

How labile is gastric infection with *H pylori*?

M Hobsley, FI Tovey, J Holton

M Hobsley, FI Tovey, J Holton, Departments of Surgery and Medical Microbiology, Royal Free and University College Medical School, United Kingdom

Correspondence to: FI Tovey, Departments of Surgery and Medical Microbiology, Royal Free and University College Medical School, London W1W 7EJ, 5 Crossborough Hill Basingstoke RG 21 4AG, United Kingdom. frank.tovey@btinternet.com

Telephone: +44-1256-461521 Fax: +44-1256-461521

Received: 2007-06-13 Accepted: 2007-06-28

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 that is variable in time to resist, or spontaneously recover from, *H pylori* infection. Evidence suggests that the deciding factor of susceptibility is the level of gastric secretion of acid.

© 2007 WJG. All rights reserved.

Key words: *H pylori*; Lability of infection; Serology; Conversion; Reversion

Hobsley M, Tovey FI, Holton J. How labile is gastric infection with *H pylori*? *World J Gastroenterol* 2007; 13(35): 4665-4668

<http://www.wjgnet.com/1007-9327/13/4665.asp>

EVIDENCE OF LABILITY OF *H PYLORI* INFECTION

Evidence from indirect tests: Spontaneous seroconversion and seroreversion

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 in periods 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^[15-17] from Japan where, on the published evidence, the prevalence is variable (36%-87%), and only one^[15] of these papers gives data for children; and two from Brazil where the prevalence is very high (80%) - one for children^[18] and one for adults^[19]. Regression analysis to determine whether length of follow-up is related to the conversion rates is inappropriate. However, 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^[20-23]. Moreover there is a known time lag of 6-12 mo^[24-27] or even longer between eradication of infection and reversion of serology to normal^[20-23].

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^[28,29] and one reporting such changes within 6 mo in both children and adults^[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^[31], and another reporting 9% of patients becoming positive and 9% becoming negative over a 6 years period^[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^[33] involving adults. Some aspects of this study have been reported^[34]. Two hundred and eight patients undergoing endoscopy for dyspepsia were categorized as *H pylori*-positive or -negative, using the biopsy-rapid 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 ¹³C-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^[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^[41], and that both tests can be used to determine not only the presence of, but also the weight of infection with, the organism^[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^[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^[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^[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^[22-25] between eradication of infection and reversion of serology to normal compared with 6 wk for UBT^[22], and the unknown time lag between the inception of infection and seroconversion, are features that cast some doubt on whether serology could have demonstrated this lability.

REFERENCES

- Xia HH, Talley NJ. Natural acquisition and spontaneous elimination of *Helicobacter pylori* infection: clinical implications. *Am J Gastroenterol* 1997; **92**: 1780-1787
- 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
- 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
- Fawcett JP, Shaw JP, Brooke M, Walker A, Barbezat GO. Seroprevalence of *Helicobacter pylori* in a longitudinal study of New Zealanders at ages 11 and 21. *Aust N Z J Med* 1998; **28**: 585-589
- Ashorn M, Mäki M, Hällström M, Uhari 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
- Granquist A, Bredberg A, Sveger 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
- Cullen DJ, Collins BJ, Christiansen KJ, Epis J, Warren JR, Surveyor I, Cullen KJ. When is *Helicobacter pylori* infection acquired? *Gut* 1993; **34**: 1681-1682
- 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
- Veldhuyzen van Zanten SJ, Pollak PT, Best LM, Bezanson GS, Marrie T. 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
- 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
- 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
- Valle J, Kekki M, Sipponen P, Ihmäki 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
- Menegatti M, Landi F, Palli D, Massardi B, Ricci C, Holton J, Ali A, Farinelli S, Mucci F, Saieva 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)
- Cilla G, Pérez-Trallero E, Montes M, Darío Piñeiro L, Beristain X. Seroconversion and seroreversion rate of *Helicobacter pylori* infection in women attended at hospital for delivery. *Med Clin (Barc)* 2003; **121**: 86-88
- Kumagai T, Malaty HM, Graham DY, Hosogaya S, Misawa K, Furihata 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
- Kikuchi S, Ohgihara A, Hasegawa A, Miki K, Kaneko E, Mizukoshi H. Seroconversion and seroreversion of *Helicobacter pylori* antibodies over a 9-year period and related factors in Japanese adults. *Helicobacter* 2004; **9**: 335-341
- Banatvalu N, Kashiwagi S, Abdi Y, Hayashi J, Hardie JM, Feldman RA. *Helicobacter pylori* seroconversion and seroreversion in an Okinawan cohort followed for 10 years. *Am J Gastroenterol* 1994; **39**: 1300 (Abst 62)
- Rocha GA, Oliveira AMR, Queiroz DMM, Mendes EN, Moura SB, Rabello ALT, Amorin MN. High seroconversion for *Helicobacter pylori* infection in children. *Gut* 1995; **37** Suppl 1: A27
- Oliveira AMR, Queiroz DMM, Rocha GA, Mendes EN, Moura SBI, Rabello ALT. High seroconversion for *Helicobacter pylori* in adults from a developing country. *Gut* 1996; **39** Suppl 2: A86
- Meyer B, Werth B, Beglinger C, Dill S, Drewe J, Vischer WA, Eggers RH, Bauer FE, Stalder GA. *Helicobacter pylori* infection in healthy people: a dynamic process? *Gut* 1991; **32**: 347-350
- Karnes WE, Samloff IM, Siurala M, Kekki M, Sipponen P, Kim SW, Walsh JH. Positive serum antibody and negative tissue staining for *Helicobacter pylori* in subjects with atrophic body gastritis. *Gastroenterology* 1991; **101**: 167-174
- 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* infection after antibiotic treatment. *Am J Gastroenterol* 1997; **92**: 1268-1274
- Musgrove C, Bolton FJ, Kryptczyk AM, Temperley JM, Cairns SA, Owen WG, Hutchinson DN. *Campylobacter pylori*: clinical, histological, and serological studies. *J Clin Pathol* 1988; **41**: 1316-1321
- Loffeld RJ, Stobberingh E, Flendrig JA, van Spreeuwel JP, Arends JW. Diagnostic value of an immunoassay to detect anti *Campylobacter pylori* antibodies in non-ulcer dyspepsia. *Lancet* 1989; **1**: 1182-1185
- Mégraud F. Advantages and disadvantages of current diagnostic tests for the detection of *Helicobacter pylori*. *Scand J Gastroenterol Suppl* 1996; **215**: 57-62
- Rautelin H, Lehours P, Mégraud F. Diagnosis of *Helicobacter pylori* infection. *Helicobacter* 2003; **8** Suppl 1: 13-20
- Makristathis A, Hirschl AM, Lehours P, Mégraud F. Diagnosis of *Helicobacter pylori* infection. *Helicobacter* 2004; **9** Suppl 1: 7-14
- Klein PD, Gilman RH, Leon-Barua R, Diaz F, Smith EO, Graham DY. The epidemiology of *Helicobacter pylori* in Peruvian children between 6 and 30 months of age. *Am J Gastroenterol* 1994; **89**: 2196-2200
- Thomas JE, Dale A, Harding M, Coward WA, Cole TJ, Weaver LT. *Helicobacter pylori* colonization in early life. *Pediatr Res* 1999; **45**: 218-223
- 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 reinfections of *Helicobacter pylori* in a population with high prevalence of infection. *Am J Gastroenterol* 2003; **98**: 2395-2402
- Niemelä S, Karttunen T, Kerola T. *Helicobacter pylori*-associated gastritis. Evolution of histologic changes over 10 years. *Scand J Gastroenterol* 1995; **30**: 542-549
- Villako K, Maards H, Tammur R, Keevallik R, Peetsalu M, Sipponen P, Kekki M, Siurala M. *Helicobacter* (*Campylobacter*) *pylori* infestation and the development and progression of chronic gastritis: results of long-term follow-up examinations of a random sample. *Endoscopy* 1990; **22**: 114-117
- Oshowo AO. The direction of the relationship between *Helicobacter pylori* and duodenal ulcer. Master of Surgery Thesis. University of London 1999
- Boulos PB, Botha A, Hobsley M, Holton J, Oshowo AO, Tovey FI. Possible absence of *Helicobacter pylori* in the early stages of duodenal ulceration. *QJM* 2002; **95**: 749-752
- Shimoyama T, Fukuda Y, Fukuda S, Munakata A, Yoshida Y, Shimoyama T. Validity of various diagnostic tests to evaluate cure of *Helicobacter pylori* infection. *J Gastroenterol*

- 1996; **31**: 171-174
- 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, Krogfelt 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 Zwet 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 **Dykhuisen 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, McGeachie DB, Glancy 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