ACUTE LIVER FAILURE

• Rare but potentially fatal disease

• Mortality without supportive management +/- liver is > 70%
ACUTE LIVER FAILURE (ALF)

• DEFINITION:
The development of hepatic necrosis leading to failure of liver function (coagulopathy and encephalopathy) within 8 weeks of the onset of liver disease and the absence of any pre-existing liver disease in any form. In children, particularly in infancy, encephalopathy may occur late.
PROPOSED DEFINITIONS: (Kings’ College) (Onset of jaundice to encephalopathy)

- Hyperacute liver failure $\leq 7$ days - prognosis ‘better’
- Acute liver failure 8-28 days
- Subacute liver failure 8-12 weeks

- Many definitions but common to them all is the absence of pre-existing liver disease.
- Need to standardise nomenclature.
• Acute hepatic necrosis leading to hepatic encephalopathy + coagulopathy develops 2° to a virus, toxin or immune mediated attack. It is associated with failure of hepatic regeneration. Processes leading to hepatic damage are unknown but are multifactorial.
AETIOLOGY

• Varies depending on the age of child
• Metabolic liver disease and infections most common in neonates and infants
• Viral disease, drug-induced hepatitis, autoimmune disease, wilsons disease are more common in older children and adolescents
• Important for prognosis as well as specific management options
CAUSES OF ALF

- Infective
  - Viral hepatitis – A, B, D
    - Non-A, Non-B
    - E
  
  CMV
  EBV
  Echo
  Varicella
  Measles
  Malaria
  Lassa, Ebola, Marburg
DRUGS/TOXINS

Paracetamol
Carbon tetrachloride
Halothane
Amanita phalloides
Isoniazid
Valproate
Phenytoin
Carbamazapine

Toxins (‘Impela’)
Galactosaemia
Tyrosinaemia
Fructosaemia
Alpha-1-antitrypsin deficiency
Wilsons disease
# Aetiology and Mortality of AFF (n=89) at RXH

<table>
<thead>
<tr>
<th>Cause of ALF</th>
<th>No.</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>%</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>22</td>
<td>16  73%</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>25</td>
<td>18  74%</td>
</tr>
<tr>
<td>Drug Toxicity</td>
<td>6</td>
<td>5   80%</td>
</tr>
<tr>
<td>Metabolic</td>
<td>1</td>
<td>1   100%</td>
</tr>
<tr>
<td>Unknown</td>
<td>35</td>
<td>26  75%</td>
</tr>
<tr>
<td>Overall Mortality Rate</td>
<td></td>
<td>75%</td>
</tr>
</tbody>
</table>
EVALUATION ON ADMISSION

Full history including information on:
- IV injections, needles and needlestick injury
- Infusions of blood products
- Contact with jaundice
- Family history of liver disease
- Sexual contacts
- Parents drug habits and medications
- Patients medications or other suspect poisons (e.g. mushrooms)
Full Clinical Examination:
- Pay particular attention to and record Degree of encephalopathy
- State of hydration
- Evidence of spontaneous bleeding
- Evidence of chronic liver disease
- Mark upper and lower margins of liver onto abdomen with waterproof marker
POOR PROGNOSTIC FACTORS:

1. Age < 10 years
2. Infants < 1yr with severe coagulopathy secondary to metabolic liver disease or familial erythrophagocytosis
3. Seronegative hepatitis
4. Severe coagulopathy (PT>55secs)
5. Prolonged duration of illness before onset of hepatic encephalopathy
6. Degree of encephalopathy:
   - Grade I-II : 44% mortality
   - Grade III-IV : 78% mortality
7. Shrinking liver size
8. Associated renal failure
MANAGEMENT OF MEDICAL PROBLEMS/COMPLICATIONS:

1. Hypoglycaemia
2. Coagulopathy and Haemorrhage
3. Encephalopathy /Raised Intracranial Pressure
4. Convulsions
5. Renal dysfunction
6. Cardiovascular problems
7. Metabolic Acidosis
1. HYPOGLYCAEMIA:

• General:
  - Hypoglycaemia results from:
    - substrate depletion
    - Defective glycolysis
    - Hyperinsulinaemia
  - Severe hypoglycaemia (blood glucose < 3.5mmol/L) is common
  - Many contribute to CNS impairment and other organ dysfunction
  - Refractory hypoglycaemia carries a poor prognostic implication
HYPOGLYCAEMIA:

• Management:
  - Minimal 4-hourly BG monitoring
  - Intravenous glucose administration (10-50% dextrose)
  - Maintain glucose > 4mmol/L
2. COAGULOPATHY AND HAEMORRHAGE:

- General:
  - Profound coagulopathy can develop secondary to:
    - Failure of hepatic synthesis of clotting and fibrinolytic factors
    - Reduction in platelet numbers (depending on diagnosis)
    - Intravascular coagulation (if sepsis present)
  - Prothrombin time (PT) is the most sensitive measure of hepatic synthesis of clotting factors
COAGULOPATHY AND HAEMORRHAGE

• Management:
  - Daily dose of **intravenous** Vitamin K (2.5 -10mg/day)
  - Do not routinely correct coagulopathy with blood products (eg FFP or cryoprecipitate) as PT is a sensitive guide to prognosis and need for liver transplantation.
  - Once decision to list for transplant has been made start correcting PT>40 secs (increased risk of bleeding).
  - Use FFP (10-15ml/kg every 6 hours), cryoprecipitate and platelets (if indicated)

  - Consider use of Recombinant factor VIIa (rFVIIa)
  - Haemofiltration may be required to control fluid balance
3. ENCEPHALOPATHY/: RAISED INTRACRANIAL PRESSURE

- **General:**
  - Deranged cerebral function associated with hepatic failure
  - Possible causes include:
    1. accumulation of toxic substances and toxic damage of the brain
    2. rising intracranial pressure (cerebral oedema) secondary to
       - Fluid overload from therapeutic efforts to correct coagulopathy and hypotension
       - Failure to maintain blood glucose concentrations
       - Failure to maintain systemic blood pressure (cerebral ischaemia)
1. Raised toxic products not metabolised by the liver.
2. Changes in blood brain barrier which increases access of toxic substances to the brain allowing substances that normally can’t enter the brain to do so.
3. Raised ammonia
   - increases intestinal production
   - increased hepatic production from amino acids
   - in CNS due to increased cerebral catabolism of some amino acids
4. Neurotoxic amino acids
   i) glutamine and alpha ketoglutarate
   ii) tryptophan
   iii) methionine/merceptans
5. FFA
6. Abnormal neurotransmitter balance
   i) false neurotransmitters
   ii) excitatory amino acids
ENCEPHALOPATHY/: RAISED INTRACRANIAL PRESSURE

- Brain death associated with cerebral oedema is the commonest cause of death in fulminant liver failure
- Prognosis is poor once it is evident (even after technically successful liver transplantation)
- May be exacerbated by sepsis, GI bleeding, electrolyte disturbances, etc
- Children may fluctuate rapidly from one stage to the other
# Clinical Stages of Hepatic Encephalopathy

<table>
<thead>
<tr>
<th>Stage</th>
<th>Asterixis</th>
<th>EEG Changes</th>
<th>Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (prodrome)</td>
<td>Slight</td>
<td>Minimal</td>
<td>Mild intellectual impairment, irritable, lethargy/midly obtunded, disturbed sleep awake cycle</td>
</tr>
<tr>
<td>II (impending coma)</td>
<td>Easily elicited</td>
<td>Generalized slowing of rhythm</td>
<td>Drowsiness, confusion, inappropriate/odd behaviour, disorientation/not recognizing parents, mood swings, photophobia</td>
</tr>
<tr>
<td>III (stupor)</td>
<td>Present if patient co-operative</td>
<td>Grossly abnormal Slowing</td>
<td>Drowsy, unresponsive to verbal commands, markedly confused, delirious, hyperreflexia, positive Babinski sign</td>
</tr>
<tr>
<td>IV (coma)</td>
<td>Usually absent</td>
<td>Delta waves, decreased amplitudes</td>
<td>Unconscious, initial response to pain present, later decerebrate or decorticate response to pain present or absent, areflexia</td>
</tr>
</tbody>
</table>
Management stage I and II:
- Every effort should be made to prevent cerebral oedema!!
- Nurse child with head elevated at 20° and no neck flexion (to decrease ICP and minimize cerebral irritability)
- Maintain oxygenation
- Restriction of dietary protein
- Carefully review fluid balance:
  - fluid restrict to 50-75% maintenance
  - Maintain urine output~0.5-2mls/kg/hour
- Minimize formation of nitrogenous substances by the intestine:
  - Lactulose (2-4mls/kg/dose TDS)
- Avoid sedation (this may mask encephalopathy), unless patient is violent/aggressive and/or needing prevention from self-injury:
  - Use short-acting barbiturates or opiates
  - Avoid benzodiazepines
Management stage III and IV:
- As management of stage I and II
- Give Mannitol:
  0.5-2gram/kg over 1 hour (7mls/kg of 20% mannitol)
Repeat every 6-8 hours for a maximum of 48 hours
Measure osmolarity every 12 hours (max 310 mosmol/kg)
At RXH we don’t admit children with ALF to ICU. In other units with larger liver transplantation programmes management would include:

- **CT-Scan:**
  1. Very likely hazardous than justified in cerebral oedema
  2. Consider if focal cerebral lesion suspected

- Elective ventilation (hyperventilate, aim for pCO$_2$ < 3.5)
- Intracranial pressure monitoring (under debate)
- Maintain cerebral perfusion pressure >50mmHg
- Consider Thiopentone
Management of Encephalopathy

1. Dietary protein withdrawal
2. Lactulose (dose to give 2 loose acidic stools per day), golytely 10ml/kg, neomycin
3. Avoid sedation (if essential – midazolam 0.05 – 0.15mg/kg)
4. Prevent GIT bleeding with H\textsubscript{2} antagonists. Sucralfate may be necessary to keep gastric ph +/-5.0.
Cerebral Oedema

Complicates stage 3 to 4 encephalopathy in the setting of ALF in 50-85% of patients.

It is the leading course of death in these patients.

Clinical signs appear when ICP is greater than 30mmHg;
4. CONVULSIONS:

- **General:**
  - Clinical presentation may be atypical or occult in children
  - May be caused by:
    - Underlying cause of ALF (toxic injury, viral, metabolic, etc)
    - Electrolyte imbalance
    - Cerebral oedema
    - Hypoglycaemia
• **Management:**
  - Correct electrolyte imbalance (if present)
  - Carefully review fluid balance
  - Consider Mannitol infusion if caused by possible cerebral oedema and plasma sodium less than 135mmol/L:
    - 0.5-2 gram/kg over 1 hour (7mls/kg of 20% mannitol)

Repeat every 6-8 hours for a maximum of 48 hours
Measure osmolarity every 12 hours (max 310 mosmol/kg)
5. RENAL DYSFUNCTION:

• General:
  - Defined as: urine output < 0.5ml/kg/hour in 2 consecutive hours
  - Possible causes: Hepato-renal syndrome, Dehydration, Low CVP/ Low cardiac output
6. CARDIOVASCULAR PROBLEMS/LOW CARDIAC OUTPUT:

- **General:**
  - Consider following cases:
    - Hypovolaemia
    - Hypoxia
    - Hypoglycaemia
    - Sepsis

- **Management:**
  - Colloid challenge: 10-20mls/kg over 30-60mins
  - Inotrope support should be discussed with PICU staff
7. METABOLIC ACIDOSIS

- **General:**
  - Consider following causes:
    - Hypovolaemia
    - Hypoxia
    - Sepsis
    - Renal failure

- **Management:**
  - Generally TREAT is base excess (BE) >10 and pH< 7.25
  - Give 8.4% Sodium Bicarbonate intravenously as follows:
    - mls bicarbonate = weight (kg) x base deficit (i.e. half correct)
      
      \[
      \text{mls bicarbonate} = \text{weight (kg)} \times \text{base deficit (i.e. half correct)}
      \]

      \[-
      \]

      \[6\]
8. SEPSIS

- General:
  Signs of sepsis may be subtle, e.g. rise in heart rate or core-toe temperature gradient, fall in blood pressure or urine output, hypo-or hyperglycaemia, hypothermia, deterioration in mental state, fits, increasing acidosis.

- Management:
  - Do full septic screen, omitting LP and supra-pubic puncture.
  - Start broad spectrum antibiotics “blind” (cerfuroxime, Ampicillin and Metronidazole).
<table>
<thead>
<tr>
<th></th>
<th>Base Line Drugs</th>
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<tbody>
<tr>
<td>1</td>
<td>Vitamin K</td>
</tr>
<tr>
<td></td>
<td>&lt; 1 year</td>
</tr>
<tr>
<td></td>
<td>&gt; 1 year</td>
</tr>
<tr>
<td></td>
<td>&gt; 10 year</td>
</tr>
<tr>
<td>2</td>
<td>Antacids</td>
</tr>
<tr>
<td></td>
<td>Omeprazole 0.5 mg/kg/dose BD i/v or orally</td>
</tr>
<tr>
<td></td>
<td>Sucralfate 250-500 mg/dose QDS (if PH &lt;5 after PPI)</td>
</tr>
<tr>
<td>3</td>
<td>Lactulose</td>
</tr>
<tr>
<td></td>
<td>2-4 mls/kg/dose TDS</td>
</tr>
<tr>
<td>4</td>
<td>N-acetylcysteine</td>
</tr>
<tr>
<td></td>
<td>150mg/kg/day continuous infusion</td>
</tr>
<tr>
<td>5</td>
<td>Broad-spectrum antibiotics:</td>
</tr>
<tr>
<td></td>
<td>• Amoxicillin</td>
</tr>
<tr>
<td></td>
<td>• Cefuroxime</td>
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<tr>
<td></td>
<td>• Metronidazole</td>
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<tr>
<td></td>
<td>30 mg/kg/dose TDS i/v</td>
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<tr>
<td></td>
<td>50 mg/kg/dose TDS i/v</td>
</tr>
<tr>
<td></td>
<td>8 mg/kg/dose TDS i/v</td>
</tr>
<tr>
<td>6</td>
<td>Antifungals:</td>
</tr>
<tr>
<td></td>
<td>• Mycostatin or</td>
</tr>
<tr>
<td></td>
<td>• Fluconzole or</td>
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<tr>
<td></td>
<td>• Amphotericin</td>
</tr>
<tr>
<td></td>
<td>2 mls QID orally</td>
</tr>
<tr>
<td></td>
<td>3-6 mg/kg/day i/v</td>
</tr>
<tr>
<td></td>
<td>1-3 mg/kg/day i/v</td>
</tr>
</tbody>
</table>
9. OTHER THERAPIES:

1. **MARS therapy** *(molecular absorbant recirculating system)*
   - Consider in ventilated patients, when renal support is needed and before severe encephalopathy
   - Give for 8 hours on a daily basis until either:
     a) liver transplantation
     b) patient recovers

2. Liver Transplantation
Patient selection and timing are critical for successful transplantation

Refer early for assessment

Who is a candidate?
1. Is spontaneous recovery probable?
   Recovery unlikely if:
   - PT greater than 100 seconds irrespective of grade of encephalopathy
   OR
   - Any of the following:
     - Age: <10 yr or > 40 yr
     - Liver failure induced by Non-A, Non-B hepatitis, halothane or idiosyncratic drug reactions
     - Duration of jaundice before onset of encephalopathy more than 7 days
     - PT more than 50 seconds
     - Serum bilirubin more than 300 umol/l
     - Factor V <15%
2. Is transplant feasible?
   - Disease
   - Family
   - Facilities
   - Donors
3. Are there other complications?
   - Exclusion criteria:
     - Overwhelming infection
     - Sustained impairment in cerebral perfusion
Alternative Treatments for ALF

- Auxillary liver transplantation
  - Heterotopic
  - Orthotopic
- Artificial hepatic support systems
  - Haemodialysis
  - Human hepatoblastoma cell line
  - Pig hepatocytes
- Hepatocyte transplantation
- Extracorporeal liver support
  - to bridge the period of ALF until OLT can be performed
- Xenotransplantation