Influence of metronidazole resistance on efficacy of quadruple therapy for Helicobacter pylori eradication

EDITOR,—van der Hulst and colleagues (Gut 1998;42:166–9) suggest that apparent metronidazole resistance predicts response to anti-helicobacter therapy regimens containing this antibiotic. However, the cure rate with their regimen of omeprazole, bismuth, tetracycline, and metronidazole for one week was only 90% (74/82). This is different from previous reports of this regimen given for seven days. 

helicobacter pylori urease positive patients with spontaneous duodenal ulcer treated with a regimen of lasaprazole, tetracycline, clarithromycin, and metronidazole, the antibiotics being given for one week. Encouraging results can be obtained with vigorous regimens if the right drug combination is selected, but laboratory studies may not be as helpful as they first appear.

The buried bumper syndrome: a complication of percutaneous endoscopic gastrostomy

EDITOR,—We would like to bring to attention a complication of percutaneous endoscopic gastrostomy (PEG) that presented in two patients in one afternoon. Both patients were male, and they both had a Freesius PEG tube placed two years previously. One patient was 88 years old with a history of stroke who, despite being given antibiotics because it continued to discharge pus.
this study. The data are retrospective and incomplete and based on the study of only 25 patients (the under 55 group) out of 319 with gastric cancer. There is no comparison of this group with the remaining 296 patients over 55 with regard to pattern of presentation or symptoms.

Perhaps more importantly there is no mention of the number of patients who actually presented for endoscopy or were picked up on the open access service. Surely the only way to set protocols for this service would be to analyse the data from it. In contrast this study seems merely to describe 25 patients below the age of 55 presenting in the Gloucester region, drawn from a pathology database, most of whom had advanced gastric cancers.

We would hope that better awareness of the importance of early referral and increased use of diagnostic endoscopic facilities should result in all those presenting with early disease. Based on our experience and that of centres such as Leeds, we would advocate open access endoscopy in anyone with new dyspeptic symptoms over the age of 40.

Finally and perhaps most worryingly the authors state in their discussion that early detection does not necessarily mean improved survival. Those of us involved in the treatment of gastric cancer realise that the only significant factor that is going to improve survival from this disease is early detection and treatment. There is overwhelming and irrefutable evidence to support this. In the UK the detection and treatment of early gastric cancers has led to a five year survival rate of over 90% in these patients. In Japan, where mass radiological screening of the over 40s, ready to endoscopy and population awareness of the disease has meant detection of early gastric cancer in more than half of all gastric cancer cases and again a five year survival of over 90% in these patients.

Early detection means improved survival.

Until we have adequate prospective data from a large open access endoscopy unit we cannot agree with the interpretation and findings of this study and urge other centres to continue to endoscope symptomatic patients under the age of 55.

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Reply

EDITOR,—Most of the arguments raised by Karat and colleagues were covered in our paper. However, we consider that the epidemiological principles underlying our paper are important, we think it is worth reiterating.

The data are retrospective but there are no comparable prospective data. Unlike other studies ours was of a defined population based on postcodes. The importance of this for determining presentation characteristics and natural history of disease cannot be over-emphasised. Most other studies emanate from referral centres that receive selected patients. The reported survival has invariably influences the type of patient seen and interpretations made. Thus we believe our study is a better reflection of the real world.

We went to great lengths to ensure completeness (e.g. searching several databases) of patient care. Our incidences are comparable to OPCS data and therefore we think it unlikely that many, if any, patients were missed. The small number (25 in seven years) of patients aged less than 55 just emphasises how rare the disease is in this age group.

Karat et al advocate better awareness of the importance of early referral to improve the chance of finding early disease. A point we stressed in our paper was that referral by general practitioners and subsequent investigation were not significantly delayed.

We did not determine the source of patients (clinic or open access) because general practitioners use clinic referrals rather than open access endoscopy for all sorts of reasons unrelated to symptoms. There would be too many confounders to make a meaningful exploration of differences in these groups.

The point about the open access service in Gloucester is that it has been in operation for 20 years. The local doctors are relatively experienced in its use. The experience of its effects in the past 10 years in our district is relevant to experience in the next 10 years in other districts (the majority) that have introduced an open access service more recently.

In the UK there is no “overwhelming and irrefutable evidence” that early detection improves survival from gastric cancer. Only a randomised controlled trial can give this level of certainty and none has been done in the UK. The case series quoted from Leeds was not based on a geographically defined population and it is subject to the biases of all referral bases) of patient capture. Our incidences are demonstrated that RelA (p65) is present in nuclear extracts of biopsy specimens or lamina propria mononuclear cells from patients with active inflammatory bowel disease (IBD). Furthermore, they show NFkB binding activity and a corresponding decrease in IxBu in lamina propria mononuclear cells treated with lipopolysaccharide (LPS). In contrast, treatment with dexamethasone pretreated LPS induced nuclear translocation of NFkB due to persistence of IxBu. The authors conclude from these data that corticosteroids inhibit NFkB activation in vitro by stabilising the cytosolic inhibitor IxBu against activation induced degradation.

Firstly, this conclusion cannot be drawn from the data presented in the paper. Secondly, their conclusion contradicts a number of previously published observations.

Two models of corticosteroid mediated NFkB inhibition have been proposed. The first proposes that down modulation of NFkB driven genes results from a physical interaction between the glucocorticoid receptor and the RelA (p65) subunit. Negative cross-talk between the glucocorticoid receptor and RelA is due to direct interaction via the Rel homology domain of RelA and the DNA binding domain of the glucocorticoid receptor in combination with interference by the transactivation domain of RelA with the transcriptional activity of the glucocorticoid receptor.

The second model proposes that the inhibitory effect of glucocorticoids is mediated by the induction of the IxBu protein, which traps activated NFkB in inactive cytoplasmic complexes. It has been shown that dexamethasone induces IxBu upregulation of the IxBu gene, although a glucocorticoid responsive element has not been identified in the IxBu promoter. Thus, in the presence of dexamethasone NFkB quickly reassociates with newly synthesised IxBu which results in notably reduced amounts of NFkB that translocates to the nucleus.8,9

So far there is no evidence that steroids stabilise IxBu. However, we have recently shown that sulphasalazine interferes with IxBu phosphorylation and promotes a self-perpetuating degradation of IxBu in vitro. Therefore, the available data indicates that different levels of interference with NFkB activation by sulphasalazine and corticosteroids.

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4 Wissink S, van Heerde EC, Schmitz ML, et al. Distinct domains of the RelA NF-kappaB subunit are required for negative cross-talk and direct


7 Schreiber S, Nikolaus S, Hampe J. Activation of NFκB by glucocorticoids induces IκBα degradation in human colonic carcinoma (SW620) and Jurkat T cell lines, adding an important aspect to the mechanistic action of anti-inflammatory drugs in IBD but also underline the importance of the experimental system. J Immunol 1996;156:3961-9.

8 Schreiber S, Nikolaus S, Hampe J. Activation of NFκB may be a central element in the pathophysiology of Crohn's disease. Inhibition of NFκB activation offers an attractive hypothesis for the action of numerous drugs with clinically relevant effects in IBD. The exact mechanisms involved have yet to be determined in the relevant cell systems and in further ex vivo studies using affected tissues of diseased patients.

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BOOK REVIEWS


This book will be a bench mark by which others on the subject of pancreatitis will be judged. This is no ordinary volume assembled by two hard-pressed editors from an array of international experts with differing styles and experience but a testament to the careful editing by two eminent authors. The gestation period was 10 years, the evidence base is 1900 citations and the bias is distinctly clinical—that is, this is a reference book for the working gastroenterologist or surgeon with an interest in pancreatitis.

The two diseases, acute and chronic pancreatitis, are dealt with in a similar format, beginning with clinical features, pathogenesis, and treatment. And on the back of this come recommendations, each one, sensitivity and specificity, and practical tips bringing clarity to an often muddled view giving practical guidance. For two disease processes whose pathogenesis is poorly understood and for which there are few specific therapies, it is mandatory for guidance to be more than anecdotal. Thus, where there is controversy the literature has been carefully sifted through, debated and a bottom line recommendation reached. The approach is not without criticism, but thoroughly positive in its analysis of international efforts to solve the conundrum of pancreatitis.

So what gems can be extracted to whet your appetite? Firstly a riveting discussion of scoring systems and prognostic signs in acute pancreatitis, a topic which often switches off the relative newcomer to this area but which holds the key to stratification and new treatment options. Ransos, Imrie and APACHE II take on a new life, literally illustrated with explanatory figures and tables. Secondly, there is a clear and detailed discussion of the merits and practical value of the various pancreatic function tests which can be used in chronic pancreatitis. When to use each one, sensitivity and specificity, and practical tips bring clarity to an often muddled area. And on the back of this comes an eclectic and comprehensive opinion giving practical guidance. For two disease processes whose pathogenesis is poorly understood and for which there are few specific therapies, it is mandatory for guidance to be more than anecdotal. Thus, where there is controversy the literature has been carefully sifted through, debated and a bottom line recommendation reached. The approach is not without criticism, but thoroughly positive in its analysis of international efforts to solve the conundrum of pancreatitis.

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Any doctor treating patients with pancreatitis can be recommended to buy and enjoy this exceptional book.

A N KINGSNORTH


In just under a decade since the hepatitis C virus was first discovered the proliferation of research publications has been overwhelming. Although this is an appropriate reflection of the prevalence and clinical importance of the disease, the high prevalence of this infection and its variable outcome, I felt that the chapter on natural history of infection had been a bit longer. It also feels that all aspects of clinical trials are thorough it would have been helpful to have included, at the end of the treatment chapter, a recommendation on best current clinical practice. Of course I realise that this is changing all the time but this book is already on its second edition we presumably can expect an update in reasonable time.

As I mentioned before this book is concise and comprehensive. This combination usually implies that it would also be unreadable but this is not the case. Inevitably a lot of detail has been edited away from the concise summaries but this is counterbalanced by excellent referencing which guides the interested reader to key publications in the literature.

I am not really sure at whom this book was originally aimed but I have my own ideas about who would benefit from having a copy on their bookshelf. I recommend this book to the specialist registrars who are starting in the viral hepatitis clinic and to PhD students who are beginning their hepatitis C research in the laboratory. For the general gastroenterologist it could well provide a more accessible source of background information than other textbooks I have read.

M THURSZ


The relationship between general practitioners and gastroenterologists has, generally, been a better one than with most other specialists. In the UK, this has in part been due to long fostered relationships between the British Society of Gastroenterology and the Primary Care Society for Gastroenterology. Also, there is a closely shared and common clinical agenda between general practitioners and gastroenterologists. Some aspects of gastroenterology, particularly dyspepsia, are managed essentially in primary care and there is a healthy, if sometimes competitive, dialogue between the professions.

This book reflects this ethos, exploring common ground through a patient centred approach. In doing so it meets the new challenges facing clinicians through the restructuring of the NHS and the advent of the Primary Care Groups, which are likely to seek closer and more meaningful dialogue across the primary care interface.

The authors, a general practitioner and two specialists, offer an intelligent entree into the concepts of shared and managed care, both of which are likely to be the basis of much future health transactions within the NHS.

The authors have managed to cover the gamut of gastroenterological problems without mimicking a traditional topic based textbook. They draw upon the experiences of mixed groups of general practitioners and specialists who have discussed shared care in specific situations. The book contains copies of shared care cards and other materials of practical use—for example, for inflammatory bowel disease in children. A whole chapter on polyps is particularly well described with a review of management options of value from both general practice and hospital viewpoints. An early section on clinical skills is especially engaging, although it might have been augmented by reference to the relatively poor predictability of clinical diagnoses. In a world of increasing use of diagnostic and referral facilities a closer examination of the uncertainty and dilemmas faced by the general practitioner would have been welcome. Many general practitioners believe that gastroenterologists rarely make clinical diagnoses at the initial consultation; they merely order tests! Equally, the authors have managed to evade a critical review of one of the most contentious areas in reflux management: whether to step “up” or “down” therapy, and the appropriateness of long term treatment with potent drugs.

This does not, however, take away from an excellent book presented in compact softback version. It is likely to appeal to the general practitioner for diagnosis and management, to the specialist registrar for easy reference and to the consultant seeking closer collaboration with primary care. It does extend beyond the basics, even has a section on patient support groups and recognises the realities of the changing environment of the NHS. It’s worth buying.

P HUNGIN


Very early in my career I told a senior colleague that I was interested in trying to treat patients with hepatocellular carcinoma (HCC). “Oh, that is easy,” he replied, “Give them a bottle of whiskey and send them home!” In those days HCC was seldom even diagnosed during life let alone treated. Gut readers, many of whom will have been brought up on single authored textbooks of gastroenterology, may be dismayed to find that treatment and diagnosis of HCC can now fill an entire book of more than 400 pages. That this task requires more than 60 authors will compound their dismay. Indeed, it is probably the size of the book that tells the main story. There is no consensus on how best to diagnose, screen for, or treat this tumour, with the result that each diagnostic approach, and each of the numerous treatment options, is described individually by their own proponents.

This is not to imply that HCC is not worthy of such detailed examination. In high incidence areas HCC management will occupy very considerable resources. For example, about a quarter of all beds in this author’s wards will be taken up by patients with HCC. In the West, the implication of the rate at which HCC develops among the increasing number of patients who are carriers of the hepatitis C virus (HCV) is only just sinking in. Decisions on whether or not to screen them all, and then what to do when the tumour is found, will have major resource implications for gastroenterologists and hepatologists. As noted above, gastroenterologists in the past have placed a high value on (justified) therapeutic nihilism. Now, however, it is clear that long term survival following resection can be achieved and long term results following liver transplantation are very impressive.

Within this volume the reader will be able to find information on all aspects of the diagnosis and management of HCC. The book is comprised of 32 chapters arranged in five sections: basic aspects, clinical aspects, diagnosis, treatment and fibrolamellar HCC with an international, though predominantly Italian and Japanese authorship. The individual chapters are perhaps best read as a series of good reviews on the various topics rather than constituting a coherent text book. This is because in several instances—for example, in the chapter on chemoebolisation, the authors tend to recount their own, single institution experience without reference to randomised controlled trials when these are done elsewhere.

There are some areas where tighter editing would have helped clarify clinical practice. For example, under the heading of “Besides therapies” we are told that “non-randomized trials (of tamoxifen) supplied contradictory results regarding the value of its use...” But of the three references supplied at that contention, three were, in fact, clearly randomised and at least two of these suggested that tamoxifen did increase survival.

Gut readers will find a good analysis (Cotone and D’Antoni), but no easy answers, as to how to often and by what means to screen their high risk patients. Whether screening will help the individual or the community remains unclear. Italian authors are pessimistic, Japanese more positive. Perhaps readers from both correct in relation to the tumour as seen within their own countries. The authors’ conclusion that, “The lack of evidence that early detection translates into improved clinical outcome strengthens the belief that the primary goal in the battle against HCC should focus on the prevention of cirrhosis by vaccinating against hepatitis, by minimizing the risk of hepatitis C and decreasing the risk of alcoholism”, is probably correct but likely to be of little solace to current carriers of hepatitis B or C.

With regard to an overall approach to therapy, individual units will find the wealth of information in this well produced and lav
ishly illustrated book. They will, however, have to sift the data very carefully to develop approaches suitable for their own institutions. The editors conclude, under the heading “Therapeutic guidelines”: “To sum up, the possible combinations (of treatments) are many and it is not easy to lay down strict rules for the management of patients whose HCC is not advanced . . . the most opportune treatment has to be decided in the light of each individual patient’s characteristics, evaluating every variable, and the expertise available at each centre and the resources of the national health services”.

It seems that HCC is not a single entity but rather several different types. Each may need its own approach, both in relation to different geographical areas of the world and to different aetiologies. This makes the task of editors wishing to give an overall view of HCC extremely difficult, but Livraghi, Makuuchi and Buscarini have, by and large, succeeded.

P JOHNSON

NOTES

European Mucosal Immunology Meeting. The Cells and Molecules Important in Mucosal Tolerance and Inflammation

The European Mucosal Immunology Meeting. The Cells and Molecules Important in Mucosal Tolerance and Inflammation will be held at the Charterhouse Square Campus of St Bartholomew’s and the Royal London School of Medicine and Dentistry, London, UK, on 2–3 October 1998. Further information from: Professor T T MacDonald, Department of Paediatric Gastroenterology, St Bartholomew’s Hospital, London EC1A 7BE. Email: t.t.macdonald@mds.qmw.ac.uk.

Laparoscopic Surgery

A Course on Laparoscopic Surgery will be held at the University Hospital Saint Pierre, Brussels, Belgium, on 17–20 November 1998. Further information from: Conference Services S.A., Avenue de l’Observatoire 3, bte 17, B-1180 Brussels, Belgium. Email: conference.services@skynet.be.

Second Inflammatory Bowel Disease Meeting

The Second Inflammatory Bowel Disease Meeting will be held at Chester Town Hall, Chester, UK, on 23–24 November 1998. Further information from: Professor J M Rhodes, Royal Liverpool University Hospital, Prescot Street, Liverpool L7 8XP. Tel: +44 151 706 3558; Fax: +44 151 706 5832.

13th International Workshop on Therapeutic Endoscopy

The 13th International Workshop on Therapeutic Endoscopy will be held at the Endoscopy Centre, Prince of Wales Hospital, Hong Kong, on 1–3 December 1998. Further information from: Professor Sydney Chung, Endoscopy Centre, Prince of Wales Hospital, The Chinese University of Hong Kong, Sha tin, N.T., Hong Kong. Tel: +852 2632 2233; Fax: +852 2635 0075.

European Postgraduate Gastro-Surgical School Symposia

The 7th Course on Digestive Endoscopy - Live will be held at the Academic Medical Centre, Amsterdam, The Netherlands, on 3–4 September 1998. Registration fee: NLG 450.00.

H. pylori: from Bench to Bedside will be held at the Academic Medical Centre, Amsterdam, The Netherlands, on 24–25 September 1998. Registration fee: NLG 300.00.

Minimally Invasive Surgery: A Critical Evaluation will be held at the Academic Medical Centre, Amsterdam, The Netherlands, on 13 November 1998. Registration fee: NLG 200.00.

From Gene to Cure II: Bilio-pancreatic malignancy will be held at the Academic Medical Centre, Amsterdam, The Netherlands, on 4–5 February 1999.

Further information from: Helma Stockmann, Managing Director, European Postgraduate Gastro-Surgical School, G-4-4zuid, Academic Medical Centre, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands. Tel: +31 20 566 3926; Fax: +31 20 566 6596 or 691 4858; Email: w.j.stockman@amc.uva.nl.

Sir Francis Avery Jones BSG Research Award 1999

Applications are invited by the Education Committee of the British Society of Gastroenterology who will recommend to Council the recipient of the 1999 Award. Applications (TWENTY COPIES) should include:

- A manuscript (2 A4 pages ONLY) describing the work conducted.
- A bibliography of relevant personal publications.
- An outline of the proposed content of the lecture, including title.
- A written statement confirming that all or a substantial part of the work has been personally conducted in the UK or Eire.

Entrants must be 40 years or less on 31 December 1998 but need not be a member of the BSG. The recipient will be required to deliver a 40 minute lecture at the Annual Meeting of the Society in March 1999. Applications (TWENTY COPIES) should be made to the Honorary Secretary, BSG, 3 St Andrews Place, London W1 4LB, by 1 December 1998.

34th Annual Meeting of the European Association of the Study of the Liver (EASL)

The 34th Annual Meeting of the European Association of the Study of the Liver (EASL) will be held in Naples, Italy, on 8–12 April 1999. Topics covered include: The Liver and Systemic Disorders, Infection and Liver Diseases, Gene Therapy in Liver Diseases, and Aspects, SBP, Hepatorenal Syndrome. The president of the 1999 meeting is Professor Giuseppe Giusti. EASL will offer 120 Travel Bursaries to selected young investigators and 30 to Eastern Europeans, dependent on submission of an abstract. In addition, registration is free for first authors under 35 years of age who submit abstracts. This is part of EASL’s policy to encourage young investigators to attend and present at its scientific meeting. Abstract deadline: 30 November 1998. Application deadline for 1999 EASL Fellowships: 31 December 1998.

Further information from: EASL Liaison Bureau, Hepatology, Neckher Hospital, 149 rue de Sèvres, 75743 Paris Cedex 15, France. Fax: +33 1 44 49 51 65; Email: isabelle.porteret@nck-ap-hop-paris.fr.

Second International Workshop on Helicobacter pylori

The Second International Workshop on Helicobacter pylori will be held in Hong Kong on 24 and 25 April 1999. Further information from: Professor Joseph Sung, Endoscopy Centre, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong. Tel: +852 2632 2233; Fax: +852 2635 0075; Email: info@hksdc.org.

International Conference at the Hong Kong Academy of Medicine

The Hong Kong Academy of Medicine will host its first International Conference on 26–29 November 1999. Further information from: Congress Secretariat, 9/f, Multicentre Block A, Pamela Youde Nethersole Eastern Hospital, 3 Lok Man Road, Chai Wan, Hong Kong. Tel: +852 2515 5755; Fax: +852 2503 3149; Email: hkam@hkam.org.hk; Website: http://www.hkam.org.hk.

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Influence of metronidazole resistance on efficacy of quadruple therapy for *Helicobacter pylori* eradication

M C BATESON

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