Clinical opinons in general medicine

This edition of clinical opinions looks at recent developments in the fields of asthma management, alcohol-related liver disease and the link between obesity and non-alcoholic liver disease. We hope readers find these articles informative and useful and, as always, we welcome comments.

Clinical opinion: SIGN/BTS guidelines – implications for practice

TITLE: British Guideline on the Management of Asthma.
KEYWORDS: Asthma, guidelines, treatment.
AUTHORS: Scottish Intercollegiate Guidelines Network and the British Thoracic Society.
JOURNAL: *Thorax* 2003; **58:**supplement 1.

OPINION

'Guidelines or tramlines?' the cynics amongst us often ask. There are those who find the profusion of guidelines intrusive and restrictive and certainly the new BTS/SIGN asthma guidelines will cause many to reflect on their current, and in most cases comfortable, practice. The guideline is a weighty document running to some 94 pages, which may be off-putting for some, but the quick-reference guide is comprehensive and well-suited to busy day-to-day practice. The guideline is the result of an evidence-based review of the available literature with some 1,500 abstracts being identified and examined in the initial review. As one might expect, the strength of the evidence is not always sufficient to make strong recommendations, as in the case of complementary medicines. The guideline does, however, give clear guidance on the importance of accurate initial diagnosis, the use of alternatives to higher and higher doses of ICS, the importance of agreed Asthma Action Plans and advice on how to carry out quality audit of asthma care. Given that asthma still carries a significant mortality rate, and that a recent Confidential Inquiry into Asthma Deaths in Scotland found that inadequate routine care was a factor in 35% of deaths and poor compliance a factor in 18%, the importance of evidence-based guidelines for primary and secondary care seems incontrovertible. The guidelines represent a significant step forward and are to be commended.

Clinical opinion: the evidence base for stepping down inhaled steroids in moderate to severe asthma

TITLE: Stepping down inhaled corticosteroids in asthma: randomised controlled study.
KEYWORDS: Asthma, inhaled steroids, dose.
AUTHORS: Hawkins G, McMahon A, Twaddle S *et al.*
JOURNAL: *BMJ* 2003; **326:**1115.

SUMMARY

The authors tested whether a step-down approach to the use of high-dose inhaled corticosteroid (ICS) can be used safely in adults with stable chronic asthma. A multicentre, randomised, double-blind, parallel group trial was carried out over a one-year period. The study was conducted in a variety of general practices in central Scotland. Two hundred and fifty-nine adult asthmatics receiving high-dose inhaled coticosteroids (mean dose 1430 ug beclomethasone) were enrolled and randomised to receive either no change to their usual dose of ICS (control) or a 50% reduction in ICS dose if they met the criteria for stable asthma (stepdown). The main outcome measures were: comparison of exacerbation rates; asthma-related visits to general practice and hospital; health status measures and ICS dose in the two groups. No significant differences were found between the two groups except that the step-down group received 348 ug (95% CI 202–494 ug) of beclomethasone less per day than controls. The authors conclude that it is possible to step down high-dose ICS in stable chronic asthma without compromising control.

OPINION

Previous studies have indicated that it is possible to reduce the dose of ICS in the short term in mild asthmatics but this is the first study to specifically examine the effect of reducing ICS dosage in moderate to severe asthma over the longer term. Inhaled steroids are the most effective treatment for asthma but there has been increasing concern about their safety profile, especially in high dose; with bone loss, cataracts and adrenal suppression being possible side-effects. This provides practitioners with a much-

improved evidence base for a practice which had hitherto been really only based on little more than 'expert opinion' and as such is to be welcomed. Whilst it is undoubtedly true that optimal asthma control is best achieved using the lowest possible dose of inhaled steroid, it is probably worth remembering that the biggest problem in asthma is not that patients are receiving too much treatment, but too little. Nevertheless this paper, when taken in conjunction with the new BTS/SIGN guidelines, offers practitioners in primary and secondary care sensible evidence-based advice.

Dr Calum MacLeod, Consultant Paediatrician, Co. Antrim

Clinical opinion: combined drug therapy not superior to propranolol alone in treatment of oesophageal varices

TITLE: Propranolol plus placebo versus propranolol plus isosorbide-5-mononitrate in the prevention of a first variceal bleed: a double-blind RCT.
KEYWORDS: Isosorbide mono-nitrate, variceal bleeding, variceal band ligation
AUTHORS: García-Pagán JC, Morillas R, Bañares R *et al.*
JOURNAL: *Hepatology* 2003; **37:**1260–6.

SUMMARY
Nonselective blockers are very effective in preventing first variceal bleeding in patients with cirrhosis. Whilst treatment with isosorbide-5-mononitrate (IS-MN) and propranolol achieves a greater reduction in portal pressure than propranolol alone, there is no evidence that this confers additional clinical benefit. This multicentre, prospective, double-blind RCT evaluated whether combined drug therapy would be more effective than propranolol alone in preventing variceal bleeding. A total of 349 consecutive cirrhotic patients with gastro-oesophageal varices were randomised to receive propranolol + placebo (n = 174) or propranolol + IS-MN (n = 175). There were no significant differences in the one and two-year actuarial probability of variceal bleeding between the two groups (propranolol + placebo, 8·3% and 10·6%; propranolol + IS-MN, 5% and 12·5%). Survival was also similar. Adverse effects were significantly more frequent in the propranolol + IS-MN group due to a greater incidence of headache. There were no significant differences in the incidence of new-onset or worsening ascites or in impairment of renal function. In conclusion, propranolol effectively reduces variceal bleeding, but adding IS-MN does not further decrease the risk of bleeding in patients receiving propranolol.

OPINION
Variceal bleeding is one of the most severe complications of patients with cirrhosis and portal hypertension. At diagnosis more than 40% of cirrhotic patients already have oesophageal varices, and approximately 30% of those patients with large (>Grade I) oesophageal varices will bleed by two years. Currently, nonselective-blockers are the most widely used drugs to treat portal hypertension; however, problems with their usage persist. The effectiveness of nonselective-blockers in this setting has been shown in several controlled trials; further, meta-analyses have revealed a 40–50% reduction in the risk of the first episode of bleeding (from 22–35% to 17–22%, pooled odds ratio = 0·54) and a trend towards improved survival. Indeed, whilst treatment with -blockers decreases the risk of first haemorrhage by 50%; the risk is not completely abolished. For this reason the role of adjunctive or alternative therapies has been explored. This study demonstrates no additional reduction in variceal bleeding in those patients receiving IS-MN as well as propranolol. A recent study comparing endoscopic variceal band ligation (VBL), propranolol and IS-MN for primary prophylaxis demonstrated that VBL and propranolol significantly reduced bleeding/mortality compared with IS-MN.[1] Notably up to 30% of patients in the drug arms were intolerant of their medication and were switched to VBL.

In the meantime, until further data are available in patients undergoing primary prophylaxis, combined treatment with nonselective-blockers and nitrates should be limited to clinical research. Patients should be offered propranolol or VBL in the first instance and, should they be intolerant of medication, they should be switched to VBL.

REFERENCES
1 Lui HF, Stanley AJ, Forrest EH *et al.* Primary prophylaxis of variceal hemorrhage: A randomized controlled trial comparing band ligation, propranolol, and isosorbide mononitrate. *Gastroenterology* 2002; **123(3):**735–44.

Clinical opinon: obesity as a cause of liver disease

TITLE: Determinants of the association of overweight with elevated serum alanine aminotransferase activity in the United States.
KEYWORDS: Waist–hip ratio, ALT, cirrhosis, non-alcoholic fatty liver disease.
AUTHORS: Ruhl CE, Everhart JE.
JOURNAL: *Gastroenterology* 2003; **124(1):**71–9.

SUMMARY
In the absence of other causes, overweight and obesity increase the risk of liver disease. This study examined whether central adiposity and metabolic markers explain the association of body mass index (BMI as kg/m2) with abnormal serum alanine aminotransferase (ALT) activity in a national, population-based study.

Adult participants (5,724) in the third US National Health and Nutrition Examination Survey (1988–94) underwent anthropometric measures and phlebotomy after an overnight fast. Participants with excessive alcohol consumption, hepatitis B, hepatitis C, iron overload or known diabetes were excluded. Standing waist circumference was measured at the high point of the iliac crest, and hip circumference at the maximum circumference of the buttocks.

Elevated ALT levels were found in 2·8% of the population. The proportion of elevated ALT activity due to overweight and obesity (BMI 25 kg/m2) was 65%. Mean waist–hip ratio (WHR) in patients with normal and abnormal ALT values were 0·90 ± 0·2 and 0·96 ± 0·7 respectively. Abnormal ALT activity was most strongly associated with higher WHR (odds ratio [OR], 1·32; 95% CI, 1·12–1·56) and leptin (OR, 1·12; 95% CI, 1·01–1·24) and insulin (OR, 1·27; 95% CI, 1·01–1·60) concentrations, whereas BMI was not independently related.

In conclusion, this study established being overweight as a major risk factor for elevated ALT activity. It was possible to explain the association with overweight through its correlation with central adiposity, hyperinsulinemia, and hyperleptinemia, which were strongly related to elevated ALT activity. Waist–hip ratio is correlated with visceral adipose tissue, which provides a greater supply of potentially hepatotoxic fatty acids to the liver. These findings provide support for a central role for abdominal obesity and insulin resistance in non-alcoholic fatty acid liver disease (NAFLD).

OPINION
In this study the prevalence of an abnormal ALT, defined as an ALT>43 U/L for men or women, was used as a surrogate for NAFLD. The authors found that 2·8% of the population had an elevated ALT. In multivariate analyses central adiposity, insulin and leptin concentrations were the most highly associated factors. The authors conclude that these factors are the major determinants of the association between elevated ALT concentration and higher body weight. The WHR can accurately predict central adiposity and, unlike BMI, is an independent predictor of abnormal ALT.

Using ALT alone, the authors estimate the prevalence of NAFLD in the US to be 2·8%, a figure that is much lower than general population estimates of NAFLD in other countries (16–20%: based on ultrasound and histological evidence for hepatic steatosis). Furthermore, it is substantially lower than that predicted by a recent population-based study of seemingly healthy Italian blood donors. Given that a patient can have NAFLD on biopsy and have a normal ALT, it is reasonable to assume that this figure is an underestimate. This raises the question of which, if any, patients we should biopsy.

More importantly, what does a diagnosis of NAFLD mean? Is this condition merely NAFL, or is it NAFLD? Fatty liver is considered by many to be an incidental condition with a benign prognosis. However, a growing body of literature disputes this, with studies indicating that the natural history of NAFLD may include progression to cirrhosis and hepatocellular carcinoma. That such varying opinions exist would suggest that we don't know enough about the natural history of these patients. Indeed it is important to remember that many of these patients die of vascular diseases related to their metabolic syndrome before their NAFLD becomes an issue.

Dr Philip Newsome, Specialist Registrar, Edinburgh

Clinical opinon: advice for the general physician treating end-stage alcoholic liver disease

TITLE: Influence of superimposed alcoholic hepatitis on the outcome of liver transplantation for end-stage alcoholic liver disease.
KEYWORDS: Alcoholic liver disease, alcoholic hepatitis, cirrhosis, liver transplantation
AUTHORS: Tomé S, Martinez-Rey C, González-Quintela A *et al.*
JOURNAL: *J Hepatol* 2002; **36:**793–8

SUMMARY
Survival in 68 patients transplanted for alcoholic cirrhosis was compared to 101 patients transplanted for other reasons (1994–9). 'Patients with overt signs of acute alcoholic hepatitis (recent alcohol abuse, fever, leucocytosis, cholestasis) were not considered for transplantation.' Out of 68 alcoholic cirrhosis patients 36 showed histological alcoholic hepatitis (at least three of focal necrosis, neutrophilic infiltrate, Mallory's hyaline, steatosis) in the explanted (removed) liver, but their survival over six years and their alcohol recidivism rate was as good as those alcoholic-cirrhosis patients without histological hepatitis or those transplanted for other liver diseases.

OPINION
Alcoholic liver disease patients are often looked after by general physicians who should be aware that liver transplantation can be life-saving for some such patients. Unfortunately, there is no consensus on how patients appropriate for transplantation should be identified. Best known is the requirement for a period of abstinence, usually three to six months, and the view that clinically-evident alcoholic hepatitis is a strong, some would say an absolute, contraindication.[1] This interesting paper seems to challenge the second of these criteria without actually doing so and could lead to confusion at the bedside.

Alcoholic liver disease is characterised by a spectrum of overlapping syndromes (alcoholic fatty liver, alcoholic hepatitis, alcoholic cirrhosis) associated with a spectrum of clinical and laboratory features and histological findings in the liver which are, unfortunately, not co-terminus.[2] Accordingly, patients with alcoholic cirrhosis who have none of the clinical or laboratory features of alcoholic hepatitis may show histological features of alcoholic hepatitis in the liver (which likely means continuing or very recent drinking).

In this study, Tomé *et al.* excluded patients with 'overt (i.e. clinical and laboratory) signs of acute alcoholic hepatitis' from transplantation, and showed that in those transplanted for end-stage alcoholic cirrhosis the finding of histological features of alcoholic hepatitis in the removed liver did not adversely affect the outcome of the transplantation. They applied the discriminant function Maddrey devised for clinically-evident alcoholic hepatitis to their patients with histological alcoholic hepatitis on their explanted livers and the majority had relatively low scores. Accordingly, finding histological features of alcoholic hepatitis on biopsy in patients with no clinical or laboratory evidence of alcoholic hepatitis just prior to transplantation would not in itself contraindicate transplantation but should lead to a review of recent alcohol intake. Whether this constitutes evidence that patients with clinically evident alcoholic hepatitis should be transplanted is quite another matter,[1,3] and indeed Tomé *et al.* state that 'from our data it cannot be concluded that cases with florid acute alcoholic hepatitis should be considered as suitable candidates for liver transplantation'. At present, evidence on this point is lacking.

What is the general physician to do in the face of this confusion? Patients with end-stage alcoholic cirrhosis do as well as any others after liver transplantation, and considering transplantation in all such patients is important. Those with overt alcoholic hepatitis are very unlikely to be suitable, but seeking more specialised advice from a gastroenterologist/hepatologist, or from a liver transplant unit where this is available, is worthwhile. To obtain the best advice, it is important to provide information about the patient's clinical status, previous abstinence, evidence of alcohol dependency, cooperation with and results of previous treatment for alcoholism and the outcome of any previous psychiatric assessments. Assessment of alcohol abuse by liver transplant units is increasingly sophisticated and any such unit which does not involve an experienced interested psychiatrist still has a lesson to learn.

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2 Lucey MR. Is liver transplantation an appropriate treatment for acute alcoholic hepatitis? *J Hepatol* 2002; **36:**829–31.
3 Bathgate A and Hayes P. Transplantation for alcoholic liver disease: lessons from the explant? *Gut* 2003; **52:**462–3. A further comment on this paper.

Dr Niall DC Finlayson, Consultant Gastroenterologist, Edinburgh

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