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REVIEW

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Clinical management of acute hepatic failure

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Abstract Acute hepatic failure is a rare clinical syndrome associated with high mortality. Hepatic failure leads to a well-recognised pattern of clinical signs and symptoms, sometimes with rapid deterioration and progression to multi-organ failure. Early recognition of this syndrome is essential for appropriate treatment; once identified, patients benefit from early interventional support and treatment in the intensive care unit. Aggressive management may allow stabilisation of patients before their transfer to specialist liver units. At present, orthotopic liver transplantation is the only treatment modality that provides significant improvement in outcome. This review examines the aetiology and clinical presentation of acute hepatic failure, providing guidelines regarding patient management. We present a critical appraisal of specific clinical areas, including the management of cardiovascular, cerebral, renal, coagulopathic and infective complications. Liver transplantation is discussed as well as emerging therapies including *non-biological* and *hybrid* liver support systems that may provide a "bridge to transplantation".

Key words Liver failure · Hepatic failure · Cerebral · Hepatorenal · Transplantation · Bioartificial

Introduction

The management of acute hepatic failure (AHF) remains a challenge. Both acute and chronic hepatic failure may present difficult clinical scenarios and problems that are associated with high morbidity and mortality. Jaundice, hepatic encephalopathy and coagulopathy were described by Trey and Davidson [1] who introduced the terms *fulminant* and *sub-fulminant* hepatic failure. Advances in intensive care unit (ICU) monitoring, management and pharmacological therapy have made a significant impact on survival. Currently, liver transplantation remains the only definitive treatment for patients who fail supportive care management and who meet the appropriate criteria. Improved techniques and immunosuppressive regimens have improved long-term survival post-transplantation, although organ availability remains a limiting factor. Artificial liver support aims to provide a "bridge to transplantation" and is currently under investigation, although its usefulness remains to be proved.

Definitions

O'Grady et al. [2] introduced a robust and functional classification incorporating factors such as aetiology clinical pattern and prognosis. They divided AHF into three sub-groups: *hyperacute*, *acute*, and *subacute*. Hyperacute describes those patients who develop encephalopathy within 7 days of the onset of jaundice (survival 36%). Acute liver failure describes patients who develop encephalopathy 8–28 days after the onset of jaundice (survival 7%). Subacute describes the onset of encephalopathy 5–26 weeks after the onset of jaundice (survival 14%).

Aetiology

Drugs may induce hepatic failure in a dose-dependent manner (e.g. paracetamol) or through an idiosyncratic drug reaction (e.g. halothane). Paracetamol overdose remains the leading cause of AHF in the United Kingdom, comprising up to 50–60 % of all referrals [3]. Other drugs that cause AHF include monoamine oxidase inhibitors, anti-inflammatory drugs, gold, sodium valproate, cotrimoxazole, sulphonamides and disulphiram. The global increase in tuberculosis has led to an increasing incidence of AHF related to isoniazid, rifampicin and pyrazinamide [4].

On a worldwide basis the hepatitis B virus remains the leading cause of AHF, followed by non-A non-B hepatitis. This describes a clinical presentation similar to a viral cause but without an identifiable pathogen. Hepatitis A virus is less common and carries a 70 % survival rate. Hepatitis C infection remains a rare cause in the western world while hepatitis E virus may complicate the third trimester of pregnancy and is more frequently reported in Asia [5].

Acute fatty liver of pregnancy, the syndrome of haemolysis, abnormal liver enzymes and low platelets, pre-eclampsia, hepatic rupture and/or hepatic infarction may lead to AHF, requiring early delivery of the foetus, supportive care, and even transplantation for the mother [6]. Hypercoagulable conditions and pro-coagulant disorders range from small vessel veno-occlusive disease to hepatic vein thrombosis (e.g. Budd-Chiari syndrome). Metabolic disorders, for example, Wilson's disease, may occur with non-specific symptoms. The increasing use of recreational drugs such as cocaine and ecstasy has been associated with AHF [7]. Other less frequent causes include ischaemic hepatitis, lymphoma, malignant infiltration, sepsis, ingestion of *Amanita phalloides* and, rarely, autoimmune chronic hepatitis [8].

Clinical syndrome

Initial presentation may be with non-specific symptoms such as nausea, vomiting, abdominal pain, dehydration and jaundice. A thorough history should examine all travel, sexual, social and drug aspects. Full clinical examination, specifically looking for stigmata of chronic liver disease, evidence of drug abuse and careful assessment of neurological status should take place. The patient's clinical condition should be monitored regularly, including frequent observations of vital signs, blood glucose and neurological status.

Full blood count, biochemical, haematological, immunological, microbiological (viral hepatitis screen, including core antibody status for hepatitis B) and toxic drug screens should be undertaken, including arterial blood gas and blood lactate analysis to assess metabolic disturbance. Further investigations may include abdominal ultrasound, paying particular interest to hepatic and portal venous flow patterns. Spiral computed tomography allows rapid evaluation of the hepato-biliary anatomy; hepatic volume measurements have been used as indicators for the need for transplantation

Blood analysis for paracetamol should be interpreted with extreme caution. The use of nomograms in the decision to treat or not treat borderline cases with *N*-acetylcysteine (NAC) must be influenced by several factors: an accurate/inaccurate history from the patient, degree of malnourishment, presence of chronic alcohol abuse, and concurrent use of drugs that induce hepatic enzymes [9]. In the case of paracetamol overdose the commencement of NAC is recommended prior to obtaining blood levels. Patients who already display symptoms of AHF may have no detectable paracetamol in their blood as this is often cleared before symptoms appear. By contrast, patients developing encephalopathy within 24 h of paracetamol consumption should have other cause for encephalopathy excluded.

All abnormal blood results should be discussed with senior colleagues, if not with a specialist centre for liver transplantation. Any deterioration in the patient's condition may warrant urgent referral. Worsening hepatic encephalopathy, metabolic acidosis, and hypoglycaemia in the presence of a coagulopathy and/or renal failure requires urgent transfer to a specialist unit. As deterioration is often rapid, patients should be sedated and intubated if they deteriorate to grade III encephalopathy. Particular attention should be paid to the prothrombin time and to renal function, both of which are prognostic markers (see the criteria for liver transplantation, below).

Patients may present in incipient or full-blown AHF, manifesting with severe metabolic acidosis, profound hypoglycaemia, marked coagulopathy and hepatic coma. Patient stabilisation requires resuscitation, mechanical ventilation, haemodynamic and/or renal support, and urgent liaison and transfer to a transplant centre [10]. These patients require specialist intensive care, as demonstrated by a 20 % reduction in mortality due to improved ICU facilities and advances in pharmacological treatment. Early identification of worsening prognostic indicators may improve survival with early intervention [11].

Encephalopathy

Hepatic encephalopathy results from failure of biotransformation and excretion of toxins normally processed by the liver. Raised plasma ammonia levels have been implicated; however, other chemicals involved include mercaptans, fatty acids, aromatic chain amino acids, benzodiazepine-like substances, γ-aminobutyric

acid, glutamate [12] and toxic metals (e.g. zinc, copper, manganese). Complex changes in blood-brain barrier permeability may also contribute [13].

Hepatic encephalopathy is classified as grades I–IV, describing the progression from normal mentation to hepatic coma [14]. The grades of hepatic encephalopathy and the common clinical features are as follows:

- I: slow mentation
- II: inappropriate disinhibited behaviour (agitation, aggression and drowsiness)
- III: somnolence
- IV: coma

Grade I/II encephalopathy has a better prognosis than those progressing to grade III/IV encephalopathy, in whom development of cerebral oedema is more frequent. Elective intubation and ventilation is undertaken when patients progress to grades II–III and become unmanageable. Unexplained cerebral deterioration may also be explained by clinical or sub-clinical epileptiform activity; this may require treatment with phenytoin or other agents such as thiopentone. The incidence of cerebral oedema in patients with chronic liver disease is less frequent.

Cerebral oedema

Patients with grade IV encephalopathy risk developing cerebral oedema (80 %) and raised intracranial pressure (ICP), the primary cause of death [15]. Clinical signs of raised ICP include systemic hypertension, bradycardia, pupillary abnormalities, decerebrate posturing, epileptiform activity, and brainstem respiratory patterns.

Disruption of complex relationships involving brain metabolism, tissue and microcirculatory autoregulation, neurotransmission and blood-brain barrier integrity contribute to cerebral oedema and raised ICP [16]. These changes lead to reduced metabolite removal, accumulation of osmolytes and increased local cytokine release. One case report describes successful treatment of cerebral oedema with indomethacin, supporting the role of vasogenic autoregulation in the pathogenesis [17]. The advent of cyclo-oxygenase 2 inhibitors may prove therapeutically useful in the treatment of raised ICP.

Wendon et al. [18] measured cerebral blood flow (CBF) and cerebral metabolic rate for oxygen ($CMRO_2$) in 30 AHF patients in grade IV encephalopathy. CBF varied widely, from 14 to 71 ml 100 g^{-1} min^{-1} (normal range: 41–66 ml 100 g^{-1} min^{-1}), whereas $CMRO_2$ was consistently low at 0.16–2.03 ml 100 g^{-1} min^{-1} (normal range: 3.12–3.96 ml 100 g^{-1} min^{-1}). Of the 30 patients 21 had increased cerebral lactate production. Increases in CBF and $CMRO_2$ and a decrease in cerebral lactate production have been recorded in patients infused with NAC and prostacyclin. This may be explained by augmentation of microcirculatory perfusion and oxygen delivery, leading to reduction in tissue hypoxia, free radical generation and cytokine release.

Management of cerebral oedema

Patients at risk of cerebral oedema (AHF grades III/IV) are electively sedated, intubated and mechanically ventilated, all helping to reduce cerebral irritation. This allows monitoring and optimises further management. Davenport et al. [19] suggested that 30° head elevation provides optimal cerebral perfusion pressure [CPP (mmHg) = MAP (mean arterial pressure) – ICP]. Patients with cerebral oedema benefit from minimal intervention (physiotherapy, suction through the endotracheal tube) and a quiet environment; however, a compromise between the risk and benefit of these procedures should be exercised.

Monitoring

Improved survival in AHF has been achieved by close monitoring, reduction in ICP, and supportive treatment on specialist units. In experienced hands, to monitor ICP, intracranial transducers may be placed in brain parenchyma, subdural or extradural spaces. Epidural devices have lower complication rate (3.8 %) than subdural bolts (20 %) or parenchymal monitors (22 %) [20]. Non-invasive monitoring of ICP and cerebral lactate with computed tomography, transcranial Doppler, positive-emission tomography and magnetic resonance imaging has proved relatively insensitive to fluctuations in ICP [21].

A raised ICP and a prolonged CPP below 50 mmHg, or an ICP above 40 mmHg, are associated with poor neurological recovery in AHF patients [22]. It is desirable to maintain ICP lower than 20 mmHg and CPP higher than 60 mmHg. Some regard a CPP below 40 mmHg for longer than 1 h as a contraindication to liver transplantation. However, Davies et al. [23] reported four AHF patients making full neurological recovery following prolonged intracranial hypertension (> 35 mmHg for 24–38 h) and impaired cerebral perfusion pressures refractory to standard therapy.

The *jugular venous bulb saturation* is measured by sampling from an indwelling catheter sited in the jugular bulb. This may be used to determine oxygen utilisation by the brain. Low venous saturations in AHF patients may reflect a reduction in CPP with or without increased oxygen utilisation, for example, due to epileptifom activity. Alternatively, jugular saturations may be greater than mixed venous saturations suggesting hyper-

aemia, ischaemia and/or failure of oxygen utilisation [24].

Treatment

Raised ICP is initially treated with *mannitol*, an osmotic diuretic that reduces brain water and decreases ICP. Clinical trials on AHF patients with intracranial hypertension have demonstrated mortality reduction [18]. It may be given as repeated boluses but its use is limited by the need to keep serum osmolality below 320 mOsm/l. It may be used in anuric renal failure when adequate renal replacement therapy has been initiated [18, 25].

Thiopentone, a barbiturate agent used as an anticonvulsant in the treatment of status epilepticus, has been used in mannitol-resistant cases in which CBF remains satisfactory. It is thought to cause cerebral vasoconstriction, reducing brain hyperaemia and $CMRO_2$. It may also act as an antioxidant and an anticonvulsant. Side effects include precipitous hypotension that may require fluid resuscitation and inotropic support [26].

Hyperventilation reduces carbon dioxide tension and ICP in patients with head injuries and AHF. Wendon et al. [18] compared the effects of hyperventilation, mannitol, NAC and prostacyclin in the treatment of raised ICP in patients with AHF. Hyperventilation resulted in a significant decrease in both CBF (median 36–28 ml 100 g^{-1} min^{-1}) and $CMRO_2$ (median 0.92–0.65 ml 100 g^{-1} min^{-1}), and thus a corresponding increase in cerebral lactate production. Prostacyclin infusion did not significantly alter CBF but produced a significant increase in $CMRO_2$. However, mannitol and NAC infusions resulted in significant increases in both CBF and $CMRO_2$. Thus mannitol is the recommended treatment for raised ICP in AHF.

In contrast, Strauss et al. [27, 28] assessed CBF autoregulation in seven AHF patients using transcranial Doppler measurement of mean flow velocity (V_{mean}) in the middle cerebral artery. After 15 min hyperventilation five of the seven patients had restored cerebral autoregulation, supporting the role of hyperventilation as a therapeutic modality. The use of hyperventilation remains controversial, although it may have a role in short-term management, closely guided by jugular venous saturations.

Moderate hypothermia was successful in maintaining four AHF patients, with raised ICP resistant to treatment with mannitol and ultrafiltration, until transplantation [29]. This involved cooling them to a core temperature of 32–33 °C for a mean of 13 h. ICP was reduced from 45 mmHg (25–49) to 16 mmHg (13–17), CBF decreased from 103 ml 100 g^{-1} min^{-1} (25–134) to 44 ml 100 g^{-1} min^{-1} (24–75). Corresponding changes were also seen in the CPP which increased from 45 mmHg (37–56) to 70 mmHg (60–78). Arterial ammonia levels and cerebral uptake of ammonia were also reduced with cooling. This technique successfully reduced cerebral oedema, providing a bridge to transplantation.

Prolonged treatment-resistant intracranial hypertension has led, *in extremis,* to total hepatectomy and portacaval shunt insertion. The successfully reduced ICP and improved haemodynamic stability, however, obviously limit patient survival unless transplantation takes place within 12–24 h [30].

Coagulopathy

The normal liver is responsible for the synthesis of several clotting factors involved in the clotting cascade. In AHF decreased production and increased consumption of these factors and their inhibitors is also associated with platelet abnormalities. The prothrombin time is an important prognostic indicator therefore correction by administration of vitamin K and/or fresh-frozen plasma is discouraged unless patients are haemodynamically unstable or actively haemorrhaging. Factor V is used in France as a prognostic marker in AHF and is useful if prothrombin abnormalities have been corrected [31].

Haemorrhage from oesophageal, gastric, rectal and peritoneal varices complicated by coagulopathy results in high mortality. This is seen more frequently in patients with chronic liver disease, with gastric erosions being more common in AHF. Morbidity and mortality have been reduced with acid suppression regimens, including H_2-antagonists, proton pump inhibitors and sucralfate. The use of these pharmacological agents is encouraged upon patient admission, regardless of whether they are actively bleeding [32].

The systemic circulation

Nausea, vomiting and loss of appetite are part of the prodrome of AHF. Patients may present with severe dehydration. Loss of autoregulation of vasogenic tone, and reduction in systemic vascular resistance is characteristic of AHF, resulting in vasodilatation and systemic hypotension associated with an increased cardiac output. Reduction in intravascular volume leads to decreased tissue perfusion exacerbated by small vessel occlusion and the development of shunts [33, 34]. Oxygen delivery increases, but the oxygen extraction ratio and oxygen consumption decrease, resulting in tissue hypoxia, increased anaerobic metabolism and lactic acid accumulation (normally metabolised by the liver). This series of physiological changes may be complicated by sepsis, gastrointestinal bleeding and dysrhythmias. Poor tissue perfusion exacerbates hepatic injury, activating Kupffer cells which increase release of cytokines, free radicals

and reactive oxygen species. Studies have demonstrated increased local concentrations of platelet activating factor, tumour necrosis factor-α, interleukin-1α and nitric oxide [35].

Keays et al. [36] demonstrated improved survival in patients given the antidote NAC after paracetamol overdose. Paracetamol is metabolised in the liver generating a toxic metabolite that is normally bound to cellular glutathione. Depletion of glutathione leads to free radical induced hepatic necrosis. NAC acts as a glutathione donor, replenishing depleted stores and neutralising the toxic metabolite, thereby reducing hepatic damage. The administration of NAC in AHF was shown to improve oxygen delivery, oxygen consumption, haemodynamic parameters, the incidence of cerebral oedema and survival, even in those who received late administration [37]. However, more recently, contrasting data suggest that NAC does not improve oxygen consumption [38].

Management of the systemic circulation

Appropriate monitoring is required to maintain adequate central venous pressures (8–10 cmH_2O). The use of human albumin solutions is controversial, and therefore other colloidal fluids may be used and complemented with crystalloid to resuscitate patients [39]. In contrast to established practice, recent studies have indicated an association between maintaining adequate serum sodium levels and a reduction in the incidence of cerebral oedema in AHF [40]. Hypotension (MAP < 60 mmHg) requires the use of inotropic or pressor support, arterial pressure monitoring and either pulmonary artery catheterisation or alternative, less invasive, monitoring [41].

The hypotension and vasodilatation associated with AHF are sensitive to peripheral α-receptor agonists, thus supporting the use of epinephrine and norepinephrine [42]. Norepinephrine, although commonly used, may increase arteriolar vasoconstriction and profoundly reduce microcirculatory delivery and oxygen utilisation. In an animal study this caused significant architectural damage to mitochondria and endoplasmic reticulum [43]. Reduced oxygen utilisation may be offset by the concurrent use of prostacyclin, which reduces platelet clumping, promotes fibrinolysis, and decreases postcapillary tone.

Clinical studies demonstrate benefit from the concurrent use of dopexamine, a drug with dopaminergic receptor agonist activity and β_2-adrenergic effects. Dopexamine increases splanchnic and renal blood flow and improves oxygen delivery [44]. In addition, it has an anti-inflammatory effect and may attenuate leucocyte adherence to the splanchnic bed microvasculature [45].

Renal failure

The reported incidence of renal failure in AHF varies from 40% to 85%. Causes include pre-renal failure due to volume depletion, renal ischaemia, acute tubular necrosis (e.g. paracetamol) and hepatorenal syndrome (common among patients with chronic liver disease). Following paracetamol overdose, renal failure may occur in the absence of AHF and has a good prognosis. In non-paracetamol cases the incidence of renal failure is usually accompanied by worsening encephalopathy and is associated with a poor outcome.

The pathophysiology of AHF-associated renal failure is complex. The reduction in systemic vascular resistance and MAP affects the pressure-dependent part of the autoregulatory curve of renal blood flow, resulting in renal hypoperfusion. Homeostatic mechanisms fail to correct and restore afferent pressures with the release of hormones (e.g. aldosterone, norepinephrine and vasopressin) and other vasoconstrictors [46]. Increased levels of arginine, vasopressin, endothelin, eicosanoids, and cysteinyl leukotrienes have been demonstrated in cirrhotic patients with hepatorenal syndrome [47].

Management of renal failure

Oliguria requires resuscitation using central venous monitoring. Fluid challenge to elevate central venous pressure and ensure adequate filling is an essential step in assessing oliguria. The use of low-dose ("renal dose") *dopamine* infusion (1–3 $\mu g\ kg^{-1}\ min^{-1}$) in acute renal failure management is controversial [48]. Dopamine increases glomerular filtration rate, sodium excretion, and renal plasma flow in healthy human subjects and in animal models of acute renal failure. At low dose it is an agonist of β_1 and dopamine 1 and 2. More specific dopamine agonists are presently being tested [49]. In hepatorenal syndrome associated with cirrhosis the use of splanchnic vasoconstrictors, notably terlipressin, appears much more promising and has reversed deteriorating renal function [50].

Studies of *loop diuretics* are largely retrospective, anecdotal and poorly controlled. Shilliday et al. [51] performed a prospective, randomised, placebo-controlled, double-blind study examining the effect of loop diuretics on renal recovery, dialysis, and death in 92 patients with ARF. Patients given a loop diuretic had a significantly higher in urine flow rate in the first 24 h than those receiving placebo ($p = 0.02$) but no improvement in outcome. Their use in AHF remains controversial.

Anuria, acidosis, hyperkalaemia, hyponatraemia, fluid overload and a rising creatinine requires renal support. Conventional haemodialysis may cause volume and electrolyte shifts that exacerbate cerebral oedema.

Continuous veno-venous haemofiltration is preferred, offering haemodynamic stability and allowing predictable and gradual control of any metabolic disturbance [52]. The substitution solution may be lactate free, bicarbonate buffered, or acetate as dictated by acid-base homeostasis. Anticoagulation of circuits may be performed using heparin, low molecular weight heparin, or prostacyclin if thrombocytopenia exists. Beneficial effects include immunomodulation with removal of vasoactive substances from the circulation, including immunoglobulins, interleukin-1, interleukin-6, tumour necrosis factor-α, C1q, C3a, C5a and platelet-activating factor. Bellomo et al. [53, 54] described improved survival in animal and clinical studies in sepsis using high volume exchange; similar studies have shown a reduced requirement for inotropic support in AHF. Adverse effects of these systems include complement activation, activation of the coagulation cascade and release of vasoactive and chemoattractant fragments.

Infection

The liver is the site of complement synthesis. Low levels of C3a and C5a have been reported in AHF of various causes. Reduced complement has been associated with impaired opsonisation of yeast and bacteria. Polymorphonuclear cells have poor killing ability due to reduced superoxide and free radical generation, while impaired phagocytosis and reduced cytokine production by Kupffer cells reduces clearance of endotoxin and other gut-derived toxins from the portal circulation. High concentrations of endotoxin, tumour necrosis factor-α and interleukin-6 have been shown to be correlated with increased encephalopathy and mortality [55].

Rolando et al. [56] demonstrated 50% incidence of pneumonic episodes, 26% bacteraemias, and 22% urinary tract infections in patients with AHF. Gram-positive infection was most common, with *Staphylococcus aureus* infection in 70% of pneumonias. *Eschericia coli* caused most urinary tract infections. The incidence of multi-resistant bacteria, methicillin-resistant *S. aureus*, vancomycin-resistant *S. aureus*, vancomycin-resistant *Enterococcus* and multi-resistant *Acinobacter* has increased.

Immunosuppression in AHF leads to a 30% incidence of fungal septicaemia, predominantly *Candida albicans*. Presentation is often late and is associated with renal failure. Clinical suspicion should remain high as many patients may be neutropenic and unable to mount a leukocytosis and/or pyrexic response [57]. AHF patients are subject to extensive instrumentation; early use of guided broad-spectrum therapy, including the use of anti-fungal regimens, is advocated [57].

Enteral nutrition via a nasogastric or naso-jejunal tube offers optimal delivery of nutrition. The use of immunomodulatory feeding regimens (containing arginine, taurine and ω-fatty acids) have led to reductions in episodes of sepsis, reduced ventilator days and shorter post-operative recovery times in general ICU patients [58] although benefits in AHF patients have still to be specifically addressed.

Liver transplantation

The definitive treatment for a patient in AHF who has met the recognised criteria for transplantation is an orthotopic liver transplant (OLT). This was first performed by Starzl et al. [59]. Before 1980 the 1-year survival post-OLT was 30–50%; this can be compared to a 80–90% 1-year survival and more than 70% 5-year survival by the 1990s [60]. By 1994, 1,821 transplants (median age 32.5 years) had been registered with the European Liver Transplant Registry; of these AHF represented 8–11%. The 1-year and 5-year survival rates were 60% and 55%, respectively [60]. Recent data from the United States also report 70% survival after 1-year, decreasing to 60% graft survival by 3 years [61].

Patient selection

Unsuitable patient selection will reduce the already diminished pool of organs for transplantation. The King's College Hospital criteria [62] were identified following the analysis of 588 patient records with AHF of various causes between 1973 and 1985. They have a positive predictive value of 0.98, negative predictive value of 0.82 and an accuracy of 0.82. Recent re-evaluation of these criteria suggests that the predictive value is lower [63]. The King's College Liver Unit criteria for liver transplantation are as follows:

Paracetamol-induced hepatic failure:
- Arterial blood pH < 7.3 (irrespective of grade of encephalopathy)
- Otherwise, *all* three of the following criteria:
  - Prothrombin time > 100 s
  - Serum creatinine > 300 μmol/l
  - Grade III/IV encephalopathy

Non-paracetamol-induced hepatic failure:
- Prothrombin time > 100 s
- Otherwise, *any* three of the following criteria (irrespective of grade of encephalopathy):
  - Drug induced, non-A/non-B halothane hepatitis
  - Jaundice > 7 days before encephalopathy
  - Age < 10 or > 40 years
  - Prothrombin time > 50 s
  - Serum bilirubin > 300 μmol/l

Contraindications to OLT include raised ICP in cases in which neurological damage is suspected, refractory hypotension, overwhelming sepsis, acquired immunodeficiency syndrome and advanced cardiopulmonary disease. Psychiatric illness, human immunodeficiency virus positivity, active alcohol and substance abuse, portal venous thrombosis, pulmonary hypertension, cholangiocarcinoma and age over 70 years are relative contraindications that will be assessed by the transplanting centre.

Auxiliary partial orthotopic liver transplantation

The novel regenerative capacity of the liver and the lack of donor organ availability formed the platform for the development of auxiliary partial orthotopic liver transplantation. Partial resection of the host liver followed by transplantation of a reduced size donor graft is performed. This performs normal functions while the host organ regenerates. Immuno-suppression may then be withdrawn and the graft allowed to atrophy as a result of acute or chronic rejection [64, 65]. Chenard-Neu et al. [66] demonstrated an overall survival rate of 63 % after a 3- to 67-month follow- up; 13 of 19 patients had immunosuppression withdrawn with full recovery.

Artificial liver support

The role of hepatic support

AHF leads to deranged intracellular metabolism, failure of interconversion of carbohydrates, lipids, amino acids, synthesis of plasma proteins, coagulation factors and lipoproteins, and is associated with loss of detoxification and biotransformation. The role of artificial hepatic support is therefore complex. Ideally, hepatic support should prevent or halt acceleration of the cytokine cascade, provide metabolic, synthetic and detoxicating functions while allowing time for organ regeneration. Where this is not possible, hepatic support may provide a "bridge to transplantation".

Non-biological hepatic support

Technology initially developed and used successfully for the treatment of renal failure has been applied to AHF. *Haemodialysis* and the use of adsorbents have been shown to be ineffective in AHF. The molecular adsorbents recirculating system [67], an adaptation of haemodialysis, was introduced in 1993 and incorporates a polysulphone membrane impregnated on both sides with albumin. Clinical studies have demonstrated improved parameters (encephalopathy and renal function) which parallels reductions in bilirubin, urea, and creatinine in patients with chronic liver disease. *High-flow haemofiltration* is currently the subject of investigation following encouraging in vivo studies in sepsis and AHF, respectively [53, 54]

Plasma exchange and plasmapheresis involve removal of toxic plasma and replacement with plasma from healthy individuals. Large controlled studies have demonstrated improved haemodynamic parameters, reduced cerebral oedema and prolonged survival in those awaiting OLT [68].

Hybrid hepatic support

Hybrid hepatic support combines the use of biological tissue with the use of non-biological materials. The hybrid systems are dependent on a hepatocyte component (human and xenogeneic), matrix support (extracellular matrix, co-culture, and three-dimensional cell culture) and, finally, bioreactor design (optimal oxygenation, toxin removal, and blood/plasma flow). Two systems have been used clinically: the bioartificial liver and the extracorporeal liver-assist device. Although conceptually very similar, there are three major differences: the cell source, namely cryopreserved primary pig hepatocytes attached to collagen-coated dextran microcarriers; the perfusate, which is plasma rather than blood; and the presence of a charcoal column filtering the plasma prior to its entry to the bioreactor [69]. The results of clinical trials are presented in Table 1.

The extra-corporeal liver-assist device incorporates the C3A cell line [70]. This is a highly differentiated clonal population isolated from a human hepatoblastoma cell line (HepG2). Cells (200 g) were originally seeded and grown in the extracapillary space of a haemodialysis cartridge containing approximately 10,000 hollow fibres with a surface area of 2 m^2 and perfused with whole blood. The device has since been modified, now being perfused with the patient's plasma, while the cartridge contains a greater number of hepatocytes. Results of the single clinical trial are shown in Table 1.

In conclusion, these results demonstrate biocompatibility, some detoxification, no synthetic function, and possible survival benefit. However, no randomised controlled trials have successfully demonstrated this.

Hepatocyte transplantation

The clinical use of hepatocyte transplantation has been limited and small studies have been reported. Soriano et al. [71] reported three children in AHF who were treated with intraportal injection of cryopreserved hepatocytes taken from unused donor segments. One child survived and some biochemical parameters improved post-transplantation. Bilir et al. [72] demonstrated im-

Table 1 Clinical trials of bioartificial liver and extra-corporeal liver-assist devices for hybrid hepatic support. Bioartificial liver: plasma-perfused cryopreserved pig hepatocytes (6×10^9) attached to dextran-coated microcarrier beads packed into extracapillary space of a hollow fibre bioreactor; extra-corporeal liver-assist device: blood perfused 200 g C3A hepatoblastoma cells in attachment culture on outer surface of hollow fibre membranes

	Patients	Outcome	Morbidity and mortality
Bioartificial liver device			
Chen et al. [74]	Group 1: $n = 12$, AHF	Improved ICP, CPP; improved NH_3, bilirubin and glucose	12 patients survived to OLT
	Group 2: $n = 8$, chronics		6/8 patients died
Watanabe et al. [75]	Group 1: $n = 18$, AHF	Improved ICP, CPP; improved NH_3, bilirubin and glucose	16/18 patients to OLT
	Group 2: $n = 3$, primary graft non-function		3 patients to OLT
	Group 3: $n = 10$, chronics		2 patients to OLT
Extra-corporeal liver-assist device			
Ellis et al. [76]	Group 1: $n = 9$, 50 % chance of survival on admission (controls, $n = 5$)	1 patient decreased ICP; galactose elimination after the first 6 h not different between groups, as was NH_3	8/9 patients (89 %) survived; 4/5 controls (80 %) survived
	Group 2: $n = 3$, met criteria for OLT on admission (controls, $n = 3$)	Factor V levels and arterial ketone body ratios	1/3 patients (33 %) survived; 1/3 controls (33 %) survived

proved encephalopathy, and decreased serum ammonia and prothrombin times following percutaneous cryopreserved human hepatocyte transplantation in three patients. Strom et al. [73] reports a prospective controlled trial of transplanted isolated fresh and cryopreserved human hepatocytes as a bridge to transplantation. Those receiving hepatocyte transplants maintained normal cerebral perfusion and haemodynamic stability with significant reductions in blood ammonia and liver injury markers. All were transplanted within 2–10 days.

Conclusion

AHF carries a high mortality. Raised awareness has increased the proactive care of these patients while the development of specialist centres allows for early transfer. Improved monitoring, continuing new developments in multi-organ support and improved intensive care nursing and multi-disciplinary patient management have significantly reduced mortality. Liver transplantation has progressed from offering little hope to now offering every hope to individuals. The concurrent refinement of surgical techniques and development of immunosuppressive pharmacological agents has taken 5-year survival to greater than 70 % in a 30-year period. Auxiliary partial orthotopic liver transplantation may offer full recovery with only a short time dependency on immunosuppressive medication; recent trials indicate that even those having had OLT may expect to withdraw from medication after a number of years.

We are now seeing more novel therapeutic approaches to AHF. Hybrid hepatic support has been applied clinically and the results show reason for optimism. A large multi-centre trial of the bioartificial liver device is awaited; however, the results will have to be interpreted with caution. Differences in classification, aetiology and availability of specialist care and organs cannot be corrected for. Several other confounding factors will also complicate the results. Hepatocyte transplantation still appears to be in its infancy; however, greater understanding of cell biology coupled with advances in biotechnology are allowing improved hepatocyte delivery and effective cellular function following transplantation.

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