Transplantation for acute liver failure: perioperative management

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Purpose of review

A number of conditions can lead to acute liver failure. Determining the cause has important prognostic implications that guide decisions regarding the likelihood of spontaneous recovery, or conversely, the need for transplantation.

Recent findings

Neurological deterioration is associated with intracranial hypertension, which requires meticulous management. The decision to employ invasive intracranial pressure monitoring is controversial because of associated risks and the lack of controlled studies. Recent literature addressing the use of intracranial pressure monitoring is reviewed.

Summary

Even tertiary care units that specialize in liver disease treat acute liver failure patients infrequently. Knowledge of the latest guidelines and treatment protocols can lead to improved patient care.

Keywords

acute liver failure, cerebral edema, fulminant hepatic failure, intracranial hypertension, liver transplantation

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Introduction

Acute liver failure (ALF) is a condition with a variety of causes. It is defined as sudden and severe liver cell dysfunction leading to the onset of coagulopathy and hepatic encephalopathy within 26 weeks of the appearance of jaundice in an individual without previous liver disease [1]. It is an uncommon condition with an incidence of 2000 cases per year in the USA, making it very difficult to study and to compare the effects of different treatments on outcome [2]. Two recent reports [3,4] highlight the most common causes of ALF in the USA and the UK (Table 1).

In the UK single-center study, the spontaneous (transplant-free) survival was 56%. By comparison, the US Acute Liver Failure Study Group reported 43% survival without transplant among 308 patients at 17 centers in the USA [5]. The 3-week survival for those who received a transplant (24% of patients) was 84%. Treatment consists of management of the underlying causal factor, and the active prevention and treatment of multisystem and organ complications. Between 20 and 30% of patients with ALF will undergo liver transplantation. It is difficult to predict who will recover without liver transplantation. Several scoring systems have been developed to help predict outcome in ALF, the most notable is the King's College Criteria. This risk stratification, based on cause [6], age [7], encephalopathy, acid–base status (acetaminophen) [8], coagulopathy and renal function, can be used to identify patients with a poor chance of spontaneous survival. Liver transplantation is indicated for these patients. Others scoring systems include international normalized ratio (INR), alpha-fetoprotein, arterial lactate, arterial ammonia, phosphate and factor V [1,9]. Most units use prognostic scoring indices as a general guide and also take into account progress of individual patients and specific experience by individual tertiary centers. One of the biggest challenges for patients in whom transplantation is indicated is to find an available donor in a timely fashion, before complications such as infection, sepsis, multiple organ failure or permanent brain damage preclude transplantation. Outcome after transplantation for ALF is comparable to that of transplantation for cirrhosis, with 1-, 5- and 10-year survival reported as 77, 66 and 48%, respectively [4]. Another study [10] reported patient survival at 1, 3 and 5 years as 72, 70 and 67%, respectively. Living-related donation (LRD) is an option in some centers to overcome the problems of urgency and the shortage of acceptable donors. Acceptable LRD outcomes have been achieved with patient and graft survival similar to that seen after transplantation for chronic liver disease [11].

Preoperative management

The intensivist's role in ALF is four-fold: recognize that ALF may be the precipitant of multiple systems organ

Table 1 Cause of acute liver failure in the USA and the UK

Cause of ALF	% of USA cases ($n = 1033$)	% of UK cases ($n = 1237$)
Acetaminophen/paracetamol	46	61
Other drugs	12	6.7
Hepatitis B	7.4	2.6
Hepatitis A	3	1.1
Ischemic	4.2	
Autoimmune	5.3	15
Wilson's disease	1.7	0.6
Budd–Chiari syndrome	0.9	1.5
Pregnancy	0.8	
Other	4.8	
Indeterminate	14.6	7.8

ALF, acute liver failure. Data from [3,4].

failure (MSOF), identify the patient who will benefit from orthotopic liver transplantation (OLT) and determine the optimal timing of surgery, recognize the patient who is too ill to benefit and to secure the promise of a technically successful transplant operation with skilled postoperative management. Patients may present to the ICU in a transplant center with ALF recognized and cause defined. However, in a community setting, patients with ALF may present with multisystem organ failure. Abnormal liver function tests may be mistaken as part of the MSOF rather than the precipitant *per se*. In the USA, where acetaminophen intoxication accounts for 50% of ALF and 50% of these patients overdose unintentionally because of a therapeutic misadventure, there is significant potential for missing acetaminophen intoxication as the cause of MSOF.

Once ALF is recognized, the intensivist must identify patients for whom liver transplant is indicated and arrange transfer of patients to an appropriate facility. In the transplant center, while resuscitating the patient and instituting appropriate monitoring, the intensivist must assess the tempo of deterioration. This factor will allow for determination of the urgency of OLT as well as recognition of the patient too ill to transplant. It will also facilitate appropriate risk–benefit analysis if native hepatectomy or high-risk donors are considered. Subtle signs of spontaneous recovery of liver function may also be appreciated and thereby obviate OLT. Once the decision is made that the patient will need to undergo transplantation, the goal is to maintain all other organ function.

Cerebral edema

Cerebral edema leading to intracranial hypertension (ICH) is one of the major causes of morbidity and mortality in patients with ALF. Ammonia is converted in the astrocytes to osmotically active glutamine causing osmotic cerebral edema. Other factors such as loss of cerebral vascular autoregulation, release of inflammatory mediators and ischemic and hypoxic injury have also been proposed. As liver function deteriorates, cerebral hyperemia develops such that ICH is initially secondary to increased cerebral blood volume. This presages the development of cytotoxic cerebral edema, which results in falling cerebral blood flow and increased intracranial pressure (ICP). Cerebral edema presents clinically as hepatic encephalopathy due to ICH. The severity of ICH correlates with the severity of hepatic encephalopathy.

Diagnostic modalities include physical examination, which is superior to invasive monitoring until the point when coma supervenes. A computed tomography (CT) scan of the head is indicated to rule out any other potential causes of high ICP, most importantly bleeding. However, the CT is insensitive to ICH [12]. Loss of gray–white differentiation and ventricular compression indicate cerebral edema but occur relatively late in the course, long after elevated ICP is identified by direct monitoring. MRI and PET provide tremendous insight into structure, blood flow and metabolism in the experimental setting but are poorly attuned to the needs of the critically ill patient.

Infection, hypoxemia, hemodynamic instability and metabolic disturbances can lead to a further deterioration of neurological status. There is no recommendation for the use of seizure prophylaxis, but seizures should be actively treated.

Monitoring and management of intracranial pressure

Invasive monitoring is currently the only way to measure ICP and to guide the treatment of ICH. The indication for placement of an ICP monitor remains a very contentious issue. These monitors are used to accurately detect and intervene when the ICP is elevated. The US Acute Liver Failure study group recommends the placement of an ICP monitor in patients listed for transplantation with grades III–IV hepatic encephalopathy (confusion, sleepiness or coma). Although ICP placement is associated with increased interventions in patients with ALF, it remains to be demonstrated that survival is improved [13]. In part, this reflects the risk of hemorrhage related to the invasiveness of the technique as well as the risks of aggressive correction of coagulopathy and use of antimicrobials for prophylaxis. External ventricular drainage, the standard in neurointensive care, is considered too invasive by many because of the risk of parenchymal hemorrhage. However, this approach is utilized routinely by one of the authors (D.K.). It has the potential advantage of avoiding spikes in ICP by draining cerebrospinal fluid and avoiding transient cerebral ischemia. Epidural catheters have the lowest rate of complications but are not found to be reliable. Complications increase with subdural and intraparenchymal devices.

In a prospective case series of 22 ALF patients managed with an intraparenchymal ICP monitor, three cases of monitor-related intracranial hemorrhage occurred [14••]. In this series, there were no deaths related to cerebral edema, survival with transplant was 88% and survival without transplant was 30%. This group used therapeutic hypothermia (target 33–34°C) more aggressively than most other series. Other authors have reviewed the therapeutic use of hypothermia for the management of ICH and concluded that it appears to have benefits, but that controlled trials are needed [6,15••].

Cerebral blood flow correlates with ICP and can be measured noninvasively with xenon-133 using multiple external detectors at the bedside or xenon-enhanced CT. However, these techniques are predominantly used as research tools. Transcranial Doppler (TCD) ultrasonography is widely available and useful for monitoring for the presence of cerebral vasospasm after subarachnoid hemorrhage. Although algorithms have been developed to predict the ICP from TCD measurements [16,17], the shape of the middle cerebral artery velocity–time curve provides better insight into cerebral compliance [18]. Therapeutic intervention can be titrated with continuous TCD monitoring. Catheterization of the jugular bulb allows measurement of oxygen saturation in the venous effluent of the brain, providing insight into the balance of oxygen delivery and consumption. Cerebral blood flow is inversely related to the arterial–jugular venous oxygen content difference [19]. Narrowing of the arterial–jugular venous oxygen content difference suggests cerebral hyperemia (luxuriant flow) and presages ICH [20,21]. EEG monitoring permits detection of akinetic seizures (nonconvulsive epilepsy), which will increase ICP and cerebral edema [22]. Continuous EEG monitoring is useful to avoid overdosage of propofol and barbiturates, as the infusion can be titrated to burst suppression.

Deterioration of neurological function can happen over a very short time with progression to higher grades of ICH and hepatic encephalopathy. Mild grades of hepatic encephalopathy (grades I and II) are managed by placing the patient in a quiet setting and avoiding stimulation. Sedation should be minimized. Benzodiazepines should be avoided due to the slow clearance and potential worsening of hepatic encephalopathy. Lactulose is believed to reduce the high levels of blood ammonia and may be beneficial in the treatment of hepatic encephalopathy. The effectiveness of this treatment, however, has not been demonstrated, and abdominal distension may make liver transplantation more challenging.

As hepatic encephalopathy progresses to grades III–IV, patients should be managed in a 30% head-up position. The neck should be maintained in a neutral position. Intubation of the trachea should considered to blunt responses that would adversely affect cerebral compliance and homeostasis; for example, straining, coughing and valsalva can all cause an increase in ICP and decrease in cerebral perfusion pressure (CPP). Sedation makes frequent neurological testing more difficult; if needed, sedation with short-acting agents (propofol or short-acting narcotic) is preferred.

Once ICH develops, cerebral blood flow should be determined. Elevations in ICP should be actively treated. As cerebral edema develops and cerebral blood flow falls, maintenance of mean arterial blood pressure (BP) is of paramount importance to preserve adequate CPP (mean arterial pressure – ICP). Some centers aim for a CPP of 75 mmHg, others a value of more than 60 mmHg. Vasopressor support is often required. Hypertonic saline will reduce cerebral edema and ICP. The serum sodium should be maintained between 145 and 155 mmol/l [23]. Osmotic diuresis is particularly valuable in this setting so long as renal function is preserved. Mannitol should be administered in boluses of 0.5–1 g/kg while maintaining serum osmolality below 320 mosm/l. Complications include potential volume overload in patients with renal dysfunction, hypernatremia and hyperosmolality. The prophylactic use of mannitol is not recommended. Mannitol can result in an increase in ICP if renal failure is present [24]. Cautious administration is indicated for management of cerebral edema if intravascular volume can be controlled with continuous renal replacement therapy (CRRT).

ICH with cerebral hyperemia responds to reduction of CVP, hyperventilation, sedation and hypothermia [25••] as well as correction of metabolic acidemia and anemia. Indomethacin may be effective in refractory cases of ICH, though some have questioned its benefit [26]. Drug-induced coma with barbiturate or propofol can be alternative options for ICH refractory to mannitol. Maintenance of CPP is essential as hypothermia and barbiturates may exacerbate myocardial dysfunction and hypotension. Those patients with high ICP in the presence of hypotension face a dismal neurologic prognosis.

Respiratory

Management of the airway and mechanical ventilation are dictated in large part by neurologic status. Patients with grade III encephalopathy usually require endotracheal intubation and mechanical ventilation. Acute lung injury is common in ALF and may presage the development of cerebral edema. Management is guided by the experience of lung-protective strategies, which reduce mortality and decrease extrapulmonary organ dysfunction in acute lung injury. These strategies include tidal volume restricted to 6 ml/kg ideal body weight and maintenance of low airway pressures. This option may result in hypercapnia. The conflicting imperatives of mild hypocapnia to address cerebral hyperemia and hypercapnia,

which results from a lung-protective strategy may be resolved by transient hyperventilation while other ICP-reducing measures are initiated. Reasonable pretransplant ventilation targets include FiO_2 below 0.6, positive end-expiratory pressure below 12 cmH_2O and mean pulmonary artery pressure below 40 mmHg. In the event of severe acute lung injury and elevated pulmonary artery pressures, prone positioning may improve gas exchange and pulmonary artery pressures. Nitric oxide may provide additional benefit.

Cardiovascular

Hypotension in ALF requires assessment of cardiac preload and contractility but usually reflects progressive loss of arterial tone as liver function worsens and/or as infection and systemic inflammatory response syndrome (SIRS) develop. Adequacy of preload may be difficult to assess without invasive monitors. As in sepsis, elevated cardiac output may mask decreased contractility. Myocardial depression may be exacerbated by hypothermia, barbiturates or both. Echocardiography provides real-time assessment of ventricular filling and contractility, as resuscitation is continued. Measurement of stroke-volume variation with positive pressure ventilation can guide fluid resuscitation prior to placement of invasive monitors in the patient who is not spontaneously breathing.

Vasopressor selection is somewhat arbitrary. Norepinephrine is the vasopressor of choice in managing septic shock [27], as it avoids tachycardia and the disadvantageous effects of epinephrine on the splanchnic circulation. Vasopressin is controversial in the setting of ALF. In the management of septic shock, it proves to be norepinephrine sparing, thereby mitigating side effects. It may even have a benefit in mild septic shock with respect to mortality. However, vasopressin and terlipressin have been reported to increase ICP [28]. When cerebral autoregulation is impaired, however, it is probable that any vasopressor that increases mean arterial BP will increase ICP [29].

Infection

The failing liver is associated with acute portal hypertension and mesenteric congestion. This outcome is frequently associated with SIRS [30] and infection, which remains one of the major causes of mortality in patients with ALF. Untreated infection is a contraindication to liver transplantation. Pneumonia, urosepsis and central venous catheter-related sepsis account for almost 85% of infections. Infective organisms are mainly Gram-negative enteric bacilli, Gram-positive cocci and *Candida* species. Empiric antibiotics against both bacteria and yeasts are currently recommended for all patients listed for liver transplantation. If a patient's clinical condition changes suddenly, infection should be ruled out. Sterile precautions should be followed with placement and management of these lines. Infection with *Aspergillus* is a particular concern in patients with ALF combined with acute renal failure [31]. Antifungal therapy with voriconazole requires significant modification of calcineurin inhibitor doses.

Coagulopathy

A decrease in the synthesis of coagulation proteins, an increase in consumption of clotting factors and low serum fibrinogen levels manifest as a laboratory coagulopathy. Typically, patients present with high INR, low serum fibrinogen and low platelet counts. However, clinically significant bleeding only occurs in up to 5% of patients, with spontaneous intracranial bleeding occurring in less than 1%. Most patients have near-normal portal pressures, and gastrointestinal bleeding is from superficial gastric and gastroesophageal mucosal lesions rather than from esophageal and gastric varices seen in patients with cirrhosis. The risk of bleeding due to invasive procedures is unknown. The US Acute Liver Failure Study Group recommends an INR lower or equal to 1.5, and a minimum platelet count of 50 000 platelets/μl for these invasive procedures. There is no recommendation that supports the prophylactic correction of an abnormal coagulation profile in the absence of active bleeding. However, all patients should receive parenteral vitamin K (10 mg parenterally), as deficiency can occur in more than 25% of patients. Options for correcting the INR are the administration of fresh frozen plasma (FFP), recombinant factor VIIa (FVIIa) or both. Large volumes of FFP might be needed to achieve the desired INR; potential side effects include fluid overload, dilutional anemia and thrombocytopenia. FVIIa avoids these complications; however, it carries a risk of thrombotic complications.

Renal function and fluid management

Intravascular volume depletion due to inadequate intake, gastrointestinal losses and transudation of fluid are frequently present. Cautious resuscitation should be attempted to optimize intravascular volume status and to prevent volume overload. Colloid (albumin or FFP) is the preferred solution. Preserving renal function is achieved by optimizing renal perfusion, avoidance of nephrotoxic drugs and early identification and treatment of infection. Renal failure can be due to dehydration, acute tubular necrosis or hepatorenal syndrome. Oliguria should be assessed by urinalysis, fractional excretion of sodium and ultrasonography to rule out hydronephrosis. Protracted acidosis and volume overload are indications for renal replacement therapy. When indicated, continuous venovenous hemodialysis is the method of choice, as it is less likely to exacerbate cerebral edema than intermittent dialysis [32,33].

Liver function

Interventions targeted specifically at improving liver function are limited. *N*-Acetylcysteine infusion is indicated

Table 2 Suggested criteria for deferral of liver transplantation

Deferral of liver transplantation for ALF – extrahepatic organ dysfunction		
Neurologic		CPP <40 for >2 h Herniation (radiographic and clinical criteria)
Cardiovascular		Norepinephrine >1 μg/kg/min
Respiratory	ALI/ARDS	PEEP >12 and FiO_2 >60%
	Pulmonary arterial hypotension	Mean pulmonary artery pressure >40 mmHg
	Intrapulmonary shunt (HPS)	p_aO_2/FiO_2 <100
Functional status		Bedbound >10 days

ALF, acute liver failure; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; CPP, cerebral perfusion pressure; HPS, hepatopulmonary syndrome; PEEP, positive end-expiratory pressure.

in ALF due to acetaminophen intoxication, even late after ingestion, and in ALF due to other causes, as transplant-free survival is improved [34]. Heroic measures such as recipient hepatectomy in advance of donor identification, cross-blood group donation and high donor risk index organs increase the probability of postoperative liver allograft dysfunction. Ongoing graft dysfunction will perpetuate MSOF and ICH.

Too sick to transplant

The threshold at which patients are considered too sick to transplant is poorly defined. Several factors come into play and include recipient acuity, donor quality, surgical and anesthesia resources and the risk aversion philosophy of the transplant program. Thresholds to consider are outlined in Table 2. Patients can be reconsidered if sufficient stabilization occurs.

Intraoperative management

As ALF is rare, and only 20–30% of ALF patients undergo transplant, few data exist to guide intraoperative patient management [35]. The intraoperative mortality has been quoted as 1.5% in 204 patients undergoing liver transplantation for ALF [10]. In this study, the median time from encephalopathy to transplantation was 4 days (range 0–72 days) and the median time from listing to transplantation was 2 days (range 0–88 days). The majority of patients will arrive in the operating room mechanically ventilated, 68% in the above study [10].

Patients should be monitored with intraarterial pressure monitors and some form of central venous pressure or pulmonary artery pressure monitoring. Transesophageal echocardiogram as a monitoring device is becoming more popular for liver transplantation [36]. Patients should be managed in the head up and neutral neck position. The hemodynamic and ventilatory goals are the same as in the ICU. A primary volatile anesthetic technique is relatively contraindicated due to the cerebral vasodilating properties of the inhalational anesthetic agents. However, below one minimum alveolar concentration of volatile agent and a p_aCO_2 of 30–40 mmHg, there should be no adverse effect on cerebral compliance. Osmotherapy with mannitol is indicated when ICP is more than 25 mmHg for more than 10 min. A study [37] of six patients showed an ICP rise during the pre-anhepatic phase, decrease during the anhepatic phase and rise again with reperfusion and during the early postoperative period. In a small case series [38], hypothermia has been suggested as a possible therapeutic option for refractory ICP elevations during transplantation. There are no data on the effect of veno-venous bypass on ICP and CPP. Nor does data exist on the effects of partial inferior vena cava clamping during the so called 'piggyback technique' used in some centers during deceased donor graft implantation and typical during living-related transplantation.

Postoperative management

After OLT, cerebral edema resolves slowly as the allograft function improves. Modifiable clinical parameters include level of sedation, body temperature, mean arterial pressure, tension of carbon dioxide, intravascular volume and osmolality. There is no study that demonstrates superiority of any one specific approach. Indeed management often lacks consistency within a single program. The overarching goal is to maintain cerebral perfusion until liver function is restored. The major postoperative complications are neurological dysfunction, affecting up to 10% of patients, and infection [38].

Immunosuppression is ideally calcineurin inhibitor-based with recognition that young, previously healthy patients have a higher propensity for rejection. Renal failure may warrant induction with interleukin-2 receptor antagonists to permit a delay in the introduction of calcineurin inhibitors. Early mycophenolate and corticosteroids provide cover while calcineurin inhibitor levels are optimized. Steroid use may need to be limited in the presence of critical illness-induced myopathy. Infection of the allograft with hepatitis B is preventable by the perioperative administrative of hepatitis B immune globulin and specific antiviral medications such as lamivudine and entecavir.

Conclusion

Patients with ALF who fail to recover spontaneously require liver transplantation. Once selected for liver transplantation, the focus is on maintaining extrahepatic

organ function, especially brain integrity, and to prevent and treat infection. After transplantation, a smooth transition of care between the operating room and ICU requires close communication between the anesthesiologist and intensivist. With well coordinated, meticulous care, patients with ALF can experience posttransplant survival rates comparable with those of patients with end-stage liver disease.

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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:

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- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 401).

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