Critical Care Management of Acute Liver Failure

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30.1 Introduction

Acute liver failure (ALF) is a severe and complex condition that results from acute and massive hepatocellular destruction with very poor prognosis, with an approximately 80% mortality rate in historical series. ALF is an infrequent condition, with an incidence of 1–8 cases per million inhabitants, and it is responsible for 6% of deaths due to liver disease and up to 7–8% of liver transplants [1]. ALF mainly affects young adults, with a peak age between 35 and 45 years. Women account for approximately 60% of cases [2]. The development of cerebral oedema, sepsis and multiple organ failure are the main causes of mortality [3].

30.1.1 Definition and Classification

Acute liver failure was first described by Trey C and Davidson [4] as "hepatocellular dysfunction of such severity that encephalopathy occurs within eight weeks of appearance of first symptoms in the absence of pre-existing liver disease." In 1993, O'Grady et al. [5] based on data from King's College subdivided ALF into hyperacute, acute, and sub-acute presentation depending on the interval from onset of disease to onset of encephalopathy. The most widely accepted definition is by American association of study of liver disease [6] who in 2005 defined ALF as a clinical syndrome characterized by evidence of coagulopathy (international normalized ratio [INR] >5) and any degree of altered mental status in a patient without pre-existing liver disease and duration of illness <26 weeks. Hepatic encephalopathy (HE) is usually considered the hallmark of Hyderabad, Telangana, India this disease and differentiates ALF patients from those with acute liver injury [7] (Fig. 30.1).

O'Grady's classification possesses the advantage of having prognostic value [5] (Fig. 30.2). Thus, the time between the presentation of jaundice and the onset of HE subdivides patients into three categories (hyperacute, acute, and sub-acute), which are useful to define the prognosis. The hyperacute form has a better prognosis but a higher incidence of cerebral oedema. On the other hand, acute and sub-acute presentations have a worse prognosis, but a lower incidence of cerebral oedema [8].

Critical care management of acute liver failure can be sub-divided into etiological and organ specific management (Table 30.1).

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V. Vohra et al. (eds.), *Peri-operative Anesthetic Management in Liver Transplantation*,
https://doi.org/10.1007/978-981-19-6045-1_30

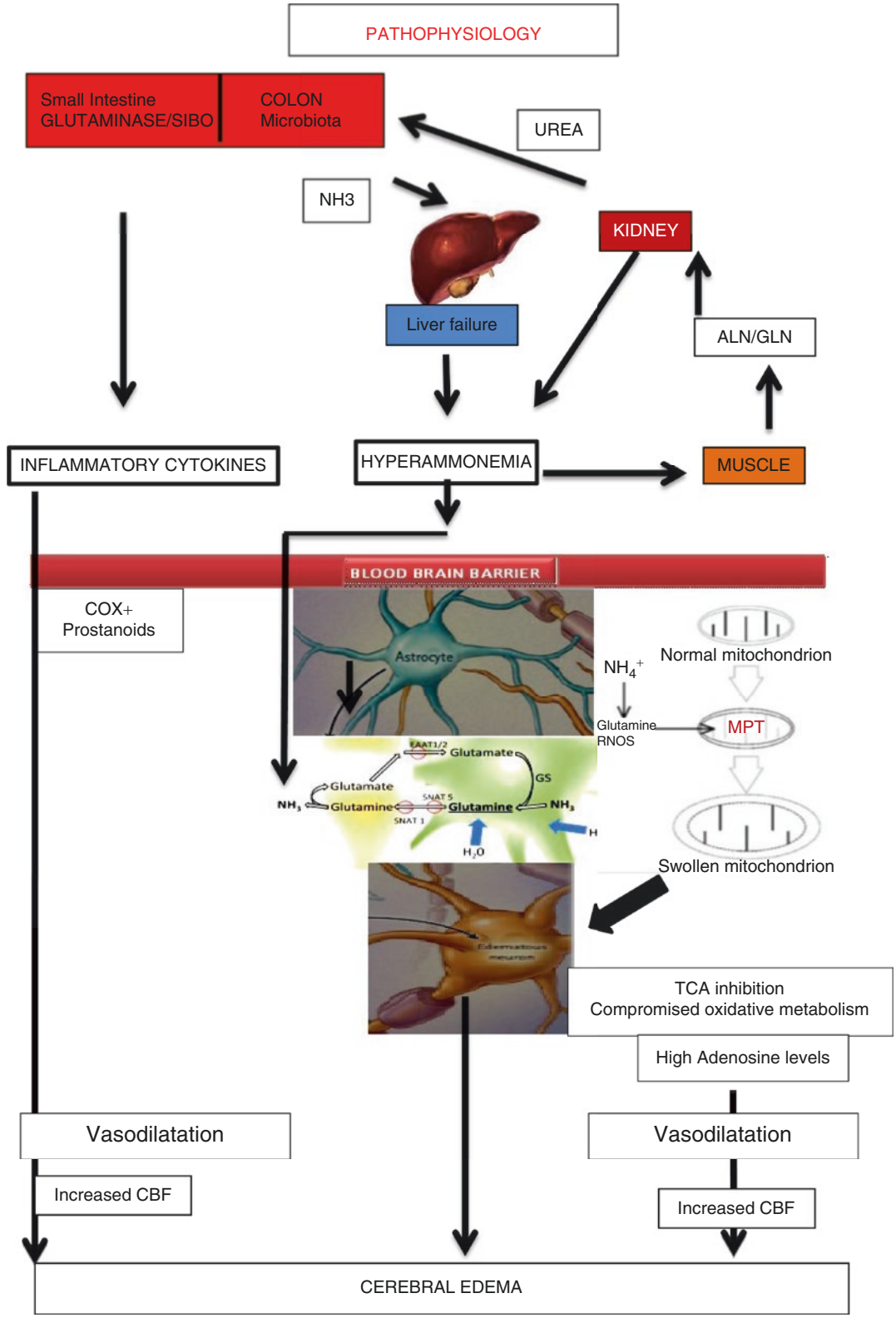

Fig. 30.1 Pathophysiology of acute liver disease

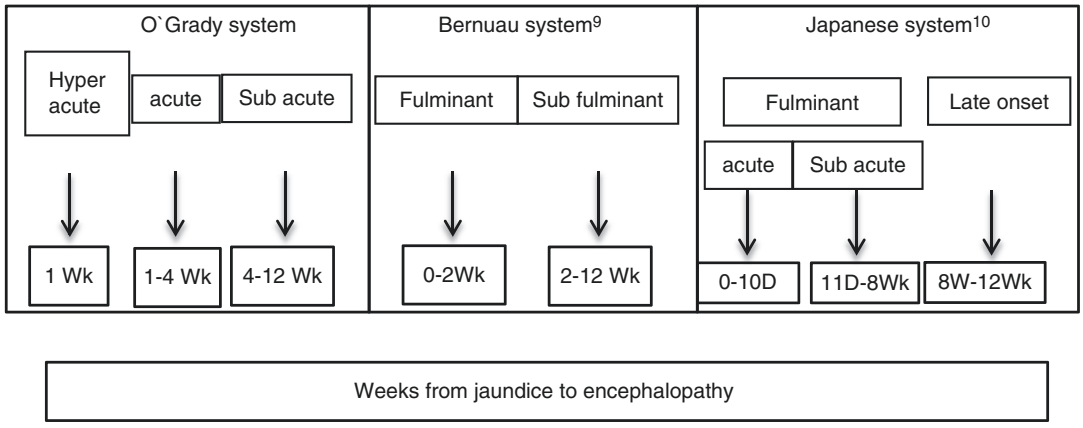

Fig. 30.2 Classification systems of acute liver failure

Table 30.1 Etiological management of acute liver failure

Category	Etiology	Common c/f	Treatment
Viral hepatitis	Hepatitis A virus	Hyperacute presentation; ALF is more common in older patients or those with underlying liver disease	Supportive
	Hepatitis B virus ± delta virus		Entecavir (taken on an empty stomach) or tenofovir at standard renal adjusted Doses
	Hepatitis E virus	History of travel to endemic areas or those with exposure to porcine farm animals; has a higher risk during pregnancy, especially in the third trimester	
	Herpes simplex virus	Immuno compromised patient	Acyclovir: 10 mg/kg IV every 8 hours (using IBW) adjusted for kidney Function
	Varicella zoster virus	Manifested by a vesicular rash	
	Cytomegalovirus	Rare and controversial as to the potential for causing ALF	Ganciclovir: 5 mg/kg IV every 12 h (using IBW) adjusted for kidney function
	Epstein–Barr virus		
	Human herpesvirus-6		
	Adenovirus, coxsackie B virus, hemorrhagic fever virus	Rare causes of ALF	

Table 30.1 (continued)

Category	Etiology	Common c/f	Treatment
Drugs	Idiosyncratic reactions	Isoniazid, nonsteroidal anti-inflammatory drugs, carbamazepine	
	Dose-dependent hepatotoxicity	Acetaminophen, sulfonamides, tetracycline	Oral NAC: 140 mg/kg loading dose, then 70 mg/kg every 4 h
			IV NAC: 150 mg/kg loading dose, then 50 mg/kg IV over 4 h, then 100 mg/kg IV over 16 h as a continuous infusion
	Herbal supplements	Patients' families must be asked about treatment history	
Vascular diseases	Right heart failure		
	Sinusoidal obstruction syndrome	Most common following systemic chemotherapy in preparation for bone marrow transplantation	
	Budd-Chiari syndrome		TIPS/anticoagulation/liver transplantation
	Ischemic hepatitis (shock liver)		
Toxins	Amanita phalloides toxin	Acute gastroenteritis; renal failure and pancreatitis	Charcoal: via NGT every 4 h alternating with silymarin Penicillin G: 1 g/kg/day IV and NAC (Dosing as for acetaminophen overdose) Silymarin: 300 mg PO/NGT every 12 h Legalon-SIL: 5 mg/kg/day IV (given in 4 divided doses) or 5 mg/kg IV Loading dose followed by 20 mg/kg/day via continuous infusion
	Bacillus cereus toxin	Fried rice syndrome	
	Carbon tetrachloride		
	Yellow phosphorus		
Metabolic diseases	Wilson disease	Younger patients; Coombs negative hemolytic anemia, hypouricemia, and a low alkaline phosphatase level with a high bilirubin level	
	Reye syndrome	Occurs in young children with viral syndrome and salicylate ingestion	
	Acute fatty liver of pregnancy	Associated with defects in fetal and maternal mitochondrial long-chain 3-hydroxyacyl coenzyme A dehydrogenase	Delivery of fetus
Malignant infiltration	Metastatic breast cancer	The most common solid organ metastasis to cause liver failure	
	Lymphoma		
Autoimmune diseases	Autoimmune hepatitis		Methylprednisolone: 60 mg/day IV

30.2 Intracranial Hypertension (ICH), Hepatic Encephalopathy in ALF and Management

The most lethal complication associated with ALF is the *development of Hepatic encephalopathy (HE) and cerebral edema*. (CE) As a consequence of cerebral edema and increased intracranial pressure (ICP), CNS complications may range from ischemic and hypoxic injury to uncal herniation and death. ICH accounts for 20–35% of the mortality in ALF [9]. The presence of severe HE is associated with a high frequency of ICH (25–35% in grade III and up to 75% in grade IV) [8]. ICH (defined as an ICP above 20–25 mmHg for >15 min) is one of the most severe complications of ALF and is associated with a poor prognosis [10]. Additional factors that may worsen the neurological outcome are the coexistence of infection or presence of inflammation without sepsis alongside the presence of other organ failure [10–12].The risk of developing intracranial hypertension (ICH) is higher in female and younger patients with severe liver failure (MELD >32), presenting in acute or hyperacute state [5] with renal failure, ionotropic therapy, and ammonium concentrations above 200 mmol/L [11, 13, 14].

30.2.1 ICP Monitoring

The rationale for ICP measurement is based on retrospective trials that showed a prevalence of over 50% of ICH in ALF patients and an association with elevated mortality risk [15]. Nonetheless, there is no randomized data available to evaluate the benefit of ICP monitoring [15–17].

30.2.2 Methods of ICP Monitoring

Direct and Invasive:-Invasive ICP monitoring can be obtained through two different approaches: intraparenchymal microtransducers and direct catheters (intraventricular, subdural or epidural). Epidural transducers are a relatively safe method [17]. However, it has a less-than-optimal degree of precision compared with other methods due to the damping effect of the surrounding dura mater. ICP evaluated by an intraparenchymal catheter has a good correlation with values obtained with intraventricular catheters [18]. The rates of infection from intraparenchymal catheters are minimal but are associated with a bleeding rate of 7% and bleeding-related deaths of approximately 3% [15], but there was no 21-day mortality benefit in acetaminophen-related ALF and a worse prognosis in the non-acetaminophen group [15]. Therefore, placement of ICP devices remains a matter of intense debate, with their use reserved for patients at high risk of ICH, and in centers with large neurosurgical experience in ALF management [19–21].

All Indirect and Non-invasive techniques are complex and demonstrate considerable *"inter and intra-assay" variability*. Changes in CBF reflecting ischemia and vasodilation of the cerebral circulation and resistance to flow, with increased ICP, can be assessed using MCA Doppler [22]. An increase in CBF usually precedes the rise of ICP. Indirect data can be obtained by monitoring reverse jugular vein oxygen saturation; values over 80% usually indicate hyperemia and under 55% relative ischemia. The latter suggests a scenario where cerebral oxygen consumption is in excess of supply due to epileptiform activity (increased demand) or inadequate supply (hyperventilation and hypocapnia, inadequate blood pressure or cardiac index). The measurement of optic nerve sheath diameter is also representative of ICP, according to a recent assessment [23].The optic nerve sheath is anatomic continuity to meninges, is distensible and the ICP influences its diameter [24]. Thus, literature suggests the utility of ONSD measurement as screening method to ICH diagnosis, with a cut-off of 5.7 mm measured 3 mm behind the globe. CT and MRI may show radiological signs of brain oedema. However, the absence of these signs does not rule out ICH [25].

30.2.3 Therapeutic Interventions

30.2.3.1 General Supportive Strategies

- Head end elevation to 30 degree with neck in neutral position.
- Intubation and mechanical ventilation in grade III and IV HE.
- Use propofol and low-dose fentanyl, and if needed cisatracurium once intubated [26]. Intermediate or long acting benzodiazepines should be avoided [27].
- Deploy low-tidal volume lung protective strategy to prevent ARDS. High-intrathoracic pressures result in cerebral venous outflow obstruction [28].
- For non-invasive approach for BP monitoring in suspected ICH - target a higher mean arterial pressure goal (>80 mmHg).
- In case of concern of seizure activity, EEG monitoring should be undertaken and antiepileptic drugs administered;
  - Phenytoin has traditionally been the medication of choice; however, agents without risk of hepatotoxicity and more easily achieved therapeutic levels such as levetiracetam or lacosamide are now more frequently utilized.
- Avoid acid-base and electrolyte disturbances.
  - Hypokalemia, and metabolic acidosis which increases renal proximal tubule ammoniagenesis [29].
  - Metabolic alkalosis promotes formation of NH3+ from (NH4+) augmenting its passage across the blood–brain barrier [30].
  - Hyponatremia, which is a risk factor for cerebral edema via reduced extracellular osmolarity [31],
- Prevent hypoglycemia by initiating 10% or 20% dextrose infusion in central line.

30.2.4 Specific Strategies

30.2.4.1 Strategies to Reduce Hyperammonemia

Lactulose: It is a nonabsorbable disaccharide. It is metabolized in caecum by enteric bacteria to lactate and acetate. This in turn lowers the cecal pH leading to increased fecal nitrogen excretion and decrease in serum ammonia levels [32, 33]. However, there have been no studies showing mortality benefit in ALF [34]; avoid lactulose via oral or NG route in ALF as it may cause bowel distention, worsening ileus, and complicating transplant surgery. If used, it is safer to be given rectally.

Rifaximin: It is an oral antibiotic with a broad spectrum activity against enteric bacteria. Its possible benefit in lowering ammonia in patients with ALF has not yet been explored [34].

LOLA & LOPA: LOLA (L ornithine L aspartate) is a stable salt of the amino acids ornithine and aspartic acid. These two amino acids get converted to glutamate in the muscles and hepatocytes. Glutamate is the substrate on which the enzyme glutamine synthase (present in the muscle as well as liver), acts and combines it with ammonia to make glutamine and thereby reduces blood ammonia levels [35]. A recent placebo controlled double blind RCT [36] in ALF showed that LOLA did not decrease ammonia levels, and improved neither encephalopathy nor survival. In the above mentioned study ammonia levels were measured for 6 days among patients receiving LOLA as well as placebo, however, the rate of decline of ammonia was also similar between the two arms. Peculiarly, patients receiving LOLA had more frequent seizures. Very high glutamine levels in the systemic circulation are found in ALF [37, 38]. LOLA could theoretically further increase ammonia detoxification by the skeletal muscle by increased glutamine synthesis. This glutamine is recirculated back to the intestine and kidney where it is broken down to ammonia and glutamate by glutaminase, thus LOLA is ineffective in reducing the ammonia levels.

LOPA (L ornithine phenyl acetate):- Phenyl acetate combines with glutamine to form phenylacetyl glutamine which is water soluble and is excreted in urine, but human studies are yet to find a beneficial effect and is contraindicated in renal failure.

Renal replacement therapy: Continuous renal replacement therapy (CRRT) is recommended over intermittent hemodialysis [39] because of

lower fluctuations in ICP and improved hemodynamic stability in the setting of AKI and other conventional indication for dialysis therapy (e.g., metabolic acidosis and hyperkalemia) [40, 41]. CRRT using continuous veno venous hemofiltration with high-filtration volume (90 ml/kg/h) has been shown to be an effective method of rapidly lowering serum plasma ammonia levels [42, 43]. Early CRRT helps to maintain euvolemia, augment ammonia clearance [42, 43], correction of electrolyte and in acidosis correction. Initiating CRRT with isotonic dialysate in patient with intracranial hypertension and induced hypernatremia can cause rebound edema from dialysis disequilibrium syndrome and precipitate brain herniation, so use hypertonic dialysate or hypertonic saline infusion in post filter return arm of CRRT.

30.2.5 Prophylactic Strategies

- Hypertonic saline used to prophylactically elevate serum sodium level between 145 and 155 meq/l has been demonstrated to reduce the incidence and severity of intracranial hypertension in grade 3 and 4 hepatic encephalopathy patients is a single center study [44]. Prophylactic hyperventilation does not provide a benefit in terms of reducing the incidence of cerebral oedema [45].
- The prophylactic use of antiepileptic drugs is not warranted [46].
- Prophylactic antibiotics have been shown to reduce the risk of infection that later stages of encephalopathy are associated with increased incidence of cerebral edema, and that fever may worsen intracranial hypertension [47].
- Recently, the role of prophylactic hypothermia was evaluated in a randomized trial. This study [48] included 46 patients with intracranial pressure monitoring that were randomized to hypothermia (targeted temperature of 33–34 °C) or normothermia (36 °C) treatments. Interestingly, although the target temperature was consistently achieved in both groups, there was no difference in the incidence of sustained elevation of ICP (35% vs. 27% in intervention and control group, respectively) or in overall survival.

30.3 Specific Strategies to Reduce Cerebral Edema and ICH

ICP should be maintained below 20–25 mmHg and the difference between MAP and ICP (cerebral perfusion pressure, CPP) should remain above 50 mmHg [49]. Sustained surges in ICP (>25 mmHg) or development of clinical signs should be treated immediately, with Osmotherapy.

Hypertonic saline with sodium goal of 145–150 meq/l can be used either as:

1. Continuous infusion: 3% NaCl titrated between 30 and 100 ml/h or.
2. Intermittent bolus dosing: 200 ml of 3% sodium chloride.

Mannitol reduces brain water through its osmotic effect and improves cerebral perfusion through RBC rheological effect, in a dose of 0.5–1 g/kg bodyweight bolus. It should be avoided if plasma osmolarity >320 mOsm/l or osmolar gap >20 mOsm/l. High doses can result in acute renal failure and damage to the BBB. Mannitol [50] works best in mild to moderate intracranial hypertension and is less effective when the ICP is greater than 60 mmHg.

Hyperventilation [51] produces cerebral vasoconstriction secondary to CSF alkalosis, reduces vascular inflow, and eventually decreases ICP although its effect is short-lived and cerebral vasoconstriction can generate areas of cerebral ischemia, which can potentially worsen cerebral edema by causing cerebral hypoxia [52]. Based on available evidence, there is no role for prophylactic hyperventilation in patients with ALF. If life-threatening ICH is not controlled with osmotherapy and other general management, hyperventilation may be instituted acutely to delay impending herniation; beyond this acute situation, forced hyperventilation cannot be recommended as routine management.

Hypothermia reduces CBF and the entry of ammonia into the brain, decreases the availability

of glutamate in the cerebral extracellular space, and diminishes anaerobic glycolysis [53]. In 1999, Jalan et al. [54] showed that a temperature reduction to 32–33 °C was associated with a significant decrease in ICP. A recent retrospective study [55] showed that therapeutic hypothermia had no impact on overall or transplant-free survival. However, this warrants an RCT to evaluate the role of hypothermia on overall survival. Also, hypothermia has not been compared to normothermia in a controlled trial, and has not been shown to improve transplant-free survival. Potential deleterious effects of hypothermia [56] include increased risk of infection, coagulation disturbance, and cardiac arrhythmias; while concern about the effect of hypothermia on hepatic regeneration [57] has also been raised. Its utility in controlling ICP remains an attractive and useful intervention in the ICU, and perhaps should be reserved for refractory intracranial hypertension or refractory hyperammonemia. Considering the risk and benefits, a reasonable approach [58] would be to use a milder goal for hypothermia starting at 35 °C. Though literature reports that hypothermia decreases ICP there is no beneficial effect on mortality.

Indomethacin inhibits endothelial cyclooxygenase, produces cerebral vasoconstriction, and decreases CBF. Toefteng et al. [59] evaluated the effect of indomethacin ICP in 12 ALF patients and reported significant reduction in ICP and an improvement in CPP. While further studies are awaited its use may be considered in refractory cases. A Randomized Control Trial [60] ALF patients corticosteroids failed to improve cerebral edema or survival, and is not advocated. Based on head injury data, IV thiopental [61] was assessed in 13 patients with Fulminant Hepatic Failure complicated by unresponsive intracranial hypertension. The ICP was reduced in all cases, and in eight cases thiopentone infusion achieved stable normal intracranial and cerebral perfusion pressure. Five patients made a complete recovery. The recommended dose of pentobarbital is a loading dose of 3–5 mg/kg (maximum 500 mg) over 15 min, followed by a continuous infusion of 0.5–2.0 mg/h. Barbiturate therapy must be used with simultaneous continuous ICP and arterial blood pressure monitoring.

Hepatectomy is a theoretical possibility as a bridging procedure to liver transplant for those patients with devastating and medically uncontrolled ICH in whom there is no perceived chance of spontaneous recovery.

30.4 Hemodynamic Derangement in ALF and Management

Cardiovascular and circulatory abnormalities are a common feature of ALF. ALF is characterized by a hyperdynamic circulation with high cardiac output, low MAP, and low systemic vascular resistance [62]. Troponin elevation [63, 64] is seen in approximately 60–70% of patients with ALF and is likely related to systemic stress versus true myocardial injury. Elevation of troponin in the setting of ALF did correlate positively with requirements for vasopressors, renal failure, and organ failure scores and did not correlate with evidence of cardiac dysfunction on ECHO studies [63].

The initial step in management of hemodynamic abnormalities is aimed at the restoration of effective circulating volume, as most patients are relatively volume depleted due to various causes.

Invasive monitoring devices are often used to optimize circulating volume and cardiac output [65]. Arterial pressure monitoring from a central artery is preferable. As intravascular volume assessment in ALF poses a challenge, dynamic measures utilizing echocardiography are superior to static hemodynamic measurements [66].

There is considerable data to suggest that a persistent positive fluid balance is associated with higher mortality in ALF. Elevated right sided cardiac pressures may be detrimental to liver venous outflow and hence liver function and regeneration, gut integrity and renal functions [67–69]. Therefore, volume overload should be avoided as much as volume depletion. The choice of fluid should be normal saline or balanced salt solutions, being guided by the patient's acid-base and electrolyte status with and preventing hyper-

chloremic acidosis, as it has been associated with an increased risk of renal failure and other morbidities [70, 71].

In case of increasing tissue and cerebral edema and need for volume therapy, albumin [72–74] infusion can be considered which will enhance plasma oncotic pressure and maintain intravascular volume.

Noradrenaline [75] is typically the vasopressor of choice as it effectively raises mean arterial pressure and can increase hepatic blood flow in parallel with less tachycardia. Vasopressin may augment noradrenaline effect and allow titrating down its dose, but vasopressin, according to animal studies [76], may exacerbate cerebral hyperemia, hyperammonemia, and consequent edema associated with ALF.

In 2007, Eefesen et al. [77] compared noradrenalin and terlipressin in ten ALF patients with ICP monitoring and cerebral microdialysis, and found terlipressin increased CPP without changing ICP, decreased brain lactate, and unchanged lactate/pyruvate ratio. In the absence of advanced hepatic encephalopathy a MAP of at least 65 mmHg, and with advanced encephalopathy and suspected intracranial hypertension, a MAP of at least 80 mmHg is recommended to maintain optimal CPP.

While ALF exhibits hyperdynamic circulation, those with hypoxic hepatitis may have both right and left sided cardiac dysfunction, with or without valvular heart disease. Minimizing right sided pressures, by treating PAH with pulmonary vasodilators (Prostaglandins and sildenafil) and ensuring adequate MAP should be the strategy. In patients with profound and reversible acute cardiac dysfunction, venoarterial extracorporeal membrane oxygenation [78] (VA ECMO) may be appropriate. Hypoxic hepatitis is a secondary form of ALF and as such, the primary presenting organ failure needs to be addressed and managed to facilitate liver recovery. Liver transplantation is not indicated.

About 62% of ALF exhibit adrenal insufficiency [79] which is not impacted by etiology and it correlate with the severity of illness. They are less responsive to the pressor effects of norepinephrine and which is restored when physiologic doses of hydrocortisone are added [80]. Thus patients with ALF who experience refractory hypotension should be evaluated for adrenal insufficiency and when adrenal insufficiency is identified, hydrocortisone should be administered at 200–300 mg daily in divided doses.

30.5 Nutritional and Metabolic Support in ALF

About half of ALF patients develop recurrent hypoglycemia due to glycogen depletion and defective glycogenolysis and gluconeogenesis [81], which can be sudden and can misinterpretation of mental changes. Blood sugar should be monitored at 2–3 h intervals and whenever it is lower than 60 mg/dl, an iv bolus of 50–100 ml of 50% dextrose administered. Glucose transport across the blood–brain barrier is increased because of upregulation of glucose carriers in ALF and hyperglycemia contributes to raised ICP because this increased glucose influx leads to cerebral lactic acid accumulation [82], thereby emphasizing the need for maintaining euglycemia. Low systemic blood pressure and poor systemic microcirculation in ALF result in a build-up of lactate, compounded by failing lactate metabolism. Hyperlactataemia [81] can not only aggravate hemodynamic instability, but also cause cerebral hyperemia and should be treated aggressively.

ALF increases energy requirements are by 60%, and further by complicating infection. Whole body protein catabolism may be increased up to four times the normal rate and results in massive amino acid losses in urine. Owing to the hypercatabolic state of ALF, nutrition is vital and enteral feedings should be initiated early. Only where enteral feeding is contraindicated, partial or total parenteral nutrition should be considered. Initially, combination of parenteral dextrose and lipid emulsions, with 40 gm protein/day can be administered. Lipid emulsions [83] may be used safely in patients with ALF. Avoid severe restrictions of protein [84] and provide normal protein intake of about 1 g/kg per day. Branched chain amino acids (BCAA) offer no additional advan-

tage, except during frequent dialysis, in whom large BCAA losses may occur. Serum levels of phosphorus, potassium, and magnesium are usually low and should be supplemented. Critically ill patients with ALF are at high risk for GI bleeding. In patients who are ventilated or with severe coagulopathy related to hepatic dysfunction, initiation of GI prophylaxis with H_2 blockers or proton pump inhibitors is recommended [27].

30.6 Respiratory Derangement in ALF and Management

The earlier reported incidence [85, 86] of ALI in ALF is between 33 and 37%. Prevention and modern critical care management of ALI and ALF has resulted in current prevalence of ALI in ALF to 21%, though this does not have significant impact on outcomes [87].

Non-invasive ventilator (NIV) should be avoided in ALF patients at risk of hepatic, metabolic or septic high risk of encephalopathy, aspiration, and poor compliance. Invasive airway management to protect airway should be instituted in cases of high grade HE, followed by ventilatory support for hypoxia and respiratory failure.

Rapid sequence induction technique to minimize elevation in ICP using of nondepolarizing agents such as cisatracurium is preferred for endotracheal intubation. Cisatracurium is largely independent of renal or hepatic function for metabolism. Short acting opiate fentanyl for analgesia and propofol for sedation are usually preferred. Although propofol may decrease propofol in hypovolemic patients, it decreases cerebral metabolic rate and also acts as an anticonvulsant.

The balance of hypoxia, hypercarbia and risk of increased ICP are determining factors while choosing the modality of ventilation.

Protective ventilatory strategy with low tidal volumes [88] (6 ml/kg/ideal body weight) and appropriate levels of PEEP to maintain an open lung should be chosen. A target of pCO_2 between 34 and 41 mmHg is ideal. Judicious airway care, head up positioning and careful respiratory therapy minimize risk of ventilator associated pneumonia. Protocol based microbiological cultures of endotracheal secretions and broncho-alveolar lavage should be followed.

Acute respiratory distress syndrome (ARDS) is uncommon ALF patients which may not impact mortality [89]. But in the unlikely patients who develop ARDS prone ventilation [90] does improve oxygenation and potentially decreases mortality, though fraught with the risk of increasing cerebral complications. High PEEP, i.e., >12, which can enhance ICP, can be monitored with middle cerebral artery Doppler. One can consider VV-ECMO in centers with expertise, keeping in view the increased risk of bleeding in ALF.

Hypoxemia is rather common and its etiological assessment is difficult. In some patients with hypoxic hepatitis there is evidence of hepatopulmonary syndrome [91] and this should be excluded with bubble ECHO. HPS is characterized by triad of chronic liver disease, gas exchange abnormalities with significant hypoxemia and/or increased A-a O2 gradient and evidence of right to left intrapulmonary shunt. In patients with intra-cardiac shunts, a small amount of contrast is usually recorded in the left chambers within 1 or 2 cardiac cycles after its appearance in the right side chambers. On the contrary, late arrival of contrast in the left atrium after a time delay of 4–8 cardiac cycles is diagnostic of intra-pulmonary shunt, and is due to the time required for passage through the pulmonary circulation [92].

There also may be evidence of a toxic liver syndrome with increased lung water and ARDS. Assessment of lung water, utilizing advanced hemodynamic monitoring such as volume view or PiCCO may optimize managing these patients.

30.7 Renal Derangement in ALF and Management

Etiology [93] of renal dysfunction in ALF is multifactorial with drug-induced nephrotoxicity, acute tubular necrosis, and abdominal compartment syndrome being the common causes.

Paracetamol [94] may also be one of the causes. The various other risk factors [95] for renal dysfunction in ALF are increased age, hypotension, systemic inflammatory response Syndrome [96] (SIRS), and infection.

Acute kidney injury also develops in 55–68% of all ALF patients and it resolves along with resolution of liver injury or with transplantation [97]. Early AKI develops due to direct injury pattern, whereas late onset typically is more akin to hepatorenal syndrome characterized by functional impairment [98, 99] which is due to a complex interplay between extrarenal vasodilation and renal arteriolar vasoconstriction coupled with inadequate cardiac output [100].

Avoiding nephrotoxic agents, aggressively handling infection and sepsis, deploying various techniques to maintain adequate renal perfusion and instituting timely renal replacement therapy are the mainstays of managing renal dysfunction in ALF [101]. Early targeted volume replacement and vasoactive agent administration, utilizing the hemodynamic management principles above, are keys to avoiding hypotension and to ensure adequate renal perfusion. Renal replacement therapy should be deployed judiciously and timely, rather than a last resort.

30.7.1 Renal Replacement Therapy

Although no study to date has clearly determined ideal and optimal timing for initiation of RRT, rational arguments for early initiation are favored by many liver centers. Studies [40] comparing CRRT versus IHD have noted greater variations in hemodynamic parameters and ICPs with IHD. This has led to the *preference for CRRT over IHD* in these patients and early initiation prevents or allows treatment of these disturbances with consequent complications. High dose CRRT [42] has been shown to decrease arterial ammonia as well. Low-urine output in spite of adequate intravascular volume, fluid overload, and rise in serum creatinine of 0.3 mg/dl have been advocated as indications [3] for CRRT in ALF and even post-transplant.

CRRT vs. IHD:-A retrospective analysis of 1604 patients in the U.S. ALFSG [15] showed that 70% of patients developed AKI with almost 30% requiring RRT. CRRT is recommended over intermittent hemodialysis, in most ALF patients, due to poor tolerance of HD owing to circulatory instability, sudden fluid shifts, and ICP rise [40]. Lactate free bicarbonate buffer as the dialysate and biocompatible dialysis membranes like polysulfone or polyacrylonitrile should only be used [93]. ALF patients require standard heparinization for dialysis in spite of the coagulopathy, due to coexisting antithrombin III deficiency. While cirrhotic patients tolerate citrate anticoagulation [102–104], those with acute and hyperacute ALF may not, due to deranged metabolism of citrate. If citrate is used, close monitoring of total calcium compared with ionized calcium is warranted. Full recovery of AKI is seen in most ALF patients either by the time of discharge or following liver transplantation [94]. Female gender, lower day three MELD scores, admission hypotension and lower grades of AKI are predictive factors for complete renal recovery following paracetamol induced ALF [96, 105].

30.8 Hemostasis in ALF and Management

Since liver synthesizes majority of coagulation factors and proteins required for fibrinolysis, disordered coagulation is an essential diagnostic component of ALF. Deranged international normalized ratio (INR) and prothrombin time are common and are essential to the diagnosis of ALF. Thrombocytopenia [106] is a frequent feature of ALF and is associated with increased incidence of multisystem organ failure and death. In spite of this, clinically significant bleeding events are rare and are seen only in 5% of ALF patients [107]. In depth analysis of coagulation pathophysiology in patients with ALF suggests that they have "*rebalanced hemostasis"* and despite prolongation of measured INR or PT they have a "normal coagulation state," and a significant proportion are actually hypercoagulable. This is due

to significant increases in endogenous heparinoids, procoagulant microparticles, von Willebrand factor and factor VIII, reduced pro- and anticoagulant factors and release of "younger" more reactive platelets in patients with ALF [108–112]. In cases of both acute and chronic liver failure, decreased synthetic capacity of the liver results in decreased production of both procoagulant and anticoagulant proteins [113]. Compared to CLD and cirrhosis, ALF patients have more pronounced reductions in levels of factors II, V, VII, and X with increased levels of factor VIII, likely owing to acute inflammation and tissue factor-mediated consumption of these factors (with the exception of factor VIII) [114].

Recent studies [112] in ALF have identified platelet derived microparticles as being potentially responsible for thrombocytopenia, which may create a hypercoagulable state in the microcirculation and lead to systemic complications and poor outcomes. The "rebalanced state of hemostasis" [115, 116] of ALF can be measured by thromboelastography and thrombin generation studies which explains the low rate of bleeding complications.

Monitoring of coagulation in ALF requires standard and extended laboratory techniques (thrombin generation, factor VIII, etc.), in addition to thromboviscous technology, which is becoming a standard method in many liver centers.

The balanced hemostasis concept reinforces the recommendation that prophylactic correction of deranged coagulation or platelets is unnecessary. It may adversely affect prognostication as well as increase the risk of thrombosis or transfusion related acute lung complications. However, there are two situations that require such measures. (1) ICP monitor insertion requires correction of coagulation and platelet deficiencies, as guided by neurosurgical specialist societies. Some suggest prophylactic recombinant factor VIIa, without any evidence of mortality benefit, but an increased risk of thrombosis [15, 16, 111, 117]. (2) Significant active hemorrhage also necessitates correction, apart from source control of the hemorrhage. Although indications in the specific setting of ALF are not available, it seems reasonable to target plasma fibrinogen levels 1.5–2 g/L by infusing fibrinogen concentrate at an initial dose of 25–50 mg/kg body weight, and a platelet count >60,000 [118]. Supportive therapies such as tranexamic acid can also be considered. Hemoglobin level of 7 g/dl is usually acceptable, though packed cell transfusion may be considered in severe cardiorespiratory failure or subarachnoid hemorrhage [119]. Finally, vitamin K (5–10 mg) should be considered in all patients with ALF, because its deficiency can occur in >25% of patients.

30.9 Infection and SIRS in ALF

ALF is associated with dynamic immune dysfunction. An altered balance between opposing systemic pro- and anti-inflammatory immune profiles can contribute to organ failure and death in ALF [120]. Any type of liver injury leads to activation of the innate immune system, altered macrophage and neutrophil function, initial activation and subsequent reduction of complements, impaired phagocytosis and opsonization resulting in functional immunoparesis.

Liver cell death leads to a release of pro-inflammatory mediators, with elimination of pathogens and tissue regeneration, which may also initiate propagation of further tissue damage. This may lead to "spill over" phenomenon of chemotactic mediators and pro-inflammatory cytokines, with subsequent recruitment of monocytes, lymphocytes, and polymorphonuclear leukocytes [112]. They secrete vasoactive mediators, which by activating platelets and coagulation cascade, increase vascular permeability alongside microcirculatory failure and thrombosis [112] and eventual SIRS. Release of damage associated molecular patterns, e.g., HMGB1, from injured hepatocytes may also contribute to the development of SIRS [121]. SIRS leads to a vicious cycle wherein an increase in vascular permeability further contributes to tissue injury. Over time, the balance tilts towards the anti-inflammatory response, which is associated with immune suppression, recurrent infections, sepsis,

and death [122].SIRS appears to be involved in the worsening of HE, reduces the chances of transplantation, and confers a poorer prognosis, independent of infection [123].

ALF patients are at increased risk of developing infections, sepsis, and septic shock. Though bacteremia is not independent predictor of mortality in ALF [124], infectious complications [125] are a leading cause of death. Bacterial infections [126] are seen in 60–80% of ALF patients, commonest being pneumonia (50%), followed by urinary tract infections (22%), intravenous catheter-induced bacteremia (12%), and spontaneous bacteremia (16%). Gram-negative enteric bacilli and Gram-positive cocci are the most common pathogens. Fungal infections [127] occur in about one-third of ALF patients requiring prolonged critical care, mostly with candida species, with concurrent bacterial infections. Viral infections and reactivation of CMV [128] is common in ALF patients.

30.9.1 Biomarkers

High level of clinical suspicion of infection should be maintained in patients with ALF. Diagnosis of infection in ALF patients poses many challenges. Clinical features are nonspecific and lab indicators like C reactive protein [129] and procalcitonin [130] measurements are unreliable. Routine microbiologic surveillance may aid early detection and treatment of infections [126]. Frequent screening of blood, urine, and representative samples for cultures should be performed as indicated. Admission HE and SIRS score >2 are significant predictors of bacteremia. Deterioration of mental status, unexplained fever, and leukocytosis may herald the onset of infection [124]. Deterioration in hepatic coma grade after initial improvement, pyrexia unresponsive to antibiotics, established renal failure, and marked elevation in white cell count should prompt aggressive investigation for fungal, bacterial, or viral infection. This is especially important in patients already on broad spectrum antibiotics. Use of biomarkers for fungal infection [131] should be utilized, while recognizing their high false positive rate, but low risk of false negative results.

Empirical broad spectrum antibiotics should be administered to ALF patients with SIRS, refractory hypotension or unexplained worsening of hepatic encephalopathy [132]. Though prophylactic [133] parenteral antimicrobial therapy reduces the incidence of infection in certain groups of ALF patients, resultant survival benefit has not been shown. Selective digestive decontamination [134] using nonabsorbable antibiotics and parenteral antibiotics also does not impact survival. There are no controlled trials confirming that the use of prophylactic antimicrobials decreases the likelihood of progression of HE or the development of raised ICP. Therefore, there is no sufficient data to support a generalized antibiotic prophylactic [133] practice in ALF. Empiric antibiotics are recommended for patients listed for super-urgent liver transplantation, since the development of infection and sepsis may prompt delisting. Decisions surrounding antimicrobial choice should be based on knowledge of local microbiological data.

30.9.2 Prognosis and Liver Transplantation

Liver transplantation has improved survival in ALF. The 1-year post-LT survival in ALF in less than that of elective LT performed for chronic liver disease. This is primarily due to increased ICH and sepsis resulting in increased mortality in the first 3 months following LT in ALF. Beyond the first year, ALF patients have better long-term survival [135].

Both whole organ deceased donor and living donor LT have been performed in ALF with great success. Another type of LT is auxiliary transplantation in which the recipient liver is left in place and a partial left or right lobe from the donor is transplanted, thus providing hepatic function until the native liver regenerates. Good survival rates of 60–65% have been reported with this procedure and immunosuppression can be withdrawn in 65–85% of patients at the end of 1-year post-LT.

Prognostic factors in ALF assist in the early identification of patients who would benefit from liver transplantation. They also help identify patients who may recover on their own with supportive care without the need for transplantation. Unfortunately, despite the presence of numerous clinical indicators and prognostic models, a successful prognostic scoring system has yet to be determined. This is mainly due to the varying etiologies of ALF and the variability in the course and complications of ALF.

The Kings College Criteria (KCC) was the first validated scoring system (introduced in 1989) and is currently one of the most widely used prognostic tools for ALF (Table 30.2). Modern medical management has modified KCC performance proven with its dropping sensitivity to studies done after 2005 (46–71%) compared with studies before 1995 (76–82%) [136]. Arterial blood lactate [137] greater than 3.5 mmol/L is an early predictor of mortality in APAP associated ALF (sensitivity 67%, specificity 95%, positive predictive value 79%, negative predictive value 91%) and when added may increase the predictive accuracy of the KCC.

In a systematic analysis [138] of the MELD (modified end stage liver disease) score in ALF, 526 patients with ALF from six studies (all did not have LT support) were included and overall 304 died (58%). By using a MELD score cut-off of 30.5–35, the pooled sensitivity was 77% (95% CI, 72–82%) and specificity was 72% (95% CI, 62–80%).

In a meta-analysis done by Mcphail et al. [136] comparing KCC and MELD score for predicting outcome in ALF, found that The Diagnostic Odds Ratio (DOR) for KCC in cases of AALF was 10.4(4.9–22.1) and for MELD 6.6 (2.1–20.2) whereas for NAALF the DOR for KCC was 4.16 (2.34–7.40) and 8.42 (5.98–11.88) for MELD. Concluding that Although KCC performs better for AALF, MELD has improved prognostic accuracy in NAALF.

Accordingly, the American Gastroenterological Associates [139] suggests using the MELD score rather than the KCC as a prognostic scoring system in patients presenting with ALF (a cut-off MELD score of 30.5 should be used for prognosis and higher scores predict a need for LT). A more recent European Association for the Study of the Liver guideline [7] recommends that LT be considered in those patients fulfilling either the KCC or Clichy criteria. A factor V level of less than 20% may indicate a poor prognosis necessitating consideration of LT in patients of 30 years of age or younger, and a higher threshold of less than 30% is of equivalent significance in older patients [139].

Important prognostic variables for predicting the lack of spontaneous recovery and the need for liver transplantation include: (1) advanced grades 3 and 4 HE and (2) severe coagulopathy defined as an INR >6.5. Additional unfavorable prognostic variables include unfavorable etiologies (e.g., AIH, WD, HSV, and HAV) and the rate of disease progression.

More recently, a retrospective analysis [140] done by the US Acute Liver Failure Study Group (ALFSG) developed a logistic regression model to predict transplant-free survival using admission variables include hepatic encephalopathy (HE) grade, ALF etiology, vasopressor use, bilirubin, and International Normalized Ratio showed good performance characteristics (C-statistic 0.84, specificity 95%, sensitivity 37.1%) in 1974 patients in the ALFSG registry (Fig. 30.3).

Table 30.2 King's college criteria for transplantation in acute liver failure – Acetaminophen induced and Non-acetaminophen induced

Acetaminophen-induced ALF	Nonacetaminophen-induced ALF
Arterial pH <7.30 after fluid resuscitation	Prothrombin time >100 s (INR >6.5)
Or all of the following:	*Or* any 3 of the following:
• Prothrombin time >100 s (INR >6.5)	• Non-A, non-B viral hepatitis, drug-induced or indeterminate etiology of ALF
• Serum creatinine >3.4 mg/dL	• Time from jaundice → encephalopathy >7 days
• Grade 3 or 4 hepatic encephalopathy	• Age <10 years or >40 years
	• Prothrombin time >50 s (INR >3.5)
	• Serum bilirubin >17.4 mg/dL

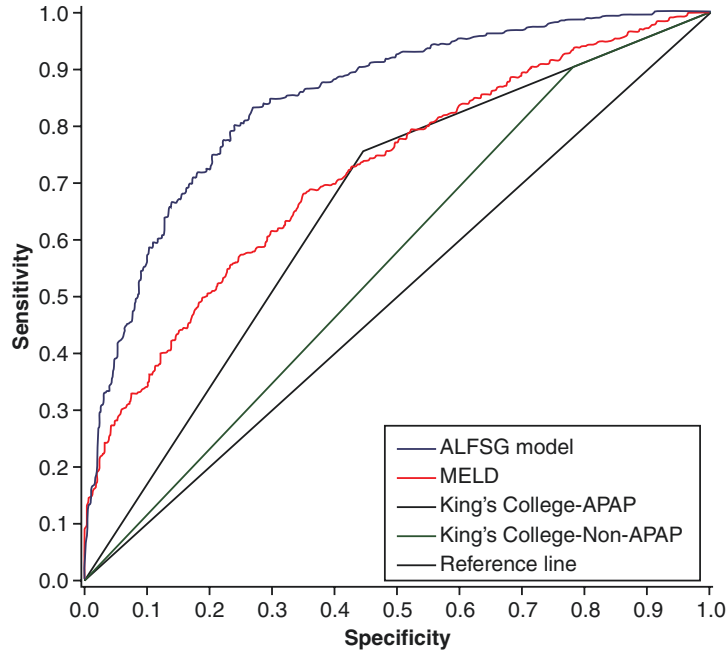

Fig. 30.3 ALFSG model, King's college model (APAP and Non-APAP) and MELD as prognostic models in acute liver failure

The latest model from the King's Liver Intensive Care Unit is a dynamic outcome prediction model [141] developed and validated for use in patients with paracetamol-induced ALF. It is based on prospective data including analysis of more than 20 daily variables sequentially assessed for 3 days after ICU admission in 912 un-transplanted patients between 2000 and 2012. The variables included in the final models to predict death-included age, hepatic encephalopathy, cardiovascular failure, INR, creatinine, and arterial pH on admission and dynamic variables of changing arterial blood lactate and INR. On validation in independent datasets from four transplant centers, the models showed good discrimination between survivors and non-survivors, improving with the inclusion of changes in INR and Lactate over time. Innovative in this approach was its access though a dedicated website and the generation of continuous survival estimates rather than a binary survival outcome, with the intention that the model should act as a decision-support tool to support clinical judgment rather than a sole arbiter as to proceeding with transplantation.

Platelet count has been shown to be closely linked to outcome. In a recent study [142] from the USALFSG, the evolution of thrombocytopenia was closely associated with development of multiorgan failure and a poor outcome in ALF. Recent studies [143] suggest that in some non-paracetamol etiologies, loss of liver volume in adults to less than 1000 cm^3 may indicate irreversible damage and serve as an early indicator of poor prognosis, often in advance of the development of encephalopathy.

Apart from these scoring systems, other serum laboratory parameters (e.g., alfa-fetoprotein [144], galectin-9 [145], procoagulant microparticles [112] soluble CD163 [146], and liver-type fatty acid binding protein [147]) for predicting outcomes [148] in ALF have also been proposed.

Finally, it is important to emphasize that prognostic models should be only part of the overall functional evaluation of the very sick patient with ALF and an experienced multi-disciplinary team in an intensive care setting is required for correct interpretation. Rather than providing an absolute

arbiter, these models should support decision making and the multifactorial team assessment.

30.10 Liver Support Devices in Acute Liver Failure [149]

Many ALF patients die either waiting for a donor liver or they are not suitable for transplantation. Extracorporeal liver support devices (LSD) have been developed to support this kind of patients. These devices help to either stabilize the patient while liver is recovering from insult or act as a bridge to liver transplantation. An effective artificial liver support device should be able to do three functions, namely, detoxification, synthesis of proteins, and regeneration. An ideal LSD would also replace the need for transplantation and may offer chronic replacement for end stage liver disease, but such support device is not yet available in market.

The liver support devices are classified into two basic groups as artificial liver support devices and bio-artificial liver support devices. While the artificial liver support devices are purely mechanical devices or non-cell based liver support devices, the bio-artificial liver support devices are cell-based liver support devices and have a cellular component such as primary hepatocytes or hepatic cell line. The artificial liver support devices only detoxify while the cellular component in bio-artificial liver support devices try replacing liver functions such as oxidative detoxification, biotransformation, excretion, and synthesis (Table 30.3).

Table 30.3 Characters of liver assist devices

Type of device	Artificial liver support	Bio-artificial liver support
Cellular component	No	Yes
Functions achieved	Detoxification only	All hepatic functions
Cost	Comparatively less	High cost
Ease of use	Relatively easier	Complexity of maintaining living components
Efficacy	Limited	Expected results more promising

30.11 Artificial Liver Support Devices (Non-cell Based)

Molecular adsorbents recirculating system (MARS), fractionated plasma separation and adsorption (Prometheus), single pass albumin dialysis (SPAD), and selective plasma filtration therapy (SEPET) are the current non-cell based artificial liver support devices.

Human blood contains toxins which are either water soluble (ammonia, aromatic amino acids, creatinine, interleukin, Interleukin-6, GABA, urea, tryptophan) or bound to albumin (bilirubin, bile acids, cytokines, protoporphyrin, middle and short-chain fatty acids, para-cresol, protoporphyrin, nitric oxide) toxins. Since hemodialysis and hemofiltration remove only water soluble toxins, albumin has been added to existing dialysis devices to remove albumin bound toxins, as in MARS and SPAD. Large pore filters have also been used to retain cellular components and separate plasma proteins including albumin as in Prometheus and SEPET. The filtrate either undergoes readsorption and then cleans the toxin-attached albumin, which is recycled in MARS and Prometheus or discarded in SPAD and SEPET.

MARS (Gambro GmbH, Hechingen, Germany) was introduced in 1990s, which is a combination of conventional hemodialysis against an Albumin dialysate solution over an Albumin impermeable membrane, and consists of a blood circuit and a secondary circuit. Blood passes through a high flux dialyzer over albumin impermeable membrane against 600 ml of 20% Human Albumin dialysate in the secondary circuit. The secondary circuit refreshes albumin by passing through anion-exchange resin and activated charcoal columns. A meta-analysis looking at four RCTs of MARS in ALF did not show any survival benefit, while mortality rates of MARS patients without transplantation are about 78–100%. MARS decreases bilirubin levels and encephalopathy, but may worsen coagulopathy. MARS does not improve non-transplantation ALF survival and can be used as a bridge to transplantation.

Prometheus, the Fractional plasma separation and adsorption (FPSA, Bad Homburg, Germany)

system has a 250 kDa pore size filter and albumin-permeable membranes, the albumin-bound toxins diffuse across and the filtrate which is then passed over two columns of neutral resin and anion-exchange and returned to the patient. Prometheus provides higher clearance for most albumin liver Toxins, compared to MARS. When studied in alcoholic liver disease, MAP and SVR were better preserved compared to MARS.

Single pass albumin dialysis (SPAD) uses 5% albumin concentration which is discarded against a single countercurrent pass against the patient's blood in a hemofilter and is comparable to MARS in clinical and laboratory parameter efficiency. Selective plasma filtration therapy (SEPET) deploys a membrane pore size, allowing passage of molecules of less than100 kDa, size and thus preserves immunoglobulins, complement proteins, clotting factors and hepatocyte growth factor, but albumin is lost and is replaced along with FFP and electrolytes. Clinical trials of SEPET are underway currently.

30.12 Bio-Artificial Liver Support Devices (Cell-Based)

The systems of BAL, which are currently under clinical evaluation, include HepatAssist, Extracorporeal Liver Assist Device (ELAD), Modular Extracorporeal Liver support (MELS), Bio-artificial Liver support system (BLSS), and Amsterdam Medical Centre Bio-artificial Liver (AMCBAL).

The aim of BALs is to provide both detoxification and synthetic functions. Human hepatocytes may be the best cells for use in BAL, but their lack of availability, decreased efficacy in cell culture and inability to readily regenerate in vitro, limits their use. The alternatives are immortal cell lines such as C3A human hepatoblastoma cell lines and porcine hepatocytes. However, there are concerns oncogenesis and xenozoonosis. Moreover, hepatoblastoma cells (C3A) do not exhibit normal metabolic efficiency like ureagenesis and are inferior to primary hepatocytes in metabolic activity.

HepatAssist by Arbios has a hollow fiber extracorporeal bioreactor loaded with cryopreserved porcine hepatocytes. Overall safety was demonstrated across all groups while survival benefit was shown only in subgroup of patients with fulminant or subfulminant hepatic failure. Extracorporeal Liver Assist Device (ELAD) by Vital Therapies (San Diego, California, USA) utilizes hollow fiber cartridges loaded with C3A human hepatoblastoma cell lines. ELAD shas shown improvement in ammonia, bilirubin in HE, survival benefit is yet to be demonstrated through a large multicenter trial. The Modular Extracorporeal Liver support (MELS) system.

(Charite Berlin, Germany) utilizes hollow fibers with fresh porcine hepatocytes. A limited sample study in ALF has shown its safety as a bridge to transplant. Bio-artificial Liver Support System (BLSS) by Excorp Medical (Minneapolis, Minnesota, USA) is under phase II and III studies, which utilizes porcine hepatocytes in a single hollow fiber cartridge. Amsterdam Medical Center Bio-artificial Liver (AMC-BAL) utilizes porcine hepatocytes bound to a spiral-shaped polyester fabric with integrated hollow fiber, which showed some promise in preliminary studies, but larger trials are yet to be done.

In conclusion, excellent evidence proved critical care practices and progress in liver transplantation have improved the survival of ALF significantly. Clarity in definition and classification of ALF have aided in targeting therapies of for ALF subsects. Artificial liver assist devices and coming in are the scope for current research and possible future therapy of ALF.

Key Points

- Although etiological management is important organ supportive management also plays a pivotal role in ALF management.
- For worsening intracranial hypertension with hyperammonemia early continuous renal replacement therapy is the major salvage tool.
- "Rebalanced homeostasis" should always be born in mind warranting judicious use of blood products to correct prolonged clotting parameters.
- Though a lot of prognostic scoring systems are available still one universal prognostic score is still yet to be concluded.
- An ideal liver support device is still impractical at this point.

References

1. Germani G, Theocharidou E, Adam R, Karam V, Wendon J, O'Grady J, et al. Liver transplantation for acute liver failure in Europe: outcomes over 20 years from the ELTR database. J Hepatol. 2012;57:288–96.
2. Donnelly MC, Davidson JS, Martin K, Baird A, Hayes PC, Simpson KJ. Acuteliver failure in Scotland: changes in aetiology and outcomes over time (the Scottish Look-Back Study). Aliment Pharmacol Ther. 2017;45:833–43.
3. Stravitz RT, Kramer DJ. Management of acute liver failure. Nat Rev Gastroenterol Hepatol. 2009;6:542–53.
4. Trey C, Davidson CS. The management of fulminant hepatic failure. Prog Liver Dis. 1970;3:282–98.
5. O'Grady JG, Schalm SW, Williams R. Acute liver failure: redefining the syn-dromes. Lancet. 1993;342:273–5.
6. Polson J, Lee WM. AASLD position paper: the management of acute liver failure. American Association for the Study of Liver Disease. Hepatology. 2005;41(5):1179–97.
7. Wendon J, Panel members, Cordoba J, Dhawan A, Larsen FS, et al. European Association for the Study of the Liver. Electronic address:easloffice@easloffice.eu; Clinical practice guidelines panel, EASL Clinical Practical Guidelines on the management of acute (fulminant) liver failure. J Hepatol. 2017;66:1047–1081.
8. Ostapowicz G, Fontana RJ, Schiødt FV, Larson A, Davern TJ, Han SHB, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med. 2002;137:947–54.
9. Bernuau J, Rueff B, Benhamou JP. Fulminant and subfulminant liver failure: definitions and causes. Semin Liver Dis. 1986;6:97–106. https://doi.org/10.1055/s-2008-1040593.
10. Mochida S, Takikawa Y, Nakayama N, Oketani M, Naiki T, Yamagishi Y, et al. Diagnostic criteria of acute liver failure: a report by the Intractable Hepato-Biliary Diseases Study Group of Japan. Hepatol Res. 2011;41:805–812. https://doi.org/10.1111/j.1872-034X.2011.00860.x.
11. 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;46:1844–52.
12. Larsen FS, Wendon J. Alternative pathway therapy for hyperammonemia in liver failure. Hepatology. 2009;50:3–5.
13. Clemmesen JO, Larsen FS, Kondrup J, Hansen BA, Ott P. Cerebral herniation in patients with acute liver failure is correlated with arterial ammonia concentration. Hepatology. 1999;29:648–53.
14. Bhatia V, Singh R, Acharya SK. Predictive value of arterial ammonia for complications and outcome in acute liver failure. Gut. 2006;55:98–104.
15. Karvellas CJ, Fix OK, Battenhouse H, Durkalski V, Sanders C, Lee WM, et al. Out-comes and complications of intracranial pressure monitoring in acute liver failure: a retrospective cohort study. Crit Care Med. 2014;42:1157–67.
16. Vaquero J, Fontana RJ, Larson AM, Bass NM, Davern TJ, Shakil AO, et al. Complications and use of intracranial pressure monitoring in patients with acute liver failure and severe encephalopathy. Liver Transpl. 2005;11:1581–9.
17. Blei AT, Olafsson S, Webster S, Levy R. Complications of intracranial pressure monitoring in fulminant hepatic failure. Lancet. 1993;341:157–8.
18. Gelabert-González M, Ginesta-Galan V, Sernamito-García R, Allut AG, Bandin-Diéguez J, Rumbo RM. The Camino intracranial pressure device in clinical practice. Assessment in a 1000 cases. Acta Neurochir (Wien). 2006;148:435–41.
19. Wendon JA, Larsen FS. Intracranial pressure monitoring in acute liver failure. A procedure with clear indications. Hepatology. 2006;44:504–6.
20. Bernuau J, Durand F. Intracranial pressure monitoring in patients with acute liver failure: a questionable invasive surveillance. Hepatology. 2006;44:502–4.
21. Fortea JI, Banares R, Vaquero J. Intracranial pressure in acute liver failure: to bolt or not to bolt-that is the question. Crit Care Med. 2014;42:1304–5.
22. Larsen FS, Strauss G, Moller K, Hansen BA. Regional cerebral blood flow autoregulation in patients with fulminant hepatic failure. Liver Transpl. 2000;6:795–800.

23. Krishnamoorthy V, Beckmann K, Mueller M, Sharma D, Vavilala MS. Perioperative estimation of the intracranial pressure using the optic nerve sheath diameter during liver transplantation. Liver Transpl. 2013;19:246–9.
24. Helmke K, Hansen HC. Fundamentals of transorbital sonographic evaluation of optic nerve sheath expansion under intracranial hypertension I. Experimental study. Pediatr Radiol. 1996;26:701–5.
25. Wijdicks EF, Plevak DJ, Rakela J, Wiesner RH. Clinical and radiologic features of cerebral edema in fulminant hepatic failure. Mayo Clin Proc. 1995;70:119–24.
26. Raghavan M, Marik PE. Therapy of intracranial hypertension in patients with fulminant hepatic failure. Neurocrit Care. 2006;4:179–89.
27. Kandiah PA, Olson JC, Subramanian RM. Emerging strategies for the treatment of patients with acute hepatic failure. Curr Opin Crit Care. 2016;22(02):142–51.
28. Citerio G, Vascotto E, Villa F, et al. Induced abdominal compartment syndrome increases intracranial pressure in neurotrauma patients: a prospective study. Crit Care Med. 2001;29:1466–71.
29. Weiner ID, Wingo CS. Hypokalemia–consequences, causes, and correction. J Am Soc Nephrol. 1997;8(7):1179–88.
30. Taboada J, Dimski DS. Hepatic encephalopathy: clinical signs, pathogenesis, and treatment. Vet Clin North Am Small Anim Pract. 1995;25(2):337–55.
31. Iwasa M, Sugimoto R, Mifuji-Moroka R, et al. Factors contributing to the development of overt encephalopathy in liver cirrhosis patients. Metab Brain Dis. 2016;31(5):1151–6.
32. Rabinowich L, Wendon J, Bernal W, Shibolet O. Clinical management of acute liver failure: results of an international multicentre survey. World J Gastroenterol. 2016;22(33):7595–603.
33. Quero Guillén JC, Carmona Soria I, García Montes JM, Jiménez Sáenz M, Herrerías Gutiérrez JM. Hepatic encephalopathy: nomenclature, pathogenesis and treatment. Rev Esp Enferm Dig. 2003;95(02):135–42, 127–134.
34. Cordoba J. Hepatic encephalopathy: from the pathogenesis to the new treatments. ISRN Hematol. 2014:236–68.
35. Olde Damink SW, Deutz NE, Dejong CH, Soeters PB, Jalan R. Interorgan ammonia metabolism in liver failure. Neurochem Int. 2002;41:177–88.
36. Acharya SK, Bhatia V, Sreenivas V, Khanal S, Panda SK. Efficacy of L-ornithine L-aspartate in acute liver failure: a double-blind, randomized, placebo-controlled study. Gastroenterology. 2009;136:2159–68.
37. Clemmesen JO, Kondrup J, Ott P. Splanchnic and leg exchange of amino acids and ammonia in acute liver failure. Gastroenterology. 2000;118:1131–9.
38. Rosen HM, Yoshimura N, Hodgman JM, Fischer JE. Plasma amino acid patterns in hepatic encephalopathy of differing etiology. Gastroenterology. 1977;72:483–7.
39. Gupta S, Fenves AZ, Hootkins R. The role of RRT in hyperammonemic patients. Clin J Am Soc Nephrol. 2016;11(10):1872–8. https://doi.org/10.2215/CJN.01320216.
40. Davenport A, Will EJ, Davidson AM. Improved cardiovascular stability during continuous modes of renal replacement therapy in critically ill patients with acute hepatic and renal failure. Crit Care Med. 1993;21:328–38.
41. Lee WM, Larson AM, Stravitz T. AASLD position paper: the management of acute liver failure: update 2011. Baltimore, MD: American Association for the Study of Liver Diseases; 2011. http://www.guideline.gov/content.aspx?Id=36894.
42. Slack AJ, Auzinger G, Willars C, et al. Ammonia clearance with haemofiltration in adults with liver disease. Liver Int. 2014;34:42–8.
43. Cordoba J, et al. Determinants of ammonia clearance by hemodialysis. Artif Organs. 1996;20:800–3.
44. Murphy N, Auzinger G, Bernel W, et al. The effect of hypertonic sodium chloride on intracranial pressure in patients with acute liver failure. Hepatology. 2004;39:464–70.
45. Ede RJ, Gimson AE, Bihari D, et al. Controlled hyperventilation in the prevention of cerebral oedema in fulminant hepatic failure. J Hepatol. 1986;2:43–51.
46. Bhatia V, Batra Y, Acharya SK. Prophylactic phenytoin does not improve cerebral edema or survival in acute liver failure–a controlled clinical trial. J Hepatol. 2004;41:89–96.
47. Kodakar SK, Gopal PB, Wendon JA. Intracranial pressure is related to body temperature in acute liver failure. Liver Transpl. 2001;7:C87.
48. Bernal W, Murphy N, Brown S, Whitehouse T, Bjerring PN, Hauerberg J, et al. Amulticentre randomized controlled trial of moderate hypothermia to prevent intracranial hypertension in acute liver failure. J Hepatol. 2016;65:273–9.
49. Helbok R, Olson DM, Le Roux PD, Vespa P, Participants in the International Multidisciplinary Consensus Conference on Multimodality Monitoring. Intracranial pressure and cerebral perfusion pressure monitoring in non-TBI patients: special considerations. Neurocrit Care. 2014;21:S85–94.
50. Munoz SJ. Difficult management problems in fulminant hepatic failure. Semin Liver Dis. 1993;13:395–413.
51. Strauss GI. The effect of hyperventilation upon cerebral blood flow and metabolism in patients with fulminant hepatic failure. Dan Med Bull. 2007;54:99–111.
52. Curley G, Kavanagh BP, Laffey JG. Hypocapnia and the injured brain: more harm than benefit. Crit Care Med. 2010;38:1348–59.
53. Vaquero J, Rose C, Butterworth RF. Keeping cool in acute liver failure: rationale for the use of mild hypothermia. J Hepatol. 2005;43:1067–77.

54. Jalan R, Olde Damink SW, Deutz NE, Hayes PC, Lee A. Moderate hypothermia in patients with acute liver failure and uncontrolled intracranial hypertension. Gastroenterology. 2004;127:1338–46.
55. Karvellas CJ, Todd Stravitz R, Battenhouse H, Lee WM, Schilsky ML, US Acute Liver Failure Study Group. Therapeutic hypothermia in acute liver failure: a multicenter retrospective cohort analysis. Liver Transpl. 2015;21:4–12.
56. Schubert A. Side effects of mild hypothermia. J Neurosurg Anesthesiol. 1995;7:139–47.
57. Munoz SJ. Hypothermia may impair hepatic regeneration in acute liver failure. Gastroenterology. 2005;128:1143–4.
58. Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, et al. Targeted temperature management at 33 degrees C vs. 36 degrees C after cardiac arrest. N Engl J Med. 2013;369:2197–206.
59. Tofteng F, Larsen FS. The effect of indomethacin on intracranial pressure, cerebral perfusion and extracellular lactate and glutamate concentrations in patients with fulminant hepatic failure. J Cereb Blood Flow Metab. 2004;24:798–804.
60. Rakela J, Mosley JW, Edwards VM, Govindarajan S, Alpert E. A double- blind randomized trial of hydrocortisone in acute hepatic failure. Dig Dis Sci. 1991;36:1223–8.
61. Forbes A, Alexander GJ, O'Grady JG, et al. Thiopental infusion in the treatment of intracranial hypertension complicating fulminant hepatic failure. Hepatology. 1989;10:306–10.
62. Siniscalchi A, Dante A, Spedicato S, Riganello L, Zanoni A, Cimatti M, et al. Hyperdynamic circulation in acute liver failure: reperfusion syndrome and outcome following liver transplantation. Transplant Proc. 2010;42:1197–9. https://doi.org/10.1016/j.transproceed.2010.03.097.
63. Jaber S, Paugam-Burtz C. Acute liver failure and elevated troponin-I: controversial results and significance? Crit Care. 2013;17:102.
64. Parekh NK, Hynan LS, De Lemos J, et al. Elevated troponin I levels in acute liver failure: is myocardial injury an integral part of acute liver failure? Hepatology. 2007;45:1489–95.
65. Møller S, Bernardi M. Interactions of the heart and the liver. Eur Heart J. 2013;34:2804–11.
66. Olson JC, Wendon JA, Kramer DJ, et al. Intensive care of the patient with cirrhosis. Hepatology. 2011;54:1864–72.
67. Legrand M, Dupuis C, Simon C, Gayat E, Mateo J, Lukaszewicz AC, et al. Association between systemic hemodynamics and septic acute kidney injury in critically ill patients: a retrospective observational study. Crit Care. 2013;17:R278.
68. Mitchell KH, Carlbom D, Caldwell E, Leary PJ, Himmelfarb J, Hough CL. Volume overload: prevalence, risk factors, and functional outcome in survivors of septic shock. Ann Am Thorac Soc. 2015;12:1837–44.
69. Chen H, Wu B, Gong D, Liu Z. Fluid overload at start of continuous renal replacement therapy is associated with poorer clinical condition and outcome: a prospective observational study on the combined use of bioimpedance vector analysis and serum N-terminal pro-B-type natriuretic peptide measurement. Crit Care. 2015;19:135.
70. Young P, Bailey M, Beasley R, Henderson S, Mackle D, McArthur C, et al. Effect of a buffered crystalloid solution vs. saline on acute kidney injury among patients in the intensive care unit: the SPLIT randomized clinical trial. JAMA. 2015;314:1701–10.
71. Yunos NM, Bellomo R, Glassford N, Sutcliffe H, Lam Q, Bailey M. Chloride liberal vs. chloride-restrictive intravenous fluid administration and acute kidney injury: an extended analysis. Intensive Care Med. 2015;41:257–64.
72. Finfer S, Myburgh J, Bellomo R. Albumin supplementation and organ function. Crit Care Med. 2007;35:987–8.
73. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med. 2004;350:2247–56.
74. Caironi P, Tognoni G, Masson S, Fumagalli R, Pesenti A, Romero M, et al. Albumin replacement in patients with severe sepsis or septic shock. N Engl J Med. 2014;370:1412–21.
75. Lee WM, Stravitz RT, Larson AM. Introduction to the revised American Association for the Study of Liver Diseases Position Paper on acute liver failure 2011. Hepatology. 2012;55:965–7. https://doi.org/10.1002/hep.25551.
76. Chung C, Vaquero J, Gottstein J, et al. Vasopressin accelerates experimental ammonia-induced brain edema in rats after portacaval anastomosis. J Hepatol. 2003;39:193–9.
77. Eefsen M, Dethloff T, Frederiksen HJ, et al. Comparison of terlipressin and noradrenalin on cerebral perfusion, intracranial pressure and cerebral extracellular concentrations of lactate and pyruvate in patients with acute liver failure in need of inotropic support. J Hepatol. 2007;47:381–6.
78. Auzinger G, Willars C, Loveridge R, Best T, Vercueil A, Prachalias A, et al. Extracorporeal membrane oxygenation for refractory hypoxemia after liver transplantation in severe hepatopulmonary syndrome: a solution with pitfalls. Liver Transpl. 2014;20:1141–4.
79. Harry R, Auzinger G, Wendon J. The clinical importance of adrenal insufficiency in acute hepatic dysfunction. Hepatology. 2002;36:395–402.
80. Annane D, Bellissant E, Sebille V, et al. Impaired pressor sensitivity to noradrenaline in septic shock patients with and without impaired adrenal function reserve. Br J Clin Pharmacol. 1998;46:589–97.
81. Wang DW, Yin YM, Yao YM. Advances in the management of acute liver failure. World J Gastroenterol. 2013;19:7069–77.

82. Murphy ND, Kodakat SK, Wendon JA, et al. Liver and intestinal lactate metabolism in patients with acute hepatic failure undergoing liver transplantation. Crit Care Med. 2001;29:2111–8.
83. Nagayama M, Okuno M, Takai T, et al. Effect of fat emulsion in patients with liver disorders. Nutrition. 1991;7:267–70.
84. Montejo González JC, Mesejo A, Bonet Saris A. Guidelines for specialized nutritional and metabolic support in the critically-ill patient: update. Consensus SEMICYUCSENPE: liver failure and liver transplantation. Nutr Hosp. 2011;26(Suppl 2):27–31. https://doi.org/10.1590/S0212-16112011000800006.
85. Baudouin SV, Howdle P, O'Grady JG, et al. Acute lung injury in fulminant hepatic failure following paracetamol poisoning. Thorax. 1995;50:399–402.
86. Trewby PN, Warren R, Contini S, et al. Incidence and pathophysiology of pulmonary edema in fulminant hepatic failure. Gastroenterology. 1978;74(5 Pt 1):859–65.
87. Audimoolam VK, McPhail MJ, Wendon JA, et al. Lung injury and its prognostic significance in acute liver failure. Crit Care Med. 2014;42:592–600.
88. Malhotra A. Low-tidal-volume ventilation in the acute respiratory distress syndrome. N Engl J Med. 2007;357:1113–20.
89. Audimoolam VK, McPhail MJ, Wendon JA, Willars C, Bernal W, Desai SR, et al. Lung injury and its prognostic significance in acute liver failure. Crit Care Med. 2014;42:592–600.
90. Gattinoni L, Pesenti A, Carlesso E. Body position changes redistribute lung computed-tomographic density in patients with acute respiratory failure: impact and clinical fallout through the following 20 years. Intensive Care Med. 2013;39:1909–15.
91. Fuhrmann V, Madl C, Mueller C, Holzinger U, Kitzberger R, Funk GC, et al. Hepatopulmonary syndrome in patients with hypoxic hepatitis. Gastroenterology. 2006;131:69–75.
92. Gudavalli A, Kalaria VG, Chen X, Schwarz KQ. Intrapulmonary arteriovenous shunt: diagnosis by saline contrast bubbles in the pulmonary veins. J Am Soc Echocardiogr. 2002;15:1012e4.
93. Devauchelle P, Page M, Brun P, Ber CE, Crozon J, Baillon JJ, Allaouchiche B, Rimmelé T. Continuous haemodialysis with citrate anticoagulation in patients with liver failure: three cases. Ann Fr Anesth Reanim. 2012;31:543–6. https://doi.org/10.1016/j.annfar.2012.01.036.
94. O'Riordan A, Brummell Z, Sizer E, Auzinger G, Heaton N, O'Grady JG, et al. Acute kidney injury in patients admitted to a liver intensive therapy unit with paracetamol-induced hepatotoxicity. Nephrol Dial Transplant. 2011;26:3501–8.
95. Tujios SR, Hynan LS, Vazquez MA, Larson AM, Seremba E, Sanders CM, et al. Risk factors and outcomes of acute kidney injury in patients with acute liver failure. Clin Gastroenterol Hepatol. 2015;13:352–9.
96. Leithead JA, Ferguson JW, Bates CM, et al. The systemic inflammatory response syndrome is predictive of renal dysfunction in patients with non paracetamol- induced acute liver failure. Gut. 2009;58:443–9.
97. Moore K. Renal failure in acute liver failure. Eur J Gastroenterol Hepatol. 1999;11:967–75.
98. Davenport A. Management of acute kidney injury in liver disease. Contrib Nephrol. 2010;165:197–205.
99. Munoz SJ. The hepatorenal syndrome. Med Clin North Am. 2008;92:813–37, viii–ix. https://doi.org/10.1016/j.mcna.2008.03.007.
100. O'Brien Z, Cass A, Cole L, et al. RENAL Study Investigators and the Australian and New Zealand Intensive Care Clinical Trials Group. Higher versus lower continuous renal replacement therapy intensity in critically ill patients with liver dysfunction. Blood Purif. 2018;45(1–3):36–43.
101. Leventhal TM, Liu KD. What a nephrologist needs to know about acute liver failure. Adv Chronic Kidney Dis. 2015;22(05):376–81.
102. Schultheiss C, Saugel B, Phillip V, Thies P, Noe S, Mayr U, et al. Continuous venovenous hemodialysis with regional citrate anticoagulation in patients with liver failure: a prospective observational study. Crit Care. 2012;16:R162.
103. Slowinski T, Morgera S, Joannidis M, Henneberg T, Stocker R, Helset E, et al. Safety and efficacy of regional citrate anticoagulation in continuous venovenous hemodialysis in the presence of liver failure: the Liver Citrate Anticoagulation Threshold (L-CAT) observational study. Crit Care. 2015;19:349.
104. Patel S, Wendon J. Regional citrate anticoagulation in patients with liver failure time for a rethink? Crit Care. 2012;16:153.
105. Moore JK, Love E, Craig DG, Hayes PC, Simpson KJ. Acute kidney injury in acute liver failure: a review. Expert Rev Gastroenterol Hepatol. 2013;7:701–12.
106. Stravitz RT, Ellerbe C, Durkalski V, et al. Thromobcytopenia is associated with multiorgan system failure in patients with acute liver failure. Clin Gastroenterol Hepatol. 2016;14(4):613–620.e4.
107. Munoz SJ, Stravitz RT, Gabriel DA. Coagulopathy of acute liver failure. Clin Liver Dis. 2009;13:95–107.
108. Hugenholtz GC, Adelmeijer J, Meijers JC, Porte RJ, Stravitz RT, Lisman T. An unbalance between von Willebrand factor and ADAMTS13 in acute liver failure: implications for hemostasis and clinical outcome. Hepatology. 2013;58:752–61.
109. Lisman T, Bakhtiari K, Adelmeijer J, Meijers JC, Porte RJ, Stravitz RT. Intact thrombin generation and decreased fibrinolytic capacity in patients with acute liver injury or acute liver failure. J Thromb Haemost. 2012;10:1312–9.
110. Stravitz RT, Lisman T, Luketic VA, Sterling RK, Puri P, Fuchs M, et al. Minimal effects of acute liver injury/acute liver failure on hemostasis as assessed by thromboelastography. J Hepatol. 2012;56:129–36.
111. Agarwal B, Gatt A, Riddell A, Wright G, Chowdary P, Jalan R, et al. Hemostasis in patients with acute

kidney injury secondary to acute liver failure. Kidney Int. 2013;84:158–63.
112. Stravitz RT, Bowling R, Bradford RL, Key NS, Glover S, Thacker LR, et al. Role of procoagulant microparticles in mediating complications and outcome of acute liver injury/acute liver failure. Hepatology. 2013;58:304–13.
113. Lisman T, Leebeek FW, de Groot PG. Haemostatic abnormalities in patients with liver disease. J Hepatol. 2002;37:280–7.
114. Kerr R, Newsome P, Germain L, et al. Effects of acute liver injury on blood coagulation. J Thromb Haemost. 2003;1:754–9.
115. Lisman T, Porte RJ. Rebalanced hemostasis in patients with liver disease: evidence and clinical consequences. Blood. 2010;116:878–85.
116. Habib M, Roberts LN, Patel RK, Wendon J, Bernal W, Arya R. Evidence of rebalanced coagulation in acute liver injury and acute liver failure as measured by thrombin generation. Liver Int. 2014;34:672–8.
117. Munoz SJ, Rajender Reddy K, Lee W, Acute Liver Failure Study Group. The coagulopathy of acute liver failure and implications for intracranial pressure monitoring. Neurocrit Care. 2008;9:103–7.
118. Kozek-Langenecker SA, Afshari A, Albaladejo P, Santullano CA, De Robertis E, Filipescu DC, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology. Eur J Anaesthesiol. 2013;30:270–382.
119. Lelubre C, Vincent JL, Taccone FS. Red blood cell transfusion strategies in critically ill patients: lessons from recent randomized clinical studies. Minerva Anestesiol. 2016;82:1010–1.
120. Antoniades CG, Berry PA, Wendon JA, Vergani D. The importance of immune dysfunction in determining outcome in acute liver failure. J Hepatol. 2008;49:845–61.
121. Antoine DJ, Jenkins RE, Dear JW, Williams DP, McGill MR, Sharpe MR, et al. Molecular forms of HMGB1 and keratin-18 as mechanistic biomarkers for mode of cell death and prognosis during clinical acetaminophen hepatotoxicity. J Hepatol. 2012;56:1070–9.
122. Possamai LA, Antoniades CG, Anstee QM, Quaglia A, Vergani D, Thursz M, et al. Role of monocytes and macrophages in experimental and human acute liver failure. World J Gastroenterol. 2010;16:1811–9.
123. Bernal W, Wendon J. Acute liver failure. Curr Opin Anaesthesiol. 2000;13:113–8.
124. 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;35:1390–6.
125. Vaquero J, Polson J, Chung C, Helenowski I, Schiodt FV, Reisch J, et al. Infection and the progression of hepatic encephalopathy in acute liver failure. Gastroenterology. 2003;125:755–64.
126. Rolando N, Philpott-Howard J, Williams R. Bacterial and fungal infection in acute liver failure. Semin Liver Dis. 1996;16:389–402.
127. Rolando N, Harvey F, Brahm J, Philpott-Howard J, Alexander G, Casewell M, et al. Fungal infection: a common, unrecognised complication of acute liver failure. J Hepatol. 1991;12:1–9.
128. Lopez Roa P, Hill JA, Kirby KA, Leisenring WM, Huang ML, Santo TK, et al. Coreactivation of human herpesvirus 6 and cytomegalovirus is associated with worse clinical outcome in critically ill adults. Crit Care Med. 2015;43:1415–22.
129. Silvestre JP, Coelho LM, Povoa PM. Impact of fulminant hepatic failure in creactive protein? J Crit Care. 2010;25:e7–e12.
130. Rule JA, Hynan LS, Attar N, Sanders C, Korzun WJ, Lee WM, et al. Procalcitonin identifies cell injury, not bacterial infection, in acute liver failure. PLoS One. 2015;10:e0138566.
131. Farmakiotis D, Kontoyiannis DP. Emerging issues with diagnosis and management of fungal infections in solid organ transplant recipients. Am J Transplant. 2015;15:1141–7.
132. Bernal W, Auzinger G, Dhawan A, Wendon J. Acute liver failure. Lancet. 2010;376:190–201.
133. Karvellas CJ, Cavazos J, Battenhouse H, Durkalski V, Balko J, Sanders C, et al. Effects of antimicrobial prophylaxis and blood stream infections in patients with acute liver failure: a retrospective cohort study. Clin Gastroenterol Hepatolol. 2014;12:1942–11949.
134. Rolando N, Gimson A, Wade J, Philpott-Howard J, Casewell M, Williams R. Prospective controlled trial of selective parenteral and enteral antimicrobial regimen in fulminant liver failure. Hepatology. 1993;17:196–201.
135. Fontana RJ, Ellerbe C, Durkalski VE, et al. Two-year outcomes in initial survivors with acute liver failure: results from a prospective, multicentre study. Liver Int. 2015;35(2):370–80.
136. McPhail MJ, Farne H, Senvar N, Wendon JA, Bernal W. Ability of King's College Criteria and model for end-stage liver disease scores to predict mortality of patients with acute liver failure: a meta-analysis. Clin Gastroenterol Hepatol. 2016;14(4):516–525.e5.
137. Bernal W, Donaldson N, Wyncoll D, et al. Blood lactate as an early predictor of outcome in paracetamol-induced acute liver failure: a cohort study. Lancet. 2002;359(9306):558–63.
138. Herrine SK, Moayyedi P, Brown RS Jr, et al. American Gastroenterological Association Institute technical review on initial testing and management of acute liver disease. Gastroenterology. 2017;152(3):648–64.e5.
139. Flamm SL, Yang YX, Singh S, et al. American Gastroenterological Association Institute guidelines for the diagnosis and management of acute liver failure. Gastroenterology. 2017;152(3):644–7.
140. Koch DG, Tillman H, Durkalski V, Lee WM, Reuben A. Development of a model to predict transplant-free survival of patients with acute liver failure. Clin Gastroenterol Hepatol. 2016;14(8):1199–1206.e2.

141. Stravitz RT, Ellerbe C, Durkalski V, et al. Thrombocytopenia is associated with multi-organ system failure in patients with acute liver failure. Clin Gastroenterol Hepatol. 2016;14(4):613–20.
142. Shakil AO, Jones BC, Lee RG, Federle MP, Fung JJ, Rakela J. Prognostic value of abdominal CT scanning and hepatic histopathology in patients with acute liver failure. Dig Dis Sci. 2000;45(2):334–9.
143. Schmidt LE, Dalhoff K. Alpha-fetoprotein is a predictor of outcome in acetaminophen-induced liver injury. Hepatology. 2005;41(1):26–31.
144. Rosen HR, Biggins SW, Niki T, et al. Association between plasma level of Galectin-9 and survival of patients with drug-induced acute liver failure. Clin Gastroenterol Hepatol. 2016;14(4):606–12.e3.
145. Moller HJ, Gronbaek H, Schiodt FV, et al. Soluble CD163 from activated macrophages predicts mortality in acute liver failure. J Hepatol. 2007;47(5):671–6.
146. Karvellas CJ, Speiser JL, Tremblay M, Lee WM, Rose CF, US Acute Liver Failure Study Group. Elevated FABP1 serum levels are associated with poorer survival in acetaminophen-induced acute liver failure. Hepatology. 2017;65(3):938–49.
147. Ichai P, Samuel D. Etiology and prognosis of fulminant hepatitis in adults. Liver Transpl. 2008;14(Suppl 2):S67–79.
148. Puri P, Anand AC. Liver support devices. Medicine update; 2012. p. 489–3.
149. Mochida S, Takikawa Y, Nakayama N, Oketani M, Naiki T, Yamagishi Y, et al. Diagnostic criteria of acute liver failure: a report by the Intractable Hepato-Biliary Diseases Study Group of Japan. Hepatol Res. 2011;41:805–12. https://doi.org/10.1111/j.1872-034X.2011.00860.x.