Non-polyposis Colon Cancer (HNPCC) management

The French Ad-Hoc Committee on Hereditary Non-polyposis Colon Cancer (HNPCC) management meeting on behalf of the French Health Minister has recently released its statement. The report on prophylactic colorectal resections for HNPCC related adenocarcinomas (Gut 2003;52:1752–5) is in contrast with ours and we would like to discuss this point.

Use of decision analysis models is a smart approach in dealing with such complex situations. However, life expectancy related to the occurrence of metachronous colorectal carcinoma should be balanced against the negative impact on quality of life in the case of prophylactic extensive colorectal resections. Thus quality adjusted life expectancy, integrating the individual patient’s choice, might be a more accurate approach. Comprehensive, fair, and loyal information of what the patient can hope for is mandatory.

Compliance with ethical standards

Our committee has no conflicts of interest.

References


Serum pro-hepcidin: measuring active hepcidin or a non-functional precursor?

We read with great interest the paper “Pro-hepcidin: expression and cell specific localisation in the liver and its regulation in hereditary haemochromatosis, chronic renal insufficiency, and renal anaemia” (Gut 2004;53:733–43).

We have two observations. Firstly it was shown that pro-hepcidin and hepcidin were localised within the liver and in Hep-G2 cells. However, it was not possible, using serum ELISA, to identify the C terminus of hepcidin (the mature form of hepcidin 25). Is it possible that the functional N terminal antibody used for serum analyses represents non-functional precursor amino acids and not the active molecule? This might explain the lack of correlation between iron parameters and hepcidin seen from the patient data.

Furthermore, the authors comment on the paradoxically elevated levels of pro-hepcidin in patients with chronic renal insufficiency on erythropoietin (EPO). All of these patients were reported to have normal haemoglobin levels. Previous studies have shown that EPO inhibits hepatic hepcidin expression. The authors speculate that the elevated circulating hepcidin levels may reflect reduced renal clearance of the molecule in these patients. However, other studies have suggested chronic inflammatory diseases are associated with elevated serum hepcidin (in animal models) and urine hepcidin in human beings. Another possibility, therefore, is that patients have elevated iron stores, in relation to chronic disease, and this may have a direct effect on hepcidin release. It would be interesting to know the iron metabolic parameters in these patients, as obviously haemoglobin in isolation is not an accurate measure of iron stores. It is unclear from the paper whether fig 8 represents data from patients with haemochromatosis (HFE) patients, in whom hepcidin expression is likely to be dysregulated due to direct effects of the HFE gene product.
Clearly future clinical studies in this field hold much promise.

M J Brookes, N K Sharma, C Tselepis, T H Iqbal
City Hospital, Birmingham, UK

Correspondence to: Dr M J Brookes, City Hospital, Dudley Rd, Birmingham B18 7QH, UK; mbro453399@oal.com

References

Use of oesophageal dilatation in clinical practice
Drs Riley and Attwood are to be commended for their recent publication (Gut 2004;53:1–6). We share their difficulty with one recommendation related to dilatation. Under 6.1, it is stated that during oesophageal dilatation the endoscopist should be supported by at least two endoscopy assistants. We agree that this is certainly desirable when the complications encountered are dilated or if one is dealing with an achalasia patient.

However, for dilatation of Schatzki’s rings or simple peptic strictures, one endoscopy assistant generally is sufficient. At our institution, over the years numerous dilatations have been done with only one assistant and without any adverse consequences.

As written, your guidelines seem to indicate that the standard of care would be to have two endoscopy assistants present and I think this is both unrealistic and unwarranted.

S J O Veldhuizen van Zanten
Correspondence to: Dr S J O Veldhuizen van Zanten, Division of Gastroenterology, Dalhousie University, Queen Elizabeth II Health Sciences Centre, Room 928, Centennial Building, 1278 Tower Rd, Halifax, Nova Scotia B3H, Canada; zanten@dalu.ca

Variant Creutzfeldt-Jakob disease: update
Two years ago we reported current thinking on the potential for gastrointestinal endoscopy to act as a vector for patient to patient transmission of variant Creutzfeldt-Jakob disease (vCJD) in that article we stressed that the advice would be updated if new evidence became available. Gastroenterologists may be aware of a recently published article in the Lancet in which the tissue distribution of abnormal prion protein (PrPSc) in monkeys that have been inoculated with brain homogenate from first passage animals with bovine spongiform encephalopathy (BSE) via the oral route, which is the route by which the vast majority of patients developing vCJD will have become infected. As the prion protein responsible for vCJD is found in all lymphoid tissue, our advice was to reduce “random” biopsies to an absolute minimum and ensure that useable biopsy forceps were meticulously cleaned and decontaminated according to the strict British Society of Gastroenterology (BSG) guidelines. We also advised on the use of disposable biopsy forceps, particularly in the ileum, as it was felt that biopsies from this area posed the greatest risk to both endoscope and forceps becoming contaminated. Other inexpensive accessories such as cleaning brushes and the rubber cap covering the biopsy port were also to be disposed of if a biopsy had been taken.

The paper from Herzig and colleagues1 is the first to look specifically at the tissue distribution of PrPSc after oral and intravenous inoculation in a primate model utilising Cynomolgus macaques. The findings confirm that the highest concentration of PrPSc is in the tonsil but that it is also abundantly present in the terminal ileum and ileocaecal fold where gut associated lymphoid tissue is present in large amounts. The whole of the gastrointestinal tract was positive for PrPSc from the duodenum to the rectum. Both gut associated lymphoid tissue and the autonomic nervous system were highly involved, including nerve fibres lying just below the mucosal border. The authors suggested that the possible risk of transmitting vCJD via endoscopic procedures could be further underestimated as the detection of PrPSc is the best marker for infectivity in prion diseases.

This new information should help to inform gastroenterologists that the risk of transmitting vCJD via an endoscopic procedure remains a distinct possibility and the advice of two years ago remains as relevant today as it was then. All patients undergoing gastrointestinal endoscopy should be considered potential carriers of vCJD in the context that the majority of the UK population is likely to have had dietary exposure to the BSE agent during the 1980s. Perhaps the most important aspect of this new information is the increasing realisation that any biopsy from anywhere in the gastrointestinal tract is “high risk” as a biopsy of the terminal ileum. It is not logical to reserve disposable biopsy forceps for this one area; it seems more appropriate for endoscopy units to move entirely into using disposable forceps for all procedures and phase out the use of re-usable equipment that might be difficult to trace or decontaminate. Biopsies should only be performed where this is likely to influence clinical management.

Although one recent case of vCJD has been associated with blood transfusion,2 no case of vCJD has so far been attributed to an endoscopic procedure. However, we would urge all staff involved in endoscopy decontamination to remain vigilant and adhere strictly to guidelines already issued by the BSG in order to minimise this risk.

M G Bramble
James Cook University Hospital, Middlesbrough, UK

I Ironside
National CJD Surveillance Unit, Western General Hospital, Edinburgh, UK

Correspondence to: Professor M G Bramble, James Cook University Hospital, Marton Rd, Middlesbrough TS4 3BW, UK; mike.bramble@stees.nhs.uk

References

Is mesalazine really safe for use in breastfeeding mothers?
Mesalazine containing preparations are commonly used for the treatment and maintenance of remission of inflammatory bowel disease. The young age of many inflammatory bowel disease sufferers means that the issue of whether to continue therapy in nursing mothers often arises.

We report a small study that was instigated after a nursing mother with Crohn’s disease approached us concerned about the safety of continuing to breastfeed while taking mesalazine. She had a cracked bleeding nipple and was worried about the dose of the drug that her baby would be receiving. We agreed to analyse this for her and to undertake a small study.

We obtained breast milk samples from four breastfeeding mothers with inflammatory bowel disease who were taking a 5-ASA preparation. Ethics approval for the study was obtained from the local ethics committee. Breast milk analysis was performed using high performance liquid chromatography. Concentrations of 5-ASA in the breast milk of 5-ASA treated patients were 0–40 ng/ml while those of N-Ac-5-ASA were 5.0–14.9 μg/ml (some 1000 times higher). These results are similar to levels found by other investigators.3,4

Based on an average intake of a breastfeeding infant of 150 ml of milk/kg of body weight/day, concentrations of 5-ASA found in breast milk samples equate to a dosage of 0.0006–0.006 mg/kg. This falls well below 10% of the standardised therapeutic dose, and therefore by this conventional criteria the risk of 5-ASA to the infant is considered clinically unimportant. However, our finding of high levels of metabolite (N-Ac-5-ASA) in breast milk suggests that the metabolite is greatly enriched in breast milk. Differences in the physical properties of 5-ASA and N-Ac-5-ASA may well account in part for some difference in their rate of transfer into breast milk. It is more likely that the findings reflect the result of active metabolism of 5-ASA taking place within the glandular cells of the breast.

We have shown that the concentration of 5-ASA in the breast milk of patients receiving 5-ASA therapy is low. It is therefore interesting to speculate whether the low levels of 5-ASA may, in part, be due to metabolism of 5-ASA to N-Ac-5-ASA by breast tissue as a
mechanism to prevent high levels of active 5-ASA from accumulating in milk. N-Ac-5-ASA is a relatively inactive metabolite and is therefore unlikely to have a toxic effect on the infant, although to our knowledge the effect of N-Ac-5-ASA on infants has not been studied. We therefore cautiously support the view that 5-ASA containing medication is safe for breastfeeding mothers with inflammatory bowel disease. In addition to our specific findings relating to 5-ASA, the discovery of active drug metabolism in the breast has potentially wider implications. Based on our findings we would recommend that future studies looking at breast milk drug levels explore the possible effects of metabolism by breast tissue and the potential toxic effects of any metabolites produced.

D A Silverman, J Ford, I Shaw, C S J Probert
University of Bristol Division of Medicine, Bristol Royal Infirmary, Bristol, UK
Correspondence to: Dr C S J Probert, University of Bristol Division of Medicine, Bristol Royal Infirmary, Bristol BS2 8BW, UK; c.s.j.probert@bristol.ac.uk

References
2 Nesi G. Diarrhoea due to 5-aminosalicylic acid in breast milk. Lancet 1993;338.

Duodenal adenoma and cancer in FAP
We congratulate the authors (Gut 2004; 53:381–6) on gathering this large cohort of patients in this important area in familial adenomatous polyposis (FAP) but would like to express some concerns regarding the study. Our first concern relates to the means of endoscopic assessment. Standard forward viewing endoscopy was used, whereas in clinical practice side viewing endoscopy is recommended as duodenal polyposis in FAP is more severe in the periampullary region and this is likely to be missed with standard endoscopy. This will therefore underestimate both adenoma sta-
ging and frequency. This matter is raised in their discussion where they describe side viewing endoscopy as unrealistic. We however feel this is unreasonable in an era where ERCP services are available in most hospitals, at least in the UK.

Furthermore, the need for appropriate endoscopy technique and biopsy protocols has been highlighted in a recent study1 which reveals the impact of side effects related to duodenal disease when comparing biopsy specimens and resected specimens, in addition to the finding of invasive cancer in a number of specimens resected for “severe duodenal adenomatosis” (that is, Spigelman stage 3 with high grade dysplasia or stage 4). The need to operate before biopsy proven carcinoma is demonstr-
ated by the high mortality rates from metastatic disease in those with duodenal carcinoma. Accurate staging and assessment for endoscopic or surgical intervention is, in our opinion, not possible by standard forward viewing endoscopy.

Our other concern relates to the quoted cancer incidence, which we feel must be biased. The cohort was not followed up from a young age and therefore underestimated both adenoma sta-
ging and frequency. In this important area in familial adenomatous polyposis in FAP is more severe in the periampullary region and this is likely to be missed with standard endoscopy. This will therefore underestimate both adenoma staging and disease progression. In the discussion, the authors mention that a few patients may have been on periodic sulindac and therefore underestimate both adenoma staging and cancer. As such, these older patients in this group we would expect to be self selected and to have less severe disease. Those who were destined to develop severe duodenal disease or cancer may well have developed it prior to screening. Of note, the median age of those developing cancer was 52 years (range 26–58).

In addition, those patients undergoing open duodenotomy and polyectomy are likely to be those with most advanced disease and a highest risk of malignant transforma-
tion, thus again biasing the likely natural incidence of duodenal carcinoma.

There are also few details regarding to medical intervention which may affect duode-

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tion, thus again biasing the likely natural incidence of duodenal carcinoma.
Octreotide is mainly used in acromegaly and in gastrointestinal and pancreatic tumours. Nevertheless, it has also been proposed to be effective in controlling bleeding from the gastrointestinal tract due to angio-dysplasia and variceal bleeding. It is postulated that it exerts its actions through a reduction in splanchnic and portal blood flow. Octreotide LAR, compared with conventional octreotide, has the advantages that it is administered once monthly, does not require hospitalisation, and has a similar efficacy and safety profile.

Only one report on the effectiveness of octreotide therapy in two patients with vWD was found in the literature. In one of these patients, vWF was increased after administration of octreotide. In our patient, octreotide did not cause any increase in the synthesis or release of vWF. We can therefore assume that the combined administration of octreotide LAR and propranolol was effective in preventing bleeding in our patient through the treatment of angiodysplasia of the gastrointestinal tract, particularly when other therapeutic modalities have failed.

N Krikis, K Tziomalos, V Perifanis, S Vakalopoulou, A Karagiannis, V Garipidou, F Harsoulis
Second Propedeutic Department of Internal Medicine, Aristotle University of Thessaloniki, Hippokration General Hospital, Thessaloniki, Greece
Correspondence to: Dr K Tziomalos, Second Propedeutic Department of Internal Medicine, Aristotle University of Thessaloniki, 63 Solanos St, Thessaloniki 54248, Greece; k.tziomalos@yahoo.com

References

Antiviral treatment initiation costs in chronic hepatitis C
We thank Dr Poynard for his comments highlighting the role of pretreatment evaluation costs prior to antiviral treatment of patients with chronic hepatitis C (Gut 2003;52:1352). The rate of fibrosis progression varies among patients with chronic hepatitis C, so liver biopsy can identify those with advanced disease who are at greatest risk for progressing to decompensated cirrhosis when therapeutic options are limited. Other testing, such as genotyping and viral load, can help estimate the likelihood of antiviral response or determine the duration of therapy, and still others are obtained for baseline values to monitor for potential side effects from therapy.

In our cost effectiveness analyses of antiviral treatment strategies for chronic hepatitis C, treatment initiation costs included those related to procedures performed before the beginning of antiviral therapy: pregnancy test, quantitative hepatitis C virus (HCV)-RNA testing, HCV genotyping, thyroid stimulating hormone, thyroxine, and liver biopsy, as well as partial inpatient costs for initiation of antiviral treatment. Previously published cost effectiveness studies have applied different biopsies costs depending on the country and health care system. The costs in our study are based on the German Hepatitis C Database and reflect the German health care system. However, there are different options for defining these costs. Liver biopsy can be performed as an inpatient or outpatient procedure. The German Uniform Assessment Standard (Einheitlicher Bewertungsmassstab, EBM), which is the fee for service coding system in social health insurance for outpatient care in Germany, assigns a total of 1450–1630 score points to the performance of outpatient liver biopsy. This includes ultrasound guidance (530 points), biopsy (700 points), and histology (220–400 points), and translates to a cost between €49 and €55. The German Hepatitis C Model Clinical Expert Panel (n = 16) estimated that inpatient liver biopsy requires an average hospital stay of one day or less. Based on administrative per diem costs, a one day hospital stay in Germany costs €234. To bias our analysis against antiviral therapy, we estimated a conservative estimate of the cost effectiveness of antiviral treatment, we applied a full hospital day for all patients undergoing liver biopsy in our base case analysis.

When we performed sensitivity analyses on all cost parameters, we found little variation in the incremental cost effectiveness ratios of antiviral treatment compared with no antiviral treatment. When comparing combination therapy with interferon and ribavirin plus weight based ribavirin with a combination of standard interferon plus ribavirin, pretherapeutic costs do not alter the incremental cost effectiveness ratios. However, if the costs occur for all antiviral treatment strategies, they cancel each other out when we calculate the incremental cost of antiviral treatment (that is, the difference in treatment costs between antiviral treatment strategies).

This is not however the case when combination therapy with pegylated interferon plus weight based ribavirin is compared with no antiviral treatment. In response to Dr Poynard’s comment, if the cost of liver biopsy were €1000, the discounted incremental cost effectiveness ratio of treatment with pegylated interferon and ribavirin rose from our base case of €3820 to €4070 per quality adjusted life year (QALY) gained. If we assumed that non-invasive measurement of biochemical markers of liver fibrosis reduced the test related mortality by 3/10 000 and had the same accuracy as liver biopsy but at a cost of €90, the discounted incremental cost effectiveness ratio of treatment with pegylated interferon and ribavirin fell to €3760 per QALY gained. Varying biopsy related mortality from 0 to 5 per 10 000 did not affect the incremental cost effectiveness ratios when rounded to two significant figures but clearly has a major impact on the individual basis for those affected. To bias our results against no antiviral treatment, our analysis did not consider periodic repeat liver biopsy, in which case disease related costs and morbidity and mortality from liver biopsy would be higher. In such an analysis, the use of non-invasive biochemical markers would have a greater effect on hepatitis C related morbidity, mortality, and costs.

These additional analyses suggest that even for countries with substantially higher initial pretherapeutic costs than exist in Germany, the expected long term clinical benefits and cost savings from antiviral treatment induced prevention of future adverse health outcomes outweighs the initial pretherapeutic and antiviral treatment costs in patients with chronic hepatitis C. If inexpensive and accurate fibrosis markers replaced liver biopsy, the cost effectiveness of antiviral treatment would improve even further.

U Siebert, J Wasem, S Rossol, G Sroczynski, P Aidelburger, U Ravens-Sieberer, B M Kurth, M P Mannis, J G McHutchison, J B Wong
Harvard School of Public Health, Boston, Massachusetts, USA
Correspondence to: Dr U Siebert, Harvard School of Public Health, 718 Huntington Ave, Boston, Massachusetts 02115, USA; usiebert@hsph.harvard.edu

References
Adherence to BSG adenoma surveillance guidelines will reduce colonoscopic workload

There is an ever increasing demand for colonoscopy nationally which will increase further when colorectal cancer screening is rolled out nationally. To accommodate this, a marked improvement in the efficiency of endoscopy units is required. One simple way of reducing demand is to reduce the number of repeat procedures performed. We have found that by following the British Society of Gastroenterology (BSG) polyp follow up guidelines, our unit could prevent a significant number of unnecessary colonoscopies.

Our unit’s three month retrospective audit found that 79 of 528 patients undergoing colonoscopy had colonic polyps; 130 polyps in total were detected of which 65 were histologically confirmed adenomas (45 tubular, 18 tubulovillous, and two villous). Over two thirds were in the rectum/sigmoid.

By classifying patients with polyps according to BSG guidelines:

- 32 were low risk, of which 16 had too short a follow up interval and 16 had correct follow up (of the 16 with too short a follow up, 10 had no follow up and six had a five year follow up);
- 13 were intermediate risk, with three having correct follow up, six too short a follow up interval, one too long a follow up, and three had no follow up;
- one patient was high risk and received too short a follow up interval;
- 11 had incomplete polyp removal of which four received appropriately rapid follow up, two had late follow up, and five received no follow up;
- of 22 patients with non-adenomatous polyps, only eight had an unnecessary repeat procedure arranged.

Strict adherence to the BSG guidelines would have added eight apparently overlooked procedures but could have saved up to 30 other surveillance procedures (if a policy of no follow up for low risk polyps was used), resulting in a net reduction of 22 procedures. This is equivalent to a 47% reduction in surveillance colonoscopies.

The simple measure of reviewing repeat requests for surveillance procedures to ensure they adhere to BSG guidelines should reduce the number of unnecessary procedures performed, creating additional capacity within our endoscopy unit and reducing the exposure of patients to unnecessary risk.

R C Thomas, C Seilinger, M D Rutter
University Hospital of North Tees, Stockton, UK

Correspondence to: Dr R C Thomas, Department of Gastroenterology/GIM, University Hospital of North Tees, Hardwich, Stockton TS9 6ED, UK; rcht72@aol.com

Conflict of interest: None declared.

Reference

6th International Symposium on Functional Gastrointestinal Disorders

This symposium will be held 7-10 April 2005, in Milwaukee, Wisconsin, USA, and is jointly sponsored by the University of Wisconsin Medical School and the International Foundation for Functional Gastrointestinal Disorders, in cooperation with the Functional Brain-Gut Research Group. An international audience of clinicians and investigators will gather to exchange information on the latest advancements in the areas of functional gastrointestinal disorders. The symposium will offer a format of plenary sessions, interactive workshops and mini symposia on both adult and paediatric functional gastrointestinal disorders. Further details: Terese Bailey, Office of Continuing Medical Education, 2701 International Lane, #208, Madison, WI 53704; tel: +1 (608) 240 2141; fax +1 (608) 240 2151; email: tmbailey@wisc.edu.

CORRECTION
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In the Editor’s quiz: GI snapshot entitled “An unusual treatment for a colonic polyp” (Gut 2004; 53(7):1000, 1019) the last two authors were listed incorrectly. The correct order is M Crobu and then MG Porpora.
An alternative to prophylactic colectomy for colon cancer prevention in HNPCC syndrome

S Olschwang, P Laurent-Puig, F Eisinger and B Millat

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