DISEASES OF THE LIVER

Acute liver disease

By Paul Richardson, MBBS, MRCP and John G. O'Grady, MD, FRCPI

This article focuses on acute liver failure as a form of acute liver disease and includes a discussion on its aetiology, management and complications.

The most basic classification of liver disease is as acute and chronic. The definition of acute liver disease (such as acute hepatitis and acute liver failure [ALF]) is based on duration, with the history of the disease does not exceed six months. Diseases of longer duration are classified as chronic (such as chronic viral hepatitis, cirrhosis). An additional term, “acute-on-chronic” is used to describe a sudden clinical complication in a previously stable patient with chronic liver disease, such as bleeding from oesophageal varices in a patient with cirrhosis.

Acute viral hepatitis and drug reactions account for the majority of cases of acute liver disease. Hepatitis A and B are the commonest causes of viral hepatitis in Europe and hepatitis E is common in India. Hepatitis C is not usually recognised as an acute infection because it rarely causes jaundice at this stage.

Idiosyncratic reactions to recreational drugs such as “ecstasy”, or therapeutic drugs may occur. Such reactions (e.g., cholestasis, hepatitis, ALF) are relatively common with antituberculous drugs and non-steroidal anti-inflammatory drugs, but also occur less frequently with some other drugs (see Panel 1, p132). Paracetamol toxicity is an example of a semi-quantitative reaction (the risk of a reaction increases with the dose but this is neither universal nor linear) and it is often used intentionally in suicide attempts.

Patients with acute hepatitis usually present with jaundice and this can last for several weeks. Spontaneous recovery is the norm and there is no specific treatment. The severity of the liver damage is most accurately assessed by measuring coagulation activity (international normalised ratio [INR], prothrombin time, Factor V). Once coagulation becomes abnormal, the patient is at risk of developing acute liver failure.

ACUTE LIVER FAILURE

Acute liver failure was originally described as the appearance of hepatic encephalopathy associated with severe liver dysfunction, coagulopathy and jaundice, within a time frame of six months following the onset of symptoms. Since then, the classification of ALF has been revised to take into account the heterogeneous nature of the syndrome with regards to aetiology, frequency of complications, and outcome. The need to update and re-define the syndrome has been, in part, driven by the requirement to identify patients who would be appropriate candidates for liver transplantation.

A recent classification has defined the syndrome by proposing three classes: hyperacute, acute and subacute liver failure (Table 1, p132).

1. In hyperacute liver failure the appearance of encephalopathy is recorded within seven days of the onset of jaundice. There is a high incidence of cerebral oedema but paradoxically this is the cohort most likely to survive with medical treatment.

2. Acute liver failure is where the appearance of encephalopathy is within eight to 28 days of the onset of jaundice.
high prevalence of viral hepatitis makes this infection the predominant cause of the disease. In the UK, the most common cause of ALF is deliberate or accidental paracetamol overdose.

In the majority of cases, the underlying aetiology has limited impact on management because there are few treatment options available to address the initial cause. One notable exception is paracetamol overdose, where prompt (within 16 hours) and later administration of intravenous N-acetylcysteine has been shown to prevent or ameliorate liver damage and improve overall survival.11 The recognition of the importance of paracetamol as a major cause of ALF in the UK has prompted the repackaging of tablets into blister packs with limited quantities and appears to have reduced the incidence of ALF secondary to paracetamol overdose.12

HAEMODYNAMIC MONITORING

One of the cardinal signs of ALF is the marked disturbance in systemic circulation.19 This is characterised by hypovolaemia, reduced systemic vascular resistance and a compensatory increase in the cardiac output. The circulatory changes are analogous to those seen in septic shock. ALF also affects the microcirculation, with arterio-venous shunting and impaired end-organ perfusion. The consequences of these changes are tissue hyperperfusion, tissue hypoxia, lactic acidosis and multiple organ failure.11,12

To enable observation of these effects, and to target treatment, invasive monitoring is required despite the associated complications of bleeding because of poor clotting profiles and low platelet counts. Central venous catherisation is generally mandatory but is limited in terms of the amount of data that can be generated.

Pulmonary artery (PA) catherisation allows recording of pulmonary capillary wedge pressure, which is a more accurate reflection of volume resuscitation than central venous pressure. The use of a PA cather also allows measurement of cardiac index and systemic vascular resistance, which will guide the use of inotropic and arterial pressor agents.

A recent addition to the monitoring armamentarium has been the “cold catheter” which when inserted in the femoral artery, allows measurement of the total blood volume and lung water indices.

GENERAL MANAGEMENT

Treatment in the first instance is adequate fluid replacement. The choice of fluid replacement is controversial, and there is considerable debate in light of a recent meta-analysis comparing crystalloid with albumin.21 Albumin was associated with a higher mortality but the study may not be pertinent to ALF. It must be recognised that no prospective studies have been reported comparing the form of replacement agent in ALF. Despite adequate fluid replacement, many patients remain hypotensive due to the low systemic vascular resistance (SVR), and require treatment with a vasopressor agent, most commonly noradrenaline. In the situation of a low SVR with a low cardiac output, the combined pressor and inotropic effects of adrenaline may be more appropriate. Similarly, a combination of noradrenaline and dobutamine may give a similar result.

As stated above, the abnormalities in the microcirculation have profound consequences for local tissue perfusion, and both N-acetylcysteine and proscystin have been demonstrated to exert a beneficial effect on the microcirculation in ALF.22

Liver transplantation. Liver transplantation cannot be regarded as a panacea for ALF, since the procedure itself is associated with an appreciable mortality.

The one-year survival rates vary between 60–90 per cent, but these figures do not take into account patients deemed either inappropriate or too ill for transplantation and those who die while waiting for a suitable graft. With the limited window of opportunity for successful transplantation and the shortage of cadaveric organs, there is a need for early recognition of those patients who will benefit from transplantation and those who are best managed medically. There are currently two main predictive criteria in general use, the King’s College Hospital (KCH) criteria and the Clichy criteria.

The KCH criteria are the most commonly used (see Panel 2, p133).11 The criteria are divided into two subsets: for paracetamol induced and non-paracetamol induced ALF.

### Table 1: Features of subtypes of acute liver failure

<table>
<thead>
<tr>
<th>Feature</th>
<th>Hyperacute</th>
<th>Acute</th>
<th>Subacute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaundice to encephalopathy (days)</td>
<td>0–7</td>
<td>8–28</td>
<td>29–84</td>
</tr>
<tr>
<td>Cerebral oedema</td>
<td>Common</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Renal failure</td>
<td>Early</td>
<td>Late</td>
<td>Late</td>
</tr>
<tr>
<td>Ascites</td>
<td>Rare</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Coagulation disorder</td>
<td>Marked</td>
<td>Marked</td>
<td>Modest</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Moderate</td>
<td>Poor</td>
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There is a significant incidence of cerebral oedema, but unlike the hyperacute group the outcome is poorer without liver transplantation.

3. Subacute liver failure is defined by the development of encephalopathy from 12 weeks after the onset of jaundice, and is characterised by a high mortality, despite a low incidence of cerebral oedema.1

The incidence of ALF ranges from 0.1–5 per cent, depending on the underlying aetiology, and this diagnosis is made once encephalopathy manifesting as impairment of consciousness or coma develops. The mortality from ALF is high and many patients require urgent liver transplantation.

ALF is one of the most devastating clinical syndromes observed in clinical practice. It is associated with a high overall mortality, ranging from 30–80 per cent, depending on the underlying aetiology.1 This high mortality is a consequence of the profound disturbances in circulatory control, cerebral pressure and blood flow, susceptibility to renal failure and overwhelming sepsis, as well as the generalised derangements in metabolism such as hypoglycaemia.

The overall poor outlook in ALF conceals the widespread differences in aetiology, clinical course, complications encountered, prognosis, and the need for liver transplantation. It is therefore important to define the subsets of ALF and recognise the underlying aetiology. The clinical management is still a combination of critical care medicine and liver transplantation. The treatment of these patients is multidisciplinary with pharmacists, specialist nurses, hepatologists, intensivists and transplant surgeons all having vital roles in the provision of care.

AETIOLOGY

The aetiology of ALF is heterogeneous and shows widespread geographic variability. Within the developing world, the

### Commonest causes

Paracetamol, halothane, isoniazid, rifampicin, non-steroidal anti-inflammatory drugs, sulphonamides, sodium valproate, carbamazepine, flutamide, 3,4-methylene dioxymethamphetamine (“Ecstasy”)

### Less frequent or historical causes

Phenytoin, isoflurane, enflurane, tetracycline, allopurinol, ketoconazole, monoamine oxidase inhibitors, dapsone, methyldopa, amiodarone, tricyclic antidepressants, propylthiouracil, gold, 2,3-dioxoxyinosine (ddl)

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Panel 1: Drugs causing ALF

<table>
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These criteria have been independently validated and give predictive accuracy of 71 per cent and 68 per cent, respectively. The KCH criteria base their predictions on prothrombin time, arterial pH 24 hours post-overdose, serum creatinine and grade of encephalopathy for the paracetamol-induced ALF group. For all other causes of ALF (non-paracetamol induced), aetiology, interval from appearance of jaundice to evidence of encephalopathy, prothrombin time, age, aetiology and serum bilirubin are used.

The Chichy (French) criteria rely on the degree of encephalopathy and serum factor V levels below 30 per cent of normal.25 Despite these selection criteria, a significant number of patients die waiting for a suitable organ, or clinical deterioration precedes a successful outcome. This situation, together with the remarkable regenerative capacity of the liver, has generated interest in the development of additional strategies to maintain the patient in a stable condition long enough for an appropriate graft to become available, or until spontaneous regeneration and clinical improvement occurs.

One such approach has been the development of artificial liver devices analogous to renal dialysis, where the patient is connected to an extracorporeal circuit containing hepatocytes. This may prove to be a pivotal approach in the coming years, but at present there is a paucity of data demonstrating clear improvement in outcome with these devices.23,26 One reason for the lack of data is the difficulty in designing good clinical trials due to the heterogeneous nature of ALF and the problem of selecting suitable clinical end points.

Non-biological support systems include charcoal haemoperfusion (circulation of blood through a cartridge containing charcoal adsorbent),10,20 and high volume plasmapheresis (replacement of the plasma fraction of blood).20,21 A recent addition to the therapeutic armamentarium has been the molecular adsorb recirculating system (MARS), which is an extracorporeal device using albumin-enhanced diasylate to remove albumin-bound toxins.22 This novel treatment has been demonstrated to be of benefit in ALF and in patients with HRS, and may again offer time for hepatic recovery or act as a bridge to transplantation.23,25

### Cerebral complications

Cerebral oedema is a feared complication of ALF with a high mortality rate being observed in patients who fail to respond to conventional treatment.20 Its occurrence is higher in the hyperacute and acute groups, with a combined incidence of 60–70 per cent in these groups.20 The pathophysiology of cerebral oedema is still unclear, but various theories have been postulated. The simplest explanation is that as brain volume is restricted by the size of the cranium, any increase in the brain volume will cause a rise in intracranial pressure (ICP).25

**Panel 2: KCH criteria for liver transplantation in ALF**

<table>
<thead>
<tr>
<th>Paracetamol induced</th>
<th>Non-paracetamol induced</th>
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</thead>
<tbody>
<tr>
<td>Arterial pH &lt;7.3</td>
<td>Prothrombin time &gt;100s</td>
</tr>
<tr>
<td>OR</td>
<td>or INR &gt;6.7</td>
</tr>
<tr>
<td>All three of the following:</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Prothrombin time &gt;100s</td>
</tr>
<tr>
<td></td>
<td>or INR &gt;6.7</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Serum bilirubin &gt;300µmol/L</td>
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On the other hand, it should be noted that with the loss of autoregulation, the brain may be rendered relatively ischaemic by reduction of cerebral blood flow due to decrease in the mean systemic arterial blood pressure. It is a precarious balance trying to avoid an increased cerebral blood flow and a raised ICP, while recognising that a lower BP is associated with the risk of reduced cerebral blood flow and cerebral ischaemia.

**Monitoring** The mainstay of monitoring is measurement of the ICP and cerebral perfusion pressure (CPP). This is the mean arterial pressure minus the ICP. The accuracy of the measurements is influenced by the method chosen, with an epidural monitor being the safest but least accurate. These procedures are not without risk, and the benefits of monitoring and response to treatment must be carefully weighed against the risks.20 A sustained reduction of CPP was once considered a contraindication for transplantation due to a potentially large risk of serious neurological sequelae. This position has been refuted.22 Measurement of jugular vein oximetry enables direct estimation of cerebral oxygenation. Low saturation scores, that is, less than 55 per cent, may indicate relative ischaemia secondary to reduced blood flow or an excessive cerebral metabolic rate seen in seizures or hypoglycaemia. A persistently raised oximetry, that is, higher than 75 per cent, indicates a high cerebral blood flow and, in conjunction with a raised ICP, generally indicates a poor prognosis. Different strategies exist to control cerebral oedema.23

**Management** The mainstay of treatment for raised ICP is osmotherapy with mannitol infusion. This causes an increase in colloidal osmotic pressure within cerebral capillaries and a reduction in cerebral water content. Mannitol has been shown to reduce ICP and raise cerebral blood flow.25 The same study demonstrated no benefit in the use of dexamethasone.

The marked reduction of ICP and stabilization of patients when rendered anhepatic (absence of the liver) before transplantation has led to suggestions that the necrotic liver produces an as yet unidentified agent that is able to cross the blood brain barrier and cause increased cerebral blood flow and/or cerebral oedema. Improvement in ICP has been demonstrated in patients rendered anhepatic generally to prevent irreversible neurological damage when it is known that a suitable organ will become available for transplantation.25

Hyperventilation by reducing $P_{CO_2}$ induces cerebral vasosnstriction and thus reduces both cerebral blood flow and ICP. Hyperventilation has to be used carefully, as the reduction in cerebral blood flow can induce cerebral ischaemia.26 Barbbiturates reduce cerebral metabolic rate. This leads to...
arteriolar vasoconstriction and possible reduction in cerebral blood flow. Thiopeptone has been shown to be effective in reducing ICP, although this may be at the expense of increasing the future risk of fungal infections due to neutrophil inhibition. 37

Hypothermia has been shown to be effective in reducing ICP in cerebral trauma patients, and this observation led to its trial in ALF. 38,39 Mild hypothermia with cooling to 32°C has also been shown in a small study to reduce cerebral blood flow and ICP and was suggested as a potential bridge to transplantation for those patients with raised ICP who do not respond to mannitol and ultrafiltration. 40 The same group has recently suggested that the response to cooling may reside in the restoration of cerebral blood flow autoregulation. 40

Prospects As the basic pathophysiology of cerebral oedema becomes clearer, the possibility of a more directed approach becomes increasingly likely. Direct inhibition of cerebral glutamine synthetase could, in future, prevent astrocyte swelling. In addition, skeletal muscle glutamine synthetase can be induced so that it is used as an alternative site for ammonia metabolism. These goals can be achieved by the infusion of ornithine aspartate which, in rat models of ALF, reduced ICP and ammonia levels and also increased muscle glutamine synthetase enzyme activity. In patients with cerebral trauma, indomethacin has been demonstrated to cause profound vasoconstriction and reduction in ICP by inhibiting cyclo-oxygenase. 41 A recent case report described the benefits of indomethacin in ALF from paracetamol poisoning. 42 This initial case report has been confirmed in animal models, but further clinical studies are still required before this treatment modality can be recommended. 43 The potential renal complications and risk of gastric ulceration may, however, preclude its clinical application.

RENA L COM P L IC AT I O NS

Renal failure develops in approximately 35 per cent of patients with ALF. 44 The aetiology of renal failure in ALF is multi-factorial and includes hepatorenal syndrome (HRS), direct toxicity from paracetamol, hypovolaemia, use of nephrotoxic drugs, and sepsis.

HRS is defined as the development of acute renal failure secondary to liver disease. 45 It can occur in acute or chronic liver disease. The kidneys are microscopically normal and recover if the underlying liver diseases are eliminated. HRS is divided into two categories: type 1 and 2.

Type 1 HRS is characterised by rapidly progressive renal failure, with a sharp rise in plasma creatinine to more than 200 µmol per litre or a fall in creatinine clearance to less than 20 ml per minute.

Type 2 HRS is characterised by a slower deterioration in renal function and is not associated with acute liver failure. The diagnosis of HRS can only be made with the exclusion of other causes of renal failure. The occurrence of HRS is a poor prognostic sign and has an associated mortality of 50–100 per cent depending on the aetiology of the underlying liver disease.

The marked circulatory changes in ALF are the most likely underlying pathogenesis of HRS. The relative hypovolaemia and hypotension causes activation of the angiotensin-renin-aldosterone axis, increased vasopressin release, production of local renal vasoconstrictors and increased sympathetic nervous system activity, all of which tend to reduce renal blood flow and perfusion and lead to the development of HRS. 46

Management Managing HRS is difficult and outcome ultimately resides in reversing the underlying liver disease. Despite the reliance on an improvement of the liver dysfunction to promote renal recovery in HRS, co-existent causes of renal dysfunction should be actively sought. Hypovolaemia should be corrected and blood pressure maintained (with or without the use of pressor agents) to provide adequate renal perfusion. All nephrotoxic medication should be stopped and a thorough search made for a septic focus by culture of blood, urine and ascitic fluid. The patient should be started on broad spectrum antibiotics until the results of the cultures are known, when the antibiotic regimen can be tailored appropriately.

Attempts to prevent the progression of the hepatorenal syndrome or multiple organ failure on the background of sepsis have involved a range of pharmacological agents. 47,48 These have included dopamine, 49–51 terlipresin, 52–54 N-acetylcysteine, 55 and octreotide, 56,57 with varying degrees of benefit. However, it is important to note that the trials have, in the main, been undertaken in patients with underlying chronic liver disease and predominantly consist of small study cohorts. Although it is encouraging that benefits have been reported with these drugs, it is difficult to extrapolate these results to ALF. Another interesting observation is the potential for terlipresin to maintain renal function. Larger studies in patients with ALF are required before firm conclusions can be drawn and treatment recommendations offered. 58,59

Sepsis

Many of the systemic manifestations of ALF are analogous to those observed in septicemic shock. In fact, the incidence of sepsis in ALF is also high, with bacterial infections occurring in approximately 80 per cent of patients and fungal infection (predominantly candidiasis) in 32 per cent. 60

ALF renders the patient susceptible to infection due to low complement levels, reduced neutrophil phagocytosis, impaired superoxide and hydrogen peroxide production, and the increased translocation of gut organisms across the bowel mucosa. 61

Patients requiring endotracheal intubations are at greater risk of developing respiratory system sepsis (which accounts for about 50 per cent of infective episodes). A perplexing observation is the lack of cardinal signs of sepsis, (that is, elevated white cell count and pyrexia) in up to 30 per cent of cases.

Management Prophylactic intravenous antibiotics have been demonstrated to reduce the incidence of infective episodes but have not translated into reduced mortality or reduced length of stay in an intensive care setting. Use of selective decontamination of the gastrointestinal tract to reduce the risk of translocation of gut flora has no

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additional benefit to prophylactic antibiotics alone. The emergence of multiresistant organisms has potentially major implications for future management both of ALF and patients in intensive care units.

Whether the development of new antibiotics will keep pace with neo-resistance remains to be seen, but in the meantime prudent antibiotic usage both in hospitals and in the community is warranted. The “old-fashioned” methods of reducing spread between patients such as regular hand washing by staff also have a place in preventing infection. More inventive strategies to address the resistance issue may include novel treatments such as introducing a bacteriophage specifically to target the resistant organism.

Poor neutrophil function is undoubtedly a significant contributor to the risk of sepsis and improvement in function has been described with the use of granulocyte colony-stimulating factor, but whether this translates into reduced septic episodes and improved survival is unclear at present.76,77

### NUTRITIONAL DEFECTS

Two hallmarks of ALF are hypoglycaemia and a high catabolic rate. To manage both of these complications, enteral nutrition with a high protein content should be instituted early via the nasogastric or naso-jejunal route. Despite adequate calorific intake, significant hypoglycaemia can develop, necessitating intravenous glucose infusions.

Electrolyte levels also need to be monitored, since hypomagnesaemia, hypokalaemia and hypophosphataemia are all common in ALF.

### THE FUTURE

Progress has undoubtedly been made in the management of ALF; with higher survival rates linked to improved intensive care management and the development of liver transplantation. The ongoing development of artificial devices will continue to increase survival rates.

Potentially, the greatest influence on outcomes in ALF will be the expanding field of molecular biology. For example, the observation of the involvement of Fas ligand expression and the serum levels of soluble Fas may offer future treatment options with either monoclonal antibodies, soluble ligand infusion, nuclease acids, or combinations of these agents.78,79 Insight into their potential was glimpsed with description of the prevention of ALF in an animal model with prior treatment of anti-Fas antisense oligonucleotides.80 As the basic molecular mechanisms involved in the pathophysiology of ALF are teased out, it is still possible to interfere directly with these processes. This interference, along with the expanding field of stem cell technology and the recognition of the trans–differentiation potential of these cells, offer innumerable possibilities.

Another interesting report has demonstrated improved survival in septicemic shock patients with the use of activated protein C. Whether this will be equally effective in ALF patients remains to be seen. The prevention of multi-organ failure in hepatocellular rat treated with activated protein C does offer some hope for this form of treatment.72

### REFERENCES

HOSPITAL PHARMACIST