AN ESICM MULTIDISCIPLINARY DISTANCE LEARNING PROGRAMME FOR INTENSIVE CARE TRAINING

Acute hepatic failure

Organ specific problems

Update 2012 (pdf)

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LEARNING OBJECTIVES

After studying this module on Acute hepatic failure, you should be able to:

1. Describe the clinical, laboratory and radiological features used to diagnose acute liver failure (ALF) and determine its aetiology.

2. Assess the severity and prognosis of the patient with ALF and institute appropriate monitoring and immediate management.

3. Understand the differences between ALF and Acute on Chronic Liver Failure (ACLF).

4. Choose therapies to optimise support of the liver and other organ systems.

5. Determine which patients with ALF should be considered for transplantation or other advanced treatment options.

6. Discuss the prognosis of ALF.

FACULTY DISCLOSURES

The authors of this module have not reported any disclosures.

DURATION

6 hours

INTRODUCTION

The liver is the largest visceral organ and makes up 2.5% of body weight. The functions of the normal liver are:

- Bile formation
  - Bile acid transport
  - Bilirubin metabolism and transport
  - Gall bladder function and enterohepatic circulation
- Cholesterol and lipoprotein metabolism
- Drug metabolism
- Carbohydrate metabolism
- Fatty acid metabolism
- Ammonia metabolism
  - Protein synthesis
  - Cell volume regulation
- Storage
  - Glycogen
  - Vitamin A, B12, D, Iron
- Immunological
  - Reticuloendothelial system.

Bacon BR, O'Grady JG, DiBisceglie AM, Lake JR. Comprehensive Clinical Hepatology: Textbook with CD-ROM. 2nd ed. Mosby; 2005. ISBN-13: 978-0323036757

O'Grady JG, Lake JR, Howdle PD. Comprehensive Clinical Hepatology. Mosby; 2000. ISBN-10: 072343106X. p. 3.1–3.16.

In this module, the term Acute Hepatic Failure (AHF) will include both acute liver failure (ALF) and acute on chronic liver failure (ACLF); although these conditions share a number of aetiologies, they are distinct entities with important differences both in terms of clinical presentation and management.

ALF is a broad term used to describe the development of severe hepatic dysfunction within six months of the onset of symptoms, while chronic liver disease is said to be manifest when cirrhosis or another inflammatory/fibrotic process has been present for more than six months.

Chronic liver disease is more common than ALF; causes include chronic infection with hepatitis B and C viruses, alcohol, cholestatic diseases, immune-mediated and metabolic processes amongst others. Acute exacerbations, with deterioration in both hepatic and extra-hepatic organ failures are most often caused by infection (often spontaneous bacterial peritonitis), variceal bleeding, alcohol excess (alcoholic hepatitis), vascular thrombosis and drug therapies.

The incidence of cirrhosis is continuing to rise, related to viral hepatitides, non-alcoholic fatty liver disease (as a component of the metabolic syndrome) and alcohol-related liver disease.

1. AN INTRODUCTION TO ALF AND ACLF

Acute liver failure

Acute liver failure is a rapidly progressive, life-threatening condition which occurs when there is massive liver injury, with necrosis of the liver parenchyma.

The condition is characterised by coagulopathy and encephalopathy which occurs within days or weeks, usually preceded by a prodromal illness of nausea and vomiting.

It is often complicated by multi-organ failure. Liver necrosis triggers an inflammatory cascade, which drives vasoplegic cardiovascular collapse, renal failure and, to some extent, cerebral oedema. Aggressive resuscitation of the circulation ameliorates hepatic parenchymal ischaemic injury and promotes regeneration. Hypoglycaemia must be actively sought, monitored and treated.

The key to a successful outcome rests in timely recognition, resuscitation and referral to a specialist centre for consideration of transplantation.

Patients with ALF may initially appear relatively well, but can rapidly progress to develop multi-organ failure. The diagnosis of the cause of these patients' ALF must go hand in hand with basic resuscitative manoeuvres.

Failure to recognise subacute/acute liver failure is not uncommon and is potentially disastrous for the patient who will not then be considered for urgent liver transplantation.

Classification

Hinds CJ, Watson JD. Intensive Care: A Concise Textbook. 3rd edition. Saunders Ltd; 2008. ISBN: 978–0–7020259–6–9. p. 381; Types of acute liver failure

The classification of ALF is important. In general, the incidence of cerebral oedema is higher in hyperacute liver failure, and the prognosis without transplantation is worst in the subacute group.

- **Hyperacute** – in which encephalopathy occurs within seven days of jaundice.
- **Acute** – with an interval of eight to 28 days from jaundice to encephalopathy.
- **Subacute** – with encephalopathy occurring 28 days to 12 weeks after jaundice.

When liver failure arises from a toxic cause, such as acetaminophen overdose or *Amanita phalloides,* or ischaemia then encephalopathy may precede the development of deep jaundice and the prodromal illness is absent.

All patients suspected of taking an overdose of any medication should have serum acetaminophen levels measured because ALF due to acetaminophen toxicity can be avoided by timely treatment with *N*-acetylcysteine (NAC).

For further information see the references below.

Bernal W, Auzinger G, Dhawan A, Wendon J. Acute liver failure. Lancet 2010; 376(9736): 190–201. PMID 20638564

Auzinger G, Wendon J. Intensive care management of acute liver failure. Curr Opin Crit Care 2008; 14(2): 179–188. PMID 18388681

Epidemiology

ALF is a rare condition. There are approximately 400 cases of ALF each year in the UK, and around 2800 in the USA. Viral hepatitis (particularly hepatitis B) is the most common precipitant in the developing world, but acetaminophen toxicity, idiosyncratic drug reactions and seronegative hepatitis are more common in developed nations. Seronegative hepatitis is said to be the cause when the history suggests a viral or immune-mediated aetiology but all serological tests are negative. A uniform investigative pathway helps to determine aetiology and whether disease-specific therapy may be available.

The decision to proceed to transplantation is made by a multidisciplinary team on the basis of aetiology, presentation and agreed prognostic criteria. The availability of donor organs is under continued pressure worldwide.

Aetiology

Hinds CJ, Watson JD. Intensive Care: A Concise Textbook. 3rd edition. Saunders Ltd; 2008. ISBN: 978–0–7020259–6–9. pp. 381–382; Causes

Causes of acute liver failure:

- Viral hepatitis
    - Hepatitis A, B, C, D, E, seronegative hepatitis
    - Herpes simplex, cytomegalovirus, chickenpox – usually limited to immunocompromised hosts
- Drug related
    - Acetaminophen
    - Antituberculous drugs
    - Recreational drugs (ecstasy, cocaine)
    - Idiosyncratic reactions – anticonvulsants, antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs)
    - Aspirin in children may lead to Reye (or Reye's) syndrome
    - Kava Kava
- Toxins
    - Carbon tetrachloride, phosphorous, *Amanita phalloides*, Alcohol
- Vascular events
    - Ischaemia, veno-occlusive disease, Budd–Chiari syndrome (hepatic vein thrombosis)
    - Hyperthermic liver injury
- Pregnancy
    - Acute fatty liver of pregnancy, HELLP syndrome (Haemolysis, Elevated Liver enzymes, Low Platelets), liver rupture
- Other
    - Wilson's disease, auto-immune, lymphoma, carcinoma, haemophagocytic syndrome
    - Trauma.

Bacon BR, O'Grady JG, DiBisceglie AM, Lake JR. Comprehensive Clinical Hepatology: Textbook with CD-ROM. 2nd ed. Mosby; 2005. ISBN-13: 978-0323036757

Acetaminophen overdose

Hinds CJ, Watson JD. Intensive Care: A Concise Textbook. 3rd edition. Saunders Ltd; 2008. ISBN: 978–0–7020259–6–9. pp. 514–515; Paracetamol

Acetaminophen (paracetamol) is an oral analgesic which is readily available over-the-counter in the UK, USA and Europe. Amidst suggestions that this medication may be linked to overdose, the Medicine Control Agency has sought to limit its availability. On the basis that overdose is frequently an impulsive act, acetaminophen is now sold in packets of no more than 8 g in the UK in an attempt to limit total quantities ingested.

In the UK, acetaminophen overdose is responsible for half of all hospital admissions due to poisoning. Following massive ingestion, relatively small doses are absorbed and *N*-acetylcysteine (NAC) is efficacious when administered early; less than 1% of cases result in significant hepatotoxicity.

Acetaminophen overdose may be intentional, unintentional, staggered (multiple ingestions over time) or mixed. Combined analgesics confer a risk of inadvertent overdose when they are abused for their narcotic content.

The risk of developing hepatotoxicity is related to the quantity ingested, the time to presentation and treatment with NAC.

Cytochrome P450 enzymes convert ~5% of acetaminophen to *N*-acetyl p-benzoquinoneimine (NAPQI), a metabolite which is normally detoxified by conjugation with hepatic glutathione. Hepatocellular glutathione becomes rapidly depleted in overdose, and NAPQI persists, causing damage to cell membranes leading to hepatocyte death.

NAC augments glutathione levels and is highly effective when administered within 8–12 hours of a single acute overdose.

A clear history of the timing and quantity of the overdose is essential. It should be established whether tablets were ingested in a single sitting, or the overdose was staggered.

> **NOTE** Negative acetaminophen levels do not exclude hepatotoxicity if obtained more than 16–24 hours after ingestion. Timing of reported ingestion of tablets and dose should always be considered in the context of the clinical scenario and may not be accurate.

Overdose is frequently mixed, accompanied by co-ingestion of opiates/narcotics (e.g. co-dydramol) or by alcohol ingestion. Notwithstanding this, every attempt should be made to investigate the circumstances surrounding any suicidal attempt.

Anorexia, malnutrition, chronic alcohol consumption and enzyme inducing drugs (phenytoin, carbemazepine, etc) may all potentiate overdose by lowering glutathione levels and/or increasing P450 activity.

The Prescott nomogram (http://pmj.bmj.com/content/81/954/204.full) is used in the UK and Europe to determine the risk of acetaminophen toxicity. The Rumack–Matthew nomogram is used in the USA. They can only be applied to a single acute overdose presenting within 16–24 hours.

If in doubt, commence treatment. NAC administration can be life-saving, and adverse reactions and unpleasant side effects are rare.

> **NOTE** Patients with features of moderate to severe acetaminophen toxicity should be managed in a critical care environment. Appropriate early volume resuscitation can impact enormously on outcome. Early contact should be made with a transplant centre and decisions to transfer made in a timely fashion.

Risk factors:

See nomogram curve B (http://pmj.bmj.com/content/81/954/204.full) which designates a high-risk group whose threshold (acetaminophen plasma level) for treatment is much lower than (about half) the 'non high-risk group'.

Decreased hepatic glutathione stores	Induction of cytochrome P450 microenzymes
Anorexia nervosa	Phenytoin
Bulimia	Carbamazepine
HIV	Rifampicin
Cystic fibrosis	Phenobarbitone
Malnourishment	? Long-term ethanol ingestion

Viral hepatitis

Hepatitis A and B are the most frequently implicated causes of ALF worldwide.

The risk of a bout of viral hepatitis precipitating acute liver failure is lowest with hepatitis A. The incidence of hepatitis A is decreasing in Western countries, presumably due to vaccination and improvements in sanitation and food hygiene.

Hepatitis B progresses to ALF in ~1% of cases. Around 50% are associated with hepatitis D co-infection. The role of antiviral agents in management is lacking a large evidence base but these drugs are commonly administered. Those patients who are carriers of hepatitis B and are then treated with high dose steroids and or chemotherapy may reactivate their hepatitis B and develop ALF. This complication can be prevented by appropriate screening and treatment with antiviral agents.

Hepatitis E is common in Asia and Africa. Like hepatitis A, it is also transmitted by the faecal–oral route and has caused epidemics after heavy rainfalls. It carries a mortality risk of 0.5–4% in developed countries, although this figure

may be as high as 75% in less developed countries. The risk of ALF consequent to hepatitis E infection is highest if the virus is contracted in the third trimester of pregnancy (>20%).

Viruses such as cytomegalovirus (CMV), Epstein–Barr virus (EBV), Herpes Simplex virus (HSV) and Varicella Zoster (VZ) have all been implicated in cases of ALF, and should be considered particularly in the immunocompromised. The mortality associated with atypical viral hepatitis is ~75%. Acyclovir and valganciclovir are used to treat HSV and CMV.

Drug-Induced Liver Injury

The liver is the primary site of drug metabolism and elimination. The hepatic portal vein is usually formed by the confluence of the superior mesenteric and splenic veins and also receives blood from the inferior mesenteric, gastric and cystic veins. It is responsible for ~75% of the liver blood supply. This close anatomical relationship renders the liver susceptible to the potential toxicity of substances absorbed across the gut mucosa.

Hepatotoxicity is one of the most common reasons for the withdrawal of medicines from the market. More than 1000 drugs and herbal remedies have been implicated in drug-induced liver injury (DILI).

DILI includes acetaminophen toxicity and is one of the most common causes of ALF. Acetaminophen toxicity is a phenomenon related to the quantity of drug ingested. Most other cases of DILI are idiosyncratic reactions.

DILI is unpredictable. Allergic DILI is characterised by fever, skin reactions, eosinophilia and autoantibody formation. Risk factors include age, female gender, polypharmacy and active co-morbidity. Genetic polymorphisms have been associated with diclofenac hepatotoxicity.

DILI is most frequently diagnosed following a rise in aspartate aminotransferase (AST)/alanine aminotransferase (ALT) and in gamma-glutamyltransferase (GGT).

Specific causes of DILI:

Most of the anti-TB drugs have hepatotoxic potential. The greatest incidence of DILI is seen with isoniazid/rifampicin in combination, although the pyrazinamide/rifampicin combination is also particularly toxic. Toxicity is most often seen in the elderly, pregnant and Asian male cohorts. If DILI develops in the context of anti-TB treatment, then all drugs should be stopped and expert advice sought. Drugs are often re-introduced sequentially once transaminases decline, although decisions are made based on the severity of the TB infection and the time for normalisation of the liver function tests (LFTs).

Khat is a flowering plant native to East-Africa which contains the amphetamine-like stimulant cathionine and may be chewed to induce mild euphoria. Use is particularly common in males in Somalia and Yemen. It can cause ALF and is illegal in many European countries, although it is not classified as a controlled substance in the UK.

Other drugs such as antimicrobials e.g. flucloxacillin, recreational drugs e.g. MDMA/'ecstasy' and halothane (a volatile anaesthetic) are other noteworthy causes of DILI. The risk of liver injury may be greatest with concomitant acetaminophen use, long-standing viral hepatitis and other forms of chronic liver disease. Sodium valproate is also implicated in DILI. Halothane is no longer in regular clinical use and therefore is less relevant.

Toxins

The toxins in *Amanita phalloides* and *Bacillus cereus* (food poisoning/'fried rice syndrome') are naturally occurring causes of ALF. Carbon tetrachloride is sometimes used experimentally to induce ALF in animal models.

Amanita phalloides   *Bacillus cereus*

Malignancy

Both solid and haematological tumours are causes of ALF. Infiltration, ischaemia, infarction and vascular attenuation cause parenchymal injury.

The images below were obtained from a previously well 63-year-old man who felt non-specifically unwell for about four weeks prior to presentation with a sepsis-like syndrome, transaminitis and only modestly elevated bilirubin. CT imaging demonstrated what appeared to be a large necrotic, gas-filled liver abscess; histology revealed this to be adenocarcinoma with abundant surrounding mucous ('colloid carcinoma').
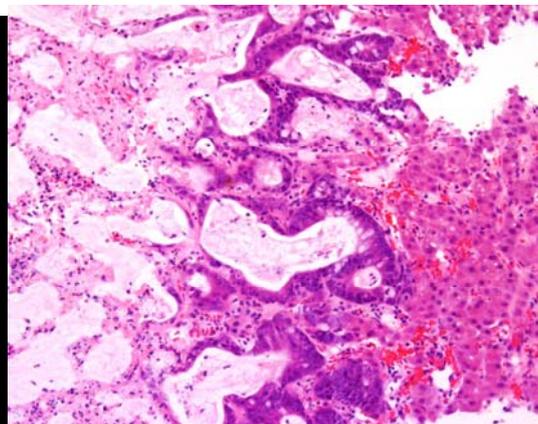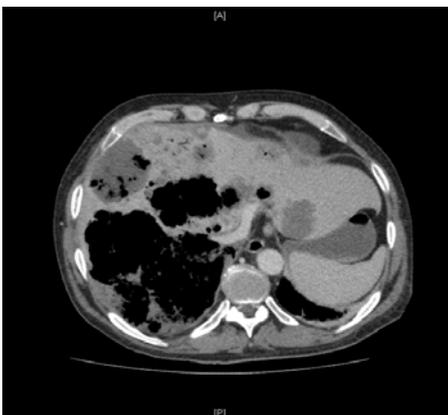
Patients with underlying malignancy are often older, and features such as enlarged lymph nodes, or radiological evidence of infiltration should prompt further investigation. AST and ALP (alkaline phosphatase) are frequently elevated, but serum bilirubin elevation is less predictable. Transjugular liver biopsy, bone marrow aspiration/trephine, or biopsy of lymph nodes or other involved tissues are necessary to make a definitive diagnosis.

The presence of malignancy is a contraindication to liver transplantation. The diagnosis should be clear – if ALF is manifest, then the prognosis is often extremely poor.

Ischaemic hepatitis

Ischaemic hepatitis is common in low cardiac output states and in the context of severe respiratory failure. The biochemical picture is one of massive elevation in transaminases (ALT, AST), followed some days later by more modest elevations in ALP and bilirubin. Treatment is essentially resuscitative, with correction of the low perfusion state/any congestive element and with appropriate respiratory support.

Budd–Chiari syndrome is caused by occlusion of the hepatic veins. It is very uncommon (incidence 1:1 million) and presents with ALF in approximately 20% of cases. Chronic venous thrombosis may present with a cirrhotic type picture. Thrombosis secondary to inherited and acquired procoagulant states is the most common cause in Europe and the USA, although extrinsic venous compression by tumour may also occur. Congenital venous webs are a more common cause in the Asian population.

Procoagulant screening should be directed towards Factor V Leiden deficiency, Protein C and Protein S deficiency, antithrombin deficiency, anti-phospholipid syndrome, paroxysmal nocturnal haemoglobinuria and JAK2 mutation. Myeloproliferative disorders, polycythaemia, pregnancy/post-partum, oral contraceptive use and trauma are additional risk factors.

Metabolic disorders

These include acute fatty liver of pregnancy (AFLP – see below), fructose intolerance, galactosaemia, Reye's syndrome, tyrosinaemia and Wilson's disease.

Wilson's disease is an inherited, autosomal recessive, condition. Defective coding of a copper-transporting ATPase leads to inefficient copper excretion in the bile, and subsequent accumulation in the brain, liver and cornea. It is often suspected when ALF occurs in the presence of psychiatric symptoms.

Presentation is often acute, particularly in younger patients. The condition can present chronically as late as the eighth decade of life.

The diagnosis is made by measuring serum copper and caeruloplasmin (although the latter is acute phase and may be elevated in ALF), and elevated urinary copper levels (although ALF patients are frequently anuric). Kayser–

Fleischer rings may be evident on ophthalmoscopy because of corneal copper accumulation.

In patients with sudden unexplained deterioration in level of consciousness, consideration should be given to urea cycle defects which can present in later life and result in significant elevation of arterial ammonia levels.

Hepatic complications of pregnancy

Making the diagnosis of abnormal liver function in pregnancy is challenging. There is considerable clinical and biochemical overlap between syndromes. Hyperemesis gravidarum, AFLP, Intrahepatic cholestasis of pregnancy (IHCP) and HELLP syndrome (Haemolysis, Elevated Liver enzymes, Low Platelets) are unique to pregnancy. Other hepatic conditions, such as viral infection or Budd–Chiari syndrome, may occur during pregnancy and should be considered when reaching a differential diagnosis.

Acute fatty liver of pregnancy carries a significant maternal mortality. It is often complicated by pre-eclampsia. Defective β-oxidation of long chain fatty acids in the fetus can cause elevated serum levels of circulating fatty acids in the mother. Mothers who are heterozygous for long-chain-3 hydroxyacyl CoA dehydrogenase are at risk of hepatotoxicity. The presentation is non-specific, with nausea and vomiting, followed by jaundice and encephalopathy. Early delivery of the fetus is recommended.

Other

Falciparum malaria may also cause ALF. Mortality is around 25%.

Acute on chronic liver failure

The management of stable chronic liver disease is rarely the responsibility of the intensive care physician, except in specialist centres where planned interventions and/or surgical procedures are performed in patients with stable CLD (chronic liver disease). Increasingly, however, patients with stable, often unrecognised cirrhosis will present with decompensation following elective surgical procedures.

Decompensations in chronic liver disease are often precipitated by an acute event – commonly infection and bleeding.

Sepsis in chronic liver disease

Classical definitions of sepsis may not be applicable in chronic liver disease. The compensated and decompensated cirrhotic may demonstrate components of the Systemic Inflammatory Response Syndrome (SIRS) under resting conditions. Tachycardia and a bounding, vasodilated hyperdynamic circulation with hyperventilation (due to the evolution of hepatic encephalopathy) and reduced baseline polymorphonuclear leukocyte (PMN) count due to hypersplenism are common in 'stable' cirrhotics. Sepsis may be characterised only by exacerbation of circulatory changes already present at baseline.

A majority of cirrhotic patients with SIRS will have intercurrent infection and their mortality is higher than those who do not fulfil SIRS criteria.

The increased incidence of sepsis in those with underlying liver disease is multifactorial. Patients are frequently physically debilitated, deconditioned, malnourished and cachectic. Bactericidal and opsonic activity is reduced. Monocyte function is altered and there is depression of the phagocytic activity of the reticuloendothelial system due to the presence of intra- and extra-hepatic shunts through sinusoids without Kupffer cells, and reduced Kupffer cell number and function. Immune paresis, chronically upregulated endotoxin signalling and bacterial translocation are associated with the acquisition of infection.

Karvellas CJ, Pink F, McPhail M, Austin M, Auzinger G, Bernal W, et al. Bacteremia, acute physiology and chronic health evaluation II and modified end stage liver disease are independent predictors of mortality in critically ill nontransplanted patients with acute on chronic liver failure. Crit Care Med 2010; 38(1): 121-126. PMID 19770744

The main sites of infection in cirrhosis are the peritoneal space (ascites), urinary tract, lungs and blood. The commonest organisms are *E. coli*, followed by *Staph. aureus*, *E. faecalis*, *Strep. pneumoniae*, *Pseudomonas* and *Staph. epidermidis*. MRSA, VRE and ESBL-producing enterobacteria are becoming increasingly common and 1st and 2nd generation cephalosporins therefore fail in a substantial proportion of patients.

An exaggerated and damaging inflammatory response may provoke single or multiple organ failures. Tissue hypoperfusion occurs secondary to systemic hypotension, microvascular dysfunction, shunting, vasoplegia, formation of microthrombi, reduced RBC deformability and tissue oedema.

Sepsis has the potential to worsen liver function itself – exposure to endotoxin can cause hepatic inflammation mediated by Kupffer cells and hepatic fibrosis mediated by hepatic stellate cells.

Sepsis in cirrhosis (see figure 3 http://gut.bmj.com/content/54/4/556.full) is associated with a failure to control variceal bleeding and with early variceal re-bleeding.

Thalheimer U, Triantos CK, Samonakis DN, Patch D, Burroughs AK. Infection, coagulation, and variceal bleeding in cirrhosis. Gut 2005; 54(4): 556–563. PMID 15753544
doi: 10.1136/gut.2004.048181

Infection may predispose to variceal bleeding because of an elevation in sinusoidal pressure – and hence portal pressure and a worsening of

coagulopathy. It is recommended that patients with bleeding complications also be treated with antibiotics. Choice of antibiotic therapy is informed by local prescribing policy and drug resistances, but should include broad Gram-negative cover.

Spontaneous bacterial peritonitis

Spontaneous bacterial peritonitis (SBP) is infection of cirrhosis-related ascites. It may cause a florid sepsis syndrome with shock and renal failure, or have an onset which is insidious and only detected at paracentesis. Pyrexia, changes in mental state and abdominal tenderness are common. It is extremely important to differentiate SBP from secondary peritonitis.

Multi-organ failure

Encephalopathy may either be a precipitating factor or a consequence of ACLF. Its course often depends on the absence or presence of other organ failures. Aspiration pneumonia may be a consequence of high-grade encephalopathy. Clinical cerebral oedema is extremely rare compared to that of ALF.

Circulatory failure in ACLF is characterised by a vasodilated, hyperdynamic circulation and a need for vasopressor support. It is associated with metabolic acidosis and high lactate levels. It may be associated with cardiac systolic/diastolic dysfunction.

Pneumonia and pulmonary infiltrates are common in ACLF. Intubation and ventilation may be indicated for respiratory failure and for airway protection in advanced encephalopathy.

Changes in renal blood flow occur at an early stage during cirrhosis. Intense renal vasoconstriction may eventually lead to the so-called hepatorenal syndrome characterised by a steady (pre-renal like) deterioration in renal function with no response to volume expansion.

Relative adrenal insufficiency may contribute to the development of multiple organ failure (MOF), although the indications for steroid treatment in this cohort remain the subject of controversy.

See the PACT modules on Altered consciousness, Sepsis and MODS, Oliguria and anuria (Acute Kidney Injury Part I) and Electrolytes and Homeostasis.

2. HOW I MAKE THE DIAGNOSIS

History

As in all fields of medicine, a good clinical history and collation of all facts relating to this clinical presentation and past medical events are extremely important.

The history of the current illness should include the type and duration of symptoms leading to presentation. Not only is the duration of symptoms before the development of encephalopathy related to the incidence of cerebral oedema and prognosis without transplantation, but it may also help to localise the precipitating event. It is important to establish whether there has been any contact with viral hepatitis. It is also essential to obtain a full drug history, including prescribed, over-the-counter, herbal and recreational drugs. Drugs may have been taken for some months before the presentation of liver symptoms (amiodarone, methotrexate, NSAIDs). Other drug ingestion may result in a more acute presentation (acetaminophen, ecstasy).

History of travel is essential, as viral hepatitis is more common in some countries e.g. hepatitis E in the Indian subcontinent. It is important to determine if there is a family history of liver disease, particularly with regard to haemochromatosis, α-1 antitrypsin deficiency, Wilson disease and cystic fibrosis. In children, AHF can be caused by several other genetic–metabolic diseases, such as Reye-like inherited metabolic disorders, Gaucher disease, Niemann–Pick disease, Tangier disease, Fabry disease or Hurler disease. Early treatment with venesection/phlebotomy in an individual with Wilson disease may prevent the development of cirrhosis.

> Remind yourself of the inherited forms and causes of chronic liver disease. Review how they may present to your practice. These are becoming increasingly common as patients who have survived neonatal and childhood liver disease are presenting to adult services with decompensation. It is important to recognise these patients and their associated co-morbidities, e.g. Alagille syndrome and peripheral pulmonary stenosis.

http://www.geneclinics.org/profiles/alagille

> **NOTE** Screening of family (members) is important with inherited forms of liver disease.

In the social history it is important to establish whether there has been drug use, foreign travel or exposure to industrial chemicals. The patient's occupation may be relevant. A history of alcohol intake should be obtained, but it is inappropriate for all patients who consume alcohol to be labelled as having alcohol-related liver disease.

ANECDOTE A 45-year-old woman who drank several glasses of wine per night presented with malaise, clinical jaundice and abnormal liver function tests. The possibility of alcohol-related liver disease was raised, and she was told to stop drinking, with re-evaluation in two weeks. However, she deteriorated, with increasing jaundice, confusion and coagulopathy, and was eventually diagnosed with ALF due to seronegative hepatitis. She survived after a successful liver transplant operation.

A past history of jaundice, biliary surgery or trauma may suggest subsequent parenchymal liver injury or portal hypertension. A history of thrombosis or first trimester pregnancy loss may suggest the diagnosis of Budd–Chiari syndrome, whereas a history of systemic chemotherapy may indicate veno-occlusive disease or reactivation of hepatitis B infection.

> *Not all patients with jaundice will have liver disease but assume that they do in the first instance and order a full screen for liver disease and haemolysis*

Presentation

Acute liver failure

Hinds CJ, Watson JD. Intensive Care: A Concise Textbook. 3rd edition. Saunders Ltd; 2008. ISBN: 978–0–7020259–6–9. pp. 383–388; Clinical features, investigations and diagnosis

The common presentation of ALF is with jaundice, coagulopathy and encephalopathy, usually preceded by a prodromal illness characterised by nausea and vomiting.

Because the rate of development of encephalopathy is variable (see above), it may not be present when the patient is first seen. Similarly, when liver failure develops quickly (e.g. from a toxic cause such as acetaminophen), encephalopathy may precede the development of deep jaundice and the prodromal illness is absent.

Q. What is the importance of assaying for acetaminophen level when managing acute overdose patients?

A. All suspected overdose patients should have their serum acetaminophen level measured, because ALF due to acetaminophen can be avoided by timely treatment with *N*-acetylcysteine (NAC).

Clearly, a history suggestive of a cause, such as contact with hepatitis, should alert clinicians to the possibility of ALF.

Acute on chronic liver failure

The diagnosis of ACLF is usually clearer. Patients frequently have stigmata of chronic liver disease, ascites, jaundice and encephalopathy.

NOTE It is important to think: Why (has) the patient with chronic liver disease deteriorated?

Is there sepsis, dehydration, electrolyte abnormalities, sedative drugs, portal vein thrombosis, liver tumour or a gastrointestinal bleed? These should be actively sought in the patient with chronic liver disease (CLD) who has deteriorated acutely.

In a patient without a prior history of liver disease, assure yourself that this is not subacute liver failure.

Q. A 38-year-old male presents with ascites and jaundice. Investigations for viral hepatitis are negative. Ultrasound reveals splenomegaly. Creatinine is normal. He is assumed to have liver cirrhosis and started on diuretics. Is this appropriate?

A. No, this is not appropriate management as a diagnosis should first be determined. This will start with a detailed history examining risk factors for liver disease.

It will include seeking evidence of previous blood or other blood product transfusions, family history of jaundice/liver diseases, previous hepatitis infections, alcohol intake, recent travel history, drug ingestion/administration – including herbal remedies, tattoos or body piercing and sexual orientation.

Careful examination may give clues as to the chronicity of his signs and symptoms.

Investigations performed indicate negative viral serology. Always exclude acute hepatitis B by requesting an anticore antibody (IgM). Other investigations will be needed, auto-immune screens, ferritin, serum caeruloplasmin, immunoglobulins and α-1 antitrypsin deficiency.

There are many causes of splenomegaly. Request Doppler signals in hepatic veins and portal vein.

Once a diagnosis has been established then diuretics for treatment of ascites may be appropriate.

Discuss with colleagues and ensure appropriate investigations and imaging. Practise interpreting investigations and confirm with appropriate specialists.

Bacon BR, O'Grady JG, DiBisceglie AM, Lake JR. Comprehensive Clinical Hepatology: Textbook with CD-ROM. 2nd ed. Mosby; 2005. ISBN-13: 978-0323036757

Viral serology for hepatitis B infection must be requested and interpreted in the clinical context. A 19-year-old presents with a three-week history of malaise, bilirubin 350 μmol/l (20.5 mg/dl), AST 600 IU/L, international normalised ratio (INR) 3.0 and grade III encephalopathy. There was no history of drug ingestion. HAVIgM and HBVsAg were negative. Does this exclude hepatitis B (HBV) as a cause of infection?

No; patients with ALF secondary to HBV have a supra-immunological response to the virus in an attempt to clear it resulting in hepatocyte necrosis. Some patients will have already cleared the surface antigen at the time of presentation and test negative for HBVsAg. The diagnosis should be confirmed by demonstrating positive IgM anticore status. Of note this patient does not fit the picture for acetaminophen toxicity, the bilirubin level being too high in relation to AST.

Clinical features

Jaundice is a frequent presenting feature in patients with liver disease. It occurs in both ALF and in ACLF. Other clinical signs of ALF are relatively non-specific. Encephalopathy may be present and may range in grade from I to IV (see below). It can progress to cerebral oedema and brain-stem herniation in ALF.

Altered level of consciousness should always be considered to be a manifestation of encephalopathy in a patient with liver disease. Hypoglycaemia must also be considered.

Kayser–Fleischer rings may be seen in Wilson disease, though this will normally require slit lamp examination.

In ACLF there will often be signs of pruritis, especially with biliary disease. Loss of muscle mass is frequent, as is loss of secondary sexual characteristics and gynaecomastia in men. Other features include altered level of consciousness, parotid swelling (in alcohol-related disease) and spider naevi. Imaging will demonstrate established portal hypertension.

NOTE Spider naevi do not always indicate chronic liver disease (CLD) because they may also be seen in ALF.

Hepatomegaly may be present or the liver may be small and shrunken. A shrinking liver is a poor prognostic sign in patients with acute and subacute liver failure. Hepatomegaly is particularly seen in alcoholic hepatitis and in infiltrative diseases. Bruising may be seen, and in patients with acute coagulation disturbances subconjunctival haemorrhage may be present. Peri-umbilical veins, ascites and oedema are often present. The hands may reveal palmar erythema, clubbing and leukonychia, and a liver flap (asterixis) may be demonstrated as an early sign of encephalopathy.

> ⚠ The presence of small volume ascites, a slightly enlarged spleen and small liver do not guarantee that the diagnosis is CLD as opposed to subacute liver failure. It is often a difficult diagnosis even for experts in the field and discussion at an early stage is essential along with review of recent investigations and imaging.

Bacon BR, O'Grady JG, DiBisceglie AM, Lake JR. Comprehensive Clinical Hepatology: Textbook with CD-ROM. 2nd ed. Mosby; 2005. ISBN-13: 978-0323036757

Vincent J-L, Abraham E, Moore FA, Kochanek PM, Fink MP (eds). Textbook of Critical Care. 6th ed. Elsevier; 2011. ISBN 978–1-4377–1367–1

Laboratory tests and their interpretation

Liver function tests (LFTs) are simple tests performed on serum. Increased serum bilirubin concentration reflects increased production or reduced hepatic uptake or biliary excretion. In acute liver disease, the absolute bilirubin level reflects the severity of the process to some degree, but a rising serum bilirubin concentration is particularly significant in patients with CLD. It is important to measure the conjugated and unconjugated fractions of bilirubin to determine whether haemolysis is contributing.

The hepatic intracellular enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are also present in non-hepatic tissues. ALT is more specific for the liver. In acute toxic injury and ischaemic hepatitis, the serum concentration of aminotransferase enzymes may be increased to several thousand IU/l, whereas in CLD, levels may be modestly increased or even normal. In alcohol-related liver disease AST activity is frequently twice that of ALT.

> ⚠ Falling plasma aminotransferase concentrations in a patient with ALF do not necessarily imply that liver function is improving. In the setting of worsening jaundice, coagulopathy and encephalopathy, it rather suggests that necrosis is massive, especially if the liver volume is decreasing.

An elevated serum concentration of alkaline phosphatase (ALP) is seen in many forms of liver disease, but most frequently in patients with biliary disease (extra- and intrahepatic) and in those with an infiltrative process involving the liver. A low plasma albumin concentration may be a sign of deteriorating liver function in patients with CLD, but in the critical care setting it is influenced by many other factors, and cannot be used as a marker of prognosis or disease progression. A number of the coagulation factors are synthesised by the liver (I, II, V, VII, IX, X). If the international normalised ratio (INR) remains prolonged after intravenous vitamin K repletion it is likely that there is significant liver dysfunction, assuming there is not disseminated intravascular coagulation,

although the two may co-exist. Elevated serum gamma-glutamyltransferase (GGT) concentration may be seen in patients with enzyme induction as well as in biliary obstruction.

Abnormalities of full blood count are frequent. Pancytopaenia occurs with hypersplenism. Erythrocytes are commonly macrocytic, and hypochromia may be seen if there is chronic low-grade blood loss, such as with portal hypertensive gastropathy. Eosinophilia may be present in liver disease caused by drugs, but its absence should not preclude this diagnosis.

Other tests that may be undertaken depending on the clinical context are plasma immunoglobulin profile and hepatitis virus serology viz. A (IgM), B (sAg, eAg, core IgM and DNA), C (antibody and viral load), delta, E), autoantibodies, viral serology (CMV, EBV, HSV, zoster). Further tests such as caeruloplasmin, serum copper, urinary copper (pre and post penicillamine), α-1 antitrypsin phenotype, ferritin and iron studies, procoagulant profile and alpha fetoprotein (AFP) may be indicated.

> *The aetiology of ALF must be sought with appropriate tests because prognosis is linked to the cause as well as to physiological and laboratory variables*

The latter (AFP) is elevated in a significant proportion of patients with hepatocellular carcinoma and with increased cell turnover, as may occur in ALF with necrosis and chronic viral hepatitis. In infants and children, screening for metabolic diseases is mandatory.

Some diseases have a classical pattern of LFTs such as leptospirosis where there is a markedly elevated serum bilirubin concentration with only marginally elevated AST and INR often with a normal GGT.

⚠️ Haemolysis (Coombs negative) in a young person with signs and stigmata of CLD, but often with no preceding history should suggest a diagnosis of acute Wilson disease – this is the one form of CLD that should be treated as a case of ALF in regard to transplantation and management when it presents acutely.

Q. An 18-year-old female presents with decreased level of consciousness. She has a small liver and splenomegaly on clinical examination. Haemoglobin is 5 g/dl, WBC 4.0 x 103/mm³ and platelet count is 50 x 10⁵/mm³, INR is 2.5. Bilirubin is elevated at 500 µmol/l (29.2 mg/dl), AST is 150 IU/l and ALP is 35 U/l. The low Hb is ascribed to bleeding from varices. Is this appropriate? Give your reasons.

A. No, this is not appropriate. Bleeding from varices is a possibility but not at the top of the list.

> **Q. The blood results demonstrate a reduction in Hb, WBC and platelets. What is your assessment and the next tests you request in this patient?**

A. This appearance may be in keeping with a poorly functioning bone marrow but her bilirubin is high and so haemolysis is a possibility.

> **Q. How would you exclude haemolysis?**

A. Request a split on the bilirubin (conjugated/unconjugated) and a haemolysis screen – reticulocyte/haptoglobin/blood film.

Liver biopsy

Liver biopsy may be required in order to establish a diagnosis. It is rarely undertaken in the critical care or acute setting, as the principles of management are infrequently determined by the aetiology of the process, and the decision to proceed to transplantation is normally based on a clinical diagnosis and markers of illness severity. A biopsy may be required for patients suspected of having malignancy, particularly lymphoma where systemic chemotherapy may be required. Haemodynamic observations following liver biopsy are essential to detect bleeding. Expert interpretation by a liver histopathologist is essential.

In many patients with ALF, diagnostic features may not be found within the liver biopsy – this is in contrast to the setting of chronic liver disease and ACLF

Review the anatomical considerations, techniques and complications of liver biopsy. Liver biopsy is not likely to be a skill of a Critical Care physician as the skill is acquired in a separate structured, specialist hepatology environment. The risk–benefit with regard to coagulopathy should always be considered. Liver biopsy should be undertaken under ultrasound guidance or by the transjugular route (see below).

Bacon BR, O'Grady JG, DiBisceglie AM, Lake JR. Comprehensive Clinical Hepatology: Textbook with CD-ROM. 2nd ed. Mosby; 2005. ISBN-13: 978-0323036757

Percutaneous liver biopsy is dangerous in coagulopathic patients. These patients should be transferred to the Radiology Department, where an interventional radiologist can perform the biopsy by the transjugular route.

Radiology

Radiology is an important aspect of the assessment of a patient with liver disease. Ultrasound is readily available and easy to perform. It allows assessment of the liver parenchyma (whether homogeneous or heterogenous, high reflectivity associated with fatty infiltration). The biliary tree may be examined for dilation, and the parenchyma for abnormal areas suggestive of tumour deposits. However, this may be difficult to determine in a patient with a nodular cirrhotic liver. The examination must also include assessment of the vascular supply of the liver, assessing patency of the hepatic artery and veins. This is particularly important in the diagnosis of the Budd–Chiari syndrome, as patients may be misdiagnosed with CLD because of jaundice, ascites and hepatomegaly. The vascular signal in the hepatic veins may also mimic ischaemic hepatitis if the patient exhibits significant tricuspid regurgitation. It is also important to determine the patency of the portal vein, as in some patients portal hypertension is secondary to portal vein thrombosis without any associated liver disease.
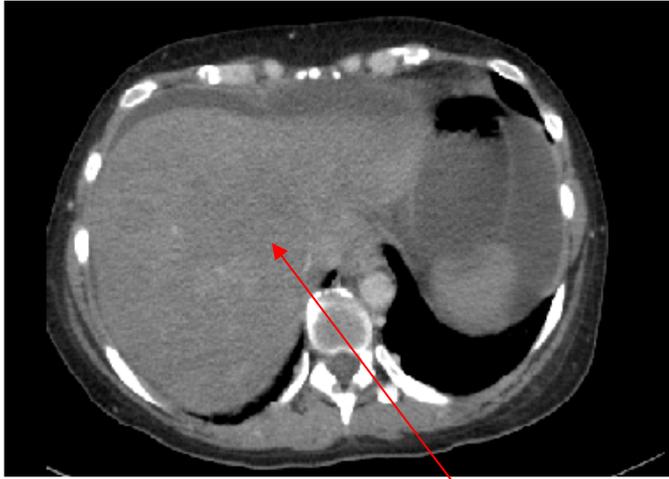
Acute Budd Chiari syndrome. The intrahepatic IVC is grossly attenuated.

CT and magnetic resonance imaging allow further detailed visualisation of the abdominal anatomy. These modalities provide further information regarding vascular supply and possible areas of tumour infiltration. Endoscopic retrograde cholangiography is used in patients with biliary obstruction who require decompression of their biliary system and may be required in patients with traumatic liver injuries where there is leakage of bile from the liver rupture site.

CT scan in a patient with a major hepatic tear

Endoscopic ultrasound may be indicated to assess the pancreas and abdominal lymph nodes, particularly in the context of malignancy.

Endoscopic retrograde cholangiopancreatography (ERCP) examination demonstrating traumatic bile leak (arrow) in a patient who had been kicked by a horse.
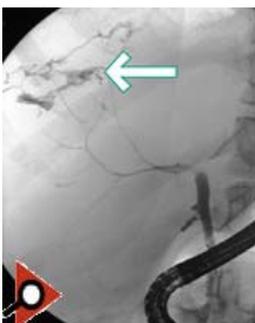
THINK of pseudoaneurysm formation after liver trauma, especially when there is an associated biliary or pancreatic injury. This complication may present with catastrophic bleeding and/or melaena with blood decompressing through the biliary tree and into the GI tract. Endoscopy, if undertaken, must visualise the sphincter of Oddi. Treatment is normally with angiographic embolisation.

Q. A patient in the ICU is recovering from a traumatic liver injury that was managed conservatively. He has a parenchymal haematoma that is regressing on sequential CT imaging. He develops fever (38 °C) and abdominal pain. Liver function tests are improving (bilirubin 20 μmol/l (1.2 mg/dl), AST 150 IU/l, alkaline phosphate 45 U/l). CT shows a collection in the sub-hepatic space, the parenchymal injury is regressing. What are your management plans?

A.
- Septic screen and broad-spectrum antibiotics
- Daily liver function tests
- Discuss findings with surgeons responsible for the patient
- Further imaging may be necessary to follow the resolution of this collection (USS or CT).

Q. If a bile leak suspected, what further diagnostic imaging might be appropriate?

A. A magnetic resonance cholangiopancreatogram (MRCP) or endoscopic retrograde cholangiopancreatogram (ERCP) may be indicated

For more information on imaging, see the PACT module on Clinical imaging.

3. HOW I MANAGE THE ACUTE SITUATION

Staff protection

No particular extra staff protection is required in patients with ALF/ACLF. Universal precautions should be applied to all patients whether or not they are regarded as infectious. In addition, patients with liver disease are susceptible to infections and infection control procedures should be stringently applied.

See the PACT module on Infection prevention and control.

All staff working with patients with ALF should be immunised and immune to hepatitis B infection. However, vaccination does not protect from infection with mutant versions of hepatitis B virus or hepatitis C. Hepatitis A and E viruses are spread by the faecal–oral route; hepatitis B and C viruses are transmitted via blood and other bodily fluids. Strict hand washing and use of a chlorhexidine/alcohol hand wash before and after contact with the patients, appropriate use of aprons, and use of gloves if there is the possibility of contact with secretions, should be routine and essential clinical practice.

> ⚠️ Healthcare workers should use appropriate eye protection with face shields.

Insertion of cannulae, central venous catheters, chest tubes and other procedures put healthcare staff at risk not only of needle stick injury but also of splash contamination by potentially infected blood and secretions. In the case of needle stick injury, local Infection Control and Occupational Health protocols are immediately activated.

Assessment of severity and prognosis – ALF

The severity of ALF (and consequently the prognosis without liver transplantation) can be assessed using pre-existing characteristics of the patient (e.g. age), the cause of the ALF, the rapidity with which symptoms develop (particularly encephalopathy) and certain key markers on testing–INR, pH, serum bilirubin and creatinine concentration. In general, the prognosis is worse in patients who are younger than 10 years or older than 40 years, those who have causes other than acetaminophen toxicity or hepatitis A and B virus infection, and when there is a long period between the development of symptoms and encephalopathy. Persistent acidosis, INR >3.5 and increasing serum bilirubin and creatinine concentrations also suggest a worse prognosis in those with non-acetaminophen aetiologies.

O'Grady JG, Alexander GJ, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology 1989; 97(2): 439–445. PMID 2490426

The most frequently used prognostic models are those of O'Grady and the French (Clichy) criteria. Other useful models recently published utilise phosphate level in those with acetaminophen toxicity or a combination of bilirubin, lactate and aetiology as the BiLE criteria. Liver volume is also used by some, particularly in patients with subacute liver failure.

Bacon BR, O'Grady JG, DiBisceglie AM, Lake JR. Comprehensive Clinical Hepatology: Textbook with CD-ROM. 2nd ed. Mosby; 2005. ISBN-13: 978-0323036757

Vincent J-L, Abraham E, Moore FA, Kochanek PM, Fink MP (eds). Textbook of Critical Care. 6th ed. Elsevier; 2011. ISBN 978–1-4377–1367–1

Assessment of severity and prognosis – ACLF

Severity of CLD may be assessed with the Child–Pugh score or the model end stage liver disease (MELD) score. The MELD score was developed as a scoring system to assess likely outcome from TIPS (transjugular intrahepatic portosystemic shunt) in the chronic liver disease population. Although it is often used in the acute liver failure patients, it is not particularly reliable for this group. This score, ranging from 6 to 40, is highly predictive of three-month mortality in hospitalised cirrhotic patients without transplantation.

Child–Pugh score

	1	2	3
Encephalopathy	0	I/II	III/IV
Ascites	absent	mild	>moderate
Bilirubin (μmol/l)	<34 (<2 mg/dl)	34-51 (2-3 mg/dl)	>51 (>3 mg/dl)
Albumin (g/l)	>35 (>3.5 g/dl)	28-35 (2.8-3.5 g/dl)	<28 (<2.8 g/dl)
INR	<1.3	1.3-1.5	>1.5

A total score of:
5–6 = Grade A (well-compensated disease)
7–9 = Grade B (significant functional compromise)
10–15 = Grade C (decompensated disease)

MELD score

$$3.8 \times \log_e (\text{bilirubin (mg/dl)}) + 11.2 \times \log_e (\text{INR}) + 9.6 \times \log_e (\text{creatinine (mg/dl)})$$
$$+ 6.4 \times (\text{aetiology: 0 if cholestatic or alcoholic, 1 otherwise})$$

In broad terms, dysfunction and failure of other organs have adverse prognostic implications in both ALF and ACLF. SOFA score appears to be the best predictor of outcome in cirrhotics admitted to critical care as opposed to liver based scoring systems.

Wehler M, Kokoska J, Reulbach U, Hahn EG, Strauss R. Short-term prognosis in critically ill patients with cirrhosis assessed by prognostic scoring systems. Hepatology 2001; 34(2): 255–261. PMID 11481609

NOTE Organ failure and requirement for ventilatory, renal and vasopressor support do not preclude a patient with ALF proceeding to transplantation whereas it may well do so in a patient with ACLF.

Monitoring key variables and trends in organ dysfunction

Management of the patient with ALF involves aggressive supportive care and ongoing assessment of clinical, physiological and laboratory variables.

Trends are more important than absolute measures

⚠️ In ALF clinical deterioration can occur rapidly. Criteria for transplantation may be met in hours.

Because of the potential for rapid deterioration, early discussion with a transplant centre can facilitate optimal timing of transfer. Similarly, once listed for transplantation, patients require ongoing assessment as to their suitability for liver grafting. In patients with ACLF it is important to consider the severity and rate of progression of liver disease in the individual patient when deciding on treatments for renal failure, variceal bleeding, ascites and encephalopathy.

Clinical variables

Modified Parsons-Smith scale of hepatic encephalopathy

GRADE	CLINICAL FEATURES	NEUROLOGICAL SIGNS	GLASGOW COMA SCALE
0/subclinical	Normal	Only seen on neuro-psychometric testing	15
1	Trivial lack of awareness, shortened attention span	Tremor, apraxia, incoordination	15
2	Lethargy, disorientation, personality change	Asterixis, ataxia, dysarthria	11-14
3	Confusion, somnolence to semi-stupor, responsive to stimuli, fits of rage	Asterixis, ataxia	8-10
4	Coma	± Decerebration	< 8

In ALF, as encephalopathy worsens from grade I through to IV there is a classic progression of clinical signs:

- Reducing level of consciousness
- Development of brisk reflexes
- Clonus
- Coma
- Elevated intracranial pressure
- Pupillary abnormalities – sluggish then fixed
- Brain-stem coning/herniation

It is therefore important to monitor the grade of encephalopathy, and to perform regular clinical examinations to assess progression. Assessment of pupillary reactions should be performed hourly or more frequently if the patient is unstable. Monitoring of intracranial pressure (ICP) and jugular bulb oxygen saturation are indicated in specific circumstances (see Task 3 – Monitoring – in the PACT module on Traumatic brain injury).

> ⚠ Be suspicious if you are told a patient with ALF is 'asleep'. It may be so, but the patient is more likely demonstrating early signs of encephalopathy. Similarly, a patient who becomes aggressive and pulls out vascular catheters and other tubes is also likely to be encephalopathic.

Cardiovascular variables are assessed using standard invasive haemodynamic monitoring. Heart rate, arterial blood pressure and central venous pressure should be measured at least hourly. Cardiac output measurement, pulmonary artery and pulmonary artery wedge pressure monitoring and echocardiography may be indicated in some patients. Hypovolaemia is common in patients with ALF, and should be corrected promptly using sodium-containing resuscitation fluids. The high cardiac output state combined with reduced oxygen extraction by the failing liver makes central or mixed venous saturations an unreliable guide to hypovolaemia.

Renal function is assessed clinically by monitoring urine output. Intra-abdominal pressure monitoring may be useful in patients with tense ascites (see the PACT module on Abdomen in acute/critical care medicine).

> **THINK** how you could measure the intra-abdominal pressure in a patient with oliguria and tense ascites. In such patients the urine output may respond to low volume paracentesis.

Respiratory function is monitored by recording the respiratory rate and continuous measurement of oxygen saturation, in conjunction with regular arterial blood gas estimations. There is a high risk of infection in patients with liver failure, and temperature should be monitored closely. Surveillance cultures for infection control are useful in these patients.

Laboratory variables

To evaluate whether transplant criteria are met and to assess liver function, full blood count, liver and renal biochemistry and coagulation profiles should be

determined regularly. In patients with ALF, transfusion to correct coagulation abnormalities should be avoided unless there is active bleeding in view of the importance of the INR in defining prognosis. By contrast, transfusion in patients with ACLF can be given if clinically indicated. Arterial blood ammonia may also be monitored. Urinary Na is low in hepatorenal failure.

> **NOTE** Blood urea is not a good guide to renal function in patients with liver disease.

Blood and other biological fluids should be cultured if there is suspicion of infection. In patients with ascites, ascitic fluid should be obtained. A white blood cell count greater than 250 PMN/mm^3 in ascitic fluid is indicative of infection and should prompt the administration of antibiotics and volume resuscitation. The ascitic fluid culture will facilitate specifically targeted antimicrobial therapy once culture/antibiogram results are known.

Point-of-care testing should allow regular blood gas analysis incorporating blood lactate assessment. Because blood lactate concentration is a composite measure of lactate production and metabolic capacity, it can be used to assess both haemodynamic status and liver function.

As described above, specific tests to determine the aetiology of liver disease should also be undertaken.

Imaging

Chest X-ray and ultrasound of the liver should be performed in all patients; this includes checking the patency of, and direction of flow in vessels. In some patients more detailed imaging may be required.

Providing a safe physiological environment

As in all critically ill patients, control of airway, breathing and circulation is paramount and is the first consideration.

All patients with grade III and IV encephalopathy should be treated in an intensive care unit, and those with grade I/II encephalopathy should be in a high-dependency environment where escalation of care can be offered if required.

> **NOTE** Grade III/IV encephalopathy is an indication for intubation (for airway protection), even when gas exchange is normal.

Intravascular volume status can be difficult to assess in patients with liver disease, especially when complicated by ascites. Patients with ALF are not normally salt overloaded, unlike those with ACLF, in whom saline-containing solutions should be avoided. Most patients with liver disease have a high cardiac output state with low peripheral vascular resistance, and vasopressors such as noradrenaline should be the normal first-line drug infusion for hypotension once intravascular volume has been restored.

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Hypoglycaemia is common in patients with ALF and should be prevented by appropriate dextrose infusion – ensuring that hyponatraemia is not potentiated. Iatrogenic hyponatraemia and failure to correct hypovolaemia are the most common errors.

Infection is a common complication of acute liver failure. The progression of hepatic encephalopathy can be caused by sepsis.

Respiratory tract infection, including ventilator-associated pneumonia is most prevalent although intravascular catheter-related sepsis, urinary sepsis, abdominal sepsis secondary to bacterial translocation and *de novo* severe sepsis/septic shock are also common. Fungal infections are common, and may occur in a third of ALF patients. It is routine practice to treat early and aggressively with antifungal therapy. Antibiotic 'prophylaxis' is instituted as a matter of routine in all patients with advanced encephalopathy.

The antimicrobial regimen should encompass commonly responsible organisms given the likely site of infection, the known bacterial flora of the intensive care unit at the time, resistance patterns and the results of blood, urine and sputum cultures, chest radiographs and other surveillance modalities. Azoles, polyenes and echinocandins are suitable antifungal agents.

Karvellas CJ, Pink F, McPhail M, Cross T, Auzinger G, Bernal W, et al. Predictors of bacteraemia and mortality in patients with acute liver failure. Intensive Care Med 2009; 35(8): 1390-1396. PMID 19343322. Full text (pdf)

Nutrition should be given to all patients, as most patients with liver disease have high nutritional requirements. Oesophageal varices are not a contraindication to nasogastric tube insertion for feeding.

ANECDOTE A patient presents 48 hours following an acetaminophen overdose. She has been vomiting profusely and is fluid depleted. Blood tests show a serum creatinine of 230 µmol/l (2.6 mg/dl), Na 136 mmol/l, urea 2.0 mmol/l (5.6 mg/dl) and INR 4.5. Because of the liver disease she is prescribed 5% dextrose at 150 ml/hr. Over the next 48 hours she develops progressive hyponatraemia (Na 123 mmol/l), decreasing level of consciousness, anuria and INR >6. Although she was at high risk of neurological deterioration, the iatrogenic hyponatraemia was an avoidable contributor.

Toxin removal or treatment

Specific treatment options for AHF are sadly few. *N*-acetylcysteine is an effective antidote for acetaminophen-induced hepatotoxicity and appears to be effective if started up to 24 hours after ingestion. Some reports suggest lack of benefit after this time, whilst others show ongoing benefit with improved organ function. *Amanita phalloides* may be treated with penicillin or silibinin. Other specific treatments are more relevant to CLD than AHF or ACLF. Patients with Wilson disease may be offered chelating therapies with penicillamine or trientene. Those with Budd–Chiari syndrome are anticoagulated and may be

treated with TIPS if organ failure is not present. Lamivudine therapy should be commenced in patients with past HBV infection undergoing chemotherapy, steroid or other immunosuppressive therapies because of the risk of reactivation of disease.

Q. A patient undergoing chemotherapy for lymphoma presents with transaminitis (AST 500 IU/l), jaundice (bilirubin 450 µmol/l (26.3 mg/dl)), alkaline phosphatase 120 U/l (N<150 U/l), INR 2.1 and altered level of consciousness (GCS 10). Is this progressive lymphomatous infiltration? Give reasons.

A. This may be progressive lymphomatous disease but it is unlikely if the liver function tests have deteriorated rapidly.

Q. Outline other causes of this acute deterioration which require exclusion in this setting?

A. Veno-occlusive disease associated with chemotherapy; chemotherapy induced cardiomyopathy causing marked hepatic congestion; Budd–Chiari syndrome may be associated with procoagulant disorders, chemotherapy and/or dehydration.

Q. Any hepatic disorder which may be triggered by the chemotherapy?

A. Recrudescence of hepatitis B following systemic chemotherapy may be a possibility.

4. MINIMISING COMPLICATIONS AND PROVIDING ORGAN SUPPORT

See ESICM Flash Conference: J Wendon. Conservative management of acute liver failure, Lisbon 2008.

Optimum support of the liver involves maximising oxygen delivery, avoiding hepatotoxins and using antidotes if appropriate.

One of the main difficulties in optimising liver support is the lack of a time-responsive indicator of changes in liver function in the critical care setting. Blood lactate and coagulation parameters, in addition to standard biochemistry, may be used, but the response time is slow. The plasma decrement rate of indocyanine green is a simple but non-specific bedside test of function but is not widely used in clinical practice. Breath identification studies using 13C-methacetin have yet to be validated.

Minimising complications

Patients are prescribed proton-pump inhibitors as prophylaxis against gastrointestinal bleeding but, interestingly, patients with liver disease and coagulopathy are normally excluded from trials assessing such interventions.

Nutrition is commenced as soon as feasible. Protein intake should normally be between 1 and 1.5 g protein/kg/day.

Córdoba J, López-Hellín J, Planas M, Sabín P, Sanpedro F, Castro F, et al. Normal protein diet for episodic hepatic encephalopathy: results of a randomized study. J Hepatol 2004; 41(1): 38–43. PMID 15246205

Variceal bleeding is an important cause of decompensation of CLD. Management of the acute bleed requires control of the airway, ventilation and restoration of circulating volume with colloid and coagulation factors. Administration of intravenous proton-pump inhibitor is usual. Decreased splanchnic inflow and hence pressure may be achieved with drug therapy (terlipressin or somatostatin) and bleeding may then be controlled with endoscopy. If there is re-bleeding despite these measures or the portal pressure is >20 mmHg early consideration should be given to a Transjugular Intrahepatic Portosystemic Shunt (TIPS). Early TIPS should also be considered in those with Child–Pugh score B or C and active bleeding at endoscopy.

> *Variceal bleeding is frequently associated with sepsis and requires aggressive concomitant treatment of the varices, sepsis and coagulopathy*

García-Pagán JC, Caca K, Bureau C, Laleman W, Appenrodt B, Luca A, et al.; Early TIPS (Transjugular Intrahepatic Portosystemic Shunt) Cooperative Study Group. Early use of TIPS in patients with cirrhosis and variceal bleeding. N Engl J Med 2010; 362(25): 2370-2379. PMID 20573925

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The risk of re-bleeding can also be reduced with concurrent use of terlipressin and endoscopic therapy. Many patients with cirrhosis take non-selective β-blockers to decrease their risk of bleeding and these should be restarted once the patient has been stabilised.

Goulis J, Burroughs AK. Chapter 31 Portal hypertensive bleeding. In: McDonald JWD, Burroughs AK, Feagan BG, editors. Evidence-Based Gastroenterology and Hepatology. 2nd ed. Wiley-Blackwell; 2005. ISBN-10 072791751X

Groszmann RJ, Garcia-Tsao G, Bosch J, Grace ND, Burroughs AK, Planas R, et al.; Portal Hypertension Collaborative Group. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. N Engl J Med 2005; 353(21): 2254–2261. PMID 16306522

Q. You are asked to assess a 42-year-old man with major upper GI haemorrhage and haemodynamic compromise (HR 130/min, BP 90/40 mmHg, postural drop). He is known to have auto-immune liver disease and is drowsy. He has ascites and has recently become oliguric. The admitting team wishes to undertake an upper GI endoscopy – what is your advice?

A. Resuscitation prior to the endoscopy. He is likely to have oesophageal varices.

Q. What pre-procedure measure would you consider appropriate?

A. Consider:
- Central venous access/large bore cannulae/cross-match blood
- Correction of coagulopathy with blood products and vitamin K
- If drowsiness persists, he is at risk of aspiration, therefore tracheal intubation/ventilation prior to endoscopy likely to be pre-emptively required
- Consider terlipressin/broad-spectrum antibiotics/anti-fungals after blood cultures/septic screen taken.

Central nervous system

Encephalopathy

Hinds CJ, Watson JD. Intensive Care: A Concise Textbook. 3rd edition. Saunders Ltd; 2008. ISBN: 978–0–7020259–6–9. p. 383; Encephalopathy, pp. 388–389; Pathogenesis of encephalopathy and cerebral oedema

Hepatic encephalopathy encompasses a wide spectrum of neuropsychiatric disturbances associated with liver dysfunction. It occurs in patients with both acute and chronic liver disease. It may also be seen in patients with large portosystemic shunts in the absence of liver disease (as with portal vein thrombosis).

> *The diagnosis of encephalopathy is essentially clinical: EEG and evoked potentials are only used to diagnose sub-clinical encephalopathy and as research tools*

See ESICM Flash Conference: J Wendon. Hepatic encephalopathy, Barcelona 2010.

Although encephalopathy may be chronic (that is low grade and often only diagnosed with neuropsychiatric tests), it is patients with the acute form who are most likely to present to the ICU. Acute encephalopathy is usually precipitated by:

- Infection.
- Metabolic disturbances (electrolyte abnormalities, excessive diuretic therapy or fluid restriction, excessive paracentesis, uraemia, alkalosis, anaemia, hypoxaemia).
- Gastrointestinal disturbances (haemorrhage, constipation, excessive protein load).
- Hepatic abnormalities (acute liver necrosis, disease progression, portal vein thrombosis, ischaemia, hepatoma, spontaneous portosystemic shunting that may not be associated with liver disease, TIPS or surgical shunts).
- Psychoactive drugs.
- Medication non-compliance.

ANECDOTE A 56-year-old woman with known CLD secondary to alcohol consumption was admitted with severe encephalopathy (GCS 5/15). CT scan of the head was normal. Liver function tests were unchanged from clinic (bilirubin 50 µmol/l (2.92 mg/dl), AST 50 U/l, GGT 150 U/l). There was no ascites or peripheral oedema (unusual for her) and she was clinically dehydrated. Na was decreased at 129 mmol/l, creatinine 135 µmol/l (1.53 mg/dl), urea 6 mmol/l (16.8 mg/dl). Diuretics were discontinued, crystalloid administered and lactulose prescribed for constipation. Within 48 hours she had a GCS of 15/15. The aetiology of encephalopathy is often multifactorial requiring simple but urgent therapies.

Although the precise pathophysiology of encephalopathy is unclear, it is generally believed that the neurological dysfunction is caused by accumulation of toxins. In CLD there is abnormal cerebral astrocytic and neuronal function, with derangement of multiple neurotransmitter systems. Shunting of blood from the portal circulation into the systemic circulation may expose the brain to substances that are neurologically active (false neurotransmitter hypothesis).

Putative toxins include ammonia, mercaptans, gamma-aminobutyric acid, endogenous benzodiazepines and serotonin/tryptophan. Ammonia has been the most studied and probably is a relevant putative toxin along with an inflammatory milieu which appears to potentiate the risk of encephalopathy.

Shawcross DL, Wright G, Olde Damink SW, Jalan R. Role of ammonia and inflammation in minimal hepatic encephalopathy. Metab Brain Dis 2007; 22(1):125–138. PMID 17260161

Seyan AS, Hughes RD, Shawcross DL. Changing face of hepatic encephalopathy: role of inflammation and oxidative stress. World J Gastroenterol 2010; 16(27):3347–3357. PMID 20632436

The primary source of ammonia is the gastrointestinal tract; it is metabolised in health in the liver and then excreted as urea and ammonium. In liver disease, ammonia may access the systemic circulation directly, both through portosystemic shunts and through failure of hepatic metabolism. When the liver is unable to adequately metabolise ammonia some metabolism will occur in skeletal muscle. Most treatments of encephalopathy associated with CLD aim to decrease cerebral exposure to ammonia.

Management options

Management of encephalopathy associated with CLD may involve:

- Resuscitative measures e.g. control of airway, support of circulation.
- Diagnosis and treatment of the precipitant.
- Treat infection and biochemical abnormalities.
- Protein intake of 1–1.5 g protein/kg/day depending on level of encephalopathy (can be reduced to 0.5 g/kg/day transiently). Vegetable protein is preferable to animal protein.
- Lactulose/lactilol. The cathartic effect removes endogenous and exogenous ammonia-generating compounds from the bowel and maintains an acidic environment that retains ammonia within the bowel lumen.
- Neomycin may have an additive benefit but is not often used because of the risk of oto-and nephrotoxicity.
- Zinc supplementation is recommended as zinc is a necessary substrate in the metabolism of ammonia to urea and many patients are zinc deficient.

- There is no evidence to support the use of benzodiazepine antagonists.
- Recent studies suggest benefit with rifaxamin in preventing encephalopathy in an outpatient setting.
- Use of ammonia lowering agents such as L-ornithine and L-arginine have some role in chronic liver disease but had no beneficial effect when studied in the context of ALF.

Bass NM, Mullen KD, Sanyal A, Poordad F, Neff G, Leevy CB, et al. Rifaximin treatment in hepatic encephalopathy. N Engl J Med 2010; 362(12): 1071-1081. PMID 20335583

Q. A patient is admitted with encephalopathy (grade II/III). There is a history of heavy alcohol consumption. Jaundice, moderate ascites and hepatomegaly are present and there is peripheral oedema. The temperature is 38 °C. Serum bilirubin is 150 µmol/l (8.76 mg/dl), AST 40 U/l, albumin 30 g/l, Na 128 mmol/l, creatinine 120 µmol/l (1.36 mg/dl), urea 3 mmol/l (8.4 mg/dl). White blood count is 25 x 10^9/l, Hb 12 g/dl, platelet count 68 x 10^9/l. Ultrasound reveals a bright liver, 15 cm spleen and ascites. All vessels are patent. What is your likely diagnosis?

A.
This patient is likely to have alcoholic hepatitis.

By clinical history and examination, you assess for risk factors for liver disease from relatives, friends and general practitioner and perform investigations to exclude concomitant and other causes of liver disease. As you are concerned that the fever may reflect infection, you conduct a septic screen and start broad-spectrum antibiotics.

See the PACT module on Pyrexia.

You start IV thiamine/B vitamin complex and commence NG Nutrition and start a detoxification regimen (e.g. with diazepam/lactulose).

Q. Which specific therapy would you consider?

A. Pentoxifylline or steroids but you are aware that pentoxifylline has been shown to be more effective for alcoholic hepatitis.

Q. If a confirmatory tissue diagnosis was required, what would you consider?

A. Consider specialist hepatology opinion re liver biopsy if specifically required for diagnostic purposes. In this patient's case, a transjugular biopsy might be safer.

Acute liver failure and cerebral oedema

Encephalopathy in ALF is associated with development of cerebral oedema in patients who deteriorate to grade IV coma. Its pathogenesis involves both vasogenic and cytotoxic mechanisms. There is marked variability of cerebral blood flow in patients with ALF, and hyperaemia is often seen in those with cerebral oedema. Ammonia has been implicated in the pathogenesis – and appears to diminish neutrophil function.

> *Cerebral oedema is rarely seen in patients with CLD and encephalopathy*

Shawcross DL, Wright GA, Stadlbauer V, Hodges SJ, Davies NA, Wheeler-Jones C, et al. Ammonia impairs neutrophil phagocytic function in liver disease. Hepatology 2008; 48(4):1202–1212. PMID 18697192

Higher levels of ammonia are seen in patients who die a cerebral death compared with those who do not. Fever appears to worsen encephalopathy and hypothermia decreases brain ammonia uptake.

Bernal W, Hall C, Karvellas CJ, Auzinger G, Sizer E, Wendon J. Arterial ammonia and clinical risk factors for encephalopathy and intracranial hypertension in acute liver failure. Hepatology 2007; 46(6): 1844–1852. PMID 17685471

Sepsis and SIRS have a detrimental effect on the progression of encephalopathy and cerebral oedema.

Hinds CJ, Watson JD. Intensive Care: A Concise Textbook. 3rd edition. Saunders Ltd; 2008. ISBN: 978–0–7020259–6–9. pp. 402–404; Changes in cerebral blood flow

Because of the rigidity of the skull, the intracranial pressure (ICP) is determined by the volumes of the brain substance, cerebrospinal fluid and blood within it. An ICP that is persistently >25 mmHg and cerebral perfusion pressure (CPP) <50 mmHg are associated with a poor prognosis. Autoregulation is rarely intact in patients with ALF, and increases in mean arterial pressure are often mirrored by increased ICP.

For more information see the PACT module on Traumatic brain injury.

> ⚠ Avoid fever, seizures, agitation, jugular venous compression and coughing associated with endotracheal suction in encephalopathic patients with ALF. They are all associated with increases in intracranial pressure.

Monitoring

Vigilant monitoring by experienced nursing and medical staff is mandatory for optimal outcome in patients with ALF. Pupil responses and size should be documented at least half-hourly, and GCS and level of encephalopathy noted regularly. Patients may develop increased tone, hyper-reflexia and sustained clonus.

Practice varies with regard to invasive cerebral monitoring in ALF. Some centres use aggressive multimodal monitoring for all patients with grade III/IV coma, whereas others avoid invasive monitoring because of the risk of intracerebral bleeding and the lack of clear data demonstrating a mortality benefit. The risks of ICP monitoring were reported several years ago from the results of a questionnaire. This showed the lowest morbidity and mortality to be associated with an extradural system (5% and 1%, respectively).

> *Most liver units place a reverse jugular line in all patients with ALF who require ventilation*

Willars C, Auzinger G Liver Transplantation – The Patient with Severe Co-morbidities: CNS Disease and Increased Intracranial Pressure. In: Wagener G, editor. Liver Anesthesiology. Springer (in press)

In general, it appears prudent to place ICP monitors only in patients most at risk. These include those who:

- Are pressor dependent and in renal failure
- Have arterial ammonia >150 µmol/l
- Have pupillary abnormalities
- Have acute and hyperacute liver failure
- Have reverse jugular (jugular bulb) saturations outside the normal range (55% to 80%).

The decision to place a monitor needs to take into account the risk and benefit for the individual patient.

Bernal W, Hall C, Karvellas CJ, Auzinger G, Sizer E, Wendon J. Arterial ammonia and clinical risk factors for encephalopathy and intracranial hypertension in acute liver failure. Hepatology 2007; 46(6): 1844–1852. PMID 17685471

The decision to place an intracranial pressure monitor should be taken by experienced staff in the context of overall patient care. Expose yourself to clinical scenarios to develop experience in making these decisions.

Although the coagulopathy associated with ALF should not be routinely corrected in view of its value as a prognostic marker, fresh frozen plasma (15

ml/kg) and cryoprecipitate, if required, should be given prior to insertion of an ICP monitor. Platelets are given if the count is <50 000/mm^3 (<50 x 10^9/l) in the authors' institution. Other centres may have differing thresholds for platelet administration.

Management of patients with grade III/IV encephalopathy

- Tracheal intubation and mechanical ventilation
- Provide adequate sedation – propofol or a benzodiazepine and an opiate
- Normalise serum sodium
- Prevent fever
- Maintain normocapnia
- Maintain in the head up position
- Maintain normovolaemia.

The role of hypothermia has not been tested in an RCT, but in individual cases the institution of hypothermia (32–35 °C) when the ICP is resistant to standard therapies may be beneficial.

Stravitz RT, Larsen FS. Therapeutic hypothermia for acute liver failure. Crit Care Med 2009; 37(7 Suppl): S258–S264. Review. PMID 19535956

Management of increased intracranial pressure

Treatment is required when there is a sustained rise in ICP to >25 mmHg or when pupillary abnormalities occur. It includes:

- Mannitol bolus: 0.5–1.0 g/kg, normally using 20% (20 g/100 mls) mannitol. Serum osmolality should be monitored and should not be allowed to increase to above 320 mosmol/kg.
- Hypertonic saline: slow infusion to maintain sodium levels of 145–155 mmol/l.
- Cooling: there are some data to suggest that aggressive cooling to 32–33 °C is beneficial.
- Thiopentone (thiopental): one case series suggests benefit in resistant intracranial hypertension, but there are significant haemodynamic side effects.
- Hyperventilation: may be used for short periods if ICP is increased with associated high jugular venous oxygen saturations.

For more information see the following references and the PACT module on Acute brain ischaemia.

Murphy N, Auzinger G, Bernal W, Wendon J. The effect of hypertonic sodium chloride on intracranial pressure in patients with acute liver failure. Hepatology 2004; 39(2): 464–470. PMID 14767999

Jalan R, Olde Damink SW, Deutz NE, Davies NA, Garden OJ, Madhavan KK, et al. Moderate hypothermia prevents cerebral hyperemia and increase in intracranial pressure in patients undergoing liver transplantation for acute liver failure. Transplantation 2003; 75(12): 2034–2039. PMID 12829907

⚠️ Always be aware that patients with ALF may deteriorate rapidly in terms of their level of consciousness.

Cardiovascular system

Patients with ALF and ACLF characteristically have a hyperdynamic circulation. Hypotension secondary to hypovolaemia is common. There is a significant incidence of adrenal dysfunction in ALF, and consideration should be given to treatment with pharmacological doses of hydrocortisone (200–300 mg/day) in those who require vasopressor support. The preferred pressor is noradrenaline.

Hinds CJ, Watson JD. Intensive Care: A Concise Textbook. 3rd edition. Saunders Ltd; 2008. ISBN: 978–0–7020259–6–9. pp. 60–63; Pulmonary artery pressure

Monitoring is usually with a central venous catheter initially. A pulmonary artery catheter provides a means of monitoring cardiac output and measuring pulmonary artery pressure and pulmonary artery occlusion pressure (PAOP). As in other settings, there are limitations to using PAOP as an indicator of fluid status because of compliance changes within the ventricle and the effects of elevated intra-abdominal pressure (IABP), which is common in ACLF. A monitoring technique that provides an index of fluid responsiveness is preferable in this clinical setting.

This may be particularly relevant in patients with ACLF who have significant right ventricular dysfunction – so-called cirrhotic cardiomyopathy. For more information see the PACT module on Haemodynamic monitoring.

Q. A patient with portal hypertension and large varices on CT imaging is admitted following a variceal haemorrhage. He is found to be hypoxic with PaO_2 8 kPa (60 mmHg) on 40% oxygen by face-mask. Chest X-ray is clear with no evidence of focal consolidation. Oxygen saturation deteriorates when the patient sits up. What is the likely diagnosis?

A. Hepatopulmonary Syndrome

Pulmonary hypertension is a complication of CLD (portopulmonary hypertension). Hepatopulmonary syndrome is characterised by abnormal gas exchange and orthodeoxia resulting from intrapulmonary vascular dilatation. Either can be an indication for liver transplantation.

Variceal haemorrhage is a significant cause of cardiovascular instability in patients with portal hypertension. Management includes restoration of blood volume and aggressive control of coagulopathy. First-line treatment is normally terlipressin (splanchnic vasoconstrictor) or octreotide (a long acting somatostatin analogue that reduces gastric acid secretion and splanchnic blood flow) and subsequent endoscopy, ideally with banding therapy. Gastric varices may be amenable to glue therapy. If control cannot be achieved, balloon tamponade is indicated, with inflation of a gastric balloon and traction on the gastro-oesophageal junction. The complications of this procedure are significant (misplacement of the gastric balloon with oesophageal injury and aspiration) and intubation and ventilation will be required if the patient is encephalopathic.

Balloon tamponade

The Sengstaken–Blakemore tube is most commonly used in the authors' institution. Normally only the gastric balloon is inflated, providing control of both local gastric and oesophageal varices by virtue of controlled pressure tamponade in the stomach at the gastro-oesophageal junction. Other devices for balloon tamponade of varices include the Minnesota tube (has an oesophageal suction port) and the Linton–Nachlas tube (has a gastric balloon only).

⚠️ Don't tie the Sengstaken–Blakemore tube to a bag of fluid over the end of the bed – this results in variable traction. Traction should be applied in a steady manner and should be secured from a 'helmet' or by applying tape to the patient's face. The 'tamponading' balloon should ideally be filled not with air but a mixture of saline and contrast media.

Chest radiograph in a patient presenting with a 10 cm oesophageal tear, bilateral pneumothoraces and surgical emphysema following the insertion of a Sengstaken tube.

> ⚠️ Failure to place the Sengstaken tube appropriately may result in oesophageal rupture following balloon inflation. The development of subcutaneous emphysema should be urgently investigated as the cause is likely to be oesophageal injury.

Bacon BR, O'Grady JG, DiBisceglie AM, Lake JR. Comprehensive Clinical Hepatology: Textbook with CD-ROM. 2nd ed. Mosby; 2005. ISBN-13: 978-0323036757

Respiratory system

As discussed earlier, patients with ALF may require tracheal intubation for control of the airway even when gas exchange is normal. This is usually necessary in grade III encephalopathy. In ALF, pulmonary complications are generally those of the unconscious state and include aspiration and infection. All patients with liver disease have increased susceptibility to infection and a high incidence of nosocomial infection.

Non-invasive ventilation is almost never indicated in patients with ALF and ACLF because of rapid progression of encephalopathy accompanying the onset of organ dysfunction

Pleural effusions are a common finding in patients with liver disease, and in many situations represent ascites passing through physical defects in the diaphragm. Managing hepatic hydrothorax and referral to specialised units is suggested. Acute lung injury and ARDS are seen in patients with liver disease and management is as for other patients except that permissive hypercapnia is not advisable in patients at risk of cerebral oedema.

Consideration should be given to specific cardiorespiratory complications that may present in ACLF and cirrhosis. Hepatopulmonary syndrome (HPS) results from shunting through the pulmonary capillary system with hypoxaemia and orthodeoxia. It is seen in up to 20% of patients and may be diagnosed with bubble echocardiography with the bubbles being seen after 2–3 cardiac cycles. Mild and moderate HPS may be reversed with liver transplantation but can be associated with significant morbidity.

Significant pulmonary hypertension with mean pulmonary artery pressures greater than 50 mmHg presents a significant mortality risk at transplantation (especially at reperfusion of the donor liver). Treatment may be with pulmonary vasodilators.

Renal

Hinds CJ, Watson JD. Intensive Care: A Concise Textbook. 3rd edition. Saunders Ltd; 2008. ISBN: 978–0–7020259–6–9. p. 387; Renal dysfunction

The most common cause of renal failure in patients with ALF is acute tubular necrosis. Consequently, strategies for preventing renal failure in this setting involve prevention and prompt treatment of hypovolaemia and hypotension and avoidance of nephrotoxic agents, including NSAIDs. In some cases, the agent causing the liver failure may have direct nephrotoxic effects (e.g. acetaminophen, carbon tetrachloride and other industrial toxins).

Renal failure may also be related to the underlying disease process, e.g. glomerulonephritis associated with HBV and hepatitis C virus (HCV) infection or an IgA nephropathy. Elevated intra-abdominal pressure (IAP) may also cause renal dysfunction, contributing to decreased renal perfusion pressure. Drainage of a small amount of ascites may have dramatic effects in decreasing abdominal pressure and improving renal function. For more information see the PACT module on Oliguria and anuria (Acute Kidney Injury Part I) and the PACT module on Abdomen in acute/critical care medicine.

Hepatorenal syndrome

O'Grady JG, Lake JR, Howdle PD. Comprehensive Clinical Hepatology. Mosby; 2000. ISBN-10: 072343106X. p. 8.1–8.16.

See the PACT module on Oliguria and anuria (Acute Kidney Injury Part I)

Hepatorenal syndrome (HRS) is seen in patients who have a decrease in renal perfusion pressure related to abnormal renal autoregulation and decreased renal prostaglandin synthesis, in addition to stimulation of the sympathetic nervous system and an increase in synthesis of humoral and renal vasoactive mediators.

HRS is a pre-renal failure that does not respond to fluid therapy. Type-1 HRS is rapidly progressive and may appear spontaneously, but often develops in the context of sepsis/SBP and hypotension. The natural prognosis of type-1 HRS is very poor. Type-2 HRS is usually more moderate, and often occurs in association with ascites. See references below.

Salerno F, Gerbes A, Ginès P, Wong F, Arroyo V. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. Gut 2007;56(9): 1310–1318. PMID 17389705

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1954971/figure/fig2/

Alessandria C, Ozdogan O, Guevara M, Restuccia T, Jiménez W, Arroyo V, et al. MELD score and clinical type predict prognosis in hepatorenal syndrome: relevance to liver transplantation. Hepatology 2005; 41(6):1282–1289. PMID 15834937

http://onlinelibrary.wiley.com/doi/10.1002/hep.20687/full

The diagnostic criteria for HRS in cirrhosis include:

- Cirrhosis with ascites
- Creatinine>1.5 mg/dl (133 micromol/L)
- No improvement in serum creatinine after 2 days of diuretic withdrawal and volume expansion with albumin
- Absence of shock
- No nephrotoxins
- Absence of parenchymal kidney disease.

There is an association with renal vasoconstriction. Infections, bleeding and large volume paracentesis without adequate volume replacement are common precipitating factors.

> **NOTE** HRS is reversible. After successful liver transplantation, for example, renal function will improve. Indeed, if the kidneys from someone with hepatorenal failure are transplanted into another individual, they function well.

A number of treatments for HRS have been investigated but have not been proven to be successful in randomised controlled trials. These include colloid infusion, mannitol, paracentesis with re-infusion, Levin shunt, porto-caval shunt, pressor agents such as angiotensin and noradrenaline, and renal vasodilators. Recent uncontrolled trials suggest that milrinone in combination with octreotide infusion, noradrenaline infusion in combination with albumin and furosemide, *N*-acetylcysteine infusion and TIPS have some beneficial effects in HRS.

Albumin may be effective as prophylaxis for HRS in SBP. Terlipressin appears to have significant benefit in patients with HRS when combined with albumin as volume therapy – see Cochrane systematic review below.

Gluud LL, Kjaer MS, Christensen E. Terlipressin for hepatorenal syndrome.
Cochrane Database of Systematic Reviews 2006, Issue 4. Art. No.:
CD005162. DOI: 10.1002/14651858.CD005162.pub2.

http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005162.pub2/figures

Renal replacement therapy

Renal replacement therapy (RRT) is normally undertaken as a continuous intervention (CVVH, CVVHD, CVVHDF) using dialysate buffered with bicarbonate. Intermittent dialysis is often associated with hypotension, with a concomitant decrease in cerebral perfusion pressure and possible worsening of cerebral oedema.

There are no absolute rules for institution of RRT, and much will depend on the clinical setting. However, it is usually indicated earlier in HRS than in patients with isolated renal failure.

Anticoagulation of the RRT circuits in patients with liver disease may be complicated by coagulopathy or bleeding. The preferred regimen will depend on the clinical setting and the experience of the unit, but options include low-dose heparin, regional heparinisation, citrate or prostacyclin. The authors would advocate a trial of unrestricted intensive care, including renal replacement therapy in ACLF. Prognosis is discussed later in the text.

> ⚠ NSAIDs should not be given to patients with liver failure, as prostaglandins are essential for maintaining renal blood flow in advanced liver disease.

See ESICM Flash Conference: J Wendon. RRT in liver failure: current indications, Barcelona 2010.

Coagulopathy

Coagulopathy is almost universal in patients with AHF. The liver plays a central role in haemostasis, and liver failure results in reduced synthesis and low circulating concentrations of fibrinogen, prothrombin and factors V, VII, IX and X, resulting in an increase in the prothrombin time (PT) or international normalised ratio (INR) for prothrombin. There may also be disseminated intravascular coagulation (DIC) and qualitative as well as quantitative defects in platelet function. As previously discussed, the PT and INR are vital markers of prognosis in ALF.

In patients with CLD, trends in coagulation parameters are less important with regard to prognosis. There is no evidence that support of coagulation with transfusion of fresh frozen plasma (FFP), platelets or cryoprecipitate has any

beneficial impact on outcome, and should not be undertaken without clear clinical indication.

In patients who have variceal haemorrhage it is conventional practice to maintain the INR below 1.5 and the platelet count above 70 x 10^9/l (70 x 10^3/mm^3). For more information see the PACT module on Bleeding and thrombosis.

> **THINK** Before giving FFP to a patient with acute liver failure – is correction of the INR necessary? Will it obscure an important prognostic indicator?

In patients with traumatic liver injury or with acute fatty liver of pregnancy and HELLP, coagulation support should be given because of the high risk of bleeding, even in those with only moderate coagulopathy.

5. PLANNING ADVANCED TREATMENT OPTIONS AND AVAILABILITY

Specialist referral – criteria

> ⚠️ Severely ill patients with ALF are best treated in a specialised unit with the capacity to provide liver transplantation!

All patients with non-acetaminophen-induced acute liver disease should be considered for transfer to a regional transplant centre for assessment. Specific criteria for transfer in this group include encephalopathy, coagulopathy (INR >1.8), jaundice (bilirubin >150 μmol/l (8.76 mg/dl)), renal failure, hyponatraemia and ascites. Trends are often more important than absolute values. Metabolic acidosis or blood lactate >2 mmol/l following initial resuscitation should prompt urgent discussion. The clinical finding of a shrinking liver also is a poor prognostic indicator and a reason for transfer.

Early discussion with a transplant centre is essential in order to optimise decisions regarding transfer or management at the local hospital

For acetaminophen-induced ALF, discussion with a specialist unit should take place if:
- The INR is greater than 3.0 or the prothrombin time in seconds is greater than the number of hours since overdose or INR of 2.0 at 24 hours, 4.0 at 48 hours, 6.0 at 72 hours
- There is an elevated creatinine (>200 μmol/l (2.26 mg/dl)) and INR >2.5
- There is any evidence of encephalopathy
- Mean arterial pressure <60 mmHg following volume resuscitation
- Evidence of a metabolic acidosis, pH <7.3 or HCO_3 <20 mmol/l
- Elevated blood lactate (>2.0 mmol/l)

Patients should be transferred before criteria for transplantation are met (see 'King's' criteria below). The major risk is that patients are not recognised as having ALF, so maintain an open mind and question! Nothing is lost by having early discussions with specialist centres.

Transfer of patients with CLD is dependent upon the clinical scenario. It may be that specialist endoscopic management is required or that the patient may be suitable for TIPS or transjugular liver biopsy.

> ⚠️ Liver trauma should be managed in a hospital with the capacity to undertake interventional radiology for control of arterial bleeding, with appropriate surgical expertise and the capacity to undertake ERCP. Obstetric liver patients are best managed in combined units.

Transportation

Patients with ALF can deteriorate rapidly; transportation to a liver unit must involve appropriate accompanying personnel, cardiac and respiratory monitoring and the equipment and capacity to initiate new treatments during transfer.

Although some patients may be suitable for transfer with a nursing or paramedical crew (stable CLD, early acute liver failure with isolated coagulopathy), the majority, particularly those with variable or fluctuating levels of consciousness, need transfer with suitably qualified medical staff with airway/critical care skills.

Venous access must be secured in all patients. Those with rapidly deteriorating levels of consciousness and ALF should be intubated and ventilated prior to transfer. Patients at risk of cerebral oedema should be transferred with normal $PaCO_2$ levels and equipment should be carried to administer 150 ml 20% (30 g) mannitol should the patient develop dilated or sluggish pupils.

Patients with severe metabolic acidosis should be considered for ventilation prior to transfer to reduce work of breathing. Treatment may be required in the form of intravenous bicarbonate and/or renal replacement therapy prior to transfer.

Equipment should be available to initiate a noradrenaline infusion if required; along with adequate volumes of colloid should hypotension develop during transfer. Normoglycaemia should be maintained. This may require administration of 10–50% dextrose – often by infusion.

Coagulation support is not indicated in ALF unless there is evidence of overt bleeding. In patients with variceal bleeding who are being transferred, blood products should accompany the patient as should a Sengstaken–Blakemore tube or similar device.

All patients with AHF failure who are transferred should be discussed with senior/consultant staff, and close communication should be maintained between both centres.

For more information see the PACT module on Patient transportation.

Liver transplantation

Criteria for transplantation in acute liver failure

In ALF, criteria for transplantation are different depending on whether the ALF is caused by acetaminophen toxicity or other non-acetaminophen aetiologies. The widely used King's College Hospital criteria are outlined in the O'Grady and McPhail references below.

> *The prognostic models of O'Grady et al. and the Clichy criteria (below) have been shown to be equally sensitive and specific*

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Vincent J-L, Abraham E, Moore FA, Kochanek PM, Fink MP (eds). Textbook of Critical Care. 6th ed. Elsevier; 2011. ISBN 978–1-4377–1367–1

O'Grady JG, Alexander GJ, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology 1989; 97(2): 439-445. PMID 2490426

McPhail MJ, Wendon JA, Bernal W. Meta-analysis of performance of Kings's College Hospital Criteria in prediction of outcome in non-paracetamol-induced acute liver failure. J Hepatol 2010; 53(3): 492-499. PMID 20580460

See ESICM Flash Conference: J Wendon. Liver dysfunction in the critically ill, acalculous cholecystitis & acute liver failure. Lisbon 2008 (slides 30 and 31)

NOTE Patients with non-acetaminophen aetiologies are the more difficult group to assess. They may present with multiple potential aetiologies and may be difficult to distinguish from chronic liver disease.

These criteria may be difficult to apply in the face of drug ingestion, including sedatives, salicylates, tricyclics and non-steroidal anti-inflammatory agents. The issue of acidosis may be clouded by the use of bicarbonate haemofiltration replacement fluids, which were not available when the criteria were developed. In recent studies, application of these criteria has been shown to result in improved sensitivity, specificity, and positive and negative predictive value.

It should be noted, however, that these criteria were not developed in patients with acute Budd–Chiari syndrome, Wilson disease or pregnancy-related liver failure. Nor have they been applied in the setting of trauma-related or paediatric liver failure.

The Clichy criteria

Criteria for liver transplantation have also been developed for non-acetaminophen aetiologies by the group in Clichy, France. These were generated from data from 115 patients with ALF secondary to hepatitis B and indicate that liver transplantation is necessary if:

- There is encephalopathy (coma or confusion)

and

- Factor V level <20% (if aged <30)

or

- Factor V level <30% (if aged 30 or above)

In the USA, decisions to transplant are also influenced by liver biopsy findings – specifically the percentage of viable hepatocytes found at the time of biopsy. There are concerns that this criterion is potentially unreliable because of sampling error, especially in acute and subacute liver failure.

Blood lactate levels, although not incorporated into any specific criteria for transplantation, are important prognostic indicators. For example, elevated levels despite volume loading of >3.5 mmol/l at four hours after transfer or admission and >3 mmol/l at 12 hours or following volume therapy are indicative of a very poor outcome and suggest that early liver transplantation is required.

Bernal W, Donaldson N, Wyncoll D, Wendon J. Blood lactate as an early predictor of outcome in paracetamol-induced acute liver failure: a cohort study. Lancet 2002; 359(9306): 558–563. PMID 11867109

Disease-specific criteria

French data suggest that in acute Budd–Chiari syndrome the combination of encephalopathy and renal failure should lead to transplantation. Increasingly, TIPS has a place in the earlier management of acute Budd–Chiari syndrome, in patients without renal failure and encephalopathy. There are no specific criteria for patients with fatty liver of pregnancy. In children the finding of an isolated INR >4.5 suggests the need for transplantation assuming the child has not ingested acetaminophen (in this setting the acetaminophen criteria would be applied). In acute Wilson disease, encephalopathy will normally result in transplantation.

> *The criteria for transplantation in children are different*

> **Q. A 50-year-old patient with hepatitis C-related cirrhosis presents with their first episode of decompensation. The patient is found to have bacterial peritonitis and is appropriately treated with good recovery. Renal function is maintained throughout. Imaging shows a cirrhotic liver, ascites, portal vein is patent and spleen is 16 cm. There is a nodule within the liver of 4 cm raising the possibility of hepatocellular carcinoma. What are the investigations and options available to this patient?**

A.
Investigations: alpha feta protein usually elevated in the presence of hepatocellular carcinoma (HCC); triple phase CT scan of the liver gives a characteristic filling pattern for HCC; MRI liver.
Orthotopic liver transplantation is the most appropriate therapy for a single lesion thought to be hepatocellular carcinoma in the presence of hepatitis C.

> **THINK** Am I excluding this patient for consideration for transplantation? Nothing is lost by discussion with a transplant centre.

Artificial liver support

Clinical experience dates back over several decades. The role of the liver is extremely complex, and support systems can be divided into those that aim to undertake the role of detoxification and those that in addition attempt to provide a synthetic component using hepatocytes in a bioartificial system.

One of the difficulties in assessing the data on these systems is that studies have included patients with both ALF and ACLF. The other confounding factor, particularly in ALF, is the use of liver transplantation, making interpretation of survival data difficult. Case series are frequent but the findings are difficult to extrapolate given the nature of the disease and the high incidence of transplantation.

Detoxifying systems

The first detoxifying system studied in AHF was haemodialysis, but no improvement in outcome was shown. Charcoal haemoperfusion was evaluated subsequently, and although the initial case series suggested significant benefit, a controlled clinical trial of patients in grade III and IV coma failed to demonstrate any improvement in outcome. Combined haemofiltration and plasma exchange in ALF may improve haemodynamic variables. Plasmapheresis has been shown to improve haemodynamic and neurological parameters.

Albumin dialysis is a mode where the patient's blood is dialysed against a variable concentration of albumin in the diasylate. In the MARS albumin dialysis circuit, detoxifying and de-ionising columns are incorporated in a closed dialysis circuit of 20% albumin. Two randomised controlled trials have been performed in ACLF:

In the first, 12 patients with hepatorenal failure were randomised to receive standard care or albumin dialysis. All patients died in the standard care group, with one survivor at 30 days in the treatment limb.

A second study examined 24 patients with acute on chronic liver injury. Biochemical markers and encephalopathy were significantly improved in the MARS group and a survival benefit was seen at three months but not at six months.

Recent data on plasmapheresis in ALF has suggested benefit, but has thus far only been presented in abstract form. The use of MARS in ALF has similarly only been presented as an abstract (benefit only in the acetaminophen subgroup).

Heemann U, Treichel U, Loock J, Philipp T, Gerken G, Malago M, et al. Albumin dialysis in cirrhosis with superimposed acute liver injury: a prospective, controlled study. Hepatology 2002; 36(4 Pt 1): 949–958. PMID 12297843

Bioartificial systems

Extracorporeal liver perfusion has been used for many years. In case reports, this approach appears to result in haemodynamic, biochemical and neurological improvement. Its application is, however, time-consuming and expensive.

There are several other systems utilising hepatocytes. Case series suggest benefit in terms of biochemical parameters. A large randomised controlled trial has been published that describes results with the bioartificial liver device.

Demetriou AA, Brown RS Jr, Busuttil RW, Fair J, McGuire BM, Rosenthal P et al. Prospective, randomized, multicenter, controlled trial of a bioartificial liver in treating acute liver failure. Ann Surg 2004; 239(5): 660–667; discussion 667–670. PMID 15082970

This study combined patients with acute liver failure and primary graft non-function. In the total group of 147 patients there were no significant improvements seen with or without liver transplantation. In subgroup analysis, however, there was benefit in the ALF group when the diagnosis was known.

The ELAD (extracorporeal liver assist device) study is pending publication, as are results of a trial examining the efficacy of plasmapheresis in ALF.

Only data from RCTs and published in peer-reviewed journals can be used to inform the application of potential treatment strategies. At present there is no definitive role for artificial liver support systems in patients with AHF.

6. WHAT IS THE OUTCOME FROM AHF?

Relevance of background psychosocial factors

> **NOTE** In patients with liver disease who are being assessed for transplantation, a multidisciplinary approach is paramount.

The acceptance of patients onto a transplant list in terms of psychosocial and dependency issues varies among centres – some will accept patients who are dependent on methadone, for example, but only as part of an established programme, whilst others would not consider such patients.

A multidisciplinary approach is also needed to support patients with alcohol-related disease to become abstinent. Abstinence is important because of the ability of the liver to regenerate. Over a period of three to six months' abstinence, an individual may improve from Child–Pugh C to Child–Pugh A and no longer require transplantation.

This is one of the main reasons why a period of six months' abstinence is required before listing a patient with alcohol-related liver disease for transplantation. Abstinence from alcohol is also of great importance in patients with hepatitis C-related liver disease due to synergistic hepatotoxic effects.

> ⚠️ Take care when assessing psychosocial problems in patients with ALF who may need transplantation and access as many sources as possible promptly. Accurate information may be difficult to obtain and the physical condition of the patient may change rapidly.

Different centres may have different views about offering acute liver transplantation to patients who have taken recreational drugs or to those who have taken an overdose of, for example, acetaminophen. It should be emphasised that the vast majority of patients who have taken an overdose do so as part of a 'cry for help' and have no suicidal intent, and express regret at their actions.

Supporting the family

The families of all critically ill patients require support and understanding. This is particularly true of patients with liver disease. For those with ALF, the onset of the disease may be very sudden and a patient may be functioning normally one day and require mechanical ventilation and multiple organ support soon thereafter.

Family members may have particular problems understanding the reason for their relative's confusion and the concept of encephalopathy. The risk of cerebral oedema should be explained early and fully. As with all critically ill patients, the changes in the patient's appearance and the functions of all the tubes and catheters should also be explained to the family.

Family members also need to be reassured that there is no stigma associated with liver disease. Many are under the impression that liver disease only occurs in people who abuse alcohol or drugs. Another frequent concern is the risk of an infectious process affecting other family members. This may particularly be the case when it is not possible to give a definitive diagnosis, as in patients with seronegative hepatitis.

Perceived stigma is a real issue for the relatives of patients with liver disease as are the issues of risk to themselves in regard to infection

The role of transplantation also needs to be explained. In ALF, transplantation is only offered to those who fulfil poor prognostic criteria (predicted mortality >90%). This does not mean that patients who do not fulfil transplant criteria will all survive, and relatives require support through these difficult times.

In the setting of chronic liver disease there are the same concerns regarding the cause of liver disease and associated stigma. In many cases, the episode of decompensation may be the first time liver disease has been diagnosed. In patients with chronic liver disease and established multiple organ failure, it is unlikely that transplantation would be offered unless the patient first improved significantly. In contrast, patients with ALF are transplanted from the ICU setting with organ failure. Family members may find the decision on whether to offer transplant or not difficult to understand. This may be compounded by the assumption that transfer to a specialist centre is expressly for transplantation.

Patients who undergo transplantation for ALF require significant psychological support – unlike patients with CLD they frequently have no memory of being ill and thus their dependence on drug therapy may be difficult to deal with

Relatives often express anger that a diagnosis or recognition of severity of disease was not made earlier. Support again is needed, and it should be explained that many people with liver disease are asymptomatic until their episode of decompensation.

For more information see the PACT modules on Communication and Organ donation and transplantation.

Prognosis and outcomes following transplantation

Prognostic factors are well described for patients with ALF, and when applied appropriately, accurately define a cohort of patients with a less than 10% chance of surviving with medical therapy alone. The negative and positive predictive factors are well defined for patients with acetaminophen-induced ALF. When blood lactate is incorporated into the criteria, a poor outcome can be predicted earlier.

In the non-acetaminophen group, the criteria accurately predict patients who will have a poor outcome. Sepsis and multiple organ failure are common and are a frequent cause of death in those awaiting transplant and in those who do not fulfil transplant criteria.

Aggressive support is indicated in all patients with ALF, whether or not transplantation is planned. Patients who survive ALF without the need for transplantation should be reassured that their liver has the capacity to return to its 'pre-illness condition'.

The decision to proceed to transplantation in an individual with ALF and multiple organ failure depends to a great extent on trends in clinical parameters rather than any given level of support or physiological derangement. Most centres would not proceed to liver grafting in a patient with dilated pupils that were non-responsive to light, but decisions regarding level of pressor support or gas exchange are assessed on an individual basis.

> *Although transplantation solves the problem of end-stage liver disease it brings with it other complications, e.g. immunosuppressive drugs and their side effects, renal dysfunction, disease reoccurrence, biliary complications, cardiovascular risk*

Patients undergoing liver transplantation for ALF have a worse one-year survival rate than patients undergoing elective transplantation (75–80% vs 90–95%, respectively). An individual who has only encephalopathy prior to liver grafting is likely to have a better chance of three-month survival than a patient on noradrenaline, high-level respiratory support, in renal failure with grade IV coma and intracranial hypertension. It is of note that most of the 12-month mortality in ALF patients is seen in the first three months after transplantation, unlike patients with CLD, whose co-morbidities may contribute to ongoing morbidity and mortality over the subsequent years.

Q. What background and acute factors are considered before proceeding to transplantation in a patient with AHF?

A.
1. Background:
The patient's wishes (known after discussions with family and referring team).
Psychological factors (premorbid mental state, suitability for transplant programme and alcohol).

2. Acute:
Degree of multi-organ failure.
Brain including brain-stem function (?fixed dilated pupils).
Meeting criteria for transplantation.

Prognosis in ACLF

The outcome of patients with CLD admitted to the ICU does not appear to be determined by the aetiology of the liver disease. Patients admitted with a variceal bleed normally have a better prognosis than those admitted with multiple organ failure and sepsis. A recent study examined the outcome of patients with CLD admitted to the ICU. Das et al determined that the most important risk factor for in-hospital mortality was the severity of non-haematologic organ failure, best assessed after three days. Overall survival at 12 months was under 40% and at 24 months was under 30%.

For more information see the following reference and the PACT module on Clinical outcome.

Das V, Boelle PY, Galbois A, Guidet B, Maury E, Carbonell N, et al. Cirrhotic patients in the medical intensive care unit: early prognosis and long-term survival. Crit Care Med 2010; 38(11): 2108-2116. PMID 20802324

> ⚠ Studies such as these should not be used to refuse admission but to examine practice, to optimise care and to identify patients who need earlier and more aggressive support. The authors concluded that the in-hospital survival rates seemed acceptable, even in those with MOF on admission. They state that a trial of unrestricted intensive care could be proposed for select critically ill cirrhotic patients.

Transplantation and chronic liver disease

Outcome for patients with CLD undergoing elective transplantation is excellent, and is quoted as 90–95% survival at 12 months. In general, however, the outcome of patients with CLD who undergo transplantation from the ICU with multiple organ failure is poorer, with survival figures lower than in ALF. Primary graft dysfunction and non-function contribute to the mortality and following liver grafting and also the presence of co-morbidities (renal, cardiac or respiratory dysfunction).

Survival Functions
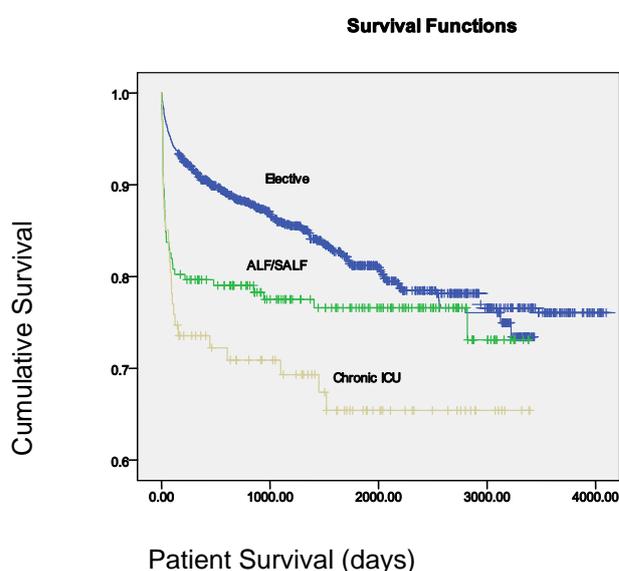
Kaplan–Maier survival curves comparing survival of patients transplanted electively for chronic liver disease, emergently for acute/subacute liver failure and patients with chronic liver disease transplanted from the ICU. Source – Institute of Liver Studies, King's College Hospital (unpublished data).

CONCLUSION

Acute liver failure is an uncommon condition and most patients should be treated in a liver unit where management of complications and assessment for and management of liver transplantation can be undertaken by teams experienced in the management of liver disease. However, optimum management involves early identification of these patients and consequently it is vital that all intensivists are able to recognise the condition, assess severity, liaise with a liver unit if necessary and provide appropriate supportive and specific medical treatment through the period of assessment and transfer.

Chronic liver disease is relatively common, particularly in the context of alcohol and viral infection. Decompensation is often due to sepsis or bleeding, and admission to ICU should be sought. Again, centres offering expertise in the management of these episodes can add to patient management and advice should be sought at an early stage.

SELF-ASSESSMENT

EDIC-style Type K

1. Regarding the occurrence of acute liver failure:
A. The incidence is rising
B. Viral hepatitis is the most common precipitant in Europe
C. The incidence is approximately 100/million inhabitants/year
D. The disease is more common in the very old (>80 years)

2. Regarding acetaminophen (paracetamol) overdose and acute liver failure:
A. A total dose of at least 25 g is necessary to lead to acute liver failure
B. *N*-acetylcysteine is a very effective antidote if administered early
C. Most of the ingested paracetamol is converted to a toxic metabolite causing cell damage
D. A negative paracetamol level does not rule out hepatotoxicity

3. Ichaemic hepatitis may occur after low cardiac output states and have the typical findings:
A. Massive elevation of transaminases in the days after the ischaemic insult
B. Massive elevation of bilirubin immediately (1–2 days) after insult
C. Normal INR
D. Hypoglycaemia indicates near total liver failure

4. The hepatic intracellular enzymes are important in the diagnosis of liver diseases. Regarding the interpretations of ALT and AST:
A. They are only present in hepatic tissues
B. In chronic liver disease the elevations of ALT and AST are often moderate
C. Very high levels (>5000 IU) are not seen in acute ischaemic hepatitis
D. In alcohol liver disease AST is usually two-fold higher than ALT

5. Staff protection in an acute ward treating acute liver failure includes:
A. Special whole body gown
B. Use of gloves if possibility of contact with secretions
C. Immunisation to hepatitis B
D. Immunisation to hepatitis C

6. Worse prognosis in acute liver failure (ALF) includes:
A. Age between 10 and 40 years
B. ALF caused by acetaminophen (paracetamol)
C. Long period between symptoms and encephalopathy
D. Persistent acidosis

7. Usual precipitants of acute encephalopathy is/are:
   A. Infection
   B. Hypoxaemia
   C. Beta-blockers
   D. Gastrointestinal haemorrhage

8. Management options in hepatic encephalopathy include:
   A. Abstention from all exogenous protein sources
   B. Lactulose
   C. Airway control
   D. Anaerobic coverage (antibiotics)

9. Regarding transplantation as an option in acute liver failure (ALF):
   A. The one-year survival rate is similar to patients undergoing elective liver transplantation
   B. Patients with encephalopathy and fixed dilated pupils are not considered for transplantation
   C. Transplantation is only offered to patients with a survival prognosis >30%
   D. Transplantation criteria are different in patients with paracetamol-induced ALF and other types of ALF

EDIC-style Type A

10. The classification of acute liver failure, as subacute, acute and hyperacute, depends primarily upon:
   A. The degree of encephalopathy
   B. The level of bilirubin
   C. Elapsed time between jaundice and encephalopathy
   D. Speed of rise of INR
   E. The level of organ dysfunction (SOFA score)

11. Causes of acute liver failure include all of the following except:
   A. Seronegative hepatitis
   B. Acetaminophen (paracetamol) overdose
   C. Methanol ingestion
   D. Veno-occlusive disease
   E. HELLP syndrome

12. Acute on chronic liver failure may be complicated by circulatory failure. Typical findings are the following EXCEPT:
   A. High lactate level
   B. High systemic vascular resistance (SVR)
   C. Severe metabolic acidosis
   D. Cardiac systolic or diastolic dysfunction
   E. Elevated cardiac output

13. Important diagnostic tests in acute liver failure include the following EXCEPT:
   A. Alkaline phosphatase (ALP)
   B. International normalised ratio (INR)
   C. Conjugated bilirubin
   D. Troponin-T
   E. Gamma-glutamyltransferase (GGT)

14. The Child–Pugh score is often used to assess the severity and hence prognosis in liver failure. Which is the correct answer?
   A. It is used for acute liver failure
   B. It is divided into five classes of severity
   C. INR is a part of the score
   D. The lower the score, the worse is the prognosis
   E. Assessment of metabolic acidosis is a part of the score

15. Variceal bleeding is an important complication in chronic liver disease. Of the following treatment options what is not considered standard care?
   A. Rapid intubation and control of the airway
   B. Use of terlipressin or somatostatin
   C. Endoscopy with control of the bleeding
   D. ERCP
   E. TIPS (transjugular intrahepatic portosystemic shunt)

16. The preferred vasopressor in hypotension in acute liver failure is:
   A. Adrenaline
   B. Dobutamine
   C. Dopamine
   D. Dopexamine
   E. Noradrenaline

17. The most common cause of renal problems in a patient with acute liver failure is:
   A. Toxic effect from hyperbilirubinaemia
   B. Hepato-renal syndrome
   C. Acute tubular necrosis
   D. Glomerulonephritis from underlying disease
   E. Elevated intra-abdominal pressure

18. The diagnostic criteria for hepatorenal syndrome includes the following EXCEPT:
   A. Cirrhosis without ascites
   B. Absence of shock
   C. No nephrotoxins
   D. No parenchymal kidney disease
   E. No effect of two days of treatment with diuretic withdrawal and volume expansion with albumin

Self-assessment Answers

1. TFFF
2. FTFT
3. TFFT
4. FTFT
5. FTTF
6. FFTT
7. TTFT
8. FTTF
9. FTFT
10. Correct C
11. Correct: C
12. Correct B
13. Correct D
14. Correct: C
15. Correct: D
16. Correct: E
17. Correct C
18. Correct A

PATIENT CHALLENGES

Patient 1

A 68-year-old patient was hospitalised due to diffuse abdominal pain, somnolence and acute worsening of his overall physical condition. You are requested to evaluate him in the general ward for a possible admission to the ICU.

The patient has a history of chronic alcohol abuse, and has drunk more heavily over the last three weeks. In the last five days, he has been abstinent, but with loss of appetite, jaundice and progressive sleepiness. The patient is somnolent, partially oriented and cooperative and while more awake, restless with a flapping tremor. He has no dyspnoea, but appears to hyperventilate and has moderate diffuse abdominal pain on palpation, and probably ascites.

LEARNING ISSUES

History taking in guiding diagnosis
Clinical features of acute hepatic failure
Aetiology of acute hepatic failure

Q. Which diagnoses should be considered in this patient and why?

A. Based on the history and clinical signs it is likely that the patient has decompensated acute on chronic liver disease (ACLF), as suggested by the relatively acute onset of jaundice, worsening general condition and altered neurology. Alcoholic hepatitis is possible.

Q. Is there specific therapy for alcoholic hepatitis that may be introduced from the outset?

A. Specific therapies include the use of steroids and/or pentoxifylline depending on clinical and biochemical criteria.

Q. Presuming hepatic encephalopathy and you have ruled out alternative diagnoses for altered level of consciousness, is sepsis a possible trigger?

A. Yes, sepsis is a recognised exacerbating factor and should be considered.

Q. Is there a specific source of sepsis which is peculiar to this category of patient?

A. Yes, spontaneous bacterial peritonitis may acutely worsen the condition of the patient with liver disease even if no liver failure is present.

See the PACT module on Altered consciousness.

You observe that the patient is slightly tachycardic, his blood pressure is 90/50 mmHg, and his hands and feet are cool, with poor capillary circulation and venous filling. There is no information available on his urine flow or renal function.

Q. Does this patient require urgent resuscitative and specific interventions or should he be 'allowed to sleep it off'?

A. He requires urgent acute medical care.

Q. Which urgent clinical problem have you observed? Which therapeutic/diagnostic interventions should be done immediately?

A. You have observed the classical signs of hypovolaemia; the patient needs volume resuscitation.

Q. The hyperventilation suggests the possible presence of a gas exchange disorder, metabolic acidosis, or both. Which test will best elucidate? Which other blood tests will you request?

A. An arterial blood gas. You should also take samples for liver function and coagulation tests in order to evaluate the severity of the liver damage. Renal function should also be assessed.

See the PACT module on Electrolytes and Homeostasis.

Q. Where should this patient be treated?

A. This patient requires urgent intervention and intensive monitoring. In most hospitals, such care is available only in the intensive care unit. In some institutions, high-dependency care areas (e.g. intermediate care units) may offer an alternative, providing that access to intensive care without delay can be ensured.

Q. Why the urgency?

A. Patients with acute liver failure may deteriorate rapidly, and, due to the onset of severe hepatic encephalopathy, need intubation. This patient also needs optimisation of haemodynamics and further diagnostics. Hence, intensive care is indicated.

Managing the acute situation
Indications for intensive care/transfer to specialised units in acute liver failure

You admit the patient to the intensive care unit, insert an arterial cannula, start pressure monitoring and a peripheral intravenous infusion.

Providing a safe physiological environment
Monitoring key variables and trends in organ dysfunction
Laboratory features of acute hepatic failure

Q. Which organ functions are likely to be most at risk for acute further deterioration? Outline three likely imminent organ dysfunctions.

A.
1. You have already observed clinical signs of hypovolaemia. Hence, the circulation is at risk, and consequently also the kidneys. Acute liver failure is associated with an increased risk of acute renal failure.
2. Cerebral oedema may rapidly develop, but less commonly in patients with decompensated ACLF.
3. Severe coagulation abnormalities may also develop, especially if sepsis is the cause for deterioration.

Organ system support

See the PACT modules on Oliguria and anuria (Acute Kidney Injury Part I) and Altered consciousness

The patient remains moderately hypotensive and is oliguric despite volume expansion. He has a progressive metabolic acidosis and hyperlactataemia, and his level of consciousness is deteriorating rapidly. You need to intubate the patient and start mechanical ventilation. Meanwhile, the initial laboratory diagnostics have become available, and reveal a high bilirubin, moderately elevated transaminases, markedly elevated INR and prolonged prothrombin time.

Interpretation of laboratory tests of acute hepatic failure

Due to progressive hypotension and oliguria, a pulmonary artery catheter is inserted and reveals a cardiac output of 10 l/min and normal filling pressures.

> Q. What can explain the haemodynamic situation?
>
> A. Patients with acute liver failure often have a hyperdynamic circulation due to abnormal distribution of vascular resistance. An alternative or additional explanation would be septic shock.

See the PACT modules on Haemodynamic monitoring and Sepsis and MODS.

Further volume loading using colloids fails to restore the urine output and norepinephrine is started to improve the perfusion pressure. Despite this, the patient remains oliguric. Renal replacement therapy is started using continuous haemodiafiltration. Over the next 12 hours, blood lactate levels stabilise, but the patient requires moderate doses of norepinephrine and volume boluses as the renal failure persists. The INR and prothrombin time remain pathologically elevated and the platelets are slightly reduced.

LEARNING ISSUES

Monitoring laboratory variables
Renal replacement therapy

See the PACT module on Acute renal failure (Acute Kidney Injury Part II).

> Q. Would you treat the abnormal coagulation?
>
> A. If there is no clinically evident bleeding, coagulation support is not routinely indicated. Reduced hepatic synthesis of coagulation factors rarely results in bleeding problems from catheter insertion sites, unless accompanied by low platelets or disseminated intravascular coagulation. For more invasive procedures, support with fresh frozen plasma and platelets should be considered.

LEARNING ISSUES

Coagulopathy in acute liver failure

The patient deteriorates neurologically, the liver function tests also deteriorate, and the gas exchange also progressively worsens.

> Q. How might you investigate the acute neurological deterioration?
>
> A. A CT of the head.

The CT confirms diffuse cerebral oedema and despite moderate hyperventilation and mannitol boluses, there is no improvement in neurological status due to presumed persistence of cerebral oedema and intracranial hypertension.

In consultation with the hepatology service, it is considered that due to the history of chronic alcohol abuse, the fulminant course of the acute hepatic failure, the rapidly progressive multi-organ failure, and the age of the patient, the prognosis is poor.

Severe encephalopathy
Intracranial hypertension as a complication of acute hepatic failure
Consideration of CNS/ICP monitoring
Prognosis of acute hepatic failure
Indications for liver transplantation in acute hepatic failure

After discussions with the family, intensive care intervention is withdrawn, and comfort therapy instituted. The patient dies after the norepinephrine infusion has been stopped.

Outcome of ACLF

See the PACT module on Organ donation and transplantation.

Patient 2

A 34-year-old female was found in a park in a comatose state and brought into the emergency department. Clinical examination reveals a GCS of 6 and no external signs of injury. The patient has repeated convulsions and needs emergency intubation.

The blood glucose and electrolytes are normal. Head CT scan is also considered normal. There were no signs of infection or bleeding. Different empty drug bottles are found in the patient's bag, including benzodiazepines, salicylates and acetaminophen. A toxicology screen and blood concentration measurements confirm all three, including a high acetaminophen concentration.

ABCs
Investigation of coma
Importance of measuring acetaminophen level

See the PACT module on Altered consciousness.

> **NOTE** Acute comatose state may hide multiple diagnoses, which all may need an immediate intervention. For example hypoglycaemia-induced loss of consciousness may cause a head injury, intoxication may cause multiple organ damage, the unconscious patient may have rhabdomyolysis due to pressure injury. Be alert and search systematically for alternative causes for the coma and signs of secondary injuries and organ damage.

The patient is admitted to the intensive care unit where resuscitation is continued. The patient is hypotensive but responds promptly to volume expansion. Liver function tests reveal markedly elevated INR and transaminases, and a slightly increased bilirubin.

LEARNING ISSUES

Laboratory variables of ALF

Q. What is your next therapeutic intervention and why?

A. Start *N*-acetylcysteine infusion to reduce the liver damage. There is good evidence that starting *N*-acetylcysteine as soon as possible following an acetaminophen overdose will limit hepatic toxicity and also reduce morbidity and mortality.

LEARNING ISSUES
Toxin removal or treatment
Acetaminophen-induced hepatotoxicity

Due to the positive opiates and benzodiazepines in the toxicology screen, you attempt a reversal using flumazenil and naloxone but this produces only a moderate improvement in neurologic status. No adverse effect occurs.

NOTE Flumazenil may precipitate convulsions in patients who ingest benzodiazepines chronically!

The patient is acidotic and has an elevated blood lactate. Despite the volume expansion, diuresis is moderate at 20–40 ml/hr, and the serum creatinine is slightly elevated (150 µmol/l; 1.96 mg/dl). Your institution has a wide variety of specialty services available, but no transplantation service.

Q. Is this patient a candidate for transplantation, or should you proceed with a conservative therapy?

A. Markedly elevated INR, poor neurologic status (even if the mixed intoxication is considered), renal impairment and hyperlactataemia all suggest severe liver damage. It is advisable to contact a transplantation centre at this stage, and discuss the strategy.

LEARNING ISSUES

Specialist referral – criteria
Transplant criteria for acetaminophen-induced acute liver failure
Transferring the patient

After contacting the specialist centre, you decide to observe the clinical course and the development of laboratory values over the next 12 hours. Meanwhile, you consider the requirements for possible transportation.

Q. What specific precautions would be needed for the transfer of this patient to the specialist liver transplant institution, which is about two hours away by ambulance?

A. The patient would be intubated and ventilated for transfer, if this is not already done. A doctor with appropriate experience would accompany the patient on the transfer. Care would be taken to avoid deterioration and/or complications during the transfer. In particular, the importance of maintaining normoglycaemia, preventing surges in intracranial pressure and managing cardiovascular disturbances en route would be appreciated.

LEARNING ISSUES

How to transfer

See the PACT module on Patient transportation.

However, the patient improves somewhat neurologically, the liver function tests remain elevated but the INR does not increase further. Haemodynamics remain stable and there is a slight decrease in serum creatinine and improvement of urinary output. When the GCS improved to 12–13, weaning the patient from mechanical ventilation was started. In the next 12 hours, the patient was extubated and the liver function tests had started to normalise. Following 96 hours in the ICU, the patient was discharged to the normal ward.

LEARNING ISSUES

Prognosis and outcome

On reflection, patients presenting with acute liver failure can be extremely sick and often have multiple organ involvement. The prognosis is very dependent on aetiology and subsequent appropriate management.