Hepatic Hell: Acute Liver Failure causes and management **Twitter/Instagram: @emboardbombs**

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Introduction

Acute liver failure: some type of severe liver injury leads to near-immediate failure of the synthetic function of the liver with a high risk of permanent liver infarction and mortality. There are 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, NASH etc) are 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 drives management decisions.

Grade	Encephalopathy	Asterixis	EEG
I	Mild confusion/slurred speech	variable	usually normal
II	Moderate confusion/lethargy	yes	Abnormal
III	Marked confusion/incoherent	yes	Abnormal
IV	Coma	no	Abnormal

Presentation

Nonspecific symptoms and signs. Lethargy, anorexia, nausea/vomiting, pruritus, jaundice, abdominal distention, RUQ pain, mental status changes.

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

GENERAL MANAGEMENT

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

Workup: the obvious liver studies- CMP, PT/PTT/INR, CBC, and ABG. Serial fingerstick glucoses are important because hypoglycemia can be a cause of altered mental status given the liver's inability to provide stress hyperglycemia.

Patients should be monitored and treated for hypoglycemia, hypokalemia, and hypomagnesemia. Worsening ALF and worsening prognosis is indicated by rising bilirubin & PT/INR.

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 will be unable to metabolize the lactate and therefore it will worsen the patient's acidosis). If the patient is already severely acidotic, one can use ½ -NS with 75 mEq/L Na bicarbonate. There is no right answer here- these patients are usually very sick and any volume resuscitation can be helpful, although one must be cautious due to high risk of volume overload from venous congestion and low oncotic 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.

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

Bleeding prevention: Patients with ALF can develop severe coagulopathy. Interestingly, 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. 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 fluoroquinolone. Gram negative and anaerobe coverage is needed.

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 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 (both used

more for chronic liver failure). Neomycin is nephrotoxic, thus avoid. If the need arises, intubate patient before administering lactulose, especially patients who are unable to maintain their airway protection and there is concern for aspiration.

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.

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

If concern for increased ICP and Cushing triad, prophylactic administration of 3% hypertonic saline (in grade IV encephalopathy, and patients with ammonia >150 micromol/L should be performed.

Treatment 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, use sedatives with anti-seizure activity. First line: phenytoin, second line is short activating benzodiazepines. Prophylaxis with an AED is not recommended.

INTERVENTION FOR SOURCE OF ALF (SEE NEXT PAGE)

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Acetaminophen toxicity: #1 cause of ALF in the USA

The recommended max dose of acetaminophen is 4g/day but this can be toxic in people with underlying liver damage. It is a dose-related toxin, and most ingestions leading to ALF exceed 10 gm/day. Findings: very high ALT/AST

Tx: if ingestion within ~4hr of presentation, activated charcoal (standard dose of 1gm/kg) may be useful for GI decontamination. N-acetylcysteine (NAC), has been shown to be effective as late as 48 hrs of ingestion. The standard acetaminophen toxicity nomogram may aid in determining the likelihood of serious liver damage; regardless, have a low threshold to start NAC. Controversy exists over when to stop use of NAC, after 72 hrs or until LFTs normalize? Coordinate with your local poison control center.

Viral hepatitis: #2 most common cause of ALF in the USA

Hepatitis A is the most common cause of viral hepatitis; HBV is a close second. HCV and HDV are not significant causes of ALF unless coinfection with HBV. IVDU is the #1 risk factor for all (except Hep A). Hep E ALF is mainly significant in infection of pregnant women.
Consider HSV1, HSV2, VZV, CMV, EBV, & adenovirus mostly in immunocompromised px.

DX: viral serology
TX: ALF from Hepatitis A/E treated with supportive care. Patients with known or suspected herpes virus or varicella ALF should be treated with acyclovir (5-10 mg/kg IV every 8 hours).

Wilson's Disease

History young patient (rarely >20 years old) with no predisposition to hepatic injury, with history of anemia, kidney issues, parkinsonian/psychiatric issues.

Dx: ceruloplasmin (low), serum and urinary copper levels (high), slit lamp examination for Kayser-Fleischer rings, and total bilirubin (high) to alkaline phosphatase (low) ratio (>2.0, quick, reliable way for screening Wilson). Coombs negative hemolytic anemia. *These patients must be promptly considered for transplant*. In the acute setting, while awaiting transplant, dialysis and/or plasmapheresis will be needed. Penicillamine has not been shown to be as effective in the acute setting.

Autoimmune hepatitis

History: family history of autoimmune diseases, most commonly in females, 30s-40s.

Dx: autoantibodies (anti LKM-1, anti SMA, ANA)
Tx: prednisone starting at 40-60 mg/day. Do not wait for steroid to take effect- plan for possible transplant as indicated.

Increased INR (≥ 1.5)
Change in mental status
Less than <26 weeks

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Acute Liver failure

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Initial labraoty analysis	
Prothrombin time/INR	Acetaminophen level
CMP	Toxicology screen
Amylase/ lipase	Ceruplasmin level
ABG	Pregnancy test
Arterial lactate	
Arterial ammonia	Type and Screen
CBC	
viral serologies	

↓

Indeterminate Etiology When the etiology of ALF cannot be determined after routine evaluation, biopsy using a transjugular approach may be helpful (helps with diagnosing malignant infiltration, autoimmune hepatitis, certain viral infections, Wilson disease). The lack of a clear diagnosis suggests that the history may have been inadequate regarding toxin or drug exposures.

N-acetylcysteine — NAC is used for the tx of acetaminophen toxicity, but it may be beneficial in other forms of acute liver failure and to patients with an indeterminate cause of ALF.

Acute Ischemic Injury "shocked liver"

History after any period of significant hypovolemia/hypotension. Source: CHF (relative hypovolemia), traumatic injury, cardiac arrest. There will likely be evidence of multi-organ ischemia

Dx: very high AST/ALT, high LDH, EKG, ECHO
Tx: fluid resuscitation +/- blood products if trauma, maintaining MAP >65.

Drug induced Liver injury

History A careful drug/herbal history should include listing of all agents taken, the time period involved, and quantity ingested. *Most drug hepatotoxicity occur within the first 6 months after drug initiation.* A potentially hepatotoxic medication that has been used continually >1 year is unlikely to cause de novo liver damage.

Drugs other than acetaminophen rarely cause dose-related toxicity.
Tx: corticosteroids are not indicated unless a drug hypersensitivity such as DRESS or an autoimmune reaction is suspected. NAC may be beneficial.

Drugs that my cause ALF	
Abacavir	Amiodarone
Didanosine	Valproic acid
Efavirenz	Phenytoin
Ciprofloxacin	Carbamazepine
Nitrofurantoin	Isoflurane
Doxycycline	Tolcapone
Augmentin	Imipramine
Allopurinol	Methyldopa
Etodolac	Labetelol
Sulfasalzine	Propylthiouracil
Gemtuzumab	Statin
Diclofenac	Cocaine
Rifampin	Nicotinic acid
Isoniazid	MDMA
Dapsone	**herbal supp**
Pyrazinamide	Kava Kava
Itraconazole	Herbalife
Ketoconazone	hydrocut
Terbinafine	Comfrey

Amanita phalloides

History: recent mushroom ingestion/ recent camping, presenting w/ *delayed onset* of severe GI symptoms.

Tx: If early: gastric lavage and activated charcoal via NG tube. Consider administration of N-acetylcysteine. Discuss transplant.

Budd-Chiari

History of hypercoagulable state (Polycythemia vera, Waldenstrom, malignancy).
Exam: rapid onset of abdominal distention pain, ascites & hepatomegaly

Dx: ultrasound with Doppler, CT.
Tx: venous decompression but discuss transplant

Malignant infiltration

History of breast or lung cancer, lymphoma, melanoma, myeloma and other malignancies
Exam: hepatomegaly

Dx: CT and/or biopsy
Tx: appropriate for underlying malignancy.

Acute Fatty Liver of Pregnancy/HELLP

History/Exam: pregnancy, abdominal tenderness, bleeding, hypertension, vision changes.

Dx: Hemolysis, elevated liver enzymes, low platelets
Tx: expeditious delivery of the infant. Magnesium sulfate and blood pressure control until then. Transplantation may need to be considered if hepatic failure does not resolve quickly following delivery