Hepatic Hell: Acute Liver Failure

Introduction
Acute liver failure (ALF): some type of severe liver injury leads to near-immediate failure of the synthetic liver function with a high risk of permanent liver infarction. Obviously, there is an associated high mortality. ALF has strict criteria and the following MUST be met:

- **Encephalopathy**
- **Impaired synthetic function (INR of ≥1.5)** in a patient without preexisting liver disease
- **Duration of < 26 weeks** (differentiates from chronic)

Someone with preexisting cirrhosis for >26 weeks (due to alcohol, chronic hepatitis, NASH, etc.) is diagnosed with acute-on-chronic injury. This is not ALF.

The true determinants of prognosis are the causes, which vary greatly depending on the pathology. **Viral and drug-induced hepatitis are the most common causes in adults.** In the USA, acetaminophen is the most common cause of acute liver failure.

See the table to the right to understand the grading of encephalopathy. **Cerebral edema is the most common cause of death in ALF, therefore this should drive management decisions.**

### Encephalopathy:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Encephalopathy</th>
<th>Asterix</th>
<th>EEG</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Mild confusion/slurred speech</td>
<td>variable</td>
<td>usually normal</td>
</tr>
<tr>
<td>II</td>
<td>Moderate confusion/lethargy</td>
<td>yes</td>
<td>Abnormal</td>
</tr>
<tr>
<td>III</td>
<td>Marked confusion/incoherent</td>
<td>yes</td>
<td>Abnormal</td>
</tr>
<tr>
<td>IV</td>
<td>Coma</td>
<td>no</td>
<td>Abnormal</td>
</tr>
</tbody>
</table>

Presentation
Nonspecific symptoms and signs. Lethargy, anorexia, nausea/vomiting, pruritus, jaundice, abdominal distention, RUQ pain, mental status changes. Depending on the cause, specific findings may be present. For example, Budd Chiari often presents with abdominal distention, Wilson Disease presents with profound psychiatric changes and even Parkinsonism. See the table on the next page for details.

Laboratory findings: nonspecific and depends on time of presentation and cause. Most commonly seen are elevated aminotransferase levels, elevated bilirubin, elevated INR (required for diagnosis), thrombocytopenia, hyperammonemia, and multiple electrolyte deformities as described below.

General Approach

**Setting:** Only 40% of patients with acute liver failure recover spontaneously, leaving many needing liver transplantation. Whenever possible, patients with ALF should be managed at a facility capable of performing liver transplantation. Transport patients early!

**Workup:** the obvious- CMP, PT/PTT/INR, CBC, and ABG. Serial fingerstick glucose are important because hypoglycemia can be a cause of altered mental status given the liver’s inability to provide stress hyperglycemia. Hypoglycemia is seen in more than 40% of ALF patients. Labs should be serially drawn about every 4-6 hours as major electrolyte shifts can occur with resuscitation and worsening condition.

Patients should be monitored and aggressively treated for hypoglycemia, hypokalemia, and hyponatremia. Rising bilirubin & PT/INR are ominous and are associated with worse prognosis. Hypokalemia specifically raises renal production of serum ammonia, and hyponatremia can lead to tissue hypoperfusion with impaired renal free water excretion.

**Hemodynamic management:** The goal is to maintain a MAP > 75 mmHg or a CPP >50 to 60 mmHg; initial volume replacement is with normal saline (LR should not be used as the liver (theoretically) will be unable to metabolize the lactate and therefore worsening the patient’s acidosis). If the patient is already severely acidic, one can use ½ -NS with 75 mEq/L Na-bicarbonate. There is honestly no right answer here. These patients are critically ill and any volume resuscitation can be helpful, although one must be cautious due to high risk of volume overload from venous congestion and low oncocytic pressure.

If unresponsive to IV fluids, norepinephrine is preferred as the vasopressor of choice. If refractory, Vasopressin can be considered along with stress dose hydrocortisone as many patients can develop adrenal insufficiency.

Acute kidney injury is seen in 30-70% of patients. The percentage is higher in those with acetaminophen toxicity and ischemic hepatitis. Similar pathophysiology as hepatorenal syndrome.

**Coagulopathy:** Patients with ALF can develop coagulopathy. Interestingly though, even with an elevated INR, the majority of patients are either hypercoagulable or have normal coagulation. Therefore, prophylactic FFP is not recommended as it can interfere with assessments of liver function and may lead to fluid overload. It also has been shown to not change mortality. Correct low platelets and increased PTT only in the setting of bleeding or pre-procedure. The most common site of bleeding is GI.

**Infection surveillance/ prevention:** studies have shown no benefit for prophylaxis. If there is evidence of infection use piperacillin/tazobactam or a fluorquinolone +/ metronidazole. Avoid aminoglycosides! Gram negative and anaerobic coverage is needed. **If ascites is present, this should without a doubt be sampled via diagnostic paracentesis.**

Management of Complications

**Metabolic abnormalities:** initially patients present with alkalosis (mixed respiratory and metabolic abnormality) in early ALF then acidosis as lactic acid accumulates. The most common electrolyte disturbances as mentioned above are hypokalemia, hyponatremia, and hypoglycemia.

**Hepatic encephalopathy:** ALF can lead to high ammonia, which accumulates in astrocytes causing cytotoxic edema. The table above refers to the grading of encephalopathy. Patients with acute liver failure are not routinely treated with lactulose or rifampin (controversial and has no clear mortality benefit). Neomycin is nephrotoxic, thus avoid. If the need arises in the critically ill patient, intubate before administering lactulose, as they are high risk for aspiration.
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Cerebral edema: uncommon in patients with grade I or II encephalopathy, but it is present in 30% of those with grade III encephalopathy and in approximately 75% of those with grade IV encephalopathy. Besides the uncommon Cushing Triad, neurologic manifestations may include increased muscle tone, hyperreflexia, and altered papillary responses.

Preventing intracranial pressure elevation: immediate steps in those with grades III-IV include minimizing patient agitation, elevating the head of the patient's bed and maintaining optimal fluid balance.

If concern for increased ICP and Cushing triad, administer of 3% hypertonic saline (in grade IV encephalopathy and/or patients with ammonia >150 micromol/L).

General management of ICP: please refer to our more detailed guide on managing elevated ICP on our website.

Seizures: Seizures are common in ALF, especially with worsening encephalopathy, and can raise ICP. In patients who require sedation, avoid opioids as they lower the seizure threshold. Low dose, short acting benzodiazepines are preferred for sedation. If seizures occur, first line is phenytoin, followed by short acting benzodiazepines (2nd line). Routine AED prophylaxis is not recommended.

"Throwing in the kitchen sink": N-acetylcysteine has clear benefit in those with acetaminophen overdose, yet it might be beneficial to those with acute liver failure where the cause is unknown in the early stages of encephalopathy. In a placebo-controlled trial with ALF patients not due to acetaminophen, NAC significantly lowered the mortality rate (40 versus 27 percent). We support the use of NAC in those with undifferentiated ALF as there is a potential for decreased mortality and NAC itself has no major side effects.

Transplant indications: King’s College Criteria were developed after measuring patients treated for ALF in 1973-1985. In short, their recommendations are below:

Acetaminophen-induced ALF: 
- Arterial pH <7.30 alone
- Grade III/IV encephalopathy AND PT >100 seconds AND serum Cr >3.4

All other ALF causes:
- PT >100 seconds alone
- Any 3 of the following: Age <10 or >40, poor prognostic disease (non-A/non-B viral hepatitis, drug-induced, Wilson disease), duration of jaundice before development of encephalopathy > 7 days, PT > 50 seconds, bilirubin > 18 mg/dL (308 micromol/L)

A couple of noteworthy comments here. Several studies have been performed analyzing King’s College Criteria, finding it to be greatly specific but poorly sensitive along with a high positive predictive value and low negative predictive value. In short, it is more effective at predicting patients with a poor prognosis than a good prognosis.

As for the debate regarding MELD (not posted here) vs King’s College Criteria, there is extensive data cross-examining their performances and honestly results over the past several years seems conflicting, especially when discussing acetaminophen-induced injury vs other causes. In summary, as an emergency physician, these scores should NOT play a major role in deciding acute care. Any patient with ALF should be transferred to a transplant capable hospital and upon arrival there will be a detailed discussion at the ICU-level with critical care physicians and the transplant team.
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References: