Critical hepatic encephalopathy

November 9, 2016 by Josh Farkas

**CONTENTS**

- **Introduction** ([#introduction](#introduction))
- **Clinical features** ([#clinical_features_of_hepatic_encephalopathy](#clinical_features_of_hepatic_encephalopathy))
- **Diagnosis**
  - Labs ([#laboratory_studies_don't_really_help](#laboratory_studies_don't_really_help))
  - Hepatic encephalopathy vs. EtOH withdrawal ([#hepatic_encephalopathy_versus_alcohol_withdrawal](#hepatic_encephalopathy_versus_alcohol_withdrawal))
  - Diagnostic approach ([#diagnostic_approach](#diagnostic_approach))
- **Causes & evaluation of cause** ([#causes_&_evaluation_of_cause](#causes_&_evaluation_of_cause))
- **Treatment**
  - Cathartic ([lactulose_and/or_polyethylene_glycol](#lactulose_and/or_polyethylene_glycol))
  - Rifaxamin ([#rifaxamin](#rifaxamin))
  - Manage triggers & coexisting problems ([#manage_triggers_&_coexisting_problems](#manage_triggers_&_coexisting_problems))
  - Avoid sedatives like the plague ([#avoid_sedating_medications_like_the_plague](#avoid_sedating_medications_like_the_plague))
  - Nutritional support & gut access ([#nutritional_support_&_gut_access](#nutritional_support_&_gut_access))
  - Treatments of desperation ([#treatments_of_desperation](#treatments_of_desperation))
- **Checklist** ([#checklist](#checklist))
- **Podcast** ([#podcast](#podcast))
- **Questions & discussion** ([#questions_&_discussion](#questions_&_discussion))
- **Pitfalls** ([#pitfalls](#pitfalls))
what this chapter is about

- Severe hepatic encephalopathy – stupor or coma requiring ICU admission.
- Hepatic encephalopathy in the context of chronic cirrhosis: This shouldn't be confused with encephalopathy due to acute hepatic failure, a more malignant process requiring different treatment (which will be discussed in the chapter on acute hepatic failure).

overall philosophy for the patient intubated due to severe hepatic encephalopathy

- The overall prognosis of these patients is generally quite poor, unless they are candidates for hepatic transplantation.
- Discussions regarding prognosis and goals of care should be pursued with the patient’s family.
- Generally, an organized and aggressive strategy can be successful in waking up the patient sufficiently to extubate.
  - Although the long-term prognosis is usually poor, in the short term these patients can often survive their ICU course.
  - For patients with true hepatic decompensation and acute-on-chronic liver failure, the outlook is worse.

clinical features of hepatic encephalopathy

overall presentation: delirium

- Non-focal, metabolic delirium with symptoms ranging from subtle alterations of consciousness to frank coma.
- Overall this may present similarly to other forms of delirium. However, it tends to cause more of a hypoactive form of delirium (rather than hyperactive delirium).

clues to hepatic encephalopathy as the etiology of delirium

- (1) Asterixis
  - Defined as the inability to maintain a stable posture. When asked to hold hands outstretched, this generates a “flapping tremor” (video below).
  - Hallmark of hepatic encephalopathy, but also seen in other metabolic derangements (including uremia, hypercapnia, and hypoglycemia).
  - May be lost in the most severe stages of hepatic encephalopathy (e.g. coma).
  - Hyperreflexia and clonus may also occur.
- (2) Cirrhosis may lead to respiratory alkalosis due to an increased respiratory drive. This can be a useful clue to hepatic encephalopathy for a patient intubated due to hypoactive delirium.
- (3) Prior history of hepatic encephalopathy
  - Patients often have recurrent episodes.

Laboratory studies don't really help

liver function tests

- Will generally be abnormal, reflecting underlying cirrhosis.
Hepatic encephalopathy can occur with normal liver tests.

- Unfortunately, liver tests aren't tremendously sensitive to cirrhosis.

ammonia level

- The use of ammonia to diagnose hepatic encephalopathy in the context of chronic liver disease is controversial (ammonia is far more useful in acute liver failure).
- Ultimately the evidence just doesn't support the use of this test (25117134, 28786433).
- Some patients can have hepatic encephalopathy with normal ammonia levels.
- Other patients may have elevated ammonia levels without hepatic encephalopathy.

CHOOSING WISELY®: THINGS WE DO FOR NO REASON

Ammonia Levels and Hepatic Encephalopathy in Patients with Known Chronic Liver Disease

Jacob Niran, MD**, Leonard Feldman, MD, SHFM, FACP, FAAP

1Department of Hospital Medicine, Mayo Clinic Health Systems, La Crosse, Wisconsin; 2Johns Hopkins School of Medicine, Baltimore, Maryland.

RECOMMENDATIONS

- HE is a diagnosis of exclusion and is made on clinical grounds.
- Do not check serum ammonia levels in patients with CLD to diagnose HE, to assess the severity of HE, or to determine whether HE is resolving.

CONCLUSION

The attraction of the ammonia theory to explain HE continues to lead physicians to check and follow blood ammonia levels in patients with CLD and suspected HE. However, ammonia measurement, as in the clinical vignette, should be replaced by a thorough clinical evaluation to rule out other causes for altered mental status. Serial exams of the patient should guide management, not ammonia levels.

hepatic encephalopathy versus alcohol withdrawal

Occasionally, in a patient with cirrhosis due to alcoholism there will be a question of sorting out hepatic encephalopathy versus alcohol withdrawal. These are fundamentally nearly opposite pathologies:

<table>
<thead>
<tr>
<th>Hepatic encephalopathy vs. alcohol withdrawal</th>
<th>Alcohol withdrawal</th>
<th>Hepatic encephalopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathophysiology includes...</td>
<td>- Neuronal damage due to excessive stimulation of GABA receptors</td>
<td>- Excessive activity of inhibitory GABA receptors by various toxins</td>
</tr>
<tr>
<td>Typical clinical presentation to ICU</td>
<td>- Agitated delirium</td>
<td>- Hypertensive delirium</td>
</tr>
<tr>
<td>- Seizure(s)</td>
<td></td>
<td>- Somnolence, coma</td>
</tr>
<tr>
<td>Epidemiology</td>
<td>- Occurring within days of EOGH cessation</td>
<td>- Often not seen due to drinking significant EOGH, may have stopped drinking or been sent home</td>
</tr>
<tr>
<td>- History of prior episodes of withdrawal upon cessation of alcohol.</td>
<td></td>
<td>- History of prior episodes of hepatic encephalopathy</td>
</tr>
<tr>
<td>Physical examination</td>
<td>- Generalized ongoing tremor</td>
<td>- Asterixis (&quot;flapping tremor&quot;)</td>
</tr>
<tr>
<td>- Hypertension</td>
<td>- History of prior episodes of withdrawal</td>
<td></td>
</tr>
<tr>
<td>- Visual hallucinations</td>
<td>- May cause somnolence.</td>
<td></td>
</tr>
<tr>
<td>Response to low-dose benzodiazepine</td>
<td>- May have minimal effect (patients generally resistant to benzodiazepines)</td>
<td></td>
</tr>
</tbody>
</table>

Generally, this differentiation can be made on the basis of a thoughtful history and physical examination. The importance of an accurate drinking history cannot be over-emphasized (many patients will have a history of "alcoholism" in their electronic medical records despite having stopped drinking).

Be careful about over-diagnosing patients with alcohol withdrawal, because the treatment for alcohol withdrawal can be disastrous in a patient who actually has hepatic encephalopathy:

- 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 is a challenging diagnosis for two reasons

- #1: There is no test which can prove the presence of hepatic encephalopathy.
  - The closest we have to a definitive “test” for hepatic encephalopathy is improvement following therapy – but even this isn't 100% specific. Many forms of metabolic encephalopathy will improve with supportive care.
- #2: Hepatic encephalopathy may often coexist with other causes of delirium.
  - As with ICU-acquired delirium, patients with hepatic encephalopathy often have multifactorial delirium.
  - Thus, discovering one cause of delirium (e.g. hyponatremia) doesn't necessarily exclude coexisting hepatic encephalopathy.

general approach

- Patients should be approached with a broad differential diagnosis, as outlined in the chapter on delirium https://emcrit.org/ibcc/delirium/.
- Particular attention should be given to the following differential diagnostic possibilities:
  - Subdural hematoma (may present without localizing findings)
  - Infection (including meningitis or encephalitis)
  - Hypoglycemia
  - Alcohol intoxication or withdrawal; Wernicke's encephalopathy
- Ultimately, hepatic encephalopathy is a diagnosis of exclusion.

empiric therapy

- The treatments for hepatic encephalopathy are fairly benign.
- In situations of diagnostic uncertainty, a reasonable approach is to empirically treat for hepatic encephalopathy (while continuing to evaluate for alternative causes of delirium).

causes & evaluation of cause

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics/dehydration (case n)</td>
<td>36</td>
<td>-</td>
<td>29</td>
<td>39</td>
<td>-</td>
<td>104</td>
</tr>
<tr>
<td>Constipation (case n)</td>
<td>22</td>
<td>23</td>
<td>19</td>
<td>8</td>
<td>94</td>
<td>1</td>
</tr>
<tr>
<td>Electrolyte disturbance (case n)</td>
<td>-</td>
<td>12</td>
<td>10</td>
<td>4</td>
<td>39</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal haemorrhage (case n)</td>
<td>-</td>
<td>28</td>
<td>27</td>
<td>6</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Infections (case n)</td>
<td>25</td>
<td>40</td>
<td>43</td>
<td>10</td>
<td>57</td>
<td>1</td>
</tr>
<tr>
<td>Total preceding events/total points</td>
<td>83/96</td>
<td>103/120</td>
<td>99/120</td>
<td>57/50</td>
<td>241/193</td>
<td>4/20</td>
</tr>
</tbody>
</table>

Infection is a common trigger of hepatic encephalopathy, contributing to nearly a third of cases. In patients without an obvious trigger, consider further evaluation for infection

(Nardelli 2018 PMID 29705917)

precipitating factors

- Most common
  - #1 = Infection (delirium can be the presenting symptom)
    - Spontaneous bacterial peritonitis
    - Urinary tract infection
    - Pneumonia
  - GI bleed
  - Nonadherence with lactulose or rifaxamin (or constipation)
  - Volume depletion (e.g. over-diuresis)
  - Electrolyte abnormalities (especially hyponatremia or hypokalemia)
  - Renal failure (including hepatorenal syndrome)
Deleriogenic medications

- Less common
  - Transhepatic intravascular portosystemic shunt (TIPS), or spontaneous portosystemic shunts.
  - Hepatic or portal vein thrombosis

**basic evaluation for etiology (appropriate in most patients)**

- Basic labs (electrolytes, liver function tests)
- Paracentesis if substantial ascitic fluid on bedside ultrasonography
- Chest X-ray
- Urinalysis and possibly blood cultures

**advanced evaluation for etiology (consider based on context)**

- Lumbar puncture (may be challenge in context of coagulopathy)
- MRI of the brain
- EEG to exclude seizures
- Right upper-quadrant ultrasonography with Doppler to exclude hepatic vein or portal vein thrombosis (if acutely deteriorating hepatic function)

**cathartic (lactulose and/or polyethylene glycol)**

**lactulose**

- Traditionally the cornerstone of therapy for hepatic encephalopathy.
  - Promotes growth of non-ammonia-producing, benign bacteria (e.g. lactobacillus).
  - Numerous potential mechanisms (e.g., lowers the colonic pH which traps ammonia in the gut, laxitive agent).
  - Supported by reasonable amount of evidence ([27081787](https://www.ncbi.nlm.nih.gov/pubmed/27081787)).
- Aggressive dosing is needed, with an ultimate goal of achieving >4 bowel movements per day.
  - If the patient isn't having adequate bowel movements, then lactulose won't work.
  - Start at a high dose and then titrate downwards (e.g. 30 ml Q2hr until frequent bowel movements, then decrease to 30 ml Q6hr and titrate).
  - Typically, an intubated patient will require an orogastric tube.

**Lactulose enemas**

- Theoretically may be used in a patient without enteral access (one regimen is 300 ml lactulose in 700 ml water twice daily as a retention enema).

**polyethylene glycol**

- Polyethylene glycol (PEG) is an inert osmotic cathartic agent. It is widely used to prepare the colon prior to colonoscopy. When provided in a large volume of water, it induces minimal electrolyte shifts and is very safe (11246353).
Recently two RCTs found that polyethylene glycol was superior to lactulose, in terms of achieving more rapid resolution of hepatic encephalopathy (25243839, 30234645). One further study found that the addition of polyethylene glycol to lactulose also accelerated recovery (28316761).

Reasons that polyethylene glycol was superior to lactulose may include the following:

1. These studies used a standard pre-colonoscopy regimen of polyethylene glycol (~4 liters). This will undoubtedly cause more rapid and complete bowel evacuation compared to standard regimens of lactulose.
2. When diluted in large volumes of water, polyethylene glycol has little effect on electrolyte levels of volume status. In contrast, aggressive lactulose therapy will cause hypernatremia.

These studies are small, so it may be premature to conclude that polyethylene glycol is definitively superior to lactulose. The following conclusions may be reasonable at this point in time:

1. Bowel cleansing with large-volume polyethylene glycol is used widely on patients prior to colonoscopy and is accepted to be extremely safe.
2. Polyethylene glycol is a reasonable and evidence-based approach to treating hepatic encephalopathy that could be superior to lactulose. If polyethylene glycol is used, it should initially be administered with a large volume of water to avoid electrolyte shifts (e.g. using a standard 3-4 liter commercial preparation as is done prior to colonoscopy).
3. Polyethylene glycol may be used as add-on therapy for a patient who has been started on lactulose and isn't responding adequately.

For patients who are intubated or severely stuporous, dual therapy should immediately be initiated using a laxative (typically lactulose) plus rifaxamin.

Combination therapy with rifaximin plus lactulose has been shown to reduce length-of-stay, compared to lactulose monotherapy (23877348, 24849268).

Possible doses are 550 mg PO BID or 400 mg TID.

Manage triggers & coexisting problems

Hyponatremia

Mild to moderate hyponatremia is often seen upon admission (it's a common problem in the context of cirrhosis). This may sometimes function as a precipitating cause of hepatic encephalopathy.

Lactulose alone is generally a very effective treatment for both hyponatremia and also hepatic encephalopathy (more on this here).

- Lactulose is an osmotic cathartic agent, so it removes water from the body and increases the sodium concentration.
- Hypertonic saline is generally unnecessary in this situation (unless hyponatremia is uncommonly severe).

Hypernatremia

Commonly develops during treatment of hepatic encephalopathy as a side-effect of lactulose therapy.

Hypernatremia must be managed aggressively (with enteral water or IV D5W), otherwise it will contribute to the patient's encephalopathy and agitation.

More on hypernatremia management here.

Hypokalemia

Hypokalemia may increase ammonium reabsorption by the kidneys, potentially exacerbating hepatic encephalopathy.

(Of course, hypokalemia should be treated regardless.)

Renal support

Adequate renal function is essential to allow patients to clear toxins and emerge from encephalopathy.
Renal function should be supported aggressively (e.g. with avoidance of nephrotoxins or volume depletion).

- If the kidney starts failing, consider aggressive support as described in the chapter on hepato-renal syndrome.

### Avoid sedating medications like the plague

Patients with hepatic encephalopathy are often exquisitely sensitive to sedating medications (e.g. benzodiazepines, opioids, antipsychotics).

- For an intubated patient with hepatic encephalopathy, it is best to avoid any sedative or analgesic, except agents with extremely short half-lives (e.g., propofol or dexmedetomidine) ([19394004](https://www.ncbi.nlm.nih.gov/pubmed/19394004)).

  - Even small doses of a long-acting sedative may delay extubation.
  - One trick to facilitate extubation is to allow all other sedating medications to wash out of the patient.
  - Patients who are comatose due to hepatic encephalopathy are usually very sensitive to sedation, so they often don't require much propofol to achieve comfort (they are somnolent to begin with — that's their problem).

- For patients with stable cirrhosis, a total of two grams of acetaminophen daily may be used daily for analgesia.

- (If a patient with hepatic encephalopathy can't be rendered comfortable with low-dose propofol, it's probably time for extubation.)

### Nutritional support & Gut Access

**Nutritional Support**

- Intubated patients with hepatic encephalopathy should receive enteral nutrition just like any other intubated patient.
- Recent guidelines don't recommend restricting protein intake among these patients.

**Empiric thiamine for Wernicke's encephalopathy in alcoholism**

- Patients with alcoholism and cirrhosis may be at risk for Wernicke's encephalopathy.
- Differentiation of Wernicke's encephalopathy from hepatic encephalopathy is basically impossible.
  - There are no lab tests capable of doing this promptly.
  - Physical examination signs of Wernicke's encephalopathy (nystagmus, ataxia) may be absent in a comatose patient.
- If there is significant concern for Wernicke's encephalopathy, the safest thing is to treat empirically with thiamine (500 mg IV q8hrs).
  - IV thiamine is entirely safe.

**Place a small-bore nasal feeding tube prior to extubation**

- Patients will often be unable to take oral medications immediately following extubation due to somnolence. However, it is essential to continue lactulose and rifaximin therapy without interruption. Inability to give PO medications following extubation is a potential cause of relapse & reintubation.
• It may be easiest and best-tolerated to place a small-bore nasal feeding tube early in the patient’s course, while the patient is intubated. During extubation, care should be taken to remove the endotracheal tube while leaving the nasal feeding tube in place.

### treatments of desperation

Fundamentally, there are two causes of hepatic encephalopathy:

1. Hepatic dysfunction (blood flowing through the liver isn’t fully detoxified)
2. Shunting of blood around the liver

One approach to treatment of hepatic encephalopathy is to close any anatomic shunts which are allowing blood to bypass the liver. This may be done in the following ways

#### #1: ligation of TIPS (trans-hepatic intra-portal shunt)

- TIPS shunting may precipitate or worsen hepatic encephalopathy.
- In a patient with a TIPS shunt who has refractory hepatic encephalopathy, encephalopathy may be treated by closing the shunt entirely or revising it (to reduce its size).
- This is rarely done, because it would potentially aggravate other problems (e.g. the indication for the TIPS in the first place).

#### #2: ligation of anatomic shunts

- **Spontaneous** shunts may develop which allow portal blood to flow into systemic circulation, bypassing the liver. Some series suggests that spontaneous shunts are present in the majority of patients with refractory hepatic encephalopathy ([29705917](https://www.ncbi.nlm.nih.gov/pubmed/29705917)).
  - Shunt may be suggested by refractory hepatic encephalopathy which seems disproportionate to the degree of derangement in liver function tests and coagulation.
  - Spontaneous shunts may be found on CT scanning and ligated via interventional radiology. Unfortunately, shunt closure may increase portal pressures – which may promote the formation of ascites and/or variceal bleeding.

### checklist

Critical Hepatic Encephalopathy

- **Evaluation of cause**
  - Immediate fingerstick glucose
  - Basic labs (liver function tests, electrolytes including Ca/Mg/Phos)
  - Paracentesis if ascites present (to exclude SBP)
  - CT head if intracranial hemorrhage possible
  - Review medication list
  - Consider basic infection workup (e.g. chest X-ray, urinalysis, possibly blood cultures)
  - Consider: Lumbar puncture, MRI, EEG
- **Empiric therapy for Wernicke’s encephalopathy in alcoholism**
  - Empiric therapy: thiamine 500 mg IV q8hr
- **Core therapies for hepatic encephalopathy**
  - Cathartic: one or both of the following
    - Lactulose: Start 30 ml q2-4 hr; titrate to >4 bowel movements per day
    - Polyethylene glycol: 3-4 liters (same preparation as used prior to colonoscopy)
  - Rifaximin 550 mg BID (initiate immediately)
- **Avoid any long-acting neuroactive medications**
  - Review medication list and d/d heterogenic medications
- **For intubated patient:** Avoid any sedation or analgesia other than Propofol or dexmedetomidine
- **Aggressive treatments of any coexisting problems**
  - Follow electrolytes and treat abnormalities (especially sodium abnormalities).
  - Treat any coexisting renal failure (may include therapy for hepato-renal syndrome).
  - Treat any coexisting infection

Hepatic encephalopathy is a diagnosis of exclusion, so make sure to evaluate broadly for other problems. Ammonia levels aren’t reliable enough to guide clinical management. For patients with coma or stupor, don’t delay treatment with rifaxamin to wait until the lactulose fails — start both treatments up-front immediately. Make sure to treat any coexisting electrolyte disorders (especially lactulose-induced hypernatremia). Avoid sedative medications if possible (even benign-seeming medications like PRN opioids).

One-minute recap:

- Hepatic encephalopathy is a diagnosis of exclusion, so make sure to evaluate broadly for other problems.
- Ammonia levels aren’t reliable enough to guide clinical management.
- For patients with coma or stupor, don’t delay treatment with rifaxamin to wait until the lactulose fails — start both treatments up-front immediately.
- Make sure to treat any coexisting electrolyte disorders (especially lactulose-induced hypernatremia).
- Avoid sedative medications if possible (even benign-seeming medications like PRN opioids).
Going further:

- [Hepatic encephalopathy: Common precipitants, sneaky precipitants, and clinical pearls](http://www.emdocs.net/hepatic-encephalopathy-common-precipitants-sneaky-precipitants-and-clinical-pearls/) (Setareh Mohammadie and Amy Zeidan, emDocs)
- [Hepatic Encephalopathy in the ED](https://www.nuemblog.com/blog/hepatic-encephalopathy) (Daniella Ohnemus, NU EM blog)
- [5 pearls on hepatic encephalopathy](https://www.clinicalcorrelations.org/2017/12/13/core-im-podcast-5-pearls-on-hepatic-encephalopathy/) : John Hwang, Marty Fried, and Shreya Trivedi, Core IM podcast

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.