTRA MENENDEZ S., FERNANDEZ RODRIGUEZ E., FERNANDEZ VELAZQUEZ M.R., GARCIA ALONSO S., LAURET BRANA M.E. Epidemiological study of the prevalence of *Helicobacter pylori* infection in the general population of Asturias, Spain. *Rev. Esp. Enferm. Dig.*, 1997, **87** : 511-22.
52. KEHRT R., BECKER M., BROSICKE H., KRUGER N., HELGE H. Prevalence of *Helicobacter pylori* infection in Nicaraguan children with persistent diarrhea diagnosed by the ^{13}C-urea breath test. *J. Pediatr. Gastroenterol. Nutr.*, 1997, **25** : 84-88.
53. PELSER H.H., HOUSEHAM K.C., JOUBERT G., VANDERLINDE G., KRAAIJ P.?. MEINARDI M., MC LEOD A., ANTHONY M. Prevalence of *Helicobacter pylori* antibodies in Bloemfontein, South Africa. *J. Pediatr. Gastroenterol. Nutr.*, 1997, **24** : 135-9.