COMPLICATIONS OF CIRRHOSIS: ASCITES & HEPATIC ENCEPHALOPATHY

OBJECTIVES

- Understand the prognosis of End Stage Liver Disease (ESLD)
- Identify the common complications of cirrhosis
- Understand the pathogenesis of each complication
- Identify pharmacological treatment options for portal hypertension & ascites
- Discuss cost-effective treatments for hepatic encephalopathy
WHAT IS CIRRHOSIS?

- Late stage scarring of the liver
- Replaces normal healthy tissue
- Irreversible

COMMON CAUSES CIRRHOSIS

- Chronic viral hepatitis
- Alcohol related liver disease
- Non alcoholic fatty liver disease (NAFLD)
STATISTICS

- 35,000 deaths per year in the U.S
- 9th leading cause of death in the U.S & 14th most common death worldwide
- 1.2% of all U.S deaths
- Over 2.1% of hospice admissions annually (NHPCO statistics)

PROGNOSIS

The Model for End-Stage Liver Disease (MELD Score)
- Measures 3-month mortality risk
- Transplant planning

Child-Pugh Classification for Severity of Cirrhosis
- Likelihood of developing complications
- One year and two year patient survival

A MELD score calculator is available at:
https://www.mayoclinic.org/medical-professionals/model-end-stage-liver-disease/meld-model
COMPLICATIONS OF CIRRHOSIS

- Portal hypertension
- Ascites
- Spontaneous bacterial peritonitis (SBP)
- Hepatic encephalopathy

PORTAL HYPERTENSION

- Portal Hypertension
  - ↑ in portal pressure
  - ↑ resistance to portal flow
  - ↑ splanchnic vasodilation
- Variceal Hemorrhage prophylaxis
  - High risk- medium/large varices present
  - Non-selective beta-blockers
- Leads to ascites & hepatic encephalopathy
### Portal Hypertension Cont’

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Recommended Dose</th>
<th>Therapy Goals</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol $</td>
<td>• 20-40 mg PO BID&lt;br&gt;• Adjust every 2-3 days until &lt;br&gt;treatment goal is achieved&lt;br&gt;• MDD &lt;br&gt;• 320 mg/day without ascites&lt;br&gt;• 160 mg/day with ascites</td>
<td>• Resting HR 55-60 BPM&lt;br&gt;• SBP should not decrease &lt; 90 mm Hg</td>
<td>Continue indefinitely</td>
</tr>
<tr>
<td>Nadolol $$</td>
<td>• 20-40 mg PO QD&lt;br&gt;• Adjust every 2-3 days until &lt;br&gt;treatment goal is achieved&lt;br&gt;• MDD &lt;br&gt;• 160 mg/day without ascites&lt;br&gt;• 80 mg/day with ascites</td>
<td>• Resting HR 55-60 BPM&lt;br&gt;• SBP should not decrease &lt; 90 mm Hg</td>
<td>Continue indefinitely</td>
</tr>
<tr>
<td>Carvedilol $</td>
<td>• Start with 6.25 mg QD&lt;br&gt;• After 3 days increase to 6.5 mg BID&lt;br&gt;• MDD 12.5 mg/day</td>
<td>• SBP should not decrease &lt; 90 mm Hg</td>
<td>Continue indefinitely</td>
</tr>
<tr>
<td>EVL- Endoscopic Variceal Ligation</td>
<td>• Every 2-8 weeks until the eradication of varices</td>
<td>• Variceal eradication</td>
<td>First EGD performed 3-6 months after eradication and every 6-12 months thereafter</td>
</tr>
</tbody>
</table>

### Ascites

- Accumulation of fluid in the peritoneal cavity
- Splanchnic vasodilation → Sodium & water retention
- 50% develop ascites
- Physical examination:
  - Presence of a full, bulging abdomen with flank dullness
  - Abdominal ultrasound
TREATMENT OF ASCITES

- Non-pharmacological treatment
  - Reduce sodium intake: less than 2g/day
  - Discontinue alcohol
  - Discontinue medications that decrease renal perfusion: NSAIDs, BB, ACEI, ARBs
  - Fluid restriction: not necessary
  - Abdominal paracentesis (second line)

TREATMENT OF ASCITES CONT’

- Pharmacological treatment
  - First line treatment: dual diuretics
  - Titrate upward q3-5 days as needed
  - Maintain ratio of 100mg Spironolactone to 40mg Furosemide
  - Alcohol-induced liver disease
    - Baclofen 5mg PO TID 3 days then 10mg TID

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Starting Dose</th>
<th>AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spironolactone</td>
<td>100mg PO QD, MDD: 400mg/day</td>
<td>Aldosterone antagonist, Avoid if CrCl &lt;10ml/min, Gynecomastia possible, especially at higher doses</td>
</tr>
<tr>
<td>Furosemide</td>
<td>40mg PO QD, MDD: 160mg/day</td>
<td>Inhibits reabsorption of Na &amp; Cl in the ascending loop of Henle and proximal/distal renal tubules</td>
</tr>
</tbody>
</table>
TREATMENT OF ASCITES CONT’

- Refractory/recurrent ascites OR diuretic resistant ascites
  - Continue Na restriction
  - D/C beta blockers
  - **Midodrine 7.5mg PO TID** in addition to diuretics – hypotensive patients
    - ↑ blood pressure/MAP
    - ↑ urine volume
    - ↑ urine sodium excretion
- Serial therapeutic paracentesis
  - Large volume paracentesis: 3-5L
  - Small volume paracentesis: 1-2L
  - TIPS (transjugular intrahepatic portasystemic stent-shunt)- invasive for hospice
  - Liver transplantation

SPONTANEOUS BACTERIAL PERITONITIS (SBP)

- Ascitic fluid infection
- Clinical manifestation
  - Fever
  - Abdominal pain/tenderness
  - Altered mental status
  - Diarrhea
- Diagnosis
  - Paracentesis
    - Elevated absolute polymorphonuclear leukocyte (PMN) count ≥250 cells/mm^3
    - Positive bacterial culture- most common *Escherichia coli* and *Klebsiella* (minimum *Streptococcal/Staphylococcal*)
SPONTANEOUS BACTERIAL PERITONITIS (SBP)

- Empiric treatment
  - Drug: **IV Cefotaxime 2g every 8 hours**
  - Alternatives
    - Third generation cephalosporins (IV Ceftriaxone 2g/day)
    - Fluoroquinolones (IV Ciprofloxacin 400mg BID)
- Duration: **5 or 10 days**
- Prophylaxis
  - Bactrim DS QD
  - Cipro 500mg QD
  - D/C PPIs

HEPATIC ENCEPHALOPATHY (HE)

- Encephalopathy
  - Diffuse disturbances of brain function
- Clinical presentation
  - Disorientation ***
  - Acute confused state
  - Inappropriate behavior
  - Unconsciousness/insensitivity
  - Coma
- Motor system abnormality
  - Asterixis***
  - Hyperreflexia
  - Positive Babinski sign
  - Muscle rigidity
  - Bradykinesia
  - Slowness of speech
  - Dyskinesia
  - Diminished voluntary movements
PATHOGENESIS OF HE

- Gut derived Ammonia: neurotoxin that precipitates HE

CLASSIFICATION OF HE

- Underlying disease
  - **Type A**: HE associated with acute liver injury
  - **Type B**: HE associated with portal systemic bypass with no intrinsic hepatocellular disease
  - **Type C**: HE associated with cirrhosis and portal hypertension
- Severity of manifestations – West Haven Criteria
- Time course
  - Episodic
  - Recurrent
  - Persistent
- Precipitating factors
HEPATIC ENCEPHALOPATHY

- West Haven Criteria

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Changes in behavior</td>
<td>• Marked confusion (stupor)</td>
</tr>
<tr>
<td>• Mild confusion</td>
<td>• Incoherent speech</td>
</tr>
<tr>
<td>• Slurred speech</td>
<td>• Sleeping but arousable</td>
</tr>
<tr>
<td>• Disordered sleep</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade 2</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Lethargy</td>
<td>• Coma</td>
</tr>
<tr>
<td>• Moderate confusion</td>
<td>• Unresponsive to pain</td>
</tr>
</tbody>
</table>

HEPATIC ENCEPHALOPATHY

- Laboratory Testing
  - High blood-ammonia levels

- Diagnosis
  - Clinical examination
  - Differential diagnosis

- Treatment
  - Reversible
  - Drug therapy

- Protein intake
  - 1.2 to 1.5 g/kg/day
### TREATMENT OF HE

<table>
<thead>
<tr>
<th>Drug Therapy</th>
<th>MOA</th>
<th>Dosage Forms</th>
<th>Dosing Range</th>
<th>Comments</th>
</tr>
</thead>
</table>
| **Lactulose** *(Kristalose®, Constulose®, Enulose®, Generlac®)* | • Nonabsorbable disaccharide  
• Lowers colonic pH  
• \( \text{NH}_2 \rightarrow \text{NH}_4^+ \)  
• Excreted through feces | • Packets: 10g, 20g/pack  
• Solution: 10g/15ml  
AWP price \$0.03 - \$0.10/ml  
\$9/pack | • 25ml PO q1-2 hours until at least two soft or loose BM/day  
• Titrate dose to maintain 2-3 BM/day  
• Can use rectal enema | • First line  
• FDA approved for treatment and prevention |
| **Rifaximin** *(Xifaxan®)* | • Antibiotic  
• Eliminates gut bacteria-derived ammonia  
• Anti-inflammatory effects | • Tablets: 200mg, 550mg  
• Brand only  
AWP price  
\$23.03/tablet (200mg)  
\$43.90/tablet (550mg) | • 400mg PO TID or 550mg PO BID | • Alternative therapy/add on  
• FDA approved for prevention  
• Off-label for treatment  
• Minimal AEs |
| **Neomycin** | • Antibiotic  
• Eliminates gut bacteria-derived ammonia | • Tablets: 500mg  
AWP price  
\$1.40-$2/tablet | • 500mg PO TID or 1g PO BID | • Alternative therapy/add on  
• FDA approved for treatment  
• BBW: ototoxicity and nephrotoxicity |

### RIFAXIMIN VS LACTULOSE

- **Jiang et al.**
  - Rifaximin vs. nonabsorbable disaccharides in the management of HE
  - Meta-analysis of 5 randomized controlled trials involving 264 patients
  - Rifaximin was not superior to nonabsorbable disaccharides except that it may be better tolerated for acute or chronic hepatic encephalopathy
- **Bass et al.**
  - Rifaximin for the prevention in hepatic encephalopathy
  - Randomized, double-blind, placebo-controlled trial involving 299 patients
  - More than 90% of patients in both arms were taking lactulose
  - Over a 6-month period, patients experienced reduction in breakthrough HE in the Rifaximin group (31 of 140) compared to placebo (73 of 159)
  - 50% reduction in hospitalization for the Rifaximin group (19 of 140) compared with placebo group (36 of 159)
NEOMYCIN VS. LACTULOSE AND RIFAXIMIN VS. NEOMYCIN

- Conn et al.
  - Comparison of neomycin and lactulose in the treatment of chronic portal-systemic encephalopathy
  - A double blind controlled trial involving 33 patients
  - Mental status, asterixis and ammonia levels was improved significantly by neomycin and lactulose
  - Both lactulose and neomycin are effective in the treatment of chronic portal-systemic encephalopathy

- Miglio et al.
  - Rifaximin in comparison to neomycin in short and long-term treatment of HE
  - Double-blind, randomized trial involving 49 patients
  - Patients were randomly assigned to rifaximin 400 mg PO TID & neomycin 1g PO TID
  - In both groups the disturbances in speech, memory, behavior and mood, gait, asterixis, all showed the highest proportion of improvement
  - Ammonia levels were decreased in both groups
  - In all patients a progressive and important reduction in HE grade was observed, and no statistically significant difference between the two treatments was detected

OTHER THERAPIES

- Metronidazole or vancomycin
  - Limited studies
  - Not commonly used
  - Neurotoxicity w/ metronidazole
  - Bacterial resistance w/ vancomycin

- Polyethylene Glycol 3350-Electrolyte Solution (PEG)
  - The HELP Randomized Clinical Trial (2014)
    - Improvement of 1 or more in HE grading (HESA grading) was met in both arms (primary endpoint)
    - Medium time for resolution was 2 days for lactulose & 1 day for PEG (secondary outcome)

- Primary prophylaxis
  - High risk patients only

- Secondary prophylaxis
  - Lactulose +/- Rifaximin
  - Neomycin- avoid long term use
SUMMARY

Portal Hypertension
- No varices ➔ No NSBBs
- Small varices ➔ Low or high risk of bleeding ➔ NSBBs/EVL
- Medium/Large varices ➔ NSBBs/EVL

Ascites
- Diuretic sensitive ➔ Spironolactone AND Furosemide
- Diuretic resistant (recurrent) ➔ Add Midodrine

Spontaneous Bacterial Peritonitis
- Third generation cephalosporin ➔ Cefotaxime or Ceftriaxone
- Fluoroquinolones ➔ Ciprofloxacin

Hepatic Encephalopathy
- First line ➔ Lactulose
- Second line ➔ Add Rifaximin or Neomycin
- Prophylaxis ➔ Lactulose +/- Rifaximin

QUESTIONS?
REFERENCES

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- https://www.uptodate.com/contents/model-for-end-stage-liver-disease-meld#subscribeMessage
- https://www.mayoclinic.org/medical-professionals/model-end-stage-liver-disease/meld-model

- https://www.uptodate.com/contents/hepatic-encephalopathy-in-adults-clinical-manifestations-and-diagnosis?search=hepatic%20encephalopathy&source=search_result&selectedTitle=2-150&usage_type=default&display_rank=1