and there is usually complete recovery[11]. Transmission is unknown and prevention impracticable.

It is likely that a number of viruses remain to be identified in this group and may then add to the alphabetic list.

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Acute liver failure

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Acute liver failure is one of the most challenging conditions to treat. Its outcome has been improved by a multidisciplinary approach that encompasses management in intensive care and liver transplantation. The treatment of acute liver failure may undergo further evolution if the newer extracorporeal systems prove to be effective in prolonging survival or acting as bridges to transplantation. A better understanding of its natural history has led to a revised categorisation of these patients and streamlined choice of management options. The new terminology uses the core term 'acute liver failure' which is prefixed by hyper- or sub- to describe the two ends of the temporal spectrum[1].

Terminology

Hyperacute liver failure: encephalopathy develops within seven days of the onset of jaundice. Paradoxically, this group has the highest likelihood of recovery with medical management, despite the characteristic rapid deterioration, high incidence of cerebral oedema and severe prolongation of prothrombin time.

Acute liver failure: encephalopathy develops 8–28 days after the onset of jaundice. This group has a high mortality, high incidence of cerebral oedema and marked prolongation of prothrombin time.

Subacute liver failure: the interval between the onset of jaundice and the development of encephalopathy ranges from 4–12 weeks. This state is also characterised by a high mortality, despite a low incidence of cerebral oedema and much less severe prolongation of prothrombin time.

Assessment of prognosis and monitoring

The most important management decisions are those concerning the need for referral to specialist centres and the indications for transplantation. Indications for transfer to specialist units for paracetamol overdose and other causes of acute liver failure are shown in Tables 1 and 2[2]. Separate criteria have been identified for use within specialist centres to identify the patients most in need of liver transplantation. The widely used King's College criteria[3] (Table 3) are early indicators of prognosis that do not rely on progression to the advanced stages of encephalopathy. In the original analysis, the discriminatory power of a metabolic acidosis with an arterial pH below 7.30 on the second or subsequent day after a paracetamol overdose was very strong (95% mortality), but the more liberal use of N-acetylcysteine and

Key Points

- Earlier referral and refinements of medical management continue to result in improved survival
- Liver transplantation options are widening through the use of auxiliary liver transplantation
- A new phase of interest in extracorporeal liver support may yield benefits in the near future

Table 1. Guidelines for referral of patients to specialist centres following paracetamol induced acute liver failure

Day 2	Day 3	Day 4
Arterial pH <7.30	Arterial pH <7.30	INR >6.0 or PT >75 sec
INR >3.0 or PT >50 sec	INR >4.5 or PT >60 sec	Progressive rise in PT
Oliguria	Oliguria	Oliguria
Creatinine >200 μmol/l	Creatinine >200 μmol/l	Creatinine >300 μmol/l
Hypoglycaemia	Encephalopathy	Encephalopathy

INR = international normalised ratio PT = prothrombin time

Table 2. Guidelines for referral of patients to specialist centres for non-paracetamol induced acute liver failure

Hyperacute	Acute	Subacute
Encephalopathy	Encephalopathy	Encephalopathy
PT >30 sec	PT >30 sec	PT >20 sec
Renal failure	Renal failure	Renal failure Serum sodium <130 μmol/l Shrinking liver volume

PT = prothrombin time

aggressive early rehydration appear to have improved the outcome in these patients. As a result, a transient acidosis in isolation from other prognostic indicators has to be more cautiously interpreted.

General measures

The principles of medical management are to prevent or treat the numerous complications that contribute to this medical emergency (Table 4). *Hypoglycaemia*, one of the earlier complications, can predate and mimic the development of encephalopathy. *Progressive vasodilatation* leads to increased fluid requirements and makes early monitoring of central venous pressures important. When patients develop *advanced encephalopathy* more sophisticated haemodynamic monitoring is required to optimise the management of the haemodynamic problems and the associated alterations in oxygen metabolism. Gastric protection (eg with sucralfate, 2 g three times a day) reduces the risk of *gastrointestinal haemorrhage*. The clinical problem of bleeding is considerably less than might be expected from the extent of derangements of the clotting tests; prophylactic administration of fresh frozen plasma is not recommended unless it precedes an invasive procedure.

The transfer of patients to specialist units requires high quality support; the accompanying team should be able to deal with sudden changes in conscious state, episodes of cerebral oedema, respiratory compromise and haemodynamic instability.

N-acetylcysteine is extensively used in the management of paracetamol induced acute liver failure. Initially, it was given to patients presenting within 16 hours of the overdose, but a retrospective study of 100 patients suggested some benefit up to 36 hours after drug ingestion[4]. This was confirmed in a prospective controlled trial of 50 patients, in which patients given N-acetylcysteine 36–80 hours after drug ingestion had fewer instances of cerebral oedema and haemodynamic instability, and there were more survivors[5]. Adequate studies of the overall effect of N-acetylcysteine on survival have not been performed for other causes of acute liver failure. No other drug subjected to controlled trial has been shown to be beneficial in acute liver failure.

A number of extracorporeal bioartificial liver support systems have been developed for clinical assessment in recent years. The *hybrid bioartificial liver* intermittently exposes separated plasma to a cartridge containing porcine hepatocytes attached to collagen-coated microcarriers after the plasma has been passed through a charcoal column designed to remove substances toxic to the hepatocytes[6]. The *extracorporeal liver assist device* continuously exposes whole blood to cartridges containing well differentiated human hepato-

Table 3. Selection criteria for liver transplantation[3]

Paracetamol	Other causes
Arterial pH <7.30*	INR >6.7 or PT >100 sec
OR *All 3* of the following:	OR *Any 3* of following:
PT >100 sec	Unfavourable cause (seronegative hepatitis, halothane hepatitis or drug reaction)
Creatinine >300 μmol/l	Jaundice >7 days before encephalopathy
Grade 3–4 encephalopathy	Age <10 or >40 years
	INR >4.0 or PT >50 sec
	Serum bilirubin >300 μmol/l

NB: All patients with Wilson's disease developing encephalopathy should be considered for transplantation.
INR = international normalised ratio
PT = prothrombin time
* Interpret with caution (see text).

blastoma cells[7]. Pilot studies have demonstrated some neurological improvement and modest biochemical changes with the use of these devices, but without prolonging survival[6–8].

Further appraisal of these systems is needed in properly constructed trials that take note of the heterogeneity of acute liver failure, and assess their impact on survival as well as their potential role as a bridge to transplantation.

Liver transplantation

Orthotopic liver transplantation has revolutionised the management of acute liver failure. Survival rates after transplantation average 61–63%, but have reached 93% in some exceptional series[9–11]. Excluding paracetamol induced acute liver failure, 45–51% of patients admitted with acute liver failure undergo transplantation[12–14]. The equivalent figures for paracetamol cases in the UK are only 7–9%[9,15,16]. Up to 27% of patients are considered to have contraindications to transplantation at the time of admission, and up to another 18% develop contraindications while they are waiting for a suitable graft to become available[12–14]. The principal contraindications to transplantation are irreversible neurological damage, sepsis and severe haemodynamic instability.

Table 4. Important general principles of management

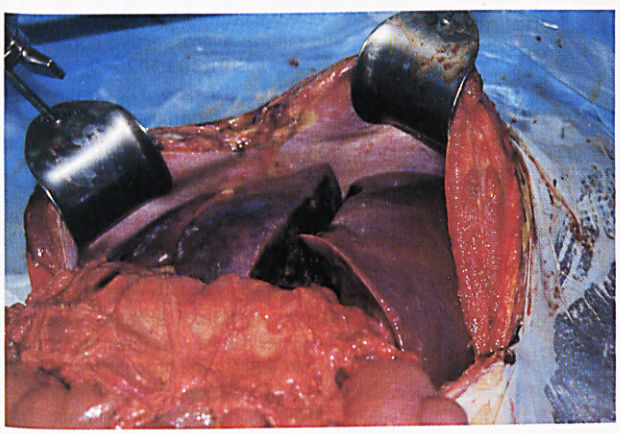
- Establish diagnosis
- Classify patient and make preliminary assessment of prognosis
- Establish contact with specialist centre
- Resuscitate patient and transfer safely to specialist unit
- Monitor for hypoglycaemia
- Protect the airways as encephalopathy progresses beyond grade 2
- Maintain adequate intravascular volumes, and support with inotropes when necessary
- Establish need for transplantation and intracranial pressure monitoring
- Reduce risk factors for, and treat, cerebral oedema and other neurological complications
- Institute aggressive surveillance for sepsis and early antimicrobial therapy
- Treat the other major complications, including renal failure, respiratory failure, clinical coagulopathy, metabolic derangements, pancreatitis

Heterotopic auxiliary liver transplantation has considerable potential in cases with the capacity to regain normal liver function after recovery from acute liver failure[17]. The theoretical advantage of this approach is that immunosuppression can be withdrawn after the native liver has recovered, sparing the patient the need for lifelong immunosuppressive therapy. A multicentre experience of 30 patients reported a survival rate of 63%, with 68% of these survivors ultimately weaned off immunosuppression[17]. The challenge is to identify appropriate patients with the capacity to regenerate to normal morphology, but who are not in need of the therapeutic advantage of removing the entire necrotic native liver.

Management of complications: new and controversial features

Encephalopathy

One of the main thrusts of management is the control of the neurological events that may complicate



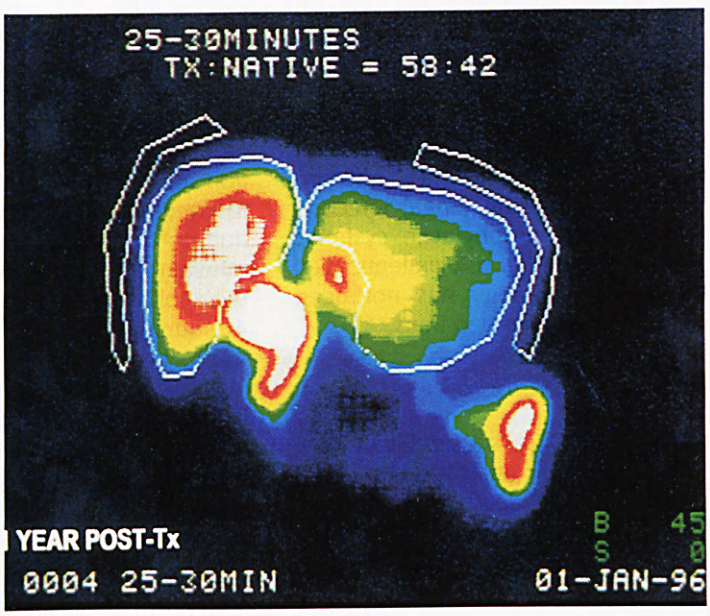


Figure 1. Auxiliary liver transplant: **(a)** the appearance on completion of the transplant (left lobe); **(b)** functional scan a year later, demonstrating 58% of function in the graft (left lobe) and 42% in the recovering native liver (right lobe).

grade 4 encephalopathy (ie cerebral oedema, hypoxic brain damage and occult seizure activity). Intravenous mannitol, 0.3–1 g/kg, remains the mainstay of management of increased intracranial pressure, but once cerebral perfusion pressure becomes compromised (<50 mmHg), aggressive inotropic support and optimisation of oxygen delivery to the brain is indicated. Cerebral oedema resistant to these measures may respond to sodium thiopentone or acute hyperventilation using low tidal volumes. Subclinical seizure activity, which occurs in up to 45% of patients, is now recognised as an aggravating factor for cerebral oedema, and the prophylactic use of phenytoin decreases the incidence and severity of cerebral oedema[18]. Patients *in extremis* have been subjected to hepatectomy, with dramatic improvements in neurological and haemodynamic stability facilitating successful transplantation up to 24 hours later[19,20].

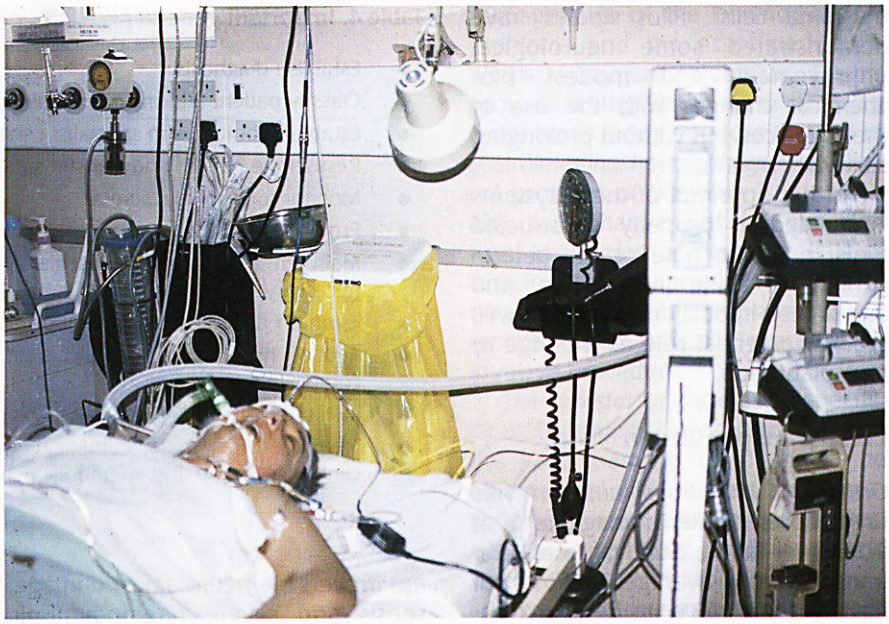


Figure 2. Patient with acute liver failure undergoing intracranial pressure monitoring.

Infection

Infection is common in acute liver failure (up to 82% bacterial and 34% fungal) and has been implicated in 50% of deaths[21,22]. Selective intestinal decontamination has convincingly lowered the incidence of bacterial infection. In one study the infection rate was reduced to 26% with the prophylactic use of broad spectrum antibiotics[23]. However, these regimens were associated with the emergence of multiple strains in 9% of patients[22]. The difficulties encountered in diagnosing fungal infection justify giving prophylactic systemic antifungals in high risk patients even though this strategy has not been validated by controlled trials.

Circulatory failure

Circulatory failure is a significant contraindication to transplantation and a major mode of death in acute liver failure, often occurring against the background of sepsis or multi-organ failure. Hypotension occurring despite adequate intravascular volumes (pulmonary capillary wedge pressure 10–14 mmHg) is treated with vasopressor agents, with noradrenaline if the cardiac index exceeds 4.5 l/min/m^2, or adrenaline if the cardiac output needs to be boosted above this threshold[24]. The initial stabilising dose to achieve a mean arterial pressure above 60 mmHg is 0.2–1.8 mg/kg/min of adrenaline and 0.2–2.0 mg/kg/min of noradrenaline[24]. Vasopressor agents may cause or aggravate an oxygen debt, and prostacyclin infused at a rate of 5 ng/kg/min improves indices of oxygen metabolism (delivery, consumption and extraction ratio) when used in conjunction with both adrenaline and noradrenaline[24]. N-acetylcysteine infusion (10 mg/kg/min for 15 minutes, followed by 0.2 mg/kg/min for 4 hours) causes less vasodilatation than prostacyclin, independently increases mean arterial pressure, and is as effective as prostacyclin in improving oxygen metabolism[25]. The combination of prostacyclin and N-acetylcysteine improves oxygen metabolism more than either drug alone[25].

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Investigation and management of gastrointestinal motility disease

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Gastrointestinal motility disorders vary from the rare and well defined, such as achalasia, to the common but nebulous, such as irritable bowel syndrome (IBS). Motility tests have made their biggest impact in the management of oesophageal and gastric disorders and have also found some use as tests of biliary and intestinal motility. Patients needing such investigations should be referred to a gastroenterologist once the preliminary investigations have been performed.

Oesophageal motility

Swallowing requires the coordinated, initially voluntary, action of the striated muscle of the tongue and pharyngeal constrictors, followed by the relaxation of the cricopharyngeus which forms the upper oesophageal sphincter. The bolus is then moved on by coordinated contraction of the smooth muscle of the oesophagus. Distension of the oesophagus induces a descending inhibition mediated by nitric oxide-releasing neurons and an ascending stimulation of the circular muscle by cholinergic neurons. The net effect is to produce a powerful aboral propulsion. Swallowing induces descending inhibition with an anticipatory relaxation of the lower oesophageal sphincter (LOS); this begins simultaneously with the contraction of the pharyngeal muscles. Once the bolus has passed the LOS, the sphincter returns to its resting state of tonic contraction just above intragastric pressure.

Disordered swallowing and peristalsis

Oropharyngeal disorders

Choking, nasal regurgitation and prolonged chewing with a fear of attempting to swallow are characteristic of diseases affecting the oropharyngeal muscle such as myopathies, motor neuron disease, and bulbar and 'pseudobulbar' palsies affecting the vagus and ninth cranial nerve. These disorders can usually be diagnosed by history and neurological examination.

Investigation

A cineradiographic contrast study shows oropharyngeal incoordination and frequently aspiration into the trachea. Rarely a fibrotic 'cricopharyngeal bar' may be detected which fails to distend as the bolus passes. This is often associated with high pharyngeal pressures and the development of a hypopharyngeal diverticulum.