Pathology of acute liver failure

Alberto Quaglia

BSG Annual Liver Pathology Update Meeting, Cheltenham, 6th October 2016
“A potentially reversible condition, the consequence of severe liver injury, with a onset of encephalopathy within 8 weeks of the appearance of the first symptoms and in the absence of pre-existing liver disease “

Figure 1. Clinical Features of Acute Liver Failure.

- **Brain**
  - Hepatic encephalopathy
  - Cerebral edema
  - Intracranial hypertension

- **Lungs**
  - Acute lung injury
  - Acute respiratory distress syndrome

- **Liver**
  - Loss of metabolic function
  - Decreased:
    - Gluconeogenesis → hypoglycemia
    - Lactate clearance → lactic acidosis
    - Ammonia clearance → hyperammonemia
    - Synthetic capacity → coagulopathy

- **Heart**
  - High output state
  - Frequent subclinical myocardial injury

- **Pancreas**
  - Pancreatitis, particularly in acetaminophen-related disease

- **Adrenal gland**
  - Inadequate glucocorticoid production contributing to hypotension

- **Kidney**
  - Frequent dysfunction or failure

- **Bone marrow**
  - Frequent suppression, particularly in viral and seronegative disease

- **Circulating leukocytes**
  - Impaired function, with immunoparesis contributing to high risk of sepsis

- **Portal hypertension**
  - May be prominent in subacute disease and confused with chronic liver disease

- **Systemic inflammatory response**
  - High energy expenditure or rate of catabolism
A – O’Grady system

Hyper-acute

Acute

Subacute

Weeks from jaundice to encephalopathy

B – Bernau system

Fulminant

Subfulminant

Weeks from jaundice to encephalopathy

C – Japanese system

Fulminant

Late-onset

Subclass:

Acute

Subacute

Weeks from jaundice to encephalopathy

Figure 3. Worldwide Causes of Acute Liver Failure.
HAV denotes hepatitis A virus, HBV hepatitis B virus, HEV hepatitis E virus, and NT not tested.
Other Causes

Acute ischemic hepatocellular injury, or hypoxic hepatitis, may occur in critically ill patients with primary cardiac, circulatory, or respiratory failure. It may be caused by severe sepsis accompanied by signs of cardiac failure and major, transient elevations in blood aminotransferase levels.\textsuperscript{24,25} This condition primarily requires supportive cardiorespiratory management rather than specific interventions targeted at the liver injury. The prognosis depends on both the cause of hepatic hypoxia and the severity of liver injury. A similar liver-injury pattern may also be seen in drug-induced liver injury caused by recreational drugs such as MDMA (3,4-methylenedioxy-N-methylamphetamine, also known as ecstasy) or cocaine.

Other causes of acute liver failure are neoplastic infiltration, acute Budd–Chiari syndrome, heatstroke, mushroom ingestion, and metabolic diseases such as Wilson’s disease.\textsuperscript{15,16} Acute liver failure that occurs during pregnancy may require early delivery of the fetus; management should be discussed with specialists at a referral center that has capabilities for both neonatal care and intensive management of the mother’s liver disease.

In many cases, the cause of acute liver failure remains unknown, despite intensive investigation; potential causes include infection with a novel...
<table>
<thead>
<tr>
<th>Neonates</th>
<th>n = 31</th>
<th>Children</th>
<th>n = 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal hemochromatosis</td>
<td>15</td>
<td>Non-A-E hepatitis</td>
<td>45</td>
</tr>
<tr>
<td>Hemophagocytic lymphohistiocytosis</td>
<td>4</td>
<td>Hepatitis A/B</td>
<td>7</td>
</tr>
<tr>
<td>Disseminated herpes simplex virus</td>
<td>5</td>
<td>Other viral infection</td>
<td>3</td>
</tr>
<tr>
<td>Metabolic</td>
<td>4</td>
<td>Metabolic</td>
<td>18</td>
</tr>
<tr>
<td>Transplacental acetaminophen toxicity</td>
<td>1</td>
<td>Paracetamol toxicity</td>
<td>8</td>
</tr>
<tr>
<td>Endocrine (isolated cortisol deficiency)</td>
<td>1</td>
<td>Other drug/toxin</td>
<td>5</td>
</tr>
<tr>
<td>Sepsis/shock</td>
<td>1</td>
<td>Sepsis/hypoxia</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Miscellaneous</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Hyperacute</td>
<td>Acute</td>
<td>Subacute</td>
</tr>
<tr>
<td>--------------------------</td>
<td>------------</td>
<td>------------</td>
<td>------------</td>
</tr>
<tr>
<td>Time from jaundice to encephalopathy</td>
<td>0-1 week</td>
<td>1-4 weeks</td>
<td>4-12 weeks</td>
</tr>
<tr>
<td>Severity of coagulopathy</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Severity of jaundice</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Degree of intracranial hypertension</td>
<td>++</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>Survival rate without emergency liver transplantation</td>
<td>Good</td>
<td>Moderate</td>
<td>Poor</td>
</tr>
<tr>
<td>Typical cause</td>
<td>Paracetamol, hepatitis A and E</td>
<td>Hepatitis B</td>
<td>Non-paracetamol drug-induced liver injury</td>
</tr>
</tbody>
</table>

Data from O’Grady and colleagues and Ichai and Samuel. +++= high severity. ++= medium severity. + = low severity. +/- = present or absent.

Table 1: Classification, clinical features, and prognosis of the three subtypes of acute liver failure

Bernal et al. Lancet 2010; 376:190-201
Histology of ALF

Multiple aetiologies, limited morphologic repertoire of tissue response and macroscopic and histological patterns

Limited role for the histopathologist in clinical practice

Histopathological basis of syndrome

CRITICAL CARE IN ACUTE LIVER FAILURE

Editors: Roger Williams and Julia Wendon
Patterns of injury

- Confluent hepatocyte loss
  - Terminology: coagulative, eosinophilic, zonal, panlobular, multiacinar, massive
    - Centro-midlobular with periportal sparing
    - Periportal necrosis
    - Geographic/random with viral inclusions
    - No residual hepatocytes
    - Map-like

- Venous outflow block
- Malignant infiltration
- Microvescicular steatosis
- “Giant cell” hepatitis and neonatal haemochromatosis

Histopathological basis of syndrome

**CRITICAL CARE IN ACUTE LIVER FAILURE**

*Editors: Roger Williams and Julia Wendon*
Acute liver failure due to hepatic malignant infiltration

• Very rare cause of ALF
• Compared 24 ALF-MI patients with 72 ALF patients
  – 13 Haematological
  – 10 Carcinoma
  – 1 Angiosarcoma
• Higher ALP, LDH, urea, ferritin and lower platelets in the ALF-MI
• Hepatomegaly on imaging

Patterns of injury

• Confluent hepatocyte loss
  – Terminology: coagulative, eosinophilic, zonal, panlobular, multiacinar, massive
    • Centro-midlobular with periportal sparing
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    • Geographic/random with viral inclusions
    • No residual hepatocytes
    • Map-like
Courtesy of Bernard Portmann
“map-like” pattern
“map-like” pattern
"map-like" pattern
“map-like” pattern
Median age = 19 years (range 1-40), 19 children, 22 female.

Cause:
- 24 = seronegative liver failure;
- 15 = paracetamol overdose;
- 4 = HBV infection in 4;
- 3 = drug-induced liver failure;
- 2 = autoimmune hepatitis;
- 1 = mushroom poisoning;
Panel: Definitions of acute-on-chronic liver failure

World Congress of Gastroenterology (consensus definition)\(^5\)
“A syndrome in patients with chronic liver disease with or without previously diagnosed cirrhosis which is characterized by acute hepatic decompensation resulting in liver failure (jaundice and prolongation of the INR [International Normalized Ratio]) and one or more extrahepatic organ failures that is associated with increased mortality within a period of 28 days and up to 3 months from onset”

Asia-Pacific Association for the Study of Liver Disease\(^{17}\)
“Acute hepatic insult manifesting as jaundice and coagulopathy, complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease”

European and American associations for the study of liver disease\(^{18}\)
“Acute deterioration of pre-existing, chronic liver disease, usually related to a precipitating event and associated with increased mortality at 3 months due to multi-system organ failure”

*Lancet* 2015; 386: 1576–87
Acute on chronic liver failure

Acute on chronic liver failure

Acute on chronic liver failure

# Alcoholic Hepatitis Histological Score (AHHS) for Prognostic Stratification of Alcoholic Hepatitis

## Points

### Fibrosis stage
- None Fibrosis or Portal fibrosis 0
- Expansive fibrosis 0
- Bridging fibrosis or Cirrhosis +3

### Bilirubinostasis
- No 0
- Hepatocellular only 0
- Canalicular or ductular +1
- Canalicular or ductular plus Hepatocellular +2

### PMN infiltration
- No/Mild +2
- Severe PMN Infiltration 0

### Megamitochondria
- No Megamitochondria +2
- Megamitochondria 0

### AHHS categories (0–9 points)
- Mild: 0–3
- Intermediate: 4–5
- Severe: 6–9

Note: Histological features included in the AHHS where product of the multivariate logistic regression analysis (Table 2). Weighting of each histological feature was based in the odds ratio of the updated model (training plus test set samples. See model building in Supplementary Data).

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