

Acute liver failure

Andy Slack and Julia Wendon

Introduction

Acute liver failure (ALF) is an unpredictable and rapidly progressive life threatening multisystem condition that ensues when an insult causes diffuse necrosis of liver parenchyma disrupting hepatocyte function in patients who have no pre-existing liver injury. The subsequent development of encephalopathy and coagulopathy within days or weeks represents the key features of ALF, but critically often culminates with multi-organ failure (MOF), which impacts significantly on mortality. Timely referral to specialist centres with specialist expertise in the management of ALF and liver transplantation is crucial.

The availability of donor organs is under continued pressure in the UK and worldwide. Patients with ALF must fulfil a strict set of selection criteria based on published risk factors for prioritisation before being established on the national super-urgent transplantation waiting list.

Classification and incidence of ALF

The two most common definitions for ALF concentrate on the time period from jaundice to the onset of encephalopathy (Table 1).¹ ALF is rare with around 400 and 2,800 cases of ALF per year in the UK and USA, respectively.¹ In the developing world the leading cause of ALF is predominated by the viral hepatitises, particularly hepatitis B and in the UK, like the USA, paracetamol (acetaminophen) overdose (POD) is the leading cause.

Aetiologies of ALF

Paracetamol (acetaminophen) overdose

In the UK, POD comprises up to 50% of all poisoning admissions and around 10% of admissions in the USA.⁴ The assessment of the risk of developing ALF from POD, whether accidental or deliberate, is intimately related to the total dose ingested and the time from ingestion to presentation. The pathophysiological reasons behind this relate to the length of time exposed to the active unstable N-acetyl p-benzoquinone imine (NAPQI) metabolite that depletes hepatic glutathione levels. Once NAPQI is unopposed by hepatic glutathione hepatocellular damage ensues unless the antidote, a glutathione precursor, N-acetylcysteine (NAC) or methionine, is given in a timely fashion.

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Viral hepatitises

All the hepatitises except for possibly hepatitis C have been implicated in cases of ALF.¹ Viral hepatitis A and B are the most common causes of ALF worldwide including France and Japan with hepatitis E predominant in India. Hepatitis E is common in Asia and Africa with the risk of ALF greatest in pregnancy at more than 20%, particularly during the third trimester.

Idiosyncratic drug reactions

The administration of medicines directly affects the liver because it is the primary site of drug metabolism and elimination. Drug-induced liver injury (DILI), including cases of acetaminophen toxicity, is the leading cause of ALF and indication for liver transplantation. The remainder of DILI cases comprise idiosyncratic reaction, which occurs in around 1 in 10,000 exposed patients. However, more than 1,000 drugs and herbal remedies have been implicated in DILI and altogether comprise 10% of ALF cases.⁵

Other

Malignancy has featured in a number of case reports in the literature that have documented a wide range of solid and haematological tumours as rare causes of ALF. Vascular insults as a cause of ALF are uncommon; however, these include ischaemic hepatitis associated with low cardiac output states and variable degrees of left and right ventricular cardiac dysfunction. Both inherited and acquired procoagulant disorders can cause veno-occlusive disorders, such as Budd-Chiari (BC) and portal vein thrombosis. Metabolic disorders are also uncommon but can be due to both inherited and acquired disorders, which include acute fatty liver of pregnancy, fructose intolerance, galactosemia,

Table 1. Classifications of acute liver failure (ALF) (time from jaundice to onset of encephalopathy).

Definition ²	Time (days)	Most common aetiologies	Definition ³	Time (weeks)
Hyperacute	< 7 days	POD, Hepatitis A and B	Fulminant	<2 weeks
Acute	8–28 days	POD, Hepatitis A, B, E,		
Subacute	29 days–8 weeks	Idiosyncratic drug reactions, seronegative hepatitis	Subfulminant	>2 weeks

POD = paracetamol (acetaminophen) overdose.

lecithin-cholesterol acyltransferase deficiency, Reye's syndrome, tyrosinemia and Wilson's disease (WD). Other rare but important causes of ALF include HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome of pregnancy.

Clinical features and management

General

The management of ALF should follow some general principles implemented on initial presentation. Establishing a diagnosis of the underlying insult is crucial in determining potential therapies that could halt the injurious process and reverse liver failure. Prompt testing of hepatitis and atypical viral serology, autoantibodies, along with an illicit drugs screen, paracetamol levels, urine and serum copper where appropriate are frequently indicated. Additionally, ultrasonography of the liver and its vasculature is important. Where possible, if the history and investigations do not suggest a viral or drug-induced insult then axial imaging with contrast enhanced triple-phase computer tomography is advisable. Early recognition and the treatment of sepsis along with the support and prevention of organ dysfunction are vital in order to increase the potential for hepatic regeneration. Finally, a timely decision regarding listing for super-urgent liver transplantation is needed when it becomes clear sufficient hepatic regeneration is not going to occur. The huge potential for clinical deterioration and the limited availability of organs accounts for the narrow window of opportunity to undertake this procedure.

Cardiovascular

The circulatory hallmarks of established ALF mirror the haemodynamic changes of sepsis with an elevated cardiac output and vasoplegia. The management goals for the circulation in established ALF intuitively, in view of the similarities and despite formal validation, should follow the initial resuscitation recommendations outlined in the Surviving Sepsis Campaign (SSC). The early use of haemodynamic monitoring is recommended as it often forms a vital aspect of management providing important additional clinical indices about central circulating volumes and cardiac output. Furthermore, interrogation of myocardial function with echocardiography to evaluate left and right ventricular filling and function is also important.

There are problems associated with some the SSC parameters; central venous oxygen saturation (scvO₂) is often significantly elevated reflecting the hyperdynamic circulation and microvascular shunting. The SSC threshold for lactate of 4 mmol/l, is unlikely to reflect sole circulatory disarray in ALF, but it should be assumed to be so until adequate volume resuscitation has been implemented. Relative adrenal insufficiency (RAI), defined as a total cortisol (TC) level less than 248 nmol/l after corticotropin administration, has a reported prevalence of 62% in ALF. Hydrocortisone replacement therapy is therefore, frequently indicated as it is associated with reductions in vasopressor requirements, albeit without any mortality benefit.⁶

Respiratory

The development of hepatic encephalopathy in ALF is one of the primary indications for intubation and ventilation to establish airway protection. Patients will also develop a spectrum of respiratory complications associated with both mechanical ventilation and critical illness. These include pleural effusions, atelectasis and poor compliance due to raised intra-abdominal pressure (IAP) or reduced thoracic compliance due to chest wall oedema. Acute lung injury (ALI) and adult respiratory distress syndrome (ARDS) complicate up to 30% of paracetamol-induced ALF cases,⁷ particularly those with significant intracranial hypertension (ICH) and vasopressor requirements. ICH is associated with the use of deep sedation, limited endotracheal suctioning and hypothermia that can lead to secretion retention contributing to the high incidence of gram-negative ventilator-associated pneumonias and ALI.

Conventional protective ventilation manoeuvres employed for ALI/ARDS can impact on cerebral perfusion exacerbating ICH due to elevations in CO₂. Consequently, a balanced approach is often required. High positive end expiratory pressures (PEEP) are necessary to optimise recruitment and prevent atelectasis of basal lung segments. The opportunity to wean patients from the ventilator is usually once the acute phase of the liver injury has subsided or in the post-transplant period when ICH has settled. The insertion of a tracheostomy percutaneously to facilitate weaning from the ventilator can be performed safely despite the occurrence of coagulopathy and thrombocytopenia in ALF.⁸

Nutrition

Numerous metabolic abnormalities and their associated complications are encountered in ALF, however few studies have assessed and identified best practice. Hypoglycaemia is a significant metabolic abnormality encountered in ALF, due to the loss of hepatic glycogen stores, impaired gluconeogenesis and hyperinsulinaemia. It is important to establish early and maintain normoglycaemia with infusions of 20–50% dextrose that will continue until enteral nutrition is commenced usually within 24 hours of admission aiming to achieve 25–30 kcal/kg/day. If gut failure and poor absorption become a problem, it is safe to use total parenteral nutrition (TPN) in patients with ALF.⁹ The use of continuous renal replacement therapy (CRRT) necessitates supplementation with vitamins, trace elements and phosphate.¹⁰

Immunity and bacteraemia

The innate immunity undergoes significant changes in response to acute liver injury and many of these resemble the clinical features of systemic sepsis with a systemic inflammatory response syndrome. These complex immune responses include complement deficiency, neutrophil dysfunction and macrophage-mediated release of cytokines, which are all responsible for the increased incidence of bacteraemia and can affect the degree of

encephalopathy. The use of empirical broad-spectrum antibiotics, the attention to appropriate nutrition, gut decontamination, oral hygiene, use of ventilator care bundles, intense daily scrutiny of the indwelling intravenous catheters and vigilant infection control measures are all important in limiting the occurrence of bacteraemia.

Acute kidney injury

The incidence of acute kidney injury (AKI) in ALF is significantly higher than that of the general critically ill population, ranging from 40–85% depending on aetiology, with POD associated with a higher incidence at around 75%.¹¹ The mechanisms involved in

Table 2. Criteria for referral/discussion to specialist centres.^{2,15}

Organ system	Paracetamol overdose (Time from ingestion, days)			Non-paracetamol overdose (ALF classification, time from jaundice to encephalopathy)		
	Day 2	Day 3	Day 4	Hyperacute	Acute	Subacute
Liver	INR >3.0 or PT >50s	INR >4.5 or PT >75 s	INR >6 or PT >100s	INR > 2.0 or PT >30s	INR > 2.0 or PT >30s	INR >1.5 or PT >20s or Shrinking liver volume
Metabolic	pH <7.3 or HCO ₃ <16 or Lactate >3.0 or Hypoglycaemia	pH <7.3 or HCO ₃ <16 or Lactate >3.0		Hypoglycaemia or Hyperpyrexia	Hypoglycaemia	Hypoglycaemia or Hyponatraemia <130 umol/l
Kidney	Oliguria or SCr >200 umol/l	Oliguria or SCr >200 umol/l	Oliguria or SCr >300 umol/l	AKI	AKI	AKI
Brain	HE	HE	HE	HE	HE	HE
Haematology		Severe thrombocytopenia	Severe thrombocytopenia			

AKI = acute kidney injury; HE = hepatic encephalopathy; INR = international normalised ratio; PT = prothrombin time; SCr = serum creatinine.

Table 3. Criteria for super-urgent listing for orthotopic liver transplantation.^{2,15}

Organ system	Paracetamol overdose	Seronegative hepatitis (SNH), hepatitis A, hepatitis B, or an idiosyncratic drug reaction (IDR)
Liver	MUST occur within 24-hour time window INR >6.5 or PT >100s with both AKI Stage 3 and Grade 3/4 HE	INR >6.5 or PT >100s WITH any grade of HE Three of the following: INR >3.5 or PT >50s, bilirubin >300 umol/l, jaundice to HE >7 days, unfavourable aetiology SNH or IDR, age >40
Metabolic	pH <7.25 or Lactate >3.0 mmol/l (after >24 hours after overdose despite aggressive fluid resuscitation usually in addition to OI Grady criteria ¹⁵ to increase sensitivity and specificity)	
Kidney	AKI Stage 3 (SCr >300 umol/l or anuria) with both (INR >6.5 or PT >100s AND Grade 3/4 HE)	
Brain	Grade 3/4 HE with both (INR >6.5 or PT >100s AND AKI stage 3)	Any grade of HE with INR >6.5 or PT >100s
Cardiac	In the UK increased inotrope or vasopressor requirement in the absence of sepsis with 2 out of 3 (INR >6.5 or PT >100s, AK Stage 3, Grade 3/4 HE)	

AKI = acute kidney injury; HE = hepatic encephalopathy; INR = international normalised ratio; PT = prothrombin time; SCr = serum creatinine.

the development of AKI in ALF resemble the pathophysiological models of hepatorenal syndrome and septic AKI. Vasoactive mediator-induced changes cause heightened homeostatic sympathetic nervous and renin-angiotensin system (RAS) responses culminating in intrarenal arterial vasoconstriction. Both acute tubular necrosis and septic AKI mechanism with microcirculatory changes that result in renal venous congestion and disturbed cellular energy mechanisms are all likely to play a role.¹² Paracetamol nephrotoxicity is responsible for the higher incidence of AKI in POD and is due to increased renal proximal tubules cell death by mechanisms that differ to those causing hepatotoxicity.

The high incidence of AKI leads to an increased requirement for CRRT for both renal- and non-renal-related reasons. The anticoagulation of CRRT circuits is still required, despite the coagulopathy of ALF, which usually relies on the safe use of prostacyclin due to its short half-life, along with other measures such as good vascular access and pre-dilution to achieve extended filter life spans.

Coagulation

The integral relationship between clotting factor production and acute hepatocyte necrosis is key to determining both bleeding risk and prognosis. The prothrombin time (PT) is used for the prognostic assessment of ALF with a PT >36 seconds at 36 hours after ingestion predicting that 50% of patients will go on to develop ALF. Furthermore, a PT increasing on day 4 and peaking at PT >180 seconds is predictive of a 65% mortality.¹³ However, the role of PT in assessing bleeding risk needs to be cautioned in the context of ALF as both thrombocytopenia and platelet function seem to correlate better with bleeding risk.

Neurology

Intracranial hypertension (ICH) is still frequently responsible for cerebral death in ALF, despite a decline over the past two decades. Adverse outcomes with ICH are more common in the young where brain volumes are higher and intracranial space is at a minimum. The cause of cerebral oedema in ALF is multifactorial, but integrally related to ammoniogenesis and the inflammatory responses of ALF. A blood ammonia >200 $\mu\text{mol/l}$ is associated with an increased risk of cerebral herniation.¹⁴ Blood ammonia is converted to glutamine in the brain, which accumulates within astrocytes raising osmolality leading to swelling. The standards of care for ICH used in neurosurgical patients are the mainstays of treatment of ICH encountered in ALF. These include maintaining the head elevated at 30 degrees, a mean arterial pressure to achieve a cerebral perfusion pressure >55 mmHg and a partial pressure of carbon dioxide (pCO_2) <4.5 KPa when autoregulation is preserved, hypothermia with a core body temperature <36°C, heavy sedation and hypernatraemia, maintained with hypertonic saline to achieve a serum sodium concentration >145 mmol/l. Often, monitoring of intracranial pressure with an intracranial pressure bolt along

with additional information regarding cerebral perfusion utilising cerebral dopplers is warranted, particularly when patients are to undergo liver transplantation.

Prognostication of ALF

Spontaneous recovery in ALF is largely determined by the underlying pathology, therefore, establishing a diagnosis is important in determining prognosis and can influence management. Clinical criteria predicting prognosis in patients with ALF were first described at King's College Hospital, London. There are other criteria, which have been developed and used, which include Clichy, BiLE score and even the modified end-stage liver disease (MELD) score. The most widely used are the King's College Criteria (KCC), which were developed from a retrospective analysis of patients with acute liver failure medically managed between 1973–85. The identified prognostic variables were then assessed prospectively with the subsequent development of the KCC. They do not perform perfectly with up to 25% of ALF cases that fulfil KCC surviving without transplantation. The KCC were developed for both paracetamol- and non-paracetamol-related ALF and assist decisions regarding when to refer or discuss cases with specialist centres that perform OLT or to decide whom to priority list for transplantation (Table 2 and 3).

Summary

ALF is a multisystem disorder necessitating both predictive and reactive management strategies to support and protect organs from the initial and subsequent insults encountered. Early referral to a specialist liver centre with the option of liver transplantation is recommended. Furthermore, a good understanding of the poor prognostic variables is necessary to determine those most at risk of developing ALF in order to facilitate timely, safe transfer and listing for liver transplantation.

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■ CONFERENCE SUMMARIES

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Dyslipidaemia: integration between primary and secondary care

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It is the implementation of guidelines, not the guidelines themselves, that change clinical practice. This session examined some of the issues that were faced when interpreting national guidelines for local implementation. Local guidelines for the use of lipid lowering drugs have been in place and regularly updated for more than 10 years and were recently reviewed to incorporate the recommendations in the National Institute for Health and Clinical Excellence (NICE) lipid modification guideline¹ and the relevant section of the NICE type 2 diabetes guideline.² The process formed the basis of this talk.

Lipid lowering drugs impact on practice in primary care and in a range of specialty areas. Membership of the local guideline development group reflected this with colleagues from primary care and a wide range of specialties, including those perhaps less likely to be represented, such as from mental health services and rheumatology. Integration and a common agreed approach

across primary and secondary care aims to avoid confusion and inconsistency.

The local guideline identified three main groups: those with vascular disease, those with diabetes, and those with neither of these conditions, ie primary prevention. In addition, the guideline included additional notes to supplement the recommendations.

Some recommendations are routine and were unchanged from previous iterations of the guideline. All patients with vascular disease have a lipid profile and liver function tests measured, and any secondary causes identified at baseline and, in the absence of contra-indications, are treated with a statin. In the absence of a recent acute coronary syndrome, simvastatin 40 mg od is first line treatment, with further titration being considered if total cholesterol remains above 4 mmol/l, and low-density lipoprotein (LDL) cholesterol above 2 mmol/l. This is consistent with the NICE lipid modification guideline. Recognising the importance of management directed at atherogenic components of the lipid profile and, in the spirit of considering some of the practical barriers to guideline implementation, a corresponding threshold

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