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REVIEW

Neurological Management of Fulminant Hepatic Failure

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Abstract Acute liver failure (ALF) is uncommon in the United States, but presents acutely and catastrophically, often with deadly consequences. Hepatic encephalopathy, cerebral edema, elevated intracranial pressure, and intracranial hemorrhage due to coagulopathy are common occurrences in patients with ALF. Appropriate management of multi-system organ failure and neurological complications are essential in bridging patients to transplant and ensuring satisfactory outcomes.

Keywords Acute liver failure · Fulminant liver failure · Intracranial pressure · Coagulopathy

Introduction

Often used interchangeably, the terms acute liver failure (ALF) and fulminant hepatic failure are both defined by the new onset of hepatocellular dysfunction as reflected by coagulopathy (INR $>$ 1.5) and encephalopathy in the absence of pre-existing liver disease [1]. By convention, the further stratification of fulminant hepatic failure is based on the rapidity of encephalopathy onset in the course of illness: less than 2 weeks for acute fulminant liver failure and 8 weeks for sub-fulminant liver failure [2].

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Epidemiology of Fulminant Hepatic Failure

In North America, acetaminophen accounts for nearly half of the ALF caused by drug toxicity, followed distantly in etiologic prevalence by anti-tuberculous (particularly INH and pyrazinamide), anti-seizure (particularly valproic acid), and antibiotic medications [3]. Liver failure due to acetaminophen toxicity is typically associated with single ingestion in excess of 10 g, and unlikely with less than 4 g [4]. However, in the setting of polypharmacy, alcohol abuse, co-ingestion or chronic ingestion, a far lower intermittent dosage may result in hepatocellular loss. Other identifiable causes of ALF include acute hepatitis B virus (HBV) infection (7%), other viral infections (3%), autoimmune hepatitis (5%), ischemic hepatitis (4%), and various other causes (5%) such as Wilson's disease, pregnancy-associated ALF, and other metabolic pathway abnormalities. Of importance, up to 15% of ALF cases remain of indeterminate etiology [3]. Attempts should be made to identify all non-prescription therapy, illicit drug use, alternative/non-traditional and herbal remedy use, and to inquire about non-medicinal ingestions (e.g., amanita mushroom, nutritional, or fitness supplements) that are new or noteworthy [5].

Pathophysiology of Hepatic Encephalopathy

Hepatic encephalopathy is a reversible form of neurological dysfunction, and though its pathogenesis is not entirely understood, it is thought to be primarily due to ammonia-induced neurotoxicity. Ammonia, produced either by catabolism of nitrogenous sources or by glutamine metabolism at a mitochondrial level, has been shown to lead to astrocyte swelling and dysfunction [6]. Metabolism of

glutamine into glutamate and ammonia may additionally cause stimulation of NMDA receptors triggering nitric oxide release and subsequent vasodilation. This vasodilation may lead to hyperemia and cerebral edema [7]. In addition, cerebral autoregulation has been found to be impaired in patients with fulminant hepatic failure [8–10]. A variety of other mechanisms may be involved in the pathogenesis of hepatic encephalopathy including activation of the aquaporin-4 water channel protein on astrocytes, oxindole, a tryptophan metabolite, as well as catecholamine and other neurotransmitter abnormalities. Inflammation may play a role in fulminant patients, as elevated TNFa levels have been documented in patients with elevated ICP compared to those without [11].

The result of this abnormal neurochemical milieu is cerebral edema, which occurs in 80% of comatose patients with acute hepatic failure [3] and is the leading cause of death among fulminant patients [12, 13]. Hepatic encephalopathy grading is shown in Table 1.

Diagnostic Evaluation

Suggested laboratory and imaging studies for the evaluation of ALF are listed in Table 2. When an initial exam suggests another etiology, ultrasound or abdominal CT examination may provide clues to biliary tract obstruction, infiltrative hepatopathy, tumor, hepatic vein obstruction, or acute exacerbation of chronic liver disease. Non-primary hepatic disease such as sepsis, hemolytic crisis, acute pericardial constriction may mimic ALF if coagulation abnormalities or hyperbilirubinemia are prominent. Warfarin ingestion and consumptive coagulopathy must be considered with isolated coagulopathy. Also, adverse drug reactions may occur in the context of superimposed or concomitant illness that may further cloud the distinction between hepatocellular injury and another systemic illness.

Any patient with an acute deterioration in mental status or focal findings on exam should undergo a non-contrast head CT to assess for intracranial hemorrhage. Apart from this, a head CT is recommended in any patient with stage III/IV encephalopathy to evaluate for cerebral edema [14]. A normal head CT does not rule out elevated ICP and should not be used as a surrogate for ICP monitoring [15, 16]. In addition to a baseline CT, a head CT should be performed after insertion or removal of an ICP monitor to check for hemorrhage and positioning. Though MRI may detect cerebral edema with more sensitivity and specificity than CT, the risks of transport and the time involved in obtaining an MRI outweigh the benefits in diagnostic accuracy.

Management

Airway and Breathing

Encephalopathy can lead to aspiration and elevated PaCO2, exacerbating cerebral edema and elevated ICP. Non-command following (typically grade III/IV) patients should be considered for intubation. In order to avoid spikes in ICP that can occur with laryngeal stimulation, intubation should occur in a controlled setting. Either propofol or etomidate are appropriate induction agents. Ketamine should be avoided because it can elevate ICP. Lidocaine spray or 1 ml/kg IV bolus can be given before laryngoscopy to blunt increases in ICP. Succinylcholine should be avoided in patients that have been sedentary for >24 h. Use of a video-assisted laryngoscope can facilitate intubation with fewer complications than direct laryngoscopy [17, 18].

Assist control volume control modes are reasonable in patients with hepatic encephalopathy. Since increasing PEEP will increase mean intrathoracic pressure as well, elevated PEEP that exceeds central venous pressure can theoretically lead to elevations in ICP, though studies with

Table 1 Hepatic encephalopathy grade

Grade	Level of consciousness/cognitive function	Psychiatric symptoms	Neuromuscular function
1	Sleep disturbance, mild confusion, impaired computations	Euphoria/depression	Tremor, incoordination, ±asterixis
2	Inattentive, moderate confusion, disorientation to time	Irritability, decreased inhibitions, personality changes	Asterixis, slurred speech, impaired handwriting
3	Marked confusion, completely disoriented. Lethargic, but arousable command following	Anxiety or apathy, inappropriate or bizarre behavior, paranoia, anger or rage	Slurred speech, ataxia, asterixis, nystagmus, hypo or hyperactive reflexes
4	Non-command following, coma	Coma	Dilated pupils, loss of cranial nerve reflexes, signs of herniation, flexor or extensor posturing, loss of reflexes

Table 2 Laboratory and imaging evaluation

	Admission studies	Etiologic evaluation	Serial studies
Serologic studies	Liver function panel, PT/INR, complete blood count w/differential, fibrinogen, D-dimer, acetaminophen level (adduct if available), toxicology screen, electrolytes/creatinine/uric acid, blood cultures	Cytomegalovirus IgG, Epstein Barr virus IgG, hepatitis A virus IgM, hepatitis B virus-DNA (quant), hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, hepatitis C antibody, hepatitis C virus-RNA (quantitative), alpha-fetoprotein, ceruloplasmin, serum protein electrophoresis, alpha smooth muscle antibody, antimitochondrial antibody, anti-nuclear antibody, liver kidney microsome antibody	Arterial blood gas, arterial lactate, ABO (two separate tests, 2 h apart), repeat PT/INR q6 h, repeat transaminase level q6 h, repeat total and direct bilirubin q6 h, serum Na q6 h, serum osmolarity or osmolality gap (if using Mannitol), repeat fibrinogen and D-Dimer if patient received PCC or rFVIIa
Imaging studies	CXR, non-contrast Head CT (in stage 3–4 encephalopathy), CT abdomen with liver volume or MRI abdomen with liver volume. If a CT or MRI cannot be done safely and in a timely manner, then bedside abdominal sonogram with doppler should be ordered to assess for portal vein patency, ECG, TTE		CXR, non-contrast HCT if patient received intracranial monitor or if intracranial hemorrhage present (repeat HCT every 6 h until hemorrhage size stable)

Q6 h Every 6 h; *PCC* prothrombin complex concentrates; *rFVIIa* recombinant factor VIIa; *CXR* chest X-ray; *HCT* head CT; *MRI* Magnetic Resonance Imaging; *TTE* transthoracic echocardiogram

PEEP up to 15 cm H_2O do not show a significant effect on ICP or cerebral perfusion pressure (CPP) [19]. Permissive hypercapnia should be avoided as this will elevate ICP. Similarly, inverse ratio modes with elevated pressures for a significant duration of the respiratory cycle may inhibit jugular venous outflow and lead to increased ICP. Many fulminant liver failure patients will spontaneously hyperventilate as part of an autoregulatory response [14]. This should not be treated. Conversely, induced hyperventilation is not recommended except in acute cases of herniation since this can lead to ischemia due to vasoconstriction. Maintenance of a PaCO2 between 30 and 40 mm Hg is reasonable.

Sedation

Minimizing sedation and sedation interruption are essential for continuous assessment of the neurological exam. Adequate treatment of pain and anxiety should be addressed to minimize elevation of ICP. When selecting a sedative, renal and hepatic clearance should similarly be considered. Propofol is a typical agent with a short half life that allows for frequent exam assessment. Propofol does not provide any analgesia, however. Other reasonable options include fentanyl, which can minimally lower seizure threshold, and dexmetetomidine, a centrally acting alpha 2 agonist, that provides anxiolysis and analgesia with minimal respiratory or neurological suppression. Midazolam is a reasonable choice in anxious patients and, like propofol, has anticonvulsant effects. Midazolam does, however, have active metabolites that can accumulate with prolonged use. All of the aforementioned agents can lower blood pressure. Paralysis is seldom necessary for adequate ventilation, but if required, it should be used judiciously for as brief a period of time as necessary as it can substantially increase the risk for critical illness neuropathy/myopathy, mask seizure activity and completely obscure the neurological exam.

Lactulose and Non-Absorbable Antibiotics

Frequently used in chronic liver failure, lactulose and non-absorbable antibiotics, such as neomycin and rifaximin, help modulate the production and absorption of nitrogenous moieties that can contribute to hepatic encephalopathy. However, the use of either lactulose or non-absorbable antibiotics in ALF is controversial. Lactulose can lead to gaseous abdominal distention, which can obscure the operating field during orthotopic liver transplant, and in rare cases, can lead to megacolon and bowel ischemia [20]. In one retrospective study, lactulose had no impact on outcome [14]. Intravascular volume depletion due to excessive diarrhea must be avoided if lactulose is used. Similarly, little data exists to support the use of either rifaximin or neomycin in ALF. Neomycin is not recommended due to the risks of nephrotoxicity [14, 21].

Monitoring Intracranial Pressure

Elevated ICP occurs in 86–95% of patients with grade III/IV encephalopathy [22, 23]. Given the insensitivity of head CT to assess for cerebral edema [15, 16], ICP monitoring

should be considering in all non-command following patients, typically grade III/IV encephalopathy patients. Monitoring ICP is the only way to diagnose elevated ICP and assess the efficacy of cerebral edema treatment in patients with marginal neurological exams. Though there are no randomized trials to support the use of ICP monitoring, data suggests that monitoring can identify ICP spikes that are subclinical, can lead to therapeutic changes and provide important prognostic information [22, 24]. In a recent study of fulminant liver failure patients, 95% of patients had elevated ICP, with a median value of 33 mm Hg for a median duration of 60 min. Patients were monitored for a median of 6 days and 82 elevated ICP episodes occurred in 21 patients [22]. Such frequent and severe elevations in ICP mandate evaluation and medical management. A protocolized response to elevated ICP can lead to good neurological outcomes [22]. ICP monitoring is recommended by the US Acute Liver Failure Study Group in grade III/IV patients who are candidates for OLT and in some patients with advanced encephalopathy who are not OLT candidates, but may have survival benefit with aggressive neurological management [14].

In the past, epidural ICP monitors have been commonly used to continuously measure ICP. In a survey of centers treating fulminant liver failure conducted in 1992, hemorrhage occurred in 3% of patients undergoing epidural ICP monitoring compared to 18% with subdural monitors and 13% with "parenchymal" monitors [25]. In most centers in this study, "parenchymal" monitors referred to intraventricular drains, and no information is given specifically regarding ICP monitors that are purely in the parenchyma. In addition, the authors do not provide information about coagulopathy reversal used before monitor placement. Epidural ICP monitors are not used in common neurosurgical practice and have an orphan indication in coagulopathic patients requiring ICP monitoring. Their accuracy is limited [25, 26] and since the indications for use is limited, many centers do not stock such ICP monitors and many practitioners have limited experience in insertion. In a study of fulminant liver failure patients undergoing ICP monitoring with parenchymal monitors, 14% had a hemorrhagic complication at the site of the ICP monitor, though none of these hemorrhages was a cause of death or neurological impairment [22]. Since it is not clear that the risk of hemorrhage after adequate correction of coagulopathy is higher with intraparenchymal monitors compared with epidural ICP monitors, and since parenchymal monitors are more accurate [27, 28], our practice is to place intraparenchymal monitors. Intraventricular monitor placement is not recommended due to the increased risk of bleeding [14].

In patients who are unable to undergo ICP monitor placement, transcranial Doppler assessment of pulsatility index (peak-end diastolic flow velocity/mean flow velocity) can provide a rough assessment of whether ICP is elevated or not, but cannot quantify the ICP. Pulsatility indices >1.5 are considered abnormal. It is important to note that transcranial Doppler does not provide quantifiable or continuous ICP monitoring and in some studies has shown suboptimal sensitivity and specificity [29].

Adequate reversal of coagulopathy is essential before ICP monitor placement. Patients in fulminant liver failure can present with abnormalities at multiple levels of the coagulation cascade. Aside from coagulation factor and fibrinogen deficiency due to synthesis disorders, patients may also present with thrombocytopenia due to splenic sequestration, disseminated intravascular coagulopathy or platelet abnormalities due to uremia and acute renal insufficiency. Though recombinant Factor VIIa has been recommended for coagulopathy reversal before ICP monitor placement [14, 30–33], use of rFVIIa does not replete other depleted coagulation factors and carries a higher risk of DIC than other agents. In addition, the rate of arterial thrombotic events with rFVIIa is as high as 8.5% [34]. Unactivated prothrombin complex concentrates (PCC) (marketed as Bebulin and Profilnine in the US and Octaplex in Europe, and sometimes referred to as Factor IX concentrates) include varying amounts of factors II, VII, IX, X, and protein C and S. PCC, typically dosed as 50 μ/kg, comes as a powder that requires reconstitution in 20 ml of sterile water per vial. Coagulopathy reversal of multiple factors can be achieved quickly with minimal volume and a lower expense than rFVIIa. Since PCC does not contain Factor V, some hematologists recommend additional FFP to replace this factor. All the patients should receive vitamin K 10 mg IV once [14]. In addition, if fibrinogen is <100 mg/dl, the patients should be repleted with cryoprecipitate. The patients who have renal insufficiency should receive DDAVP 0.3 mcg/kg once for uremia-induced platelet dysfunction. Adequate laboratory values for placement of an intracranial monitor include INR <1.5, platelets $>50{,}000$/mm3, fibrinogen >100 mg/dl, and a normal PTT. It should be noted that multiple doses of rFVIIa or combining rFVIIa with PCC is not recommended as this can dramatically increase the risk of DIC and DIC-related complications. In patients with persistent coagulopathy, plasma exchange has been shown to be effective [35]. This may be an especially attractive option in patients who already have a dialysis catheter in place and who can tolerate an interruption from renal replacement therapy to undergo plasma exchange.

It is unclear if coagulation factors need to be corrected for the entire duration of time an ICP monitor is in place or if correction is only necessary during placement and removal of devices [22]. Continued aggressive coagulopathy correction can lead to volume overload, thrombosis, or DIC and may mask spontaneous liver recovery. In addition, the expense of continued correction should be considered.

Management of Elevated Intracranial Pressure

A flow diagram for management of elevated intracranial pressure in the context of fulminant hepatic failure is illustrated in Fig. 1. The first step in managing elevated ICP (defined as sustained ICP > 20 mm Hg or 25 cm H2O) involve simple measures to maximize venous outflow and avoid increases in intrathoracic or intraabdominal pressure that can come with agitation, coughing, or ventilator dyssynchrony. All the patients should have the head of the bed elevated at least 30° (unless contraindicated by hypotension), the head should be maintained midline to promote venous drainage, bilateral jugular venous catheterization should be avoided, and the patients should be maintained in a comfortable pain free state with the minimal amount of analgesics or anxiolytics required to avoid agitation or pain. Lidocaine spray can be used before suctioning to avoid a cough response and an adequate bowel regimen should be prescribed to avoid straining during defecation. Generally, patients should be maintained in an euthermic [36], euvolemic state.

Since cerebral autoregulation has been found to be impaired in patients with fulminant hepatic failure [8–10], it is important to recognize the relationship between ICP and mean arterial pressure (MAP). In patients with a global loss of autoregulation, cerebral blood flow (CBF) and cerebral blood volume will vary passively with mean arterial pressure. Since cerebral blood volume (CBV) is one component of intracranial volume, increases in CBV may increase ICP. Thus, MAP should not be excessively high. However, if autoregulation is partially or regionally intact, under circumstances of low MAP, small cerebral arterioles will dilate in an attempt to maintain CBF. When these arterioles dilate in the vasodilatory cascade zone, CBV increases and, as a consequence, so can ICP. Thus, at very high and very low MAPs, ICP may be elevated. For this reason, a CPP (MAP–ICP) of at least 50 mm Hg is recommended. The upper limit of CPP is not well established and may vary based on individual. Attempts to maintain CPP > 70 mm Hg in traumatic brain injury patients have led to complications such as ARDS [37]. In most neurological patients a CPP > 50 mm Hg has been favored [14, 37–39].

In the patients with persistently elevated ICP osmotic therapy can be considered. Mannitol (20%, 1.0 g/kg or 100 g IV bolus) is a traditional agent that can be used for induction of a hyperosmotic state. Mannitol will cause diuresis and may cause hypotension or renal insufficiency. Alternately, hypertonic saline (23.4%, 30 ml over 10–20 min via a central line) may be used. Hypertonic saline will improve CPP to a greater extent than mannitol, but can cause flash pulmonary edema and/or hypotension if administered too quickly. Though hypertonic saline can also cause renal insufficiency, it is not as offensive as mannitol. Both mannitol and hypertonic saline have rheologic effects that can improve ICP. Maintenance of a hyperosmotic state can be achieved with either mannitol boluses or hypertonic saline (2 or 3% saline) as a bolus or continuous infusion. Mannitol is typically redosed every 6 h for elevated ICP or serum osmolality <320 mOsm/l or osmolal gap <50 mOsm/kg [14]. Renal insufficiency due to mannitol is typically seen with doses >200 g/24 h or with a serum osmolal gap >60–75 mOsm/kg. Hypertonic saline is typically dosed using 3% saline at 1 mg/kg/h titrated to a serum sodium of 150–155 meq/l. Serum sodium values should be evaluated every 6 h and drips should be titrated accordingly. Care should be taken to avoid abrupt withdrawal of hyperosmolar treatment as this can lead to rebound cerebral edema. Hypertonic saline can be decreased in rate and weaned from 3 to 2% based on sodium values. An upper limit of Na of 160 meq/l is generally recommended to avoid complications (seizure, mental status changes) associated with extreme hypernatremia [40].

Since acute renal failure complicates up to 50% of patients with fulminant liver failure [41, 42], an elegant way to maintain a hyperosmolar state is by adjusting the dialysis bath or using hypertonic saline as the replacement fluid if CVVH is used. In general, early introduction of renal replacement therapy is recommended for patients with progressive oliguria, particularly in the setting of electrolyte disturbance or volume overload and to assist the management of plasma administration or osmotic therapies [4]. Continuous veno-venous hemofiltration (CVVH) is the preferred modality by Acute Liver Failure Study Group (ALFSG) recommendations, based on its smoother hemodynamic profile, less precipitous fluid shifts, the ability to rapidly and continuously address electrolyte disturbance, and manage osmotic therapy [4]. Renal replacement therapy itself may provide additional ICP benefits apart from allowing for hyperosmolar therapy. Albumin dialysis has been shown to attenuate increases in ICP in a porcine model apart from its effects on cerebral edema [43].

The patients who are refractory to maximal osmolar therapy should be considered for induced hypothermia targeted to a core body temperature of 32–34°C [44]. Surface cooling ± induction with a cold saline bolus (30 ml of 4°C saline) is preferred in fulminant hepatic failure patients given the risks of bleeding complications with catheter-induced hypothermia. Hypothermia lowers cerebral metabolic demand and reduces splanchnic ammonia production, thus lowering ICP. Though hypothermia has been shown in multiple studies to reduce ICP in fulminant liver failure patients [12, 45–53], it has not been studied in large randomized trials and is associated with serious complications including infections, bleeding diathesis and arrhythmias.

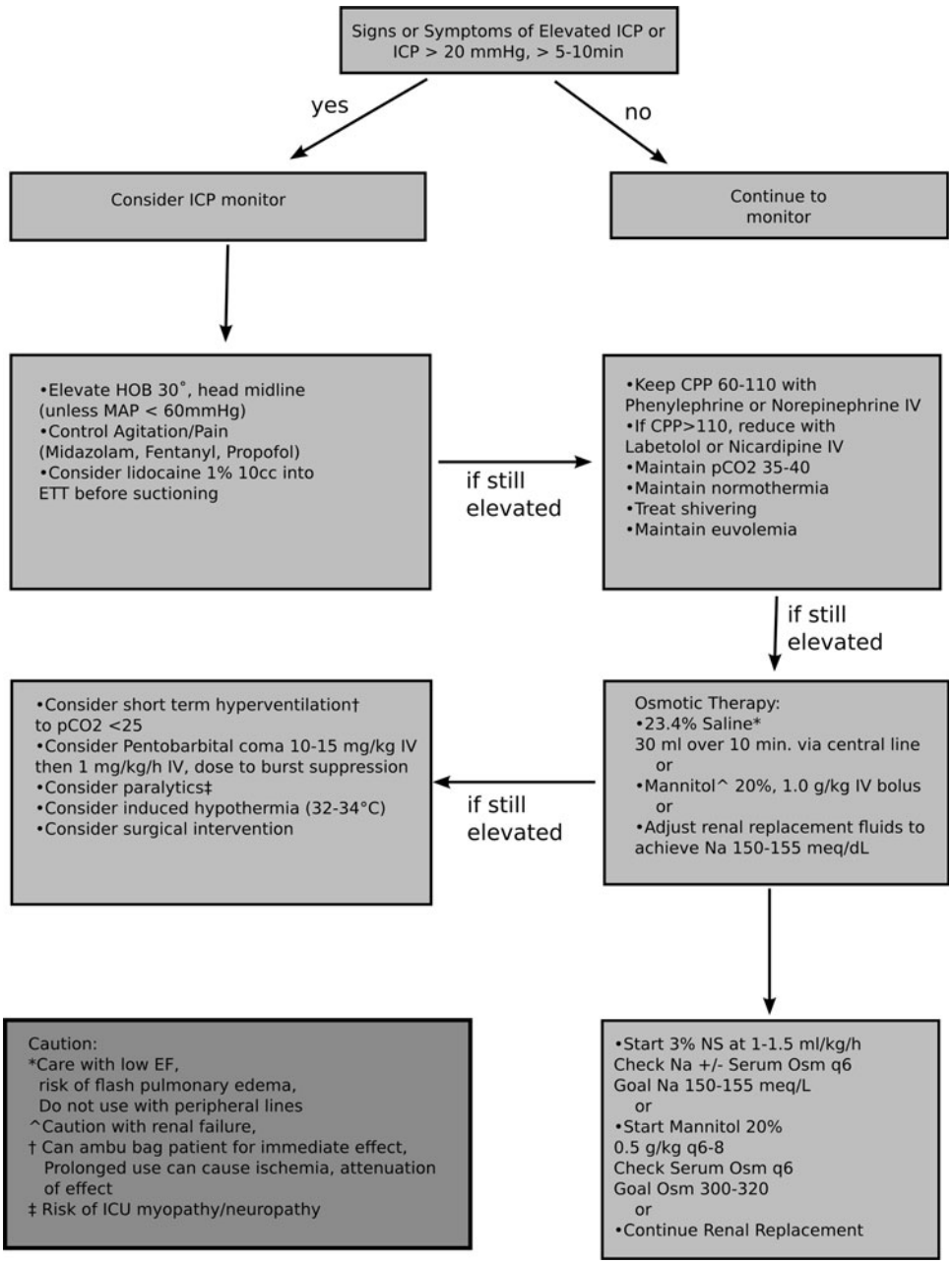

Fig. 1 Management of increased intracranial pressure or malignant edema. *ICP* Intracranial pressure; *HOB* head of bed; *MAP* mean arterial pressure; *ETT* endotracheal tube; *CPP* cerebral perfusion pressure; *Osm* osmolarity; *EF* ejection fraction; *q6* every 6 h

Shivering should be aggressively managed with Bair hugger skin counter-rewarming, and sedation such as dexmetetomidine, fentanyl, or midazolam. The patients who are allowed to shiver will have substantial increases in their metabolic rate and ICP. It should be noted that hypothermia-induced coagulopathic bleeding is typically refractory to blood product replacement. In circumstances of serious hemorrhage patients should be rewarmed at a rate of 0.33–0.5°C/h. Faster rates of rewarming can lead to rebound cerebral edema and herniation.

Other options for ICP control include hyperventilation and barbiturate coma. Hyperventilation should only be used acutely during herniation. For immediate effect, patients can be removed from the ventilator and ambu-bagged to a goal PCO2 of 25–30 mm Hg. Since every 1 mm Hg reduction in PaCO2 will reduce CBF by 3%, prolonged and drastic reductions in PaCO2 can precipitate ischemia. The effect of hyperventilation is short lived (1–24 h) [54]. since the CSF will rapidly buffer the alkalotic effect. Barbituate coma is considered the last course of action for ICP control in liver failure patients. Pentobarbital (5–20 mg/kg IV bolus followed by 1–4 mg/kg/h) is typically used and titrated to burst suppression on continuous EEG. Barbituates cause loss of the entire neurological exam including brainstem reflexes and, in addition, carry the complications of cardiosuppression,

immunosuppression, and profound hypotension. However, barbiturates can be powerfully effective in lowering ICP by the mechanism of metabolic suppression, when patients are refractory to all other agents.

Seizure Prophylaxis and Management

The patients should be monitored for seizures and treated appropriately since this can elevate ICP. The true incidence of seizure in fulminant liver failure patients is not clear. Hypoglycemia, hyponatremia, uremia, and intracranial hemorrhage, which are all co-morbidities of acute liver failure, are common causes of seizure. Typically, fulminant liver failure induces a GABAnergic state, with concomitant low NMDA activity, which is generally protective against seizures. However, mitochondrial dysfunction induced by an acute hyperammonemic states can lead to seizures, as it does in Reye syndrome and other inborn errors of metabolism [55]. In a study conducted in 42 patients with acute liver failure, seizure activity was identified in up to 32% of patients [56]. The authors do not provide any imaging, medication or metabolic data to determine if other etiologies for seizure were present. In addition, some patients included in this study were post-transplant. The post-transplantation state is accompanied by acute GABAnergic withdrawal, and is actually a higher risk time for seizure activity. The rate of seizure in this study may actually be an underestimate since the authors used a hairline EEG montage and patients were paralyzed, thus minimizing detection of clinical seizures. Another study found a seizure rate of 25% in acute liver failure patients, but similarly did not account for confounders and did not use continuous EEG monitoring [57]. Our recommendation is to utilize continuous EEG monitoring in all grade III/IV patients, patients with intracranial hemorrhage or patients with clinical seizure episodes. Since non-convulsive seizures occur in 10–20% of critically ill patients [58–60], full montage continuous EEG monitoring is the best form of detection. In addition, paralysis should be avoided, if possible, to allow for detection of subtle clinical spells. There is mixed data on the utility of phenytoin prophylaxis [56, 57]. The patients who have seized should receive antiepileptic treatment. Prophylaxis can be considered for those who have intracranial hemorrhage or very severe cerebral edema, in whom a seizure might cause herniation due to elevated intracranial pressure.

Other Therapeutic Interventions

The toxic acetaminophen metabolite *N*-acetyl *P*-benzoquinoneimine (NAPQI) is normally detoxified by glutathione conjugation. *N*-acetylcysteine (NAC) for acetaminophen overdose by either oral or intravenous (IV) route is indicated to replenish glutathione stores, and may further act by antioxidant and vasoactive mechanisms. The IV route has the advantage of improved GI tolerance and eliminates problems related to absorption [14]. Moreover, based on accumulating evidence for transplant-free survival benefit and its generally favorable safety profile, intravenous NAC should be strongly considered for patients with early stage non-acetaminophen-induced acute liver failure [61]. Treatment should be initiated immediately when ALF or hepatotoxicity is established, with a loading dose of 150 mg/kg in 500 ml dextrose 5% over 30 min, followed by maintenance dose 50 mg/kg over 4 h, then 125 mg/kg in 1000 ml dextrose 5% over 19 h. Most experts recommend a continuous intravenous infusion of NAC until the INR is less than 1.5. Because of risk of hypersensitivity reaction, IV NAC should always be administered in a monitored setting, and the patients with mild allergic symptoms should have the infusion rate decreased by 50% and receive corticosteroids and antihistamines.

Other therapies in use, but of unproven benefit, include activated charcoal and high-dose IV penicillin for mushroom poisoning and corticosteroids for autoimmune hepatitis. However, corticosteroids had no demonstrated benefit in drug-induced ALF. Other emergent interventions that apply to specific etiologies include prompt delivery for pregnancy-related ALF. Consultation with the transplantation team should be conducted before initiation of etiology specific therapy with unproven initiatives such as copper chelation, plasmapheresis, and antioxidant therapy for Wilson'a disease; lamivudine or entecavir for acute hepatitis B; acyclovir for herpes simplex virus infection; and decompressive surgery or transjugular intrahepatic portosystemic shunts (TIPS) for acute Budd-Chiari syndrome [3].

Emerging Therapeutic Options in ALF

Hemofiltration and hemodialysis have limited capacity to remove protein bound toxins, but newer, experimental techniques have been developed to deal with these substances. Several configurations of so-called liver support modalities have been reported in non-randomized studies, and the results of multicenter trials are awaited. Both cell-free and bioartificial systems have been developed with the aim of removing known and unknown toxins that are released and not cleared in ALF. At present the use of these devices has not been reported to change mortality, though endpoints such as reduced encephalopathy have raised interest in pursuing this line of research, however, their use should be considered experimental [62].

Bridging therapies such as auxiliary orthotopic transplant and two stage transplantation where hepatectomy precedes transplantation by a variable interval up to days, are controversial, and have only been reported anecdotally.

These extraordinary procedures are attempted only in specialized centers under dire circumstances, as in the setting of unavailable allograft in a patient with unmitigated intracranial hypertension [63].

Prognosis

Etiology has a measurable effect on outcome. ALF from acetaminophen overdose, pregnancy, and hepatitis A have a more favorable outcome with transplant-free survival approaching 50% [64]. Spontaneous recovery is least likely with Wilson's disease, non-acetaminophen idiosyncratic drug reactions, and indeterminate causes [65]. Patients who suffer ALF due to antiepileptic medications have a significantly higher death rate after liver transplant than patients who have ALF due to other drugs [66]. The most commonly used prognostic classification scheme, the King's College Hospital criteria (see Table 3) uses simple measures that negatively predict transplant-free survival, originally derived from a cohort of acetaminophen-induced ALF [67]. The model for end-stage liver disease (MELD) score is a prospectively developed chronic liver disease score that is currently used by UNOS to prioritize chronic liver failure patients for liver transplantation [68]. The MELD score is calculated by the formula:

$$\begin{aligned}\text{MELD} = {} & 3.8[\text{Ln serum bilirubin}(\text{mg/dl})] \\ & + 11.2(\text{Ln INR}) \\ & + 9.6[\text{Lnserum creatinine}(\text{mg/dl}) + 6.4]\end{aligned}$$

where Ln is the natural logarithm. Three-month survival decreases precipitously with MELD scores greater than 20. UNOS does not currently apply MELD scores to transplant prioritization for fulminant liver failure patients. Studies have found that increasing MELD scores correlate with decreased survival among the patients with fulminant liver failure [69], however, MELD scores do not seem to be more accurate than King's College Criteria or INR alone [64, 70]. Data that support the additive value of additional serum markers of poor outcome have been debated among the transplant community [71–73]. Likewise, disease-specific prognostic indices have been evaluated in relatively small cohorts that require further validation [64]. Overall, the predictive value of any modality, including the King's College Hospital criteria, may be influenced by the interruption of the natural history of disease by transplant itself.

Table 3 Predictors of increased mortality without emergent transplant: King's College Criteria [67]

Acetaminophen-induced ALF	Non-acetaminophen-induced ALF
Arterial pH $<$ 7.30	Prothrombin time greater than 100 s (INR $>$ 6.5)
OR	OR 3 OF THE 5 FOLLOWING:
Grade 3 or 4 encephalopathy AND	Patient age $<$10 or $>$40 years
Serum creatinine $>$300 mcg/ml (3.4 mg/dl) AND	Hepatitis due to non-A/non-B virus, halothane, or drug reaction
Prothrombin time greater than 100 s (INR $>$ 6.5)	Delayed onset of encephalopathy ($>$1 week after onset of jaundice)
	Serum total bilirubin $>$18 mg/dl (308 mmol/l)
	PT greater than 50 s (INR $>$ 3.5)

Conclusions

Grade III/IV encephalopathy patients should undergo imaging with a non-contrast head CT to evaluate for cerebral edema and/or hemorrhage due to coagulopathy. ICP monitoring should strongly be considered in these patients. Coagulopathy reversal before ICP monitor placement can be achieved using prothrombin complex concentrates, vitamin K, DDAVP, and platelet transfusion, depending on the presence of renal failure and the degree of coagulopathy. Utilizing renal replacement therapy to adjust serum sodium levels is an elegant way of addressing cerebral edema and elevated ICP. Additional effects of hemodialysis include removal of protein bound toxins, which may have beneficial cerebral sequelae. Seizure prophylaxis and continuous EEG monitoring should be considered in the patients with elevated ICP and/or malignant cerebral edema or intracranial hemorrhage. Long term outcomes are strongly tied to the etiology of ALF, but may be improved by aggressive neurological management.

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References

1. Trey C, Davidson CS. The management of fulminant hepatic failure. Prog Liver Dis. 1970;3:282–98.
2. O'Grady JG, Schalm SW, Williams R. Acute liver failure: redefining the syndromes. Lancet. 1993;342(8866):273–5.
3. Lee WM. Acute liver failure. N Engl J Med. 1993;329(25):1862–72.
4. Nourjah P, Ahmad SR, Karwoski C, et al. Estimates of acetaminophen (Paracetomal)-associated overdoses in the United States. Pharmacoepidemiol Drug Saf. 2006;15(6):398–405.
5. Estes JD, Stolpman D, Olyaei A, et al. High prevalence of potentially hepatotoxic herbal supplement use in patients with fulminant hepatic failure. Arch Surg. 2003;138(8):852–8.
6. Albrecht J, Norenberg MD. Glutamine: a Trojan horse in ammonia neurotoxicity. Hepatology. 2006;44(4):788–94.
7. Larsen FS, Gottstein J, Blei AT. Cerebral hyperemia and nitric oxide synthase in rats with ammonia-induced brain edema. J Hepatol. 2001;34(4):548–54.

8. Larsen FS, Ejlersen E, Strauss G, et al. Cerebrovascular metabolic autoregulation is impaired during liver transplantation. Transplantation. 1999;68(10):1472–6.
9. Larsen FS, Knudsen GM, Hansen BA. Pathophysiological changes in cerebral circulation, oxidative metabolism and blood-brain barrier in patients with acute liver failure. Tailored cerebral oxygen utilization. J Hepatol. 1997;27(1):231–8.
10. Strauss G, Hansen BA, Kirkegaard P, et al. Liver function, cerebral blood flow autoregulation, and hepatic encephalopathy in fulminant hepatic failure. Hepatology. 1997;25(4):837–9.
11. Jalan R, Olde Damink SW, Hayes PC, et al. Pathogenesis of intracranial hypertension in acute liver failure: inflammation, ammonia and cerebral blood flow. J Hepatol. 2004;41(4):613–20.
12. Jalan R. Intracranial hypertension in acute liver failure: pathophysiological basis of rational management. Semin Liver Dis. 2003;23(3):271–82.
13. Ostapowicz G, Fontana RJ, Schiodt FV, 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(12):947–54.
14. Stravitz RT, Kramer AH, Davern T, et al. Intensive care of patients with acute liver failure: recommendations of the US. Acute liver failure study group. Crit Care Med. 2007;35(11): 2498–508.
15. Lidofsky SD, Bass NM, Prager MC, et al. Intracranial pressure monitoring and liver transplantation for fulminant hepatic failure. Hepatology. 1992;16(1):1–7.
16. Munoz SJ, Robinson M, Northrup B, et al. Elevated intracranial pressure and computed tomography of the brain in fulminant hepatocellular failure. Hepatology. 1991;13(2):209–12.
17. Serocki G, Bein B, Scholz J, et al. Management of the predicted difficult airway: a comparison of conventional blade laryngoscopy with video-assisted blade laryngoscopy and the GlideScope. Eur J Anaesthesiol. 2010;27(1):24–30.
18. Nouruzi-Sedeh P, Schumann M, Groeben H. Laryngoscopy via Macintosh blade versus GlideScope: success rate and time for endotracheal intubation in untrained medical personnel. Anesthesiology. 2009;110(1):32–7.
19. McGuire G, Crossley D, Richards J, et al. Effects of varying levels of positive end-expiratory pressure on intracranial pressure and cerebral perfusion pressure. Crit Care Med. 1997;25(6): 1059–62.
20. Wright RA. Lactulose-induced megacolon. Gastrointest Endosc. 1988;34(6):489–90.
21. Greenberg LH, Momary H. Audiotoxicity and nephrotoxicity due to orally administered neomycin. JAMA. 1965;194(7):827–8.
22. Raschke RA, Curry SC, Rempe S, et al. Results of a protocol for the management of patients with fulminant liver failure. Crit Care Med. 2008;36(8):2244–8.
23. Ede RJ, Gimson AE, Bihari D, et al. Controlled hyperventilation in the prevention of cerebral oedema in fulminant hepatic failure. J Hepatol. 1986;2(1):43–51.
24. Keays RT, Alexander GJ, Williams R. The safety and value of extradural intracranial pressure monitors in fulminant hepatic failure. J Hepatol. 1993;18(2):205–9.
25. Blei AT, Olafsson S, Webster S, et al. Complications of intracranial pressure monitoring in fulminant hepatic failure. Lancet. 1993;341(8838):157–8.
26. Bacher A. Intracranial hypertension in fulminant hepatic failure. Transplant Proc. 2006;38(3):783–5.
27. Fernandes HM, Bingham K, Chambers IR, et al. Clinical evaluation of the Codman microsensor intracranial pressure monitoring system. Acta Neurochir Suppl. 1998;71:44–6.
28. Gray WP, Palmer JD, Gill J, et al. A clinical study of parenchymal and subdural miniature strain-gauge transducers for monitoring intracranial pressure. Neurosurgery. 1996;39(5):927–31. discussion 931-922.
29. Figaji AA, Zwane E, Fieggen AG, et al. Transcranial Doppler pulsatility index is not a reliable indicator of intracranial pressure in children with severe traumatic brain injury. Surg Neurol. 2009; 72(4):389–94.
30. Jeffers L, Chalasani N, Balart L, et al. Safety and efficacy of recombinant factor VIIa in patients with liver disease undergoing laparoscopic liver biopsy. Gastroenterology. 2002;123(1):118–26.
31. Pavese P, Bonadona A, Beaubien J, et al. FVIIa corrects the coagulopathy of fulminant hepatic failure but may be associated with thrombosis: a report of four cases. Can J Anaesth. 2005;52(1): 26–9.
32. Porte RJ, Caldwell SH. The role of recombinant factor VIIa in liver transplantation. Liver Transpl. 2005;11(8):872–4.
33. Shami VM, Caldwell SH, Hespenheide EE, et al. Recombinant activated factor VII for coagulopathy in fulminant hepatic failure compared with conventional therapy. Liver Transpl. 2003;9(2):138–43.
34. Mayer SA, Brun NC, Begtrup K, et al. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. N Engl J Med. 2008;358(20):2127–37.
35. Munoz SJ, Ballas SK, Moritz MJ, et al. Perioperative management of fulminant and subfulminant hepatic failure with therapeutic plasmapheresis. Transplant Proc. 1989;21(3):3535–6.
36. Munoz SJ, Moritz MJ, Bell R, et al. Factors associated with severe intracranial hypertension in candidates for emergency liver transplantation. Transplantation. 1993;55(5):1071–4.
37. Robertson CS, Valadka AB, Hannay HJ, et al. Prevention of secondary ischemic insults after severe head injury. Crit Care Med. 1999;27(10):2086–95.
38. Contant CF, Valadka AB, Gopinath SP, et al. Adult respiratory distress syndrome: a complication of induced hypertension after severe head injury. J Neurosurg. 2001;95(4):560–8.
39. Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. IX. Cerebral perfusion thresholds. J Neurotrauma. 2007;24(Suppl 1):S59–64.
40. Aiyagari V, Deibert E, Diringer MN. Hypernatremia in the neurologic intensive care unit: how high is too high? J Crit Care. 2006;21(2):163–72.
41. Caraceni P, Van Thiel DH. Acute liver failure. Lancet. 1995; 345(8943):163–9.
42. Munoz SJ. Difficult management problems in fulminant hepatic failure. Semin Liver Dis. 1993;13(4):395–413.
43. Sen S, Rose C, Ytrebo LM, et al. Effect of albumin dialysis on intracranial pressure increase in pigs with acute liver failure: a randomized study. Crit Care Med. 2006;34(1):158–64.
44. Stravitz RT, Larsen FS. Therapeutic hypothermia for acute liver failure. Crit Care Med. 2009;37(7 Suppl):S258–64.
45. Jalan R. Pathophysiological basis of therapy of raised intracranial pressure in acute liver failure. Neurochem Int. 2005;47(1–2): 78–83.
46. Jalan R, Davies NA, Olde Damink SW. Hypothermia for the management of intracranial hypertension in acute liver failure. Metab Brain Dis. 2002;17(4):437–44.
47. Jalan R, Olde Damink SW. Hypothermia for the management of intracranial hypertension in acute liver failure. Curr Opin Crit Care. 2001;7(4):257–62.
48. Jalan R, Olde Damink SW, Deutz NE, et al. Moderate hypothermia prevents cerebral hyperemia and increase in intracranial pressure in patients undergoing liver transplantation for acute liver failure. Transplantation. 2003;75(12):2034–9.
49. Jalan R, Olde Damink SW, Deutz NE, et al. Restoration of cerebral blood flow autoregulation and reactivity to carbon dioxide in acute liver failure by moderate hypothermia. Hepatology. 2001;34(1):50–4.
50. Jalan R, Olde Damink SW, Deutz NE, et al. Moderate hypothermia in patients with acute liver failure and uncontrolled intracranial hypertension. Gastroenterology. 2004;127(5):1338–46.

51. Jalan R, Rose C. Hypothermia in acute liver failure. Metab Brain Dis. 2004;19(3–4):215–21.
52. Jalan R, OD SW, Deutz NE, et al. Moderate hypothermia for uncontrolled intracranial hypertension in acute liver failure. Lancet. 1999;354(9185):1164–8.
53. Stadlbauer V, Jalan R. Acute liver failure: liver support therapies. Curr Opin Crit Care. 2007;13(2):215–21.
54. Laffey JG, Kavanagh BP. Hypocapnia. N Engl J Med. 2002;347(1): 43–53.
55. Felipo V, Butterworth RF. Mitochondrial dysfunction in acute hyperammonemia. Neurochem Int. 2002;40(6):487–91.
56. Ellis AJ, Wendon JA, Williams R. Subclinical seizure activity and prophylactic phenytoin infusion in acute liver failure: a controlled clinical trial. Hepatology. 2000;32(3):536–41.
57. 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(1):89–96.
58. Claassen J, Mayer SA, Kowalski RG, et al. Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. Neurology. 2004;62(10):1743–8.
59. Towne AR, Waterhouse EJ, Boggs JG, et al. Prevalence of nonconvulsive status epilepticus in comatose patients. Neurology. 2000;54(2):340–5.
60. Oddo M, Carrera E, Claassen J, et al. Continuous electroencephalography in the medical intensive care unit. Crit Care Med. 2009;37(6):2051–6.
61. Lee WM, Hynan LS, Rossaro L, et al. Intravenous *N*-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. Gastroenterology. 2009;137(3):856–64. 864 e851.
62. McKenzie TJ, Lillegard JB, Nyberg SL. Artificial and bioartificial liver support. Semin Liver Dis. 2008;28(2):210–7.
63. Ferraz-Neto BH, Moraes-Junior JM, Hidalgo R, et al. Total hepatectomy and liver transplantation as a two-stage procedure for toxic liver: case reports. Transplant Proc. 2008;40(3):814–6.
64. Taylor RM, Davern T, Munoz S, et al. Fulminant hepatitis A virus infection in the United States: incidence, prognosis, and outcomes. Hepatology. 2006;44(6):1589–97.
65. Fontana RJ. Acute liver failure including acetaminophen overdose. Med Clin North Am. 2008;92(4):761–94. viii.
66. Mindikoglu AL, Magder LS, Regev A. Outcome of liver transplantation for drug-induced acute liver failure in the United States: analysis of the United Network for Organ Sharing database. Liver Transpl. 2009;15(7):719–29.
67. O'Grady JG, Alexander GJ, Hayllar KM, et al. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology. 1989; 97(2):439–45.
68. Freeman RB Jr, Wiesner RH, Harper A, et al. The new liver allocation system: moving toward evidence-based transplantation policy. Liver Transpl. 2002;8(9):851–8.
69. Kremers WK, van IJperen M, Kim WR, et al. MELD score as a predictor of pretransplant and posttransplant survival in OPTN/UNOS status 1 patients. Hepatology. 2004;39(3):764–9.
70. Schmidt LE, Larsen FS. MELD score as a predictor of liver failure and death in patients with acetaminophen-induced liver injury. Hepatology. 2007;45(3):789–96.
71. 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.
72. Katoonizadeh A, Decaestecker J, Wilmer A, et al. MELD score to predict outcome in adult patients with non-acetaminophen-induced acute liver failure. Liver Int. 2007;27(3):329–34.
73. 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.