

HOW I DIAGNOSE AND TREAT ACUTE (FULMINANT) LIVER FAILURE

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INTRODUCTION

Acute (fulminant) liver failure (ALF) is a rare but devastating clinical condition resulting in massive hepatocyte cell death. The clinical syndrome is characterised by hepatic encephalopathy (HE) in the presence of significant liver injury as evidenced by deranged coagulation and elevated serum transaminases. ALF can rapidly progress to multi-organ failure and death. The causes of ALF vary according to geographical area; paracetamol or acetaminophen hepatotoxicity (POD) is more common (70-80% cases series) in the developed world, and in contrast, viral hepatitis is more frequently found in other countries. However, in most case series' the cause of ALF cannot be identified in a significant proportion of patients, so-called seronegative or nonA-E hepatitis. The ALF syndrome is classified further according to the period between the development of clinical jaundice and HE; hyperacute ALF (≤ 7 days), acute ALF (8-28 days), and sub-acute ALF (5-12 weeks). POD characteristically causes hyperacute ALF and is associated with greater risk of fatal complications such as cerebral oedema (CO), but relatively increased spontaneous survival. In contrast, viral and seronegative hepatitis causes acute or subacute ALF, the risk of CO is lower but the chances of spontaneous survival are relatively reduced.

How do I Recognise Patients with ALF?

Because POD is the most common cause of ALF in the UK, this seems a rather easy-to-answer question. However, in the UK the proportion of cases following single time point suicidal consumption of excessive amounts of paracetamol is becoming less frequent. Suicidal consumption of paracetamol and subsequent hepatotoxicity follows a recognisable clinical course; the patients usually present because they have taken an overdose, a significant elevation of serum

transaminases develops, reaching a peak level of several 100-fold increase by 3 days, increasing coagulopathy, acidosis, kidney injury, and HE follow with multi-organ failure and death. In contrast, after accidental consumption of excessive paracetamol patients present significantly unwell, possibly unconscious, hypothermic, hypotensive with significant acidosis, kidney injury, and hypoglycaemia. Serum transaminases may not be significantly elevated in such cases, but paracetamol may still be detectable in the blood and the patients are usually significantly jaundiced with coagulopathy. Paradoxically, patients with accidental overdoses have a significantly worse outcome compared with suicidal overdose.

In contrast, patients with acute or sub-acute ALF can be difficult to differentiate from those with decompensated chronic liver or acute-on-chronic liver failure. These patients may have jaundice, encephalopathy, ascites, and portal hypertension. Often radiological imaging shows a small and shrunken liver, due to parenchymal collapse rather than cirrhotic nodules. A relatively short clinical course may be the only clue and such cases require a high index of suspicion to be identified. Where there is doubt, liver biopsy is essential, although this may have to be acquired via the transjugular route due to the coagulopathy and ascites. Wilson's disease may present with ALF; this is an extraordinarily rare but characteristic clinical syndrome. The patients are usually in their late teens, presenting with encephalopathy, very high serum bilirubin due to haemolytic anaemia, and low serum alkaline phosphatase levels. These patients have liver cirrhosis, but are managed in similar fashion to other cases of ALF.

How do I Manage Patients without HE or with Low-Grade HE?

Patients with significant acute liver injury and coagulopathy require management in high dependency or intensive care environments.

Close monitoring of organ systems, particularly renal, cardiovascular, and neurological systems, is essential. Frequent biochemical monitoring of blood glucose, phosphate, coagulation, creatinine, and other liver functions is required, sometimes as frequently as 4-times per day. Blood glucose may be measured even more frequently in hyperacute cases, where 2-hourly measurements would not be excessive. Careful attention to fluid balance, correction of electrolyte disturbance (especially hyponatraemia), and avoidance of significant hypotension are important. Coagulation monitoring mostly utilises measuring the prothrombin time (PT) and impressive prolongation of PT can be observed. Routine correction of PT should be avoided as this is an important prognostic marker. More complete assessment of the coagulation and fibrinolytic systems in ALF has revealed a balance that results in no increased risk of spontaneous bleeding. In fact, invasive monitoring can be safely inserted in patients with ALF and prolonged PT. We only routinely administer coagulation factors when inserting intracranial pressure monitors. N-acetylcysteine may be helpful in both POD and other causes of ALF. Specific treatments such as anti-viral therapy, transjugular intrahepatic stent shunts, or delivery may be appropriate for viral hepatitis, acute Budd-Chiari syndrome, and pregnancy associated ALF, respectively. Early psychiatric involvement, before the development of HE in cases of POD, are often crucial in assisting decisions regarding emergency liver transplantation (LTx) should a patient deteriorate.

When do I Decide to Refer to a Transplant Centre?

There are few data to guide decisions regarding transfer of patients to liver transplant centres. Transfer of patients following the development of HE can be risky, with the significant potential for deepening HE, development of CO, or cardiovascular instability. Patients with HE should be ventilated for transfer. Waiting until patients have achieved national criteria for transplantation in referring units before transfer should be avoided; this limits assessment in transplant centres and may fatally delay listing for emergency LTx. Early discussion with a transplant centre should be undertaken where there is doubt. Published guidelines from the British Society of Gastroenterology suggest early acidosis (pH <7.3), rising international normalised ratio (>3.5 and rising), or PT (>number of hours after the overdose), HE, rising serum creatinine (>200 µmol/l), or

hypoglycaemia are worrying clinical features and should prompt discussion with transplant units in patients with POD. Elevated arterial lactate (>3.5 mmol/l) especially if not responsive to fluid resuscitation is another sign of potential for deterioration in patients following POD. Recently we have suggested that sequential organ failure assessment (SOFA) scoring may assist transfer decisions in patients with POD; SOFA scores of <7 are rarely associated with significant extra-hepatic organ failure and HE.

Timing transfer of patients with non-paracetamol ALF is more problematic and again early discussion with transplant centres is advocated. Rising bilirubin and shrinking liver volume are signs of potential deterioration in patients with non-POD severe liver injury. Patients who have otherwise reached the UK non-paracetamol ALF transplant listing criteria, but without HE should be discussed. Infection in these patients can cause rapid and fatal deterioration. Within the UK there are discussions regarding potential for emergency transplant listing in such cases in the absence of HE.

How do I Manage Patients with ALF in the Intensive Therapy Unit (ITU)?

Managing patients with ALF in ITU is a complex and challenging topic. Locally a team of physicians and intensivists manages our patients. Several guidelines have been published, EASL are due to publish more up-to-date guidelines shortly. Early renal replacement therapy, protective ventilation strategies, and cardiovascular support (with norepinephrine) are often required. Continued controversy regards prophylactic antibiotic therapy and use of intracranial pressure monitoring. Locally we use prophylactic antibiotic and anti-fungal therapy in all ventilated patients. Our hyperacute ALF patients have intracranial pressure monitoring guided by arterial ammonia concentration; significantly elevated ammonia is associated with increased risk of raised intracranial pressure in hyperacute ALF. We use mannitol and hypertonic saline as our first-line treatment of CO. Use of plasmapheresis may improve survival, but this trial has not been published as a full paper yet. There is continued hope for the development of an effective liver support device for use in ALF cases; a meta-analysis of the currently published data suggested survival advantage but the introduction of liver support into routine clinical management presents a considerable logistical challenge.

How do I Decide if Patients with ALF need Emergency LTx?

A recent provocative review challenged conventional criteria for emergency LTx in patients with ALF, especially in POD-ALF. LTx has never been the subject of a randomised trial in ALF. Improved spontaneous survival in POD cases with careful ITU management have been reported in one specialist unit, but it is not clear if this occurs elsewhere. In the UK the modified King's College criteria are used to identify patients for emergency LTx, but these were first published in 1989. Two recent systematic reviews and meta-analysis of these transplant criteria have highlighted reduced sensitivity and also some reduction in specificity over the intervening years. A national review of emergency LTx criteria has been commissioned in the UK and this group is due to report soon.

Currently my approach to deciding candidacy for LTx of an individual ALF patient depends on collecting as much information regarding the patients previous history before onset of HE; alcohol, drug, and previous psychiatric issues are most relevant in POD patients and may exclude up to 25-30% of cases from further consideration. Some patients are just too unstable to consider transplantation (25-30%), a situation that is more common in POD cases. I will not list POD cases without HE that achieve the 'lactate criteria' (arterial lactate >24 hours post-overdose >3.5 mmol/l on admission or >3.0 mmol/l after overdose and after fluid resuscitation). I am also reluctant to use these criteria alone when listing POD cases after they have developed HE and prefer to see other evidence of clinical deterioration. Otherwise I would use the conventional King's College criteria to decide if patients have better survival with emergency LTx.

FURTHER READING

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