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GUIDELINES

Diagnosis and management of pediatric acute liver failure: consensus recommendations of the Indian Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ISPGHAN)

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Abstract

Timely diagnosis and management of pediatric acute liver failure (PALF) is of paramount importance to improve survival. The Indian Society of Pediatric Gastroenterology, Hepatology, and Nutrition invited national and international experts to identify and review important management and research questions. These covered the definition, age appropriate stepwise workup for the etiology, non-invasive diagnosis and management of cerebral edema, prognostic scores, criteria for listing for liver transplantation (LT) and bridging therapies in PALF. Statements and recommendations based on evidences assessed using the modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) system were developed, deliberated and critically reappraised by circulation. The final consensus recommendations along with relevant published background information are presented here. We expect that these recommendations would be followed by the pediatric and adult medical fraternity to improve the outcomes of PALF patients.

Keywords Guidelines · Pediatric acute liver failure · Acute liver failure · Non-invasive assessment of cerebral edema · Bridging therapies · Therapeutic plasma exchange · Continuous renal replacement therapy · Molecular adsorbent recirculating system · Diagnosis · Management · Liver transplantation

Abbreviations

AIH	Autoimmune hepatitis
ALF	Acute liver failure
APAP	Acetaminophen
CBF	Cerebral blood flow
CLD	Chronic liver disease
CMV	Cytomegalovirus
CPPe	Estimated cerebral perfusion pressure
CRRT	Continuous renal replacement therapy
DILI	Drug-induced liver injury
EDV	End-diastolic volume
ELSS	Extracorporeal liver support systems
HAV	Hepatitis-A virus
HBV	Hepatitis-B virus
HE	Hepatic encephalopathy
HTS	Hypertonic saline
ICP	Intracranial pressure
ICU	Intensive care unit
INR	International normalized ratio
KCH	King's College Hospital
LOE	Level of evidence
LT	Liver transplantation
MARS	Molecular adsorption and recirculation system
MLD	Metabolic liver disease
NAC	N-acetylcysteine
NIRS	Near Infrared spectroscopy
NLS	Native liver survival
ONSD	Optic nerve sheath diameter
PALF	Pediatric acute liver failure

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PALFSG	Pediatric acute liver failure study group
RCT	Randomized controlled trial
SIRS	Systemic inflammatory response syndrome
SjvO2	Jugular venous oxygen saturation
TBI	Traumatic brain injury
TCD	Transcranial Doppler
TJLB	Transjugular liver biopsy
TPE	Therapeutic plasma-exchange

Introduction

Pediatric acute liver failure (PALF) is potentially fatal and may lead to rapid deterioration of hepatic function and synthetic liver failure. The preceding period may last for days or weeks; however, once PALF is established, the clinical course is unpredictable and often rapidly progressive. Large multicenter data from the west reported native liver survival (NLS) of around 50% about 2 decades ago, whereas recently the PALF study group (PALFSG) re-analyzed 1144 cases and reported an increase in NLS from 47.5% to 68.5% in the present era [1, 2]. Data from the PALF study group reported 60% NLS among young infants less than 90 days old [3]. On the other hand, data from India report NLS of 47.7%, a greater proportion of deaths (42.2%), and only 10% of liver transplantation (LT) [4]. The proportion of patients with NLS is even lower in younger Indian children and infants [5].

PALF is characterized by coagulopathy and hepatic encephalopathy (HE) in children without an underlying chronic liver disease (CLD). It results from rapid and massive hepatocyte necrosis or injury, leaving behind a liver parenchymal mass insufficient to sustain liver functions, resulting in high rates of mortality. PALFSG has defined PALF in an infant or child according to the following criteria: (i) no known evidence of CLD, (ii) biochemical evidence of acute liver injury, and (iii) corrected (6 h post1–10-mg of parenteral vitamin K) coagulopathy defined as an international normalized ratio (INR) ≥ 1.5 in the presence of clinical HE or INR ≥ 2, regardless of the presence or absence of clinical HE [1].

Age-based protocols are required in the diagnostic workup of PALF to reduce the number of indeterminate cases. Indeterminate PALF accounted for about half of the cases in older studies, but the proportion is now decreasing due to improved diagnostic work-up [6]. Although there has been a significant reduction in mortality over time in the West, the mortality rate in PALF remains close to 50% in India. This could be due to a delay in diagnosis, a poor referral system, and a limited number of formally trained pediatric hepatologists, pediatric intensivists, and pediatric LT programs in the country. Cerebral edema and systemic inflammation continue to be the major pathophysiologic mechanisms driving multi-system organ failure in PALF. There are newer non-invasive diagnostic modalities, such as optic nerve sheath diameter (ONSD) and transcranial Doppler (TCD), to detect elevated intracranial pressure (ICP) in PALF. Moreover, the use of newer therapeutic modalities such as therapeutic plasma exchange (TPE) and continuous renal replacement therapy (CRRT) has improved outcomes. Guidelines are needed to direct the appropriate use of these new modalities in the management of PALF. The ideal prognostic models and LT listing criteria for PALF have not been well established. There are no consensus guidelines on the diagnosis and management of PALF, although few review articles or position papers have been published previously [6, 7].

Hence, a consensus meeting was planned on February 25, 2024, at the Department of Pediatric Hepatology, Institute of Liver and Biliary Sciences, under the aegis of the Indian Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ISPGHAN) to develop recommendations on the diagnosis and management of PALF. The scientific committee invited international and national experts to participate in a consensus meeting. Before the meeting, questions were identified by a subgroup of experts and allotted to participants to review and analyze the published literature. Literature search, level of evidence (LOE), and grade of recommendations for each question were reviewed by a subgroup of experts based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system (Table 1) [8]. A 1-day meeting was held on February 25, 2024, in New Delhi, India, to discuss and finalize the consensus statements, recommendations, and guidelines. A large group of experts deliberated on each question, reviewed the literature, discussed the contentious issues, and deliberated to prepare the consensus statement deciding the LOE and grade of recommendations on the particular question. The final statements and recommendations were circulated to all experts for their suggestions. The manuscript with consensus recommendations was prepared by a subgroup of experts, and the final manuscript was re-circulated for comments. The experts' suggestions were used to revise and finalize the recommendations. A brief background of each question has been included, providing recommendations and evidence from the published literature.

Pediatric ALF definition

All adult definitions of acute liver failure (ALF) have three common features: (i) the presence of HE and coagulopathy, (ii) a specified interval (from onset of illness to HE), and (iii) no pre-existing liver disease [9]. Although initially meant to be used only as study entry criteria (and not primarily for diagnosis), the PALFSG criteria have now gained almost universal acceptance for defining PALF [1]. However,

Table 1 Level of evidence and strength of recommendations used for the Indian Society of Pediatric Gastroenterology, Hepatology and Nutrition guidelines on pediatric acute liver failure (adapted from GRADE recommendations) [8]

	Criteria	Notes
Level of evidence		
1	Systematic reviews (with homogeneity) of randomised-controlled trials	Further research is unlikely to change our confidence in the estimate of benefit or risk
2	Randomised-controlled trial or observational studies with dramatic effects, systematic reviews of lower quality	
3	Non-randomised controlled cohort/follow-up study/control arm of randomised trial	Further research is likely to have an impact on our confidence in the estimate of benefit and risk
4	Case-series, case–control, or historically controlled studies	
5	Expert opinion (mechanism-based reasoning)	Any estimate of effect is uncertain
Strength of recommendations		
Strong	Evidence, consistency of studies, risk–benefit ratio, presumed patient-important outcomes, and cost	
Weak	Depends on patient preferences, ethical obligations, feasibility, higher cost or resource consumption	

GRADE Grading of recommendations assessment development and evaluation

even though any known evidence of CLD is an exclusion criterion, patients with Wilson disease, autoimmune liver disease, etc. (with underlying cirrhosis in the majority) are commonly included in the PALF groups considering them as an acute presentation of underlying CLD [6, 10]. There is a need to differentiate between pure PALF and PALF associated with CLD since they are discrete in their natural course of illness and outcome. The negative impact of including patients with cirrhosis in PALF studies is further evident from the placebo-controlled clinical trial on the use of intravenous N-acetylcysteine (NAC) in patients with non-acetaminophen (APAP) PALF [11]. The negative outcome of the study, particularly among those aged < 2 years, formed the basis of non-usage of NAC in PALF patients worldwide. However, closer scrutiny of the study's methodology revealed that more than half of the patients in both study groups (with known etiology) had underlying potential cirrhosis (including metabolic liver diseases such as Wilson disease, tyrosinemia, galactosemia, etc.). While a similar study in adult ALF majorly including patients with potentially non-cirrhotic etiologies such as drug-induced liver injury and hepatitis B showed a beneficial effect of intravenous NAC in non-APAP ALF [12]. The results of this trial led to NAC being recommended as standard medical management in non-APAP ALF in adults [10]. The regeneration potential differs depending on the underlying hepatic fibrosis/cirrhosis [13]. Thus, any study evaluating therapies (e.g., extracorporeal liver support systems (ELSS) like TPE and CRRT) is likely to be confounded if patients with underlying CLD are included. Therefore, all efforts should be made to include only 'pure ALF' cases, especially in studies on therapeutic modalities in PALF patients.

HE is one of the most important prognostic markers in patients with ALF. Therefore, all adult ALF definitions include HE as a mandatory diagnostic criterion [9]. However, the difficulties in incorporating HE in PALF patients are well known including suboptimal assessment in early stages of HE and it may not be apparent until terminal stages in infants/young children [1]. Almost all children with ALF have HE, however, it is difficult to detect early HE in younger children. All possible efforts should be made to identify early HE in suspected PALF cases using the modified HE assessment scale by the PALFSG for optimal management [1]. The modified HE assessment scale in children as proposed by the PALFSG is depicted in Table 2. There is an urgent need to evaluate potential biomarkers for the early detection of HE in children.

1. Recommendations:

1.1. Pediatric acute liver failure should be defined as per pediatric acute liver failure study group criteria:

- Children with no known evidence of chronic liver disease,
- Biochemical evidence of acute liver injury, and
- Hepatic-based coagulopathy defined as an INR ≥ 1.5 not corrected by Vitamin K with clinical hepatic encephalopathy or an INR ≥ 2, regardless of the presence or absence of clinical encephalopathy (LOE 5, strong recommendation).

1.2. Efforts should be made to suspect and diagnose hepatic encephalopathy early, even in younger populations using the modified encephalopathy assessment scale (LOE 5, strong recommendation).

Table 2 Modified hepatic encephalopathy assessment scale for children upto 3 years of age as recommended by the pediatric acute liver failure study group [1]

Grade	Clinical	Asterixis/reflexes	Neurological signs
Early (I andII)	Inconsolable crying, sleep reversal, inattention to task	Unreliable/normal or hyper-reflexic	Untestable
Mid (III)	Somnolence, stupor, combativeness	Unreliable/hyper-reflexic	Most likely untestable
Late (IV)	Comatose, arouses with painful stimuli (IVa) or no response (IVb)	Absent	Decerebrate or decorticate

Etiology of PALF

The etiology of PALF is diverse and varies across different age groups and geographical locations. As per the PALFSG cohort, three different age groups were defined to segregate etiologies—0–90 days, 91 days to 3 years, and 3 years–18 years [2]. APAP, hepatotropic viruses, non-APAP drug-induced liver injury, and autoimmune hepatitis are common in older children [2, 4, 14–24]. In contrast, infants commonly have cardiac or ischemia-induced liver failure, non-Wilsonian metabolic liver disease (MLD), non-hepatotropic viruses (herpes simplex and enterovirus), gestational alloimmune liver disease or hemophagocytic lymphohistiocytosis [2, 3, 5, 25–28]. Etiological distribution of PALF also appears to vary based on the incidence of hepatitis-A virus (HAV) infection in different regions of the world [29]. Figure 1 summarizes the etiologies of PALF in children among various age groups.

Metabolic liver diseases presenting as ALF

MLD constitutes approximately 28% of PALF in children less than 5 years of age with galactosemia, mitochondrial respiratory chain defects, tyrosinemia, ornithine transcarbamylase deficiency, Niemann–Pick disease being the common ones [30]. Red flags for MLD in PALF include infantile presentation, failure to thrive, hepatosplenomegaly, disproportionate synthetic dysfunction, consanguineous parents, history of miscarriages or sib-death, family history of similar illness, abnormal body fluid odors, extrahepatic features in the form of rickets, diarrhea, developmental delay or regression, nystagmus, seizures, hypotonia, bone marrow suppression, cardiomyopathy, or recurrent PALF with infection or catabolic stress [5, 30].

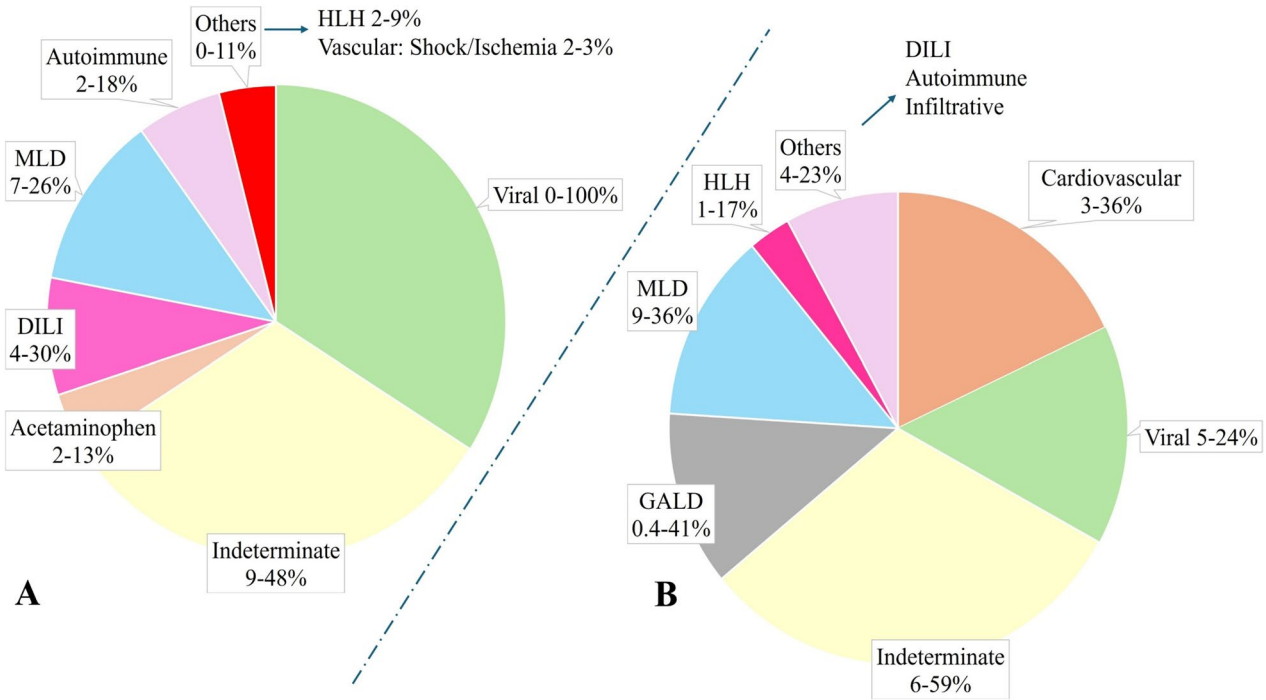

Fig. 1 Etiologies of pediatric acute liver failure in older (≥3 years age) (**A**) and younger children (<3 years age) (**B**)

Indeterminate PALF

Around 9–52% of children with PALF above 3 years of age and 6–52% under 3 years of age have indeterminate etiology [2–5, 14–28]. With the application of etiology-specific algorithms on a set of 303 'indeterminate' labeled adult ALF patients, it was shown that nearly half (46.9%) got a diagnostic label, thus decreasing the prevalence of indeterminate ALF to 5.5% [31]. A similar concept was utilized by PALFSG, where a collaborative learning approach for age-specific diagnostic tests was applied using an electronic medical record admission order set at hospital admission in three phases from 1999 to 2014. It was found that the diagnosis of indeterminate PALF decreased significantly from 48 to 30.8%, along with a decrease in the 21-day cumulative incidence rate for LT from 34.6 to 20.2%. This decline was present in all three age groups, but most significantly in the older (above 3 years) age group [2]. A modified version of the age-based stepwise algorithm is presented in Table 3.

Extended viral testing in PALF

Testing for an extended panel of viruses in the patients of the PALFSG cohort showed a positive viral (IgM, PCR or antigen) test in 166 (20.2%) of the 820 children tested for a causative or an associated virus. In the under-6 months age group, herpes simplex virus and Epstein–Barr virus were the common causative viruses, and cytomegalovirus and human herpes virus-6 were commonly associated viruses. In the older age group, herpes simplex virus, adenovirus, and parvovirus were the commonly detected causative viruses, and human herpes virus-6, Epstein–Barr viruses, and cytomegalovirus were the commonly associated viruses [32]. The study emphasizes that testing for viruses is often incomplete, and it should be more comprehensive to detect treatable viral etiologies of PALF.

There has been a sudden surge in cases of severe acute hepatitis/PALF since 2021. There are speculations of their association with adenovirus type 41, adeno-associated virus-2, and COVID-19. In a recent systematic review of 1643 children presenting with severe acute hepatitis, 120 (7%) required LT, and 24 (1%) died. There were inconsistent results for serological testing or testing of explants for these viruses, and considering the existing evidence, it was concluded that no definite explanation for causality could be made [33]. Another report from King's College Hospital (KCH), London mentioned that the presence of indeterminate PALF had a similar prevalence and association with adenovirus over the previous 5 years, although with a severe phenotype but similar survival to native liver in the year 2022 [34]. This again emphasizes the need for extensive viral testing of PALF cases.

Genetic testing for PALF

Genetic testing for PALF is important for identifying MLDs with a diverse or unrecognized phenotype. In a study from KCH, a next-generation sequencing (NGS) panel of 64 candidate genes identified homozygous or compound heterozygous variants in 12 (26.7%) out of 45 children tested by targeted and whole exome sequencing [35, 36]. A recent multicenter data on whole exome sequencing of 260 children with indeterminate PALF (22.7% recurrent PALF) from 19 countries showed the establishment of genetic diagnosis in 37%, with the highest diagnostic yield in infants (46%) and with recurrent PALF (64%). Common defects were linked to 36 genes related to mitochondria, vesicular trafficking, and cytosolic t-RNA synthetase and the common ones were *NBAS* (21%), *MPV17* (8%), and *DGUOK* (7%), followed by *TRMU, SCYL1, DLD, SERAC1, YARS1, LARS1 and ZNFX1* [36]. A prolonged turnaround time for genetic analysis is currently a potential limitation for any timely therapeutic intervention.

2. Recommendations:

   2.1. Etiological evaluation of pediatric acute liver failure should be undertaken based on the age and geographic location of the patient (LOE 3, strong recommendation).
   2.2. Genetic testing using whole-exome sequencing should be considered for children with pediatric acute liver failure of indeterminate etiology (LOE 4, strong recommendation).

Diagnosis of cerebral edema

The intracranial volume is contributed by three compartments: the brain, blood, and cerebrospinal fluid. According to the Monroe-Kellie doctrine, the intracranial volume is constant, and any increase in the volume of one of the compartments would lead to a compromise of the other 2 compartments. Hence, cerebral edema caused by ALF leads to compromised cerebral perfusion (ischemia). Cerebral edema can be present in as high as 55%–74% of adult ALF and is associated with high mortality [37, 38]. Factors associated with raised ICP are hyperacute ALF, younger age, higher grade HE, serum ammonia > 150 mmol/L, systemic inflammatory response syndrome, concurrent infection, and requirement for vasopressors [37, 39]. To reduce the mortality associated with PALF, all possible attempts should be made towards early detection and appropriate management of cerebral edema.

Table 3 Step-wise age-based diagnostic evaluation of pediatric acute liver failure* (Modified from reference [3])

		Age Group		
Tests	***Specific disease***	***0-90 days***	***3 mo – 3 years***	***3-18 years***
Step 1				
Herpes simplex PCR in blood	Systemic Herpes	■		
Urine NGRS	Galactosemia, HFI	■	■	
GALT assay	Galactosemia	■	■	
AFP	Tyrosinemia, GALD	■	■	
Urinary succinyl acetone	Tyrosinemia	■	■	
Lactate / Pyruvate	Mitochondriopathy	■	■	
Ferritin & Transferrin saturation	GALD	■		
Echocardiogram	Cardiac dysfunction	■		
Ferritin, Fibrinogen, Triglycerides	HLH	■	■	■
IgM HAV	Hepatitis-A		■	■
IgM HEV	Hepatitis-E		■	■
IgM Anti-HBc, HBsAg	Hepatitis-B		■	■
ANA, SMA, LKM, IgG	Autoimmune hepatitis		■	■
Ceruloplasmin, 24-hour Urine Cu, K-F Ring on Slit lamp examination#	Wilson disease			■
Step 2				
Lip biopsy	GALD	■		
MRI for extrahepatic siderosis	GALD	■		
Bone marrow aspiration / biopsy	HLH / NPC	■	■	■
Urine orotic acid	UCD	■	■	
Aminoacidogram (serum / urine)	UCD	■	■	
Enterovirus blood PCR	Enterovirus infection	■		
Carnitine / Acylcarnitine on TMS	FAOD	■	■	
EBV VCA IgM or PCR	EBV infection	■	■	■
CMV PCR	CMV infection	■	■	
HHV-6 PCR	HHV-6 infection	■	■	■
Parvo IgM or PCR	Parvovirus infection	■	■	■
Acetaminophen adducts level	APAP toxicity	■	■	■
Liver biopsy	AIH / Indeterminate / GCH	■	■	■
Careful history taking for Drug exposure	DILI	■	■	■
Step 3				
Soluble CD 25 (IL-2 receptor)	HLH	■	■	■
NK cell activity	HLH	■	■	■
Targeted or Whole exome sequencing	Specific Genetic disorder	■	■	■
Liver Copper estimation				■

Shaded boxes indicate essential tests as per step-wise approach in a particular age-group.

*These age-groups are not water-tight compartments; hence testing may be extended when there is a high index of suspicion for a certain disorder. The step-wise testing leads to resource utilization in an economically constrained setting but may have a limited role in the setting of an imminent liver transplantation.

#Kayser-Fleischer ring should be looked up on Slit-lamp examination by an experienced ophthalmologist in a conscious child. It won't be easy to perform in an encephalopathic child, where a hand-held slit lamp device can be used.

Abbreviations: AFP = Alpha-fetoprotein; ANA= Antinuclear antibody; CMV = Cytomegalovirus; DILI = Drug induced liver injury; EBV = Epstein-Barr virus; FAOD = Fatty-acid oxidation defect; GALD = Gestational alloimmune liver disease; GALT = Galactose-1-Phosphate uridyl transferase; GCH = Giant cell hepatitis; HAV

Shaded boxes indicate essential tests as per step-wise approach in a particular age-group

AFP Alpha-fetoprotein; *ANA* antinuclear antibody; *CMV* cytomegalovirus; *DILI* drug induced liver injury; *EBV* Epstein-Barr virus; *FAOD* fatty-acid oxidation defect; *GALD* gestational alloimmune liver disease; *GALT* galactose-1-phosphate uridyl transferase; *GCH* giant cell hepatitis; *HAV* hepatitis-A virus; *HBV* hepatitis-B virus; *HEV* hepatitis-E virus; *HFI* hereditary fructose intolerance; *HHV-6* human herpes virus-6; *HLH* hemophagocytic lymphocytosis; *IgG* immunoglobulin G; *IgM* immunoglobulin M; *K-F ring* Kayser-Fleischer ring; *LKM* anti-liver kidney microsomal antibody; *NGRS* non-glucose reducing substances; *NPC* Niemann–Pick type-C; *SMA* anti-smooth muscle antibody; *UCD* urea cycle defects

Table 3 (continued)

*These age-groups are not water-tight compartments; hence testing may be extended when there is a high index of suspicion for a certain disorder. The step-wise testing leads to resource utilization in an economically constrained setting but may have a limited role in the setting of an imminent liver transplantation

#Kayser–Fleischer ring should be looked up on Slit-lamp examination by an experienced ophthalmologist in a conscious child. It won't be easy to perform in an encephalopathic child, where a hand-held slit lamp device can be used

Clinical assessment of HE and cerebral edema

HE assessment is best performed using the West Haven Criteria in older children and using a modified HE assessment scale in children up to 3 years of age [1, 40]. The classical symptoms of cerebral edema include headache, blurred vision, vomiting, and alterations in mental status (somnolence to coma). Assessment of these classical signs and symptoms in PALF may be difficult due to HE, ventilation, and sedation. Physical signs that suggest significant cerebral edema are unilateral or bilateral false localizing sign i.e., 6th nerve palsy, Cushing response (hypertension, bradycardia), irregular respiration, spasticity, and decerebrate posture. Neurological examination including pupil size should be regularly monitored as per the grade of HE (q2 hourly in grade I, q60 min in grade II, q30 min in grade III–IV) [6]. Clinical signs of raised ICP are frequently late in emergence, hence all attempts should be made to detect raised ICP early by using a range of non-invasive techniques [41]. Direct monitoring of ICP is invasive, requires technical expertise [42] and is associated with a risk of intracranial bleeding. Therefore, non-invasive reproducible methods are gaining importance. The different non-invasive modalities for the assessment of ICP and cerebral perfusion include ONSD, TCD, reverse jugular venous oxygen saturation ($S_{jv}O_2$), and near-infrared spectroscopy (NIRS) (Table 4). A combination of two or more modalities may be used, depending on the availability, expertise, and experience at the center.

Optic nerve sheath diameter

Optic nerve sheath has anatomical continuity with the intracranial duramater; hence, any fluctuation in ICP is directly and rapidly reflected in the ONSD. Data on the correlation between ONSD and ICP have been established in studies on traumatic brain injury (TBI), pseudotumor cerebri, and raised ICP due to diabetic ketoacidosis. The cut-off values established in adult studies vary between 5.5 and 5.7 mm and a good correlation has been found between ONSD and invasive monitoring [43, 44]. ONSD values vary with age [45]. A recent study demonstrated that ONSD > 4.6 mm suggests raised ICP in children with PALF and a persistent elevation at this level beyond 24 h predicted poor outcome [46]. Further ONSD was found to be a reliable dynamic parameter to assess the therapeutic response to ICP lowering measures. Another study in PALF also demonstrated a cut off of 4.6 mm to differentiate PALF with HE vs without HE [47]. The same group could also differentiate non-transplant outcomes by ONSD when the cut-off considered was 5.1 mm with ≥ 80% sensitivity and specificity [47]. More studies are needed to establish the efficacy of ONSD in infants and young children.

Transcranial Doppler

TCD is a non-invasive neuromonitoring tool widely used to assess cerebral perfusion and guide therapy [41]. Cerebral perfusion is primarily dependent on two opposing forces: arterial blood pressure, which is the primary driving force for cerebral blood flow (CBF), and ICP, which opposes it [48]. Therefore, a rapid rise in ICP would alter CBF, which can be assessed using TCD. The skull has several potential windows that are used to evaluate intracranial vessels in the circle of Willis. Middle cerebral artery (MCA) is most commonly evaluated vessel in adults with ALF and is examined through the transtemporal window [49–52]. Raised ICP results in increased peak systolic velocity, decreased end-diastolic flow velocity (EDV), and decreased mean flow velocity (MFV), resulting in an increased pulsatility index (PI). Falsely elevated PI may be seen in arterial hypotension and hypocapnia. Another important finding in raised ICP is the loss of the Windkessel effect on TCD tracings, although none of the findings have conclusively been shown to correlate with the outcome [49–52]. Estimated ICP calculated using the flow velocity parameters obtained through TCD and mean arterial pressure (MAP) has been shown to correlate well with invasive ICP in adults with ALF [48–50]. The estimated cerebral perfusion pressure (CPPe) is first estimated using the formula CPPe = MAP * EDV/MFV + 14. The estimated ICP is then calculated using the following formula: $ICP_{TCD} = MAP - CPPe$. Larsen et al. demonstrated improvement in the MFV of the MCA after TPE [53]. There is only 1 study in PALF that showed a lower nadir of EDV and a higher peak of PI in non-survivors [54]. Recently introduced automated TCD machines have the potential advantages of a smaller learning curve, less inter-observer variability, and the possibility of using it as a continuous monitor.

Table 4 Modalities for non-invasive assessment of intracranial pressure in children

Modalities	Principle	Interpretation	Pros and cons
Optic nerve sheath diameter (ONSD)	Optic nerve sheath has anatomical continuity with the intracranial dura mater and reflects fluctuation in ICP as changes in the diameter of the nerve sheath Uses regular Ultrasound machine with 6.5-10 MHz probe 3 readings in both the eyes are taken to minimize intraobserver variability	ONSD > 4.6 mm indirect evidence of raised ICP in PALF ONSD > 4.6–5.1 mm suggests poor outcome	Dynamic, changes within minutes of change in ICP, thus can be used to assess therapeutic response Operator dependent, difficult to measure in combative patient
Transcranial Doppler (TCD) (Automated & non-automated)	Assesses cerebral perfusion by measuring the flow velocities in the intracranial arteries ICP calculated using the formula: $ICP_{TCD} = MAP - (MAP*EDV/MFV + 14)$	Increased ICP leads to decreased diastolic velocity, mean flow velocity; and increased peak systolic velocity and pulsatility index	Continuous monitoring feasible Automated TCD devices expensive but have shorter learning curve
Reverse Jugular venous oxygen saturation ($S_{jv}O_2$)	$S_{jv}O_2$ measures O_2 saturation in the venous drainage from the brain through the jugular vein. It reflects the balance between cerebral oxygen supply and demand, offering an indirect indicator of cerebral metabolic rate Normal $S_{jv}O_2$: 60–80%	$S_{jv}O_2 < 60\%$: increased oxygen extraction by brain due to increased cerebral metabolism (raised ICP, seizure, fever) $S_{jv}O_2 > 80\%$: decreased cerebral oxygen extraction due to cerebral hyperemia	Can guide appropriate therapy whether osmotherapy or measures to reduce cerebral blood flow Invasive lines needed increasing risk of infection
Near infra-red spectrometry (NIRS)	Spectroscopic analysis of regional perfusion changes based on hemoglobin content At the near infrared spectrum of light there is low absorptivity that allows deep tissue penetration	Asymmetric values indicate intracranial hemorrhage Lower values indicate poor cerebral perfusion	No data on its utility in neuro-monitoring in pediatric acute liver failure
Continuous Electroencephalography (EEG)	Measurement of electrical activity of brain and detection of seizures, particularly non-convulsive	Burst suppression; decreased frequency/amplitude indicate raised ICP Useful to detect non-convulsive seizures in cases of refractory cerebral edema	Can be monitored continuously Requires neurologist to interpret Findings affected by drugs like propofol and thiopentone

ICP Intracranial pressure; *EDV* early diastolic velocity; *MAP* mean arterial pressure; *MFV* mean flow velocity; *ONSD* optic nerve sheath diameter; $S_{jv}O_2$ reverse Jugular venous oxygen saturation; *TCD* transcranial doppler; *NIRS* near infra-red spectrometry; *EEG* electroencephalogram

Reverse jugular venous oxygen saturation ($S_{jv}O_2$)

$S_{jv}O_2$ monitoring involves measuring oxygen saturation in venous drainage from the brain through the jugular vein. This reflects the balance between cerebral oxygen supply and demand and offers an indirect indicator of cerebral oxygen extraction. Normal $S_{jv}O_2$ varies between 60 and 80%. A decreased value of < 60% suggests increased oxygen extraction by brain due to increased cerebral metabolism, which could be either due to seizures, fever, or raised ICP. On the other hand, increased $S_{jv}O_2$ beyond 80% indicates decreased cerebral oxygen extraction due to cerebral hyperemia. This information can guide the planning of appropriate therapies. Limited data in adult ALF have suggested that $S_{jv}O_2$ may have a potential role in guiding the therapy of raised ICP [55, 56]. Measuring $S_{jv}O_2$ needs skill, special equipment, optical sensors, is invasive and a surrogate test for cerebral oxygen extraction.

Near infrared spectroscopy (NIRS)

NIRS provides a measure of cerebral oxygenation and can detect changes in cerebral blood volume (CBV), brain tissue oxygenation and CBF. In the near-infrared spectrum of light, there is low absorption that allows deep tissue penetration. The variability of absorption helps quantify the detected changes in the concentrations of deoxyhemoglobin and oxyhemoglobin. Asymmetrical or extreme values in children attending the emergency department without a history of trauma have been found to correlate with evidence of intracranial hemorrhage on head computed tomography [57, 58]. It has been used as a surrogate marker of cerebral perfusion in studies of cerebral autoregulation in adult ALF [59, 60].

Electroencephalogram

About 25–30% of all ALF may have focal or generalized seizures [61]. There are also chances of subclinical seizures that may remain undetected unless electrical brain wave patterns are continuously assessed. Electroencephalography (EEG) can also help guide prognostication. However, EEG is affected by drugs commonly used in ALF, such as propofol, thiopentone, and requires expert interpretation by a neurologist.

3. Recommendations:

   3.1. Clinical assessment is essential but not always reliable for the assessment of raised intracranial pressure because classical clinical signs appear late in the course of the disease (LOE 5, strong recommendation).

   3.2. Measurement of optic nerve sheath diameter, is useful for the diagnosis of raised intracranial pressure in pediatric acute liver failure. It can be helpful in monitoring the course and outcome of therapies for cerebral edema (LOE 3, strong recommendation).

   3.3. Transcranial Doppler can be a useful dynamic, non-invasive modality for the diagnosis and monitoring of elevated intracranial pressure in pediatric acute liver failure (LOE 4, strong recommendation).

   3.4. Reverse jugular venous oxygen saturation and near infrared spectroscopy may be used for assessing cerebral oxygen extraction as a marker of cerebral blood flow in pediatric acute liver failure (LOE 4, weak recommendation).

Management of cerebral edema

Cerebral edema in PALF results from various factors including ammonia buildup, blood–brain barrier disruption, systemic inflammation, and electrolyte imbalances, leading to vasogenic and cytotoxic edema. Managing this condition is crucial for ALF patients' outcomes [62]. Mortality rates in PALF are 20%–35%, highlighting the importance of timely and aggressive management of cerebral edema. Strategies such as minimal stimulation, head elevation, and hyperosmolar therapy with mannitol or hypertonic saline (HTS) are essential interventions. All patients should be nursed in a quiet environment with a 20–30° head-up position to improve cerebral venous drainage. Raising the head-end of the bed also decreases the risk of ventilator-associated pneumonia. Frequent suctioning, patient turning, and other tactile stimulation should be cautiously performed. The patients should be kept well oxygenated. Osmotherapy (mannitol and HTS) is the first-line treatment for cerebral edema in PALF. Refractory cerebral edema may warrant deep sedation using propofol and/or thiopentone although it needs to be kept in mind that these agents can cause fall in MAP, which might actually worsen the CPP. Addition of vasoactive agents may be considered in such patients to maintain adequate CPP while using these medications. The role of therapeutic hypothermia and hyperventilation (P_aCO_2: 30–35 mmHg) in the management of cerebral edema has not been well established.

Mannitol and hypertonic saline in cerebral edema

Meta-analyses in adults with TBI favor HTS over mannitol for reducing ICP and improving short-term survival [63, 64]. However, evidence supporting their use in ALF is limited,

with potential side effects including acute kidney injury and metabolic disturbances associated with both treatments [65]. It is usually recommended to avoid mannitol in the presence of AKI or serum osmolality greater than 320 mOsm/L.

Experience in children with neurocritical illness Two randomized controlled trials (RCT) [66, 67] showed that both mannitol and HTS reduce ICP in children. While one study found HTS to be superior in acute meningitis, showing greater ICP reductions and improved outcomes [66], the other found no significant difference in patients with TBI [67]. HTS, particularly at 3% concentration, correlates with shorter mechanical ventilation and intensive care unit (ICU) stays, but mortality differences remain statistically insignificant [68, 69]. A recent meta-analysis found no significant differences in mortality or key outcomes between HTS and mannitol but noted increased serum osmolality with HTS [70]. The target serum sodium concentration is 145–155 mEq/L; while levels exceeding 160 mEq/L pose higher risk of hyperchloremic acidosis [70, 71].

Experience in ALF No RCTs have examined the efficacy of mannitol and HTS in the context of PALF. An RCT demonstrated that patients treated with 30% HTS aiming at serum sodium levels of 145–155 meq/L, showed significant improvement in response, although this did not translate into significant differences in overall survival or NLS [72]. Another RCT in adult patients found no significant difference between mannitol bolus and 3% HTS infusion (with serum sodium less than 160 meq/L) in reducing ICP, length of stay in ICU, and NLS [73]. A prospective cohort study involving PALF patients observed that 66% of patients who received a combination treatment of mannitol followed by continuous infusion of 3% HTS experienced a significant decrease in ONSD [46].

4.1. Recommendations:

4.1.1. Hypertonic saline should be used for the prevention and treatment of cerebral edema in pediatric acute liver failure. The target serum sodium level should be maintained at 145–155 meq/L (LOE 3, strong recommendation).

4.1.2. Mannitol should be used for the treatment of cerebral edema in pediatric acute liver failure. Care should be taken in patients with renal impairment or those with serum osmolality greater than 320 mOsm/L (LOE 3, strong recommendation).

Role of propofol, barbiturates, fentanyl and other therapies (hypothermia and hyperventilation) in the management of cerebral edema.

There is a lack of adult and pediatric data evaluating the role of propofol, thiopentone, and other therapies aimed at decreasing the metabolic activity of the brain in ALF. Propofol is a potent short-acting sedative-hypnotic as well as an anticonvulsant that decreases the cerebral metabolic rate. It is widely used for managing increased ICP, and continuous monitoring of ICP guides titration, although caution should be exercised when using it for mitochondrial defects [74]. Studies, including an RCT on ALF, support its efficacy in controlling ICP, making it a common choice in clinical practice [75–77]. Dexmedetomidine is a highly selective alpha agonist with sedative, anxiolytic, hypnotic, and analgesic properties and is used for ICU sedation in children at some centers. Thiopental, an ultra-short-acting barbiturate historically used for ICP, decreases cerebral metabolic rate, potentially lowers ICP, and provides cerebral protection. Limited research supports its effectiveness in reducing ICP leading to positive outcomes in head trauma and craniotomy [78–80]. There are issues in the follow-up assessment of the pupillary size and reaction after the administration of thiopentone, propofol, and fentanyl. Although theoretically beneficial, the use of flumazenil has not been studied in this context [81, 82]. Concurrent usage of opioid analgesics, such as fentanyl, can reduce the required doses of anesthetic agents, thereby improving cardiovascular stability [83].

Therapeutic hypothermia in ALF aims to lower cerebral metabolism and reduce cerebral blood flow to alleviate cerebral edema. A multicentric RCT did not show any significant benefits of therapeutic hypothermia [84]. However, large multicentric retrospective and small prospective observational studies suggest a beneficial effect of therapeutic hypothermia as a bridge to LT [85–87]. Controlled hyperventilation can temporarily reduce ICP, but risks cerebral vasoconstriction with prolonged use, potentially worsening cerebral ischemia. Studies on ALF are limited, inconclusive, and lack randomized controlled trials [56, 88].

4.2. Recommendations:

4.2.1. There is no consensus on the use of propofol/dexmedetomidine infusion for sedating intubated patients with pediatric acute liver failure (LOE 2, weak recommendation).

4.2.2. Fentanyl is useful for analgesia in patients with increased intracranial pressure (LOE 5, strong recommendation).

4.2.3. Thiopentone infusion can be considered in refractory cases of raised intracranial pressure in pediatric acute liver failure (LOE 4, weak recommendation).

4.2.4. Normocarbia and euthermia should be maintained in patients with pediatric acute liver failure (LOE 4, strong recommendation).

Fluid management in PALF

Fluid management in ALF is important as dehydration can occur due to repeated vomiting and poor oral intake. This state of hypovolemia is complicated by fluid redistribution due to systemic inflammatory response syndrome (SIRS) and sepsis [89]. Therefore, the goal of fluid management is to ensure euvolemia. There have been no studies on fluid therapy in the setting of PALF. The hemodynamic changes (vasoplegic hyperdynamic) seen in ALF resemble those seen in septic shock, and advanced ALF is characterized by vasogenic and cytotoxic cerebral edema as seen in TBI [90]. Thus, studies conducted in children with septic shock and TBI may be used to guide fluid management in PALF patients.

Fluid balance

Studies in adult patients with TBI have shown that a net positive daily fluid balance is associated with a higher risk of pulmonary edema and mortality while a negative fluid balance is also associated with high mortality [91–93]. A recent meta-analysis of euvolemic versus hypervolemic fluid balance strategies in pediatric sepsis showed higher respiratory dysfunction and mortality rates in children with hypervolemia [94]. This suggests that in PALF, both positive and negative fluid balances may be detrimental, and euvolemia should be targeted. The hazards of fluid bolus without checking for fluid responsiveness in pediatric septic shock were demonstrated in the FEAST trial [95]. A meta-analysis of fluid responsiveness following fluid bolus in adult ICU patients has shown that half of the patients show an increase in cardiac preload [96]. No studies have assessed fluid bolus resuscitation in PALF patients with shock; however, since fluid overload is associated with adverse outcomes. Fluid bolus without checking for fluid responsiveness, should be avoided.

Assessment of fluid responsiveness and type of fluid

Use of advanced hemodynamic variables such as respiratory variation in aortic blood peak velocity, inferior vena-cava distensibility index, and stroke volume variation, have good sensitivity and specificity in predicting fluid requirement in pediatric patients and may be used to guide fluid therapy [97–101]. As liver dysfunction leads to lactate accumulation, using trends in blood lactate levels to guide fluid resuscitation should be avoided [89]. The post hoc analysis of SAFE trial, which randomized adult ICU patients to receive either 4% albumin or normal saline, showed significantly higher mortality in the albumin group for patients with TBI, especially in severe brain injury and cerebral edema [102]. Extrapolating data from a recent meta-analysis in children with sepsis has shown that the use of balanced crystalloids leads to a significantly lower overall mortality and incidence of acute kidney injury than isotonic saline [103]. Since the metabolism of lactate is compromised in liver failure, Ringer's lactate should be avoided [89]. The use of starches has been associated with an increased need for blood transfusion and renal replacement and should also be avoided in PALF [104].

Enteral nutrition

Adequate calories and protein (1–1.5 g/kg/day) can be safely administered as tube feeds to patients on ventilator support. Concentrated solutions of intravenous dextrose (25% or 50% dextrose) may be added to maintain blood sugar without causing fluid overload. Keeping in mind the suspected inborn error of metabolism, the specific component can be removed from the diet until the disorder is confirmed, for example, hereditary fructose intolerance, galactosemia, fatty acid oxidation defect, etc.

5. Recommendations:

5.1. Euvolemia should be targeted using balanced crystalloids in pediatric acute liver failure patients with careful avoidance of hypovolemia and hypervolemia (LOE 1, strong recommendation).

5.2. Advanced hemodynamic monitoring in expert hands should be considered to assess fluid responsiveness and tolerance for fluid therapy in pediatric acute liver failure (LOE 2, weak recommendation).

Coagulopathy in PALF

Acute liver failure is a state of rebalanced hemostasis in which there is a proportional reduction in both pro-and anticoagulant factors [105–107]. ALF patients do not bleed spontaneously unless this balance is disturbed by sepsis, disseminated intravascular coagulation, thrombocytopenia, or hypofibrinogenemia [108]. The most common spontaneous bleeding sites in ALF are the self-limiting upper gastrointestinal mucosal bleeds. More importantly, deranged

INR values are not associated with spontaneous bleeding [42, 109]. This is because the INR does not consider concomitant reduction in antithrombotic factors. Routine correction of INR by prophylactic transfusion of fresh frozen plasma must be avoided, as this disturbs serial monitoring for prognostication and causes fluid overload. Major bleeding events during low-risk invasive procedures are rare and more dependent on the technique used to perform the procedure. Minor bleeding events such as superficial hematoma or persistent oozing from the puncture site are also uncommon [110–112]. Bleeding rates of 3–18% reported post high-risk procedures (intra cerebral monitor placement) in adult ALF can be reduced by targeted correction of INR, platelet count, and fibrinogen [113–118]. Viscoelastic tests measure clot formation in real-time and reduce blood component requirements without increasing bleeding rates in adults and children with CLD [119–123]. In ALF, these tests are more hypocoagulable in patients with bleeding events and LT/death than in those with NLS [124]. As PALF is a state of rebalanced hemostasis, the use of viscoelastic tests in this setting may decrease unnecessary transfusions.

6. Recommendations:

   6.1. Routine correction of the INR is not recommended for low-risk invasive procedures (central venous cannulation, hemodialysis catheter insertion, ascitic tap, pleural tap) (LOE 3, weak recommendation).
   6.2. Targeted correction of conventional coagulopathy parameters (INR, platelet count, and fibrinogen levels) should be done prior to high-risk invasive procedures (percutaneous or transjugular liver biopsy) (LOE 3, strong recommendation).
   6.3. Viscoelastic tests should be used, if available, for assessment and correction of coagulopathy before invasive procedures (LOE 2, strong recommendation).

Laboratory investigations to assess severity and extrahepatic involvement in PALF

A complete blood count, liver profile, prothrombin time-INR, and renal profile are required daily. Arterial blood gas and lactate need frequent monitoring especially in patients on ventilator, CRRT or hemodynamic instability. Frequent monitoring of blood sugars is recommended until the sugar values stabilize and spontaneously improving blood sugars is a good prognostic sign in ALF [125]. The North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition suggested that blood sugars should be maintained between 90 and 120 mg/dl to prevent seizures but experts opined that instead of this narrow range, we should target levels of 100–150 mg/dl [6].

Ammonia levels > 100 µmol/L on admission predict the risk of developing advanced HE [37], and a level > 200 µmol/L is strongly associated with risk of cerebral herniation [126]. For testing ammonia levels, blood should be collected in a heparinized syringe, either an arterial sample (preferably) or a free-flowing venous sample. The specimen must be placed in an ice pack and sent immediately to the laboratory. Plasma should be separated within 15 to 30 min of collection and processed to avoid erroneous results. Refractory hypotension secondary to relative adrenal insufficiency was identified by a positive short synacthen test in 62% of 45 adults with ALF [127]. Serum cortisol may be performed in refractory hypotension with PALF, although there is no pediatric data to support the recommendation.

7. Recommendations:

   7.1. INR is a sensitive marker of acute liver failure and should be done every 8–12 h, till a declining trend is observed (LOE 5, strong recommendation).
   7.2. Complete blood counts, ammonia, and biochemistry (transaminases, bilirubin, albumin, creatinine, electrolytes, phosphorus, blood gas/lactate) should be closely monitored (LOE 5, strong recommendation).
   7.3. The target blood sugar should be maintained between 100 and 150 mg/dL and should be monitored every 8–12 h (LOE 5, strong recommendation).

Role of liver biopsy in children with ALF

Knowing the etiology of ALF helps to offer specific therapies such as immunosuppression in autoimmune hepatitis (AIH), identifying conditions where LT is contraindicated (e.g., mitochondrial disorders, leukemia, etc.), and prognosticating the outcome [6]. Liver biopsy, including immunohistochemistry and electron microscopy) is one of the modalities used to determine etiology and help differentiate between ALF and acute-on-chronic liver failure [111, 128]. Transjugular liver biopsy (TJLB) is feasible, safe, and provides adequate tissue both in children and adults with coagulopathy and ascites. However, it is expensive and requires expertise, and most of the experience with it is in older children, mostly older than 2–3 years of age. Additionally, the facilities for TJLB are available at a few centers only. Several studies in children including a systematic review have confirmed the safety of TJLB [129–132]. Plugged percutaneous liver biopsy where the biopsy tract is plugged

with gel foam/coils to reduce the risk of bleeding has been safely performed in infants/young children. Most studies included patients with mild coagulopathy after blood product transfusion or after paracentesis for ascites [133–135]. There is a need to define the cut-off of INR/platelet count for the safe performance of plugged percutaneous liver biopsy in children and for transfusion of blood products. Data on both transjugular and plugged percutaneous liver biopsies in PALF is limited.

In adults, the severity of necrosis on liver biopsy has been shown to predict outcomes, with cases having more than 70% necrosis requiring LT [136]. A single pediatric study with 94 biopsies, 22 of which were antemortem, showed that increasing severity of hepatocyte loss (adjusted OR 9.95, 95% CI 4.22–23.45, $p < 0.001$) was an independent predictor of poor outcome. Eighty percent of children with more than 50% hepatocyte loss had a poor outcome (death/LT) within 10 days of admission [137]. We need to accept the limitations of the size of tissue sampled and variability in histology due to sampling bias. The published data on liver biopsy in ALF are limited, mostly in the form of retrospective case series [111, 129, 130, 137, 138]. No RCTs have examined the utility of biopsy in ALF.

8. Recommendations:

    8.1. Liver biopsy, preferably via the transjugular route, may be considered under expert hands, in select cases of acute liver failure of indeterminate origin, suspected autoimmune hepatitis, or systemic diseases such as malignancy (LOE 2, weak recommendation).

Infections in acute liver failure

Children with PALF are at an increased risk of infection due to underlying immune dysregulation. Hepatocyte injury releases damage-associated molecules that initially activate the innate immune system. The release of pro-inflammatory cytokines results in SIRS and anti-inflammatory cytokines can cause monocyte dysfunction and inactivation. Poor fibronectin production affects Kupffer cell function and poor complement secretion impedes opsonization [139]. The incidence of infections in ALF in adult studies varied between 26.6 and 76.9% among those who were already treated with prophylactic antibiotics [140, 141]. Among the PALF patients, sepsis was reported in 20 to 68.9% [4]. Sepsis is attributed as the cause of death in 8% of PALF [142].

Types of infection

Infection at admission is seen in 22% of adults, and 59% of children are infected within 48 h of admission [140, 143]. Among adults with ALF, bacterial infections are found in 70 to 80% and fungal infections in 4 to 28% [139–141]. Bacterial infections account for 60–100% of infections in PALF and fungal infections for 40% [143, 144]. The average time to bacteremia was 2 days, and that to fungemia was 4 days [144]. The predominance of gram-negative bacteria is reported among adults in India from 73 to 90% [140, 141]. However, data from the West indicate a higher incidence of gram-positive bacteria up to 44% [145]. Among children, gram-positive infections are found in 6% to 47% [143, 144]. Commonly identified gram-negative organisms include *Acinetobacter baumannii* (9–39%), *Klebsiella pneumoniae* (9–25%), Escherichia coli (2–15%), and *Pseudomonas aeruginosa* (9–19%), and common gram-positive organisms include *Staphylococcus aureus* (3–13%) and Enterococcus (3–15%) [140, 141, 145]. Extended-spectrum beta-lactamase-producing organisms have been isolated in 40%, carbapenem resistance in 56%, and multidrug resistance in 13% of adults with ALF [141]. In an Indian study among children resistance to 3rd generation cephalosporin has been identified in 89%, quinolones (79%), carbapenems (33%), vancomycin (10%), and multiple-drugs (26%) [143]. The major sites of infection are the bloodstream (8–62%), respiratory (14–45%), urinary tract (14–37%), and ascitic fluid (3–12%) [140, 141, 143, 144, 146].

Infections and outcome

Arterial ammonia, model for end-stage liver disease (MELD), advanced HE, cerebral edema, creatinine, PT-INR, invasive catheters, and mechanical ventilation have been identified as predictors of infection in adults with ALF [140, 141, 145]. There are contradictory results regarding the impact of infections on outcomes in adults with ALF [145, 147]. None of the pediatric studies have shown a higher risk of mortality in infected children with ALF, although the number of days of ventilation, hospitalization, and intensive care unit stay was higher in patients with infection [4, 143, 144, 146]. The threshold for starting antibiotics may be lower in patients with worsening grades of HE/cerebral edema, hyperammonemia, central venous and urinary catheterization, and more than 2 SIRS components.

Laboratory investigation to assess infections

Relevant body fluids (blood, urine, tracheal/sputum, ascitic fluid) are sent for aerobic and fungal cultures [6]. In the presence of central venous access, blood needs to be collected from the peripheral line and central venous catheter

to diagnose catheter-associated bloodstream infection. Surveillance cultures may be performed at regular intervals or when an infection is suspected. This could be when there are localized symptoms or general indicators of infection, such as fever, hypothermia, hypotension, high WBC count, or deterioration in the form of worsening encephalopathy and renal or cardio-respiratory function. Studies in adults have reported fungal infections in approximately 1/3rd of patients [148], although they are not common in children [146]. PCR-based tests may be used if cultures are negative and clinical suspicion is high. Procalcitonin is used as a marker of bacterial infections and is produced by many organs, especially the liver. Procalcitonin levels are often high in ALF due to inflammation and massive hepatic necrosis [149]. Therefore, high procalcitonin values do not necessarily correlate with the presence of SIRS or infection [149]. Bolia et al. showed that procalcitonin and CRP had better diagnostic accuracy for predicting infection in patients with decompensated CLD than ALF [150].

Antibiotics—prophylaxis vs treatment

Antibiotic prophylaxis administered to 39% of adults with ALF showed no difference in the incidence of bloodstream infections (15.7% vs 12.8%, $p=0.12$). Although those who developed bacteremia had higher 21-day mortality, antimicrobial prophylaxis did not have any impact on survival [140]. Antimicrobial prophylaxis in combination with gut decontamination does not offer any additional survival benefits [140]. There are no data available to assess whether the administration of antimicrobial prophylaxis will predispose patients to more resistant bacterial or fungal infections. Surveillance culture-guided treatment of specific infections and escalation or de-escalation as per the sensitivity is prudent. Local sensitivity patterns should be used to guide the choice of antibiotics.

9. Recommendations:

    9.1. Cultures: blood, urine, tracheal/bronchioalveolar lavage (bacterial, fungal) should be performed at presentation depending upon the clinical status. Polymerase chain reaction-based tests may be used if cultures are negative and clinical suspicion remains high (LOE 3, strong recommendation).
    9.2. There should be a low threshold for initiating prophylactic antimicrobials (antibiotics and antifungals) in patients with pediatric acute liver failure awaiting cultures (LOE 5, strong recommendation).
    9.3. Antimicrobials should cover gram-positive, and gram-negative bacteria and fungus (LOE 3, strong recommendation).
    9.4. Modification (escalation and de-escalation) of antibiotics should be performed in hospitalized patients with pediatric acute liver failure based on the clinical course, biomarkers, culture, and sensitivity (LOE 3, strong recommendation).

Bridging therapies in PALF

Liver failure in PALF is associated with high mortality in the absence of LT. The mechanisms of liver failure are thought to be driven by SIRS, which in turn dysregulates the immune activation triggered by both microbial and non-microbial factors. ELSS is the extracorporeal removal of large compounds and toxins (both albumin bound and water soluble) from the blood and replacement with plasma and/or albumin. In recent years, some non-biological and biological ELSS have gained popularity in bridging PALF to spontaneous recovery or LT. Table 5 describes the principles and characteristics of various non-biological and biological ELSS.

Therapeutic plasma exchange in pediatric acute liver failure

TPE is a promising intervention for PALF, aimed at mitigating the systemic inflammatory response, removing toxins, and improving coagulopathy [151–153]. Although there is limited data to compare the efficacy of centrifugation and membrane filtration techniques of TPE, a recent study demonstrated the superiority of the centrifugation technique due to its higher plasma clearance capacity [154]. The amount of plasma volume exchanged can vary from high-volume TPE [2 to 3 times the plasma volume], standard-volume TPE (1.5 to 2 times plasma volume), or low-volume TPE (0.5 to 1 times plasma volume) [151, 152, 155, 156]. The plasma volume is calculated as follows: blood volume × (100 − hematocrit), where the blood volume ranges from 60 to 80 ml per kg depending on the age. Low-volume TPE has been exclusively evaluated in ALF caused by toxic ingestions such as yellow phosphorus poisoning [155, 156].

Mechanism of action of TPE in ALF The various mechanisms demonstrated for the action of TPE in ALF include the removal of pro-inflammatory cytokines, inflammatory macromolecules, and toxins in addition to the replenishment of coagulation factors and other plasma proteins synthesized in the liver [151–153]. High-volume TPE leads to the removal of damage-associated molecular patterns, endotoxins, and circulating pro-inflammatory mediators, such as TNF-α, IL-6, and IL-8, resulting in the improvement of the phagocytic function of monocytes and marked amelioration of

Table 5 Various extracorporeal liver support systems in pediatric acute liver failure

Biologic Principles	Key features	Pros/cons and considerations for use
Non-cellular/non-biologic		
Continuous renal replacement therapy (CRRT)		
Removes low molecular weight water-soluble substances like ammonia, potassium, lactate, urea, and creatinine Correction of hyperammonemia, fluid overload, metabolic acidosis and electrolyte imbalance is the key in PALF	Reduces ammonia levels without rapid fluid shifts Maintains acid–base and electrolyte balance Could be used in smaller children (< 10 kg) through adult machines with the use of an appropriate-size catheter for vascular access and a smaller filter	Does not remove albumin- bound toxins, bile acids, or bilirubin Continuous anticoagulation (heparin, citrate or prostacyclin) is required to prevent circuit clotting Blood priming is needed for infants Dialysis catheter is required, thereby increasing risk of bleeding, clotting, infections
Therapeutic plasma exchange (TPE)		
TPE removes the pro-inflammatory cytokines, DAMPs, inflammatory macromolecules, and all other toxins present in the plasma of PALF patients It replenishes the coagulation factors and other plasma proteins	Patient plasma is separated and eliminated from whole blood, and replaced by fresh frozen plasma Maintains fluid and protein neutrality High volume TPE exchanges 2–3 times plasma volume, standard volume (1.5–2 times) and low volume (0.5–1 times volume) Feasible and safe in children	Since TPE is intermittent, the effect is short-lived There is exposure to plasma products since exogenous FFP is given Increases the load on the blood bank Artificially alters INR, bilirubin, etc. making prognostication difficult Immunoglobulins and beneficial growth factors may be removed
Molecular adsorbent recirculating system (MARS)		
Removal of water bound as well as protein bound toxins that accumulate in the blood in PALF, without exposing the child to exogenous blood products	Blood is circulated across an albumin permeable (5–60 kDa) membrane against a 20% human albumin dialysate Toxins bind to albumin in the dialysate, which is then subject to hemodialysis to remove water soluble toxins The albumin passes through a charcoal column where protein-bound toxins are adsorbed and cleansed in an anion exchange resin column before being recirculated	Minimize exogenous protein (albumin/plasma) load Ability of exogenous albumin to adsorb toxins wanes with time Resource intensive, extremely expensive
Cellular/Biologic		
Extracorporeal assist device		
Hepatocytes obtained from human hepatoblastoma cell line are integrated into a device to provide functional activity to a patient with PALF Can provide the synthetic functions of liver in addition to the toxins removal	Comprised of hollow fiber dialysis cartridges that are lined with the cells. Blood comes in contact with the cells while flowing through the cartridges	Can generate albumin and metabolize drugs Not efficient for ammonia detoxification No added benefit in survival compared to standard therapy, thus production of these devices has been halted
Spheroid reservoir bio-artificial liver		
Primary healthy swine hepatocytes in a bioreactor are capable of providing functional activity	Hollow fiber dialyzer detoxifies blood, while primary swine hepatocytes spheroids enhance detoxification and protein synthesis	Can generate albumin, metabolize drugs in swine models of D-galactosamine induced liver failure Human trials pending

CRRT Continuous renal replacement therapy; *DAMPs* damage associated molecular patterns; *INR* international normalized ratio; *MARS* molecular adsorbent recirculating system; *PALF* pediatric acute liver failure; *FFP* fresh frozen plasma; *TPE* therapeutic plasma exchange

SIRS [151, 152]. TPE has also been shown to remove acute inflammatory macromolecules, such as Von Willebrand factor, which are postulated to accumulate in the hepatic sinusoids, resulting in a functional sinusoidal obstruction and compromised microcirculation [152, 155, 156]. Amelioration of SIRS results in improved systemic vascular resistance index (SVRI), improved MAP, decreased vasopressor requirement, improved cerebral and hepatic blood flow, and decreased organ failures [151, 152, 157]. TPE also lowers ammonia levels, leading to improvement in HE, and reduction in cerebral edema [152, 158].

Studies in adults Two important RCT in adults have demonstrated the efficacy of TPE. Larsen et al. conducted an RCT showing improved NLS and decreased requirement for renal replacement therapy in patients treated with high-volume TPE [151]. Similarly, Maiwall et al. reported improved NLS with standard-volume TPE in ALF with cerebral edema and no available donor for LT [152]. Apart from these two RCTs, several retrospective studies using matched or unmatched historical controls demonstrated improved NLS with the use of TPE in ALF [159, 160]. A recent systematic review by Beran et al. included five studies (343 patients) and concluded that TPE led to higher survival rates than SMT alone [161]. Recently, TPE has been recommended as a first-line stand-alone treatment modality for adult ALF patients by the European Association for the Study of the Liver (EASL) and American Society for Apheresis [10, 162]. Due diligence is required in light of the finding that TPE also clears growth factors present in the plasma of patients with patients [152]. However, NLS was improved in the TPE group despite this fact, suggesting that the timing of TPE may be crucial and may be more beneficial in the early phase of ALF when SIRS is predominant and regenerative factors are minimal.

Studies in children Unlike adults, no RCTs evaluate TPE's efficacy in children with ALF. Except for one recent propensity-matched analysis [163] and another prospective study in children with Wilson disease [164], most pediatric studies have been retrospective studies without a control arm [165–171]. Most pediatric studies have found that TPE is feasible and safe even in young children [165–171]. A recent analysis including 65 patients in the TPE arm and an equal number of propensity-matched controls demonstrated improved NLS and OS in the TPE arm [163]. On subgroup analysis, the survival benefit was predominantly seen in HAV-related PALF [163]. Importantly, Chien et al. showed the futility of performing extra sessions of TPE in PALF not responding to the initial six sessions of TPE [166]. Standard volume TPE led to improved NLS compared to SMT in a controlled study in children with Wilson disease presenting with ALF [164]. Even low-volume TPE (0.5 × the plasma volume) led to improved NLS (75%) in rodenticide poisoning related PALF, where mortality was high before the introduction of TPE [156]. Table 6 lists various studies evaluating TPE as a standalone treatment modality in adults and children with ALF. There is an urgent unmet need to conduct RCT in children to assess the efficacy of TPE and to compare the various volumes (high, standard, and low) and protocols (once daily vs. twice daily) to determine the optimal TPE protocols for therapeutic benefit without adding burden to the already strained blood banks in resource-limited settings.

10.1. Recommendations:

10.1.1. Therapeutic plasma exchange may be considered as a bridge to recovery of native liver or to liver transplantation in pediatric acute liver failure fulfilling listing criteria if transplant options are available (LOE 4, weak recommendation).

10.1.2. Therapeutic plasma exchange should be considered in pediatric acute liver failure fulfilling listing criteria if the liver transplant option is not available (LOE 4, strong recommendation).

10.1.3. Therapeutic plasma exchange should be considered in pediatric acute liver failure due to Wilson disease, hepatitis A, or yellow phosphorus poisoning (LOE 3, strong recommendation).

Role of continuous renal replacement therapy in the management of pediatric acute liver failure

CRRT is increasingly being recognized as one of the most common and easily available extracorporeal support systems for ALF [172]. In ALF, ammonia and various other toxins start accumulating in the body due to impaired hepatic detoxification mechanisms. These toxins, along with inflammatory cytokines, initiate a devastating complex pathophysiological process that culminates in sepsis, cerebral edema, and multiorgan failure. The high efficacy of CRRT in removing water-soluble toxins such as ammonia, potassium, lactate, urea, and creatinine forms the basis for its use as an extracorporeal support system [173]. However, there is still much debate regarding the indication, timing, duration, type, and optimal dose of CRRT in PALF due to the paucity of well-designed and adequately powered prospective studies.

Standard renal indications for initiating CRRT in PALF include AKI with oligo-anuria leading to fluid overload (> 10%), metabolic acidosis (pH < 7.1), persistent hyperlactatemia and dyselectrolytemia [172]. Apart from renal

Table 6 Summary of prominent studies evaluating the role of therapeutic plasma exchange in adults and children with acute liver failure:

Study	Study design & sample size	Methods	Summary of major results
Important controlled studies in adults			
Larsen et al. J Hepatol 2016 [151]	RCT: 3 centers TPE: 92 vs SMT: 90	• High volume TPE • ALF, Gr 2 HE • APAP ALF (54% TPE; 64% SMT) • Listed for LT: 50% vs 49%	NLS: 58.7% (TPE) vs 47.8% (SMT), $p=0.0083$ Improved survival in those listed for LT but had contraindications; no difference based on etiology Decreased INR, bilirubin, ammonia, vasopressors—Day 7
Maiwall et al. Clin Gastroenterol Hepatol 2022 [152]	RCT TPE: 20 vs SMT: 20	• Standard volume TPE • ALF, cerebral edema on CT, No donor for LT • 78% viral hepatitis	NLS at day 21: 75% (TPE) vs 45% (SMT), $p=0.04$, HR 0.30, 95% CI 0.01–0.88 TPE independent predictor of survival ($p=0.045$) Reduction in SIRS, pro-inflammatory cytokines
Stahl et al. J Clin Apheresis 2019 [159]	Retrospective Historical matched controls TPE: 20 vs SMT: 20	• Low/standard volume TPE (3-4L/session) • All ALF • Toxin induced ALF (40%)	NLS: 54% (TPE) vs 33% (SMT); HR 0.639, 95% CI 0.226–1.807, $p=0.398$; 30 days OS: 65% (TPE) vs 50% (SMT) HR (mortality): 0.637; 95% CI 0.238–1.706, $p=0.369$
Kim et al. J Clin Apheresis 2020 [160]	Retrospective Historical unmatched controls TPE: 16 vs SMT: 16	• High volume TPE • ALF on LT waitlist	OS: 94% (TPE) vs 69% (SMT), $p=0.068$ OS in high SOFA (≥ 13) patients: 91% vs 29%, $p<0.05$ NLS: 28% (TPE) vs 19% (SMT), $p=0.083$
Beran A et al. Liver Transpl 2024 [161]	Systematic review and metaanalysis TPE: 174 vs SMT: 169	• 5 studies on ALF including 343 patients • Studies evaluating TPE + SMT vs TPE alone	Higher 30-day (RR 1.41, 95% CI 1.06–1.87, $p=0.02$) and overall (RR 1.35, 95% CI 1.12–1.63, $p=0.002$) survival in TPE group No difference based on type of study (RCT vs others) and type of TPE (HVP vs SVP)
Studies in children			
Biswas et al. J Clin Apher 2024 [163]	Propensity matched study TPE: 65 vs SMT: 65	• PALF with INR > 2.5 (> 3.1 for HAV-PALF) & Increasing INR/HE at 6–12 h • Volume exchanged: 1.5 to 2 times the plasma volume	NLS: 46.15% (TPE) vs 26.15% (SMT), Log rank, $p=0.001$ OS: 50.8% (TPE) vs 35.4% (SMT), Log rank, $p=0.004$ Subgroup analysis: NLS benefit predominantly seen in hepatitis A-related PALF
Singer et al. Ann Surg 2001 [165]	Retrospective cohort, no controls TPE: 28 (PALF)	• High volume TPE • Listed for LT, PT > 20 s (included non-PALF also)	NLS: 3/49 of the total cohort; data for PALF not described separately Transfusion reaction: 11/243 (4.5%) sessions, positive blood or catheter tip cultures: 5/243 (2.1%) sessions
Chien M-M et al. Pediatr Neonatol 2019 [166]	Retrospective cohort No controls TPE: 23 (Age > 2 years)	• PALF with persistent coagulopathy and HE • Mostly indeterminate (61%) • High volume TPE (2–4 times plasma volume)	NLS: 11 (48%), Death: 9 (39.1%) Lower number of TPE sessions in NLS patients suggesting futility of increased sessions of TPE

Table 6 (continued)

Study	Study design & sample size	Methods	Summary of major results
Jorgensen et al. J Pediatr Gastroenterol Nutr 2021 [167]	Observational Cohort No controls TPE: 16	• PALF with bilirubin > 200 µmol/L or toxic etiology • Standard volume (10% of body weight) • Safety and feasibility study	No catheter related complications Metabolic alkalosis: 18.75% No new infections, dyselectrolytemia NLS: 50%
Pawaria et al. J Clin Apheresis 2021 [164]	Prospective, controlled, non-randomized TPE: 19 vs SMT: 18	• Wilson disease—PALF • INR > 2.5 listed for LT with worsening HE or hemolysis • Standard volume TPE (> 1.5 times plasma volume)	NLS at 90 days: 47.4% (TPE) vs 16.7% (SMT), $p = 0.049$ 15 (29.4%) sessions—asymptomatic dyselectrolytemia No increase in sepsis or transfusion related complications
Pham et al. J Clin Apheresis 2016 [168]	Observational cohort No controls TPE: 10 (5 children)	• Wilson disease • INR: median 3.33 (1.69–8.88) • Standard volume TPE (1–1.25 times plasma volume)	Ultimately 9 (90%) underwent LT
Chowdhry M et al. Transfus Apher Sci. 2023 [169]	Retrospective cohort No controls TPE: 14	• Standard volume TPE (1.5 times plasma volume) • PALF with HE and worsening liver parameters • Included 4 Wilson disease	NLS: 35.7% Decreased bilirubin, INR, ammonia
Balasubramanian KK et al. Indian J Crit Care Med. 2023 [170]	Retrospective cohort No controls TPE: 6	• Standard volume in 5, high volume TPE in 1 • Indication not mentioned	NLS: 4/6 (66.7%) SAE: 4.3% (related to fluid overload)—resolved after discontinuation
Thomas L et al. J Clin Exp Hepatol. 2023 [156]	Retrospective cohort No controls TPE: 8	• Low volume TPE • ALF meeting Kochi criteria	NLS: 6/8 (75%)
Gokce S et al. Turk J Pediatr. 2021 [171]	Retrospective cohort TPE: 3	• Volume of TPE not specified • Autoimmune ALF with HE ≥ grade 2	2 progressed to HE grade 3 after prednisolone and 1 had HE grade 2 at admission All 3 showed resolution of HE and NLS after TPE

ALF Acute liver failure; *CI* confidence interval; *CT* computed tomography; *HE* hepatic encephalopathy; *HR* hazard ratio; *HVP* high volume plasma exchange; *INR* international normalized ratio; *LT* liver transplantation; *NLS* native liver survival; *PALF* pediatric acute liver failure; *FFP* fresh frozen plasma; *RCT* randomized controlled trial; *RR* relative risk; *SAE* serious adverse event; *SIRS* systemic inflammatory response syndrome; *SMT* standard medical therapy; *SOFA* Sequential Organ Failure Assessment; *SVP* standard volume plasma exchange; *TPE* therapeutic plasma exchange

indications, CRRT is beneficial for patients with advanced HE and those with persistent hyperammonemia with or without HE. Various adult and pediatric studies have documented a significant reduction in ammonia levels within 1–7 days of CRRT and improved overall survival as well as NLS [174–179]. Deep et al. analyzed 45 PALF patients from KCH who underwent CRRT and reported a significant decline in ammonia from 153 to 90 µmol/L (41% decline) in 48 h. The overall survival rate of the cohort was 26/45 (58%), the majority of whom (19/26, 73%) were bridged to LT with native liver survival in (7/26, 27%) [180].

However, there is lack of robust evidence regarding the threshold ammonia level at which CRRT should be initiated. Nonetheless, the Pediatric Continuous Renal Replacement Therapy Workgroup and the International Collaboration of Nephrologists and Intensivists for Critical Care Children (ICONIC) consensus statement recommend administering CRRT at an absolute ammonia level > 200 µmol/l or > 150 µmol/l which is not being controlled with medical management [172, 181].

Among the various modalities available for CRRT, continuous venovenous hemofiltration is the most widely used [172, 181]. The optimal dose of CRRT in PALF remains a matter of debate owing to the lack of head-to-head trials comparing different doses of CRRT. A significantly greater ammonia clearance was observed in the high-volume CRRT (90 ml/kg/h) compared to the low-volume CRRT (35 ml/kg/h) in a study on 10 adult ALF [182]. The efficacy of high-dose CRRT in the rapid dramatic reduction of serum ammonia levels has also been reported in neonatal hyperammonemia cases due to various inborn metabolic errors [183, 184]. High-volume CRRT at a dose of 119 mL/kg/h in PALF led to a significant improvement in HE grade and ammonia levels after 48 h [177]. KCH group also suggested starting CRRT at a standard dose of 60 mL/kg/h and sequentially increasing the dose up to 120 ml/kg/h if ammonia concentrations did not decrease within 6 h of initiation of CRRT [172, 180, 185]. Heparin, prostacyclin, or citrate could be used as an anticoagulant in CRRT to increase the circuit life in PALF; however, the decision regarding anticoagulation use and type of anticoagulant may be made depending on the individual risk assessment, availability of the drug, trained manpower, and cost [172, 181, 186, 187]. CRRT could also be administered to smaller children, especially those weighing < 10 kg, through adult machines using an appropriate-sized catheter for vascular access and a smaller filter [188]. CRRT has also been used in combination with other extracorporeal liver assist systems, such as TPE, either in series or parallel [178, 189, 190]. One has to be mindful of removal of drugs and nutrients whilst using high volume CRRT and TPE.

10.2. Recommendations:

10.2.1. Continuous renal replacement therapy should be performed in patients with pediatric acute liver failure with persistent acidosis, dyselectrolytemia, fluid overload, or persistent hyperammonemia (ammonia > 150 µmol/L) (LOE 3, strong recommendation).

Molecular adsorption and recirculation system (MARS)

MARS is a modality of augmented clearance system, which can achieve removal of water-bound (measured and unmeasured) as well as protein-bound (measured and unmeasured) toxins that accumulate in the blood in PALF, without the need to expose a child to exogenous blood products in a sustained fashion to provide maximal and longer-lasting benefits of blood purification [172, 191]. The risks, benefits, and comparisons between MARS and other available modalities that allow augmented clearance are listed in Table 5.

Evidence on use of MARS as modality to support ALF and PALF MARS and other forms of albumin-assisted dialysis have been studied in adults for over two decades. Several RCTs, systematic reviews, and cohort control studies have been conducted on various modalities of extracorporeal liver support. Overall, no single modality is effective and no modality offers a greater advantage than other modalities in PALF [192–197]. However, there may be a potential role for combination (hybrid) intervention based on the need for a critically ill child with liver failure [198].

10.3. Recommendations:

10.3.1. Infants and children with advanced encephalopathy and multi-organ failure may benefit from advanced/augmented modes of blood detoxification (LOE 4, weak recommendation).

10.3.2. Albumin-assisted dialysis may be considered as a bridge to native liver recovery or liver transplantation in pediatric acute liver failure and grade 3–4 hepatic encephalopathy (LOE 4, weak recommendation).

10.3.3. Albumin-assisted dialysis may be considered for poisoning and toxin-mediated acute liver failure with advanced encephalopathy (LOE 3, weak recommendation).

Prognostic scores for pediatric acute liver failure

PALF is associated with considerable morbidity and mortality [1, 4, 19, 199–201]. Patients with PALF require early referral to a center equipped with a multidisciplinary team to manage such cases and having facility for LT. Families should be assessed to ensure that financial, social, and psychosocial support systems are adequate for LT candidates to optimize post-transplantation outcomes. The decision to perform LT depends on both the accurate prediction of survival chances in its absence and the survival potential after LT to avoid transplanting an extremely sick child with contraindications. Scoring tools alone are not sufficient to evaluate the prognosis of individual cases of PALF. Therefore, scoring tools should be interpreted together with patient-specific conditions when deciding whether to wait, list and wait, or go ahead for LT.

Various prognostic models

An ideal prognostic model would correctly identify patients unlikely to respond to medical and supportive management who would thus be listed for LT while also avoiding unnecessary LT in those likely to improve on medical therapy. In other words, an ideal prognostic model should have 100% sensitivity and specificity for predicting the outcomes. A prognostic model should ideally be derived from a large representative population using well-defined outcome measures (death and survival), and its components should preferably have objectively quantifiable clinical and/or laboratory parameters that are repeatable, simple, economical, and applicable at the bedside or using an app-based model [202, 203]. Most existing scores lack the dynamic ability to adapt to the rapidly evolving nature of liver injury and are not designed to predict irreversible brain injury or cardiovascular collapse. Table 7 lists various prognostic models, along with their strengths and limitations evaluated in PALF.

The most widely used KCH criteria have poor sensitivity in predicting death or poor outcomes in non-APAP related ALF in adults as well as pediatric ALF [199–201, 204, 205]. The sensitivity of KCH in predicting poor outcomes in children is low (29 to 61%) across studies [199–201, 204]. Table 8 shows the prognostic accuracy of commonly used prognostic models for PALF. An INR > 4 is a more sensitive criterion than KCH and is utilized for organ allocation in the UK [201, 203]. Other scores that have been evaluated as prognostic models include the pediatric end-stage liver disease score, MELD score, liver injury unit, admission liver injury unit, and the recent Children's Hospital of Los Angeles—Acute Liver failure score [19, 166, 199, 200, 202, 206–210]. Liver injury unit scores based on admission or peak values are not user-friendly and have not been extensively evaluated clinically [207–209].

Etiology specific prognostication

Etiology is among the most important factors determining outcomes in PALF; thus, the listing criteria ought to be etiology-specific based on the epidemiology of the region [4]. While APAP is the most common etiology of PALF in the US and Europe, HAV is the leading cause of PALF, accounting for nearly half of pediatric ALF cases in developing countries [1, 199]. The distinct KCH criteria developed for APAP-induced ALF continue to have good discrimination value [211]. The low sensitivity of the KCH criteria is further lowered in HAV-induced PALF, as two of the five KCH criteria (age and non-A hepatitis) cannot be met in older children (> 10 years) with HAV-induced PALF [199, 212]. Peds-HAV model, which is an etiology-specific listing criterion in HAV-PALF, was derived from a large population of HAV-PALF patients and used three simple bedside parameters to decide listing for LT: (i) INR > 3.1, (ii) HE grade 3 or 4, and (iii) jaundice to HE interval > 10 days [199]. Patients fulfilling two or more of these criteria were listed for LT [199]. The model has recently been externally validated in HAV-PALF from two Indian non-LT centers and has been shown to have better sensitivity than KCH [212]. Peds-HAV model has been recommended as an etiology specific, simple to use, dynamic model validated in pediatric age groups [213]. Other etiology-specific models, such as the New Wilson Index (NWI) and AARC (APASL ACLF Research Consortium)—ACLF score for Wilson disease and the Kochi criteria for yellow phosphorus (rodenticide) poisoning induced PALF exhibit reasonable prognostic accuracy in PALF [208, 214–216].

Contraindications for proceeding to LT in a child with ALF

LT is not without short- and long-term risks. Although imminently lifesaving, it involves the risk of surgery, fluid shifts, hemodynamic derangements, remote organ injuries, periods of ischemia and reperfusion that can further injure organs, and, more importantly, immunosuppressive therapies that can set up a child for opportunistic infections in the future. Hence, there is a consensus that the liver should not be offered to recipients where LT is not curative or short- or long-term outcomes are unlikely to improve after LT [6, 10]. The contraindications include severe multisystem mitochondrial disease, irreversible brain injury and uncal herniation, and multisystem organ failure with uncontrolled sepsis needing escalating inotropes to maintain perfusion to organs.

11. Recommendations:

    11.1. Contact with a pediatric liver transplantation center should be initiated for children with acute liver failure, and emergent referral for liver transplantation evaluation may be required. A multi-

Table 7 Various prognostic scoring systems used in children with pediatric acute liver failure

Prognostic scores	Strengths	Limitations
Non etiology specific Prognostic models		
Kings College Criteria (non-APAP): INR > 6.5 or ≥ 3 out of 5 of the following: patient age < than 11 years (or > 40 years) Non-A, Non-E, Non-B viral hepatitis, drug induced, or indeterminate PALF Serum bilirubin > 17.5 mg/dl (> of greater than 300 µmol/L) Jaundice to encephalopathy > 7 days INR > 3.5	Simple, bedside objective parameters Most widely used Good specificity Can be used dynamically to de-list, re-list a patient	Low sensitivity (29 to 61%) Parameters (Bilirubin, INR) get affected by TPE Jaundice to encephalopathy interval difficult to assess in children with delayed identification of HE The derivation cohort were mainly adults (only 29 children) and most of them were APAP related ALF (311/588) Older children (> 10 years) with viral (HAV, HEV, HBV) induced ALF need to meet all 3 remaining criteria to get listed
Pediatric end stage liver disease (PELD) score = 4.80[Ln serum bilirubin (mg/dL)] + 18.57[Ln INR] − 6.87[Ln albumin (g/dL)] + 4.36(< 1 year old) + 6.67(growth failure) Model end stage liver disease (MELD) score = 3.78 × Log_e serum bili (mg/dl) + 11.20 × Log_e INR + 9.57 × Log_e serum creatinine (mg/dl) + 6.43 Calculator: https://unos.org/resources/allocation-calculators/	High sensitivity at lower cut-offs Dynamic score	Derived from patients with end stage liver disease PELD and MELD cannot be used interchangeably Poor Specificity at lower cutoffs and poor sensitivity and higher cut-offs Growth failure and albumin incorporated in PELD are not usually predictive No clear cut-off for listing Parameters get affected by plasmapheresis
Liver injury units (LIU): = (3.507 × peak total bilirubin) + (45.51 × peak INR) + (0.254 × peak ammonia)	Higher score suggests poor prognosis Admission LIU is more practical than LIU which uses peak values of the variables Externally and internally validated	LIU used peak variables which can only be known once outcome has occurred Risk stratification score rather than direct risk of death Not used clinically Requires an app/computer for calculation
Children's Hospital of Los Angeles liver failure (CHALF) score: CHALF score = ½ × [1 − (1.8846 + 2.773 ln(albumin) − 0.8103 ln (total bilirubin) − 0.8615 ln (ammonia))] × 15 + 50	Acceptable sensitivity and specificity in the training and validation cohorts App based Uses objective biochemical parameters	Low specificity in training and low sensitivity in validation cohorts Doesn't include INR which is the most dynamic prognostic variable in patients with PALF due to the short half-life of factor VII
Etiology specific prognostic models		
Kings College Criteria for APAP: Arterial ph < 7.3 or Grade III or IV hepatic encephalopathy and creatinine > 3.4 mg/dl and INR > 6.5 at time of initial presentation	Etiology specific model for the most common etiology of PALF in western world (acetaminophen) Derived from a large cohort of acetaminophen related ALF Can be used dynamically Simple, bedside, objective parameters	Does not account for co-ingestions, pre-existing liver diseases which may lead to acidosis
Peds-HAV model for Hepatitis A: presence of ≥ 2 out of 3 criteria indicates listing for liver transplantation • INR > 3.1 • Jaundice to HE interval > 10 days • HE Grade III or IV	Etiology specific model for the most common etiology of PALF in developing countries (Hepatitis A) Reasonable sensitivity and specificity Internally and externally validated Can be used dynamically Easy to use at bedside	Jaundice to encephalopathy interval may not be accurate in children INR may get affected by therapeutic plasma exchange

Table 7 (continued)

Prognostic scores	Strengths	Limitations
New Wilson's Index for Wilson Disease Utilizes a combination of scores for bilirubin, INR, aspartate aminotransferase, total leucocyte count, and albumin. Each parameter is assigned a score from 1 to 5. Maximum score can be 15 and minimum score of 5	NWI > 11 has acceptable sensitivity and specificity for predicting poor outcome Externally validated	Limited data with variable sensitivity and specificity
AARC ACLF score in Wilson disease Utilizes a combination of scores for bilirubin, INR, grades of hepatic encephalopathy, lactate and creatinine. Each parameter is assigned a score from 1 to 5. Maximum score can be 15 and minimum score of 5	Score ≥ 11 suggests need of liver transplantation in Wilson disease related acute-on-chronic liver failure Validated in pediatric acute-on-chronic liver failure	Limited data in PALF
Kochi Criteria for yellow phosphorus poisoning MELD ≥ 36 or a combination of international normalized ratio > 6 and hepatic encephalopathy	Etiology specific for a common cause of ALF in South India	No data in PALF Yellow phosphorus poisoning induced ALF limited to a particular region of India MELD can only be used in children older than 12 years Affected artificially by therapeutic plasma exchange which is an important therapeutic modality in yellow phosphorus poisoning

AARC-ACLF Asia Pacific Association for study of liver disease—acute-on-chronic liver failure research consortium; *ALF* acute liver failure; *APAP* acetaminophen; *LIU* liver injury unit score; *CHALF score* Children's hospital of Los Angeles Acute Liver Failure score; *HAV* hepatitis A virus; *HBV* hepatitis B virus; *HEV* hepatitis E virus; *HE* hepatic encephalopathy; *INR* international normalized ratio; *KCH* King's College Hospital; *LIU* liver injury unit score; *LT* liver transplantation; *MELD* model for end stage liver disease score; *PALF* pediatric acute liver failure; *PELD*: pediatric end stage liver disease score; *PPV* positive predictive value; *NPV* negative predictive value; *NWI* New Wilson Index; *TPE* therapeutic plasma exchange

Table 8 Studies evaluating the various prognostic scores in cohorts of pediatric acute liver failure

Study	Study design	Sample Size	Etiology of PALF	Evaluation of various prognostic models
Studies evaluating KCH criteria in PALF				
Sundaram V et al. J Pediatr. 2013 [204]	Retrospective study from PALF study group	$n=522$	Non-APAP PALF (all other etiologies)	Sensitivity 61% & Specificity 70% to predict death PPV: 33%, NPV: 88%
Pop TL et al. J Clin Med 2022 [200]	Retrospective study	$n=161$	Toxic: 64 (39.6%) (Drug induced: 51, 31.7%; mushroom poisoning: 13 (8.1%)	Sensitivity 29.1%, Specificity 94.3% to predict poor outcome; PPV: 72.7%, NPV: 71.9%
Amatya P et al. Front Pediatr 2022 [201]	Retrospective study	$n=125$	Infections: 40 (32%) (Dengue: 22, 17.6%)	Sensitivity 34.5%, Specificity 72.2% to predict poor outcome (death/LT); PPV: 42.1%, NPV: 65.5%
Lal BB et al. Hepatol Int. 2020 [199]	Retrospective study	Derivation: 75 Validation: 45	Hepatitis A only	Derivation cohort: sensitivity 58.1% & Specificity 87.3% to predict poor outcome (death/LT) PPV: 75.8%, NPV: 75.3%, Accuracy: 75.5% Validation cohort: sensitivity 38.9% & specificity 100% to predict poor outcome (death/LT)
Walabh P et al. BMC Pediatr 2022	Retrospective study	$n=45$	Infective etiology: 30 (66.7%) (Hepatitis A: 19, 42.2%)	Sensitivity 84.6%, Specificity 50% to predict poor outcome; PPV: 91.7%, NPV: 33.3%
Studies evaluating PELD score in PALF				
Rajanayagam J et al. Pediatr Transplant. 2013 [19]	Retrospective study	54 children	All etiologies	PELD/MELD > 27 predicted poor outcome with 76% sensitivity and 60% specificity PELD/MELD > 42 predicted poor outcome with 66% sensitivity and 92% specificity
Sanchez MC et al. J Pediatr Gastroenterol Nutr. 2012 [206]	Retrospective study	40 children	Mixed etiology predominantly Hepatitis A	PELD > 33 score predicted poor outcome (death/LT) with 86% sensitivity and 81% specificity PPV: 92%; NPV: 69%
Ascher-Bartlett JM et al. Transplantation. 2023 [202]	Retrospective study	Training cohort: 135 Validation cohort: 492	All etiologies	PELD predicted poor outcome with an area under ROC of 0.76; 95% CI 0.68–0.83
Lal BB et al. Hepatol Int. 2020 [199]	Retrospective study	131 children	Hepatitis A only	PELD ≥ 27 predicted poor outcome with 89.3% sensitivity and 56.5% specificity PELD ≥ 35 predicted poor outcome with 67.4% sensitivity and 90.5% specificity
Walabh P et al. BMC Pediatr 2022	Retrospective study	$n=45$	All etiologies	Admission PELD 23.2 ± 11.6 in survivors, 32.2 ± 10.8 in transplanted, and 32.8 ± 10.9 in death ($p=0.162$) Peak PELD/MELD significantly different between different outcome groups ($p=0.009$)

Table 8 (continued)

Study	Study design	Sample Size	Etiology of PALF	Evaluation of various prognostic models
Pop TL et al. J Clin Med 2022 [200]	Retrospective study	$n=161$	Toxic: 64 (39.6%) (Drug induced: 51, 31.7%; mushroom poisoning: 13 (8.1%)	PELD > 20: Sensitivity 60%, Specificity 75.4%, PPV: 58.5%, NPV: 76.5%
Chien M-M et al. Pediatr Neonatol 2019 [166]	Retrospective	$n=23$	Predominantly indeterminate (60.8%)	PELD comparable between survivors & non-survivors (39 vs. 41, $p=0.76$)
Fang W-Y et al. World J Clin Cases 2021 [208]	Retrospective study	$n=41$	Wilson disease only	MELD/PELD > 31 predicted poor outcome (death/LT) with 100% sensitivity and 94.3% specificity (similar sensitivity but higher specificity than NWI)
Studies evaluating LIU score in PALF				
Liu E et al. J Hepatol 2006 [209]	Prospective	81 children	All etiologies	LIU 296–367: moderate risk, LIU > 368: high risk Sensitivity 88.5 and Specificity 90.5%
Lu BR, et al. J Pediatr 2013 [207]	Prospective study	$n=709$	All etiologies	LIU score INR C statistic: 0.76 for poor outcome and 0.84 for LT
Ascher-Bartlett JM et al. Transplantation. 2023 [202]	Retrospective study	Training: 135 Validation: 492	All etiologies	aLIU score predicted poor outcome with an area under ROC of 0.76; 95% CI 0.68–0.83 aLIU score had higher sensitivity than CHALF score in the validation cohort
Chien M-M et al. Pediatr Neonatol 2019 [166]	Retrospective	$n=23$	Predominantly indeterminate (60.8%)	Medium/high risk LIU score in NLS vs non-NLS: 63.6% vs. 91.7%, $p=0.16$
Fang W-Y et al. World J Clin Cases 2021 [208]	Retrospective study	$n=41$	Wilson disease only	aLIU score (PT based) > 290 predicted poor outcome (death/LT) with 100% sensitivity and 94.3% specificity (similar sensitivity but higher specificity than NWI)
Studies evaluating CHALF score in PALF				
Ascher-Bartlett JM et al. Transplantation. 2023 [202]	Retrospective study	Training cohort: 135 Validation cohort: 492	All etiologies	Training cohort: CHALF score > 30 predicted poor outcome with 81% sensitivity and 67% specificity Validation cohort: CHALF score > 30 predicted poor outcome with 56% sensitivity and 85% specificity
Yadav D et al. Transplantation. 2024 [210]	Retrospective	$n=391$	All etiologies, predominantly Hepatitis A (49.1%)	CHALF score more than 48.5 predicted poor outcomes (death/LT) with 67% sensitivity and 74.9% specificity
Studies evaluating etiology specific models in PALF				
Prognostic model in Hepatitis A				
Peds-HAV model				

Table 8 (continued)

Study	Study design	Sample Size	Etiology of PALF	Evaluation of various prognostic models
Lal BB et al. Hepatol Int. 2020 [199]	Prospective study	Derivation cohort: 75 Validation cohort: 45	Hepatitis A only	Derivation cohort: Peds-HAV model: 90% sensitivity, 81.4% specificity for predicting death; PPV: 76.6%, NPV: 92.3% Validation cohort: Peds-HAV model: 83.3% sensitivity, 92.6% specificity for predicting death
Verma S et al. Indian J Gastroenterol. 2024 [212]	Prospective/retrospective		Hepatitis A only	Peds-HAV score ≥ 2 predicted death with 89.7% sensitivity and 89.6% specificity; PPV: 78.8%, NPV: 95.2%
Prognostic model in Wilson disease				
New Wilson Index				
Dhawan A et al. Liver Transpl. 2005 [215]	Retrospective + prospective	Derivative: $n=74$ (27 ALF) Prospective: $n=14$	Wilson disease	NWI > 11; Sensitivity: 75%, Specificity: 91% Derived from a mixed cohort (Among ALF—only 2 survived while 25 died or received LT)
Chanpong A et al. J Pediatr Gastroenterol Nutr. 2022 [214]	Prospective	$n=18$ (AHD)	Acute hepatic decompensation (AHD/ACLF) Wilson disease	In AHD, NWI had sensitivity of 80%, specificity of 100%, PPV 100% & NPV: 80% for predicting LT
Pop TL et al. J Clin Med 2022 [200]	Retrospective study	$n=9$	Wilson disease only	NWI > 11 predicted poor outcome with 100% sensitivity, 100% specificity & 100% accuracy
Fang W-Y et al. World J Clin Cases 2021 [208]	Retrospective study	$n=41$	Wilson disease only	Sensitivity 100%, Specificity 71.4% to predict poor outcome (death/LT)
AARC-ACLF score				
Alam S et al. Hepatol Int 2019 [216]	Retrospective study	$n=66$	Wilson disease only	AARC ACLF score ≥ 11 predicted poor outcome with 92.6% sensitivity and 84.6% specificity
Prognostic model in Yellow Phosphorus (rodenticide) poisoning related ALF: Kochi Criteria—No pediatric studies				

AARC-ACLF Asia Pacific Association for study of liver disease—acute-on-chronic liver failure research consortium; *ACLF* acute-on-chronic liver failure; *AHD* acute hepatic decompensation; *APAP* acetaminophen; *aLIU* admission liver injury unit score; *CHALF score* Children's hospital of Los Angeles Acute Liver Failure score; *CI* confidence interval; *INR* international normalized ratio; *KCH* King's College Hospital; *LIU* liver injury unit score; *LT* liver transplantation; *MELD* model for end stage liver disease score; *NLS* native liver survival; *PALF* pediatric acute liver failure; *PELD* pediatric end stage liver disease score; *PPV* positive predictive value; *NPV* negative predictive value; *NWI* New Wilson Index; *PT* prothrombin time; *ROC* receiver operating characteristic curve

disciplinary team should be skilled in the management of acutely ill pediatric acute liver failure patients (LOE 5, strong recommendation).

11.2. To optimize post transplantation outcomes, the family members should be sensitized and assessed to ensure adequate social and psychosocial support (LOE 5, strong recommendation).

11.3. The King's College Hospital criteria should be used for liver transplantation listing in pediatric acute liver failure despite its low sensitivity (LOE 3, strong recommendation). In patients not fulfilling the King's College Hospital criteria, INR > 4 carries a high mortality, and these patients need to be closely monitored at a liver transplant center (LOE 3, strong recommendation).

11.4. Etiology-specific prognostic models relevant to the population, such as the Peds-HAV model for hepatitis A, New Wilson Index for Wilson disease, and Kochi criteria for yellow phosphorus poisoning-related pediatric acute liver failure should be preferred for liver transplantation listing in children (LOE 3, strong recommendation).

11.5. Children with irreversible brain damage, uncal herniation, uncontrolled sepsis, multi-system organ failure requiring escalating inotropic support, and mitochondrial illnesses where liver transplantation is either detrimental or unlikely to change outcomes, should not be considered for transplantation (LOE 3, strong recommendation).

Liver transplantation on extracorporeal liver support systems

With the advent of ELSS, the challenge that clinicians are facing is regarding the monitoring of these PALF patients while on ELSS. With or without ELSS, the goal remains that we should not transplant those who are likely to recover spontaneously; on the other hand, one should not be late for LT in those who need it. Since the ELSS can artificially alter crucial prognostic parameters, immediately after the initiation of CRRT, it is difficult to comment on ammonia and lactate, but INR and bilirubin can be used for prognostication. However, TPE artificially alters bilirubin and INR, which are the components of most prognostic models. INR is the most crucial parameter for prognostication; hence, some centers guide prognostication based on rebound values of INR after TPE. After a session of MARS, one needs to be cautious about interpreting the INR and bilirubin.

Experts opined to follow the rule that if the INR value rebounds 50% in 12 h or 100% in 24 h after a session of TPE/MARS, then the patient should be considered to be a candidate for LT. However, there is no adult or pediatric data to support this. A recent pediatric study reported that TPE performed more than six sessions was probably associated with poor outcome [166]. Hence, the experts suggested that clinicians should judiciously use clinical parameters, etiology, and the trajectory of the illness to determine the need for LT (while on ELSS) on a patient-to-patient basis.

12. Recommendations:

12.1. While on continuous renal replacement therapy for pediatric acute liver failure, besides clinical assessment, standard parameters of listing (INR, bilirubin) can be used in children with acute liver failure if fresh frozen plasma/cryoprecipitate has not been administered (LOE 5, weak recommendation).

12.2. While being on therapeutic plasma exchange sessions, one needs to be cautious in interpreting INR in the first 12–24 h after plasma exchange (LOE 5, weak recommendation).

12.3. While being on albumin assist devices (such as molecular absorbent recirculating system) as a bridge to liver recovery/LT, one needs to be cautious in interpreting INR/bilirubin in the first 12–24 h (LOE 5, weak recommendation).

12.4. One needs to judiciously use clinical acumen based on the age, etiology, and trajectory of the patient's illness while deciding the listing of a child with acute liver failure while on extracorporeal liver support systems (LOE 5, strong recommendation).

Specific medical therapies in PALF

Few etiologies of PALF have specific medical therapy which should be offered promptly. Some metabolic disorders like galactosemia and hereditary fructose intolerance may just require simple dietary modifications, while others like tyrosinemia can be treated by specific drugs like nitisonone. Neonatal ALF caused by herpes simplex virus should be urgently treated with acyclovir, while gestational alloimmune liver disease has improved outcomes with exchange transfusion followed by intravenous immunoglobulin. Wilson disease having PALF like presentation may be treated with chelation in addition to TPE. Table 9 lists the various etiologies of PALF which have specific medical therapies. Possibly, the best outcomes in PALF have been demonstrated with use of N-acetylcysteine (NAC) in APAP-related PALF.

Role of N-acetylcysteine (NAC) in ALF

NAC in acetaminophen toxicity and ALF Two studies, including an RCT, showed a significant reduction in the risk

Table 9 Specific medical therapies available for management of various causes of pediatric acute liver failure

Etiology of pediatric acute liver failure	Specific medical therapy
Acetaminophen	N-acetylcysteine
Herpes simplex virus	Acyclovir
Hepatitis B virus	Entecavir (≥ 2 years), tenofovir disoproxil fumarate (≥ 2 years), tenofovir alafenamide (≥ 6 years)
Cytomegalovirus	Intravenous ganciclovir followed by valganciclovir (oral)
Autoimmune hepatitis	Steroids ± immunosuppression (mycophenolae mofetil/azathioprine)
Gestational alloimmune liver disease	Exchange transfusion followed by intravenous immunoglobulin (IVIG)
Hemophagocytic lymphohistiocytosis	Chemotherapy (HLH-94 protocol), intravenous immunoglobulin (IVIG), corticosteroids, therapeutic plasma exchange
Metabolic liver diseases	
Galactosemia	Galactose free diet
Hereditary fructose intolerance	Fructose free diet
Tyrosinemia	Nitisonone + low tyrosine and phenylalanine diet
Urea cycle defect	Ammonia scavengers, protein free diet with essential amino acids supplementation
Wilson disease	Chelation therapy with D-penicillamine or trientene ± zinc
Cholesteryl ester storage disease/wolman disease	Enzyme replacement (sebelipase-alfa)

of hepatotoxicity when NAC was initiated for APAP toxicity [217, 218]. Due to the high adverse effect rates with the traditional NAC infusion protocol, a recent systematic review compared the traditional 3 bag regimen and simplified 2 bag regimen NAC regimen and concluded that there was no difference in liver injury between the two regimens [219]. A meta-analysis confirmed similar efficacy with both oral versus intravenous routes [220]. The dose of NAC to be used in APAP related PALF is infusion at a rate of 6.25 mg/kg/h until normalization of the INR.

NAC in non-APAP ALF NAC has been shown to be beneficial in non-APAP ALF in early HE [12, 221]. Two meta-analyses, which included seven studies ($n = 883$, both pediatric and adult) and five prospective studies (adults only), concluded that overall survival and NLS were better in the NAC group [222] and that NLS and length of stay were improved in the NAC group; however, overall survival was similar between the groups [223]. Guidelines on the management of ALF in various societies, namely the American Association for Study of Liver Disease in 2011, EASL in 2017, and the Indian National Association for Study of Liver in 2020, recommended the use of NAC in drug-induced liver injury-related ALF [10, 224, 225].

A double-blind placebo-controlled RCT in 184 children concluded that NAC did not improve 1-year survival in non-APAP PALF [11]. One-year LT-free survival was significantly lower with NAC, particularly among those aged < 2 years. A Cochrane review in 2020 also concluded that there is no difference in mortality or LT rates in children with non-APAP ALF treated with NAC or placebo [226]. A Cochrane review and the North American Society of Pediatric Gastroenterology Hepatology and Nutrition suggested NAC use in APAP PALF only [6, 226].

13.1. Recommendations:

13.1.1. N-acetylcysteine is indicated in preventing hepatotoxicity and reducing mortality in acetaminophen-induced pediatric acute liver failure (LOE 3, strong recommendation).

13.1.2. Evidence on the role of N-acetylcysteine in non-acetaminophen related pediatric acute liver failure is inconclusive (LOE 2, weak recommendation).

Steroids in autoimmune hepatitis induced PALF setting (AIH-PALF)

AIH presenting as PALF (AIH-PALF) constitutes 2–6% of all PALF. However, there is a paucity of high-quality data on corticosteroid use in children with AIH-PALF. Data were mainly limited to retrospective case reports or small case series with varying inclusion criteria [227–234]. There is a good volume of data on corticosteroid use in AIH-ALF/ACLF in adults, but this is mainly limited to retrospective studies [235, 236]. Collating results from the literature, 51.4% (18/35) cases of AIH-PALF showed a response (NLS) to steroids whereas adult studies reported response (NLS) to steroids in 8% to 97% of patients [235, 236]. There is no strong evidence to suggest that the intravenous route is superior to the oral route.

13.2. Recommendations:

13.2.1. Patients with coagulopathy and no or early encephalopathy in autoimmune hepatitis related pediatric acute liver failure may be considered for corticosteroid therapy (oral prednisolone, 2 mg/kg/day; max: 60 mg/day or an equivalent dose of intravenous methylprednisolone) (LOE 3, strong recommendation).

13.2.2. The presence of grade III or IV hepatic encephalopathy or lack of response within seven days of corticosteroid administration implies poor prognosis and necessitates liver transplantation (LOE 4, strong recommendation).

Acute liver failure due to hepatitis B

Acute hepatitis B accounts for 4% of ALF in adults [10]. Acute hepatitis B related ALF (HBV-ALF) is rare in children [4]. It is generally acute-on-chronic liver failure due to reactivation of hepatitis B viral infection. The clinical history and signs of chronicity can help differentiate acute infection from reactivation. Biochemical markers do not help differentiate between these two conditions. Compared to reactivation, patients with HBV-ALF have higher levels of anti-HBc IgM (titers > 1:1000 in 78%), lower levels of HBV-DNA ($< 10^4$ IU/mL) and lower HBsAg, which suggests rapid clearance of the virus as a result of a robust immune response [237, 238]. A combination of anti-HBe positivity, low anti-HBc IgM titers, and high HBV-DNA is more likely to be observed in the reactivation of chronic hepatitis B [237, 239, 240]. Studies on the use of antiviral therapy for adult patients with HBV-ALF are contradictory [241–244]. Although the use of lamivudine led to lower HBV-DNA at 4 weeks, it did not provide survival benefit in an RCT in adults with hepatitis B-related ALF [245]. Despite the contradictory evidence, the World Health Organisation (WHO) has recommended antiviral therapy to improve viral clearance and reduce the risk of recurrent hepatitis B [246]. Tenofovir disoproxil fumarate and entecavir are the two most widely used antivirals which are approved for use in children beyond 2 years of age. Lamivudine is not commonly used due to its low barrier to development of resistance. WHO recommends continuing antiviral therapy for at least three months after HBsAg seroconversion or at least 12 months after HBeAg seroconversion in patients failing to achieve HBsAg seroconversion [246]. There are no studies evaluating the efficacy of antivirals in children with HBV related ALF.

13.3. Recommendations:

13.3.1. Liver transplantation may be considered in patients with hepatitis B related pediatric acute or acute-on-chronic liver failure as per the standard indication (LOE 4, strong recommendation).

13.3.2. Although there are conflicting data, antivirals may be used in children with hepatitis B related pediatric acute liver failure (LOE 3, weak recommendation).

Conclusion

This consensus guidance from the Indian Society of Pediatric Gastroenterology, Hepatology, and Nutrition, the first of its kind, is based on extensive and critical evaluation by global experts of the published data and the evidences emerging from the data, on the diagnosis and management of pediatric acute liver failure. An age-appropriate stepwise algorithmic approach for etiological workup has been developed for improving bed-side management approaches. Seminal advancements in the assessment and management of cerebral edema have been incorporated. Particular emphasis has been placed on the impact of various extracorporeal liver support systems on improving native liver survival in PALF. A critical review of the indications and timing of LT with and without extracorporeal liver support systems was presented. Since none of the studies examined the effect of extracorporeal liver support systems on the prognostic models/listing criteria, we need to identify cytokine signatures or other models for predicting the need for LT patients on extracorporeal liver support systems.

Unresolved issues and potential areas for research

Despite the progress made in the last decade, several recommendations continue to be based upon little or no evidence or based upon extrapolation from the literature on adults with ALF. The high rates of indeterminate etiology points to inadequate workup and recent studies have suggested evaluation for genetic disorders in patients where etiology remains elusive after initial investigations. While recent pediatric literature has focused on ONSD, other non-invasive modalities for the assessment of cerebral edema in children need to be evaluated in clinical setting before their widespread acceptance. The role of TCD, $S_{jv}O_2$, NIRS, and EEG for neuromonitoring in PALF could be the areas of potential interest for future research. There is scarce data on infections in PALF and their impact on the natural course and outcome. On the therapeutic front, there is an urgent unmet

need to conduct an RCT in children to assess the efficacy of TPE alone or in combination with CRRT. Studies are also needed to determine the optimal plasma exchange protocol and volumes in children with ALF. Studies should also focus on pharmacokinetics of drugs, particularly antibiotics and their optimum administration doses and protocol while the patient is on concomitant bridging therapies. As most bridging therapies artificially alter important prognostic biochemical variables like INR, bilirubin, and ammonia complicating the decision about the need and timing of LT, research on cytokine signatures and other clinical/biochemical prognostic models in those on bridging therapies is the need of the hour. Other potential areas of interest to researchers in PALF could be the biochemical and omics-based signatures for liver regeneration, hepatocyte transplantation, studies assessing efficacy and safety of NAC, safety of prolonged propofol infusion as an ICP lowering agent, PALF-specific modifications of LT like auxiliary LT, and evaluation of modalities to decide coagulopathy correction in PALF.

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