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Childhood *Helicobacter pylori* Infection and Growth Impairment in Developing Countries: A Vicious Cycle?

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ABSTRACT

We hypothesize that infection with the gastric pathogen *Helicobacter pylori* in children in developing countries is the initiator of a vicious cycle of events that result ultimately in malnutrition and growth impairment. Acute infection with *H pylori* is accompanied by hypochlorhydria, which facilitates the acquisition of other enteropathogens because of removal of the gastric acid barrier, which then results in diarrheal disease and iron-deficiency anemia. This is likely to occur most frequently in developing regions where the prevalence of *H pylori* infection is disproportionately high and multiple enteric coinfections are common. The consequent synergistic impact of diarrheal disease and micronutrient deficiency on growth and cognitive function in children has significant public health implications for socioeconomic development in these countries.

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Key Words

H pylori, hypochlorhydria, diarrhea, enteric infections, iron-deficiency anemia, malnutrition

Abbreviations

IDA—iron-deficiency anemia
IL-1—interleukin 1

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THE ACQUISITION OF *Helicobacter pylori* infection occurs primarily in early childhood. Acute infection, at least in adults, results in a transient or extended period of hypochlorhydria. We hypothesize that this period represents a critical phase for pediatric cohorts in developing countries because, within this window, the individual becomes more susceptible to (1) acquiring other enteropathogenic infections, which results in diarrheal illness, and (2) developing iron-deficiency anemia (IDA). The combined impact of these extragastric manifestations of *H pylori* infection ultimately results in impaired childhood growth and cognitive function caused by the comorbidity associated with malnutrition, micronutrient deficiency, and diarrheal disease.

EVIDENCE FOR OUR HYPOTHESIS

Since the discovery of *H pylori* by recent Nobel Laureates Marshall and Warren¹ in 1982, the pathogen has been shown to be a causative agent of disease states of varying degrees of severity including chronic gastritis, peptic ulcer disease, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue (MALT) lymphoma. Host genetics, host immune responses, and bacterial virulence factors contribute to the multifactorial nature of disease progression.^{2–4} Interleukin (IL)-1 β is a potent suppressor of gastric acid secretion, and polymorphisms in the *IL-1* gene cluster resulting in high IL-1 β production are associated with hypochlorhydria with chronic *H pylori* infection.² More severe disease is also associated with specific bacterial factors such as the *cag* pathogenicity island⁵ and carriage of specific alleles of the vacuolating cytotoxin.⁶

Although the discovery of *H pylori*¹ heralded a major reevaluation of the etiology of peptic ulcer disease and distal gastric cancer, the major global impact of *H pylori* infection may yet be largely unrecognized. In developing countries the incidence of *H pylori* infection in infancy is high^{7–10} and has been associated with malnutrition and growth faltering.^{11,12} Indeed, the incidence of *H pylori* infection in malnourished children is greater than in adequately nourished subjects.¹³ Moreover, there is an inverse relationship between early *H pylori* colonization, infant malnutrition, and socioeconomic status.¹⁴ It is believed that the acquisition of *H pylori* in infancy/childhood in developing countries has a more severe impact on general health compared with developed countries. We believe that the acquisition of *H pylori* in childhood in developing countries is the initiator of a vicious cycle of events that makes an impact on childhood morbidity and mortality, as summarized in Fig 1.

First, the association between acute *H pylori* infection and transient hypochlorhydria in adults is well documented.^{15–24} Hypochlorhydria usually resolves within several months. Experimental infection of animals with gastric *Helicobacter* species also results in initial hypochlorhydria,^{25–27} which in gerbils was reversible by treatment

FIGURE 1

Potential cycle induced by childhood *H pylori* infection in developing countries. *H pylori* infection and hypochlorhydria result in development of IDA and acquisition of other enteric infections, which promotes a vicious cycle of malnutrition and growth impairment. Polymorphisms in the *IL-1β* gene cluster may control the extent and duration of hypochlorhydria with initial *H pylori* infection.

with recombinant IL-1 receptor antagonist.²⁶ It is interesting to note that animal models have shown that hypochlorhydria can promote fecal transmission of infection,²⁷ an observation that may have implications for *H pylori* transmission among humans. However, although there is less direct evidence to support an association between acute *H pylori* infection and hypochlorhydria in pediatric cohorts, accumulating evidence indicates that *H pylori*-infected children also have impaired gastric acid secretion.^{28–33}

Second, hypochlorhydria increases susceptibility to enteric infections^{34,35} such as typhoid and nontyphoidal salmonellosis,^{36,37} cholera,^{38–42} giardiasis,⁴³ and other infections. Other organisms (eg, *Escherichia coli*, *Shigella flexneri*) are less susceptible to gastric acid and can survive exposure to acidic pH.⁴⁴ Evidence from case-controlled studies that examined the association between proton pump inhibitor-induced hypochlorhydria and increased relative risk of acquiring enteric infections including *Clostridium difficile*, *Giardia*, and *Salmonella* supports the view that a reduction in gastric acid secretion may result in the acquisition of infections, as reviewed elsewhere^{45,46} (see Table 1). Thus, *H pylori*-induced hypochlorhydria may predispose to enteric infections,⁵⁸ particularly in regions of the developing world where enteric infections are endemic. Evidence from develop-

TABLE 1 Association of Proton Pump-Inhibitor Use With Increased Risk of Gastrointestinal Infection/Gastroenteritis

Infecting Organism	Odds Ratio	References
<i>C difficile</i>	1.9–2.9	47–52
Gastroenteritis (ND)	1.8–5	53
<i>Salmonella</i>	4.6	54
<i>Campylobacter</i>	11.7	55
<i>Giardia</i>	—	52 and 56
Gastroenteritis (ND)	3.58	57

ND indicates no infecting organism determined; —, not reported.

ing countries indicates that *H pylori* infection may increase the risk of acquisition of coinfection with other pathogens including *Vibrio cholerae*,^{59,60} *Salmonella typhi*,^{61,62} *Shigella*,⁶³ and various parasites.⁶⁴ The resultant diarrhea post-acute *H pylori* infection^{13,29,65} leads to malnutrition and growth retardation in children.^{29,66–70} The recent linking of enteric protozoal infections in developing countries with impaired cognitive function in children⁷¹ further emphasizes the importance of the vicious cycle initiated by *H pylori* on childhood morbidity and potential for socioeconomic impairment.

Another potential consequence of hypochlorhydria is IDA. IDA is a major public health issue, particularly in children, in developing countries where the prevalence in these regions exceeds 50%. In addition to poor nutritional sources of iron in many regions, absorption of bioavailable iron can be compromised if there are alterations to gastric acid secretion (eg, see ref 58). Acidic pH is essential for the efficient reduction and complexation of iron (and other micronutrients) before absorption.^{72,73}

A possible causal role for *H pylori* in the onset of IDA is supported by epidemiologic studies in adults^{74–78} and children.^{79–84} A combination of the (1) hypochlorhydria-associated *H pylori* infection and (2) direct competition between *H pylori* and the host for iron are the likely main contributors to IDA.^{85–89} In developing regions, the micronutrient deficiency and clinical sequelae would be further exacerbated by malnutrition and concurrent enteric infections.^{90,91} Manifestations of clinically advanced IDA include increased childhood mortality and susceptibility to disease, reduced growth,^{11,18} and cognitive function.⁹² However, the impact of *H pylori* on acquisition of diarrheal pathogens and pediatric growth in developing countries has not yet been evaluated rigorously. Studies in developed countries on the role of *H pylori* in diarrheal illness^{93,94} have yielded conflicting results compared with those in developing countries.^{59,61–63} This is perhaps not surprising, given the markedly contrasting exposure to diarrheal pathogens in developing countries. To date, few studies have focused on children during the first few years of life, which is when acute *H pylori* infection and associated hypochlorhydria occur.

CONCLUSIONS

A combination of micronutrient deficiency and coinfection with diarrhea-inducing enteropathogens acquired as a consequence of *H pylori*-induced hypochlorhydria is likely to have a profound impact on pediatric populations in developing countries where the prevalence of *H pylori* is high and reliable nutritional sources of bioavailable iron are low. Thus, prevention of *H pylori* infection could potentially have an important impact on diarrheal diseases in the developing world.

TESTING THE HYPOTHESIS

Whether the hypochlorhydria induced by acute *H pylori* infection in childhood is associated with an increase in enteric infections and diarrheal disease, IDA, and growth impairment remains an important unanswered question. The impact of *IL-1β* gene cluster polymorphisms on acute *H pylori* infection-related hypochlorhydria in pediatric populations is unknown. These factors require evaluation by a multicountry longitudinal observational prospective cohort study in developing countries to determine the impact of *H pylori* and other enteropathogen infections on the epidemiology of diarrheal disease, IDA, and childhood growth. As a causative agent of human disease, the global impact of *H pylori* on childhood morbidity in developing countries may far outreach its role in causing peptic ulcer disease and gastric cancer.

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REFERENCES

1. Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet*. 1984;1(8390):1311–1315
2. Furuta T, El-Omar EM, Xiao F, Shirai N, Takashima M, Sugimura H. Interleukin 1beta polymorphisms increase risk of hypochlorhydria and atrophic gastritis and reduce risk of duodenal ulcer recurrence in Japan. *Gastroenterology*. 2002;123:92–105
3. Queiroz DM, Bittencourt P, Guerra JB, Rocha AM, Rocha GA, Carvalho AS. IL1RN polymorphism and cagA-positive *Helicobacter pylori* strains increase the risk of duodenal ulcer in children. *Pediatr Res*. 2005;58:892–896
4. Peek RM Jr, Crabtree JE. *Helicobacter* infection and gastric neoplasia. *J Pathol*. 2006;208:233–248
5. Crabtree JE, Taylor JD, Wyatt JL, et al. Mucosal IgA recognition of *Helicobacter pylori* 120 kDa protein, peptic ulceration, and gastric pathology. *Lancet*. 1991;338:332–325
6. 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;270:17771–17777
7. Mergraud F, Brassens-Rabbe MP, Denis F, Belbourni A, Hoa DQ. Seroepidemiology of *Campylobacter pylori* infection in various populations. *J Clin Microbiol*. 1989;27:1870–1873
8. Kehrt R, Becker M, Brosicke H, Kruger N, Helge H. Prevalence of *Helicobacter pylori* infection in Nicaraguan children with persistent diarrhoea, diagnosed by the C-13 urea breath test. *J Pediatr Gastroenterol Nutr*. 1997;25:84–88
9. Goodman K, Correa P, Tengana Aux HJ, et al. *Helicobacter* infection in the Columbian Andes: a population based study of transmission pathways. *Am J Epidemiol*. 1996;144:290–299
10. Sarker SA, Rahman MM, Mahalanabis D, et al. Prevalence of

- Helicobacter pylori* infection in infants and family contacts in a poor Bangladeshi community. *Dig Dis Sci*. 1995;40:2669–2672
11. Thomas JE, Dale A, Bunn JEG, et al. Early *Helicobacter pylori* colonisation: the association with growth faltering in the Gambia. *Arch Dis Child*. 2004;89:1149–1154
 12. Mera RM, Correa P, Fontham EE, et al. Effects of a new *Helicobacter pylori* infection on height and weight in Columbian children. *Ann Epidemiol*. 2006;16:347–351
 13. Sullivan PB, Thomas JE, Wight DGD, et al. *Helicobacter pylori* in Gambian children with chronic diarrhoea and malnutrition. *Arch Dis Child*. 1990;65:189–191
 14. Webb PM, Knight T, Greaves S, et al. Relation between infection with *Helicobacter pylori* and living-conditions in childhood. *BMJ*. 1994;308:750–753
 15. Graham DY, Alpert LC, Smith JL, Yoshimura HH. Iatrogenic *Campylobacter pylori* infection is a cause of epidemic achlorohydria. *Am J Gastroenterol*. 1988;83:974–980
 16. McColl KE, El-Omar EM, Gillen D. Interactions between *H. pylori* infection, gastric acid secretion and anti-secretory therapy. *Br Med Bull*. 1998;54:121–138
 17. McColl KE, El-Omar EM, Gillen D. Alterations in gastric physiology in *Helicobacter pylori* infection: causes of different diseases or epiphenomena? *Ital J Gastroenterol Hepatol*. 1997;29:459–464
 18. El-Omar EM, Oien K, El-Nujumi A, et al. *Helicobacter pylori* infection and chronic gastric acid hyposecretion. *Gastroenterology*. 1997;113:15–24
 19. Morris A, Nicholson G. Ingestion of *Campylobacter pyloridis* causes gastritis and raised fasting gastric pH. *Am J Gastroenterol*. 1987;82:192–199
 20. Sobala GM, Crabtree JE, Dixon MF, et al. Acute *Helicobacter pylori* infection: clinical features, local and systemic immune response, gastric mucosal histology, and gastric juice ascorbic acid concentrations. *Gut*. 1991;32:1415–1418
 21. Ramsey EJ, Carey KV, Peterson WL, et al. Epidemic gastritis with hypochlorhydria. *Gastroenterology*. 1979;76:1449–1457
 22. Gledhill T, Leicester R, Addis B, et al. Epidemic hypochlorhydria. *Br Med J (Clin Res Ed)*. 1985;290:1383–1386
 23. Harford WV, Barnett C, Lee E, Perez-Perez G, Blaser MJ, Peterson WL. Acute gastritis with hypochlorhydria: report of 35 cases with long term follow up. *Gut*. 2000;47:467–472
 24. Iijima K, Ohara S, Sekine H, et al. Changes in gastric acid secretion assayed by endoscopic gastrin test before and after *Helicobacter pylori* eradication. *Gut*. 2000;46:20–26
 25. Fox JG, Otto G, Taylor NS, Rosenblad W, Murphy JC. *Helicobacter mustelae*-induced gastritis and elevated gastric pH in the ferret (*Mustela putorius furo*). *Infect Immun*. 1991;59:1875–1880
 26. Takashima M, Furuta T, Hanai H, Sugimura H, Kaneko E. Effects of *Helicobacter pylori* infection on gastric acid secretion and serum gastrin levels in Mongolian gerbils. *Gut*. 2001;48:765–773
 27. Fox JG, Blanco MC, Yan L, et al. Role of gastric pH in isolation of *Helicobacter mustelae* from the feces of ferrets. *Gastroenterology*. 1993;104:86–92
 28. Sarker SA, Davidsson L, Mahmud H, et al. *Helicobacter pylori* infection, iron absorption, and gastric acid secretion in Bangladeshi children. *Am J Clin Nutr*. 2004;80:149–153
 29. Dale A, Thomas JF, Darboe MK, Coward WA, Harding M, Weaver LT. *Helicobacter pylori* infection, gastric acid secretion, and infant growth. *J Pediatr Gastroenterol Nutr*. 1998;26:393–397
 30. Weaver LT. Royal Society of Tropical Medicine and Hygiene Meeting at Manson House, London, 16 February 1995: Aspects of *Helicobacter pylori* infection in the developing and developed world—*Helicobacter pylori* infection, nutrition and growth of West African infants. *Trans R Soc Med Hyg*. 1995;89:347–350
 31. Park JH, Kim SY, Kim DW, Lee WG, Rhee KH, Youn HS. Correlation between *Helicobacter pylori* infection and vitamin C levels in whole blood, plasma, gastric juice, and the pH of gastric juice in Korean children. *J Pediatr Gastroenterol Nutr*. 2003;37:53–62
 32. McCallion WA, Ardill JE, Bamford KB, Potts SR, Boston VE. Age dependent hypergastrinaemia in children with *Helicobacter pylori* gastritis: evidence of early acquisition of infection. *Gut*. 1995;37:35–38
 33. Baysoy G, Ertem D, Ademoglu E, Kotiloglu E, Keskin S, Pehlivanoglu E. Gastric histopathology, iron status and iron deficiency anaemia in children with *Helicobacter pylori* infection. *J Pediatr Gastroenterol Nutr*. 2004;38:146–151
 34. Howden CW, Hunt RH. The relationship between gastric acid secretion and infection. *Gut*. 1987;28:96–107
 35. Gilman RH, Partanen R, Brown KH, et al. Decreased gastric acid secretion and bacterial colonisation of the stomach of severely malnourished Bangladeshi children. *Gastroenterology*. 1988;94:1308–1314
 36. Giannella RA, Broitman SA, Zamcheck N. Salmonella enteritis: role of reduced gastric secretion in pathogenesis. *Am J Dig Dis*. 1971;16:1000–1006
 37. Khosla SN, Jain N, Khosla A. Gastric acid secretion in typhoid fever. *Postgrad Med J*. 1993;69:121–123
 38. Nalin DR, Levin RJ, Levine MM, et al. Cholera, non-*Vibrio cholera* and stomach acid. *Lancet*. 1978;2(8095):856–859
 39. Sack GH, Pierce NF, Hennessey KN, Mitra RC, Sack RB, Mazumder DNG. Gastric acidity in cholera and noncholera diarrhoea. *Bull World Health Organ*. 1972;47:31–36
 40. Cash RA, Music SI, Libonati JP, Snyder MJ, Wenzel RP, Hoenick RB. Response of man to infection with *Vibrio cholera*: clinical, serological, and bacteriologic responses to a known inoculum. *J Infect Dis*. 1974;129:45–52
 41. Evans CA, Gilman RH, Rabbani GH, Salazar G, Ali A. Gastric acid secretion and enteric infection in Bangladesh. *Trans R Soc Trop Med Hyg*. 1997;91:681–685
 42. Shahinian ML, Passaro DJ, Swerdlow DL, Mintz ED, Rodriguez M, Parsonnet J. *Helicobacter pylori* and epidemic *Vibrio cholera* O1 infection in Peru. *Lancet*. 2000;355:377–378
 43. Cook GC. Infective gastroenteritis and its relationship to reduced gastric acidity. *Scand J Gastroenterol Suppl*. 1985;111:17–23
 44. Lin J, Lee IS, Frey J, Slonczewski JL, Foster JW. Comparative analysis of extreme acid survival in *Salmonella typhimurium*, *Shigella flexneri*, and *E. coli*. *J Bacteriol*. 1995;177:4097–4104
 45. Martinsen TC, Bergh K, Waldum HL. Gastric juice: a barrier against infectious disease. *Basic Clin Pharmacol Toxicol*. 2005;96:94–102
 46. Laine L, Ahnen D, McLain C, Solcia E, Walsh JH. Review article: potential gastrointestinal effects of long-term acid suppression with proton pump inhibitors. *Aliment Pharmacol Ther*. 2000;14:651–668
 47. Dial S, Alrasadi K, Manoukian C, Huang A, Menzies D. Risk of *Clostridium difficile* diarrhea among hospital inpatients prescribed proton pump inhibitors: cohort and case-control studies. *CMAJ*. 2004;171:33–38
 48. Dial S, Delaney JA, Barkun AN, Suissa S. Use of gastric acid-suppressive agents and the risk of community-acquired *Clostridium difficile*-associated disease. *JAMA*. 2005;294:2989–2995
 49. Yearsley KA, Gilby LJ, Ramadas AV, Kubiak EM, Fone DL, Allison MC. Proton pump inhibitor therapy is a risk factor for *Clostridium difficile*-associated diarrhoea. *Aliment Pharmacol Ther*. 2006;24:613–619
 50. Cunningham R, Dale B, Undy B, Gaunt N. Proton pump inhibitors as a risk factor for *Clostridium difficile* diarrhoea. *J Hosp Infect*. 2003;54:243–245
 51. Black RE, Levine MM, Clements ML, Hughes TP, Blaser MJ.

- Experimental *Campylobacter jejuni* infections in humans. *J Infect Dis*. 1988;157:472–479
52. Khatami SS, Mukunda B, Ravakhah K. Co-infection with *Giardia lamblia* and *Clostridium difficile* after use of ranitidine. *Am J Med Sci*. 2004;327:91–93
 53. Nwolo C, Loft D, Holder R, Langman M. Increased incidence of bacterial diarrhoea in patients taking gastric acid antsecretory drugs. *Eur J Clin Gastroenterol Hepatol*. 1994;6:693–699
 54. Neal KR, Briji SO, Slack RC, Hawkey CJ, Logan RF. Recent treatment with H2 antagonists and antibiotics and gastric surgery as risk factors for salmonella infection. *BMJ*. 1994;308:176
 55. Neal KR, Scott HM, Slack RCB, Logan R. Omeprazole as a risk factor for *Campylobacter* gastroenteritis: a case control study. *BMJ*. 1996;312:414–415
 56. Reynaert H, Fernandes E, Bourgain C, Smekens L, Devis G. Proton pump inhibition and gastric giardiasis: a causal or casual association? *J Gastroenterol*. 1995;30:775–778
 57. Canani RB, Cirillo P, Roggero P, et al. Therapy with gastric acidity inhibitors increases the risk of acute gastroenteritis and community acquired pneumonia in children. *Pediatrics*. 2006;117(5). Available at: www.pediatrics.org/cgi/content/full/117/5/e817
 58. Sarker SA, Gyr K. Non-immunological defence mechanisms of the gut. *Gut*. 1992;33:987–993
 59. Clemens J, Albert MJ, Rao M, et al. Impact of infection by *Helicobacter pylori* on the risk and severity of endemic cholera. *J Infect Dis*. 1995;171:1653–1656
 60. Leon-Barua R, Recavarren-Arce S, Chinga-Alayo E, et al. *Helicobacter pylori*-associated chronic atrophic gastritis involving the gastric body and severe disease by *Vibrio cholerae*. *Trans Roy Soc Trop Med Hyg*. 2006;100:567–572
 61. Bhan MK, Bahl R, Sazawai S, et al. Association between *Helicobacter pylori* infection and increased risk of typhoid fever. *J Infect Dis*. 2002;186:1857–1860
 62. Vollaard AM, Verspaget HW, Ali S, Visser LG, et al. *Helicobacter pylori* infection and typhoid fever in Jakarta, Indonesia. *Epidemiol Infect*. 2006;134:163–170
 63. Shmueli H, Samra Z, Ashkenazi S, Dinari G, Chodick G, Yahav J. Association of *Helicobacter pylori* infection with *Shigella* gastroenteritis in young children. *Am J Gastroenterol*. 2004;99:2041–2045
 64. Torres J, Perez GP, Ximenez C, et al. Association of intestinal parasitosis and *H. pylori* infection in children and adults from a Mexican community with high prevalence of parasitosis. *Helicobacter*. 2003;8:179–185
 65. Passaro DJ, Taylor DN, Meza R, Cabrera L, Gilman RH, Parsonnet J. Acute *Helicobacter pylori* infection is followed by an increase in diarrheal disease among Peruvian children. *Pediatrics*. 2001;108(5). Available at: www.pediatrics.org/cgi/content/full/108/5/e87
 66. Bravo LE, Mera R, Reina JC, et al. Impact of *Helicobacter pylori* infection on growth of children: a prospective cohort study. *J Pediatr Gastroenterol Nutr*. 2003;37:614–619
 67. Passaro DJ, Taylor DN, Gilman RH, Cabrera L, Parsonnet J. Growth slowing after acute *Helicobacter pylori* infection is age-dependent. *J Pediatr Gastroenterol Nutr*. 2002;35:522–526
 68. Choe YH, Kim SK, Hong YC. *Helicobacter pylori* infection with iron deficiency anaemia and subnormal growth at puberty. *Arch Dis Child*. 2000;82:136–140
 69. Demir H, Saltik IN, Kocak N, Yuce A, Ozen H, Gurakan F. Subnormal growth in children with *Helicobacter pylori* infection. *Arch Dis Child*. 2001;84:89–90
 70. Tasar A, Kibrisli E, Dallar Y. Seroprevalence of *Helicobacter pylori* in children with constitutional height retardation. *Turk J Gastroenterol*. 2006;17:7–12
 71. Berkman DS, Lescano AG, Gilman RH, Lopez SL, Black MM. Effects of stunting, diarrhoeal disease, and parasitic infection during infancy on cognition in late childhood: a follow-up study. *Lancet*. 2002;359:564–571
 72. Skikine BS, Lynch SR, Cook JK. Role of gastric acid in food iron absorption. *Gastroenterology*. 1981;81:1068–1071
 73. Conrad ME, Umbreit JN, Moore EG. Iron absorption and transport. *Am J Med Sci*. 1999;318:213–219
 74. Yakoob J, Jafri W, Abid S. *Helicobacter pylori* infection and micronutrient deficiencies. *World J Gastroenterol*. 2003;9:2137–2139
 75. Cardenas VM, Mulla ZD, Ortiz M, Graham DY. Iron deficiency and *Helicobacter pylori* infection in the United States. *Am J Epidemiol*. 2006;163:127–134
 76. DuBois S, Kearney DJ. Iron-deficiency anaemia and *Helicobacter pylori* infection: a review of the evidence. *Am J Gastroenterol*. 2005;100:453–459
 77. Milman N, Rosenstock S, Andersen L, Jorgensen T, Bonnevie O. Serum ferritin, hemoglobin, and *Helicobacter pylori* infection: a seroepidemiologic survey comprising 2794 Danish adults. *Gastroenterology*. 1998;115:268–274
 78. Parkinson AJ, Gold BD, Bulkow L, et al. High prevalence of *Helicobacter pylori* infection in the Alaska native population and association with low serum ferritin levels in young adults. *Clin Diagn Lab Immunol*. 2000;7:885–888
 79. Konno M, Muraoka S, Takahashi M, Imai T. Iron-deficiency anemia associated with *Helicobacter pylori* gastritis. *J Pediatr Gastroenterol Nutr*. 2000;31:52–56
 80. Choe YH, Kim SK, Son BK, Lee DH, Hong YC, Pai SH. Randomized placebo-controlled trial of *Helicobacter pylori* eradication for iron-deficiency anemia in preadolescent children and adolescents. *Helicobacter*. 1999;4:135–139
 81. Barabino A, Dufour C, Marino CE, Claudiani F, De Alessandri A. Unexplained refractory iron-deficiency anemia associated with *Helicobacter pylori* gastric infection in children: further clinical evidence. *J Pediatr Gastroenterol Nutr*. 1999;28:116–119
 82. Baggett HC, Parkinson AJ, Muth PT, Gold BD, Gessner BD. Endemic iron deficiency associated with *Helicobacter pylori* infection among school aged children in Alaska. *Pediatrics*. 2006;117(3). Available at: www.pediatrics.org/cgi/content/full/117/3/e396
 83. Dufour C, Brisigotti M, Fabretti G, Luxardo P, Mori PG, Barabino A. *Helicobacter pylori* gastric infection and sideropenic refractory anaemia. *J Pediatr Gastroenterol Nutr*. 1993;17:225–227
 84. Marignani M, Angeletti S, Bordini C, et al. Reversal of long standing iron deficiency anaemia after eradication of *Helicobacter pylori*. *Scand J Gastroenterol*. 1997;32:617–622
 85. Annibale B, Capurso G, Lahner E, et al. Concomitant alterations in intragastric pH and ascorbic acid concentration in patients with *Helicobacter pylori* gastritis and associated iron deficiency anaemia. *Gut*. 2003;52:496–501
 86. Ratledge C, Dover LG. Iron metabolism in pathogenic bacteria. *Annu Rev Microbiol*. 2000;54:881–941
 87. Weinberg ED. Iron and susceptibility to infectious disease. *Science*. 1974;184:952–956
 88. Velayudhan J, Hughes NJ, McCollm AA, et al. Iron acquisition and virulence in *Helicobacter pylori*: a major role for FeoB, a high-affinity ferrous iron transporter. *Mol Microbiol*. 2000;37:274–286
 89. Choe YH, Oh YJ, Lee NG, et al. Lactoferrin sequestration and its contribution to iron-deficiency anemia in *Helicobacter pylori*-infected gastric mucosa. *J Gastroenterol Hepatol*. 2003;18:980–985
 90. Stoltzfus RJ, Chwaya HM, Tielsch JM, Schulze KJ, Albonico M, Savioli L. Epidemiology of iron deficiency anaemia in Zanzibari schoolchildren: the importance of hookworms. *Am J Clin Nutr*. 1997;65:153–159
 91. Oppenheimer SJ. Iron and its relation to immunity and infec-

- tious disease. *J Nutr.* 2001;131(2S-2):616S-633S; discussion 633S-635S
92. Grantham-McGregor S, Ani C. A review of studies on the effect of iron deficiency on cognitive development in children. *J Nutr.* 2001;131(2S-2):649S-666S; discussion 666S-668S
 93. Rothenbacher D, Blaser MJ, Bode G, Brenner H. Inverse relationship between gastric colonization of *Helicobacter pylori* and diarrheal illness in children: results of a population-based cross-sectional study. *J Infect Dis.* 2000;182:1446-1449
 94. Perry S, Sanchez L, Yang S, Haggerty TD, Hurst P, Parsonnet J. *Helicobacter pylori* and risk of gastroenteritis. *J Infect Dis.* 2004; 190:303-310

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