



## EM CASES SUMMARY

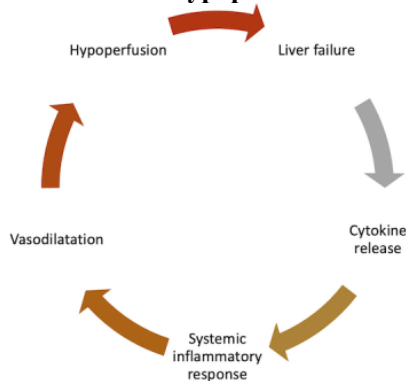
### Episode 148 Liver Emergencies Part 1: Acute Liver Failure, Hepatic Encephalopathy, Hepatorenal Syndrome, Liver Test Interpretation & Drugs to Avoid

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#### Acute Liver Failure

Patients with acute liver failure in the ED may progress to multiorgan failure unless treatment is initiated early. The cytokine release in liver failure and necrosis kicks off a systemic inflammatory response, causing vasodilation and **hypoperfusion**.



Patients with liver cirrhosis have an increased susceptibility to **bacterial infections** due to a compromised immune system, **portal hypertension** due to increased portal venous flow and hepatic resistance, **thrombosis** due to complex alterations in the coagulation factors and hypoalbuminemia, and **bleeding** due to portal hypertension as well as complex alterations in the coagulation factors. Liver patients may have decreased gluconeogenesis (leading to **hypoglycemia**), decreased lactate clearance (leading to **metabolic acidosis**) and decreased ammonia clearance (leading to **hyperammonemia**). All of these need to be considered in the ED management of patients with acute liver failure.

#### **Triggers for decompensation in patients with liver disease: Search carefully for infections**

**Infections** are a common high-risk trigger for acute liver failure in patients with chronic liver disease and may present in a subtle manner, similar to the immunocompromised patient. It is therefore incumbent upon the emergency physician to conduct a thorough search for underlying infection in the sick liver patient. **Pneumonia, ARDS and sepsis** are the most common diagnoses of ESLD patients admitted to ICU. These patients are also at high risk for **urinary tract infections, C. Diff and spontaneous bacterial peritonitis**. Have a low threshold to treat for sepsis on speculation.

Other common triggers include ongoing **alcohol use, acetaminophen overdose, adverse drug effects, trauma, GI bleed and electrolyte disturbances**. Common vague triggers include **constipation** (decreased gut transit time increases ammonia levels) and **malnutrition**.

#### **Causes of acute liver failure in the absence of known liver disease**

**Hepatic ischemia** from any shock state (“shock liver”) is a common cause of acute liver failure in the ED where treatment is aimed at the underlying cause of shock.

**Common disease states that cause fulminant acute liver failure** that should be considered in the ED:

- Acetaminophen toxicity
- Drug induced liver injury
- Viral hepatic diseases
- Autoimmune diseases
- Mushroom toxicity
- Wilson’s disease

***Pearl:** As recommended by The Association for the Study of Liver Diseases, draw an acetaminophen level on all patients with acute liver failure (recognizing that a “therapeutic” level does not rule out acetaminophen toxicity) and have low threshold for starting NAC in those suspected of acetaminophen toxicity*

**Misconception:** a common misconception is that patients with acute liver failure will be jaundiced. Jaundice may not be present despite severe decompensated acute liver failure.

## **Treatment of Acute Liver Failure in the ED**

**Hypoperfusion/vasodilatation** – our experts recommend **blood products** for the bleeding patient in shock, **fluid resuscitation with normal saline** for the non-bleeding liver failure patient, and to consider **IV albumin** in patients with hepatorenal syndrome, hepatic encephalopathy and low albumin, post-paracentesis >5L and bacterial peritonitis.

**Bacterial infections** – have a low threshold for initiating **antibiotics** in patients with acute liver failure suspected of infection as a trigger.

**Hypoglycemia** – a common pitfall in managing acute liver failure patients in the ED is the inadequate treatment of hypoglycemia.

Maintaining normal glucose levels can help prevent starvation ketosis, ketoacidosis and lactic acidosis. One bolus of 50% dextrose may not be adequate therapy because of depleted glycogen stores; **maintenance infusions of D10W or D25W** should be administered after the D50W bolus.

**Hyperammonemia** – ammonia levels are unreliable and may be misleading; patients with acute liver failure and hepatic encephalopathy should be presumed to have elevated ammonia levels and be treated with lactulose and/or PEG and rifaximin accordingly

## **Demystifying Liver Enzymes and Liver Function Tests in Liver Emergencies**

**Liver enzymes** (AST, ALT, ALP, GGT) and liver function tests – **LFTs** (INR, PTT, albumin, bilirubin) are terms that are often mistakenly used interchangeably. Simply put, the main difference between *liver enzymes* and *LFTs* is that the former is a measure of the degree of cell death/damage to the liver, whereas the latter involves the *synthetic capability of liver* – liver metabolism.

### **Liver enzymes**

Insults to hepatocytes lead to necrosis and cause elevated transaminases. ALT is most specific for liver disease. ALP is found in bone and liver and is usually elevated in obstructive biliary disease. An elevated GGT that is proportional to an elevated ALP can help distinguish liver disease from bone disease.

The degree of elevation of liver enzymes can help guide the differential diagnosis:

- Mild elevation: up to 5 x of normal – fatty liver, end-stage liver cirrhosis, infiltrative liver disease
- Moderate elevation: 5-10 x of normal – alcohol related liver disease, chronic hepatocellular and cholestatic disease
- Severe elevation: >15 x of normal – acute liver failure including viral hepatitis, acetaminophen toxicity, shock liver, HELLP

The commonly known ratio of 2:1 AST:ALT is suggestive of alcoholic liver disease, with the caveat that other conditions such as NASH, hepatitis C and rhabdomyolysis may have a similar liver enzyme ratio.

**Pearl:** in cholestasis, the first enzyme to increase is often ALT, which occurs prior to the elevation of ALP.

Liver Disease Class	AST and ALT Levels	ALP Levels	Bilirubin Levels	Albumin Levels	Prothrombin Time
Acute Hepatocellular Conditions	Highly elevated	Normal to elevated to < 3 times ULN	elevated	Normal	Usually normal; INR > 1.5 indicates severe injury
Chronic Hepatocellular	Moderately elevated	Normal to elevated to < 3 times ULN	Normal or elevated	Normal or decreased	Normal or prolonged (will not correct with parenteral vitamin K administration)
Acute Cholestatic	Normal to highly elevated	Normal to elevated	Normal to elevated	Normal	Normal
Chronic Cholestatic	Normal to moderately elevated	Elevated > 4 times ULN	Elevated	Normal or decreased	Normal or prolonged, (may correct with vitamin K administration)
Infiltrative	Normal to mildly elevated	Elevated > 4 times ULN	Normal to mild elevations	Normal	Normal to mild changes

Adapted from: Woreta TA, Alqahtani SA. Evaluation of abnormal liver tests. Med Clin North Am. 2014;98(1):1-16.

## LFTs

**Albumin** – hypoalbuminemia is found not only in patients with liver disease, but also in those with nephrotic syndrome, protein losing enteropathy, heart failure and malnutrition.

**INR** – while the INR is elevated in many patients with liver disease and may help to predict prognosis, a liver patient with an elevated INR is not necessarily at increased risk for bleeding, and an elevated INR in a liver patient does not rule out the possibility of thrombosis

**Bilirubin** – serum conjugated bilirubin level does not become elevated until the liver has lost 50% of its excretory capacity; while an elevated bilirubin may suggest poor liver function it cannot distinguish between hepatocellular, cholestatic, or infiltrative liver disease and may be normal or elevated in each

**MELD score** stratifies severity of end-stage liver disease for transplant planning and includes Creatinine, INR, bilirubin, sodium and renal replacement therapy. It has poor sensitivity, but its constituents are useful in the ED to get a general sense of severity of disease.

## ED Medications to Adjust or Avoid in Liver Patients and Liver Emergencies

Susceptibility to adverse effects from medications increases with worsening liver function. In general, try to avoid **sedative drugs** (benzodiazepines, opioids, antihistamines, antiemetics) in patients with severe liver disease.

### Opioids

No opioid is ideal in the liver patient. Morphine has toxic metabolites that may accumulate in liver patients; hydromorphone has impaired elimination. If opioids are required, our experts recommend IV fentanyl in the ED and oral hydromorphone at lower doses with longer time in

between doses (e.g. hydromorphone 0.5mg po q8h) after discharge. Consider IV ketamine as an alternative to opioids for analgesia in the liver patient in the ED.

### **Acetaminophen**

A common misperception is that acetaminophen is strictly contraindicated in all liver patients. In those with *mild* liver disease, it is generally safe to prescribe acetaminophen at a lower dose (500mg q6h, max 2g daily). Acetaminophen should be avoided in patients with severe liver disease and those with active alcohol use.

### **NSAIDs**

- NSAIDs can cause renal impairment and even lead to hepatorenal syndrome in liver patients in addition to triggering GI bleeding
- NSAIDs should be avoided in patients with cirrhosis and in patients with acute liver failure, but can be considered in low doses/short courses in patients with mild liver disease

### **Benzodiazepines**

Benzodiazepines should generally be avoided in patients with severe liver disease and dosages should be lowered in those with mild liver disease. Patients with even mild hepatic encephalopathy are very sensitive to GABAergic medications. The exception, of course, is alcohol withdrawal. Lorazepam is the benzodiazepine of choice for alcohol withdrawal in patients with severe liver disease – see [Episode 87 Alcohol Withdrawal & Delirium Tremens](#) for details.

### **Antiepileptic medications**

Carbamazepine and valproate are contraindicated in patients with severe liver disease and phenytoin should be used with caution. Expert opinion dictates that if ALT values exceeding 5x the upper limit of normal (or lesser elevations associated with any rise in bilirubin or any associated symptoms of hepatitis), phenytoin should be discontinued. The

antiepileptic medication of choice in patients with liver disease is levetiracetam.

### **Antiemetics**

Sedating antiemetics should be avoided in patients with severe liver disease. Metoclopramide and ondansetron require significant dose reduction in patients with cirrhosis.

### **Antibiotics**

While most antibiotics are safe in liver patients, macrolides, ciprofloxacin, nitrofurantoin, trimethoprim-sulfamethoxazole should be avoided in liver patients, and amoxicillin/clavulanic acid can cause liver failure even when taken at therapeutic doses.

### **Cardiac medications**

Medications such as beta-blockers, diltiazem and amiodarone are metabolized through first-pass metabolism. If starting these medications, start low, go slow.

***Pearl:** if prescribing a drug that may be constipating, consider starting a laxative empirically to decrease transit time in the GI tract and minimizing the risk of hepatic encephalopathy*

### **Antibiotics to avoid in liver patients**

- Patients with hepatic encephalopathy have excess GABA stimulation, so they are very sensitive to GABAergic medications (e.g. benzodiazepines or barbiturates).
- Administration of benzodiazepines or barbiturates to a patient with hepatic encephalopathy risks inducing a prolonged stuporous/comatose state.

## Hepatic Encephalopathy: A Diagnosis of Exclusion

**Step 1: Rule out other causes of altered level of awareness (LOA)** including sepsis, renal failure, alcohol withdrawal and subdural hematoma.

**Step 2: Assess for and address common precipitants of hepatic encephalopathy** which include:

- Medications – noncompliance/use of diuretics/benzodiazepines
- GI bleeding
- Hypokalemia
- Alkalosis
- Volume depletion
- Sepsis

**Step 3: Make the diagnosis**

- After excluding other causes of altered LOA look for **asterixis** (nonspecific – also seen in renal failure) and signs of cirrhosis
- **Diurnal sleep pattern reversal** may help support a diagnosis of hepatic encephalopathy
- In general, the more altered the patient is, the more severe the disease

**Step 4: Correct presumed hyperammonemia (without the need for a serum ammonia level)**

- **Lactulose** 20 g (30mL) po, titrated to 3 to 4 soft stools per day (reduces mortality, serious complications)
- If patient is NPO, **Polyethylene glycol (PEG)** via NG tube 4L over 4 hours (more rapid resolution of hepatic encephalopathy

compared to lactulose in 2 small RCTs) or **lactulose enema** with 1–3 L of 20% solution

**Step 5: Replace fluid and glucose deficits**

- NS is our experts' crystalloid of choice for fluid replacement in hepatic encephalopathy
- Consider **albumin** in patients with low serum albumin given some weak RCT evidence that it may improve outcomes in hepatic encephalopathy
- One bolus of 50% dextrose may not be adequate therapy for hypoglycemia because of depleted glycogen stores; **maintenance infusions of D10W or D25W** should be administered after the D50W bolus

**Step 6: Treat even the mildest hypokalemia**

- **Hypokalemia** contributes to hyperammonemia by decreasing ammonia excretion; correcting hypokalemia is thought to decrease ammonia levels in patients with hepatic encephalopathy

**Step 7: Assess for and treat cerebral edema**

- **Cerebral edema** is the most common cause of death in patients with hepatic encephalopathy due to the rapid accumulation of ammonia
- Cerebral edema may be clinically subtle; if suspected, keep the head of the bed elevated at 45 degrees and consider hypertonic saline (20 ml of 30% NaCl targeting a serum Na level between 145-150 mmol/L)

**Step 8: Consider refaximin**

- **Rifaximin** 400-550 mg po daily – this antibiotic is not absorbed through the gut, eradicates *E. Coli* which produces ammonia, and is used for long term maintenance of patients with recurrent hepatic encephalopathy

***Pearl:** Diurnal Sleep Pattern Reversal: Could it be Hepatic Encephalopathy? This can present with a patient who may be up all night and sleeping during the day. It is not 100% sensitive or specific for the diagnosis but may help support a diagnosis of hepatic encephalopathy.*

### **The myth of ammonia**

The #1 recommendation by [Choosing Wisely Canada – Hepatology](#) is “don’t order serum ammonia to diagnose or manage hepatic encephalopathy”. Elevated ammonia levels do not add diagnostic or prognostic value in liver patients suspected of hepatic encephalopathy. Encephalopathy can precede the rise in ammonia levels.

***Pitfall:** a common pitfall is ruling out hepatic encephalopathy with a normal ammonia level; ammonia levels can be normal or near-normal in hepatic encephalopathy; as such they can be misleading*

***Pearl:** a trick to eliciting asterixis in a patient who is unable to follow commands involves placing their forearm on the stretcher and forcibly dorsiflexing the wrist to bring out asterixis*

### **Hepatorenal Syndrome: Another Diagnosis of Exclusion**

Hepatorenal Syndrome carries a mortality rate of >50% in the absence of liver transplant. It is a **diagnosis of exclusion**.

It is difficult to diagnose Hepatorenal Syndrome in the ED because the diagnostic criteria include:

1. Cirrhosis with ascites
2. Creatinine > 132 umol/L

3. No improvement in serum Creatinine after 2 days of diuretic withdrawal and albumin volume expansion
4. Absence of shock
5. Absence of nephrotoxic medications
6. No parenchymal renal disease (no proteinuria > 500 mg/day, microhematuria, or renal US abnormality)

Patients typically have **decreased urine output, elevated creatinine, low urine sodium, and no/little urine sediment**.

Many liver patients are on diuretics which may alter sodium excretion. While low urine sodium is typical in hepatorenal syndrome, it can only be interpreted accurately after several days of discontinuation of diuretics, long after the patient has left the ED.

**Clinical clue:** suspect Hepatorenal Syndrome in a patient with liver disease in whom volume status does not improve with fluids or albumin

**Beware:** the excessive use of diuresis, underuse of albumin and underperformance of paracentesis increase the risk of Hepatorenal Syndrome

### **ED Management of Hepatorenal Syndrome**

- This is a complex disease – get help from your ICU and GI colleagues
- Avoid give diuretics and benzodiazepines
- Replace low serum albumin with IV **albumin** 1.5 g/kg
- Manage hypotension aggressively as these patients are significantly vasodilated; consider **norepinephrine**
- Discuss giving **octreotide** and/or **midodrine** with admitting physician
- Consider if patient is a liver transplant candidate based on the [MELD score](#)

## Take home points for Liver Emergencies: Acute Liver Failure, Hepatic Encephalopathy, Hepatorenal Syndrome, Liver Test Interpretation & Drugs to Avoid

- Have a low threshold to order acetaminophen levels in the sick liver patient
- Sepsis is a common trigger of acute liver failure and may be subtle – when in doubt, treat on speculation
- ED medications requiring dose adjustment or avoidance in the liver patient: NSAIDs, opioids, acetaminophen, benzodiazepines, antiepileptics (except levetiracetam), macrolides, B-blockers, amiodarone
- Watch out for hypoglycemia in sick liver patients and start an infusion of D10W after you have corrected the hypoglycemia
- Serum ammonia levels are unreliable and can be misleading; assume high ammonia levels in the patient suspected of hepatic encephalopathy and treat with lactulose and/or polyethylene glycol and rifaximin
- IV albumin needs to be considered in the patient with acute liver failure, hepatorenal syndrome and hepatic encephalopathy
- Have a low threshold to treat for hepatic encephalopathy and hepatorenal syndrome on speculation as they are both diagnoses of exclusion
- Some patients with hepatic encephalopathy will develop cerebral edema and this may be subtle; keep the head of bed at 45 degrees and give hypertonic saline if there are any clinical signs of cerebral edema

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