Managing Complications of Portal Hypertension

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Varices Increase in Diameter Progressively

- No varices
- Small varices
- Large varices

7-8%/year

Merli et al. J Hepatol 2003;38:266
Screening for Varices

- Current recommendations for screening
  - AASLD:
    - All cirrhotic patients especially with
      - mod-severe cirrhosis (Child B/C)
      - Child A with signs of portal hypertension (plts <140,000, PV >13mm, or evidence of collaterals)
  - ACG: All patients with cirrhosis upon diagnosis of cirrhosis
Capsule Endoscopy for Screening for Varices

Grade 3 Varices

Grade 1 Varices
Capsule Endoscopy vs. EGD for Variceal Screening: EGD is Superior

- If EGD is the gold standard for variceal detection:
  - Sensitivity of CE = 84%
  - Specificity of CE = 88%
  - PPV = 92%
  - NPV = 77%
  - CE missed 13.3% of small varices and 2.2% of large varices

DeFranchis et al, Hepatology 2008;47:1595-1603
Treatment of Varices / Variceal Hemorrhage

- **No varices**
  - Prevention of variceal development
- **Varices**
  - No hemorrhage
- **Variceal hemorrhage**
- **Recurrent hemorrhage**
Pre-Primary Prophylaxis

- Multicenter, randomized, placebo-controlled trial of timolol (non-selective beta-blocker) vs. placebo in patients

- Beta-blockers did not prevent the development of varices and were associated with a higher rate of serious adverse events

- Hepatic venous pressure gradient was the strongest predictor of the development of varices

Groszmann, et al., NEJM 2006
Treatment of Varices / Variceal Hemorrhage

- **No varices**
  - No specific therapy
  - Repeat endoscopy in 2-3 yrs*

- **Varices**
  - **No hemorrhage**
  - Repeat endoscopy in 2-3 yrs*

- **Variceal hemorrhage**

- **Recurrent hemorrhage**

* Sooner with cirrhosis decompensation
Treatment of Varices / Variceal Hemorrhage

- No varices
- Varices
  - No hemorrhage
  - Variceal hemorrhage
  - Recurrent hemorrhage
- Prevention of first variceal hemorrhage
Treatment of Varices / Variceal Hemorrhage

No varices

Varices
No hemorrhage

Variceal hemorrhage

Recurrent hemorrhage

Management depends on the size of varices
## Non-Selective Beta-Blockers Prevent First Variceal Hemorrhage

<table>
<thead>
<tr>
<th>Bleeding rate (~2 year)</th>
<th>Control</th>
<th>Beta-blocker</th>
<th>Absolute rate difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>All varices</td>
<td>25%</td>
<td>15%</td>
<td>-10%</td>
</tr>
<tr>
<td>(11 trials)</td>
<td>(n=600)</td>
<td>(n=590)</td>
<td>(-16 to -5)</td>
</tr>
<tr>
<td>Large varices</td>
<td>30%</td>
<td>14%</td>
<td>-16%</td>
</tr>
<tr>
<td>(8 trials)</td>
<td>(n=411)</td>
<td>(n=400)</td>
<td>(-24 to -8)</td>
</tr>
<tr>
<td>Small varices</td>
<td>7%</td>
<td>2%</td>
<td>-5%</td>
</tr>
<tr>
<td>(3 trials)</td>
<td>(n=100)</td>
<td>(n=91)</td>
<td>(-11 to 2)</td>
</tr>
</tbody>
</table>

*D’Amico et al., Sem Liv Dis 1999;19:475*
Variceal Band Ligation (VBL) vs. Beta-Blockers (BB) in the Prevention of First Variceal Bleed

First hemorrhage

Survival

Favors VBL  Favors BB
Favors BB  Favors VBL

Chen 1998
Sarin 1999
De 1999
Jutabha 2000
De la Mora 2000
Lui 2002
Lo 2004
Schepke 2004
Total

Relative risk

Treatment of Varices / Variceal Hemorrhage

- No varices
- Small varices
  - No hemorrhage
- Medium/large varices
  - No hemorrhage
  - *1) β-blockers (propranolol, nadolol) indefinitely
  - 2) Endoscopic variceal ligation in patients intolerant to β-blockers
- Variceal hemorrhage
- Recurrent hemorrhage

*β-blocker vs EBL based on expertise, availability, preference
Treatment of Varices / Variceal Hemorrhage

- **No varices**
- **Small varices**
  - No hemorrhage
- **Medium/large varices**
  - No hemorrhage
- **Variceal hemorrhage**
- **Recurrent hemorrhage**

**? Prevention of variceal growth**
Nadolol May Prevent the Growth of Small Varices

Merkel et al., Gastroenterology 2004;127:476
Treatment of Varices / Variceal Hemorrhage

- No varices
- Small varices
  - No hemorrhage
  - Repeat endoscopy in 1-2 years*
  - Beta-blockers+
- Medium/large varices
  - No hemorrhage
- Variceal hemorrhage
- Recurrent hemorrhage

* Sooner with cirrhosis decompensation
+ If varices have high risk signs or Child-Pugh B/C patients
Predictors of hemorrhage:

- Variceal size
- Red signs
- Child B/C

Variceal hemorrhage

Varix with red signs

Treatment of Varices / Variceal Hemorrhage

- No varices
- Small varices
  - No hemorrhage
- Medium/large varices
  - No hemorrhage
- Variceal hemorrhage
- Recurrent hemorrhage

Control of hemorrhage
Treatment of Acute Variceal Hemorrhage

General Management:
- IV access and fluid resuscitation
- Do not overtransfuse (hemoglobin ~ 8 g/dL)
- Antibiotic prophylaxis

Specific therapy:
- Pharmacological therapy: terlipressin, somatostatin and analogues, vasopressin + nitroglycerin
- Endoscopic therapy: ligation, sclerotherapy
- Shunt therapy: TIPS, surgical shunt
# Prophylactic Antibiotics Improve Outcomes in Cirrhotic Patients with GI Hemorrhage

<table>
<thead>
<tr>
<th></th>
<th>Control (n=270)</th>
<th>Antibiotic (n=264)</th>
<th>Absolute rate difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>45%</td>
<td>14%</td>
<td>-32% (-42 to –23)</td>
</tr>
<tr>
<td>SBP / Bacteremia</td>
<td>27%</td>
<td>8%</td>
<td>-18% (-26 to –11)</td>
</tr>
<tr>
<td>Death</td>
<td>24%</td>
<td>15%</td>
<td>-9% (-15 to –3)</td>
</tr>
</tbody>
</table>

*Bernard et al., Hepatology 1999;29:1655*
Combination Drug / Endoscopic Therapy is More Effective Than Endoscopic Therapy Alone in Achieving Five-Day Hemostasis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sclero + Octreotide</td>
<td>Besson, 1995</td>
</tr>
<tr>
<td>Ligation + Octreotide</td>
<td>Sung, 1995</td>
</tr>
<tr>
<td>Sclero + Octreotide / ST</td>
<td>Signorelli, 1996</td>
</tr>
<tr>
<td>Sclero + Octreotide</td>
<td>Ceriani, 1997</td>
</tr>
<tr>
<td>Sclero + Octreotide</td>
<td>Signorelli, 1997</td>
</tr>
<tr>
<td>Sclero + ST</td>
<td>Avgerinos, 1997</td>
</tr>
<tr>
<td>Sclero + Octreotide</td>
<td>Zuberi, 2000</td>
</tr>
<tr>
<td>Sclero / ligation + Vapreotide</td>
<td>Cales, 2001</td>
</tr>
</tbody>
</table>

**TOTAL**

Favors endoscopic therapy alone

Favors endoscopic plus drug therapy

Relative Risk

Bañares R et al., *Hepatology* 2002;35:609
Endoscopic Variceal Band Ligation

- Bleeding controlled in 90%
- Rebleeding rate 30%
- Compared with sclerotherapy:
  - Less rebleeding
  - Lower mortality
  - Fewer complications
  - Fewer treatment sessions
Endoscopic Variceal Band Ligation

- Banding ulcers
  - Significant and severe complication
- PPI compared placebo*
  - Post-banding ulcers smaller, $p<0.05$
  - Banding ulcer bleeds lower, $p>0.05$

*Shaheen et al., Hepatology 2005;41:588-594
TIPS in the Treatment of Variceal Hemorrhage

- TIPS is rescue therapy for recurrent variceal hemorrhage
  (at second rebleed for esophageal varices, at first rebleed for gastric varices)

- TIPS is indicated in patients who rebleed on combination endoscopic plus pharmacologic therapy

- In patients with Child A/B cirrhosis, the distal spleno-renal shunt is as effective as TIPS
  (dependent on local expertise)
Early Use of TIPS in Patients with Cirrhosis* and Variceal Bleeding

![Graph A: Freedom from Uncontrolled Bleeding or Rebleeding (Early TIPS vs. Drugs+EBL)](image)

![Graph B: Survival (Early TIPS vs. Drugs+EBL)](image)

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Months</th>
<th>Early TIPS</th>
<th>Drugs+EBL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early TIPS</td>
<td>32</td>
<td>24</td>
<td>15</td>
</tr>
<tr>
<td>Drugs+EBL</td>
<td>31</td>
<td>13</td>
<td>7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Months</th>
<th>Early TIPS</th>
<th>Drugs+EBL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early TIPS</td>
<td>32</td>
<td>24</td>
<td>17</td>
</tr>
<tr>
<td>Drugs+EBL</td>
<td>31</td>
<td>18</td>
<td>13</td>
</tr>
</tbody>
</table>

*Child-Pugh Class C (10-13 points) or Child-Pugh Class B with active bleeding on initial endoscopy

Garcia-Pagan et al. NEJM 2010;362:2370-2379
Treatment of Varices / Variceal Hemorrhage

- No varices
- Small varices \(\rightarrow\) No hemorrhage
- Medium/large varices \(\rightarrow\) No hemorrhage
- Variceal hemorrhage
- Recurrent hemorrhage

1) Safe vasoactive drug + endoscopic therapy + antibiotic prophylaxis
2) Early TIPS for Child-Pugh B/C
3) TIPS / Shunt (rescue therapy)
Lowest Rebleeding Rates are Obtained in HVPG Responders and With Ligation + β-Blockers

Bosch and García-Pagán, Lancet 2003;361:952

* ↓ HVPG <12 mmHg or >20% from baseline
Treatment of Varices / Variceal Hemorrhage

- No varices
- Varices
  - No hemorrhage
- Variceal hemorrhage
  - Recurrent hemorrhage
  
1) β-blockers + ISMN or EVL
2) β-blockers + EVL may be preferable
3) TIPS / shunt surgery
Evolution of Varices

Cirrhosis with no varices

Small varices
No hemorrhage

Medium / large varices
No hemorrhage

Variceal hemorrhage

Recurrent variceal hemorrhage

Level of Intervention

Pre-primary prophylaxis

Primary prophylaxis

Secondary prophylaxis

Management Recommendations

- Repeat endoscopy in 2-3 years
- No specific therapy

Small varices

- Repeat endoscopy in 1-2 years
- No specific therapy
- ? beta-blocker to prevent enlargement

Medium/Large varices

- Non-selective beta-blockers
- EVL in those intolerant to drugs

- Endoscopic/pharmacologic therapy
- Antibiotics in all patients
- TIPS or shunt surgery as rescue therapy

- Beta-blockers + nitrates or EVL
- Beta-blockers + EVL ?
- TIPS or shunt surgery as rescue therapy
Pathophysiology of Hepatic Encephalopathy

↑ Ammonia

Upregulation of astrocytic peripheral benzodiazepine receptors (PBR)

Neurosteroid production

Modulation of $\text{GABA}_A$ receptor

Hepatic encephalopathy
Hepatic Encephalopathy is a Clinical Diagnosis

- Clinical findings and history important
- Ammonia levels are unreliable
- Measurement of ammonia not necessary
- Measurement of ammonia levels may be supportive when diagnosis is in doubt
## Stages of Hepatic Encephalopathy

<table>
<thead>
<tr>
<th>Stage</th>
<th>Mental state</th>
<th>Neurologic signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mild confusion: limited attention span, irritability, inverted sleep pattern</td>
<td>Incoordination, tremor, impaired handwriting</td>
</tr>
<tr>
<td>2</td>
<td>Drowsiness, personality changes, intermittent disorientation</td>
<td>Asterixis, ataxia, dysarthria</td>
</tr>
<tr>
<td>3</td>
<td>Somnolent, gross disorientation, marked confusion, slurred speech</td>
<td>Hyperreflexia, muscle rigidity, Babinski sign</td>
</tr>
<tr>
<td>4</td>
<td>Coma</td>
<td>No response to pain, decerebrate posture</td>
</tr>
</tbody>
</table>
Minimal Hepatic Encephalopathy

- Occurs in 30-70% of cirrhotic patients without overt hepatic encephalopathy
- Detected by psychometric and neuro-psychological testing
- May improve with lactulose or synbiotics (probiotics and fermentable fiber)
Treatment of Hepatic Encephalopathy

- Identify and treat precipitating factor
  - Infection
  - GI hemorrhage
  - Prerenal azotemia
  - Sedatives
  - Constipation
- Protein restriction should be avoided
Treatment of Hepatic Encephalopathy

- Lactulose (adjust to 2-3 bowel movements/day)

- Long-term therapy assessment
  - Higher likelihood of recurrent encephalopathy
  - Assessment of need for liver transplantation
## Current HE Treatment Options

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Drug Class</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactulose</td>
<td>Poorly absorbed disaccharide</td>
<td>• Decrease blood ammonia concentration&lt;br&gt;• Prevention and treatment of portal-systemic encephalopathy</td>
</tr>
<tr>
<td>Rifaximin</td>
<td>Non-aminoglycoside semi-synthetic, nonsystemic antibiotic</td>
<td>Reduction in risk of overt hepatic encephalopathy (HE) recurrence in patients ≥ 18 years of age.</td>
</tr>
<tr>
<td>Neomycin</td>
<td>Aminoglycoside antibiotic</td>
<td>Adjuvant therapy in hepatic coma&lt;br&gt;Ototoxicity and nephrotoxicity</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Synthetic antiprotozoal and antibacterial agent</td>
<td>Not approved for HE&lt;br&gt;Peripheral neurotoxicity</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Aminoglycoside antibiotic</td>
<td>Not approved for HE&lt;br&gt;Bacterial resistance and renal toxicity</td>
</tr>
</tbody>
</table>

Lactulose

• Currently the mainstay of therapy of HE; ~70% to 80% of patients with acute and chronic HE improve with lactulose treatment

• Administered orally, by mouth or through a nasogastric tube or via retention enemas

• Adjust to 2-3 bowel movements/day

• Principal side effects include abdominal distension, cramping, diarrhea, electrolyte changes, and flatulence

Bajaj JS. *Aliment Pharmacol Ther* 2010;31:537-547
Rifaximin

- Minimally absorbed (<0.4%) oral antibiotic
- No clinical drug interactions reported
- No dosing adjustment required in patients with liver disease or renal insufficiency
- In registration trials, 91% of patients were given lactulose concomitantly
  - 58% reduction in risk of recurrent hepatic encephalopathy (NNT=4)
  - 50% reduction in risk of hospitalizations (NNT=9)

Cirrhosis

- Hepatic venous outflow block
  - Sinusoidal pressure (HVPG ≥ 10-12 mmHg)
  - Ascites

- Arteriolar resistance (vasodilation)
  - Effective arterial blood volume

- Sodium and water retention
  - Activation of neurohumoral systems (renin, angiotensin, aldosterone)
Natural History of Ascites

Portal Hypertension
No Ascites

- HVPG <10 mmHg
  - Mild Vasodilation

Uncomplicated
Ascites

- HVPG >10 mmHg
  - Moderate Vasodilation

Refractory
Ascites

- HVPG >10 mmHg
  - Severe Vasodilation

Hepatorenal
Syndrome

- HVPG >10 mmHg
  - Extreme Vasodilation
# Ascitic Fluid Analysis

## Ascitic Fluid Laboratory Data

<table>
<thead>
<tr>
<th>Routine</th>
<th>Unusual</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell count and differentials</td>
<td>Acid fast bacillus smear and culture</td>
</tr>
<tr>
<td>Albumin</td>
<td>Cytology</td>
</tr>
<tr>
<td>Total protein</td>
<td>Triglyceride</td>
</tr>
<tr>
<td>Serum-ascites albumin gradient (calculated)</td>
<td>Bilirubin</td>
</tr>
<tr>
<td>Optional</td>
<td>Unhelpful</td>
</tr>
<tr>
<td>Culture in blood culture bottles</td>
<td>pH</td>
</tr>
<tr>
<td>Glucose</td>
<td>Lactate</td>
</tr>
<tr>
<td>Lactate dehydrogenase</td>
<td>Cholesterol</td>
</tr>
<tr>
<td>Amylase</td>
<td>Fibronectin</td>
</tr>
<tr>
<td>Gram’s stain</td>
<td>Glycosaminoglycans</td>
</tr>
</tbody>
</table>

Serum-Ascites Albumin Gradient

<table>
<thead>
<tr>
<th>Serum-Ascites Albumin Gradient (SAAG)</th>
<th>Low Gradient (&lt; 1.1 g/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Gradient (≥ 1.1 g/dl)</td>
<td>Peritoneal carcinomatosis</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>Peritoneal tuberculosis</td>
</tr>
<tr>
<td>Alcoholic hepatitis</td>
<td>Pancreatic ascites</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>Biliary ascites</td>
</tr>
<tr>
<td>Massive liver metastases</td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Fulminant hepatic failure</td>
<td>Serositis</td>
</tr>
<tr>
<td>Budd-Chiari syndrome</td>
<td>Bowel obstruction or infarction</td>
</tr>
<tr>
<td>Portal-vein thrombosis</td>
<td></td>
</tr>
<tr>
<td>Veno-occlusive disease</td>
<td></td>
</tr>
<tr>
<td>Fatty liver of pregnancy</td>
<td></td>
</tr>
<tr>
<td>Myxedema</td>
<td></td>
</tr>
<tr>
<td>“Mixed” ascites</td>
<td></td>
</tr>
</tbody>
</table>

Treatment of Ascites

- Portal Hypertension
  - No ascites
    - Uncomplicated ascites
    - Refractory ascites
      - Hepatorenal syndrome
    - No specific therapy
      - Consider salt restriction
Treatment of Ascites

Portal Hypertension
No ascites

Uncomplicated ascites

Refractory ascites

Hepatorenal syndrome
Management of Uncomplicated Ascites

Sodium Restriction 2 g (or 5.2 g of dietary salt) a day

Fluid restriction is not necessary unless there is hyponatremia (<125 mmol/L)

Diuretics
- Spironolactone 100-400 mg/day
- Furosemide (40-160 mg/d) for inadequate weight loss or if hyperkalemia develops
- Increase diuretics if weight loss <1 kg in the first week and < 2 kg/week thereafter
- Side effects
  - Renal dysfunction, hyponatremia, hyperkalemia, encephalopathy, gynecomastia
Treatment of Ascites

Portal Hypertension
No ascites

Uncomplicated ascites

Refractory ascites

Hepatorenal syndrome
Definition and Types of Refractory Ascites

Occurs in ~10% of cirrhotic patients

- **Diuretic-intractable ascites** 80%
  Therapeutic doses of diuretics cannot be achieved because of diuretic-induced complications

- **Diuretic-resistant ascites** 20%
  No response to maximal diuretic therapy (400 mg spironolactone + 160 mg furosemide/day)

*Arroyo et al. Hepatology 1996;23:164*
Meta-Analysis of TIPS vs. LVP + Albumin for Refractory Ascites

- Ascites control (month 4)
- Ascites control (month 12)
- Survival (month 12)
- Encephalopathy

More with LVP

Risk Difference

More with TIPS

Deltenre et al., Liver International 2005;25:349
Treatment of Ascites

Portal Hypertension
No Ascites

Uncomplicated
Ascites

Refractory
Ascites

Hepatorenal
Syndrome

1) LVP + albumin
2) TIPS
3) PVS (in non-TIPS, non-transplant candidates)

LVP = large volume paracentesis
TIPS = transjugular intrahepatic portosystemic shunt
Take Home Points

• Three Major Complications of Portal Hypertension
  • Varices
    • Primary prophylaxis
    • Management of acute bleeding
    • Secondary prophylaxis
  • Hepatic Encephalopathy
    • Clinical diagnosis
    • Identify precipitating factors
    • Identify and then treat patients with recurrent encephalopathy
Take Home Points

- **Ascites Management**
  - Diagnose portal hypertension related ascites using SAAG
  - Sodium restriction is important
  - Judicious use of diuretics

- **Refractory Ascites**
  - Make sure definition is fulfilled before ‘giving up’

- **Spontaneous Bacterial Peritonitis**
  - Diagnosis: **PMN count >250/mm³**
  - Secondary prophylaxis