Invasive or non-invasive methods for the diagnosis of subclinical coeliac disease?

I read with great interest the letters published in Gut on the role of small bowel biopsies and antiretail antibodies (EMA) as methods for diagnosing coeliac disease in patients with iron deficiency anaemia (IDA) (Gut 2001;49:595). In particular, Pearce et al seem to prefer EMA instead of histological evaluation because of the considerable resource implications for histology departments, and Scott seems to agree with Pearce’s affirmation even if he takes into consideration the important role of histological evaluation. However, I do not completely agree with the conclusions of these authors.

Firstly, I would debate the role of non-invasive methods in diagnosing subclinical/silent coeliac disease. In my experience, IDA is the main indication of subclinical forms of coeliac disease and thus it should be taken into consideration in clinical practice. Although EMA are a well known hallmark of coeliac disease and the prevalence is more than 90% in classical forms of coeliac disease, our study and other recent studies clearly showed that the prevalence of EMA (as well as AGA) is lower than expected in clinical practice,²⁸ probably due to the high prevalence of slight histological lesions in these patients (Marsh I-IIIa lesions according to the Marsh classification). In contrast, the sorbitol H₂-breath test (H₂-BT) seems to be more effective than EMA in diagnosing this form of coeliac disease, probably due to the better correlation with slight histological lesions.²⁸ In the light of these experiences, sorbitol H₂-BT may be a good alternative to small bowel biopsy in identifying coeliac disease in patients with IDA but unfortunately this is not always true. In fact, in clinical practice, it is easy to observe patients with IDA EMA – and a negative small bowel biopsy – who show slight histological lesions (Marsh I-III type lesions) with disappearance of IDA and improvement in histology after a gluten free diet (GFD) in these cases the use of non-invasive methods (such as EMA) may be a serious misfortune as we may run the risk of not identifying hidden coeliac disease. These experiences are very important and should be considered in the cost/benefit ratio of diagnosing coeliac disease.

Other important points are the patchiness of the disease, obvious for pathologists obtaining biopsies orientated sufficiently and the cost of small bowel biopsy. Pearce et al are not in favour of biopsy. Firstly, many patients suspected of having coeliac disease have upper gastrointestinal symptoms as an initial investigation which provides an opportunity to perform a biopsy on the second part of the duodenum. Although routine biopsies in all patients undergoing endoscopy would have significant cost implications, endoscopic abnormalities of the second portion of the duodenum associated with coeliac disease have been described, and these may be used to select patients for biopsy, even if recent studies have re-evaluated the accuracy of endoscopic markers of the disease.²⁹ Secondly, multiple biopsy samples obtained from the second portion of the duodenum overcome the problem of the patchiness of the histological lesions (and we routinely take at least six endoscopic biopsies from the descending duodenum). Also, the pathologist’s expertise in the Marsh classification of histological lesions in coeliac disease may certainly overcome the problem of incorrectly orientated biopsies. Thirdly, I disagree about the excessive expensive of histological evaluation. In Italy the cost of histological evaluations from a single biopsy (in this case descending duodenum) is about $12.40: I do not believe that this is an excessive additional cost to a routine upper gastrointestinal endoscopy.

In light of these considerations, the final question is: should we always perform small bowel biopsies in patients with IDA or other pathologies hiding a subclinical/silent form of coeliac disease? I believe that small bowel biopsy remains the gold standard in diagnosing subclinical forms of coeliac disease (such as IDA), even if the sorbitol H₂-BT test is promising as a non-invasive method: the sorbitol H₂-BT test seems to be more promising in the follow-up of these patients after a GFD (unpublished data). It remains to be determined whether serological testing for antibodies to antiretail transglutaminase improves the diagnosis in cases of mild mucosal lesions. I think that patients at high risk for coeliac disease (such as those with unexplained IDA) should always undergo duodenal biopsy. The costs could be quite high due to the high number of endoscopies that need to be performed but is cost-effective if we consider the significant proportion of patients with coeliac disease who may be missed if screened by serology alone.

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References


Authors’ reply

We would like to thank Dr Tursi for his comments. We suggest that Dr Tursi’s and our opinions on the use of antiretail antibodies (anti-EMA) and duodenal biopsy (DDB) in the management of coeliac disease are convergent.

We agree that at present anti-EMA can be a flawed diagnostic test and its results must be treated with caution. However, we believe that there is potential for close to 100% sensitivity and specificity, as has been obtained in some laboratories.¹ This highlights the fact that there is a difference in accuracy between centres due to the nature of the test, as discussed in our first letter (Gut 2001;49:595). The reasons for these differences are not always easily addressed and may be related not just to the laboratory itself but also to the local population. In centres that have 100% accuracy in anti-EMA testing for coeliac disease, it is clear that its use in the management of coeliac disease will be different in centres that achieve much lower accuracy, some of which are cited in Dr Tursi’s letter.

In our letter we were attempting to raise the question as to whether DDB should be obtained in all patients with suspected coeliac disease, and to suggest that if anti-EMA is as accurate as pooled published data, suggesting sensitivity and specificity of 94% and 98%, respectively,¹ it theoretically could be used as a firstline investigation. To put this in context, at present in our biochemistry laboratory, in a hospital serving 350 000, 400 anti-EMA tests are performed per month. Currently at our hospital there is not the capacity to perform 400 extra duodenoscopies each month, and if there were a clinical need, the department would have to be reorganised to do so. Anecdotally, other regions of the UK carry out similar numbers of serological tests for coeliac disease diagnosis.
At present in our patient population, anti-EMA is therefore used as a screening tool, and if positive, patients are offered DDB. This is likely to be the case across the country. Our regional teaching centre has formalised this: tissue transglutaminase (tTG) is used as a screening tool, and anti-EMA and subsequently duodenal biopsy are offered to selected patients. We believe that this approach has merit, although the routine use of tTG lacks confirmation in the clinical setting.

We agree that currently DDB is the gold standard investigation and that at this moment in time, on the basis of current clinical evidence, should be obtained in all patients with anti-EMA positivity.

Although we are aware of the benefits of other diagnostic methods, such as sorbitol H2 breath testing (H2 BT), this is still a "resource intensive" test; a quick, cheap, and accurate screening test is required. If sorbitol H2 BT, when thoroughly evaluated, was found to be more effective than DDB in the diagnosis of coeliac disease, we would welcome its introduction.

Better education of primary care physicians in anti-EMA testing may also be required. We have become aware that in our region only a minority of patients with positive anti-EMA are biopsied. This situation should be corrected; it has arisen as a result of anti-EMA being available on a direct access basis to primary care physicians. We wonder if the difference between published guidelines, and what is currently practicable, has contributed to some of the confusion.

On the subject of duodenal biopsies, we believe, as discussed in our letter, that at some point in the future its validity as a gold standard should be reviewed. However, we accept it must remain as such until other methods are thoroughly evaluated, hopefully in well-designed controlled trials. If performing an endoscopy for iron deficiency, and a duodenal biopsy is not feasible, one would certainly accept that it makes sense to biopsy the duodenum.

In summary, the numbers of patients who are tested at present using anti-EMA means that it has effectively become a screening tool for suspected coeliac disease. However, as the gold standard, we believe that DDB should be offered to all anti-EMA positive patients to confirm the diagnosis and other patients in whom the diagnosis in doubt, which could include patients who are iron deficient but with negative anti-EMA. We suggest that guidelines for the management of coeliac disease should reflect this.

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observed, although the surveillance programme has not changed over the years (liver ultrasonography and α-fetoprotein determination every six months). As Bruix and Llovet affirm, this increase in survival may be due to advances in diagnosis even in the absence of effective treatment, to the availability of multiple treatment, or both.

However, it must be emphasised that HCC stage (parameter of the tumour) and residual liver function (parameter of the affected patient) were closely related and influence each other, and that both can influence the choice of treatment and prognosis. Therefore, what should improved survival over the years be attributed to since surveillance programmes after 2–3 cm able to detect a minority of “early” HCCs?

Bolondi et al analysed the outcome and cost effectiveness of HCC surveillance programmes. They compared the outcome of a cohort of mixed aetiology cirrhotic patients screened by means of biannual liver ultrasonography and serum α-fetoprotein measurement to the outcome of patients who had not been under surveillance and those who had not been transplanted. However, survival at three years was significantly better in the group that had been kept under surveillance. Lastly, both liver function and tumour stage were selected in multivariate analysis as predictors of survival.

We recently performed a similar study in a cohort of hepatitis C virus positive cirrhotic patients. We compared studies of clinical parameters, eligibility for treatment, and survival of patients whose HCC had been discovered during a surveillance programme (biannual liver ultrasonography and α-fetoprotein measurement) with patients whose HCC had been incidentally diagnosed. Although age, serum α-fetoprotein levels, and unifocality of the tumour were no different between the two subgroups of patients, we found that more patients in the group under surveillance were eligible for treatment (32/33 vs 18/27, p=0.003, Fisher's exact test). Moreover, we found that clinical status at diagnosis was better in the group under surveillance compared with patients with an incidental diagnosis of HCC. Lastly, we observed that longer survival was obtained in treated patients, regardless of diagnosis modality or treatment modality. On the basis of these findings, we attempted to determine whether the longer survival observed in the group under surveillance might be due to better basal conditions, or perhaps they were more likely to benefit from treatment due to their improved clinical status. We thus compared patients treated with the same procedures and analysed the results on the basis of modality of diagnosis. We observed that there was no difference in overall survival between the groups, and that overall survival was not better related (72%) than tumour related. Both of these points suggested that the better outcome observed in the group under surveillance was due to the better basal conditions of the patients and not to the procedures themselves. Lastly, multivariate analysis showed that liver function, tumour stage, treatment, and not HCC surveillance were independent predictors of better survival.

Thus what emerges from our study as well as from that of Bolondi et al is that survival of HCC patients is mainly linked to preserved liver function. This probably allows patients to undergo treatment even when this is not classically considered “curative” as even therapeutically considered “non-curative” have reportedly obtained increasingly positive results in terms of survival. In an era of multimodal therapeutic approaches to HCCs, these findings further support the results of screening programmes. Indeed, almost a decade ago on patients with compensated cirrhosis. They compared the outcome of a retrospective study of 435 patients. Hepatology 1998; 28: 751–5.


Gastric cancer and H pylori

We would like to comment on the relationship of chronic Helicobacter pylori infection and gastric cancer risk discussed in the recent combined analysis of prospective serological studies presented by the Helicobacter and Cancer Collaborative Group (1994; 49: 347–53). It is our opinion that the null association between H pylori seropositivity and gastric cancer risk reported in this analysis is due to a lack of combination of observational studies with (a) different definitions of gastric cancer and (b) diverse subject populations, particularly with respect to the prevalence of gastrooesophageal reflux disease (GORD), which we believe may affect the perceived H pylori–gastric cancer relationship. By definition, the gastric cardia represents only the proximal 2–3 cm of the stomach. This small anatomical region can easily be overgrown by tumours that originate from adjacent mucosal sites. Thus in this setting, both oesophageal and gastric adeno carcinoma are common, tumours described as “cardia cancers” undoubtedly include a mixture of neoplasms arising from the lower oesophagus as well as the gastric cardia (and perhaps even the more distal stomach). Classification of gastric cardia cancer has been further confused by the inclusion of malignant lesions situated 2–3 cm above the gastro-oesophageal junction in some previous reports.

With respect to disease aetiology, adenocarcinoma of the oesophagus appears to be strongly associated with GORD, while adenocarcinoma of the distal stomach has been positively linked with chronic H pylori carriage (1991; 49: 347–53). It is therefore not surprising that both GORD and H pylori have been suggested as potential “risk factors” or “defining features” for “gastric cardia cancer”. In our opinion, GORD is probably associated with most oesophageal adenocarcinomas and some true gastric cardia cancers whereas chronic H pylori infection appears to be a predisposing factor for most non-cardia adenocarcinomas and some gastric cardia cancers. Additionally, chronic H pylori carriage is thought to reduce the risk of GORD associated with reflux oesophagitis by lowering the amount of refluxed gastric contents while GORD is not thought to affect the risk of H pylori associated tumours.

Since 1985, our group has collaborated on multicentre studies of chronic H pylori and gastric cancer in Linxian, China. Residents of this region are known to be at high risk for oesophageal squamous cell carcinoma and gastric cardia cancer, whereas chronic H pylori carriage appears to be a predisposing factor for most oesophageal adenocarcinomas. In this setting, screening for H pylori seropositivity among cancer free adults has been reported as 56%.[1] Based on the endoscopic evaluation of nearly 7000 asymptomatic adults in our studies in Linxian, reflux oesophagitis is uncommon in this population. Moreover, no cases of Barrett's oesophagus or oesophageal adenocarcinoma have been histologically confirmed. In contrast, we have detected more than 175 cases of early gastric cardia adenocarcinoma, almost all of which were confined to the 2–3 cm region below the squamocolumnar junction at the time of diagnosis. Other groups have also reported that reflux oesophagitis and its complications are uncommon and that the H pylori carriage rates are high among Asian adults.[2] Therefore, such populations seem well suited to the investigation of H pylori and gastric cardia cancer risk, as the potential disease modifying effects of GORD are virtually non-existent. In the combined analysis of the Helicobacter and Cancer Collaborative Group (1994; 49: 347–53), our analysis of the pooled data from the three Asian studies revealed a summary odds ratio estimate of 1.67 (95% confidence interval (CI) 1.06–2.64) for H pylori seropositivity and gastric cardia cancer risk. Interestingly, each of the Asian studies further reported similar risk estimates for gastric cardia and gastric non-cardia cancers among H pylori positive subjects, which suggests that the bacterium’s putatively carcinogenic effects may be uniform throughout the stomach.

In most Western populations, GORD is a relatively common disorder whereas H pylori infection is on the decline.[3] In this setting,
estimating the risk of *H pylori* associated gastric carcinoma becomes substantially more challenging. Our further analysis of the combined data from the seven western studies alone yielded a summary odds ratio of 0.60 (95% CI 0.38–0.93) for *H pylori* seropositivity and gastric carcinoma risk. Because the proportion of oesophageal, gastric, and gastric non-cardia cancers included in these studies cannot be readily determined, we believe that this risk estimate is in some way showing a protective (or null) association is problematic. Consistent with the discussion offered above, the apparent lack of association between *H pylori* exposure and gastric cancer in Western populations may be due to an over representation of misclassified GORD associated lower oesophageal malignancies in these studies. The appropriateness of combining the existing Western and Asian studies of *H pylori* and gastric cancer risk is further called into question by formal statistical testing. When we do a heterogeneity test that allows for potential differences between Western and Asian studies, we find that the odds ratio is significantly different (p=0.002).

In summary, we believe that *H pylori* carriage is a risk factor for adenocarcinoma throughout the stomach, including the gastric cardia. The different conclusion reached by the recently published combined analysis seems likely to have been influenced by pooling data from subject populations with demonstrated or plausible differences in disease classification and disease activity, respectively. More specifically, we believe it is difficult to accurately judge the relationship between *H pylori* seropositivity and gastric and gastric cardia cancer risk among populations wherein tumour location has not been rigorously defined and GORD is highly prevalent (due to the potentially misleading biological effects associated with this condition). Thus we respectfully disagree with the conclusion proposed by the Helicobacter and Gastric Carcinoma Collaborative Group that “*H pylori does not appear to increase the risk of cardia cancer”. However, we do agree that additional prospective studies, with larger case numbers and longer follow up intervals, would be useful in clarifying this issue.

Sir Francis Avery Jones BSG Research Award 2003

Applications are invited by the Education Committee of the British Society of Gastroenterology who will recommend to Council the recipient of the 2003 Award. Applications (TWENTY COPIES) should include:

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Entrants must be 40 years or less on 31 December 2002 but need not be a member of the Society. The recipient will be required to deliver a 30 minute lecture at the Annual meeting of the Society in Birmingham in March 2003. Applications (TWENTY COPIES) should be made to the Honorary Secretary, British Society of Gastroenterology, 3 St Andrews Place, London NW1 4LB by 1 December 2002.

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Funds for inflammatory bowel disease (IBD) research are available immediately from the Broad Medical Research Program of The Eli and Edythe L. Broad Foundation for innovative projects regarding etiology, therapy, or prevention. Grants totalling approximately US$100,000 per year are available for basic or clinical projects. Larger requests may be considered. Initial letter of interest (no submission) should be received by 15 February 2003. Further information: Marciana Poland, Research Administrator, Broad Medical Research Program, 10900 Wilshire Blvd., 12th Floor, Los Angeles, CA 90024-6532, USA. Tel: +1 310 954 5091; email: info@broadmedical.org; website: www.broadmedical.org

ESPEN 2002

The European Society for Parenteral and Enteral Nutrition will be hosting its annual meeting on 31 August to 4 September 2002 in Oxford, UK. The course has been designated for consultants and registrars, including those who do not specialise in gastroenterology. Topics will include: Barrett’s Oesophagus; The Case for Endoscopic Surveillance—A Debate; Liver Disease; Bacteria and the Gut; IBD Therapeutics, Gastrointestinal Bleeding, Endoscopic Training. Further information: Professor Derek P Jewell, University of Oxford, Nuffield Department of Medicine, Gastroenterology Unit, Gibson Laboratories, 2nd Floor, Radcliffe Infirmary, Block 21, Woodstock Road, Oxford OX2 6HE. Tel: +44 (0)1865 224829; fax: +44 (0)1865 790792; email: derek.jewell@ndm.ox.ac.uk; website: www.medicine.ox.ac.uk/gastro

British Association for the Study of the Liver

The 2002 BASH meeting will be held on 11–12 September in Newcastle, UK. Further information: Mrs Jackie Carter, Centre for Liver Research, University of Newcastle, Floor 4, William Leech Building, Medical School, Framlington Place, Newcastle upon Tyne, NE2 4HH, UK. Tel: +44 (0)191 222 5640; fax: +44 (0)191 222 0723; email: j.a.carter@ncl.ac.uk

3rd World Chinese Congress of Digestology

This congress will take place on 23–25 September 2002 in Beijing, China. Further information: Lian-Sheng Ma, President of WCCD, PO Box 2345 Beijing 100230, China. Tel: +86 6099 1893; email: wcjd@public.bta.net.cn

Xth European Course on Therapeutic Digestive Endoscopy and Radiology

This course will take place on 24–25 October 2002 in Rome, Italy. Further information: SC. Studio Congressi, Via Francesco Ferrari 40, 00191 Roma, Italy. Tel: +39 06 3290150; fax: +39 06 36306897; email: sc.congressi@stm.it; website: www.sctudiocongressi.it

Advances in the Inflammatory Bowel Diseases

This conference will take place on 6–7 December 2002 in New York, USA. Further information: Heather Drew, Imedex, 70 Technology Drive, Alpharetta, GA 30005-7969, USA. Tel: +1 770 751 7332; fax: +1 770 751 7334; email: h.drew@imedex.com; website: www.imedex.com

15th European Intensive Course (SMIER) Digestive Endoscopy

This course will take place on 16–17 December 2002 in Strasbourg, France. Further information: Michele Centonze Conseil, 6 bis Rue des Cendariers, 75020 Paris, France. Tel: +33 1 44 62 68 80; fax: +33 1 43 49 68 58.

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Intravenous immunoglobulin for recurrent *Clostridium difficile* diarrhoea

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