How labile is gastric infection with *H pylori*?

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Abstract

It is known that patients infected with *H pylori* can spontaneously become free from infection, and that the reverse change can occur. The time-scale of these conversions is expressed as percentages per year. Since they have been investigated in terms of serology, the changes are called sero-reversion and sero-conversion respectively. Using serological evidence to investigate these phenomena is open to the criticisms that positive serology can be present in the absence of all other evidence of infection, and that a time-lag of 6-12 mo or longer can occur between eradication of the infection and sero-reversion. Investigations using direct evidence of current infection are sparse. The few that exist suggest that some individuals can seroconvert or sero-revert within six to twelve weeks. If these findings are confirmed, it means that some patients have an ability to recover from, *H pylori* infection. Evidence suggests that the deciding factor of susceptibility is the level of gastric secretion of acid.

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EVIDENCE OF LABILITY OF *H PYLORI*

INFECTION

Evidence from indirect tests: Spontaneous seroconversion and sero-reversion

In papers concerned with human infections of the gastroduodenum with *H pylori*, it is usually tacitly assumed that infection is stable, i.e., that a subject infected at any one moment will remain infected until the organism is eradicated with pharmacological agents. There is considerable evidence based on serological studies that *H pylori* infection can be more labile, with subjects undergoing spontaneous sero-reversion as well as sero-conversion. Reports from countries where the prevalence of *H pylori* infection is moderate (40%-60%) show that spontaneous cures may occur even more frequently than fresh infections, and more often in children and teenagers than in adults[1-14]. The question is, do these figures adequately reflect the rates of the changes?

In children, of a total of 1134 children who were *H pylori* negative, 92 had converted to *H pylori*-positive during intervals ranging from 9 to 14 years[2-6]. The percentage conversion rates differed from 40 percent after 10 and 14 years to 5% or less after 2, 10 and 14 years. The same publications documented that of a total of 141 *H pylori*-positive patients 58 reverted to *H pylori* negative over the same periods. The sero-reversion rates in the five studies varied between 15% at 14 years and 80% at 10 years.

In these reports of children, there is no evidence that the length of follow-up is related to sero-conversion or sero-reversion rates. The lack of evidence of a link between the rates and the length of follow-up may be due to the (necessarily) small range of follow-up in an age group defined as children and teenagers. The salient feature of these results is that the sero-conversion rate overall was 92/1134 (8.1%), while the sero-reversion rate was 58/141 (41%). A small tendency for children to develop the infection as time passed was considerably outweighed by a five-fold tendency towards natural cure.

In adults, there is strong evidence that both sero-conversion and sero-reversion rates increase with the duration of follow-up. Eight publications[7-14] yielded the following statistical results. Over a time-interval of 3-32 years, 94 (2.7%) of 3489 subjects sero-converted; regression analysis indicated that the number converting increased by 0.311 per cent per annum ($r^2 = 0.836, P = 0.0015$). The corresponding figures for sero-reversion were 109 (6.04%) of 1806 subjects; the regression values were an increased rate of reversion of 0.676 per cent per annum ($r^2 = 0.747, P = 0.0056$). In adults, therefore, conversion rates per annum were outweighed by a doubled rate of sero-reversion.

Comparisons between the two rates in adults and the two in children are strictly impossible because of the lack of correlation in children with length of follow-up. However, if one is prepared to accept that the yearly rates in children (in whom the average length of follow-up was...
about 11 years) were, for sero-conversion 8.1/11 = 0.74%, for sero-reversion 41/11 = 3.73%, it is clear that infection status derived from antibody information in children is more labile in both directions than it is in adults.

The evidence from countries with a high prevalence of infection with H. pylori is scanty. There are only three papers\cite{15-17} from Japan where, on the published evidence, the prevalence is variable (36%-87%), and only one of these papers gives data for children; and two from Brazil where the prevalence is very high (80%) - one for children\cite{18} and one for adults\cite{19}. Regression analysis to determine whether length of follow-up is related to the conversion rates is inappropriate. Moreover, it is clear that in Japan sero-conversion rates are only slightly lower than sero-reversion rates, 5/86 (5.8%) versus 2/22 (8.1%) in children and 66/1038 (6.4%) versus 149/2103 (7.1%) in adults, whereas in Brazil the rates of sero-conversion are high 5/78 (6.41%) in less than 2 years in children, 5/46 (10.87%) in 3 years in adults, while in children there was a zero reversion rate and in adults only 1 of 173 H. pylori-positive subjects reverted.

There seems little doubt that the sero-conversion rate rises with the overall prevalence of the infection in the population, that where the prevalence is moderate the tendency to spontaneous cure overtakes the rate of new infections, but where the prevalence is high there is practically no spontaneous cure. These conclusions depend on the assumptions that sero-positivity means the presence of infection, sero-negativity means its absence.

The time periods of the quoted studies range from 20 mo to 32 years. It is tacitly assumed by the authors that sero-reversion and sero-conversion rates represent the averages of a slow single rate in each direction. However, it is also conceivable that during these times changes in infection status might have occurred several times in both directions.

These reports seem to assume that serological evidence of the presence or absence of antibodies to H. pylori indicates the presence or absence of the infection. The fact is that the presence of antibodies indicates exposure to the infecting organism in the past, but does not indicate current infection. Indeed, there are reports of positive serology in the absence of other positive tests for infection\cite{20-23}. Moreover there is a known time lag of 6-12 mo\cite{24-27} or even longer between eradication of infection and reversion of serology to normal\cite{20,21}.

**Evidence from direct tests: Histology and urea breath test**

Only a few reports base their opinions on direct methods such as the urea breath test (UBT) or histology. There are two reports of children showing changes either way within 3 mo\cite{28,29} and one reporting such changes within 6 mo in both children and adults\cite{30} using the urea breath test. There are two reports based on histology in adult patients, one showing 5/39 patients becoming H. pylori negative over a ten year period\cite{31}, and another reporting 9% of patients becoming positive and 9% becoming negative over a 6 years period\cite{32}. However, there is some direct evidence that infection can be even more labile than the above evidence suggests. There is one significant report in a Master of Surgery Thesis\cite{33} involving adults. Some aspects of this study have been reported\cite{34}. Two hundred and eight patients undergoing endoscopy for dyspepsia were categorized as H. pylori-positive or -negative, using the biopsy-urease, culture and polymerase chain reaction tests. The patients received no anti-H. pylori treatment. The first hundred of these patients to volunteer (14 duodenal ulcer, 5 gastric ulcer, 16 oesophagitis, 46 non-ulcer dyspepsia (NUD) and 19 Others) were examined between 6 and 12 wk later and re-categorized as positive or negative, using a non-invasive C-urea breath test. Of 42 patients positive for H. pylori at endoscopy, 8 (19%) had become negative at the later breath test; and of 58 patients negative at endoscopy, 15 (26%) had become positive at the later breath test. The results suggest that H. pylori-status in the adult can alter in both directions within a few weeks. The PCR test was done at the time of the endoscopy but, at the time of the follow-up, because it was not clinically justifiable to repeat endoscopy, the UBT was used.

It may be criticised that the results from two different tests may not be comparable. There is considerable evidence, however, that PCR and UBT vie with each other as the gold standard for H. pylori-status, and therefore are highly unlikely to give divergent results\cite{24-26,35-40}. Indeed, it has been shown that PCR results can be used to determine the optimal cut-off point for the breath test results\cite{41}, and that both tests can be used to determine not only the presence of, but also the weight of infection with, the organism\cite{42}. The evidence from the later breath tests can, therefore, be relied on as at least as satisfactory as that from the PCR tests at the time of endoscopy. It follows that in this study during a period of 6 to 12 wk there was a 20%-25% change of H. pylori-status in both directions.

**The possible effect of gastric pH on H. pylori infection**

One possible explanation is that the ability of H. pylori to colonize the stomach (and gastric-type epithelium in the duodenum) is dependent on the local luminal pH. Extremes of pH in either direction kill the organism\cite{43,44}. The patients with peptic ulcer (whether gastric or duodenal), with reflux oesophagitis, and some of those with other lesions would have received acid-suppression agents during the period between the two examinations, and this fact might explain why patients negative at endoscopy later became positive. There is evidence that acid-suppression promotes gastritis associated with H. pylori infection\cite{45}. For movements in status in the opposite direction, in patients given a clean bill of health (NUD) or those in the group with diagnoses that did not seem related to gastric hyperacidity, the later withdrawal of acid-suppressing agents given prior to the endoscopy that excluded an ulcer might be the cause of the reversion from positive to negative. It is interesting to recall that, when Marshall\cite{46} in 1985 swallowed a culture of H. pylori, he took 600 mg of cimetidine 3 h before to reduce the acidity. Thereafter, stomach acidity would have returned to normal, and whilst stomach biopsies taken one week later were positive for H. pylori, those taken at two weeks had become negative.
CONCLUSION

The above findings show that the H pylori-status of adults can alter in both directions in a matter of a few weeks and that the infection is much more labile than previously realised. The known time lag of 6-12 mo between eradication of infection and seroconversion to normal compared with 6 wk for UBT, and the unknown time lag between the inception of infection and seroconversion, are features that cast some doubt on whether seroconversion could have demonstrated this lability.

REFERENCES

1 Xia HH, Talley NJ. Natural acquisition and spontaneous elimination of Helicobacter pylori infection: clinical implications. Am J Gastroenterol 1997; 92: 1780-1787

2 Granström M, Tindberg Y, Blennow M. Seroepidemiology of Helicobacter pylori infection in a cohort of children monitored from 6 months to 11 years of age. J Clin Microbiol 1997; 35: 468-470

3 Malaty HM, El-Kasabany A, Graham DY, Miller CC, Reddy SG, Srinivasan SR, Yamaoka Y, Berenson GS. Age at acquisition of Helicobacter pylori infection: a follow-up study from infancy to adulthood. Lancet 2002; 359: 931-935

4 Fawcett JP, Shaw JP, Brooke M, Walker A, Barbezat GO. Sero-prevalence of Helicobacter pylori in a longitudinal study of New Zealanders at ages 11 and 21. Aust N Z J Med 1998; 28: 585-589

5 Ashorn M, Mäki M, Hallström M, Uhart M, Akerblom HK, Viikari J, Miettinen A. Helicobacter pylori infection in Finnish children and adolescents. A serologic cross-sectional and follow-up study. Scand J Gastroenterol 1995; 30: 876-879

6 Granquist A, Bredberg A, Seger T, Axelsson I. A longitudinal cohort study on the prevalence of Helicobacter pylori antibodies in Swedish children and adolescents. Acta Paediatr 2002; 91: 636-640

7 Cullen DJ, Collins BJ, Christiansen KJ, Epi J, Warren JR, Surveyor I, Cullen KJ. When is Helicobacter pylori infection acquired? Gut 1993; 34: 1681-1682

8 Rosenstock SJ, Anderson LP, Bonnevie O, Jørgensen J. Sero-conversion and sero-reversion in IgG antibodies to Helicobacter pylori: an 11-year follow-up of 2523 randomly selected Danes. Gut 1996; 39 Suppl 2: A3

9 Veldhuizen van Zanten SJ, Pollak PT, Best LM, Bezanson MR. Increasing prevalence of Helicobacter pylori infection with age: continuous risk of infection in adults rather than cohort effect. J Infect Dis 1994; 169: 434-437

10 Kuipers EJ, Peña AS, van Kamp G, Uytterlinde AM, Pals G, Pels NF, Kurz-Pohlmann E, Meuwissen SG. Seroconversion for Helicobacter pylori. Lancet 1993; 342: 328-331

11 Parsonnet J, Blaser MJ, Perez-Perez GI, Hargrett-Bean N, Tauxe RV. Symptoms and risk factors of Helicobacter pylori infection in a cohort of epidemiologists. Gastroenterology 1992; 102: 41-46

12 Valle J, Kekki M, Sipponen P, Ihamaki T, Siurala M. Long-term course and consequences of Helicobacter pylori gastritis. Results of a 32-year follow-up study. Scand J Gastroenterol 1996; 31: 546-550

13 Menegatti M, Landi F, Palli D, Massardi B, Ricci C, Holton J, Ali A, Farinetti S, Mucci F, Sanvi C, Miglioli M, Vaira D. Seroconversion of Helicobacter pylori. A five-year follow-up in asymptomatic donors living in a Western country. Gut 1996; 39 Suppl 3: A60 (367)

14 Cilla G, Pérez-Trallero E, Montes M, Dario Pineiro L, Beristain X. Seroconversion and seroreversion rate of Helicobacter pylori pylori infection in women attended at hospital for delivery. Med Clin (Barc) 2003; 121: 86-88

15 Kumagai T, Malaty HM, Graham DY, Hosogaya S, Misawa K, Furuhata K, Ota H, Sei C, Tanaka E, Akamatsu T, Shimizu T, Kiyosawa K, Katsuyama T. Acquisition versus loss of Helicobacter pylori infection in Japan: results from an 8-year birth cohort study. J Infect Dis 1998; 178: 717-721

16 Kikuchi S, Ogihara A, Hasegawa A, Miki K, Kaneko E, Mizukoshi H. Seroconversion and seroreversion of Helicobacter pylori pylori antibodies over a 9-year period and related factors in Japanese adults. Helicobacter 2004; 9: 335-341

17 Banatvala N, Kashiwagi S, Abdi Y, Hayashi J, Hardie JM, Feldman RA. Helicobacter pylori pylori seroconversion and seroreversion in an Okinawan cohort followed for 10 years. Am J Gastroenterol 1994; 39: 1300 (Abst 62)

18 Rocha GA, Oliveira AMR, Queiroz DMM, Mendes EN, Moura SB, Rabello ALT, Amorim MN. High seroconversion for Helicobacter pylori pylori infection in children. Gut 1995; 37 Suppl 1: A27

19 Oliveira AMR, Queiroz DMM, Rocha GA, Mendes EN, Moura SB, Rabello ALT. High seroconversion for Helicobacter pylori pylori in adults from a developing country. Gut 1996; 39 Suppl 2: 886

20 Meyer B, Werth B, Beglinger C, Dill S, Drewe J, Vischer WA, Eggers RH, Bauer FE, Stalder GA. Helicobacter pylori pylori infection in healthy people: a dynamic process? Gut 1991; 32: 347-350

21 Kares WE, Samloff IM, Siurala M, Kekki M, Sipponen P, Kim SW, Walsh JH. Positive serum antibody and negative tissue staining for Helicobacter pylori pylori in subjects with atrophic body gastritis. Gastroenterology 1991; 101: 167-174

22 Rollán A, Giancaspero R, Arrese M, Figueroa C, Vollrath V, Schultz M, Duarte I, Vial P. Accuracy of invasive and noninvasive tests to diagnose Helicobacter pylori pylori infection after antibiotic treatment. Am J Gastroenterol 1997; 92: 1268-1274

23 Musgrove C, Bolton FJ, Kryszczyn AM, Templemer JM, Cairns SA, Owen WG, Hutchinson DN. Campylobacter pylori pylori: clinical, histological, and serological studies. J Clin Pathol 1988; 41: 1316-1321

24 Loffeld RJ, Stoberbring E, Flendrig JA, van Spreeuwel JP, Arends JW. Diagnostic value of an immunocassay to detect anti Campylobacter pylori pylori antibodies in non-ulcer dyspepsia. Lancet 1989; 1: 1182-1185

25 Mégraud F. Advantages and disadvantages of current diagnostic tests for the detection of Helicobacter pylori pylori. Scand J Gastroenterol Suppl 1996; 215: 57-62

26 Rautelin H, Lehours P, Mégraud F. Diagnosis of Helicobacter pylori pylori pylori infection. Helicobacter 2003; 3 Suppl 1: 13-20

27 Makristathis A, Hirschl AM, Lehours P, Mégraud F. Diagnosis of Helicobacter pylori pylori infection. Helicobacter 2004; 8 Suppl 1: 7-14

28 Klein PD, Gilman RH, Leon-Barua R, Diaz F, Smith EO, Graham DY. The epidemiology of Helicobacter pylori pylori in Peruvian children between 6 and 30 months of age. Am J Gastroenterol 1994; 89: 2196-2200

29 Thomas JE, Dale A, Harding M, Coward WA, Cole TJ, Weaver LT. Helicobacter pylori pylori colonization in early life. Pediatr Res 1999; 45: 218-223

30 Leal-Herrera Y, Torres J, Monath TP, Ramos I, Gomez A, Madrazo-de la Garza A, Dehesa-Violante M, Muñoz O. High rates of recurrence and of transient re-infections of Helicobacter pylori pylori in a population with high prevalence of infection. Am J Gastroenterol 2003; 98: 2395-2402

31 Niemelä S, Karttunen T, Kerola T. Helicobacter pylori pylori-associated gastritis. Evolution of histologic changes over 10 years. Scand J Gastroenterol 1995; 30: 542-549

32 Villako K, Maards H, Tammm R, Kevallik R, Peetsalu M, Sipponen P; Kekki M, Siurala M, Helicobacter (Campylobacter) pylori pylori infection and the development and progression of chronic gastritis: results of long-term follow-up examinations of a random sample. Endoscopy 1990; 22: 114-117

33 Oshowo AO. The direction of the relationship between Helicobacter pylori pylori and duodenal ulcer. Master of Surgery Thesis. University of London 1999

34 Boulos PB, Botha A, Hobsley M, Holton J, Oshowo AO, Tovey FL. Possible absence of Helicobacter pylori pylori in the early stages of duodenal ulceration. QJM 2002; 95: 749-752

35 Shimoda Y, Fukuda S, Munakata A, Yoshida Y, Shimoyama T, Validity of various diagnostic tests to evaluate cure of Helicobacter pylori pylori infection. J Gastroenterol
36 Kobayashi D, Eishi Y, Ohkusa T, Ishige T, Minami J, Yamada T, Takizawa T, Koike M. Gastric mucosal density of Helicobacter pylori estimated by real-time PCR compared with results of urea breath test and histological grading. J Med Microbiol 2002; 51: 305-311

37 Wong BC, Wong WM, Wang WH, Tang VS, Young J, Lai KC, Yuen ST, Leung SY, Hu WH, Chan CK, Hui WM, Lam SK. An evaluation of invasive and non-invasive tests for the diagnosis of Helicobacter pylori infection in Chinese. Aliment Pharmacol Ther 2001; 15: 505-511

38 Monteiro L, de Mascarel A, Sarrasqueta AM, Bergey B, Barberis C, Talby P, Roux D, Shouler L, Goldfain D, Lamouliatte H, Mégraud F. Diagnosis of Helicobacter pylori infection: noninvasive methods compared to invasive methods and evaluation of two new tests. Am J Gastroenterol 2001; 96: 353-358

39 Andersen LP, Kiilerick S, Pedersen G, Thoreson AC, Jørgensen F, Rath J, Larsen NE, Børup O, Krosgfild K, Scheibel J, Rune S. An analysis of seven different methods to diagnose Helicobacter pylori infections. Scand J Gastroenterol 1998; 33: 24-30

40 Thijs JC, van Zweet AA, Thijs WJ, Oey HB, Karrenbeld A, Stellaard F, Luijt DS, Meyer BC, Kleibeuker JH. Diagnostic tests for Helicobacter pylori: a prospective evaluation of their accuracy, without selecting a single test as the gold standard. Am J Gastroenterol 1996; 91: 2125-2129

41 Yoshida H, Hirota K, Ogura K, Maeda S, Shiratori Y, Sasaki Y, Omata M. Determination of the optimal cut-off value for the [13C]-urea breath test based on a Helicobacter pylori-specific polymerase chain reaction assay. J Gastroenterol Hepatol 2000; 15: 155-160

42 Furuta T, Kaneko E, Suzuki M, Arai H, Futami H. Quantitative study of Helicobacter pylori in gastric mucus by competitive PCR using synthetic DNA fragments. J Clin Microbiol 1996; 34: 2421-2425

43 Dykhuizen RS, Fraser A, McKenzie H, Golden M, Leifert C, Benjamin N. Helicobacter pylori is killed by nitrite under acidic conditions. Gut 1998; 42: 334-337

44 Sjöström JE, Larsson H. Factors affecting growth and antibiotic susceptibility of Helicobacter pylori: effect of pH and urea on the survival of a wild-type strain and a urease-deficient mutant. J Med Microbiol 1996; 44: 425-433

45 Meining A, Bosseckert H, Caspary WF, Nauert C, Stolte M. H2-receptor antagonists and antacids have an aggravating effect on Helicobacter pylori gastritis in duodenal ulcer patients. Aliment Pharmacol Ther 1997; 11: 729-734

46 Marshall BJ, Armstrong JA, McGeoch DB, Claney RJ. Attempt to fulfil Koch’s postulates for pyloric Campylobacter. Med J Aust 1985; 142: 436-439

S- Editor Liu Y  L- Editor Alpini GD  E- Editor Lu W