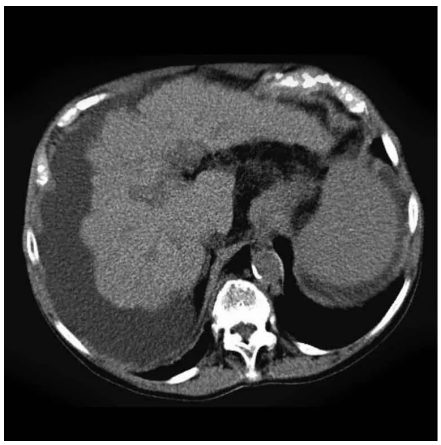
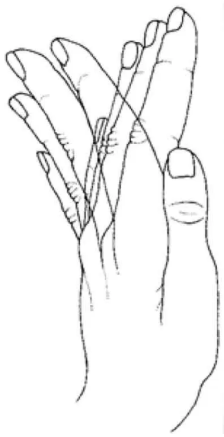
Search the site ...

The Internet Book of Critical Care

Critical hepatic encephalopathy

November 9, 2016 by Josh Farkas


CONTENTS

introduction

(back to contents) (#top)

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

(back to contents) (#top)

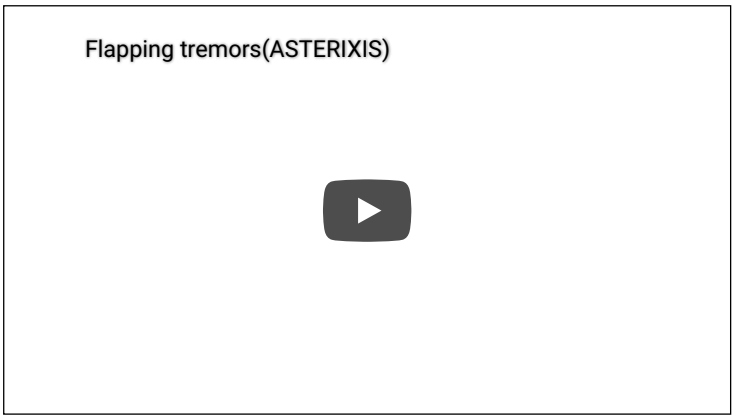
---

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

(back to contents) (#top)

---

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 (https://www.ncbi.nlm.nih.gov/pubmed/25117134), 28786433 (https://www.ncbi.nlm.nih.gov/pubmed/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 Ninan, MD[1]*, Leonard Feldman, MD, SHFM, FACP, FAAP[2]

[1]*Department of Hospital Medicine, Mayo Clinic Health Systems, La Crosse, Wisconsin;* [2]*Johns 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

(back to contents) (#top)

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:

Hepatic encephalopathy vs. alcohol withdrawal

	Alcohol withdrawal	Hepatic encephalopathy
Pathophysiology includes…	- *Neuroexcitation* due to inadequate stimulation of GABA receptors	- Excessive activity of inhibitory GABA receptors by various toxins
Typical clinical presentation to ICU	- Agitated delirium - Seizure(s)	- Hypoactive delirium - Somnolence, coma
Epidemiology	- Occurring within days of EtOH cessation - History of prior episodes of withdrawal upon cessation of alcohol.	- Often patients too sick to drink significant EtOH, may have stopped drinking in remote past (obtain a good history!) - History of prior episodes of hepatic encephalopathy
Physical examination	- Generalized ongoing tremor - Sympathetic activation (e.g. hypertension, tachycardia) - Visual hallucinations	- Asterixis ("flapping tremor")
Response to low-dose benzodiazepine	- May have minimal effect (patients generally relatively *resistant* to benzodiazepines).	- May cause somnolence.

The Internet Book of Critical Care, by @PulmCrit

(https://emcrit.org/wp-content/uploads/2016/11/againcirr.svg)

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.

diagnostic approach

(back to contents) (#top)

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

(back to contents) (#top)

Table 2. Published randomized controlled trials on episodic hepatic encephalopathy treatment

Precipitant(s)	Simon-Talero [5]	Sharma [6]	Sharma [7]	Rahimi [8]	Sidhu [9]	Bajaj [10••]	Total
Diuretics/dehydration (case n)	36	-	-	29	39	-	104
Constipation (case n)	22	23	19	8	94	1	167
Electrolyte disturbance (case n)	-	12	10	4	39	1	66
Gastrointestinal haemorrage (case n)	-	28	27	6	12	1	74
Infections (case n)	25	40	43	10	57	1	176
Total preceding events/total points	83/56	103/120	99/120	57/50	241/193	4/20	587/559

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)

(back to contents) (#top)

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 (https://www.ncbi.nlm.nih.gov/pubmed/25243839), 30234645 (https://www.ncbi.nlm.nih.gov/pubmed/30234645)). One further study found that the *addition* of polyethylene glycol to lactulose also accelerated recovery (28316761 (https://www.ncbi.nlm.nih.gov/pubmed/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, agressive 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.

---

rifaxamin

(back to contents) (#top)

- 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 (https://www.ncbi.nlm.nih.gov/pubmed/23877348); 24849268 (https://www.ncbi.nlm.nih.gov/pubmed/24849268)).
- Possible doses are 550 mg PO BID or 400 mg TID.

---

manage triggers & coexisting problems

(back to contents) (#top)

---

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 (https://emcrit.org/pulmcrit/unconventional-therapies-for-hyponatremia-thinking-outside-the-collecting-duct/)).
  - 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 (https://emcrit.org/squirt/hypernatremia/).

hypokalemia

- Hypokalemia may increase ammonium reabsorption by the kidneys, potentially exacerbating hepatic encephalopathy.
- (Of course, hypokalemia should be treated regardless.)

renal support

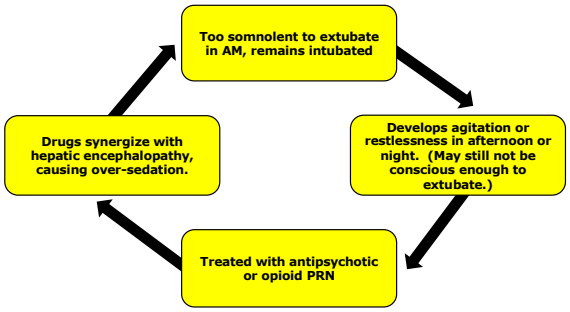
- Adequate renal function is essential to allow patients to clear toxins and emerge from encephalopathy.

- 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

(back to contents) (#top)

Vicious cycle of opioids or long-acting sedatives in severe hepatic encephalopathy



Successful extubation in profound hepatic encephalopathy may require complete avoidance of long-acting drugs (even fentanyl can accumulate over time). This may seem inhumane, but comfort can be ensured with short-acting and non-sedating agents (e.g. acetaminophen, propofol and/or dexmedetomidine).

The Internet Book of Critical Care, by @PulmCrit

(https://emcrit.org/wp-content/uploads/2016/11/hecycle.svg) **avoid sedating medications!**

- 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

(back to contents) (#top)

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 rifixamin 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

(back to contents) (#top)

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

(back to contents) (#top)

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)
  - ❑ Rifaxamin 550 mg BID (initiate immediately)
- ❑ **Avoid any long-acting neuroactive medications**
  - ❑ Review medication list and d/c deleriogenic 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

The Internet Book of Critical Care, by @PulmCrit

(https://emcrit.org/wp-content/uploads/2016/11/heversion2.svg)

podcast

(back to contents) (#top)

(https://i1.wp.com/emcrit.org/wp-content/uploads/2016/11/apps.40518.14127333176902609.7be7b901-15fe-4c27-863c-7c0dbfc26c5c.5c278f58-912b-4af9-88f8-a65fff2da477.jpg)

Follow us on iTunes (https://itunes.apple.com/ca/podcast/the-internet-book-of-critical-care-podcast/id1435679111)

The Podcast Episode

00:00 00:00 /javascript:void(0);)

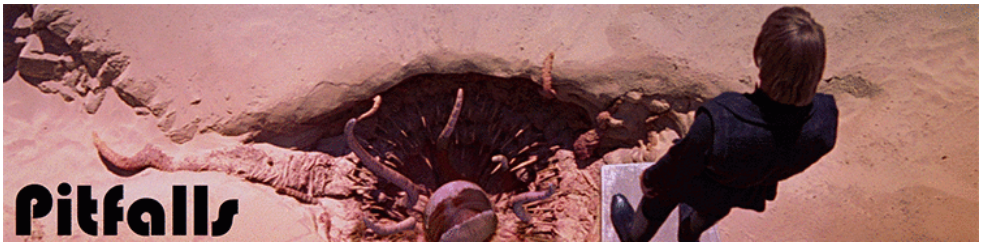
Want to Download the Episode?

Right Click Here and Choose Save-As (http://traffic.libsyn.com/ibccpodcast/IBCC_EP_38_-_Hepatic_Encephalopathy.mp3)

questions & discussion

(back to contents) (#top)

To keep this page small and fast, questions & discussion about this post can be found on another page ***here*** (https://emcrit.org/pulmcrit/HE/) .



(https://i1.wp.com/emcrit.org/wp-content/uploads/2016/11/pitfalls2.gif)

- 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:

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

Internet Book of Critical Care
@iBookCC

many FOAM sites including IBCC are currently in the process of upgrading to wordpress-Gutenberg. eventually the IBCC will be fully renovated (& hopefully better than before), but for now the formatting won't be perfect.

7 9:28 AM - May 14, 2019

See Internet Book of Critical Care's other Tweets

Edits: DGI

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.