Antibiotic use and the development of Crohn’s disease: methodological issues

Card and colleagues (Gut 2004;53:246–50) reported that the use of antibiotics could increase the risk of Crohn’s disease, particularly those prescribed 2–5 years prior to the diagnosis (odds ratio 1.32 (95% confidence interval 1.05–1.65)). As the use of drugs acting on the central nervous system and of other prescription drugs such as oral contraceptives was also associated with a diagnosis of Crohn’s disease, the authors concluded that this association is non-specific. Nevertheless, some methodological issues could have had an important impact on the results.

One methodological aspect of the study design that could have biased the findings is that calendar time was not accounted for properly. This is highlighted by the fact that the median time available prior to the index date, the period during which exposure to antibiotics was measured, was 6.4 years for the cases compared with 8.2 years for the controls. This difference of almost two years is due to the fact that the index date was correctly taken to be the date of diagnosis of Crohn’s disease for the cases but was taken to be the date of the end of data analysis for the controls. Consequently, a case diagnosed in 1992 could potentially be compared with a control whose date of end of data analysis was in 1998. As a result, the odds ratio based on the comparison of cases and controls for exposure to antibiotics may be biased by comparing exposures to antibiotics that may have changed over calendar time. Thus any trend over time in the patterns of use of antibiotics during the calendar time span of the study, namely the 1990s, would bias the estimate. Such bias cannot be excluded, particularly for an odds ratio as small as 1.32, because the design did not match the index date on calendar time nor did the data adjust for calendar time. In fact, the study, namely the 1990s, would bias the study, particularly those prescribed 2–5 years prior to the diagnosis (odds ratio 1.32 (95% confidence interval 1.05–1.65)). As the use of drugs acting on the central nervous system and of other prescription drugs such as oral contraceptives was also associated with a diagnosis of Crohn’s disease, the authors concluded that this association is non-specific. Nevertheless, some methodological issues could have had an important impact on the results.

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A second limitation of the study is the unclear accounting of age. On the one hand, there is the issue of matching on age of cases and controls, while on the other there is the issue of adjustment for age in the analysis. Firstly, it is not clear at what time these two ages were measured, and particularly whether age was taken at the index date. We suspect this choice because cases were 2.1 years younger than controls, which is similar to the difference of almost two years in the index dates of cases and controls. Secondly, age matching was based on 20 year age bands, which may be too wide to control fully for confounding, unless the precise age was used in adjustment.

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in cirrhosis. This concept is supported by the findings that β2 adrenoceptor density is reduced in blood lymphocytes from patients with cirrhosis and that there is reduced β2 adrenoceptor mediated relaxation in human cirrhotic hepatic artery segments.  

In summary, intrinsic arterial hyporesponsiveness to vasopressors cannot be detected in isolated mesenteric vessels. Hyporesponsiveness of these vessels in vivo may be related to other factors, such as neurohumoral activation, or the effects of circulating vasodilators and vasoactive peptides.

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Population based screening for coeliac disease: patient’s choice or doctor’s decision

I read with interest the debate on population based screening for coeliac disease (Gut 2003;52:168–9 and 170–1). Antagonists of population based screening hold the view that there is no evidence that screening the general population or instituting a gluten free diet in asymptomatic coeliac disease will reduce mortality.

Contrary to early beliefs, coeliac disease is one of the most common disorders affecting up to 1% of the general population, regardless of ethnic or geographical origin. In patients with coeliac disease, mortality rate is higher than the general population by a factor of 1.9–3.8, mainly due to complications (table 1) such as malignancy.

The important fact is that this increased mortality can be reduced to that of the general population after 1–5 years on a gluten free diet. Moreover, there has been concern about the increased risk of osteoporosis and current autoimmune disease in patients with untreated coeliac disease.  

Recently available sensitive serological assays have led to awareness that the typical form of coeliac disease (diarrhoea, weight loss, and abdominal distension) may be silent, although the condition that thrives represents only a small proportion of coeliac disease patients. Additionally, most diagnosed cases in adult life have an atypical presentation (table 1) or often clinically silent.

A combination of high prevalence and atypical presentation (table 1) has led to under diagnosis of this condition, resulting in a ratio of known (previously diagnosed) to undiagnosed coeliac disease cases as high as 1 to 7. Cases detected with screening usually manifest atypical or minimal complaints, such as abdominal pain, fatigue, mood changes, and iron deficiency.

It is important to recognise that some asymptomatic undiagnosed cases may emerge later on due to development of symptoms. This aspect of coeliac disease has been clearly shown in a recent Finnish study in a cohort of 3634 children. At the time of the first blood collection in 1994, none of the subject had received a diagnosis of coeliac disease. However, 56 (1.5%) cases had a positive test for coeliac disease when anti-tissue transglutaminase (tTG) and anti-endomysial antibody tests were performed on sera seven years later. Interestingly, 10 of 56 (17%) anti-tTG positive cases had already received a diagnosis between 1994 and 2001 because of abdominal complaints.

These results raise many questions. Although the natural history of the silent form of coeliac disease remains unclear, there is growing evidence that, if untreated, it may be associated with symptoms and complications such as anaemia, osteoporosis, stunted growth, autoimmune disease, and small bowel lymphoma, leading to increased morbidity compared with the general population.

The ethical dilemma that the medical world faces today is whether we should move our focus on one of the most common genetic conditions, that is easy to diagnose, and in which complications could be prevented by adherence to a gluten free diet. In view of the usual delay in diagnosis and the high morbidity related to untreated coeliac disease, there should be a low threshold for usage of serological testing in both primary
and secondary care settings. There is also a pressing need to have an open debate not only within the medical community but also involving the general public to address the appropriateness of population based screening of this easily treatable common genetic condition.

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References

Table 1: Clinical presentations of coeliac disease

<table>
<thead>
<tr>
<th>Typical symptoms</th>
<th>Complications</th>
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<tr>
<td>Diarrhoea</td>
<td>Enteropathy associated</td>
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<td>Weight loss</td>
<td>T cell lymphoma</td>
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<td>Abdominal distension</td>
<td>Ulcerative jejunitis</td>
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<td>Nervous system failure</td>
<td>Carbohydrate intolerance</td>
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<td>Atypical symptoms</td>
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<tr>
<td>Anaemia</td>
<td>Hypersplenism</td>
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<td>Dermatitis herpetiformis</td>
<td>Refractory sprue</td>
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<td>Autoimmune disorders</td>
<td>Microscopic colitis</td>
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<tr>
<td>Fatigue</td>
<td>Increased prevalence of diabetes</td>
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<tr>
<td>Liver disease</td>
<td>Carbohydrate intolerance</td>
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<td>Gastrointestinal cancer</td>
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<td>Mood change</td>
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<td>Irritable bowel</td>
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<td>Abdomina</td>
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<td>Epilepsy</td>
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<td>Dental enamel</td>
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<td>Hypoplasia</td>
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<td>Malignancy</td>
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<td>Metabolic bone disease</td>
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<td>Short stature</td>
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The enteric nervous system is not essential for the propulsion of gut contents in fetal mice

Hirschsprung’s disease is a congenital disorder in which enteric neurones are absent from variable lengths of the terminal region of the bowel. The condition presents as failure to pass meconium, severe constipation, colonic distension, and sometimes enterocolitis. Treatment for Hirschsprung’s disease requires the surgical removal of the aganglionic segment. Mutant mice lacking enteric neurones in all or a major part of the gastrointestinal tract die soon after birth. Thus, after birth, the enteric nervous system is crucial for normal intestinal motility in both mice and humans.

During fetal development, amniotic fluid is swallowed, while epithelial cells, mucus, and bile are discharged into the intestine, and progress in an anal direction. Little is known about the mechanisms controlling gastrointestinal motility in fetal life. Some infants with aganglionosis extending into the ileum present with features of meconium ileus, suggesting that enteric neurones are required for the propulsion of meconium prior to birth.

In this study, we first examined the progression of intestinal contents in fetal wild-type (C57Bl/6) mice. As the wall of the fetal mouse gut is transparent and bile pigment is yellow, location of bile can be readily observed. Bile was first detected at embryonic day (E) 16.5 in the duodenum but there was no evidence of bile in the distal small intestine or colon. At E17.5, bile was present throughout the small intestine and extended into the proximal colon. Little or no bile was observed in the proximal duodenum (close to the stomach), indicating that luminal contents move predominantly or exclusively in an anal direction. At E18.5 (one day prior to birth), bile (meconium) was present in the distal hindgut. Thus, as in humans, intestinal contents move analy during mouse fetal development.

In mice lacking the receptor tyrosine kinase, Ret, the enteric nervous system fails to develop in the small and large intestine but mice heterozygous for the Ret mutation have normal numbers of enteric neurones. To determine whether propulsion of intestinal contents in fetal mice requires enteric neurones, we examined the location of meconium in E18.5 mice lacking Ret (R/2R/+/+ mice). The post-caecal hind-gut of wild-type (+/+), heterozygous (+/-), and Ret null (−/−) littermates was photographed. The fetuses were genotyped using polymerase chain reaction, and NADPH diaphorase histochemistry was also performed on samples of proximal duodenum. All fetuses lacking NADPH diaphorase stained neurones in the duodenum were confirmed by polymerase chain reaction to be Ret null mice. There was no significant difference between Ret null, wild-type, and heterozygous mice in the length of the hindgut (data not shown), number of meconium boluses in the post-caecal hindgut, length of the hindgut occupied by meconium, or the distance from the caecum to meconium (fig 1). Thus progression of contents through the fetal mouse gut does not require enteric neurones. Slow waves do not appear in the murine colon until after birth, so it is unlikely that propulsion of gut contents during fetal life depends on slow waves and their propagation.

Our data show that enteric neurones are not required for the anally directed propulsion of gut contents in fetal mice. Although there are some data from infants with long segment Hirschsprung’s disease suggesting that neurones contribute to the propulsion of gut contents in the fetus, humans are born at a developmentally later stage than mice, and there may be neurone independent propulsive motor patterns in fetal humans that are replaced by neurone dependent motor patterns prior to birth.

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References

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Figure 1  (A–C) Analysis of the presence and location of meconium in the hindgut of embryonic day 18.5 (E18.5) wild-type (+/+; n = 25), heterozygous (+/−; n = 39), and Ret null (−/−; n = 24) mice. There was no significant difference between the three groups in the number of meconium boluses in the post-caecal hindgut (A), length of the hindgut occupied by meconium (B), or distance from the caecum to the meconium (C) (one way ANOVA; p = 0.05).  (D–F) Hindgut from E18.5 wild-type (D), heterozygous (E), and Ret null (F) mice. Meconium containing bile pigment is present in the caudal hindgut (asterisk) of mice of all three genotypes. A, anus; C, caecum; SI, small intestine. Scale bar = 1 mm.

Risk of duodenal cancer in patients with familial adenomatous polyposis

Bülow et al published results of a prospective multicentre study on analysis of the natural history of duodenal adenomas in familial adenomatous polyposis (FAP) (Gut 2004;53:381–6).

A total of 368 patients were examined over a mean period of 7.6 years (range 0.5–10.4). They showed significant progression of Spigelman stage over time (p < 0.0001). At the end of the study, the incidence of Spigelman stage IV was 7.0%. These results are lower than those reported in a similar study published very recently (35% incidence of Spigelman stage IV) of 368 patients who entered into a study of biological markers some years ago. The available literature on this issue is inconsistent. Our own experience is somewhat different. In 30 FAP patients who entered into a study of biological markers some years ago, the development of the most severe Spigelman stage was negligible after 7–18 years of surveillance (only one case, from stage II to stage III). We found no cases with stage IV or cancer. This could be due to differences in the selection of patients. For example, in the studies of both Bülow and colleagues and Saurin and colleagues, data on colorectal surgery were not reported. Proctocolectomy affects bile acid metabolism and circulation. Bile acids are involved in the development of duodenal neoplasia.

All of the patients we have under surveillance have undergone a proctocolectomy with J-pouch ileoanal anastomosis. They probably have impairment of the bile acid pool thus leading to a smaller risk of duodenal neoplasia. In Bülow’s group, a separate analysis on patients who were operated on and those who were not may be more informative in this regard.

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References


Author’s reply

In response to the letter of Biasco et al, in our study (Gut 2004;53:381–6) of 368 patients with a median follow up of 91 months, the cumulative incidence of duodenal adenomatosis Spigelman stage IV was 52% at age 70 years, which is in fact almost the same lifetime risk as the 50% found by Saurin and colleagues and the 20–30% risk in the Swedish and Finnish series.

All of major studies have found that the risk of advanced duodenal adenomatosis increases with age, thereby indicating an increasing risk of duodenal carcinoma and justification of regular endoscopic surveillance.

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BOOK REVIEWS

Molecular Pathogenesis of Cholelithiasis


This book represents a timely and up to date review of a rapidly developing field. The pattern is generally one of concise overviews which are extensively referenced. Those who
have always regarded bile as dark and unfathomable would find a large array of related subjects which have been illuminated to provide clinically meaningful insights into health and disease, albeit the compilation of the book had the cognoscenti in mind. The future plan is to have the book available in electronic format to allow for regular updating.

The historical introductory chapter brings home the almost startling rapidity with which the field has developed. Less than half a century ago it was first understood that bile secretion was an active process which could be sustained against a pressure gradient in contradistinction to urine. The energy which drives secretion is now known to emanate from an array of ATP binding cassette transporters responsible for secretion of osmotically active bile solutes. Many of those transporters have been cloned and characterised and disease associations worked out.

Similarly, the function and feedback regulation of a host of genes whose products control bile composition and secretion of bile is explained, along with the changes induced by various cholestatic perturbations. The scope of the book is comprehensive, including all aspects of cell physiology pertinent to formation for the hepatocyte and cholangiocyte, and extensive data on the causes and consequences of cholestasis. The basic science chapters, written by leading authorities in their field, are informative and amply referenced to lead the serious student of basic science chapters, written by leading authorities in their field, are informative and amply referenced to lead the serious student into any background literature of their choosing. The excellent clinical chapters on pruritus, PBC, PSC, etc, are more discursive and are aimed at an audience of physician, the book's foreword stresses the emphasis on recent updates, and as such some of the omissions (such as CT colonography, advances in surgery) are slightly disappointing. Nevertheless, the author is to be congratulated overall for his success in including such a wealth of information in a mere 200 pages of a pocket sized book.

A Emmanoul

Gastrointestinal and Liver Disease, 7th Edn Online. Pathophysiology/Diagnosis/Management
Edited by M Feldman, L S Friedman, M H Sleisenger, Amsterdam: Elsevier, £65.99. ISBN 0 7216 8973 6

The mighty Sleisenger and Fordtran textbook now comes in three varieties: two volume hardback, online only access, or both. Evolving at the speed of medicine'' sounded good but the internet version be any use for me? All three of the hospitals I currently work at now have easy computer access at the clinic desk and on the wards, so it seemed an appealing prospect to carry around just a password rather than seven kilos of weighty tome.

The 7th edition online is exactly as described, and although—confusingly—there is also a CD, this contains only slide images/illustrations. My confusion with the CD meant I was unable to use the lovely interruption free time provided by the plane to DDW to write this review and was forced to watch movies instead. In this version, the site is solely available through the internet via a web browser. The quality of the website is therefore critical to the success of the "book", and I thought it was fairly good. The site (www.sgastro.com) was fast loading without fancy graphics (unless specifically chosen) and so would also work at home with a modem, and was simple to use with clear clearly labelled sections last year. There are also a few bonuses, including a drug database, patient information leaflets (albeit scanty and with US specific information), and useful website links. Both the website and CD image collection (provided only I suspect for speed of use) were pretty good for making rapid PowerPoint presentations—for example, to teach medical students on a topic with an hour's notice.

Would I buy it? Yes, having quick access to an easy to use and up to date textbook in the clinic is I think very valuable. Reviewing information on the website is fast enough that it can be done in a few minutes with the clinical notes at hand before calling a patient in. Access to the 7th edition online, however, is as soon as the edition was published—so the book version remains as a comfort to have on the shelf, and will at least always be there. If resources were no problem I'd have both!

D A van Heel

Nutritional Support for Adults and Children

On behalf of BAPEN (British Association of Parenteral and Enteral Nutrition), Tim Bowling has managed to bring together three doctors (one physician, one paediatrician, and one surgeon), two nurse specialists, two pharmacists, as well as four dieters as joint authors of this book. This is far from easy, especially as the authors individually contributed by writing a chapter each but by contributing throughout the book.

The book is laid out in two principle sections: adult and paediatric nutrition support with the same headings repeated in each section. This makes it easy to follow and there is a lot of information in this book that is very simply and clearly presented. Tables are clear and useful, and practical guidance is given—for example, nasogastric tube placement, issues around bowel sounds and feeding, and practical aspects of administering parenteral nutrition and dealing with line sepsis.

My only criticism is the number of forwards to the book. There are a record five forwards, which seems a little excessive but does not detract from the book. Overall this is a practical hands-on book. It is clear and informative without being too large or weighty. It is well referenced for further reading. I can see nurses, dietitians, and pharmacists carrying this book around with them and hope also to see a copy on each ward. What about doctors? Well, it certainly should be essential reading for every junior doctor.

S Gabe

www.gutjnl.com
Risk of duodenal cancer in patients with familial adenomatous polyposis

G Biasco, M A Pantaleo, G Di Febo, C Calabrese and G Brandi

Gut 2004 53: 1547

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