Management of acute liver failure in Intensive Care

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Key words

Acute liver failure, intensive care medicine, update on management

Key points

1. Acute Liver Failure (ALF) is a rare but severe life threating emergency warranting a multidisciplinary approach and early referral to a liver transplantation centre
2. lLiver transplantation has significantly improved ALF outcomes
3. Transplant free survival, particularly for paracetamol overdose related ALF, has also improved due to better organ system support measures
4. Globally hepatitis B and E are leading causes of ALF whereas in the UK paracetamol induced liver injury remains the predominant aetiology of ALF
5. The incidence of Intracranial Hypertension (ICH) has been continuously decreasing over the last few years and it is no longer the leading cause of mortality in ALF
6. Infections and septic complications are common and are associated with high mortality

Learning objectives

By reading this article, you should be able to:

1. Recall the common aetiologies of ALF both in the UK and globally
2. Describe the pathophysiology of ALF leading to multiorgan failure
3. Formulate a clear management plan for patients with ALF

A.Introduction

ALF is a highly specific liver condition, characterised by a rapidly progressive life-threatening illness. It is defined as the presence of coagulopathy (International Normalised Ratio (INR) > 1.5) and Hepatic Encephalopathy (HE) in an otherwise healthy liver.[1] Coagulopathy alone, in the absence of HE, is termed Acute Liver Injury (ALI), which carries much better prognosis.

This is a rare illness with a rate of less than 10 cases per million person years, and in severe cases is associated with multi-organ failure and high mortality.[2] The overall incidence is declining worldwide due to better vaccination programmes for hepatitis B and fewer drug related cases.[3] Emergency Liver Transplantation (LT) remains the definitive treatment for those progressing to severe disease.

Acute on Chronic Liver failure (ACLF) is characterised by acute decline in liver function in patients with pre-existing chronic liver disease and progression to extrahepatic organ failure associated with high short-term mortality. This should be differentiated from ALF.

Exceptions to this rule is *de novo* presentation of liver failure in patients with autoimmune hepatitis, Budd-Chiari syndrome and acute Wilson's disease, where the underlying chronic pathology would have previously gone undiagnosed and acute presentation mimics ALF phenotype.

A.Aetiology

The aetiology of ALF varies across the world, with viral infections being the common culprits in the developing world and Drug Induced Liver Injury (DILI) in the developed settings. Paracetamol toxicity accounts for 50-70% of all DILI, however since the UK restriction on purchasing, there has been a 43% reduction in deaths.[3,4] Globally in developing

countries, hepatitis B and E are responsible for majority ALF cases, with a predominance of hepatitis E in the Indian subcontinent.[3] ALF is also seen with hepatitis A, particularly in some Asian and Mediterranean counties.[5] The syndrome of ALF can be subclassified using the time period between the onset of jaundice to developing HE ; Hyperacute ALF (HALF, HE within 7 days of developing jaundice), ALF (HE within 8 and 28 days of developing jaundice) and Subacute ALF (SALF, HE within 28 days and 12 weeks of developing jaundice).[6] This classification can sometimes provide clues to the potential underlying aetiology (Figure 1) and prognosis. However in up to 20% of the cases, despite rigorous investigation, the cause of the ALF remains unidentified and is referred to as indeterminate or cryptogenic.[3]

A.Prognosis

The outcomes from ALF have improved significantly over the last few decades in developed countries. This has been driven by parallel improvements in the understanding of disease pathophysiology, early referrals to specialist centres equipped with transplantation facility, better organ system support in Intensive Care Units (ICU) and the availability of emergency LT. This has led to improved outcomes for those managed medically or receiving a LT.[7] Mode of death has also changed over time with ICH replaced by sepsis and multiple organ failure as the leading cause of death.[7] Patient's age (older patients do less well), disease aetiology (pregnancy related ALF has excellent transplant free survival, whereas acute Wilson's disease has very poor prognosis without transplantation) and the speed of disease progression (figure 1) can provide prognostic determinants. Hyperacute ALF is associated with rapid onset with development of severe coagulopathy, higher grades of encephalopathy and greater incidence of ICH, and multi-organ dysfunction. However, offset is also rapid with excellent rates of transplant free recovery. Subacute ALF, on the other hand, develops over a

much longer period and is often associated with only modest rise in serum transaminases and mild coagulopathy. These patients can present with splenomegaly, ascites and shrinking liver volumes, mimicking cirrhosis, which can make the diagnosis challenging.[1] Once HE develops in these patients there is little chance of spontaneous recovery and the prognosis is very poor without transplantation.[3]

A. Pathophysiology

ALF is characterised by direct hepatocyte damage, necrotic or apoptotic cell damage, and development of an immune response which is mediated through activated monocytes, macrophages, dendritic cells and natural killer T cells. The cells express Toll-Like Receptors (TLRs) which recognise Pathogen Associated Molecular Patterns (PAMPS) of infectious, and Damage Associated Molecular Patterns (DAMPS) from non-infectious insults. This results in a strong inflammatory response, both locally within the liver and systemically. Systemic inflammation contributes to the development of extra hepatic manifestations and Multiple Organ Dysfunction Syndrome (MODS).[8] This is similar to the Systemic Inflammatory Response Syndrome (SIRS) seen in sepsis, with an initial pro-inflammatory response causing MODS, followed by an anti-inflammatory response characterised by immune paresis which predisposes to new infections.

HE, a hallmark feature of ALF, is characterised by altered cerebral blood flow and dysregulated cerebral autoregulation. The exact pathological basis of subsequent progression to cerebral oedema and ICH is not completely understood and is likely a complex interplay between systemic inflammation, circulating neurotoxins (ammonia in particular) and osmolar perturbations such as one caused by hyponatraemia, the end result being astrocyte swelling, brain oedema and ICH.[3,7,8]

A.Management

B.Diagnosis

Patients present with a range of symptoms including non-specific features of nausea, vomiting, lethargy, abdominal pain and feeling generally unwell. The diagnosis may also be delayed if the primary presenting features are those of confusion and agitation, particularly in the hyperacute cases related to paracetamol poisoning where, in some instances, there may be little jaundice with only mild elevation of serum bilirubin, and those with subacute disease which can be mistaken for Chronic Liver Disease (CLD).[2] A clinical history should focus on features of mental alterations/HE, the presence and timing of jaundice in relation to HE, other stigmata of CLD and a drug and travel history to establish a causative agent. HE is graded and should be clearly documented for all patients.

Grade I: Mild confusion, decrease attention, irritability

Grade II: Disorientation, drowsiness, inappropriate behaviour

Grade III: somnolent but arousable, incoherent

Grade IV: Coma

Table 1 details laboratory test that should be performed in all patients when a diagnosis of ALF is considered. All women of childbearing age should have a pregnancy test. Imaging will often include ultrasound and triple phase CT of the liver. These can show changes in liver echogenicity, splenomegaly, ascites, liver surface nodularity, collateral vessel formation, hepatomegaly or liver atrophy, reversed portal blood flow and vascular patency. It is important to note that initial studies can be normal and therefore serial images should be considered.[9,10]

B.Referral to a specialist centre

ALF is a rapidly progressive condition and early escalation to critical care is essential. The care of these patients should be discussed within a multidisciplinary team involving hepatology, critical care and the transplant team. This can offer insight into the trajectory of the condition and timing of transfer to a specialist centre. Threshold for referral varies but generally includes an INR > 3.0 or PT > 50 seconds or rising, HE, hyperlactatemia/hypotension despite resuscitation, pH < 7.35, acute kidney injury, bilirubin > 300 µmol L^{-1} and shrinking liver volume on imaging.[11]

B.Treatment

C.Airway and breathing

Early elective tracheal intubation of patients with higher grades of HE (III/IV) is recommended for airway protection especially if being transferred. This allows protection from aspiration, control of agitation and optimal management of Intracranial Pressure (ICP). Standard airway strategies to minimise elevations in ICP should be employed during the intubation process. Further unwarranted surges in ICP can be avoided by using lung protection ventilation with tidal volumes of 6 ml kg^{-1} with a maximum of 8 ml kg^{-1} to maintain P_{CO_2} between 4.5-5.5 kPa and appropriate levels of PEEP.[1] A balanced approach must be taken with optimization of ventilation versus optimal cerebral perfusion and avoiding increases in ICP.[1,9,12] Standard bundles to avoid ventilator associated pneumonia should be strictly adhered as these patients are at a greater risk of developing infections.[1,9] The incidence of Acute Respiratory Distress Syndrome (ARDS) is low in this specific patient population, and venous-venous Extra Corporal Membrane Oxygenation (ECMO) is an option in selected patients in centres with expertise in both ECMO and ALF.[1,13] However the use of

ECMO is very rare and the subgroup of patients for which it may be useful has not been defined and requires further studies.

C.Circulation

Most patients with ALF have profoundly reduced systemic vascular resistance presenting with vasodilatory shock, high cardiac output state and a clinical picture similar to that seen in SIRS/sepsis.[9] Therefore, the aim of cardiovascular support is to restore circulating volume and enhance oxygen delivery to tissue by targeting a MAP > 65 mmHg.[1] A higher MAP of 80 mmHg should be targeted if there are signs of raised ICP and for patients with uncontrolled chronic hypertension. A balanced crystalloid solution with regular monitoring of acid base status and electrolytes is recommended for volume restoration. Albumin does not have an impact on mortality but improves haemodynamic status and can also be used as a colloid volume expander.[1] Starch substances should be avoided due to the increased risk of renal impairment.[1] Fluid management should be directed by cardiac output monitoring, the choice of devise is often driven by the individual unit preference.[9] Noradrenaline is recommended as first line agent for vasopressor support.[1] Terlipressin, a commonly used splanchnic vasoconstrictor in patients with cirrhosis , has been implicated in potentially worsening ICP and is not widely used in ALF.[14] Adrenaline may be added as an inotrope where there is evidence of a cardiac dysfunction/failure. Cortisol deficiency is common in ALF and the degree of deficiency correlates with disease severity.[15] Supraphysiological doses of cortisol have been shown to reduce vasopressor requirement but they do not impact survival and increase risk of infection.[16]

C.Renal

Acute Kidney Injury (AKI) is seen in 40% -85% of patients with ALF. The incidence is higher in ALF secondary to paracetamol poisoning due to direct tubular toxicity mediated by

paracetamol. ALF associated with AKI is associated with worsening of HE and poorer outcomes.[17] Risk factors for developing AKI include older age, paracetamol induced ALF, hypotension, SIRS and infections.[1] Early initiation of Renal Replacement Therapy (RRT) is advised for renal support but also for non-renal indications including hyperammonaemia (ammonia levels >150 µmol L^{-1}), sodium imbalances, temperature and metabolic control.[1] Continuous RRT is preferred to prevent cerebral complications of fluid shifts. Refractory hyperammonaemia has been shown to respond to higher intensity ultrafiltration with rates of up to 60- 90 ml kg^{-1} hr^{-1} with additional benefit of reduction in the vasopressor requirements.[18] This is in contrast to septic shock where higher intensity ultrafiltration is not shown to be effective. The need and choice of anticoagulation of the circuit remains controversial. Evidence suggests frequent clotting of circuits and therefore despite coagulopathy, most patients will require anticoagulation. Unfractionated heparin and/or prostacyclin are the commonest options.[19] Regional citrate anticoagulation is generally avoided due to the diminished ability of the liver to metabolise the citrate load. However it is used in liver failure patients in some centres, but careful monitoring is required.[1,20]

C.Central Nervous System

ICH as a result of cerebral oedema is a major concern for patients with ALF with a mortality of 55%. However, the incidence of ICH in the UK has fallen from 76% in the 1980's to 19.8% in 2004-2008 due to improved understanding of the pathophysiology, pre-emptive institution of targeted cerebral care and improved organ support.[7] Risk factors for ICH include hyperacute or acute presentation, younger ages, renal and cardiac dysfunction, systemic inflammatory response and persistent ammonia levels > 200 µmol L^{-1}.[1,12] Elevated levels of ammonia lead to astrocyte swelling, mitochondrial dysfunction and cerebral oedema, and correlate with the development of raised ICP and HE.[12] Therefore, patients should have regular monitoring of arterial ammonia as levels > 124 µmol L^{-1} have a 77.5% of

predictive accuracy of mortality.[12] Clinical signs have low sensitivity and specificity for detecting increases in ICP, and in the ICU setting are masked by the medication and organ support. Abnormal pupillary responses, spasticity, extensor posturing, and Cushing's reflex are all late signs of raised ICP. 25% of patients with ALF have clinical signs of seizure activity with the incidence of subclinical activity higher, however there is no evidence for using seizure prophylaxis therapy.[12] Invasive ICP monitoring is associated with a 1-4% risk of non-fatal and 1% risk of fatal haemorrhage. The incidence varies on operator and centre expertise as well as placement location, and there is little evidence of its impact on long term survival.[12] The use of invasive ICP monitoring is therefore only recommended for patients at a very high risk of developing ICH.[1,2] Other means of monitoring ICP include jugular venous oxygen saturations, transcranial doppler, optic nerve sheath diameter and near Infrared Spectrophotometry (NIS), however the accuracy of these modalities is not fully established..[12] CT is useful to exclude other aetiologies but is insensitive to detecting elevated ICP. MRI is more sensitive but is often not logistically possible. The management and prevention of raised ICP include reduction of cerebral oxygen consumption through adequate sedation, normocapnia, normoglycemia, minimise venous congestion through 30-degree head elevation, loosen endotracheal ties, and avoid hyperthermia. Serum sodium should be maintained between 145-150 mmol L^{-1} using boluses or a continuous infusion of 30% sodium chloride if needed.[1,9] RRT should be initiated early with the aim of keeping the serum ammonia <100 µmol L^{-1}.[9] Acute surges of ICP can be managed with a bolus of hypertonic saline (200 ml 3% or 20 ml of 30%) or rarely mannitol (150 ml, 20%) given over 20 minutes with the aim to keep sodium ≥ 150 mmol L^{-1} and osmolality < 320 mOsm L^{-1}.[1,2] In resistant cases a short period of hyperventilation can be used with the aim to reduce $PaCO_2$ to ≤ 4 kPa. There is little evidence in support of cooling in the context of ALF and raised ICP. The goal is to avoid fever and maintain a core temperature of 35-36 ^{0}C. Profound

hypothermia ($\leq 33^0$ C) has been shown to reduce severe refractory ICH and should be reserved as a rescue intervention in selected patients.[1,2]

C.Coagulation

ALF often presents with deranged INR/PT, thrombocytopenia, reduced circulating pro- and anticoagulant proteins and fibrinogen levels. These patients are therefore often assumed to have a higher incidence of spontaneous and procedure related bleeding but this is often not the case.[2] Reduced synthesis of procoagulant clotting factors by the diseased liver is compensated by a simultaneous reduction of natural anticoagulants (proteins c and s and antithrombin) and an increased expression of endothelium derived factor VIII ,von willebrand factor and circulating procoagulant microparticles. This collectively leads to a state of rebalanced haemostasis.[21] Point Of Care (POC) tests of coagulation such as Thromboelastography (TEG) or Rotational Thromboelastometry (ROTEM) have demonstrated complex coagulation profiles in ALF which do not correlate with PT derangement; hypocoagulable state in 20%, normal in 45% and hypercoagulable 35%.[21] Therefore POC testing is recommended as standard laboratory measurements of coagulation such as INR measurements may fail to reveal the true haemostatic picture. Routine correction of INR/PT should be avoided as these are important markers of liver's synthetic function. Platelets and fibrinogen are more sensitive indicators of bleeding risk and should be corrected as required. For invasive lines insertion, platelet count > 30,000 µL and fibrinogen level >1-1.5g L^{-1} is generally adequate, but for invasive ICP monitoring or if there is active haemorrhage it is reasonable to aggressively correct all clotting including INR, platelets and fibrinogen.

C.Sepsis

ALF is associated with an immune dysfunction leading to altered macrophage and neutrophil function, reduction in complement, impaired phagocytosis and opsonisation.[1,9] SIRS without infection itself worsens HE and leads to generally poorer outcomes.[22] Sepsis is now considered the leading cause of death in ALF but may also prevent patients getting transplant or complicate the post-operative recovery period. Bacteraemia is reported in 80% of cases with pneumonia (50%) being the most common site followed by urinary tract infection (22%) and catheter induced bacteraemia (12%). Gram negative enteric bacilli and gram-positive cocci are the most frequently isolated. Fungaemia is seen in 32% of cases of ALF with candida species being the main culprit.[22] These patients will also frequently have bacterial co-infections. Reactivation of viral infections is also seen particularly Cytomegalovirus (CMV).[1] Diagnosis can be challenging as clinical features such as elevated temperature and increased inflammatory biomarkers can be absent. Therefore, a high level of suspicion and regular microbiological surveillance is recommended. Prophylactic use of antibiotics and antifungals does not have an impact on survival outcome but does reduce the incidence of sepsis and HE , and therefore is recommended.[1,9] This is particularly important for those listed for super urgent liver transplants as development of infections may lead to delisting.[1]

C.Metabolic and nutrition

Hypoglycaemia is frequently present in ALF and is associated with increased mortality. The clinical presentation is often similar to that of HE and therefore blood sugar should be monitored regularly. Prompt treatment should be provided in the form of intravenous low volume high concentration glucose solutions and therefore avoiding infusion of large volume of hypotonic solutions which could worsen cerebral oedema and hyponatraemia.[2,9] Derangements of magnesium, calcium, potassium and phosphate are also frequently observed and should be correctly appropriately.[1]

ALF leads to increased energy expenditure and protein catabolism; therefore, early initiation of nutritional support is needed. Enteral feeding is often the preferred route with a daily calorie target of 25-30 Kcal kg^{-1} day^{-1}.[9] Prokinetics are frequently required to aid absorption which is often impaired due to a variety of ICU related factors. Post pyloric feeding can be considered if absorption remains suboptimal and is preferred to parental feeding which is associated with higher rates of infections. Some liver units will continue to give 1.0-1.5g kg^{-1} day^{-1} of enteral protein with regular monitoring of ammonia and adjusts level appropriately.[2] Stress ulcer prophylaxis in the form of PPI is frequently administrated to patients and consideration should be given to stopping when enteral feeding has been established.[1]

B.Specific therapies

C.N- Acetyl cysteine (NAC)

There is strong evidence for the early use of NAC in patients with established paracetamol overdose.[1] NAC provides cysteine which is a glutathione precursor. This neutralises N-Acetyl P-Benzoquinone Imine (NAPQI) which is responsible for hepatocyte toxicity. In 2012 the UK's Commission on Human Medicine (CHM) offered simpler guidelines with a single nomogram treatment line (patient risk stratification no longer required) resulting in greater treatment consistency among different centres. There is also evidence of improved transplant free survival in non- paracetamol related ALF when using NAC specifically in those in the early stages of the disease with lower grades of HE.[23]

C.Autoimmune Hepatitis (AIH) and steroids

AIH is a hepatic necrotic- inflammatory condition which often presents chronically but approximately 20% of the cases present as ALF with extensive necrosis.[24] The diagnosis is often challenging, and a significant proportion of patients will require a LT. If diagnosis is

suspected, early referral to a specialist centre is crucial for a diagnostic biopsy and potential steroid therapy.

C.Antivirals and Hepatitides

There is evidence for the use of antiviral drug lamivudine in ALF secondary to Hepatitis B infection. This has improved survival outcomes, but it is important that the therapy is initiated early before advanced stages of ALF develop. There is less robust data on the use of other antivirals such as entecavir and tenofovir. There is currently no evidence of the use of interferon in this specific patient population.[25] There is currently no evidence to support the use of antivirals in the ALF secondary to Hepatitis E.

C.Wilsons disease and chelating agent

D- penicillamine is a chelating agent that promotes the urinary excretion of copper. Its early administration has been shown to be effective in restoring liver function and preventing disease progression in the context of ALF and potentially avoiding the need for LT.[26]

B.Other therapeutic options

C.Plasma exchange

This is often utilised for a range of other immunologically mediated conditions and replaces the patient's plasma with donor fresh frozen plasma. Multiorgan failure associated with ALF results in a range of proinflammatory cytokines due to the SIRS and accumulation of a metabolites and toxins exacerbated by hepatocyte death. High Volume Plasmas exchange (HVP) is defined as exchange of 15% of body weight. HVP has shown to increase overall survival in ALF, but specifically in patients that do not undergo emergency transplantation, due to contraindications and patients listed for a transplant but deteriorated while waiting for a graft.[27]

C.Mechanical assist devices

These devices are broadly divided into biological and non-biological and are not used in routine clinical settings.[28] The non-biological devices work on the principle of haemodialysis using an artificial membrane to detoxify the blood. Molecular Absorbent Recirculating System (MARS) and Single Pass Albumin Dialysis (SPAD) use albumin-based dialysate across a highly selective membrane (< 50kDa). These devices result in improved haemodynamic parameters and HE but have failed to show any survival benefit in ALF.[1] The biological devices are much more complex and consist of porcine or human hepatic cells. These devices aim to enable not only clearance of toxins but also to support hepatocyte function. The two devices Hepat Assist and Extracorporeal Liver Assist Devise (ELAD) are currently only used in clinical trial settings.

C.Liver transplant

Liver transplant has been a significant leap in the management of ALF with dramatic effects on survival outcomes. 10% of all liver transplants are performed for ALF and the 5-year survival of these patients in the UK is 82 % (83% for elective liver transplant).[29] Risk factors for poorer outcomes post-transplant include age > 60, cardiac dysfunction, high vasopressor and FIO_2 > 0.8 pre operatively.[10] Patients with ALF meeting the criteria are listed for super-urgent transplants and table 2 shows the most frequently used Kings College criteria for patient selection. It is important that this prognostication is performed early and discussed with a specialist centre. Auxiliary liver transplant is also an option in selected patients and offers the benefit of not having to take lifelong immunosuppression.[30]

Liver transplant is contraindicated in irreversible brain damage, malignancy and uncontrolled sepsis. It also commits the patients to a lifetime of immunosuppression and therefore even

when listed, continuous assessment of suitability should be made within a MDT setting. Patients who spontaneously recover have better outcomes when compared to those that have a transplant. If there are signs of clinical improvement or even further deterioration (irreversible brain damage, severe infections and worsening haemodynamic parameters) it is acceptable to hold the transplant.

In conclusion ALF is an acute severe life-threatening condition which carries high mortality but is potentially reversible. The outcomes of ALF have improved significantly over the last few decades due to a better understanding, improved intensive care and availability of transplants.

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