https://doi.org/10.15360/1813-9779-2025-2-2532

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Intensive Care for Acute Liver Failure in Pediatric Practice (Review)

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For citation: *Georgy A. Avakyan, Yuri V. Bykov, Alexander N. Obedin.* Intensive Care for Acute Liver Failure in Pediatric Practice (Review). *Obshchaya Reanimatologiya = General Reanimatology.* 2025; 21 (2): 42–54. https://doi.org/10.15360/1813-9779-2025-2-2532 [In Russ. and Engl.]

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Summary

Acute liver failure (ALF) is a rare pathologic syndrome in pediatric practice with a high risk of multiple organ failure and death. Despite extensive research on risk factors and clinical manifestations, there are no standardized critical care protocols for ALF in children and adolescents. Anesthesiologists and intensivists face significant challenges in the diagnosis and prevention of ALF.

The aim of this review is to analyze the main triggers, etiology, pathogenesis, clinical manifestations and both specific and supportive treatment approaches for ALF in pediatric intensive care units.

The Cochrane Library, PubMed, Medscape and Library.ru databases were used to conduct a systematic search and analysis of the scientific literature using the keywords «acute liver failure, children and adolescents, hepatic encephalopathy, cerebral edema, extracorporeal methods, liver transplantation». A total of 81 sources were selected for review. Inclusion criteria were studies that described the pathogenesis, clinical manifestations, diagnosis and treatment of ALF in the pediatric intensive care unit. Exclusion criteria were studies that focused on the diagnosis and treatment of ALF in adult patients.

This review summarizes the most common etiologic factors and clinical presentations of ALF based on the child's age, as well as the diagnostic tools used in the pediatric intensive care unit. It also focuses on the primary supportive and disease-specific management strategies for ALF in the ICU, taking into account the unique physiological characteristics of pediatric patients.

Conclusion. Infectious and idiopathic causes are the most common etiologies of ALF, leading to hyperammonemia, inflammatory response, and hepatocyte death. The primary clinical manifestations of ALF in children vary with age and include jaundice, abdominal pain, nausea, vomiting, and encephalopathy. Specific treatment in the intensive care unit focuses on correcting fluid and electrolyte imbalances, administering antibacterial therapy, and providing enteral nutrition. Supportive therapy is aimed at stabilizing vital organ function, implementing extracorporeal treatment methods, and performing liver transplantation when indicated.

Keywords: acute liver failure; children and adolescents; hepatic encephalopathy; cerebral edema; extracorporeal methods; liver transplantation

Conflict of interest. The authors declare no conflict of interest.

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Introduction

Acute liver failure (ALF) is a rare condition in pediatric practice that can rapidly progress to multiple organ failure with fatal outcome [1–7]. It is characterized by acute hepatocellular injury in the absence of pre-existing liver disease [1, 2, 8, 9]. The exact incidence of ALF in children remains unknown, but is estimated to range from 1 to 10 cases per million people per year in all age groups (including adults), with a mortality rate of approximately 5–10% [1, 10–14]. Notably, ALF is observed more frequently in children aged 1 to 5 years than in other pediatric age groups [15].

In adults, ALF is defined by severe liver dysfunction manifested by jaundice and coagulopathy, accompanied by the development of hepatic encephalopathy (HE) within eight weeks of symptom onset [1]. However, among young children, challenges in accurately assessing mental status and establishing the precise duration of illness limit the applicability of this definition [1, 16].

A generally accepted definition of pediatric ALF was formulated in 1999, characterizing it as a «rare multisystem disorder characterized by severe hepatic dysfunction, with or without hepatic encephalopathy, associated with hepatocellular necrosis in the absence of pre-existing chronic liver disease» [2, 13, 17].

Biochemical criteria for the diagnosis of ALF in children should include at least one of the following [1, 4, 10]:

- An international normalized ratio (INR) >1.5 that is not corrected with vitamin K administration in the presence of hepatic encephalopathy (HE).
- An INR>2.0 that does not respond to vitamin K supplementation, even in the absence of HE.

Management of this rare yet complex syndrome requires a comprehensive diagnostic eval-

uation, as well as continuous monitoring, prognostication, and treatment of the multiple organ failure that often develops as a secondary complication of ALF [1, 6, 8]. Diagnostic criteria for ALF in children vary according to age and clinical presentation, necessitating pediatric-specific intensive care algorithms that differ from those used in adults [1, 2, 4, 9, 13].

The importance of this review is underscored by the rarity of ALF in the pediatric ICU and the limited awareness among anesthesiologists and intensivists regarding emergency management strategies for this patient population.

The aim of this review is to examine the major triggers, etiopathogenesis, clinical manifestations, and both specific and supportive treatment approaches for ALF in pediatric intensive care practice.

Materials and Methods

A systematic search and analysis of the scientific literature was performed using the Cochrane Library, PubMed, Medscape, and Library.ru databases. The search was conducted using the following keywords: «acute liver failure, children and adolescents, hepatic encephalopathy, brain edema, extracorporeal therapies, liver transplantation».

The search yielded 350 publications from international and national journals published between 2014 and 2024. Studies were included in the review if they provided data on the pathogenesis, clinical presentation, diagnosis, and treatment strategies in pediatric intensive care. Articles that focused on the clinical characteristics, diagnosis, and ICU management of adult patients were excluded. After screening, 81 studies directly related to the objectives of this review were selected for analysis.

Etiology and Pathogenesis

Acute liver failure in children and adolescents is a potentially life-threatening condition caused by a variety of factors, making its accurate diagnosis and treatment difficult [10, 18]. The etiology of ALF varies depending on the child's age, geographic region, and socioeconomic status [17, 19]. Infectious causes are the most common etiology of ALF in developing countries, whereas undetermined causes are more common in Europe and North America [13, 15, 19–22].

In neonates, ALF may result from conditions such as gestational alloimmune liver disease, herpes simplex virus infection, and metabolic disorders [21, 22]. In adolescents, common causes include drug-induced liver injury (with acetaminophen overdose accounting for over 75% of ALF cases), ingestion of toxic Amanita phalloides mushrooms, herbal and dietary supplements, and autoimmune diseases [1, 2, 9, 15, 23].

Certain causes of ALF are specific to the pediatric population. These include metabolic disorders such as type 1 tyrosinemia, mitochondrial cytopathies, galactosemia, hereditary fructose intolerance, and genetic disorders such as neonatal hemochromatosis [7]. In addition, autoimmune hepatitis, acute leukemia, Wilson's disease, and Reye's syndrome are well recognized causes of pediatric ALF [7, 17].

Despite diagnostic advances, a substantial proportion of ALF cases (35–45%) remain of unknown etiology (indeterminate ALF), particularly in children aged 1 to 5 years [4, 9, 10, 17, 24–27].

Despite the diverse etiology of pediatric acute liver failure (PALF), the underlying mechanisms of hepatocellular injury and regeneration share common pathways regardless of the initiating factor. The interplay between innate and adaptive immune mechanisms plays a central role in this process [17]. Damage to individual hepatocytes triggers an integrated stress response (ISR), leading to increased activation of caspases and NF-κB, as well as Fas ligation [28, 29].

The pathophysiological cascade underlying ALF is primarily driven by two key mechanisms [30]. The first is the development of hyperammonemia due to the inability of the liver to produce urea [30, 31]. The second mechanism is hepatocyte necrosis, which results in the release of large amounts of degradation proteins such as damage-associated molecular patterns (DAMPs), including DNA and RNA fragments, S-100 proteins, hyaluronan, and purine metabolites [30].

This release of DAMPs triggers a proinflammatory response in intrahepatic macrophages, leading to systemic circulation of these molecules, which in turn activate monocytes and macrophages, resulting in further secretion of proinflammatory cytokines [30]. The excessive accumulation of DAMPs contributes to a clinical syndrome similar to septic shock, which is exacerbated by severe HE and cerebral edema (CE) [32].

Clinical Manifestations

The clinical presentation of PALF is highly variable and often atypical [3]. Symptoms vary depending on the underlying cause and the age of the child [33–35]. The most common signs include jaundice, abdominal pain, nausea, vomiting, and generalized weakness [10, 15].

In newborns, the clinical presentation is closely related to the etiology of neonatal liver failure, so that early symptoms are nonspecific and often limited to changes in general condition such as lethargy, weight loss, and vomiting [33–35]. Jaundice is not always present, especially in cases of inborn errors of metabolism [33–35]. Hepatic encephalopathy, which may manifest as behavioral changes such as irritability and sleep-wake disturbances, typically

occurs in later stages and is particularly difficult to diagnose in newborns [33–35]. Seizures may indicate meningoencephalitic brain involvement or be associated with hypoglycemia [33–35]. Hepatomegaly is common in neonatal ALF, whereas splenomegaly and ascites are uncommon [33–35].

In infants and older children, ALF often begins with a prodromal phase characterized by malaise, nausea, and anorexia [33–35]. Jaundice is a common sequela, but may be absent, particularly in the presence of metabolic disorders or toxic liver injury, making clinical diagnosis difficult [33–35]. Other signs include hepatomegaly, ascites, and cerebral edema (CE) [36]. While ascites is more typical of chronic liver disease, it can occasionally be seen in ALF, particularly in Budd-Chiari syndrome [36]. A characteristic hepatic odor on breath may be subtle or absent [33, 36].

Coagulopathy is a characteristic feature of ALF [37]. Although spontaneous bleeding may occur, primarily in the gastrointestinal tract [33–35], clinically significant bleeding is observed in less than 5% of patients, and spontaneous intracranial hemorrhage is diagnosed in less than 1% of children [37, 38]. Severe hypoglycemia is common and can lead to seizures if left untreated [33–35].

HE in children is classified into four stages [33]:

- Stage 1: Behavioral changes without altered consciousness, along with sleep disturbances (sleepiness, insomnia, or disrupted sleep-wake cycles in neonates).
- Stage 2: Disorientation, marked drowsiness, and inappropriate behavior.
- Stage 3: Stupor with weak response to pain and auditory stimuli.
- Stage 4: Coma with decorticate posturing [33].

HE may be absent despite severe liver dysfunction or may develop over hours, days, or weeks after the onset of ALF [33–35].

The most common cause of mortality in ALF is CE, which leads to intracranial hypertension (ICH) and ischemic brain injury [37]. Triggers of CE include hypoxia, systemic hypotension, and decreased cerebral perfusion pressure, all of which result from increased ammonia levels and excessive glutamine production in the brain [37]. Pathologic pupillary reflexes, muscle rigidity, and decerebrate posturing indicate the presence of ICH [37]. ALF often results in multisystem organ dysfunction, with acute kidney injury (AKI) and acute respiratory failure (ARF) being among the most common early complications [36].

The major complications of ALF in children and adolescents are summarized in Table.

Diagnosis

All children suspected of having ALF must undergo an immediate evaluation to determine the underlying cause and assess the severity of liver injury and dysfunction [1, 39]. A thorough history should be obtained, focusing on the onset of hepatic symptoms, changes in mental status, exposure to infectious agents, blood transfusions, medication use, and any family history of liver or autoimmune disease [1]. A comprehensive physical examination, including a detailed neurological assessment, is essential [1].

CBC, absolute platelet count, prothrombin time (PT) with international normalized ratio (INR), coagulation factors V and VII, blood glucose, and serum electrolytes (potassium, sodium, calcium, and phosphate) should be checked every 12 hours [37, 40]. Serum bilirubin, AST/ALT, alkaline phosphatase, albumin, and globulin should also be assessed routinely [37, 40]. Blood and urine cultures and chest radiography are essential to identify potential sources of infection [37, 39, 40]. Cranial computed tomography (CT) should be performed in children with grade 3–4 HE to exclude intracranial hemorrhage and CE [37]. Continuous monitoring of clinical and biochemical parameters is necessary until the child's condition stabilizes [41].

Recommended monitoring includes

1. Continuous monitoring of hemoglobin oxygen saturation (SpO_2).
2. Assessment of vital signs (respiratory rate, heart rate, blood pressure) every 4 hours; more frequently in hemodynamically unstable children.

Table. Common complications of acute liver failure (ALF) in children [2].

System	Complications
Brain	• Hepatic encephalopathy • Cerebral edema
Blood	• Coagulopathy • Aplastic anemia
Gastrointestinal	• Ascites • Gastrointestinal bleeding • Pancreatitis
Urinary	• Hypovolemia • Hepatorenal syndrome
Metabolic	• Hypokalemia, hypophosphatemia, hypoglycemia • Acid-base disorders
Immune	• Bacterial infection and sepsis
Cardiovascular	• Pulmonary edema • Hypovolemia • Shock

3. Hourly neurological examination for 12 hours, including assessment of consciousness level.

4. Regular monitoring of electrolytes, glucose levels, and arterial blood gas analysis.

5. Daily coagulation studies and complete blood count.

6. Daily liver size measurements (palpation and ultrasonography).

7. Twice weekly monitoring of cholesterol, urea, creatinine, calcium, and phosphate levels.

Intensive Therapy

The management of PALF is complex due to the risk of multi-organ dysfunction and requires a multidisciplinary approach [1]. Close collaboration between anesthesiologists, intensivists, pediatricians, hepatologists, neurologists, nephrologists, and hematologists is essential [1].

Children with worsening coagulopathy and/or altered mental status must be admitted to the ICU for continuous neurological, cardiorespiratory, and laboratory monitoring, as PALF can deteriorate rapidly [1, 39, 42]. ICU admission is indicated if INR >1.5 with evidence of HE or if INR >4 without HE [40].

After initial assessment and stabilization, management should focus on the identification and treatment of complications [23, 36]. Venous access is required for fluid administration, acid-base balance correction, and electrolyte maintenance [37, 41]. If consciousness deteriorates to coma, endotracheal intubation should be performed to protect the airway and prevent aspiration [37].

Fluid Therapy and Electrolyte Correction

Metabolic, electrolyte, and acid-base disturbances are common in PALF and require careful monitoring and correction [1, 39, 43]. Fluid support is essential for patients who are unable to receive adequate enteral nutrition [44]. Intravenous fluid therapy should be started at ¾ of the calculated daily requirement to prevent fluid overload [40, 41, 45]. Overhydration can lead to pulmonary edema, ascites, and CE, while underhydration increases the risk of hepatorenal syndrome, acute tubular necrosis, worsening HE, and arterial hypotension [45].

Balanced crystalloids are the preferred fluid choice for ALF [44]. The initial fluid solution in hemodynamically stable patients consists of 10% glucose with sodium (0.5–1.0 mmol/kg) and potassium (2–3 mmol/kg) [40, 45]. Lactated Ringer's solution should be avoided as it may worsen lactic acidosis and contribute to CE [40].

Hypoglycemia occurs due to impaired glycogenolysis and gluconeogenesis and requires continuous glucose infusion at a rate of 10–15 mg/kg/min [37, 39, 45, 46]. Intravenous lipid emulsions can be used for caloric support, but fat metabolism may be impaired in certain conditions that lead to ALF (e. g., mitochondrial diseases) [47].

Plasma concentrations of sodium, potassium, phosphate, calcium, and magnesium are often low and require careful correction [1]. Hyponatremia and hypokalemia may occur as a result of aggressive fluid therapy, ascites, and AKI when diuretics are used [1, 39]. It is very important to avoid hyponatremia to avoid exacerbation of CE [39]. Serum phosphate levels should be monitored and corrected as hypophosphatemia can be severe [37, 45, 48].

Severe symptomatic cases of hypophosphatemia require intravenous administration of *P* when the serum level is <1.0 mg/dL (or <0.32 mmol/L); oral preparations should be started when the serum phosphate exceeds 2.0 mg/dL (or 0.48 mmol/L).

Sodium phosphate and potassium phosphate preparations with an equivalent phosphate content of 0.011 g/mL are commonly used according to the following scheme [37, 45, 48]:

— If serum P < 1.0 mg/dL: 0.6 mmol/kg intravenously over 6 hours;

— If serum P 1.0–1.7 mg/dL: 0.4 mmol/kg intravenously over 6 hours;

— If serum P 1.7–2.2 mg/dL: 0.2 mmol/kg intravenously over 6 hours.

Hypocalcemia and hypomagnesemia are common in ALF and require timely correction [39]. For hypocalcemia, oral calcium supplementation is indicated for mild cases (asymptomatic, with serum calcium >1.9 mmol/L), whereas intravenous administration of calcium gluconate is required for severe cases (serum calcium <1.9 mmol/L) [39]. Hypomagnesemia should be treated with slow intravenous infusion of magnesium sulfate (25% $MgSO_4$) administered under close clinical and hemodynamic monitoring. In pediatric patients, the recommended dose of 25% $MgSO_4$ is 25–50 mg/kg (0.2–0.4 mEq/kg), with a maximum single dose of 2 g administered over 1–5 minutes [39].

Enteral Nutrition

ALF is a hypercatabolic state characterized by negative nitrogen balance and increased caloric expenditure, which increases energy requirements in children by approximately 20% [43]. The goals of enteral nutrition in ALF include providing adequate calories to limit protein catabolism, maintaining euglycemia, and ensuring adequate protein delivery without inducing hyperammonemia [1, 39]. However, the lack of randomized controlled trials (RCTs) has resulted in the absence of standardized, evidence-based nutritional guidelines for pediatric ALF. Instead, most nutritional protocols are based on approaches used in the management of chronic liver disease or cirrhosis [1, 49, 50].

To reduce complications such as CE, enteral nutrition should utilize high-calorie formulas that minimize the administration of free water. Recommended daily caloric intake targets are 50–80 kcal/kg/day for older children and 120–160 kcal/kg/day for neonates and infants less than one year of age [40, 49, 51]. When selecting enteral formulas for patients with ALF, products such as Nutrien Hepa are beneficial. These formulas contain medium-chain triglycerides (MCTs), which are efficiently metabolized without storage in adipose tissue or accumulation in the liver [52].

The target blood glucose concentration during enteral nutrition should be maintained between 110–130 mg/dL [40]. Children should receive approximately 1.5–1.9 g/kg of protein per day, while neonates of normal birth weight require 3.0–3.3 g/kg/day [40].

Antibacterial Therapy

Recommendations for the prophylactic use of antibacterial agents in children and adolescents with ALF remain uncertain [51]. Several RCTs in adults have examined the role of prophylactic antibiotics in liver failure, but the results remain inconclusive [53]. The lungs and kidneys are the most common sites of bacterial infection, with gram-positive cocci (staphylococci, streptococci) and gram-negative enterobacteria being the most commonly isolated pathogens [54]. Empiric therapy with broad-spectrum antibiotics is indicated in children with sepsis or worsening HE [37, 51].

Anesthetics and Muscular Blocking Agents

Sedatives, analgesics, and neuromuscular blocking agents are important components of the intensive care management of children with ALF in the ICU, especially if mechanical ventilation is required [39]. Data on pharmacologic agents that can be used for sedation and/or analgesia in children with ALF are limited, but drugs with short duration of action are preferred [1, 39]. The use of sedatives in agitated, spontaneously breathing children with ALF should be carefully considered, balancing the potential benefits of reducing agitation with tranquilizers against the risk of worsening HE [1, 39].

Benzodiazepines and propofol may worsen encephalopathy by increasing gamma-aminobutyric acid (GABA) neurotransmission in the brain [1, 39]. In addition, benzodiazepines may have prolonged sedative effects in the setting of impaired liver function and should be avoided [39]. Recovery time in children after propofol administration is significantly shorter than with benzodiazepines, and propofol may provide some neuroprotection by reducing cerebral blood flow and intracranial pressure [1, 39, 55]. Concomitant use of opioid analgesics may reduce the required anesthetic doses [1, 39]. Opioid analgesics with a shorter half-life, such as fentanyl or remifentanil, are preferred [39]. If neuromuscular blockade is used, vecuronium and rocuronium should be avoided as they are metabolized in the liver [56]. Atracurium and cisatracurium are the preferred neuromuscular blockers in children with ALF on mechanical ventilation because of their short duration of action [56].

Symptomatic Therapy and Correction of Brain Dysfunction

Cerebral dysfunction is the most important predictor of outcome in PALF [1]. Early recognition of neurological deterioration allows timely initiation of intensive therapy and minimizes mortality [1]. Seizures increase cerebral oxygen demand and may exacerbate CE in children with ALF [41]. Phenytoin has been used in adults with ALF to control seizures, but no clear benefit of its use in preventing BE has been demonstrated [37, 41].

Hepatic Encephalopathy

Early diagnosis and intensive therapy in ALF are crucial to prevent the onset and progression of HE [1, 39]. It is necessary to perform frequent neurological examinations and to minimize the influence of exogenous noise and pain factors [1, 39]. Children with HE greater than grade 2 should undergo endotracheal intubation for airway protection due to decreased level of consciousness and assisted ventilation. [1, 37, 39]. Elevating the head of the bed by 20–30° helps improve CSF drainage [1, 37, 39]. Fever and chills can lead to increased intracranial pressure and should be treated promptly, avoiding the prescription of acetaminophen, which is hepatotoxic [1, 39]. The use of antibiotics such as rifaximin and neomycin is a widely used strategy to reduce ammonia production in the treatment of HE, but RCTs confirming their efficacy in PALF are currently lacking [46, 51]. In HE, rifaximin is given at a dose of 400 mg every 8 hours to children over 12 years of age [57]. Lactulose is given at a dose of 0.3–0.4 ml/kg orally or rectally 3–4 times/day for the treatment of HE; alternatively, lactilol 30–40 g/day or sodium benzoate at a dose of 250 mg/kg/day may be used [40]. L-ornithine-l-aspartate (LOLA) and l-ornithine-phenylacetate (LOPA), as major components of ammonia deamination, are currently being investigated for use as agents to reduce ammonia production in ALF [1]. Promising results have been reported in an adult study [51]; however, there are no data on their use in PALF [58].

Intracranial Hypertension and Cerebral Edema

The goal in the treatment of ICH and CE is to reduce ICP while maintaining cerebral perfusion

pressure (the difference between ICP and mean arterial pressure), which helps prevent hypoxic brain injury [1]. Osmotic agents such as mannitol and hypertonic saline (HS) are among the primary treatments for CE [1, 37, 59]. Mannitol is used as a first-line treatment for elevated ICP in children with ALF [1, 46]. It works by increasing serum osmolality, thereby facilitating the passage of water from neurons into the bloodstream [1, 39]. Mannitol also reduces blood viscosity, resulting in vasoconstriction and a decrease in cerebral blood volume [39]. The drug is recommended to be administered intravenously as a bolus at a dose of 0.25–1.0 g/kg, with the possibility of one or two repeated doses as long as serum osmolality remains below 320 mOsm/L [1, 46]. In children, it is recommended only for acute ICP elevation and should not be used prophylactically [1, 39]. Most information on the use of mannitol has been extrapolated from the adult literature, and there are no RCTs evaluating its efficacy in PALF [1, 39].

HS (3-30%) is a second-line agent that reduces intracranial pressure by decreasing brain water content via an osmotic effect and improves cerebral blood flow by reducing edema [39, 60, 61]. The advantages of HS include an increase in serum osmolarity without the hemodynamic side effects observed with the use of mannitol [39]. A 3% HS is administered at a dose of 2–6 mL/kg, followed by 0.1–1.0 mL/kg/hour (administration should be stopped if serum sodium concentration exceeds 155 mOsm/L or osmolality exceeds 360 mOsm/L) [40, 62]. HS has been studied as a therapeutic agent to prevent elevated intracranial pressure in adult patients with ALF; however, its use as a treatment for elevated ICP in this disease has not been studied in children [39, 63, 64]. Importantly, HS administration is associated with electrolyte imbalance, hyperchloremic metabolic acidosis, worsening coagulopathy, deep vein thrombosis, and increased risk of bleeding [61].

Management of Cardiovascular Dysfunction

ALF is associated with elevated cytokine levels leading to hyperdynamic circulatory failure [39]. In most cases, peripheral vasodilation develops, often accompanied by low mean arterial pressure (MAP) [39]. The first-line treatment for relative hypovolemia is to restore adequate intravascular volume by fluid resuscitation [39]. In cases of massive blood loss, transfusion of blood components is indicated [45]. If arterial hypotension persists despite adequate fluid resuscitation, vasopressor therapy should be initiated [1, 39].

Vasopressors are essential to maintain MAP within or above the physiologic range to ensure adequate renal and cerebral perfusion [37]. In adults, norepinephrine is the preferred agent because it optimally improves peripheral organ perfusion while minimizing tachycardia and preserving splanchnic circulation [51]. Although RCTs in PALF are lacking, norepinephrine is considered a rational first-line vasopressor in volume-refractory hyperdynamic circulatory failure because it helps maintain adequate central perfusion pressure in children [1, 39, 46].

Vasopressin and its analogues may be used as adjunctive therapy in children who do not respond to norepinephrine and fluid resuscitation. If the norepinephrine infusion exceeds 3 μg/kg/min without achieving the target MAP, vasopressin may be started at 0.0001 IU/kg/min to augment the pressor effect [1, 40].

Focused cardiac ultrasound is a valuable tool for rapid assessment of myocardial function, particularly in the evaluation of cardiac output and diagnosis of fluid overload in hemodynamically unstable pediatric patients. This method can be integrated with clinical assessment to differentiate the etiology of shock and guide decisions regarding fluid administration, vasopressor use, inotropic support, and other therapeutic interventions [65].

Management of Respiratory Dysfunction

Children with ALF may develop acute respiratory failure (ARF) due to sepsis, fluid overload-induced pulmonary edema, pulmonary hemorrhage, or acute respiratory distress syndrome (ARDS) [1, 37, 39]. Endotracheal intubation and mechanical ventilation (MV) may be required in ALF-associated ARF due to these causes or to protect the airway in cases of progressive HE [66].

Ventilation strategies in ALF should be both lung and neuroprotective, especially in the presence of elevated ICP [39]. The standard of care for ventilated pediatric patients with elevated ICP includes maintaining normocapnia and preventing hypoxemia [1]. Low tidal volumes (3–6 mL/kg) and moderately elevated positive end-expiratory pressure (PEEP>6 cm H_2O) are recommended to maintain adequate oxygenation (SpO_2>94%) [39, 40]. Excessively high levels of PEEP may increase intrahepatic and intracranial pressures, so minimally effective PEEP should be used to achieve adequate oxygenation [5, 40].

Hyperventilation may be used as an emergency measure to reduce elevated ICP refractory to mannitol therapy. However, prolonged hyperventilation should be avoided in pediatric patients due to its potential adverse effects [1, 39].

Management of Renal Dysfunction

Acute kidney injury (AKI) in the setting of ALF may develop due to hypovolemia, acute tubular necrosis, or hepatorenal syndrome [37]. Preventive strategies focus on maintaining adequate fluid balance, avoiding volume overload, minimizing the

use of nephrotoxic drugs or intravenous contrast, and ensuring optimal renal perfusion pressure [1, 67]. Renal replacement therapy (RRT) is considered an important intervention in patients awaiting liver transplantation (LT) [37]. However, the criteria for initiating RRT in pediatric ALF remain poorly defined [68, 69]. Continuous RRT is generally preferred to intermittent hemodialysis in critically ill patients because it minimizes hemodynamic instability and reduces the risk of ICP elevation [1, 37]. The decision to initiate RRT in children and adolescents is based on the severity of renal impairment and associated metabolic and electrolyte imbalances [1]. AKI typically resolves either after RRT when liver function is restored or after LT [70–72].

Management of Hematologic Disorders

In ALF, hepatic synthesis of coagulation factors (II, V, VII, IX, and X) is impaired, leading to fibrinolytic abnormalities and hemostasis disorders [73]. Correction of hemodynamic disorders should be guided by clear clinical indications, taking into account not only standard coagulation tests but also thromboelastography (TEG) or rotational thromboelastometry (ROTEM) parameters [74].

There are only two scenarios that require active correction of coagulopathy and thrombocytopenia. First, if ICP monitoring is required, the administration of fresh frozen plasma (FFP), cryoprecipitate, and platelets should be considered based on the degree of coagulopathy. Second, if there is significant active bleeding, coagulation abnormalities must be corrected in addition to local hemostatic measures to control the source of bleeding [75].

Routine correction of coagulopathy in PALF is not recommended except in cases of active bleeding or before invasive procedures [1, 33, 37, 76]. Transfusion of platelets, FFP, and cryoprecipitate may be used when indicated [33, 37].

FFP is given at a dose of 15–20 mL/kg every 6 hours or 3–5 mL/kg/hour intravenously in cases of bleeding [40]. However, FFP infusion alone may not be sufficient to correct severe coagulopathy and carries the risk of fluid overload [1]. Recombinant factor VIIa (80 mcg/kg) is recommended when FFP fails to normalize PT INR to acceptable levels or when volume overload is a concern [40, 77]. It is important to note that administration of recombinant factor VIIa increases the risk of thrombosis [37].

Platelet transfusion is indicated when the platelet count falls below 50,000/mm³ before an invasive procedure or prophylactically when the platelet count falls below 20,000/mm³ [40]. Vitamin K is used to correct coagulopathy at a dose of 0.2 mg/kg intravenously (maximum dose 10 mg) [33, 40].

FFP and/or platelet transfusions carry risks, including transfusion-related lung injury (TRALI) and volume overload, and may mask a rising INR, which is an important prognostic marker in ALF [1]. Thromboelastography is considered a superior method to assess bleeding risk in ALF, but its routine use in pediatric patients remains limited due to availability issues [78].

Gastrointestinal Management

The use of H_2-receptor antagonists or proton pump inhibitors (PPIs) is recommended for the prevention of stress-induced gastrointestinal bleeding in children with ALF admitted to the ICU [1, 33, 37]. Sucralfate (10–15 mg/kg orally every 6 hours) or omeprazole (10 mg/kg twice daily) are preferred for prophylaxis of gastric bleeding [33, 40].

A small proportion of children with ALF may develop ascites, for which spironolactone is the diuretic of choice [66].

Specific Treatment Based on ALF Etiology

For children with ALF due to acetaminophen toxicity, activated charcoal and prompt administration of N-acetylcysteine (NAC) are indicated [37, 40]. The oral NAC regimen consists of a loading dose of 140 mg/kg followed by 70 mg/kg every 4 hours for 17 doses [40]. The intravenous NAC protocol includes an initial dose of 150 mg/kg diluted in 200 mL 5% dextrose infused over 15 minutes, followed by 50 mg/kg over the next 4 hours and 100 mg/kg over the next 15 hours [40].

Patients with suspected Amanita phalloides mushroom poisoning require gastric lavage, activated charcoal, and intravenous penicillin-G at a dose of 1 g/kg/day [37].

For ALF associated with hepatitis A or E, supportive care remains the mainstay of treatment, as specific antiviral therapies have not been established [37, 40]. Patients with acute or reactivated hepatitis B should receive nucleotide analogues (entecavir or tenofovir) for at least six months [37, 40]. Children with suspected autoimmune hepatitis should be treated with intravenous methylprednisolone at a dose of 60 mg/day [37, 40].

For chronic hepatitis E, interferon and ribavirin therapy may be considered [40]. Children with herpes simplex virus (HSV) hepatitis or ALF caused by varicella-zoster virus (VZV) should receive intravenous acyclovir at a dose of 5–10 mg/kg every 8 hours [37]. Patients with cytomegalovirus (CMV)-induced hepatitis should be treated with intravenous ganciclovir at a dose of 5 mg/kg every 12 hours [37, 40].

Extracorporeal Treatment Modalities

Several extracorporeal liver support systems have been studied in pediatric patients with ALF to determine their potential impact on clinical outcomes [45]. These methods include albumin dialysis, plasmapheresis, bioartificial liver support

systems (using human hepatoblastoma cells), and molecular adsorbent recirculation systems (MARS), each of which has demonstrated varying degrees of efficacy [79–81].

In adult patients with ALF, high-volume plasma exchange (HVPE) has been shown to exert beneficial effects by removing hepatotoxic substances from the circulation while enhancing liver regeneration [30, 82]. However, data on its efficacy in pediatric ALF remain limited. Although HVPE may improve coagulation parameters, there is no conclusive evidence to support its role in improving neurological outcomes or facilitating spontaneous recovery [45].

Most RCTs in pediatric patients suggest that plasmapheresis, sometimes in combination with other extracorporeal therapies, may serve as a «therapeutic bridge» to LT [83]. Plasmapheresis has been associated with a reduction in multi-organ dysfunction and HE, while increasing survival in the absence of LT [72, 84].

Despite its theoretical advantages, MARS has not demonstrated significant clinical benefit in pediatric ALF [85]. Limited studies, including a cohort of 20 children undergoing MARS therapy, have reported improvements in biochemical markers such as ammonia, bilirubin, and creatinine levels, with good overall tolerability of the procedure [86]. However, further RCTs are needed to determine whether this modality provides meaningful clinical benefit in pediatric patients [45].

Liver Transplantation

The decision to proceed with LT in children with ALF is urgent when the likelihood of spontaneous recovery is extremely low and before the development of irreversible neurological or respiratory complications [87]. A progressive increase in serum aminotransferases, coupled with worsening coagulopathy, indicates progressive liver necrosis and the potential need for LT [37].

Currently, the Model for End-Stage Liver Disease (MELD) score is used to assess transplant eligibility in PALF patients, replacing the Child-Pugh classification [33, 88].

In some cases, the decision-making process for LT can take several hours to days [89]. Many centers prefer to list patients for transplantation while continuing ICU management and further diagnostic evaluation within the first 24–48 hours [89]. Prior to the introduction of LT, mortality in PALF was 70–95% [89]. However, with the advent of transplantation, mortality has decreased to 11% [90]. Currently, up to 10.3% of all pediatric liver transplants are performed for ALF [90]. Given the success of living-donor liver transplantation (LDLT) in PALF, this approach should be actively considered for children listed for transplantation, particularly in multidisciplinary centers where LDLT is feasible [89].

A major limitation of LT is the shortage of viable donor organs and the need for lifelong immunosuppressive therapy to prevent graft rejection [91]. Hepatocyte transplantation (HT) has emerged as a promising alternative to LT, either as a potential replacement therapy or as a bridge treatment until a donor liver becomes available. HT involves the infusion and engraftment of human hepatocytes, typically from organs unsuitable for whole organ transplantation, into the recipient's liver parenchyma to temporarily restore liver function [89].

Conclusion

Pediatric acute liver failure (PALF) is a rare and life-threatening condition that many anesthesiologists and intensivists rarely encounter. As a result, optimizing its management remains a challenge that can negatively impact the quality of emergency care. Increased awareness and education about PALF are essential to improve outcomes. In addition, more clinical research is needed to advance therapeutic strategies, including the development of novel approaches such as hepatocyte transplantation.

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Received 21.11.2024
Accepted 25.02.2025
Accepted in press 25.02.2025