Seminar Summary - “Management of advanced liver disease, liver failure, and hepatoma in people with substance use disorders”.

In the Sydney Addiction Seminar of October 2011, Associate Professor Simone Strasser, Senior Staff Specialist at Royal Prince Alfred Hospital, took us through the management of advanced liver disease, liver failure, and HCC, with an emphasis on people with substance use disorders.

Summary by Richard Hallinan with assistance from Dr Simone Strasser.

Key points

- Cirrhosis and liver failure are on the increase in Australia, the main causes being chronic viral hepatitis, alcoholic liver disease and non-alcoholic fatty liver disease.
- Early diagnosis and management has a major impact on the outcomes of cirrhosis.
- Ascites is generated by a vicious cycle of portal hypertension and porto-systemic shunting. Management is by salt restriction and spironolactone. Refractory ascites may require a transjugular intrahepatic porto systemic shunt.
- The presentation of spontaneous bacterial peritonitis may be non-specific and there should be a low threshold of suspicion for diagnosis, referral and treatment.
- Gastrointestinal bleeding in cirrhosis may be caused by varices, portal hypertensive gastropathy, peptic ulcer disease, coagulopathy and thrombocytopenia. NSAIDS can cause disaster - people should be specifically warned against their use.
- Endoscopic banding is carried out repeatedly until varices are obliterated. Beta blockers should be used in haemodynamically effective doses, aiming to get the pulse rate down to about 60.
- Hepatic encephalopathy occurs in response to ammonia, inflammatory cytokines, and benzodiazepine-receptor-like agonist and cannabinoid-receptor agonists. Sleep disturbance is an early sign. Benzodiazepines, cannabis and alcohol must be avoided, and doses of other psychoactive medications reviewed. Lactulose and Rifaximin are used to reduce the nitrogenous load arising from the gut.
- Malnutrition, ascites, a catabolic state and reduced appetite form a vicious cycle, and reduce the chances of survival. A high protein, high energy (fats,
carbohydrates) diet is required. Salt restriction is required if there is ascites, and fluid restriction if there is hyponatraemia.

- Patients with cirrhosis or chronic HBV should have hepatoma surveillance with 6 monthly abdominal ultrasound. The measurement of alpha fetoprotein (AFP) is more useful for HCC surveillance in chronic HBV.

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Seminar summary

Fibrotic liver disease is now the 8th leading cause of death worldwide. The major causes of cirrhosis are alcoholic liver disease, hepatitis B and C, and non-alcoholic fatty liver disease. Less common causes (part of the standard screen performed by liver specialists) include autoimmune disease, haemochromatosis and Wilson’s disease, alpha-1 antitrypsin deficiency, toxins and drugs.

Dr Strasser pointed to disturbing trends in hospitalisations for alcoholic cirrhosis and liver failure in Australia, with increases especially in younger people, right down to those in their 20s. Projections are for large increases in HCV-related cirrhosis over the next 20 years.

In 2008, Australia overtook the USA to become world leader in prevalence of obesity. Dr Strasser pointed out that there are increasing numbers of cases of cirrhosis and hepatocellular carcinoma (HCC) from fatty liver alone. Overweight and obesity are also strong risk factors for the development of liver failure in people with viral hepatitis and alcoholic liver disease.

Diagnosis and assessment of advanced liver disease

Diagnosis of cirrhosis can be made from clinical examination, blood tests, imaging, liver biopsy, and now fibroscan. It is important to make the diagnosis early to inform the need for antiviral treatment, monitoring for complications, and referral for specialist care and transplantation in some cases. Pro-active identification and management of complications has a major impact on the outcomes of cirrhosis.

The clinical indicators of cirrhosis are well known: spider naevi, palmar erythema, muscle wasting with loss of fat deposits and thinning of the skin, fluid retention with peripheral oedema and ascites, jaundice and scratch marks, splenomegaly, feminisation including loss of
body hair and gynaecomastia in men; raised bilirubin, prolonged INR, low albumin, low platelet count. Ultrasound can show splenomegaly, ascites, and portal vein dilatation. CT scan additionally may show nodularity of the liver and oesophageal varices, if large.

Liver biopsy not only stages fibrosis, but also grades necroinflammation, and shows steatosis, iron overload and indicators of less common causes of liver disease (such as Wilson’s disease, autoimmune disease). However biopsy is costly, can cause bleeding (especially where platelets are low and coagulation impaired) and pain, and is subject to sampling error. Further, the information is “static”, as biopsy is generally not done serially.

Numerous tests using serum/blood markers have been developed to identify liver fibrosis non-invasively. The two most commonly used, AST/ALT ratio >2:1 and APRI (an index of AST to platelet ratio) >1.5 suggest cirrhosis. More complicated algorithms exists using additional data like age and BMI, GGT, cholesterol, INR (Forns’ index, Lok index) or other tests which are commercially available (Fibrotest, Hepascore). Fibroscan has made these less important.

Fibroscan measures the stiffness of the liver by the velocity of ultrasound waves, producing a score that can broadly categorise people into having little to no fibrosis (up to 7 kilopascals), significant fibrosis (7-13kPa) or cirrhosis (>13kPa), but cannot be interpreted more precisely – especially with readings in the 7-13kPa range. Fibroscan is validated for HCV, alcoholic liver disease and fatty liver, but obesity can cause technical difficulties with the procedure. In chronic HBV, fibroscan readings vary with intensity of liver inflammation, so different cut-offs are used, depending on transaminases. Fibroscan can be done serially and thus potentially indicate stable fibrosis or rapid progression. 5 year survival drops from about 70% for people with liver stiffness 20-30kPa, to around 30% for liver stiffness 50kPa.

Both fibroscan and blood test algorithms are good at telling who doesn’t have cirrhosis (its “negative predictive value” is high).

In “compensated” cirrhosis, there is no ascites or encephalopathy, albumin and bilirubin are normal, and the person may be asymptomatic, the diagnosis being suspected by low platelets, AST>ALT, and confirmed on imaging or fibroscan. 80% remain compensated at 10 years follow up.

The Child-Turcotte Pugh (CTP) grading of cirrhosis uses ratings of ascites, encephalopathy, albumin, bilirubin and INR. Grades 2 and 3 are “decompensated” and predict lower survival rates. The MELD score (calculated from bilirubin, creatinine and INR) is designed to predict 3 month survival and is used to monitor urgency of need for transplant.

The major complications of liver failure are caused by hepatic synthetic failure, portal hypertension and portosystemic shunting. Dr Strasser dealt with them in turn.

Ascites and oedema

Ascites is generated by a vicious cycle of portal hypertension and porto-systemic shunting due to the nodularity of the liver and presence of vasoactive substances, leading to splanchnic and arteriolar vasodilatation, lowered systemic resistance and compensatory fluid retention. Management is by salt restriction (no-added salt) and spironolactone (100-200mg/day, increasing to 400mg/day and adding frusemide up to 160mg/day. If ascites becomes more
severe, large volume paracentesis and IV albumin may be needed, as often as weekly.

Refractory ascites has a poor prognosis – only a third are alive at 2 years – and may require a transjugular intrahepatic porto systemic shunt (TIPSS) placed by an interventional radiologist. A needle is placed within the liver to allow blood flow from the obstructed portal circulation into the inferior vena cava. There needs to be well preserved liver synthetic function, and TIPSS is contra-indicated where there is hepatic encephalopathy, which it can exacerbate.

TIPSS is indicated for refractory ascites, portal hypertensive bleeding, hepatic hydrothorax and Budd Chiari syndrome. It is contra-indicated in severe and progressive liver failure, portal vein thrombosis, right heart failure and pulmonary hypertension, or HCC.

Diuretics must be used carefully in liver failure, with close monitoring to avoid hyponatremia, hypo- or hyperkalemia, renal impairment. Dr Strasser suggested fortnightly electrolyte monitoring. Diuretics can also cause muscle cramps, gynaecomastia and precipitate hepatic encephalopathy. Dilutional hyponatremia (where water retention exceeds sodium retention) often complicates advanced cirrhosis and worsens prognosis. It too can worsen hepatic encephalopathy and limits the use of diuretics. Increasing dietary salt does not help: fluid restriction is the only management available.

**Spontaneous bacterial peritonitis**

Spontaneous bacterial peritonitis (SBP) is caused by bacteria moving from the intestinal lumen to the systemic circulation. The presentation may be non-specific (eg encephalopathy), or with fever and abdominal pain (late). Diagnosis is based on increased white cells (>500/mL) or neutrophils (>250/mL) in ascitic fluid. An episode of SBP doubles mortality rates in 18 month follow up.

There should be a low threshold for referral and treatment of possible SBP, with intravenous antibiotics ± IV albumin in hospital. Prophylaxis with norfloxacin or Bactrim is indicated if there is: low ascitic protein concentration; upper GI bleeding; or where there has been a previous episode of SBP.

**Hepatorenal syndrome**

Hepatorenal syndrome is progressive renal failure, which tends to develop over time with advanced cirrhosis and ascites. The kidneys are structurally normal, and the renal failure is due to vasoconstrictor substances. Creatinine gradually rises while urine output falls. Type-1 hepatorenal syndrome comes on suddenly, causes acute renal failure and has a dismal prognosis. Type-2 hepatorenal syndrome develops more insidiously and causes refractory ascites. In each case it is important to look for any precipitant. Management is highly specialised, and liver transplant may be needed.

**Portal hypertensive bleeding**

Gastrointestinal bleeding in cirrhosis is caused by a combination of factors. Portal hypertension causes oesophageal or gastric varices or portal hypertensive gastropathy. There may be peptic ulcer disease, coagulopathy and thrombocytopenia are common and NSAIDs and alcohol use can exacerbate bleeding. Over the counter NSAIDS can cause disaster -
people should be specifically warned against their use.

Bleeding from varices can present catastrophically and require resuscitation with octreotide, endoscopic banding and antibiotics. Primary prevention of bleeding involves beta blockers and endoscopic band ligation, and secondary prevention may additionally require TIPSS, a surgical shunt, or liver transplantation. Endoscopic banding is carried out repeatedly until varices are obliterated. Dr Strasser advised that beta blockers should be used in haemodynamically effective doses, not homeopathic, doses, aiming to get the pulse rate down to about 60.

Cardiorespiratory complications

There are also pulmonary sequelae of liver cirrhosis. Hepatopulmonary syndrome comprises pulmonary vascular dilatations + hypoxaemia, whereas porto-pulmonary hypertension results from pulmonary vasoconstriction with eventual right heart failure. Hepatic hydrothorax involves migration of ascites with the risk of subsequent atelectasis

Hepatic encephalopathy (HE)

Dr Strasser gave us a definition: “Hepatic encephalopathy reflects a spectrum of neuropsychiatric abnormalities seen in patients with liver dysfunction after exclusion of other known brain disease” (Ferenci et al. Working group on hepatic encephalopathy. Hepatology 2002).

Hepatic encephalopathy is a clinical manifestation of low grade cerebral oedema, with swelling of astrocytes. It occurs in response to ammonia and other precipitating factors, including inflammatory cytokines, (endogenous or exogenous) benzodiazepine-receptor-like agonist and cannabinoid-receptor agonists.

Enteric bacteria are the main source for generation of ammonia. Serum ammonia levels are not helpful in diagnosis of HE as some patients with HE have normal ammonia levels, and many patients with cirrhosis have elevated ammonia levels without HE. HE is often, but not always, accompanied by typical electroencephalographic changes, and these don’t correspond to ammonia levels.

HE can be precipitated by events in the gut (including upper GIT bleeding, a protein load, or even constipation), electrolyte disturbances (vomiting, diarrhoea, use of diuretics), infection or metabolic disturbances, and psychoactive substances including sedatives and alcohol. Sleep disturbance is an early sign of HE, and one must be careful to identify this, as the use of any benzodiazepine can worsen HE.

West Haven Criteria for HE have 4 grades. HE becomes detectable at “grade 1”, where the person is alert, euphoric, with poor concentration, slow mentation and sleep inversion but the flapping tremor is not usually seen. In Grade 2 the person is drowsy, inappropriate and disoriented, grade 3 stuporose but rousable and markedly confused – flapping tremor is seen in both these grades, but is usually absent in grade 4 HE, which is coma. The grade of HE also predicts survival.

HE may be episodic, with the person dipping in and out of clinically detectable HE, persistent (always detectable but often fluctuating) or minimal (fluctuating below the level of clinical
detection). Intermittent encephalopathy is more common than constant encephalopathy. Minimal encephalopathy, which is not clinically detectable, can be assessed by computerized psychometric tests, or paper-based tests such as the number connection test.

It is important to identify “Minimal HE”, and to be aware that it:

- predicts later development of overt HE (56% with MHE vs 8% without MHE)
- impacts on ability to work - 55% of blue collar workers and 20% white collar workers are unable to work.
- impairs driving skills (44-100% of patients with MHE are unsafe drivers) with increased rates of motor vehicle accidents (17% with MHE vs 3% without MHE)
- increases rate of falls, often with injury (36% with MHE vs 6% without MHE)

The goals of therapy are to identify and treat precipitants, prevent recurrent episodes of overt HE, and reduce risks to patient and others. HE is associated with increased risk of falls and accidents, so “blue collar” workers may actually be more disabled in their work capacity than “white collar” workers. A person who has had any episode of hepatic encephalopathy must not drive.

The principles of management of Hepatic Encephalopathy (Modified from Am College Gastro Practice Guidelines: 2001) are

1. **Nutritional** - avoid long periods of dietary protein restriction and receive the maximum tolerable protein intake, aiming at 1.2 g of protein/kg/day.
2. **Reduction in the nitrogenous load arising from the gut** - Lactulose (a non-absorbable disaccharide) is a first-line pharmacological treatment of HE. An alternative is non-absorbable antibiotics. Neomycin no longer used for this purpose. Rifaximin is now rated as second-line pharmacological treatment of HE (approved in Australia in 2012, but not yet available on the PBS). Both Lactulose and Rifaximin have RCT evidence that they reduce time to first breakthrough episode of HE. There may be a role for probiotics to restore normal gut flora and prevent episodes of overt HE.
3. **Avoid sedating drugs and substances**: this means avoiding benzodiazepine, cannabis and alcohol. Dr Strasser suggests aiming to reduce opioid doses, and review doses of anti-depressants and other psycho-active drugs.

**Malnutrition**

Malnutrition in liver disease is common in patients with cirrhosis and has major impact on complications (particularly ascites and HE), and clinical outcomes. The reasons include reduced appetite from include portal hypertensive gastritis, abdominal bloating and fullness from ascites, continuing alcohol use, or bad medical advice. Dr Strasser finds often patients have been advised to restrict protein intake. This is absolutely wrong. Malnutrition, ascites, a catabolic state and reduced appetite form a vicious cycle.

Accurate assessment using blood markers of malnutrition is difficult because of fluid retention and hypoproteinaemia. Like other indicators mentioned above, malnutrition is shown to reduce the chances of survival.

Referral to an experienced dietician is essential. Encourage intake of high protein, high
energy (fats, carbohydrates) diet in small frequent meals (5-7/day) – a late-evening snack can work wonders. Dr Strasser showed a photo of a man with extreme ascites and muscle wasting, remarking that the ascites went away without medical intervention: “all we did was feed him up”.

Salt restriction is required if there is ascites, and fluid restriction if there is hyponatraemia.

Supplements may be indicated including polymeric glucose, protein supplements (eg Ensure / Resource and branched-chain amino acids (eg hepatamine).

**Bone disease**

Bone disease is a frequent complication of end-stage liver disease, with a prevalence of 9-60%. Mechanisms include reduced bone formation, low bone turnover, and Vitamin D deficiency. Dr Strasser finds Vitamin D deficiency is virtually universal in people with cirrhosis. All patients with cirrhosis should be assessed for bone disease, including measurement of 25(OH) Vitamin D, parathyroid hormone and mineral bone density (DEXA). Management of bone disease includes Vitamin D3 replacement to reach serum levels of 25(OH) Vit D3 >60, ensuring adequate calcium intake, and bisphosphonates if indicated (for progressive loss of BMD, or osteoporosis, or prior fracture history. Standard contraindications apply – active dental disease, renal impairment etc).

**Hepatocellular carcinoma (HCC):**

80% of cases of HCC are now due to HCV or HBV. The HBV virus is oncogenic, so risk of HCC is increased in people with chronic HBV regardless of whether or not they have cirrhosis. Patients with cirrhosis or chronic HBV should have surveillance with 6 monthly abdominal ultrasound. 4-phase CT or MRI will be required to characterise any lesions that are identified. The value of measurement of alpha fetoprotein (AFP) is less clear, as this can be increased due to liver disease without HCC, especially HCV; AFP is more useful for HCC surveillance in chronic HBV. Surveillance recommendations in USA and Europe include only 6 monthly US without AFP levels.

There are several therapeutic options for HCC. Surgical resection is possible, but most people with severe liver disease are not suitable, and access to liver transplantation is limited. Local therapies include chemo-embolisation, radiofrequency ablation and systemic therapy with sorafenib.

Radiofrequency ablation (RFA) has a one year survival of 90-97%, 3 yr survival 63-81%. Tumour control is achieved for 93-100% small lesions, and RFA is equivalent to surgery for lesions <3cm.

Transarterial chemo-embolisation (TACE) involves intra-arterial delivery of chemotherapy + occlusion of arterial supply. It can be used for larger tumours, and people on a liver transplant waiting list. It is palliative, rather than curative.

Survival rates are reported by Perry et al (Liv Intern 2007) as greatest for liver transplantation, followed by resection > ablation > no therapy > TACE > systemic therapy.

The indication for referral of patients for consideration of transplantation is decompensated
cirrhosis (if CTP score ≥8, MELD ≥14).

If there is alcoholic liver disease, transplant will generally not be performed prior to 6 months alcohol abstinence, however early referral is important so that patient can meet the team, and specific management issues can be addressed. Patients with significant malnutrition or with major psychosocial issues should also be referred early. Methadone treatment is not a contraindication to liver transplantation.

Case studies

In the second half of the seminar two cases were presented. One was a woman with chronic HCV, heavy alcohol use, decompensated cirrhosis and frequent emergency department presentations with intoxication or overdose. Small doses of oxazepam were sufficient to manage alcohol withdrawal. On one hospital admission her mental state deteriorated with no apparent precipitant, and when low grade fever developed 36 hours later she was treated with expectantly with parenteral antibiotics in case of bacterial peritonitis. Ascitic fluid showed polymorphs but there was no growth on culture. Dr Strasser commented that they would be inclined to treat any unexplained deterioration in this situation as bacterial peritonitis until proven otherwise. It was noted that the patient was discharged without arrangements for long term antibiotic prophylaxis (corrected the day after the seminar!).

The other case was of a 48 year old alcohol, opioid and benzodiazepine dependent man on high dose methadone maintenance, with decompensated cirrhosis but no history of demonstrated ascites, no oesophageal varices on endoscopy, and no imaging indications of portal hypertension. He was having 6 monthly endoscopy for surveillance for varices, and Dr Strasser questioned whether this was necessary in the absence of evidence of portal hypertension. The patient had, since decompensated cirrhosis was identified 10 years ago, also been treated with supervised diazepam maintenance 15mg/day on a “no-alcohol contract”, which he however breached on numerous occasions, including presentations to emergency department with intoxication or injury. Supervised disulfiram had not been a success, with the patient taking the medication but sometimes drinking alcohol on top: “after the first four I’d have an up-and-under (= chunder, or vomit) and I’d be alright after that”. In retrospect the use of disulfiram had been risky in this case. A general view was expressed that there was no justification for the prescription of diazepam. The contrary view was that he had been drinking up to 360g alcohol/day prior to the current regimen was started, had clearly reduced his alcohol consumption, and survived for a decade against the odds of his severe liver disease.