

COMPLICATIONS OF CIRRHOSIS: ASCITES & HEPATIC ENCEPHALOPATHY

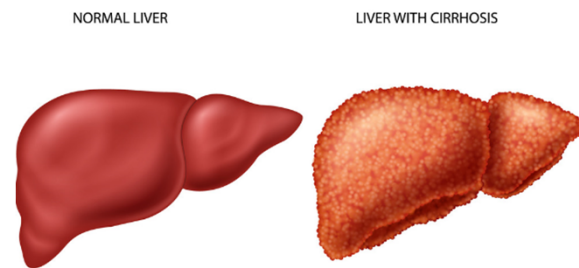
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OBJECTIVES

- 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

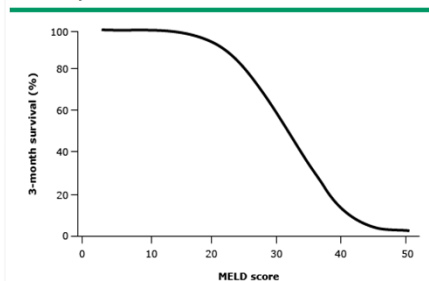
- 35,000 deaths per year in the U.S
- 9th leading cause of death in the U.S & 14th most common death worldwide
- 1.2% of all U.S deaths
- Over 2.1% of hospice admissions annually (NHPCO statistics)

PROGNOSIS

The Model for End-Stage Liver Disease (MELD Score)

- Measures 3-month mortality risk
- Transplant planning

Estimated 3-month survival as a function of the MELD score in patients with cirrhosis



Child-Pugh Classification for Severity of Cirrhosis

- Likelihood of developing complications
- One year and two year patient survival

Score	1	2	3
Encephalopathy	None	Mild	Marked
Bilirubin (mg/dl)	< 2.0	2.0-3.0	> 3.0
Albumin (g/dl)	> 3.5	3.0-3.5	< 3.0
Prothrombin time (seconds prolonged)	< 4	4-6	> 6
Ascites	None	Mild	Marked
Add the individual scores:	< 7 = Child's A		
	7-9 = Child's B		
	> 9 = Child's C		

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

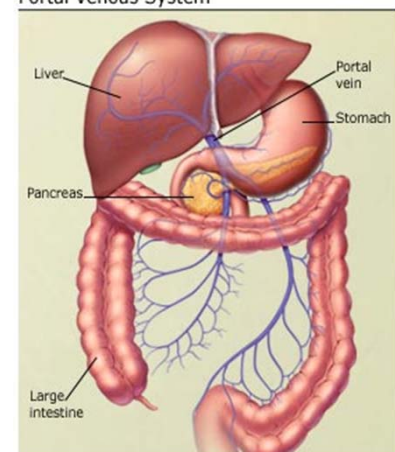
COMPLICATIONS OF CIRRHOSIS

- 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 Venous System

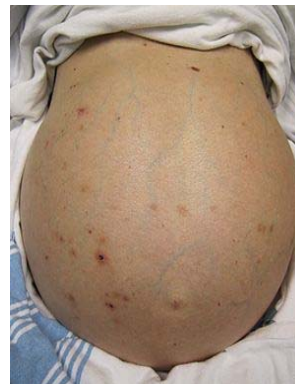


PORTAL HYPERTENSION CONT'

Therapy	Recommended Dose	Therapy Goals	Maintenance
Propranolol \$	<ul style="list-style-type: none"> 20-40 mg PO BID Adjust every 2-3 days until treatment goal is achieved MDD <ul style="list-style-type: none"> 320 mg/day without ascites 160 mg/day with ascites 	<ul style="list-style-type: none"> Resting HR 55-60 BPM SBP should not decrease <90 mm Hg 	Continue indefinitely
Nadolol \$\$	<ul style="list-style-type: none"> 20-40 mg PO QD Adjust every 2-3 days until treatment goal is achieved MDD <ul style="list-style-type: none"> 160 mg/day without ascites 80 mg/day with ascites 	<ul style="list-style-type: none"> Resting HR 55-60 BPM SBP should not decrease <90 mm Hg 	Continue indefinitely
Carvedilol \$	<ul style="list-style-type: none"> Start with 6.25 mg QD After 3 days increase to 6.5 mg BID MDD 12.5 mg/day 	<ul style="list-style-type: none"> SBP should not decrease <90 mm Hg 	Continue indefinitely
EVL- Endoscopic Variceal Ligation	<ul style="list-style-type: none"> Every 2-8 weeks until the eradication of varices 	<ul style="list-style-type: none"> Variceal eradication 	<ul style="list-style-type: none"> First EGD performed 3-6 months after eradication and every 6-12 months thereafter

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 ↓ 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

Therapy	Starting Dose	AEs
Spironolactone	<ul style="list-style-type: none"> • 100mg PO QD • MDD: 400mg/day 	<ul style="list-style-type: none"> • Aldosterone antagonist • Avoid if CrCl <10ml/min • Gynecomastia possible, especially at higher doses
Furosemide	<ul style="list-style-type: none"> • 40mg PO QD • MDD: 160mg/day 	<ul style="list-style-type: none"> • Inhibits reabsorption of Na & Cl in the ascending loop of Henle and proximal/distal renal tubules

TREATMENT OF ASCITES CONT'

- Refractory/recurrent ascites OR diuretic resistant ascites
 - Continue Na restriction
 - D/C beta blockers
 - **Midodrine 7.5mg POTID** 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 portosystemic 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/mm³
 - Positive bacterial culture- most common *Escherichia coli* and *Klebsiella* (minimum *Streptococcal/Staphylococcal*)

SPONTANEOUS BACTERIAL PERITONITIS (SBP)

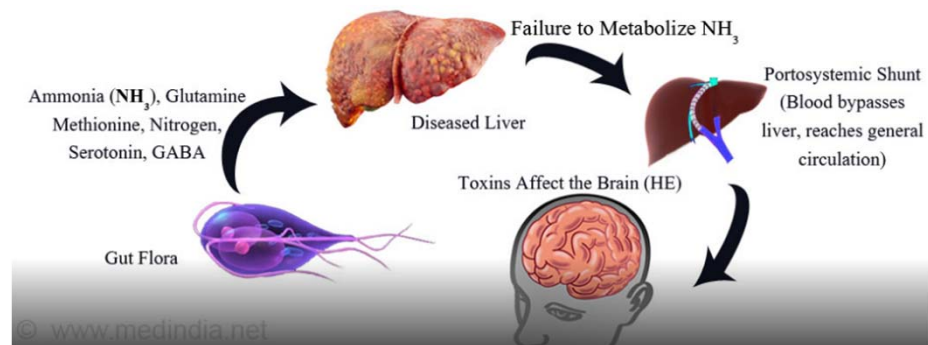
- Empiric treatment
 - Drug: **IV Cefotaxime 2g every 8 hours**
 - Alternatives
 - Third generation cephalosporins (IV Ceftriaxone 2g/day)
 - Fluoroquinolones (IV Ciprofloxacin 400mg BID)
- Duration: **5 or 10 days**
- Prophylaxis
 - Bactrim DS QD
 - Cipro 500mg QD
- D/C PPIs

HEPATIC ENCEPHALOPATHY (HE)

- | | |
|--|--|
| <ul style="list-style-type: none"> ■ Encephalopathy <ul style="list-style-type: none"> ■ Diffuse disturbances of brain function ■ Clinical presentation <ul style="list-style-type: none"> ■ Disorientation *** ■ Acute confused state ■ Inappropriate behavior ■ Unconsciousness/insensibility ■ Coma | <ul style="list-style-type: none"> ■ Motor system abnormality <ul style="list-style-type: none"> ■ 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

Grade 1 <ul style="list-style-type: none"> Changes in behavior Mild confusion Slurred speech Disordered sleep 	Grade 3 <ul style="list-style-type: none"> Marked confusion (stupor) Incoherent speech Sleeping but arousable
Grade 2 <ul style="list-style-type: none"> Lethargy Moderate confusion 	Grade 4 <ul style="list-style-type: none"> Coma Unresponsive to pain

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

Drug Therapy	MOA	Dosage Forms	Dosing Range	Comments
Lactulose (Kristalose® Constulose® Enulose® Generlac®)	<ul style="list-style-type: none"> Nonabsorbable disaccharide Lowers colonic PH $\text{NH}_3 \rightarrow \text{NH}_4^+$ Excreted through feces 	<ul style="list-style-type: none"> Packets: 10g, 20g/pack Solution: 10g/15ml <u>AWP price</u> \$0.03 - \$0.10/ml \$9/pack 	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> First line FDA approved for <u>treatment and prevention</u>
Rifaximin (Xifaxan®)	<ul style="list-style-type: none"> Antibiotic Eliminates gut bacteria-derived ammonia Anti-inflammatory effects 	<ul style="list-style-type: none"> Tablets: 200mg, 550mg Brand only <u>AWP price</u> \$23.03/ tablet (200mg) \$43.90/tablet (550mg) 	<ul style="list-style-type: none"> 400mg PO TID or 550mg PO BID 	<ul style="list-style-type: none"> Alternative therapy/add on FDA approved for <u>prevention</u> Off-label for treatment Minimal AEs
Neomycin	<ul style="list-style-type: none"> Antibiotic Eliminates gut bacteria-derived ammonia 	<ul style="list-style-type: none"> Tablets: 500mg <u>AWP price</u> \$1.40-\$2/tablet 	<ul style="list-style-type: none"> 500mg PO TID or 1g PO BID 	<ul style="list-style-type: none"> Alternative therapy/add on FDA approved for <u>treatment</u> BBV- 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 POTID & neomycin 1g POTID
 - 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?



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