

SUMMARY

Helicobacter pylori infection is a common and universally distributed bacterial infection. It is predominately acquired in childhood, and more than three fourths of the population in developing countries is infected during childhood. In developed countries, infection in children is less frequent. It is the most frequent cause of chronic gastritis and peptic ulcer, and is directly associated with gastric carcinoma.

Our aim in the present study is to correlate the main bacterial virulence factors *babA2*, *vacA*, and *cagA* with the histopathological parameters of *h pylori* related gastritis, the endoscopic picture and with the clinical presentations. This will be important for the future policies for the eradication of *h pylori* in order to prevent severe diseases in children and adults. Our study adds new pieces of information in this respect.

To achieve this goal, the present study was carried out on 95 symptomatic children who referred for endoscopy suffering from hematemesis, abdominal pain and/or vomiting. 50 of those children were diagnosed to have *H. pylori* infection by rapid urease test, histopathology and PCR and 45 children were diagnosed as *H. pylori* negative. A third group of 25 asymptomatic children were diagnosed as *H. pylori* positive using the stool antigen test.

Statistical analysis of data obtained from the present study showed the following results:

- 1- Hematemesis is the most common clinical manifestation in patients who referred to our pediatric gastroenterology clinic for upper gastrointestinal endoscopy (54.7%) with statistically significant association between *h pylori* and hematemesis.
- 2- Antral nodularity is a significant predictor of *H. pylori* infection.
- 3- The histological picture of symptomatic *H. pylori*-infected children was characterized by a more severe inflammatory cell infiltrate, highly active inflammation and an increased number of lymphoid follicles compared with those who were *H. pylori* negative.
- 4- The histological picture of *H. pylori* infected children with RAP and those with hematemesis, characterized by significantly more inflammation compared with those not complaining .
- 5- The most prevalent virulent gene is *vacA* (72%) then *cagA* (52%) then *babA2* (44%) among *H. pylori* positive cases.
- 6- As regard *vacA* s/m combined genotypes, s2/m2 is the most common, then s1/m1 then s1/m2 and s2/m1 with equal prevalence.
- 7- Significant relations are found between *babA2*, *cagA*, *vacA* s1, s1/m1 and s2/m2 positivity and presence of symptoms among *H. pylori* infected children.
- 8- Antral nodularity was more common in *cagA*-positive and in *vacA* s1 positive samples.
- 9- Among virulence factors, *cagA* and *vacA* s1 are correlated with some clinical presentations and histopathological findings
- 10- We could not detect statistical association between the *babA2* status and the severity of the endoscopic and histopathological picture.
- 11- The triple positive (simultaneous presence of *vacA* s1, *cagA*, and *babA2*) was found in 5 of our symptomatic cases and not found in the asymptomatic children.

CONCLUSION

1. The most frequent gastrointestinal complaint in children referred for endoscopy is hematemesis, and *H. pylori* has an important role. However, neither of abdominal pain nor vomiting is associated with *H. pylori*.
2. Nodular gastritis is the most common endoscopic findings of *H. pylori* infection, and most probably associated with *cagA* and *s1* allele positivity.
3. Antral predominant gastritis seems to be the main pattern of gastritis in *H. pylori* positive cases.
4. There is a statistically significant difference between *H. pylori* infected and non infected groups as regard the severity, activity and presence of lymphoid follicles.
5. It seems that hematemesis and abdominal pain are associated with severe inflammation in antral samples.
6. It would appear that there is a high prevalence of *babA2*, *cagA*, *vacA* *s1*, *s1/m1*, and *s2/m2* among symptomatic *H. pylori* positive patients especially those complaining of abdominal pain and hematemesis.
7. We had confirmed, a significant correlation between the severity of histological changes and the presence of the *vacA* *s1* and *cagA* in the *H. pylori* genome.
8. The present study could not detect any association between *babA2* and the severity of histopathological or endoscopic changes.

RECOMMENDATION

- 1- The critical period of *H. pylori* acquisition is in childhood so, genotyping at childhood is important in future policies for the identification of those at risk of severe disease and will help in planning of eradication programme.
- 2- The relation between the genotypes of causative strain and clinical outcome should be considered in different geographic regions in order to make a true estimation of prognosis.
- 3- Further studies are needed to clarify the exact pathogenicity role of babA2 gene also with the use of animal models and with in vitro studies.

REFERENCES

1. Ruuws EAJ, Langengerg W, Houthoff HJ, Zanen HC, Tytgat GN. Campylobacter pyloridis associated chronic antral gastritis. *Gastroenterol* 1988; 94: 33-40.
2. Drumm B, Shermann P, Cutz E, Karmali M. Association of campylobacter pylori on gastric mucosa with antral gastritis in children. *N Engl J Med* 1987; 316. 1557-61.
3. Warren J, Marshall B. Unidentified curved bacillus on gastric epithelium in chronic active gastritis. *Lancet* 1983; I: 1273-5.
4. Veldhuyzen van Zanten S, Shermann p. A systemic overview of helicobacter pylori infection as the cause of gastritis, duodenal ulcer, gastric cancer, non-ulcer dyspepsia: applying eight diagnostic criteria in establishing causation. *Can Med Assoc J* 1994; 150:177.
5. Suerbaum S, Achtman M. Helicobacterpylori: recombination , population structure and human migrations. *Int J Med Microbial* 2004; 294: 133-9.
6. Yamaoka Y, Kato M, asaka M. Geographic differences in gastric cancer incidence can be explained by differences between helicobacter pylori strains. *Inter Med* 2008; 47:1077-83.
7. Wroblewski LE, Peek RM, Wilson KT. Helicobacter pylori and gastric cancer: factors that modulate disease risk. *Clin Microbial Rev* 2010; 23:713-39.
8. Yamoaka Y, Kodama T, Gutierrez O, kim G, Kashima K and Graham ay. Relationship between helicobacter pylori ice, cagA, and vacA status and clinical outcome: studies in four different countries. *J Clin Microbial* 1999; 37:2274-9.
9. Suzuki T, Matsuo K, Sawaki A, Ito H, Hirose K, Wakai K, et al. Systematic review and metaanalysis : importance of cagA status for successful eradication of helicobacter pylori infection. *Aliment Phamacol The* 2006;24(2):273-80.
10. Sugimoto m, yamaoka Y. Virulence factor genotypes of helicobacter pylori affect cure rates of eradication therapy. *Arch Immunol Ther Exp (Warsz)* 2009;57:45-56.
11. Mendall MA, Pajares-Garcia. Epidemiology and transmission of helicobacter pylori. *Curr opin gastroenterol* 1995; 11(1): 1-4.
12. Logan rph, hiscal am. Epidemiology of helicobacter pylori infection. *Curr opin gastroenterol* 1996; 12(1): 1-5.
13. Kung JSL, hob, chan sh. Biotyping of campylobacter pylori. *J med microbial* 1989; 29: 203-6.
14. Megraud F. microbiological characteristics of characteristics of campylobacter pylori. *Eur j gastroenterol hepatol* 1989; 1:5-12.

15. Linz B, Balloux F, Moodley Y, Manica A, Liu H, Roumagnac P, et al. An African origin for the intimate association between humans and *Helicobacter pylori*. *Nature* 2007; 445(7130):915-8.
16. Salles N, Megraud F. Current management of *Helicobacter pylori* infections in the elderly. *Expert Rev Anti Infect Ther* 2007; 5(5):845-56.
17. Rowland M, Daly L, Vaughan M, Higgins A, Bourke B, Drumm B. Age-specific incidence of *Helicobacter pylori*. *Gastroenterology* 2006; 130(1):65-72.
18. 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(6):1348-55.
19. Mitchell H, Megraud F. Epidemiology and diagnosis of *Helicobacter pylori* infection. *Helicobacter* 2002; 7 (Suppl 1):8-16.
20. Bardhan PK. Epidemiological features of *Helicobacter pylori* infection in developing countries. *Clin Infect Dis* 1997; 25(5):973-8.
21. Kawakami E, Machado RS, Ogata SK, Langner M. Decrease in prevalence of *Helicobacter pylori* infection during a 10-year period in Brazilian children. *Arq Gastroenterol* 2008; 45(2):147-51.
22. Omran M. Prevalence of *helicobacter pylori* in the first year of life. Master Thesis. Faculty of Medicine, University of Alexandria, Alexandria, Egypt; 2003.
23. Sherif M, Mohran Z, Fathy H, Rockabrand D, Rozmajzl PJ, Frenck RW. Universal high-level primary metronidazole resistance in *Helicobacter pylori* isolated from children in Egypt. *J Clin Microbiol* 2004; 42: 4832-4.
24. Mohammad MA, Hussein L, Coward A, Jackson SJ. Prevalence of *Helicobacter pylori* infection among Egyptian children: impact of social background and effect on growth. *Public Health Nutr* 2008; 11(3):230-6.
25. Georgopoulos SD, Mentis AF, Spiliadis CA, Tzouvelekis LS, Tzelepi E, Moshopoulos A, et al. *Helicobacter pylori* infection in spouses of patients with duodenal ulcers and comparison of ribosomal RNA gene patterns. *Gut* 1996; 39:634-8.
26. Schutze K, Hentschel E, Dragosics B, Hirschl AM. *Helicobacter pylori* reinfection with identical organisms: transmission by the patients' spouses. *Gut* 1995; 36:831-3.
27. Mitchell HM, Hazell SL, Kolesnikow T, Mitchell J, Frommer D. Antigen recognition during progression from acute to chronic infection with a *cagA*-positive strain of *Helicobacter pylori*. *Infect Immun* 1996; 64:1166-72.
28. Chalkauskas H, Kersulyte D, Cepulienė I, Urbonas V, Ruzeviciene D, Barakauskiene A, et al. Genotypes of *Helicobacter pylori* in lithuanian families. *Helicobacter* 1998; 3: 296-302.

References

29. Leung WK, Sung JJ, Ling TK, Siu KL, Cheng AF. Use of chopsticks for eating and *Helicobacter pylori* infection. *Dig Dis Sci* 1999; 44:1173-6.
30. Li C, Musich PR, Ha T, Ferguson DA Jr, Patel NR, Chi DS, et al. High prevalence of *Helicobacter pylori* in saliva demonstrated by a novel PCR assay. *J Clin Pathol* 1995; 48: 662-6.
31. Li C, Ha T, Ferguson DA Jr, Chi DS, Zhao R, Patel NR, et al. A newly developed PCR assay of *H. pylori* in gastric biopsy, saliva, and feces. Evidence of high prevalence of *H. pylori* in saliva supports oral transmission. *Dig Dis Sci* 1996; 41: 2142-9.
32. Namavar F, Roosendaal R, Kuipers EJ, de Groot P, van der Bijl MW, Peña AS, et al. Presence of *Helicobacter pylori* in the oral cavity, oesophagus, stomach and faeces of patients with gastritis. *Eur J Clin Microbiol Infect Dis* 1995; 14:234-7.
33. Shimada T, Ogura K, Ota S, Terano A, Takahashi M, Hamada E, et al. Identification of *Helicobacter pylori* in gastric specimens, gastric juice, saliva, and faeces of Japanese patients. *Lancet* 1994; 343:1636-7.
34. Mapstone NP, Lynch DA, Lewis FA, Axon AT, Tompkins DS, Dixon MF, et al. Identification of *Helicobacter pylori* DNA in the mouths and stomachs of patients with gastritis using PCR. *J Clin Pathol* 1993; 46: 540-3.
35. Gramley WA, Asghar A, Frierson HF Jr, Powell SM. Detection of *Helicobacter pylori* DNA in fecal samples from infected individuals. *J Clin Microbiol* 1999; 37:2236-40.
36. van Zwet AA, Thijs JC, Kooistra-Smid AM, Schirm J, Snijder JA. Use of PCR with feces for detection of *Helicobacter pylori* infections in patients. *J Clin Microbiol* 1994;32:1346-8.
37. Webb PM, Knight T, Newell DG, Elder JB, Forman D. *Helicobacter pylori* transmission: evidence from a comparison with hepatitis A virus. *Eur J Gastroenterol Hepatol* 1996;8:439-41.
38. Hulten K, Han SW, Enroth H, Klein PD, Opekun AR, Gilman RH, et al. *Helicobacter pylori* in the drinking water in Peru. *Gastroenterology* 1996; 110:1031-5.
39. Fan XG, Chua A, Li TG, Zeng QS. Survival of *Helicobacter pylori* in milk and tap water. *J Gastroenterol Hepatol* 1998; 13: 1096-8.
40. Dubois A, Berg DE, Incecik ET, Fiala N, Heman-Ackah LM, Perez-Perez GI, et al. Transient and persistent experimental infection of nonhuman primates with *Helicobacter pylori*: implications for human disease. *Infect Immun* 1996;64:2885-91.
41. Fox JG. Non-human reservoirs of *Helicobacter pylori*. *Aliment Pharmacol Ther* 1995; 9(Suppl 2):93-103.

References

42. Handt LK, Fox JG, Dewhirst FE, Fraser GJ, Paster BJ, Yan LL, et al. *Helicobacter pylori* isolated from the domestic cat: public health implications. *Infect Immun* 1994; 62: 2367-74.
43. Axon AT. Disinfection of endoscopic equipment. *Baillieres Clin Gastroenterol* 1991; 5: 61-77.
44. Fantry GT, Zheng QX, James SP. Conventional cleaning and disinfection techniques eliminate the risk of endoscopic transmission of *Helicobacter pylori*. *Am J Gastroenterol* 1995; 90: 227-32.
45. Mohamed EI. *Helicobacter pylori* infection in childhood: effect on growth. Master Thesis. Faculty of Medicine, University of Alexandria, Alexandria, Egypt; 2004.
46. Toloa V. *Helicobacter pylori* in pediatric non ulcer dyspepsia. Pathogen or commensal? *Am J Gastroenterol* 1995; 30: 865-8.
47. Glassman MS, Schwartz SM, Medow MS, Beneck D, Halata M, Berezin S, et al . *Campylobacter pylori* related gastrointestinal disease in children. *Dig Dis Sci* 1989; 34: 1501-4.
48. Kusters JG, van Vliet AH, Kuipers EJ. Pathogenesis of *Helicobacter pylori* infection. *Clin Microbiol Rev* 2006;19(3):449-90.
49. Granstrom 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(2):468-70.
50. Malaty HM, Graham DY, Wattigney WA, Srinivasan SR, Osato M, Berenson GS. Natural history of *Helicobacter pylori* infection in childhood: 12-year follow-up cohort study in a biracial community. *Clin Infect Dis* 1999;28(2):279-82.
51. Perz-Perz GL, Sack RB, Reid R, Santosham M, Croll J, Blaser MJ. Transient and persistent *helicobacter pylori* colonization in native American children. *J Clin Microbial* 2003; 41:2401-7.
52. Talley NJ. *Helicobacter pylori* and non-ulcer dyspepsia. *Scand J Gastroenterol Suppl* 1996; 220:19.
53. McColl K, Murray L, El-Omar E, Dickson A, El-Nujumi A, Wirz A, et al. Symptomatic benefit from eradicating *Helicobacter pylori* infection in patients with nonulcer dyspepsia. *N Engl J Med* 1998; 339: 1869-74.
54. Blum AL, Talley NJ, O'Moráin C, van Zanten SV, Labenz J, Stolte M, et al. Lack of effect of treating *Helicobacter pylori* infection in patients with nonulcer dyspepsia. *N Engl J Med* 1998; 339:1875-81.
55. Moayyedi P, Soo S, Deeks J, Delaney B, Harris A, Innes M, et al. Eradication of *Helicobacter pylori* for non-ulcer dyspepsia. *Cochrane Database Syst Rev* 2001; 1:1-39.

References

56. Tally Nj, Hunt RH. What role does helicobacter pylori play in dyspepsia and nonulcer dyspepsia? Arrangements for and against h pylori being associated with dyspeptic symptoms. *Gastroenterology* 1997; 113:67-77.
57. Ford AC, Qume M, Moyyedi P, Arents NI, Lassen AT, Logan RF, et al. Helicobacter pylori "test and treat" or endoscopy for managing dyspepsia:an individual patient data meta-analysis. *Gastroenterology* 2005; 128:1838-44.
58. Meining A, Kiel G, Stolte M. Changes in Helicobacter pylori-induced gastritis in the antrum and corpus during and after 12 months of treatment with ranitidine and lansoprazole in patients with duodenal ulcer disease. *Aliment Pharmacol Ther* 1998;12:735-40.
59. Moayyedi P, Bardhan C, Young L, Dixon MF, Brown L, Axon AT. Helicobacter pylori eradication does not exacerbate reflux symptoms in gastroesophageal reflux disease. *Gastroenterology* 2001;121:1120-6.
60. Schwizer W, Thumshirn M, Dent J, Guldenschuh I, Menne D, Cathomas G, et al. Helicobacter pylori and symptomatic relapse of gastro-oesophageal reflux disease: a randomised controlled trial. *Lancet* 2001;357:1738-42.
61. Ruiz B, Correa P, Fontham ETH, Ramakrishnan T. Antral atrophy, Helicobacter pylori colonization, and gastric Ph. *Am J Clin Pathol* 1996;105:96-101.
62. Prieto G, Polanco I, Larrauri J, Rota L, Lama R, Carrasco S. Helicobacter pylori infection in children: clinical, endoscopic, and histologic correlations. *J Pediatr Gastroenterol Nutr* 1992;14(4):420-5.
63. Glassman MS, Dallal S, Berezin SH, Bostwick HE, Newman LJ, Perez-Perez GI, et al. Helicobacter pylori-related gastroduodenal disease in children. Diagnostic utility of enzyme-linked immunosorbent assay. *Dig Dis Sci* 1990;35(8):993-7.
64. Drumm B, O'Brien A, Cutz E, Sherman P. Campylobacter pyloridis-associated primary gastritis in children. *Pediatrics* 1987;80(2):192-5.
65. Shalaby S. Upper gastrointestinal bleeding in children an etiological study. Master Thesis. Faculty of Medicine, University of Alexandria, Alexandria, Egypt; 2004.
66. Blecker U, Renders F, Lanciers S, Vandenplas Y. Syncopes leading to the diagnosis of a Helicobacter pylori positive chronic active haemorrhagic gastritis. *Eur J Pediatr* 1991;150(8):560-1.
67. American Academy of Pediatrics Subcommittee on Chronic Abdominal Pain. Chronic abdominal pain in children. *Pediatrics* 2005;115(3):812-5.
68. McArthur C, Saunders N, Feldman W. Helicobacter pylori, gastroduodenal disease, and recurrent abdominal pain in children. *JAMA* 1995; 273:729.
69. Hardikar W, Feekery C, Smith A, Oberklaid F, Grimwood K. Helicobacter pylori and recurrent abdominal pain in children. *J Pediatr Gastroenterol Nutr* 1996; 22:148.

References

70. De Giacomo C, Fiocca R, Villani L, Lisato L, Licardi G, Diegoli N, et al. *Helicobacter pylori* infection and chronic gastritis: clinical, serological, and histologic correlations in children treated with amoxicillin and colloidal bismuth subcitrate. *J Pediatr Gastroenterol Nutr* 1990; 11(3):310-6. *J Pediatr Gastroenterol Nutr* 1992; 11: 310-6.
71. Chong SK, Lou Q, Asnicar MA, Zimmerman SE, Croffie JM, Lee CH, et al. *Helicobacter pylori* infection in recurrent abdominal pain in childhood: comparison of diagnostic tests and therapy. *Pediatrics* 1995; 96(2 Pt 1):211-5.
72. Blecker U, Vandenplas Y. *Helicobacter pylori* seropositivity in symptom-free children. *Lancet* 1992; 339(8808):1537.
73. van der Meer SB, Forget PP, Loffeld RJ, Stobberingh E, Kuijten RH, Arends JW. The prevalence of *Helicobacter pylori* serum antibodies in children with recurrent abdominal pain. *Eur J Pediatr* 1992;151(11):799-801.
74. Heldenberg D, Wagner Y, Heldenberg E, Keren S, Auslaender L, Kaufshtein M, et al. The role of *Helicobacter pylori* in children with recurrent abdominal pain. *Am J Gastroenterol* 1995;90(6):906-9.
75. Hardikar W, Feekery C, Smith A. *Helicobacter pylori* and recurrent abdominal pain in children. *J Pediatr Gastroenterol Nutr* 1996; 22(2): 148-52.
76. Macarthur C, Saunders N, Feldman W. *Helicobacter pylori*, gastroduodenal disease, and recurrent abdominal pain in children. *JAMA* 1995;273(9):729-34.
77. Perri F, Pastore M, Leandro G, Clemente R, Ghooos Y, Peeters M, et al. *Helicobacter pylori* infection and growth delay in older children. *Arch Dis Child* 1997; 77: 46-9.
78. Sood MR, Joshi S, Akobeng AK, Mitchell J, Thomas AG. Growth in children with *Helicobacter pylori* infection and dyspepsia. *Arch Dis Child* 2005; 90: 1025-8.
79. Isomoto H, Ueno H, Nishi Y, Wen C, Nakazato M, Kohno S. Impact of *Helicobacter pylori* infection on ghrelin and various neuroendocrine hormones in plasma. *World J Gastroenterol* 2005; 11: 1644–8.
80. Cummings DE, Shannon MH. Roles for ghrelin in the regulation of appetite and body weight. *Arch Surg* 2003; 138: 389–96.
81. Kostaki M, Fessatou S, Karpathios T. Refractory iron-deficiency anemia due to silent *Helicobacter pylori* gastritis in children. *Eur J Pediatr* 2003; 162: 177-9.
82. Choe YH, Kim SK, Hong YC. The relationship between *Helicobacter pylori* infection and iron deficiency: seroprevalence study in 937 pubescent children. *Arch Dis Child* 2003; 88: 178.
83. 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.

References

84. Gasbarrini A, Carloni E, Gasbarrini GM, Chisholm SA. *Helicobacter pylori* and extragastric diseases-other *Helicobacters*. *Helicobacter* 2004; 9(Suppl. 1):57-66.
85. Oleastro M, Santos A, Cordeiro R, Nunes B, Mégraud F, Ménard A. Clinical relevance and diversity of two homologous genes encoding glycosyltransferases in *Helicobacter pylori*. *J Clin Microbiol* 2010;48:2885-91.
86. Tomb JF, White O, Kerlavage AR, Clayton RA, Sutton GG, Fleischmann RD, et al. The complete genome sequence of the gastric pathogen *Helicobacter pylori*. *Nature* 1997;388:539-47.
87. Alm RA, Ling LS, Moir DT, King BL, Brown ED, Doig PC, et al. Genomic-sequence comparison of two unrelated isolates of the human gastric pathogen *Helicobacter pylori*. *Nature* 1999; 397:176-80.
88. Falush D, Kraft C, Taylor NS, Correa P, Fox JG, Achtman M, et al. Recombination and mutation during long-term gastric colonization by *Helicobacter pylori*: estimates of clock rates, recombination size, and minimal age. *Proc Natl Acad Sci USA* 2001; 98: 15056-61.
89. Suerbaum S, Smith JM, Bapumia K, Morelli G, Smith NH, Kunstmann E, et al. Free recombination within *Helicobacter pylori*. *Proc Natl Acad Sci USA* 1998; 95: 12619-24.
90. Mobley HLT. *Helicobacter pylori* urease. In: Achtman M, Suerbaum S (eds). *Helicobacter pylori: molecular and cellular biology*. Wymondham, UK: Horizon Scientific Press; 2001. 155-70.
91. Bujanover Y, Reif S, Yahav J. *Helicobacter pylori* and peptic disease in the pediatric patient. *Pediatr Clin North Am* 1996;43(1):213-34.
92. Hazell SL, Evans DJ Jr, Graham DY. *Helicobacter pylori* catalase. *J Gen Microbiol* 1991;137(1):57-61.
93. Josenhans C, Suerbaum S. *Helicobacter* motility and chemotaxis. In: Achtman M, Suerbaum S (eds). *Helicobacter pylori: molecular and cellular biology*. Wymondham, UK: Horizon Scientific Press; 2001. 171-84.
94. Gerhard M, Hirno S, Wadstrom T. *Helicobacter pylori*, an adherent pain in the stomach. In: Achtman M, Suerbaum S (eds). *Helicobacter pylori: molecular and cellular biology*. Wymondham, UK: Horizon Scientific Press; 2001. 185-206.
95. Ilver D, Arnqvist A, Ogren J, Frick IM, Kersulyte D, Incecik ET, et al. *Helicobacter pylori* adhesin binding fucosylated histo-blood group antigens revealed by retagging. *Science* 1998; 279: 373-7.
96. Falk PG, Bry L, Holgersson J, Gordon JJ. Expression of a human alpha-1, 3/4-fucosyltransferase in the pit cell lineage of FVB/N mouse stomach results in production of Leb-containing glycoconjugates: a potential transgenic mouse model for studying *Helicobacter pylori* infection. *Proc Natl Acad Sci USA* 1995; 92:1515-9.

References

97. Guruge JL, Falk PG, Lorenz RG, Dans M, Wirth H P, Blaser MJ, et al. Epithelial attachment alters the outcome of *Helicobacter pylori* infection. *Proc Natl Acad Sci USA*. 1998; 95(7):3925-30.
98. Montecucco C, Papini E, de Bernard M. *Helicobacter pylori* VacA vacuolating cytotoxin and HP-Nap neutrophil activating protein. In: Achtman M, Suerbaum S (eds). *Helicobacter pylori: molecular and cellular biology*. Wymondham, UK: Horizon Scientific Press; 2001. 245-63.
99. De Bernard M, Papini E, de Filippis V, Gottardi E, Telford J, Manetti R, et al. Low pH activates the vacuolating toxin of *Helicobacter pylori* which becomes acid and pepsin resistant. *Biol Chem* 1995; 270: 23937-40.
100. Szabo I, Brutsche S, Tombola F, Moschioni M, Satin B, Telford JL, et al. Formation of anion-selective channels in the cell plasma membrane by the toxin VacA of *Helicobacter pylori* is required for its biological activity. *EMBO J* 1999; 18: 5517-27.
101. Galmiche A, Rassow J, Doye A, Cagnol S, Chambard JC, Contamin S, et al. The N-terminal 34 kDa fragment of *Helicobacter pylori* vacuolating cytotoxin targets mitochondria and induces cytochrome c release. *EMBO J* 2000; 19: 6361-70.
102. Salama NR, Otto G, Tompkins L, Falkow S. Vacuolating cytotoxin of *Helicobacter pylori* plays a role during colonization in a mouse model of infection. *Infect Immun* 2001; 69: 730-6.
103. Atherton JC, Cao P, Peek RM Jr, Tummuru MK, Blaser MJ, Cover TL. Mosaicism in vacuolating cytotoxin alleles of *Helicobacter pylori*, association of specific vacA types with cytotoxin production and peptic ulceration. *J Biol Chem* 1995; 270: 17771-7.
104. Atherton JC, Peek RM, Tham KT, Cover TL, Blaser MJ. Clinical and pathological importance of heterogeneity in vacA, the vacuolating cytotoxin gene of *Helicobacter pylori*. *Gastroenterology* 1997; 112: 92-9.
105. Ji X, Fernandez T, Burrone D, Pagliaccia C, Atherton JC, Reyrat JM, et al. Cell specificity of *Helicobacter pylori* cytotoxin is determined by a short region in the polymorphic midregion. *Infect Immun* 2000; 68:3754-7.
106. Covacci A, Censini S, Bugnoli M, Petracca R, Burrone D, Macchia G, et al. Molecular characterization of the 128-kDa immunodominant antigen of *Helicobacter pylori* associated with cytotoxicity and duodenal ulcer. *Proc Natl Acad Sci USA* 1993; 90: 5791-5.
107. Peek RM, Miller GG, Tham KT, Perez-Perez GI, Zhao X, Atherton JC, et al. Heightened inflammatory response and cytokine expression in vivo to cagA* *Helicobacter pylori* strains. *Lab Invest* 1995; 73: 760-70.
108. Akopyants NS, Clifton SW, Kersulyte D, Crabtree JE, Youree BE, Reece CA, et al. Analyses of the cag pathogenicity island of *Helicobacter pylori*. *Mol Microbiol* 1998; 28: 37-53.

References

109. Qiao W, Hu JL, Xiao B, Wu KC, Peng DR, Atherton JC, et al. CagA and vacA genotype of *Helicobacter pylori* associated with gastric diseases in Xi'an area. *World J Gastroenterol* 2003; 9: 1762-6.
110. Wen S, Moss SF. *Helicobacter pylori* virulence factors in gastric carcinogenesis. *Cancer Lett* 2009; 282: 1-8.
111. Figura N, Guglielmetti P, Rossolini A, Barberi A, Cusi G, Musmanno RA, et al. Cytotoxin production by *Campylobacter pylori* strains isolated from patients with peptic ulcers and from patients with chronic gastritis only. *J Clin Microbiol* 1989; 27: 225-6.
112. Jackson S, Beck PL, Pineo GF, Poon MC. *Helicobacter pylori* eradication: novel therapy for immune thrombocytopenic purpura? A review of the literature. *Am J Hematol* 2005; 78: 142-50.
113. Suerbaum S, Michetti P. *Helicobacter pylori* infection. *N Eng J Med* 2002; 347: 1175-86.
114. Torres J, Pérez-Pérez G, Goodman KJ, Atherton JC, Gold BD, Harris PR, et al. A comprehensive review of the natural history of *helicobacter pylori* infection in children. *Arch Med Res* 2000;31(5):431-69.
115. Black DD, Haggitt RC, Whittington PF. Gastroduodenal endoscopic-histologic correlation in pediatric patients. *J Pediatr Gastroenterol Nutr* 1988;7(3):353-8.
116. Dixon MF, Genta RM, Yardley JH, Correa P. Classification and grading of gastritis. The updated Sydney System. International Workshop on the Histopathology of fmGastritis, Houston 1994. *Am J Surg Pathol* 1996;20(10):1161-81.
117. Price AB. The Sydney system: histological division. *J Gastreterol Hepatol* 1991; 6: 209-22.
118. Drumm B. *Helicobacter pylori* in the pediatric patient. *Gastroenterol Clin North Am* 1993;22(1):169-82.
119. Kuipers EJ, Uytterlinde AM, Pena AS, Hazenberg HJ, Bloemena E, Lindeman J, et al. Increase of *Helicobacter pylori*-associated corpus gastritis during acid suppressive therapy: implications for long-term safety. *Am J Gastroenterol* 1995;90(9):1401-6.
120. El-Omar EM, Oien K, El-Nujumi A, Gillen D, Wirz A, Dahill S, et al. *Helicobacter pylori* infection and chronic gastric acid hyposecretion. *Gastroenterology* 1997;113(1):15-24.
121. Verdu EF, Armstrong D, Fraser R, Viani F, Idstrom JP, Cederberg C, et al. Effect of *Helicobacter pylori* status on intragastric pH during treatment with omeprazole. *Gut* 1995;36(4):539-43.
122. Holtmann G, Cain C, Malfertheiner P. Gastric *helicobacter pylori* infection accelerates healing of reflux esophagitis during treatment with the proton pump inhibitor pantoprazole. *Gastroenterology* 1999; 117:11-6.

References

123. El-Omar EM, Carrington M, Chow WH, McColl KE, Bream JH, Young HA, et al. Interleukin-1 polymorphisms associated with increased risk of gastric cancer. *Nature* 2000; 404: 398–402.
124. Ernst PB, Gold BD. The disease spectrum of *Helicobacter pylori*: the immunopathogenesis of gastroduodenal ulcer and gastric cancer. *Annu Rev Microbiol* 2000; 54: 615–40.
125. Kuipers EJ. Review article: exploring the link between *Helicobacter pylori* and gastric cancer. *Aliment Pharmacol Ther*. 1999; 13: 3–12.
126. Kuipers EJ, Thijs JC, Festen HP. The prevalence of *Helicobacter pylori* in peptic ulcer disease. *Aliment Pharmacol Ther* 1995; 9(Suppl. 2): 59–69.
127. Soll AH. *Gastrointestinal disease: pathophysiology, diagnosis, management*. Philadelphia: Wound Saunders; 1993.
128. Nomura A, Stemmermann GN, Chyou PH, Perez-Perez GI, Blaser MJ. *Helicobacter pylori* infection and the risk for duodenal and gastric ulceration. *Ann Intern Med* 1994; 120: 977–81.
129. Cullen DJE, Collins J, Christiansen KJ, Epis J, Warren JR, Cullen KJ. Abstract from the digestive diseases week. *Gastroenterology* 1993; 104: A60.
130. Veldhuyzen van Zanten, SOJ, Dixon MF, Lee A. The gastric transitional zones: neglected links between gastroduodenal pathology and *Helicobacter* ecology. *Gastroenterology* 1999; 116:1217–29.
131. Sonnenberg A. Temporal trends and geographical variations of peptic ulcer disease. *Aliment Pharmacol Ther* 1995; 9: 3–12.
132. Sonnenberg A. The US temporal and geographic variations of diseases related to *Helicobacter pylori*. *Am J Public Health* 1993; 83:1006–10.
133. Crowe SE, Alvarez L, Sherman PM, Jin Y, Dytoc M. Expression of interleukin-8 and CD54 by human gastric epithelium after *H. pylori* infection in vitro. *Gastroenterology* 1995; 108: 65-74.
134. Borody TJ, George LL, Brandl S, Andrews P, Ostapowicz N. *Helicobacter pylori*-negative duodenal ulcer. *Am J Gastroenterol* 1991; 86: 1154-7.
135. Nensey YM, Schubert TT, Bologna SD, Ma CK. *Helicobacter pylori*-negative duodenal ulcer. *Am J Med* 1991; 91: 15-8.
136. Malfertheiner P, Megraud F, O'Morain C, Bazzoli F, El Omar E, Graham D, et al. Current concepts in the management of *Helicobacter pylori* infection: the Maastricht III consensus report. *Gut* 2007; 56(6):772-81.
137. Drumm B, Day AS, Gold B, Gottrand F, Kato S, Kawakami E, et al. *Helicobacter pylori* and peptic ulcer: Working Group Report of the second World Congress of Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr* 2004; 39 (Suppl 2):S626-31.

References

138. Koletzko S, Jones NL, Goodman KJ, Gold B, Rowland M, Cadranel S, et al. Evidencebased guidelines from ESPGHAN and NASPGHAN for *Helicobacter pylori* infection in children. *J Pediatr Gastroenterol Nutr* 2011; 53(2):230-43.
139. Hassall E, Dimmick JE. Unique feature of *helicobacter pylori* disease in children *Dig Dis Sci* 1991; 36: 417-23.
140. Bujanover Y, Kanikoff F, Baratz M. Nodular gastritis and *helicobacter pylori*. *J Pediatr Gastroenterol Nutr* 1990; 11: 41-4.
141. Gray SF, Wyatt JJ, Rathbone BJ. Simplified techniques for identifying *campylobacter pyloridis*. *J Clin Pathol* 1986; 39: 1279.
142. Yardly JH, Paull H. *Campylobacter pylori*: a newly recognized infectious agent in the gastrointestinal tract. *Am J Surg Pathol* 1988; 12(Suppl.1):89.
143. Genta RM, Hammer HW, Ghaham DY. Gastric lymphoid follicles in *helicobacter pylori* infection: frequency. Distribution and response to triple therapy. *Hum Pathol* 1993; 24: 577-83.
144. Sternberg SS, Antonili DA, Cater D. Diagnostic surgical pathology. 3rded. Philadelphia: Lippincott Williams & Wilkins; 1999.
145. Riddel RH, Goldman H, Ransohoff DF. Dysplasia in inflammatory bowel disease. *Hum Pathol* 1983; 14: 16-20.
146. Genta RM, Lew GM, Graham Dy. Changes in the gastric mucosa following eradication of *Helicobacter pylori*. *Mod Pathol* 1993; 6: 281-9.
147. Witteman EM, Mravunac M, Becx MJ. Improvement of gastric inflammation and resolution of epithelial damage one year after eradication of *helicobacter pylori*. *J Clin Pathol* 1995; 48: 250-6.
148. Craanen ME, Dekker W, Block P, Ferwerda J, Tytgat GN. Intestinal metaplasia and *helicobacter pylori*: an endoscopic bioptic study of the gastric antrum. *Gut* 1992; 33:16-20.
149. Karnes WE, Smaloff IM, Siurala M, Kekki M, Sipponen P, Kim SW, et al. Positive serum antibody and negative tissue staining for *helicobacter pylori* in subjects with atrophic body gastritis. *Gastroenterology* 1991; 101: 167-74.
150. Correa P. Chronic gastric a clinic pathological classification. *Am J Gastroenterol* 1988; 83: 504-9.
151. Parsonnet J, Freidman GD, Vandersteen DP, Chang Y, Vogelmann JH, Orentreich N, et al. *Helicobacter pylori* infection and the risk of gastric carcinoma. *N Engl J Med* 1991; 325: 1127-31.
152. Recavarren-Arce S, León-Barúa R, Cok J, Berendson R, Gilman RH, Ramírez-Ramos AR. *Helicobacter* and progressive gastric pathology that predisposes to gastric cancer. *Scand J Gastronterol* 1991; 181: 1-7.

153. Villako K, Kekki M, Tamm A, Savisaar E. Development and progression of chronic gastritis in the antrum and body mucosa: results of long term follow-up examinations. *Ann Clin Res* 1986; 18: 121-3.
154. Caygill CP. Epidemiology relating N-nitroso compounds to human cancer. *Eur J Cancer Prev* 1996; 5(1):125-30.
155. Xu GP, SO PJ, Reed PI. Hypothesis on the relationship between gastric cancer and intragastric nitrosation: n-nitrosamines in gastric juice of subjects from a high risk area for gastric cancer and the inhibition of N-nitrosamine of formalin by fruit juices. *Eur J Cancer Prev* 1993; 25-36.
156. Chen VW, Abu-Elyazed RR, Zvala DE, Haenszel W, Ktsanes VK, Rice J, et al. Risk factor of gastric precancerous lesion in high risk Columbian population: II. Nitrate and nitrite. *Nutr Cancer* 1990; 13: 67-72.
157. Negrini R, Savio A, Poiesi C, Appelmelk BJ, Buffoli F, Paterlini A, et al. Antigenic mimicry between helicobacter pylori and gastric mucosa in the pathogenesis of body atrophic gastritis. *Gastroenterology* 1996; 111: 655-65.
158. Chen XY, Rene-Hulst WM, Bruno MJ, Ende A, Xiao Sh, Tytgat D, et al. Interobserver variation on the histopathological scoring of helicobacter pylori related gastritis. *J Clin Pathol* 1999; 52: 612-5.
159. Yukihiko T, Hiroyuki SH, Takatoshi H, Akihiro K, Atsuo T, Kiyosi O. Density of helicobacter pylori infection evaluated semiquantitatively in gastric cancer. *J Clin Gastroenterology* 2000; 31: 217-21.
160. Misiewicz JJ. The Sydney system a new classification of gastritis. *Introduction J Gastroenterol Hepatol* 1991; 6: 207-8.
161. Apley J. The child with recurrent abdominal pain. *Pediatr Clin North Am* 1967; 14: 63-72.
162. Kauser, F., hussain, M,-A., Ahmed, I., et al (2005): comparing genomes of *Helicobacter pylori* strains from the high-altitude desert of ladakh, india. *J. Clin. Microbiol.*, 43,1538-1545.
163. Shi-Ying Xuan, Ning Li, Xin Qiang, Rong-Rong Zhou, Yong-Xin Shi, Wen-Jie Jiang. *Helicobacter* infection in hepatocellular carcinoma tissue. *World J Gastroenterol* 2006 April 21; 12(15):2335-2340.
164. Chattopadhyay S, Patra R, Ramamurthy T, Chowdhury A, Santra A, Dhali G.K. et al. Multiplex PCR assay for rapid detection and genotyping of *Helicobacter pylori* directly from biopsy specimens. *J Clin Microbiol* 2004, 24, 2821-24.
165. Sheu BS, Sheu SM, Yang HB, Huang AH, Wu JJ. Host gastric lewis expression demtermine the bacterial densty of *Helicobacter pylori* in babA2 genopositive infection *Gut* 2003;52:927-932.
166. Kotz S, Balakrishnan N, Read CB, Vidakovic B. *Encyclopedia of statistical sciences*. 2nd ed. Hoboken, N.J.: Wiley-Interscience; 2006.

References

167. Kirkpatrick LA, Feeney BC. A simple guide to IBM SPSS statistics for version 20.0. Student ed. Belmont, Calif.: Wadsworth, Cengage Learning; 2013.
168. Peterson WL, Graham DY. *Helicobacter pylori*. In: Feldman-Sleiseneger MH (ed). Sleiseneger and Ford trans gastrointestinal and liver disease: pathophysiology, diagnosis, management. 8thed. Philadelphia: WB Saunders Company; 2006. 732-49.
169. Queiroz DM, Rocha GA, Mendes EN, Carvalho AS, Barbosa AJ, Oliveira CA, et al. Differences in distribution and severity of *Helicobacter pylori* gastritis in children and adults with duodenal ulcer disease. *J Pediatr Gastroenterol Nutr* 1991; 12:178-81.
170. Cave DR. How is *Helicobacter pylori* transmitted? *Gastroenterology* 1997; 113: S9-4.
171. Huang IF, Wu TC, Wang KS, Hwang B, Hsieh KS. Upper gastrointestinal endoscopy in children with upper gastrointestinal bleeding. *J Chin Med Assoc* 2003; 66(5):271-5.
172. Houben CH, Chiu WY, Lau JY, Lee KH. Duodenal ulcer dominates acute upper gastrointestinal tract bleeding in childhood: A 10-year experience from Hong Kong. *J Dig Dis* 2008; 9; 199-203.
173. Nijevitch AA, Shcherbakov PL. *Helicobacter pylori* and gastrointestinal symptoms in school children in Russia. *J Gastroenterol Hepatol* 2004; 19(5):490-6.
174. Drum B, Rhoads JM, Stringer DA, Sherman P, Ellis L, Durie P. peptic ulcer disease in children: etiology, clinical findings, and clinical course. *Pediatrics* 1988;82:410.
175. Chiang BL, Chang MH, Lin MI, Hsu JY, Wang CY, Wang TH. Chronic duodenal ulcer in children: clinical observation and response to treatment. *J Pediatr Gastroenterol Nutr* 1989;8:161.
176. Lamireau T, Rigot A, Megraud F, De Mascarel A. *Helicobacter pylori* gastritis in children. *Arch Pediatr* 1995; 2: 310-6.
177. Gremse DA, Sacks AI. Symptoms of gastritis due to *helicobacter pylori* in children. *South Med J* 1996; 89: 278-81.
178. Sonnenberg A, Lash RH, Genta RM. A national study of *Helicobacter pylori* infection in gastric biopsy specimens. *Gastroenterology* 2010; 139:1894–901.
179. Abdollahi A, Morteza A, Khalilzadeh O, Zandieh A, Asgarshirazi M. The role of *Helicobacter pylori* infection in gastro-oesophageal reflux in Iranian children. *Ann Trop Paediatr* 2011;31:53–7.
180. Blecker U, Hauser B, Lanciers S, Keymolen K, Vandenplas Y. Symptomatology of *Helicobacter pylori* infection in children. *Acta Paediatr* 1996; 85(10):1156-8.
181. Mahony MJ, Wyatt JI, Littlewood JM. Management and response to treatment of *helicobacter pylori* gastritis. *Arch Dis Child* 1992; 67: 940-3.

182. Maherzi A, Fendri C, Ben Jilani S, Bousnina S. Symptomatic *Helicobacter pylori* infection: prospective study of epidemiological, diagnostic and therapeutic aspects in children in Tunisia. *Arch Pediatr* 1996; 3: 329-34.
183. Conti-Nibali S, Sferlazzas C, Fera M-T, Saitta G, Tedes-Chi A, Magazzu G. *Helicobacter pylori* infection: a simplified diagnostic approach. *Am J Gastroenterol* 1990; 85:153-5.
184. Oderda G, Figura N, Bayeli P, Basagni C, Bugnoli M, Armellini D. et al. Serologic IgG recognition of *Helicobacter pylori* cytotoxin-associated protein, peptic ulcer and gastroduodenal pathology in childhood. *Eur J Gastroenterol Hepatol* 1993; 5: 695-9.
185. Bourke B, Ceponis PM, Chiba N, Czinn S, Ferraro R, Fischbach L, et al. Canadian helicobacter study group consensus conference: update on the approach to *Helicobacter pylori* infection in children and adolescents-an evidence-based evaluation. *Can J Gastroenterol* 2005; 9: 399-408.
186. McCallion WA, Bailie AG, Ardill JES, Bamford KB, Potts SR, Boston VE. *Helicobacter pylori*, hyppergastrinemia and recurrent abdominal pain in children. *J Pediatr Surg* 1995; 30: 427-9.
187. Rindi G, Annibale B, Bonamico M, Corleto V, Delle Fave G, Solcia E. *Helicobacter pylori* infection in children with antral gastrin cell hyperproduction. *J Pediatr Gastroenterol Nutr* 1994; 18: 152-8.
188. Warren JR, Marshall B. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. *Lancet* 1983; 1:1273-5.
189. Czinn SJ, Dahms BB, Jacobs GH, Kaplan B, Rothstein FC. *Campylobacter*-like organisms in association with symptomatic gastritis in children. *J Pediatr* 1986;109:80-3.
190. Cadranel S, Goossens H, De Boeck M, Malengreau A, Rodesch P, Butzler JP. *Campylobacter pyloridis* in children. *Lancet* 1986;1:735-6.
191. Luzzza F, Contaldo A, Imeneo M, Mancuso M, Pensabene L, Giancotti L, et al. Testing for serum IgG antibodies to *Helicobacter pylori* cytotoxin-associated protein detects children with higher grades of gastric inflammation. *J Pediatr Gastroenterol Nutr* 1999;29:302-7.
192. Prieto Bozano G, Lorente Minarro M, Bejarano Lopez A, Carrasco Gandía S, Lama Moré R, Polanco Allué I. Antritis nodular y infeccion por *Helicobacter pylori* en el nino. *An Esp Pediatr* 1993; 39:428-30.
193. Luzzza F, Pensabene L, Imeneo M, Mancuso M, Contaldo A, Giancotti L, et al. Antral nodularity identifies children infected with *Helicobacter pylori* with higher grades of gastric inflammation. *Gastrointest Endosc* 2001; 53:60-4.
194. Motamed F, Doroudian R, Najafi M, Monajemzade M, Marashi SM, Arastoo L, et al. *Helicobacter pylori* infection: clinical, endoscopic and pathological findings in Iranian children. *Int J Pediatr* 2014; 2(S4):9-17.

195. Lame L, Cohen H, Sloane R, Marin-Sorensen M, Weinstein WM. Interobserver agreement and predictive value of endoscopic finding for *h pylori* and gastritis in normal volunteers. *Gastrointest Endoscopic* 1995; 42:420-3.
196. Sbeih F, Abdullah A, Sulllivan S, Merenkov Z. Antral nodularity, gastric hyperplasia, and *H. pylori* in adult. *J Clin Gastroenterol* 1996; 22: 227-30.
197. Grellier L, Tanner P, Grainger SL. Anti-al nodularity: Macroscopic marker for *Helicobacter pylori* gastritis. *Gut* 1993; 34 (suppl):S35.
198. Mitchell HM, Bohane TD, Tobias V, Bullpitt P, Daskalopoulos G, Carrick J, et al. *Helicobacter pylori* infection in children: potential clues to pathogenesis. *J Pediatr Gastroenterol Nutr* 1993;16(2):120-5.
199. Aeri Moon MD, Aliza Solomon DO, Cunningham-Rundles S. Positive Association between *Helicobacter pylori* and Gastroesophageal Reflux Disease in Children. *J Pediatr Gastroenterol Nutr* 2009; 49(3): 283–8.
200. Sonnenberg A, Lash RH, Genta RM. A national study of *Helicobacter pylori* infection in gastric biopsy specimens. *Gastroenterology* 2010; 139:1894–901.
201. Abdollahi A, Morteza A, Khalilzadeh O, Zandieh A, Asgarshirazi M. The role of *Helicobacter pylori* infection in gastro-oesophageal reflux in Iranian children. *Ann Trop Paediatr* 2011;31:53–7.
202. Daugule I, Rumba I, Alksnis J. *Helicobacter pylori* infection among children with gastrointestinal symptoms: a higher prevalence of infection among patients with reflux oesophagitis. *Acta Paediatr* 2007; 96:1047–9.
203. Moon A, Solomon A, Beneck D, Cunningham-Rundles S. Positive association between *Helicobacter pylori* and gastroesophageal reflux disease in children. *J Pediatr Gastroenterol Nutr* 2009;49:283–8.
204. Emiroglu HH, Sokucu S, Suoglu OD, Gulluoglu M, Gokce S. Is there a relationship between *Helicobacter pylori* infection and erosive reflux disease in children?. *Acta Paediatr* 2010; 99: 121–5.
205. O’connor HJ. Review article, *helicobacter pylori* and gastroesophageal reflux disease—clinical implications and management. *Aliment Pharmacol Ther* 1999;13:1-11.
206. Schenk BE, Kuipers EJ, Klinkenberg-Knol EC, Eskes SA, Meuwissen SG. *Helicobacter pylori* and the efficacy of omeprazole therapy for gastroesophageal reflux disease. *Am J Gastroenterol* 1999; 94:884-7.
207. Wu JC, Sung JJ, Chan FK. *Helicobacter pylori* infection is associated with milder gastro-esophageal reflux disease. *Aliment Pharmacol Ther* 2000; 14:427-32.
208. Loffeld RJ, Werdmuller BF, Kuster JG. Colonization with *cagA*_positive *helicobacter pylori* strains inversely associated with reflux esopgagitis and Barrett’s esophagus. *Digestin* 2000; 62: 95-9.

209. Recavarren-Arce S, León-Barúa R, Rodríguez C, Cok J, Berendson R, Gilman RH. *Helicobacter pylori*-associated chronic gastritis in Peruvian adolescents is very common and severe. *J Clin Gastroenterol* 1995; 20:335–7.
210. Bedoya A, Garay J, Sanzo'n F, Bravo LE, Bravo JC, Correa H, et al. Histopathology of gastritis in *Helicobacter pylori*-infected children from populations at high and low gastric cancer risk. *Hum Pathol* 2003;34:206–13.
211. Kato S, Nakajima S, Nishino Y, Ozawa K, Minoura T, Konno M, et al. Association between gastric atrophy and *Helicobacter pylori* infection in Japanese children: a retrospective multicenter study. *Dig Dis Sci* 2006;51:99–104.
212. Sgouras DN, Panayotopoulou EG, Papadakos K, Martinez-Gonzalez B, Roumbani A, Panayiotou J, et al. CagA and VacA polymorphisms do not correlate with severity of histopathological lesions in *Helicobacter pylori*-infected Greek children. *J Clin Microbiol* 2009;47:2426–34.
213. Azuma T, Ito S, Sato F, Yamazaki Y, Miyaji H, Ito Y, et al. The role of the HLA-DQA1 gene in resistance to atrophic gastritis and gastric adenocarcinoma induced by *Helicobacter pylori* infection. *Cancer* 1998; 82:1013–8.
214. Arents NL, van-Zwet AA, Thijs JC, Kooistra-Smid AM, van Slochteren KR, Degener JE, et al. The importance of vacA, cagA, and iceA genotypes of *Helicobacter pylori* infection in peptic ulcer disease and gastroesophageal disease. *Am J Gastroenterol* 2001; 96:2603–8.
215. Atherton JC. *Helicobacter pylori* virulence factors. *Br Med Bull* 1998; 54:105–20.
216. Yahav J, Fradkin A, Weeisselberg B, Diver-Haver A, Shmueli H, Jonas A. Relevance of cagA positivity to clinical course of *Helicobacter pylori* infection in children. *J Clin Microbiol* 2000;38:3534–7.
217. Yamaoka Y, Kodama T, Gutierrez O, Kim G, Kashima K, Graham Y. Relationship between *Helicobacter pylori* ice, cagA, and vacA status and clinical outcomes: studies in four different countries. *J Clin Microbiol* 1999; 37:2274–9.
218. Queiroz DM, Mendes EN, Carvalho AS, Rocha GA, Oliveira AM, Soares TF, et al. Factors associated with *Helicobacter pylori* infection by a cagA-positive strain in children. *J Infect Dis* 2000;181(2):626–30.
219. Oleastro M, Gerhard M, Lopes AI, Ramalho P, Cabral J, Sousa Guerreiro A, et al. *Helicobacter pylori* virulence genotypes in Portuguese children and adults with gastroduodenal pathology. *Eur J Clin Microbiol Infect Dis* 2003;22:85–91.
220. Karhukorpi J, Yan Y, Kolho KL, Rautelin H, Lahti M, Sirviö A, et al. cagA, vacA and iceA virulence genes of *Helicobacter pylori* isolates of children in Finland. *Eur J Clin Microbiol Infect Dis* 2000;19:790–3.
221. Saltik IN, Demir H, Engin D, Ertunç OD, Akyön Y, Koçak N. The cagA status of *Helicobacter pylori* isolates from dyspeptic children in Turkey. *FEMS Immunol Med Microbiol* 2003;36:147–9.

222. Sökücü S, Ozden AT, Süoğlu OD, Elkabes B, Demir F, Cevikbaş U, et al. CagA positivity and its association with gastroduodenal disease in Turkish children undergoing endoscopic investigation. *J Gastroenterol* 2006; 41: 533–9.
223. Ghotaslou R, Milani M, Akhi MT, Nahaei MR, Hasani A, Hejazi MS, et al. Diversity of *Helicobacter Pylori* cagA and vacA Genes and Its Relationship with Clinical Outcomes in Azerbaijan, Iran. *Adv Pharm Bull* 2013;3(1):57-62.
224. Hussein NR. *H. pylori* and gastric cancer in the Middle East: anew enigma? *World J Gastroenterol* 2010; 16(26):3226-34.
225. Covacci A, Telford JL, Giudice GD, Parsonnet J, Rappouoli R. *Helicobacter pylori* virulence and genetic geography. *Science* 1999; 284: 1328-33.
226. Yamaoka Y, El-Zimaity HM, Gutierrez O, Figura N, Kim JG, Kodama T, et al. Relationship between the cagA3' repeat region of *Helicobacter pylori*, gastric histology, and susceptibility to low pH. *Gastroenterology* 1999; 117:342-9.
227. Yamaoka Y, El-Zimaity HM, Gutierrez O, Figura N, Kim JG, Kodama T, et al. *Helicobacter pylori* in North and South America before Columbus. *FEBS Lett* 2002; 517: 180-4.
228. Husson MO, Gottrand F, Vachee A, Dhaenens L, de la Salle EM, Turck D, et al. Importance in diagnosis of gastritis of detection by PCR of the Cag A gene in *Helicobacter pylori* strains isolated from children. *J Clin Microbial* 1995; 33: 3300-3.
229. Plebani M, Guariso G, Fogar P, Basso D, Gallo N, Zambon CF, et al. Effects of cagA status on the sensitivity of enzyme immunoassay in diagnosing *helicobacter pylori*-infected children. *Helicobacter* 1999;4(4):226-32.
230. Nogueira C, Figueiredo C, Carneiro F, Gomes AT, Barreira R, Figueira P, et al. *Helicobacter pylori* genotypes may determine gastric histopathology. *Am J Pathol* 2001; 158: 647-54.
231. Demirturk L, Ozel AM, Yazgan Y, Solmazgul E, Yildirim S, Gultepe M, et al. CagA status in dyspeptic patients with and without peptic ulcer disease in Turkey: association with histopathological findings. *Helicobacter* 2001; 6: 163-8.
232. Martins LC, Corvelo TC, Demachki S, Araujo MT, Assumpcao MB, Vilar SC, et al. Clinical and pathological importance of vacA allele heterogeneity and cagA status in peptic ulcer disease in patients from North Brazil. *Mem Inst Oswaldo Cruz* 2005;100(8):875-81.
233. Boyanova L, Yordanov D, Gergova G, Markovska R, Mitov I. Benefits of *Helicobacter pylori* cagE genotyping in addition to cagA genotyping: a Bulgarian study. *Antonie Van Leeuwenhoek* 2011;100: 529–35.
234. Gold BD, van Doorn LJ, Guarner J, Owens M, Pierce-Smith D, Song Q, et al. Genotypic, clinical, and demographic characteristics of children infected with *Helicobacter pylori*. *J Clin Microbiol* 2001; 39: 1348–52.

235. Benenson S, Halle D, Rudensky B, Faber J, Schlesinger Y, Branski D, et al. *Helicobacter pylori* genotypes in Israeli children: the significance of geography. *J Pediatr Gastroenterol Nutr* 2002; 35: 680–4.
236. Lopes AI, Palha A, Monteiro L, Olcastro M, Pelerito A, Fernandes A. *Helicobacter pylori* genotypes in children from a population at high gastric cancer risk: no association with gastroduodenal histopathology. *Am J Gastroenterol* 2006; 101: 2113–22.
237. Shimoyama T, Crabtree JE. Mucosal chemokines in *Helicobacter pylori* infection. *J Physiol Pharmacol* 1997; 48: 315-23.
238. Selimoglu MA, Karabiber H, Otlu B, Yildirim O, Ozer A, Samdanci E. Correlation of clinical, endoscopic, and histological findings with virulence factors in children with *Helicobacter pylori* gastritis. *Eur J Gastroenterol Hepatol* 2014;26(6):602-6.
239. Homan M, Luzar B, Kocjan BJ, Orel R, Mocilnik T, Shrestha M, et al. Prevalence and clinical relevance of *cagA*, *vacA*, and *iceA* genotypes of *Helicobacter pylori* isolated from Slovenian children. *J Pediatr Gastroenterol Nutr* 2009;49:289-96.
240. Podzorski RP, Podzorski DS, Wuerth A, Tolia V. Analysis of the *vacA*, *cagA*, *cagE*, *iceA*, and *babA2* genes in *Helicobacter pylori* from sixty-one pediatric patients from the Midwestern United States. *Diagn Microbiol Infect Dis* 2003; 46: 83–8.
241. Zhou J, Zhang J, Xu C, He L. *cagA* genotype and variants in Chinese *Helicobacter pylori* strains and relationship to gastroduodenal diseases. *J Med Microbiol* 2004; 53 (Pt 3):231–5.
242. Strobel S, Bereswill S, Balig P, Allgaier P, Sonntag HG, Kist M. Identification and analysis of a new *vacA* genotype variant of *Helicobacter pylori* in different patient groups in Germany. *J Clin Microbiol* 1998;36(5):1285-9.
243. Van Doorn LJ, Figueiredo C, Megraud F, Pena S, Midolo P, Queiroz DM, et al. Geographic distribution of *vacA* allelic types of *Helicobacter pylori*. *Gastroenterology* 1999;116(4):823-30
244. Sugimoto M, Yamaoka Y. The association of *vacA* genotype and *Helicobacter pylori*-related disease in Latin American and African population. *Clin Microbiol Infect* 2009; 15: 835-42.
245. Al Qabandi A, Mustafa AS, Siddique I, Kaajah AK, Madda JP. Distribution of *vacA* and *cagA* genotype of *Helicobacter pylori* in Kuwait. *Acta Trop* 2005; 93:283-8.
246. Sgouras DN, Panayotopoulou EG, Papadacos K, Martinez-Gonzalez B, Roumbani A, Panayiotou J, et al. *CagA* and *VacA* polymorphisms do not correlate with severity of histopathological lesions in *Helicobacter pylori*-infected Greek children. *J Clin Microbiol* 2009; 47(8):2426-34.
247. Gerhard M, Lehn N, Neumayer N, Boren T, Rad R, Schepp W, et al. Clinical relevance of the *Helicobacter pylori* gene for blood-group antigen-binding adhesin. *Proc Natl Acad Sci USA* 1999; 96:12778–83.

248. Rudi J, Kolb C, Maiwald M, Kuck D, Sieg A, Galle PR, et al. Diversity of *Helicobacter pylori* vacA and cagA genes and relationship to VacA and CagA protein expression, cytotoxin production, and associated diseases. *J Clin Microbiol* 1998; 36: 944–8.
249. Ito Y, Azuma T, Ito S, Miyaji H, Hirai M, Yamazaki Y, et al. Analysis and typing of the vacA gene from cagA-positive strains of *Helicobacter pylori* isolated in Japan. *J Clin Microbiol* 1997; 35:1710–4.
250. Pan ZJ, Berg DE, van der Hulst RW, Su WW, Raudonikienė A, Xiao SD, et al. Prevalence of vacuolating cytotoxin production and distribution of distinct vacA alleles in *Helicobacter pylori* from China. *J Infect Dis* 1998; 178:220–6.
251. De Gusmão VR, Nogueira Mendes E, De Magalhães Queiroz DM, Aguiar Rocha G, Camargos Rocha AM, Ramadan Ashour AA, et al. Vaca genotypes in *Helicobacter pylori* strains isolated from children with and without duodenal ulcer in Brazil. *J Clin Microbiol* 2000; 38:2853–7.
252. Warbuton VJ, Everett S, Mapstone NP, Axon AT, Hawkey P, Dixon MF. Clinical and histological association of cagA and vacA genotypes in *Helicobacter pylori* gastritis. *J Clin Pathol* 1998; 51:55–61.
253. Hussein NR, Mohammadi M, Talebkhan Y, Doraghi M, Letley DP, Mohammad MK, et al. Differences in virulence markers between *Helicobacter pylori* strains from Iraq and those from Iran: potential importance of regional differences in *Helicobacter pylori*-associated disease. *J Clin Microbiol* 2008; 46:1774–9.
254. Umit H, Tezel A, Bukavaz S, Unsal G, Otkun M, Soyulu AR, et al. The relationship between virulence factors of *Helicobacter pylori* and severity of gastritis in infected patients. *Dis Sci* 2009; 54:103–10.
255. Nimri LF, Mataka I, Bani Hani K, Ibrahim M. *Helicobacter pylori* genotypes identified in gastric biopsy specimens from Jordanian patients *BMC Gastroenterol* 2006; 6:27–32.
256. Marie MA. Relationship between *Helicobacter pylori* virulence genes and clinical outcomes in Saudi patients. *J Korean Med Sci* 2012; 27(2):190–3.
257. Ozbey G, Dogan Y, Demiroren K. Prevalence of *Helicobacter pylori* virulence genotypes among children in Eastern Turkey *World J Gastroenterol* 2013;19(39):6585–9.
258. Podzorski RP, Podzorski DS, Wuerth A, Tolia V. Analysis of the vacA, cagA, cagE, iceA, and babA2 genes in *Helicobacter pylori* from sixty-one pediatric patients from the Midwestern United States. *Diagn Microbiol Infect Dis* 2003; 46: 83–8.
259. Garcia GT, Aranda KR, Gonçalves ME, Cardoso SR, Iriya K, Silva NP, et al. High prevalence of clarithromycin resistance and cagA, vacA, iceA2, and babA2 genotypes of *Helicobacter pylori* in Brazilian children. *J Clin Microbiol* 2010; 48: 4266–8.

260. Singh M, Prasad KN, Yachha SK, Krishnani N. Genotypes of *Helicobacter pylori* in children with upper abdominal pain. *J Gastroenterol Hepatol* 2003; 18: 1018-23.
261. Fox JG, Correa P, Taylor NS, Thompson N, Fontham E, Janney F, et al. High prevalence and persistence of cytotoxin-positive *Helicobacter pylori* strains in a population with high prevalence of atrophic gastritis. *Am J Gastroenterol* 1992; 87: 1554-60.
262. Yamoaka Y. Roles of *helicobacter pylori* babA IN gastrodudenal pathogenesis. *World J Gastroenterol* 2008; 14: 4265-72.
263. Talarico S, Gold BD, Fero J, Thompson DT, Guarner J, Czinn S, et al. Pediatric *helicobacter pylori* isolates display distinct gene coding capacities and virulence gene marker profiles. *J Clin Microbial* 2009; 47:1680-8.
264. Olfat FO, Zheng QM, Oleastro M, Voland P, Boren T, Karttunen R, et al. Correlation of the *helicobacter pylori* adherence factor babA with duodenal ulcer disease in four European countries. *FEMS Immunol Med Microbial* 2005; 44:151-6.
265. Han YH, Liu WZ, Zhu HY, Xiao SD. Clinical relevance of iceA and babA2 genotypes of *Helicobacter pylori* in a Shanghai population. *Chin J Dig Dis* 2004;5(4):181-5.
266. Henning EE, Mernaugh R, Edl J, Cao P, Cover TL. Heterogenicity among *helicobacter pylori* strains in expression of the outer membrane protein babA. *Infect Immune* 2004; 72:3429-35.
267. Pride DT, Meinersmann RJ, Blaster MJ. Allelic variation within *helicobacter pylori* babA AND BAB b. *Infect Immun* 2001;69:1160-71.
268. Mizushima T, Sugiyama T, Komatsu Y, Ishizuka J, Kato M, Asaka M. Clinical relevance of the babA2 genotype of *Helicobacter pylori* in Japanese clinical isolates. *J Clin Microbiol* 2001; 39(7): 2463–5.

RELATIONSHIP BETWEEN HELICOBACTER PYLORI
GENOTYPES, CLINICAL MANIFESTATION AND
SEVERITY OF GASTRITIS IN CHILDREN

العلاقة بين موروثةات الميكروب الحلزوني وشدة المظاهر السريرية والتهابات المعدة
عند الأطفال

Protocol of a thesis submitted
to the Faculty of Medicine
Alexandria University
In partial fulfillment of the
requirements of the degree of
Master of Pediatrics

خطة بحث مقدمة
لكلية الطب
جامعة الإسكندرية
إيفاء جزئياً لشروط
الحصول على درجة
الماجستير في طب الأطفال

by

من

Amira Hamed Hasab El-Naby
MBBCh, Alex
Resident
Alexandria University Children's Hospital
Department of Pediatrics
Faculty of Medicine
Alexandria University
2011

أميرة حامد حسب النبى
بكالوريوس الطب والجراحة، الإسكندرية
طبيب مقيم
مستشفى الأطفال الجامعى الإسكندرية
قسم طب الأطفال
كلية الطب
جامعة الإسكندرية
٢٠١١

2.

SUPERVISORS

Prof. Dr. Sana Hosny Mohamed Barakat
Professor of Pediatrics,
Faculty of Medicine,
University of Alexandria.

مشرفون

د/ سنا حسنى بركات
مناظ طب الأطفال
كلية الطب
جامعة الإسكندرية

Prof. Dr. Nahed Mohamed Baddour
Professor of Pathology,
Faculty of Medicine,
University of Alexandria.

د/ ناهد محمد بدور
استاذ علم الأمراض
كلية الطب
جامعة الإسكندرية

Dr. Reem Abd El Hamid Harfoush
Assistant Professor of Medical Microbiology and
Immunology,
Faculty of Medicine,
University of Alexandria.

د/ ريم عبد الحميد حرفوش
استاذ مساعد قسم الميكروبيولوجيا الطبية
والمناعة
كلية الطب
جامعة الإسكندرية

3.

CO-RESEARCHER

Amir Alaa Rabal

5th year student,

Faculty of Medicine,

University of Alexandria.

Mobile Phone: 0100266277

E-mail: amirahal@yahoo.com

الباحث المساعد

أمير علاء رحال

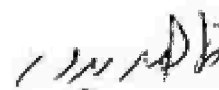
طالب بالفرقة الخامسة

كلية الطب

جامعة الإسكندرية







INTRODUCTION

Helicobacter pylori is a spiral, microaerophilic, gram negative bacterium that permanently colonizes gastric epithelial cells in approximately 25% of the population in developed countries and 70% - 90% in developing countries.⁽¹⁾

Humans appear to be the only reservoir of *H.pylori* infection and therefore human contacts remain the major mode for its transmission. Iatrogenic spread through contaminated gastrointestinal equipment has been documented.⁽²⁾ Water has been shown to be a source for *H.pylori* infection.⁽³⁾

Histological gastritis is essential universal among *H.pylori* infected individuals. Whereas most infected individuals are asymptomatic, chronic *H.pylori* infection in susceptible individuals is associated with a variable degree of mucosal damage ranging from mild gastritis and ulcer disease to gastric carcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma.⁽⁴⁾ One reason for this phenomenon may be the different pathogenicity of infective *H.pylori* strains.⁽⁵⁾

The most important virulence determinants of *H. pylori* are CagA protein and the vaculating cytotoxin A (VacA)^(6,7). Approximately 50% to 60% of *H. pylori* contain the *cagA* gene, encoding the CagA protein. The *cagA* gene is part of *cag* pathogenicity island (*cagPAI*), which contains many genes that are related to the virulence and pathogenicity of *H. pylori* strain. The presence of *cagA* is a confirmed marker for *cag PAI* and is associated with more virulent *H. pylori* strains.⁽⁸⁻¹⁰⁾

5.

The vaculating cytotoxin A gene, which is another important virulence factor of *H. pylori*, encodes an 87 kD protein that induces vaculation of epithelial cells⁽¹¹⁾. The *vacA* gene is present in all strains of *H. pylori* and comprises two variable parts. The *H. pylori* strains have one of two types of *vacA* signal sequence (s1 and s2) and two types of mid region (m1 and m2).^(12,13)

Among the bacterial factors, the ability to adhere to epithelial cells is crucial in the initiation of a gastric inflammatory response.⁽¹⁴⁻¹⁶⁾ The blood group antigen-binding adhesion BabA has been shown to mediate adherence of *H. pylori* to human Lewis b (a-1,3/4-difucosylated) blood group antigens on gastric epithelial cells⁽⁵⁾. This attachment resulted in the development of chronic gastritis and gastric atrophy.⁽¹⁶⁻¹⁸⁾

Cir

7/8/01 (11/11/01)

The aim of the work is to correlate the virulence factor, (cagA, VacA and BabA2) with:

- 1- The histologic parameters of *H.pylori* related gastritis.
- 2- The clinical presentations.

٢١

_____ *condit*

PATIENTS

Fifty patients infected with H.pylori (stool Ag positive) referred for endoscopy with upper gastrointestinal symptoms (mostly recurrent abdominal pain, haematemesis...etc.), suggestive of organic disease and severe enough to require endoscopic evaluation, will be included in the study.

Informed consent from the parents will be obtained.

Exclusion criteria were treatment with antisecretory, antimicrobial, or anti-inflammatory medication, for the 3 months preceding the endoscopy.

Twenty five clinically health children (no gastrointestinal symptoms) with H.pylori stool antigen positive will be included as a control group.

METHODS

All patients of this study will be subjected to the following:

- 1- Through history taking and clinical examination with special stress on age and clinical manifestation, exclusion of patients who received proton pump inhibitor or antibiotic for the last three months.
- 2- Upper GIT endoscopy (after written consent):

Biopsy specimens will be systemically taken from duodenum, gastric antrum, and body. One of gastric biopsies will be processed for rapid urease test, other biopsy specimen will be processed, paraffin blocked, sectioned into 5µm thick section and submitted for the following:

- 1- Histopathological assessment according to Sydney classification for gastritis.
- 2- The Polymerase chain reaction will be used to detect *cagA*, *vacA* and *babA₂* genes of *H.pylori* using specific primers.
- 3- In the stool specimens of the control group, polymerase chain reaction will be used to detect *cagA*, *vacA* and *babA₂* genes of *H.pylori* using specific primers.



9.

RESULTS

The results will be tabulated and analyzed using appropriate statistical methods.

Handwritten signature

10.

DISCUSSION

Results will be discussed in view of achievement of the aim and compared with other studies published in the literature.

[Handwritten signature]

[Handwritten signature]

[Handwritten signature]

REFERENCES

1. Dunn BE, Cohen H, Blaser MJ. *Helicobacter pylori*. Clin Microbial Rev 1997; 10:720-41.
2. Logan RP, Hiscail AM. Epidemiology of *Helicobacter pylori* infection. Curr Opin Gastroenterol 1996; 12(suppl 1):1-5.
3. Parsonnet J, Hansen S, Rodriguez L, Gelb AB, Warnke RA, Jellum E, et al. *Helicobacter pylori* infection and gastric lymphoma. N Engl J Med 1994; 330:1267-71.
4. Israel DA, Peek RM. Pathogenesis of *Helicobacter pylori*-induced gastric inflammation. Aliment Pharmacol Ther 2001; 15:1271-90.
5. McGee DJ, Mobley HLT. Pathogenesis of *Helicobacter pylori* infection. Curr Opin Gastroenterol 2000; 16:24-31.
6. Atherton JC, Cao P, Peek RM Jr. Mosaicism in vacuolating cytotoxin alleles of *Helicobacter pylori*-association of specific *vacA* types with cytotoxin production and peptic ulceration. J Biol Chem 1995; 270: 777-7.
7. Zhu Y, Zhong X, Du Zheng SO, Xu W. Transformed immortalized gastric epithelial cells by virulence factor CagA of *Helicobacter pylori* through Erk mitogen -activated protein kinase pathway. Oncogen, 2005; 24: 3886-95.
8. Qiao W, Hu JL, Xiao B. CagA and VacA genotype of *Helicobacter pylori* associated with gastric disease in Xi'an area. World J Gastroenterol 2003;9: 1762-6.





- 12.
9. Van Doorn LJ, Figueiredo C, Sanna R. Clinical relevance of the *cagA*, *vacA*, and *iceA* status of *Helicobacter pylori*. *Gastroenterol* 1998;115:58-66.
10. Konturek P, Konturek S, Pierzchalski P. Cancerogenesis in *Helicobacter pylori* infected stomach-role of growth factors, apoptosis and cyclooxygenases. *Med Sci Monit* 2001; 7(5):1092-107.
11. Ito Y, Azuma T, Ito S, Miyaji H, Hirai M, Yamazaki Y, et al. Analysis and typing of the *vacA* gene from *cagA*-positive strain of *Helicobacter pylori* isolated in Japan. *J Clin Microbiol* 1997; 35:1710-14.
12. Van Doorn LJ, Figueiredo C, Sanna R, Pena S, MidoloNg EK, Atherton JC, et al. Expanding allelic diversity of *Helicobacter pylori vacA*. *J Clin Microbiol* 1998; 36:2597-603.
13. Atherton JC, Cao P, Peek RM Jr, Tummuru MK, Blaser MJ. Cover TL Mosaicism in vaculating cytotoxin alleles of *Helicobacter pylori*. Association of specific *vacA* types with cytotoxin production and peptic ulceration. *J Biol Chem* 1995; 270:771-7.
14. Hessey SJ, Spencer J, Wyatt JJ, Sobala G, Rathbone BJ, Axon AT, et al. Bacterial adhesion and disease activity in *Helicobacter*-associated chronic gastritis. *Gut* 1990; 31:134-8.
15. Logan RP. Adherence of *Helicobacter pylori*. *Aliment. Pharmacol Ther* 1996; 10: 3-15.
16. Ilver D, Arnqvist A, Ogren J, Frick IM, Kersulyte D, et al. *Helicobacter pylori* adhesin binding fucosylated histo-blood group antigens revealed by retagging. *Science* 1998; 279:373-7.

13.

17. Falk PG, Roth KA, Boren T, Westblom TU, Gordon JI, Normark S. An in vitro adherence assay reveals that *Helicobacter pylori* exhibits cell lineage-specific tropism in the human gastric epithelium. *Proc Natl Acad Sci USA* 1993; 55: 122-8.
18. Falk PG, Bry L, Holgersson J, Gordon JI. Expression of a human alpha-1, 3/4-fucosyltransferase in the pit cell lineage of FVB/N mouse stomach results in production of Leb-containing glycoconjugates: a potential transgenic mouse model for studying *Helicobacter pylori* infection. *Proc Natl Acad Sci USA* 1995; 92:1515-9.

—

محمود محمد

المخلص العربي

تعتبر الاصابه بالعدوى بالميكروب الحلزوني من العدوى البكتيرية الشائعة عالميا. وقد اصاب اكثر من ثلثه ارباع السكان في الدول الناميه وتم حيازته في الغالب في مرحله الطفوله. اما في البلدان المتقدمه فالعدوى في الاطفال اقل توترا. انها السبب الاكثر شيوعا لالتهاب المعده المزمن وايضا قرحة المعده وهي مرتبطه مباشرة بسرطان المعده.

وهدفنا في هذه الرساله هو ربط العوامل الرئيسيه لضراره البكتيريا وهي الجينات (*cagA*, *vacA*, *babA*) مع كلا من الاعراض المرضيه والمحددات النسيجييه والمرضييه لالتهاب المعده المرتبط بالميكروب الحلزوني وأيضا بالصوره المنظاريه وهذا سوف يكون مهما لوضع سياسات مستقبليه للقضاء على الميكروب الحلزوني من اجل منع الامراض الاكثر شده في كلا من الاطفال والبالغين ولدراسه اضافات جديده في هذا الصدد.

ولتحقيق هذا الهدف اجريت هذه الدراسه على ٩٥ من الاطفال الذين احيلو لعمل منظار علوي بسبب معاناتهم من الام البطن والرجيع والقئ الدموي. ٥٠ من هؤلاء الاطفال تم اثبات اصابتهم بالميكروب الحلزوني بواسطه اختبار اليورباز السريع والفحص الدقيق للانسجه (هستوباثولوجي) والفحص الجيني PCR وايضا ٤٥ طفلا تم اثبات خلوهم من العدوى وقد تم تشخيص ٢٥ طفلا لا يشتكون باعراض مرضيه انهم حالات ايجابيه بواسطه اختبار المولد المضاد للميكروب الحلزوني في البراز.

واظهر التحليل الاحصائي للبيانات التي تم الحصول عليها من هذه الدراسه النتائج التاليه:

- ١- القئ الدموي هو عرض من الاعراض المرضيه الاكثر شيوعا في الاطفال الذين احيلو الى عياده الجهاز الهضمي للاطفال لعمل التنظير العلوي (٥٤.٧%) وتوجد علاقه ذات دلالة بين القئ الدموي والاصابه بالميكروب الحلزوني.
- ٢- وجود العقيدات المعديه هو مؤشر كبير على الاصابه بالبكتيريا الحلزونييه.
- ٣- قد تميزت الصوره النسيجييه للاطفال ذوي الاعراض المرضيه والمصابين للميكروب الحلزوني بوجود التهاب شديد واكثر عمقا مع زياده في عدد البصيلات الليمفاويه مقارنة بالحالات السالبيه.
- ٤- الصوره النسيجييه للحالات المصابه بالميكروب الحلزوني والتي تعاني من الام البطن المتكرره وأيضا التي تعاني من القئ الدموي تتميز بالتهاب حاد بشكل ملحوظ مقارنة بالذين لا يشتكون من نفس الشكاوى.
- ٥- الجينات الاكثر شيوعا في حالات الميكروب الحلزوني الايجابيه هي *vacA* (٧٢%) ثم *cagA* (٥٢%) ثم *babA2* (٤٤%).
- ٦- توجد علاقات هامه بين وجود كلا من الجينات *vacA s1*, *cagA*, *babA2* و *s1 / m1* و *s2 / m2* ووجود الأعراض المرضيه في الحالات المصابه بالميكروب الحلزوني.
- ٧- تعتبر العقيدات المعديه اكثر شيوعا في العينات الايجابيه لكلا من *cagA* و *vacA S1*.
- ٨- ترتبط الجينات *cagA* و *vacA s1* ببعض الاعراض المرضيه والتغيرات النسيجييه.
- ٩- لا توجد علاقه ذات دلالة بين الجين *babA2* والتغيرات في الصوره المنظاريه والصوره النسيجييه بالمجهر.
- ١٠- تم العثور على الثلاثي (*cagA*, *vacA*, *babA2*) في خمس حالات تشكي من أعراض الميكروب الحلزوني من عدم وجود هذا الثلاثي في الاطفال بدون أعراض.



جامعة الإسكندرية
كلية الطب
قسم طب الأطفال

العلاقة بين موروثةات الميكروب الحزوني وشدة المظاهر السريرية والتهابات المعدة عند الأطفال

رسالة مقدمة

لقسم طب الأطفال - كلية الطب - جامعة الإسكندرية
ضمن متطلبات درجة

الماجستير

فى

طب الأطفال

من

أميرة حامد حسب النبى
بكالوريوس الطب والجراحة ،
كلية الطب، جامعة الإسكندرية

[٢٠١٥]



جامعة الإسكندرية
كلية الطب
قسم طب الأطفال

العلاقة بين موروثةات الميكروب الحلزوني وشدة المظاهر السريرية والتهابات المعدة عند الأطفال

رسالة مقدمة من

أميرة حامد حسب النبى

للحصول على درجة

الماجستير

فى

طب الأطفال

التوقيع

.....

.....

.....

لجنة المناقشة والحكم على الرسالة

أ.د/ سنا حسنى بركات
أستاذ طب الأطفال
قسم طب الأطفال
كلية الطب
جامعة الإسكندرية

أ.د/ شويكار محمود عبد السلام
أستاذ الميكروبيولوجيا الطبية والمناعة
قسم الميكروبيولوجيا الطبية والمناعة
كلية الطب
جامعة الإسكندرية

أ.د/ محمد سامى الحكيم
أستاذ علم الأمراض
قسم علم الأمراض
كلية الطب
جامعة الأزهر بنين

التاريخ / /

لجنة الإشراف

موافقون

أ.د/ سنا حسنى بركات

.....

أستاذ طب الأطفال
قسم طب الأطفال
كلية الطب
جامعة الإسكندرية

أ.د/ ناهد محمد بدور

.....

أستاذ علم الأمراض
قسم علم الأمراض
كلية الطب
جامعة الإسكندرية

د/ ريم عبد الحميد حرفوش

.....

أستاذ مساعد الميكروبيولوجيا الطبية والمناعة
قسم الميكروبيولوجيا الطبية والمناعة
كلية الطب
جامعة الإسكندرية