Hepatology Manual

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• General
  o Meld score: INR, Creatinine, & Bilirubin
  o Enter “.meld” in Epic to auto-calculate
  o This predicts mortality and should be calculated daily – every liver patient needs a CMP, PT/INR daily
  o Know if transplant work up is initiated, the patient’s blood type, etiology of liver disease, pending studies needed
  o Know if patient is a transplant recipient
  o Know the etiology of liver disease
  o Know if there is a history of HCC; if yes, prior treatments/procedures (ie TACE); if no, when was the last screening modality (ie U/S or CT) & the results of this study
  o Know if there is a history of esophageal varices (EV), any prophylaxis, last EGD, any prior bleeding
  o Know if the patient had a TIPS
  o Consider sending a tox screen and ETOH level on admission when the history or clinical scenario warrants.

• HRS Cocktail
  o Octreotdie 50-100mcg TID, albumin 25% 50mL TID, midodrine 5-10mg TID
  o Initiate if the patient failed a fluid challenge of albumin or normal saline, consider initiating
  o Be careful not to use excessive amounts of albumin, which can cause pulmonary edema and increase portal pressures.

• Alcohol
  o For alcoholic hepatitis (AH), calculate the Maddrey Discriminant Function— this is a prognosticator & marker for initiating treatment for AH exacerbations
  o If the Maddrey Discriminant Function is >32, initiate therapy; this includes prednisone if there is no uncontrolled infection, renal failure, or GI bleeding
  o If suspecting alcohol abuse or recent use, order a send out lab – ethyl glucuronide

• Ascites
  o For evaluation of SBP via a diagnostic or therapeutic paracentesis, collect fluid count, anaerobic cultures, gram stain, ± cytology (goes to the 2nd floor above the ED in separate collection system), albumin, protein. Of these, fluid count (ordered as fluid cnt) is most important
  o When doing a large volume paracentesis (LVP), replace 6-8g of albumin/L if more than 4L of volume is removed. Do not remove more than 6L. Avoid large volume paracentesis in patients with SBP.
Do not make repeated attempts at paracentesis unless there is obvious fluid without use of an ultrasound machine.

**SBP**
- Active infection – indicated by fluid count analysis of absolute PMN count >250 cells/mm$^3$ or >500 WBC. Do this by calculating WBC x %PMNs
- There is a correction for the # of RBC – take 1 PMN for every 250 RBCs in the fluid analysis
- If active infection, stop BB as this worsens outcomes
- Treat with Ceftriaxone 2g q12hr x5d (or renal dosing); 1.5g/kg albumin should be given on days 1 & 3 (depending on the attending physician preference)
- Prevention/prophylaxis: oral norfloxacin 400mg QD or Cipro 250mg daily (or renal dosing)

**Esophageal Varices**
- In cirrhatics without varices or small varices, a non-selective BB is not recommended
- In cirrhatics, if large varices (Child A), a non-selective BB should be started to prevent hemorrhage (ie nadolol or propranolol). Higher risk of hemorrhage includes Child B, Child C, or red wale markings found on EGD
- If unable to tolerated BB, consider variceal band ligation in medium/large varices that haven’t bled
- Active bleed – *Call for MICU Eval immediately*. Achieve adequate IV access and transfuse for Hgb >8. Treat with IV Ceftriaxone 1g x5d. Start Octreotide gtt with EGD performed in the first 12 hours
- For secondary prophylaxis (to prevent re-bleeding) – consider banding to obliterate, add a nonselective BB is first line, then TIPS for patients with have recurrent bleeding
  - TIPS is contraindicated if severe hepatic encephalopathy (can worsen), portal vein thrombosis (alters vascular access in future transplant patients), severe R Heart Failure ie severe TR, pulm HTN, uncontrolled infection

**Hepatic Encephalopathy (HE)**
- Reversible, impaired mentation secondary to decreased metabolism of toxins (including ammonia)
- Treat with lactulose oral or enemas for goal 3-4 bowel movements a day
- Do not check ammonia levels, improvement is assessed via clinical status, exam
- If no significant improvement, consider adding Xifaxan/Rifaximin 550mg BID or Zinc

**Hepatocellular Carcinoma (HCC)**
- Surveillance in patients with cirrhosis – every 6 months via ultrasound. Evaluate liver nodule identified by US with MRI abdomen with gadolinium (or triple phase CT if patient is not a candidate for MR)
o TACE – trans-arterial chemoembolization of lesions are indicated if HCC is not a candidate for local radiofrequency ablation or if patients are awaiting orthotopic liver transplantation

o Liver transplantation can be used for treatment if it fits Milan criteria
  - 1 lesion < 5 cm, up to 3 lesions < 3 cm, no evidence of extra-hepatic manifestations or vascular invasion

o Do not biopsy a potential HCC lesion as it enhances on arterial phase and washes out in the venous phase of CT scan – this is very sensitive and specific

o Chemotherapy or radiation is limited in de-compensated cirrhosis
**Midodrine** - treats hypotension. Also seen with dialysis/ESRD patients

**Mechanism of Action (MOA):** A selective alpha adrenergic agonist – treats neurogenic orthostatic hypotension, a systemic vasoconstrictor, and persistent intra-dialytic hypotension.

**Journal Reference:** *Journal of Hepatology, 2012 56(2): 348-354* – A randomized pilot study evaluating midodrine in patients with cirrhosis and refractory or recurrent ascites. Long term administration of midodrine + standard medical therapy vs standard medical therapy alone in RCT. Results showed there was a significant decrease in plasma renin at 1 month, a decrease in cardiac output with increase in SVR, and decrease in ascites at 3 months after midodrine + standard therapy use vs control. (Standard medical therapy includes – Na restriction, diuretics, LVPs).

**Lactulose** – treats Hepatic Encephalopathy

**MOA:** a non-digestible sugar; helps to trap ammonia in the colon by using gut flora to acidify the colon – transforming ammonia to ammonium so it cannot be diffused back into the blood. Diarrhea and flatulence are common side effects.

**Journal Reference:** *JAMA Intern Med, 2014 Nov 174(11): 1727-1733* – the HELP study (Hepatic Encephalopathy: Lactulose vs Polyethylene glycol); a RCT study evaluating Lactulose vs Miralax/PEG for tx of overt HE. This essentially tested rapid clearance of gut ammonia via the HESA scale (a neuro-clinical scoring algorithm) in 24 hrs. Found that PEG led to more rapid HE resolution than standard therapy.

**Rifaximin/xifaxan** – treats Hepatic Encephalopathy

**MOA:** An oral antibiotic - It is minimally absorbed (based on rifamycin; poor oral bioavailability). It interferes with transcription by binding to bacterial RNA polymerase.

**Journal Reference:** *NEJM, Mar 2010 362:1071-1080* - A RCT, double blind study looking at efficacy of prevention of disease (HE) of placebo vs drug in remission from recurrent HE. Studies showed significant reduction in recurring HE vs placebo (both groups received lactulose); 22.1% vs 45.9%.

**Zinc** – treats Hepatic Encephalopathy

**MOA:** may enhance hepatic conversion of amino acids into urea and may modulate ion channel function and neurotransmission. Deficient in chronic liver patients, especially those with HE.

**Journal Reference:** *Nutrition Journal, 2013 12:74* – systemic review and metanalysis of use of Zinc in treatment of HE. Use was associated with Zinc Long term zinc supplementation showed significant improvement of severe recurrent HE that has been refractory protein restriction, lactulose, and neomycin

**Octreotide/sandostatin** – treats EV Bleed, Hepatorenal syndrome (HRS) cocktail

**MOA:** an octapeptide that mimics somatostatin - an inhibitor of GH, glucagon, insulin. Used as an infusion for mngmt of acute hemorrhage from esophageal varices by reducing portal venous pressure. Also a splanchnic vasoconstrictor for HRS

**Journal Reference:** *AM J Gastroenterol, 2009 Mar 104(3):617-623* – a RCT evaluating Terlipressin (a vasopressin analog used to treat low BP, HRS, EV bleed) vs octreotide in patients with EV bleed as an adjuvant therapy with band ligation. Found terlipressin group had more deaths from acute bleed
otherwise showed similar rates of control of bleed, # of pRBC, length of hospital stay. Overall not inferior to octreotide, had less hospital stay but not of clinical importance.

**Propanolol** – treats prophylaxis for EV

**MOA:** a non cardioselective vasodilating BB with mild anti alpha activity. Decreases portal flow (vaso-constricts), increases portal resistance, lowers portal pressure.

**Journal Reference:** *Hepatology, 2007 Sept 46*(3):922-938 - there have been 2 studies that investigated efficacy of nonselective BB in preventing enlargement of small varices. A large multicenter placebo, single blinded study showed that tx with nadolol had slower progression to larger varices at 3 years vs placebo but no differences in survival. Also had lower risk of bleed at 5 years.
**Model for End Stage Liver Disease (MELD) score**: A scoring system to assess severity of chronic liver disease. Initially developed to predict death within 3 months of surgery who had a TIPS procedure then found to be useful in determining prognosis and prioritizing for receipt of liver transplant.

- Now used by UNOS (United Network for Organ Sharing) instead of older Child-Pugh score.
- \[ MELD = 3.78 \ln(\text{serum bili}) + 11.2 \ln(\text{INR}) + 9.57 \ln(\text{serum Cr}) + 6.43 \times \text{etiology} (0–\text{cholestatic/alcoholic, 1 other}). \]
- UNOS added value for dialysis twice in the last 7d.
- Interpretation: \(>40 = 71.3\%, 30-39 = 52.6\%, 10-19 = 6\%, <9 = 1.9\% \) mortality.
- **Journal Reference**: J Gastroenterol Hepatol, 2014 Mar 29(3):581-588 – a prospective study evaluating MELD vs Maddrey score for short term outcomes in patients with alcoholic hepatitis. Both were equally good predictors with equal mortality rates

**Milan Criteria** – a basis for selecting patients ± cirrhosis with HCC for liver transplantation

- Eligible for transplant if: 1 lesion < 5cm, up to 3 lesions < 3cm, no extra hepatic manifestations, no vascular invasion.
  Found that overall 5 year survival for patient’s s/p transplantation and resection were 63% and 53% respectively.

**Yttrium**\(^90\) – radioembolization using 90-Yttrium tagged glass or resin microspheres in patients with HCC

- Used for unresectable HCC; Injection of microspheres in hepatic arteries allows for high doses of radiation to tumor while sparing the remaining liver tissue.
- Improves survival and is also used as a down-staging procedure to transplantation or resection.
- **Journal Reference**: J Clin Oncol 32, 2014, ASCO Annual Meeting – a retrospective study evaluating HCC patients treated with TACE vs Y\(^90\). Yttrium used more in advanced age and more advanced cancer; also used less in patients with cirrhosis complications and fewer comorbidities. No evidence that Yttrium will improve outcomes compared to TACE.

**Transcatheter Arterial Chemoembolization (TACE)** – a minimally invasive procedure which takes small embolic particles coated with chemotherapy agents and injects them selectively into the artery directly supplying a HCC tumor (neovascularization).

- This also directly interrupts the blood supply and allows for higher doses of chemotherapy. The drug is not washed out from the tumor bed by blood flow after embolization.
- Used for HCC pts not eligible for transplantation under the Milan criteria, an alternative to surgery for resectable early HCC, patients with regional recurrence, and down-staging HCC outside Milan criteria for transplantation, resection.
- Contraindication – advanced cirrhosis, decompensated cirrhosis; leads to acute ischemic change with worsened HE, ascites, death.
• **Journal Reference:** Hepatology, 2012 June 56(6):1330-1335 – a retrospective study analyzing survival of HCC patients treated with drug eluting beads via TACE. Showed better survival expectancy – 50% survival at 4 years compared with standard TACE

**Transjugular Intrahepatic Portosystemic Shunt (TIPS)** – an artificial channel in the liver that establishes communication between the inflow portal vein and outflow hepatic vein, treats portal HTN.

• Decreases the effective vascular resistance of the liver by making an alternate pathway to improve collaterals and ascetic fluid accumulation.
• Indications – acute variceal bleed uncontrolled with standard medical tx, refractory or recurrent bleed, refractory ascites, or portal decompression with outflow obstruction ie HRS, hepatic hydrothorax & Budd-Chiari syndrome.
• Contraindications – R Heart Failure with increased central venous pressure, severe TR, polycystic liver disease, severe hepatic failure, severe HE, hyper-vascular liver tumors, PV thrombus (more technically demanding), active intrahepatic or systemic infection.
• Complications – 25% have new or worsened HE, bile duct or hepatic artery injury, site PTX, fistulas, shunt stenosis and occlusion, acute increase CO, CVP wedge pressures -> congestive heart failure.
• **Journal Reference:** Gut, 2000 Aug 47(2):288-295 – a prospective study looking at long-term outcomes for patients with HRS after TiPs. Analyzed 41 non-transplantable cirrhotics with either type of HRS and found reduced portal pressure, improved Cr Clearance, 35% 18 month survival rate.

**Lille model** – a prognostic score which predicts survival probability at 6 months for patients with severe alcoholic hepatitis not responding to steroids

• Formula = 3.19 – 0.101(age) + 0.147(albumin day 0 g/L) + 0.0165(Bilirubin day 7) – 0.206(Cr day 0) – 0.0065(Bilirubin day 0) - 0.0096(PT day 0)
• Interpretation – 6 month survival is 25% with a score of >0.45 vs 85% if <0.45.
• **Journal Reference:** Hepatology, 2007 Jun 45(6): 1348-1254 – a prospective study used to generate this prognostic model. Total 320 patients with alcoholic hepatitis treated with steroids measuring day 0 and 7 Bilirubin, Cr, age, PT successfully predicted mortality in patients with cutoff score 0.45.

Can use to determine if steroids are not working.
**Etiologies of cirrhosis:**

1. **Hepatitis C (26%)** - percutaneous exposure i.e. IVDA (50%), tattoo, body piercing, acupuncture; less risk with sexual transmission, vertical transmission, M>F, minority. Genotype 1a (50-60%), 1b (15-20%), 2a-c 10-15%. No bx mandatory before tx but assesses severity. Tx interferon, polymerase inhibitor

2. **Alcoholic liver disease (21%)** – common in white males, min daily EtOH intake is 40g for males, 20g for females older than 20yo. 5 yr survival 30% for Female, 70% Males. Alcohol causes centrilobular necrosis with toxic effect on cell membranes, generation of free radicals, & cytokine damage. AST>ALT 2:1. Treat prednisone or PTX as above

3. **NASH (Non-alcoholic steatohepatitis)(18%)** risk factors include metabolic syndrome ie diabetes, obesity, hyperlipidemia

4. **Hepatitis B, +/- Hep D (15%)** transmitted via birth, sex, sharing needles

5. **Others** - Autoimmune, PBC, Secondary biliary cirrhosis, PSC, Hemochromatosis, Wilson’s disease, Alpha 1 AT def, granulomatous disease i.e. sarcoidosis, drug induced liver disease, chronic RHF or TR

**Portal HTN** – increased portal pressure 2/2 architectural distortion of the liver, fibrous tissue and regenerative nodules

- Leads to active intrahepatic vasoconstriction due to decrease in endogenous NO production along with formation of porto-systemic collaterals or varices
- Varices are formed via increased venous inflow with concomitant splanchnic arteriolar vasodilation and insufficient portal decompression - porto-systemic shunts
- Normal hepatic venous pressure gradient is 3-5mmHg.

**Esophageal Varices**

- Dilated submucosal veins in the lower third of the esophagus caused by portal HTN
  - Diagnosis – EGD = gold standard
  - See Quick Guide section
  - **Endoscopic Variceal Ligation (EVL)** has been compared to β-blockers in several randomized trials in patients with high-risk varices (large varices with or without red wale markings). Two recent meta-analyses of these trials have been performed: the first included 8 trials and comprised 596 subjects (285 with EVL, 311 with β-blockers) (61); and the second included 12 studies comprising 839 subjects (410 with EVL, 429 with β-blockers) (62). Both showed that EVL is associated with a small but significant lower incidence of first variceal hemorrhage without differences in mortality.

**Hepatorenal syndrome (HRS)** – renal failure in advanced liver disease;

- Portal HTN-> splanchnic vasodilation-> decreased effective circulatory volume → RAAS activation → renal vasoconstriction decreased GFR, CCI with renal sodium avidity - ascites.
- At least 40% of cirrhotics will develop HRS; liver transplant is curative.

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1 See Table 3
• Diagnosis – major criteria include portal HTN with kidney failure, absence of shock, infection, use of nephrotoxin therapy with absence of sustained improvement in kidney function despite tx with 1.5L of IV NS
  o No evidence of proteinuria, no kidney disease or obstruction of outflow on U/S.
  o Minor criteria – low urine vol <500cc/d, low Una, UOSM>SOSM, no RBC in urine
• Type I – rapid progressive kidney failure with doubling serum Cr or halving CCl in < 14d. Associated with 50% mortality in 1 month.
• Type II – slower onset and progression. Increase SCr or CCl <40mL/mn, 6 month prognosis unless transplant.

Ascites – accumulation of fluid in peritoneal cavity.

• A consequence of portal HTN -> vasodilation affecting splanchnic bed, decrease effective arterial pressures-> activate vconstrictor and antinatriuertic mechanisms to restore normal perfusion ie RAAS, vasopressin/ADH leading to sodium and water retention -> dilutional hyponatremia and ascites.
• SAAG serum- ascitic fluid albumin, if >1.1g/dL = portal HTN.
• Tx sodium retention, Aldactone, Lasix, albumin, fluid restriction.

SBP An acute bacterial infection of ascitic fluid.

• Possibly due to bacterial translocation across gut lumen or hematogenous spread, gut bacterial overgrowth with low complement levels.
• Mainly E coli, aerobic GN bugs ascitic fluid. Diagnose
• Diagnose via fluid analysis - PMN leukocyte >250 cells
• Treat with cefotaxime and albumin 1.5kg/body weight within 6 hrs of detection and 1g/kg on d3 or oral fluoroquinolone.
• Ppx includes bactrim or norfloxacin or Cipro as above

Hepatic Encephalopathy – reversible decrease in neuropsychiatric function caused by liver disease, mainly in pt with portal HTN.

• Insidious onset with subtle intermittent changes in personality, memory, concentration, reaction times; a diagnosis of exclusion
• Ammonia is detoxified in the liver and converted to urea (relies on activity of glutamine synthetase). In patients with decreased liver function and porto-systemic shunting, there can be diverting of ammonia buildup to systemic circulation causing hyperammonemia
• Tx involves removal of nitrogenous load from gut via bowel cleansing with lactulose orally or with enemas.
• RCT study showed no benefit of protein restriction diet in HE episodes.

Coagulopathy – present in moderate to advanced liver disease
• Most commonly see low platelets with impaired humoral coagulation.
• Liver makes clotting factors, coagulation inhibitors, fibrinolytic proteins.
• Increased bleeding risk via decreased production of non-endothelial cell-derived coag factors ie Vit K dependent clotting factors 2,7,9,10 that disrupt hemostasis. This leads to decreased platelets with altered function, inhibition by NO, and fibrinogen abnormalities.
• Also associated with decreased thrombopoietin production and splenic sequestration of plts due to portal HTN
• Increased thrombotic risk via decreased levels of liver-synthesized natural AC proteins ie PC, PS, antithrombin levels, decreased plasminogen, elevated vWF. Increased risk of VTE, portal vein thrombosis, microthrombi with localized ischemia. Prevention via enoxaparin or LMWH.
• Treatment – Vit K, FFP - has all the coag factors, cryo – has fibrinogen, vWF, fibronectin, plt transfusion, recombinant factor 7a, Amicar for refractory bleeding
**Table 3.** Effect on Portal Flow, Resistance and Pressure with the Different Therapies for Varices/Variceal Hemorrhage

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Portal Flow</th>
<th>Portal Resistance</th>
<th>Portal Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasoconstrictors (e.g. β-blockers)</td>
<td>↓↓</td>
<td>↑</td>
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</tr>
<tr>
<td>Venodilators (e.g. nitrates)</td>
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<td>↓*</td>
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<tr>
<td>Endoscopic therapy</td>
<td>-</td>
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<tr>
<td>TIPS/Shunt therapy</td>
<td>↑</td>
<td>↓↓↓</td>
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*Although theoretically nitrates act by decreasing resistance, they actually act by decreasing portal flow through a decrease in mean arterial pressure.*

**References**

[https://aasld.org](https://aasld.org); available online