Diagnosis of *H. pylori* infection: which is the best test? Stool test

Dino Vaira, Chiara Ricci, F. Perna, L. Gatta, A. Tampieri, M. Miglioli

Helicobacter pylori (*H. pylori*) is a human pathogen that causes chronic gastritis, has a role in gastric and duodenal ulcer, is involved in gastric carcinogenesis (so that the germ has been classified as a class I definite gastric carcinogen to human) and is regarded as a possible important factor in at least, a subset of patients with functional dyspepsia. *H. pylori* infection can be diagnosed by both invasive, i.e. requiring endoscopy, and non-invasive technique, i.e. techniques, which do not require endoscopy with biopsy sampling. Each of the available diagnostic technique has advantages as well as disadvantages and it is now clear that the discussion over the different diagnostic methods cannot be oversimplified by thinking just in term of "which is the best diagnostic tool?" The problem should be more connectedly addressed by asking "which is the best diagnostic tool in each definite situation?" This means that the choice has to take into account different factors such as: are we dealing with normal subjects screened for epidemiological purposes or with patients referred to the gastroenterologists? Is the patients already failed eradication attempt/s and are we looking for susceptibility to antibodies? Are we aiming only at diagnosing the infection in a clinical setting or are we interested in other possibly relevant factors (i.e. putative markers of increased virulence/pathogenicity of the strain as *cagA* e or *vacA)* in a research setting? Eventually we should also ask "when is the cost of the diagnostic tech-

nique employed?" Obviously taking into account all the factors involved as the need for the endoscopy or for technician/nurse to assist the patient, the need of dedicated laboratory instrumentation/material's (i.e. to evaluate breath sample) or the possibility to use facilities already widely available even in small hospital or in developing countries (as it is usually the case of serology). It is bearing in mind these and other similar questions that we will discuss the possibility of testing stool samples to non-invasively diagnose *H. pylori* infection.

Over the last few years it has been obtained the culture of *H. pylori* from stool samples but it has been also shown that viable organism are present only in a small percentage of cases.[1] Despite the difficulties encountered in colture from stool samples the fact that the organism was present at all raised the possibility of developing a new non-invasive diagnostic test on the detection of bacterial antigen in stool. Over the last two years an enzymatic immunoassay (EIA) which detects the presence of *H. pylori* antigen in stool specimen has become available (HpSA™- *H. pylori* Stool Antigen Meridian Diagnostics Inc., Cincinnati USA) and begun to be tested in clinical practice to evaluate its performance compared to that of the other already available diagnostic tests.

The HpSA test has recently received from the United States Food and Drugs Administration (FDA) with two indication for use: diagnosis of *H. pylori* infection in adults symptomatic patients and 2) monitoring response and post-therapy in adult patients. It is clear that such a test, which detects bacterial antigen in an actual ongoing infection, is theoretically useful not only for screening, but also as an early predictor of successful treatment. In this section we will briefly consider the currently available evidences supporting a possible role for non-invasive diagnostic test. There appears agreement that this HpSA is highly accurate in untreated patients.[2-20] The case at issue, however, concerns its value as a test of successful bacterial eradication.

The case at issue, however, concerns its value as a test of successful bacterial eradication.[3,4,8,16,20-24] Controversial results were reported by two authors. The first author,[4] by Makristathis et al. reports a specificity of 68.3% for HpSA in 55 patients tested 4 weeks following treatment. Surprisingly, in this study, PCR had an even lower specificity of 48.8%. These findings coat some doubts on the validity of the histology and culture results obtained. In contrast to the above report a recent study published by Trevisani et al[3] achieved a sensitivity and specificity of 93% and 82% respectively in 116 patients after treatment. They obtained 12 false positive results by HpSA but used a fixed cut-off without grey zone. In our experience, the wash-step is critical and may produce a high background. In fact most of the false positive cases in their study are borderline. A key point in our study is that we recognised a grey zone from 0.140 to 0.159. We undertook a

multicenter study, involving dedicated centres, and can not envisage a more appropriate experimental design. In the 501 patients the sensitivity and the specificity of UBT, were performed independently in each centre, as well as the HpSA, giving values of 95.3% and 97.7% respectively with 13 false positive and 5 false negative for UBT.

We have recently presented our completed post therapy follow-up study[21] using the 10 European centres, involved in the first paper. We were able to confirm sensitivity and a specificity of the HpSA and UBT of 93.8% and 96.9%, and 90.6% and 99.2%. These evaluation were assessed against endoscopy based tests for *H. pylori* status. Three other papers support our findings. The first from Germany, reports a sensitivity and specificity of 91.3% and 94.6% in 115 patients assessed four weeks after treatment.[8] The second, (on children with a mean age of 7 years), reports a sensitivity and specificity of 100% and 97.2% respectively[23] and the third one from Japan reporting a sensitivity and specificity of 90 and 98 respectively in 112 patients.[22]

From the data available it seems that the *H. pylori* stool assay represents a highly accurate diagnostic tool to detect *H. pylori* infection both before and shortly after therapy. As a test which is non invasive, accurate, simple and cost-effective it has the potential to become the preferred diagnostic tools in many different clinical setting from epidemiological studies to paediatric investigation, from pre-endoscopic screening policies to post-therapy monitoring.

REFERENCES

1 Thomas JE, Gibson GR, Darboe MK, et al. Isolation of *Helicobacter pylori* from human faeces. Lancet 1992;340:1194-5.
2. Trevisani L, Sartori S, Galvani F, et al. Detection of *Helicobacter pylori* in faeces with a new enzyme immunoassay method: preliminary results. Scand J Gastroenterol 1998;33: 893.
3. Trevisani L, Sartori S, Galvani F, et al. Evaluation of a new enzyme immunoassay for detecting *Helicobacter pylori* in faeces; a prospective pilot study. Am J Gastroenterol 1999;94:1831-3.
4. Makristathis A, Pasching E, Schùtze K, et al. Detection of *Helicobacter pylori* in stool specimens by PCR and Antigen Enzyme Immunoassay. J Clin Microbiol 1998;36:2772-4.
5. Vaira D, Malfertheiner P, Mégraud F, et al. Diagnosis of *Helicobacter pylori* infection using a novel, non-invasive antigen based assay in a European multicentre study. Lancet 1999;354:34-9.

6. Fanti L, Mezzi G, Cavallero A, et al. A new simple immunoassay for detecting *Helicobacter pylori* infection: antigen in stool specimens. Digestion 1999;60:456-60.
7. Archimandritis A. Diagnosis of *Helicobacter pylori* infection by HpSA test. Lancet 1999;ii:1209.
8. Braden B, Teuber G, Dietrich CF, et al. Stool test may defeat breath test: new faecal antigen detects *Helicobacter pylori* infection and eradication. BMJ 2000;320:148.
9. Oderda G, Rapa A, Ronchi B, et al. High accuracy if the *Helicobacter pylori* stool antigen test for detection of the infection in children. A multicentre Italian study. BMJ 2000;320:347-8.
10. Puspok A, Bakos S, Oberhuber G. A new non invasive method for detection of *Helicobacter*: validity in the routine clinical setting. Eur J Gastroenterol Hepatol 1999;11:1139-42.
11. Lehmann F, Drewe J, Terraciano L, et al. Comparison of stool immunoassay with standard methods for detecting *Helicobacter pylori* infection. BMJ 1999;319:1409-13.
12. Trevisani L, Sartori S, Ruina M, et al. *Helicobacter pylori* stool antigen test. Clinical evaluation and cost analysis of a new enzyme immunoassay. Dig Dis Sci 1999;44:2303-6.
13. Okhura R, Miwa H, Murai T, et al. Usefulness of a novel enzyme immunoassay for the detection of *Helicobacter pylori* in feces. Scand J Gastroenterol 2000;36:48-52.
14. Vakil N, Rhew D, Soll A, et al. Cost effectiveness of non invasive strategies for *Helicobacter pylori*. Am J Gastroenterol 2000;95:1691-8.
15. Braden B, Posselt HG, Ahrens P, et al. New immunoassay in stool provides an accurate noninvasive diagnostic method for *Helicobacter pylori* screening in children. Pediatrics 2000;106:115-7.
16. Masoero G, Lombardo L, Della Monica P, et al. Discrepancy between *Helicobacter pylori* stool test antigen assay and urea breath test in the detection of *Helicobacter pylori* infection. Dig Liv Dis 2000;32:285-90.
17. Manes G, Balzano A, Iaquinto G, et al. Accuracy of the stool antigen test in the diagnosis of *Helicobacter pylori* infection in the pre-treatment assessment and in patients on omeprazole therapy. Aliment Pharmacol and Ther 2000, in press.
18. Ni YH, Lin JT, Huang SF, et al. Accurate diagnosis of *Helicobacter pylori* infection by stool antigen test and other currently available tests in children. J Pediatr 2000;136:823-7.
19. Shepherd AJ, Williams CL, Doherty CP, et al. Comparison of an enzyme immunoassay for the detection of *Helicobacter pylori* antigens in the faeces with the urea breath test. Arch Dis Child 2000;83:268-70.
20. Fornè M, Dominguez J, Frenandez-Banares F, et al. Accuracy of an enzyme immunoassay for the detection of *Helicobacter pylori* in stool specimens in the diagnosis of infection and post-treatment check-up. Am J Gastroenterol 2000;95:2200-5.
21. Vaira D, Malfertheiner P, Mégraud F, et al. Non invasive antigen based assay for assessing *Helicobacter pylori* eradication. A European multicenter study. Am J Gastroenterol 2000;95:925-9.

22. Ishihara S, Kaji T, Kawamura A, et al. Diagnostic accuracy of a new non-invasive enzyme immunoassay for detecting *Helicobacter pylori* in stools after eradication therapy. Aliment Pharmacol Ther 2000;14:611-4.
23. Oderda G, Rapa A, Marinello D, et al. Usefulness of *Helicobacter pylori* stool antigen test to monitor response to eradication treatment in children. Aliment Pharmacol and Ther 2001;15:203-6.
24. Makristathis A, Barousch W, Pasching E, Binder C, Kuderna C, Appalter P, Rotter M, Hirschl A. Two enzyme immunoassays and PCR for detection of *Helicobacter pylori* in stool specimens from pediatric patients before and after eradication therapy. J Clin Microbiol 2000;38:3710-4.