Intensive therapy of the patient with liver disease

Liver disease is a subject of increasing importance in the UK, with a steadily rising incidence. It is an important cause of death in young adults, and the initial presentation of liver disease is frequently complicated by critical illness.

In 2007, 15 203 people died from liver disease and it is now the fifth biggest killer after heart disease, cancer, stroke and respiratory disease. The number of deaths from liver disease in the UK now compared to 1991 has doubled, and it is the only major cause of death still increasing year on year (British Liver Trust, 2008). There are approximately 400 cases of acute liver failure in the UK every year.

With an increasing incidence of decompensated liver disease, the number of referrals for intensive care of patients with liver disease will increase. Liver disease has multisystem effects and causes profound physiological insult. The supportive treatment required to facilitate recovery or specific treatment is only available in an intensive care setting.

There are four categories of liver injury encountered in the intensive care environment. These are:
1. Transaminitis or cholestatic jaundice associated with critical illness
2. Acute ischaemic hepatitis
3. Acute liver failure (coagulopathy and encephalopathy in a patient without pre-existing cirrhosis and less than 6 months' illness)
4. Acute decompensation of severe (end-stage) chronic liver disease.

This article outlines the care of patients with liver disease in general intensive care units.

Diagnosis and evaluation

The correct categorization of liver failure is a key task of the attending physician – it is crucial to decide which category a patient falls into, as each carries a different aetiology, pathogenesis, treatment and prognosis.

The history is nearly always key to the underlying aetiology of liver failure. This should elicit use of medication and exposure to other drugs as well as the risk of exposure to blood-borne viruses. In cases where the patient is already encephalopathic, the history will need to be gained from other sources.

Examination needs to focus on assessment of mental function and the grading of encephalopathy, and also as to whether the patient is protecting his/her airway. Patients with marked encephalopathy (grade III–IV) should be admitted to intensive care proactively, as they are at high risk of further deterioration. The physical examination should be used to help support the diagnosis, and to attempt to differentiate between acute and acute on chronic liver disease.

Laboratory investigations should be comprehensive and used to assess aetiology. Although the aetiology will hopefully come from the history, these investigations may reveal underlying disorders amenable to treatment or factors predisposing to liver failure. The investigations can be divided into functional and investigatory (*Table 1*).

Table 1. Laboratory investigations

Functional	Prothrombin time or international normalized ratio	
	Biochemistry	Sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphate glucose , urea, creatinine
		Aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma glutamyl transferase, total bilirubin, albumin
	Arterial blood gas	Lactate
	Full blood count	
	Blood type and screen	
	Ammonia	
Investigatory	Paracetamol level	
	Toxicology screen	
	Viral hepatitis serology	Anti-hepatitis A virus IgM, hepatitis B surface antigen, anti-hepatitis B core IgM, anti-hepatitis C virus IgM, anti-hepatitis E virus IgM, Epstein–Barr virus, cytomegalovirus
	Ceruloplasmin level	
	Ferritin level	
	Pregnancy test (females)	
	Autoimmune markers	Anti-nuclear antibodies
		Anti-smooth muscle antibodies
	Alfa-fetoprotein	

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An ultrasound of the liver is the initial imaging modality of choice. This can be used to assess for the appearance of cirrhosis and help to exclude hepatocellular carcinoma.

It is always worth early discussion with the local transplant unit if the patient fulfills the criteria for liver transplantation or other specialist therapy (e.g. transjugular intrahepatic portosystemic shunt; TIPPS). Transfer is much more easily arranged and safer the lower the grade of encephalopathy. Consideration should be given to elective intubation before transfer if there is any doubt about airway protection.

Management

Wherever possible treatment should be aimed at the underlying cause. Where the aetiology is not found, treatment is supportive. Specific management is shown in *Table 2*.

Liver disease has multisystem effects and these patients are usually very unwell. They are often looked after on general wards but high dependency unit or intensive care unit care is often required to optimize the therapy of these patients.

Encephalopathy

The physiological mechanisms of encephalopathy have never been clearly elicited. Cerebral oedema and intracranial hypertension are well recognized in liver failure. This can result in ischaemic brain injury. The pathological process behind the development of cerebral oedema is not fully understood, but probably results from osmotic brain disturbances and loss of cerebral autoregulation. Cerebral oedema rarely occurs in patients with grade I–II encephalopathy. The risk of oedema rises to 30% in grade III and 70% in grade IV encephalopathy (Munoz, 1993).

As encephalopathy increases to grade III–IV, airway protection is likely to be required. Relatively low doses of sedation are often all that are required for the patient to tolerate the endotracheal tube, as a result of reduced metabolism of sedative drugs. Measures aimed at cerebral protection and avoidance of secondary brain injury should be instituted.

As cerebral perfusion pressure = mean arterial pressure – intracranial pressure it may be necessary to support the cardiovascular system with vasopressors to maintain cerebral perfusion pressure >60 mmHg (Richardson and Bellamy, 2002). It must be remembered that patients with liver disease are often relatively hypotensive.

Experimental studies have shown that ammonia can result in the development of cerebral oedema (Blei et al, 1994). Ammonia levels greater than 200 μg/dl have been associated with cerebral herniation (Clemmesen et al, 1999). In view of these findings and clinical experience in patients with chronic liver disease, reducing ammonia plasma levels with the use of lactulose seems a reasonable treatment but there has never been a demonstrated survival benefit to this action in acute liver failure (Alba et al, 2002). There is evidence that ammonia levels do not relate to severity of encephalopathy but more reliably to the degree of inflammation, which may help explain why encephalopathy does not resolve with lactulose therapy (Shawcross et al, 2007). There is no value to additional lactulose should the patient be opening his/her bowels twice daily.

Hyperventilation has been used previously in an attempt to reduce intracranial pressure, and although there was a longer time to cerebral herniation, there was no reduction in cerebral oedema or mortality. As with head injuries there is no place for hyperventilation in encephalopathy (Ede et al, 1986; Strauss et al, 1998). A lung-protective strategy of ventilation, aiming for normocapnoea, should be instituted.

Seizures may occur as a result of the process leading to increased intracranial pressure. There is a balance to be found in the treatment of seizures. Sedative medication will make assessment of encephalopathy more difficult, while there is a need to terminate seizures as they may acutely increase intracranial pressure. Phenytoin is a reasonable choice for preventing seizures.

Hypertonic saline has been used to maintain sodium levels 145–155 mmol/litre in patients with acute liver failure and was found to prevent increases in intracranial pressure (Murphy et al, 2002). This study also revealed a reduction in vasopressor requirements when hypernatraemia is produced. The number of patients involved in the study was small, and no survival benefit was seen.

There is no place for corticosteroids in the management of raised intracranial pressure associated with liver disease (Canalese et al, 1982).

Coagulopathy

Clotting abnormalities are almost universal in the patient with liver failure, resulting from deranged synthetic function but also from increased consumption of both clotting factors and platelets. As a general guide, fresh frozen plasma should not be used to correct the coagu-

Table 2. Specific treatments of liver failure

Disease	Treatment
Paracetamol overdose	N-acetylcysteine
Viral hepatitis	Supportive therapy
Chronic hepatitis B	Nucleoside analogues
Wilson's disease	Transplant
Autoimmune hepatitis	Corticosteroids
HELLP (haemolysis, elevated liver enzymes, low platelets)	Delivery of fetus
Ischaemic hepatitis	Cardiovascular support
Budd–Chiari	Transplant (exclude malignancy)
Unclear diagnosis	Consider biopsy

lopathy, as these factors will be rapidly consumed (Gazzard et al, 1975), and the administration of clotting factors also makes clotting investigations uninterpretable for assessing liver synthetic function. However, it is reasonable to use fresh frozen plasma to cover the periods during which invasive procedures are to be performed, or when there is active bleeding and the patient's international normalized ratio is >1.5. Cryoprecipitate can be used to maintain a fibrinogen of >1 mg/dl where there is a reluctance to use fresh frozen plasma. This has the advantage of lower volume and sodium load.

Vitamin K is routinely given, for 3 days, to try and correct the coagulopathy. This will be to varying success and have no effect acutely, but is a reasonable course of action.

Platelet transfusions are rarely indicated if the levels are greater than 20 000/mm^3 (Drews and Weinberger, 2002). However, for invasive procedures levels greater than 50 000/mm^3 are desirable. If patients develop significant bleeding with platelets less than 50 000/mm^3 then a platelet transfusion should be instituted to maintain that level.

Further investigation of the role of recombinant activated factor VII is required, but a small study has shown beneficial short-term effect on correction of clotting abnormalities, with the added advantage of only administering small volumes to these patients, where fluid balance is often critical (Shami et al, 2003).

Gastrointestinal haemorrhage

Gastrointestinal bleeding is a common cause of death in patients with liver disease and is usually more complicated to manage because of the presence of coagulopathy. Endoscopy will allow diagnosis and treatment of these patients with this complication. Varices are more likely to be present in acute on chronic liver failure, but patients with acute liver failure are at risk of ulceration.

Coagulopathy and mechanical ventilation for more than 48 hours are risk factors for gastrointestinal bleeding in all groups of intensive care patients (Cook et al, 1994). Liver failure has been identified as an independent risk factor for stress ulceration (Martin et al, 1992).

All these patients should be on gastric acid prophylaxis. Histamine antagonists have demonstrated proven gastric protection for many years but there is now convincing evidence that proton pump inhibitors provide more profound and longer lasting gastric acid suppression (van Rensburg et al, 2003). The reduced gastric acid assists platelet aggregation, decreases clot lysis and fibrinolytic enzymatic activity. These benefits are maximized in high dose proton pump inhibitor infusions where there is active upper gastrointestinal bleeding (Lau et al, 2000). The effects of proton pump inhibitors may be more prolonged in liver failure as a result of their metabolism by the cytochrome P450 enzymes.

More specifically, haemorrhage from oesophageal varices carries a high mortality. There is a known association with sepsis and variceal haemorrhage as a result of the release of endotoxin and worsening coagulopathy.

Cardiovascular resuscitation should be initiated promptly with appropriate blood products as required, being mindful that bleeding from varices rarely occurs with portal vein pressures <12 mmHg. However, there is little evidence for a threshold above which bleeding is more likely (Jalan et al, 2008) and measuring this value is mostly a research tool. Central venous pressure is unlikely to be a reliable surrogate.

Endoscopy should be arranged as soon as possible. This will facilitate banding of the varices, which eradicates varices faster than sclerotherapy. There is no benefit to sclerotherapy as an adjunct to banding (Al-Traif et al, 1999).

Terlipressin assists with haemostasis and is additive to endoscopic intervention. The effects of terlipressin reduce portal hypertension by reducing portal blood flow. This is the only pharmacological agent which reduces mortality in variceal bleeding (Ioannou et al, 2002). The use of terlipressin has been associated with increased cerebral blood flow and intracranial pressure (Shawcross et al, 2004). Terlipressin is relatively contraindicated in patients with ischaemic heart disease.

TIPSS is an interventional radiology procedure which aims to reduce portal pressure by creating a connection within the liver between the portal and systemic circulations. TIPSS should be considered in acute variceal bleeding uncontrolled by medical and endoscopic therapy or where there is recurrent or refractory variceal bleeding (Colombato, 2007). TIPSS is associated with a 25% incidence of acute encephalopathy. Patients are likely to require transfer to a tertiary referral centre for this procedure.

Sepsis

Patients with liver failure are immunocompromised and therefore at risk of both bacterial and fungal infections. Prophylactic antibiotics reduce the incidence of infection in some subgroups but there has been no improvement seen in survival and therefore there is no role for prophylactic antibiotics (Rolando et al, 1993).

Deterioration of cognitive function or development of delerium may be the initial presenting sign of sepsis. It is vital to be proactive in looking for infection and have a low threshold for starting appropriate antibiotics and/or antifungals. Meticulous aseptic technique with line insertion and handling is essential. There is an association between the systemic inflammatory response syndrome and worsening grades of encephalopathy.

Renal failure

Fluid management and control of electrolytes is a challenge in these patients, particularly when there is renal involvement and/or elevated intracranial pressure.

Prevention of renal failure is vital as it has such a profound prognostic effect. These patients have multiple reasons for being intravascularly deplete; poor oral intake secondary to encephalopathy, extracellular transudation of fluid and gastrointestinal blood losses. Most patients will require fluid resuscitation, usually with a colloid, but there is no evidence that this is better than appropriate crystalloids. These patients may have chronic hyponatraemia and this must be considered when selecting fluids for resuscitation and the rate of correction of sodium considered.

As a consequence of repeated bacterial endotoxaemia, these patients may be peripherally vasodilated and, even when fluid resuscitated, often remain relatively hypotensive. Cardiovascular monitoring may be beneficial to guide fluid therapy and initiation of vasopressors if required. Alpha-adrenergic agents reduce peripheral oxygen delivery (Wendon et al, 1992), and although oxygen delivery is vital, appropriate perfusion pressures are required to maintain renal function, and a mean arterial pressure of 60 mmHg would be an appropriate target. In patients with deteriorating renal function both terlipressin and noradrenaline are beneficial (Alessandria et al, 2007). The dose for terlipressin is 0.5–2 mg 6-hourly.

Where renal replacement therapy is required and appropriate, continuous modes rather than intermittent modes should be used to help maintain consistent cardiovascular and intracranial conditions by preventing dramatic fluid shifts. Early institution of renal replacement therapy may aid appropriate fluid balance.

Avoiding nephrotoxic agents should be a priority, although this may be complicated by the need for specific antibiotics when treating sepsis and appropriate radiological investigations requiring the administration of contrast.

Ascites and ventilation

Ascites creates a number of challenges to different systems. Within the abdomen there is the risk of abdominal compartment syndrome and exacerbation of compromise in renal function.

Ventilation is difficult with tense ascites because of diaphragmatic splinting. In the mechanically ventilated patient a high positive end expiratory pressure strategy with relatively high mean airway pressures may cause less damage to the lung parenchyma, as the transpulmonary gradient is reduced by the raised intra-abdominal pressure.

Drainage of tense ascites by paracentesis will assist ventilation but the balance of risk needs to be weighed. If paracentesis is used, the drain should not remain in situ for any longer than 6 hours because of the risk of introducing infection.

The question of which plasma expander to use is still unanswered. Plasma expansion should always be used when draining greater than 5 litres of ascites. Synthetic plasma expanders are clinically effective at preventing hyponatraemia and renal impairment. In comparison to albumin, the synthetic plasma expanders cause greater activation of the renin–angiotensin system and an increased incidence of liver-related complications (Moore and Aithal, 2006).

Where the facility is available, paracentesis should be carried out with real-time ultrasound guidance to avoid trauma to abdominal wall varices and administration of terlipressin to prevent hyperaemia of gastric varices and subsequent gastric bleeding.

Nutrition

Hypoglycaemia is a common problem with liver failure, and should be managed with glucose infusions as symptoms and signs can be masked by the presence of encephalopathy and the multisystem effects of liver failure. Repeated supplementation of ions (potassium, magnesium and phosphate) may be necessary to correct abnormalities. Assessment of plasma levels of electrolytes should be frequent (at least daily).

Wherever possible, enteral nutrition should be initiated as soon as possible. Immunonutrition has not shown any benefit in critically ill patients with liver disease. Although protein load has traditionally been minimized, 60 g/day is reasonable in most patients (Polson and Lee, 2005).

Parenteral nutrition may be an alternative should enteral nutrition not be possible, but the risks of subsequent infections need to be considered.

Molecular adsorbent recirculating system

The molecular adsorbent recirculating system (MARS) uses two separate dialysis circuits, the first of which consists of human albumin in exchange with the patient's blood via a semi-permeable membrane. This circuit has filters incorporated which remove the adsorbed toxins from the circuit albumin before it is recirculated. A number of toxins such as ammonia, bilirubin, copper, iron and bile acids can be removed.

MARS requires the insertion of an appropriate central venous catheter and for cardiovascular stability it is advisable to stop haemofiltration during this period.

Although this system would seem to be a solution to liver failure in the same way that dialysis is used to treat renal failure, it remains to be seen exactly where this system should be used. Although excretory function can be produced in this manner, the many other hepatic functions are still missing.

The MARS system has been used for patients awaiting liver transplant as a measure to provide more time for a donor to be found. In spite of this technological advance overall mortality is still very high (Lee et al, 2005). However, a more recent study with longer durations of MARS therapy meant some patients listed for urgent liver transplant avoided this intervention as their liver function improved (Camus et al, 2009). The numbers

involved in both trials were small and so the exact indications for MARS therapy may yet change.

There are risks associated with the MARS system, particularly in unstable or septic patients, where it can precipitate cardiovascular collapse.

Conclusions

In spite of many advances in the care of patients with liver disease, most management is supportive and good basic intensive care is at the heart of this treatment. Further work is required in providing treatments that provide synthetic function substitution as well as the excretory function provided by MARS. **BJHM**

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Alba L, Hay J, Angulo P, Lee W (2002) Lactulose therapy in acute liver failure. *J Hepatol* **36:** 33

Al-Traif I, Fachartz F, Al Jumah et al (1999) Randomised trial of ligation versus combined ligation and sclerotherapy for bleeding oesophageal varices. *Gastrointest Endosc* **50**(1): 1–6

Alessandria C, Ottobrelli A, Debernardi-Venon W et al (2007) Noradrenaline vs terlipressin in patients with hepatorenal syndrome: a prospective, randomized unblended pilot study. *J Hepatol* **47**(1): 499–505

Blei A, Olafsson S, Therrien G, Butterworth R (1994) Ammonia induced brain oedema and intracranial hypertension in rats after portocaval anastamosis. *Hepatology* **19:** 1437–44

British Liver Trust (2009) Facts about liver disease. www.britishlivertrust.org.uk/home/media-centre/facts-about-liver-disease.aspx (accessed 4 June 2010)

Camus C, Lavoue S, Gacouin A et al (2009) Liver transplantation avoided in patients with fulminant hepatic failure who received albumin dialysis with the molecular adsorbent recirculating system while on the waiting list: impact of the duration of therapy. *Thera Apher Dial J* **13**(6): 549–55

Canalese J, Gimson A, Davis C, Mellon PJ, Davis M, Williams R (1982) Controlled trial of dexamethasone and mannitol for the cerebral oedema of fulminant hepatic failure. *Gut* **23:** 625–9

Clemmesen JO, Larsen FS, Kondrup J et al (1999) Cerebral herniation in patients with acute liver failure is correlated with arterial ammonia concentration. *Hepatology* **29:** 648–53

Colombato L (2007) The role of transjugular intrahepatic portosystemic shunt (TIPS) in the management of portal hypertension. *J Clin Gastroenterol* **41**(Suppl 3): S344–51

Cook DJ, Fuller HD, Guyatt GH et al (1994) Risk factors for gastrointestinal bleeding in critically ill patients. *N Engl J Med* **330:** 377–81

Drews R, Weinberger S (2000) Thrombocytopenic disorders in critically ill patients. *Am J Respir Crit Care Med* **162:** 347–51

Ede R, Gimson A, Bihari D, Williams R (1986) Controlled hyperventilation in the prevention of cerebral oedema in fulminant hepatic failure. *J Hepatol* **2:** 43–51

Gazzard B, Henderson J, Williams R (1975) Early changes in coagulopathy following paracetamol overdose and a controlled trial of fresh frozen plasma therapy. *Gut* **16:** 617–20

Ioannou G, Doust J, Rockey D (2002) Terlipressin in acute oesophageal haemorrhage. *Aliment Pharm Ther* **17**(1): 53–64

Jalan R, Redhead D, Forrest E, Hayes P (2008) Relationship between directly measured portal pressure gradient and variceal haemorrhage. *Am J Gastroent* **90**(11): 1994–6

Lau J, Sung J, Lee K et al (2000) Effect of intravenous omeprazole on recurrent bleeding after endoscopic treatment of bleeding peptic ulcers. *N Engl J Med* **343:** 310–16

Lee K, Lee M, Sutedja D, Lim S (2005) Outcome from molecular adsorbent recycling system (MARS) liver dialysis following drug induced liver failure. *Liver Int* **25**(5): 973–7

Martin LF, Booth FVM, Reines D et al (1992) Stress ulcers and organ failure in intubated patients in surgical intensive care units. *Ann Surg* **215:** 332–7

Moore KP, Aithal GP (2006) Guidelines on the management of ascites in cirrhosis. *Gut* **55:** 1–12

Munoz SJ (1993) Difficult management problems in fulminant hepatic failure. *Semin Liver Dis* **13(4):** 395–413

Murphy N, Auzinger G, Bernal W, Wendon J (2002) The effect of hypertonic sodium chloride on intracranial pressure in patients with acute liver failure. *Hepatology* **39:** 464–70

Polson J, Lee W (2005) AASLD Position Paper: The management of acute liver failure. *Hepatology* **42:** 1179–97

Richardson D, Bellamy M (2002) Intracranial hypertension in acute liver failure. *Nephrol Dial Transplant* **17:** 23–7

Rolando N, Gimson A, Wade J, Philpott-Howard J, Casewell M, Williams R (1993) Prospective controlled trial of selective parenteral and enteral antimicrobial regimen in fulminant liver failure. *Hepatology* **17:** 196–201

Shami V, Caldwell S, Hespenheide E, Arseneau K, Bickston S, Macik B (2003) Recombinant activated factor VII for coagulopathy in fulminant hepatic failure compared with conventional therapy. *Liver Transpl* **9:** 138–43

Shawcross D, Davies N, Mookerjee R et al (2004) Worsening of cerebral hyperemia by the administration of terlipressin in acute liver failure with severe encephalopathy. *Hepatology* **39:** 471–5

Shawcross D, Wright G, Olde Damink S, Jalan R (2007) Role of ammonia and inflammation in minimal hepatic encephalopathy. *Metabolic Brain Disease* **22**(1): 125–38

Strauss G, Hansen B, Knudsen G, Larsen F (1998) Hyperventilation restores cerebral blood flow autoregulation in patients with acute liver failure. *J Hepatol* **28:** 199–203

van Rensburg CJ, Hartmann M, Thorpe A et al (2003) Intragastric pH during continuous infusion with pantoprazole in patients with bleeding peptic ulcer. *Am J Gastroenterol* **98:** 2635–41

Wendon J, Harrison P, Keays R, Gimson A, Alexander G, Williams R (1992) Effects of vasopressor agents and epoprostenol on systemic hemodynamics on oxygen transport variables in patients with fulminant hepatic failure. *Hepatology* **15:** 1067–71

KEY POINTS

- Liver disease is an increasing problem with younger groups of patients being affected.
- Aetiology helps determine prognosis.
- Encephalopathy results from mixed mechanisms: toxins and raised intracranial pressure.
- Blood products should be used appropriately to allow assessment of synthetic function.
- Management of gastrointestinal bleeding is multimodal and may require transfer to tertiary centres.
- Discuss patients with tertiary centres early, as transfer is safer with lower grades of encephalopathy.
- If the aetiology is unclear, unidentified viral infection must be considered and early discussion with transplant centres is warranted.