Acute liver failure

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Acute liver failure is a rare disorder with high mortality and resource cost. In the developing world, viral causes predominate, with hepatitis E infection recognised as a common cause in many countries. In the USA and much of western Europe, the incidence of virally induced disease has declined substantially in the past few years, with most cases now arising from drug-induced liver injury, often from paracetamol. However, a large proportion of cases are of unknown origin. Acute liver failure can be associated with rapidly progressive multiorgan failure and devastating complications; however, outcomes have been improved by use of emergency liver transplantation. An evidence base for practice is emerging for supportive care, and a better understanding of the pathophysiology of the disorder, especially in relation to hepatic encephalopathy, will probably soon lead to further improvements in survival rates.

Introduction

Acute liver failure is the clinical manifestation of sudden and severe hepatic injury and arises from many causes. After abrupt loss of hepatic metabolic and immunological function, it leads to hepatic encephalopathy, coagulopathy, and, in many cases, progressive multiorgan failure (panel 1). Although uncommon, this critical illness occurs mostly in young adults and is associated with high mortality and resource cost. In many countries it is the most frequent indication for emergency liver transplantation.

In the past 10 years, there have been major changes in the understanding of the cause and pathogenesis of the disease, and an evidence base for treatment has evolved. In this Seminar, we summarise these changes, present approaches to management, and suggest future developments.

Definitions

The term fulminant hepatic failure was first used[11] in 1970 to describe a potentially reversible disorder that was the result of severe liver injury, with an onset of encephalopathy within 8 weeks of symptom appearance and in the absence of pre-existing liver disease. The key elements of this definition remain relevant, although classifications have changed to recognise that prognosis and complications vary in relation to the rate of evolution of illness.

The terminology developed by O'Grady and colleagues[12] in 1993 is still used for description of acute liver failure in adults. This classification recognises the central prognostic importance of the development of encephalopathy and altered consciousness after initial hepatic injury and divides the presentation into three groups: hyperacute, acute, and subacute, dependent on the interval between development of jaundice and onset of encephalopathy. This description remains clinically important, and can help to identify the cause of disease, probable complications, and prognosis (table 1). Similarly, the classification by Bernuau and colleagues[14] is useful, dividing the disorder into fulminant and subfulminant categories dependent on the jaundice to encephalopathy interval.

In young children, clinical encephalopathy can be absent or late in the course of illness, thus the definition does not depend on this symptom but only on coagulopathy due to liver injury. A designation accepted for clinical and research studies is that of a multisystem disorder in which severe impairment of liver function, with or without encephalopathy, occurs with hepatocellular necrosis in a patient with no reported underlying chronic liver disease.[15]

Incidence

Acute liver failure is rare. Reports from the developed world suggest an overall incidence of between one and six cases per million people every year.[16–18] Data for other regions are sparse, although rates are probably high in locations where infective hepatitis is common and medical therapies that interrupt progression of hepatic injury and development of extrahepatic organ dysfunction are not readily available.

Causes

Viral infections

The main causal agents for the hepatic injury that triggers the onset of liver failure show wide geographical variation, and depend on the prevalent hepatotropic virus infections and patterns of drug use (table 2).[13,27,28] In the developing world, viral causes predominate, with infection by hepatitis A, B, and E viruses accounting for most cases. By contrast, acute viral infection is an uncommon cause in the USA and much of western Europe, where drug-induced liver injury predominates.

Hepatitis A virus is transmitted via the faecal–oral route, either through personal contact or consumption

Search strategy and selection criteria

We searched Medline with the terms "acute liver failure" and "fulminant hepatic failure" between 1997 and 2009. We also reviewed reference lists of publications we identified and selected those most relevant to practice. We have not attempted to give a comprehensive review of all features of acute liver failure, but have focused on areas in which there have been substantial advances in understanding of the disorder and in which there have been major new developments in treatment.

of contaminated food or water, with high incidence of infection closely associated with poor hygiene and sanitation.[29] In much of the developed world, frequency of acute infection has fallen strikingly, after effective use of hepatitis A vaccination (figure 1).[30–32] Concomitantly, the importance of hepatitis A virus as a cause of acute liver failure has substantially declined in many regions, and accounted for fewer than 3% of cases in a recent US study.[33]

Although about 1·5 million clinical cases of acute hepatitis A viral infection occur worldwide every year, fewer than 1% of patients will develop liver failure.[29,34] Viral infection follows a more severe course in adults than it does in children—in whom asymptomatic infection is common—and case fatality rates rise with advanced age.[35] An increased risk of death from acute viral infection has also been noted in patients with underlying chronic liver disease, especially that resulting from hepatitis C virus infection, which suggests that such patients without naturally acquired immunity to type A virus might particularly benefit from targeted vaccination.[36–38] Acute liver failure that is induced by hepatitis A virus most often follows a hyperacute or acute clinical course, although in elderly patients a more subacute pattern of disease can occur, which is often associated with a worse outcome.[33]

Similar to type A, hepatitis E virus is transmitted via the faecal–oral route and is endemic throughout tropical and subtropical countries, with periodic epidemics that are mostly caused by contaminated water supply.[39] Sporadic cases of viral hepatitis E infection also arise at much higher rates in endemic than in non-endemic regions.[40,41] Hepatitis E is now the most common cause of acute liver failure in India and Pakistan, China, and southeast Asia.[39] In some developed countries, acute hepatitis E virus infection is more common than is type A, with a higher frequency of locally acquired than imported disease.[42,43] Although the source of such infections remains unknown, evidence suggests a porcine origin.[39]

Similar to hepatitis A, mortality rates from acute hepatitis E viral infection are low—probably less than 1%—with a worse outcome in elderly patients and those with established chronic liver disease.[25,44] Infection is common in pregnant women, particularly in the third trimester, and initial reports suggested a strikingly high mortality rate. However, recent data suggest that pregnancy might not adversely affect liver failure outcomes resulting from hepatitis E infection, with mortality not increased above that recorded in pregnant women with other viral causes of the disorder.[27,45,46] Vertical transmission of hepatitis E from women with acute infection results in acute liver failure in more than half of neonates.[47]

Hepatitis E viral infection typically results in a hyperacute pattern of liver failure, although the course can also be indolent.[25,45] Additionally, and unlike in hepatitis A, transition from acute to chronic infection with persistent hepatic inflammation and viraemia can occur in immunosuppressed patients.[48] Although overall outcomes for liver failure related to hepatitis E can be good, mortality can exceed 50% when emergency liver transplantation is unavailable.[25,27]

Hepatitis B is transmitted vertically or horizontally by exposure to blood or other body fluids of an infected person. The disease accounts for nearly 30% of acute liver failure in parts of Europe, and is a main cause in Asia, sub-Saharan Africa, and the Amazon basin.[18,28,49,50] Fewer than 4% of cases of acute hepatitis B viral infection will lead to development of the acute liver failure, but mortality is higher than that with hepatitis A or E infections.[25,34] Similar to the situation with hepatitis A, initiation of public health measures (eg, vaccination) has led to large decreases in hepatitis B

***Panel 1:* Clinical features of acute liver failure**

Whole body
- Systemic inflammatory response[1,2]
- High energy expenditure and catabolism[3,4]

Liver
- Loss of metabolic function
- Decreased gluconeogenesis leading to hypoglycaemia
- Decreased lactate clearance leading to lactic acidosis
- Decreased ammonia clearance leading to hyperammonaemia
- Decreased synthetic capacity leading to coagulopathy

Lungs
- Acute lung injury
- Adult respiratory distress syndrome

Adrenal gland
- Inadequate glucocorticoid production contributing to hypotension[5]

Bone marrow
- Frequent suppression, especially in viral and seronegative disease[6]

Circulating leucocytes
- Impaired function and immunoparesis contributing to high risk of sepsis[7]

Brain
- Hepatic encephalopathy
- Cerebral oedema
- Intracranial hypertension[8]

Heart
- High output state
- Frequent subclinical myocardial injury[9]

Pancreatitis
- Particularly in paracetamol-related acute liver failure[10]

Kidney
- Frequent dysfunction or failure[2]

Portal hypertension
- Might be prominent in subacute disease and confused with chronic liver disease

	Hyperacute	Acute	Subacute
Time from jaundice to encephalopathy	0–1 week	1–4 weeks	4–12 weeks
Severity of coagulopathy	+++	++	+
Severity of jaundice	+	++	+++
Degree of intracranial hypertension	++	++	+/–
Survival rate without emergency liver transplantation	Good	Moderate	Poor
Typical cause	Paracetamol, hepatitis A and E	Hepatitis B	Non-paracetamol drug-induced liver injury

Data from O'Grady and colleagues[12] and Ichai and Samuel.[13] +++=high severity. ++=medium severity. +=low severity. +/–=present or absent.

Table 1: **Classification, clinical features, and prognosis of the three subtypes of acute liver failure**

	Drug		Viral			Unknown	Other
	Paracetamol	Non-paracetamol	HAV	HBV	HEV		
Spain 1992–2000[18]	2%	17%	2%	32%	..	35%	12%
Sweden 1994–2003[19]	42%	15%	3%	4%	..	11%	25%
UK 1999–2008[20]	57%	11%	2%	5%	1%	17%	7%
Germany 1996–2005[21]	15%	14%	4%	18%	..	21%	28%
USA 1998–2001[22]	39%	13%	4%	7%	..	18%	19%
Australia 1988–2001[23]	36%	6%	4%	10%	..	34%	10%
Pakistan 2003–05[24]	0%	2%	7%	20%	60%	7%	4%
India 1989–96[25]	0%	1%	2%	15%	44%	31%	7%
Sudan 2003–04[26]	0%	8%	0%	22%	5%	38%	27%

..=not reported. HAV=hepatitis A virus. HBV=hepatitis B virus. HEV=hepatitis E virus.

Table 2: **Selected reports of causes of acute liver failure**

incidence, with a concomitant fall in acute liver failure and mortality (figure 1).[30,50]

Acute liver failure associated with hepatitis B can result not only from novel acute infection but also in chronic infection when viral status changes. These state changes include seroconversion with transition from a phase of stable viral replication or inactive carriage to viral clearance, superinfection with hepatitis D virus, or after a replication surge or reactivation. Reactivation can arise spontaneously, but more commonly happens during or after treatment-induced immunosuppression for solid-organ or haematological malignant disease.[51,52] Virus reactivation is associated with a much higher risk of progression to liver failure and death than is novel acute infection, and preliminary identification of patients at risk and administration of antiviral prophylaxis reduces mortality.[52,53]

Acute liver failure has a longer incubation and prodrome when associated with hepatitis B virus than with hepatitis A or E viruses, and typically has an acute rather than hyperacute presentation.[54] Increased age is consistently associated with a worse prognosis in disease from all viral causes.[25,30,34,54]

Uncommon but well documented viral causes of acute liver failure include herpes simplex virus types 1 and 2, human herpes virus 6, varicella zoster virus, Epstein-Barr virus, cytomegalovirus, and parvovirus B19. Acute hepatitis C infection is very rarely implicated as a cause in Europe and the USA, although cases have been reported in Japan and India. Few data suggest a major pathogenic role for SEN, TT (transfusion transmitted), or hepatitis G viruses.[55–59]

Causation cannot be established in many cases; such seronegative or indeterminate liver failure happens worldwide, and are associated with especially poor survival with medical therapy alone, and frequently need emergency transplantation.[60,61] Often associated with a subacute presentation, seronegative disease is a diagnosis of exclusion and its pathogenesis is poorly understood. Clinical features and associated haematological abnormalities can suggest viral infection, but serological testing for established and putatative hepatotropic viruses can be negative.[55,61–63] Some patients can progress to chronic hepatitis with recurrence after liver transplantation.[56,62]

Demographic profile, HLA genotype, presence of autoantibodies, and histological findings suggest an autoimmune pathogenesis for seronegative disease in some patients.[64,65] In the absence of a clear definition of the disease, many causative agents are implicated in this heterogenous group of patients, with possible roles for toxic or autoimmune hepatic insults, undescribed viral infections, and undefined metabolic disorders in children.

Drug-induced injury

Drug-induced injury is the second main cause of acute liver failure and predominates in much of the developed world. In the USA and northern Europe, non-prescription paracetamol (acetaminophen) is the analgesic that is

most commonly consumed in overdose, either inadvertently or with intent for deliberate self-harm.

Paracetamol-induced hepatoxicity is the characteristic hyperacute form of acute liver failure. The clinical course is often rapidly progressive multiorgan failure, with a greater severity of illness than that seen in liver failure from other causes.[17,66] Paradoxically, in patients who do not meet criteria for transplantation, outcomes with medical management alone are better than for patients with acute liver failure of other causes but equally severe extrahepatic organ failure, because of an increased potential for hepatic regeneration and recovery.[17,22]

In the UK, the availability of paracetamol has contributed to its popularity as the drug taken most often for deliberate self-harm. An epidemic of self-poisoning happened during the 1980s and 1990s, with nearly 40 000 hospital admissions and 500 deaths occurring yearly by 1997.[60] Legislation to restrict sales was instituted in 1998 with the intention to reduce domestic stocks of paracetamol and the dose consumed at impulsive overdose; consequently, the hepatotoxic potential would be lowered. This legislation probably succeeded in reduction of serious hepatotoxicity, with a 40% fall in paracetamol-related admissions to specialist liver units.[67] Whether this effect has been sustained is unknown, since studies have shown poor compliance with sales restrictions and regional variation in effects on mortality.[68,69]

In the USA, paracetamol is the commonest cause of acute liver failure and incidence seems to be increasing.[70] By contrast with the UK, half of overdose cases are apparently unintentional, with most from simultaneous consumption of many paracetamol-containing products for analgesic effect. Concerns also exist about possible hepatotoxicity of therapeutic doses of the drug, especially in patients at high risk of hepatotoxicity from chronic alcohol use.[71]

Sustained consumption of paracetamol at therapeutic doses (4 g daily) can lead to asymptomatic increases of blood hepatic aminotransferase concentrations after more than 4 days of consumption.[72–74] Such changes do not necessarily suggest an increased risk of progression to acute liver failure, and a systematic review found no prospective study of sustained therapeutic dosing that reported serious liver injury or death.[75] However, enhanced liver injury has been described in patients who have taken paracetamol at therapeutic doses for symptom relief at the onset of acute liver disease resulting from other causes.[76,77] The presence in serum of paracetamol-protein adducts, a specific biomarker of drug-related toxic effects, has also been noted in some adults and children with liver failure not otherwise attributable to paracetamol.[78,79]

The US Food and Drug Administration has recommended labelling changes and more explicit package warnings to discourage simultaneous consumption of many paracetamol-containing formulations, and is considering lowering the suggested therapeutic dose of paracetamol.

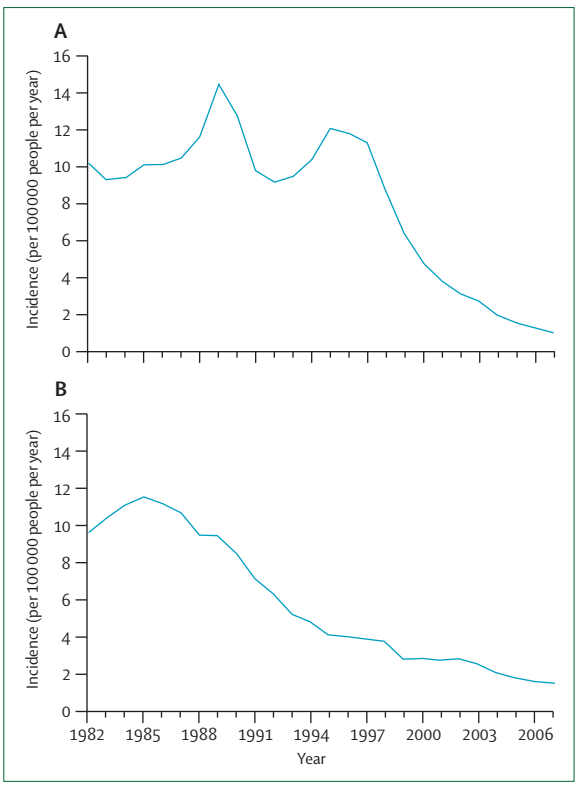

Figure 1: **Incidence of acute hepatitis per 100 000 people per year in USA, 1982–2007**
(A) Hepatitis A and (B) hepatitis B. Data from reference 30.

Liver damage induced by drugs other than paracetamol has been the most frequent cause of safety-related marketing withdrawals in the past 50 years.[80] Fewer than 10% of drug-induced liver injuries progress to acute liver failure, with an estimated incidence of only one to two cases per million people per year.[81–83] However, up to 80% of patients who develop liver failure might die or require transplantation.[81,84] The drugs responsible vary by location and prevailing drug use, with anti-infectives, anticonvulsants, and anti-inflammatory drugs most commonly implicated; herbal or adulterated traditional or complementary medications are also a notable cause in east Asia (figure 2).[84,86]

Unlike for other causes of acute liver failure, drug-induced liver failure arises more often in older than younger patients, especially those aged 60 years or more.[81,83] Most non-paracetamol drug-induced liver failures are individual and unpredictable, with some patients having months of uneventful treatment before presentation and rarely have pre-existing overt liver disease. Many cases follow a subacute course, with progression to hepatic failure despite drug discontinuation.[81,82] Conventional hypersensitivity is seen in fewer than a third of patients,[87,88] and can show a cholestatic or hepatocellular pattern of liver biochemistry, which has a worse prognosis.[81,82] High mortality is associated with deep jaundice, raised concentrations of aminotransferases, and increased age.[81]

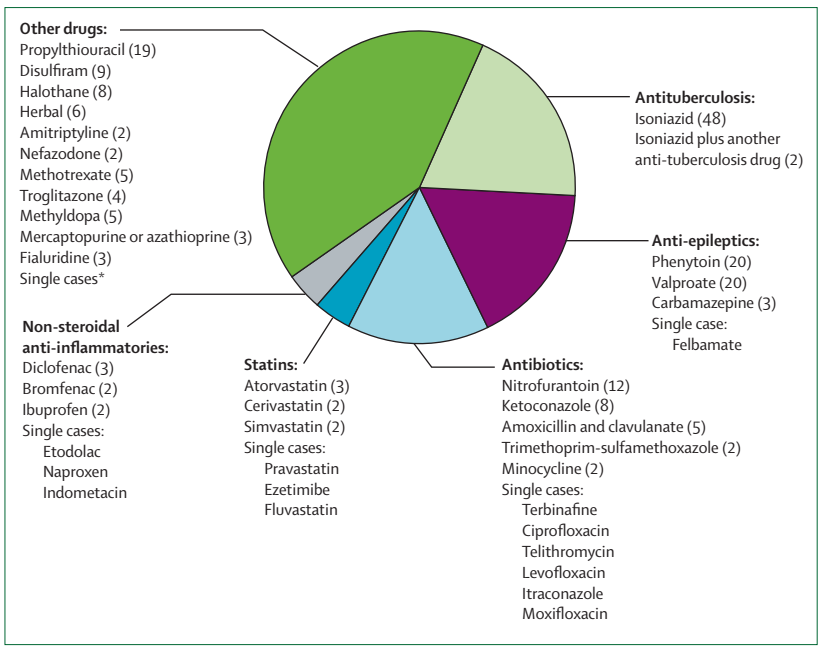

Figure 2: **Non-paracetamol-based drugs causing acute liver failure in patients requiring emergency liver transplantation in USA, 1987–2006**

Data from Mindikoglu et al.[85] Number of cases is shown in parenthesis. *Single cases noted with sertraline, cyclobenzaprine, paroxetine, bupropion, tamoxifen, asparaginase, dactinomycin, unknown antineoplastic agents, iron, nicotinic acid, infliximab, pemoline, carbon tetrachloride, sulfasalazine, zafirlukast, loratadine, clonazepam, dapsone, diltiazem, isoflurane, labetolol, butorphanol, steroids, angiotensin converting enzyme inhibitor, efavirenz, nevirapine-lamivudine, valsartan, retinol, lisinopril, allopurinol, and terbinafine.

There might be genetic predisposition to non-paracetamol drug-induced liver injury. An increased incidence has been seen with glutathione S-transferase and manganese superoxide dismutase gene polymorphisms, and specific HLA-genotype associations with drug-induced liver injury from flucloxacillin and amoxicillin.[89–91] Polymorphic variations of enzymes associated with the metabolism of diclofenac and isoniazid have also been linked with liver injury.[92,93] However, no study so far has linked genetic variation with severity of illness or outcomes.

Other causes

Other rare causes of acute liver failure include hyperthermic injury from heat shock or after protracted seizures, specific toxic insults such as *Amanita spp* (mushroom) poisoning, metabolic disorders such as Wilson's disease, immunological insults from autoimmune hepatitis, ischaemic injury as a result of systemic hypotension in sepsis or cardiac failure, or Budd-Chiari syndrome.[13] Malignant infiltration of the liver is a rare but notable cause of acute liver failure, and most often happens in elderly people. Pregnancy-related disease is associated with a good outcome with appropriate management.[94]

In children, inherited disorders merit special attention as a differential diagnosis, especially in newborn babies. Although these children have a variable degree of liver damage before clinical presentation, overt signs of chronic liver disease are usually absent. As such, urgent intervention with dietary manipulation or other disease-specific treatment might be lifesaving and, for some diagnoses, liver transplantation might be contraindicated.[15]

Clinical management

Principles of care

Acute liver failure leads to a unique combination of often rapidly progressive, severe multiorgan failure with unpredictable complications, and necessitates urgent decision making about use of the only effective treatment for those with advanced disease: emergency liver transplantation. However, the general principles of care are straightforward. Standard intensive care is delivered with additional specific measures aimed at identification and removal or amelioration of the insult that caused hepatic injury. Organ-system support is used to improve the patient's condition to achieve maximum hepatic regeneration, to return to premorbid hepatic function while medical staff anticipate and prevent development of complications. Patients who will not achieve sufficient regeneration need to be identified early in the course of their disease to increase the probability of successful emergency transplantation.

Although these principles are straightforward, their practical application is more complex and outcomes seem best for patients treated in centres experienced in management of acute liver failure.[95] Since intensive care management has been reviewed in detail;[96,97] we will focus on several specific areas of particular importance and interest.

Cause-specific interventions

If a particular agent responsible for liver injury can be identified, in some circumstances cause-specific treatments might be used to limit the severity of liver injury and potentially prevent progression from isolated hepatic failure to multiorgan damage and acute liver failure. The rare and severe nature of the disease means that few randomised trials have been done to establish best practice and the evidence base is therefore small.[97] Treatments should probably start early in the course of the disease for best effect, and careful assessment of disease severity and response to treatment is necessary to prevent delay or preclusion of successful emergency transplantation. For example, corticosteroids have been given in case series[98–100] of liver failure attributable to autoimmune hepatitis, although inappropriately prolonged therapy might worsen outcome. Lamivudine antiviral therapy for hepatitis B-associated disease, or aciclovir for disease associated with herpes simplex virus might improve outcomes, but randomised trial data are scarce.[101–104]

When given within 24 h of paracetamol ingestion, N-acetylcysteine can prevent or reduce liver damage even after large overdoses.[105] Early randomised trials suggested reductions in mortality from late administration of

N-acetylcysteine, and intervention studies showed improvements in systemic and cerebral haemodynamics and oxygen uptake.[106,107] A multicentre double-blind randomised trial[108] of N-acetylcysteine in non-paracetamol acute liver failure was completed after 8 years of recruitment. N-acetylcysteine was well tolerated and associated with improved non-transplanted survival, but only in patients treated early in the course of disease and with low-grade encephalopathy.

Encephalopathy and ammonia

In acute liver failure, hepatic encephalopathy encompasses many neuropsychiatric disturbances, ranging from minor confusion and disorientation to frank coma and cerebral oedema, resulting in intracranial hypertension. Although the frequency of clinically overt cerebral oedema has decreased over the past 20 years, such hypertension still accounts for 20–25% of deaths.[8] Survival without transplantation for patients with acute liver failure is poor in those with severe encephalopathy, and the risk of substantial cerebral oedema and intracranial hypertension is greatest in those with hyperacute or acute presentations. In patients with subacute disease, even the presence of modest hepatic encephalopathy suggests critically impaired liver function that, although infrequently associated with intracranial hypertension, is a sign of poor outlook.

The pathogenesis of hepatic encephalopathy in acute liver failure is only partly understood, but clinical and experimental evidence suggests an important role for raised concentrations of circulating neurotoxins, especially ammonia.[109] Results from laboratory studies[110–112] have shown ammonia-induced changes in neurotransmitter synthesis and release, neuronal oxidative stress, impaired mitochondrial function, and osmotic disturbances resulting from astrocytic metabolism of ammonia to glutamine. The overall result is a change in cerebral function and astrocytic swelling.[109,111,112] Findings from clinical studies[113–115] have suggested a link between the development of high grades of hepatic encephalopathy and arterial ammonia concentrations. However, although intracranial hypertension probably represents the most severe manifestation, factors other than ammonia seem to be important in hepatic encephalopathy pathogenesis.

Severe hepatic encephalopathy and cerebral oedema tend to arise in systemic inflammatory states, often precipitated by development of infection, providing a strong argument for use of prophylactic antimicrobial therapy.[1,115,116] Systemic circulation of proinflammatory mediators might have permissive or direct effects on development of hepatic encephalopathy and cerebral oedema through modulation of cerebral endothelial permeability to neurotoxins or via initiation of endothelial inflammatory responses and changes in cerebral blood flow.[109,117]

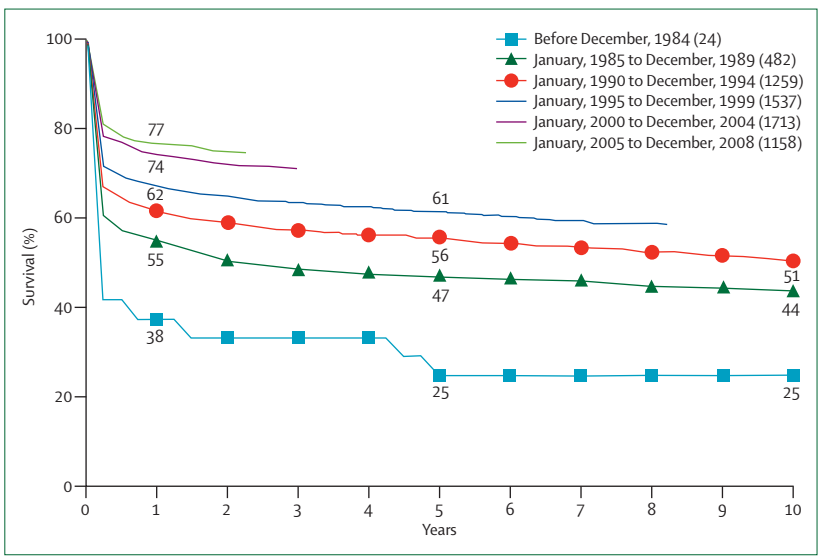

Figure 3: **Survival after liver transplantation for acute liver failure by date of surgery in Europe, 1984–2008**
Data from the European liver transplant registry.[129] Numbers are completed 1, 5, and 10-year survival rates. Numbers in parentheses are surgeries done in each group.

In view of the close relation between blood ammonia concentrations and cerebral complications of acute liver failure, treatments that reduce ammonia concentration could interrupt progression of hepatic encephalopathy or development of intracranial hypertension. Ammonia concentrations in the circulation point to the complex interorgan metabolism that occurs in liver failure. Ammonia is primarily produced in the small bowel from glutamine, metabolised by glutaminase to ammonia and glutamate.[118,119] Ammonia is converted to urea by the healthy liver, but in liver failure concentrations rise, and an alternative pathway for detoxification in muscle becomes available, in which glutamine synthetase metabolises ammonia back to glutamine.[120]

The drug ornithine aspartate might aid this conversion and represents an attractive agent for reduction of circulating ammonia, and seems effective in the treatment of hepatic encephalopathy in chronic liver disease.[121] However, a large randomised trial[122] of ornithine aspartate in Indian patients with acute liver failure did not show improvements in ammonia concentration, hepatic encephalopathy, or survival compared with placebo. Glutamine might be converted back to glutamate and ammonia by glutaminase in the gut, kidneys, liver, and brain in this disease.[123] Alternative agents that might help with ammonia metabolism in muscle without an increase in circulating glutamine are being investigated,[124] although present strategies to reduce ammonia concentrations rely on extracorporeal removal via conventional renal replacement therapies or control of body temperature.

Therapeutic hypothermia slows whole body metabolism and might reduce both systemic production and cerebral uptake of ammonia.[8] Beneficial effects in

Panel 2: King's College criteria for selection of recipients of emergency liver transplants

Paracetamol

Arterial pH less than 7·3 following adequate volume resuscitation, or combination of encephalopathy grade 3 or more, creatinine 300 μmol/L or more, and international normalised ratio more than 6·5

Non-paracetamol

Any grade encephalopathy and international normalised ratio 6·5 or more, or any three of: international normalised more than 3·5, bilirubin 300 μmol/L or more, age less than 10 or more than 40 years, unfavourable cause (drug-induced liver injury, seronegative disease)

Modified from reference 130.

Panel 3: Clichy-Villejuif criteria for selection of recipients of emergency liver transplants

- Encephalopathy grade 3 or more and factor V concentrations less than 20% in patients aged less than 30 years
- Encephalopathy grade 3 or more and factor V concentrations less than 30% in patients aged more than 30 years

Modified from reference 13.

relation to severity of cerebral oedema and intracranial hypertension have been shown in animal models of acute liver failure and in uncontrolled clinical series.[111] Moderate (32–33°C) hypothermia has been reported to effectively control refractory intracranial hypertension in patients awaiting transplantation,[125] with improvements in systemic haemodynamic variables. Potential adverse effects include coagulation disturbance, impairment of hepatic regeneration, and increased infection risk.[8] Widespread introduction of therapeutic hypothermia in patients with acute liver failure awaits the results of an international multicentre trial of prophylactic moderate hypothermia.[126]

In patients with established hepatic encephalopathy, other strategies to prevent the onset of severe cerebral oedema and intracranial hypertension aim to maintain freedom from sepsis, adequate sedation, cerebral perfusion, and correct hypo-osmolality.[96] Hypo-osmolality mainly results from hyponatraemia, and evidence from a randomised trial[127] suggested that treatment with hypertonic saline solutions could delay onset of intracranial hypertension to enable successful emergency liver transplantation. Seizures might complicate advanced hepatic encephalopathy and worsen prognosis; however, results from one study did not suggest any benefit from phenytoin prophylaxis.[128]

Liver transplantation

Survival has been transformed by the introduction of emergency transplantation, which is now part of routine care in many countries for those patients with acute liver failure who meet criteria indicative of a poor prognosis. However, emergency transplantation outcomes are consistently lower than are those of elective surgery, with high early post-transplant mortality, mainly as a result of sepsis and multiorgan failure. Nonetheless surgical outcomes have shown progressive and substantial improvement, and in present series, 1 year survival exceeds 80% (figure 3).[62,66]

The ideal means for identification and selection of patients who are likely to benefit from emergency liver transplantation remains controversial. Inaccurate selection will have serious effects—a patient who would otherwise have survived with medical management and who has incorrectly received a transplant will be subjected to an unnecessary surgical procedure and lifelong immunosuppression, which is associated with major resource cost and increased risk of death. Furthermore, a graft that could be used in a more appropriate candidate will be lost. The result of failure to identify a patient with acute liver failure who would survive only with emergency liver transplantation is of equal magnitude, because a potentially preventable death will ensue.

Different selection criteria for emergency transplantation are used worldwide. Although details vary, most rely on factors of common prognostic importance on multivariate analysis of survival in non-transplanted patients, specifically presence of severe hepatic encephalopathy, patient's age, and severity of liver dysfunction as assessed by extent of coagulopathy or jaundice.[130–132] Criteria developed at King's College Hospital (London, UK) also consider the presentation and cause of disease and are among the most commonly applied, and form the basis for registration for emergency liver transplantation in the UK and elsewhere.[133] The Clichy-Villejuif criteria are also in widespread use in northern Europe for patients with severe encephalopathy, and assess outlook with consideration of coagulation factor V concentrations and patient's age (panels 2 and 3).[13,131]

Most criteria validation studies have assessed the King's College criteria. Findings from case series[66,134] and meta-analysis[135] have confirmed that these criteria have clinically acceptable specificity, with survival without transplantation in patients meeting criteria of less than 15%. However, sensitivity might be low and be unable to identify some patients who would die without emergency transplantation.[134,135] In recognition of these limitations, there have been many proposals to improve selection techniques either through replacement with alternative systems—such as the model for end-stage liver disease or bilirubin lactate and aetiology scores—or by addition of supplemental markers such as lactate,

phosphate, and α-fetoprotein.[136–139] However, no other criteria have so far has shown consistent and reproducibly better performance or have been as widely adopted as have the King's College criteria. Nevertheless, an urgent need to improve selection exists and remains a key area of investigation.

Three interacting factors affect the outcome of emergency liver transplantation: age of recipient, severity of pretransplant illness, and the nature of graft used. The more unwell a patient is, the less probable that transplantation will be done or be successful.[66] Severity varies by reason for liver failure, and is greatest in patients with paracetamol-related disease; deaths before transplantation are more than twice as common as in patients with acute liver failure due to other causes.[17,66] Recipient's age also has a strong effect on the outcome of emergency transplantation, with postoperative mortality more than doubled in those over 50 years of age.[62,66] An age-related reduction in physiological reserve probably explains this finding, and reminds us of the extreme physiological stress caused by acute liver failure and emergency liver transplantation. The third main factor that determines outcome is the nature and quality of the graft used. There are strong cumulative effects of adverse graft factors on survival of the patient and graft, with inferior outcomes in those patients receiving size-reduced, ABO-incompatible, or steatotic grafts.[66,140] Impaired early graft-function is poorly tolerated in acutely unwell recipients and might predispose to the development of sepsis—the main cause of postoperative death.

Successful transplantation requires individual matching of recipient and graft; the most ill patients might only respond to the best possible graft. A difficult decision has to be made between risking delay of transplantation until an ideal graft is available—with the likelihood of further clinical deterioration—and early acceptance of a suboptimum graft that might be associated with a poor outcome.[66]

Auxiliary liver transplantation is theoretically a promising treatment for acute liver failure. In this technique, a partial liver graft is placed either heterotopically or orthotopically, and all or part of the native liver is left in place. With resolution of the insult that caused the liver failure, the native liver could subsequently regenerate, allowing withdrawal of immunosuppression and graft atrophy or removal, and avoiding long-term side-effects and costs. This process might be possible in more than half of auxiliary liver recipients.[141–143]

Because auxiliary liver transplantation is a technically demanding procedure, findings from initial reports showed high rates of complication and retransplantation.[141] Outcomes have improved substantially, in part caused by improvements in surgical technique, but also from selection of patients. Most centres now consider auxiliary liver transplantation only for young patients with liver failure of specific causes and with restricted and stable extrahepatic organ dysfunction, along with the availability of an optimum graft. Regeneration of native liver depends on presence of sufficient residual native hepatocytes and occurs most commonly in young patients who have a hyperacute presentation from a viral or paracetamol-related cause.[142]

Living-donor transplantation is a recognised part of elective transplantation of paediatric recipients, and use in children with acute liver failure is well established.[144] The potential advantages of living-donor transplantation are the increased speed of availability of a high-quality graft and that rapid medical assessment of the donor seems practical.[145,146]

Case series[145,146] about selective use of living-donor transplantation in adults report 5-year survival rates of up to 80%. Similar to elective transplantation, the main dilemma in adults is procurement of an adequately sized liver graft. Since this is usually impossible to achieve with a left-lobe or left-lateral-segment graft, most successful reported cases of living-donor transplantation in acute liver failure have used right-lobe grafts. The ethical considerations are more complex in adult than in paediatric transplantation, in which the donor is often a parent who provides a left lobe.[147,148] Because complications might be more common in people donating a right rather than left lobe, and because candidate donors are often not the parents, the predonation ethical and psychological assessment is even more difficult.[149,150]

Future directions

A range of extracorporeal supportive devices has been advocated to replace liver function in patients with acute liver failure, either to stabilise the patient before transplantation, or to improve native liver regeneration. Despite many uncontrolled case series and individual randomised trials,[151–153] conclusive evidence of benefit to patients has not been reported. There are no published data to support the use of either biological or non-biological systems as sole treatment when emergency transplantation is available, outside a trial setting.

Hepatocyte transplantation has also been proposed for treatment of acute liver failure. In this technique, human hepatocytes are infused into the splenic or hepatic portal vascular beds or peritoneal cavity to provide adjunctive hepatic function for the failing liver. Although there have been reports of successful treatment of inborn errors of hepatic metabolism with this technique,[154] challenges for extension to acute liver failure are sizeable. The hepatocyte mass needed to support or replace lost liver function will probably be at least an order of magnitude greater than that needed for correction of isolated metabolic defects, and sustaining viability and function of infused cells in acutely sick patients with acute liver failure will probably be difficult. Although experience has suggested the technique is practical to undertake, a review of cases reported worldwide showed survival without

conventional emergency transplantation to be 35%.[154] Successful clinical application of hepatocyte transplantation in acute liver failure needs further improvement of the process in the non-acute setting; this treatment will probably be appropriate only in the most stable patients, and will serve initially as a means to support liver function while awaiting definitive liver transplantation.

Outcomes should continue to improve, with clinical advances resulting from an increased knowledge of the mechanisms of liver cell injury, hepatic regeneration, and the pathogenesis of encephalopathy and extrahepatic organ failure. Early recognition and treatment of patients with worsening liver failure and further development of intensive care and transplantation selection methods will also help to improve outcomes.

However, the greatest benefits in terms of reduced mortality and morbidity will probably result from public health measures to control drug-induced liver injury and, most importantly, through application of the effective and available methods to reduce the incidence of infection by hepatitis A, B, and E viruses.

Contributors

WB and JW conceived the Seminar. WB wrote the first draft and all authors contributed to the writing of the final version.

Conflicts of interest

We declare that we have no conflicts of interest.

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