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Acute liver failure – practical management

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Abstract

The three most important components of the management of Acute Liver Failure are :-

1) Identification of causes requiring specific treatment including hepatic lymphoma, the Budd-Chiari syndrome, ischaemic hepatic necrosis, fulminating septicaemia, Wilson's disease and reactivation of HBV in chronic carriers.

2) Institution of early monitoring and optimal intensive care for multi-organ involvement to improve chances of spontaneous recovery or of transplantation. Deteriorating encephalopathy with cerebral oedema is related to a systemic inflammatory response and infections need to be treated aggressively.

3) Assessment of the need for transplantation based on strong positive predictive values provided by the King's or Clichy criteria. A significant percentage of those not fulfilling criteria also progress. The MARS liver support device has corrective effects on the disturbed pathophysiology of ALF and may be used to enhance spontaneous recovery or as a bridge to transplant, although the latter is not yet proven by controlled clinical trial. (Acta gastroenterol. belg., **2006**, 69, **210-213**).

Three key areas of management need to be addressed when confronted with, or asked for advice on the treatment of an established case of acute liver failure (ALF). The first is whether the cause has been sufficiently investigated, using the full range of virological, toxicological and imaging modalities and including in selected instances the obtaining of liver histology, so that those cases potentially amenable to specific measures are identified, eg. Budd-Chiari syndrome or Wilson's disease. Along with this is the determination of the likely category of ALF-hyperacute, acute or subacute which gives an indication of the prognosis and of the clinical features that are most likely to require treatment. The second area is the establishment of early monitoring and optimal care for the multiorgan failure that is so characteristic of the later stages of ALF. Transfer to a specialized liver unit should be done early. With progression of disease transportation becomes more difficult on account of deleterious effects on encephalopathy and the risks of precipitating cardio-respiratory arrest. The third key area is early recognition of the need for liver transplantation based on the well established King's or Clichy criteria.

The latest data from the Acute Liver Failure cooperative study in the USA, gives a more optimistic outcome for survival than in most standard textbooks (Fig. 1) (1). Overall survival was 43% without a transplant and figures for the UK are similar (Fig. 2) (2). The better survival is largely due to the number of paracetamol hepatotoxicity cases (hyperacute category), where despite the rapidity of onset and the severity of manifestations, spontaneous recovery is more likely. A potentially important finding from the USA group was the detection of acetaminophen in the serum of about 40% of patients with ALF attributed to hepatitis A and B infections, the drug presumably having been ingested for relief of viral associated symptoms. Serum alanine-aminotransferase levels were higher in this group (5,400 v 1,367 IU/L) as was prolongation of INR (5.3 v 2.6), suggesting an additive effect of the acetaminophen on the viral hepatitis injury and raising questions as to use of the antidote N-acetylcysteine in such cases (3).

Data from 17 Tertiary Care centres

- 308 Consecutive patients admitted over 41 mts
- Acetaminophen overdose 39% (*suicide 37%, accidental 57%*) idiosyn. drug reaction 13%, viral hepatitis A & B 12%, indeterm. 17%
- 29% had OLT (*6% only for Acetamin.*) and 43% survived without transplant giving overall survival of 67%

Fig. 1. — Prospective study of Acute Liver Failure in the USA from Liver Failure Study group

Optimal care for multi-organ failure

The underlying hepatic necrosis in ALF has effects on a number of other organs and systems in the body with multiorgan failure as the final event leading to demise (Fig. 3) (4). Severe coagulopathy, encephalopathy and haemodynamic instability are major components of the clinical syndrome. Each can to some extent be controlled as can manifestations in more distantly affected organs including the kidneys as well as the metabolic and nutritional disturbances that result from severe liver failure. The occurrence of infection consequent on an early major depression of the body's phagocytic and immune defence mechanisms is increasingly recognised as an important factor in the progression of encephalopathy and development of cerebral oedema (5,6,7,8). Our findings showing correlations with

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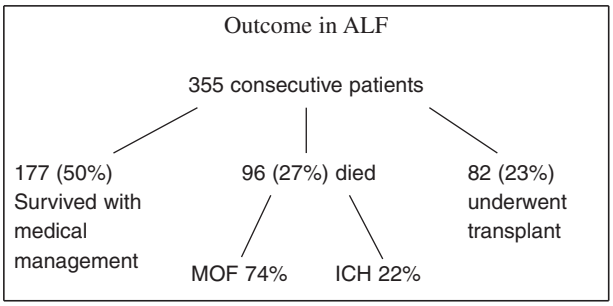

Fig. 2. — Single centre experience of (King's College Hospital) of outcome in Acute Liver Failure.

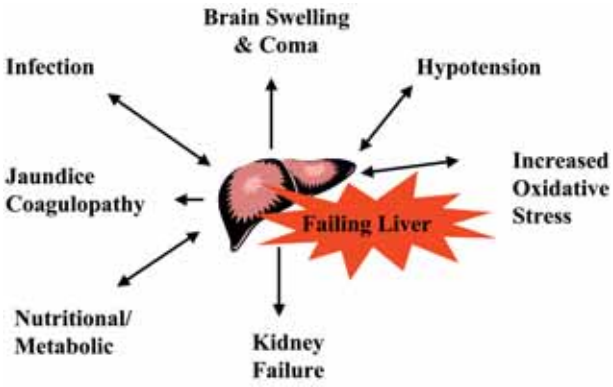

Fig. 3. — Cartoon illustrating main features of clinical syndrome of Acute Liver Failure and associated multiorgan involvement.

components of the systemic inflammatory response may also point to some of the mechanisms involved (through cytokine release) (Fig. 4) (7). Infections, circulatory instability, nutritional and metabolic changes may all have additional damaging effects on the underlying processes of liver damage, possibly through common mechanisms of oxidative stress thus emphasising the need for instituting corrective measures at the earliest possible time.

Important aspects of the intensive care management are based on results of randomized controlled trials of ICU outcomes in other critical care situations as well as in ALF and for more detailed consideration the reader is referred to the recent reviews by Sizer *et al.* (9) and Blei (10) (Fig. 5 & Fig. 6). Sedation is with opiates and propofol ; paralysing agents are best avoided as they may mask seizure activity and signs of raised ICP (11,12). In endeavouring to maintain an adequate circulatory volume in the face of progressive systemic vasodilatation, volume replacement whether based on colloids or crystalloid is essential but has to be carefully monitored as over-repletion may be equally dangerous. If vasopressor drugs have to be added noradrenaline is probably the safest. Terlipressin/glypressin has been shown to worsen cerebral hyperaemia in ALF with severe encephalopathy (13). Intravenous hydrocortisone

COMPONENTS OF SIRS –

Temperature > 38° or < 36°C, Heart rate >90/min, Respiratory rate > 20/min or $PaCO_2$ < 4.3kPa, WBC > 12 or < 4 x 10^9/L

In series of 887 patients -

- Those manifesting increase in encephal. grade or ICP more often infected & with > two SIRS components
- Those with SIRS (57%) more likely to have worsening encephalopathy – 77% v 68% (p = .003)

Fig. 4. — Relationship between components of systemic infection response (SIRS), and encephalopathy in ALF.

Basic ICU Care :

- Early restoration of circulating volume & low threshold for invasive monitoring
- Active control of blood glucose target 4 - 6 mmol/L with insulin infusion as required
- CVS support with steroids in those on vasopressors if Synacthen response inadequate
- Continuous veno-venous haemofiltration at least 35ml/kg/hr & started early when NH_4 high & metabolic acidosis severe

Fig. 5. — Practical management of ALF I – Basic care in Intensive Care ward.

Encephalopathy & raised ICP :

- Intubate & ventilate at Grade III, Nurse at 15°
- Sedate with Propofol, no paralysis as masks seizure activity, IV magnesium for hypertonicity or clonus
- Cerebral monitoring by reverse jugular oximetry. ICP bolts if proceeding to OLT
- Maintenance of moderate hypernatraemia (Na 145-50 µmol/L), bolus mannitol
- Patients cooled to around 36°C
- IF REFRACTORY → aggressive cooling, bolus indomethacin, short-term hyperventilation

Fig. 6. — Practical management II – Specific measures in slowing progression of encephalopathy and cerebral oedema.

may also be required as adrenal insufficiency – shown by a short synacthen test (14), is common in ALF and similar to the situation in sepsis impairs the response to pressor agents. Insulin resistance is a feature of ALF and hyperglycaemia is known within the ICU population to be detrimental to outcome. Tight blood glucose control (target 4-6 mmol/L) with an insulin infusion is essential.

The management of infection is all important because of the adverse effects on encephalopathy already referred to and with infective episodes often the immediate cause of death in association with multiorgan failure. The patient may already be infected by the time of referral to the liver centre and antibiotics should be started (or continued) whilst awaiting blood culture results on the basis that during the first week of illness,

infections with gram positive organisms predominate. Gram negative ones are subsequently more frequent and fungal infections are increasingly likely, and to be of clinical importance, from the second week onwards. Prophylactic antibiotics were shown in one study when started early in the course to reduce the incidence of septic episodes and improve encephalopathy but without any effect on mortality (6).

A useful and safe technique in monitoring for the development of cerebral oedema and elevation in ICP is serial measurement of jugular bulb venous saturation through an indwelling catheter or by continuous oximetry. Low values in comparison with mixed venous oxygen saturations are indicative of reduction in cardiac output or increased utilisation as with convulsive activity. High saturations reflect hyperaemia, ischaemia or failure of oxygen utilisation. The insertion of a subdural intracranial bolt is not without risk but can be of considerable value in guiding management decisions particularly with considerably raised ICP levels and if the patient is proceeding to orthotopic liver transplantation (15,16). In a recent study, it was shown to provide no survival advantage though it did result in more frequent treatment of cerebral oedema (17). Bolus administration of hypertonic mannitol is a proven value in the early stages of cerebral oedema and the maintenance of moderate hypernatraemia (serum sodium 145-150 µmol/L) by infusion of 30% saline IV has been shown to reduce ICP without altering mean arterial pressure (18). For patients refractory to these measures, bolus doses of propofol can give a prolonged reduction in ICP. Indomethacin administration again in bolus doses has been shown to be of value in single case reports (19) and recently received confirmation in an experimental model of liver failure. Short-term hyperventilation can also be effective in controlling otherwise uncontrollable surges in ICP (20). The use of hypothermia is a potentially valuable approach. Its effectiveness in lowering ICP was first shown by Jalan and colleagues in describing 7 patients unresponsive to conventional therapy (21). Core temperatures were reduced to 32° or 33°C, using cooling blankets for 8 hours. ICP was lowered (mean 45 → 16 mmHg) consequent on a parallel decrease in cerebral blood flow (103 → 44 ml/100 g^{-1}/min^{-1}), and cerebral perfusion pressure brought up to safe levels.

The effectiveness of IV N-acetylcysteine (NAC) infusion in lessening the incidence and progression of multiorgan failure in ALF with a reduced frequency of cerebral oedema, hypotension and renal failure as originally reported (22) is currently being re-examined in multicentre trial in the USA. Underlying the effectiveness may be an enhanced tissue perfusion with reduction in tissue hypoxia although the original clinical studies in ALF (23,24), have been questioned by workers in Edinburgh on the basis of the methodology used for determining oxygen consumption (25). Nevertheless, there is considerable clinical evidence attesting to its value in other ICU situations of multiorgan failure and it continues to be widely used. As an antidote to paracetamol hepatotoxicity, its value when given early cannot be questioned and in such cases it is also worth giving up to 24 hours after the overdose.

Modification of KCH criteria
for acetaminophen-induced ALF

- CONSIDER LISTING IF :- Arterial lactate concentration > 3.5 mmol/l after early fluid resuscitation
- LIST FOR TRANSPLANTATION IF :- Arterial pH < 7.3 OR arterial lactate concentration > 3.0 mmol/l after adequate fluid resuscitation, OR concurrently :- Serum creatinine > 300 µmol/l, INR > 6.5 & grade III encephalopathy or above

Fig. 7. — Modification of KCH criteria for acetaminophen-induced ALF.

Assessment of the likely need for liver transplant

Validation of the King's and Clichy prognostic criteria for ALF confirms strong positive predictive values of 90-95% (26). Unfortunately, a considerable number of cases not fulfilling criteria do deteriorate and negative predictive values in some of the more recent validation studies have been in the order of 50% - 60% only. Arterial lactate levels have been shown recently to be of added value in acetaminophen-induced liver failure with modification of the King's criteria for this group (Fig. 7) (27). The early identification of irreversible hepatic injury is of the utmost importance for even in the best centres survival figures for an emergency liver transplant are 10%-20% lower than for an elective transplant because of the associated multiorgan failure.

The use of an effective liver support device could enhance the rate of spontaneous recovery in ALF as well as maintaining or even improving the condition of those awaiting transplant thereby providing additional critical time for a donor organ to be obtained – a true bridge to the procedure (28). The Molecular Adsorbents Re-circulating System (MARS) based on albumin dialysis in an extracorporeal circuit, in which the patient's blood dialysed against an albumin impregnated membrane, is one such technique (29). Effective removal of protein bound toxic substances from the blood is obtained. With daily 8 hour perfusions, correction of other aspects of the disturbed pathophysiology in ALF has been reported by Schmidt and his group (30,31) notably a rise in systemic vascular resistance and a decrease in the abnormal elevations of blood amino acids.

In summary, ALF remains one of the most demanding disorders in medicine to treat in terms of the need for specialised knowledge, investigatory facilities, and high level intensive care. Transplantation currently offers the only chance of survival for a substantial number of cases but is limited by its availability of Cadaver organs. Only by a better understanding of the basic mechanisms responsible for the liver injury and of the process leading

to multiorgan failure is the continuing high mortality likely to be reduced.

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