

## HELICOBACTER PYLORI INFECTION IN CHILDREN

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### Rezumat:

Există o corelație între HP și gastrita cronică atât la adulți cât și la copii, precum și între HP și neoplazmele gastrice la adulți.

Boala asociată de HP se caracterizează prin vărsături, greață, epigastralgi și chiar hematemază.

Infecția cronică are o simptomatologie slab reprezentată și semne nespecifice.

Tratamentul de primă alegere constă în omeprazol la care se asociază două antibiotice, amoxicilină, claritromicină sau metronidazol).

Profilaxia specifică prin vaccinare este în continuare în discuție.

Cuvinte cheie: *Helicobacter pylori*, gastrită cronică, eradicare, vaccin.

### Abstract:

There is a proven relationship between HP and chronic gastritis, both in adults and children, and between HP and non-cardial gastric neoplasms in adult. Acute HP infection in children manifests through nausea, vomiting, epigastralgia, associated in infants with poor feeding or even hematemesis. Chronic infection has poor and unspecific signs. Long term effects on growth are deleterious, HP infected children being smaller than uninfected ones. Eradication is mandatory, even in asymptomatic children, in case of family history of gastric cancer. First choice regimens use omeprazole and 2 antibiotics (amoxicilline, claritromycine or metronidazole). Specific prophylaxis through vaccination is under study.

Keywords: *Helicobacter pylori*, chronic gastritis, gastric cancer, eradication, vaccine.

### ETIOLOGY

*Helicobacter pylori* (HP) is a spiral-shaped microaerophilic Gram negative bacteria, very mobile due to its multiple flagella. It was first cultured and described by Warren and Marshall (Perth, Australia) in 1982, discovery which brought them the Nobel Prize for Medicine and Physiology in 2005. Initially named *Campylobacter pylori*, it received its present name in 1989.

According to a recent paper published in *Nature* by a research team from UK and Germany, the relationship between humans and HP dates more than 60000 years back (1).

The only known reservoir are the humans. There are equivalent species in animals but they can only transiently infect humans.

This bacteria's biology has several particularities, which enable it to survive the acidic intragastric medium and to avoid immunologic defense mechanisms.

Before HP discovery, it was believed that no bacteria is able to live and multiply within a such strongly acid medium (pH as low as 1.5) as the intragastric medium is. An HP genom coded protein – the urease – allows it to deny this concept. This enzyme is capable of urea lysis,

with bicarbonate and ammonium production, which provide acid buffering. Another enzyme essential for HP survival is the catalase, which confers defense against reactive oxygen species produced by leucocytes.

HP lives and develops in the inner mucus layer, a place hard to reach for the immunologic cells and molecules.

Unlike other Gram negative bacteria, HP's membrane lipopolysaccharides have lower immunogenicity (poor activation of complement classic path).

HP virulence seems to depend on *cag* gene presence (cytotoxin associated gene), this gene's product, the *cagA* protein, being associated by some authors with a higher neoplastic risk (2,3,4) while others haven't found such association (5,6,7).

### EPIDEMIOLOGY

#### GASTRIC CANCER – HP RELATIONSHIP

HP infection is widely spread, especially in developing countries. Children get infected generally before 5 years of age (8-13), with a lowering incidence thereafter (8). Recognized risk factors are an infected

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sibling or mother, poverty, large family, crowded home, late bottle weaning (after 2 years of age) (8). Infection transmission route is fecal-oral or oral-oral.

There is no sex difference in HP infection.

There are no epidemiologic data about pediatric HP infection in Romania.

There is a proven relationship between HP and chronic gastritis, both in adults and children, and between HP and non-cardial gastric neoplasms in adult. Only 1% of HP infected individuals develop gastric cancer (14), which means that there are other factors responsible for gastric carcinogenesis, possible equally important (A blood group (15), high salted (16) or smoked (17) food intake, poor vitamin C (18) or carotenoids (19) intake).

According to a 2001 review (20), there is no proven benefit for the introduction of an active screening for detection and treatment of the HP infected children, nor is HP infected children treatment compulsory if they are asymptomatic. Still, information about HP and gastric cancer relationship should be provided for these children's parents and they should be offered the choice. Eradication is mandatory, even in asymptomatic children, in case of family history of gastric cancer (21-23).

Particular cases are  $\beta$ -cell gastric lymphomas, the so-called MALT lymphomas (mucosa associated lymphoid tissue), their relationship with HP being suggested by several research works (24,25). They even regress after HP eradication within the host (26-29), so they represent a strong indication for this treatment.

The natural history of HP infection in asymptomatic children was studied by Ganga-Zandzou P et al. in Lille, France. They followed 18 HP infected children for a period of two years (32). Spontaneous clearance of infection was observed only in one case; the other 17 children remained infected with the same HP strain (assessed by DNA studies) and, although bacterial density never changed, histopathology turned worse. The most frequent histopathologic finding was nodular gastritis, with a prevalence increasing with infection's age.

### **PATHOGENY. PATHOLOGY**

Gastric colonization with HP generally manifests as an acute disease, followed by chronic infection. Part of the bacteria attach to gastric epithelium but most of them resides in the inner mucus layer.

Due to HP antigens release, immun system is activated and proinflammatory and chemotactic factors are secreted. As a consequence, leukocytes (macrophages and mononucleares) migrate and submucosal lymphoid tissue proliferates. During this stage interleukines profile is dominated by IFN-gamma and IL-8, with an immunity deviation toward a cytotoxic, TH1 - type reaction (33).

Reactive oxygen species released by neutrophils and CD8 lymphocytes do not succeed to kill HP (protected by its own catalase) but produce gastric epithelium injury.

During the acute phase of the infection these phenomena could lead to acute gastritis or even gastric or duodenal ulcerations (only rarely seen in children 34).

In a few years a chronic gastritis develops. The patient's immunologic mechanisms produce lesions of

the gastric epithelium. Its regeneration capacity is overwhelmed, eventually leading to gastric atrophy and intestinal metaplasia. This process can have neoplastic implications, but in this stage HP is no longer detectable at lesions site.

The most frequently encountered lesion in HP positive patients is nodular antral gastritis 34-36, some of the authors even stating that they have found HP in virtually all cases with this morfo-pathological type 34 of lesion.

### **CLINICAL PRESENTATION**

Acute HP infection in children manifests through nausea, vomiting, epigastralgia, associated in infants with poor feeding or even hematemesis (37).

Chronic infection has poor and unspecific signs. There is a controversial relationship between chronic HP infection and recurrent abdominal pain (RAP), some authors sustaining and others denying it (35,39,40). Beside RAP, other signs of chronic HP infection in children are anorexia, descending weight curve or failure to thrive, palour, sunken eyes or vomiting.

Long term effects on growth are deleterious, HP infected children being smaller than uninfected ones (41,42).

Two recent papers raise the concern of anemia associated to HP infection (43,44), related both to iron consumption by HP and to absorption impairment due to gastric achlorhydria.

Another type of lesion, rarely encountered in children, is the peptic ulcer, manifested through nausea, vomiting, epigastralgia or by its complications' signs (gastric hemorrhage, perforation, peritonitis). In time gastric carcinoma or MALT lymphoma may occur and manifest themselves by local and general signs.

In children with insuline dependent diabetes mellitus HP infection may raise the insuline requirements (45).

### **BIOLOGIC AND IMAGISTIC PROCEDURES**

Amongst imagistic tests, the most accurate information is provided by digestive endoscopy. Beside the lack of radiation exposure, endoscopic exploration is better than radiological procedures in providing topographic and morphologic data and it offers the possibility of performing biopsies. Types of lesions which are easily diagnosed by endoscopy are: gastritis, ulcer, perforation, hemorrhage, pyloric stenosis.

On the bioptic fragment one can perform direct microscopy (for HP or neoplastic cells, on smear or fragment section), bacterial cultures (on special media), urease test or polymerase chain reaction (PCR).

Bacterial culture and antibiogram are important in recurrent or resistant infections and for epidemiologic reason (regional antibiotic resistance pattern).

The most sensitive and widely available non invasive test (46-49,51) is respiratory urease test. It is done by oral administration of radioactive labeled urea (13C and 14C), which will be decomposed by HP's urease to bicarbonate. This will enter the blood stream, it will be partially transformed to CO<sub>2</sub>, which can be detected in

the exhaled air. A variant of this test can be performed also *in vitro*, on the biptic fragment.

On the next place in terms of sensitivity and specificity is the stool HP antigens detection technique, with 91.6% sensitivity and 98.6 specificity (47,51).

As for the blood HP serology, it has a lower sensitivity than the two methods already mentioned (46,48) but a very good specificity. ELISA tests and methods must be locally validated, in order to have good results<sup>51</sup>.

Due to IgG life-time, one serology result does not offer much information. Repeated tests, on the other hand, gives important information about the evolution. The antibodies' level remains constant or increase in persistently infected children and it has a descending tendency in spontaneously or post-therapeutic HP clearance. Anti-HP IgG level falls below detection limit by 6-9 (even 12) months thereafter (47). Some authors' opinion is that anti-HP IgG could be used as an infection clearance marker, provided that more than 6 months have passed since conclusion of the treatment (50). The sensitivity is even higher if IgA are used.

AntiHP IgG can be detected in urine, too (49), with a sensitivity and specificity ratio compared to blood assays of 85.4% and 95.5% respectively.

In HP positive patients usual lab tests may also be altered - neutrophilia, elevated ESR and CRP, hypochromic anemia, low proteinemia.

## DIFFERENTIAL DIAGNOSIS

Resembling diseases enter two categories:

- Eso-gastro-enteral diseases: hiatal hernia, gastroesophageal reflux, esophagitis, gastric/duodenal ulcer, stress ulcer, Zollinger-Ellison syndrome, chronic gastritis, pyloric stenosis, enteral duplication, eosinophilic gastroenteritis, celiac disease, inflammatory bowel disease, parasitic disorders
- Biliary and pancreatic disorders: pancreatitis, cystic fibrosis, bile ducts malformations, angiocholitis, pancreatic pseudocyst

## TREATMENT

Treatment indications are as follows (see also Epidemiology. Gastric cancer – HP relation) (51):

- Symptomatic infection;
- Patients with gastroesophageal reflux who will need chronic proton pump inhibitors (because of increase added risk of gastric atrophy);
- HP+ patients with impaired nutrition state;
- HP+ patients with family history of gastric cancer;
- HP+ patients who need chronic steroid or non-steroid antiinflammatory treatment;
- MALT lymphoma;
- HP+ patients with cancerophobia;
- Parents' special demand for treatment;
- Treatment can be achieved by association of 3 or 4 of the drugs presented in table 1.

**Table 1.** Drugs indicated for *Helicobacter pylori* eradication in children

Drug	Dose
● bismuth subsalicylate	30 ml q 6 h, in children over 10 y.o.
● bismuth citrate	480 mg/1,73m <sup>2</sup> /day
● proton pump inhibitors (omeprazol)	1 mg/kgc/day, q 12 h
● amoxicilline	50 mg/kgc/day, q 12 h
● claritromycine	15 mg/kgc/day, q 12 h
● metronidazole	20 mg/kgc/day, q 12 h
● tetraciline (in children over 8 y.o.)	25-50 mg/kgc/day, q 6 h

According to NASPGHAN (*North American Society for Pediatric Gastroenterology, Hepatology and Nutrition*), there are three first choice regimens for HP eradication<sup>51</sup>:

- Omeprazole + amoxicilline + claritromycine
- Omeprazole + amoxicilline + metronidazole
- Omeprazole + metronidazole + claritromycine

Second choice regimens, reserved for first line treatment failure (51):

- Bismuth subsalicylate + metronidazole + proton pump inhibitors + antibiotic (amoxicilline or tetracycline or claritromycine)
- Ranitidine + bismuth citrate + claritromycine + metronidazole

Antibiotics must be given for 14 days and omeprazole for 1 month.

Treatment failure predictive factors are: numerous crowded family, lack of treatment compliance, bacterial resistance to antibiotics, previous use of a proton pump inhibitor (51,52).

HP resistance to antibiotics is an important issue. In a paper published in 1999, Nilsson F. *et al* showed that in Sweden clarithromycin-resistance among HP strains increased in prevalence from 1 to 7% over the previous four years, and always resulted in treatment failure (53). In 2004 Hartzel S. presented data about antibiotic resistance of HP in Denmark within an interval of 10 years, comparing 180 strains from 1990–93 and 180 strains from 2000–02. His results showed that over a period of 10 years only the development of resistance to metronidazole appeared to constitute a problem, HP remaining remarkably susceptible to amoxicillin, clarithromycin and tetracycline (54).

A more recent Iranian study performed on 24 HP infected patients stressed that many HP strains were resistant to metronidazole (Table 2) (55).

**Table 2.** Resistance of *Helicobacter pylori* to antibiotics (Fallahi G, 2007) (55)

Antibiotic	Resistance
● Metronidazole	54.16%
● Amoxicilline	8.33%
● Eritromicine	4.16%
● Claritromycine	4.16%
● Tetraciline, furazolidone	0

## VACCINATION

HP infection is generally a chronic one, with a reduced probability for spontaneous clearance of the bacteria. The effects of this infection on humans may be important on short term but they are crucial on long term.

In 1994 the International Agency for Research on Cancer (USA) has included HP in 1st order class carcinogens, a decision later confirmed by WHO, due to its association with non-cardial gastric carcinomas and MALT lymphomas.

Specific prophylaxis through vaccination is under study. Due to the low prevalence of gastric cancer among HP infected patients (only 1%), this vaccine should be easy to obtain, cheap and highly protective in order to be epidemiologically efficient.

So far, performed studies have used the following methods (56):

- Recombinant attenuated Salmonellas expressing *H. pylori* urease; poor immunogenicity;
- An oral whole-cell vaccine adjuvanted with wild-type LT; discontinued due to side effects;
- Purified urease co-administered with LT; studies were also interrupted;
- A recombinant VacA, CagA and NAP vaccine (alum); proved safe and strongly immunogenic.

All these are phase I studies and an anti-HP vaccine for clinical use is still waiting to be produced.

## Bibliografie

1. Bodo Linz, Franois Balloux, Yoshan Moodley, Andrea Manica, Hua Liu, Philippe Roumagnac, Daniel Falush, Christiana Stamer, Franck Prugnolle, Schalk W. van der Merwe, Yoshio Yamaoka, David Y. Graham, Emilio Perez-Trallero, Torkel Wadstrom, Sebastian Suerbaum, Mark Achtman. An African origin for the intimate association between humans and *Helicobacter pylori*. *Nature* 445, 915 - 918 (07 Feb 2007)
2. Crabtree JE, Wyatt JI, Sobala GM, Miller G, Tompkins DS, Primrose JNM. Systemic and mucosal humoral responses to *Helicobacter pylori* in gastric cancer. *Gut*. 1993;34:1339-1343
3. Blaser MJ, Perez-Perez GI, Kleanthous H, et al. Infection with *Helicobacter pylori* strains possessing *cagA* is associated with an increased risk of developing adenocarcinoma of the stomach. *Cancer Res*. 1995; 55:2111-2115
4. Parsonnet J, Friedman GD, Orentreich N, Vogelman H. Risk for gastric cancer in people with CagA positive or CagA negative *Helicobacter pylori* infection. *Gut*. 1997;40:297-301
5. Mitchell HM, Hazell SL, Li YY, Hu PJ. Serologic response to specific *Helicobacter pylori* antigens: antibody against CagA antigen is not predictive of gastric cancer in a developing country. *Am J Gastroenterol*. 1996;91:1785-1788
6. Shimoyama T, Fukuda S, Tanaka M, Mikami T, Saito Y, Munakata A. High prevalence of the CagA-positive *Helicobacter pylori* strains in Japanese asymptomatic patients and gastric cancer patients. *Scand J Gastroenterol*. 1997;32:465-468
7. Perez-Perez GI, Bhat N, Gaensbauer J, et al. Country-specific constancy by age in *cagA1* proportion of *Helicobacter pylori* infections. *Int J Cancer*. 1997;72:453-456
8. Rowland M; Daly L; Vaughan M; Higgins A; Bourke B; Drumm B. Age-specific incidence of *Helicobacter pylori*. *Gastroenterology*. 2006; 130(1):65-72.
9. The Gastrointestinal Physiology Working Group. *Helicobacter pylori* and gastritis in Peruvian patients: relationship to socio-economic level, age and sex. *Am J Gastroenterol*. 1990;85:819-823
10. Raymond J, Bargaoui K, Kalach N, Bergeret M, Barbet P, Dupont C. Isolation of *Helicobacter pylori* in a six-day-old new-

born. *Eur J Clin Microbiol Infect Dis*. 1995;14:727-728

11. Pattison CP, Marshall BJ, Young TW, Vergara GG. Is *Helicobacter pylori* the missing link for sudden infant death syndrome? *Gastroenterology*. 1997;112:A254
12. Thomas JE, Gibson GR, Darboe MK, Dale A, Weaver LT. Isolation of *Helicobacter pylori* from human faeces. *Lancet*. 1992;340:1194-1195
13. Gottrand F, Turck D, Vincent P. *Helicobacter pylori* infection in early infancy. *Lancet*. 1992;340:495
14. Kuipers EJ. Relationship between *Helicobacter pylori*, atrophic gastritis and gastric cancer. *Aliment Pharmacol Ther*. 1998;12(suppl 1):25-36
15. Aird I, Bentall HH, Roberts JAF. A relationship between cancer of the stomach and the ABO blood groups. *BMJ*. 1953;1:799
16. Joossens JV, Hill MJ, Elliott P, et al. Dietary salt, nitrate and stomach cancer mortality in 24 countries. European Cancer Prevention (ECP) and the INTERSALT Cooperative Research Group. *Int J Epidemiol*. 1996;25:494-504
17. Palli D. Epidemiology of gastric cancer [review]. *Ann Ist Super Sanita*. 1996;32:85-99
18. Mackerness CW, Leach SA, Thompson MH, Hill MJ. The inhibition of bacterially mediated N-nitrosation by vitamin C: relevance to the inhibition of endogenous N-nitrosation in the achlorhydric stomach. *Carcinogenesis*. 1989;10:397-399
19. Haenszel W, Correa P, Lopez A, et al. Serum micronutrient levels in relation to gastric pathology. *Int J Cancer*. 1985;36:43-48
20. Cameron Imrie, Marion Rowland, Billy Bourke and Brendan Drumm. Is *Helicobacter pylori* Infection in Childhood a Risk Factor for Gastric Cancer? *Pediatrics* 2001;107:373-380
21. Brenner H, Bode G, Boeing H. *Helicobacter pylori* infection among offspring of patients with stomach cancer. *Gastroenterology*. 2000;118: 31-35
22. El-Omar EM, Oien K, Murray LS, et al. Increased prevalence of precancerous changes in relatives of gastric cancer patients: critical role for *H. pylori*. *Gastroenterology*. 2000;118:22-30
23. Parsonnet J. When heredity is infectious. *Gastroenterology*. 2000;118: 222-227
24. Wotherspoon AC, Ortiz-Hidalgo C, Falzon MR, Isaacson PG. *Helicobacter pylori*-associated gastritis and primary B-cell gastric lymphoma. *Lancet*. 1991;338:1175-1176
25. Parsonnet J, Hansen S, Rodriguez L, et al. *Helicobacter pylori* infection and gastric lymphoma. *N Engl J Med*. 1994;330:1267-1271
26. Wotherspoon AC, Doglioni C, Diss TC, Pan L, Moschini A, de Boni M. Regression of primary low-grade B-cell gastric lymphoma of mucosa-associated lymphoid tissue type after eradication of *Helicobacter pylori*. *Lancet*. 1993;342:575-577
27. Wotherspoon AC, Doglioni C, de Boni M, Spencer J, Isaacson PG. Antibiotic treatment for low-grade gastric MALT lymphoma. *Lancet*. 1994;343:1503-1503
28. Montalban C, Manzanal A, Boixeda D, Redondo C, Bellas C. Treatment of low-grade gastric MALT lymphoma with *Helicobacter pylori* eradication. *Lancet*. 1995;345:798-799
29. Thiede C, Morgner A, Alpen B, et al. What role does *Helicobacter pylori* eradication play in gastric MALT and gastric MALT lymphoma? *Gastroenterology*. 1997;113:S61-S64
30. Blecker U, McKeithan TW, Hart J, Kirschner BS. Resolution of *Helicobacter pylori*-associated gastric lymphoproliferative disease in a child. *Gastroenterology*. 1995;109:973-977
31. European *Helicobacter pylori* Study Group [review]. Current European concepts in the management of *Helicobacter pylori* infection. The Maastricht Consensus Report. *Gut*. 1997;41:8-13
32. Ganga-Zandzou P, Michaud L, Vincent P, Husson MO, Wizla-Derambure N, Delassalle E, Turck D, Gottrand F. Natural Outcome of *Helicobacter pylori* Infection in Asymptomatic Children: A Two-year Follow-up Study. *Pediatrics* 1999;104:216-221
33. Shimizu T; Haruna H; Ohtsuka Y; Kaneko K; Gupta R; Yamashiro Y. Cytokines in the gastric mucosa of children with *Helicobacter pylori* infection. *Acta Paediatr*. 2004; 93(3):322-6
34. Sonny K. F. Chong, Qinyuan Lou, Mark A. Asnicar, Sarah E. Zimmerman, Joseph M. Croffie, Chao-Hung Lee and Joseph F.

Fitzgerald. *Helicobacter pylori* Infection in Recurrent Abdominal Pain in Childhood: Comparison of Diagnostic Tests and Therapy. *Pediatrics* 1995;96:211-215

35. Nicolas Kalach; Karine Mention; Dominique Guimber; Laurent Michaud, Claire Spycykerell; and Frederic Gottrand. *Helicobacter pylori* Infection Is Not Associated With Specific Symptoms in Nonulcer-Dyspeptic Children. *Pediatrics* 2005;115:17-21

36. Menachem Moshkowitz; Shimon Reif; Shlomo Brill; Yehuda Ringel; Nadir Arber; Zamir Halpern and Yoram Bujanover. One-Week Triple Therapy With Omeprazole, Clarithromycin, and Nitroimidazole for *Helicobacter pylori* Infection in Children and Adolescents. *Pediatrics* 1998;102:14-

37. Gilger MA., Feigin RD, Cherry JD. *Helicobacter pylori*. In: *Textbook of Pediatric Infectious Diseases*. 4th ed. 1998:1488-1495

38. Mitchell JD, Mitchell HM, Tobias V. Acute *Helicobacter pylori* infection in an infant associated with gastric ulceration and serological evidence of intrafamilial transmission. *Am J Gastroenterol*. 1992;87:382-386

39. Malaty HM; Abudayyeh S; Graham DY; Gilger MA; Rabeneck L; O'Malley K. A prospective study for the association of *Helicobacter pylori* infection to a multidimensional measure for recurrent abdominal pain in children. *Helicobacter*. 2006; 11(4):250-7

40. Gunter Bode; Dietrich Rothenbacher; Hermann Brenner and Guido Adler. *Helicobacter pylori* and Abdominal Symptoms: A Population-based Study Among Preschool Children in Southern Germany. *Pediatrics* 1998;101:634-637

41. Richter T; Richter T; List S; Müller DM; Deutscher J; Uhlig HH; Krumbiegel P; Herbarth O; Gutschmuths FJ; Kiess W. Five- to 7-year-old children with *Helicobacter pylori* infection are smaller than *Helicobacter*-negative children: a cross-sectional population-based study of 3,315 children. *J Pediatr Gastroenterol Nutr*. 2001; 33(4):472-5

42. Bravo LE; Mera R; Reina JC; Pradilla A; Alzate A; Fonham E; Correa P. Impact of *Helicobacter pylori* infection on growth of children: a prospective cohort study. *J Pediatr Gastroenterol Nutr*. 2003; 37(5):614-9

43. Kurekci AE; Atay AA; Sarici SU; Yesilkaya E; Senses Z; Okutan V; Ozcan O. Is there a relationship between childhood *Helicobacter pylori* infection and iron deficiency anemia? *J Trop Pediatr*. 2005; 51(3):166-9

44. Henry C. Baggett, Alan J. Parkinson, Pam T. Muth, Benjamin D. Gold, Bradford D. Gessner. Endemic Iron Deficiency Associated With *Helicobacter pylori* Infection Among School-Aged Children in Alaska. *Pediatrics* 2006;117:396-404

45. Rodolfo E. Begue; Ayesha Mirza; Terry Compton; Ricardo Gomez and Alfonso Vargas. *Helicobacter pylori* Infection and Insulin Requirement Among Children With Type 1 Diabetes Mellitus. *Pediatrics* 1999;103:83-

46. Sonny K. F. Chong, Qinyuan Lou, Mark A. Asnicar, Sarah E. Zimmerman, Joseph M. Croffie, Chao-Hung Lee and Joseph F. Fitzgerald. *Helicobacter pylori* Infection in Recurrent Abdominal Pain in Childhood: Comparison of Diagnostic Tests and Therapy. *Pediatrics* 1995;96:211-215

47. Barbara Braden, Hans-Georg Posselt, Peter Ahrens, Richard Kitz, C. F. Dietrich and Wolfgang F. Caspary. New Immunoassay in Stool Provides an Accurate Noninvasive Diagnostic Method for *Helicobacter pylori* Screening in Children. *Pediatrics* 2000;106:115-117

48. Robert W. Frenck, Jr, Hanan Mohamed Fathy, May Sherif, Zaynab Mohran, Hanan El Mohammedy, Wagdy Francis, David Rockabrand, Bahaa Ihab Mounir, Patrick Rozmajzl, Henry F. Frierson. Sensitivity and Specificity of Various Tests for the Diagnosis of *Helicobacter pylori* in Egyptian Children. *Pediatrics* 2006;118:1195-1202

49. Seiichi Kato; Tetsuya Tachikawa; Kyoko Ozawa; Mutsuko Konno; Masumi Okuda; Takuji Fujisawa; Yutaka Nakazato; Hitoshi Tajiri and Kazuie Iinuma. Urine-Based Enzyme-Linked Immunosorbent Assay for the Detection of *Helicobacter pylori* Infection in Children. *Pediatrics* 2001;107:87-

50. Seiichi Kato; Noriko Furuyama; Kyoko Ozawa; Kenji Ohnuma and Kazuie Iinuma. Long-term Follow-up Study of Serum Immunoglobulin G and Immunoglobulin A Antibodies After *Helicobacter pylori* Eradication. *Pediatrics* 1999;104:22-

51. Singapore Minister of Health Clinical Practice Guidelines 9/2004. Management of *Helicobacter pylori* infection.

52. Benjamin D. Gold, Richard B. Colletti, Myles Abbott, Steven J. Czinn, Yoram Elitsur, Eric Hassall, Colin Macarthur, John Snyder and Philip M. Sherman. *Helicobacter pylori* Infection in Children: Recommendations for Diagnosis and Treatment. *J Pediatr Gastroenterol Nutr*, Vol. 31, No. 5, November 2000, 490-497

53. Nilsson F, Walder M. Antibiotic resistance of *Helicobacter pylori* in Malmö. Therapeutic success in spite of antibiotic resistance. *Lakartidningen*. 1999 Feb 3;96(5):460-3

54. Hartzen S. The prevalence and consequences of antibiotic resistance in Danish *H. pylori* strains isolated with an interval of 10 years. Abstract, 14th European Congress of Clinical Microbiology and Infectious Diseases, Prague / Czech Republic, May 1-4, 2004

55. Fallahi G, Maleknejad S. *Helicobacter pylori* culture and antimicrobial resistance in Iran. *Indian J Pediatr* 2007;74:127-130

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## ● RECENZIE ● RECENZIE ● RECENZIE ●

### Dr Grigore Buşoi – Din adânc spre cele înalte

O carte cu totul deosebită, nu numai pentru medici, cu un conţinut greu de ordonat în tiparele medicale obișnuite tocmai pentru ca abunda în corelații multidisciplinare multiculturale și pentru ca prezintă o problematică proteiformă; este o încercare încordată de a stăpâni o suită de idei sub care pulsează o inimă plină de dragostea pentru bogățiile minții și sufletului românesc – (de la folclorul genial și peren până la mari personalități medicale cunoscute de autor), încărcată de pasiunea și devoțiunea pentru profesia sa de medic, nu numai al trupului ci și al sufletului omului bolnav. Autorul vadește și o mare dragoste de înțelepciune și frumos, alimentată de o uriasă cultură filozofică și estetică.

Este vorba de apariția editorială a distinsului coleg dr Grigore Busoi, unul dintre valoroșii fondatori ai specialității de medicină a familiei din țara noastră, în același timp fondator și animator al Revistei Române de Medicină, careia i-a imprimat o orientare în consens cu pluralenta umanista a medicului și în paginile careia, în special în editorialele scrise de domnia sa, a încercat și încercă în mod conștient – cu armele scriitorului care este – sa descopere și sa valorifice nenumăratele conexiuni între variatele credințe și obiceiuri ale poporului nostru și problemele de baza ale medicinei: etiopatogenia bolilor (adeseori psihogena), ecoul acestora în sufletul bolnavului, mentalitatea pacientului supus unor interdicții (de stil de viață) greu de acceptat, etc.

Dintre aceste concepte legitime pentru o revista medicală, se strecoara (dar la vedere!) veritabile miniesuri cu o tematică frecvent axată pe contribuțiile romanesti, inca insuficient relevate, la tezaurul de idei și valori estetice la umanității, ca și pe concepții/concepte medicale – filozofice sintetizate sau reformulate într-o manieră originală uneori cu tentatii esoterice rigurose ținute în frâu.

Tocmai aceste caracteristici ale medicului și scriitorului Grigore Buşoi se regăsesc în această lucrare, extrem de atractivă prin bogăția uriașă de informații și stilul clar și firesc. O carte pe care – în această vreme, ostilă unor lecturi prelungite – o citești pe nerăsuflăte.

Chiar dacă timpul nu permite o lectură „dintr-o sorbitură”, cele 3 mari secțiuni ale cărții permit o distribuie a materialului lucrării după cum urmează, partea I: probleme culturale învăstăte medicale, partea a II-a: deschideri medicale, și partea a III-a: repere în munți; citite în etape pline de atractivitate intelectuală. Paragrafele și subcapitolele cărții ne permit să realizăm o îmbogățire complexă a universului nostru spiritual.