Paediatric Acute Liver Failure

Where it differs from adults

Tim De Maayer
Not just small adults
Content

• Definitions
• Encephalopathy
• Aetiology & diagnostic testing
• Medical Management
• Outcome prediction scores

No disclosures
The PALF study group

• Study entry criteria:
  • Evidence of acute liver injury
  • Liver induced coagulopathy:
    • INR > 2.0 if no encephalopathy
    • INR > 1.5 with encephalopathy
  • Absence of chronic liver disease
Hepatic encephalopathy in children

- Not always clinically apparent
- Non-specific
- Often a late/pre-terminal sign

The Whitington scale for encephalopathy in children <3y

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical</th>
<th>Asterixis/Reflexes</th>
<th>Neurological Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early (I and II)</td>
<td>Inconsolable crying, sleep reversal, inattention to task</td>
<td>Unreliable/normal or hyperreflexic</td>
<td>Untestable</td>
</tr>
<tr>
<td>Mid (III)</td>
<td>Somnolence, stupor, combativeness</td>
<td>Unreliable/hyperreflexic</td>
<td>Most likely untestable</td>
</tr>
<tr>
<td>Late (IV)</td>
<td>Comatose, arouses with painful stimuli (IVa), or no response (IVb)</td>
<td>Absent</td>
<td>Decerebrate or decorticate</td>
</tr>
</tbody>
</table>
21 day outcomes of PALF by encephalopathy

In 59% of early LTx patients, peak encephalopathy was mild (grade I or II)

Aetiology and diagnostic testing
Neonatal/infant specific diagnoses

**Herpes Simplex virus**
- Most common cause of neonatal PALF.
- Intrapartum transmission
- ↑↑ transaminases
- Vesicles not always present

**GALD**
- Maternal antibody to foetal liver
- Recurs in subsequent pregnancies
- Presents in utero / first few days of life
- Treated with gamma globulins
Specific diagnoses

**HLH**

- Abnormal immune activation
- Primary or secondary
- Fever, HSM and cytopaenia
- Raised ferritin & triglycerides
- Haemophagocytosis
- Rx: immune suppression
Specific diagnoses

Tyrosinaemia
- FAH deficiency
- ↑↑INR, ↑SBR, ↑transaminases
- High HCC risk
- Rx: Nitisinone, low tyrosine diet
- Tx if treatment fails

Mitochondrial neuro-hepatopathies
- Defect in electron transport chain
- Impaired ATP generation, fat oxidation
- Elevated lactate, microvesicular steatosis
- Novel MPV17 mutation in black South Africans
Aetiology varies by age (N= 985)

Squires, PALF study group
The etiology of pediatric acute liver failure (PALF) is identified in approximately 55 percent of cases, leaving an indeterminate cause in 45 percent. Indeterminate cases are likely composed of a number separate conditions including immune dysregulation, with the latter condition having a variety of manifestations.

%: percent; APAP: acetaminophen (paracetamol).

Age specific diagnostic testing algorithms

• PALF study phase 1 & 2:
  • Neonates <91d old:
    • HSV, GALD, Metabolic (galactosaemia & respiratory chain disorders) most common
    • No EBV
    • No AIH
  • >3 months:
    • AIH, drugs (incl paracetamol)
  • Wilson’s only from 4y onwards
<table>
<thead>
<tr>
<th>Recommended tests</th>
<th>Indication</th>
<th>&lt;3 mo</th>
<th>3 mo to 3 y</th>
<th>3 mo to 18 y</th>
<th>4–18 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and urine tests</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Herpes blood PCR</td>
<td>Systemic herpes infection</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Serum amino acid profile</td>
<td>Urea cycle; other metabolic defects</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Ferritin</td>
<td>GALD screen</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate, pyruvate</td>
<td>Mitochondrial screen</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Plasma acylcarnitine profile</td>
<td>FAO defects</td>
<td></td>
<td>X</td>
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<tr>
<td>Urine succinylacetone</td>
<td></td>
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<tr>
<td>Enterovirus blood PCR</td>
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<td></td>
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<td></td>
<td>X</td>
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<tr>
<td>Acetaminophen level</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis A virus IgM</td>
<td></td>
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<tr>
<td>Hepatitis B surface antigen</td>
<td></td>
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<tr>
<td>EBV VCA IgM or PCR</td>
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<tr>
<td>Antinuclear antibody</td>
<td></td>
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<td></td>
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<tr>
<td>Anti–smooth muscle ab</td>
<td></td>
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<tr>
<td>Liver kidney microsomal ab</td>
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<tr>
<td>IgG</td>
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<tr>
<td>Ceruloplasmin</td>
<td></td>
<td></td>
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<td></td>
<td>X</td>
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<tr>
<td>24-hour urine copper</td>
<td>Wilson disease screen</td>
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<td></td>
<td></td>
<td>X</td>
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<tr>
<td>Historical information</td>
<td></td>
<td></td>
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<td></td>
<td>X</td>
</tr>
<tr>
<td>Drug history</td>
<td>APAP other drug or HDS exposure</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Confirm newborn screen results</td>
<td>Galactosemia and tyrosinemia</td>
<td></td>
<td></td>
<td>X</td>
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<tr>
<td>Confirm maternal hepatitis B serology</td>
<td>Hepatitis B in newborn</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
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<tr>
<td>Procedures</td>
<td></td>
<td></td>
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<tr>
<td>Abdominal ultrasound with Doppler</td>
<td>Vascular anomalies</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
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<tr>
<td>Echocardiogram</td>
<td>Cardiac dysfunction</td>
<td></td>
<td></td>
<td>X</td>
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</tbody>
</table>
Age specific testing improves diagnostic yield
Medical management
Intravenous N-acetylcysteine in Pediatric Patients With Nonacetaminophen Acute Liver Failure: A Placebo-Controlled Clinical Trial


**Primary Outcome: 1 Year Survival**

- Placebo: 82%
- NAC: 73%

**Secondary Outcome: Liver Transplant-Free Survival**

- Placebo: 53%
- NAC: 35%
Predicting outcomes
### King's College Hospital Criteria for Non-Acetaminophen Induced Acute Liver Failure in an International Cohort of Children

- **Acetaminophen-induced disease**
  - Arterial pH < 7.3 (irrespective of the grade of encephalopathy)
  - Grade III or IV encephalopathy AND Prothrombin time > 100 seconds AND Serum creatinine > 3.4 mg/dL (301 µmol/L)

- **All other causes of acute liver failure**
  - Prothrombin time > 100 seconds (irrespective of the grade of encephalopathy)
  - Any three of the following variables (irrespective of the grade of encephalopathy)
    1. Age < 10 years or ≥ 40 years
    2. Etiology: non-A, non-B hepatitis, halothane hepatitis, idiosyncratic drug reactions
    3. Duration of jaundice before onset of encephalopathy > 7 days
    4. Prothrombin time > 50 seconds
    5. Serum bilirubin > 18 mg/dL (308 µmol/L)


![Flowchart showing criteria and outcomes](chart.png)
LIU, Clichy, PELD/MELD, ...

**LIU, Clichy, PELD/MELD, ...**

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**Evaluation of the Liver Injury Unit Scoring System to Predict Survival in a Multinational Study of Pediatric Acute Liver Failure**

Brandy R. Lu, MD,1 Song Zhang, MS2, Michael R. Narkewicz, MD1,3, Steven H. Belle, MD2, Robert H. Squires, MD1, Ronald J. Sokol, MD1,3, and on behalf of the Pediatric Acute Liver Failure (PALF) Study Group.

\[ LIU = (3.507 \times \text{peak total bilirubin}) + (45.51 \times \text{peak INR}) + (0.254 \times \text{peak ammonia}) \]

- Small numbers of deaths in Tx era
- Death & Tx groups combined
- Don’t account for dynamic nature of PALF
- Don’t help individual patients
The future
Thank you WDGMC