Acute Liver Failure (ALF)

February 14, 2021 by Josh Farkas

(https://emcrit.org/ibcc/alf/attachment/alftop/)

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definition & classification

definition

- Acute Liver Failure (ALF) is generally defined as:
  - (1) Synthetic liver failure (INR > 1.5) with hepatic encephalopathy.
  - (2) No underlying cirrhosis.
Acute Liver Failure (ALF) - EMCrit Project

- (3) Hepatic encephalopathy beginning within roughly <26 weeks.

**Subclassification of acute liver failure**

- Subclassification is based on the time delay between the initial onset of symptoms (usually jaundice) and the development of hepatic encephalopathy.
- **Hyperacute ALF**
  - Delay from symptoms to hepatic encephalopathy is below ~1 week.
  - Common causes include acetaminophen or viral hepatitis.
  - Carries a higher risk of immediate deterioration due to cerebral edema.
  - If patients can survive the immediate illness, they may have a greater likelihood of experiencing hepatic recovery and thus avoiding transplantation.
- **Longer** durations of time between symptom onset and hepatic encephalopathy indicate a smoldering process ("subacute ALF"). As this time-interval increases (e.g., to >4-6 weeks),
  - Hepatic failure is less likely to cause cerebral edema or cause immediate death.
  - Clinically this may appear a bit more like cirrhosis (e.g., a gradual process with ascites).
  - There is a lower likelihood of hepatic recovery, so patients are more likely to ultimately require transplantation.

**Diagnosis**

**Signs & Symptoms**

- Jaundice, although this may not be prominent.
- Encephalopathy, graded as follows:
  - Grade I: Patient shows altered behavior with normal level of consciousness, reduced attention span.
  - Grade II: Patient displays altered behavior with disorientation, drowsiness.
  - Grade III: Patient is confused, incoherent, mostly sleeping but arousable to painful stimuli.
  - Grade IV: Patient is comatose and unresponsive to pain.
- Other findings may include fatigue, nausea/vomiting, right upper quadrant pain, anorexia, pruritus, and distension due to ascites.

**Laboratory indications of hepatic failure**

- Labs suggesting active or *impending* hepatic failure may include:
  - INR >1.5
  - Marked hyperbilirubinemia.
  - Severe elevation of transaminases.
- Frank metabolic failure of the liver may eventually cause:
  - Lactic acidosis (although there are many potential causes of lactic acidosis, discussed [here](https://emcrit.org/ibcc/agma/#evaluation&_treatment_of_lactate_elevation)).
  - Hypoglycemia.
  - Hyperammonemia.

**Causes & investigation of etiology**

**Most common causes**

- Acetaminophen.
- Other drugs & toxins:
  - Sympathomimetics, including cocaine and MDMA ("ecstasy").
  - Numerous drugs are implicated (see [livertox.nih.gov](https://livertox.nih.gov)). Overall, non-acetaminophen drug-induced liver injury may be less likely to resolve, so transplantation may be an earlier consideration. ([31885843](https://pubmed.ncbi.nlm.nih.gov/31885843/)).
- Amanita phalloides mushroom poisoning.
Always ask patients about over the counter medications and herbal or other supplements, as well as chemical exposures. (Note: Alcohol does not cause acute liver failure; rather, this is classified as acute-on-chronic liver failure).

Viral hepatitis:
- Mostly HBV & HAV (especially reactivation of HBV in patients starting chemotherapy or immunosuppressive regimens).
- HEV is more common in some areas.
- Herpesviruses
  - HSV can occur in immunocompetent patients
  - CMV, EBV, or VZV in immunosuppression.
- Autoimmune hepatitis.

Less common causes
- Wilson's disease.
- Budd-Chiari syndrome (hepatic vein thrombosis).
- Pregnancy-associated.
  - Acute fatty liver of pregnancy.
  - Preeclampsia/HELLP syndrome.
- Ischemic hepatitis (may especially occur in presence of biventricular dysfunction, causing congestion and poor perfusion; frank hypotension isn't always noted).
- Hyperthermia including heat stroke.
- Malignant infiltration of the liver (e.g., lymphoma or metastatic adenocarcinoma).
- Veno-occlusive disease following bone marrow transplantation.
- Hemophagocytic lymphohistiocytosis (HLH).
- Reye's Syndrome.

Investigations for patient with acute hepatic failure
- Basic labs:
  - Complete blood count.
  - Chemistries, including magnesium and phosphate.
  - Liver function tests.
  - Coags (including INR, PTT, fibrinogen, thromboelastography).
  - Lactate.
  - Ammonia (>150 uMol/L correlates with increased risk of herniation). (17685471)
- Viral panel
  - HIV.
  - HAV IgM.
  - HBV panel (surface antigen, surface antibody, IgM anti-core antibody).
  - HCV antibody (HCV rarely causes acute liver failure, but could be an underlying disorder). If concerned for acute HCV, consider checking HCV RNA.
  - HSV IgM, HSV-1 and HSV-2 PCR.
- Additional testing:
  - In immunocompromised patients: testing for VZV, CMV, and EBV.
  - If recent travel to endemic area or pregnancy, HEV IgM antibody.
- Autoimmune markers: ANA, anti-smooth muscle antibody, immunoglobulin levels.
- Toxicologic labs:
  - Acetaminophen level (Note, however, that this is usually zero by the time liver failure occurs).
  - Serum ethanol level.
  - May consider urine toxicology screen.
  - Wilson's disease: suggested if alkaline phosphate (in IU/L) is less than four times the bilirubin (in mg/dL), or the presence of Coombs negative hemolytic anemia.
  - Beta-HCG if potentially pregnant.
- Imaging:
- EKG, chest X-ray.
- Right upper-quadrant ultrasound (including Doppler to exclude Budd-Chiari).

**liver transplantation**

**consider transfer to a liver transplant center**

- Patients with acute hepatic failure can deteriorate rapidly. Especially if the patient is a potential transplant candidate, it is often safest to pursue early transfer to a liver transplant center.
- Criteria for transfer vary widely. The most important aspect is early and clear communication between centers regarding eligibility and timing of transfer.

**treatment of inciting cause & N-acetylcysteine**

**treatment of any identifiable cause of hepatic failure**

- Treat any medication/toxin exposures:
  - Review all medications regarding potential hepatotoxicity (compare to livertox.nih.gov (https://livertox.nih.gov/php/searchchem.php)).
  - Discontinue any potentially hepatotoxic medications.
  - Make sure to discontinue PRN acetaminophen orders (which are often part of prefabricated order sets).
- Steroid therapy is occasionally indicated:
  - Autoimmune hepatitis (1 mg/kg IBW prednisone daily) (https://pubmed.ncbi.nlm.nih.gov/32334790/)
  - Alcoholic hepatitis (more on this here (https://emcrit.org/ibcc/alcoholic-hepatitis/)).
  - Some forms of drug-induced liver injury.
- Antiviral therapy for acute HBV, HSV, VZV, or CMV.

**N-acetylcysteine**

- N-acetylcysteine should be given for both acetaminophen and non-acetaminophen liver failure. (32068578)
  - Acetaminophen toxicity is the #1 cause of liver failure in many developed nations. This may result from suicide attempts or medication errors (e.g., simultaneous use of several acetaminophen-containing cold medications).
  - N-acetylcysteine improves transplant-free survival even in hepatic failure not due to acetaminophen toxicity. (19524577, 23325162)
- Generally, the regimen is the same as for acetaminophen intoxication:
  - N-acetylcysteine is easiest to administer intravenously. MDcalc (https://www.mdcalc.com/acetaminophen-overdose-nac-dosing) has a calculator for the dose.
  - Repeat the third dose (as a continuous infusion) until the patient is improving (and, if the patient did take acetaminophen, until the acetaminophen level is negative). If improvement doesn't occur, the infusions shouldn't be continued longer than five days. (32068578)

**cardiovascular**

- Acute hepatic failure tends to cause a vasodilatory shock state. Clinically this may be nearly indistinguishable from septic shock (if doubt exists regarding the possibility of septic shock, cultures should be obtained and empiric broad-spectrum antibiotics initiated).
  - Norepinephrine is often a front-line pressor.
  - Targeting a high Bp (e.g., MAP>75 mm) may be beneficial. This may promote cerebral perfusion in the face of elevated intracranial pressure, and may also be beneficial to renal perfusion in patients with hepatorenal physiology. (31915608, 30694840)
Acute hepatic failure may cause relative adrenal insufficiency, so **stress-dose steroids** may be considered. (28131021)

- If hypovolemic, **5% albumin** might be a preferred fluid. (31394283, 33205036)
- There should be a low threshold to **discontinue antihypertensives & diuretics**.

### Pulmonary

- Intubation may be required in patients with worsening hepatic encephalopathy, to achieve several purposes:
  - Airway protection from aspiration.
  - Avoid hypercapnia (which could worsen ICP elevation); for intubated patients, target a low-normal PaCO2. (28417882)
  - Propofol sedation may reduce intracranial pressure.
- For patients with deteriorating encephalopathy and worsening hepatic function, there is little role for BiPAP (given high risks of deterioration and aspiration).

### Nutritional Support

- **Stress ulcer prophylaxis** should be considered, even in nonintubated patients.
- Avoid constipation, with a low threshold to initiate **lactulose** as the cathartic agent of choice.

### Renal

- Avoid nephrotoxins.
- Treat **electrolyte abnormalities** (especially hypokalemia or sodium abnormalities, if they seem to be contributing to encephalopathy).
  - Hypokalemia may increase renal ammoniagenesis, so it should be treated promptly.
- Treat **acute kidney injury** early (defined as a creatinine rise by 0.3 mg/dL or 1.5 times baseline):
  - Consider empiric therapy for hepatorenal syndrome, including albumin and vasopressors (more on this [here](https://emcrit.org/ibcc/hrs)).
- **Early initiation of dialysis** may assist in ammonia clearance, so this is recommended by the SCCM guidelines and European guidelines. (28417882, 32058375, 32058375)
  - Early renal replacement therapy may be used to target an ammonia level <100 uM/L (32068578)
  - Continuous renal replacement is generally preferred over intermittent dialysis, to avoid rapid electrolyte shifts which may cause fluctuations in intracranial pressure. If citrate is used to prevent filter clotting, ionized calcium levels should be monitored (citrate may be poorly metabolized by the liver, leading to its accumulation and chelation of calcium).

### Infectious Diseases

- Bacterial superinfection is a substantial problem. However, these typically occur later on during the ICU course (e.g., after >1 week).
- There should be a low threshold for obtaining cultures and initiating empiric antibiotics (especially if septic shock is suspected).
empiric vitamin K

- Consider 10 mg vitamin K intravenously daily for three days (to exclude vitamin K deficiency and thereby promote accurate prognostication based on INR values).
- Realistically, vitamin K usually has minimal effect among patients with acute liver failure (who rarely will be vitamin K deficient).

DVT prophylaxis is generally indicated

- Despite the elevated INR, patients in acute liver failure have a tendency towards coagulation (more-so than patients with chronic liver disease). ([32334790](https://pubmed.ncbi.nlm.nih.gov/32334790/))
- When doubt exists (e.g., in patients with profoundly elevated INR), thromboelastography may be helpful to understand the patient’s coagulation balance. If the R-time is normal or low, then DVT prophylaxis should be administered.

avoid giving fresh frozen plasma (FFP), for the following reasons:

- (1) Giving plasma makes it impossible to use the INR as a measurement of hepatic synthetic function.
- (2) Most patients with elevated INR aren’t truly coagulopathic.
- (3) For patients with liver dysfunction who are bleeding, plasma rarely helps the bleeding (fibrinogen supplementation or platelet infusion is more likely beneficial, depending on the patient’s coagulation status).

endocrine

avoid hypoglycemia

- Hypoglycemia can result from the liver’s inability to synthesize glucose.
- Follow glucose levels regularly, especially if patients are NPO.
- Don’t aggressively control hyperglycemia.
- Intubated patients should ideally receive nutrition, if possible (see above [gastrointestinal]).
- Some patients will require infusions of dextrose to prevent hypoglycemia (e.g., D10W via peripheral line or higher concentrations via central line).

neurology

The greatest life threat is often acute hepatic encephalopathy, which is frequently associated with increased intracranial pressure and herniation. This is far more dangerous than hepatic encephalopathy seen in chronic cirrhosis (which isn’t associated with cerebral edema or herniation).

basic measures

- Whenever possible, avoid sedating medications that may cloud the picture or exacerbate encephalopathy.
- Correct electrolyte abnormalities.
- Lactulose has not been proven to reduce mortality, but it may decrease ammonia levels and remains a rational therapy (if it can be safely tolerated).

intracranial pressure (ICP) elevation: epidemiology & detection

- ICP elevation occurs in 20-30% of patients with acute liver failure. ([32334790](https://pubmed.ncbi.nlm.nih.gov/32334790/), 32068578)
- Risk factors for ICP elevation:
  - Younger age.
  - Hyperacute presentation (shorter duration from jaundice to encephalopathy).
  - Renal replacement therapy (more severe renal injury results in greater NH3 retention).
Hypotension requiring vasopressor support.

Ammonia levels may be the strongest risk factor, as this seems to be the primary driver of cerebral edema. Levels >100 uM/L predict the onset of severe hepatic encephalopathy, with the risk of herniation increasing at levels >150-200 uM/L. (30694840)

Clinically, ICP elevation manifests mostly as severe encephalopathy. Other signs which may occur include hypertension, bradycardia, and mydriasis. (28417882)

CT scan may be falsely negative, due to uniformly elevated pressure throughout the brain (which doesn't cause tissue shifts).

Optic nerve ultrasonography (https://emcrit.org/emcrit/optic-nerve-sheath-ultrasound-for-detecting-increased-icp/) may be useful. Transcranial Doppler is another option, but it requires a very high skill level.

Invasive ICP monitoring is controversial. This may be considered in highly selected patients who are at the greatest risk for elevated intracranial pressure. An additional use is as a prognostic tool while awaiting transplantation (cerebral perfusion pressure <40mm for >4 hours predicts irreversible brain injury).

ICP elevation: management

Basic interventions:
- Maintain pCO2 within a low-normal level. (28417882)
- Avoid catheterization of the internal jugular veins when able: elevate the head of the bed.
- Avoid fever, with a low threshold to institute definitive temperature control using an external adaptive cooling system (e.g., Arctic Sun system targeted to 36C).
- Generally target a high-normal sodium level (140-145 mM).
- Deep sedation with propofol.
- Avoid hypotension (as this may cause a profound drop in the cerebral perfusion pressure).
- Avoid systemic venous congestion (which may further reduce cerebral perfusion).

Management of hyperammonemia:
- Hyperammonemia seems to be the primary driver of elevated intracranial pressure in acute liver failure.
- Renal replacement therapy may be useful to clear ammonia. (32334790, 30694840)
  Continuous renal replacement therapy initiation when ammonia levels are >150 uM/L may be associated with improved survival. (32068578)
- Lactulose or polyethylene glycol may be considered for reducing ammonia absorption from the bowel. (discussed further in the chapter on hepatic encephalopathy).

seizure management

- Subclinical seizure is often present in grade III-IV encephalopathy, so video EEG should be considered.
- Prophylactic antiepileptic agents are generally not recommended.
- Propofol is a preferred sedative among intubated patients, with the advantage of providing antiepileptic activity.

podcast


questions & discussion

To keep this page small and fast, questions & discussion about this post can be found on another page here.
Any patient with acute hepatic failure should receive a consultation with transplant hepatology and/or discussion with a regional liver transplant center.

Give N-acetylcysteine to all hepatic failure patients. Don't allow the infusion to stop until the patient has recovered.

Do not fail to aggressively diagnose and treat hepatorenal syndrome. Supporting the kidney function may promote ammonia clearance and thereby prevent other organ failures (e.g., hepatic encephalopathy).

Beware of acute hepatic encephalopathy and consider initiation of treatment early.

Consider video EEG for intubated patient with hepatic encephalopathy. Seizure is a common event in this context, which may exacerbate ICP elevation and promote herniation.

References


The Internet Book of Critical Care is an online textbook written by Josh Farkas (@PulmCrit), an associate professor of Pulmonary and Critical Care Medicine at the University of Vermont.