Introduction

Severe acute liver failure is defined as the development of overt liver failure with encephalopathy over eight weeks or less in previously healthy individuals. In hyperacute liver failure, deterioration occurs in less than 14 days. Whilst it is a relatively uncommon reason for admission to the intensive care unit (ICU), acute liver failure is important because it often occurs in previously well young adults and carries a high mortality. Management of these patients presents considerable challenges within the ICU due to the extreme nature of the associated pathophysiological processes, which affect multiple systems. Integrated management strategies have been poorly studied and treatment is often center-specific [1]. Clinical manifestations include a reduced conscious state, jaundice with abnormal liver function tests (especially elevations in amino acid transferase levels more than 25 times the upper limit of normal) and coagulopathy. Further deterioration can involve marked cerebral edema, hypoglycemia and severe shock with lactic acidosis and multiple organ failure. The use of clinical management guidelines may assist in the treatment of these patients by providing an evidence-based framework for care by staff at the bedside, which ensures that all important priorities are adequately addressed. It is possible that a coordinated combination of specific and general therapies may reduce mortality and the need for liver transplantation. Consideration for transfer to a unit with expertise in liver transplantation may be appropriate in order for this option to be available as a life-saving treatment should supportive care fail to arrest deterioration.
Etiology of Severe Acute Liver Failure

Hepatotropic viral infections, drug-induced liver injury, autoimmune processes, metabolic disorders and vascular thrombosis are responsible for most cases of acute liver failure [2] (Table 1). Causes of severe acute liver failure requiring ICU admission vary across regions, with drug-induced liver injury more common in industrialized nations and viral pathogens more common in developing countries. Up to a fifth of cases have no clear cause and may be due to as yet unrecognized viral entities, unusual presentations of autoimmune processes or unrecognized drug complications. Patients in whom critical illness develops rapidly (e.g., hyperacute liver failure from paracetamol [acetaminophen] toxicity) may recover completely without the need for liver transplantation if not overwhelmed by multiple organ failure, severe cerebral edema or complications, such as sepsis. For patients who exhibit a less fulminant course (e.g., as a result of idiosyncratic drug reactions), death is a frequent outcome unless transplantation is undertaken. Severe liver injury can sometimes also occur as a consequence of prolonged shock, where situations of advanced hemodynamic compromise result in ischemic hepatitis and considerable derangement of liver function. In this setting, ICU management is most appropriately directed to addressing the cause of the shocked state and its consequences, with specific liver failure directed therapies rarely required.

| Major causes of acute liver failure | Examples |
|-----------------------------------|----------|
| Drugs                             | Dose related: |
|                                   | – Paracetamol |
|                                   | Idiosyncratic: |
|                                   | – Isoniazid |
|                                   | – Beta-lactams |
|                                   | – NSAIDS |
|                                   | – Herbal remedies |
| Toxins                            | Amanita mushroom |
| Viral                             | HAV, HBV, HEV, HSV, CMV, EBV |
| Vascular thrombosis               | Budd-Chiari syndrome |
| Inherited metabolic disorders     | Wilson’s disease |
| Pregnancy-related                 | Acute fatty liver of pregnancy |
| Other                             | Autoimmune hepatitis |
|                                   | Reye Syndrome |

NSAID: non-steroidal anti-inflammatory drug; HAV: hepatitis A virus; HBV: hepatitis B virus; HEV: hepatitis E virus; HSV: herpes simplex virus; CMV: cytomegalovirus; EBV: Epstein-Barr virus.
Management Problems

The rapid onset, severity and complexity of organ failure in patients with severe acute liver failure necessitate urgent admission to the ICU in the majority of cases. Patients with acute liver failure exhibiting any combination of encephalopathy, acute renal failure, hypotension, lactic acidemia or hypoglycemia should be admitted to the ICU as fulminant deterioration is likely.

Cerebral Edema and Intracranial Hypertension

Cerebral edema occurs in many patients with high-grade encephalopathy. Brainstem herniation is a common cause of death in acute liver failure and occurs because of severe cerebral swelling causing refractory intracranial hypertension. The pathophysiology of acute liver failure-associated cerebral edema is complex, but the accumulation of metabolic toxins, such as ammonia [3], and the loss of cerebral autoregulation resulting in hyperemia [4] are two key drivers.

Ammonia is a waste product of nitrogen metabolism and undergoes detoxification via the urea cycle. The liver is responsible for most of this detoxification activity and hyperammonemia is a cardinal feature of severe liver failure. Ammonia readily crosses the blood brain barrier and the increasing brain tissue concentrations cause neuroexcitation, astrocyte swelling and disruption of many crucial neuronal processes. A range of crucial astrocyte signaling and intracellular functions are also impacted, causing further central nervous system (CNS) impairment. Ammonia concentrations more than 117 µmol/l are highly associated with the development of severe cerebral edema and intracranial hypertension [5]. Severe acute liver failure also results in the accumulation of false neurotransmitters, CNS depressants, and inflammatory mediators, which may reduce consciousness. Like ammonia, these neurotoxic substances are generally small and water-soluble and may, therefore, be removed by extracorporeal therapy.

Cerebral blood flow is normally tightly regulated across a wide range of systemic arterial pressures. Autoregulation is lost in patients with severe acute liver failure due to abnormal regulation of vasoactive mediators within the CNS. This leads to cerebral hyperemia and vasogenic edema in severely encephalopathic patients.

Features of severe cerebral edema with resultant intracranial hypertension are difficult to detect in critically ill patients with multiple organ failure and regular clinical evaluation is necessary.

Vasodilatory Shock

A vasodilated, hyperdynamic circulation is present in most patients with acute liver failure. Relative or absolute hypovolemia may develop due to poor fluid intake prior to presentation, abnormal external fluid losses, loss of intravascular volume into the interstitium and vasodilatation. Many patients will be shocked and require
Occasional patients may exhibit a low cardiac output state, (for example, due to pre-existing cardiac pathology), and require inotropic support. Circulatory failure results in generalized malperfusion ultimately leading to critical dysfunction in multiple organ systems.

**Sepsis**

Acute liver failure patients with multi-organ dysfunction are at high risk of infective complications [6], especially overwhelming Gram-negative and fungal sepsis. Pathogens may emerge from a patient’s own microbiological flora or may be acquired from the hospital environment. Common sites of infection include the lower respiratory tract, the urinary tract and invasive vascular access devices.

**Coagulopathy**

Coagulopathy is one of the defining features of hepatic decompensation. Hepatic synthesis of clotting factors fails and many patients also develop significant thrombocytopenia. Bleeding may complicate the insertion of invasive devices, or occur spontaneously. While spontaneous intracranial hemorrhage is very rare, the consequences can be devastating. Sometimes, despite severe derangement of measured clotting parameters, a hypercoaguable state develops [7] and may result in thrombotic complications, such as digital ischemia, portal vein thrombosis or lower limb deep venous thrombosis. A patient’s clotting profile can be a guide to the severity of their liver failure and normalization of a prolonged prothrombin time or international normalized ratio (INR) in the absence of clotting factor support suggests hepatic regeneration and recovery of synthetic function.

**Renal Failure**

Whether as a result of the primary pathology that also affects the liver (e.g., paracetamol overdose) or as a consequence of systemic inflammatory response with shock, renal failure is a common problem in patients with acute liver failure. Consequences of renal failure include electrolyte derangement and fluid balance problems, both of which contribute significantly to the complex pathophysiology of acute liver failure. Severe uremia is relatively uncommon due to disruption of the urea cycle.

**Fluid and Electrolyte Management**

Patients with acute liver failure will tend to accumulate a positive fluid balance and electrolyte abnormalities due to the administration of fluid boluses for circulatory
support, clotting factors and various other intravenous therapies, such as antimicrobials. This can have several undesirable consequences including a predisposition to cerebral edema.

**Initial Evaluation and Investigations**

Critically ill patients with acute liver failure with airway compromise or respiratory failure should be urgently intubated and appropriately ventilated. Shocked patients must be resuscitated with intravenous fluid and vasoactive infusions. Hypoglycemia should be checked for and reversed with prompt parenteral glucose administration. A careful history, clinical examination and series of investigations should follow.

**History**

It is often necessary to obtain important details from friends and relatives of critically ill patients. Important details include: Previous general health, history of chronic liver disease (to differentiate from decompensated cirrhosis), family history of liver disease, and risk factors for viral hepatitis (illicit drug use, tattoos, sexual history, travel). A comprehensive discussion of drug therapies (prescription and non-prescription pharmaceuticals, herbal remedies, illicit drugs, alcohol use) must occur and a specific history of mushroom ingestion should be sought. Female patients should be asked about the possibility of pregnancy.

**Examination**

After initial resuscitation, patients must be checked for evidence of chronic liver disease (e.g., wasting, clubbing, leukonychia, gynecomastia, spider nevi, advanced ascites, prominent abdominal wall veins). Encephalopathy can be graded according to the West Haven criteria, but critical care physicians may be more familiar with the Glasgow Coma Scale (GCS) for describing abnormal conscious states. Whichever approach is utilized, a base-line assessment will allow for subsequent repeated appraisal so that deterioration may be detected. The skin should be assessed for herpetic lesions, tattoos and needle tracks. Eye examination should include looking for Kayser-Fleischer rings. Abdominal examination should evaluate liver and spleen size as well as the presence of ascites.

**Investigations**

All acute liver failure patients should have a full blood examination (including a blood film), electrolyte profile and renal function tests. Blood levels of bilirubin, transaminases, albumin, clotting profile and glucose will help determine the extent of liver injury and function. Arterial blood gas analysis (including lactate)
is extremely useful in guiding therapy and assessing the severity of the patient’s illness. Serum lipase should be checked to detect associated pancreatitis. Blood ammonia levels may be predictive of encephalopathy and samples should be transported to the pathology laboratory in ice. All of the above investigations should be repeated regularly to guide treatment. Paracetamol levels must be checked in all patients, even in the absence of a documented overdose. Levels of other drugs may also be appropriate depending on circumstances. Viral testing for hepatitis A, B and E as well as Epstein-Barr virus (EBV), herpes simplex virus (HSV) and cytomegalovirus (CMV) should be undertaken. Copper studies, autoimmune testing and an abdominal ultrasound (including Doppler assessment of flow in the hepatic vessels) should be completed early during admission along with pregnancy testing of female patients. In shocked patients on vasoactive infusions, a bed-side hemodynamic assessment using echocardiography may guide the approach to circulatory support. If there is concern about intracranial pathology (e.g., possible head trauma), computed tomography (CT) imaging should be arranged.

Treatments for Specific Causes of Acute Liver Failure

Specific therapies directed towards the cause of acute liver failure have limited utility except in a few instances. N-acetylcysteine (NAC) should be started in all patients with known or suspected paracetamol-induced acute liver failure. Continuation of NAC by infusion is recommended until the resolution of critical illness. Nucleoside analogs are indicated for acute hepatitis B infection and acyclovir for HSV. A trial of corticosteroids may be appropriate for autoimmune hepatitis, although resolution of acute liver failure is rare in this situation. Emergency cesarean section delivery is indicated for critically ill women with acute fatty liver of pregnancy. High doses of intravenous penicillin or silibinin may be useful in amanita mushroom poisoning, although the latter may be difficult to source.

Prevention and Management of Neurological Complications in Acute Liver Failure

The risk of death from cerebral edema and associated refractory intracranial hypertension from acute liver failure is considerable. A number of treatments have been trialed and it may be that the utilization of combination therapy offers the most effective approach. The combination of mild hyperventilation, high dose hemodiafiltration, hypernatremia and mild hypothermia has been termed quadruple-H therapy [8] (Table 2) and may be readily delivered in most ICUs.
### Table 2
Summary of quadruple-H interventions and therapeutic targets for acute liver failure patients with severe encephalopathy. From [8] (with permission)

| Neuroprotective Intervention | Therapeutic Target | Method of Therapy | Mechanism |
|------------------------------|--------------------|-------------------|-----------|
| Hyperventilation             | PaCO₂ = 35 mmHg or that achieved by the patient prior to intubation (whichever is lower) | Set mechanical ventilation to achieve sufficient minute ventilation | Attenuates cerebral hyperemia Lowers ICP |
| Hemodiafiltration           | Blood ammonia < 60 µmol/l and even daily fluid balance | High volume CRRT utilizing dialysis and filtration | Reduces blood ammonia concentration Allows precise metabolic, electrolyte and fluid management Cooling effect |
| Hypernatremia                | Serum sodium 145–155 mmol/l | Continuous infusion of concentrated saline via central venous catheter | Increased serum tonicity and reduces cerebral edema |
| Hypothermia                  | Core temperature 33–35 °C | CRRT circuit and external cooling blanket | Reduces ammonia production and CNS uptake Attenuates cerebral hyperemia and reduces cerebral metabolic rate Reduces neuro-excitation Anti-inflammatory effects |

CRRT: continuous renal replacement therapy; ICP: intracranial pressure; CNS: central nervous system.

### Hyperventilation

Even when in an advanced state of coma, patients with acute liver failure tend to hyperventilate [9]. It is important when undertaking intubation and initiating mechanical ventilation that sufficient support is provided in order to target a PaCO₂ equivalent to the lower of that achieved by the patient prior to intubation, or at least a value at the low end of the normal range [1]. Hypercarbia must be assiduously avoided. Mild hyperventilation helps attenuate cerebral vasodilatation and associated hyperemia and can be safely guided by regular arterial blood gas analysis and end-tidal exhaled CO₂ (EtCO₂) monitoring. Hyperventilation to PaCO₂ values significantly lower than the normal range offer little additional benefit and tend to become ineffective over a short time with risk of rebound intracranial hypertension [10]. Aggressive hyperventilation should be reserved for use only as a rescue therapy in cases where severe intracranial hypertension is evident and rapid transplantation is planned.
**Hemodiafiltration**

All intubated patients with acute liver failure should have urgent placement of a dual lumen vascular access catheter for initiation of continuous renal replacement therapy (CRRT). Clotting factor support may be required to facilitate insertion of large venous catheters. Modalities incorporating both diffusive and convective clearance (e.g., hemodiafiltration) may be more effective than filtration alone. Lactate-free replacement fluid (i.e., bicarbonate buffered) must be used for hemofiltration to avoid contributing to elevations in blood lactate concentrations. Modern integrated CRRT machines used in the ICU have integrated heating mechanisms, which may be turned off or run at the lowest permitted temperatures as a way of lowering the patient’s core temperature. Anticoagulation is rarely required, especially if good circuit blood flows can be achieved. The use of an extracorporeal blood purification therapy, such as CRRT, can rapidly lower blood ammonia concentrations and is a key neuroprotective strategy [8]. Ammonia undergoes similar clearance to urea when CRRT is applied and treatment should be given at sufficient intensity to lower levels to near the normal range. Treatment should not be delayed until overt renal failure or uremia is evident. Additional benefits of CRRT include achievement of an even fluid balance, correction of electrolyte disturbances, improvement of acid-base abnormalities and prevention of fever. High dose CRRT may result in hypophosphatemia and measurements should be undertaken at least daily with low serum levels being treated as required. Intermittent dialysis is less preferred in acute liver failure [11] because of the undesirable impact on already compromised hemodynamics and problems associated with discontinuous therapies, such as rebound hyperammonemia.

**Hypernatremia**

Osmotherapies have a long established role in the management of cerebral edema. The continuous administration of hypertonic saline (e.g., 20% sodium chloride at 5–10 ml/hour) via a central line is an effective and straightforward approach to increasing serum tonicity and inducing dehydration of brain parenchyma [8]. Serum sodium concentrations of 145–155 mmol/l should be targeted and can be readily checked using point-of-care blood gas analysis within the ICU. Additional potential benefits include anti-inflammatory effects, reduced cerebral hyperemia [12] and maintenance of the systemic circulatory volume [13]. Hypertonic saline may be preferred to other osmotherapies, such as mannitol. Mannitol has also been used in acute liver failure-associated intracranial hypertension, but repeat dosing might result in delayed worsening of cerebral edema as it enters into brain tissue through a damaged blood-brain-barrier, inducing a ‘reverse’ osmotic gradient.
Hypothermia

The therapeutic lowering of core body temperature reduces both ammonia production and its entry into the CNS [14]. CNS inflammation and toxic injury to astrocytes are also attenuated at sub-normal body temperatures. Therapeutic hypothermia is safe to apply in the ICU and most studies have aimed for a core temperature range of 32 to 33 °C, but higher targets of up to 35 °C are also effective [15] and may be safer. Lower temperatures may provide further cerebral protection, but with an increased theoretical risk of complications, such as bleeding, immunosuppression and sepsis. More extreme hypothermia should be relegated to use as a rescue therapy when severe cerebral edema is present and urgent liver transplantation is available. External cooling is usually effective, and servo-controlled cooling blankets using continuous core temperature monitoring are recommended in order to achieve effective temperature regulation.

Other Therapies for Severe Cerebral Edema in Acute Liver Failure

A range of treatments have been proposed for refractory cerebral edema and may be trialed as rescue therapies. In addition to more aggressive application of the quadruple-H measures outlined above, deep sedation (e.g., with propofol) and muscle relaxants may acutely lower intracranial pressure (ICP) [16]. Other options include the administration of indomethacin, which has been shown to transiently reduce cerebral hyperemia and lower ICP [17]. Unless life-saving liver transplantation can be urgently arranged, however, these strategies are unlikely to impact on outcomes.

Quadruple-H neuroprotective therapy should continue for the period of most severe encephalopathy, which generally lasts 4 to 7 days for paracetamol related-acute liver failure, but may persist for significantly longer when the hepatic injury results from other causes. The role of invasive ICP monitoring has been increasingly questioned given a lack of evidence for benefit [18, 19]. The routine application of neuroprotective measures for acute liver failure patients in ICU may render the insertion of ICP monitors unnecessary.

Other Neurological Care

A range of additional ammonia lowering therapies may be considered, but limited evidence of benefit and lack of availability may deter their use. Enteral administration of lactulose can be tried, but may produce significant abdominal distension without substantial benefit in acute liver failure. L-ornithine-L-aspartate [20] and L-ornithine-phenylacetate [21] accelerate ammonia metabolism and have shown promise in limited animal and clinical studies. Complex blood purification technologies such as Coupled Plasma Filtration Adsorption (CPFA) [22], Molecular Adsorbent Recirculation System (MARS) [23], the bio-artificial Extracorporeal Liver
Assist Device (ELAD) and Normothermic Extracorporeal Liver Perfusion (NELP) [24] may have a place, but have yet to be demonstrably beneficial as routine care in the setting of acute liver failure and their use should be confined to clinical trials.

Seizures may occur in the setting of severe acute liver failure-associated cerebral edema and may be difficult to detect clinically [25]. Electroencephalography (EEG) assessment is necessary to establish the diagnosis definitively and guide treatment with anticonvulsants, such as propofol, benzodiazepines or levetiracetam.

Supporting the Circulation in Acute Liver Failure

Patients with severe acute liver failure usually have a vasodilated, hypotensive and hyperdynamic circulation with preservation of cardiac output. Loss of vascular tone results in failure to maintain adequate end-organ perfusion pressure in a manner very similar to advanced states of septic shock. In addition to vasodilatory shock, microvascular dysfunction causes the loss of fluid into the interstitium, intravascular thrombosis and abnormalities of blood flow within capillary beds. While the exact mechanisms underlying the loss of normal hemodynamic homeostasis are incompletely understood, severe inflammation, abnormal neurohormonal control and endothelial injury are all likely to contribute to the evolution of severe shock. Coupled with mitochondrial dysfunction and generalized inflammation, lactic acid levels rise as production increases and clearance (mainly hepatic) decreases [26].

Intra-arterial catheters are required for adequate monitoring in critically ill acute liver failure patients. Central venous access allows assessment of the central venous pressure (CVP) in response to fluid challenges and the safe administration of vasoactive infusions. Given the number of infusions required by critically ill acute liver failure patients, several multi-lumen central venous catheters may be necessary. Continuous or intermittent measurement of cardiac output (e.g., intra-arterial pulse contour measuring technologies) may be useful to guide treatment of severely shocked acute liver failure patients. The insertion of vascular catheters may necessitate the administration of clotting factors to prevent major bleeding related to the procedure. If such administration is provided, the additional volume should be removed by CRRT in order to avoid fluid overload and more cerebral edema and/or acute respiratory distress syndrome (ARDS). Focused bedside hemodynamic assessment using echocardiography is an increasingly available technology, but requires skill and experience to perform reliably.

After adequate fluid resuscitation has been administered, the majority of patients will remain hypotensive and shocked such that vasopressor therapy is indicated. Norepinephrine by continuous infusion through a central venous catheter and titrated to effect is a common approach to supporting the systemic arterial pressure. In situations where large doses of intravenous catecholamine infusions are required (e.g., norepinephrine > 0.5 µg/kg/min), it may be reasonable to commence vasopressin by infusion as a means of improving vascular tone. Concerns that similar drugs can worsen cerebral edema [27] need to be considered against the need to respond to a severely compromised circulation. Moreover, many of these patients
are young and a mean arterial pressure (MAP) of 60 mmHg may be acceptable. Of interest, although never formally studied, the hyperemic cerebral edema of acute liver failure may be increased when higher MAP values are targeted.

The administration of large volumes of fluid to critically ill patients is routine during the resuscitation phase of ICU management. Ongoing accumulation of fluid after this period is also common, especially in the setting of multiple drug infusions, clotting factor support and artificial nutrition. Coupled with reduced plasma protein levels, this may lead to severe generalized interstitial fluid overload resulting in a propensity for edema in vulnerable organs such as the lungs and brain. Efforts to carefully manage fluid therapy in order to avoid an escalating positive fluid balance might be beneficial, as may be the utilization of concentrated albumin (e.g., 20% human albumin solution) to maintain intravascular volume without associated fluid overload. Hypotonic solutions (e.g., 5% dextrose) must be carefully avoided in acute liver failure patients in order to minimize the risk of exacerbating cerebral edema.

The exact role of corticosteroid therapy for circulatory support in critical illness currently remains somewhat unresolved. While the use of low dose corticosteroids in septic shock may not impact on patient-centered outcomes, such as mortality, few adverse events have been associated with the administration of relatively low doses in this context. It may be that absolute or relative adrenal insufficiency with potential end-organ cortisol resistance does occur in severe acute liver failure [28], such that corticosteroid administration does have a specific role in this context.

Prolonged infusion of NAC is absolutely indicated in patients with paracetamol-induced acute liver failure, and there could be a role in patients with severe acute liver failure from other causes also. Continuous infusion of NAC may improve hemodynamic parameters and provide other benefits in shocked acute liver failure patients [29] and has few associated risks with extended use.

**General Supportive Care in Acute Liver Failure**

Critically ill patients with multiple organ failure require carefully coordinated care by all members of the ICU multidisciplinary team. In addition to acute liver failure-specific neurological care and circulatory support, other aspects of management may be influenced by the presence of hepatic dysfunction.

**Sepsis**

Serious infection is a major cause of death in patients admitted to the ICU with acute liver failure. Nosocomial pneumonia, catheter-related blood stream infections, intra-abdominal sepsis and urinary tract infection commonly develop in the context of acute liver failure-associated multiple organ failure with shock. Gram-negative and fungal pathogens are major culprit organisms and may be acquired from the hospital environment or arise from the patient’s own flora. The role of
early empiric antimicrobial therapy is not fully established; however, given the high risks of overwhelming sepsis contributing to cerebral edema and circulatory failure, the routine use of early broad spectrum antibiotics and antifungal therapies has been suggested [2]. Stringent surveillance for possible infection should always be undertaken, including chest X-rays and regular cultures of blood, urine and sputum.

**Respiratory Support**

Patients with advanced encephalopathy (e.g., West Haven grade III or IV or a GCS of < 8) should be intubated to minimize the risk of airway obstruction or aspiration. The need for sufficient minute ventilation required to optimize PaCO₂ is an important component of neuroprotective care and hypoventilation must be carefully avoided. Periods of risk include during intubation, the initiation of mechanical ventilation and patient transport (e.g., between hospitals or to the radiology department). Regular arterial blood gas testing and measurement of exhaled EtCO₂ is mandatory to guide ventilatory support.

**Renal Support**

The early initiation of CRRT may more correctly be considered as part of a CNS protective strategy and control of ammonia levels, rather than renal replacement therapy and as such, treatment should not be delayed until problems associated with overt renal dysfunction are evident. The maintenance of high blood flow (e.g., > 250 ml/min), the use of pre-dilution hemofiltration replacement fluid and optimal vascular access are important factors in ensuring adequate circuit life. Anticoagulation treatment may not significantly improve filter life [30] and is best avoided in patients with severe coagulopathy. Hemofiltration fluid exchange rates of 40 to 50 ml/kg/hour may be necessary to achieve adequate ammonia clearance. With high intensity CRRT, close monitoring and replacement of electrolytes (e.g., potassium, phosphate, magnesium) and supplementation of water-soluble vitamins is advisable. Frequent interruptions to CRRT are undesirable and should prompt a careful evaluation for preventable causes. Phosphate supplementation in particular should be started early (within 24 hours of initiation of CRRT) because high volume therapy will remove approximately 1 mmol/l and liver regeneration will also consume significant amounts of phosphate.

**Hematological Support**

Marked abnormalities in laboratory-based measurements of clotting are a hallmark of severe acute liver failure. Despite sometimes gross prolongation of the prothrombin time, significant hypofibrinogenemia and severe thrombocytopenia, spontaneous major hemorrhage is uncommon. Parenteral vitamin K should be adminis-
tered to all patients with acute liver failure-associated coagulopathy. Many patients may actually manifest a strong tendency to pro-thrombotic complications and caution is, therefore, warranted regarding the administration of clotting factors except where invasive procedures are necessary or actual bleeding occurs. In the absence of major bleeding events, reasonable targets include an INR of < 6, platelet count of > 20/mm³, and a fibrinogen concentration of more than 1.0 g/l. Clotting factor support may include fresh-frozen plasma (FFP), prothrombin concentrate, pooled platelets and cryoprecipitate.

**Metabolic, Gastrointestinal Care and Nutritional Support**

Hypoglycemia is common in severe acute liver failure and should be immediately corrected as part of initial management. Patients with persisting low blood glucose levels will require the continuous infusion of concentrated glucose (e.g., 25% dextrose solution) via a central venous catheter, aiming for a blood glucose concentration of between 6 and 10 mmol/l. Once hepatic recovery is established, many patients will exhibit a tendency to hyperglycemia and require continuous infusion of short acting insulin to avoid excessive elevations in blood glucose concentrations.

Patients with acute liver failure are at high risk of gastrointestinal hemorrhage. The routine use of H₂-blockers (e.g., ranitidine) or proton-pump-inhibitors (e.g., pantoprazole) is appropriate.

Enteral tube feeding is recommended for patients with acute liver failure and is achievable in most situations. Evidence supporting specific recommendations for the content of enteral feeds in acute liver failure patients is poor. Branch-chain amino acid-enriched formulations are significantly more expensive and may confer little benefit beyond standard formulations used within the ICU.

**The Role of Liver Transplantation in Acute Liver Failure**

Orthotopic liver transplantation has been shown to be life-saving in some circumstances [31]. For patients with severe acute liver failure from Wilson’s disease, autoimmune hepatitis or idiosyncratic drug reactions, survival in the absence of transplantation is rare. Optimal treatment may, however, offer an extension on the period of time available to source a suitable organ for transplantation and maintain patients in a state suitable to undergo the rigors of major surgery. The decision to transplant a patient with acute liver failure is extremely challenging and must involve extensive evaluation by experienced hepatologists, transplant surgeons and intensivists. The development of better prognostic scoring systems is needed [2]. For other causes of severe acute liver failure, such as paracetamol toxicity or viral hepatitis, effective supportive care will ideally result in a live patient discharged from hospital with their own liver fully recovered.
### Table 3  General management of patients with severe acute liver failure in the ICU

| Intervention                                      | Goals/Approach                          | Method/Examples                                                                 |
|--------------------------------------------------|----------------------------------------|---------------------------------------------------------------------------------|
| Treatment for specific causes of acute liver failure | Reversal of/prevention of further hepatic injury | NAC infusion for paracetamol overdose  
Nucleoside analogues for acute HBV  
Penicillin or silibinin for amanita mushroom poisoning  
Emergent delivery for AFLP |
| Circulatory support                               | Hemodynamic parameters according to patient’s clinical progress:  
CVP 6–10 mmHg  
MAP 65–70 mmHg  
Even daily fluid balance | Fluid administration  
Vasoactive infusions e.g. norepinephrine  
Low dose corticosteroid administration |
| Sepsis care                                       | Empiric broad spectrum antibiotics and antifungal therapy  
Regular culture of blood, urine and sputum  
Daily CXR | Extended spectrum beta-lactams  
Liposomal amphotericin |
| Ventilatory support                              | See hyperventilation section of Table 2 | Intubate patients with advanced encephalopathy  
Provide adequate ventilation to achieve neuroprotective PaCO₂ |
| Renal support                                    | See hemodiafiltration section of Table 2 | Run blood flow > 200 ml/min  
Use pre-dilution to minimize filter clotting  
Use high exchange rates of lactate free replacement fluid (40–50 ml/kg/h)  
Turn off heater  
Monitor electrolytes (especially phosphate, potassium, magnesium) |
| Hematological support                            | Hb > 7.0 g/dl  
INR < 6  
Platelet count > 20/mm³  
Fibrinogen > 1.0 g/l | Do not attempt to normalize abnormal clotting values unless extreme derangement, active bleeding or need for invasive procedures  
Administer Vitamin K 10 mg i.v. daily  
Use FFP, platelets and cryoprecipitate if factor support is required |
| Metabolic/gastrointestinal/nutritional support   | Blood glucose 6–10 mmol/l  
Stress ulcer prophylaxis  
Enteral feeding | Concentrated dextrose infusion via central line  
H₂-blocker or PPI therapy  
Enteral feeding via nasogastric tube |

CVP: central venous pressure; MAP: mean arterial pressure; CXR: chest X-ray; Hb: hemoglobin; NAC: N-acetylcysteine; HBV: hepatitis B virus; AFLP: acute fatty liver of pregnancy; FFP: fresh frozen plasma; PPI: proton pump inhibitor.
Conclusion

Despite the severe and complex nature of critical illness resulting from acute liver failure, good patient outcomes may be achieved through the use of an integrated management plan (Table 3) that targets specific pathophysiological processes. The combination of quadruple-H therapy and comprehensive general intensive care support can be provided in most critical care settings and may reduce mortality and the need for liver transplantation. In extremely unwell patients, transfer to a major transplant center may be appropriate in order to optimize care, even if need for transplantation is not considered a likely ultimate outcome.

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