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Reply

EDITOR.—We thank Drs Heaton and Emmett for their interest in our paper (*Gut* 2000;47:144–7) and the insightful comments. We regret not having cited their previous research findings on the relationship between plasma insulin and prevalent gall stones.¹ We agree that waist to hip ratio may be an important variable to consider. However, waist to hip ratio and insulin are intimately related in the pathophysiological pathways linking insulin resistance to gall stone formation, therefore the interpretation of results from analytical models, including both of these variables, may be problematic. In addition, we concur with the potential importance of physical fitness, and would like to add that physical activity may also play a role in the aetiology of gall stones. Our conclusion is based on the findings from a previous paper by our group showing a strong association between physical activity and incident gall stones in a population based case control study.²

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Heparin as an anti-inflammatory agent: it's no GAG to forget about chemokines

EDITOR.—We approached with enthusiasm the report by Salas and colleagues (*Gut* 2000;47:88–96) showing that heparin prevented tumour necrosis factor α induced leucocyte rolling, adhesion, and migration in vivo, as demonstrated using intravital microscopy. The novelty and potential importance of the report were emphasised by the appearance of an accompanying commentary by Perretti and Page (*Gut* 2000;47:14–15). Our enthusiasm was tempered, however, by the authors' selective invocation of potential explanations for heparin as an anti-inflammatory agent. While an effect of heparin on the neutrophil integrin adhesion molecule CD11b was described in elegant experiments, heparin almost certainly exerts its anti-inflammatory effects through a range of activities beyond an adhesion molecule target. One of these targets is the superfamily of cytokines known as chemokines, over 40 of which have now been identified.¹

Chemokines are small, basic, chemotactic cytokines that mediate leucocyte recruitment to sites of inflammation and immune responses.^{2,3} In addition, it is now clear that

they are crucial to routine immune surveillance and homeostasis.⁴ They have a capacity to bind selectively to a range of glycosaminoglycans, or GAGs, including heparin, in tissues and on the surface of both endothelial cells and leucocytes. This interaction heightens migration along a fixed gradient, or so-called haptotaxis,⁵ and favours receptor binding.⁶ There is strong evidence that soluble GAGs, including heparin, prevent chemokines binding to their receptors, thus abrogating their chemotactic potential.⁷

Neither Salas and colleagues nor Perretti and Page chose to mention an anti-chemokine mechanism for the anti-leucocyte migration activity of heparin. We ignore chemokines at our peril though, as their sheer number and abundance, and the intensity of the effort being directed at discovering pharmacological inhibitors of their function, highlight their critical role in inflammation.

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Management of variceal haemorrhage in cirrhotic patients

EDITOR.—We have serious concerns about several of the recent UK guidelines for the management of variceal haemorrhage in cirrhotic patients (*Gut* 2000;46(suppl 3 and 4):iii1–iii115), particularly those that contradict current published evidence. We highlight below the ones we feel are the most important.

In the management of acute variceal bleeding, variceal ligation is not the method of first choice which was given an AI recommendation. Meta-analysis of all trials of acute bleeding of banding versus injection sclerotherapy have shown no statistically significant difference between the two treatments for either control of bleeding or survival (data derived from 12 studies with 419 patients), with no statistical heterogeneity.¹

The implication of recommending ligation for acute bleeding is that double intubation would be necessary in a patient who is actively bleeding so as to attach the ligation device after the initial diagnostic endoscopy. Although there is no evidence, this would create more risk to the patient; it is common

sense that a single intubation would be preferable and would take less time. At best the recommendation should be that either endoscopic technique could be used as first choice, dependent on operator expertise and facilities.

Secondly, there is evidence from randomised studies of vasoactive drug therapy combined with endoscopic techniques that combination therapy is superior in terms of control of bleeding. This is based on five randomised studies with 610 patients (pooled odds ratio 0.42, 95% confidence interval 0.29–0.6).¹ Publication bias assessment has shown that 29 null or negative studies would be needed to render the results non-significant, and thus this effect is fairly robust. Moreover, in several of these studies vasoactive drugs were given before diagnostic endoscopy, demonstrating their utility during the period of resuscitation before endoscopy could be safely performed, which in practice may be several hours after admission. This goes against the recommendation that drugs can be used if endoscopy is not available. Drugs should be used first followed by therapeutic endoscopy.

As regards the prevention of rebleeding from sources due to portal hypertension, the treatment of first choice, unless there are contraindications, is either non-selective β blockers as they are equivalent to sclerotherapy,¹ or band ligation. No fully published randomised studies are available with regard to β blockers versus banding. If banding is not available, β blockers should be used, not sclerotherapy, as recommended. If there are contraindications or intolerance to β blockers, banding should be used. One can argue cogently that as non-selective β blockers are cheap and do not involve repeated endoscopy sessions, they always should be considered the treatment of first choice.

The recommendation of measuring hepatic venous pressure gradient (HVPG) in patients given β blockers cannot be one for current practice. Only two Spanish groups have suggested this, and it is unclear when a repeat measurement should be performed. Moreover, both a 20% reduction from baseline HVPG or an absolute reduction to less than 12 mm Hg are "protective" from rebleeding, so both end points, and not just the absolute reduction, need to be mentioned if this management strategy is used. In any case the randomised studies versus sclerotherapy used non-selective β blockers empirically to the maximum tolerated by patients so that use of drugs without pressure measurement was effective. Lastly, if the recommendation of using drugs with re-measurement of pressure is taken to its logical conclusion, all patients should be tried on drugs first, as those who respond have far less rebleeding (10% or less) than patients who receive banding, and secondly, a recommendation of what to do next would need to be made for those who do not reduce their portal pressure (for which as yet there is no evidence).

Lastly, two meta-analyses comparing TIPS with endoscopic techniques showed that TIPS did not improve survival.^{2,3} The increased encephalopathy, greatly increased cost, as well as poor availability of TIPS treatment does not make it a first choice treatment for rebleeding, even in centres with expertise such as the authors' own, as stated in the guidelines. Thus the AI recommendation grading is particularly inappropriate.

With respect to primary prevention of portal hypertensive bleeding in cirrhotics, the

recommendation that nitrates should be used if neither β blockers nor banding are available or contraindicated is potentially dangerous. A long term randomised study has shown that at least in elderly patients, nitrates on their own decrease survival.¹ Thus to err on the side of caution, nitrates cannot be recommended as a substitutive therapy.

Finally, the guidelines should have included some issues of general management—for example, resuscitation with fluids, early assessment of portal vein patency, and presence of hepatocellular carcinoma—and an AI recommendation for the use of prophylactic antibiotics in acute bleeding based on the meta-analysis the authors quoted.⁵ A corrected and improved update of these guidelines is needed soon.

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Reply

EDITOR,—We thank Dr Burroughs and Dr Patch for their interest and helpful comments on the UK guidelines in the management of variceal bleeding. A number of the points raised by them reflects the fact that it is not always possible to directly translate the evidence that is gleaned from clinical trials into clinical practice because of the subjectivity in the definition of evidence based medicine. There is a lot of argument in the literature about what constitutes research evidence. Indeed, there is ongoing debate whether the results of a good randomised controlled trial are more reliable than a meta-analysis on the same subject because the latter often suffers from problems introduced by heterogeneity between studies.^{1,2}

For the preparation of the present “guidelines”, about 300 papers were reviewed and 208 have been referred to in the paper. It is clear that the vast majority of these studies were not adequately powered to detect differences in mortality and a number of points that have been raised by Dr Burroughs and Dr Patch represent alternative interpretation of the available data which are not necessarily at variance with the “guidelines”.

Before discussing the specific points raised by them, it is important to point out that:

- Although the guidelines were written by us, they have undergone several revisions based on peer review organised by the

British Society of Gastroenterology (BSG), Liver Section. This review process we believe was extensive and largely anonymous. The guidelines therefore represent the views of the BSG.

- The guidelines were first commissioned in 1996 but finally accepted for publication following several alterations in mid-1998. Some of the more important data were added into the text (the antibiotic prophylaxis section) during the proof stage.

With respect to the specific comments:

(a) We agree with Dr Burroughs and Dr Patch that studies have not shown any significant differences between band ligation and sclerotherapy in their ability to control bleeding. Also, most patients who have had a variceal bleed and are undergoing endoscopy are not bleeding actively. It is therefore relatively easy to band in these situations and a double intubation using the new multi-band ligation devices is not necessarily a problem. Studies have also shown that complications from endoscopic therapy in the form of oesophageal ulcers, mediastinitis, and pneumonia are significantly less in the group treated with band ligation compared with sclerotherapy. This is associated with reduced mortality in patients treated with band ligation. It stands to reason therefore that band ligation should be used where possible as there is no significant difference between treatments in their ability to control bleeding but the rate of complications has been shown to be significantly less in the band ligation group.^{3–6}

(b) Interpretation of data regarding the combination of vasoactive drugs with endoscopic therapy in the setting of acute bleeding is fraught with difficulties and there is no clear evidence that the combination reduces mortality. This is despite a large number of trials in this area. The meta-analysis that Burroughs and Patch (published in 1999) refer to as a justification for the combination treatment shows no differences in survival between groups.⁷ The role of vasoactive drugs in the management of variceal bleeding is an area of intense research by a number of groups and data are needed before the combination treatment can be recommended in routine clinical practice.

(c) With respect to secondary prophylaxis of variceal haemorrhage, the literature suggests that various treatments such as sclerotherapy, β blockers, or a combination of these are similar in the long term (reviewed by D'Amico and colleagues⁸). Most patients that we treat in the UK with variceal bleeding have underlying alcoholic liver disease and who have a questionable compliance. The recommendation is that if only a β blocker is used we should ensure that this is having some effect on the most important parameter predictive of rebleeding, a portal pressure gradient <12 mm Hg (about 30% of patients in different studies show inadequate portal pressure response to β blocker therapy). It has been shown in a prospective study that in patients being treated with β blockers, none with a hepatic venous pressure gradient <12 mm Hg bled and only 8% of those whose hepatic venous pressure gradient fell by more than 20% on therapy bled during follow up.⁹ However, if portal pressure studies are included in patients being treated with β blockers, this is likely to increase both the cost and invasiveness. We do agree that we should add to the guidelines that a reduction in portal pressure gradient by 20% or more from baseline is acceptable.

(d) The guidelines clearly state what Dr Burroughs and Dr Patch suggest in their letter: “TIPSS is more effective than endoscopic treatment in reducing variceal rebleeding but does not improve survival and is associated with more encephalopathy”. Three studies have shown that TIPSS is as cost effective as endoscopic treatment.^{10–12} The only study that suggests that TIPSS is more expensive is an Italian study in which TIPSS was not strictly being used for secondary prophylaxis with patients being randomised for as long as six months after their initial variceal bleed.¹³ Studies that have compared TIPSS with band ligation have not shown any significant differences in encephalopathy between groups.^{10,14} This has, however, not been borne out in a meta-analysis.¹⁵ But it is clear from individual trials and also from the meta-analysis that TIPSS significantly reduces the rate of rebleeding.

(e) The recommendation grade for the use of isosorbide-5-mononitrate (ISMN) in case of failure of propranolol or band ligation is grade B1 and is based on the equivalence study of ISMN and propranolol by Angelico and colleagues.¹⁶ The paper that Dr Burroughs and Dr Patch refer to is a post hoc analysis of data from a study that was first reported in 1993.¹⁷ A preliminary report of another study has not confirmed these findings¹⁸ and it is clear that more data are needed before nitrates can be suggested as being dangerous in the primary prophylaxis of variceal bleeding.

(f) Our brief was to develop guidelines about the management of variceal bleeding and not about the detailed intensive care management. We have however included some pointers in the guidelines which we thought were likely to be useful. We accept that the use of prophylactic antibiotics should be a grade 1A recommendation. This section on the use of antibiotics following a variceal bleed was added during the proof stage following the availability of the meta-analysis by Bernard *et al* in 1999.¹⁹

We do agree with Dr Burroughs and Dr Patch that the treatment options in portal hypertension are continuously evolving and with the emergence of new data, “guidelines” should be revised to incorporate the advances that have occurred in that time.

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Long term follow up of interferon responder children with chronic hepatitis B

EDITOR,—We read Bortolotti *et al*'s article (*Gut* 2000;46:715-18) reporting the long term effect of interferon (IFN) alpha in children with chronic hepatitis B (HBV). Briefly, a total of 107 children with chronic HBV who received IFN alpha for three or six months in two clinical trials were followed for a mean period of 69 months. In the first trial 19 and 20 cases received IFN alpha at a dose of 3 and 7.5 MU/m² three times a week for six months, respectively. In the second trial 34 cases received lymphoblastoid IFN at a dose of 5 MU/m² for 12 weeks and 30 cases received IFN at the same dose but preceded by a four week course of prednisolone. Response to treatment was defined as loss of hepatitis B e antigen (HBeAg) within 12 months after stopping treatment. A control group of 59 patients was also followed for a mean period

Table 1 Number (%) of patients who cleared HBeAg at different times in the four treatment groups

Time	Group 1 (n=8)	Group 2 (n=34)	Group 3 (n=5)	Group 4 (n=12)	Total (n=59)
End of treatment	6 (75%)	23 (67.6%)	3 (60%)	6 (50%)	38 (64.5%)
12 months after stopping treatment	6 (75%)	32 (94.1%)	5 (100%)	12 (100%)	17 (28.8%)
End of follow up	8 (100%)	34 (100%)	5 (100%)	12 (100%)	59 (100%)

Interferon alpha dosage and duration: group 1, 10 MU/m² three times a week for six months; group 2, 5 MU/m² three times a week for six months; group 3, 5 MU/m² three times a week for 12 months; group 4 (non-responders to previous interferon alpha treatment), 10 MU/m² three times a week for six months.

of 46 months without any therapy. Sixteen (15%) treated children responded during therapy and 18 (17%) during post-treatment follow up; 31 (29%) non-responders lost HBeAg during subsequent years. The cumulative HBeAg clearance rates at five years were similar between treated patients (60%) and controls (65%). Loss of hepatitis B surface antigen (HBsAg) occurred in only four patients who responded during treatment.

We also wish to report on the long term follow up of 59 IFN responder children with chronic HBV (table 1).¹⁻³ At the beginning of IFN therapy, all children (44 males; 74.6%) had abnormal or fluctuating transaminases for at least six months and were positive for HBV DNA. Mean age of the patients at diagnosis of chronic HBV was 6.8 (3.4) years (range 1-15). They were followed for a mean period of 19.9 (21.5) months (range 6-100) before treatment. Liver biopsy was performed on 29 patients; 15 (51.7%) had mild, 12 (41.4%) moderate, and two (6.9%) severe hepatitis. Forty three (84.3%) of 51 patients had at least one family member with positive HBV serology. Eight patients (group 1) had received IFN alpha at a dose of 10 MU/m² three times a week for six months,¹ 34 (group 2) at a dose of 5 MU/m² three times a week for six months² or 12 months (five patients, group 3). Twelve patients (group 4) who were unresponsive to IFN therapy at a dose of 5 MU/m² received IFN alpha again at a dose of 10 MU/m² three times a week for six months.³ Response to treatment was defined as loss of HBeAg during the treatment period or within 12 months after stopping treatment. All patients were followed for a mean period of 35.3 (10.8) months (range 18-62) after starting treatment. Thirty eight (64.5%) patients cleared HBeAg at the end of IFN therapy and 17 (28.8%) within 12 months after stopping treatment. Four (6.7%) patients were late responders (HBeAg clearance was observed between 21 and 30 months after stopping therapy). The mean period of HBeAg clearance was 8.2 (7.0) months. Within the follow up period, antibody to hepatitis B surface antigen (anti-HBs) occurred in seven (18.4%) patients who responded during therapy and all but one lost HBsAg. After HBeAg clearance, anti-HBe seroconversion and loss of HBV DNA was observed in all patients. Alanine aminotransferase values normalised in 98.3% of patients. None had biochemical or serological relapse within the follow up period.

The majority of our patients cleared HBV DNA and HBeAg during therapy whereas only 15% of patients in the study of Bortolotti *et al* responded during therapy. They followed patients for an average of 69 months and observed that all IFN responders remained HBeAg and HBV DNA negative. Although our observation period was shorter than theirs, we also observed that all responders had sustained results at the end of follow up. Similar to Bortolotti *et al*'s results, all HBsAg cleared patients were early responders to IFN

therapy in our group. In conclusion, response to IFN alpha in children with chronic hepatitis B is permanent. It is necessary to follow these patients for longer periods to see the long term effects of IFN alpha therapy, such as prevention of cirrhosis and/or hepatocellular carcinoma.

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Renal sodium handling in preascitic cirrhosis

EDITOR,—We read with interest the commentary by Clària and Rodés (*Gut* 1999;45:639) on our paper published in *Gut* which re-examined the mechanisms of renal sodium retention in patients with preascitic cirrhosis.¹ In summary, in our patients we observed indirect evidence of expanded central vascular fluid volume compared with healthy controls and thought this physiopathological alteration was due to slightly reduced values of glomerular filtration rate (measured as creatinine clearance) and, mainly, to increased distal tubular retention of sodium when expressed as a fraction of the filtered sodium load that is reabsorbed by the distal nephron (26.9 (6.7)% v 12.5 (3.4)%, respectively; $p < 0.05$).¹

Clària and Rodés advanced two criticisms and affirmed that our results, obtained by means of the lithium clearance and fractional excretion technique, may be influenced by two fundamental flaws. Firstly, the reliability of lithium clearance as a marker of distal fluid delivery in clinical conditions characterised by low fractional sodium excretion (below 0.40%) has not been proved due to possible lithium reabsorption in the distal nephron.² Secondly, in Clària and Rodés's opinion, our observation of more avid fractional sodium reabsorption by the distal nephron in compensated cirrhosis merely reflects diminished delivery of fluid and sodium to the distal segments (due to reduced glomerular filtration) rather than increased distal tubular sodium reabsorption.