THE CIRRHOTIC PATIENT: MANAGEMENT OF CHRONIC LIVER DISEASE AND MINIMIZING COMPLICATIONS

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CIRRHOSIS ETIOLOGIES

Liver Institute of Virginia database
9/2015
LIVER ANATOMY
LIVER LOBULE

- Pentagonal shape
- Portal triad
  - Portal vein
  - Bile duct
  - Hepatic artery
- Central area
  - Central vein

PORTAL HYPERTENSION
ETIOLOGY IN CIRRHOSIS

Hepatocytes

Space of Disse

Kupffer and endothelial cells

Stellate cells
PORTAL HYPERTENSION ETIOLOGY IN CIRRHOSIS

Stellate cells secrete collagen matrix

Kupffer and endothelial cells

Fenestrations close

Stellate cells secrete collagen matrix

Endothelial cells fatten
PORTAL HYPERTENSION
SEQUENCE OF EVENTS

- Sinusoidal fibrosis and loss of endothelial fenestrations
- Loss of sinusoidal compliance
- Sinusoidal pressure increases
- Salt and water retention
- Portal hypertension develops when HVPG exceeds 12 mm Hg
- Collateral circulation
- Shunting portal blood
- Ascites
- Varices
- Hepatic encephalopathy

CIRRHOSIS
COMPLICATIONS

- Hepatocellular carcinoma
- Variceal hemorrhage
- Ascites and edema
  - Hepato-renal syndrome
  - Hyponatremia
  - Malnutrition
- Hepatic encephalopathy
- Infections
IMPACT OF CURING HCV  
HCC, LIVER FAILURE, MORTALITY

AJ van der Meer et al.  
JAMA  2012; 308:2584-2593.

SVR REVERSES FIBROSIS 
RESOLUTION OF CIRRHOSIS

ML Shiffman et al.  
SVR IN ADVANCED CIRRHOSIS
THE POINT OF NO RETURN

- N=120 patients
- Advanced cirrhosis
- Treated 12 weeks
- SOF+SMV
- Overall SVR = 81%
- Patients with MELD >20 did not appear to improve
- HCC developed in some patients that appeared to improve

Adapted from ML Shiffman et al. Am J Gastroenterol 2015; 110:1179-1185

RISK OF HCC
PLATELET COUNT

- Chronic HCV
- HALT-C trial
- N= 1,005
- P<0.0001

Platelet Count:
- <100
- 100-149
- >150

CASE 1
CIRRHOSIS AND HCC

LF is a 65-year-old female with cryptogenic cirrhosis, metabolic syndrome and BMI of 30. Liver biopsy demonstrates cirrhosis and <5% steatosis and no inflammation. Liver transaminases, ALP, TBILI, albumin, and INR all normal. Platelet count 98. No ascites, edema, HE, or esophageal varices. She is told she is clinically stable and to return if she develops any complications of cirrhosis. She is referred back 4 years later with a 8 cm liver mass, portal vein invasion, and an ALP of 1,052. She asks how did this happen?

IMPACT OF SURVEILLANCE
SIZE OF HCC AT DIAGNOSIS

**Impact of Surveillance Effect on Survival**

![Graph showing survival rates for different surveillance methods](image1)


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**Esophageal Varices: The Need for Surveillance**

![Graph showing frequency of new varices and varices enlargement](image2)

**CHRONIC HCV VARICES AND PLATELET COUNT**


**PREVENTING VARICES FROM FORMING BETA-BLOCKERS**

# Preventing First Variceal Bleed

## Beta-Blockers

### All Varices (11 trials)
- Control: 25% (N=600)
- Beta-Blockers: 15% (N=590)
- Absolute Difference: -10% (-16% → -5%)

### Large Varices (8 Trails)
- Control: 30% (N=411)
- Beta-Blockers: 14% (N=400)
- Absolute Difference: -16% (-24% → -8%)

### Small Varices (3 Trials)
- Control: 7% (N=100)
- Beta-Blockers: 2% (N=91)
- Absolute Difference: -5% (-11 → 2%)

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G D’Amico, et al.  

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## Preventing First Variceal Bleed

### Band Ligation vs Beta-Blockers

<table>
<thead>
<tr>
<th>Study</th>
<th>Beta-blockers</th>
<th>Banding</th>
<th>Delta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen 1998</td>
<td>1/26 (4%)</td>
<td>2/30 (7%)</td>
<td>3%</td>
</tr>
<tr>
<td>Sarin 1999</td>
<td>4/45 (9%)</td>
<td>12/44 (27%)</td>
<td>18%</td>
</tr>
<tr>
<td>De 1999</td>
<td>2/15 (13%)</td>
<td>1/15 (7%)</td>
<td>-6%</td>
</tr>
<tr>
<td>Jutabha 2000</td>
<td>0/18 (0%)</td>
<td>1/17 (6%)</td>
<td>6%</td>
</tr>
<tr>
<td>De la Mora 2000</td>
<td>1/12 (8%)</td>
<td>2/12 (17%)</td>
<td>9%</td>
</tr>
<tr>
<td>Lui 2002</td>
<td>3/44 (7%)</td>
<td>9/66 (14%)</td>
<td>7%</td>
</tr>
<tr>
<td>Lo 2004</td>
<td>10/50 (20%)</td>
<td>16/50 (32%)</td>
<td>12%</td>
</tr>
<tr>
<td>Schepke 2004</td>
<td>19/75 (25%)</td>
<td>22/77 (29%)</td>
<td>4%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>40/285 (14%)</td>
<td>65/311 (21%)</td>
<td>7%</td>
</tr>
</tbody>
</table>

MS Khuroo, et al.  
ESOPHAGEAL VARICES APPROACH

- Cirrhosis
  - Endoscopy if platelets < 150,000
    - No Varicies
      - Follow-up EGD Q 2-3 years
    - Small Varicies
      - Follow-up EGD Q 1-2 years
    - Medium-Large Varicies
      - Beta-Blockers or Band Ligation


BETA-BLOCKERS IMPACT OF ASCITES

- Survival (%)
  - Beta-Blockers
    - No
    - Yes

Use of beta-blockers significantly increased the risk of AKI and HRS in patients who developed SBP:

- RCT, N=602
- Mean age 57 years
- ETOH cirrhosis 55%
- Mean MELD 17
- Child class C 50%
- 90 day mortality with AKI in patients on beta-blockers and h/o SBP = 80%


The most common complication of cirrhosis and portal hypertension:

- Leads to other complications:
  - Hepatorenal syndrome
  - Hyponatremia

ASCITES COMPLICATIONS AND SURVIVAL

<table>
<thead>
<tr>
<th></th>
<th>Median Survival (mos)</th>
<th>Median Survival (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP</td>
<td>&gt;80</td>
<td>46</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>&lt;1.2</td>
<td>25</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>&gt;130</td>
<td>27</td>
</tr>
<tr>
<td>Urine Na</td>
<td>≥10</td>
<td>46</td>
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</tbody>
</table>


COMPLICATIONS OF ASCITES MORTALITY

ASCITES AND EDEMA

CASE 2

JB is a 45-year-old female with cirrhosis secondary to NASH. She developed ascites for the first time 1 year ago. This initially resolved with step 1 diuretics. This is her 6th hospitalization in the past 3 months for ascites and AKI. She has had 6 paracentesis removing 5-8 liters each. HE is controlled with lactulose and rifaxamine.

EXAM: 5'2"; 250 pounds, distended abdomen with obvious ascites, 4+ edema to the hips. Mild HE. No muscle wasting.

LABS: Sodium 115, K 4.5, albumin 1.8 gm, creatinine 2.1 mg

HYPONATREMIA AND AKI

INTRAVENOUS ALBUMIN

PA McCormick et al.
Gut 1990; 31:204-207.
SEVERE ASCITES AND EDEMA

IV ALBUMIN

• Start IV albumin 25 gms
• Q6 hours
• Large volume paracentesis on admission
• Role of albumin:
  ▪ Expands vascular space
  ▪ Enhances renal perfusion
  ▪ Increases urine output
• Use for several days until serum albumin increasing then add IV diuretics
• Continue IV albumin until serum albumin 4 gm/dl
• Discharge on oral diuretics

ASCITES MANAGEMENT

• Sodium restriction
  ▪ Avoid IV saline when hospitalized
• Diuretics
  ▪ Spironolactone 100 200 300 400 mg
  ▪ Furosemide 40 80 120 160 mg
  ▪ Paracentesis - Remove as much as possible
• Limiting factors:
  ▪ Acute Kidney Injury
  ▪ Hyponatremia
  ▪ TIPS when refractory because of
    ▪ Hyponatremia
    ▪ AKI

Intravenous 25% albumin Tolvaptan
CALORIC CONSUMPTION IMPACT OF ASCITES

<table>
<thead>
<tr>
<th>Maximal Tolerated Volume (ml)</th>
<th>Caloric Intake (kcal q 3d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>738 (469-1078)</td>
</tr>
<tr>
<td>After LVP</td>
<td>3110* (2160-3860)</td>
</tr>
</tbody>
</table>


PROTEIN CALORIE MALNUTRITION PREVALENCE IN CIRRHOSIS

- 50 consecutive patients with cirrhosis
- Patients with HTN or functional GI disorders matched for age, race, sex
- PCM assessed by:
  - Subjective Global Assessment
  - Prognostic Nutrition Index
  - Hand grip

**Protein Calorie Malnutrition Complications of Cirrhosis**

- **PCM**:
  - Yes
  - No

<table>
<thead>
<tr>
<th>Complications</th>
<th>Transplantation</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of Patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>No</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>


**TIPS vs Total Paracentesis NASTRA Study**

- **ASCITES (%)**
  - TP: 100, 80, 60, 40, 20
  - TIPS: 100, 80, 60, 40, 20

- **Survival (%)**
  - TP: 100, 80, 60, 40, 20
  - TIPS: 100, 80, 60, 40, 20

CIRRHOSIS
COMMON RECOMMENDATIONS

- Caloric restriction
- Protein restriction
- Activity restriction

Promotes:
- Physical decline
- Muscle wasting
- Worsens HE

AMMONIA METABOLISM
NORMAL

Brain

Normal Liver
NH3

Skeletal Muscle
AMMONIA METABOLISM
CIRRHOSIS

Brain

Cirrhosis

NH3

Skeletal Muscle

MALNUTRITION AND MUSCLE WASTING FACTORS IN CIRRHOSIS

Portal hypertension

Ascites

Shunting of hepatic blood

Decreased caloric intake

Inefficient hepatic caloric utilization

Fatigue

Muscle Wasting

Reduced activity
AMMONIA METABOLISM
CIRRHOSIS AND MUSCLE WASTING

Brain

Skeletal Muscle Wasting

NH3

CIRRHOSIS
COMMON RECOMMENDATIONS

WRONG
- Caloric restriction
- Protein restriction
- Activity restriction

CORRECT
- Maintain adequate caloric intake
- Push protein as much as tolerated
- Promote activity
**DIETARY PROTEIN EFFECT ON HE**

![Graph showing dietary protein effect on HE stages from Day 0 to Day 14.](image1)

- Low Dietary Protein: Red bars
- Normal Dietary Protein: Blue bars


**HIGH CALORIE AND PROTEIN DIET IMPACT ON HE**

![Graph showing high calorie and protein diet impact on HE.](image2)

- % of Patients Improved by:
  - 2 Stage: Red bars
  - 1 Stage: Blue bars

- Serum NH3:
  - Initial: Blue bars
  - Final: Green bars

HEPATIC ENCEPHALOPATHY
LACTULOSE

- Do not treat the ammonia level
- Treat symptoms of HE
- Do not overdose:
  - Diarrhea
  - Dehydration
  - Electrolyte abnormalities
  - Precipitate HE

Before After

IVer

HEPATIC ENCEPHALOPATHY
WHEN CANNOT AFFORD RIFAXAMINE

- DO NOT USE Neomycin
  - Most oto- and nephrotoxic aminoglycoside
  - Small amounts can be absorbed across edematous bowel
  - Associated with renal failure
- Metronidazole
- Vancomycin
- Ampicillin
RB is a 45-year-old male with alcohol induced cirrhosis. He has been abstinent from alcohol for 3 years. Ascites and edema have resolved on step 2 diuretics. Varices have been banded to obliteration. After being stable for 2 years he has been hospitalized every month for the past 6 months with HE. He is on lactulose TID and rifaxamine. Serum ammonia never declines below 100 (but lucid at this level). MRI performed during the current hospitalization demonstrated a spontaneous spleno-renal shunt.

**SPONTANEOUS SPLENO-RENAL SHUNT**

**BRTO**

Gastric Varices (GOV 1 or 2)
25% of all GOV

SMV

BALLON OCCLUDED RETROGRADE TRANSVENOUS OBLITERATION
MANAGEMENT OF CIRRHOSIS

SUMMARY

- Screen all patients with cirrhosis for HCC
- Patients with a platelet count below 150,000 need to be screened for esophageal varices
- Band ligation or beta-blockers in patients with medium-large varices to prevent first variceal hemorrhage
- Avoid beta-blockers in patients with Child class B and C cirrhosis and/or ascites
- Treat ascites aggressively to resolution
- Do not restrict protein in patients with HE unless necessary