Acute Liver Failure

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INTRODUCTION

Acute liver failure (ALF) in children

- Is associated with multi organ involvement
- Has a high mortality rate, without transplantation
- Aetiology is age-dependent and varies with geographical location
- Mainstay of management is supportive care

DEFINITION

Severe hepatic dysfunction and hepatocelluar necrosis in the absence of chronic liver disease. Extent of hepatic encephalopathy (HE) is variable.

Paediatric Acute Liver Failure (PALF) study group criteria:

1. No known evidence of chronic liver disease
2. Biochemical evidence of acute liver injury
3. Hepatic-based coagulopathy
   (a) PT $\geq$ 15s or INR $\geq$ 1.5, uncorrectable by vitamin K, in the presence of HE
   (b) PT $\geq$ 20s or INR $\geq$ 2.0, uncorrectable by vitamin K, regardless of the presence or absence of HE

AETIOLOGY

1. Indeterminate or seronegative (non-A-E) hepatitis (41%)
   – usually diagnosis of exclusion once other causes are eliminated
   – associated with worse prognosis
2. Infections (27%)
   – Hepatotrophic viruses eg Hepatitis A–E, CMV, EBV, VZV, HSV (esp neonates – can be fatal), parvovirus, HHV-6, Echovirus and Coxsackie Virus (esp neonates)
3. Inborn errors of metabolism (27%)
4. Drugs/Toxins, including paracetamol overdose (6%)
5. Wilson disease (3%)
6. Autoimmune hepatitis*
7. Gestational alloimmune liver disease (previously termed as neonatal haemochromatosis)*
8. Haemophagocytic lymphohistiocytosis (HLH)*

*uncommon based on our local series

CLINICAL FEATURES

Pertinent history to elicit includes,

- Recent prodromal illness (fever, abdominal pain, rashes, ‘flu’-like illness)
- Onset of jaundice (late feature)
- Alteration in mental status
- Evidence of bleeding tendency, easy bruising

- Drug ingestion and doses (acetaminophen, anti-TB treatment, traditional medication)
- Developmental delay or seizures
- Relevant family history (consanguinity, spontaneous abortions, early infantile death, liver/ autoimmune/ metabolic diseases)

Physical examination may reveal evidence of

- bruises,
- hepatomegaly, ascites
- encephalopathy, signs of raised intracranial pressure from cerebral oedema.
- signs that are diagnostic hallmarks of specific conditions eg. Kayser-Fleischer ring (Wilson disease)
- evidence of heart failure (myocarditis, cardiomyopathy)
- splenomegaly in the presence of persistent fever and characteristic biochemical profile (HLH).

Table 1. Assessment of encephalopathy for young children; birth to age 3 years [3]

Grade	Clinical	Asterixis / Reflexes	Neurological signs
Early (I and II)	Inconsolable crying Sleep reversal / Disturbed sleep rhythm Inattention to task / Mild drowsiness	Unreliable / normal, or hyperreflexic	Untestable
Mid (III)	Somnolence Stupor Combativeness	Unreliable, or hyperreflexic	Most likely untestable
Late (IV)	Comatose, Arouses with painful stimuli (IVa) No response to painful stimuli (IVb)	Absent	Decerebrate or decorticate

INVESTIGATIONS

A systematic diagnostic workup is paramount to help identify conditions which have specific directed therapy, like acetaminophen toxicity, tyrosinemia and autoimmune hepatitis, as well as differentiate patients in whom liver transplantation is contraindicated.

Table 2.

First line investigations	
General FBC, peripheral blood film, GXM Na, K, Cl, Urea, Creatinine Calcium, Phosphate, Magnesium Blood gas Acetaminophen level CRP, ESR Amylase, Lipase	*Liver synthetic function tests* PT/INR Glucose Albumin Ammonia Conjugated bilirubin *Tests for liver injury* ALT, AST, GGT, ALP, LDH
Second line investigations	
Infectious screen Blood culture Urine FEME and culture Viral hepatitis serology	*Metabolic screen* Serum amino acids, Urine organic acids Cu, Caeruloplasmin levels Lactate *Autoimmune markers*

anti-HAV IgM, HBsAg, anti HBc IgM, anti HEV, anti HCV HSV serology/PCR EBV serology HIV serology Paracetamol levels	ANA, SMA (Smooth muscle antibody), LKM (liver-kidney-microsomal) Immunoglobulins *Imaging* Abdominal ultrasound

POOR PROGNOSTIC FACTORS

- Period of onset of illness prior to liver failure > 7 days
- Seronegative (non-A-E) hepatitis
- Shrinking liver size, rising bilirubin with decreasing liver enzymes
- Renal failure / Hepatorenal syndrome
- Higher grade of encephalopathy
  - Grade IV : 90% mortality
  - Grade II–III : 85% mortality
- ARDS

GOALS OF MANAGEMENT

1. Optimal organ systems support
2. Anticipation, prevention and treatment of potential complications
3. Maximise chances of spontaneous hepatocyte recovery and maintain optimal clinical condition for best post-transplant survival

GENERAL SUPPORTIVE MANAGEMENT

Early identification and immediate initiation of appropriate supportive therapy is crucial to maximise potential for recovery. After stabilisation, ill-looking patients should be promptly sent to the critical care setting.

Acute resuscitative measures

- Assess and support airway and breathing accordingly. Oxygen therapy, if required. Need for definitive airway and ventilation more likely in Grade III-IV HE.
- Obtain venous access for volume resuscitation, if required.
  Consider central venous access for monitoring central venous pressure (CVP) and delivery of high dextrose concentration solution or inotropes.
- HD/ICU admission depending on clinical status. Consider timely transfer to liver transplant center after stabilisation

General measures

- Nurse in a quiet environment.
- Monitor vitals (HR,RR,BP), blood parameters (electrolytes, glucose) and neurological status (for presence of encephalopathy) 4 – 6 hourly.

Fluids / Haemodynamics

- Fluid restrict to 70% maintenance.
  Avoid fluid overload (can worsen cerebral oedema).
- Use colloid for volume expansion.
- If hypotensive with normal circulating volume (CVP 4–8 cmH_20), consider vasoactive drugs (noradrenaline, alpha agonist) in view of low systemic vascular resistance.

Metabolic & Nutrition

- Maintain normoglycaemia (Blood glucose > 4 mmol/L). Monitor 1 – 2 hourly initially. Consider higher dextrose concentrations if necessary
- Nasogastric tube insertion for early enteral feeding. Consider TPN if ileus present. Provide protein intake of about 1-2 g/kg/day (titrate protein intake based on patient's clinical status)

Renal

- Urinary catheterisation for accurate intake/output monitoring
- Maintain urine output of 1 ml/kg/h. If oliguric, consider
  - Low cardiac output
  - Hepatorenal syndrome
  - Dehydration (low CVP)
- CVP low – colloid challenge 10 ml/kg
  CVP high – IV frusemide 1-2 mg/kg/dose
- Hemofiltration may be considered for renal failure(CVVHD) or hyperammonaemia > 200 mcg/dL

Gastrointestinal

1. Gastric acid suppression
   - Omeprazole (proton-pump inhibitor) IV 1 mg/kg/dose BD
   - Esomprazole (proton-pump inhibitor) IV 0.5mg/kg/dose OD

   Note: dose adjustment may be needed in severe liver impairment

2. Suppression of ammonia production (by bowel flora)
   - Oral neomycin.50-100 mg/kg/day divided every 6 hours for a maximum of 7 days with or without lactulose. Maximum daily dose: 12 g/day
   - Lactulose 2 – 4 ml/kg/dose (max=30ml/dose) 6H (Aim for 3 – 5 bowel output/day).
     Monitor for bowel distension and intravascular depletion. Excessive use increases risk of pneumatosis intestinalis
3. N-acetylcysteine (NAC) infusion
   - For paracetmaol-induced ALF, to refer to toxicology guidelines
   - Role of NAC in non-paracetamol-induced paediatric ALF is controversial, please discuss with Gastroenterologist-on-call; Suggested dose of IV NAC infusion for non-paracetamol PALF: 100 mg/kg/day over 24h, review after 24-48h

MANAGEMENT OF SPECIFIC COMPLICATIONS

Hepatic encephalopathy (HE) & Cerebral Oedema

Hepatic encephalopathy is a spectrum of altered cerebral function secondary to hepatic failure. The most serious complication of ALF is cerebral oedema resulting in raised intracranial pressure. The risk of cerebral oedema increases with increasing severity of HE.

- HE Grade I–II : Minimal risk
- HE Grade III : 25 – 35 % risk
- HE Grade IV : 65 – 75 % risk

- Elective intubation in patients with
  - HE Grade II but agitated

  - HE Grade III – IV

- Institute neuroprotective measures in the presence of raised ICP to maintain cerebral perfusion pressure (CPP) and oxygenation
  - Head elevated to 30 degrees, in neutral position
  - Maintain normothermia.
  - Keep well sedated (low dose fentanyl preferred because of its short half life and its elimination half-life is less affected in liver impairment than morphine Consider muscle relaxant. Atracurium is preferred in liver failure as it undergoes ester hydrolysis and Hofmann elimination and is independent of both liver and renal function. No dosage adjustment is required in liver failure
  - Maintain normocarbia pCO_2 35 mmHg and pO2 80 – 100 mmHg
  - Keep Na 145 – 150 mmol/L with hyperosmolar therapy
    - Hypertonic saline IV 3% NaCl 4 ml/kg over 30 mins.
    - Mannitol 0.5–1 g/kg over 30 mins. Repeat 6-8Hly, only if good urine output. Keep serum osmolarity < 320 mOsmol/kg
  - Consider ICP monitoring (Correct coagulopathy first).
    - Keep CPP > 50 mmHg and ICP < 20 mmHg.
    - Consider volume expansion and/or vasopressors.
    - Consider thiopentone for recalcitrant raised ICP
      Aim for burst suppression if EEG monitoring is utilised.

- Exclude other non-hepatic causes of altered mental status
  - Hypotension
  - Hypoglycaemia
  - Hyponatraemia
  - Seizures
  - Cerebral oedema
  - Intracranial haemorrhage (Urgent CT head)

- Contributory factors
  - Hyperammonemia. Consider CVVHD for serum ammonia > 200 umol/L.
  - Fluid overload
  - Metabolic derangements (hypoglycaemia, hyponatraemia)
  - Hypotension and ischaemia
  - Alteration in cerebral vascular permeability
  - Failure of intracellular homeostasis (disrupted neuronal Na-K pump)

Seizures
May be subtle in children with hepatic encephalopathy.

- Causes include
  - electrolyte imbalances (hypoNa, hypoMg)
  - raised ICP
  - intracranial haemorrhage
  - encephalitis
- Consider intracranial imaging.
- Correct electrolyte imbalance if any
- Mannitol or hypertonic saline if there is suspected cerebral oedema
- For status epilepticus, 1st-line treatment with benzodiazepines (diazepam, lorazepam).
- For recurrent seizures, treat with phenobarbitone (loading and maintenance doses)

Coagulopathy and Haemorrhage

- ALF is characterised by reduced synthesis of coagulation factors (II,V,VII,IX,X), accelerated fibrinolysis and impaired hepatic clearance of activated clotting factors and fibrin degradation products.
- Thrombocytopenia with depressed platelet function is tolerated, as long as platelet level > 20 000 /mm^3 and there is no active bleeding.
- Hypofibrinogenemia results from reduced both decreased hepatic synthesis and increased catabolism.

- Parenteral Vitamin K is recommended empirically for 3 days
  - IV 250 – 300 mcg/kg/day OM (max 10 mg)

- In the absence of haemorrhage, no prophylaxis FFP is recommended, unless discussed with hepatology team, as it
  - does not reduce risk of significant bleeding
  - obscures trending of PT as prognostic marker
  - increases risk of volume overload

- In the presence of bleeding or in anticipation of an invasive surgical procedure,
  - Transfuse FFP to achieve INR < 1.5
  - Keep platelets > 50 000 /mm^3
  - Consider cryoprecipitate if fibrinogen < 100 mg/dL

- Recombinant factor VIIa (40 mcg/kg) can be given when FFP fails to correct INR
  - Must be administered immediately before a procedure
  - Procedure must be performed within 30-60 mins (effect persists for >2h)
  - FFP must be given before rFVIIa if fibrinogen <100 mg/dL
- Plasma exchange can be considered where rFVIIa is contraindicated.

Gastrointestinal bleeding

Upper GI bleeding can be improved with gastric acid suppression such as with a proton pump inhibitor (eg. Omeprazole).

Ascites

Clinically evident ascites (not common in ALF) occurs in less than half of ALF patients. Therapy is not usually indicated, apart from correction of oncotic pressure with IV 20% Albumin (with frusemide) and general fluid management.

Renal insufficiency

- Ensure urine output 1 ml/kg/h. If oliguric, consider
  - Low cardiac output
  - Intravascular volume depletion with low CVP (Give colloid challenge)
  - Hepatorenal syndrome
- Can also be precipitated by overzealous use of diuretics and/or nephrotoxic drugs.

- Hepatorenal syndrome is the most common cause of renal insufficiency in acute-on-chronic liver failure. It is related to renal hypoperfusion in response to splanchnic vasodilatation due to portal hypertension. Management is with vasoconstrictor drugs (for example noradrenaline, octreotide or terlipressin) and albumin replacement.

- Institute early haemofiltration if
    - Oliguria with fluid overload, in the presence of cerebral oedema
    - Symptomatic uraemia, intractable hyperkalemia or metabolic acidosis

Metabolic and electrolyte abnormalities

- High risk of hypoglycaemia (approx 40%) due to failure of hepatic gluconeogenesis. Keep blood glucose > 4 mmol/L. Monitor 1 – 2 hourly initially.
  Glucose infusion rates up to 12 – 15 mg/kg/min may be required.
  Consider higher dextrose concentration with fluid restriction.
- Metabolic acidosis can be caused by hypoxia, hypovolemia, sepsis and renal failure. Consider correctable parameters.
  If refractory, correct with IV sodium bicarbonate if BE > -10 and pH < 7.25
- Avoid metabolic alkalosis and hypokalemia as this enhances conversion of NH_4 to ammonia which can cross the blood brain barrier.
- Hyponatraemia, hypokalemia, hypophosphataemia, hypocalcaemia and hypomagnesaemia are often observed.
- In the absence of HIE, fluid resuscitation and sodium management should be targeted at maintaining sodium levels at 140-145mmol/L. Conversely, hypernatraemia may occur due to excessive use of lactulose.
- Alterations in potassium, phosphate, calcium and magnesium should be monitored and corrected as clinically appropriate.
- Hypophosphataemia is postulated to be related to the amount of regenerative liver mass, as phosphate is a substrate for various enzymatic reactions that phosphorylate proteins needed during rapid liver regeneration.

Infection prophylaxis and surveillance

Susceptibility to infection is a result of impaired host immune defences. Additional risk factors include poor respiratory effort (drowsiness) and presence of ETT, urinary catheters, central line. Peritonitis from ascites must also be considered.

- Obtain surveillance cultures (sputum, urine, blood, rectal swab) at presentation and with any evidence of clinical deterioration.
- Empirical antibiotics is recommended where likelihood of infection is high
    - Surveillance cultures reveal significant isolates
    - Progression of, or advanced stage (grade III/IV) of hepatic encephalopathy
    - Refractory hypotension
    - Presence of systemic inflammatory response syndrome (SIRS)
      Temp > 38 ^oC or < 36 ^oC, WCC > 12000 or < 4000 /mm^3, Pulse > 90 beats/min
- Consider IV fluconazole prophylaxis for all patients
- Start empirical parenteral acyclovir therapy in neonates and infants < 6 months.

Nutrition

ALF is a catabolic state characterised by a negative nitrogen balance. Patients exhibit increased resting energy expenditure.

- Maintain blood glucose > 4 mmol/L.
- Ensure sufficient carbohydrates for energy metabolism.
- Provide protein intake of 1-2 g/kg/day (titrate protein intake based on patient's clinical status)

Acute pancreatitis

Is uncommon in ALF, although mildly raised amylase levels may be present. Predisposing factors include shock, viral illness or haemorrhage into /around the pancreas.

- Check amylase / lipase in the presence of abdominal pain and/or hypocalcaemia.
- Treatment is usually supportive.

Adrenal suppression
Occurs in 60% of adults with ALF.

- Consider diagnosis in fluid refractory, catecholamine resistant hypotension.
- May need further evaluation with synacthen test.
- Treat with corticosteroids.

PROPOSED INDICATIONS FOR LIVER TRANSPLANTATION ASSESSMENT

Paracetamol-induced ALF (according to King's College Criteria)	Non-Paracetamol-induced ALF
ABG pH < 7.3 ***OR*** Presence of any of 3 on the same day 1. PT >100s 2. Creat 300 micromol/L 3. Grade III/IV encephalopathy	PT > 100s, INR > 6.5 ***OR*** Presence of 3 of the following 1. Age < 10y , > 40y 2. Aetiology of non-A non-B hepatitis 3. Bilirubin > 300 micromol/L 4. INR >3.5

CONTRAINDICATION TO LIVER TRANSPLANTATION

- Diseases not cured by transplantation (metastatic cancer, HLH)
- Reye syndrome
- Mitochondrial respiratory chain disorders with neurological involvement
- Uncontrolled multiorgan failure

USUAL CAUSES OF DEATH

- Cerebral oedema or haemorrhage
- Sepsis
- Haemorrhage

CHAPTER ACUTE LIVER FAILURE

Evidence of acute liver injury,
without established antecedent liver disease

INR high but < 2,
and clinically well

Give IV Vit K.

Follow up in 24 h
for repeat INR

INR > 2 without HE or
INR > 1.5 with HE

Acute resuscitation and stabilisation

- Airway, Breathing, Circulation
- Advanced Life Support, as required
- Establish venous access and consider CVL for high dextrose, CVP & inotropes

- Blood and urine investigations (See Table 3)
- Urinary catherisation and NGT insertion.
- Place in quiet, calm environment. Avoid sedation.
- Regular monitoring : Neurovitals hourly, Strict I/O.
- Urine output 1 ml/kg/h
- Hydration as clinically indicated.
- Keep CVP 4-8 cmH_20. Colloid for volume expansion.
- Fluid restriction 2/3 maintainance.
- Max Na 1 mmol/kg/day. Max protein 1 g/kg/day
- Consider vasopresssor.

For non-Acetaminophen ALF,
NAC infusion (discuss with Gastro)
IV :100 mg/kg/day for 24h

For paracetamol-related ALF:
Refer to toxicology guidelines

Consider Abd USS

Check INR +ABG q 6H
UECr, Ca, Mg, PO_4 q 6 – 12 H
FBC, LFTs, NH_3 q24H

Start IV Omeprazole
IV Unasyn
IV Fluconazole prophylaxis
IV Acyclovir for infants < 6 months
IV NAC (if indicated)
IV Vitamin K

Monitor for complications.
Hypoglycaemia : Hourly BG. Keep BG > 4 mmol/L.
Low Na, K, PO_4 & Mg : Correct as required.
Metabolic acidosis : Consider correctable parameters
Correct with HCO_3 if refractory
Coagulopathy:
Avoid FFP unless active bleeding or for op
Platelet transfusion is necessary only for active bleeding
Give IV Vit K
Hyperammonemia ± encephalopathy :
Lactulose 2 – 4 ml/kg/dose q6H (3-5x BO/day)
Neomycin 50-100mg/kg/day divided every 6 hours
(max 12g/day

Raised ICP : Hypertonic saline as first line, maintain Na 145-150 mmol/L
Neuroprotective measures
Renal impairment : If oliguric, consider:
Fluid bolus if CVP low
Frusemide if CVP high

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