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 for an odds ratio as small as 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 trends 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 analysis adjust for calendar time. In fact, such widely changing patterns have been observed in this population for oral contraceptive usage after a pill scare in the mid-1990s.

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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Enhanced vascular responses to noradrenaline in isolated omental arteries from patients with advanced cirrhosis: evidence against intrinsic vascular hyporeactivity in cirrhosis

The mesenteric and systemic vasodilatation that occurs in advanced liver disease leads to the development of a hyperdynamic circulatory state which in turn underlies many of the complications of cirrhosis. Studies of isolated vessel preparations from cirrhotic animal models have led to the concept that vasodilatation is linked to an intrinsic vascular hypersensitivity to endogenous vasoconstrictors such as noradrenaline, but whether the same holds true of human blood vessels in cirrhosis has not been established. In order to study the responses of isolated human splanchnic vessels, we obtained 21 omental arteries from 10 patients undergoing orthotopic liver transplantation for advanced cirrhosis. Fifteen control arteries were obtained from six patients at the time of hepatobiliary surgery or intestinal resection. Informed consent was obtained and the study was approved by the institutional ethics committee.

A hyperdynamic circulation was confirmed by invasive measurement of haemodynamic parameters using a pulmonary artery catheter. Micromvessels were carefully dissected free from a sample of omentum and mounted on a Mulvany-Halpern myograph in order to study isometric vascular responses. Responses were measured to potassium, noradrenaline, and the selective α1-adrenoceptor agonist phenylephrine. Endothelium dependent vasodilatation was assessed by acetylcholine and substance P, given before and after inhibition of nitric oxide and prostaglandin synthesis. Contraction responses were expressed as a percentage of the force generated by maximal potassium depolarisation. Relaxation responses were expressed as a percentage of precontraction with 30 mM KCl. Dose-response curves were fitted to a logistic equation and mean sensitivity (EC50) and maximal responses (Emax) compared between cirrhosis and control vessels by the Student’s t test. A p value <0.05 was considered significant.

Vascular responses are shown in table 1. Cricortic vessels demonstrated normal responses to potassium depolarisation. The sensitivity of contraction responses to noradrenaline and methoxamine was not affected by the presence of cirrhosis and in fact a greater maximal contraction to noradrenaline was observed in cirhotic vessels compared with controls. The presence of a functional endothelium was confirmed by demonstrating vasodilatation to the endothelium dependent vasodilator substance P. Responses following inhibition of nitric oxide and prostaglandin synthesis show that vasodilatation was mediated by the action of nitric oxide and vasodilator prostanooids but the contribution of the latter was greater in cirhotic vessels.

This study is the first of its kind to directly address the question of whether intrinsic hyporeactivity to endogenous vasospressors is present in small resistance arteries from patients with cirrhosis. Previously, only large conduit branches of the hepatic artery without an intact endothelium have been studied in the organ bath. These have produced evidence for both a reduced1 or normal2 response to adrenergic agonists. Noradrenaline produces vasoconstriction via its action on α adrenoceptors. However, in high concentrations, it can mediate a vasodilator response via β adrenoceptors. It is therefore possible that the enhanced noradrenaline response observed in the present study may relate to reduced β adrenoceptor activation.

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Reference

Table 1 Pharmacological parameters of omental arteries in advanced cirrhosis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Emax</th>
<th>Log EC50</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td>KPSS (mm Hg)</td>
<td>106.8 (11.7)</td>
<td>111.0 (8.6)</td>
</tr>
<tr>
<td>Noradrenaline (1%KPSS)</td>
<td>90.9 (9.9)</td>
<td>110.9 (3.6)*</td>
</tr>
<tr>
<td>Methoxamine (1%KPSS)</td>
<td>40.1 (11.1)</td>
<td>11.1 (1)</td>
</tr>
<tr>
<td>Acetylcholine (% relaxation)**</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Substance P (% relaxation)</td>
<td>87.4 (3.0)</td>
<td>91.3 (1.6)</td>
</tr>
<tr>
<td>Substance P + 0.1 mM NOLA</td>
<td>35.2 (6.6)</td>
<td>56.0 (6.4)*</td>
</tr>
<tr>
<td>Substance P + 0.1 mM NOLA+10μM indomethacin (% relaxation)**</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Maximal responses (Emax) and the log10 of EC50 were determined in each vessel studied by fitting the responses to a logistic equation. Data are mean (SEM).

*p<0.05 compared with control response.

Logistic curves were not fitted as no responses were observed.
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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References


Histopathology using the Vienna criteria: clinical decision making is still adequate

We thank Saito et al for their interest in our paper that prospectively examined the safety and efficacy of high magnification chromoscopic colonoscopy for the diagnosis of neoplasia in flat and depressed lesions of the colorectum (Gut 2004;53:284–90).

Their abstract data, using the modified Paris classification of superficial neoplastic lesions, as determined by the newly designated 1000m vertical mucosal extension limit, offers impressive sensitivity and overall accuracy without substantial distinguishing sm2 invasion. We look forward to publication of the full manuscript soon.

However, fundamental differences still exist between Japanese and Western histopathologists that make comparative studies between East and West difficult. Our histopathology was interpreted using the Vienna classification of gastrointestinal epithelial neoplasia, as proposed by Schlemper et al following the consensus classification workshop. The consensus terminology differentiates between non-invasive low grade neoplasia, non-invasive high grade neoplasia (which includes suspicion of invasive neoplasia), and invasive neoplasia (intramucosal carcinoma, submucosal carcinoma, or beyond) into Vienna categories 3, 4, and 5, respectively. In table 4 (Gut 2004;53:284–90), our neoplastic invasive group includes both Vienna 4 and 5 lesions together. This “collection” of data reflects current histopathological practice in the UK where sm invasion (i.e. Vienna 1–3) are not routinely specified. While we accept that the modified Paris guidelines are extremely helpful, our current practice is aimed at overall patient “risk stratification” where the natural history of low grade dysplasia (LGD) has yet to be determined but that of high grade dysplasia is more defined; assuming a high risk of progression to invasive neoplasia. Differentiation of hyperplastic (non-neoplastic/non-invasive) from LGD adenoma (neoplasic/neoplastic invasive) therefore still remains an important asset to the endoscopists (sensitivity 98%/specificity 92% in our series), as the number of inappropriate biopsies and resections can be safely limited while allowing for appropriate risk stratification permitting suitable chromoscopic follow up intervals.

We agree with the recent data of Hurlstone et al who have demonstrated that sm superficial lesions without lymphovascular invasion or poorly differentiated histological features have a low incidence of local nodal metastasis.

While we acknowledge the concerns raised by Saito et al we feel that despite adopting the Paris guidelines, our data still provide a comprehensive guide to high magnification chromoscopic colonoscopy, as is practiced within the UK.

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References

1 Matsuoka T, Fujii T, Oto A. Effectiveness of magnifying colonoscopy in diagnosing the depth of invasion of colorectal neoplastic lesions: invasive pattern is an indication for surgical treatment Gut 1997;37:575–8176.


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 concurrent 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) is 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 disease.

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 3654 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 antinuclear 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 mortality compared with the general population.

The ethical dilemma that the medical world faces today is whether screening is based 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

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, mucous, 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 aganglionsis 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 anally 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 (Rئ/ئ/Rئ/ئ mice). The post-caecal hindgut of wild-type (+/+), heterozygous (+/−), and Ret null (−/−) littersmates 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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Table 1  Clinical presentations of coeliac disease

<table>
<thead>
<tr>
<th>Typical symptoms</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td>Enteropathy associated</td>
</tr>
<tr>
<td>Weight loss</td>
<td>T cell lymphoma</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>Ulcerative jejunitis</td>
</tr>
<tr>
<td></td>
<td>Malignancy (oesophageal small bowel)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Atypical symptoms</th>
<th>Associated conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia</td>
<td>Dermatitic herpetiforms</td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
<td>Type 1 diabetes</td>
</tr>
<tr>
<td>Autoimmune disorders</td>
<td>Autoimmune thyroiditis</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Primary biliary cirrhosis</td>
</tr>
<tr>
<td>Liver disease</td>
<td>Autoimmune diseases</td>
</tr>
<tr>
<td>Gastrointestinal cancer</td>
<td>IgA deficiency</td>
</tr>
<tr>
<td>Mood change</td>
<td>Down’s syndrome</td>
</tr>
<tr>
<td>Irritable bowel</td>
<td></td>
</tr>
<tr>
<td>Ataxia</td>
<td></td>
</tr>
<tr>
<td>Epilepsy</td>
<td></td>
</tr>
<tr>
<td>Dental enamel</td>
<td></td>
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<tr>
<td>Hypoplasia</td>
<td></td>
</tr>
<tr>
<td>Mucocoele</td>
<td></td>
</tr>
<tr>
<td>Metabolic bone disease</td>
<td></td>
</tr>
<tr>
<td>Short stature</td>
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</table>

References
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%. These results are lower than those reported in a similar study published very recently (35% incidence of Spigelman stage IV). The available literature on this issue is inconsistent. Our own study published very recently (35% incidence of Spigelman stage IV) was 7%. These results show 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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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 colleagues1 and the 20–30% risk in the Swedish and Finnish series.2

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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References


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
Anal and Rectal Diseases Explained


Eli Ehrenpreis, a respected senior North American physician, has completed the latest volume in a series of “Explained” mini textbooks. The series is intended as a source of concise information for physicians. The content is comprehensive, including subjects often missed by physicians and surgeons alike, such as sexually transmitted anorectal conditions and anal neoplasia. The style is akin to highly structured student notes and as such the information provides more of an overview for trainees rather than the complete detail for higher level specialists. This brevity and conciseness towards being didactic, while a strength in some respects, can result in certain deficiencies, in particular in the introductory section on anatomy and physiology. The emphasis is towards the American model in terms of the intensity of investigation. A particular strength of future editions would be to “editorialise” to a greater degree in terms of suggesting orders of priority for investigation and management of common presentations.

A particular strength of the book is the complementary illustrations, in particular the elegantly executed line drawings. These provide an excellent demonstration of the occasionally confusing anatomical relations of the pelvic floor, and is particularly evident in the chapters covering anal fistulae. Additionally, the profusion of clinical photographs and x rays will be of help to gastroenterologists whose specialty is not coloproctology.

Another great value of the book is the patient information section. This is laid out in a question and answer style for a number of common clinical problems and is particularly helpful for those gastroenterologists/physicians. The book’s foreword stresses the emphasis on recent updates, and as such of some of the omissions (such as CT colonography, advances in surgery) are slightly disappointing. 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 Emmanuel

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 Fordran textbook now comes in three varieties: two volume hardback, online only access, or both. “Evolving at a time of ‘gastroenterology’ pretty good but would 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 text 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 clear navigation. The site was also easy to view on the left of the screen and the text pages on the middle and right. Clicking on a chapter provided a further breakdown of contents by subheading while remaining easy to change between topics. A minor grumble: the chapter headings took up too much space on my small laptop screen (although fine on a bigger desktop)—and an option to personalise the view of the site would be an ideal source for the enquirer unfamiliar with this niche interest.

E Elias

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 dietitians as joint authors of this book. This is far from easy, specially as the authors have not only 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 it 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
Molecular Pathogenesis of Cholestasis

E Elias

Gut 2004 53: 1547-1548

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