Fulminant Hepatic Failure

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Current Treatment Options in Gastroenterology 2005, **8:**503–518
Current Science Inc. ISSN 1092–8472

Opinion statement

The rare but potentially devastating clinical syndrome of fulminant hepatic failure has as its components severe encephalopathy and finally cerebral edema, hemodynamic instability, renal failure, coagulopathy, profound metabolic disturbances and a particular susceptibility to bacterial and fungal infection. Despite advances in medical management, fulminant hepatic failure in its most severe form carries a high mortality rate unless urgent orthotopic liver transplantation is carried out. However, availability of cadaveric donor organs is limited and, due to the rapidly progressive clinical course in many cases, a substantial proportion of patients will die or develop contraindications to transplantation before the procedure can be performed. Consequently, recent interest has centred on living donor transplantation and the possibility of providing temporary liver support, either through auxiliary partial organ transplantation, extracorporeal perfusion or transplantation of hepatocytes, to allow time for either a liver graft to become available or native liver regeneration, on which spontaneous survival ultimately depends, to occur.

Introduction

Management strategies for fulminant hepatic failure (FHF), a rare but potentially devastating disorder defined by the presence of hepatic encephalopathy as the consequence of severe liver injury in patients without pre-existing overt liver disease, must take into account both specific treatments for the initiating drug, viral, or other cause and supportive measures to reverse components of the resultant clinical syndrome. The latter includes not only profound metabolic disturbance and coagulopathy but also hemodynamic instability, cerebral edema, renal failure, and susceptibility to infection. Accumulation of toxins such as ammonia and lactate, along with deleterious effects of vasoactive cytokines produced in response to the initiating cause of liver injury and/or complicating sepsis, contribute to the development of multiorgan dysfunction in FHF. The severity and duration of the clinical syndromes of FHF in individual patients are determined by the extent to which impairment of the liver's various metabolic and toxin-scavenging functions can be counterbalanced by liver cell regeneration, without which spontaneous recovery cannot occur.

Despite advances in supportive measures, FHF in its most severe form continues to carry a high mortality rate unless emergency orthotopic liver transplantation (OLT) is performed. Nonetheless, the rapidity of progression of the clinical syndrome along with a worldwide shortage of cadaveric donor organs result in many patients dying or developing contraindications to transplantation before a donor liver becomes available, even with priority listing. In order to help overcome this problem, living donor OLT has been introduced as a therapeutic option for FHF both in pediatric and, more recently, adult patients. Other recent interests have centred on the possibility of providing temporary liver support based on auxiliary partial organ transplantation or the use of extracorporeal devices or hepatocyte transplantation. The latter strategies act as either a "bridge" to OLT or, ideally, to allow time for or to actively promote native liver regeneration, thereby rendering OLT unnecessary.

The most likely etiology of FHF varies according to geographical location, altering the possibility of being able to apply specific therapy. Hepatotoxicity due to

acetaminophen is by far the most frequent cause of FHF in the United Kingdom, accounting for 60% to 70% of cases in recent series [1]. In keeping with a trend towards greater numbers of cases in many Western countries, acetaminophen is also the most prevalent cause of FHF in a recent series from Denmark and the United States [2,3]. Cases of FHF after ingestion of recommended (or near recommended) doses of acetaminophen have been reported, particularly in patients with chronic exposure to enzyme-inducing drugs and alcohol. However, our experience is that the majority of instances of severe hepatotoxicity related to acetaminophen in alcoholics, as in other patients, are the direct consequence of having ingested a large dose of the drug. Most cases of hepatotoxicity occurring in relation to acetaminophen use with therapeutic rather than suicidal intent are also due to ingestion of large doses, generally over at least several days [4•]. The development of FHF due to acetaminophen may be prevented if N-acetylcysteine is given within 15 hours of exposure. Furthermore, the later use of this agent, after signs of liver necrosis have developed, has been shown in one controlled trial to ameliorate associated multi-organ failure and improve survival [5].

Infection with hepatitis B virus (HBV) (with or without delta co- or super-infection) is the most prevalent cause of FHF in the Far East, France, and many other southern European countries where carriage rates are high. Reactivation of HBV is more prevalent than new HBV infection in some FHF series. Use of antiviral agents such as lamivudine may play a role in patients with high circulating HBV DNA levels, although viral replication is characteristically low or absent by the time of clinical presentation with FHF. Hepatitis E virus, for which no specific antiviral therapy is currently available, is the cause of up to 60% of cases of FHF in India but only 6% of cases in Western countries [6]. Similarly, hepatitis C virus (HCV) has only rarely been implicated as a cause of FHF in Europe [7,8], although HCV infection is found in a substantial proportion of patients with FHF in Japan and Taiwan [9,10]. As well-recognized with HBV, instances of FHF following withdrawal of chemotherapy have been documented in patients with chronic HCV infection. Risk of FHF is increased in HCV and HIV coinfected patients treated with highly active antiretroviral therapy [11]. Irrespective of the geographical location, hepatitis A virus (HAV) is typically responsible for less than 10% of cases of FHF. The age at which HAV infection occurs influences outcome, with the risk of FHF increasing markedly in those older than 40 years. A high rate of development of FHF with a poor prognosis has been reported in patients with chronic HCV infection who acquire HAV acutely [12], implying that those with chronic HCV infection should be vaccinated against hepatitis A.

Cryptogenic (or so called non-A to E fulminant hepatitis) cases generally constitute the second largest group both in the United States and European series. Documentation of cases of FHF due to ingestion of food contaminated with the *Bacillus cereus* emetic toxin [13] inhibits hepatic mitochondrial fatty-acid oxidation that raises the possibility that other mitochondrial toxins may be responsible for many cases currently considered cryptogenic in etiology. Nonacetaminophen adverse drug reactions, mostly idiosyncratic, account for approximately 10% to 15% of cases of FHF in Western countries. "Ecstasy" (3,4-methylene-dioxymethamphetamine) and other illicit drugs are increasingly recognized as causes of FHF.

Other uncommon etiologies of FHF include autoimmune hepatitis, pregnancy-related disorders such as acute fatty liver and the hemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome, Amanita phalloides poisoning, veno-occlusive disease, acute Budd-Chiari syndrome, hepatic ischemia related to heart failure or septic shock, heatstroke, and Wilson's disease. Specific therapies and interventions to be considered in these latter disorders include a trial of corticosteroid therapy in autoimmune hepatitis, delivery of the fetus in pregnancy-related etiologies, use of penicillin and silibinin as antidotes in Amanita poisoning and decompressive vascular shunting (surgical or radiologically-achieved) in selected patients with veno-occlusive disease and acute Budd-Chiari syndrome. Investigation for an underlying procoagulant disorder is mandatory in this latter disorder. Interventional radiology including the placement of a transjugular intrahepatic portosystemic shunt (TIPS) and a hepatic venous angioplasty and stenting of the inferior vena cava may have a role in patients with hepatic venous outflow block, depending on the exact clinical context. Treatment of precipitating cardiac dysfunction is necessary in ischemic FHF due to left ventricular failure, along with appropriate antibiotics and vasopressor agents in septic shock. Circulatory collapse with resultant ischemic liver injury also contributes to the pathogenesis of FHF associated with heatstroke. Recognition of the rare fulminant presentation of Wilson's disease, suggested clinically by the presence of hemolysis, splenomegaly, and Kayser-Fleischer rings, is crucial as mortality in those with encephalopathy is virtually 100% without urgent OLT. By contrast, survival without transplantation can be achieved with early D-penicillamine treatment in most nonencephalopathic Wilson's disease patients who present acutely with other manifestations of severe hepatic insufficiency, highlighting the importance of early recognition of this disorder [14].

Infection with Epstein-Barr virus, cytomegalovirus (CMV), varicella-zoster virus, adenovirus, and herpes simplex virus (HSV) must also be considered, especially in the immunosuppressed. FHF due to HSV and CMV may respond to antiviral treatment [15•]. FHF due to infection with togavirus-like particles, Papillomavirus,

paramyxoviruses, and hemorrhagic fever viruses is also recognized. Lymphomatous infiltration of the liver is another rare but potentially treatable cause of FHF. Making a specific diagnosis is also important in view of the potential for recurrence of many of these conditions post-OLT [16•]. Many of these etiologies for which specific therapies may be applied can be established only by a liver biopsy using a transjugular approach in cases with uncontrollable coagulopathy or more than minimal ascites.

SUPPORTIVE CARE

Management in an intensive care unit, preferably in a liver transplant center if the patient is a candidate for transplantation, is mandatory in all FHF patients with more than grade I hepatic encephalopathy. Supportive medical interventions based on an understanding of underlying pathophysiology are aimed at maintaining hemodynamic, cerebral and renal function, reversing metabolic derangements, preventing or treating infection, preventing stress ulceration of gastric mucosa, and, where appropriate, treating coagulopathy.

HEMODYNAMIC DISTURBANCE

Pathophysiology Hemodynamic studies have shown that FHF is characterized by marked splanchnic and systemic arteriolar vasodilatation and low arteriovenous oxygen content difference. Recent clinical data suggest that elevated levels of interleukin (IL)-6 and IL-8 contribute to this splanchnic and systemic vasodilatation and the systemic hypotension often evident in this syndrome [17]. Adrenal insufficiency may contribute to the propensity for systemic hypotension [18], as it has been demonstrated in severe sepsis. As in patients with severe sepsis, the ability to extract oxygen at the cellular level is impaired in FHF. The pathogenesis of the microcirculatory disorder leading to impaired tissue oxygen extraction is poorly understood, but production of vasoactive cytokines and endothelial damage caused by generation of oxygen free radicals may be important. Microcirculatory plugging due to formation of microthrombi as a consequence of activation and consumption of platelets, together with increased adhesion of leukocytes to endothelium, may also be contributory, with blood being shunted through nonnutritive arteriovenous channels.

Supportive management Interventions to achieve or maintain hemodynamic stability are aimed at optimizing tissue oxygen delivery and consumption parameters. Substantial volumes of colloid may be required to attain an adequate cardiovascular filling pressure (pulmonary capillary wedge pressure 8–14 mmHg), given the often profound vasodilatation. In studies performed at King's College Hospital using the Fick method, N-acetylcysteine infusion was shown to significantly improve oxygen delivery, tissue oxygen consumption, and hemodynamic stability; prostacyclin infusion also improved oxygen delivery and consumption, whereas combined infusions led to a significant increase in oxygen delivery but not consumption compared with infusion of N-acetylcysteine alone [19]. More recently, another group used indirect calorimetry in order to avoid any possible confounding effect of mathematical coupling, and they found a more variable systemic hemodynamic response to N-acetylcysteine, with clear responders and nonresponders. Overall, a small (6%) early improvement in tissue oxygen consumption, which was not sustained throughout a 5-hour period of monitoring, was recorded [20]. Further, multicenter studies are needed to clarify the effect of N-acetylcysteine on tissue oxygenation in FHF.

Vasopressor agents are indicated if mean arterial pressure is less than 60 mmHg, despite adequate intravascular volume. Most experience is with epinephrine and norepinephrine. Oxygen consumption may fall with use of these agents, despite the increased arterial pressure, resulting from a reduction in oxygen delivery and extraction rates. The latter may be prevented by concurrent use of prostacyclin. Recent data supporting the use of vasopressin for vasodilatory shock suggest that this agent may be of value in the FHF setting [21••]. Terlipressin, the vasopressin prodrug, is less likely than vasopressin to cause myocardial ischemia. Terlipressin is sometimes used as a vasopressor agent in patients with FHF, but it may exacerbate cerebral hyperaemia and intracranial hypertension in this setting [22]. Although dopamine increases arterial pressure and oxygen delivery in FHF, reduced splanchnic oxygen consumption has been observed [23].

HEPATIC ENCEPHALOPATHY AND CEREBRAL EDEMA

Pathophysiology The pathophysiologic mechanisms responsible for hepatic encephalopathy, which are typically rapid in onset and progression in FHF, have not been fully elucidated. Accumulation of ammonia, disturbance of central glutamatergic, serotoninergic and noradrenergic pathways, production of false neurotransmitters, activation of central gamma-aminobutyric acid/benzodiazepine receptors, and altered cerebral energy metabolism may each be important. Autoregulation of cerebral blood flow (CBF) is impaired or absent in patients with advanced encephalopathy grade. The prevalence of severe encephalopathy has fallen in recent years, possibly as a consequence of the recognition that, in those requiring renal support, continuous hemodiafiltration is preferable to intermittent dialysis. Better control of infection is likely an important contributory factor [24•]. Subclinical epileptiform activity, detectable by continuous electroencephalographic monitoring and possibly related to cerebral ischemia, is common in FHF patients in grade III or IV encephalopathy and would exacerbate any imbalance between cerebral oxygen demand and supply and precip-

itate or exacerbate cerebral edema [25•]. Cerebral blood flow is often increased in FHF, especially at the stage when cerebral edema develops [26]. Accumulation of lactate has been implicated in the pathogenesis of cerebral edema in FHF [27], with the recent finding of a normal hepatic venous pyruvate/lactate ratio suggesting that accelerated glycolysis rather than tissue hypoxia accounts for the elevated lactate levels [28,29]. Increased glycolysis is a known consequence of the systemic inflammatory response syndrome (SIRS) and may be the mechanism underlying the recent observation of a significant association between the severity of the SIRS and grade of hepatic encephalopathy in FHF [24•].

Supportive management Neurologic support is aimed at optimizing CBF, cerebral perfusion pressure, and oxygen consumption, along with preventing or treating cerebral edema. Patients should be nursed in the 20 to 30 degrees head-up position. Elective mechanical ventilation with sedation and paralysis, the use propofol and atracurium, minimization of endotracheal suctioning, patient turning and other tactile stimulation prevent surges in intracranial pressure (ICP) which may provoke or exacerbate cerebral edema. Treatment with N-acteylcysteine has been reported in one study to increase cerebral oxygen consumption, with a fall in anaerobic metabolism; infusion of prostacyclin was also of benefit [30]. These findings remain to be confirmed in other studies. Extradural pressure monitoring, with sufficient fresh frozen plasma to achieve an international normalized ratio less than or equal to two and platelet transfusions to achieve a count that is greater than or equal to10^9/L at the time of insertion of the transducer, is of value in guiding further therapy in ventilated patients with grade III or IV encephalopathy, including during OLT, as the increase in CBF that occurs with reperfusion may be deleterious, especially in those with defective autoregulation [31]. Nonetheless, such monitoring does carry some risk and the transducer should be removed no longer than 5 days after insertion in view of the risk of infection. A fall in cerebral perfusion pressure (CPP), the difference between mean arterial pressure and intracranial pressure (ICP), to < 50 mmHg due to arterial hypotension should be managed with vasopressor agents, provided intravascular volume status is adequate. When CPP is reduced as a consequence of an increase in ICP, or when the latter exceeds 25 mmHg, bolus intravenous injection of mannitol is first-line treatment. Renal replacement therapy that aims to remove two to three times the volume of infused mannitol is required in patients in oliguric renal failure. Repeated doses may be given as necessary, provided that the plasma osmolarity does not exceed 320 mOsmol/L. Thiopentone may be beneficial in cases of intractable cerebral edema, although it may result in hemodynamic instability. There is considerable interest in moderate hypothermia (32–33° C), which, as in experimental animals, may be beneficial in both adults and infants with uncontrolled increases in ICP through reductions in cerebral blood flow, metabolism, and glutamine synthesis [32••,33,34]. Prophylactic phenytoin has been found in one study to reduce the incidence of subclinical epilepsy [25]. Seizure activity despite phenytoin treatment may respond to diazepam, although hypotension related to use of this drug must quickly be reversed and bezodiazepines should otherwise be avoided in view of the possible role of activation of central gamma-aminobutyric acid/benzodiazepine receptors in pathogenesis of encephalopathy. Hepatectomy with temporary portocaval shunt is a possible consideration for the short-term control of otherwise refractory intracranial hypertension during the period between organ retrieval and transplantation in patients for whom a donor liver has become available. Hyperventilation reduces CBF and is appropriate in the subgroup, with increased jugular venous oxygen saturation and elevated ICP suggestive of cerebral hyperaemia. A reverse jugular venous oxygen saturation of 55% to 75% and an arterio-jugular venous lactate difference that is less than or equal to 35 mmol/L suggest an adequate CPP. As opposed to the chronic liver disease setting, agents such as lactulose and neomycin are generally ineffective in the management of hepatic encephalopathy in patients with FHF, especially in those with more than grade I encephalopathy.

RENAL FAILURE

Pathophysiology Renal failure occurs in approximately 70% of patients with FHF, due to acetaminophen and 30% of other etiologies. Relative hypovolemia due to vasodilatation, microcirculatory disturbance, acute tubular necrosis related to complicating sepsis, and the use of nephrotoxic antibiotics are important contributing factors. Direct nephrotoxicity may also play a role in those patients with FHF from acetaminophen overdose.

Supportive management Ensuring adequate intravascular volume status and treatment of any complicating infection are important therapeutic measures. Trials of low-dose dopamine and frusemide are often instituted, although efficacy is not proven. In patients with FHF related to acetaminophen, the incidence of renal failure requiring dialysis was reduced by N-acetylcysteine infusion in one study, even after severe liver damage had occurred [5]. As with other possible beneficial effects of this agent, this finding remains to be confirmed in other studies. Indications for renal replacement therapy in FHF patients include uncontrolled acidosis, hyperkalemia, fluid overload, and oliguria associated with either a serum creatinine over 300 micromol/L or cerebral edema requiring treatment with mannitol. Continuous veno-veno hemodiafiltration (CVVHD) is preferable to intermittent hemodialysis, as complicating

hypotension with the latter results in a fall in CPP with exacerbation or precipitation of cerebral edema.

SUSPECTIBILITY TO INFECTION

Pathophysiology Patients with FHF are susceptible to infection as a consequence of impaired neutrophil and Kupffer cell phagocytic function, reduced hepatic production of complement, and the requirement for invasive procedures. Increased bacterial translocation of gut flora may also be important. Culture-proven bacterial infection, most often pneumonia, septicaemia and urinary tract sepsis, occurs in up to 80% of patients. The infecting organisms are Gram-positive in over 50% of cases. Fungal infection, predominantly with Candida species, occurs in over 30%, particularly in the later stages of the clinical syndrome and almost always in association with concurrent bacterial sepsis. Nearly one third of septic patients remain afebrile with a normal white cell count. A recent analysis of 887 FHF patients admitted to a single center over an 11-year period found a significant association between infection and progressive encephalopathy, reducing the chance of OLT and conferring a poor prognosis [24]. In the experimental situation, sepsis-related oxidative stress has been shown in rodents to both promote hepatocellular necrosis and inhibit liver cell regeneration [35], upon which spontaneous recovery ultimately depends.

Supportive management Prophylactic parenteral broad-spectrum antibiotic regimens, such as ceftazidime plus flucloxacillin or piperacillin plus tazobactam, combined with enteral amphotericin B and vaginal clotrimazole reduce the incidence of infection to 20%. The latter approach is as effective as more intensive enteral decontamination regimens. Proven bacterial infection should be treated according to in vitro sensitivies, while invasive fungal infection requires parenteral treatment with an appropriate antifungal agent. In the absence of a positive isolate, the possibility of fungal infection should be considered in the settings of a fever unresponsive to broad-spectrum antibiotics, leukocytosis or deterioration in neurologic status after initial improvement, especially in the presence of renal failure. Granulocyte colony stimulating factor improves neutrophil function in FHF [36] and may have a future role in preventing or treating infection in this group.

NUTRITIONAL IMPAIRMENT

Pathophysiology Rapid deterioration in nutritional status, with depletion of muscle and fat stores, is often seen in patients with FHF. Along with accelerated glycolysis, impairment of glycogen storage and reduced capacity for gluconeogenesis result in hypoglycemia and increased breakdown of adipose tissue and muscle. Consequently, fat and protein are used as alternative fuel sources. However, the predominant factor responsible for the exaggerated whole body protein degradation is likely reduced hepatic synthesis of insulin-like growth factor-1. Hypoglycemia occurs early in the course of FHF, whereas hypophosphatemia, hypokalemia, and hypomagnesemia are also common, especially in patients who maintain an adequate urine output. Impaired peripheral uptake of glucose consequent to insulin resistance has been documented early in the course of FHF, with insulin sensitivity typically being restored by two weeks in patients who survive [37].

Supportive management Energy requirements in FHF are increased by up to 60%. Mean energy expenditure has been estimated at 4.05 kJ/kg/hr and is further increased by complicating infection. Harris-Benedict predictions are unreliable in the setting of FHF [38]. Caloric requirements of 35 to 50 kcal/kg daily are required to meet resting metabolic demand. Protein intakes in excess of 1g/kg/d are necessary to maintain nitrogen balance. Up to 50% of nonprotein calories should be delivered as lipid. Hypoglycemia, hypophosphatemia, hypokalemia, and hypomagnesemia require aggressive replacement. Enteral nutrition is considered preferable to parenteral in view of reports of maintained integrity of gut mucosa and reduced rates of bacterial translocation and sepsis in experimental animals.

COAGULOPATHY AND BLEEDING DIATHESIS

Pathophysiology Several mechanisms contribute to the coagulopathy associated with FHF including reduced hepatic synthesis of clotting and anticlotting factors together with consumption of clotting factors and platelets due to disseminated intravascular coagulation (DIC). Although evidence of this may be obtained, as has been well demonstrated in experimental animal models from moderately raised levels of fibrinogen degradation products in a substantial proportion of patients, DIC is usually not severe, except in acute fatty liver and other pregnancy-related etiologies. The platelet count generally falls progressively day by day and is a good marker of disease stage and prognosis. In addition to thrombocytopoenia, qualitative platelet defects including increased adhesiveness and impaired aggregation have been described. Deficiencies of anticlotting factors such as protein C and antithrombin III may result in thrombosis of dialysis circuits, despite other manifestations of a bleeding diathesis.

Supportive management Since the prothrombin time is an important prognostic variable, infusion of fresh frozen plasma is indicated only for bleeding or at the time of invasive procedures such as insertion of intracranial pressure monitors. Platelet transfusions are required in the latter circumstances if the count is less than 50×10^9/L or prophylactically if less than 20×10^9/L. Risk of bleeding from stress ulceration of gastric mucosa is

reduced by prophylactic use of sucralfate. A meta-analysis of all available prospective randomized studies performed in intensive care patients up to 1996 found that stress ulcer prophylaxis with sucralfate was associated with a significantly lower rate of nosocomial pneumonia than antisecretory drugs such as histamine-2 receptor antagonists [39]. Increased risk of pneumonia was associated with the development of gastric bacterial overgrowth due to reduced gastric acidity [40]. A more recent multicenter study performed in 1200 critically ill ventilated patients in Canada found an 18% higher rate of pneumonia in rantidine-treated compared with sucralfate-treated patients, although this difference failed to reach statistical significance [41]. A reduced rate of bleeding from ulceration in the ranitidine-treated group in this latter study may have been confounded by the high rate of early commencement of enteral feeding in study patients [40]. Endoscopic treatment may be required for bleeding varices that can develop acutely in FHF or in uncontrolled hemorrhage from stress ulceration. Use of heparin or prostacyclin may be required to prevent thrombosis of dialysis circuits.

ORTHOTOPIC LIVER TRANSPLANTATION

Selection criteria for OLT are based on indices identifying patients with a poor prognosis with medical management alone. Although not standardized from center to center, those formulated at King's College Hospital are most widely used [42], although their ability to reliably identify patients who will survive without OLT, in particular, has been lower than in the original reports [43••,44]. Additional consideration of blood lactate levels modestly improved the negative predictive value of the King's College criteria in a recent report, but positive predictive value remained higher with the initial King's College criteria alone. Nonetheless, patients with a poor outcome were identified earlier when blood lactate levels were taken into consideration [45]. Other OLT criteria based on factor V levels, VIII/V ratios, serial prothrombin times, assessment of liver size on computed tomography scanning, liver histology, and the Acute Physiology and Chronic Health Evaluation (APACHE) score have alternatively been proposed. Serum levels of Gc-globulin (vitamin D-binding protein), an important liver-derived component of the extracellular actin-scavenging system, and severity of the SIRS, may also have prognostic value. Fulminant presentations (with encephalopathy) of Wilson's disease and Budd-Chiari syndrome in association with extensive hepatocellular necrosis are generally considered to represent indications for urgent OLT.

One-year patient survival rates following cadaveric OLT for FHF range from 50% to 75%. In the best centers, outcome with split liver grafts is comparable with that following use of full size organs. Survival is substantially reduced, however, in patients with sepsis and multi-organ failure prior to OLT. A recent retrospective study found costs up to 1 year associated with OLT were $110,125 for FHF, compared with $130,638 for chronic liver disease [46•]. Reduced intensive care unit-related costs in patients transplanted for FHF, resulting from a higher early mortality rate, may at least have contributed to this difference. The use of auxiliary partial OLT in selected patients may be considered a form of temporary liver support in most recipients, as immunosuppression may eventually be withdrawn, leading to graft atrophy in approximately two thirds of cases in whom adequate regeneration of the native liver has occurred. The survival rate following living donor OLT for FHF in a pediatric series using left lateral segments was 73% at a median follow-up of 28 months [47]. Left lobe, right lobe, and extended right lobe donation has also recently been used successfully in cases of adult FHF. A graft in excess of 40% or more of the recipient's standard liver weight is required for optimal chance of success [48•].

EXTRACORPOREAL LIVER SUPPORT

An increasing number of extracorporeal devices of varying complexity are being developed as potential alternatives to auxiliary partial OLT for providing temporary liver support in FHF. Early attempts at extracorporeal support based on purely artificial modalities such as exchange blood transfusion, conventional plasmapheresis, hemodialysis, and hemoperfusion over charcoal or resins were based on the premise that removal of water soluble and albumin bound toxins was of paramount importance. Improvement in survival, however, was not proven. Recent interest in artificial liver support has centered on large volume plasmapheresis and hemodiadsorption systems including the molecular adsorbents recirculating system (MARS) [49,50••]. Use of MARS in FHF has been reported in several small uncontrolled case series and case reports in which patients were successfully bridged to transplantation. The successful treatment of a patient with fulminant Wilson's disease resulted in the removal of substantial quantities of albumin-bound copper and bilirubin and reversal of multi-organ failure before OLT was performed [50••].

Several bioartificial liver devices that differ substantially in both the hepatocyte component and bioreactor design have been assessed either experimentally or clinically [51–54,55]. Most clinical experience is with the "HepatAssist" (Circe Biomedical, Lexington, MA) bioartificial liver support system which contains cryopreserved porcine hepatocytes as the cellular component and charcoal haemoperfusion [55]. Uncontrolled data suggested an impressive improvement in neurologic rather than metabolic parameters. A prospective randomized, multicenter controlled trial of the HepatAssist device in the United States and Europe demonstrated a significant survival advantage in FHF patients treated with the device, excluding those with primary graft non-

function posttransplantation, compared with controls (44% reduction in mortality) [56]. No instances of transmission of porcine retroviruses by use of porcine hepatocytes in the HepatAssist have been documented. In a pilot but controlled clinical trial of the "Extracorporeal Liver Assist Device" (ELAD), which contains a human hepatoblastoma cell line [52], no statistically significant clinical or metabolic effect was shown in treated patients. Alternative designs to the HepatAssist and ELAD have been developed in an attempt to improve diffusion and perfusion gradients by more closely simulating in vivo hepatic architecture. No device undergoing assessment incorporates scarcely available primary human hepatocytes as the cellular component. Conversely, human livers were used for extracorporeal perfusion in a report, albeit uncontrolled, that documented metabolic and neurologic improvement in a cohort of 14 patients treated with continuous perfusion using 16 livers in 18 perfusion circuits [57].

HEPATOCYTE TRANSPLANTATION

Hepatocyte transplantation hasbeen performed in only a relatively small number of patients with FHF. Instances of mostly short-term improvement in encephalopathy and some metabolic parameters have been recorded both in OLT and non-OLT candidates [58]. No randomized controlled data are currently available. The availability of suitable hepatocytes for transplantation remains problematic at present, as these are only obtainable in sufficient quantity from scarcely available cadaver organs. Lack of success in maintaining primary hepatocytes in a clinically relevant functional state in culture prior to their subsequent transplantation is another limiting factor.

Treatment

Diet and lifestyle

- Energy requirements in FHF are increased by up to 60% and are further elevated by complicating infection.
- Protein intakes in excess of 1g/kg/d are necessary to maintain nitrogen balance. Up to 50% of nonprotein calories should be delivered as lipid.
- Enteral nutrition is preferable to parenteral in view of maintained integrity of gut mucosa and reduced bacterial translocation and incidence of sepsis.
- Hypoglycemia, hypophosphatemia, hypokalemia, and hypomagnesemia require aggressive reversal.
- Intravenous drug use predisposes to FHF through exposure to hepatitis viruses.

Pharmacologic treatment

- Pharmacologic treatment options include specific measures to eradicate the cause of FHF where applicable and supportive measures to optimise hepatic function and prevent or reverse complicating multi-organ failure.

Etiology-specific pharmacologic treatments

N-acetylcystein

Standard dosage	150 mg/kg in 200 mL, 5% dextrose by intravenous infusion over 15 minutes followed by continuous intravenous infusion of 50 mg/kg in 500 mL, 5% dextrose over 4 hours then 100 mg/kg in 1 L, 5% dextrose over 16 hours. Subsequently, 150 mg/kg by intravenous infusion over 24 hours by continuous intravenous infusion until evidence of recovery.
Contraindications	History of anaphylaxis to N-acetylcysteine.
Main drug interactions	None.
Main side effects	Allergic manifestations including rash, hypotension, bronchospasm and anaphlyaxis.
Special points	Prevents hepatotoxicity due to acetaminophen if given within 15 hours of exposure. The later use of this agent, after signs of liver necrosis have developed, may ameliorate associated multi-organ failure and improves survival [5].
Cost effectiveness	No studies have specifically evaluated cost effectiveness.

Lamivudine

Standard dosage	100 mg daily by mouth; dose reduction necessary in patients with creatinine clearance less than 50 mL/minute.
Contraindications	Hypersensitivity to lamivudine.
Main drug interactions	None.
Main side effects	Safety profile similar to placebo at standard dosage.
Special points	Potentially of value by reducing viral replication in the relatively small proportion of patients with FHF due to HBV and high circulating HBV DNA levels.
Cost effectiveness	No studies have specifically evaluated cost effectiveness.

Prednisolone or methylprednisolone

Standard dosage	0.5 mg/kg daily
Contraindications	Uncontrolled infection; hypersensitivity to prednisolone or methylprednisolone.
Main drug interactions	Antidiabetic agents (oral and insulin), digitalis glycosides; drugs that induce hepatic microsomal enzymes (eg, barbiturates, phenytoin and rifampicin).
Main side effects	Susceptibility to infection, hyperglycemia, and hypertension.
Special points	A trial of corticosteroids should be considered in FHF due to autoimmune hepatitis.
Cost effectiveness	No studies have specifically evaluated cost effectiveness.

Acyclovir

Standard dosage	10 mg/kg by slow intravenous infusion over 1 hour every 8 hours for 10 days. Dose reduction is necessary in patients with renal impairment.
Contraindications	Hypersensitivity to acyclovir.
Main drug interactions	Probenecid increases the half-life and plasma concentration of aciclovir; concurrent use of diuretics increases the plasma concentration of aciclovir in patients older than 60 years.
Main side effects	Phlebitis at injection site; renal dysfunction, rash, and neurologic toxicity.
Special points	High-dose aciclovir may be beneficial in patients with FHF due to Herpes simplex virus [15•].
Cost effectiveness	No studies have specifically evaluated cost effectiveness.

Ganciclovir

Standard dosage	5 mg/kg by intravenous infusion over 1 hour every 12 hours for 14 to 21 days. Dose reduction is required in patients with renal dysfunction.
Contraindications	Pregnancy; lactation; hypersensitivity to ganciclovir or acyclovir.
Main drug interactions	Probenecid decreases clearance of ganciclovir; concurrent use of ganciclovir with zidovudine or didanosine results in reduced clearance of the latter two agents. Generalized seizures have been reported in patients receiving ganciclovir with imipenem-cilastatin.
Main side effects	Pancytopoenia, diarrhea, nausea.
Special points	Ganciclovir may be beneficial in patients with FHF due to cytomegalovirus.
Cost effectiveness	No studies have specifically evaluated cost effectiveness.

Silibinin and benzylpenicillin

Standard dosage	Silibinin, 20 to 50 mg/kg daily by intravenous infusion; Benzylpenicillin, 300,000 to 1,000,000 units/kg daily by intravenous infusion in divided doses.
Contraindications	Known hypersensitivity to silibinin or penicillin.
Main drug interactions	Clearance of penicillin is reduced by concurrent probenecid. Tetracyclines may antagonize the bactericidal effect of penicillin.
Main side effects	Hypersensitivity reactions.
Special points	May be of value in FHF due to Amanita phalloides poisoning.
Cost effectiveness	No studies have specifically evaluated cost effectiveness.

Inotropes

Dobutamine and dopamine

Standard dosage	Dobutamine, 2.5 to 40 μg/kg/min by continuous intravenous infusion, depending on hemodynamic response. Dopamine, 5 to 50 μg/kg/min by continuous intravenous infusion, depending on hemodynamic response.
Contraindications	Hypersensitivity to dobutamine or dopamine, idiopathic hypertrophic subaortic stenosis, and phaeochromocytoma.
Main drug interactions	β-adrenergic receptor antagonists, α-adrenergic receptor antagonists, cyclopropane or halogenated hydrocarbon anaesthetics, and monoamine oxidase inhibitors.
Main side effects	Tachycardia, hypertension and arrhythmias, hypotension has occasionally been reported, nausea, vomiting, and phlebitis.
Special points	Treatment of precipitating cardiac dysfunction is necessary in ischemic FHF due to left ventricular failure. Dopamine at a dose of 5 μg/kg/min increases arterial pressure and oxygen delivery in FHF, although reduced splanchnic oxygen consumption has been observed [23].
Cost effectiveness	No studies have specifically evaluated cost effectiveness.

Chemotherapy for lymphoma

Standard dosage	Chlorambucil, 0.1 to 0.2 mg/kg daily by mouth for 4 to 8 weeks initially
Contraindications	Hypersensitivity to these agents, serious untreated infection, severe depression of bone marrow function, and demyelinating Charcot-Marie-Tooth syndrome.
Main drug interactions	Toxicity of chlorambucil may be enhanced by phenylbutazone, blood levels of phenytoin may be reduced when used concurrently with vincristine, and concurrent use of vincristine and itraconazole results in reduced metabolism of vincristine.
Main side effects	Bone marrow suppression, susceptibility to infection, alopecia, and neuropathy.
Special points	Lymphomatous infiltration of the liver is a rare but potentially treatable cause of FHF [16•].
Cost effectiveness	No studies have specifically evaluated cost effectiveness.

Supportive pharmacologic treatments

N-acetylcysteine

Standard dosage	150 mg/kg by intravenous infusion over 30 minutes as loading dose followed by 150 mg/kg over 24 hours by continuous intravenous infusion until signs of recovery.
Contraindications	History of anaphylayis.
Main drug interactions	None.
Main side effects	Allergic manifestations.
Special points	Further studies are required to assess the effects of this agent on tissue oxygenation in FHF.
Cost effectiveness	No studies have specifically evaluated cost effectiveness.

Prostacyclin

Standard dosage	5 mg/kg/min by continuous intravenous infusion.
Contraindications	Hypotension and uncontrolled bleeding.
Main drug interactions	Other anticoagulant and antiplatelet agents may have additive effects.
Main side effects	Hypotension and bleeding.
Special points	A vasodilatory prostaglandin with antiplatelet properties which may improve tissue oxygen delivery and consumption and prevent a fall in global tissue oxygen consumption related to the use of vasopressor agents. Use reduces the incidence of clotting in dialysis circuits.
Cost effectiveness	No studies have specifically evaluated cost effectiveness.

Vasopressor agents

Epinephrine, norepinephrine, vasopressin, terlipressin

Standard dosage	Epinephrine and norepinephrine, 0.1 to 2.0 microg/kg/min by continuous intravenous infusion, as required; vasopressin, 0.04 to 0.10 U/min by continuous intravenous infusion as required; terlipressin 1 to 2 mg by intravenous injection every 4 to 6 hours.
Contraindications	Known hypersensitivity to these agents; unstable angina; pheochromocytoma.
Main drug interactions	β-adrenergic receptor antagonsits; α-adrenergic receptor antagonists; cyclopropane or halogenated hydrocarbon anaesthetics; monoamine oxidase inhibitors.
Main side effects	Tachycardia, hypertension and arrhythmias, mesenteric ischemia, ischemic heart disease.
Special points	Although epinephrine and norepinephrine increase mean arterial pressure, oxygen consumption may fall as a result of reduction in oxygen delivery and extraction rates. Recent data supporting the use of vasopressin for vasodilatory shock suggest that this agent may be of value in the FHF setting [21••]. Terlipressin may exacerbate cerebral hyperemia and intracranial hypertension in FHF patients with severe hepatic encephalopathy [22].
Cost effectiveness	No studies have specifically evaluated cost effectiveness.

Atracurium and propofol

Standard dosage	Atracurium, 0.4 to 0.5 mg/kg by intravenous injection initially then 5 to 10 microg/kg/min by continuous intravenous infusion. Propofol, 1 to 3 mg/kg/hr by continuous intravenous infusion.
Contraindications	Hypersensitivity to these agents, use of monamine oxidase inhibitors, myasthenia gravis.
Main drug interactions	Drugs which may enhance the neuromuscular blocking action of atracurium include enflurane, isoflurane, sevoflurane, desflurane, halothane, aminoglycosides, polymyxin, tetracyclines, lincomycin, clindamycin, lithium, propranolol, calcium channel blockers, lignocaine, procainamide, quinidine, frusemide and thiazide diuretics. Other central nervous system depressants potentiate the sedative effects of propofol.
Main side effects	Skin flushing and erythema, pruritis, cardiorespiratory depression.
Special points	Used in patients with FHF and grade III or IV encephalopathy to facilitate management of cerebral edema by preventing surges in intracranial pressure related to psychomotor agitation.
Cost effectiveness	No studies have specifically evaluated cost effectiveness.

Mannitol

Standard dosage	0.5 g/kg by intravenous injection over 10 minutes repeated as necessary provided that serum osmolarity does not exceed 320 mosmol/kg.
Contraindications	Oligoanuria in absence of renal replacement therapy.
Main drug interactions	None.
Main side effects	Dehydration.
Special points	First-line pharmacologic treatment of established cerebral edema in FHF. In patients with oligoanuric renal failure, renal replacement therapy should aim to remove two to three times the volume of infused mannitol.
Cost effectiveness	No studies have specifically evaluated cost effectiveness.

Thiopentone

Standard dosage	50 mg by bolus intravenous injection followed by infusion of 50 mg/hr for up to 6 hours.
Contraindications	Hypersensitivity to barbiturates; variegate or acute intermittent porphyria.
Main drug interactions	Probenecid prolongs the action of thiopentone; aminophylline antagonises thiopentone effect. Additive hypotensive effects with anti-hypertensive drugs.
Main side effects	Myocardial depression; cardiac arrhythmias; hypotension; tachycardia; anaphylaxis.
Special points	Role in refractory cerebral edema in FHF.
Cost effectiveness	No studies have specifically evaluated cost effectiveness.

Phenytoin

Standard dosage	15 mg/kg by slow intravenous injection at a rate not exceeding 50 mg/min followed by 100 mg doses every 8 hours.
Contraindications	Hypersensitivity to hydantoin products; sinoatrial block, second or third degree atrioventricular block.
Main drug interactions	Many drugs increase phenytoin levels, including acute alcohol intake, amiodarone, apmphtericin, diltiazem, erythromycin, fluconazole, H2-antagonists, halothane, isoniazid, itraconazole, ketoconazole, nifedipine, oestrogens, omeprazole, salicylates, sulfonamides and tolbutamide. Drugs which decrease phenytoin levels include ciprofloxacin, rifampicin, chronic alcohol use, sucralfate and theophylline. Drugs whose efficacy is impaired by phenytoin include corticosteroids, coumarin anticoagulants, cyclosporin, doxycycline, frusemide, nicardipine, nimodipine, oral contraceptives, praziquantel, quinidine, rifampicin, tetracycline, theophylline and verapamil.
Main side effects	Nystagmus, ataxia, dysarthria, inco-ordination, confusion.
Special points	Prophylactic use in patients with advanced encephalopathy was found in one study to reduce the prevalence of subclinical epileptiform activity and resultant cerebral edema [24•].
Cost effectiveness	No studies have specifically evaluated cost effectiveness.

Diazepam

Standard dosage	10 mg by intravenous infusion as required.
Contraindications	Known hypersensitivity to benzodiazepines; respiratory failure; myasthenia gravis.
Main drug interactions	Drugs which influence cytochrome P450 enzyme activity; other CNS depressant drugs; cisapride; other anti-convulsant drugs.
Main side effects	Drowsiness, hypotension, respiratory depresion.
Special points	Used to control seizure activity, although should otherwise be avoided in view of possible role of activation of central gamma-aminobutyric acid/benzodiazepine receptors in pathogenesis of hepatic encephalopathy.
Cost effectiveness	No studies have specifically evaluated cost effectiveness.

Frusemide/furosemide

Standard dosage	10 mg/hour by intravenous infusion
Contraindication	Anuria, sodium, potassium or fluid depletion, hypersensitivity to frusemide.
Main drug interactions	Aminoglycosides, lithium, NSAIDs.
Main side effects	Electrolyte disturbance, hypovolaemia, renal dysfunction.
Special points	Often used in oliguric renal failure despite adequate intravascular volume and mean arterial pressure, although efficacy has not been established in controlled trials.
Cost effectiveness	No studies have specifically evaluated cost effectiveness.

Low-dose dopamine

Standard dosage	2.5 μg/kg/min by continuous intravenous infusion.
Contraindications	Same as frusemide/furosemide.
Main drug interactions	Same as frusemide/furosemide.
Main side effects	Same as frusemide/furosemide.
Special points	Often used in oliguric renal failure despite adequate intravascular volume and mean arterial pressure, although efficacy has not been established in controlled trials.
Cost effectiveness	No studies have specifically evaluated cost effectiveness.

Prophylactic parenteral broad-spectrum antibiotic regimens

Ceftazidime, flucloxacillin, piperacillin/tazobactam, oral amphotericin B suspension, and vaginal clotrimazole.

Standard dosage	Ceftazidime: 2 g daily by intravenous injection; flucloxacillin: 1 g every 6 hours by intravenous injection; piperacillin/tazobactam, 4.5 g every 8 hours by intravenous injection; amphotericin B suspension, 100 mg by mouth or nasogastric tube every 6 hours; vaginal clotrimazole cream once daily or pessaries twice weekly.
Contraindications	Hypersensitivity to these agents.
Main drug interactions	Probenecid decreases renal clearance of flucloxacillin, piperacillin and tazobactam; piperacillin increases the elimination of tobramycin.
Main side effects	Hypersensitivity, serum-sickness reactions, diarrhea, nausea, headaches, ageusia, hepatic toxicity, pruritis.
Special points	Prophylactic parenteral broad-spectrum antibiotic regimens combined with enteral amphotericin B and clotrimazole pessaries reduce the incidence of infection from 80% to 20%.
Cost effectiveness	No studies have specifically evaluated cost-effectiveness.

Sucralfate

Standard dosage	1 g orally four times daily.
Contraindications	Known hypersensitivity to sucralfate.
Main drug interactions	Antacids, tetracycline, phenytoin, cimetidine, digoxin, norfloxacin, ciprofloxacin, warfarin.
Main side effects	Constipation, headache, and urticaria.
Special points	Risk of bleeding from stress ulceration of gastric mucosa is reduced by prophylactic use of sucralfate, especially in patients not receiving enteral nutrition. This agent is preferable to antisecretory drugs, which predispose to gastric bacterial overgrowth and nosocomial pneumonia.
Cost effectiveness	No studies have specifically evaluated cost-effectiveness.

Endoscopic treatment

- Endoscopic therapy has only a limited role in the management of FHF. Interventions such as band ligation or injection sclerotherapy are required for haemorrhage from varices, while injection of epinephrine, 1:10,000, or treatments such as argon plasma coagulation may be helpful in uncontrolled bleeding from stress ulceration of gastric mucosa.

Surgery

- Decompressive vascular shunts (meso-atrial, mesocaval or portocaval) should be considered in cases of FHF due to veno-occlusive disease and Budd-Chiari syndrome, although OLT is treatment of choice in those patients with severe degrees of hepatic necrosis fulfilling criteria for poor prognosis.
- OLT is required in the most severely affected group, in whom survival is poor with medical treatments alone.
- Hepatectomy with temporary porto-caval shunt should be considered for cerebral edema uncontrolled by other measures during the period between organ retrieval and OLT in cases for whom a donor liver has become available.

Decompressive vascular shunts

Standard procedure	Meso-atrial or portocaval anastomosis under general anaesthesia.
Contraindications	Fulfillment of transplant criteria.
Complications	Exacerbation of encephalopathy; severe liver dysfunction makes surgical intervention under general anesthesia a high risk procedure.

Special points Patients with Budd-Chiari syndrome must be investigated for a predisposing hypercoagulable state.

Cost effectiveness No studies have specifically evaluated cost-effectiveness.

Orthotopic liver transplantation

Standard procedure In conventional OLT, the transplanted liver is grafted in place of the explant, with portal venous, hepatic arterial, vena caval and biliary anastomoses. In auxiliary partial OLT, a right or left hepatectomy of the native liver is performed to prepare a space large enough to accept a right or left liver graft, which is implanted orthotopically.

Contraindications Uncontrolled sepsis; respiratory failure; fixed pulmonary hypertension; intractable hypotension; prolonged elevations of intracranial pressure to levels greater than 35 mmHg.

Complications Primary graft nonfunction, hepatobiliary ischemia, graft rejection, sepsis, other side-effects from immunosuppressive drugs.

Special points Due to limited cadaveric donor organ availability and the often rapidly progressive nature of the clinical syndrome, many patients die or develop contraindications to transplantation before OLT can be performed, prompting interest in living donors.

Cost effectiveness Despite slightly higher 1-year costs associated with OLT for chronic liver disease than FHF in a recent analysis, OLT was considered more cost-effective in the former setting due to the higher 1-year survival [46•].

Other treatments

- Urgent delivery of the baby is required in patients with FHF due to pregnancy-specific causes (acute fatty liver; HELLP syndrome).
- Mechanical ventilation is required in patients with grade 3 or 4 encephalopathy, using a volume-controlled mode with minute volume titrated to achieve a PCO_2 of 4.5 to 5.5 kPa. Hyperventilation to achieve hypocapnia is indicated in the subgroup with increased jugular venous oxygen saturation and elevated ICP suggestive of cerebral hyperaemia.
- Radiologically placed venous stents, including TIPS, and hepatic venous angioplasty may be alternatives to decompressive vascular shunts in selected patients with FHF due to veno-occlusive disease and Budd-Chiari syndrome.
- CVVHD is preferable to intermittent haemodialysis in FHF patients requiring dialysis (uncontrolled acidosis; hyperkalaemia; fluid overload; oliguria associated with a serum creatinine over 300 micromol/L or cerebral edema requiring treatment with mannitol) in view of the reduced propensity for cerebral edema.
- Induction of moderate hypothermia (32–33 degrees C) using cooling blakets may help in the treatment of uncontrolled intracranial hypertension in FHF [32••,33,34].
- Infusion of fresh frozen plasma is indicated only for bleeding or at the time of invasive procedures, such as insertion of intracranial pressure monitors. Platelet transfusions are required in the latter circumstances if the count is less than 50 X 10^9/L and prophylactically if less than 20 X 10^9/L.

Emerging therapies

- A number of extracorporeal devices have been developed and are currently undergoing clinical trial as potential alternatives to auxiliary partial OLT for providing temporary liver support (artificial or bioartificial) in FHF [51–55]. Clinical efficacy remains to be established.
- Hepatocyte transplantation has been performed in a small number of patients with FHF [58]. Randomized controlled data are awaited.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Anand AC, Nightingale P, Neuberger JM: **Early indicators of prognosis in fulminant hepatic failure: an assessment of the King's criteria.** *J Hepatol* 1997, **26:**62–68.
2. Schiodt FV, Atillasoy E, Shakil AO, *et al.*: **Etiology and outcome for 295 patients with acute liver failure in the United States.** *Liver Transpl Surg* 1999, **5:**29–34.
3. Larsen FS, Kirkegaard P, Rasmussen A, *et al.*: **The Danish liver transplantation program and patients with serious acetaminophen intoxication.** *Transplant Proc* 1995, **27:**3519–3520.
4. • Larson AM, Ostapowicz G, Fontana RJ, *et al.*: **Outcome of acetaminophen-induced liver failure in the USA in suicidal vs accidental overdose: preliminary results of a prospective multi-center trial.** *Hepatology* 2000, **32:**396A.

This study illustrates that most cases of hepatotoxicity related to acetaminophen use with therapeutic, rather than suicidal, intent nonetheless result from ingestion of large doses.

5. Harrison PM, Keays R, Bray GP, *et al.*: **Improved outcome in paracetamol-induced fulminant hepatic failure following late administration of acetylcysteine.** *Lancet* 1990, **335:**1572–1573.
6. Acharya SK, Dasarathy S, Kumer TI, *et al.*: **Fulminant hepatitis in a tropical population: clinical course, cause and early predictors of outcome.** *Hepatology* 1996, **23:**1448–1455.
7. Wright T, Hsu H, Donegan E, *et al.*: **Hepatitis C virus not found in fulminant non-a, non-B hepatitis.** *Ann Intern Med* 1991, **115:**111–115.
8. Liang TJ, Jeffers L, Reddy RK, *et al.*: **Fulminant or subfulminant non-A, non-B viral hepatitis: the role of hepatitis C and E viruses.** *Gastroenterology* 1993, **104:**556–562.
9. Yanagi M, Kanego S, Unoura M, *et al.*: **Hepatitis C virus in fulminant hepatic failure.** *N Engl J Med* 1991, **324:**1895–1896.
10. Chu CM, Sheen IS, Liaw YF: **The role of hepatitis C virus in fulminant viral hepatitis in an area with endemic hepatitis A and B.** *Gastroenterology* 1994, **107:**189–195.
11. Kramer JR, Giordano TP, Souchek J, El-Serag HB: **Hepatitis C coinfection increases the risk of fulminant hepatic failure in patients with HIV in the HAART era.** *J Hepatol* 2005, **42:**309–314.
12. Vento S, Garafano T, Renzini C, *et al.*: **Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C.** *N Engl J Med* 1998, **338:**286–290.
13. Mahler H, Pasi A, Kramer JM, *et al.*: **Fulminant liver failure in association with the emetic toxin of Bacillus cereus.** *N Engl J Med* 1997, **336:**1142–1148.
14. Durand F, Bernuau J, Giostra E, *et al.*: **Wilson's disease with severe hepatic insufficiency: beneficial effects of early administration of D-penicillamine.** *Gut* 2001, **41:**849–852.
15. • Gruson D, Hilbert G, Le Bail B, *et al.*: **Fulminant hepatitis due to herpes simplex virus-type 2 in early phase of bone marrow transplantation.** *Hematol Cell Ther* 1998, **40:**41–44.

High dose aciclovir may be beneficial in FHF due to Herpes simplex virus in immunosuppressed patients.

16. • Blakolmer K, Gaulard P, Mannhalter C, *et al.*: **Unusual peripheral T cell lymphoma presenting as acute liver failure and re-appearing in the liver allograft.** *Transplantation* 2000, **70:**1802–1805.

Previously unrecognized lymphoma as a cause of FHF may recur in the allograft after OLT.

17. Sheron N, Keane H, Goka J, *et al.*: **Circulating acute phase cytokines and cytokine inhibitors in fulminant hepatic failure: associations with mortality and haemodynamics.** *Clin Intensive Care* 2001, **12:**127–134.
18. Harry R, Auzinger G, Wendon J: **The clinical importance of adrenal insufficiency in acute hepatic dysfunction.** *Hepatology* 2002, **36:**395–402.
19. Harrison PM, Wendon JA, Gimson AES, *et al.*: **Improvement by N-acetylcysteine of haemodynamics and oxygen transport in fulminant hepatic failure.** *N Engl J Med* 1991, **324:**1852–1857.
20. Walsh TS, Hopton P, Philips BJ, *et al.*: **The effect of N-acetylcysteine on oxygen transport and uptake in patients with fulminant hepatic failure.** *Hepatology* 1998, **27:**1332–1340.
21. •• Krismer AC, Wenzel V, Mayr VD, *et al.*: **Arginine vasopressin during cardiopulmonary resuscitation and vasodilatory shock: current experience and future perspectives.** *Curr Opin Crit Care* 2001, **7:**157–169.

Vasopressin may be a useful alternative to vasopressor agents such as epinephrine and norepinephrine in vasodilatory shock and may have a role in FHF patients.

22. Shawcross DL, Davies NA, Mookerjee RP, *et al.*: **Worsening of cerebral hyperaemia by the administration of terlipressin in acute liver failure with severe encephalopathy.** *Hepatology* 2004, **39:**471–475.
23. Clemensen JO, Galatius S, Skak C, *et al.*: **The effect of increasing blood pressure with dopamine on systemic, splanchnic, and lower extremity hemodynamics in patients with acute liver failure.** *Scand J Gastroenterol* 1999, **34:**921–927.
24. • Rolando N, Wade J, Davalos M, *et al.*: **The systemic inflammatory response syndrome in acute liver failure.** *Hepatology* 2000, **32:**734–739.

The severity of the systemic inflammatory response syndrome predicts a poor prognosis in FHF patients.

25.• Ellis AJ, Wendon JA, Williams R: **Subclinical seizure activity and prophylactic phenytoin infusion in acute liver failure: a controlled clinical trial.** *Hepatology* 2000, **32:**666–669.
Subclinical seizure activity detectable by continuous electroencephalographic monitoring was found to be a common occurrence in this study. The prevalence of this complication along with cerebral oedema were reduced by prophylactic phenytoin infusion.

26. Larsen FS: **Cerebral circulation in liver failure.** *Semin Liver Dis* 1996, **16:**281–292.

27. Tofteng F, Jorgensen L, Hamsen BA, *et al.*: **Cerebral microdialyis in patients with fulminant hepatic failure.** *Hepatology* 2002, **36:**1333–1340.

28. Clemmesen O: **Splanchnic circulation and metabolism in patients with acute liver failure.** *Dan Med Bull* 2002, **49:**177–193.

29. Butterworth RF, Giguere JF, Michand J, *et al.*: **Ammonia: key factor in the pathogenesis of hepatic encephalopathy.** *Neurochem Pathol* 1987, **6:**1–12.

30. Wendon JA, Harrison PM, Keays R, *et al.*: **Cerebral blood flow and metabolism in fulminant hepatic failure.** *Hepatology* 1994, **19:**1407–1413.

31. Philips B, Armstrong IR, Pollock A, *et al.*: **Cerebral blood flow and metabolism in patients with chronic liver disease undergoing orthotopic liver transplantation.** *Hepatology* 1998, **27:**369–376.

32.•• Jalan R, Damink SW, Deutz NE, *et al.*: **Moderate hypothermia for uncontrolled intracranial hypertension in acute liver failure.** *Lancet* 1999, **354:**1164–1168.
Hypothermia is useful in FHF patients with uncontrolled cerebral oedema and may serve as a bridge to OLT.

33. Kataoka K, Yanase H: **Mild hypothermia - a revived countermeasure against ischemic neuronal damage.** *Neurosci Res* 1998, **32:**103–107.

34. Whitelaw A, Bridges S, Leaf A, *et al.*: **Emergency treatment of neonatal hyperammonaemic coma with mild systemic hypothermia.** *Lancet* 2001, **358:**36–38.

35. Weiss YG, Bellin L, Kim PK, *et al.*: **Compensatory hepatic regeneration after mild, but not fulminant, intraperitoneal sepsis in rats.** *Am J Physiol Gastrointest Liver Physiol,* **280:**G968–G973.

36. Rolando N, Clapperton M, Wade J, *et al.*: **Administering granulocyte colony-stimulating factor to acute liver failure patients corrects neutrophil defects.** *Eur J Gastroenterol Hepatol* 2000, **12:**1323–1328.

37. Clark SJ, Shojaee-Moradie F, Croos P, *et al.*: **Temporal changes in insulin sensitivity following the development of acute liver failure secondary to acetaminophen.** *Hepatology* 2001, **34:**109–115.

38. Walsh TS, Wigmore SJ, Hopton P, *et al.*: **Energy expenditure in acetaminophen-induced fulminant hepatic failure.** *Crit Care Med* 2000, **28:**649–654.

39. Cook DJ, Reeve BK, Guyatt GH, *et al.*: **Stress ulcer prophylaxis in critically ill patients. Resolving discordant meta-analyses.** *JAMA* 1996, **275:**308–314.

40. Tryba M: **Role of acid suppressants in intensive care medicine.** *Baillieres Clin Gastroenterol* 2001, **15:**447–461.

41. Cook D, Guyatt G, Marshall J, *et al.*: **A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation.** *N Engl J Med* 1998, **338:**791–797.

42. O'Grady JG, Alexander GJM, Hayllar KM, *et al.*: **Early indicators of prognosis in fulminant hepatic failure.** *Gastroenterology* 1989, **97:**439–445.

43.•• Shakil AO, Kramer D, Mazariegos GV, *et al.*: **Acute liver failure: clinical features, outcome analysis and applicability of prognostic criteria.** *Liver Transpl* 2000, **6:**163–169.
The ability of the King's College criteria to identify patients who will survive without OLT, in particular, was not as great as in the original report, in keeping with other recent series.

44. Pauwels A, Mostefa-Kara N, Florent C, Levy VG: **Emergency liver transplantation for acute liver failure.** *J Hepatol* 1993, **17:**124–127.

45. Bernal W, Donaldson N, Wyncoll D, Wendon J: **Blood lactate as an early predictor of outcome in paracetamol-induced acute liver failure: a cohort study.** *Lancet* 2002, **359:**558–563.

46.• van Agthoven M, Metselaar HJ, Tilanus HW, *et al.*: **A comparison of the costs and effects of liver transplantation for acute and for chronic liver failure.** *Transpl Int* 2001, **14:**87–94.
One of the few studies to address cost or cost-effectiveness in FHF. OLT was considered less cost-effective in the FHF than chronic liver disease setting, due to the higher 1 year survival rate in the latter group.

47. Hattori H, Higuchi Y, Tsuji M, *et al.*: **Living-related liver transplantation and neurological outcome in children with fulminant hepatic failure.** *Transplantation* 1998, **65:**686–692.

48.• Lo CM, Fan ST, Liu CL, *et al.*: **Minimum graft size for successful living donor liver transplantation.** *Transplantation* 1999, **68:**1112–1116.
A graft size in excess of 40% of the recipient's liver native volume is required for optimum chance of successful living-related OLT, a technique with which most experience is in the pediatric population.

49. Clemmesen JO, Kondrup J, Nielsen LB, *et al.*: **Effects of high-volume plasmapheresis on ammonia, urea, and amino acids in patients with acute liver failure.** *Am J Gastroenterol* 2001, **96:**1217–1223.

50.•• Kreymann B, Seige M, Schweigart U, *et al.*: **Albumin dialysis: effective removal of copper in a patient with fulminant Wilson disease and successful bridging to liver transplantation: a new possibility for the elimination of protein-bound toxins.** *J Hepatol* 1999, **31:**1080–1085.
Artificial liver support with a hemodiadsorption system based on albumin dialysis led to improvement in a patient with fulminant Wilson's disease, the mortality of which is virtually 100% with medical therapy alone, until OLT was performed.

51. Bader A, De Bartolo L, Haverich A: *Initial evaluation of the performance of a scaled up flat membrane bioreactor (FMB) with pig liver cells. In:* Crepaldi G, Demetriou AA, Muraca M, eds. Rome: Bioartificial Liver Support: the Critical Issues. CIC Edizioni Internationali, 1997:36–41.

52. Ellis AJ, Hughes RD, Wendon JA, *et al.*: **Pilot-controlled trial of the extracorporeal liver assist device in acute liver failure.** *Hepatology* 1996, **24:**1446–1451.

53. Calise F, Mancini A, Amoroso P, *et al.*: **Functional evaluation of the AMC-BAL to be employed in a multicentric clinical trial for acute liver failure.** *Transplant Proc* 2001, **33:**647–649.

54. Gerlach JC, Encke J, Hole O, *et al.*: **Hepatocyte culture between three dimensionally arranged biomatrix-coated independent artificial capillary systems and sinusoidal endothelial cell co-culture compartments.** *Int J Artif Organs* 1994, **17:**301–306.

55. Watanabe FD, Mullon CJ-P, Hewitt WR, *et al.*: **Clinical experience with a bioartificial liver in the treatment of severe liver failure.** *Ann Surg* 1997, **225:**484–494.

56. Demetriou AA, Brown RS, Busuttil RW, *et al.*: **Prospective, randomised, multicenter, controlled trial of a bioartificial liver in treating acute liver failure.** *Ann Surg* 2004, **239:**660–670.

57. Horslen SP, Hammel JM, Fristoe LW, *et al.*: **Extracorporeal liver perfusion using human and pig livers for acute liver failure.** *Transplantation* 2000, **70:**1472–1478.

58. Strom SC, Fisher RA, Thompson MT, *et al.*: **Hepatocyte transplantation as a bridge to orthotropic liver transplantation in terminal liver failure.** *Transplantation* 1997, **63:**559–569.