Management of Acute Liver Failure

Purpose

This document is intended to guide the physician in the management and investigation of children presenting to and within Sheffield Children’s Hospital with acute liver failure.

Intended Audience

It is envisaged that this will be used by all medical staff and that this would largely be in the ward and emergency room setting.
1. Introduction

Acute liver failure (as defined by the Pediatric Acute Liver Failure Study Group) is as follows

1. The acute onset of liver disease with no known evidence of chronic liver disease.
2. Biochemical and/or clinical evidence of severe liver dysfunction.
3. Hepatic based coagulopathy with a prothrombin time greater than or equal to 20 seconds or an International normalised ratio (INR) of greater than or equal to 2.0 that is not corrected by parenteral vitamin K
4. And/or hepatic encephalopathy.

The aetiology of acute liver failure is varied and is age dependent. Viral hepatitis (including non A-E hepatitis) is thought to account for the majority of cases of acute liver failure across the paediatric age group.

In the neonatal period, infections such as herpes along with metabolic and ischaemic damage are the most common causes. In older children; infection, drugs, toxins, underlying metabolic or autoimmune conditions, ischaemia and rare causes such as underlying malignancy are responsible.

These guidelines have been produced to assist with the initial investigation and management of these children. They are intended to highlight the serious nature of acute liver failure and stress that although these children can often seem clinically very well there is a significant risk of mortality/ requirement for liver transplant in this group.

Senior assistance should be sought at an early stage in children who fulfil the diagnostic criteria for acute liver failure.

| Increased AST and ALT associated with prolonged clotting +/- jaundice +/- encephalopathy |

2. Intended Audience

It is envisaged that this will be used by all medical staff and that this would largely be in the ward and emergency room setting.
3. Guideline Content

- Investigation and treatment of liver disease with acute onset
- Differential diagnosis of acute liver failure
- Investigations
- Management of acute liver failure
- Paracetamol overdose management
- Criteria for liver transplant
- Medication used in acute liver failure

**Investigation and treatment of liver disease with acute onset**

- Acute Liver Failure (ALF): defined as liver dysfunction associated with coagulopathy occurring less than 8 weeks since a diagnosis of liver disease.

- **NB MAY NOT BE JAUNDICED AT OUTSET**

- **MAY APPEAR CLINICALLY VERY WELL DESPITE BIOCHEMISTRY**

- Age of onset >3 months

Investigate and treat as neonatal conjugated jaundice (including the second line blood investigations) **before 3 months of age** (see separate protocol on intranet “neonatal conjugated jaundice, investigation of”)

- INR>2.0 due to liver dysfunction of less than 8 weeks duration without encephalopathy or >1.5 with encephalopathy requires transfer to Transplant Centre.

- Contact initially **Dr Natalia Nedelkopoulou** Monday to Friday 9am-5pm (bleep through switchboard)

- If ALF and out of hours contact Leeds General Infirmary Paediatric Hepatologist on call who will give advice +/- arrange for transfer
Differential Diagnosis of Acute Liver Failure

**Infecive**
- Hepatitis A-E (including anti HepB core antibody)
- CMV
- EBV
- Parvo B19
- Varicella
- Measles
- Herpes simplex
- HIV

*Also consider* – Leptospirosis, Q fever, Mycoplasma, Legionella, brucellosis, malaria, Entamoeba histolytica

**Drug/toxin**
- Paracetamol
- Anticonvulsants: Valproate, Carbamazepine, Phenytoin
- Antituberculous: Rifampicin, Isoniazid
- Cytotoxics
- Others: antibiotics, NSAIDs, ecstasy, etc
- Irradiation
- Carbon tetrachloride
- Halothane
- *Amanita phalloides* (Toxic mushroom)

*Remember to ask* about any medications/ substances that may be available to the child

**Metabolic**
- Galactosaemia, tyrosinaemia, neonatal haemochromatosis,
- Mitochondrial disorders
- Reye-like illnesses – organic acidurias, fatty acid oxidation defects
- Hereditary fructose intolerance
- Wilson's disease (over 3 years)
- Congenital disorders of glycosylation

**Autoimmune**

**Ischaemic**
- Congenital heart disease, Cardiac surgery
- Severe asphyxia
- Budd Chiari

**Infiltrative**
- Leukaemia or other malignancy
- Haemophagocytic lymphohistiocytosis
- X-linked lymphoproliferative syndrome
Investigations

Haematology
Full blood count including reticulocytes  EDTA 2ml

Clotting  citrate 1ml

Group and save, and Coombs test  EDTA 2.5ml

Biochemistry
Urea, electrolytes, creatinine and CRP  EDTA 4ml
Calcium, phosphate, magnesium  EDTA 4ml
Liver function tests, \( \gamma \)GT and conjugated bilirubin  EDTA 4ml
Amylase  EDTA 4ml
Cholesterol, triglycerides, urate and CPK  EDTA 4ml
Blood glucose  fluoride 0.5ml
Lactate  fluoride 0.5ml
Ammonia  Li hep on ice 0.5ml
Arterial blood gas  heparinised tube on ice
Blood for toxicology (including paracetamol level)  lith hep 0.5ml
Transferrin iso-electric focussing  seragel 1ml

Plain urine bottle (x3)
Urine metabolic screen (organic and amino acids) (less than 5 years), inc.orotic acid if \( \text{NH}_3 >100 \mu\text{mol/L} \)
Urine toxicology screen
Urinary electrolytes

Immunology 5-10ml seragel
Alpha 1 antitrypsin level and phenotype
Immunoglobulins
Autoantibodies ANA/SMA/LKM
Coeliac (EMA and TTGA)
C3,C4
Caeruloplasmin (over 3 yrs)
Alpha fetoprotein

Microbiology
Blood and urine culture  culture bottle + plain urine
Serology (Hep A,B,C, E)  seragel 3ml
PCR for infections (see list under aetiology)  EDTA 2-3ml
Stool virology

Radiology
Chest X-ray
Doppler ultrasound scan abdomen
Consider CT scan head if suspect other cause of coma eg intracranial bleed (unilateral neurology, sudden deterioration in consciousness)
Management of Acute Liver Failure

General Advice

- **DO NOT SEDATE UNLESS VENTILATED**
- Do not give FFP - except at consultant’s request e.g.
  a) before transferring a patient between hospitals
  b) before an interventional procedure
  c) if actively bleeding
- Patients with more than grade 1 encephalopathy should be transferred to PICU

**Grading of encephalopathy**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gd 1</td>
<td>irritable, apathetic, behavioural and sleep disturbance</td>
</tr>
<tr>
<td>Gd 2</td>
<td>drowsy, confused, but responds to commands</td>
</tr>
<tr>
<td>Gd 3</td>
<td>severely confused or agitated, but response to pain</td>
</tr>
<tr>
<td>Gd 4</td>
<td>unrousable, no response to pain</td>
</tr>
</tbody>
</table>

(NB ensure have clotted blood sample for IgG viral serology before giving blood products)

Monitor

**CONTINUOUSLY**
- Pulse oximetry/cardiac monitor

**HOURLY**
- Resp rate, BP, temp (core & toe) (arterial line if ventilated)
- Fluid balance – (consider CVP monitor and urinary catheter if ventilated)
- CNS obs and stage of encephalopathy (consider ICP monitor if ventilated)

**2-4 HRLY**
- BM’s
- Arterial blood gases (if ventilated)

**6-8 HRLY**
- Clotting screen

**DAILY**
- FBC
- U&E, creatinine, Ca, PO4, Mg,
- LFT’s, GGT
- CRP
- Amylase
- Lactate
- Urinary electrolytes
Management of Acute Liver Failure

Liver size by palpation (shrinking liver with no general improvement is a bad prognostic sign)

Weight

Management

(Also see drug formulary on back page)

General
- Daily IV Vit K (phytomenadione) 300 micrograms/kg/day (max 10 mg) for at least 3 days
- Ranitidine 1mg/kg/dose TDS IV or Sucralfate orally/NG if not enterally fed
- Consider infection (see later)
- Lactulose 1-2ml/kg/dose TDS to achieve BO 3-4x per day
- If signs of encephalopathy nurse with head elevated at 10-20 degrees
- If encephalopathy progresses to grade 3 or above requires ventilation and sedation

NB Acetylcysteine is no longer recommended for non-paracetamol related acute liver failure in paediatrics and should not be routinely given unless specifically advised by a hepatologist. This is particularly true in those patients under 2 years of age. (see reference)

Fluids and electrolytes
Overall aim is to maintain circulating volume and avoid fluid overload
1. Restrict crystalloid fluids to 2/3 maintenance, unless dehydrated/hypovolaemic
2. Use 10-20% glucose (or more) (start with 10% and increase as required) to keep blood glucose > 4.5 mmol/l. If >10% concentration of glucose is needed then central venous access will be necessary.
3. Maintain urinary output at > 0.5 ml/kg/hr
4. Restrict Sodium intake to 0.5-1mmol/kg/day – even if serum sodium levels low (low serum sodium usually indicates fluid retention)
5. Potassium requirements may be large – treat as guided by serum levels and renal function
6. Correct Ca, PO4, and Mg if levels are low (dosing and administration route as per BNFc)

Nutrition
If possible enteral nutrition should be maintained with a high carbohydrate, low sodium diet. Avoid protein intake of more than 2 gm/kg/day. Nasogastric feeding can be used in stable ventilated patients. If enteral feeding impossible commence TPN.

Infection
All patients should be monitored closely for infection. Broad-spectrum antibiotics and prophylactic fluconazole should be commenced if infection is suspected clinically. If the patient has renal dysfunction use AmBisome instead of fluconazole.

If Herpes Simplex infection is suspected IV Aciclovir should be commenced.

REMEMBER

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Acute liver failure can progress rapidly. If ALF present, a liver transplant centre should be involved early in order to arrange early transfer if required.
Paracetamol Overdose Treatment Protocol

If a Paracetamol overdose is suspected or known, the child should be assessed and managed as per the guideline in the SCH Emergency Department guidelines and BNFc.

Criteria for Liver Transplantation in ALF

Paracetamol overdose

pH < 7.3 (after initial fluid resuscitation)

or all of the following:
- PT > 100 secs
- creatinine > 300μmol/l
- grade 3-4 encephalopathy

(NB these are adult criteria and in young children lower levels of creatinine should be considered)

Non-Paracetamol ALF

PT > 100 secs

or

Grade 3-4 encephalopathy

or 3 of the following
- unfavourable aetiology – non A-E hepatitis, halothane, drugs
- time from jaundice to encephalopathy > 7 days
- age < 10 yrs
- PT > 50 secs
- Bilirubin > 300μmol/l
Medications Used in Acute Liver Failure

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Frequency</th>
<th>Route</th>
<th>Max. dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin K (phytomenadione)</td>
<td>300 microgram/kg/dose</td>
<td>OD</td>
<td>IV</td>
<td>10mg</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>1 mg/kg</td>
<td>TDS</td>
<td>IV</td>
<td>50mg</td>
</tr>
<tr>
<td>Lactulose</td>
<td>1-2 mls/kg</td>
<td>TDS</td>
<td>PO/NG</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>25 mg/kg</td>
<td>TDS</td>
<td>IV</td>
<td>1 G</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>30 mg/kg</td>
<td>TDS</td>
<td>IV</td>
<td>1.5 G</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>7.5 mg/kg</td>
<td>TDS</td>
<td>IV</td>
<td>500mg</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>3 mg/kg</td>
<td>OD</td>
<td>IV/PO</td>
<td>400mg</td>
</tr>
<tr>
<td>AmBisome</td>
<td>1 mg/kg</td>
<td>OD</td>
<td>IV</td>
<td></td>
</tr>
<tr>
<td>Aciclovir</td>
<td>&lt; 3 mths</td>
<td>20mg/kg</td>
<td>TDS</td>
<td>IV</td>
</tr>
<tr>
<td>Aciclovir</td>
<td>3 mths-11 yrs</td>
<td>250 mg/m²</td>
<td>TDS</td>
<td>IV</td>
</tr>
<tr>
<td>Aciclovir</td>
<td>12 yrs and over</td>
<td>5 mg/kg</td>
<td>TDS</td>
<td>IV</td>
</tr>
<tr>
<td>Sucralfate</td>
<td>&lt;2 yrs</td>
<td>250 mg</td>
<td>QDS</td>
<td>PO</td>
</tr>
<tr>
<td></td>
<td>2-11 yrs</td>
<td>500 mg</td>
<td>QDS</td>
<td>PO</td>
</tr>
<tr>
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<td>12 yrs and over</td>
<td>1 g</td>
<td>QDS</td>
<td>PO</td>
</tr>
</tbody>
</table>

Drugs for encephalopathy, renal dysfunction, cardiovascular complications – see text

4. References

Guidelines drawn up by Dr Sally Connolly based on those produced by King’s College Hospital London Paediatric Liver Unit and Leeds General Infirmary Paediatric Liver Unit.