Intensive Care Management of Pediatric Acute Liver Failure

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ABSTRACT

Pediatric acute liver failure is rare but life-threatening illness that occurs in children without preexisting liver disease. The rarity of the disease, along with its severity and heterogeneity, presents unique clinical challenges to the physicians providing care for pediatric patients with acute liver failure. In this review, practical clinical approaches to the care of critically ill children with acute liver failure are discussed with an organ system-specific approach. The underlying pathophysiological processes, major areas of uncertainty, and approaches to the critical care management of pediatric acute liver failure are also reviewed.

Key Words: acute liver failure, critical care, hepatic encephalopathy, liver transplantation, multiple organ systems, pediatric

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Acute liver failure (ALF) is an uncommon but devastating illness. ALF is caused by acute loss of hepatocellular function secondary to hepatocellular injury or death. The widely accepted definition of ALF in adults is inadequate for children owing to difficulty in assessing age-appropriate mental status and the variability in duration of illness in pediatric patients (1–3).

In an effort to address the ambiguity associated with the definition of pediatric acute liver failure (PALF), the most widely acceptable consensus defines PALF as:

- Biochemical evidence of liver injury in a child without evidence of chronic liver disease.
- Coagulopathy not corrected by vitamin K administration.
- International normalized ratio >1.5 if the patient has encephalopathy or >2.0 if encephalopathy is absent.

PALF represents one of the most challenging of all pediatric critical illnesses. It combines the management of rapidly progressive, severe multisystem organ failure, unpredictable and potential devastating complications, as well as the need for urgent decision-making in regards to emergent liver transplantation.

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ETIOLOGY AND DIAGNOSTIC EVALUATION

The etiology of PALF is variable. In the largest prospective study of children with ALF, the most common cause of PALF was indeterminate, in part due to the lack of proper diagnostic evaluation (4,5). In children younger than 7 months, metabolic and infectious diseases were the most common known etiologies for PALF with the herpes simplex virus (HSV) was the most common infectious etiology (6). Acetaminophen overdose was the most common cause of drug-induced ALF, accounting for more than three quarters of drug-induced cases. Table 1 shows various causes of ALF in children.

Children who present with features of ALF should undergo diagnostic evaluation to ascertain the cause of liver failure and extent of liver injury. All patients should undergo complete physical examination, including a thorough assessment of their neurological status. Laboratory evaluation of these patients should include assessment of liver synthetic function, a complete metabolic panel, serum ammonia, and a complete blood count (1,7). To better define the etiology of liver failure, the evaluation should include age appropriate testing for infectious causes, metabolic liver diseases, autoimmune disease, and Wilson disease (7,8). The evaluation should include ultrasound of the abdomen with Doppler examination (1,7). Liver biopsy should be considered when the diagnosis is unclear and more information is needed regarding the extent of liver injury. Liver biopsy in the setting of ALF is generally done via transjugular approach. One needs to use caution in interpreting the degree of liver necrosis as the extent of liver injury may not be uniform. Adult ALF studies have suggested that liver biopsy showing >50% to 75% necrosis as a poor prognostic factor (9,10). Table 2 summarizes the diagnostic evaluation of PALF.

ETIOLOGY SPECIFIC TREATMENT OF PEDIATRIC ACUTE LIVER FAILURE

The etiology of ALF is an important predictor of outcome. There are several etiologies that if diagnosed promptly may be amenable to specific treatments, which may dramatically improve the mortality and morbidity as well as prevent the need for liver transplantation. Table 3 summarizes the diagnostic features and therapies for specific etiologies, which cause PALF.

ROLE OF N-ACETYL CYSTEINE IN MANAGEMENT OF NON-ACETAMINOPHEN ALF

In a randomized controlled trial (RCT) involving 173 adult non-acetaminophen (non-APAP) patients with ALF, there was no difference in 21-day survival between those who received intravenous N-acetyl cysteine (NAC) versus placebo (11). The secondary analysis showed improved transplant free survival in patients with grade 1–2 encephalopathy. In a pediatric RCT involving 184 patients, there was no difference in 1-year survival between

TABLE 1. Causes of ALF (4,5)

Diagnosis	Infants younger than 7 months, % (n = 149)	Children older than 7 months, % (n = 554)
Indeterminate (incomplete evaluation)	61 (40.9)	268 (48.4)
Drug toxicity	3 (2)	108 (19.5)
Autoimmune hepatitis	0 (0)	48 (8.7)
Metabolic	27 (18.1)	41 (7.4)
Infections	20 (13.4)	25 (4.5)
Other diagnosis	38 (25.5)	64 (11.6)

ALF = acute liver failure.

those who received NAC versus placebo (73% vs 82%) (12). The 1-year transplant free survival was lower in those who received NAC (35%) compared to those who received placebo (53%), especially in children younger than 2 years. The study does not support the use of NAC in children with non-APAP ALF

MANAGEMENT OF SPECIFIC COMPLICATIONS OF PEDIATRIC ACUTE LIVER FAILURE

Transport to Tertiary Center and Admission to Pediatric Intensive Care Unit

PALF is one of the most challenging medical emergencies due to the multiorgan system involvement, potential rapid neurological deterioration, and the need for multidisciplinary supportive interventions. Pediatric patients with suspected ALF should be evaluated immediately. The immediate availability of a hepatologist and the level of expertise provided with the initial evaluation are crucial. Early transfer to a center with liver transplant capabilities is of paramount importance (13,14). Close monitoring of stable patients in routine pediatric hospital units may be appropriate. Pediatric patients with altered mental status or worsening coagulopathy, however, should be in setting where frequent laboratory, physiological and neurological monitoring can be accomplished which is often in an intensive care unit, as children with ALF can rapidly decompensate. The intensive care unit plays a pivotal role in the management of patients with PALF by providing support for failing organs while simultaneously allowing time for hepatic regeneration as well as the optimization of clinical status if liver transplantation is ultimately required. According to the US ALF study group (US ALFSG), the morality rate for adult patients with ALF has reduced, and the improvement is partly secondary to advances in critical care medicine and management strategies (15). Such strategies should also be used to improve the outcomes of pediatric patients with ALF.

Cardiovascular Dysfunction

ALF is associated with elevated levels of cytokines and subsequent hyperdynamic circulatory failure. In general, patients will develop peripheral vasodilatation with low mean arterial blood pressure. As with all other patients with hemodynamic compromise, maintaining adequate intravascular volume status should be the first step in the management. Once that target is accomplished, if the patient continues to be hypotensive based on specific age accepted metrics, vasoconstrictor medications should be initiated. Although adult literature promotes norepinephrine as the preferred agent (1,13,16), there is no pediatric data to endorse that recommendation. Despite the lack of pediatric specific data, using norepinephrine in patients with PALF with hyperdynamic circulatory failure does appear to be a logical choice (1,13). Echocardiogram to assess both systolic and diastolic function should be considered in patients with cardiovascular dysfunction.

Acute Respiratory Failure

Patients with PALF may require endotracheal intubation for airway protection subsequent to hepatic encephalopathy or due to respiratory dysfunction secondary to sepsis, volume overload, pulmonary hemorrhage, or acute respiratory distress syndrome (ARDS). The incidence of ARDS in PALF is unknown. The published consensus statement defining diagnostic criteria for the pediatric ARDS may offer a better framework to assess the incidence (17). In the prospective PALF study, 41% of all children with ALF needed ventilator support (3). ARDS was diagnosed in 20% to 30% of adult patients with ALF (18). The overall outcome was similar between those with ARDS and without ARDS. There are no pediatric trials investigating the best approach to mechanical ventilation in patients with PALF. Mechanical ventilation strategies for children with PALF must balance the risk of ventilator induced lung injury in the setting of pediatric ARDS versus neuroprotective strategies in the setting of increased intracranial pressure. Extrapolating the standard of care guidelines for patients with increased intracranial pressure includes maintaining normocapnia and avoiding hypoxemia. Hyperventilation can be used to manage sudden symptoms of increased intracranial pressure. Sustained hyperventilation, however, should be avoided. With respect to the best mechanical ventilation strategies for pediatric ARDS, the recommendations of the Pediatric Acute Lung Injury Consensus Conference propose ventilation with low tidal volumes (5–8 mL/kg predicted body weight) and moderately elevated levels of positive end-expiratory pressure titrated to maintain normal oxygenation and hemodynamic response (17). Although permissive hypercapnia and hypoxemia are generally accepted in ARDS management, these recommendations do not apply to patients with increased intracranial pressure (ICP) (11,19).

Relative Adrenal Insufficiency

Relative adrenal insufficiency (RAI)/hepatoadrenal syndrome has been described both in septic shock and in patients with ALF (20,21). There is little agreement regarding the definition of this condition. Depending on the definition used, studies have reported that one third of the adult patients with ALF may develop RAI (22). The incidence of RAI seems to parallel the severity of liver disease (22). No pediatric specific data were found to define the incidence or formulate specific recommendations for the diagnosis and management of RAI. In general, the consensus remains that additional steroid supplementation should be considered in patients with ALF with fluid refractory, catecholamine resistant shock (13).

TABLE 2. Diagnostic evaluation of PALF

Evaluation	Population	Studies
Biochemical	-All patients to assess severity of liver injury	-Coagulation profile: PT, PTT, INR, fibrinogen -Liver function test (AST, ALT, GGT, alkaline phosphatase, bilirubin, albumin, protein) -Coagulation factors: V, VII, VIII - Metabolic Panel: electrolytes, BUN, creatinine, blood glucose, calcium, phosphorous, magnesium - Blood gas - Complete blood count - Ammonia
Viral studies	-As clinically indicated.	-Viral hepatitis serology: anti-HAV IgM, HBsAg, anti-Hbc IgM and IgG, anti HCV, anti-HEV
	-Viral infections are one of the most common known etiologies of ALF in children <7 mo of age; herpes simplex virus is the most common infectious agent (6).	- Viral Studies (polymerase chain reaction): Epstein-Barr virus, Cytomegalovirus, Enterovirus, Adenovirus, Human Herpesvirus 6, Herpes simplex virus 1/2, Parvovirus.
Drugs/toxins	-Acetaminophen overdose was the most common cause of drug-induced ALF (6).	- Urine toxin screen - Serum acetaminophen level
Metabolic studies	-Metabolic diseases are the one of the most common known etiologies of ALF in children below 1 year of age.	- Lactate, pyruvate
	-Wilson disease usually presents after age 3 years.	- Serum amino acid profile - Urine amino acids/organic acids - Urine Succinylacetone - Ferritin, iron, total iron binding capacity - Carnitine level and acyl carnitine profile - Ceruloplasmin, 24-h urine copper
Immune function	-Autoimmune hepatitis typically affects adolescent patients; however, it can be seen in all age groups.	- Autoimmune hepatitis serology: antinuclear antibody, smooth muscle antibody, liver-kidney-microsomal antibody - NK cell function, perforin, granzyme B, sIL2, triglycerides
Histology/tissues studies	-As clinically indicated	- Liver biopsy - Bone marrow biopsy
Imaging studies	-As clinically indicated	- Ultrasound liver with Doppler exam - CT/MRI head (If indicated)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CT = computed tomography; HAV IgM = hepatitis A virus IgM; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HEV = hepatitis E virus; INR = international normalized ratio; MRI = magnetic resonance imaging; PALF = pediatric acute liver failure; PT = prothrombin time; PTT = partial thromboplastin time.

Acute Kidney Injury/Renal Failure

Acute kidney injury (AKI) is a common occurrence in adult patients with ALF. In a retrospective study using US ALFSG database involving 1604 patients, AKI was seen in 45% of patients (23). In adult studies, those with AKI had decreased overall survival when compared with those without AKI (57% vs 93%). The transplant free survival was 37% in those with advanced AKI (stage III) or needing renal replacement therapy versus 64% in those without AKI (23). The exact incidence of AKI in PALF is not known. In the prospective PALF study, nearly 10% of patients needed hemofiltration support; though the exact incidence of AKI/renal failure was not specified in the article (3). In an analysis involving pediatric health information system database covering 583 patients with PALF, AKI was noted in 17.5% of children with ALF and was associated with increased mortality (24).

The causes of AKI in ALF include acute tubular necrosis, hypovolemia, sepsis, acetaminophen-induced kidney injury, nephrotoxic medications, and functional renal failure (25,26). Functional renal failure results from intrarenal vasoconstriction leading to decreased renal perfusion. The mechanism is believed to be similar to hepatorenal syndrome seen in the setting of chronic liver disease (25–27). Assessment of renal dysfunction in children with ALF is difficult, and relies on changes in serum creatinine (Scr) and urine output. Experts generally agree that Scr overestimates renal function. The change of Scr over baseline is more relevant than a single SCr value alone in estimating AKI (25,28). Novel urinary biomarkers for the prediction of pediatric AKI are emerging (29,30). These biomarkers, however, are not routinely used in clinical practice and have not been studied in the setting of ALF.

Therapies used in the management of AKI in patients with PALF should focus on reducing the ongoing kidney injury by minimizing intravenous contrast or nephrotoxic drugs, avoiding over diuresis, stimulating renal recovery by effective restoration of appropriate intravascular volume, and maintaining renal perfusion pressure (1,13,25,26). An intravenous fluid challenge is recommended with suspected prerenal azotemia, but excessive fluid administration can be detrimental in the setting of ALF.

There is insufficient data to recommend specific criteria to start or discontinue renal replacement therapy (RRT) in patients with PALF. The decision to start RRT should rely on the degree of renal dysfunction, overall fluid balance, electrolyte disturbances, and metabolic derangements. RRT can prevent worsening acidosis, fluid overload, and control hyperammonemia. Continuous forms of hemofiltration or dialysis are preferred over intermittent

TABLE 3. Etiology-specific treatment of PALF

Etiology	Diagnosis	Treatment
Acetaminophen (126,127)	Confirmed or suspected history of acetaminophen ingestion	N-acetylcysteine, should be started as soon as possible after ingestion
	Elevated acetaminophen level 4 hours postingestion	NAC used in any case of ALF in which acetaminophen overdose is suspected as possible cause
	Suspect in high aminotransferases and low bilirubin.	
Hepatitis B (128–130)	Hepatitis B virus surface Ag/e antigen	Entecavir/Tenofovir/Lamivudine
	Hepatitis B PCR	Limited experience with Entecavir and Tenofovir
HSV 1,2 (131)	Viral culture/PCR from vesicles, oropharynx, conjunctiva, blood, CSF	IV Acyclovir
Autoimmune Hepatitis (132)	Positive autoimmune hepatitis serology	IV Methylprednisolone
	Elevated IgG levels	Evaluation for liver transplantation should not be delayed while awaiting response to steroids
	Liver Biopsy	
Wilson disease (133)	Low serum ceruloplasmin	Copper chelation
	High 24 hour urinary copper	Plasmapheresis
	Elevated liver copper	
	Kayser-Fleischer rings present in about 50% of patients with ALF.	
	High alkaline phosphatase/bilirubin ration (>4)	
	Evidence of hemolysis	
Tyrosinemia Type 1 (134)	Marked elevation of alpha-fetoprotein	NTBC*
	Elevated urine succinylacetone	
	Gene or enzyme testing for fumarylacetoacetate hydrolase	
Galactosemia (135)	Urine positive for non-glucose reducing substance on lactose containing feeds	Lactose free formula
	Galactose-1 phosphatase uridyl transferase enzyme assay	
Gestational Alloimmune liver disease/Neonatal Hemochormatosis	High serum ferritin	High dose IVIG
(136)	Lip/salivary gland biopsy	Possible exchange transfusion
	MRI liver/brain/pancreas with characteristic findings	
HLH (137)	High serum triglyceride	Corticosteroids
	Low fibrinogen	Chemotherapy
	Cytopenia	Bone marrow transplantation
	High serum ferritin	
	Elevated soluble interleukin-2 receptor	
	Low/absent NK cell activity	
	Genetic testing	
	Bone marrow biopsy	
Amanita toxicity (138,139)	History of mushroom Amanita phalloides and Amanita virosa ingestion	Silibinin
	Often present with vomiting/diarrhea	High dose Penicillin G
		Low survival without transplantation
Budd Chiari Syndrome (140)	Imaging studies showing hepatic venous thrombosis	TIPS (rarely possible)
		Transplantation may be necessary

HLH = Hemophagocytic lymphohistiocytosis; PALF = pediatric acute liver failure; TIPS = transjugular intrahepatic portosystemic shunt.
*NTBC: 2-(2-nitro-4-trifluoro-methylbenzoyl)-1,3-cyclohexandion.

hemodialysis due to the associated hemodynamic instability associated with the latter method (31). Intermittent hemodialysis may also be associated with increased ICP (1). Anticoagulation during continuous RRT can be challenging with either heparin or citrate depending on the local experience.

Although AKI in the context of PALF is very likely to resolve with restoration of normal liver function, concurrent kidney transplantation must be considered in special circumstances. Current adult indications for simultaneous liver/kidney transplantation are based on the degree and duration of renal injury and duration of renal replacement therapy (32). Most adult literature suggests consideration of simultaneous liver-kidney transplantation after 8 to 12 weeks of dialysis (32). There is minimal pediatric data, and most of the available guidelines are consensus statements based on data from single center experience and transplant registry information (33,34).

Fluids, Electrolytes, and Nutrition

Meticulous attention needs to be given to metabolic, electrolyte, and acid-base disturbances that are common occurrences in PALF. Frequent monitoring of serum electrolyte concentrations and prompt correction of abnormalities are recommended. Uninterrupted glucose infusion rates of 10 to 15 mg/kg/minute may be required to achieve stable serum glucose levels and prevent brain injury that results from hypoglycemia (1,13,35). Although some ICU protocols promote tight glycemic control in critically ill patients, a child with ALF lacks appropriate homeostatic responses to hypoglycemia, creating a significant risk with such interventions (1,13). Hyponatremia should be avoided, because it may exacerbate cerebral edema. Hypokalemia may occur secondary to dilution from volume overload, ascites, or renal wasting. Serum phosphorus should be monitored and corrected as hypophosphatemia can be profound (36). Hypocalcemia and hypomagnesemia are commonly observed and should be corrected.

There is very little written about nutritional support for adults or children with ALF. ALF is a catabolic state; adult data suggest that caloric requirements are increased by about 20% in ALF (37). Although most nutritional recommendations target chronic liver disease, in general the use of enteral feedings when possible is suggested (38,39). There are no clear guidelines on formula choice (39). Goals include administration of adequate calories to decrease catabolism, maintain euglycemia, and provision of enough protein for metabolic needs without causing hyperammonemia (40). Branched chain amino acids offer no advantage compared with standard amino acid solutions (41). When parenteral nutrition is necessary, many centers include intravenous lipids as a source of nutrition, while recognizing that in some disorders such as mitochondrial disease, metabolism of fat may be problematic (42).

Infection and Systemic Inflammatory Response Syndrome

The liver performs multiple immune-related functions. Patients with ALF are susceptible to infections secondary to multifactorial immune dysfunction. Bacterial infections are seen in 10% to 80% of adult patients with ALF. Infection-related complications are responsible for 10% to 37% of mortality in adult patients with ALF (43,44). In a retrospective cohort analysis involving 1551 adult patients with ALF from US ALFSG, there was increased mortality in non-APAP patients with ALF with blood stream infections (45). There is a lack of either retrospective or prospective data delineating infection-related complications in PALF.

In a retrospective study from Kings College involving 887 adult patients with ALF, systemic inflammatory response syndrome (SIRS) was seen in 56.8% patients (43). There was a direct correlation between mortality and the presence of increased SIRS components. There was also a strong association between the presence of increasing SIRS components and worsening encephalopathy. In a prospective adult study involving 96 patients with ALF, encephalopathy progressed in 80% of patients with infection (46). The encephalopathy progressed in 50% of patients with 2 or 3 components of SIRS versus 25% in patients with no SIRS (46). There is no data regarding SIRS in PALF.

Several adult studies have examined the role of prophylactic parenteral and enteral antibiotic in management of ALF (43–48), and the results are inconclusive. There are no clear guidelines in either the adult or pediatric literatures that recommend routine use of prophylactic antibiotics or antifungals in patients presenting with ALF (1,13). Close monitoring and surveillance for infection with blood and urine cultures as well as chest radiography, however, is paramount. It is reasonable to consider empiric antibiotic therapy in patients exhibiting SIRS and in those who are in advanced coma grade 3 or 4 (1,13). Some centers routinely place patients on antibiotic prophylaxis while waiting for liver transplantation.

Coagulopathy

Prolongation of prothrombin time (PT)/INR is universal in children with ALF due to a reduction in both pro and anticoagulant factors. There may also be a reduction in platelet count. Despite these laboratory abnormalities, clinically significant hemorrhage is seen in $<5\%$ of patients and $<1\%$ have spontaneous intracranial bleeding (49). Coagulopathy is traditionally assessed by measuring PT and INR. Measurement of PT/INR, however, reflects a reduction in synthetic function, but not necessarily the risk of bleeding. It is suggested that newer techniques like thromboelastography (TEG) may be superior in assessing the bleeding diathesis compared to PT/INR (50,51). These newer techniques, however, are not widely available. Vitamin K deficiency has been reported in adult patients with ALF (52) and administration of Vitamin K is recommended. The American Association for the Study of Liver Disease (AASLD) guidelines recommend against prophylactic plasma transfusion to correct PT/INR (1). The guideline recommends plasma transfusion before invasive procedures or in the setting of active bleeding. There is, however, variation from center to center in the United States with respect to the use of FFP/plasma to correct an INR >7 to 10 without evidence of overt bleeding (1). Recombinant factor VIIa may be useful to facilitate invasive procedures especially in the setting of renal insufficiency and concern for volume overload (53). Caution, however, must be used as there are reports of systemic venous thrombosis following administration of recombinant factor VIIa (54). Platelet transfusions are generally not indicated for platelet count $>50{,}000$. It is suggested that patients may need platelet transfusions if the platelet count is $<10{,}000$. Platelet transfusion is advised in patients who are bleeding with platelet count $<50{,}000$ (1,13).

Hepatic Encephalopathy and Cerebral Edema

Hepatic encephalopathy (HE) is a neuropsychiatric syndrome seen in association with liver dysfunction in ALF in the absence of a preexisting brain disease. HE is characterized by neuropsychiatric disturbances ranging from minor confusion and disorientation to frank coma (13,55,56). In children, HE can be subtle and difficult to assess; encephalopathy can range from irritability and inactivity to coma (7,8,57). Table 4 describes the HE grading adopted for infants and children.

The exact pathogenesis of HE remains incompletely understood. A number of inter-related factors are thought to be responsible. Ammonia (NH3) plays an important role in the development of HE in ALF. Ammonia, a byproduct of nitrogen metabolism, is generated in the enterocytes within the small intestine and the colon by the enzyme glutaminase. Glutaminase breaks down glutamine into ammonia and glutamate, along with urease-producing bacteria that inhabit the gut. The gut-derived ammonia enters the urea cycle and is converted to urea and excreted by the kidneys. Ammonia that bypasses the urea cycle is metabolized by glutamine synthase to glutamine in hepatocytes, skeletal myocytes and astroglial cells (58). Although ammonia plays a critical role in the pathogenesis of HE, the plasma concentrations of ammonia and the clinical manifestations of HE do not always consistently correlate in patients with HE (59).

Astrocytes are the most abundant cells in the brain and are sensitive to the rapid increase of ammonia. As increasing quantities of ammonia are detoxified to glutamine within the astrocytes, intracellular glutamine concentration increase, increasing

TABLE 4. Classification of hepatic encephalopathy in infants/children

Grade	Clinical findings	Reflexes
Grade 0	Normal	Normal
Grade 1	Confused, mood Changes, inconsolable crying; child is not acting like self	Normal or hyperreflexic
Grade 2	Drowsy, inappropriate behavior, inconsolable crying; child is not acting like self	Normal or hyperreflexic
Grade 3	Stupor, somnolence, combativeness but may obey simple commands.	Hyperreflexic, (+) Babinski
Grade 4	Comatose, arouses with painful stimuli, or no responses to painful stimuli	Absent

intracellular osmolarity and generating osmotic stress, which leads to an influx of water into astrocytes and resulting in cerebral edema (CE) (58,60). In addition to the central role of ammonia, systemic circulation of pro-inflammatory mediators, particularly cytokines such as the interleukins (IL)-1β and IL-6 and tumor necrosis factor-alpha (TNF-α), may have permissive or direct effects on development of HE and CE through modulation of cerebral endothelial permeability to neurotoxins and changes in cerebral blood flow (61–63). The occurrence of cerebral edema and intracranial hypertension (ICH) is related in part to the severity of HE.

The Pediatric Acute Liver Failure Study Group (PALFSG) database consisting of 348 patients reported that 55% of children developed HE (3). The majority (75%) of patients had grade 1 to 2 encephalopathy. Grade 3 and 4 encephalopathy were seen 17% and 7% of patients, respectively.

General Neurologic Care and Management of Hepatic Encephalopathy

The early recognition and appropriate management of pediatric patients with hepatic encephalopathy is of paramount importance to reduce the mortality and morbidity associated with cerebral edema and ICH.

In general, patients should be kept in a quiet room with minimal stimulation, and unnecessary interventions should be avoided. Frequent neurological examination and assessment of the grade of encephalopathy, however, should be routinely performed. Endotracheal intubation is recommended for airway protection and controlled ventilation in advanced grades of HE. The patient's head should be maintained in the midline position with the head of the bed elevated 20° to 30° to optimize jugular venous outflow and improve CSF drainage. Fever and shivering should be aggressively treated, as these may exacerbate intracranial pressure. Meticulous attention should be paid to maintaining adequate oxygenation, normal ventilation, and mean arterial pressure.

Given the potential correlation between arterial ammonia levels, hepatic encephalopathy and intracranial hypertension (59), one could assume that ammonia-lowering strategies may be an effective way to treat hepatic encephalopathy; however, there is insufficient evidence to support the use of lactulose or other nonabsorbable antibiotics (rifxaximin, neomycin) to treat HE in patients with PALF (1,13). Although the data to support the benefit of L-ornithine L-aspartate (LOLA) and L-ornithine phenyl acetate (LOPA) in PALF are lacking, the recent preliminary report of the adult STOP-ALF trial shows promise of ornithine phenylacetate as adjunctive therapy in ALF (64).

MANAGEMENT OF INTRACRANIAL HYPERTENSION AND CEREBRAL EDEMA

Intracranial Pressure Monitoring

The goal in the management of cerebral edema and increased ICP is to maintain ICP <20 mm Hg while maintaining adequate cerebral perfusion pressure (CPP) (65). Close clinical monitoring is strongly recommended in pediatric patients with HE. Clinical monitoring can be very challenging especially once patients progress to HE Grade 3–4. A small recent retrospective study showed that intracranial pressure monitoring in patients with PALF allowed targeted interventions to manage elevated ICP increases; however, there was no improvement in survival (57). A multicenter study of 332 adult patients from 24 centers reported a similar 30-day survival between patients with and without ICP monitoring (85% vs 85%) (66). The multicenter US ALFSG reported no overall improvement in 21-day mortality with ICP monitoring. The study, however, showed increased 21-day mortality in non-APAP patients with ALF with ICP monitoring (67). Although there is no consistent data to demonstrate the benefits of ICP monitoring, undoubtedly it carries the risk of intracranial bleeding accentuated by the coagulopathy seen in patients with ALF. Epidural catheters were associated with the least risk of hemorrhage complications (3.1%); subdural bolts and intraparenchymal monitors were associated with 18% and 13% bleeding complications, respectively (68). Fatal hemorrhage occurred in 5% of patients. The use of ICP monitoring is controversial in the management of patients with PALF. There is insufficient data to recommend the routine the use of ICP monitoring in patients with PALF.

Osmolar Therapy

The administration of osmotic agents (hypertonic saline and mannitol) is one of the principal therapies to reduce cerebral edema and thereby lower ICP (55).

Hypertonic Saline

Hypertonic saline (HTS; 3%-30%) decreases ICP by several mechanisms. It decreases the brain water content secondary to its osmotic effect. It also improves the cerebral blood flow, which in turn causes vasoconstriction and decreases ICP. It stabilizes cerebral endothelial cell volume, which also improves the circulation (69).

HTS confers the benefits of increased serum osmolarity without the associated hemodynamic side effects observed with mannitol. The HTS has been studied as a prophylactic agent to prevent development of ICP in adult patients with ALF. It, however, has not been studied as an agent to treat elevated ICP in ALF. The complications of HTS include hemorrhages, venous thrombosis, hyperchloremic metabolic acidosis, and worsening coagulopathy (70–74). In an RCT from Kings College, 30 adult patients with ALF with grade III and IV encephalopathy were randomized to receive 30% HTS or standard care. The target serum sodium was between 145 and 150 mmol/L. The patients who received HTS had decreased ICP from baseline in the first 24 hours compared with the control group ($P < 0.003$). The incidence of ICP > 25 mm Hg or greater was significantly lower in the treatment group ($P < 0.04$). The trial, however, did not show improved survival in patients who were

treated with HTS (74). It may seem reasonable to maintain serum sodium around 145 mmol/L to 150 mmol/L in patients with PALF with ICH, as HTS is now the standard of care in the treatment of ICH in pediatric patients with traumatic brain injury (71,75).

Mannitol

Mannitol is a hyperosmolar agent used commonly as a first-line therapy to treat increased ICP in adult patients with ALF (1,13). Mannitol's main effect manifests through an increase in the serum osmolality resulting in outward movement of water from brain parenchyma. Mannitol also decreases blood viscosity, which in turn causes vasoconstriction, decreased cerebral blood volume, and ICP. The current recommendation proposes doses of 0.25 to 1 gm/Kg/dose (1,13). It should be administered to manage an acute rise in ICP; prophylactic administration of mannitol is not recommended. Furthermore, it is generally not recommended to use mannitol in the presence of hypovolemia, renal failure, or a serum osmolality >320 mOsm/L (1,13). The vast majority of information regarding use of mannitol comes from adult patients with ALF. There are no published controlled trials regarding the use of mannitol in PALF. A recent guideline for management of traumatic brain injury in children and infants also has favored the use of 3% saline over mannitol in management of ICH due to insufficient evidence to support the use of mannitol (70).

Temperature Control

Hyperthermia is associated with the development of ICH (76,77). Therapeutic hypothermia (32–35^{c}) has been used to reduce ICP in adult patients with ALF. Hypothermia reduces brain energy metabolism, systemic and neuronal inflammation, and reduces ammonia, while concurrently improving cerebral blood flow and cerebral hemodynamics (78,79). Therapeutic hypothermia, however, is associated with side effects such as coagulopathy, cardiac dysrhythmias, increased risk of infection, electrolyte disturbance, hyperglycemia, and theoretically decreased hepatic regeneration (78,79). Noncontrolled trials and case series in adult patients with ALF have reported a beneficial effect of therapeutic hypothermia (78,79). Jalan et al (80) reported successful bridging of 13 out of 14 adult patients with ALF to liver transplantation with therapeutic hypothermia. Two recent studies, however, have questioned the benefit of therapeutic hypothermia in the management of adult patients with ALF. A multicenter retrospective study from US ALFSG involving 97 patients found no difference in 21-day mortality and transplant free survival between those who received therapeutic hypothermia and those who did not (81). There is no data in patients with PALF to support the use of therapeutic hypothermia. At this time, active normothermia (36–37^{c}) may offer the best risk-benefit ratio for patients.

Seizure Control

Seizure activity in patients with ALF may increase cerebral oxygen requirement and worsen cerebral edema (82). In the absence of continuous telemetry, the true frequency of seizures in patients with ALF may be underestimated. Because neurological morbidity is a major determinant of outcome following ALF, early identification of declining neurological function allows for earlier therapeutic interventions that may help to minimize morbidity and mortality. Hussain et al (83) reported their single center retrospective pediatric study examining the role of EEG in management of PALF. EEG abnormalities were seen in 59% of patients. The most common abnormality was slowing and epileptiform discharges. Clinical seizures were seen in 10% and nonconvulsive seizures were seen in 5% of patients. There was no association between EEG and CT/magnetic resonance imaging (MRI) findings. There was increased mortality in patients with EEGs showing moderate to severe slowing, epileptiform discharge and electrographic seizure. EEG may be deployed to measure declining neurological function and may serve as a sensitive measure of neurological dysfunction (83). Continuous EEG should be considered as screening tool for subclinical seizure activity especially for patients with grade III or IV encephalopathy or if clinically suspected (82). Prophylactic phenytoin has been used to suppress subclinical seizure activity in adult patients with ALF (82,84). There was no overt benefit in prevention of cerebral edema or improvement in survival. There is no pediatric data to support the use of prophylactic anti-seizure medication in management of patients with PALF.

Neuroimaging

Head imaging with CT scan is frequently used to exclude causes of sudden decline in mental status in patients with ALF such as intracranial hemorrhage (85). Studies in adults with ALF have shown various MRI findings including reduction in apparent diffusion coefficient, abnormal signal on fluid attenuated inversion recovery, and diffusion weighted sequences (86). Adult ALF studies have also shown association between MRI findings, ammonia level, and outcome (87). A recent pediatric study assessed the utility of brain imaging in patients with PALF (83). CT/MRI was abnormal in only 13% of patients. There was no association between EEG and imaging findings. CT scan was insensitive and conventional MRI techniques did not show consistent signal abnormalities indicating the presence of cerebral edema (83). Transcranial Doppler ultrasonography has been used to measure cerebral hemodynamics and also to predict the changes in ICP and CPP. In a retrospective study involving 16 adult patients with ALF, transcranial Doppler findings were found to be useful in predicting dynamic changes in ICP (88). There are no pediatric studies examining transcranial Doppler in PALF.

In rare circumstance, when it is difficult to differentiate an advanced grade of HE from brain death, ancillary studies such as radionuclide cerebral blood flow will be necessary to complete the determination of brain death (89).

Sedation, Analgesia, and Neuromuscular Blockade

Sedation and analgesia are important components of care for all children in the pediatric intensive care unit. Pain can result from numerous diagnostic and therapeutic procedures and can contribute to ICH. In the advanced stages of HE, psychomotor agitation may also increase ICP (90). Sedating nonintubated agitated patients with PALF must be carefully considered with attention to the potential benefit of reducing agitation with anxiolytics versus the risk of blunting the accuracy of the neurological examination and exacerbating encephalopathy. There is insufficient data to recommend standard agents for sedation and analgesia in patients with PALF, but short-acting agents are preferred. Benzodiazepines and propofol may worsen HE by increasing gamma-aminobutyric acid neurotransmission (91). Furthermore, benzodiazepines can have a protracted sedative effect in the context of hepatic impairment and should be avoided. The recovery time from propofol is much shorter and may offer some neurological protection through decreased cerebral blood flow and lowered ICP (92). One should consider using propofol in patients with PALF in limited doses, in older

children without mitochondrial disease and for relatively short periods. The concomitant use of opioid analgesics can reduce the doses of anesthetic agents required with improvement in cardiovascular stability. Agents with shorter half-lives, such as fentanyl or remifentanyl are preferred (13). Remifentanyl elimination is unaltered in patients with severe liver disease. Dexmedetomidine has a sedative and analgesic effect and relatively short half-life; however, it is primarily metabolized in the liver. Dose adjustments are therefore indicated when used in patients with ALF (93). If neuromuscular blockade is indicated, vecuronium and rocuronium should be avoided as they undergo hepatic metabolism. Atracurium and cisatracurium are the preferred agents in patients with ALF as they undergo Hofmann elimination and ester hydrolysis and have a duration of action similar to patients with normal liver function (94).

Liver Support Systems

Extracorporeal liver support (ELS) systems have been proposed either as a bridge to liver transplantation or to assist in recovery from ALF. Several different types of liver support systems exist. They are broadly divided into non-biologic and biologic systems. The biologic systems use human/non-human cells to detoxify the plasma or blood. The non-biologic system uses series of filters to detoxify the plasma/blood.

Molecular adsorbent recirculating system (MARS) and Prometheus are the 2 commercially available liver support systems. In adult patients with ALF, MARS has shown improvement in biochemical parameters (including improved NH3), and hepatic encephalopathy (95). A recent RCT did not show survival benefit in adult patients treated with MARS (96). An RCT examining the role of bioartificial liver in the management of adult patients with ALF found no difference in 30-day survival between treatment group and control group (97). A recent pediatric case series involving 20 children with ALF who were treated with MARS showed significantly lower levels of serum ammonia, bilirubin, bile acid, and creatinine levels; however there was no survival benefit (98).

High-volume hemofiltration (HVHF) removes cytokines such as TNF-α and IL-1β, which are also implicated in the pathogenesis of ALF and HE. HVHF was used in 22 children with ALF in a single center in Europe and showed improvement in the hemodynamic at 24 hours and decreased degree of HE at 48 hours (99).

Plasma exchange (PE), a nonselective form of blood purification, has been attempted to improve biochemical and clinical parameters of patients with ALF. Plasma exchange improves coagulation profile, serum ammonia, encephalopathy, and cerebral perfusion pressure. In a randomized controlled study involving 182 adult patients with ALF, the overall survival in the PE group was superior to control group (58.7% vs 47.8%, $P < 0.008$) (100). SIRS score and sequential organ failure assessment score decreased in the patients receiving plasmapheresis in comparison to the control group. There is limited literature describing the use of PE in PALF. In a retrospective study, 49 children with ALF underwent 243 plasma exchanges (101). PE improved the coagulation profile; however, it did not change the neurological complications and also did not improve the survival.

Various other strategies of extracorporeal support devices are being studied with modifications of the existing techniques such as ultra volume PE (102–103). Any type of extracorporeal support should be part of multidisciplinary, supportive critical care treatment offered at a liver transplant center and should not be used as a stand-alone treatment (104). There is a wide variation from center to center in the use of liver support systems in children. None of these methods can be recommended for routine use in the management of PALF at this time.

Liver Transplantation

Liver transplantation has improved the survival of patients with PALF. The indications to perform liver transplantation remain unclear. Attempts have been made to streamline the process of listing and performing liver transplantation in PALF with limited success (105–108). PALF accounted for 11.2% to 12.5% of all pediatric liver transplantation performed in the United States between the year 2010 and 2013 (109,110). The outcome of liver transplantation following ALF is poorer when compared to liver transplantation done for chronic liver disease. In the SPLIT database, 1-year patient survival was 74% for PALF compared to 88.2% for other conditions (111). There are single center case series that describe post liver transplantation survival rates ranging from 55% to 90% (112,113). In a study from the University of California, Los Angeles (UCLA), involving 122 children with ALF, 1-year, 5-year, and 10-year survival was 81%, 77%, and 73% respectively (114). The factors predicting poor outcome following liver transplantation in the SPLIT database study included age <1 year, Grade IV encephalopathy, and the need for dialysis before transplantation (111). In the UCLA study, risk factors for poor outcome included poor renal function (creatinine clearance <60 mL/min/1.73m^2) and time between the onset of jaundice and encephalopathy <7 days (114).

Prognostic Factors

Several adult prognostic scoring systems have been validated and are routinely used with mixed results. The King's College Hospital Criteria (KCHC) and the Model for End-Stage Liver Disease (MELD) score are commonly used in adult patients (115,116). The sequential organ failure assessment score (SOFA) score has been used as a triage marker in the context of acute liver injury (117). SOFA has not been sufficiently validated to allow it to influence decision-making for transplantation. Several other laboratory variables have been studied in adult patients with ALF including alpha-fetoprotein, phosphorus, ammonia, lactate, M30 level, and the APACHE II, with some promise when combined with a scoring system (13).

Prognostic factors are less well established in children than in adults. Parameters that have been found to predict outcomes in PALF have included elevated serum bilirubin, prothrombin time, blood ammonia, white blood cell count, and onset of hepatic encephalopathy (118,119). The pediatric end-stage liver disease (PELD) score has been used as a predictor of mortality in children with chronic liver disease listed for liver transplantation; however, experience with the PELD score in PALF is limited (120). KCHC, which is used extensively in adult patients with ALF, may not be applicable in patients with PALF. PALFSG used their database to validate KCHC criteria in non-APAP patients with PALF (105). The sensitivity and the positive predictive value were significantly lower than the original KCHC study. The study showed that KCHC did not reliably predict death in patients with PALF. Another pediatric scoring system is pediatric Liver Injury Unit (LIU) score that uses peak values during hospital admission of total bilirubin and PT/INR to stratify patients into low, moderate, and high risk of death or need for liver transplantation (106,121). LIU score may be a helpful, dynamic tool to predict clinical outcomes in PALF (106,121). To date, there is no single criterion that can predict outcomes with absolute certainty and be universally applicable to all patients with PALF with different etiologies.

Outcome

There is limited data regarding the outcome of children following ALF. In a case series from Kings College, the overall survival rate was 29% (122). The prognosis was poor in those with grade IV encephalopathy with only 6% surviving. This data, however, predates

the widespread adoption of liver transplantation as a treatment modality for PALF. The more recent data from the PALF network is encouraging (3). Children with acetaminophen induced liver failure had the best survival (94%). The patients with indeterminate cause and those with nonacetaminophen-induced liver failure had the worst outcome with a survival rate of 43% and 41% respectively.

There is minimal data regarding the long-term outcome of patients with PALF. The PALFSG reported worse motor coordination, executive deficits, worse attention span, and health-related quality of life in PALF survivors (123). The ALFSG also reported lower quality of life scores in adult survivors of ALF (124,125). APAP spontaneous survivors had higher psychiatric and substance abuse issues (124,125).

CONCLUSIONS

Despite recent advances in supportive care and the improvement in outcomes observed over the last few decades, the practical intensive care management of PALF remains poorly defined due to its rarity and heterogeneity. Current treatment options are merely supportive and based on incomplete adult data and local institutional experience. PALF represents one of the most challenging of all pediatric critical illnesses. Future studies on the management of PALF, should be designed by specialists from multiple disciplines including hepatologists and intensivists. Increasing the availability of liver for transplantation, developing a better prognostic scoring system, and developing effective methods of liver support system, remain the key goals to further improve the overall survival rate.

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