Learning Objectives

At the end of this presentation the participant will be able:
1. Evaluate the cause of pediatric acute liver failure, guided by the patient age
2. Prioritize the diagnosis of treatable conditions
3. Identify and treat complications

Definition

Severe liver injury in a patient without a previous history of liver disease who develops encephalopathy within 8 weeks of the initial symptoms.

Pediatric Acute Liver Failure Study Group (PALFSG)

Began 2000
Multicenter, multi-national study
- USA = 17
- Canada (Toronto) = 1
- UK (London, Birmingham) = 2

Children Are Different

1. Hepatic Encephalopathy (HE) is difficult to assess
2. HE may not develop until terminal stages
3. Uncorrectable coagulopathy is a reliable finding in children with ALF
4. Poor outcome can occur without encephalopathy

Disclosure

No relationships with commercial companies to disclose
PALFSG Consensus entry criteria:
1. LF within 8 weeks of onset of clinical liver disease (CLD), in a patient with no evidence of chronic liver disease
2. Biochemical evidence of ALF: elevated AST/ALT and/or total and conjugated bilirubin
3. Coagulopathy unresponsive to Vit K
   - PT >15 sec or INR >1.5 with HE
   - PT>20 s or INR >2 with/without HE

Incidence is unknown
30% of children with ALF < 3 years of age
24% of children who never develop clinical encephalopathy died or required liver transplant
USA, PALF accounts for 10-15% liver transplants

Metabolic (42%)
- Galactosemia, Tyrosinemia, Fatty acid oxidation, mitochondrial chain defects
- Infections (16%)
- Herpes, enterovirus, sepsis
- Indeterminate (16%)
- Biliary atresia
- Neonatal hemochromatosis (16%)
- Other (20%)
- Drugs, Myocarditis, asphyxia, HLHS

Viral hepatitis
- Hepatitis non A and Non B (27%)
- Hepatitis A (10%)
- Hepatitis B (4%)  
- EBV, CMV

Drugs and Toxins (10%)
- Acetaminophen(13%), Valproic acid, Lisinopril, mushrooms, Amiodarone

Autoimmune/Metabolic (7%)
Wilson’ s disease, Reye syndrome

Acetaminophen (10%)

Malignancy (<5%)

< 1 YEAR OLD

Indeterminate (47%)

>1 YEAR OLD

Most common cause of liver failure in school aged children
Low rate of spontaneous recovery
One year survival 50-60% with transplant

95% of drug metabolized to non-toxic by-product
5% metabolized by a different pathway which forms toxic intermediate compound
- This fraction increases dramatically in overdose
- Potential for toxicity increased by fasting and alcohol ingestion
- Depletion of anti-oxidant defense in the liver
Acetaminophen Toxicity

- Single dose of 100-150 mg/kg
- Multiple small doses of therapeutic dosing
- Acetaminophen adducts formation can be measured in chronic ingestion
- Begin N-acetylcysteine (NAC) promptly in all patients where the quantity of acetaminophen ingested, serum drug level or rising aminotransferases indicate liver injury

Clinical Presentation

Clinical presentation is variable depending on the age and etiology:

- Onset of the disease is rarely identified
- Fatigue, nausea, emesis, anorexia, abdominal pain

Clinical Presentation

PALFSG:

- Jaundice: 58%
- Encephalopathy: 53% (13% grade III and IV)
- Ascitis: 22%
- Hepatomegaly: 10%
- Seizures: 7%

Diagnosis

1. General labs: hematology, renal, pancreatic and chemistry
2. Liver specific test: LFTs, albumin, PT, INR, glucose, ammonia
3. Imaging: CXR, Abdominal u/s, Head CT or MRI, EEG
4. Diagnostic approach
   - Age appropriate/treatable causes/ liver transplant

Diagnostic Prioritization

- In the child < 8 weeks
  - Infection: herpes, enterovirus, adenovirus, CMV, EBV
  - Metabolic disease: galactosemia, tyrosinemia, fatty acid oxidation, mitochondrial/respiratory chain defects
- Older children
  - Autoimmune disease, even in the young child
  - Other infections in addition to hepatitis A, B, or C
  - Metabolic diseases in addition to Wilson’s disease
  - Drug history

Management

1. General measures and prevention of complications
2. Treat treatable conditions
3. Treatment of complications
4. Hepatic support
5. Assessment of prognosis for liver transplantation
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### General Measures

- Avoid sedation except for procedures
- Gastric pH > 5
- Acid/base/Electrolytes
- Fluid balance:
  - 75% maintenance
  - Provide adequate glucose (GIr 6-10 mg/kg/m)
  - Na: 1 mmol/kg/day
  - K: 3-6 mmol/kg/day
  - Maintain circulating volume with colloid/FFP

### General Measures

- Nutrition
  - Protein: 1-2 g/kg/day
  - Trace elements: cooper and manganese are metabolized in the liver.
- Coagulation support: bleeding or procedures
- Drugs:
  - Vitamin K: does not improve coagulation, assures the sufficiency of this cofactor
    - < 2 years: 1-2 mg/dose
    - > 2 years: 5-10 mg/dose

### General Measures

- PPI or H₂ antagonist
- N-acetylcysteine: Acetaminophen toxicity / non-acetaminophen ALF:
  - Increase hepatic oxygen delivery, consumption and extraction. Improves coagulation and decrease progression of HE
  - PALFG: NAC was not beneficial in children with non-acetaminophen-induced ALF

### General Measures

- Broad spectrum antibiotics and antifungals
  - Infection is suspected
  - There is no evidence to support prophylactic antibiotics.
- Lactulose/Neomycin: clinical evidence of encephalopathy

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**Treatable Conditions**

- **Infection**
  - HSV
  - Enterovirus
  - Parvovirus
- **Drug and Toxins**
  - Acetaminophen
  - Amanita phalloides
- **Metabolic disease**
  - Neonatal iron storage
  - Tyrosinemia type I
  - Wilson disease
  - Galactosemia
- **Immune dysregulation**
  - Autoimmune hepatitis

**Management**

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**Complications**

- Metabolic
- Coagulopathy and hemorrhage
- GI bleeding
- Encephalopathy
- Renal dysfunction
- Ascitis
- Secondary bacterial and fungal infection

**Metabolic**

**Hypoglycemia**

- Impaired hepatic gluconeogenesis and depleted glycogen stores
- Hyperinsulinemia
- Anaerobic metabolism
- Secondary bacterial infection

**Coagulopathy Associated with ALF**

- Decreased procoagulant factors: II, V, VII, IX, X
- Decreased anti-coagulants factors: Antithrombin, protein C and protein S
- Decreased function and number of platelets
- Decreased intravascular coagulation
Bleeding diathesis in liver disease is complex:
- Balance reduction of pro- and anticoagulant factors may neutralize bleeding risk
- Renal failure, portal hypertension, sepsis may precipitate bleeding

Factor VII
- First factor depleted ALF and shortest half-life (6-12 h) of the clotting factors.
- More sensitive than PT

Factor VIII
- Synthesized by vascular endothelium
- Differentiate between DIC and ALF
- ALF: normal or increase

Thrombocytopenia
- 50% adult patients and uncommon in pediatrics
- Severe thrombocytopenia:
  - hypersplenism, DIC, aplastic anemia.
  - DIC (>70%)
  - Tissue necrosis in the liver

Pro-coagulant factors synthesized by the liver are assessed
- Little or no evidence that PT/INR predicts bleeding risk
- Prolong PT usually precedes other clinical evidence of liver failure
- Evaluation of the severity of liver injury and assess prognosis

Brain dysfunction that occurs as a result of acute hepatic dysfunction
- Factors associated with onset
  - Infection
  - GI bleeding, increase dietary proteins
  - Fluid and electrolyte disturbance
  - Drugs (narcotics)
Hepatic Encephalopathy Treatment

**Therapy goal** = Decrease ammonia production and accumulation

1. Treat precipitating factors
2. Provide adequate glucose
3. Protein restriction or elimination
4. Lactulose or neomycin
5. Benzodiazepine antagonist: Flumazenil
6. Ornithine aspartate: Urea cycle activation agents

### Renal failure

Renal insufficiency: 75% ALF

**Causes:**
1. Prerenal: volumen depletion
2. Congestive heart failure
3. Renal: ATN, Toxic-drugs
4. Postrenal: Ureteral, bladder-outlet obstruction
5. Hepatorenal syndrome

### Hepatorenal Syndrome

- HRS most often occurs with advance liver disease
- No specific criteria for HRS in children
- Estimated 5% incidence in children (vs. 10-15% adults)

### Infections Associated with ALF

- 50% of children will develop infection
- Major cause of death
- Spontaneous Bacterial peritonitis
- Cholangitis
- PNA
- UTI
- Sepsis

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Hepatic Support

1. Plasmapheresis
2. Renal replacement therapy
3. Liver/renal replacement therapy
4. Liver transplant

Plasmapheresis

- Removed toxins
- Improved coagulopathy
- No sustained CNS improvement
- No impact on outcome
- Wilson disease

Renal Replacement Therapy

- May be reasonable option as bridge to transplant
  - CRRT better tolerated than HD
- Goals:
  1. Fluid and electrolyte management
  2. Removed toxic substance
  3. Optimized nutrition and minimize the loss of visceral and somatic protein pools.

Extracorporeal Liver Support Devices

- Perform some functions of the liver
- Delay or avoid the need of liver transplantation
- Composed of immobilized living hepatocytes or multiphase dialytic and plasma exchange/absorber system
- Basic Categories:
  - Artificial: MARS, Prometheus, BAL, ELAD
  - Non-artificial: Hepatocyte supported
- Few pediatric trials to date

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Liver Transplantation

Still the most definite treatment for LF
Currently available prognostic scoring systems do not adequately predict outcome and determine candidacy for liver transplantation.
1. Kings College Hospital Criteria (KCHC)
2. Clichy score
3. Pediatric End-Stage liver disease (PELD)
4. Liver injury Unit (LIU): PALFS sensitivity 74% and specificity 80%
**Prognosis**

- Spontaneous recovery more common in Acetaminophen injury
  - 91% vs. others 45%
- Laboratory predictors
  - Higher bilirubin
  - Longer clotting studies
  - Abnormal acid-base status
- Spontaneous recovery lower in younger children
  - < 3 yrs 48% vs. >3 yrs 55%

**Outcome**

- 70% mortality in pretransplant era
  - Contributing causes
    - Cerebral edema 56%
    - Bleeding 50%
    - Renal failure 30%
    - Infection 15%
- Patients with spontaneous recovery have excellent long-term prognosis

**SUMMARY**

- ALF in children is complex, dynamic and devastating condition.
- Prioritize diagnostic studies to identify treatable conditions
- The etiology of ALF is different between children and adult and also differs within pediatric age groups
- Potentially treatable causes are likely missed due to incomplete diagnostic evaluation.

**Schematic Model of the Natural Course and Outcome of Acute Liver Failure in Children**