ACUTE LIVER FAILURE IN CHILDREN - MANAGEMENT

PRACTICE GUIDELINE ©

DOCUMENT SUMMARY/KEY POINTS

- Acute Liver Failure (ALF) is a multisystem disorder that can have high morbidity and mortality.
- All presentations should be discussed early with on call gastroenterology.
- Consideration should be given to transfer to a transplant centre. This is essential in children identified to be approaching or fulfilling King's College Transplant Criteria
- Investigation and management of ALF, along with King's College Transplant Criteria is outlined below.

CHANGE SUMMARY

- N/A – new guideline.

READ ACKNOWLEDGEMENT

- This document is for all staff involved in the management of children with Acute Liver Failure.

Approved by:	SCHN Policy, Procedure and Guideline Committee	
Date Effective:	1st January 2024	**Review Period**: 3 years
Team Leader:	Staff Specialist	**Area/Dept**: Gastroenterology

Date of Publishing: 18 December 2023 3:09 PM Date of Printing: 18 December 2023

TABLE OF CONTENTS

Definition

Acute Liver Failure (ALF) is a rare but life-threatening condition in children. It occurs when there is an acute liver insult in a patient with no known pre-existing liver disease, resulting in coagulopathy and/or encephalopathy[(1)]. Features include:

1. Acute hepatic injury
2. Absence of pre-existing liver disease*
3. Coagulopathy not corrected with intravenous or intramuscular vitamin K:
    i. INR ≥ 1.5 (with encephalopathy)
    ii. INR ≥ 2 (without encephalopathy)

**Unusually ALF may occur in Wilson's Disease and autoimmune hepatitis as the first manifestation of an unknown pre-existing liver disease*

For neonates, please refer to the section on Neonatal ALF for diagnosis and management.

Hepatic encephalopathy (HE) is often difficult to assess in children, especially infants and neonates[(1)]. Tables 1 and 2 detail the grades of encephalopathy in children of different age ranges. [(2-4)]

Table 1: HE Grading Scale (Under 4 Years of Age)

Stage	Clinical	Asterixis/Reflexes	Neurological Signs	EEG Changes
Early (I and II)	Inconsolable crying, sleep reversal, inattention to task	Unreliable/normal or hyperreflexic	Untestable	Normal or mild slowing
Mid (III)	Somnolence, stupor, combativeness	Unreliable/ hyperreflexic	Most likely untestable	Abnormal generalized slowing
Late (IV)	Comatose, arouses with painful stimuli	Absent	Decerebrate or decorticate	Severe attenuation or slowing

Table 2: Standard HE Clinical Scales (4 - 10 Years of Age)

Stage	Clinical	Asterixis/Reflexes	Neurological Signs	EEG changes
I	Confused, mood changes, altered sleep habits, loss of spatial orientation, forgetful	None/normal	Tremor, apraxia, impaired handwriting	Normal or diffuse slowing
II	Drowsy, inappropriate behaviour, decreased inhibitions	None/hyperreflexic	Dysarthria, ataxia	Abnormal generalized slowing
III	Stuporous, obeys simple commands	None/hyperreflexic	Rigidity	Abnormal generalized slowing
IV	Comatose, arouses with painful stimuli, or no response	Absent	Decerebrate or decorticate	Abnormal, very slow

Aetiology of Acute Liver Failure

Broad aetiologies of ALF are categorized as infectious, immunologic, metabolic and toxin/drug related, with age-based differences (Neonatal ALF is discussed in a later section).

In up to 50% of paediatric ALF a specific cause is not identified[2], hence "non-A-G hepatitis" which implies an unrecognised infectious aetiology.

1. Infectious
   - **a.** Viral:
     - Hepatitis A, B, C, D, E
     - **i.** Epstein Barr Virus (EBV)
     - **ii.** Cytomegalovirus (CMV)
     - **iii.** Parvovirus B19
     - **iv.** Adenovirus
     - **v.** Human Herpes Virus 6 (HHV6)
     - **vi.** Enterovirus (echovirus, coxsackie)
     - **vii.** Herpes Simplex
     - **viii.** Varicella
     - **ix.** Brucella
     - **x.** Toxoplasmosis
   - **b.** Leptospirosis
   - **c.** Coxiella burneti (Q fever)
2. Hepatotoxins
   - **a.** Paracetamol (overdose or therapeutic misadventure)
   - **b.** Amanita phalloides (mushroom)
   - **c.** Drug reaction: there are many causes, including (the list below is not exhaustive):
     - **i.** anticonvulsants (sodium valproate, carbamazepine, phenytoin); consider underlying mitochondrial disease with valproate toxicity[1,5]
     - **ii.** isoniazid
     - **iii.** halothane (no longer in anaesthetic use)
   - **d.** Social or party drugs: cocaine, ecstasy, methamphetamines
3. Autoimmune hepatitis
4. Malignancy: lymphoma, leukaemia, neuroblastoma
5. Haemophagocytic lymphohistiocytosis (HLH)
6. Metabolic Diseases:
   - **a.** Mitochondrial hepatopathy
   - **b.** Fatty acid oxidation disorders
   - **c.** Wilson disease
   - **d.** Galactosaemia
   - **e.** Hereditary fructose intolerance
   - **f.** Tyrosinaemia
   - **g.** Urea cycle disorders
   - **h.** Reye syndrome (aspirin exposure)

7. Ischaemic/hypoxic:

a. Budd-Chiari syndrome; sinusoidal obstruction syndrome (formerly known as veno-occlusive disease)

b. Cardiac compromise/cardiomyopathy/pericardial tamponade

c. Acute hepatic vascular occlusion

d. Acute circulatory compromise with shock/gram negative sepsis/hypoxia

Initial Management

Urgent consultation should be made with the on call Paediatric Gastroenterologist at the closest tertiary centre for advice and discussion of further management.

It is mandatory that children identified as having ALF who are approaching or fulfil King's College Hospital (KCH) Criteria* be referred to a liver transplant centre as early as possible. [6]

Important historical features:

- Infectious
  - recent travel
  - sick contacts
- Toxicity/drug usage
  - prescribed
  - herbal supplements
  - over the counter
  - wild mushrooms
  - illicit
  - household or industrial chemicals
- Family history of autoimmune disease
- Metabolic
  - consanguinity
  - previous late miscarriage/early infant death
  - developmental delay
  - previous episodes altered mental state/confusion

Initial assessment includes:

1. Vital signs, state of hydration, haemodynamic status
2. Neurological exam, grade of encephalopathy
3. Evidence of spontaneous bleeding
4. Growth failure, dysmorphic features
5. Signs of chronic liver disease: hepatomegaly, splenomegaly, ascites, abdominal varices, clubbing, spider naevi, peripheral oedema

Baseline Investigations:

1. FBC and reticulocyte count
2. Coagulation (including fibrinogen, factors 5,7,8)
3. Blood group
4. Liver function tests including bilirubin (total and conjugated fractions)
5. Electrolytes (UEC, CMP)
6. Serum lactate, venous blood gas
7. Blood sugar level
8. Cholesterol, triglycerides
9. Serum ammonia
10. Amylase, lipase
11. Paracetamol level
12. Blood, urine, stool culture; viral throat swab
    i. If the **INR is** ≥ 1.5 (give IV Vitamin K (0.3 mg/kg, Maximum 10mg per dose) and repeat coagulation screen in 4 hours. [7]

Paracetamol Overdose

Any child with suspected or proven paracetamol hepatotoxicity should be immediately started on N-acetylcysteine therapy if:

- Known or assumed acute overdosage. [8]
- "Therapeutic misadventure" from repeated recommended doses over several days [9], which may not fulfil the criteria as per nomogram for an acute overdose; the presence of any paracetamol level supports exposure with potential toxicity and the need for treatment.
- **Paracetamol overdose with coagulopathy alone may be managed at other centres with gastroenterology advice as needed but must be transferred to paediatric liver transplant centre if approaching or satisfying King's College Criteria.**

See also SCHN Paracetamol Overdose – Assessment and Management Guideline.

Screening Investigations:

1. Infectious screen:
    i. Hepatitis A IgG, IgM; Hep B surface antigen, surface antibody, Hep B core antibody; Hep C antibody; Hep E IgG, IgM
    ii. HIV Ab
    iii. EBV IgG, IgM: (EBV VCA IgG, IgM, EBV EBNA IgG); CMV IgG, IgM; parvovirus IgM; HHV6 IgG, IgM; HSV IgM; varicella IgM
    iv. Other serology as clinically indicated; save serology for future testing.
    v. Serology IgG, IgM and blood PCR for adenovirus, enterovirus. Consider Faeces PCR for enterovirus if clinical index of suspicion is high.
    vi. Infectious screen with Gastrointestinal PCR and Culture, Respiratory PCR
2. Autoantibodies: Antinuclear Antibody (ANA), Smooth Muscle Antibody (SMA), Liver Kidney Microsomal Antibody (LKMA), perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA), immunoglobulins
3. Copper, ceruloplasmin, Ophthalmology assessment for Kayser-Fleischer rings, 24-hour urinary copper
4. Alpha fetoprotein (neonatal liver failure), ferritin, alpha-1-antitrypsin level, and genotype
5. Urine metabolic screen, plasma amino acids, acylcarnitine profile
6. Urinary drug screen
7. Chest Xray, abdominal Doppler ultrasound, DISIDA (hepatobiliary scintigraphy)

Further Investigations

As guided by Paediatric Gastroenterology and the clinical scenario, including:

- Bone marrow biopsy, especially if evidence of blood count abnormalities or suspicion of HLH
- Liver biopsy (consider transjugular depending on coagulation profile) [10]
- Cerebral imaging, EEG
- Consider urgent genomic testing early (ideally trio), in children and neonates, depending on phenotype of ALF: contact on call geneticist to discuss urgent testing.

Important conditions which may be difficult to diagnose include:

- **Autoimmune hepatitis/autoantibody positive ALF**: classic serological markers such as ANA, SMA and LKMA are reported to be positive in 28 % of ALF [11], but not necessarily diagnostic unless confirmed with liver biopsy [12], which may warrant treatment with corticosteroids.
- **Wilson disease**: haemolysis (Coombs negative), very high bilirubin with very low ALP, Kayser-Fleischer rings.
- **Malignancies such as leukaemia, lymphoma**: abnormal FBC, significantly enlarged and firm/hard liver.
- **Haemophagocytic lymphohistiocytosis**: may present with fever, splenomegaly, pancytopaenia, hyperferritinaemia, hypertriglyceridaemia. EBV is the most common infectious trigger and is positive in only 1/3 of cases.

Overview of ED Management

Child or neonate with ALF as defined as:

Acute hepatic injury

Absence of pre-existing liver disease*

Coagulopathy not corrected with intravenous or intramuscular vitamin K:

- INR ≥ 1.5 (with encephalopathy)
- INR ≥ 2 (without encephalopathy)

1. Notify on call gastroenterology immediately for advice and if in established ALF discussion of transfer.
2. Establish history, initial assessment, and baseline investigations (see initial management).
3. IV Vitamin K 0.3mg/kg (once daily), maximum 10mg and recheck coagulation profile in 4 hours[7]. If no improvement in INR and child/neonate is in ALF, follow ALF protocol.
4. IV antibiotic (eg piperacillin-tazobactam) and consider antifungal (eg fluconazole) and antiviral (aciclovir) coverage. Neonates should start on IV aciclovir immediately[1,5].
5. Prophylactic IV proton pump inhibitor.
6. Cease feeds in neonates and in children with suspected metabolic disease.
7. Fluid resuscitation as clinically appropriate and remain on 2/3 maintenance with strict fluid balance. Close monitoring of electrolytes, glucose, and lactate on blood gases and ammonia and coagulation profile.
8. In cases of paracetamol overdose: Start n-acetylcysteine as per SCHN Paracetamol Overdose Guideline or if repeated doses over several days. Discuss transfer with transplant centre if approaching or at King's College Criteria.
9. Increase glucose in maintenance IV fluid in event of hypoglycaemia.
10. Commence lactulose 1mL/kg/dose q4-6 hourly if ammonia elevated.
11. Early discussion with ICU if haemodynamically unstable or ammonia elevated with or without altered behaviour/neurological signs.
12. Ensure adequate IV access for sampling, IV fluids/drugs and safe transfer.

Overview of Ward Management

1. Ensure ED Management completed.
1. Re-assess history, physical assessment including behaviour and neurology, review investigations and medications. Ensure screening investigations are completed (See Initial Management). Discuss further investigations with on call gastroenterologist.
2. Review Principles of Management, key points of initial ward management are outlined below.
3. Venous blood gas (VBG), lactate, liver function tests (LFT), ammonia (NH3), bloods glucose and coagulation profile three times a day and electrolytes and renal function (UEC) twice daily.
4. Twice daily clinical review.
5. Regular neurological assessment with initial 2 hourly observations and nurse with head at 30 degrees and no neck flexion.
6. Careful replacement of electrolytes, avoiding hyponatraemia.
7. Daily weights and strict fluid balance.
8. No routine correction of coagulopathy with blood products.
9. Early dietitian involvement and consideration of nutrition, route dependent on suspected aetiology of ALF.
10. Discuss initiation of transplant work up if no improvement or approaching King's College criteria.

Principles of Management

Bedside management of ALF is multifactorial and complex. Paediatric Intensive Care Unit (ICU) admission and specialised therapy is often required, particularly if hepatic encephalopathy or multi-organ failure occurs. Attention to the following areas is required.

Infection

- **Patients with ALF are at risk of sepsis and the systemic inflammatory response syndrome** [1,5]
    - **i.** Piperacillin-tazobactam antibiotic prophylaxis.
    - **ii.** Antifungal cover (fluconazole) should also be considered, especially in the ICU patient requiring invasive intervention (ventilation, central venous lines, haemofiltration).
    - **iii.** Consider aciclovir.

Fluid, electrolytes, and renal function

- **i.** Fluid management is challenging in ALF.
- **ii.** Patients on initial presentation are often intravascularly depleted and require saline resuscitation.
- **iii.** Children are then typically managed on 2/3 maintenance therapy to avoid fluid overload which can lead to complications such as cerebral oedema, ascites, and pulmonary oedema. This can then be rationalised as it is important to ensure adequate nutrition is provided.
- **iv.** Daily weights and strict fluid balance should be performed.
- **v.** ALF is also associated with low systemic vascular resistance which may precipitate hypotension and renal dysfunction, “hepatorenal syndrome” [13]; inotropic support and haemofiltration may be required.
- **vi.** Indications for haemofiltration may include: oligo-anuria, potassium >5.5 mmol/L, fluid overload > 10%, ammonia > 75 and rising, sodium <130, Grade 2 encephalopathy, lactate >2 (as an indicator of liver dysfunction-not on its own) or pH < 7.1 not responding to fluid therapy. It is important not to take each factor in isolation. [5,14]
- **vii.** Electrolyte derangement requires monitoring and correction, especially low potassium, phosphate, and magnesium.
- **viii.** Hyponatraemia (<135mmol/L) can lead to increased intracranial pressure (ICP), and this should be slowly corrected.
- **ix.** Initial VBG, lactate, LFT, ammonia, blood glucose and coagulation profile three times a day and UEC twice a day. For rationalising if patient improving.
- **x.** In the event of seizures, consider the underlying cause of ALF, as well as electrolyte imbalance and cerebral oedema.

Metabolic concerns

i. Hypoglycaemia should be monitored for and treated. Ensure glucose containing IV fluid is supplied continuously.

ii. Relative adrenal insufficiency should be considered if there is refractory hypotension.

iii. **Nutrition** needs to be maintained as ALF children are usually catabolic. The enteral route is preferred but parenteral – administration may be necessary.

iv. If metabolic disease such as galactosaemia, tyrosinaemia, urea cycle disorders or fatty acid oxidation disorders are suspected, children should remain NBM until these are ruled out.

Hepatic encephalopathy (HE)

i. Regular neurological assessment starting at 2 hourly observations.

ii. Minimise stimulation, avoid sedation.

iii. Consider serum sodium 145-155 mmol/L to improve intracranial hypertension, using hypertonic saline judiciously [15,16]. This may help temporarily but hypernatraemia should not be sustained.

iv. Nurse with head of bed elevated to 30 degrees.

v. Consider cerebral imaging if acute neurological deterioration, localising signs.

vi. Children who develop Grade 2 encephalopathy should be considered for ICU admission.

vii. Intubation and ventilation if progression to Grade 3 – 4 encephalopathy.

viii. Seizures should be considered if there is neurological deterioration.

ix. Mannitol may be used in PICU for acute therapy of raised intracranial pressure. [17]

x. The use of intracranial pressure monitoring is rarely undertaken in children, usually due to risks associated with bleeding from bolt placement [18]

Ammonia

- **Ammonia (NH_3) measurement** provides a guide to worsening HE

i. Arterial ammonia < 75 micromol/L (normal < 50) is rarely associated with intracranial hypertension (ICH).

ii. Initial treatment with Lactulose 1 mL/kg/dose q 4-6 hourly, dose adjusted to produce loose stools 4-6 daily. Lactulose promotes an acidic intraluminal gut environment which favours conversion of NH_3 to NH_4^+, reducing intestinal absorption. [19]

iii. Rifaximin has been demonstrated in adults to be as efficacious as lactulose in altering the intestinal microbiome to decrease ammonia [20] but there is sparse paediatric data.

iv. Consider IV sodium benzoate + arginine though evidence for their effectiveness is limited.

v. Ammonia levels rising > 75 micromol/L despite aggressive therapy, risks the development of HE and may need haemofiltration [21]; Ammonia > 200 micromol/L is strongly associated with cerebral herniation and increased mortality. [22]

Coagulopathy, thrombocytopaenia, and bleeding

i. Give Vitamin K intravenously 0.3 mg/kg/dose daily, maximum 10 mg.

ii. Routine correction of coagulopathy is not required as both pro- and anti-coagulant factors are affected in ALF [23] and attempts to correct coagulopathy may result in fluid overload. [24]

iii. Clinically significant bleeding can occur with sepsis, or if an invasive procedure is planned, which then requires plasma and/or platelet infusions.

iv. TEG (thromboelastography) may help define clotting capabilities. [25]

v. Thrombocytopaenia related to either consumption or bone marrow suppression may occur; this is not treated unless there is bleeding. It may be treated if a high-risk invasive procedure is planned where local haemostasis is not possible and platelets < 20-50 x 10^9 /L. This must be discussed with the proceduralist as there is weak evidence that platelet count will identify patients at increased risk of procedural bleeding. [26, 27]

vi. Empiric proton pump inhibitor therapy (1mg/kg once daily) should be given as prophylaxis for upper gastrointestinal bleeding.

Neonatal Acute Liver Failure (NALF)

ALF in neonates (less than 4 weeks of age) is rare [28]. The defining feature of liver failure in neonates is coagulopathy (INR > 2) in the presence of liver disease, given that low grade encephalopathy is impossible to determine in this age group.

Causes include:

1. Gestational Alloimmune Liver Disease (GALD), formerly known as Neonatal Haemochromatosis (NH).
2. Viral infection
    i. Most common: herpes simplex virus, enterovirus (echo virus, coxsackie)
    ii. Also reported: parvovirus, adenovirus, HHV6, CMV
3. Metabolic/Inborn Errors of Metabolism
    i. Mitochondrial disorders: respiratory chain defects, fatty acid oxidation disorders
    ii. Galactosaemia, tyrosinaemia, hereditary fructose intolerance
    iii. Nieman-Pick C, congenital defects of glycosylation, urea cycle disorders

4. Malignancy: congenital leukaemia, neuroblastoma.
5. Haemophagocytic lymphohistiocytosis (HLH).

In general, the four most common aetiologies of NALF are GALD, viral infection, HLH and mitochondrial hepatopathy. The investigation and management of these often extremely sick infants is multidisciplinary, involving Neonatology, Hepatology, Immunology, Metabolic and Infectious Diseases. Some features of each disease include:

1. **GALD**
    - **i.** Most common cause of NALF
    - **ii.** In utero insult (mid-gestation) of the liver due to alloimmune injury, with subsequent disordered iron homeostasis and iron deposition in multiple organs (pancreas, kidney, myocardium, thyroid).
    - **iii.** Pregnancy associated with oligohydramnios, intrauterine growth restriction (IUGR), premature birth, family history previous maternal sibling death or miscarriage. NALF in the setting of first pregnancy is unlikely to be GALD.
    - **iv.** Liver failure presents at birth or within 3 days: ascites common.
    - **v.** Hepatomegaly and splenomegaly uncommon (10-20%)
    - **vi.** Coagulopathy, hypoglycaemia, persistent patent ductus venosus
    - **vii.** Transaminases either normal or mildly elevated
    - **viii.** Elevated ferritin and transferrin saturation
    - **ix.** High α-fetoprotein: typically, 100,000- 600,000 ng/mL. Values > 80,000ng/mL in >37-week gestation and > 200,000 in 32-week gestation are considered abnormal and suggestive of being affected. Values for 32-37-week gestation are not well established: linear extrapolation is suggested. [29]
2. **Viral Infection**
    - **i.** Presentation day 5 – 14
    - **ii.** May have significant multi-organ disease.
        - Herpes simplex commonest cause [30]
        - May not have history herpes in mother.
    - **iii.** Rash may not be present initially.
    - **iv.** Enterovirus next likely cause
        - Consider especially if mother has recent respiratory or gastrointestinal illness.
        - Infant may have gut symptoms/necrotizing enterocolitis.
    - **v.** Typically, very high transaminases
3. **HLH**
    - **i.** Hepatosplenomegaly common

ii. Fever, pancytopaenia, coagulopathy with hypofibrinogenaemia, hypertriglyceridaemia
iii. Markedly elevated ferritin levels
iv. Bone marrow involvement
v. EBV infection may be a trigger but not always.
vi. Primary and secondary forms now recognised with prognostic implications especially post liver transplant.

4. **Mitochondrial Hepatopathy**
    i. Hypoglycaemia, metabolic / lactic acidosis, coagulopathy
    ii. Hepatomegaly common, splenomegaly uncommon
    iii. Extrahepatic involvement – cardiac, muscle, neurologic

Specific investigations include:

- Full blood count + film, retics, coagulation screen, bone marrow biopsy
- Ferritin, iron studies; oral salivary gland biopsy/MRI abdomen
- Triglycerides, lactate
- Infectious screen: blood PCR for HSV, enterovirus, adenovirus, HHV-6, parvovirus
- Urine metabolic screen (succinylacetone), plasma amino acids
- Check Newborn Screen, galactose-1-phosphate uridyltransferase (galactosaemia)
- Plasma acylcarnitine
- Dietary history for Hereditary Fructose Intolerance; sucrose use in the neonatal care setting

The management of NALF is largely supportive and likely within a Neonatal Intensive Care Unit. Special considerations include:

1. Intravenous aciclovir should be commenced until HSV is excluded.
2. Current treatment of GALD includes 1g/kg intravenous immunoglobulin and double volume exchange transfusion as soon as possible.
3. Liver transplantation for NALF is rarely performed:
    i. Infants with GALD are potential candidates but the timing, graft type and size pose challenges.
    ii. Mitochondrial diseases need to be carefully evaluated as extrahepatic disease (especially neurological) may preclude transplant [31,32]
    iii. HLH and viral infection are generally contraindications to transplant.

Liver Transplantation

The key issue is whether the child with ALF requires liver transplantation. Around 10% of paediatric liver transplants are performed for ALF [33], with historical outcomes inferior to other chronic liver diseases requiring liver transplant [34].

Assessing whether transplant is needed is difficult and involves multiple clinical and biochemical predictors, all of which are imperfect. The most widely used prognostic system is the **King's College Hospital (KCH) Criteria:**

1. **In non-paracetamol induced liver failure, list for transplant if**:
   - **a.** INR > 6.5 and encephalopathy present
   - **b.** Or, 3 of the following 5 criteria:
     - **i.** Age < 10 or > 40 years
     - **ii.** INR > 3.5
     - **iii.** Bilirubin > 300 micromol/L
     - **iv.** Aetiologies such as Wilson disease, idiosyncratic drug reaction, seronegative hepatitis
     - **v.** Jaundice for > 7 days before development of encephalopathy
2. **In paracetamol induced liver failure, list for transplant if:**
   - **a.** pH < 7.3 or arterial lactate > 3.0 after fluid resuscitation
   - **b.** All 3 factors below are present within a 24-hour period:
     - **i.** grade 3 or 4 encephalopathy
     - **ii.** INR > 6.5
     - **iii.** Creatinine > 300 micromol/L
   - **c.** Arterial lactate > 3.5 after early fluid resuscitation

Essentially the decision to transplant is based on several factors including prognostic scores, clinical deterioration and the experience and judgement of the paediatric liver transplant team.

It is mandatory that children identified as having ALF who fulfil King's College Hospital (KCH) Criteria be referred to a liver transplant centre as early as possible.

References

1. Squires J, Alonso E, Ibrahim S et al. North American Society for Paediatric Gastroenterology, Hepatology, and Nutrition Position Paper on the Diagnosis and Management of Pediatric Acute Liver Failure. JPGN 2022; 74:138-158.
2. 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; 148:652–8.
3. Whitington PFAA. Fulminant Hepatitis and Acute Liver Failure. Paediatric Liver Disease. Blackwell: Oxford; 2003:107-126.
4. Squires RH Jr. Acute liver failure in children. Semin Liver Dis 2008; 28:153–66.
5. Cordoba J, Dhawan A, Stolze Larsen F et al. EASL (European Association for the Study of the Liver) Clinical Practical Guidelines on the management of acute (fulminant) liver failure. J Hepatology 2017; 66: 1047-1081.
6. Australian Government Organ and Tissue Authority. Clinical Guidelines for Organ Transplantation from Deceased Donors. Version 1.11 – May 2023.
7. Australian Medical Handbook Children's Dosing Companion- July 2023.
8. Alonso EM, James LP, Zhang S, et al., Pediatric Acute Liver Failure Study Group. Acetaminophen adducts detected in serum of pediatric patients with acute liver failure. J Pediatr Gastroenterol Nutr 2015; 61:102–7.
9. Squires RH, Dhawan A, Alonso E, et al. Intravenous N-acetylcysteine in pediatric patients with nonacetaminophen acute liver failure: a placebo-controlled clinical trial. Hepatology 2013; 57:1542–9.
10. Chapin CA, Mohammad S, Bass LM, et al. Liver biopsy can be safely performed in pediatric acute liver failure to aid in diagnosis and management. J Pediatr Gastroenterol Nutr 2018; 67:441–5.
11. Mack CL, Adams D, Assis DN, et al. Diagnosis and management of autoimmune hepatitis in adults and children: 2019 practice guidance and guidelines from the American Association for the Study of Liver Diseases. Hepatology 2020; 72:671–722.
12. Stravitz RT, Lefkowitch JH, Fontana RJ, et al. Autoimmune acute liver failure: proposed clinical and histological criteria. Hepatology 2011; 53:517–26.
13. Liu PMF, de Carvalho ST, Fradico PF, et al. Hepatorenal syndrome in children: a review. Pediatr Nephrol 2021; 36:2203–15.
14. Deep A, Stewart C, Dhawan A et al. Effect of Continuous Renal Replacement Therapy on Outcome in Paediatric Acute Liver Failure. Crit Care Med 2016; 44(10):1910-9
15. Gonda DD, Meltzer HS, Crawford JR, et al. Complications associated with prolonged hypertonic saline therapy in children with elevated intracranial pressure. Pediatr Crit Care Med 2013; 14:610–20.
16. Koenig MA, Bryan M, Lewin JL 3rd et al. Reversal of transtentorial herniation with hypertonic saline. Neurology 2008; 70:1023–9.
17. Francony G, Fauvage B, Falcon D, et al. Equimolar doses of mannitol and hypertonic saline in the treatment of increased intracranial pressure. Crit Care Med 2008; 36:795–800.
18. Maloney PR, Mallory GW, Atkinson JL, et al. Intracranial pressure monitoring in acute liver failure: institutional case series. Neurocrit Care 2016; 25:86–93.
19. Gluud LL, Vilstrup H, Morgan MY. Nonabsorbable disaccharides for hepatic encephalopathy: a systematic review and meta-analysis. Hepatology 2016; 64:908–22.
20. Wijdicks EF. Hepatic Encephalopathy. N Engl J Med 2016; 375:1660–70.
21. Bernal W, Hall C, Karvellas CJ, et al. Arterial ammonia and clinical risk factors for encephalopathy and intracranial hypertension in acute liver failure. Hepatology 2007; 46:1844–52.
22. Clemmesen JO, Larsen FS, Kondrup J, et al. Cerebral herniation in patients with acute liver failure is correlated with arterial ammonia concentration. Hepatology 1999; 29:648–53.
23. Kawada PS, Bruce A, Massicotte P, et al. Coagulopathy in children with liver disease. J Pediatr Gastroenterol Nutr 2017; 65:603–7.
24. Argo CK, Balogun RA. Blood products, volume control, and renal support in the coagulopathy of liver disease. Clin Liver Dis 2009; 13:73–85.
25. Lisman T, Stravitz RT. Rebalanced hemostasis in patients with acute liver failure. Semin Thromb Hemost 2015; 41:468–73
26. Villa E, Bianchini M, Blasi A et al. EASL Clinical Practice Guidelines on prevention and management of bleeding and thrombosis in children. J Hepatol 2022; 76:1151-1184

27. Northup PG, Garcia-Pagan JC, Garcia-Tsao G et al. Vascular liver disorders, portal vein thrombosis and procedural bleeding in patients with liver disease: Practice Guidance by the American Association for the Study of Liver Disease. Hepatology 2021; 73:366-413
28. Squires JE, McKiernan P, Squires RH. Acute liver failure: an update. Clin Liver Dis 2018; 22:773–805.
29. Taylor SA, Whitington PF. Neonatal acute liver failure. Liver Transpl 2016; 22:677–85.
30. Verma A, Dhawan A, Zuckerman M, et al. Neonatal herpes simplex virus infection presenting as acute liver failure: prevalent role of herpes simplex virus type I. J Pediatr Gastroenterol Nutr 2006;42:282–6.
31. Squires RH, Ng V, Romero R, et al. Evaluation of the pediatric patient for liver transplantation: 2014 practice guideline by the American Association for the Study of Liver Diseases, American Society of Transplantation and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. Hepatology 2014; 60:362–98.
32. Parikh S, Karaa A, Goldstein A, et al. Solid organ transplantation in primary mitochondrial disease: proceed with caution. Mol Genet Metab 2016; 118:178–84.
33. Kim WR, Lake JR, Smith JM, et al. OPTN/SRTR 2017 annual data report: liver. Am J Transplant 2019;19(Suppl 2):184–283.
34. Farmer DG, Venick RS, McDiarmid SV, et al. Fulminant hepatic failure in children: superior and durable outcomes with liver transplantation over 25 years at a single center. Ann Surg 2009; 250:484–93.

Table 1 and 2 Reference:

35. Whitington PF, Alonso EM. Fulminant Hepatitis and Acute Liver Failure Diseases of the Liver and Biliary System in Children. 2007; Oxford, UK: Blackwell Publishing Ltd, 107-126