Portal Hypertension and its Complications

Tom Frazier
What I’m Gonna Tell You

- Pathophysiology of Portal HTN and its Complications
- Review diagnostic concerns and management of...
  - Ascites
  - Gastric and esophageal varices
  - HRS
  - HPS
  - Hepatic encephalopathy

What I expect you to remember

- General Pathophys of portal htn, he, varices, hrs
- Where to find answers when they come up
- HE treatment and problems with our curent assumptions
Pathogenesis of Portal Hypertension: Hemodynamic Factors

- Cirrhosis most common etiology
- portal pressure gradient $> 5$ mm Hg
- Hallmark is a pathologic increase in the pressure gradient between the portal vein and the inferior vena cava, which is measured by the hepatic venous pressure gradient (HVPG)
- $\text{HVPG} = \text{WHVP} - \text{FHVP}$
- Ohm's law: $P = Q \times R$
- Two steps
  - Decreased outflow
  - Increased inflow
### Classification of portal hypertension

<table>
<thead>
<tr>
<th>Type</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Prehepatic</strong></td>
<td>Portal vein thrombosis – independent of cause, splenic vein thrombosis, cavernous transformation of the portal vein, splenic arteriovenous fistula, idiopathic tropical splenomegaly</td>
</tr>
<tr>
<td><strong>2. Intrahepatic</strong></td>
<td></td>
</tr>
<tr>
<td>a) presinusoidal</td>
<td>Schistosomiasis, chronic viral hepatitis HBV, HCV, cirrhosis biliaris primaria, myeloproliferative diseases, focal nodular hyperplasia, idiopathic portal hypertension, sarcoidosis, tuberculosis, Wilson’s disease, hemochromatosis, amyloidosis, remaining storing diseases, polycystic liver disease, infiltration of liver hilus - independent of cause, benign and malignant neoplasms</td>
</tr>
<tr>
<td>b) sinusoidal</td>
<td>Liver cirrhosis - independent of etiology, acute viral and alcoholic hepatitis, acute fatty liver of pregnancy</td>
</tr>
<tr>
<td>c) postsinusoidal</td>
<td>Venous-occlusion disease, alcoholic hyaline sclerosis of central veins</td>
</tr>
<tr>
<td><strong>3. Extrahepatic</strong></td>
<td>Hepatic veins thrombosis (Budd-Chiari disease), inflammatory/neoplastic infiltration cavering hepatic veins, caval inferior occlusion (thrombosis, neoplasms), cardiac diseases: chronic right ventricular failure, chronic constrictive pericarditis, tricuspid insufficiency</td>
</tr>
</tbody>
</table>
Step 1: Increased outflow resistance

- This results from 2 factors:
  - (1) mechanical obstruction to flow because of fibrotic disruption of architecture
  - (2) a dynamic component produced by active contraction of vascular smooth muscle cells and activated stellate cells

- The dynamic component accounts for approximately 30% of the intrahepatic resistance in cirrhosis
Step 1: The DYNAMIC component

- Intrahepatic ↓(eNOS) activity and NO production.
  - impaired Akt-mediated eNOS phosphorylation (which is partially reversible by statins)
  - increased caveolin expression (particularly if folate deficiency exists).
  - nitrosylation reactions secondary to oxidative stress (↓NO) and vasoconstriction mediated by endothelin, angiotensinogen, and eicosanoids.
- other vasoactive mediators such as carbon monoxide, adrenergic tone, endotoxemia, and inflammatory cytokines
Step 2: Increased Portal Venous Inflow

- Mesenteric arterial vasodilation
  - $\uparrow$ portal venous inflow
  - Systemic hyperdynamic circulatory state ($\downarrow$ svr and map with $\uparrow$ CO).
- Caused by $\uparrow$ NO
  - Shear stress, $\uparrow$ VEGF, and TNF-$\alpha$ are causes of $\uparrow$ splanchnic NO production in cirrhosis
  - $\uparrow$ heme oxygenase activity and CO production may also contribute
  - Bacteremia can $\uparrow$ vasodilation by stimulating TNF-$\alpha$ production and activation of endocannabinoids, which are potent vasodilators.
  - Blockade of VEGF signaling attenuates the increase in portal venous inflow seen in cirrhosis
Portal HTN and its Complications

Cirrhosis
- Increased Resistance to Portal Inflow
- Release of Vasodilators (NO)
  - Peripheral vasodilation
  - Arterial underfilling
    - Release of vasoconstrictive & Na retentive hormones
    - Impaired free Water clearance
      - Dilutional Hyponatremia
      - Renal vasoconstriction
        - Hepatorenal Syndrome

Increased splanchnic capillary pressure & permeability
- Lymph formation > Lymph return
  - Na & water retention
    - Expanded plasma volume
  - Impaired free Water clearance
    - Dilutional Hyponatremia
  - Renal vasoconstriction
    - Hepatorenal Syndrome

CO fails to compensate overtime

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Acites Formation

- Increased hepatic sinusoidal pressure
- Three interrelated pathophysiologic processes contribute to the development of ascites.
  - systemic arteriolar vasodilation,
  - activation of Na and H2O retention,
  - sinusoidal portal hypertension.
Acites Formation

- *splanchnic arterial vasodilation* -&gt; effective hypovolemia
  -&gt; increased CO (hyperdynamic circulation).
- Over time splanchnic arterial vasodilation \(\uparrow\) and CO \(\downarrow\) (effectively), leading to circulatory dysfunction
  - renin-angiotensin-aldosterone system,
  - sympathetic nervous system, and
  - antidiuretic hormone.
- moderate circulatory dysfunction = sodium retention.
- Severe = impairment in free water excretion and dilutional hyponatremia.
- Extreme = HRS.
Pathophysiology of ascites and hepatorenal syndrome.
The Pathway to Ascites

- Cirrhosis
  - Increased resistance to portal flow
    - Portal hypertension
      - Splanchnic vasodilation
        - Increase in splanchnic capillary pressure
          - Lymph formation that exceeds lymph return
            - Ascites
              - Sodium and water retention
                - Expansion of plasma volume
              - Impaired free-water excretion
                - Dilutional hyponatremia
              - Renal vasoconstriction
                - Hepatorenal syndrome
              - Arterial underfilling
                - Arterial and cardio-pulmonary receptors
                  - Activation of vasoconstrictor and antinatriuretic factors
Grading Ascites

- Grade 1—mild and detectable only on imaging studies
- Grade 2—moderate, manifested by symmetrical distension of abdomen
- Grade 3—large or gross with massive abdominal distension
Survival of Cirrhotics with Ascites

Classification of Ascites

- Serum-ascites albumin gradient (SAAG)
- \( \text{SAAG (g/dl)} = \text{albumin}_s - \text{albumin}_a \)
- Gradient \( >1.1 \text{ g/dl} \) = portal hypertension
- Serum globulin \( > 5 \text{ g/dl} \):
  - \( \text{SAAG correction} = (\text{SAAG mean})(0.21+0.208 \text{ serum globulin g/dl}) \)
Ascites with High SAAG

> 1.1 g/dl = portal hypertension

- Cirrhosis
- Alcoholic Hepatitis
- Cardiac ascites
- Massive hepatic metastasis
- Fulminant hepatic failure
- Budd-Chiari syndrome
- Portal vein thrombosis
- Veno-occlusive disease
- Acute fatty liver of pregnancy
- Myxedema
- Mixed ascites
Low SAAG
<1.1 g/dl

- Peritoneal carcinomatosis
- Tuberculous peritonitis (without cirrhosis)
- Biliary ascites (without cirrhosis)
- Pancreatic ascites (without cirrhosis)
- Nephrotic ascites
- Connective tissue disease
- Intestinal obstruction/infarction
Management of Uncomplicated Ascites

Cirrhotic ascites

- Treat cause of cirrhosis

Mild-Moderate ascites
- Diagnostic tap
- Na restriction
- Diuretics

- Adequate response
  - Na restriction
  - Diuretics
- Inadequate response
  - Non compliant
  - Check Na compliance
  - Compliant
    - Increase diuretic dose
    - Inadequate response/ or complications due to diuretics
    - Refractory Ascites

Large volume ascites
- LVP
- Diet
- Diuretics

- Recurrent ascites
- Adequate response
  - Na restriction
  - Diuretics
Management of Uncomplicated Ascites

- Ideal wt loss w/o peripheral edema: 500g/day
- Ideal wt loss w peripheral edema: 1000g/d
- Checking urine Na:
  - urine Na ~ Na intake
  - ↑ Na: counsel on compliance with diet
  - ↓ Na: increase diuretic
  - Only check if patient has poor diuretic response
- Starting dose for diuretics is Furosemide 40mg and spironolactone 100mg. (max 160mg/d and 400mg)
Refractory Ascites

- **Diuretic resistant ascites** = failure to lose at least 1.5 kg/week of fluid weight, despite diuretic therapy with spironolactone (400 mg/day) and furosemide (160 mg/day)

- **Diuretic intractable ascites**: failure to mobilize 2/2 diuretic-induced side effects
Treatment of Refractory Acites

- Repeated LVP (most common)
- TIPS (better for control/less cost effective/no improvement in mortality)
  - ↑ Bili, coagulopathic, and RF are all predictors of poor outcomes with TIPS
SBP and CNNA

- **SBP** = PMN >250/mm³ with (+) culture (> 90% monobacterial)
- **CNNA** = PMN >250/mm³ with (-) culture (without previous antibiotics nor other causes of increased PMN [bleeding, cancer, TB, pancreatitis])
<table>
<thead>
<tr>
<th>Symptoms and signs</th>
<th>SBP (%)</th>
<th>Bacterascites (%)</th>
<th>CNNA (%)</th>
<th>Secondary peritonitis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>68</td>
<td>57</td>
<td>50</td>
<td>33</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>49</td>
<td>32</td>
<td>72</td>
<td>67</td>
</tr>
<tr>
<td>Abdominal tenderness</td>
<td>39</td>
<td>32</td>
<td>44</td>
<td>59</td>
</tr>
<tr>
<td>Rebound</td>
<td>10</td>
<td>5</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>54</td>
<td>50</td>
<td>61</td>
<td>33</td>
</tr>
</tbody>
</table>

CNNA, culture negative neutrocytic ascites; SBP, spontaneous bacterial peritonitis.

Reproduced from Sleisenger’s & Fordtran’s gastrointestinal and liver disease, 7th ed, with permission from Elsevier.
<table>
<thead>
<tr>
<th>Microorganisms</th>
<th>SBP (%)</th>
<th>Bacterascites (%)</th>
<th>Secondary peritonitis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monomicrobial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>37</td>
<td>27</td>
<td>20</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>17</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td><em>Pneumococcus</em></td>
<td>12</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td><em>Streptococcus viridans</em></td>
<td>9</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>0</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Miscellaneous Gram-negative</td>
<td>10</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Miscellaneous Gram-positive</td>
<td>14</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Polymicrobial</td>
<td>1</td>
<td>0</td>
<td>53</td>
</tr>
</tbody>
</table>

SBP, spontaneous bacterial peritonitis.
Reproduced from *Sleisenger’s & Fordtran’s gastrointestinal and liver disease*, 7th ed, with permission from Elsevier.
SBP and CNNA

- Mortality without treatment: 78-100%
- Mortality w. Cefotaxime: 30% (HRS= 33% )
- Mortality w. Cefotaxim+albumin: 10% (HRS=10% )
- Recurrent SBP in 69%

**Treatment**
- Cefotaxime 2g TID x 5 days + Albumin 1.5 gm/ Kg @ day 1 & 1 gm/ Kg @ day 4
- Re-paracentesis at 48hrs (50% reduction in WBCs)
### Table 2. Effective Interventions for Preventing Complications in Patients with Cirrhosis and Ascites.

<table>
<thead>
<tr>
<th>Complication and Setting</th>
<th>Intervention</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal bleeding due to gastroesophageal varices</td>
<td>Propranolol or nadolol (stepwise increase in dose until the heart rate decreases by 25% or to 55–60 beats/min)</td>
<td>Reduces the risk of variceal bleeding and improves survival</td>
<td>Bosch et al.16</td>
</tr>
<tr>
<td>Spontaneous bacterial peritonitis</td>
<td>Oral norfloxacin (400 mg twice daily for 7 days), intravenous ofloxacin (400 mg daily for 7 days), or intravenous ciprofloxacin (200 mg daily) plus oral amoxicillin–clavulanic acid (1 g and 200 mg, respectively, three times daily) for 7 days</td>
<td>Reduces the risk of spontaneous bacterial peritonitis and improves survival</td>
<td>Rimola et al.17</td>
</tr>
<tr>
<td>In patients with acute variceal bleeding</td>
<td>Oral norfloxacin (400 mg daily, indefinitely); oral ciprofloxacin (750 mg weekly, indefinitely); or oral trimethoprim–sulfamethoxazole (160 mg and 800 mg, respectively, five days per week, indefinitely)</td>
<td>Reduces the risk of a first episode of spontaneous bacterial peritonitis; use of antibiotics is controversial because a beneficial effect on survival has not been demonstrated and because there is an increased risk of infections with resistant organisms</td>
<td>Rimola et al.17</td>
</tr>
<tr>
<td>In patients with ascitic-fluid protein concentration &lt;15 g/liter</td>
<td>Intravenous albumin (1.5 g/kg of body weight on diagnosis of the infection and 1 g/kg after 2 days)</td>
<td>Reduces the risk of the hepatorenal syndrome and improves survival</td>
<td>Sort et al.18</td>
</tr>
</tbody>
</table>
Formation of Varices and Mechanism of Variceal Hemorrhage

- ↑ portal vein pressures = diverting up to 90% of the portal flow through porta-systemic collaterals
  - flow-mediated remodeling and
  - enlargement of these vessels.
  - VEGF, NO-driven VEGF type II receptor expression, and platelet-derived growth factor drive this process.
Formation of Varices

- do not form until the HVPG > 10 mm Hg and
- usually do not bleed unless the HVPG > 12 mm Hg.
- Variceal rupture occurs when the wall tension exceeds the elastic limits of the variceal wall
- The wall tension is defined by Frank's modification of Laplace's law
- The wall is thinnest at the GE junction

\[ T = \left( P_{\text{varices}} - P_{\text{esophageal lumen}} \right) \times \frac{\text{radius of varix}}{\text{wall thickness}} \]
Pathophysiology of Variceal Bleeding

Ohm's law

\[ P = Q \text{ (blood flow)} \times R \]
Active variceal hemorrhage

Endoscopic + pharmacologic treatment

Bleeding stops

EVL + β blockers

OLT Eval

Bleeding continues
Early rebleeding

TIPS

OLT Eval

TIPS for recurrent bleeds

Transplant
AASLD GUIDELINES FOR GE Varices

Recommendations for Diagnosis

1. Screening EGD for the diagnosis of esophageal and gastric varices is recommended when the diagnosis of cirrhosis is made (Class IIa, Level C).

2. On EGD, esophageal varices should be graded as small or large (>5 mm) with the latter classification encompassing medium-sized varices when 3 grades are used (small, medium, large). The presence or absence of red signs (red wale marks or red spots) on varices should be noted (Class IIa, Level C).

Compensated cirrhosis w/o varices

1. nonselective β-blockers cannot be recommended to prevent their development (Class III, Level B).
2. no varices on the initial EGD, it should be repeated in 3 years (Class I, Level C).
3. If there is evidence of hepatic decompensation, EGD should be done at that time and repeated annually (Class I, Level C).
Small Varices that have not bled

1. ↑ risk of hemorrhage (Child B/C or presence of red wale marks on varices), nonselective -blockers should be used for the prevention of first variceal hemorrhage (Class IIa, Level C).

2. ↓ risk of bleeding, betablockers can be used, although their long-term benefit has not been established (Class III, Level B).
Small Varices that have not bled

1. In patients with small varices that have not bled and who are not receiving α-blockers, EGD should be repeated in 2 years (Class I, Level C).

2. If there is evidence of hepatic decompensation, EGD should be done at that time and repeated annually (Class I, Level C).

3. In patients with small varices who receive α-blockers, a follow-up EGD is not necessary.
AASLD GUIDELINES FOR GE
Varices

- Large Varices that have not bled

1. ↑ risk of hemorrhage (Child B/C or variceal red wale markings on endoscopy), nonselective -blockers (propranolol or nadolol) or EVL may be recommended for the prevention of first variceal hemorrhage (Class I, Level A).

2. ↓ of hemorrhage (Child A patients and no red signs), nonselective -blockers (propranolol, nadolol) are preferred and EVL should be considered in patients with contraindications or intolerance or non-compliance to -blockers (Class I, Level A).
Large Varices that have not bled

1. If a patient is placed on a nonselective -blocker, it should be adjusted to the maximal tolerated dose; follow-up surveillance EGD is unnecessary.

2. If a patient is treated with EVL, it should be repeated every 1-2 weeks until obliteration with the first surveillance EGD performed 1-3 months after obliteration and then every 6-12 months to check for variceal recurrence (Class I, Level C).

3. Nitrates (either alone or in combination with -blockers), shunt therapy, or sclerotherapy should not be used in the primary prophylaxis of variceal hemorrhage (Class III, Level A).
AASLD GUIDELINES FOR GE Varices

- **Acute Hemorrhage**
  1. Intravascular volume support, being careful to maintain a hemoglobin of 8 g/dL (Class I, Level B).
  2. **Short-term** (maximum 7 days) antibiotic prophylaxis should be instituted in any patient with cirrhosis and GI hemorrhage (Class I, Level A).
     - Oral norfloxacin (400 mg BID) or intravenous ciprofloxacin (in patients in whom oral administration is not possible) is the recommended antibiotic (Class I, Level A).
     - In patients with advanced cirrhosis intravenous ceftriaxone (1 g/day) may be preferable particularly in centers with a high prevalence of quinolone-resistant organisms (Class I, Level B).
AASLD GUIDELINES FOR GE Varices

- **Acute Hemorrhage**

1. Pharmacological therapy (somatostatin or its analogues octreotide and vapreotide; terlipressin) should be initiated as soon as variceal hemorrhage is suspected and continued for 3-5 days after diagnosis is confirmed (Class I, Level A).

2. EGD, performed within 12 hours, should be used to make the diagnosis and to treat variceal hemorrhage, either with EVL or sclerotherapy (Class I, Level A).

3. TIPS is indicated in patients in whom hemorrhage from esophageal varices cannot be controlled or in whom bleeding recurs despite combined pharmacological and endoscopic therapy (Class I, Level C).

4. Balloon tamponade should be used as a temporizing measure (maximum 24 hours) in patients with uncontrollable bleeding for whom a more definitive therapy (e.g., TIPS or endoscopic therapy) is planned (Class I, Level B).
Gastric Varices

1. In patients who bleed from gastric fundal varices, endoscopic variceal obturation using tissue adhesives such as cyanoacrylate is preferred, where available. Otherwise, EVL is an option (Class I, Level B).

2. A TIPS should be considered in patients in whom hemorrhage from fundal varices cannot be controlled or in whom bleeding recurs despite combined pharmacological and endoscopic therapy (Class I, Level B).
Post bleed recs.

1. Patients with cirrhosis who survive an episode of active variceal hemorrhage should secondary prophylaxis (Class I, Level A).

2. Combination of NS bblker plus EVL is the best option for secondary prophylaxis of variceal hemorrhage (Class I, Level A).

3. The NS bblker should be adjusted to the maximal tolerated dose.

4. EVL should be repeated every 1-2 weeks until obliteration with the first surveillance EGD performed 1-3 months after obliteration and then every 6-12 months to check for variceal recurrence (Class I, Level C).
AASLD GUIDELINES FOR GE Varices

Post bleed recs.

1. TIPS should be considered in patients who are Child A or B who experience recurrent variceal hemorrhage despite combination pharmacological and endoscopic therapy. (Class I, Level A).

2. Patients who are otherwise transplant candidates should be referred to a transplant center for evaluation (Class I, Level C).
Hepatorenal Syndrome

And the...
Diagnostic criteria of HRS

**MAJOR CRITERIA**

- Low GFR as indicated by serum Cr > 1.5 mg/ dL or 24-hour creatinine clearance < 40 mL/ min

- Absence of shock, ongoing bacterial infection, and fluid losses, and current treatment with nephrotoxic agents

- Lack of sustained improvement in renal function on discontinuation of diuretics and volume expansion by 1.5 L of a plasma expander

- Proteinuria less than 500mg/ d and no ultrasonographic evidence of obstructive uropathy or parenchymal renal disease.
Diagnostic criteria of HRS

- **MINOR CRITERIA**
  - Urine volume less than 500 mL/d
  - Urine sodium less than 10mEq/L
  - Urine osmolality greater than plasma osmolality
  - Urine RBCs less than 50 per high power field
  - Serum sodium concentration less than 130 mEq/L
<table>
<thead>
<tr>
<th></th>
<th>Type 1 HRS</th>
<th>Acute tubular necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of recent shock</td>
<td>No</td>
<td>Frequent</td>
</tr>
<tr>
<td>History of recent use of nephrotoxic drugs</td>
<td>No</td>
<td>Frequent</td>
</tr>
<tr>
<td>Urine findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium concentrations (mmol/L)</td>
<td>&lt;20</td>
<td>&gt;40</td>
</tr>
<tr>
<td>Fractional excretion of sodium (%)</td>
<td>&lt;1</td>
<td>&gt;1</td>
</tr>
<tr>
<td>Urine osmolality (mOsm/kg)</td>
<td>&lt;500</td>
<td>&gt;350</td>
</tr>
<tr>
<td>Beta2-microglobulin (mg/L)</td>
<td>&lt;1</td>
<td>&gt;1.5</td>
</tr>
<tr>
<td>Renal pathology</td>
<td>No cellular lesion</td>
<td>Necrotic renal tubules</td>
</tr>
</tbody>
</table>

Hepatology. 2006 Mar;43(3):385-94
Table 3. Criteria for Diagnosis of the Hepatorenal Syndrome.*

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of the hepatorenal syndrome</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine concentration &gt;1.5 mg/dl or 24-hr creatinine clearance</td>
<td></td>
</tr>
<tr>
<td>&lt;40 ml/min</td>
<td></td>
</tr>
<tr>
<td>Absence of shock, ongoing bacterial infection, and fluid loss, and no</td>
<td></td>
</tr>
<tr>
<td>current treatment with nephrotoxic drugs</td>
<td></td>
</tr>
<tr>
<td>Absence of sustained improvement in renal function (decrease in serum</td>
<td></td>
</tr>
<tr>
<td>creatinine to ≤1.5 mg/dl) after discontinuation of diuretics and a trial</td>
<td></td>
</tr>
<tr>
<td>of plasma expansion</td>
<td></td>
</tr>
<tr>
<td>Absence of proteinuria (&lt;500 mg/day) or hematuria (&lt;50 red cells per</td>
<td></td>
</tr>
<tr>
<td>high-power field)</td>
<td></td>
</tr>
<tr>
<td>Absence of ultrasonographic evidence of obstructive uropathy or paren-</td>
<td></td>
</tr>
<tr>
<td>chymal renal disease</td>
<td></td>
</tr>
<tr>
<td>Urinary sodium concentration &lt;10 mmol/liter;†</td>
<td></td>
</tr>
<tr>
<td>Type of hepatorenal syndrome</td>
<td></td>
</tr>
<tr>
<td>Type 1: progressive impairment in renal function as defined by a</td>
<td></td>
</tr>
<tr>
<td>doubling of initial serum creatinine above 2.5 mg/dl in less than two</td>
<td></td>
</tr>
<tr>
<td>weeks</td>
<td></td>
</tr>
<tr>
<td>Type 2: stable or slowly progressive impairment in renal function not</td>
<td></td>
</tr>
<tr>
<td>meeting the above criteria</td>
<td></td>
</tr>
</tbody>
</table>

* To convert the values for creatinine to micromoles per liter, multiply by 88.4.  
† Although the urinary sodium concentration is less than 10 mmol per liter in most patients with the hepatorenal syndrome, this finding is not considered a major diagnostic criterion because some patients with this syndrome may not have markedly low sodium excretion.
<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration of one of the following drugs or drug combinations</td>
<td></td>
</tr>
<tr>
<td>Norepinephrine (0.5–3.0 mg/hr intravenously)</td>
<td>Duvoux et al.⁴⁸</td>
</tr>
<tr>
<td>Midodrine (7.5 mg orally three times daily, increased to 12.5 mg three times daily if needed) in combination with octreotide (100 μg subcutaneously three times daily, increased to 200 μg three times daily if needed)</td>
<td>Angeli et al.⁴⁹</td>
</tr>
<tr>
<td>Terlipressin (0.5–2.0 mg intravenously every 4–12 hr)¹</td>
<td></td>
</tr>
<tr>
<td>Concomitant administration of albumin (1 g/kg intravenously on day 1, followed by 20–40 g daily)</td>
<td></td>
</tr>
<tr>
<td>Duration of therapy: 5–15 days</td>
<td></td>
</tr>
<tr>
<td>End point: reduction of serum creatinine concentration to &lt;1.5 mg/dl¹</td>
<td></td>
</tr>
</tbody>
</table>

* Terlipressin is not available in some countries, including the United States.

† To convert the value for creatinine to micromoles per liter, multiply by 88.4.
ENCEPHALOPATHY 101

- Reversible neuro-psychiatric manifestation of portosystemic shunting.
- One-year survival 40%.
- 1/3rd to ½ of all hospitalizations for cirrhotics.
- Decreased hepatic clearance of ammonia derived from: 1) kidney, 2) urease activity of colonic bacteria, and 3) glutamine uptake in small bowel.
What's ammonia got to do with it?

↑ permeability in cirrhatics

Neurologic impairment factors in HE

- ammonia
- oxidative stress
- cytokines
- serotonin
- histamine
- astrocyte edema
- opiates
- benzodiazepine-like
- GABA
The Trojan Horse

Glutamine

Gastroenterology
Volume 134, Issue 6, May 2008, Pages 1715-1728
Precipitating factors for hepatic encephalopathy

- Dehydration
- GIB
- Infections
- Constipation
- Excessive dietary protein
- Central nervous system acting drugs
- Hypokalemia
- Renal failure

- Hyponatremia
- Surgery
- TIPS
- Superimposed liver injury (acute hepatitis, drug-induced liver injury)
- Hepatocellular carcinoma
- Terminal liver disease
- Urinary obstruction
- ? H.Pylori
Major differential diagnoses in hepatic encephalopathy

- Metabolic encephalopathies (uremia, sepsis, hypoxia, hypoglycemia, ketoacidosis, hypercapnea, thyroid dysfunction, or cerebral edema)
- Intracranial bleeding: subdural hematoma, intracranial hemorrhage
- Ischemic brain disease: transient ischemic attack, ischemic stroke
- Central nervous system abscess, encephalitis, meningitis (bacterial, viral, fungal)
- Central nervous system neoplasm
- Delirium tremens
- Alcoholism
- Postictal state
a) The West Haven Criteria for Grading Mental State in Patients with Cirrhosis

Grade 0  No abnormality detected

Grade 1  Trivial lack of awareness
         Euphoria
         Anxiety
         Shortened attention span
         Impairment of addition and subtraction

Grade 2  Lethargy or Apathy
         Disorientation of time
         Obvious personality change
         Inappropriate behavior

Grade 3  Somnolence to semistupor
         Responsive to stimuli
         Confused
         Gross Disorientation
         Bizarre behavior

Grade 4  Coma, unable to test mental state

b) Portosystemic Encephalopathy Index

\[ PSE = (\text{grade of mental state}) \times 3 + \text{(grade of number connection test}) + \text{(grade of flapping tremor}) + \text{(grade of blood ammonia}) \]
Minimal Hepatic Encephalopathy

- Prevalence 30% and 84%
- Memory reduction, personality changes, concentration and reaction times ↓ QOL
- ? marker for future episodes of clinical HE

Hepatology. Volume 45, Issue 3, Pages 549-559
I-acyl-carnitine

- co-factor required for transport of long-chain fatty acids through the mitochondrial membrane (important for metabolism and energy production)
- maintains the intramitochondrial salvage pathways
- re-activates coenzyme A
- reduce peroxidation and intracellular malonyl-aldehyde levels
- act as a scavenger and to contribute to neurotransmitter synthesis due to the structural affinity to acetyl-choline.
l-acyl-carnitine

- Malaguarnera et al. (3 rct’s) oral carnitine
  - ↓ serum ammonia levels
  - ↑ patient performance on a variety of psychometric tests (ONLY grade 0, 1, or 2)
- In critically ill patients with hepatic coma
  - ↓ serum ammonia levels
  - ↑ Glasgow coma score appears to have worsened compared to placebo.
- All 4gm oral cartinine
- IMPORTANT LIMITATION: single center by one investigator
Mean decline in serum ammonia with carnitine versus placebo in two randomized controlled series.
Mean change in the Glasgow coma scale of critically ill cirrhotic patients treated with L-carnitine versus placebo.
Lactulose has been used as the standard treatment for hepatic encephalopathy, and its efficacy has been considered to be beyond. It was implemented in clinical practice because two trials found it "equally effective" to neomycin, which had been the standard treatment for hepatic encephalopathy since 1957.

Non-absorbable disaccharides for hepatic encephalopathy.

“There is insufficient evidence to support or refute the use of non-absorbable disaccharides for hepatic encephalopathy. Antibiotics were superior to non-absorbable disaccharides in improving hepatic encephalopathy, but it is unclear whether this difference is clinically important.”

BMJ 2004;328:1046 (1 May)
Treating HE

- Non-absorbable disaccharides for hepatic encephalopathy.
  - minimal hepatic encephalopathy appears to be the exception
### Treating HE

Fig 2 Number of patients without improvement of hepatic encephalopathy in trials on non-absorbable disaccharides versus placebo or no intervention, stratified according to quality of methods

<table>
<thead>
<tr>
<th>Study</th>
<th>Total No in group</th>
<th>Non-absorbable disaccharides</th>
<th>Placebo or no intervention</th>
<th>Relative risk (95% CI)</th>
<th>Weight (%)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High quality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simmons 1970</td>
<td>23/21</td>
<td>4/14</td>
<td>5/12</td>
<td>7.41</td>
<td>0.58 (0.24 to 1.99)</td>
<td></td>
</tr>
<tr>
<td>German 1973</td>
<td>23/21</td>
<td>4/14</td>
<td>5/12</td>
<td>6.16</td>
<td>1.73 (0.41 to 6.33)</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>46/42</td>
<td>8/28</td>
<td>10/24</td>
<td>13.87</td>
<td>0.92 (0.42 to 2.04)</td>
<td></td>
</tr>
<tr>
<td>Total events: 0 (non-absorbable disaccharides), 0 (control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Test for heterogeneity: $\chi^2=0.07$, df=1, P=0.81, $I^2=0.0$
| Test for overall effect: $z=0.19$, P=0.83 |

<table>
<thead>
<tr>
<th>Low quality</th>
<th>Total No in group</th>
<th>Non-absorbable disaccharides</th>
<th>Placebo or no intervention</th>
<th>Relative risk (95% CI)</th>
<th>Weight (%)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urba 1983</td>
<td>0/10</td>
<td>0/10</td>
<td>4/5</td>
<td>1.20</td>
<td>0.86 (0.00 to 0.65)</td>
<td></td>
</tr>
<tr>
<td>Watanabe 1992</td>
<td>12/22</td>
<td>11/14</td>
<td>11/14</td>
<td>28.04</td>
<td>0.69 (0.43 to 1.11)</td>
<td></td>
</tr>
<tr>
<td>Li 1996</td>
<td>20/48</td>
<td>22/28</td>
<td>92/98</td>
<td>19.76</td>
<td>0.62 (0.65 to 0.00)</td>
<td></td>
</tr>
<tr>
<td>Dhiman 2000</td>
<td>6/14</td>
<td>12/12</td>
<td>6/14</td>
<td>19.43</td>
<td>0.43 (0.23 to 0.78)</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>34/54</td>
<td>34/54</td>
<td>54/54</td>
<td>68.43</td>
<td>0.57 (0.40 to 0.03)</td>
<td></td>
</tr>
<tr>
<td>Total events: 40 (non-absorbable disaccharides), 54 (control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Test for heterogeneity: $\chi^2=2.36$, df=3, P=0.76, $I^2=9.5$
| Test for overall effect: $z=2.48$, P=0.03 |

| Total (95% CI) | | | | | | |
|---------------|-------------------|------------------------------|------------------------|------------|------------------------|
| 117/90 | 117/90 | 100.00 | 0.62 (0.46 to 0.84) |
| Test for heterogeneity: $\chi^2=6.22$, df=5, P=0.29, $I^2=19.6$
| Test for overall effect: $z=3.98$, P=0.002 |

**Als-Nielsen, B. et al. BMJ 2004;328:1046**
**Fig 3 Number of patients without improvement of hepatic encephalopathy in trials on non-absorbable disaccharides versus antibiotics, stratified according to type of antibiotic**

<table>
<thead>
<tr>
<th>Study</th>
<th>Non-absorbable disaccharides</th>
<th>Antibiotics</th>
<th>Relative risk (95% CI)</th>
<th>Weight (%)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>Conn 1977&lt;sup&gt;3&lt;/sup&gt;</td>
<td>3/18</td>
<td>2/15</td>
<td>1.32</td>
<td>1.25 (0.24 to 6.53)</td>
</tr>
<tr>
<td>Atterbury 1978&lt;sup&gt;6&lt;/sup&gt;</td>
<td>4/22</td>
<td>3/23</td>
<td>1.90</td>
<td>1.39 (0.35 to 5.53)</td>
<td></td>
</tr>
<tr>
<td>Orlandi 1981&lt;sup&gt;30&lt;/sup&gt;</td>
<td>63/91</td>
<td>48/82</td>
<td>69.52</td>
<td>1.18 (0.94 to 1.49)</td>
<td></td>
</tr>
<tr>
<td>Russo 1989&lt;sup&gt;31&lt;/sup&gt;</td>
<td>1/8</td>
<td>1/7</td>
<td>0.54</td>
<td>0.88 (0.07 to 11.54)</td>
<td></td>
</tr>
<tr>
<td>Blanc 1993&lt;sup&gt;32&lt;/sup&gt;</td>
<td>9/29</td>
<td>10/31</td>
<td>6.51</td>
<td>0.96 (0.46 to 2.03)</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>168</td>
<td>158</td>
<td></td>
<td>79.80</td>
<td>1.17 (0.94 to 1.44)</td>
</tr>
<tr>
<td>Total events: 80 (non-absorbable disaccharides), 64 (antibiotics)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: χ²=0.39, df=4, P=0.98, I²=0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: z=1.42, P=0.16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Non-absorbable disaccharides</th>
<th>Antibiotics</th>
<th>Relative risk (95% CI)</th>
<th>Weight (%)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifaximin</td>
<td>Fera 1993&lt;sup&gt;34&lt;/sup&gt;</td>
<td>4/20</td>
<td>0/20</td>
<td>0.44</td>
<td>9.00 (0.52 to 156.91)</td>
</tr>
<tr>
<td>Massa 1993&lt;sup&gt;36&lt;/sup&gt;</td>
<td>0/20</td>
<td>0/20</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Song 2000&lt;sup&gt;37&lt;/sup&gt;</td>
<td>7/25</td>
<td>8/39</td>
<td>4.65</td>
<td>1.37 (0.57 to 3.30)</td>
<td></td>
</tr>
<tr>
<td>Loguercio 2003&lt;sup&gt;38&lt;/sup&gt;</td>
<td>11/13</td>
<td>6/14</td>
<td>8.61</td>
<td>1.97 (1.03 to 3.77)</td>
<td></td>
</tr>
<tr>
<td>Mas 2003&lt;sup&gt;38&lt;/sup&gt;</td>
<td>12/53</td>
<td>10/50</td>
<td>6.51</td>
<td>1.13 (0.54 to 2.38)</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>131</td>
<td>143</td>
<td></td>
<td>20.20</td>
<td>1.57 (1.03 to 2.39)</td>
</tr>
<tr>
<td>Total events: 34 (non-absorbable disaccharides), 24 (antibiotics)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: χ²=2.75, df=3, P=0.43, I²=0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: z=2.08, P=0.04</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Non-absorbable disaccharides</th>
<th>Antibiotics</th>
<th>Relative risk (95% CI)</th>
<th>Weight (%)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total events: 114 (non-absorbable disaccharides), 88 (antibiotics)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: χ²=4.69, df=8, P=0.79, I²=0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: z=2.20, P=0.03</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Alts-Nielsen, B. et al. BMJ 2004;328:1046
To Lactulose or not to Lactulose

- **Als-Nielsen B, Gluud LL, Gluud C.**
  BMJ 2004;328:1046 (1 May)
- 22 trials were included.
- reduce the risk of no improvement in patients with HE
- High quality trials found no significant effect (0.92, 0.42 to 2.04, two trials).
- no significant effect on mortality
- inferior to antibiotics in reducing the risk of no improvement and lowering blood ammonia concentration
Treating HE

- Branched-chain amino acids for hepatic encephalopathy.
  - “We did not find convincing evidence that BCAA had a significant beneficial effect on patients with hepatic encephalopathy”. Cochrane Database Syst Rev. 2003;(2):CD001939
Treating HE

- Benzodiazepine receptor antagonists for hepatic encephalopathy.
  - “Flumazenil had a significant beneficial effect on short-term improvement of hepatic encephalopathy in patients with cirrhosis and a highly favourable prognosis. Flumazenil had no significant effect on recovery or survival.”
  - Cochrane Database Syst Rev. 2004
Treating HE

- Dopaminergic agonists for hepatic encephalopathy.
  - “This review does not provide evidence that dopaminergic agonists are of benefit to patients with acute or chronic hepatic encephalopathy, or fulminant hepatic failure...there is also insufficient evidence to exclude a potential beneficial effect.”
**l-ornithine-l-aspartate (LOLA)**

- Ornithine + ammonia → urea
- Aspartate + ammonia → glutamine
- LOLA thus provides for both of these ammonia detoxification pathways.
- Several randomized controlled trials with LOLA have been carried out in Germany over the last 10 years.
- All these studies showed a beneficial effect of this compound on HE.
LOLA

Review: L-Ornithine-L-Aspartate in the Management of Hepatic Encephalopathy: a Meta-analysis
Comparison: LOLA versus placebo
Outcome: LOLA in the management of Chronic HE—overall effect

<table>
<thead>
<tr>
<th>Study</th>
<th>treatment n/N</th>
<th>control n/N</th>
<th>RR (fixed) 95% CI</th>
<th>Weight %</th>
<th>RR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>[8] Stauch, S. et al</td>
<td>17/34</td>
<td>8/32</td>
<td>2.00 [1.01, 3.96]</td>
<td>29.18</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td>100.00</td>
<td>1.69 [1.32, 2.71]</td>
</tr>
</tbody>
</table>

Total events: 54 (treatment), 28 (control)
Test for heterogeneity: \( \chi^2 = 0.04, \text{df} = 1 (P = 0.85) \), \( I^2 = 0\% \)
Test for overall effect: \( Z = 3.50 \) (\( P = 0.0005 \))

Favours Placebo  | Favours LOLA
<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>LOALA in the management of SHE</th>
<th>Control</th>
<th>RR (fixed)</th>
<th>Weight</th>
<th>95% CI</th>
<th>Favours LOALA</th>
</tr>
</thead>
<tbody>
<tr>
<td>[8] Staubach, S. et al</td>
<td>0.23</td>
<td>29.37</td>
<td>0.14</td>
<td>1.52</td>
<td>0.75, 2.38</td>
<td>Favours Placebo</td>
</tr>
<tr>
<td>[9] Kitchens G. et al</td>
<td>0.70</td>
<td>1.98</td>
<td>0.65</td>
<td>1.24, 2.34</td>
<td>3.03</td>
<td>Favours LOALA</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2 = 0.02$, df = 1, p = 0.89, I² = 0%
Test for overall effect: Z = 3.14, p = 0.002

Comparisons:
01. LOALA in the management of SHE or I

LOALA

LOALA is effective in the management of SHE or I. The meta-analysis shows a significant difference in favour of LOALA, with a pooled relative risk (RR) of 0.31 (95% CI: 0.24, 0.40) compared to the control group. The heterogeneity test indicates low variability among studies (I² = 0%).
Zinc and HE

- long-term oral zinc speeds up the kinetics of urea formation from amino acids and ammonia.
- Cirrhotics have reduced Zinc levels
- Zinc levels inversely correlate with ammonia levels in cirrhotics with HE
- Diuretics reduce zinc levels
- Short term vs Long term: data suggests long term therapy is needed.
- Dose: 220 mg po qday or bid
Nutritional Management:
- Early nutrition to cover calorie needs and 1-1.5 g protein/kg/day.
- In Chronic Stable PSE: branched-chain aminoacidsenriched formula (Nutra-Hep)

Manipulation of Splanchnic Circulation:
- Radiology-guided occlusion of shunts.
Hepatopulmonary Syndrome

- Does not require portal htn
- triad of liver disease, hypoxemia, and intrapulmonary vascular dilations (IPVDs)
- s/s: cyanosis, dyspnea, platypnea, orthodeoxia (fall in PaO2 5% or 4 mm Hg while standing), and clubbing.
- Diagnosis of HPS is based on arterial deoxygenation and CEE+ in the absence of intrinsic cardiopulmonary disease.
- 15–20% of patients with chronic liver diseases
Hepatopulmonary Syndrome

- Pathophysiology
  - intrapulmonary vasodilatation
  - Cytokine-mediated injury
  - induction of inducible nitric oxide synthase

- Treatment
  - Liver transplant (not always successful)
  - Pentoxifylline 400mg PO tid
Diagnosing HPS

Liver Disease
- Portal Hypertension
  - Risk Factors for Chronic Liver Disease

Dyspnea
- Clubbing
- Low Pulse Oximetry / Hypoxemia
- OLT Evaluation

History, Exam, CXR, ABG,
Other tests as appropriate (PFTs, Chest CT)

Elevated A-a gradient (age adjusted)
- Hypoxemia
- Low DLco
- Other studies negative

HPS suspicion high
- Contrast Echocardiogram
  - Normal
    - No HPS
  - Delayed Shunting (>3 heart beats)
  - Early shunting (<3 heart beats)
    - HPS
    - Intracardiac shunt

Studies suggest intrinsic cardiopulmonary disease
  - HPS suspicion low
  - Treat as appropriate
    - Symptoms persist
    - Contrast Echocardiogram
      - MAA if hypoxia and delayed shunting
Baseline and posttherapy median (range) values of exercise-induced change in blood oxygen (EICBO)


“pentoxifylline can be considered a safe and effective therapy for HPS”