Complications of Cirrhosis

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Overview

• What is cirrhosis?
• Causes
• Pathophysiology “lite”
• Complications of cirrhosis
  – Portal Hypertensive Ascites
  – Hepatorenal Syndrome
• Implications for endoscopy
  – Spontaneous Bacterial Peritonitis
  – Gastrointestinal Varices
  – Hepatic Encephalopathy
  – Hepatocellular Carcinoma
Cirrhosis

• End stage of any chronic liver disease
• 12th leading cause of death in US
• Characterized histologically by regenerative nodules surrounded by fibrous tissue

• Clinically there are two types of cirrhosis:
  – Compensated and Decompensated
• Extraordinary economic impact
  • 2004: 2.5B direct; 10.5B indirect excluding HCV!
Common Causes of Cirrhosis

• Hepatitis C (HCV)
  – 180-200M worldwide; 5 M Americans
  – 80% chronic; 20% cirrhosis
  – 10,000-12,000 deaths/year
  – Annual cost: ~9 Billion/year
  – Leading indication for liver transplant
    • $300M/year
  – Cure does not eradicate cirrhosis
Prevalence of HCV in Select Populations

- **Incarcerated**: \(\sim 330,000 - 860,000\) (16-41%)
- **IVDU**: \(\sim 300,000\) (80% to 90%)
- **Alcoholics**: \(\sim 240,000\) (11% to 36%)
- **Homeless**: \(\sim 175,000\) (22%)
- **HIV-infected**: \(\sim 300,000\) (30%)
- **Veterans**: \(\sim 280,000\) (8%)
- **Children** (6-18 years old): \(\sim 100,000\) (0.1%)
- **Living below poverty level**: \(\sim 940,000\) (2.4%)

Adapted From the following:

Alcoholic cirrhosis

• The most deadly legal “drug”
• 14M Alcoholics in US
  – 10-15% develop cirrhosis
• Threshold to cause liver damage (10 y)
  – W:10-40 gms/day
  – M:40-80 gms/day
• Often complicated by HCV
  – Faster progression, worse prognosis
# Alcohol Content of Various Beverages

<table>
<thead>
<tr>
<th>Beverage</th>
<th>Alcohol Content</th>
<th>Serving Size</th>
<th>Amount of Alcohol</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beer</td>
<td>5%</td>
<td>12 oz</td>
<td>13.85 g</td>
<td>3-6 cans</td>
<td>1.5-3 cans</td>
</tr>
<tr>
<td>Wine</td>
<td>12%</td>
<td>4 oz</td>
<td>10.7 g</td>
<td>4-8 glasses</td>
<td>2-4 glasses</td>
</tr>
<tr>
<td>Fortified wine</td>
<td>20%</td>
<td>4 oz</td>
<td>17.8 g</td>
<td>2-4 glasses</td>
<td>1-2 glasses</td>
</tr>
<tr>
<td>Hard liquor</td>
<td>40%</td>
<td>1.5 oz</td>
<td>13.4 g</td>
<td>3-6 drinks</td>
<td>1.5-3 drinks</td>
</tr>
</tbody>
</table>

Daily Intake Needed to Exceed Threshold for Alcoholic Liver Disease
NAFLD
Spectrum of Hepatic Pathology

Steatosis

Steatohepatitis

Hepatocellular carcinoma

Cirrhosis
Natural history of NAFLD

- NAFLD
  - Isolated fatty liver no increase in mortality
  - NASH
    - 1-3%/yr
    - Increased mortality CV, malignancy, liver
  - Cirrhosis
    - 2-3%/yr
    - 3-5%/yr
    - Decompensation
    - HCC
  - >80%

Torres DM, Clin Gastro Hep 2012
Other causes of cirrhosis

- Hepatitis B
- Autoimmune Hepatitis
- Primary biliary cirrhosis (cholangitis)
- Primary sclerosing cholangitis
- Hemochromatosis
- Cystic fibrosis
- Toxins/drugs – Methotrexate, amiodarone
- Schistosomiasis
- Biliary atresia
Cirrhotic Liver

Portal system

collaterals

Distorted sinusoidal architecture leads to increased resistance

Portal vein

Splenomegaly
Factors Involved in the Development of Portal Hypertension

- Cirrhosis
- Resistance to portal flow
- Portal Hypertension
- Portosystemic shunting and liver failure
  - Na and Water Retention
  - Vasodilation
  - Plasma Volume Expansion
  - Hyperdynamic Circulation

Complications of Cirrhosis

- Portal Hypertensive Ascites
- Hepatorenal Syndrome
- Spontaneous Bacterial Peritonitis
- Gastrointestinal Varices
- Hepatic Encephalopathy
- Hepatocellular Carcinoma
Portal Hypertensive Ascites

- Most common form of clinical decompensation
Theory of Ascites Formation in Cirrhosis

Cirrhosis → Portal Hypertension → Splanchnic Arteriolar Vasodilation

- Forward Increase in Capillary Pressure and Filtration Coefficient: Lymph Formation > Lymph Return
- Decrease in Effective Arterial Blood Volume: Activation of ADH, SNS, and RAAS → Sodium and Water Retention → Continuous Ascites Formation
Features of Ascites

• ↑ Abdominal girth, fatigue, ↓ appetite, shortness of breath
• Bulging flanks, flank dullness, fluid wave
  – +/- Peripheral edema
• Lab evidence of cirrhosis
  – Deranged lytes, plts, alb, bili, INR
  – SAAG (Serum alb-ascites alb) > 1.1
Management of Ascites

**Ascites**

**Mild to moderate**
- Na restriction (< 2 g/day)
- Diuretics (spironolactone and lasix)

**Tense**
- Large Volume Paracentesis
- Diuretics
- Na restriction
- Transplant evaluation

**Refractory Ascites**
- TIPS
- LVP
TIPS – A Visual Representation
Hepatorenal Syndrome

- Renal failure in patients with cirrhosis, advanced liver failure and severe sinusoidal portal hypertension

- Absence of significant histological changes in the kidney ("functional" renal failure)

- Marked arteriolar vasodilation in the extra-renal circulation

- Marked renal vasoconstriction leading to reduced glomerular filtration rate
Signs and Symptoms of HRS

• Advanced liver disease
• All have ascites
• Low but stable SBP
• Oliguria in absence of hypovolemia
• Almost all have hyponatremia
• Benign urine sediment
• Low Na excretion (<10 mmol/L)
• Progressive rise in Cr
Activation of neurohumoral systems

Site of Action of Different Therapies for HRS

Advanced Cirrhosis

Intrahepatic resistance

Sinusoidal pressure

Hepatorenal syndrome

TIPS

Arteriolar resistance (vasodilation)

Effective arterial blood volume

Albumin

Renal vasoconstriction

↑↑Activation of neurohumoral systems

↑↑↑Effective arterial blood volume

↓↓Arteriolar resistance (vasodilation)

TIPS

↑Intrahepatic resistance

↑Sinusoidal pressure

↑Hepatorenal syndrome
Spontaneous Bacterial Peritonitis

- Infection of ascitic fluid without obvious surgically treatable cause
- Present in 10-30% hospitalized patients with ascites
- Often complicates GI bleeding, often precipitates HRS
- Primary precipitant for SBP is bacterial translocation from the intestines
Cirrhosis (Advanced)

Decreased immunity

Bacterial Translocation

Transient Bacteremia

Gut

Prolonged Bacteremia

Sources other than the gut

Ascites Colonization

Spontaneous Bacterial Peritonitis

↓ RES

↓ Complement

* RES – Reticulo-endothelial system
Clinical Characteristics of Spontaneous Bacterial Peritonitis

- Fever
- Jaundice
- Abdominal pain
- Confusion
- Abdominal tenderness
- Hypotension
- No signs or symptoms

The chart shows the percentage of patients with each symptom, with fever being the most common (80% to 100%), followed by jaundice (80% to 100%), abdominal pain (70% to 80%), confusion (60% to 70%), abdominal tenderness (60%), hypotension (20% to 30%), and no signs or symptoms (0% to 20%).
**Diagnosis and Treatment of SBP**

- **Diagnostic paracentesis**
  - Cell count
  - Culture and Gram stain
  - Albumin (serum albumin)

- If Gram stain positive or PMN > 250/μL:
  - Presumptive diagnosis of SBP

- **Begin antibiotic**
  - Gram negative aerobes
  - Non-enterococcal streptococcus
    - e.g. cefotaxime 2g IV q 8-12h for 5-10d

- Consider IV albumin (HRS, mortality benefit)
  - 1.5 gm/kg day 1, 1.0 gm/kg day 3

- Change coverage according to culture result
Prognosis of SBP

- 80-90% short-term survival
- Poor long-term prognosis without LT
- The case for prophylaxis:
  - ~30% survival benefit
  - Inpatients with advanced cirrhosis (Cr > 1.2, Bili > 3.0, Na < 130)
  - Previous SBP
  - Variceal bleeding
  - Low protein ascites

Gastrointestinal Varices
Esophageal Varix Bleeding
Management of Gastrointestinal Varices

Surveillance for development of varices
Primary Prophylaxis

Management of bleeding
Prevention of rebleeding
Screening endoscopy
~5%/yr

- Repeat endoscopy every 2 yrs if no varices
- Primary prophylaxis if large varices
- Continued endoscopic surveillance if small varices

Nutritional support

- Nonselective beta blockers
  - nadolol or propranolol
  - Reduce HVPG < 12mm Hg
  - Dose: ~40-80 mg/day
- Endoscopic variceal ligation
- Long acting nitrates + beta blockers
Management of Bleeding Esophageal Varices

Initial Evaluation of Volume, Blood Loss and Fluid Replacement

- Confirm diagnosis by esophagogastroduodenoscopy

Variceal ligation

- Controlled

Octreotide (50–100 µg/h), Somatostatin (250 µg/h) or Vasopressin infusion 0.1–0.4 U/min (+ nitroglycerin)

- Not controlled

Maintenance therapy

1. Repeated ligation to obliteration

2. β blocker (propanolol or nadolol) (reduce resting pulse to 12 mmHg or HVPG by 20%)

Consider: TIPS (or surgical shunt)

Transplantation
Endoscopic Variceal Ligation
Hepatic Encephalopathy

- Cognitive, psychiatric +/- motor impairment associated with liver disease
  - Type A: Acute liver disease
  - Type B: Portosystemic bypass with no liver disease
  - Type C: Cirrhosis and portal hypertension
    - Type C may be episodic or persistent, clinically obvious or subclinical
Hepatic Encephalopathy

Precipitants

- Excess protein
- GI bleeding
- Sedatives / hypnotics
- TIPS
- Diuretics
- Serum K⁺
- Plasma volume
- Azotemia
- Temp
- Infections
Signs and Symptoms of HE

- Sleep disturbances
- Changes in mood or personality
- Shortened attention span, forgetfulness
- Anxiety, depression
- Motor incoordination
- Flapping tremor of the hands (asterixis)
- Fetor hepaticus
- Hyperventilation
- Coma
Treatment of HE

- Airway protection
- Eliminate precipitating factors
- Lactulose
  - Acidifies stool, aim for 2 – 3 BM/day
- Nonabsorbable antibiotics (rifaximin)
- Moderate protein diet (1-1.5 gm/kg/day)
- Liver transplantation
Hepatocellular Carcinoma

- Common complication of cirrhosis
- ↑ in U.S. due to HBV and HCV
  - Highest risk with Hep C, hemochromatosis
  - 1-4% per year, 5 year risk 17-21%
- Risk factors:
  - Older age
  - Advanced liver disease
  - Male
Screening for HCC

• **Goal:** Identify HCC when small, singular, self-contained

• **Screening methods**
  – Tumor markers (AFP, DCP): poor sensitivity and specificity
  – U/S: Lesions $\geq 1$cm, less sensitive in obese
  – Triple-phase CT or MRI
    • Greatest sensitivity/specificity, higher cost
Liver cancer on MRI
Management of HCC

• Hepatic resection
• Liver transplant for small HCC
  – Milan Criteria: 1 lesion $\leq$ 5cm or $\leq$ 3 lesions $\leq$ 3 cm
• Tumor ablation
  – Radiofrequency ablation (RFA)
  – Chemoembolization (TACE)
  – Radioembolization (TARE)
• Sorafenib
Endoscopy in cirrhotics

- Increased risk of sedation:
  - Impaired hepatic function and blood flow
  - Decreased protein binding
  - Increased volume of distribution
  - Higher plasma level of drug
  - Prolonged sedative effects due to delayed clearance of midazolam (50%)
  - Increased risk of cardiopulmonary events and deterioration of HE

Is Propofol sedation safer?

- Meta-analysis of 5 RCTs
- Propofol vs midazolam+/-opioids
- 433 patients undergoing EGD only
- Comparison of time to sedation, procedure time, procedure recovery time, and adverse events
- AE: hypotension, bradycardia, hypoxemia

### 2.1.1 Time to Sedation

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Propofol Mean</th>
<th>SD</th>
<th>Total</th>
<th>Midazolam Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agrawal 2012</td>
<td>2.1</td>
<td>0.39</td>
<td>40</td>
<td>5</td>
<td>0.83</td>
<td>42</td>
<td>49.0%</td>
<td>-2.90 [-3.18, -2.62]</td>
</tr>
<tr>
<td>Khamaysi 2011</td>
<td>2.9</td>
<td>0.7</td>
<td>31</td>
<td>5</td>
<td>1.4</td>
<td>30</td>
<td>39.9%</td>
<td>-2.10 [-2.66, -1.54]</td>
</tr>
<tr>
<td>Weston 2003</td>
<td>3.6</td>
<td>1.2</td>
<td>10</td>
<td>7.3</td>
<td>2.8</td>
<td>10</td>
<td>11.1%</td>
<td>-3.70 [-5.59, -1.81]</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>81</td>
<td></td>
<td></td>
<td>82</td>
<td></td>
<td>100.0%</td>
<td></td>
<td>-2.67 [-3.38, -1.96]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.25; Chi² = 7.29, df = 2 (P = 0.03); I² = 73%
Test for overall effect: Z = 7.39 (P < 0.00001)

### 2.1.2 Time to Recovery

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Propofol Mean</th>
<th>SD</th>
<th>Total</th>
<th>Midazolam Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agrawal 2012</td>
<td>3.4</td>
<td>0.93</td>
<td>40</td>
<td>9.1</td>
<td>2.1</td>
<td>42</td>
<td>35.1%</td>
<td>-5.70 [-6.40, -5.00]</td>
</tr>
<tr>
<td>Khamaysi 2011</td>
<td>4.1</td>
<td>1.9</td>
<td>31</td>
<td>11.5</td>
<td>5</td>
<td>30</td>
<td>30.3%</td>
<td>-7.40 [-9.31, -5.49]</td>
</tr>
<tr>
<td>Riphaus 2009</td>
<td>7.75</td>
<td>2.85</td>
<td>40</td>
<td>18.38</td>
<td>6.69</td>
<td>20</td>
<td>24.2%</td>
<td>-10.63 [-13.69, -7.57]</td>
</tr>
<tr>
<td>Weston 2003</td>
<td>15</td>
<td>3.6</td>
<td>10</td>
<td>29</td>
<td>10.5</td>
<td>10</td>
<td>10.4%</td>
<td>-14.00 [-20.88, -7.12]</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>121</td>
<td></td>
<td></td>
<td>102</td>
<td></td>
<td>100.0%</td>
<td></td>
<td>-8.27 [-10.90, -5.64]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 4.99; Chi² = 16.46, df = 3 (P = 0.0009); I² = 82%
Test for overall effect: Z = 6.17 (P < 0.00001)

### 2.1.3 Procedure Time

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Propofol Mean</th>
<th>SD</th>
<th>Total</th>
<th>Midazolam Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agrawal 2012</td>
<td>9.3</td>
<td>1.8</td>
<td>40</td>
<td>8.7</td>
<td>1.3</td>
<td>42</td>
<td>56.5%</td>
<td>0.60 [-0.08, 1.28]</td>
</tr>
<tr>
<td>Khamaysi 2011</td>
<td>9.3</td>
<td>3</td>
<td>31</td>
<td>9</td>
<td>2</td>
<td>30</td>
<td>16.2%</td>
<td>0.30 [-0.98, 1.58]</td>
</tr>
<tr>
<td>Riphaus 2009</td>
<td>9.8</td>
<td>3.7</td>
<td>40</td>
<td>9.5</td>
<td>2.3</td>
<td>20</td>
<td>11.3%</td>
<td>0.30 [-1.23, 1.83]</td>
</tr>
<tr>
<td>Weston 2003</td>
<td>3.9</td>
<td>1.9</td>
<td>10</td>
<td>2.7</td>
<td>0.8</td>
<td>10</td>
<td>16.1%</td>
<td>1.20 [-0.08, 2.48]</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>121</td>
<td></td>
<td></td>
<td>102</td>
<td></td>
<td>100.0%</td>
<td></td>
<td>0.61 [0.10, 1.13]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 1.20, df = 3 (P = 0.75); I² = 0%
Test for overall effect: Z = 2.35 (P = 0.02)

### Study or Subgroup Differences

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Propofol Mean</th>
<th>SD</th>
<th>Total</th>
<th>Midazolam Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khamaysi 2011</td>
<td>38</td>
<td>9</td>
<td>31</td>
<td>110</td>
<td>42</td>
<td>42</td>
<td>50.0%</td>
<td>-72.00 [-87.36, -56.64]</td>
</tr>
<tr>
<td>Weston 2003</td>
<td>54.2</td>
<td>10.4</td>
<td>10</td>
<td>71</td>
<td>22.3</td>
<td>10</td>
<td>50.0%</td>
<td>-16.80 [-32.05, -1.55]</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>41</td>
<td></td>
<td></td>
<td>40</td>
<td></td>
<td>100.0%</td>
<td></td>
<td>-44.39 [-98.49, 9.70]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 1462.54; Chi² = 24.98, df = 1 (P < 0.00001); I² = 96%
Test for overall effect: Z = 1.61 (P = 0.11)
No difference in adverse events

- Hypotension > 20% from baseline
  ~10% both groups
- Bradycardia HR < 50-55
  ~3-6% both groups
- Hypoxemia O2 Sat < 85-90%
  < 5% both groups
- Worsening of HE
  Propofol probably better
Limitations of the study

- Meta-analysis of EGDs only
- Variable patients
- Unbalanced/small numbers
- Differences in anesthetic doses
- Methodologic weaknesses
- Most of patients were Childs-Pugh A-B
  - Not the sickest patients, most not pre-transplant
My preference

• MAC with Propofol +/- opioids
  – All decompensated patients
    • Ascites, encephalopathy, HRS
  – Known or suspected varices
  – EVL planned
  – Concomitant renal failure
  – Pre-transplant patients
Endoscopy in cirrhotics

• Diagnostic endo low-risk, safe
• Correct coagulopathy in high-risk interventions
  • INR < 1.6 , Plt > 50K
  • Don’t delay emergency interventions
• Coag status not reflected accurately by PT/INR, plts
  – Imbalance of coagulation factors
  – Worsened if renal failure

## Endoscopic findings in cirrhotics

<table>
<thead>
<tr>
<th>LESIONS</th>
<th>PREVALENCE</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophageal varices</td>
<td>&gt;50% (5-15%/yr)</td>
<td>Most likely to bleed</td>
</tr>
<tr>
<td>Gastric varices</td>
<td>20%</td>
<td>Less likely to bleed but torrential</td>
</tr>
<tr>
<td>Portal hypertensive gastropathy (PHG)</td>
<td>80%</td>
<td>8% of NVB</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Responds to BB</td>
</tr>
<tr>
<td>GAVE</td>
<td>20-30%</td>
<td>4% of NVB</td>
</tr>
<tr>
<td></td>
<td></td>
<td>APC (4 sessions) 85-90% effective</td>
</tr>
</tbody>
</table>
Endoscopic findings in cirrhotics

<table>
<thead>
<tr>
<th>LESIONS</th>
<th>PREVALENCE</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>PH enteropathy</td>
<td>65%</td>
<td>Can cause anemia</td>
</tr>
<tr>
<td>PH colopathy</td>
<td>24%</td>
<td>Can cause anemia</td>
</tr>
<tr>
<td>Rectal varices</td>
<td>44%</td>
<td>Bleeding uncommon but life-threatening</td>
</tr>
</tbody>
</table>
Endoscopy in cirrhotics

- Increased risk of post-procedure bleeding
  - Blood products help acutely
  - PPI may decrease risk of post-EVL bleeding
    - May decrease size of post-EVL ulcers
    - Decrease acid exposure from GERD
  - ERCP: Balloon dilation > sphincterotomy

Model of End Stage Liver Disease (MELD)

- Scoring system for ESLD
- Determines priority for liver transplant
- 3 components: Cr, Bili, PT/INR
- Extra points for HCC
- No points for ascites, variceal bleeding, PSE
Summary

- Cirrhosis is 12th leading cause of death
  - HCV, ETOH, fatty liver dominate
  - major clinical, personal and economic impact
- Complications of cirrhosis are myriad, require vigilant screening and management, and impact endoscopic outcomes
  - Sedation, bleeding, encephalopathy risks
THANK YOU FOR YOUR ATTENTION!