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

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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].

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Table 69.1 Non-toxicological causes of acute liver failure[a]

Infection	Ischemia	Metabolic derangements	Malignancy	Autoimmune problems	Primary graft failure after transplant
Viral hepatitis (hepatitis A&E most common)	Disruption of portal vein or hepatic artery	Acute fatty liver of pregnancy	Any malignancy causing obstruction or liver damage	Autoimmune hepatitis	Liver transplant failure
Herpes simplex, EBV, varicella zoster, CMV, parvovirus (usually immunocompromised if acute liver failure occurs from these)	Prolonged hypotension (overdose, cardiac arrest, intraoperative, AMI, PE)	HELLP syndrome			
Rare: *Coxiella burnetii*, *Plasmodium falciparum*, amebic abscesses, disseminated TB, *Bacillus cereus*	Veno-occlusive disease (chemotherapy or bone marrow transplant related)	Reye's syndrome			
	Budd-Chiari syndrome	Wilson's disease			
	Exertional heat stroke				

EBV Epstein-Barr virus, *CMV* cytomegalovirus, *TB* tuberculosis, *AMI* acute myocardial infarction, *PE* pulmonary embolism, *HELLP* hemolysis, elevated liver enzymes, low platelets
[a]Not an all-inclusive list

Table 69.2 Toxicological causes of acute liver failure[a]

Pharmaceuticals	Drugs of abuse	Chemicals	Biologic agents
Acetaminophen	Cocaine	CCl_4	Sea anemone sting
Rare/idiosyncratic/unpredictable (valproic acid, troglitazone, amiodarone)	MDMA	Chloroform	Mushrooms (cyclopeptides)
Hypersensitivity reactions (phenytoin, para-aminosalicylate, chlorpromazine, sulfonamides)	PCP	Halothane	
Halogenated anesthetics (enflurane, methoxyflurane, isoflurane, halothane): toxic hepatitis, rare FHF	TCE (inhaled)	Cleaning solvents with fluorinated or halogenated hydrocarbons	
NSAIDs: sulindac, diclofenac	Toluene (inhaled)		
Macrolides (erythromycin, clarithromycin): cholestasis, rare hepatic necrosis	Ethanol		
Other medications: aspirin, amoxicillin-clavulanate, azathioprine, infliximab, carbamazepine, captopril, tetracycline, zidovudine, dantrolene, herbal meds (kava), dapsone, diltiazem, statins, methimazole, MAOIs, methotrexate, nitrofurantoin, TCAs, phenothiazines, gold, propylthiouracil, isoniazid, rifampin, ketoconazole, methyldopa			

FHF fulminant hepatic failure, *NSAIDs* nonsteroidal anti-inflammatory drugs, *MAOIs* monoamine oxidase inhibitors, *TCAs* tricyclic antidepressants, *MDMA* 3,4-methylenedioxymethamphetamine, *PCP* phencyclidine, *TCE* trichloroethylene
[a]Not an all-inclusive list

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

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

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)

- 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 if there is active bleeding or 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.
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