Complications of end stage liver disease

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Conflict of interest disclosures

- None

“The many complications of Cirrhosis”

- Synthetic dysfunction
  - Coagulopathy
  - Hypoalbuminemia

- Portal hypertension
  - Ascites
  - Esophageal varices
  - Encephalopathy

- Metabolic defects
  - Encephalopathy

- Hepatocellular cancer

Portal Hypertension

- Portal HTN leads to 3 major complications of cirrhosis:
  - Ascites
  - Variceal hemorrhage
  - Hepatic encephalopathy

- Two steps to portal hypertension:
  - First step
    - Increased resistance to flow through the hepatic vascular bed
  - Second step
    - Splanchic vasodilation

- The increased pressure gradient between the portal vein and the intrahepatic veins and IVC result in the formation of collateral vessels (varices)

- Collaterals do not effectively reduce portal pressure because of increased portal blood flow.

Ascites and collateral formation in cirrhosis

Adapted from: Garcia-Tsao, Gastro;120:726-748(2001)

Evaluation of Ascites

- Paracentesis
  - Protein > 1.1
  - Protein < 1.1

- SAAG
  - > 2.0
  - < 2.0

- Cirrhosis
  - Fulminant hepatitis

- Noncirrhotic
  - Nephrotic Syndrome
  - Protein losing enteropathy
  - Portal Hypertension
  - Infections
  - Eosinophilic gastroenteritis
  - Miscellaneous
  - Hypothyroidism
  - Pancreatic duct disruption
  - Nephrogenic ascites
  - Lymphatic obstruction
A paracentesis is required in the evaluation of new onset ascites

- Ascitic fluid albumin and protein assessed
- The serum-ascites albumin gradient (SAAG)
  - If gradient is greater than 1.1, 98% accuracy that ascites is due to portal HTN
- Ascitic protein is helpful in distinguishing portal hypertension from hepatic and non-hepatic causes

Cirrhotic Ascites

- Most common complication of cirrhosis
- 30% risk over 5 years of cirrhosis
- 50% mortality within 2-5 years
- Treatment and subsequent eradication of ascites abolishes risk of SBP

Key Points: Management of Ascites

<table>
<thead>
<tr>
<th>INDICATION</th>
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<tbody>
<tr>
<td>Mild ascites</td>
<td>Salt restriction</td>
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<td>Diuretics</td>
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<tr>
<td>Moderate ascites</td>
<td>Salt restriction + spironolactone + furosemide</td>
<td>LVP+albumin</td>
<td>Furosemide alone</td>
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<td>Refractory ascites</td>
<td>LVP + alb + diuretics + salt restriction</td>
<td>TIPS + salt restriction +/- diuretics</td>
<td>Side to side PCS/Peritoneo venous shunts/Peritoneal catheters</td>
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</table>

New Onset Cirrhotic Ascites

- Salt restriction to 1.5 grams per day, effective in 10%-20%
- When combined with diuretics effectiveness improves to 90%
- Complications
  - Hypovolemia 25%
  - Hyponatremia 28%
  - Encephalopathy 26%
  - Painful gynecomastia
  - Initiate Spironolactone at 100 mg/day increase stepwise to max of 400 mg/day
  - Initiate Lasix 40/day and increase stepwise to max of 160 mg/day
  - For lack of response consider
    - NSAID use
    - Non-compliance esp salt restriction
    - Refractory ascites/type II hepatorenal syndrome

Refractory Cirrhotic Ascites

- 5%-10% of cirrhotic patients
- LVP plus albumin is standard of care
- Diuretics, salt restriction continued after LVP
- TIPS is superior but higher rate of complications
- Albumin infusion reduces post paracentesis circulatory dysfunction
- 6-8g/L of ascites removed

Ascites related complications in cirrhosis

- Spontaneous Bacterial Peritonitis
- Hepatorenal Syndrome
- Dilutional Hyponatremia
- Hepatic Hydrothorax
Spontaneous Bacterial Peritonitis

- **Mortality**
  - 1 yr: 50%-70%
  - 2 yrs: 70%-75%

- **Diagnosis:**
  - Ascitic fluid cell count of >250 PMNs/ML
  - +ve ascites cultures. 50%-90% (E. coli & Klebsiella most common)

- **Signs**
  - Abdominal pain
  - Fever
  - Encephalopathy
  - Rising Creatinine
  - Recent GI bleed

- **Findings % Patients**
  - Fever 69
  - Abdominal Pain 59
  - Encephalopathy 54
  - Diarrhea 32
  - Ileus 30
  - Hypotension 21
  - Hypothermia 17

Treatment of SBP

- **Antibiotics:** Third generation cephalosporins.

- **IV albumin:**
  - 1.5 g/Kg at diagnosis
  - 1.0 gm/kg at 72 hours
    - reduces type 2 HRS
    - improves hospital survival when compared to abx alone likely due to reduced risk of hepatorenal syndrome

- **Long term prophylaxis after initial episode**
  - with quinolone preferably norfloxacin

Hepatorenal Syndrome (HRS)

- A result of renal vasoconstriction leading to progressive renal impairment
- No structural kidney defects
- 20% risk in the first year of diagnosis of ascites and as high as 40% in five years

Types of HRS

- **Type 1:**
  - Rapidly progressive
  - Rise in creatinine >2.5 mg/dl or creatinine clearance <20 cc within 2 weeks
  - Often triggered by an insult
  - Median survival 1-2 weeks without OLT

- **Type 2:**
  - Slow progression
  - Often in setting of refractory ascites
  - Mean survival 2-6 months

Diagnosis of HRS

- Low GFR (rise in creatinine)
  - Including urine output <500 cc/day
- No evidence of shock, infection, hypovolemia and nephrotoxic drug injury
- No resolution despite cessation of diuretics and adequate volume resuscitation
- No obstruction, parenchymal renal disease or proteinuria
### Treatment goals in HRS
- Identify and correct the precipitating factor
- Midodrine, octreotide +/- albumin
- TIPS possibly in type 2 HRS
- Liver transplantation

### Dilutional Hyponatremia
- Consequence of enhanced ADH
- Poor prognostic marker and predicts HRS
- Free water restriction to less than 1500 cc/day
- ?Aquaratic drugs activate aquaporin receptors and enhance free water secretion

### Hepatic Hydrothorax
- Ascites passes through fenestrae in the diaphragm to pleural cavity
- 90% right sided but can occur in the left or bilaterally
- Treatment: Salt restriction, Diuretics, Thoracentesis, TIPS
- Avoid chest tube

### Esophageal varices
- Varices occurrence: 5%/yr
- Increase in size of varices: 5%/yr
- Increased intravariceal pressure and wall tension
- Rupture
- Variceal hemorrhage and life threatening bleeding
- Mortality 20-30%

### 1-yr probability of variceal hemorrhage (Percent risk)

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<th>Grade</th>
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<th>F2</th>
<th>F3</th>
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<tr>
<td>C</td>
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### Grading varices
- Small
- Large

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North Italian Endoscopic Club. NEJM 1988
Primary prophylaxis against variceal hemorrhage

- Non-selective beta blocker
- A/E
  - Fatigue
  - Bradycardia
  - Heart block
  - Exacerbate heart failure, DM, COPD

Endoscopic variceal band ligation

- A/E
  - Procedural risks
  - Band ulcers
  - Intractable bleeding

Acute Variceal Hemorrhage

- Mortality: 15%-20%
- Risk of rebleed in 6 weeks: 40%
- EVL is therapy of choice
- Octreotide infusion
- TIPS if bleeding continues

Quinolone or similar antibiotics for all cirrhosis patients with gastrointestinal hemorrhage

Prevention of Recurrent Bleeding

- Recurrence rate of 40% at 6 weeks
- Non-selective Beta blocker + EVL

Shunt surgery (Child A) or TIPS if recurrent variceal hemorrhage

Management of Esophageal varices

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<td>Prevention of first bleed</td>
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<tr>
<td>Acute Hemorrhage</td>
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<td>Prevention of re bleed</td>
<td>β-blocker and EVL</td>
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Hepatic Encephalopathy

- Neuropsychiatric syndrome in the presence of severe liver dysfunction
- Varied presentation from mild mental impairment to frank coma
- Multiple factors including ammonia play a role in its pathogenesis

Diagnosis

- Physical Exam
  - Fetor hepaticus
  - Asterixes
  - Mental Status Exams
    - Serial 7’s
    - “A” deletion test
**Hepatic Encephalopathy**

- Exacerbating Factors
  - GI bleeding
  - Sepsis
  - Hypokalemia
  - Dehydration
  - Sedatives/narcotics
  - Azotemia
  - Dietary N2 loading
  - Constipation

- Treatment
  - Identify and correct precipitant
  - Lactulose
  - Rifaximin
  - Sodium benzoate

**Hepatocellular Cancer (HCC)**

- Signs: RUQ pain, weight loss, acute abdominal catastrophe (rare).
- PE: ascites, varices, gynecomasia, hepatic bruit (10%-20%)
- Labs: Increased ALT and AST, anemia or erythrocytosis, hypoglycemia
- Imaging: US, Liver protocol CT or MRI

**Who is at Risk for HCC?**

- Cirrhosis
  - Hepatitis B
  - Hemochromatosis
  - Alcohol
  - Hepatitis C
  - PBC
  - NASH, Autoimmune hepatitis, alpha 1-antitrypsin

- Hepatitis B:
  - Africans >20 yrs,
  - Family history of HCC,
  - Asians (M:>40 yr, F:50 yr)

**Recommendations for screening**

- Ultrasonogram +/- AFP every 6 months

**Treatment**

- Liver Transplantation
  - 1 lesion <5cm or 3 lesions <3 cm.
  - 5 yr survival >70%, recurrence <15%

- Surgical Resection
  - NI bilirubin and lack of significant portal HTN
  - 5 yr recurrence >50%

- Ablative therapies

- Transarterial (chemo)embolization.

**Summary**

- Complications of cirrhosis include portal hypertension, synthetic dysfunction, metabolic changes and cancer

- Manifestations of portal hypertension dominate complications of liver disease

- Ascites is the most common manifestation of hepatic decompensation

- Preventive therapies for variceal hemorrhage are effective

- Surveillance of hepatocellular carcinoma is recommended in all patients with cirrhosis
References


Question # 1

- 51 yr old male with cirrhosis presents to the emergency room with hematemesis and hemodynamic instability. He undergoes an emergent upper endoscopy where bleeding varices were banded.

The best management to reduce his risk of recurrent bleeding is:

1. Non selective beta blocker therapy
2. Band ligation
3. Combination therapy with beta blocker and band ligation
4. TIPS

Question # 2

- 50 yr old female is a new patient with cirrhosis from Hepatitis C. She is asymptomatic. No clinical decompensation. Spider angiomas and palmary erythema on physical examination. Otherwise, history and physical exam are unremarkable. Recent EGD showed no varices and she has been vaccinated to Hepatitis A and B.

You recommend the following:

1. Refer for liver transplantation
2. Initiate anti viral therapy
3. Abdominal ultrasound +/- AFP measurement then repeated every 6 to 12 months
4. No further evaluation and return for follow-up in 6 months