Part I | of a special series of reports from

DIGESTIVE DISEASE WEEK 2007

May 19–24, Washington DC, USA

Digestive Disease Week (DDW) is considered the largest and most prestigious meeting in the world for the GI professional. This year close to 17,000 physicians, researchers and academics attended the meeting to learn about the latest advances in gastroenterology, hepatology, endoscopy and gastrointestinal surgery; prevention, diagnosis and treatment of digestive disorders; and cutting-edge technological advances. Each year DDW features about 2300 oral and 4000 poster presentations. The following report is the final part of a series based on a selection of key sessions, with commentary by leading Australian specialists

AGA state-of-the art lecture: alcoholic liver disease

Report by Dr Andrew Keegan
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In the United States, death rates from cirrhosis have been falling over recent years. However, despite the increasing prevalence of HCV-induced liver disease, alcohol remains the major cause of end-stage liver disease and liver-related mortality, as well as the primary indication for liver transplant in the USA (followed by HCV).

Dr VH Shah questioned the value of biochemical markers such as AST/ALT, MCV, GGT and carbohydrate-deficient transferrin. These tests assess alcohol excess indirectly and thus, suffer from poor sensitivity and specificity, generally less than 70%.[1]

Validated questionnaires, such as CAGE, can be of value to clarify alcohol use and abuse syndromes. CAGE asks:

- Have you ever thought you should **c**ut down on your drinking?
- Have people **a**nnoyed you by criticising your drinking?
- Have you ever felt bad or **g**uilty about your drinking?
- Have you ever drunk alcohol first thing in the morning to steady your nerves or to try to get over a hangover (**e**ye-opener)?

Any positive responses to these enquiries require more detailed investigation and raise the possibility of alcohol abuse. The more positive responses, the greater the likelihood of alcohol-related disease.

Dr Shah also noted the difficulty in differentiating between alcoholic fatty liver and non-alcoholic fatty liver as patient history is often not helpful and histology does not provide differentiation between the two conditions. A useful tool to assist in this process, AST/ALT, MCV and BMI, is available on the Mayo Clinic website http://www.mayoclinic.org/gi-rst/mayomodel10.html

Alcoholic hepatitis

Dr Shah then reviewed the value and role of "scores" in assessing the prognosis of alcoholic hepatitis.

Maddrey score Discriminant function (4.6 X prothrombin time prolongation in seconds) + bilirubin (mg/dL). Values above 32 indicate severe disease and are associated with 50% mortality. The prognostic value of this formula has been prospectively confirmed and appears to be the most clinically helpful for therapeutic decisions when severity of illness determines treatment.

The **model for end-stage liver disease (MELD) score**, with a range from 6 (less ill) to 40 (gravely ill), accurately predicts mortality. This model incorporates creatinine, INR and total bilirubin. A score of greater than 17 indicates a need for intervention. Further information is available on the Mayo Clinic website http://www.mayoclinic.org/meld/mayomodel5.html

Glasgow alcoholic hepatitis score A recent article by Louvet *et al.*[2] has attempted to generate a specific prognostic model, the so-called Lille model, enabling clinicians to identify subjects early in the course of alcoholic hepatitis who are unlikely to survive; and to propose new management based on this specific model. This model will help assess the value of continuing steroid therapy in patients. It is significantly more accurate than DF, MELD or Glasgow scores in predicting short-term mortality, and is better than ECBL at predicting subjects likely to die. The Lille model is able to identify 40% of subjects receiving prednisolone treatment who have a poor survival prognosis and who thus may be candidates for alternative treatments. The formula is available online at http://www.lillemodel.com

Each score/model works in the prognostic assessment of patients with alcoholic hepatitis. Generally, each is based on calculations including bilirubin, INR and/or creatinine. It was suggested that doctors involved in the management of such patients make themselves familiar with at least one.

Alcoholic liver disease was described as being the result of a combination of "bad genes" (complex inheritance) and "bad habits" (drinking, HCV, poor nutrition, obesity). It is estimated

that up to 90% of those who drink will develop fatty liver, but most do not go on to have alcoholic hepatitis or cirrhosis. Females require lower doses to cause liver injury.

The presence of hepatitis C will amplify the effects of alcohol on the liver. The combination of the virus and alcohol will accelerate liver injury, reduce the response to interferon-based therapy, increase the risk of HCC and reduce overall prognosis for patients. Obesity may also result in increased hepatic fibrosis in those with alcoholic liver disease.

Specific therapy for alcoholic hepatitis

In the discussion of the treatment for alcoholic hepatitis, Dr Shah highlighted the value of a high discriminant function in the absence of active GI bleeding, renal impairment or infection in identifying patients who may benefit from corticosteroid therapy. In that circumstance the NNT is 5. However, long-term benefit is uncertain and the exclusion criteria limited the value of this approach. Nutrition is important, but its precise role and value is yet to be clarified. The anti-TNF agent pentoxifylline improves mortality, although that benefit is seen mainly in patients with impaired renal function. A study into the use of infliximab was terminated due to increased mortality in the study group and etanercept is under study.

References. 1. Menon KVN, Gores GJ, Shah VH. Pathogenesis, diagnosis, and treatment of alcoholic liver disease. *Mayo Clin Proc* 2001;76:1021–29. **2.** Louvet A *et al.* The Lille model: a new tool for therapeutic strategy in patients with severe alcoholic hepatitis treated with steroids. *Hepatology* 2007;45(6):1348–54.

Shah VH. Alcoholic liver disease. State-of-the-art lecture SP302.

Maintenance PPI therapy effective as anti-reflux surgery in long-term treatment of GORD

Report by Dr Richard Holloway

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Ever since the advent of truly effective medical therapy for reflux disease, with the introduction of proton pump inhibitors (PPI), there has been ongoing debate about the relative effectiveness of long-term medical therapy compared with anti-reflux surgery. Long-term data from well-conducted randomised trials, however, are few. At DDW 2007, the results of two European randomised trials comparing anti-reflux surgery with PPI therapy were presented.

The first report (Lundell LR *et al.*) was a 12-year follow-up of a trial of open fundoplication and omeprazole in 310 patients with chronic reflux disease. Earlier follow-ups of these patients have been published in 2001 (5 years) and 2007 (7 years). The primary outcome variable was the time to treatment failure (defined as recurrence of at least moderate heartburn or recurrence of oesophagitis, or the need for further therapy). The estimated proportions of patients in sustained remission after 12 years were higher in the surgery group (53%) than in the omeprazole group (45%, p = 0.022). This difference decreased after dose adjustments were made in the omeprazole group. During the study, 38% of the surgery group required maintenance PPI therapy and 7 patients underwent re-operation. In the omeprazole group, 15% underwent surgery. Both treatments were well tolerated, but the surgery group was more likely to complain of dysphagia, inability to belch and vomit, and rectal flatulence.

As part of the above trial, 253 of the patients also underwent oesophageal function testing to assess the efficacy of medical and surgical therapy in controlling reflux (Hatlebakk JG *et al.*). Ten-year data were available in 116 patients (surgery n = 60, omeprazole n = 56). Mean lower oesophageal sphincter pressure increased after surgery, but not with omeprazole. Mean oesophageal acid exposure was reduced to within the normal range in both groups (1.6% *vs* 0.7%, ns).

The second report (Lundell LR *et al.*) was a 3-year interim analysis of a randomised trial of laparoscopic anti-reflux surgery, and medical therapy in 554 patients with chronic reflux disease. Medical therapy was esomeprazole 20 mg od increasing to twice daily in cases of incomplete control. The primary outcome variable was again the time to treatment failure. The estimated proportions of patients in remission at 3 years were similar in the surgery group (90%) to that in the medical group (93%). No major complications were experienced and esomeprazole was well tolerated.

Key messages

- These studies confirm the comparable long-term efficacy of modern medical therapy for reflux disease in comparison with surgery in well-designed head-to head comparisons.
- These studies also re-affirm the need for dose adjustment of PPI therapy in order to achieve optimal control.

Lundell LR *et al.* 754. Anti-reflux surgery compared with maintenance omeprazole for reflux esophagitis. Results after 12 years. Presentation 754. Hatlebakk JG *et al.* Manometry and 24-hour pH-metry during 10 years' follow-up in patients randomized to anti-reflux surgery or omeprazole. Presentation 755. Lundell LR *et al.* The LOTUS trial – comparing esomeprazole to laparoscopic anti-reflux surgery for the management of chronic gastroesophageal reflux disease: a 3-year interim analysis. Presentation 753.

Abstracts in review

Report by Professor Gerald Holtmann

Director, Department of Gastroenterology and Hepatology, Royal Adelaide Hospital

Can patients with diverticular disease eat nuts, corn and popcorn?

There is widespread belief that patients with diverticular disease should be advised to avoid nuts and seeds, however, there is no evidence to support this assumption. A group from Boston assessed a cohort of 47,454 males in the US health professional study for the association between onset of diverticular disease and the consumption of nuts and corn. For this purpose the consumption of corn was assessed utilising a validated 131-item semi-quantitative food frequency questionnaire. Out of the above-mentioned cohort, patients with newly diagnosed

diverticular disease received this questionnaire every 4 years. During an 18-year follow-up (732,111 patient-years), 445 incident cases of diverticular bleeding, 651 cases of symptomatic uncomplicated diverticular disease and 865 incident cases of diverticular disease were identified. For diverticular bleeding and symptomatic, uncomplicated diverticulitis, no multivariate positive associations with the consumption of nuts, corn or popcorn was found. In contrast, popcorn consumption alone appeared to be protective. In patients consuming popcorn at least twice a week, the risk of complications was significantly reduced by 30%. Thus, contrasting general beliefs, the consumption of nuts, corn or popcorn is not associated with diverticular disease. In fact, popcorn consumption appears to be protective.

Strate LL *et al.* Can patients with diverticular disease eat nuts, corn and popcorn? Presentation 769.

Post-traumatic sclerosing cholangitis: high incidence in certain ICU patients

During a 5-year period, the authors identified 18 patients with post-traumatic sclerosing cholangitis (PTSC). Eighty per cent of these patients were treated for more than 3 weeks in an intensive care unit. The majority of these patients had suffered severe trauma including cerebral trauma. Clinically these patients were characterised by elevated liver function test that occurred in the early phase of the ICU treatment. ERC findings were consistent with sclerosing cholangitis with vanishing bile ducts. During the follow-up, 6 patients improved over time or remained clinically stable, while the remainder progressively deteriorated, requiring listing for liver transplant.

Dorlar D *et al.* Post-traumatic sclerosing cholangitis (PTSC): unexpectedly high incidence in certain groups of ICU patients. Presentation S1217.

Alterations of intestinal serotonin expression in dyspepsia and irritable bowel syndrome

While some efficacious treatments for functional dyspepsia and IBS target serotonergic pathways, very little is known about potential disturbances in serotonin metabolism. The authors aimed to study regional differences in the serotonin metabolism and the association with specific symptoms. The authors tested 48 patients with C-IBS, functional dyspepsia and C-IBS plus functional dyspepsia transcript levels of mRNA for the serotonin transporter (SERT) and tryptophan hydroxylase (TpH-1). The authors observed significant alterations of the SERT and TpH-1 expression in patients with functional dyspepsia and IBS. SERT expression was reduced in the stomach of functional dyspepsia patients. In contrast, TpH-1 was significantly elevated in both duodenal and rectal mucosa of functional dyspepsia patients. In contrast, no abnormalities were found in IBS. Based upon these data it can be concluded that functional dyspepsia is associated with altered serotonin signaling. These data provide further evidence for a biologic basis of functional GI disorders. However, independent replication of the data is required and the practical implications for the management of patients with functional gastrointestinal disorders remain to be elucidated.

Foxx-Orenstein AE *et al.* Alterations in intestinal serotonin expression in dyspepsia and irritable bowel syndrome. Presentation 413.

Peptic ulcer disease: does diabetes make a difference?

It is believed that peptic ulcer disease is less common in diabetics compared to non-diabetic subjects. In a retrospective study from the Montefiore Medical Centre, Bronx, NJC, 406 patients with endoscopically verified peptic ulcer and 406 controls were compared. The prevalence of peptic ulcer disease was similar in diabetic and non-diabetic subjects. However, diabetic patients had significantly less frequent abdominal pain or dyspepsia as indications. Interestingly, diabetic subjects had more adverse short-term outcomes, including the need for surgical interventions or death. Interestingly, all deaths were attributed to bleedings or bleeding-associated complications. The authors speculate that the decreased severity of symptoms and the adverse short-term outcomes are due to the diabetic sensory neuropathy.

Korenfeld S *et al.* Peptic ulcer disease: does diabetes make a difference? Presentation M1893.

Albumin versus synthetic colloid for large volume paracentesis

Several randomised-controlled studies have compared albumin with synthetic colloids to prevent hypovolaemia following large volume paracentesis. For the meta-analysis, the authors identified 8 trials (with a total of 712 patients) that fulfilled the entry criteria. While albumin decreased the incidence of circulatory dysfunction and limited the response of the plasma renin activation, there were no significant differences with regard to the risk of renal impairment, hyponatraemia, encephalopathy or GI bleeding. Furthermore, mortality and length of hospital re-admissions were similar. Based on this large meta-analysis, synthetic colloids are safe and a cost-effective alternative to albumin for large volume paracentesis.

Othman MO *et al.* Albumin versus synthetic colloid for large volume paracentesis: a meta-analysis of RCTs. Presentation 738.

Eosinophilic oesophagitis

Report by Dr Martin Weltman

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There has been an explosion of interest in the condition of eosinophilic oesophagitis (EE) in recent times. The debate as to whether this is a "new" or a "newly recognised" disease entity is yet to be decided. There are now a number of published clinical studies available regarding both the efficacy of drug treatment, as well as the pathogenesis of this condition.

It is now apparent that the prevalence of this condition is more common then initially thought: with 1 in 1500 children and 1 in 4000 adults having EE, a strong male predominance and a significant familial clustering. The condition predominates in Caucasian people and is uncommon in other racial groups. The paediatric literature supports a "food allergy and atopy" aetiology, although this still remains controversial in adults. Familial descriptions and clustering are being increasingly described, supporting that genetics is likely to play a large role.

Although patients present with dysphagia and/or food impaction, a high proportion have associated GORD (particularly in adults). Symptoms do not always correlate with the observed oesophageal abnormalities.

Unlike other segments of the gastrointestinal tract, there is usually an absence of eosinophils in the oesophagus. Most experts now agree that for a definitive diagnosis, detecting > 20 eosinophils per high power field (x400) is necessary. Lesser amounts of eosinophils have been detected in association with GORD. There is no definitive agreement on the best site to obtain such biopsies, although most experts recommend four biopsies from the mid-oesophagus. Other histological features that have recently been described for EE are that of a thickened mucosa with basal cell hyperplasia and papillary lengthening.

A recent study revealed that the eotaxin-3 gene, an eosinophilic chemotactic factor, was the most highly induced gene in EE patients compared with its expression level in healthy individuals.[1] This protein is localised to keratinocytes in the oesophagus and in turn is stimulated by IL-13. Both animal and human studies reveal that the removal of the causative "allergen" or the use of fluticasone suppresses IL-13 levels and consequently eotaxin-3.

The few natural history studies completed to date reveal that this condition is not always progressive and many patients do not develop significant strictures. Only a proportion of patients develop the anatomic complications of a ringed oesophagus leading to either a small calibre oesophagus or stricture formation.

There is currently a debate as to whether it is best to treat patients sporadically when they present with symptomatic flares or whether treatment should be ongoing to normalise the observed tissue abnormalities, so as to prevent stricture formation. While dilatation is sometimes necessary, there is increasing evidence that the anatomic changes (even advanced strictures) can be reversed with fluticasone and in refractory cases with systemic steroids. Unfortunately, there is a subgroup of patients which are steroid resistant. Nevertheless, steroid therapy should be trialled first prior to dilatation. Elimination diets have been used in the paediatric age group with a high degree of success, but there is limited evidence for the use of this approach in adults.

Reference 1. Blanchard C *et al.* Eotaxin-3 and a uniquely conserved gene-expression profile in eosinophilic esophagitis. *J Clin Invest* 2006;116(2):536–47.

Licacoura C *et al.* Eosinophilic oesophagitis in children – understanding an epidemic from mice to men. Eosinophilic oesophagitis: what do we know, what should we do. Presentations SP177, 178, 179.

Expanded adipose-derived stem cells for complex perianal fistula

Report by Dr Martin Weltman

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The background to this study is that the management of fistulas (particularly related to Crohn's disease) is often very difficult despite recent advances in medical and surgical interventions (eg. infliximab). Fistulas have a significant impact on patients' quality of life and are often recurrent. Often, in the context of an aggressive surgical approach, a dilemma stands between permanent recurrence and faecal incontinence. On the other hand, long-term efficacy of biological treatment is sometimes limited and adverse events can occur. A recent (phase I) study evaluated the use of autologous transplantation of mesenchymal adult stem cells (derived from adipose tissue) (Cx401) to treat Crohn's fistulas. Over an 8-week follow-up, 6 of 8 patients responded with complete healing of their fistulas without any adverse outcomes. Consequently, the research has progressed to a phase II clinical trial, the first of these results were presented at DDW 2007.

The researchers enrolled 49 patients with complex perianal fistulas from either cryptoglandular or Crohn's disease. Patients received fibrin glue alone or in addition to Cx401 (20 million stem cells) intralesionally. If not healed, a second dose of fibrin glue or 40 million cells plus fibrin glue was administered. Fistula healing was evaluated at 8 weeks. Those in the stem cell arm had fat extracted with liposuction and stem cells were grown up in the lab for injection. This study found that the proportion of patients whose fistulas were healed was significantly higher with Cx401 (71%) than with fibrin glue (16%). Cx401 efficacy was observed in both the cryptoglandular and Crohn's sub-populations. Quite remarkably, at the 1-year follow-up, the recurrence rate in the Cx401 group was only 17.6% and the impact of Cx401 administration on patients' quality of life revealed a significant benefit. At 8 weeks after treatment, not a single adverse event related to the stem cells (Cx401) was observed.

The research team has set a high standard with complete healing as the primary endpoint. This strategy appears to be a novel and well-tolerated approach for the healing of patients with perianal fistula, a chronic and highly debilitating disease with unmet needs. Further studies are necessary to validate this enormously promising new therapeutic approach.

Garcia-Olma D *et al.* Expanded adipose-derived stem cells (Cx401) for the treatment of complex perianal fistula. A phase II clinical trial. SSAT plenary session III. Presentation 492.

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