



# Management of Acute Liver Failure: A Pediatric Perspective

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Published online: 15 May 2018

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## Abstract

**Purpose of Review** Pediatric acute liver failure is a rare, complex, rapidly progressing, and life-threatening illness. Majority of pediatric acute liver failures have unknown etiology. This review intends to discuss the current literature on the challenging aspects of management of acute liver failure.

**Recent Findings** Collaborative multidisciplinary approach for management of patients with pediatric acute liver failure with upfront involvement of transplant hepatologist and critical care specialists can improve outcomes of this fatal disease. Extensive but systematic diagnostic evaluation can help to identify etiology and guide management. Early referral to a transplant center with prompt liver transplant, if indicated, can lead to improved survival in these patients.

**Summary** Prompt identification and aggressive management of pediatric acute liver failure and related comorbidities can lead to increased transplant-free survival and improved post-transplant outcomes, thus decreasing mortality and morbidity associated with this potential fatal condition.

**Keywords** Acute liver failure · Pediatric · Multi-organ system failure · Hepatic encephalopathy · Coagulopathy · Liver transplantation

## Abbreviations

ALF	Acute liver failure
PALF	Pediatric acute liver failure
HE	Hepatic encephalopathy
ICH	Intracranial hypertension
CE	Cerebral edema
ICP	Intracranial pressure
CPP	Cerebral perfusion pressure
HTS	Hypertonic saline
CT	Computerized tomography
MRI	Magnetic resonance imaging
PT	Prothrombin time
INR	International normalized ratio
rFVIIa	Recombinant factor VIIa
SIRS	Systemic inflammatory response syndrome
SCr	Serum creatinine

RRT	Renal replacement therapy
CRRT	Continuous renal replacement therapy
LT	Liver transplantation
KCHC	King's College Hospital Criteria
MELD	Model for End-stage Liver Disease
SOFA	Sequential organ failure assessment
PELD	Pediatric End-stage Liver Disease

## Introduction

Acute liver failure (ALF) is a complex, uncommon illness which can rapidly progress to multisystem organ failure and death. It is characterized by acute hepatocellular injury or death, leading to rapid loss of hepatocellular function resulting in multisystem involvement and, eventually, failure. In adults, it was initially characterized by signs of severe hepatic dysfunction, including jaundice and coagulopathy, accompanied by development of hepatic encephalopathy within 8 weeks of onset of the signs and symptoms of liver disease [1]. The inability to assess the age-appropriate mental status and the exact duration of illness in children has made it challenging to apply this definition to children [2•, 3]. Pediatric acute liver failure (PALF) can be defined as:

This article is part of the Topical Collection on *Gastrology*

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- Biochemical evidence of acute liver injury in a child with no known evidence of chronic liver disease along with at least one of the following
- INR > 1.5, not corrected with vitamin K supplementation, with encephalopathy
- INR > 2.0, not corrected with vitamin K supplementation, without encephalopathy.

Pediatric ALF differs significantly from ALF in adults in both clinical presentation and etiologic spectrum. The diagnosis, evaluation, and management of this rare but complex syndrome require aggressive diagnostic evaluation along with close monitoring, anticipating, and managing the multisystem complications that happen secondary to ALF to prevent organ failure, transplantation, and death.

## Etiology and Diagnostic Evaluation

The incidence of ALF in children is largely unknown. ALF accounts for about 10–15% of pediatric liver transplants performed annually in the USA [4•]. Up to 40–50% of PALF is of indeterminate etiology, partly owing to a lack of thorough diagnostic evaluation [5, 6]. In infants, metabolic and infectious etiologies are more common, with herpes simplex virus being the most common infectious etiology [7]. In adolescents, drug-induced liver injury and autoimmune hepatitis are more common. In developing countries, infectious etiologies dominate with hepatitis A viral infection being the most common infection [5]. Acetaminophen overdose accounts for more than 75% of drug-induced ALF [3]. Diagnostic evaluation for the PALF should be tailored according to age of presentation (Table 1). Preference should be given to diagnosis of diseases that have targeted therapies, that are preventable in future, or where transplant would be contraindicated.

All children with ALF should undergo systematic evaluation for identification of a cause of liver failure along with assessment of liver injury and dysfunction. A comprehensive history with emphasis on onset of symptoms, changes in mental status, exposure to infectious contacts, blood transfusions, use of medications, and/or family history of liver disease, infant death, autoimmune conditions, and consanguinity should be obtained. Complete physical examination along with a thorough neurological status evaluation is vital. Laboratory evaluation of acute liver failure includes assessment of liver function and liver injury in addition to assessment of overall functioning of all the vital organs of the body. This would include a comprehensive metabolic panel, liver enzymes, total and fractionated bilirubin, gammaglutamyl transferase, prothrombin time with international normalized ratio, reliable serum ammonia level, and a complete blood count [8, 9]. Etiologic testing for age-appropriate causes of ALF should be tailored according to presentation of illness,

history, physical exam, and clinical course to optimize the amount of blood drawn and number of tests ordered [3, 8]. Ultrasound of the abdomen with Doppler should be a part of evaluation for all patients [9]. Further imaging studies like CT, MRI, and/or MRCP should be considered [2••]. Liver biopsy should be performed early in cases of unclear diagnosis, not only for assessment of etiology but also to help assess patient's prognosis. Trans-jugular approach should be used for liver biopsy in the setting significant coagulopathy to prevent complications. One should be cautious in interpreting the level of necrosis in liver biopsy specimens as injury may not be uniform throughout the liver [10]. (Table 1).

## Management

**Approach to Management** Management of PALF is challenging due to multi-organ system involvement necessitating multidisciplinary approach and potential for rapid deterioration. Patients with suspected PALF should undergo immediate evaluation. Close collaboration between pediatric hepatologist, intensivist, transplant surgeons, neurologist, nephrologist, and/or metabolic disease specialists is crucial. Pediatric patients demonstrating signs of worsening coagulopathy and/or altered mental status should be monitored in intensive care unit where frequent neurological, cardiorespiratory, and laboratory monitoring can be performed. Once the initial evaluation has been performed and patient has been stabilized, further patient management should be along the path of monitoring and supporting the patient and organ systems, identifying and treating complications, age-appropriate diagnostic evaluation, and optimizing treatment to maximize health and survival [3] (Table 2).

Intensive care unit plays a vital role by supporting the failing organs which in turn helps recovery as well as clinical stability for further interventions, if needed. Advances in critical care medicine and management strategies have contributed significantly towards decreasing mortality in ALF in adults [11]. Similar strategies should also be assessed to help improve outcomes in PALF [2••]. Early transfer to a transplant center is of utmost importance.

**Central Nervous System—Hepatic Encephalopathy and Cerebral Edema** Hepatic encephalopathy (HE) is a progressive but potentially reversible neuropsychiatric syndrome that occurs as a complication of liver failure. The clinical features of HE can range from subtle cognitive or motor deficits to irritability to overt cerebral edema leading to coma. Pathogenesis of hepatic encephalopathy is not completely understood. Hyperammonemia, increased cerebral blood flow, and augmented inflammatory response are pivotal in causing the increased intracranial pressure [12]. Glutamine is broken down into ammonia and glutamate by glutaminase in the enterocytes.

**Table 1** Causes of pediatric acute liver failure—age based with diagnostic evaluation

Age	Most common causes	Diagnostic evaluation
All patients	Idiopathic or indeterminate (incomplete evaluation)	Liver function tests: AST, ALT, GGT, alkaline phosphatase, fractionated bilirubin, albumin, total protein)
	Drug toxicity or ingestions	Coagulation factors and profile: PT-INR, aPTT, fibrinogen, factors V, VII, VIII
	Infectious causes	Serum ammonia level and blood gas
	Autoimmune hepatitis	Complete blood count with platelets and differential
	Metabolic causes	Complete metabolic panel including electrolytes, BUN, creatinine, blood glucose, calcium, magnesium and phosphorus
	Other causes	Imaging studies: ultrasound liver with Doppler study Tissue diagnosis: liver biopsy; muscle biopsy as indicated
Infants $\leq$ 1 year	Idiopathic or indeterminate	Viral PCR for EBV, CMV, enterovirus, adenovirus, HHV-6, HSV 1 and 2, parvovirus. Viral hepatitis serology including anti-HAV IgM, HBsAg, anti-HBe IgM and IgG, anti-HCV, and anti-HEV
	Infectious (HSV 1 and 2—most common, enterovirus, adenovirus, hepatitis B, hepatitis C, EBV, CMV, HHV 6, parvovirus, etc.)	
	Metabolic (fatty acid defects, mitochondrial defects, galactosemia, tyrosinemia, neonatal hemochromatosis, etc.)	Serum lactate, pyruvate, amino acid profile, carnitine profile, acyl-carnitine profile, ferritin, iron, TIBC; urine amino acid/organic acid profile, urine succinylacetone
	Other diseases—congenital heart defects, accidental drug overdose or ingestion	Serum acetaminophen level, urine toxicology screen
Pre-adolescent	Idiopathic or indeterminate	Serum acetaminophen level, urine toxicology screen
	Drug toxicity or accidental ingestion (acetaminophen, acetylsalicylic acid, valproic acid, etc.)	
	Metabolic diseases (Wilson's disease, fatty acid oxidation defects, mitochondrial defects, etc.)	As above, plus serum Ceruloplasmin and 24-hr urine copper.
	Infectious causes (hepatitis A, B, C, D, E, non-A, non-B viral hepatitis, EBV, CMV, enterovirus, adenovirus, HHV-6, parvovirus, etc.)	As above
	Autoimmune hepatitis	Antinuclear antibody, anti-smooth muscle antibody, anti-liver-kidney microsome antibody
Adolescent	Drug toxicity, toxin ingestion, accidental or intentional drug overdose (acetaminophen, tetracycline, ecstasy, toxic mushroom <i>Amanita phalloides</i> poisoning, etc.)	As above
	Autoimmune hepatitis	
	Wilson's disease and other metabolic diseases	
	Infectious diseases (hepatitis A, B, C, D, E, non-A, non-B viral hepatitis, EBV, CMV, etc.)	

HSV, herpes simplex virus; EBV, Epstein-Barr virus; CMV, cytomegalovirus; HHV-6, human herpesvirus 6; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma glutamyl transferase; PT-INR, prothrombin time and international normalized ratio; aPTT, activated partial thromboplastin time; PCR, polymerase chain reaction; HAV, hepatitis A virus; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HEV, hepatitis E virus; TIBC, total iron binding capacity

**Table 2** Complications in PALF

Organ system	Complications
Central nervous system	- Hepatic encephalopathy - Cerebral edema - Intracranial hypertension
Cardiovascular	- Hypotension secondary to intravascular volume depletion - Volume-refractory hyperdynamic circulatory failure
Respiratory	- Acute respiratory failure - Pulmonary edema - Pulmonary hemorrhage - Acute respiratory distress syndrome (ARDS) - Endotracheal intubation and mechanical ventilation-associated complications
Renal	- Acute kidney injury (AKI) - Hepatorenal syndrome
Adrenal	- Relative adrenal insufficiency (RAI) - Hepatoadrenal syndrome
Hematological	- Coagulopathy not corrected by Vitamin K administration - Disseminated intravascular coagulopathy (DIC)
Gastrointestinal	- Gastrointestinal bleeding
Infectious	- Systemic inflammatory response syndrome (SIRS) - Pulmonary, urinary, and hematologic infections with bacteria such as staphylococci, streptococci, and enteric gram-negative bacteria
Fluid, electrolytes, and nutrition	- Hypoglycemia - Hyperammonemia - Intravascular volume depletion - Alkalosis and acidosis - Hyponatremia - Hypokalemia - Hypophosphatemia, hypocalcemia, hypomagnesemia - Catabolic state with negative nitrogen balance and increased energy expenditure

This gut-derived ammonia then enters the urea cycle where it is detoxified and excreted by the kidneys. The ammonia that bypasses the urea cycle is then converted to glutamine in astrocytes, skeletal myocytes, and hepatocytes. Astrocytes, the predominant type of cells in the brain, are very sensitive to rapid increase in serum levels of ammonia which, in turn, cause increase in intracellular glutamine concentration, leading to increased osmotic gradient and influx of water into the astrocytes resulting in cerebral edema (CE) and, subsequently, intracranial hypertension (ICH) [2•, 13]. Plasma concentration of ammonia does not always consistently correlate with the clinical manifestations of HE [14]. Increase in circulatory pro-inflammatory cytokines, especially interleukin IL-1 $\beta$  and IL-6 and tumor necrosis factor, can cause changes to cerebral blood flow and endothelial permeability affecting the development of HE and CE [15]. The incidence of CE and ICH is partially related to the severity of hepatic encephalopathy. About 55% of children

developed HE in the PALF study group, 75% of which were grade 1 and 2 encephalopathies [3]. Grade 3 and 4 encephalopathies were observed in about 17 and 7% patients, respectively [3].

**Management of Hepatic Encephalopathy** Hepatic encephalopathy is managed with aggressive supportive care. Early diagnosis and prompt management of the same is critical to avoid progression to CE and ICH. Patients should be monitored closely with frequent neurological examinations. Patients should be minimally stimulated and unnecessary interventions should be avoided. Endotracheal intubation should be performed for airway protection and protected ventilation. Elevation of head end of the bed helps improve CSF drainage [16]. Fever and shivering may lead to increased intracranial pressure and should be treated aggressively. Lactulose and other antibiotics like rifaximin and

neomycin are commonly used ammonia-lowering strategies used to treat HE; however, data to support this use in ALF is currently lacking [17]. L-Ornithine L-aspartate (LOLA) and L-ornithine phenyl acetate (LOPA) are currently being studied for use as ammonia-lowering agents by increasing the renal excretion of the same. These have shown promising results in the adult STOP-ALF trial [18]; however, there is no data regarding their use in PALF. A recent cohort study on ALF patients in US ALF Study group registry demonstrated the benefit of continuous renal replacement therapy (CRRT) in reduction of serum ammonia and improvement in 21-day transplant-free survival [19].

**Management of Intracranial Hypertension and Cerebral Edema** The goal in management of intracranial hypertension (ICH) and cerebral edema (CE) is lowering intracranial pressure (ICP) while preserving cerebral perfusion pressure (CPP) [2•, 9]. Clinical monitoring can be very difficult in pediatric patients with grades III–IV of HE. Cushing's triad (irregular breathing, systemic hypertension, and bradycardia), a sign of ICH, is not uniformly present. Intracranial pressure monitoring allows assessment of CPP (difference between ICP and mean arterial pressure) which helps avoid hypoxic brain injury [9]. There have been multiple studies to assess safety and efficacy of invasive intracranial pressure monitoring. There has been no demonstrated improvement in survival with invasive intracranial pressure monitoring [20–22]. Invasive intracranial monitoring carries the risk of intracranial hemorrhage which can be fatal in these patients with coagulopathy [23]. The use of invasive ICP monitoring has not been studied in children and its use in PALF remains controversial. [2••].

Osmotic agents like hypertonic saline (HTS) and mannitol are amongst the principal therapies to reduce cerebral edema [24]. HTS (3–30%) reduces ICP by decreasing cerebral water content by its osmotic effect and improves cerebral blood flow by reducing endothelial swelling by dehydration [25]. As a result, HTS has now been accepted as standard of care in management of ICH in children with traumatic brain injury [26]. In an RCT from King's College, the patients who received HTS had decreased ICP from baseline in the first 24 h and incidence of ICP > 25 mmHg was also significantly lower when compared to standard care [27]. HTS has been studied and is currently recommended as a prophylactic agent to prevent ICP in adults at highest risk for cerebral edema [9]. Target serum sodium level should be maintained between 145 and 150 mmol/L [2•, 27]. HTS has not been studied as an agent to treat acute increase in ICP in ALF patients. HTS is associated with electrolyte abnormalities, hyperchloremic metabolic acidosis, worsening coagulopathy, deep venous thrombosis, and hemorrhages [25, 28, 29].

Mannitol has been used as a first-line agent to treat increased ICP in adults with ALF [9, 17]. Mannitol is a hyperosmolar agent and acts by increasing serum osmolality

which leads to movement of water from the swollen astrocytes into serum. The current recommendation is to administer 0.25–1.0 g/kg IV bolus, which can be repeated once or twice as long as serum osmolality remains less than 320 mOsm/L [9, 17]. Mannitol use has only been recommended for acute increase in ICP and it should not be used prophylactically [9]. Effect of mannitol is transient and it should not be used if serum osmolality is > 320 mOsm/L, or in the presence of hypovolemia, or renal failure. Volume overload can occur with mannitol and might necessitate dialysis [2••, 9, 17]. Most of the information on use of mannitol is extrapolated from adult literature, and there are no controlled trials to assess the same in PALF.

Neurological morbidity is a major predictor of outcome for patients with ALF. Early identification of declining neurological status will allow earlier therapeutic interventions and help minimize morbidity and mortality [2••]. Seizure activity increases cerebral oxygen requirements and in patients with ALF may worsen cerebral edema [30]. Hussain et al. [31•] reported the role of EEG in management of PALF in their single-center retrospective study consisting of 19 children. Clinical seizures occurred in about 11% of patients and subclinical seizures were found in about 5% of patients. There was increased mortality in patients with EEG findings of moderate to severe slowing, epileptiform discharge, and electrographic seizure [31•]. EEG maybe used as a sensitive tool to screen for declining neurological status or subclinical seizures especially for patients with grade III or IV encephalopathy or clinical deterioration [31•, 32]. Head imaging with computerized tomography (CT) scan has been frequently used in patients who progress to stage III/IV HE or in patients with acute change in mental status to rule out different causes like intracranial hemorrhage and infections [33]. In a recent pediatric study, CT and magnetic resonance imaging (MRI) were abnormal in 13% of the patients but failed to demonstrate consistent abnormalities indicating the presence of cerebral edema [31•]. Also, there was no association between EEG and CT/MRI findings in these patients [31•]. A small retrospective study in adults demonstrated promising results for the use of transcranial Doppler waveform to assess the state of cerebral perfusion [34]. Prophylactic phenytoin has been used in adults with ALF to suppress subclinical seizures [32] but no overt benefit has been demonstrated in prevention of cerebral edema, in prevention of seizures, or in improvement in survival [30]. There is insufficient pediatric data to support the use of prophylactic antiepileptic agents in management of PALF [2••].

Therapeutic hypothermia (32°–35°) has been shown to reduce cerebral edema by decreasing ammonia level, attenuating inflammation and oxidative stresses in brain, and restoration of normal regulation of cerebral hemodynamics [35, 36]. Multiple systemic side effects like increased risk of infection, electrolyte disturbances and cardiac dysrhythmias, and



coagulopathy have been associated with use of this modality of therapy [35, 36]. There have been studies demonstrating the use of hypothermia for successful bridging of adult ALF patients to liver transplantation [12]. There is also a conflicting study demonstrating no difference in 21-day mortality and transplant-free survival between patients who received therapeutic hypothermia and those who did not [37]. There is no data in PALF to support the use of therapeutic hypothermia; active normothermia (36°–37°), with aggressive management of hyperthermia, is the current standard of recommendation in management of PALF [2••].

Hyperventilation reduces intracranial pressure by causing vasoconstriction. According to the most recent AASLD guidelines for management of ALF, there is no role for prophylactic hyperventilation in these patients, but patients with ALF hyperventilate spontaneously and this should not be inhibited [9].

There is insufficient data regarding agents to be used for sedation and/or analgesia in PALF. In general, short-acting agents, with dose adjustments for drugs metabolized in the liver, are preferred. Level of sedation should be carefully considered with special attention to potential benefit of anxiolytics versus the risk of masking signs of neurological deterioration or exacerbating encephalopathy. Benzodiazepines can have protracted sedative effect and should be avoided [2••]. Recovery time from propofol is shorter and it may lower ICP by decreasing cerebral blood flow [38]. Propofol can be used in small doses for short periods in children without mitochondrial diseases [2••]. Concurrent use of opioid analgesics with short half-life, like fentanyl or remifentanyl, can help reduce the dose of anesthetics and improve cardiovascular stability [2••, 17]. Atracurium and cisatracurium are preferred agents for neuromuscular blockade in children with ALF [39]. Vecuronium and rocuronium should be avoided as they undergo hepatic metabolism [39].

**Cardiovascular** Acute liver failure leads to peripheral vasodilatory response secondary to elevated cytokine release. This is associated with low systemic vascular resistance and low mean arterial pressures which contribute to decreased peripheral tissue oxygenation and can contribute to multi-organ failure. Most patients with ALF present with depleted intravascular volume due decreased oral intake and transudation of fluid into the extra-vascular spaces. As with any other hemodynamically compromised patient, resuscitation should start with adequate volume replacement with intravenous normal saline in these patients [9]. If the patient continues to be hypotensive after adequate fluid resuscitation, vasoconstrictor medications should be initiated. In adults, norepinephrine has been the preferred agent as it best enhances peripheral organ perfusion while minimizing tachycardia and preserving splanchnic circulation [17]. Despite the lack of pediatric data, norepinephrine is the rational choice of vasoconstrictor in

volume-refractory hyperdynamic circulatory failure in PALF to ensure adequate central perfusion pressure (CPP) [2••]. Vasopressin and its analogs can be used to potentiate the effect of norepinephrine on patients who do not respond to the combination of volume challenge and norepinephrine [9].

**Respiratory** Patients with PALF may develop acute respiratory failure due to sepsis, pulmonary edema secondary to fluid overload, pulmonary hemorrhage, or acute respiratory distress syndrome (ARDS). About 20–30% of adult patients in ALF have been diagnosed with ARDS, but the incidence in PALF is unknown [40]. Endotracheal intubation may be required in PALF for acute respiratory failure resulting from abovementioned causes, or for airway protection subsequent to hepatic encephalopathy. About 40% of patients in the prospective PALF study required some type of ventilator support [41]. The strategies for mechanical ventilation in PALF must aim at balancing the risk of ventilator-associated lung injury and neuroprotection in the setting of increased ICP. It is suggested to maintain low tidal volumes and moderately elevated positive end expiratory pressure to maintain normal oxygenation [42]. Hyperventilation can be used in acute management of increased intracranial pressure not controlled with mannitol or other strategies mentioned above to delay impending cerebral herniation, but sustained hyperventilation should be avoided [9]. The standard of care in ventilating patients with increased ICP is maintaining normocapnia and avoiding hypoxemia.

**Renal** Acute kidney injury is a common occurrence in adults with ALF and has been associated with increased mortality. In a retrospective review of 1604 patients enrolled in Acute Liver Failure Study Group, 70% patients demonstrated some degree of kidney injury, and AKI was observed in 45% patients. Overall survival as well as transplant-free survival for patients with AKI was decreased compared to those without AKI (57 vs. 93% and 37 vs. 64% respectively) [43]. The exact incidence of AKI in PALF is unknown. It is estimated that 17.5% children with ALF have associated AKI. AKI is associated with increased risk of mortality independent of respiratory failure or cerebral edema [44]. In the prospective PALF study involving 348 children with PALF, approximately 10–20% of patients required hemofiltration support but incidence of AKI or renal failure was not specified [41].

Functional renal failure or acute kidney injury in ALF is multifactorial and related to intrarenal vasoconstriction leading to decreased renal perfusion—a mechanism similar to hepatorenal syndrome in chronic liver failure [2••]. Acetaminophen-induced kidney injury, nephrotoxic medications, hypovolemia, sepsis, and acute tubular necrosis form the most common causes of AKI in ALF [45, 46]. Serum creatinine (SCr), urine output, and fluid balance are most frequently used for assessment of renal function in children. The change in SCr over the baseline is more pertinent to estimating renal injury than a single SCr value [46, 47].

Prevention of hepatorenal syndrome is the focus of therapies used in management of AKI in PALF. These measures include adequate fluid resuscitation, avoiding excessive diuresis, avoiding volume overload, minimizing the use of nephrotoxic medications or intravenous contrast, and maintaining adequate renal perfusion pressure [9, 17, 45]. Patients with suspected prerenal azotemia should receive an intravenous fluid challenge, but volume overload can be detrimental in patients with ALF [2••]. The criteria for the use of renal replacement therapy (RRT) in PALF are ill-defined. CRRT has been shown to decrease serum ammonia levels and increase 21-day transplant-free survival in adults with ALF [19]. It can also prevent worsening acidosis and fluid overload. The degree of renal dysfunction, metabolic derangements, and electrolyte disturbances help make the decision to start RRT [2••]. Continuous forms of renal replacement therapy (hemofiltration or dialysis) are preferred over intermittent forms to avoid the hemodynamic instabilities and the risk of increased ICP associated with the later [9, 48].

AKI in PALF usually resolves with normalization of liver function or after liver transplantation (LT). Adult indications for simultaneous liver/kidney transplantation are based on degree and duration of renal failure/kidney injury and/or duration of renal replacement therapy, typically after 8 to 12 weeks of dialysis [49]. There is insufficient data to define indications for simultaneous liver/kidney transplant in children [50•, 51].

**Adrenal** Relative adrenal insufficiency (RAI) has been described in septic shock [52]. Impaired adrenal function in septic shock can depress the sensitivity to noradrenaline and this can be improved by administering physiologic doses of hydrocortisone [53]. Low HDL levels and increased levels of circulating endotoxins (i.e., lipopolysaccharides) and pro-inflammatory markers like tumor necrosis factor- $\alpha$  lead to impaired cortisol synthesis [54]. This leads to adrenal insufficiency in ALF, also known as hepatoadrenal syndrome. The incidence of hepatoadrenal syndrome correlates with severity of ALF [55]. Children with ALF are also at-risk for hepatoadrenal syndrome and vasopressor-dependent children in ALF may benefit from systemic corticosteroid administration [56, 57]. However, more research is required to make any definite recommendations. The consensus is that a trial of systemic steroids should be considered in patients with persistent shock resistant to both fluid resuscitation and vasopressor support [17].

**Fluid, Electrolytes, and Nutrition** Metabolic, electrolyte, and acid-base imbalances are common in PALF and need to be identified and corrected meticulously. ALF is a catabolic state with negative nitrogen balance with increased energy expenditure [58]. As a result, caloric requirements increase by about 20% in patients with ALF [58]. Unfortunately, due to lack of adequate studies, there are no clear guidelines on

nutritional support in ALF. Nutritional regimen in PALF should be tailored to provide adequate calories, glucose, and protein to overcome catabolism while maintaining euglycemia and preventing hyperammonemia. Most of the recommendations regarding formula choice are targeted at chronic liver diseases or liver cirrhosis [59]. Enteral nutrition with high caloric density feeds should be pursued whenever possible to avoid excess free water administration which may exacerbate cerebral edema [17]. Parenteral nutrition is a safe second-line option in patients in whom adequate nutrition cannot be provided with enteral feeding [60]. Branched-chain amino acids provide no additional benefit over standard amino acid solutions [61]. Intravenous lipid solutions are used as a source of calories but it is important to recognize that fat metabolism may be problematic in some disorders such as mitochondrial diseases [62].

Electrolyte and acid-base disturbances are common in patients with PALF. Frequent monitoring and prompt correction of these abnormalities are critical to improve morbidity and mortality in these patients. Continuous glucose infusion at rates as high as 10–15 mg/kg/min is necessary to maintain euglycemia in these patients [2••]. Both alkalosis and acidosis can occur. Sodium, potassium, phosphorus, calcium, and magnesium levels are frequently low and need to be corrected meticulously. Hyponatremia and hypokalemia can occur secondary to aggressive fluid resuscitation, ascites, and renal wasting with the use of diuretics. Avoiding hyponatremia is very critical to avoid worsening cerebral edema. [2••, 9].

**Hematology—Coagulopathy** INR > 1.5 with encephalopathy or INR > 2.0 without encephalopathy is required for diagnosis for ALF. Prolonged PT-INR is due to decrease in pro- and anticoagulant factors and is a marker for decreased synthetic function of the liver [2••]. Platelets can also be low in these patients. Despite these clinical abnormalities, clinically significant bleeding is only seen in < 5% of patients, and spontaneous intracranial bleeding happens in < 1% of patients [63]. Newer techniques like thromboelastography have been found to be better at assessing the risk of bleeding but are not widely available for regular use [64]. Vitamin K deficiency is present in about 18–24% of adults with ALF and administration of IV vitamin K is recommended [65]. Plasma and/or platelet transfusions have their own drawbacks like transfusion-related lung injury and volume overload in addition to masking the elevation of INR which is a prognostic marker in ALF. Replacement of these blood products is only recommended prior to invasive procedures or in the setting of hemorrhage [9]. However, plasma infusion might not be adequate to correct severe coagulopathy and might risk volume overload. Use of recombinant factor VIIa (rFVIIa) has been found to be transiently effective in managing the coagulopathy and facilitates performance of invasive procedures and management of spontaneous hemorrhage without increasing the risk of volume overload [66].

This may be especially important in the setting of renal insufficiency. However, rFVIIa should be used cautiously mainly due to its high cost and reports of serious thromboembolic events associated with its administration [67].

**Gastrointestinal** Clinically significant bleeding is rare even with the degree of coagulopathy in patients with ALF [63]. The AASLD guidelines recommend H2 blockers or proton pump inhibitors for prophylaxis of stress-induced acid-related gastrointestinal bleeding in ICU-admitted patients with ALF [9]. Ascites might develop in a small number of patients with ALF. Spironolactone is the diuretic of choice and diuresis should be used only in patients with respiratory compromise or discomfort due to fluid accumulation as aggressive diuresis can precipitate hepatorenal syndrome in these patients [3].

**Infections—SIRS** The liver is involved in a variety of different immune-related functions. Patients with acute liver failure can have defects in many different mechanisms of host defense, making them more susceptible to infections. In a retrospective study of 887 adults with ALF, about 10–80% patients experienced bacterial infections with 10–37% attributable mortality [68, 69]. In the same study, 56.8% patients demonstrated systemic inflammatory response syndrome (SIRS) [69]. The presence of one or more components of SIRS in patients with ALF was associated with increased mortality and worsening encephalopathy [69]. The magnitude of this was even greater when infection was present [69]. Data regarding SIRS or infection-related outcomes in PALF are currently lacking [2••].

The guidelines regarding use of prophylactic antimicrobials or antifungals remain unclear [9, 17]. There are several adult studies investigating the role of prophylactic antibiotics in ALF, but the results remain inconclusive [37, 68–70]. Lungs, followed by urinary tract and blood, are the most common sites of bacterial infection, and gram-positive cocci (*Staphylococci*, *Streptococci*) and enteric gram-negative bacilli are the commonly isolated organisms [68]. Urine and blood cultures as well as chest X-rays are of paramount importance in surveillance for these infections [2••]. Empiric antibiotics are indicated in the presence of SIRS, worsening encephalopathy, refractory hypotension, or signs of infection [17] (Table 3).

## Liver Transplantation

Liver transplantation offers a life-saving alternative to medical management in patients with PALF who have otherwise guarded prognosis. Timely liver transplantation has improved survival in patients with PALF. Currently, the indications and criteria for transplant are ill-defined

and the process of listing for transplantation in PALF has not been streamlined [2••]. Between 2013 and 2015, about 10% of all pediatric liver transplants performed in the USA were performed on patients with PALF [4•]. According to the AASLD practice guidelines for evaluation of the pediatric patient for liver transplantation, it is recommended to establish an etiology for PALF in order to recognize conditions that can be treatable without LT or are contraindicated for LT [71••]. Uncontrolled sepsis, irreversible cerebral edema with uncal herniation, and severe multisystem mitochondrial disease are some contraindications for LT in PALF [71••].

Several prognostic scoring systems like the King's College Hospital Criteria (KCHC) and the Model for End-Stage Liver Disease (MELD) score have been validated and are routinely used in adult patients [72, 73]. The sequential organ failure assessment (SOFA) score has been used as triage marker for liver injury but has not been sufficiently validated to allow decision making for transplantation [74]. KCHC has been extensively used in adults with ALF. PALF study group used their database to validate KCHC criteria in non-acetaminophen-induced PALF patients. The sensitivity and positive predictive value for use of KCHC in PALF were significantly lower than those in the original study and it did not reliably predict death in PALF [75]. The Pediatric End-stage Liver Disease (PELD) score, incorporating albumin, bilirubin, INR, growth failure, and age (< 1 year), has been used as a predictor of mortality in children with chronic liver disease listed for transplantation, but it has not been extensively studied for use in PALF [76]. Another pediatric scoring system, pediatric Liver Injury Unit (LIU) score, may prove to be a helpful dynamic tool for prediction of outcomes in PALF. It uses peak values of total bilirubin and PT/INR during hospitalization to assess the risk of death or need of liver transplantation in PALF [77, 78].

Liver transplantation for ALF is generally associated with poor outcome when compared to that for chronic liver disease. In SPLIT database, the 1-year patient survival after transplant was 74% for PALF compared to 88.2% of other conditions [79]. The factors predicting poor outcome following liver transplantation were age < 1 year, grade IV encephalopathy, and need for dialysis prior to transplantation [79]. In a single-center study involving 122 PALF patients from the University of California, Los Angeles, 1-, 5-, and 10-year patient survivals was 81, 77, and 73% respectively [80]. Poor renal function as indicated by low creatinine clearance and less than 7 days between onset of jaundice and encephalopathy were indicators for poor patient survival and low creatinine clearance, age less than 24 months, and PELD/MELD score greater than 25 were associated with increased graft loss [80].



**Table 3** Management of PALF

Problem	Management
Hyperammonemia	<ul style="list-style-type: none"> <li>- Consider lactulose and other antibiotics like rifaximin and neomycin (insufficient data to support use in ALF)</li> <li>- Ammonia-lowering agents like LOLA and LOPA are under investigation</li> </ul>
Hepatic encephalopathy	<ul style="list-style-type: none"> <li>- Consider continuous renal replacement therapy</li> <li>- Supportive care in ICU</li> <li>- Minimal stimulation; avoid unnecessary interventions</li> <li>- Endotracheal intubation especially for stage 3 or 4 encephalopathy</li> </ul>
Intracranial hypertension/cerebral edema	<ul style="list-style-type: none"> <li>- Consider CT/MRI head for any acute mental status changes</li> <li>- HTS (3–30%) to maintain target serum Na level to 145 to 150 mmol/L can be used as prophylaxis to prevent ICP and CE</li> <li>- Mannitol 0.25–1.0 g/kg IV bolus, repeated once or twice if serum osmolality &lt; 320 mOsm/L</li> <li>- Invasive intracranial monitoring is currently controversial and not routinely recommended in PALF</li> </ul>
Cardiovascular instability	<ul style="list-style-type: none"> <li>- Adequate fluid resuscitation with IV normal saline</li> <li>- Norepinephrine is the preferred choice of vasoconstrictor agent for volume-refractory instability</li> <li>- Vasopressin and its analogs can be used to potentiate the effect of norepinephrine</li> </ul>
Respiratory failure	<ul style="list-style-type: none"> <li>- Endotracheal intubation should be performed for respiratory failure or for airway protection in advanced stages of hepatic encephalopathy</li> <li>- Ventilator strategies include low tidal volumes (5–8 ml/kg of predicted weight) and moderately elevated PEEP levels</li> <li>- Sustained hyperventilation should be avoided</li> </ul>
Acute kidney injury/hepatorenal syndrome	<ul style="list-style-type: none"> <li>- Preventive measures include maintaining fluid balance while avoiding excessive diuresis, minimizing the use of nephrotoxic medications or IV contrast, and maintaining renal perfusion pressure</li> <li>- Continuous renal replacement therapy is preferred over intermittent forms</li> </ul>
Relative adrenal insufficiency/hepatoadrenal syndrome	<ul style="list-style-type: none"> <li>- Trial of systemic steroids can be considered in patients with persistent shock refractory to volume resuscitation and vasopressor support</li> </ul>
Coagulopathy	<ul style="list-style-type: none"> <li>- Plasma or platelet transfusions are only recommended prior to invasive procedure or during active bleeding</li> </ul>
Ascites	<ul style="list-style-type: none"> <li>- Spironolactone is the diuretic of choice for patients with ascites who have respiratory compromise or discomfort due to fluid accumulation</li> </ul>
Gastrointestinal bleed	<ul style="list-style-type: none"> <li>- H2 blocker or proton pump inhibitors are recommended for prophylaxis of gastrointestinal bleed</li> </ul>
Infection/SIRS	<ul style="list-style-type: none"> <li>- Use of prophylactic antimicrobials or antifungals is currently controversial and is not routinely recommended</li> <li>- Aggressive surveillance with cultures and empiric antibiotics are indicated in the presence of SIRS, worsening encephalopathy, refractory hypotension, or signs of infection</li> </ul>
Nutrition, hypoglycemia	<ul style="list-style-type: none"> <li>- Enteral nutrition with high caloric density formula to avoid excess free water</li> <li>- Parenteral nutrition can be a safe second line choice in patients who cannot be fed enterally</li> <li>- Continuous glucose infusion at 10–15 mg/kg/min might be necessary to maintain euglycemia in these patients</li> </ul>
Electrolytes	<ul style="list-style-type: none"> <li>- Frequent monitoring and correction of electrolytes and acid-base balance is critical</li> <li>- Avoiding hyponatremia is critical to prevent cerebral edema in these patients</li> </ul>

HTS, hypertonic saline; SIRS, systemic inflammatory response syndrome

**Conclusion** Management of PALF challenges our skills as physicians and intensivists. There have been promising improvements in outcomes over last few decades due to numerous recent advances in intensive care management of PALF. However, the current management of PALF still remains supportive and is either based on adult data and/or experience from local institutions. PALF remains poorly defined and incompletely studied due to its rarity and heterogeneity. Future studies designed by hepatologists and intensivists, and targeted towards improved etiological diagnosis, refined prognostic indicators, and potential for a medical cure, should be prioritized. Intensive supportive care, systematic diagnostic approach, and early transfer to

transplant center with timely liver transplantation are the current best approach to improve outcomes in patients with PALF.

### Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflicts of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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