Food elimination in IBS: the case for IgG testing remains doubtful

I read with interest the study of a diet for irritable bowel syndrome (IBS) based on serum IgG levels to foods (Gut 2004;53:148–64).

In rigorous elimination diet studies, about one third of IBS patients are found not to have food intolerance.1 2 Yet it appears that everyone tested for food specific IgG in this study had some positive reactions and was therefore subjected to dietary recommendations. This does not in itself suggest that serum IgG is a particularly useful test.

One notable finding of this study appears to be that 87% of patients gave a high level of IgG to yeast. In two large scale studies of IBS using diagnostic elimination diets, the percentages who had a symptomatic reaction to yeast when challenged were 5.5% (out of 73 unselected IBS patients)1 and 12% (out of 122 unselected IBS patients).4 It seems unlikely that yeast causes IBS symptoms in 87% of patients in Manchester but in only 5–12% of patients in Oxfordshire and Cambridgeshire. A logical implication is that high levels of IgG against yeast do not, in themselves, reveal anything significant in relation to IBS symptoms.

The same, in my view, would follow for several other foods. The numbers of patients with positive responses to eggs, cow’s milk, and cashew nuts, as judged by IgG levels, are much higher than one would expect from empirical dietary studies,1 2 while the numbers testing positive to chocolate and oranges appear far too low. Again, it seems doubtful that IgG can reveal sensitivities accurately in IBS.

The percentage of patients showing substantial benefit from this diet is disappointing. In studies using a well conducted and rigorous elimination diet, the “number needed to treat” is between 1.5 and 2.2.1 2 The “number needed to treat” in this study was 9. (The value of 2.5, calculated on the basis of those who fully complied with the diet, abrogates the intention to treat principle.)

This seemingly poor response to an IgG based diet confirms the widely held view of IBS patients that IgG testing for food intolerance is not of value.2 4 These results suggest that if IgG testing identifies food intolerances at all, it does so fortuitously and with an apparent low degree of accuracy.

I conclude that the difference in outcome between the “true diet” and the “sham diet” groups can largely be explained, not by specific identification of food reactions, but by the gross differences between the two diets. The “true diet” excluded milk products for 84% of patients and wheat for 49% (both foods are known to be common offenders in IBS) while the total number of foods avoided by the group was 498 (value calculated from table 2). For the “sham diet” group, 1.3% avoided milk, 8% avoided wheat, and the total number of foods avoided was only 453. These overall differences between the diets could easily explain the modest difference in outcome between the two diet groups. The same diet sheets, distributed randomly to the patients in each group, regardless of IgG levels, would probably have produced the same overall result.

Similarly, I consider that the effectiveness of the blinding in this trial is questionable. The “nutritional advisor” giving support by telephone may have become aware of which patients were receiving the “sham diet” as this regularly excluded potatoes and rice while the “true diet” rarely did so—the reverse being true for wheat, milk, and yeast. The views of the nutritional advisor on the likely effectiveness of the diets could inadvertently have been communicated to the patients, and unintentionally influenced their assessment of the outcome.

Before this trial was begun, in my view it would have made sense to try to answer the more basic research question: do high levels of IgG against a food predict an adverse reaction to that food? Only one very small trial has so far done this.5 It measured food specific serum IgG in individual IBS patients and compared the results with those from food challenges (following a period of avoidance); there was no correspondence between the foods identified. Such work needs to be repeated with larger sample sizes.

Despite the inconclusive results of this study, it has regrettably already been the subject of a press release and other publicity by the company that provided the IgG testing for this study, in order to promote IgG tests to the general public. On the company’s website, IgG testing is now described as “clinically proven” by the British Allergy Foundation on the basis of this study (The UK YorkTest website: www.yorktest.com). This blurring of the boundaries between what should be a disinterested scientific enquiry and the promotion of a commercial venture is regrettable.

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IgG antibodies to foods in IBS

Mawdsley et al raise the important question as to whether patients with irritable bowel syndrome (IBS) would gain as much symptomatic improvement if recommended to exclude the top four foods (yeast, milk, whole egg, and wheat) compared with an IgG antibody test based diet.1 In other words, does the test add specificity? This requires a trial which compares patients receiving an IgG antibody test based diet to those advised to eliminate some or all of the top four foods. We are currently seeking funding for such a trial.

There is some evidence however from our trial that the IgG antibody test based diet may provide a better response than simply eliminating a standard set of foods. When the change in IBS symptom severity score was compared for fully adherent true and sham diet patients who were advised to eliminate one or more of the top four foods, it was found that the true diet patients experienced a significantly greater reduction than the sham diet patients (difference = 94; 95% confidence interval 18, 170; p = 0.001).

We agree with Sewell’s comment that the food elimination diets in the true and sham groups were not similar in terms of content,2 although they were for numbers of food types excluded. This was to some extent inevitable given the high prevalence of IgG antibodies to certain foods, such as yeast (86.7%) and milk (84.3%). However, exclusion was not quite as unbalanced as implied as the so-called sugar foods were allowed in the “yeast positive” paired diet. While we accept that a more balanced comparison would have been desirable, the principal point of the sham diet was to control for placebo effect. In future, more care needs to be taken to match diets not just for number of food types excluded but also for types of food. We are still confident, however, that the difference in symptom improvement observed in our study for the true and sham diet groups is a real one. This is evidenced by the highly significant difference in worsening of symptoms between the true and sham diet groups is a real one. This is evidenced by the highly significant difference in worsening of symptoms between the true and sham diet groups (p = 0.001).

I agree with Hur et al for their interest in our article. I agree that his article,1 which appeared after the initial iterations of our article (Gut 2004;53:1736–44) has been written but prior to the acceptance of our revised manuscript, is highly pertinent to our work as it models the same clinical scenario.

There are clearly some differences in the models, which are likely due in part to the estimates used to construct it. For instance, average quality adjusted life expectancy when going from surgery to photodynamic therapy (PDT) in our model was increased by approximately 0.5 years whereas in the model by Hur et al the increase was 2.2 years, or four times our estimate. Also, some of our estimated lifetime costs for various therapies varied by as much as 25% from those estimated by Hur et al.

However, considering the number of assumptions and estimates inherent in modelling a complex clinical decision such as Barrett’s with high grade dysplasia (HGD), the model of Hur et al reports remarkably similar results to ours. An ablative approach with PDT provided an increased quality adjusted life expectancy at a reasonable cost. I agree with Hur et al that the similar findings of the models strengthens and validates the findings. More generally speaking, I feel that any model that features an intervention with some efficacy in the setting of HGD is likely to demonstrate that this intervention will be cost effective. The frequent progression of HGD to cancer, the high cost associated with caring for subjects with cancer, and the poor prognosis associated with cancer all suggest that any intervention keeping even a small fraction of patients with HGD from developing cancer is likely to be cost effective. This is true even if the intervention itself is costly (such as PDT). It probably does not matter whether the intervention is chemoprevention (as elegantly modelled recently by Sonnenberg and colleagues3) or ablative therapy, as modelled by Hur et al and ourselves.

Of course, there is a possibility that both models share the same flaws, leading them to come to similar, but erroneous, conclusions. After all, these models are only as good as the data used to create them, and good data on the natural history of various subsets of Barrett’s patients is hard to obtain given the current state of the literature. However, until good randomised data comparing the treatment modalities for HGD are available with which to make these comparisons, the models are superior to expert opinion, intuition, or just plain guessing, as to the most appropriate path.

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References

When acquired thrombophilia mattered

A 52 year old previously healthy Afro-Caribbean woman was admitted as an emergency with a 12 hour history of epigastric pain. She was a non-smoker, denied alcohol use, and had no significant comorbidity. Heart rate, respiratory rate, and temperature were normal at presentation. Abdominal examination revealed mild epigastric tenderness with guarding. Baseline investigations (full blood count, clotting, urea and electrolytes, and liver function tests) were within normal limits, except for a raised white cell count (12.1) (normal range 4–11) × 10³ l (neutrophilia)) and a raised amylase level (2409 (normal <220) U/l). Abdominal and chest x rays were also normal. She was diagnosed with acute pancreatitis and treated supportively with intravenous fluids, analgesia, and thromboprophylaxis.

Twelve hours after admission the patient deteriorated significantly, with signs of abdominal peritonitis and a marked metabolic acidosis. She underwent an emergency laparotomy where she was found to have a serious perforation of the pancreas.
perforated necrotic gall bladder with biliary peritonitis. The common bile duct was dilated but no gall stones were identified. In addition, there was necrosis of her liver were noted to be dusky. Her spleen was normal. The abdomen was washed out and a cholecystectomy performed. Histology confirmed that the gall bladder was necrotic. Several of the arteries were occluded by thrombus but there was no evidence of atheroma or vasculitis.

Following surgery she ran a prolonged septic course requiring ventilatory and renal support, and on day 13 had a large upper gastrointestinal bleed secondary to intestinal ischaemia. Serial computed tomography scans to identify the source of sepsis were normal until day 21 when a large right subphrenic collection was identified. In addition, an area of low attenuation at the site of the spleen and a cystic mass in the pancreatic tail, consistent with a pseudocyst, were noted. Radiological drainage of the abscesses was performed and over the next week the patient was successfully weaned and withdrawn from circulatory and renal support. At this stage her haemoglobin was 10.8 g/dl and her platelets were 104 000/μl, a further laparotomy was therefore performed. The collection was drained and the remnants of her auto-lysed spleen and pancreatic tail removed. At this point the possibility of a thrombotic disaster was raised. Histology showed no evidence of vasculitis and she was antineutrophilic cytoplasmic antibody and antoanti- body negative. Her thrombophilia screen revealed low levels of protein C (functional: 45 (65–250) u/dl; antigen: 52 (65–130) u/dl) and antithrombin III (functional: 99 (80–120) u/dl; antigen: 70 (80–120) u/dl). Free protein S levels were normal (73 (55–120) IU/dl). She was negative for lupus anticoagulant, APC resistance ratio was normal 2.05 (1.8–4), and neither factor V Leiden nor prothrombin gene 20210 allele was detected. Her anti-thrombin level was not suggestive of an inherited defect and levels in first degree family members were within normal limits. A presumptive diagnosis of acquired anti-thrombin deficiency was made, her low molecular weight heparin was increased to therapeutic doses, and she was commenced on warfarin.

Two months after discharge her anti-thrombin levels had returned to normal and her warfarin was stopped. She had developed no further problems on follow up at 12 months.

This case illustrates how the systemic inflammatory response can be complicated by a series of thrombotic events. Anti-thrombin is a natural anticoagulant that plays a pivotal role in coagulation and haemostasis. In addition, it has potent anti-inflammatory properties, and is protective in animal models of sepsis.4,5 Acquired anti-thrombin III deficiency is commonly present in severe sepsis and levels can be predictive of outcome.6 It should therefore be considered in non-responsive severe sepsis when the clinical course is complicated by arterial or venous thrombosis.

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may also be population specific differences in the contribution of this variant to UC susceptibility although other loci such as CARD15 and IBD5 have been widely replicated in North American and British populations. Alternatively, the original report may be a false positive: it involved multiple testing against various phenotypes and Jewish versus non-Jewish populations that has not been corrected for. However, the UC association was detected in both family based and case control study designs. Lastly, the size of the effect may be much smaller than indicated by the Karban study, requiring a very large sample size to replicate.

The NFκB activation pathway is in progress to assess its contribution to susceptibility to inflammatory bowel disease.

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Primary intestinal autoimmune disease as a cause of chronic intestinal pseudo-obstruction

The purpose of this letter is to elucidate on the pathophysiology of a disease that is often considered to be idiopathic. Chronic intestinal pseudo-obstruction (CIFO) is a clinical syndrome characterised by ineffective intestinal propulsion in the absence of organic intestinal obstruction. It is a common cause of intestinal failure requiring total parenteral nutrition (TPN). It can be either a primary/idiopathic (neurogenic or myogenic) disorder or secondary to another recognised underlying disease. Most cases of childhood CIFO are congenital enteral neuromuscular diseases; however, neurophysiological studies revealed fibrous tissue deposition around enteric nerve plexus and sensory and motor nerve axons. In adults, most cases of CIFO are secondary to progressive systemic sclerosis, dermatomyositis, systemic lupus erythematosus, rheumatoid arthritis, and Sjogren’s syndrome.

We report a case of an adult onset of CIFO secondary to an autoimmune process affecting exclusively the small intestine without any other systemic organ involvement. A 53-year-old man with an unremarkable past medical history experienced symptoms of "mechanical obstruction" (nausea/vomiting). After three abdominal explorations, including small bowel resections, he failed enteral feeding rendering him fully TPN dependent. Antitubular manometry demonstrated low amplitude contractions in the distal duodenum, and gastrointestinal scintigraphy revealed normal stomach emptying and colonic transit, but delayed small bowel transit. Trypsinoma cruzi antibodies and an extensive serological work up for collagen-vascular disease were negative, except for antinuclear antibodies (ANA 1/1280). During five years on TPN, the patient developed multiple episodes of line sepsis and progressive liver disease. He then successfully underwent isolated intestinal transplantation.

Intraoperatorically, the small bowel was dilated only in the proximal 270 cm (18 cm circumference). Microscopic examination showed marked degeneration of the muscularis propria with pronounced atrophy of muscle fibres (fig 1). Eosinophilic hyaline globular inclusions were detected within smooth muscle cells, predominantly in the perinuclear regions. Masson-trichrome stain revealed fibrous tissue deposition around atrophic muscle bundles. The neuronal plexus was entirely preserved. Histological findings were compatible with an idiopathic visceral myopathy. Positive immunofluorescence staining for anti-IgA and anti-IgG was found in degenerated muscle fibres but not in areas of intact musculature (fig 1). Nine months post transplant, a full thickness biopsy of the intestine showed no evidence of recurrent disease in the graft. The patient’s ANA became negative one month after transplant and remained undetectable after 15 months of follow up. Only one similar case of a two year old boy who developed intestinal pseudo-obstruction following an episode of gastroenteritis has been reported. In that case, ANA, anti-neutrophil cytoplasmic, and antimucosal muscle antibodies became negative on

Table 1 – 94delATTG allele and genotype frequencies in British ulcerative colitis (UC) cases and controls

<table>
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<tr>
<th></th>
<th>WW (%)</th>
<th>WD (%)</th>
<th>DD (%)</th>
<th>Frequency of D allele (%)</th>
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<tbody>
<tr>
<td>Controls</td>
<td>657</td>
<td>231 (35.2)</td>
<td>330 (50.2)</td>
<td>96 (14.6)</td>
</tr>
<tr>
<td>UC</td>
<td>472</td>
<td>170 (36.0)</td>
<td>225 (47.7)</td>
<td>77 (16.3)</td>
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WW, wild insertion homozygote; WD, heterozygote; DD, deletion homozygote; D, –94 del ATTG allele

References

Figure 1 (A) Thinning of the small bowel wall with normal appearing mucosa and inner circular muscular layer. The outer longitudinal layer is severely thinned and some muscle fibres contain cytoplasmic globules. (B, C) Immunofluorescent staining using anti-IgA (B) and anti-IgG (C). Positive green fluorescent staining is seen along the edges of degenerated muscle fibres of the outer longitudinal layer.
immunosuppressive therapy. Histology after two years of treatment showed profound loss of myocytes in the outermost circular muscle layer, with lymphocyte infiltration. Deposition of (auto)antibodies was not mentioned. Other cases of CIPO and systemic autoimmune disorders have been published."

Our report is the first to describe an adult without previous gastrointestinal symptoms or other signs of systemic autoimmune disease who developed subacute ANA positive CIPO, resulting in myocytolysis of the intestinal muscularis propria. Documentation of IgG and IgA deposits in the areas of muscle degeneration and fibrosis is suggestive of an autoimmune-type disease involving the humoral immune system. The findings however do not exclude a role for cell mediated cytotoxicity at the beginning of the disease and may only represent a late stage of a complex autoimmune disorder.

In summary, some patients with idiopathic CIPO may suffer from a primary intestinal autoimmune disease, an autoimmune process exclusively directed towards the intestine. An early full thickness intestinal biopsy may indicate the need for immunosuppressive therapy. Histology after intestinal transplantation is an acceptable option before patients develop irreversible liver disease."

HCV genotype 2 as a risk factor for reactivation of chronic HCV infection
Little information is available in the literature on the risk of reactivation of chronic hepatitis C (r-CHC). In Taiwan, Sheen et al estimated an annual incidence rate of 11.9%. In this study, 40.2% of 78 patients experienced at least one episode of reactivation during a mean observation period of six years and a total of 151 episodes of reactivation were observed, 45% of them symptomatic. The paper by Rumi et al from Milan (Gut 2005;54:402–6) on r-CHC in relation to hepatitis C virus (HCV) genotyping described it as frequent in patients with genotype 2c (39% of 100 patients) and infrequent in those with genotype 1b (7.5% of 106 patients), with a rate × 1000 persons/year of 55.6 and 15.0, respectively. From January 2002 to the present, we have enrolled 49 consecutive patients with acute hepatitis C (AHC group) and 57 consecutive patients with r-CHC (r-CHC group) in a prospective follow up study. All patients were hospitalised at our ward because the illness was symptomatic.

The criteria for a diagnosis of AHC were: (a) negative serum anti-HCV and normal serum alanine aminotransferase (ALT) levels in the four months preceding the onset of symptoms; and (b) positive anti-HCV/HCV-RNA and increased ALT (>3 times the highest value of normal) during the acute stage of the illness. The diagnosis of r-CHC was made for patients with: (a) positive serum anti-HCV and plasma HCV-RNA during the six months before the onset of symptoms and on admission; and (b) ALT increase >5 times the mean of the ALT values observed during the previous six months. As a control group for patients in the r-CHC group, 57 hepatitis B virus surface antigen (HBsAg) negative, symptom free, untreated patients with chronic hepatitis C (CHC group, hospitalised in the same period for their first liver biopsy, were pair matched by age (<5 years), sex, and risk factors for acquisition of perinatal infection.

All patients in the AHC and CHC groups lacked serum HBsAg. Antibodies to hepatitis C core antigen (anti-HBc) IgM, anti-hepatitis D virus (HDV) and anti-hepatitis A virus IgM, and IgM to the herpes viruses. Excluded were patients treated with interferon and ribavirin in the last 24 months, anti-human immunodeficiency virus (HIV) positive subjects, those with a history of alcohol abuse, and those treated with potentially hepatotoxic drugs. Plasma HCV-RNA was determined by qualitative reverse transcriptase-polymerase chain reaction (HEPA-Check; C. Nuclear Laser Medicine) and HCV genotyping by Line-Prob-Assay (INNO-LIPA HCV II; Immunogenic). Anti-HCV, anti-HIV, HBV, HDV, and HDV serum markers were determined using a commercial immunoenzymatic assay.

Statistical analysis of the results was made applying the \( z \) test with Yates’ correction. A \( p < 0.05 \) was considered statistically significant.

HCV genotype 2 was found more frequently in patients in the r-CHC group (35.1%) than in those in the AHC group (8.2%, \( p < 0.005 \)) or the CHC group (14%, \( p < 0.05 \)). Conversely, HCV genotype 1 was detected less frequently in the r-CHC group (49.1%) than in the AHC (67.3%) or CHC (65%) groups (\( p = 0.1 \)). The observation that patients with symptomatic acute exacerbation of chronic hepatitis C harbour HCV genotype 2 more frequently than asymptomatic chronic hepatitis patients and patients with acute hepatitis C is in good agreement with the more frequent occurrence described by Rumi et al (1999; Gut 1999;45:570–4) in patients with HCV genotype 2c compared with those with HCV genotype 1b. The available data seem to indicate that whether the clinical presentation is symptomatic or asymptomatic, acute exacerbation of chronic hepatitis C is associated with HCV genotype 2 chronic infection. However, a multicentre prospective study is needed to obtain more conclusive data.

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References

Management of acute pancreatitis
No account of the complications of acute pancreatitis (Gut 2005;54:426–36) would be complete without mention of diabetic ketoacidosis as an association, which is either fortuitous or one which exists as a complication in its own right. Recognition of this association has been inhibited by the complicated relationship between diabetic ketoacidosis, acute abdominal pain, and hyperamylasaemia, notwithstanding the
fact that, as long as ago as 1961, a patient with subsequent post mortem validation of acute pancreatitis did present with sudden deterioration of diabetic status, the latter being characterized by unequivocal diabetic ketoadicosis.\textsuperscript{3}

Subsequently, it was also recognized that diabetic ketoadicosis could present with acute abdominal pain and elevation in serum amylase (even beyond four times the upper limit) without necessarily signifying acute pancreatitis.\textsuperscript{2} The relationship between the two disorders was clarified by a recent study comprising 100 consecutive episodes of diabetic ketoacidosis in which all patients with either abdominal pain or elevation in serum amylase to “more than three times normal” had an abdominal computerised tomography (CT) scan.\textsuperscript{3} Eleven per cent of patients had CT evidence of acute pancreatitis, and this was associated with abdominal pain in eight.

Among the three without abdominal pain was one who was comatose on admission. Accordingly, although in the context of diabetic ketoacidosis and abdominal pain the presence of “pancreatitis levels” of serum amylase does not necessarily signify acute pancreatitis,\textsuperscript{3} it is nevertheless true that unequivocal acute pancreatitis can be associated with diabetic ketoacidosis,\textsuperscript{3} the latter being either a complication or a coincidence. Either way, this is an association which has to be acknowledged rather than ignored, given the prevalence of the association (11\% of 100 consecutive cases),\textsuperscript{3} the potential lethality of either of the two disorders, and the fact that, at least one of the complications of diabetic ketoacidosis, namely, acute respiratory distress syndrome,\textsuperscript{4} can be identical in its presentation with its counterpart in acute pancreatitis.\textsuperscript{3}

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References