Current Management

Management of acute liver failure

Roger Williams

Liver Unit, King's College Hospital, Denmark Hill, London SE5 9RS

In the management of a patient presenting with acute liver failure it is essential to identify both the cause and the type of liver failure (Table I). Patients may have established chronic liver disease and develop liver failure during intercurrent infections or variceal haemorrhage, or they may have no previous history of liver disease. With the latter group the presentation is then either as fulminant liver failure (encephalopathy within 8 weeks of onset of symptoms) or with a slower course (encephalopathy developing within 6 months of onset) which has been termed late-onset hepatic failure. The measures discussed in this paper apply only to those with no antecedent history of liver disease in whom regeneration of the liver to a normal structure is seen in the survivors. Paradoxically in fulminant hepatic failure (FHF) the prognosis is better the more rapid the onset of encephalopathy, as measured from the first appearance of jaundice.

Table I Classification of liver failure

Onset of symptoms		
Acute liver failure		Chronic/acute on chronic hepatocellular failure
FHF	'Late onset' liver failure (subacute hepatic necrosis)	Chronic liver disease
0	8 weeks	6 months

Aetiology

Aetiology should be established in all cases if at all possible (Figure 1). Paracetamol poisoning may be obvious from an indication of suicidal intent and can be confirmed by blood measurements. The clinical history may also help in the identification of other drugs causing liver failure, e.g. halothane,

Figure 1 Making a diagnosis in acute liver failure.

non-steroidal anti-inflammatory drugs (NSAIDS), anti-tuberculosis drugs, antibiotics. Infectious hepatitis may be suspected if there has been recent travel abroad or if children in the family have also had hepatitis recently. Acute type B (HBV) hepatitis should be suspected in a traveller back from high prevalence areas (Far East, Africa) or if he or she is from one of the known high risk groups, namely drug addicts or homosexual. A drug addict may also have coincident or superinfection with δ antigen. In confirming HBV infection, testing for IgM anti-HBc allows distinction of acute infection from the carrier state with superinfection by delta or even non-A, non-B infection (Figure 1). The largest group of cases of fulminant viral hepatitis now seen in the UK are non-A, non-B. Results of serological tests for hepatitis A and B will not be available to help in the middle of the night. Interferon therapy has been used by Israeli workers in treatment of fulminant viral hepatitis but its value has not been confirmed. In the context of HBV infection, anti-viral therapy would not be expected to have a beneficial effect, for in the fulminant cases it has been shown that viral replication has already ceased by the time that liver damage becomes apparent.

Rare causes of liver failure include those occurring in pregnancy, the Budd-Chiari syndrome or following ingestion of *Amanita phalloides*.

Correspondence: R. Williams, M.D., F.R.C.P., F.R.C.S.
Accepted: 7 April 1988
Based on a contribution to the Symposium on Organ Failure organised by the Royal College of Physicians and held in Edinburgh on 30th October, 1987.

Early management

Management of patients in liver failure depends on the time of presentation and on the severity of the clinical and biochemical changes that have developed. If seen early in the clinical course when the patient is only moderately jaundiced and with mild (grade 1–2) encephalopathy, dietary protein should be restricted. Most patients though are not able to eat. Lactulose is usually given, though its value has never been proven by controlled trial, and it may cause serious electrolyte disturbance if the resulting diarrhoea becomes excessive. Hypoglycaemia, leading to cerebral damage, should be prevented by intravenous infusion of glucose. A failure to maintain adequate blood glucose levels by intravenous infusion, especially when transferring a patient to another unit, would be held to be negligent if cerebral damage occurred. An adequate intravascular volume should be maintained and histamine-2 antagonists given to prevent gastrointestinal erosions. Paracetamol poisoning presents special problems including lactic acidosis, which often cannot be corrected by bicarbonate infusion. Renal failure may precede the appearance of encephalopathy and both this and the acidosis require early haemodialysis.

Middle period management

This applies to patients with Grade II or III encephalopathy and is concerned with the delaying and avoidance whenever possible of the later, severe complications, detailed below, which have a major influence on prognosis. Management includes the provision of good vascular access for haemofiltration or haemodialysis, a Swan Ganz catheter to monitor intravascular volumes and pressures, as well as cardiac output, together with serial measurement of blood gases, acid base balance and renal function.

Late phase management

Most important in management where the patient has reached the stage of grade IV encephalopathy is the treatment of complications as these become established, particularly renal failure, cerebral oedema, sepsis and coagulopathy (Table II). Renal failure requires early ultrafiltration and haemodialysis. Cerebral oedema with coning is responsible for the majority of deaths in this group of patients. Intracranial pressure should be monitored using an extradural pressure monitor. A raised intracranial pressure is treated initially by with repeated boluses of mannitol, this being combined with ultrafiltration once renal failure develops. Those patients resistant to this regime should be acutely hyperventilated and if this fails the next approach is intravenous doses of thiopentone titrated according to blood level. Any manipulation of the patient including physiotherapy, turning etc. can cause a rise in intracranial pressure; patients should be nursed with the head and thorax at 45° to the horizontal.

A recent survey of severely ill patients with liver failure treated in the Liver Failure Unit at King's College Hospital, many of whom had evidence of improving hepatic function, showed 90% to have bacterial or fungal infection, possibly a reflection of the longer survival periods being obtained with intensive liver care. At all stages sepsis should be vigorously sought for and treated aggressively (Figure 2).

Liver support and new measures including transplantation

In addition to the intensive liver care management of the patient already described, temporary liver support using haemoperfusion over activated charcoal was shown to be of benefit in early trials, although not confirmed in the most recent one carried out at King's College Hospital. In particular, the length of time (10 hours versus 5 hours)

Table II Late phase of management of grade IV encephalopathy with established complications

Urgent consideration of assisted ventilation and insertion of intracerebral pressure monitor			
Cerebral oedema	:	Initially mannitol (100 ml of 20% by rapid bolus) ± ultrafiltration (300 ml) then thiopentone bolus/infusion	
Renal failure	:	Haemodialysis – serum creatinine > 400 µmol/l	
Sepsis surveillance	:	Bacterial (early)	Cover both Gram positive and negative
			G – ve
			piperacillin and gentamicin or amoxycillin and ciprofloxacin
		Fungal (later)	5 flucytosine and amphotericin together
Coagulopathy	:	Blood, FFP, platelets as needed (not prophylactic)

Figure 2 Bacterial and fungal infection in fulminant hepatic failure. Frequency of infection in a recent series of patients (from unpublished data of Rolando and colleagues).

that patients were treated by liver support did not seem to affect outcome. In that time, the underlying aetiology of the liver failure had the greatest influence on prognosis many more of the patients with paracetamol poisoning or hepatitis A or B survived than did those with non-A, non-B hepatitis or drug-induced liver failure (Table III). Similarly, the frequency with which the various complications can be combatted by intensive care management also differs in the various aetiological sub-groups, presumably reflecting the varying ability of the liver to regenerate. With respect to the latter, Japanese workers have used glucagon and insulin to stimulate liver regeneration in acute viral hepatitis but its value in improving survival in fulminant hepatic failure is unproven. A study of this is in progress at King's College Hospital using serum α -fetoprotein as a measure of hepatic regeneration.

In patients with a poor intrinsic prognosis, e.g. non-A, non-B hepatitis, halothane hepatitis or drug idiosyncrasy (Figure 3), liver transplantation should be considered early in the course in order that as much time is given for a donor organ to become available. In a recent series of such cases in the Cambridge/King's College Hospital joint programme, 65% of patients survived and are doing

Table III Charcoal haemoperfusion trial. Overall survival in 137 patients according to aetiology

Aetiology	n	Survival (%)
Paracetamol overdose	85	52.9
Hepatitis A	6	66.7
Hepatitis B	18	38.9
Hepatitis non-A non-B	20	20.0
Halothane/drugs	8	12.5

Figure 3 Illustrates improvement in survival results for fulminant hepatic failure (grade 3-4 encephalopathy) in King's College Hospital series for certain aetiological groups since Liver Failure Unit was opened in 1973.

well following transplantation. Many of the anticipated difficulties relating to severe coagulation disturbance and presence of cerebral oedema at the time of operation did not materialize. In the non-A, non-B fulminant hepatitis group there may be a mild recurrence of the original infection at 6 weeks to 3 months after the transplant.

Summary

The principles of management for acute liver failure are:

1. Accurate diagnosis of the type – fulminant, late onset, acute on chronic – and establishment of likely aetiology.
2. Early detection and treatment of complications, particularly metabolic acidosis (early), renal failure, cerebral oedema and infections (late).
3. Optimization of conditions for regeneration by maintenance of normal metabolic milieu (? removal of toxins).
4. Early consideration of an orthotopic liver transplant for poor prognosis group.

Selected bibliography for further reading

1. *Clinics in Critical Care Medicine – Liver Failure* (Ed. Roger Williams), Churchill Livingstone, Edinburgh, London, 1986.
2. *Seminars in Liver Disease* (Eds. Paul D. Berk and Roger Williams), Vol. 6, No. 2. Thieme-Stratton, New York, 1986.
3. O'Grady, J.G. & Williams, R. Management of acute liver failure. *Hospital Update (Emergency Medicine)* 1987, 13: 481-493.
4. O'Grady, J.G., Gimson, A.E.S., O'Brien, C.J., Pucknell, A., Hughes, R.D. & Williams, R. Controlled trials of charcoal haemoperfusion and prognostic factors in fulminant hepatic failure. *Gastroenterology* 1988, 94: 1186-1192.