When Does Transaminitis Become Acute Hepatic Failure? What Is the Management of Transaminitis and Acute Hepatic Failure?

Michelle A. Hieger

Pearls and Pitfalls

- Acute liver failure is a common pathway for many conditions and insults, leading to massive hepatic necrosis and/or loss of normal hepatic function.
- Transaminases can be elevated secondary to many intra- and extrahepatic causes.
- The level of transaminitis should not be the sole determinant in management and disposition.
- Patients with acute liver failure should be considered for early transfer to a liver transplant center, ideally prior to elevation in intracranial pressure or the development of severe coagulopathy.

When Does Transaminitis Become Acute Hepatic Failure?

Transaminases (aspartate aminotransferase (AST) and alanine aminotransferase (ALT)) are frequently obtained in the acute care setting [1–3]. Non-toxicological causes of elevated transaminases include infection, ischemia, metabolic derangement, malignancy, autoimmune disease, and primary graft failure after transplant [1].

Acute Hepatic Failure

Non-toxicological causes of acute liver failure are listed in Table 69.1 [1]. Toxicological causes of acute liver failure are listed in Table 69.2 [1]. Viral hepatitis is the most common cause of acute liver failure worldwide, while acetaminophen is the most common cause of acute liver failure in the United States [3]. Acute liver failure is a common pathway for many conditions and insults, leading to massive hepatic necrosis and/or loss of normal hepatic function.

Acute liver failure can be classified into subgroups by acuity of encephalopathy. Hyperacute liver failure is encephalopathy within 1 week of jaundice onset. Acute liver failure is encephalopathy within 8–28 days of jaundice onset. Subacute liver failure is encephalopathy within 5–12 weeks of jaundice onset [4, 5].

Complications

Each subgroup has its own set of complications. Hyperacute and acute liver failure have an increased incidence of cerebral edema, but hyperacute liver failure patients are more likely to survive with supportive care, and acute liver failure patients are more likely to die without liver transplant. Subacute liver failure patients have increased mortality, less cerebral edema, and increased likelihood of portal hypertension, leading to ascites and renal failure [5].

Other complications from acute liver failure include [5]:

- Bleeding (including exsanguination)
- Cardiovascular derangements
- Pulmonary and ventilatory derangements
- Central nervous system dysfunction (temperature dysregulation causing hypothermia, disruption of the blood-brain barrier, and increased intracranial pressure leading to encephalopathy)
- Metabolic derangements
- Infection

The higher the number of complications, the more likely the patient will not survive [1].

Overall, outcomes have improved due to earlier identification of causes, earlier initiation of treatment, improved intensive care, and improved transplant science. Formerly, mortality was 55–95%, and now mortality is 30–40% [4, 6].
Laboratory Abnormalities

Liver failure generally results in laboratory abnormalities beyond transaminitis. Blood work in acute liver failure may show [1, 7]:

- Synthetic dysfunction, which is usually the first sign of impending liver failure – decreased albumin and clotting factor levels, increased coagulation profiles
- Defects in gluconeogenesis – decreased serum glucose
- Worsening toxicant metabolism – increased ammonia
- Decreased hepatic excretory function – increased bilirubin

- Decreased renal function – elevated creatinine from prerenal azotemia, acute tubular necrosis, and/or hepatorenal syndrome

Table 69.3 reviews the utility of labs, imaging, and other ancillary tests in the evaluation of potential acute hepatic failure [1, 3, 8].

Non-hepatic Transaminitis

In the appropriate clinical setting, elevations in AST and ALT should prompt the clinician to consider rhabdomyolysis
and order a creatinine kinase level. Rhabdomyolysis-induced transaminitis occurs secondary to AST (and some ALT) release from muscle breakdown. In the past, ALT was considered liver-specific, but ALT elevations may occur in patients with myopathy but no liver disease [9]. Hypoperfusion from other medical issues can lead to transaminitis as well.

**Prognostication**

The King’s College Criteria is used to determine potential for liver transplant in both acetaminophen toxicity and other causes of acute liver failure. The King’s College Criteria for acetaminophen toxicity suggests transplant if [4, 10]:

- pH < 7.3 (irrespective of other factors)
- Grade III–IV encephalopathy (Table 69.4) and protime > 100 s and serum creatinine > 3.4 mg/dL.

The King’s College Criteria for non-acetaminophen toxicity suggests transplant if [4, 10]:

- PT > 35 s
- INR > 7.7
- Any three of the following:
  - Age < 10 or > 40 years old
  - Unfavorable etiology (non-A and non-B hepatitis, idiosyncratic drug reaction, halothane hepatitis, Wilson’s disease)

### Table 69.3 Initial diagnostic testing in fulminant hepatic failure

| Parameter                  | Rationale                                                                                     |
|----------------------------|---------------------------------------------------------------------------------------------|
| Electrolytes and minerals | Imbalances are common. Abnormalities can cause arrhythmias and worsen encephalopathy. Hypophosphatemia is common in acetaminophen overdose |
| BUN/creatinine             | Renal failure is frequent and affects management and prognosis. Etiology (e.g., toxic effect of ingested substances) may alter therapy (e.g., hemodialysis) |
| Glucose                    | Hypoglycemia is common and can produce permanent neurologic sequelae                          |
| CBC with platelets         | Assess for sepsis (leukocytosis), GI bleeding (anemia), and risk of hemorrhage (thrombocytopenia) |
| Liver profile              | Assess for degree of damage and follow course of illness. Elevated transaminases are generally due to hepatocyte damage. Increase in alkaline phosphatase is usually due to cholestasis or biliary obstruction. Increased bilirubin with indirect/direct can guide differential |
| Ammonia                    | Increased in hepatic metabolic failure. Poor prognosis if significantly increased in fulminant hepatic failure |
| Coagulation profile        | Serve as prognostic indicators (protime, factor V level) and assess risk of hemorrhage         |
| Arterial blood gases       | Prognostic significance (lactic acidosis). Derangements are common                             |
| Blood group                | Preparation for transplantation. Type and crossmatch in anticipation of bleeding                |
| Toxicology, virology, autoimmunity panel, ceruloplasmin, medication history | Etiology affects management (e.g., NAC for acetaminophen, charcoal for Amanita) and prognosis |
| Blood and urine cultures   | Surveillance for sepsis; aggressive treatment warranted if positive                            |
| ECG                        | May affect management. Preparation for transplantation                                         |
| Chest radiograph           | Sepsis surveillance. Evaluate for ARDS and pulmonary edema                                       |
| Abdominal ultrasound       | Evaluate for vascular thrombosis and infection. Preparation for transplantation                 |
| Intracranial pressure      | Assess ICP if stage III–IV encephalopathy present. Cerebral edema is the most common cause of death |

**ARDS** adult respiratory distress syndrome, **BUN** blood urea nitrogen, **CBC** complete blood count, **ECG** electrocardiogram, **ALF** acute liver failure, **GI** gastrointestinal, **ICP** intracranial pressure, **NAC** N-acetylcysteine, **PT** prothrombin time

### Table 69.4 Stages of clinical hepatic encephalopathy

| Stage | Level of consciousness             | Neuromotor changes                                                                 | Behavioral/intellectual changes              |
|-------|-----------------------------------|-------------------------------------------------------------------------------------|---------------------------------------------|
| I     | Reversal of sleep pattern         | Mild asterixis                                                                      | Euphoria/depression                         |
|       | Mild confusion                    | Impaired handwriting                                                                | Short-term memory lapses                    |
| II    | Slow responses                    | Asterixis/ataxia                                                                    | Inappropriate behavior                       |
|       | Increasing drowsiness             | Slurred speech                                                                       | Loss of time/amnesia                         |
| III   | Disorientation                    | Rigidity/spasticity                                                                 | Stuporous/incoherent                        |
|       | Somnolence                        | Loss of continence                                                                  | Marked confusion/paranoia                    |
| IV A/B| Comatose                          | Decorticate/decerebrate posturing                                                   | Comatose                                    |
|       | A: Responds to pain               | Hyperreflexic                                                                        |                                             |
|       | B: No response to pain            |                                                                                    |                                             |

and order a creatinine kinase level. Rhabdomyolysis-induced transaminitis occurs secondary to AST (and some ALT) release from muscle breakdown. In the past, ALT was considered liver-specific, but ALT elevations may occur in patients with myopathy but no liver disease [9]. Hypoperfusion from other medical issues can lead to transaminitis as well.
Serum bilirubin >17 mg/dL
- Time from jaundice to encephalopathy >7 days
- INR >4

The Acute Physiology and Chronic Health Evaluation III Score (APACHE III Score) may also identify those in need of liver transplant [11].

What Is the Management of Transaminitis and Acute Hepatic Failure?

Transaminitis

Initial management of acute transaminitis includes fluid resuscitation, pain management, and nausea management. Generally, the cause of transaminitis will determine treatment and disposition. Transaminase values alone do not determine disposition. Admission is recommended for higher-risk (elderly and pregnant) patients or when there is no response or poor response to supportive care. It is also recommended for bilirubin ≥20 mg/dL, PT >50% above normal, hypoglycemia, spontaneous bacterial peritonitis, new or worsening hepatic encephalopathy, hepatorenal syndrome, or coagulopathy with bleeding. Additionally, the patient should be admitted if the he or she cannot ambulate safely or if there is an unsafe home condition. Any patient with acetaminophen toxicity (using the Rumack-Matthew nomogram) should be admitted, even if the transaminases and coagulation factors are normal [8].

Acute Hepatic Failure

Patients with acute liver failure should be considered for early transfer to a liver transplant center, ideally prior to intracranial pressure elevation or development of severe coagulopathy [1]. Prophylactic treatment of coagulopathy is unnecessary. Fresh frozen plasma or factor VII should be given before invasive procedures [12]. Patients with grade IV encephalopathy generally require intubation. Providers should elevate the head of bed to 10–20° and consider avoiding positive end-expiratory pressure if possible (grade III recommendation) [13]. With cerebral edema, intracranial pressure monitoring and decompression may be necessary.

Antidotes and Specific Treatments

Specific antidotes exist for acetaminophen toxicity (n-acetylcysteine) and for Amanita mushroom poisoning (silibinin and intravenous penicillin G). Shock liver will improve with the restoration of perfusion. Herpes causing transaminitis can be treated with acyclovir. Acute Budd-Chiari syndrome (thrombosis of the hepatic veins) can be treated with transjugular intrahepatic portosystemic shunt (TIPS), surgical decompression, or thrombolysis. Autoimmune hepatitis can be treated with steroids. Idiosyncratic drug-induced transaminitis can be treated with withdrawal of the drug. Rechallenge of the drug should not be performed unless there is no alternate therapy [1].

Suggested Resources

- Interpretation of liver function tests. (2013). http://www.oscestop.com/LFT_interpretation.pdf.
- Bernal W, Wendon J. Acute liver failure. N Engl J Med. 2013;369:2525–34.
- Farkas S, Hackl C, Schlitt HJ. Overview of the indications and contraindications for liver transplantation. Cold Spring Harb Perspect Med. 2014;4

References

1. Dalhoff K. Toxicant-induced hepatic failure. In: Brent J, et al., editors. Critical care toxicology. Cham: Springer International Publishing; 2016. p. 385–408.
2. Moore P, Burkhart K. Adverse drug reactions in the ICU. In: Brent J, et al., editors. Critical care toxicology. Cham: Springer International Publishing; 2016. p. 693–741.
3. Aghababian RV. Essentials of emergency medicine. Hepatitis. Sudbury: Jones & Bartlett Learning; 2010.
4. O’Grady JG, et al. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology. 1989;97(2):439–45.
5. O’Grady JG, Schalm SW, Williams R. Acute liver failure: redefining the syndromes. Lancet. 1993;342(8866):273–5.
6. Murali AR, Narayanan Menon KV (2017) Acute liver failure [cited 4 Mar 2018]; Available from: http://www.clevelandclinicmeded.com/medicalpubs/disease-management/hepatology/acute-liver-failure/.
7. O’Grady JG, Williams R. Management of acute liver failure. Schweiz Med Wochenschr. 1986;116(17):541–4.
8. Susan R, O’Mara KG. Hepatic disorders. In: Tintinalli JE, et al., editors. Tintinalli’s emergency medicine: a comprehensive study guide. New York: McGraw-Hill Education. p. 525–33.
9. Delaney KA. Hepatic principles. In: Hoffman RS, editor. Goldfrank’s toxicologic emergencies. New York: McGraw-Hill Education. p. 302–11.
10. McPhail MJ, Wendon JA, Bernal W. Meta-analysis of performance of King’s college hospital criteria in prediction of outcome in non-paracetamol-induced acute liver failure. J Hepatol. 2010;53(3):492–9.
11. Fikatas P, et al. APACHE III score is superior to King’s college hospital criteria, MELD score and APACHE II score to predict outcomes after liver transplantation for acute liver failure. Transplant Proc. 2013;45(6):2295–301.
12. Shami VM, et al. Recombinant activated factor VII for coagulopathy in fulminant hepatic failure compared with conventional therapy. Liver Transpl. 2003;9(2):138–43.
13. Muñoz SJ. Difficult management problems in fulminant hepatic failure. In: Seminars in liver disease. New York: Thieme Medical Publishers; 1993.