Acute liver failure

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Abstract

Acute liver failure (ALF) is a rare condition, associated with high mortality and high healthcare cost. Common causes of acute liver injury leading to ALF are viral infection or specific drugs, with significant geographic variation in epidemiology. The most frequent cause of ALF in the UK is paracetamol (acetaminophen) toxicity. Advances in the critical care management of ALF, as well as surgical techniques and organ selection for transplantation, have improved outcomes for patients with ALF over recent decades. Remaining challenges in the management of ALF relate to the use of intracranial pressure monitoring, the role of therapeutic hypothermia, and advances in living-donor transplantation. Future research will also focus on extracorporeal liver assist devices, and therapies to alter the host immune response to liver injury.

Keywords acute liver failure; critical care; hepatic encephalopathy; intensive care; liver regeneration; liver transplantation; multi-organ failure

Acute liver failure (ALF) is a rare but devastating illness, which develops after a major insult to the liver and is characterized by the rapid development of coagulopathy, encephalopathy and multi-organ failure. Unlike chronic liver failure, ALF is potentially reversible through liver regeneration. The main classification system used in the UK divides the syndrome into hyperacute, acute and subacute dependent on the length of time from hepatic injury to the development of encephalopathy (within 7 days, 8–28 days and greater than 28 days respectively). This classification not only gives clues about aetiology but also has implications for prognosis.

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Causes and epidemiology

ALF has a reported incidence of fewer than 10 cases per million people per year in the developed world,[1] although this is possibly higher in the developing world. Viral infection is the most common cause in developing countries (hepatitis A, B and E) and drug-induced liver injury (DILI) in developed countries. This probably reflects the impact of public health measures including improved sanitation and vaccination programs.

Viral infection

It is uncommon for those with viral hepatitis to develop ALF (<1%).[2] Hepatitis A and E are transmitted by the faecal-oral route. Hepatitis B virus is transmitted by exposure to infected blood or bodily fluids, and is the most common cause of ALF in Asia, sub-Saharan Africa and the Amazon basin.[3] *De-novo* infection may occur, although hepatitis B leading to ALF is more commonly a reactivation due to age, immunosuppression or cessation of oral antiviral therapy and so is an 'acute-on-chronic' presentation. Other rare viral causes of ALF include herpes simplex virus (HSV) 1 and 2, herpes virus 6, varicella, Epstein–Barr virus, cytomegalovirus and parvovirus (erythrovirus) B19. Sero-negative hepatitis is a diagnosis of exclusion, typically presenting in a delayed subacute manner, and may possibly represent an as yet unknown toxic or hepatotropic viral liver insult.

Drug-induced liver injury (DILI)

The most common cause of ALF in the developed world is DILI. Paracetamol (acetaminophen) in overdose, either inadvertently or with the intention to self-harm, is the most common drug involved (50–70%).[4] The presentation is hyperacute, and regular alcohol consumption, malnutrition or anti-epileptic therapy all increase the risk of toxicity. Idiosyncratic DILI with jaundice is rare and progression to ALF is uncommon (around 10%).[5] Antimicrobials (such as antituberculous drugs, trimethoprim/sulfamethoxazole, clavulanic acid and antifungals) and anti-epileptic medications are among the drugs most frequently implicated.[6]

Other

Other causes of ALF include Wilson's disease, autoimmune hepatitis, vascular causes such as Budd–Chiari syndrome or ischaemic liver injury, pregnancy-associated liver diseases, toxin ingestion such as *Amanita* spp. mushrooms and malignant infiltration (e.g. lymphoma).

Investigations

Investigations are listed in Table 1.

Management

Overall management aims and aetiology-specific treatments

The goals of treatment in ALF are to treat the underlying aetiology (if possible), and provide supportive care to prevent complications and facilitate liver regeneration, up to the point at which liver transplantation is deemed necessary. The process of deciding when, and in whom, to recommend liver transplantation remains a challenge. Aetiology-specific treatments to consider include acetylcysteine in paracetamol toxicity, lamivudine in hepatitis B

Table of investigations

- Full blood count, clotting profile including fibrinogen, group and save
- Standard biochemistry including electrolytes, glucose, creatine kinase and iron studies
- Arterial blood gas, lactate and ammonia
- Complete hepatitis serology — including hepatitis A, hepatitis E
- Other viral serology — including cytomegalovirus, Epstein—Barr virus, herpes simplex virus, varicella zoster
- Autoantibodies, immunoglobulins
- Paracetamol and salicylate, drug screen
- Other tests dependent on history — such as copper/caeruloplasmin for Wilson's disease
- Doppler ultrasound of the liver and liver vasculature

Table 1

infection, immunosuppression in autoimmune hepatitis, and aciclovir therapy in HSV-related disease.

Neurological

The presence of hepatic encephalopathy (HE) is central to the diagnosis of acute liver failure and covers a wide spectrum of neurological disturbance from minor disorientation to frank coma. Intracranial hypertension and cerebral oedema are feared complications of this process. The pathogenesis of HE in ALF is probably due to triggering of vasogenic and cytotoxic pathways by elevated neurotoxins including ammonia, and it is the rapid rate of ammonia accumulation that distinguishes the rapidly progressive HE in ALF from the chronic, recurrent HE of cirrhosis.[7] The goals of neuroprotective treatment are to maintain adequate cerebral perfusion, control circulating ammonia and prevent systemic infection. Intubation in an ICU setting is mandatory for those with ALF and HE grade 3 and above, due to the rapid rate of progression. Intracranial pressure-monitoring devices may provide additional information and guide the use of therapies such as mannitol or hypertonic sodium chloride, but they require neurosurgery for insertion so the risk-benefit is often unclear, and this approach has not been shown to be effective in prospective studies.[8] Similarly, therapeutic hypothermia reduces intracranial pressure in ALF, but may also adversely affect haemostasis, so that prospective studies to demonstrate effectiveness are required.[9]

Nutrition

ALF is a hypermetabolic state and as such there should be a low threshold for enteral feeding via a nasogastric tube. This is preferred to parenteral feeding because of the reduced risk of sepsis.

Cardiorespiratory

ALF is a hyperdynamic state, with both peripheral vasodilation and relative central hypovolaemia. Early and sustained aggressive fluid management is appropriate with invasive cardiac monitoring and vasopressors if required. Whilst intubation is often required for neurological indications, respiratory failure is not usually an early feature of ALF although it can occur with nosocomial chest infections.

Renal and metabolic

Significant renal dysfunction complicates around 50% of cases of ALF, and both increased age and a paracetamol aetiology confer increased risk. Assiduous fluid management, avoidance of nephrotoxic substances and early renal replacement therapy are cornerstones of management. As with any critically ill patient, metabolic parameters should be tightly controlled. Hypoglycaemia is a significant risk in ALF and this can be treated by intravenous glucose infusion, however continuous infusion should be avoided due to its effects on intracranial pressure.

Infective

Functional immunosuppression is a feature of ALF. Consequently great care must be taken with hygiene and prevention of nosocomial infections. Prophylactic antibiotic and antifungal medications are indicated in line with local antimicrobial policies (piperacillin/tazobactam and fluconazole are used in our unit).

Coagulation

Prolonged markers of clotting are central to the diagnosis of ALF. Since prothrombin time is a key prognostic marker and indicator for transplantation, correction should be avoided in the absence of major haemorrhage or significant invasive procedures. However, once a patient has been listed for transplantation, coagulation may be corrected for pragmatic reasons.

Liver transplant

The introduction of liver transplantation for ALF radically improved survival, and currently 1-year survival is around 80%.[10] Strategies for accurate patient selection and timing of super-urgent transplantation remain controversial. There are many proposed criteria, with the most commonly referred to and most studied being the King's College Criteria (Table 2).

These criteria demonstrate good specificity although their sensitivity has been called into question, implying that some patients will require transplantation despite not fulfilling these criteria.[11] No proposal to either replace or modify the criteria has been found to improve performance. Cadaveric transplantation is most common in the UK. Living-donor transplantation is increasingly performed worldwide and has the benefit of planned surgical timing, although ethical challenges exist.

The King's College Criteria

Paracetamol-induced acute liver failure (ALF)

- Arterial pH <7.3 *or*
- All three of the following: PT >100 seconds or INR >6.5, creatinine >300 μmol/litre and grade 3—4 encephalopathy

Non-paracetamol-induced ALF

- Prothrombin time >100 seconds *or*
- Any three of the following: unfavourable aetiology (seronegative hepatitis or idiosyncratic drug reaction), prothrombin time >50 seconds, serum bilirubin >300 μmol/litre, jaundice to encephalopathy time >7 days, age >40 or <10 years old

Table 2

Future directions

The concept of 'bridging' to allow spontaneous recovery or transplantation is attractive, but thus far elusive. Possible strategies include extracorporeal liver assist devices, or the use of human hepatocytes infused via intraperitoneal or portal vein infusion. This latter approach has been successful in children with inborn errors of metabolism,[12] but there are considerable challenges to overcome before this can be used widely in an adult population. Finally, immune modulation in ALF is a rapidly developing therapeutic option. Control of the initial immune response to injury would potentially prevent progression of liver injury and multi-organ failure.[13] With the continuing shortage of cadaveric organs for transplantation, such innovative approaches to the management of ALF remain the target of research for the next decade. ◆

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