



# Emerging strategies for the treatment of patients with acute hepatic failure

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## Purpose of review

The objective of this article is to review the latest developments related to the treatment of patients with acute liver failure (ALF).

## Recent findings

As the treatment of ALF has evolved, there is an increasing recognition regarding the risk of intracranial hypertension related to advanced hepatic encephalopathy. Therefore, there is an enhanced emphasis on neuromonitoring and therapies targeting intracranial hypertension. Also, new evidence implicates systemic proinflammatory cytokines as an etiology for the development of multiorgan system dysfunction in ALF; the recent finding of a survival benefit in ALF with high-volume plasmapheresis further supports this theory.

## Summary

Advances in the critical care management of ALF have translated to a substantial decrease in mortality related to this disease process. The extrapolation of therapies from general neurocritical care to the treatment of ALF-induced intracranial hypertension has resulted in improved neurologic outcomes. In addition, recognition of the systemic inflammatory response and multiorgan dysfunction in ALF has guided current treatment recommendations, and will provide avenues for future research endeavors. With respect to extracorporeal liver support systems, further randomized studies are required to assess their efficacy in ALF, with attention to nonsurvival end points such as bridging to liver transplantation.

## Keywords

acute liver failure, extracorporeal liver assist devices, hepatic encephalopathy, intracranial hypertension

## INTRODUCTION

Hepatic decompensation in the critical care setting can present in two distinct contexts, which include acute liver failure (ALF) and acute on chronic liver failure. In contrast to the multiorgan effects of chronic portal hypertension in acute on chronic liver failure, ALF is a clinical syndrome of diverse etiology (including drugs, viruses, and vascular causes) that is defined by coagulopathy and encephalopathy that occurs over a span of less than 6 months in a patient 'without preexisting liver disease'. In its extreme presentation, ALF can present as multiorgan system failure, and requires a systematic approach to management to address hepatic and extrahepatic organ dysfunction.

In this review, we discuss the current recommendations and latest developments related to the management of ALF. Given the importance of intracranial hypertension in the setting of advanced hepatic encephalopathy in ALF, a specific focus of this review will be the neurologic management of advanced hepatic encephalopathy in ALF. In

addition, we will outline the systemic management of ALF in the context of multiorgan system dysfunction. We will conclude with a brief overview of the current state of extracorporeal liver support in the treatment of ALF.

## MANAGEMENT OF ACUTE LIVER FAILURE

### Neurologic considerations

Severe ALF is a devastating disease with a mortality up to 40–50% because of progressive multiorgan

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*Curr Opin Crit Care* 2016, 22:142–151

DOI:10.1097/MCC.0000000000000291

## KEY POINTS

- Advances in the critical care management of ALF have translated to a substantial decrease in mortality related to this disease process.
- There is an increasing recognition regarding the risk of intracranial hypertension related to advanced hepatic encephalopathy in ALF, and therefore, an enhanced emphasis on neuromonitoring and neuroprotective therapies targeting intracranial hypertension.
- Growing evidence implicates a systemic inflammatory response and its associated proinflammatory cytokines as a driver for the development of multiorgan system dysfunction in ALF; a recent randomized trial that demonstrated a survival benefit with HVP further supports this theory.
- With respect to extracorporeal artificial and bioartificial liver support systems, further randomized studies are required to assess their efficacy in ALF, with attention to nonsurvival study end points such as bridging to liver transplantation.

failure [1]. Worsening hepatic encephalopathy in ALF heralds a grim prognosis. Advanced hepatic encephalopathy precedes the development of cerebral edema and intracranial hypertension, that in turn, can culminate in transtentorial herniation. Historically, the progression from hepatic encephalopathy to transtentorial herniation accounted for up to 75–80% of deaths in ALF [2,3]. With improved critical care focusing on neuroprotective interventions, the mortality attributable to intracranial hypertension has decreased to a range of 10–20% [4].

### Pathophysiology of hepatic encephalopathy and intracranial hypertension in acute liver failure

Hepatic encephalopathy and cerebral edema in ALF is a result of a complex interplay between brain ammonia, inflammation, altered neurotransmission pathways, and cerebral hemodynamic dysautoregulation. Hyperammonemia continues to play a significant role in pathogenesis of hepatic encephalopathy [5,6]. Malignant cerebral edema resulting in intracranial hypertension and brain herniation appears to rely on secondary mechanisms specific to ALF. Cerebral hyperemia because of increased cerebral blood flow (CBF) and impaired autoregulation appears to be a process specific to ALF that accounts for the development of malignant cerebral edema and intracranial hypertension. Mechanisms driving this process include the loss of integrity of blood brain barrier [7], failure of

ATPase pump with resultant hyperemia because of loss of cerebrovascular autoregulation, increased NO production because of increased activity of neuronal nitric oxide synthase [8], and upregulation of cyclooxygenase with increased production of prostaglandins and eicosanoids resulting in hyperemia and increased CBF [8]. Hyponatremia frequently occurs in ALF and likely contributes to increased interstitial water-induced cerebral edema.

### Risk factors for development of intracranial hypertension in acute liver failure

A plasma ammonia level of more than 150–200  $\mu\text{mol/l}$  is a well known risk factor for intracranial hypertension in ALF [9,10]. More recently, Kitzberger *et al.* reported that 25% of ALF patients developed intracranial hypertension despite relatively low plasma ammonia levels ( $\text{NH}_3 < 146 \mu\text{mol/l}$ ) [11]. The disproportionately higher extracerebral severity of organ failure score in these patients emphasizes the substantial role of inflammation and organ failure in the development of cerebral hyperemia and diffuse cerebral edema. Other common triggers for ICP elevation include volume overload, hyponatremia, severe hypercarbia, severe acidosis, and increased thoracic and abdominal compartment pressures.

### Management of hepatic encephalopathy and intracranial hypertension

Table 1 [12,13<sup>11</sup>,14<sup>12</sup>,15,16] outlines an algorithm which describes a diagnostic and therapeutic approach to the management of hepatic encephalopathy and intracranial hypertension. Important aspects of this algorithm include an early recognition of the implications of advanced hepatic encephalopathy with respect to evolving intracranial hypertension, the expedited initiation of neuromonitoring strategies, and aggressive management of intracranial hypertension with pharmacologic therapy targeted at decreasing intracranial hypertension. To assist with these neurologic interventions, a dedicated neurointensive care consultation is recommended highly. A more detailed description of the neuromonitoring options and therapeutic strategies is outlined below.

In addition to the interventions targeted to the neurologic system as outlined in Table 1, there are specific management strategies related to other organ systems that can be of great importance in the management of hepatic encephalopathy and intracranial hypertension. Table 2 [13<sup>11</sup>,15–20,21<sup>13</sup>] outlines these specific interventions, including those related to the cardiovascular, respiratory,

**Table 1.** Algorithm for the diagnostic and therapeutic management of acute liver failure with advanced hepatic encephalopathy and intracranial hypertension

I) Identify and treat cause of ALF to minimize further injury
II) Identify risk factors for mortality and IH, and evaluate candidacy for liver transplant if high risk
III) Elect neuromonitoring strategy
1) Invasive-intracranial monitoring devices
2) Noninvasive – Glasgow coma scale assessment, neurologic checks, pupillary exam, serial brain imaging, transcranial Doppler, jugular bulb oxygen saturation and optic nerve sonography
IV) Initiate neuroprotective strategies to delay development of cerebral edema and IH
1) Head of bed elevation with neck in neutral position
2) Initiate osmotherapy with hypertonic saline or mannitol
• Plan an effective osmotherapy strategy taking into account CRRT
• Hypertonic saline with sodium goal of 145–150 meq/l:
i) Continuous infusion: 30% NaCl infusion titrated between 5 and 20 ml/h or 3% NaCl titrated between 30 and 100 ml/h
ii) Intermittent bolus dosing: 30 ml of 23.4% sodium chloride, 20 ml of 30% sodium chloride or 200 ml of 3% sodium chloride
• 20% Mannitol 0.5–1 g/kg bodyweight bolus for elevated ICP. Avoid dose if plasma osmolarity >320 mOsm/l or osmolar gap >20 mOsm/l
3) Initiate plasma ammonia lowering strategies (goal plasma NH <sub>3</sub> <100 μmol/l)
• Consider early initiation of CRRT
• Targeted temperature management (mild hypothermia 35°C) [12,13 <sup>■</sup> ,14 <sup>■</sup> ]
• Avoid hypokalemia and metabolic alkalosis [15]
• Other plasma ammonia lowering interventions
4) Consider intensive care supportive strategies for multiorgan failure directed at treating cerebral edema (See Table 2)
V) Rescue maneuvers to control elevated intracranial pressure or refractory IH
1) Maintain adequate CPP (CPP goal > 60 mmHg)
• Vasopressors for shock – norepinephrine
• Evaluate and treat for adrenal insufficiency
• Plasmapheresis for refractory shock
2) Increased sedation for metabolic suppression
• Thiopental or pentobarbital as a salvage maneuver
3) Maximize osmotherapy with hypertonic saline
• Hypertonic saline with goal sodium of 150–155 meq/l
• 20% Mannitol 0.5–1 g/kg bodyweight bolus for elevated ICP. Avoid dose if plasma osmolarity >320 mOsm/l or osmolar gap >20 mOsm/l
4) Consider continuous neuromuscular blockade infusion for high central venous pressures (>20 mmHg) or sustained refractory ICP
5) Targeted temperature management (moderate hypothermia 33–34°C)
6) Consider using indomethacin 0.5 mg/kg bolus for refractory ICP
7) Correct severe acidosis with sodium bicarbonate infusions or tromethamine [16]
VI) Slow deescalation of neuroprotective therapies postliver transplant or in transplant-free recovery
• IH frequently lags behind liver recovery
• Slow normalization of serum sodium levels
• Monitor for rebound edema or dialysis disequilibrium syndrome
• Slow rewarming if induced hypothermia initiated

ALF, acute liver failure; CPP, cerebral perfusion pressure; CRRT, continuous renal replacement therapy; ICP, intracranial pressure; IH, intracranial hypertension.

renal, and hematologic systems. These aspects of care become particularly important in the ALF patient who progresses to multiorgan system failure, and emphasize the importance of monitoring systemic blood pressure, acid base status, and thoracic and abdominal compartment pressures during the management of intracranial hypertension.

These issues are addressed further in the systemic management of ALF that is subsequently discussed.

### Neuromonitoring strategies

Neuromonitoring strategies in the setting of ALF can include invasive and noninvasive options. The risks

**Table 2.** Intensive care supportive strategies directed at cerebral edema in acute liver failure

Organ system	Intensive care supportive strategies
Neurological	Use short-acting sedatives and opiates once intubated. Propofol and low-dose fentanyl are sedatives of choice. Avoid intermediate or long-acting benzodiazepines
Respiratory	Intubation for airway protection needs to be considered early in later stages of hepatic encephalopathy before significant aspiration and lung injury occurs Low-tidal volume lung protective strategy to prevent acute respiratory distress syndrome. High-intrathoracic pressures result in cerebral venous outflow obstruction [17] High peep → use cautiously as very high peep can theoretically add to hepatic congestion High peak and plateau pressure → indirectly worsen ICP by impeding jugular venous return CO <sub>2</sub> goal: 30–40 mmHg → hypercarbia worsens hyperemia
Cardiovascular	Noninvasive approach and IH suspected → target a higher mean arterial pressure goal (>80 mmHg) Invasive approach → CPPs should be maintained ≥60 mmHg using vasopressors [18] In refractory shock → consider plasma exchange to maintain optimal CPP. (Plasma exchange was associated with reduction in systemic inflammatory response, reduction in severity of organ failure scores, and decline in need for vasopressor support [13 <sup>■</sup> ,19]) CVP goal <20 mmHg → Increased CVP may impede venous return from the brain [20]. Maintain euolemia. Consider paralysis
Renal, acid–base disorders and electrolytes	Early CRRT → to maintain euolemia, augment ammonia clearance [21 <sup>■</sup> ], correction of electrolyte and acidosis correction Formulate strategy to maintain sodium goal at 145–150 meq/l while on CRRT. Options include preparation of hypertonic dialysate or hypertonic saline infusion in postfilter return arm of CRRT Caution: initiating CRRT with isotonic dialysate in patient with IH and induced hypernatremia can cause rebound edema from dialysis disequilibrium syndrome and precipitate brain herniation Hypokalemia and metabolic acidosis increases renal ammonia production Metabolic alkalosis promotes formation of NH <sub>3</sub> + from (NH <sub>4</sub> +) augmenting its passage across the blood–brain barrier [15,16]
GI, liver and nutrition	Abdominal compartment syndrome may indirectly worsen ICP by impeding jugular venous return Lactulose → avoid lactulose via oral or NG route in ALF as it may cause bowel distention, worsening ileus, and complicating transplant surgery. Limited evidence supporting its use in ALF. If used, it is safer to be given rectally
Endocrine	Avoid hypoglycemia → may add to metabolic injury to the brain. Initiate 10% dextrose or 20% dextrose central venous infusion preemptively in ALF
Hematologic and immune system	Disseminated intravascular coagulation → consider repeating head CT if DIC occurs as spontaneous intracranial hemorrhages may occur

CPP, cerebral perfusion pressure; CRRT, continuous renal replacement therapy; CVP, central venous pressure; ICP, intracranial pressure; IH, intracranial hypertension; NG, nasogastric.

and benefits of these different strategies are outlined below.

### Invasive neuromonitoring strategies

Intracranial pressure (ICP) monitoring has been used to identify and treat ALF-induced elevated ICP aggressively, especially when brain edema was the predominant cause of death [10,22]. With improvement in ICU interventions and lower incidence of intracranial hypertension, the utility of invasive intracranial monitoring has been

steadily decreasing. The occurrence of complications, including bleeding, has further deterred its use [23,24]. Recent reviews have shown a lower rate of bleeding in the range of 2–10%. An intracranial hemorrhage rate of 10.3% was reported by Vaquero *et al.* [23] from a prospective cohort of 92 patients who received ICP monitors with grade III–IV encephalopathy; half of these bleeds were incidental findings. Karvellas *et al.* [25] reported a hemorrhage rate of 7% among 140 patients with ICP monitors.

Recombinant factor VII<sub>a</sub> is frequently used to help correct the coagulopathy associated with ALF before the placement of the ICP monitor [26–28]. When ICP monitoring is performed, the mean cerebral perfusion pressures (CPPs) should be maintained at least 60 mmHg using vasopressors [18]. Although observational studies have not found overall survival advantages in those receiving ICP monitoring [25,29], benefit in a subset of high-risk brain edema patients remains a possibility.

### Noninvasive neuromonitoring strategies

A noninvasive neuromonitoring strategy would be reliant upon the empiric use of cerebral edema-preventing interventions as listed below without the reassurance of having a pressure reading. Monitoring strategies under this category include serial head computed tomography (CT) imaging [30,31], transcranial Doppler, jugular bulb oximetry, and pupillometry.

Transcranial Doppler ultrasound is a noninvasive method to estimate ICP based on waveform characteristics because of resistance in CBF in the proximal cerebral circulation [32]. Its utility in ICP detection in ALF has not been validated prospectively and has to be interpreted with caution. Trends in transcranial Doppler ultrasound indicating cerebral perfusion could be useful; however, an easy method for continuous monitoring is not yet available [33].

The utility of brain CT for assessment of cerebral edema and intracranial hypertension remains in question, especially when the interpretation of CT is performed without a comparator. Imaging is useful for excluding other intracranial processes or evaluating for complications of intracranial devices [30,31]. If imaging is to be used for the detection of cerebral edema and to assess the risk of herniation, serial imaging with a baseline scan early or before the onset of severe hepatic encephalopathy may be more useful [34].

Other monitoring modalities such as jugular bulb oxygen saturation, optic nerve sonography, technologies using near infrared spectroscopy and pupillometry have not been validated in ALF and could be used as adjuncts until more supportive data are available.

### NEUROTHERAPEUTIC STRATEGIES

Hyponatremia can worsen cerebral edema and thus should be treated; however, care must be taken to avoid rapid correction.

Hypertonic saline used to prophylactically elevate serum sodium level between 145–155 meq/l has been demonstrated to reduce the incidence and

severity of intracranial hypertension in grade 3 and 4 hepatic encephalopathy patients in a single center study [35]. Concentrations of hypertonic saline used have included 3%, 23.4%, and 30% preparations.

Mannitol reduces brain water through its osmotic effect and improves cerebral perfusion through red blood cell rheological effect. The routine use of mannitol in the neurosurgical patient population is applicable to ALF [36]. In total, 20% mannitol in bolus doses of 0.5–1 g/kg may be used in ALF while maintaining a serum osmolality less than 320 mOsm/l [37] or ensuring an osmolar gap of less than 20 mOsm/l before repeat dosing. The osmotic diuretic effect of mannitol is lost in oliguric renal failure and consequently can precipitate volume overload. For this reason, in addition to the nephrotoxicity associated with mannitol, it should be used with extreme caution in renal failure.

Hyperventilation causes hypocapnia that induces alkalosis, which in turn produces cerebral vasoconstriction, and thereby a decrease in CBF and ICP. However, there is a serious concern of hypocapnia causing or worsening cerebral ischemia and rebound cerebral edema [38]. Moderate short-term hyperventilation reduces global CBF without compromising cerebral oxidative metabolism [39]. PaCO<sub>2</sub> should be monitored and targeted between 30–40 mmHg [40].

Barbiturate coma may be considered with pentobarbital and thiopental in selected cases [41]. Thiopental and pentobarbital have been shown to reduce brain oxygen utilization, and thereby decrease the risk of cerebral ischemia in the presence of intracranial hypertension. However, following the administration of these medications, neurological assessment cannot be done because of induced coma and the prolonged half-life of the drugs because of impaired hepatic metabolism.

Hypothermia has been successful in decreasing ICP and has been reported to help bridge the patient to liver transplant [42–44]. However, its use in ALF remains controversial as two studies (with target temperatures of 33–34°C) have not demonstrated a transplant-free survival benefit [14,45]. Hypothermia induced reduction in plasma ammonia levels [43] and 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 would be to use a milder goal for hypothermia starting at 35°C.

Indomethacin reduced ICP by cerebral vasoconstriction in a porcine model [46]. In a physiological study of 12 patients with ALF, bolus indomethacin dose of 0.5 mg/kg reduced ICP and increased CPP

without compromising cerebral perfusion. Further studies need to be performed prior to considering it for routine use; its use may be considered in refractory cases.

Antiepileptic drugs can be used to treat seizures which can worsen cerebral edema and increase ICP. Since one third of patients with ALF have nonconvulsive seizures of unknown significance, continuous electroencephalography monitoring should be considered in patients who are both sedated and paralyzed [47]. Phenytoin was shown to reduce breakthrough seizures in one small study, while using it prophylactically was of no benefit in another [48]. Using newer antiepileptic drugs is not an unreasonable approach given their fewer side-effects and nonhepatic metabolism.

Continuous renal replacement therapy (CRRT) is recommended over hemodialysis 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) [49,50]. CRRT using continuous venovenous hemofiltration with high-filtration volume (90 ml/kg/h) has been shown to be an effective method of rapidly lowering serum plasma ammonia levels [21<sup>51</sup>]. Increasingly in many transplant centers, initiation of CRRT predominantly for hyperammonemia is being considered in ALF. When using CRRT, appropriate consideration should be given to sodium concentration in dialysate fluid and intravenous hypertonic saline dosing when determining a desired serum sodium level.

### Cardiovascular considerations

Cardiovascular and circulatory abnormalities are a common feature of ALF. These hemodynamic disturbances are often progressive in nature and become more pronounced with advancing liver failure. Typical cardiovascular disturbances are similar to those seen in sepsis and decompensated cirrhosis and include arterial vasodilation, decreased systemic vascular resistance, and peripheral vasodilation; the net effect is often profound systemic hypotension which occurs in spite of increases in cardiac output.

The exact mechanisms responsible for these hemodynamic changes are not completely understood and are likely multifactorial in nature. Gross alterations in the systemic inflammatory response system are frequent in ALF even in absence of infection but are more severe when infection is present [52] and are presumed to be a contributor to the hemodynamic alterations observed.

Troponin elevation is seen in approximately 60–70% of patients with ALF [53,54] and is likely related to systemic stress versus true myocardial injury. In a study from King's College, elevation of troponin in the setting of ALF did correlate positively with requirements for vasopressors, renal failure, and organ failure scores; it did not correlate with evidence of cardiac dysfunction as assessed by abnormalities in echocardiographic studies [53]. Furthermore, the findings of this study did not identify a prognostic significance of troponin elevation in ALF.

The initial step in management of hemodynamic abnormalities is aimed at the restoration of effective circulating volume; this may be achieved with normal saline or balanced salt solutions (e.g., PlasmaLyte), the choice being guided by the patient's acid–base and electrolyte status with efforts aimed at preventing hyperchloremic acidosis. For patients with evidence of increasing tissue and/or cerebral edema who are deemed to have ongoing requirements for plasma volume expansion, consideration of concentrated albumin solutions is appropriate in an effort to prevent further increases in total body water. Assessment of intravascular volume in patients with ALF poses a difficult challenge; dynamic measures of volume status such as echocardiography are superior to static hemodynamic measurements [55]. In patients who are determined to have adequate cardiac filling pressures and in whom hypotension is ongoing, vasopressors may be required. Norepinephrine is typically the agent of choice as norepinephrine effectively raises mean arterial pressure and is less likely to exacerbate tachycardia as compared with dopamine. Vasopressin may augment the effects of norepinephrine and allow for down titration of norepinephrine doses; however, experimental evidence suggests vasopressin and analogs may exacerbate cerebral hyperemia, cerebral hyperammonemia, and cerebral edema associated with ALF [56,57]; thus these agents should be considered second-line therapies. In the absence of advanced hepatic encephalopathy, a mean arterial pressure of at least 65 mmHg is acceptable; in the setting of advanced encephalopathy and suspected intracranial hypertension, a goal mean arterial pressure of at least 80 mmHg is recommended to ensure an optimal CPP.

Adrenal insufficiency occurs in 62% of patients presenting with ALF and is not impacted by etiology of ALF but does correlate with the severity of illness [58]. Indeed patients with adrenal insufficiency are less responsive to the pressor effects of norepinephrine and when physiologic doses of hydrocortisone are administered, the vasopressor efficacy of

norepinephrine is restored [59]. 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.

### Renal considerations

Acute renal failure develops in 55–68% of all patients who present with ALF and in the vast majority of cases reverses with resolution of liver injury or with transplantation [60,61]. It occurs more commonly in patients who suffer from acetaminophen overdose [61]. Renal dysfunction occurring in ALF arises under two different pathways though overlap between the two is likely. First, direct renal toxicity from the agent responsible for inciting ALF may occur and presents early in the course of illness with features of acute tubular necrosis. Specific examples include acetaminophen poisoning and toxicity from mushrooms in the genus *Amanita* [62,63]. With more severe cases of ALF, acute kidney injury follows a pattern similar to the functional impairment seen in the hepatorenal syndrome which occurs in decompensated cirrhosis and occurs later in the course of the illness. In this situation, systemic circulatory dysfunction secondary to extrarenal vasodilation and inadequate cardiac output combines with intense intrarenal arteriolar vasoconstriction resulting in functional renal impairment [64].

In our centers, for patients with ongoing renal dysfunction in spite of aggressive supportive care, we recommend early initiation of CRRT. Although no study to date has clearly defined the ideal measures for determining optimal timing for initiation of renal replacement therapy, rational arguments for early initiation exist. CRRT offers the intensivist a powerful tool for managing important complications of ALF including fluid overload, electrolyte abnormalities, and acid–base disturbances. Early initiation allows treatment of these disturbances before they exacerbate hemodynamic collapse and intracranial hypertension. In addition, CRRT has been shown to decrease arterial ammonia levels when dosed aggressively [21<sup>¶</sup>]. Appropriate indications for initiation of CRRT in patients with ALF include low-urine output in spite of adequate intravascular volume, fluid overload, and rise in serum creatinine of 0.3 mg/dl [65]. As mentioned previously, a study comparing CRRT to intermittent hemodialysis in patients with ALF demonstrated intermittent hemodialysis was more likely to result in deleterious hemodynamic changes and increases in intracranial pressures [49]; thus intermittent hemodialysis is not recommended.

### Hemostasis in acute liver failure

As the liver is responsible for production of the majority of coagulation factors and proteins required for fibrinolysis, it comes as no surprise that gross alterations in measured indices of coagulation exist in patients with ALF. Abnormalities in the international normalized ratio (INR) of prothrombin time are common and are essential to the diagnosis of ALF. Thrombocytopenia also is a frequent feature of ALF and is associated with increased incidence of multisystem organ failure and death [66]. In spite of these significant alterations in routine tests of coagulation, clinically significant bleeding events remain rare in ALF occurring in only ~5% of patients [67].

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 [68]. However, in the setting of ALF, additional mechanisms contribute to alterations in levels of clotting factors. Compared to chronic liver disease and cirrhosis, patients with ALF 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) which is not present in cirrhosis [69]. Recent studies have identified platelet-derived microparticles as being potentially responsible for thrombocytopenia, but more importantly may create a hypercoagulable state in the microcirculation and contribute to systemic complications and poor outcomes in patients with ALF [70]. Formation of deep vein thrombosis and thrombosis of dialysis catheters has been observed in patients with ALF in the presence of prolonged INR and thrombocytopenia. In spite of marked abnormalities in the hemostatic system, the net result observed in ALF is that of a rebalanced state of hemostasis as measured by thromboelastography and thrombin generation studies which explains the low rate of bleeding complications observed in ALF [71,72].

Though bleeding complications are rare, patients are often perceived to have significant coagulopathy and receive unnecessary infusions of blood products such as fresh frozen plasma [73], though no evidence supports this practice in absence of active bleeding. Administration of unnecessary blood products results in volume overload, increased risk of lung injury, and may exacerbate intracranial hypertension [74,75]. In addition, FFP administration impairs usage of the INR as an important marker of prognosis. Based on the current body of evidence, there are no data to support routine correction of abnormalities in routine coagulation tests in absence of

clinically significant bleeding. Usage of recombinant factor VIIa has shown to reverse coagulopathy of ALF; however, it is associated with thrombosis [76] and thus cannot be routinely recommended. Use of global assays such as thromboelastography may be a favored tool for assessment of the coagulation profile in patients with ALF as these systems evaluate clot formation in the context of pro and anticoagulant factors in whole blood.

### Respiratory considerations

The development of acute lung injury (ALI) is a known complication of ALF with older studies reporting rates of ALI between 33–37% [77,78]. Improvements in prevention and treatment of ALI combined with improved critical care management of ALF has resulted in decreased prevalence of ALI in patients with ALF with current prevalence at 21% and as compared with previous studies, does not have significant impact on outcomes [79].

Strict attention to airway compromise is a more pressing respiratory concern in patients with ALF. Encephalopathy is a central feature of ALF and may progress to a level in which the patient is unable to protect his or her airway. Thus, when a patient progresses to grade 3 encephalopathy endotracheal intubation should be considered. Rapid sequence induction techniques which minimize elevation in intracranial pressure should be used. In this regard, use of nondepolarizing agents such as cisatracurium is preferred over depolarizing agents. Furthermore cisatracurium is not dependent on renal or hepatic function for metabolism making it an attractive option in patients with ALF. Once a patient is on mechanical ventilation, use of lung protective ventilation strategies with low tidal volume (6 ml/kg predicted body weight) is recommended. As mentioned previously, titrating minute ventilation to a  $p\text{CO}_2$  of  $\sim 30$ – $40$  mmHg allows for hyperventilation in the case of transient spikes in intracranial pressures.

### Extracorporeal liver support in acute liver failure

In the setting of ALF, extracorporeal liver support systems (ECLS) provide a potential therapeutic option to temporarily support hepatic function, and thereby create a window of opportunity for intrinsic hepatic regeneration and recovery, or as a bridge to liver transplantation. Over the years, both artificial and bioartificial ECLS have been examined, with albumin dialysis in the form of the Molecular Adsorbent Recirculating System

(MARS) being the most studied device. Although multiple uncontrolled studies have demonstrated biochemical improvements following MARS therapy, a recent large randomized controlled trial did not demonstrate a benefit in 6-month survival [80<sup>\*</sup>]. However, a major limitation of this study was that 75% of enrolled patients received a transplant within 24 h of enrollment, thereby potentially limiting the findings of the study. In addition, in a subgroup analysis of acetaminophen-induced ALF (which may represent a form of ALF with a greater potential for intrinsic hepatic recovery), there was a nonstatistically significant trend toward benefit in 6-month survival; this finding raises the possibility that MARS and other ECLS may have a role in certain subgroups of ALF which have a higher rate of hepatic regeneration and recovery.

Most recently, Larsen and colleagues [13<sup>\*\*\*</sup>] published a prospective randomized controlled trial in ALF utilizing high-volume plasma exchange (HVP), which demonstrated a statistically significant benefit in transplant-free survival. In this multicenter European study, 182 patients with ALF were randomized to standard medical therapy (SMT) ( $n=90$ ) or SMT plus HVP ( $n=92$ ) for three days. The primary end point was transplantation-free survival during the hospital stay. HVP was defined as an exchange of 8–12 l or 15% of ideal body weight with fresh frozen plasma; individual sessions lasted approximately 9 h, and the mean number of HVP sessions per treated patient was 2.4. In addition, in a subgroup of patients ( $n=30$ ), the effect of HVP on immune cell function was undertaken to explore a mechanistic rationale for benefit from HVP. In an intention-to-treat analysis, survival to hospital discharge was 58.7% for patients treated with HVP versus 47.8% for the patients who received SMT alone [hazard ratio for HVP vs. SMT with stratification for liver transplantation 0.56; (95% confidence interval 0.36–0.86;  $P=0.0083$ )]. Biochemical markers (INR, bilirubin, and ammonia) improved significantly in the HVP group compared with controls. Furthermore, in the subset of 30 ALF patients who underwent analysis of their immune cell function, those undergoing HVP were found to have significantly reduced circulating levels of proinflammatory cytokines (e.g., TNF- $\alpha$  and IL-6), damage-associated molecular patterns and IL-8 expression. These findings suggest that the survival benefit noted with HVP may be mechanistically explained by a decrease in the systemic inflammatory response related to ALF. In light of this study's findings, and the current lack of evidence supporting the efficacy of other extracorporeal devices, HVP may assume an increasing role in the management of severe ALF.



## CONCLUSION

Advances in the critical care management of ALF have translated to a substantial decrease in mortality related to this disease process. The extrapolation of therapies from general neurocritical care to the treatment of ALF-induced intracranial hypertension have resulted in improved neurologic outcomes, and the prevention of catastrophic brain herniation. In addition, recognition of the systemic inflammatory response and multiorgan dysfunction in ALF has guided current treatment recommendations, and will provide avenues for future research endeavors. With respect to ECLS, further randomized studies are required to assess their efficacy in ALF, with attention to nonsurvival end points such as bridging to liver transplantation.

## Acknowledgements

None.

## Financial support and sponsorship

None.

## Conflicts of interest

There are no conflicts of interest.

## REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

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