Acute liver and renal failure

Prof. A. Gervais
Gross anatomy

The liver is a roughly triangular organ that extends across the entire abdominal cavity just inferior to the diaphragm.

Most of the liver’s mass is located on the right side of the body where it descends inferiorly toward the right kidney.
The liver consists of 4 distinct lobes

- **left, right, caudate, and quadrate** lobes.

- The left and right lobes are the largest lobes and are separated by the falciform ligament.

- The small caudate lobe extends from the posterior side of the right lobe and wraps around the inferior vena cava.

- The small quadrate lobe extends from the posterior side of the right lobe and wraps around the gallbladder.
The liver performs many essential functions related to digestion, metabolism, immunity, and the storage of nutrients within the body.

These functions make the liver a vital organ without which the tissues of the body would quickly die from lack of energy and nutrients.
The liver plays an active role in the process of digestion through the production of **bile**.

As blood from the digestive organs passes through the hepatic portal circulation, the hepatocytes remove many potentially toxic substances (i.e. **ammonium**) before they can reach the rest of the body.

The liver provides storage of many essential nutrients, **vitamins A, D, E, K, and B12**, and **minerals** (iron and copper).

The liver is responsible for the production of several vital protein components of blood plasma and coagulation: **prothrombin**, **fibrinogen** and **coagulation factors** involved in the formation of blood clots.

All these functions are affected in acute liver failure.
Acute liver failure

- **Pediatric acute liver failure** (PALF) is a complex, rapidly progressive clinical syndrome that is the final common pathway for many disparate conditions, some known and others yet to be identified.

- The estimated frequency of acute liver failure (ALF) in all age groups in the United States is about 17 cases per 100,000 population per year, but the frequency in children is unknown.

- PALF accounts for 10 to 15 percent of pediatric liver transplants performed in the United States annually.
Liver biopsy in a child with indeterminate acute liver failure

Example of a liver biopsy in a child with acute liver failure of indeterminate etiology, with falling ALT (1250 IU/L to 275 IU/L), rising total bilirubin (12.5 mg/dL to 25 mg/dL) and rising prothrombin time (rising from 20 to 26 seconds). Histology reveals a dense infiltrate dominated by lymphocytes, but with scattered neutrophils and eosinophils, and with hepatic necrosis and biliary damage.

(A) Low power view.
(B) High power view.

ALT: alanine aminotransferase; IU: international unit.

Causes of PALF

- Specific etiologies of pediatric acute liver failure (PALF) can be broadly categorized as:
  - infectious,
  - immunologic,
  - metabolic,
  - toxin or drug-related.

- In almost 50 percent of patients, a specific cause is not discovered, and in this case, the PALF is categorized as indeterminate.
### Acute liver failure

#### Etiology of acute liver failure in children worldwide (final diagnosis as percent of cases in each region)

<table>
<thead>
<tr>
<th>Etiology</th>
<th>North America and Europe*</th>
<th>Brazil</th>
<th>North Brazil</th>
<th>Argentina</th>
<th>Kolkata</th>
<th>North India</th>
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</tbody>
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Causes of acute liver failure in children worldwide, as percent of cases in each country or region. The most common causes in each region are shown in red font.

* Data from the Pediatric Acute Liver Failure Study Group (PALFSG), from 2000 to 2007.

• For the PALFSG data, this category includes all viral causes of acute liver failure. In this population, herpes simplex virus (HSV) was the most common viral cause of acute liver failure in infants; Epstein-Barr virus (EBV) and hepatitis A virus (HAV) were the most common viral causes in older children.

Δ For the PALFSG data, the “other” category includes shock/ischemia, gestational alloimmune liver disease (neonatal hemochromatosis), veno-occlusive disease, hemophagocytic syndrome, Budd-Chiari, and “other
Drug-related PALF

- **Acetaminophen** (paracetamol) is widely used in children for management of fever and pain

  Hepatotoxicity after **acute single ingestion > 100mg/kg**

  after **chronic ingestion (15mg/kg q 6h) of >1 day**

- **Intrinsic hepatotoxins** (mushroom toxins)

- **Idiosyncratic effects**
  - Isoniazid, halotane, anticonvulsivant drugs, antibiotics
Virus-related PALF

Hepatitis A, B, C, E virus

- Less than 1 percent of children with symptomatic hepatitis A virus (HAV) develop ALF.

- Nonetheless, acute HAV accounts for up to 80 percent of PALF cases in developing countries, reflecting high rates of HAV infection in the population.

- In North America and Western Europe, HAV infection causes only 0.8 percent of cases of PALF, reflecting low rates of HAV infection.
Acute liver failure

Virus-related PALF

Hepatitis A, B, C, E virus

- In areas where HBV is endemic, it accounts for up to **20 percent of PALF cases**.

- Death occurs more commonly in older patients and in individuals who acquired HBV following a blood transfusion rather than from perinatal infection.
Virus-related PALF

Hepatitis A, B, C, E virus

- **Hepatitis C** virus (HCV) infection has rarely been identified as the cause for ALF, and ALF has not been observed in large studies of transfusion-acquired HCV infection.

- **Hepatitis E** virus (HEV) appears to be a common cause of acute hepatitis and sometimes of ALF in developing countries, but the true incidence may be underestimated because serologic testing is not consistently performed.
Virus-related PALF

Viruses other than hepatitis virus

- Epstein Barr virus (EBV)
- Adenovirus
- Herpes simplex virus
- Human herpesvirus 6
- Parvovirus B19
- Enteroviruses
Given the rarity of PALF, an age-based diagnostic approach is useful to improve diagnostic yield.

**History** — A detailed history is essential

Each of the following issues should be explored:

- Time of onset of symptoms such as jaundice, change in mental status, easy bruising, vomiting, and fever
- Exposure to contacts with infectious hepatitis
- History of blood transfusions
In teenagers, a history of depression, suicide attempts, and risk-taking behaviors

A list of prescription and over-the-counter medications in the home, including complementary and alternative medicines

Use of intravenous drugs or other recreational drugs that are hepatotoxins, including ecstasy, cocaine, or solvent-sniffing.

Family history of Wilson disease, infectious hepatitis, infant deaths or autoimmune conditions, which might lead to a specific diagnosis.

In neonates, review of maternal records for TORCH infection risk, including syphilis and herpes simplex
Pediatric acute liver failure (PALF) typically presents in a previously healthy patient with a nonspecific prodrome of variable duration with features that might include abdominal discomfort and malaise with or without fever.

With the exception of acute ingestions (eg, mushrooms, acetaminophen), the precise onset of disease is rarely identified.

Common features at presentation

- Jaundice
- Pruritus
- Encephalopathy – 53 percent
- Seizure – 7 percent
- Ascites – 22 percent
Acute liver and renal failure

Jaundice

Yellow sclera
Acute liver and renal failure

Because of hepatocytes destruction

- Liver enzymes (ALT, and AST) and
- Bilirubin are increased in serum

- Loss of liver function
  - Coagulopathy
  - Hepatic encephalopathy (ammonia increase in serum)
**CLINICAL DIAGNOSIS**

- **Recent development of asthenia** (unusual and severe fatigue)
- **Icterus/ Jaundice**
  - At the eye conjunctiva
- **Pruritus**
- **Signs of hepatic encephalopathy**
  - Troubles of the consciousness (apathy, psychomotor slowing)
  - Asterixis (flapping tremor)
  - Confusion evolving towards coma, without localizing signs.
  - Convulsion (7%)
- **Hemorrhagic manifestations**
  - Ecchymoses
  - Gingival or nasal hemorrhage
  - Sometimes purpura
- **Ascites (22%)**
Differential Diagnosis

- **Other causes of icterus**
  - Gastrointestinal causes: Biliary track obstruction (tumors, calculi, etc.),
    - Rare among children, usually produces light color stools
  - Hemolysis:
    - The blood examination shows a hemolytic anemia,
    - Sickle cell disease: The red cells are crescent shaped
    - Malaria: Positive blood smears for parasites
  - Contagious Hepatitis A-B-C-D
  - Cytomegalovirus, Epstein Barr Virus, Herpes Virus
  - Toxic/medication cause
  - Metabolic cause
  - Indeterminate cause

- **Alterations in consciousness**
  - Sepsis, high fever, toxins, cranial trauma, meningitis, cerebral malaria
    - Look for infectious causes requiring urgent treatment (sepsis, malaria)
    - Look for recent trauma
  - Diabetic coma (ketoacidosis)
Acute liver failure

COMPLEMENTARY EXAMINATIONS

- **Blood**
  - Complete blood count (CBC) with differential
  - Liver function tests
    - Elevation of the total serum bilirubin ≥ 1.5 times the upper limit of normal (ULN)
    - Elevation of the serum transaminases (ALT, AST ≥ 3 times the upper limit of normal (ULN))
  - Blood glucose
  - Test for proteinuria
  - Prolongation of the prothrombin time (PT), drop in factor V.
  - Drop in the concentration of serum albumin.
  - Exclusion of Hepatitis A-B-C-D
  - HIV serologies (blood tests)
  - Thick smear test
  - Sickle cell testing

- **CSF**
  - Spinal tap if there is any doubt whatsoever and if there are neurological symptoms and in the absence of major coagulation disorders

- **Urine** N/A Not applicable
- **Stools** N/A Not applicable
- **Other** (In case of diagnostic doubt)

**Prepare an extra tube of blood for:**
- Other viral serologies (blood tests)
- Medications
- Toxic neuropathies (medications, toxins such as exposure to certain insecticides)
- Autoantibodies
Acute liver failure

**CASE DEFINITION**

**Major criteria**
- Total serum bilirubin $\geq 1.5$ times the upper limit of normal (ULN)
- OR
- Elevation of the serum transaminases (ALT, AST $\geq 3$ times the upper limit of normal (ULN))
- AND
- Coagulopathy unresponsive to vitamin K (prothrombin time (PT) $\geq 15$ seconds or INR $\geq 1.5$)
Acute liver and renal failure
Gross anatomy

The kidneys are a pair of organs found along the posterior muscular wall of the abdominal cavity.

The left kidney is located slightly more superior than the right kidney due to the larger size of the liver on the right side of the body.
Acute renal failure

The kidneys are the waste filtering and disposal system of the body. As much as 1/3 of all blood leaving the heart passes into the kidneys to be filtered before flowing to the rest of the body’s tissues.

Gross anatomy

Each kidney contains around 1 million individual nephrons, the kidneys’ microscopic functional units that filter blood to produce urine.
Acute renal failure

Physiology of the kidneys

- **The primary function of the kidneys is the excretion of waste products** resulting from protein metabolism and muscle contraction.

- Ammonia, uric acid, urea, and creatinine all accumulate in the body over time and need to be removed from circulation to maintain homeostasis.

- The glomerulus in the kidneys filter all four of these waste products out of the bloodstream, allowing us to excrete them out of our bodies in urine.
Blood from the renal arteries and their subdivisions is delivered to the glomeruli.

The glomeruli form an ultrafiltrate of plasma that is nearly free of protein and blood elements and flows into the renal tubules.

The tubules reabsorb and/or secrete solutes (eg, sodium, potassium, hydrogen, urea, and creatinine) and reabsorb almost all of the filtered water.

The final tubular fluid, the urine, leaves the kidney, draining sequentially into the renal pelvis, ureter, and bladder, from which it is excreted through the urethra.
Acute renal failure

Physiology of the kidneys (other functions)

- Filtration, reabsorption and secretion
- Water homeostasis
- Acid / base homeostasis
- Electrolyte homeostasis
- Blood homeostasis (renin)
- Production of hormones (calcitriol, erythropoietin, ADH)

All these functions are affected in renal failure
Acute renal failure

CAUSES OF ACUTE RENAL FAILURE

1. Prerenal
   - Sudden and severe drop in blood pressure (shock) or interruption of blood flow to the kidneys from severe injury or illness

2. Intrarenal
   - Direct damage to the kidneys by inflammation, toxins, drugs, infection, or reduced blood supply

3. Postrenal
   - Sudden obstruction of urine flow due to enlarged prostate, kidney stones, bladder tumor, or injury
Acute prerenal injury occurs in:

- hypovolemic states such as in acute hemorrhage, diarrhea, or unreplenished insensible losses.
- decompensated liver disease with portal hypertension
- alterations in renal vascular autoregulation, such as afferent arteriole vasoconstriction caused by nonsteroidal antiinflammatory drugs (NSAIDs) or iodinated contrast
Acute renal failure

Epidemiology of acute renal failure

- Acute tubular necrosis (drug toxicity) — 45%
- Prerenal disease — 21%
- Urinary tract obstruction — 10 percent
- Glomerulonephritis or vasculitis — 4%
- Acute interstitial nephritis — 2%
- Atheroemboli — 1%
Acute renal failure

Clinical presentation

- Patients with kidney disease may have a variety of different clinical presentations.

- Some have symptoms or signs that are directly referable to the kidney (gross hematuria, decreased urine output), or

- to associated extrarenal manifestations (edema, hypertension, signs of uremia)
Clinical presentation

- Many patients are asymptomatic and are incidentally found to have an elevated serum creatinine concentration,

- Abnormal urine studies (such as proteinuria or microscopic hematuria), or abnormal radiologic imaging of the kidneys
Acute renal failure

CLINICAL DIAGNOSIS

• Most children with acute renal insufficiency present signs and symptoms indicative of altered renal function including:
  - Bilateral Oedema in the lower extremities (due to fluid accumulation)
  - Oliguria (<0.5ml/kg/hour)
  - Hematuria
  - And/or high blood pressure
Acute renal failure

Differential Diagnosis

This is not applicable (N/A), but the etiological testing is important, and among the most frequent causes are the following:

- Post-streptococcal glomerulonephritis
- Dehydratation
- Septic shock
- Multiple organ dysfunction
- Hemolytic-uremic syndrome
- Severe malaria
- Typhoid fever
- Lymphatic filariasis
- Urinary tract obstruction
Acute renal failure

COMPLEMENTARY EXAMINATIONS

- Blood
  - Complete blood count (CBC), blood smear
  - Serum creatinine
    - ≥ 1.5 times the upper limit of normal (ULN) or
    - ≥ 1.5 times the patient’s usual value

<table>
<thead>
<tr>
<th>Normal values for infants</th>
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<tbody>
<tr>
<td>Newborn</td>
</tr>
<tr>
<td>Baby</td>
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<tr>
<td>Toddler</td>
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</table>

- Dipstick: Test for proteinuria
Acute renal failure

**COMPLEMENTARY EXAMINATIONS**

- **Urine**
  - Cytobacteriological examination of the urine (blood)
  - Proteinuria (over a 24 hour period, if possible)

- **Have a tube of extra blood for:**
  - Other viral serologies
  - Medications
  - Toxic nephropathy (medications, toxins such as exposure to certain insecticides)
  - Auto-antibodies
Acute renal failure

**CASE DEFINITION**

**Major criteria**
Creatinine ≥ 1.5 times the upper limit of normal (ULN) or 1.5 times the patient’s initial value.

**Minor criteria**
Urine production < 0.5 ml/kg/hour
Acute liver and renal failure

- Acute liver and renal failure are not common adverse event following immunization
  - It has only been reported in association with Yellow fever vaccine
  - Causing VisceroTropic Disease (VTD) > 10 d after vaccination at a frequency of 0.3 to 0.4 /100'000 vaccine dose distributed
Viscerotropic disease

VTD is characterized by hepatic dysfunction, renal failure, coagulopathy, and shock

- The midzone of the liver lobule is principally affected, with sparing of cells bordering the central vein and portal tracts
- The hemorrhagic diathesis in VTD is due to decreased synthesis of vitamin K-dependent coagulation factors by the liver, disseminated intravascular coagulation, and platelet dysfunction
- Renal damage is characterized by eosinophilic degeneration and fatty change of renal tubular epithelium without inflammation
Viscerotropic disease

Case definition of viscerotropic disease

Level 1 of diagnostic certainty
• ≥3 major criteria

Level 2 of diagnostic certainty
• 2 major criteria
  OR
• 1 major criterion AND ≥ 2 minor criteria

Level 3 of diagnostic certainty
• ≥ 3 minor criteria
  OR
• 1 major criterion and 1 minor criterion

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*a* The case definition should be applied when there is temporal association to vaccination and no clear alternative diagnosis to account for the symptoms

*b* Whenever both major and minor criteria are used to meet the case definition, they must represent different clinicopathologic categories (e.g., hepatic versus renal).

Viscerotropic disease

Major criteria

Hepatic: Total bilirubin ≥ 1.5X ULN
   [≥ 1.5X patient’s baseline value if known]
   OR
   ALT or AST ≥ 3X ULN
   [≥ 3X patient’s baseline value if known]

Renal: Creatinine ≥ 1.5X ULN
       [≥ 1.5X patient’s baseline value if known]

Musculoskeletal: CPK ≥ 5X ULN

Respiratory: Oxygen saturation ≤ 88% on room air (by pulse oximetry)
           OR
           Requirement for mechanical ventilation

Hematologic: Platelets < 100,000/µL

Hypotension: Requirement for vasopressor drugs to maintain systolic BP

Coagulopathy: INR ≥ 1.5 OR Prothrombin time ≥ 1.5X ULN OR Activated partial thromboplastin time ≥ 1.5X ULN OR elevated FDPs OR hemorrhage from more than one site
Viscerotropic disease

Minor criteria

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<tr>
<th>Hepatic</th>
<th>Jaundice</th>
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<tbody>
<tr>
<td>Renal</td>
<td>Urine output &lt; 500 ml urine/24 hours for adults</td>
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<td></td>
<td>Urine output &lt; 0.5 ml/kg/hour for children</td>
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<td>Musculoskeletal:</td>
<td>Positive urine dipstick test for blood with a negative urine microscopy exam for red blood cells</td>
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<tr>
<td>Respiratory</td>
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<td>Hematologic</td>
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<td>Systolic BP &lt; 5&lt;sup&gt;th&lt;/sup&gt; percentile for age in children &lt; 16 years</td>
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<td>- Epistaxis, Hematemesis</td>
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<td>- Melena, Hematochezia, Hemoptysis</td>
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<td>- Metrorrhagia or menorrhagia, Gingival hemorrhage</td>
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<td></td>
<td>- Persistent bleeding from needle puncture sites</td>
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<sup>c</sup> Age-specific thresholds for increased respiratory rate (breaths/min.)

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<td>6 years and older</td>
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Thank you

Prof. A. Gervaix