Acute Liver Failure
An Update

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KEYWORDS

• Acute liver failure • Children • Acute liver failure management • Encephalopathy
• Diagnosis of acute liver failure

KEY POINTS

- Pediatric acute liver failure is a dynamic, life-threatening condition of disparate etiology.
- Management is dependent on intensive collaborative clinical care and support.
- Proper recognition and treatment of common complications of liver failure are critical to optimizing outcomes.
- Identifying underlying cause and implementing timely, appropriate treatment can be life-saving.

INTRODUCTION

Acute liver failure (ALF) is a dynamic clinical condition manifested by an abrupt onset of a liver-based coagulopathy and biochemical evidence of hepatocellular injury resulting from rapid deterioration in liver cell function. The Pediatric Acute Liver Failure (PALF) Study, funded by the National Institutes of Health and the National Institutes of Diabetes and Digestive and Kidney Diseases, identified clinical and biochemical study entry criteria (**Box 1**).

These criteria were not intended to define PALF, but rather to identify subjects with acute liver injury sufficiently severe to place the child at risk for progressive clinical deterioration that could result in liver transplantation or death. Beyond the PALF study, children meeting PALF study entry criteria should prompt referral, or at least contact with, a pediatric liver transplant center, as early referral is known to improve outcome.

The ALF phenotype can be precipitated by disparate etiologies that include drug-induced, metabolic and genetic, infectious, immune-mediated, hemodynamic, and oncologic injuries; however, a definitive diagnosis is not determined in up to 50% of

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Box 1
Pediatric Acute Liver Failure (PALF) study entry criteria

- No known evidence of chronic liver disease
- International Normalized Ratio (INR), following parenteral administration of vitamin K, ≥1.5 with clinical hepatic encephalopathy (HE)
- INR is ≥2.0 with or without HE

Data from Squires RH Jr, Shneider BL, Bucuvalas J, et al. Acute liver failure in children: the first 348 patients in the pediatric acute liver failure study group. J Pediatr 2006;148(5):652–8.

cases. Proper management is dependent on intensive collaborative clinical care and support and, for a handful of conditions, specific therapy that can be life-saving. Outcomes in the pre–liver transplant era were limited to survival or death. Liver transplantation (LTx) interrupts the natural history of ALF and, consequently, this third outcome is most certainly composed of individuals who would have lived or would have died in the absence of LTx. Predicting patient outcome in the LTx era has been unfulfilling and better predictive models must be developed for proper stewardship of the limited resource of organ availability.

GENERAL MANAGEMENT AND COMPLICATIONS

General

Once a patient meets PALF study entry criteria, general management strategies should be undertaken regardless of etiology. Early transfer to a pediatric liver transplant center before development of clinical encephalopathy is associated with improved outcomes.[1] A general algorithm for patients meeting PALF study entry criteria is presented in Fig. 1.

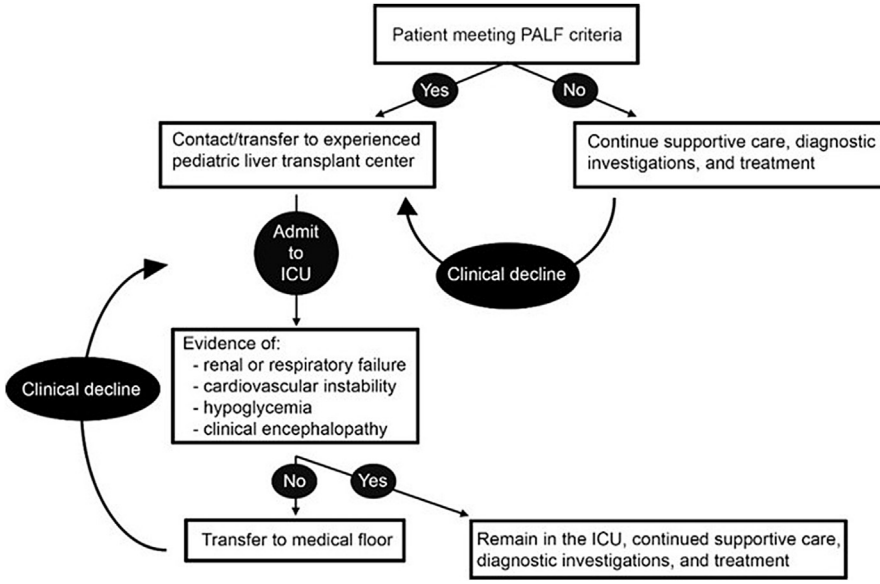

Fig. 1. A general algorithm for patients who meet the entry criteria for the PALF study. ICU, intensive care unit.

The initial history should include critical points preceding the development of PALF, while remaining focused on age-specific differential diagnoses. Physical examination is critical to assess for evidence of HE, ascites, edema, disease chronicity, heart murmur, or gallop (Box 2).

A plan for laboratory and clinical assessments should be initiated immediately and occur at least twice per day initially, then adjusted based on trends and interventions. The presence and degree of HE is critical in determining appropriate management (Table 1).

In the presence of cardiovascular instability, fluid or colloid resuscitation should occur. Once the child is stable, or if shock was not evident on presentation, total fluids should be restricted to between 90% and 100% maintenance fluids. This can be difficult to accomplish, as intravenous medications and blood product administration must be counted within the total daily volume. Accurate measurement of daily intake and output is critical. Overhydration can precipitate pulmonary edema, ascites, and cerebral edema, whereas underhydration can precipitate hepatorenal syndrome, acute tubular necrosis, worsening encephalopathy, and hypotension. A central catheter is needed for most children, and monitoring central venous pressure in the intensive care unit can assist in assessing the critically ill child. A comprehensive overview of common complications and general diagnostic and management strategies is presented (Table 2).

Hepatic Encephalopathy

HE is difficult to assess and may not be clinically apparent, particularly in infants and young children (Table 3).[26] An altered metal status due to severe illness, metabolic decompensation, electrolyte abnormality, cardiovascular instability, or fear may confound assessment of HE.[27] Pathogenesis extends beyond an elevated ammonia to include systemic inflammation and neuroinflammation.[28]

Coagulopathy

The INR is elevated in ALF and is a marker for severe hepatocellular dysfunction. However, a prolonged INR is not a measure of bleeding risk in patients with ALF.[29] Patients

Box 2
Medical history and physical examination in PALF

Important historical points:
- Onset of jaundice
- Perceived changes in mental status, such as confusion, slurred speech, agitation
- Constitution symptoms, such as nausea, vomiting, diarrhea, fever, rash
- Careful medication history, including over-the-counter medications and medications in the house
- Travel, exposure to farm animals
- Previous history of seizures, developmental delay, liver disease
- Family history of infant deaths, Wilson disease, autoimmune disease

Physical findings that suggest an underlying chronic liver disease would include the following:
- Prominent superficial abdominal vessels secondary to severe portal hypertension
- Digital clubbing
- Palmar erythema
- Xanthoma

Neurologic assessments should be frequent and, ideally, assessed by the same individual to identify subtle differences and progression.
- If able, having the child write his or her name on paper for a family member to assess the quality and subsequently to assess deterioration in handwriting over time, which can be seen with evolving encephalopathy.

Table 1
Laboratory testing and clinical assessments in pediatric acute liver failure

	Initial Testing		
Liver function	PT/INR Bilirubin (total and fractionated) Total protein and albumin Ammonia Glucose	Liver injury	ALT AST GGT Ferritin
Multisystem assessment	BMP + calcium, magnesium, phosphorus CBC + platelets and differential Amylase and lipase Blood gases (mixed, venous, or arterial)		
Frequency of testing accounting for HE			
Interval	*HE grade 0–I*	*HE grade II*	*HE grade III–IV*
Q 30 min			Neurologic checks
Q 60 min		Neurologic checks	Vital signs
Q 2 h	Neurologic checks		
Q 4 h		vital signs	Dextrostik[b]
Q 6 h	Vital signs		BMP, magnesium, ammonia, CBC[c]
Q 8 h	Dextrostik	Dextrostik,[a] BMP, magnesium, ammonia, CBC	
Q 12 h	Dextrostik, BMP, magnesium, ammonia, CBC, liver function and injury	Liver function and injury	Liver function and injury

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMP, basic metabolic panel; CBC, complete blood count; GGT, gamma glutamyl transferase; HE, hepatic encephalopathy; INR, international normalized ratio; PALF, pediatric acute liver failure; PT, prothrombin time; Q, every.

[a] No hypoglycemia in the past 48 hours.

[b] When there are acute changes in mental status. When hypoglycemia is identified, obtain serum blood sugar to ensure glucose is greater than 100 mg/dL and is stable within the normal range.

[c] When severe ascites and/or hypoalbuminemia.

Table 2
General diagnostic and management strategies of common complications in pediatric acute liver failure

Complication	Diagnosis	Management
Fluid and electrolytes		
Hyper/hypoglycemia	Routine blood monitoring/ dextrostik	• Maintain glucose levels between 90 and 120 mg/dL • Both hyperglycemia and hypoglycemia are associated with complications[2] • Protracted and profound hypoglycemia may be suggestive of an underlying metabolic defect • The glucose infusion rate may need to be 10–15 mg/kg per min and glucose concentrations in the IV fluids required to maintain proper glucose levels may need to be above 20% dextrose
Hyper/hyponatremia	Routine blood monitoring	• Maintain sodium requirements of 2–3 mEq/kg per day • Treat hyponatremia when patient is symptomatic or Na <120 mEq/L or fluid restriction not possible • Hypernatremia (145–155 mmol/L) may improve intracranial hypertension, but only temporarily and sustained hypernatremia should be avoided[3]
Hypophosphatemia	Routine blood monitoring	• Hypophosphatemia is common and should be treated to keep serum level more than 3 mg/dL[4]
HE and hyperammonemia	Physical examination, EEG, CT[a]	Clinical management • Elevate head to 30° • Dim and quiet room with no sudden noises or unnecessary chatter • Place pads on bed rails to prevent injury from sudden movements • Minimize tracheal suctioning if intubated Medical management • Reduce protein intake to 1 mg/kg • Lactulose 0.5 mL/kg per dose up to 30 mL/dose; adjust to produce 2–4 stools per day; acid environment converts ammonia produced by the gut from NH3 to NH4+ thus decreasing intestinal absorption[5] • Rifaximin to alter intestinal microbiome and decrease NH3 production; efficacy is comparable to lactulose in adults,[6] but very sparse data in children • There are conflicting studies on the efficacy of L-ornithine-L-aspartate in adults,[7,8] but has not been studied satisfactorily in children Exacerbating factors include sepsis, shock or hypotension, gastrointestinal bleeding, renal failure, electrolyte imbalance[9]

(*continued on next page*)

Table 2
(*continued*)

Complication	Diagnosis	Management
Cerebral edema	• CT: effacement of Sylvain fissures, sulci, and basil cisterns, loss of gray and white matter differentiation • Ultrasonography of optic nerve sheath diameter[10,b] • Ammonia >200 mmol/L is risk factor[6] • Clinically: rapid HE progression, abnormal pupillary responses, sustained or paroxysmal hypertension	ICP monitoring considered in • Patients with stage III or IV coma • Require mechanical ventilation • EEG with slowing • ↑↑ ammonia • CT scan with features of edema • Hemorrhage is most feared complication[11] Overall goals[12]: • Clinical stability or improvement • ICP pressure <20 mm Hg • Maintain cerebral perfusion pressure >50 mm Hg for children <4 y, >55 mm Hg for children 4–10 y, and >60 mm Hg for children >10 y Specific therapies: • Hypothermia (core body temperature 32°–33°) was reported to improve outcome in small case series, but was not found to confer benefit in 2 randomized trials[13,14] • Indomethacin has been studied for its anti-inflammatory properties,[15] but concerns regarding bleeding risk and renal toxicity have likely precluded its acceptance as a reasonable treatment option • Forced hyperventilation to reduce P_{CO_2} below 34 mm Hg; brief (eg, 20 min) bursts of forced hyperventilation may be most effective, as extended hypocapnia may place the patient at risk for hypoxia[16] • Hyperosmolar therapy[17] ◦ Mannitol 0.5–1.0 g/kg. Can be given via a peripheral vein. Can produce a brisk diuresis, so careful monitoring of cardiovascular status is needed. No additional benefit is serum osmolality >320 mOsm/kg. ◦ Hypertonic saline (2.0% to 23.4%) to maintain serum sodium between 145 and 155 meq/L. Transtentorial herniation has been reversed with 23.4% may extend the window for liver transplantation.[18]

Coagulopathy	↑↑ INR ↓ Factor V and VII ↓Fibrinogen	• Fresh frozen plasma (FFP) and or platelets for active bleeding or an invasive procedure • Avoid FFP and platelets to just correct the INR or improve platelet count in the absence of bleeding, as both are associated with transfusion-related lung injury and fluid overload[19] • Cryoprecipitate for low fibrinogen levels (eg, <100 mg/dL) • Recombinant factor VII has been used to correct the INR before placement of an intracranial monitor. It is very expensive and there is a risk of thrombosis.[20]
Kidney injury	RIFLE criteria ↓ Creatinine clearance ↓ Urine output	• Continuous renal replacement therapy[21]
Nutritional support[22–25]	Patients with PALF are likely catabolic and will required more calories than basal needs	• Enteral feeding is preferred over TPN • Oral feeding should not be interrupted if safe; nasogastric or naso-jejunal feeds should be attempted before starting TPN • TPN may be necessary to provide maximal calories with minimal volume if fluid overload is an issue and/or if ensuring euglycemia is not possible with enteral feeding • If TPN started, ◦ No protein restriction unless hyperammonemia ◦ If hyperammonemia present, protein should be restricted to 1 g protein/kg per day ◦ Lipids can be started unless suspected disorder of fatty acid oxidation or mitochondrial disease
Infections	Positive culture	Suspect infection if ◦ Onset of spontaneous bleeding ◦ Spontaneous hypothermia ◦ Worsening status of other organs (eg, pulmonary, cardiovascular, renal) ◦ Worsening mental status or progression of cerebral edema ◦ Elevation on WBC, neutrophils, or appearance of immature WBCs If clinical or biochemical changes occur, blood cultures and tracheal cultures, if intubated, should be obtained and broad-spectrum antibiotics started until cultures return negative

Abbreviations: ↑, increase in; ↓, decrease in; CT, computerized tomography; EEG, electroencephalogram; HE, hepatic encephalopathy; ICP, intracranial pressure; INR, international normalized ratio; IV, intravenous; PALF, pediatric acute liver failure; RIFLE, risk, injury, failure, loss, end-stage; TPN, total parenteral nutrition; WBC, white blood cell.

[a] Avoid contrast if evidence of renal injury.

[b] Greater than 6.1 mm is a potentially novel approach studied in pediatric traumatic brain injury, but not in PALF.

Table 3
Hepatic encephalopathy in pediatric acute liver failure

Stage		Clinical	Reflexes	Neurologic Signs	EEG Changes
0		None	Normal	None	Normal
I	Infant/child	Inconsolable, crying, inattention to task, parents describe child as "not acting like self"	Normal or hyperreflexia	Difficult or impossible to assess	Normal or diffuse slowing to theta rhythm, triphasic waves
	Adolescent/young adult	Confused, mood changes, altered sleep habits, forgetful	Normal	Tremor, apraxia, impaired handwriting	
II	Infant/child	Inconsolable, crying, inattention to task, parents describe child as "not acting like self"	Normal or hyperreflexia	Difficult or impossible to assess	Abnormal, generalized slowing, triphasic waves
	Adolescent/young adult	Drowsy, inappropriate behavior, decreased inhibitions	Hyperreflexia	Dysarthria, ataxia	
III	Infant/child	Somnolence, stupor, combativeness	Hyperreflexia	Difficult or impossible to assess	Abnormal, generalized slowing, triphasic waves
	Adolescent/young adult	Stuporous, obeys simple commands	Hyperreflexia, (+) Babinski	Rigidity	
IV	Infant/child	Comatose, arouses with painful stimuli (IVa) or no response (IVb)	Absent	Decebrate or decorticate	Abnormal, very slow, delta activity
	Adolescent/young adult	Comatose, arouses with painful stimuli (IVa) or no response	Absent	Decebrate or decorticate	

Abbreviation: EEG, electroencephalography.
Adapted from Squires RH Jr. Acute liver failure in children. Semin Liver Dis 2008;28(2):157; with permission.

with ALF appear to have a comparable decrease in both procoagulant and anticoagulant factors.[30] As a result, the overall coagulation profile, as measured by thromboelastography, typically reflects normal hemostasis.[31] However, the coagulation profile can be dynamic in ALF. Although most individuals have normal hemostasis despite a prolonged INR, some may have manifestation of a hypercoagulable state (eg, portal vein thrombosis) or hypocoagulable (eg, active bleeding episodes).[32]

Renal

As most children with ALF were healthy before presentation, renal insufficiency is a result of acute kidney injury (AKI). Settling on a consensus definition of AKI has been problematic. More recently, the *R*isk of renal failure; *I*njury to the kidney; *F*ailure of kidney function; with outcomes of *L*oss of kidney function and *E*nd-stage kidney disease (RIFLE classification) appears to be able to characterize AKI in critically ill children.[33] The RIFLE classification used estimated creatinine clearance and/or urine output to determine Risk, Injury, and Failure.[34]

The etiology of AKI in PALF includes the following:

- Acetaminophen toxicity
- Nephrotoxic medications
- Infection
- Hypovolemia

Hepatorenal syndrome (HRS) rarely, if ever, occurs in the setting of PALF. HRS can be seen in those with acute on chronic changes, such as a patient with established cirrhosis and ascites receiving aggressive diuretic therapy. This results in a contracted central blood volume resulting in reduced renal blood flow with treatment directed to expand the blood volume.[35] Expanding blood volume in PALF, in the absence of shock or hypotension, may precipitate worsening HE, cerebral edema, increased intracranial pressure, and fluid overload.

Secondary Infections

Secondary bacterial infections are not commonly reported at the time of presentation in PALF and routine administration of intravenous antibiotics are not customarily initiated on admission. A retrospective study in adults with ALF did not support antibacterial prophylaxis.[36] However, sepsis in children is more common after 2 weeks of hospitalization.[37] The clinical signs of sepsis can be subtle and often do not include an elevated temperature (see “Infections” section in **Table 2**).

Aplastic Anemia

Hepatitis-associated aplastic anemia (HAAA) is rare and presents following PALF or acute severe hepatitis of indeterminate cause. The clinical phenotype often includes serum aminotransferase values more than 3 times the upper limit of normal but often reaching well over 1000 IU/L and bilirubin levels that are more than 5 mg/dL but also reaching over 20 gm/dL at times. The etiology remains unknown, although associated viral infections have been noted. Pancytopenia develops in the weeks to months following the initial liver injury.[38] A liver biopsy without viral inclusions, but containing a marked inflammatory infiltrate with a predominance of CD8+ cytotoxic T cells, may identify an individual at risk for developing HAAA.[39] If a liver transplant interrupted the clinical course of PALF, HAAA can develop following liver transplantation.

The diagnosis is suspected by gradual diminishment of the white blood cell count, neutrophil count, platelet count, and hemoglobin accompanied by a low reticulocyte count. A bone marrow will confirm the diagnosis.

Treatment ideally uses an allogeneic bone marrow transplant from an HLA-matched sibling. Immunosuppressive therapy with antithymocyte globulin and cyclosporine is often required.[38]

Liver Support Therapy

Various iterations of extracorporeal liver support systems have been investigated in children with ALF to determine if they might have a meaningful improvement in clinical outcome. Unfortunately, virtually all of them that include albumin dialysis, plasma exchange, bioartificial liver support systems (human hepatoblastoma cells), extracorporeal liver assist device (human-based cells), HepatAssist (porcine cell-based), and molecular absorbent recirculating system (MARS) have fallen short of the mark or have been underpowered to assess benefit. Therefore, they cannot be recommended.[40]

Plasmapheresis

Plasmapheresis or plasma exchange (PE) has been used successfully in a variety of conditions, such as myasthenia gravis, Guillain-Barre, and cryoglobulinemia. Case reports and case series have suggested PE can serve as a bridge to LTx by improving coagulation and other biochemical parameters. In a study of 243 PE procedures in 49 children, coagulation parameters improved, but it had no effect on neurologic complications and only 3 of 49 recovered with their native liver.[41] In patients with Wilson disease presenting with ALF and hemolytic anemia, PE may serve to remove toxic levels of copper and stabilize the hemolytic process before LTx.[42] A recent multicenter, randomized controlled trial compared 90 participants who received standard medical therapy with 90 who received standard medical therapy plus 3 days of PE. Those who received PE experienced improved transplant-free survival, decreased frequency of systemic inflammatory response syndrome, and sequential organ failure assessment scores compared with the control group.[43] Similar studies should be performed in children.

Molecular absorbent recirculating system

Over the past 15 years, efforts to establish the relevance of this liver support system in the management of ALF have been largely unsuccessful. A recent study suggested MARS may serve to bridge patients with severe liver trauma to spontaneous recovery.[44] There is a paucity of data using MARS in children, but a recent cohort of 20 children with ALF who were MARS-treated were compared with 20 who did not receive MARS, and although the heterogeneous patient cohort precluded a statistical analysis for benefit, biochemical parameters, such as ammonia, bilirubin, and creatinine, improved and it appeared to be safe.[45] Adequately powered studies are essential to determine if children receive a meaningful benefit from MARS.

ETIOLOGY, MECHANISM OF INJURY, CLINICAL CHARACTERISTICS, DIAGNOSTIC TESTING, TREATMENT, AND PROGNOSIS

Over the course of 10 years, the PALF Study Group enrolled more than 1000 participants in North America and England. Specific diagnoses within broad diagnostic categories, such as metabolic, infectious, drug-related, and immune-mediated liver injury differ with age and geographic location. Historically, PALF in developing nations was predominantly due to viral hepatitis, as single or dual infections; however, recent publications reflect an increasing number of metabolic/genetic, immune-mediated, and drug/herbal/toxin-related causes of PALF.[46]

A diagnosis is not established for many children with PALF. This is due to a variety of reasons that include an incomplete differential diagnosis, inadequate diagnostic

testing, or clinical progression that precludes further diagnostic testing. The clinical course of PALF can be rapid, dynamic, and unpredictable. The interval between presentation and a clinical outcome, such as liver transplant, death, or spontaneous recovery, can be as short as a few hours or days for some children. Thus, there is an urgency to establishment a specific diagnosis, as timely therapeutic intervention can affect clinical outcome.

Drug-Induced Liver Injury

Acetaminophen toxicity

Acetaminophen (APAP) is one of the most frequently used medications in the United States and is the most common identified cause of ALF in children[47,48] (**Table 4**). If taken as directed (maximum dose 75 mg/kg per day for children, 4 g/d for adults), APAP is well generally well tolerated; however, a well-designed study in healthy adults taking 4 g/d of APAP found elevations in alanine aminotransferase (ALT) of more than 3 times the upper limit of normal when taken for 4 or more days, with the serum APAP level in the therapeutic range.[49]

Non-acetaminophen drug-induced or toxin-induced liver injury

Although APAP toxicity is the most common cause for drug-induced liver injury (DILI) associated with PALF, many other medications, toxins, and herbal remedies have been identified as etiologic[58–62] (**Table 5**). An excellent resource for DILI is the LiverTox Web site: https://livertox.nlm.nih.gov/.

Metabolic/Genetic Diseases

As a disease category, metabolic conditions account for approximately 10% of all cases of PALF and 18% of PALF cases among children younger than 3 years (**Table 6**).[63] Tyrosinemia, galactosemia, urea cycle disorders, mitochondrial hepatopathies, and respiratory chain defects are common in younger patients.[64] In older children, Wilson disease is the most common metabolic defect; however, mitochondrial disorders, respiratory chain defects, and partial ornithine transcarbamylase deficiency also can present in older patients.

Viral Hepatitis

In North America, a viral cause for PALF is uncommon, with the notable exceptions of herpes simplex virus and enterovirus in children younger than 90 days.[63,82] There are many reasons for this that include vaccines for hepatitis A and B, safe potable water, hygienic requirements for food processing, and a sound sanitary system. In countries or regions in which these prevention practices are not available, then infectious diseases, particularly hepatitis A, B, and E, are the most common cause of ALF (**Table 7**).

Other Viruses

A variety of other viruses have been reported to cause PALF, but their ubiquitous nature and confounding exposure to potentially hepatotoxic medications makes it difficult to invoke a cause-and-effect of the identified virus at the time of clinical presentation. Human herpes virus-6 is typically a self-limited infection associated with exanthem subitum and a mononucleosis-type syndrome,[96,99] but has been identified in liver tissue of patients with ALF.[100] Influenza virus was reported to be a cause of ALF, but all recovered with their native liver, had chronic exposure to acetaminophen, and some had a biochemical phenotype similar to acetaminophen toxicity.[101] Parvovirus B19, another ubiquitous virus, can cause mild elevations of serum aminotransferase levels when children present with Fifth disease.[102] However, parvovirus

Table 4
Acetaminophen and acute liver failure: non-acetaminophen drug-induced or toxin-induced liver injury

Etiology	Mechanism of Injury	Clinical Characteristics	Diagnosis	Treatment	Prognosis
APAP	• Hepatic glutathione depletion following acute APAP toxicity allows highly reactive APAP derivatives to exact hepatocellular injury.[50]	• Most common identifiable cause of PALF • Ingestion $\geq$ 100 mg/kg is considered potentially toxic • Most common among white, adolescent girls • Extremely ↑↑↑ AST and ALT • Modest ↑ bilirubin • Centrilobular hepatic necrosis on liver biopsy • Acute and chronic exposure can cause PALF[51,52]	• Relies heavily on a detailed history (not all patients will report a single toxic ingestion or chronic APAP ingestion) • APAP levels ○ Levels obtained before 4 h are not sufficiently reliable to predict APAP hepatotoxicity unless the level is very low or undetectable[53] ○ Level can be <10 mg/L in a third of patients with either an acute toxic ingestion or chronic exposure[54] ○ APAP adducts ■ Generated from binding of electrophilic APAP by-products to intracellular proteins ■ Have been identified in most, but not all, patients with PALF due to acute APAP toxicity ■ Present in a small percentage of those with an indeterminate diagnosis suggesting a possible role of APAP adducts in the diagnosis of APAP toxicity[55,56]	• NAC • Initial NAC bolus (between 50 and 150 mg/kg) infused over 15–60 min followed by either a continuous or intermittent infusion over the next 20–48 h[57]	Full recovery occurs in more than 90% of cases, but liver transplantation can be life-saving for those with clinical deterioration despite NAC therapy[54]

Abbreviations: ↑, increase; ALT, alanine aminotransferase; APAP, acetaminophen; AST, aspartate aminotransferase; NAC, N-acetylcysteine; PALF, pediatric acute liver failure.

Table 5
Non-acetaminophen drug-induced or toxin-induced liver injury

Classification	Drug/Toxin	Interval Between Exposure and Manifestations	Clinical Features
Analgesic	Halothane	1–30 d	Fever, jaundice
Antibiotic	Isoniazid	0–14 mo	Fatigue, anorexia, malaise, then jaundice
	Rifampin	Weeks	Jaundice, severe hepatitis
	Pyrazinamide	4–8 wk	Fatigue, anorexia, malaise, then jaundice
	Amoxicillin/clavulanic acid	Days–2 mo	DRESS, severe hepatitis, cholestasis
	Tetracycline	4–6 d into therapy	Nausea, vomiting, abdominal pain, mild jaundice
	Minocycline	Days–2 mo	DRESS, severe hepatitis
		Months to a year	Autoimmune hepatitis
	Macrolide	1–3 wk	Nausea, abdominal pain, jaundice, fever
	Sulfonomide	Days–1 mo	Fever, rash, eosinophilia, jaundice
	Ketoconazole	1–6 mo	Acute hepatitis
	Itraconazole	1–6 mo	Fatigue, jaundice, severe hepatitis
Antiepileptic	Phenytoin	2–8 wk	Hepatitis, cholestasis, atypical lymphocytes, lymphadenopathy
	Carbamazepine	1–8 wk	DRESS, severe hepatitis
	Lamotrigine	1–8 wk	DRESS, mild to moderate hepatitis, cholestasis
	Felbamate	1–6 mo	Severe hepatitis, cholestasis
	Valproate	Months to years	hyperammonemia
		1–6 mo	Jaundice, severe hepatitis
Recreational drugs	Marijuana	Days	Acute severe hepatitis
	Cocaine	Hours to a few days	Acute hepatic necrosis
	Amphetamine	3–14 d	Acute severe hepatitis
Herbal medications	Amanita phalloides	6–40 h	Nausea, vomiting, then liver and renal failure
	Germander	2–18 wk	Nausea, vomiting, fatigue, severe hepatocellular injury
	Kava	2–24 wk	Nausea, fatigue, severe hepatocellular injury, cholestasis

Abbreviation: DRESS, drug rash with eosinophilia and systemic symptoms.

Table 6
Metabolic diseases and acute liver failure

Etiology	Mechanism of Injury	Clinical Characteristics	Diagnosis	Treatment	Prognosis
Wilson disease	• Due to mutations of the *ATP7B* gene, which prevent copper incorporation into ceruloplasmin and biliary excretion of copper	• Hepatic disease may present from age 3 to 60 y, but the peak incidence is between 6 and 20 y • ALF may be accompanied by a history of school deterioration or speech abnormality • ↓ Alkaline phosphatase • Nonimmune hemolytic anemia • Liver biopsy with steatosis/fibrosis	• Pathogenic mutations in *ATP7B* • Increased urinary copper excretion • Kayser- Fleischer rings • ↑↑ Hepatic copper	• Trientene or penicillamine and zinc • Monitor Wilson disease score[65] • LTx if Wilson disease score ≥11 or encephalopathy	• Lifelong chelation therapy required
Tyrosinemia	• Defect in FAH, the final enzymatic step in the tyrosine degradation pathway[66]	• Present within the first few weeks of life with hepatomegaly, and a profound coagulopathy • ↑ bilirubin • Modest ↑ ALT and AST • *Escherichia coli* sepsis may be presenting feature • ↑↑ Risk of HCC • Risk is lowered with early treatment[67]	• Urine test for succinylacetone is diagnostic • NBS is available for tyrosinemia in most states • Diagnostic testing should be performed if the clinical phenotype is consistent with tyrosinemia regardless of the results of the NBS	• Nitisinone (NTBC, Orfadin), treatment is lifelong • Low tyrosine diet • LTx is performed for treatment failure with NTBC or clinical concern for HCC regardless of whether the patient is receiving NTBC	• Ongoing monitoring for development of HCC, even if NTBC was initiated

Galactosemia	• GALT deficiency	• Hepatosplenomegaly, coagulopathy • ↑↑ Bilirubin • *E coli* sepsis may be presenting feature • Modest ↑ ALT and AST	• NBS testing using dried blood spots includes assessment of GALT level[68] ○ Red blood cell transfusion before obtaining the test will void the usefulness of the test • + Urine reducing substances	• A galactose-restricted diet (eg, lactose free) is the lifelong therapy • Dietary restrictions appear to become lax into adulthood, but the consequences are not clear[69]	• Mild intellectual impairment is common
Urea cycle defects (UCD)	• OTCD is the most common UCD to present with PALF • Citrullinemia type 1 has also been described[70]	• Typical presentation of a metabolic crisis with poor feeding, altered mental status ± seizures, and ↑↑ serum NH3 • One-third of patients with UCD will also have a ↑ ALT, AST and INR that meets entry criteria for PALF[71] • Bilirubin usually normal • PALF can be transient or recurrent	• Quantitative serum/plasma amino acids will reveal patterns of elevation and deficiency that can lead to a suspected diagnosis • Urinary orotic acid and amino acid analysis • Single gene mutation analysis when a specific diagnosis is strongly suspected from results of the previously mentioned tests • Multigene panel that includes the 8 genes generating UCD enzymes • Enzyme activity in liver, fibroblasts, or red blood cells[72]	• Dialysis to remove NH3 • NH3 scavengers (eg, sodium phenylacetate, sodium benzoate) • Low-protein diet supplemented with amino acids, preferably administered enterally; but may require TPN • LTx will cure some UCDs (eg, CPS1, OTCD, arginosuccinate synthetase), as these enzymes are found almost exclusively in the liver; arginosuccinate lyse and arginase 1 are expressed outside the liver and more careful post-LTx monitoring is needed[73]	• Most common identifiable cause of PALF

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Table 6
(*continued*)

Etiology	Mechanism of Injury	Clinical Characteristics	Diagnosis	Treatment	Prognosis
Fatty acid oxidation defects[74]	• ≥20 individual defects are recognized • ALF described in LCHAD, ACAD9, MCAD, CACT deficiency	• Hepatomegaly, ↑ ALT and AST, and modest ↑ NH3 occur in ≥ 80% of cases • ↑Bilirubin in up to one-third • Neurologic, cardiac, and muscular symptoms are frequent	• Blood acylcarnitine profile and urinary organic analysis at the time of metabolic instability • ↑ plasma-free fatty acids/3-hydroxybutyrate ratio • Mutation detection using multigene panel • Fibroblast palmitate and myristate oxidation studies	• Treatment with intravenous carbohydrate • Avoiding fasting and use of a carbohydrate-containing emergency regimen during intercurrent illnesses • In long-chain defects, dietary long-chain fat should be restricted	• PALF recovers spontaneously with supportive care • Neurologic sequalae from hypoglycemia are common
NBAS deficiency[75]	• Normal function in retrograde transport between endoplasmic reticulum and the Golgi apparatus • Role in PALF not fully understood	• Infantile liver failure precipitated by febrile illness • Mild jaundice • Recurrent PALF	• Pathogenic mutations in *NBAS* • Liver biopsy shows steatosis	• Aggressive supportive care • Prompt antipyresis • Use of intravenous lipid during acute episodes • LTx appears to prevent recurrent episodes	• Episodes may be fatal but recovery usually occurs within days if normalization of liver function • Recurrent PALF, may become less severe with age
Hepatocerebellar neuropathy syndrome[76]	• Due to deficiency of SCYL1, which has a role in maintaining Golgi integrity	• Recurrent bouts of PALF provoked by fever starting in infancy	• MRI shows cerebellar vermis atrophy • Pathogenic mutations in *SCYL1*	• Aggressive supportive care • Prompt antipyresis • LTx has not been described	• Spontaneous recovery occurs, but progressive fibrosis and PHTN develop • Episodes decrease with age and are rare after age 10 • Delayed motor milestones are common and eventually progressive cerebellar dysfunction and motor myopathy develop

Infantile liver failure syndrome type 1[77]	• Mutations in *LARS*, which encodes a transfer RNA synthase	• Multisystem disorder with low birth weight, anemia, and seizures • PALF with fever in infancy • ↓↓ albumin • Liver biopsy with microvesicular steatosis • Microcytic anemia	• Pathogenic mutations in *LARS*	• Aggressive supportive care • Prompt antipyresis • High-protein diet during acute episodes • LTx has not been described	• Spontaneous clinical and biochemical recovery occurs over 3–4 wk • Chronic liver disease develops in some cases • Episodes decrease with age, but intermittent encephalopathy and seizures unrelated to liver dysfunction persist
Wolcot-Rallison syndrome[78]	• Due to mutations in *EIF2AK3*	• Neonatal diabetes and skeletal dysplasia • Up to 80% develop recurrent liver failure, often associated with febrile illness, from infancy	• Pathogenic mutations in *EIF2AK3*	• Aggressive supportive care • LTx has prevented recurrent episodes and has been combined with pancreas	• Up to 80% develop recurrent liver failure, often associated with febrile illness, from infancy • Most episodes are self-limiting but cumulative mortality in childhood remains high

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Table 6
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Etiology	Mechanism of Injury	Clinical Characteristics	Diagnosis	Treatment	Prognosis
Bile acid (BA) synthetic disorders[79]	• Due to defect in any of the 14 enzymes of BA synthesis • Liver injury is a consequence of decreased primary BAs that are critical for BA-dependent bile flow, combined with the production of atypical, hepatotoxic metabolites • Liver failure is reported in ○ Delta 4-3-oxosteroid 5α-reductase deficiency ○ Oxysterol 7α-hydroxylase deficiencies	• Low gamma glutamyl transferase neonatal cholestasis • Fat-soluble deficiency • Low plasma BAs	• Pathogenic mutations in select BA synthesis enzymes • Urinary fast atom bombardment spectroscopy	• Cholic and/or chenodeoxycholic acid supplementation • LTx if supplementation fails	• Excellent outcomes have been reported with initiation of early supplementation • LTx provides a metabolic cure

Hereditary fructose intolerance	• Deficiency of fructose-1-phosphate aldolase resulting in the accumulation of fructose-1 phosphate	• Symptoms occur with the introduction of sucrose or fructose into the diet and include vomiting, failure to thrive, and jaundice with hepatomegaly • Classically occurring following weaning, the widespread availability of fructose-containing feeds means that presentation can occur in early infancy • In older children and adults there is a history of avoiding fruit and sweets	• Pathogenic mutations in *ALDOB*	• Avoidance of dietary fructose	• Removal of dietary fructose results in rapid improvement, although hepatomegaly and abnormal transaminases may persist
Mitochondrial hepatopathy[80]	• Dysfunction of the electron transport chain resulting in cellular ATP deficiency, impaired fat oxidation and the generation of toxic free radicals	• Highly variable but multisystem disease is usual • ALF is most commonly caused by mtDNA depletion syndromes • Elevated lactate is sensitive but non-specific • Liver biopsy often shows microvesicular steatosis	• Tissue measurements of respiratory chain activity and mtDNA levels • Pathogenic mutations causing mtDNA depletion have been described in 10 genes to date, of which at least 4 result in liver disease ○ DGUOK ○ POLG ○ MPV17 ○ Twinkle	• Aggressive supportive care • Once considered a general contraindication to LTx, recent experience suggests a potential role of LTx in management.[81]	• Multisystem disease progresses in most cases

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Etiology	Mechanism of Injury	Clinical Characteristics	Diagnosis	Treatment	Prognosis
Alpers syndrome	• mtDNA depletion disorder due to mutations in *POLG*	• Characterized by degenerative brain and liver disease in the first decade that may be precipitated by Valproate treatment • Seizures, which are focal and refractory, usually precede liver disease • EEG may show characteristic pattern	• Pathogenic mutations in *POLG*	• Stop valproate • Intravenous carnitine and NAC if valproate associated	

Abbreviations: ↑, increase; ACAD9, Acyl-CoA dehydrogenase family member 9; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CACT, Carnitine-acylcarnitine translocase; CPS1, carbamoylphosphate synthetase; DGUOK, deoxyguanosine kinase; EEG, electroencephalogram; FAH, fumarylacetoacetase; GALT, galactose-1-phosphate uridyl transferase; HCC, hepatocellular carcinoma; LCHAD, Long-chain 3-hydroxyacyl-CoA dehydrogenase; LTx, Liver transplant; MCAD, Medium-chain acyl-CoA dehydrogenase deficiency; MRI, magnetic resonance imaging; mtDNA, mitochondrial DNA; NAC, N-acetylcysteine; NBAS, neuroblastoma amplified sequence; NBS, newborn screen; OTCD, ornithine transcarbamylase deficiency; PALF, pediatric acute liver failure; PHTN, portal hypertension; POLG, polymerase gamma; TPN, total parenteral nutrition.

Table 7
Viral infection and acute liver failure

Etiology	Clinical Characteristics	Diagnosis	Treatment/Prognosis
Herpes simplex virus[83–85]	• Most common cause of neonatal ALF • Transmission from asymptomatic mother to infant likely occurs at or shortly after birth • Symptoms generally begin in first week of life • Can occur in older children (ie, history of immunosuppression and/or sexual activity) • ↑↑ Transaminases	• PCR in the serum • HSV serologies may not be present early in the disease • Culture of vesicle, blood, liver tissue • IHC stain of the liver	• Acyclovir (should be started immediately in all newborns presenting with ALF; it can be stopped if the HSV PCR returns negative) • LTx has been successful
Enterovirus[82]	• Affects all age groups • In older children, nausea, vomiting, and/or diarrhea are common • Occasionally, more serious conditions include flaccid paralysis or cardiomyopathy • Second most common cause of neonatal ALF	• PCR for enterovirus, Coxsackie virus, echovirus • Liver tissue culture	• Supportive care • LTx has been performed • If the infant survives ALF, complete recovery without sequelae occurs in most cases
Epstein-Barr virus[86–88]	• ↑ ALT and AST • ± Cholestasis • ALF is rare • EBV can trigger HLH (see below)	• Serology helpful, but not diagnostic • PCR for EBV ± IHC increases likelihood	• Supportive care • Corticosteroids have been used for EBV-ALF
Hepatitis A virus[89]	• ALF occurs in 1% of primary infections • Incidence dramatically decreased with HAV vaccine	• HAV IgM	• Supportive care • LTx has been performed
Hepatitis B virus[48,90]	• 1% of adults with ALF, only 0.3% of children • Incidence decreased with HBV vaccine	• HBV DNA • + HBV surface antigen • + HBV surface antibody • HBV e-antigen and antibody • HBV core antibody	• Children born to HBV+ mothers should receive HBV vaccine and HBIG • Although no studies in children, entecavir or tenofovir is recommended[91,92] • LTx has been performed

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Table 7
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Etiology	Clinical Characteristics	Diagnosis	Treatment/Prognosis
Hepatitis E virus[93]	• Common cause of ALF in developing countries • Can cause ALF in pregnant women	• HEV IgM • HEV IgG + viral RNA	• Ribavirin with or without pegylated interferon[94,95] but guidelines are not established.
Cytomegalovirus[96]	• ALF more common in immunosuppressed and infant populations	• PCR + serology suggesting recent infection • Liver biopsy with CMV inclusions	• Supportive care, spontaneous resolution can occur • Reduce immunosuppression medications if possible • Ganciclovir or valganciclovir has been used[97]
Adenovirus[98]	• Common in immunosuppressed patients	• Blood PCR • Liver tissue: culture, viral inclusions, IHC	• Cidofovir

Abbreviations: ALF, acute liver failure; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HAV, Hepatitis A virus; HBIG, Hepatitis B immune globulin; HBV, Hepatitis B virus; HEV, Hepatitis E virus; HLH, hemophagocytic lymphohistiocytosis; HSV, herpes simplex virus; Ig, immunoglobulin; IHC, immunohistochemistry; LTx, liver transplantation; PCR, polymerase chain reaction.

DNA can be present in liver tissue for months following infection, raising questions about causality when found in patients with ALF.[102] A study of adult patients found no evidence that parvovirus was associated with ALF.[103]

Immune-Mediated

Immune mechanisms have been shown to play a critical role in the pathogenesis of many liver injuries in children. Immune injury can occur secondary to autoinflammation and injury (classical autoimmune hepatitis and hemophagocytic lymphohistiocytosis) or by an allogeneic immune response of maternal antibodies to antigens associated with neonatal liver cells (gestational alloimmune liver disease) (**Table 8**). Importantly, autoantibodies (auto-AB), such as antinuclear antibody, smooth muscle antibody, and liver-kidney microsomal antibody (LMK), are associated with but not exclusive to autoimmune hepatitis. In the setting of PALF, serum auto-AB can be present among disease categories that include indeterminate, autoimmune hepatitis, and other known diagnoses (particularly Wilson disease).[104] Auto-AB detected in the serum of PALF patients can be transient and reflect their release from the inflammatory milieu in the context of severe hepatocellular injury.[105] Thus, it is important to recognize differences that may exist between classic autoimmune hepatitis (AIH), which can cause ALF, and auto-AB–positive PALF.

Cardiovascular

Shock/ischemia

Ischemic hepatitis, resulting from conditions such as hypoplastic left heart, interruption of the aortic arch, and cardiomyopathy, may initially manifest as severe liver injury or ALF.[110–112] Serum aminotransferase levels are often well over 1000 IU/L associated with acute hepatic necrosis. LTx is rarely used as an intervention, as complete hepatic recovery can occur if satisfactory blood flow to the liver can be established.

Budd-Chiari syndrome

Budd-Chiari syndrome is a rare cause of PALF. Obstruction of hepatic venous outflow either from hepatic vein thrombi, intravascular web within the inferior vena cava (IVC) cephalad from the hepatic veins, or a tumor results in the clinical manifestation of hepatomegaly, ascites, and evidence of hepatocellular injury. The cause for hepatic vein thrombosis is often not determined in children, although coagulation disorders (eg, antithrombin III deficiency, protein C or S deficiency, Factor V Leiden mutations) and myeloproliferative conditions associated with Janus kinase 2 mutations should be investigated.[113,114]

Diagnosis

- Ultrasound of the liver with Doppler
- Computerized axial tomography with angiography
- Angiography of the IVC to assess for intravascular web and patency of hepatic veins

Treatment

- Anticoagulation, even if the INR is prolonged.[115]
- Angioplasty of hepatic veins
- Transhepatic portosystemic shunt
- Liver transplant

Oncologic

Congenital leukemia as well acute lymphoblastic leukemia in older children can present with ALF.[116] Physical examination revealing splenomegaly and lymphadenopathy,

Table 8
Immune-mediated disease and acute liver failure

Etiology	Mechanism of Injury	Clinical Characteristics	Diagnosis	Treatment	Prognosis
Autoimmune hepatitis	• Exact etiology unclear • Suspect that auto-antigenic peptide, with particular cytokine milieu results in Th1 cell stimulation of T lymphocytes and macrophages and Th2 stimulation of auto-AB • Possible role of regulatory T cell and Th17 dysfunction	• + abdominal pain, fatigue, arthralgia • Often other autoimmune diseases • ALF can be presenting feature • ↑↑ AST and ALT • ↑/– bilirubin • ↑↑ IgG • + Auto-AB	• + Auto-AB • ↑↑ IgG • Liver histology compatible with AIH (interface hepatitis, plasma cell infiltrate, fibrosis) • Absence of viral hepatitis	• Steroids in acute setting • Long-term management often with Imuran, 6-MP, mycophenolate mofetil • Second-line agents such as budesonide, tacrolimus, rituximab, infliximab have been used	• Variable prognosis • Infectious complications can occur due to treatment • Long-term immunosuppression therapy is needed • LTx has been performed
Auto-AB–positive PALF[48]	• Unclear, likely multiple etiologies	• Can be similar to AIH	• + Auto-AB • Liver histology with hepatic necrosis	• Steroids have been used successfully in some but not all	• Infectious complications can occur due to treatment • LKM-positive patients are more likely to receive LTx • LTx has been performed • Most patients can be weaned completely off immunosuppression without disease recurrence
Gestational alloimmune liver disease (a.k.a.	• Alloimmune disease where to-be-determined fetal antigen crosses the	• Abnormal iron deposition in ○ Liver	• Extrahepatic siderosis in salivary gland (lip biopsy) or other organ (MRI)	• Exchange transfusion with IVIG	• Spectrum of disease, but in its most severe from is

neonatal hemochromatosis)[106]	placenta, induces maternal antibody production that returns to the fetal circulation and devastates the fetal liver • High recurrence rate (~80%) in subsequent pregnancies	○ Heart ○ Brain ○ Salivary glands • Leading cause of neonatal ALF • Present in first days of life • ↑↑ INR, ↑ bilirubin • Normal AST and ALT	• + MAC stain in liver biopsy is sensitive, but not entirely specific	• Antenatal treatment with IV immunoglobulins beginning at 14–18 wk of gestation can prevent recurrence in subsequent pregnancies	universally fatal without prompt therapy or LTx • LTx has been performed
Hemophagocytic lymphohistiocytosis (HLH)[107,108]	• Disorder of immune overactivation • Primary/familial type associated with PRF1, FHL2, FHL3, syntaxin 11 mutations • Secondary type most commonly associated with EBV infection • Other conditions associated include malignancy, metabolic d/o, and autoimmune disease	• Fever, hepatosplenomegaly, and cytopenia associated with a robust hyperinflammatory state • ↑ sIL-2r • ↑ ferritin	Must meet 5 of the following 8 criteria[109]: • Fever • Splenomegaly • Cytopenia affecting $\geq$ 2 lineages ○ Hemoglobin <9 ○ Platelet count <100 $\times$ 10^9/L ○ Absolute neutrophil count <1 $\times$ 10^9/L • Hypertriglyceridemia and/or hypofibrinogenemia ○ Triglycerides $\geq$ 265 mg/dL ○ Fibrinogen $\leq$150 mg/dL • Hemophagocytosis in bone marrow, spleen, or lymph nodes • Low or absent NK cell activity • Ferritin $\geq$500 μg/L • sCD25 (sIL2Rα) $\geq$2400 U/ml	• Immunosuppression ○ Corticosteroids ○ Etoposide ○ IVIG ○ Cyclosporine ○ Antithymocyte globulin • ± Bone marrow or hematopoietic stem cell transplant • LTx should be avoided, but has been successfully reported • Antiviral therapy for example, acyclovir/valganciclovir) combined with rituximab has been used in EBV-related HLH	

Abbreviations: ↑, increase; ↓, decrease; +, positive; −, negative; AIH, autoimmune hepatitis; ALF, acute liver failure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; d/o, disorder; EBV, Epstein-Barr virus; Ig, immunoglobulins; IVIG, intravenous immunoglobulins; LKM, liver-kidney microsomal antibody; LTx, liver transplant; MAC, membrane attack complex; NK, natural killer; PALF, pediatric acute liver failure; sIL-2r, soluble interleukin 2 receptor.

abdominal ultrasonography with evidence of enlarged abdominal lymph nodes, and abnormalities noted on the peripheral blood smear would suggest examination of the bone marrow should be performed as soon as possible. Metastatic, but previously undiagnosed, tumors such as adenocarcinoma also have been reported in children.[117]

Indeterminate

An indeterminate diagnosis (IN) is one of exclusion, although oftentimes the diagnostic evaluation is either interrupted by death, liver transplant, or spontaneous recovery. Therefore, the IN cohort is likely the most heterogenous final diagnosis among all others. An IN diagnosis can occur in all age groups, but appears to be highest among children between 1 to 10 years of age.[63] Clinical features associated with an IN diagnosis include a higher total bilirubin, but comparable levels of aminotransferase elevation and encephalopathy grade compared to those with an established diagnosis. However, those with an IN diagnosis are much more likely to receive a liver transplant that those with an established diagnosis.

Recent studies have hypothesized an underlying immune dysregulation as a mechanism of injury associated with an IN diagnosis.[118,119] Children with an IN diagnosis often have clinical features similar to other hyperinflammatory conditions such as macrophage activation syndrome and HLH. However, the hyperinflammatory milieu does not appear to be a genetic disorder of the immune or inflammatory response, as episodes of ALF do not recur after spontaneous recovery with the native liver.

Treatment

- Supportive therapy.
- Anecdotal reports and small case series report a benefit from corticosteroids, but given the severe complications associated with steroid treatment in ALF, further study is needed before a recommendation can be made.
- LTx.

PROGNOSIS

There are no satisfactory tools or models to predict outcome in PALF. Efforts to construct such a model are hampered by LTx. Most models include both death and LT into a single outcome. However, these 2 outcomes are not the same, as the LTx cohort includes patients who would have lived or would have died had LTx not interrupted the natural course of ALF. Existing models such as King's College Hospital Criteria and the Liver Injury Unit score that combined outcomes were unable to be validated when the outcomes of death and LTx separated.[120,121] Examination of dynamic inflammatory networks do appear to segregate outcomes of death and survival, whereas those who received an LTx had an inflammatory network that appeared to have features seen in those who died and those who survived.[122,123] Using a growth mixture model that included clinical data (INR, encephalopathy, total bilirubin) collected over 7 days, 5 different trajectories were generated with differing likelihoods for death or survival.[124] Other models using the trajectory of data collected over time suggest dynamic models hold some promise.[125,126]

OUTCOME

Most patients who meet PALF entry criteria are alive with their native liver at 21 days after enrollment. Very rarely, recurrent episodes of ALF are noted and have been associated with disorders of long-chain fatty acid oxidation, dihydrolipoamide dehydrogenase (E3) deficiency, Wolcott-Rallison syndrome, as well as children with mutations in

the *LARS* (leucyl-tRNA synthase) gene[127] and *NBAS* (neuroblastoma amplified sequence) gene.[128] The frequency of LTx has decreased since 2000, and currently is performed in approximately 38% of patients. Outcome following LTx for both patient and graft survival has improved, but remains lower than patients receiving LTx for chronic cholestatic diseases. For those patients who survive with their native liver or received an LTx, neurocognitive testing has identified deficits in executive functions, fatigue, motor skills, attention, and health-related quality of life.[129] The frequency of death among those who met entry criteria for the PALF study has remained between 3% and 5%.

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