Cirrhosis

Pharmacotherapy I

Dr. Abdallah Abukhalil

Objectives

- Define cirrhosis
  .
- Discuss pharmacotherapy and therapeutic goals for cirrhosis and the associated complications.
- Apply current treatment guidelines for cirrhosis to a patient case.
- Manage or recommend treatment for an adult patient with cirrhosis and cirrhosis complications, including pharmacologic and non-pharmacologic therapies, goals of treatment and monitoring
- Associate symptoms of a cirrhotic patient with compliance to medication therapy.

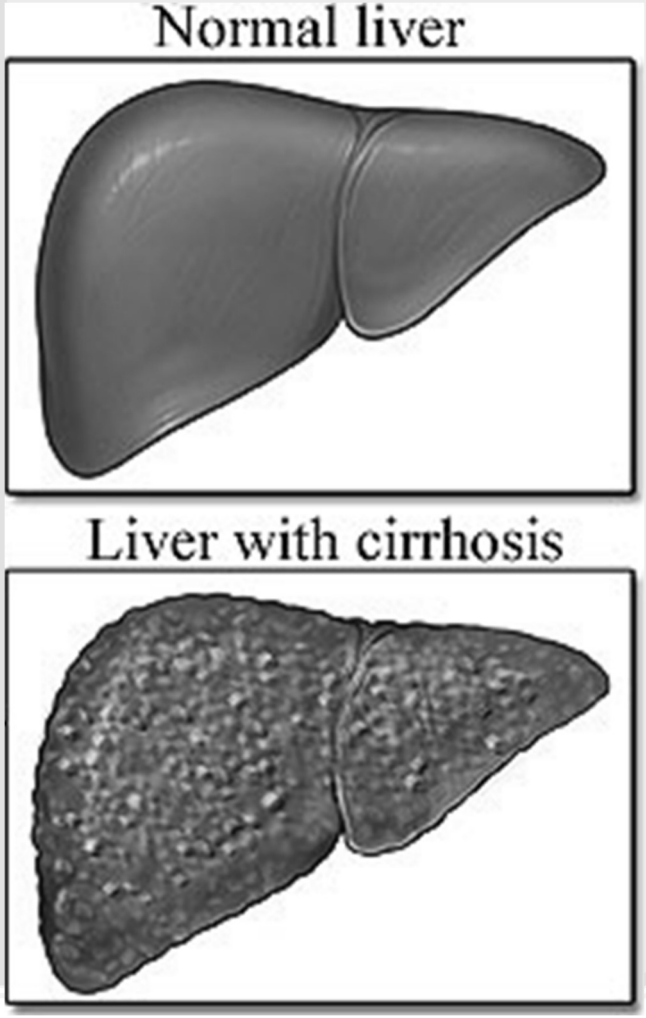
The liver is the largest organ inside the body weighing in at 3 pounds and can auto regenerate.

True False

The main function(s) of the liver include which of the following?

- Purification
- Synthesis
- Storage
- Transformation
- All of the above

What is cirrhosis?



Cirrhosis is scarring of the liver leading to impaired liver function.

- Chronic damage to the liver causes replacement of hepatocytes by fibrotic tissue

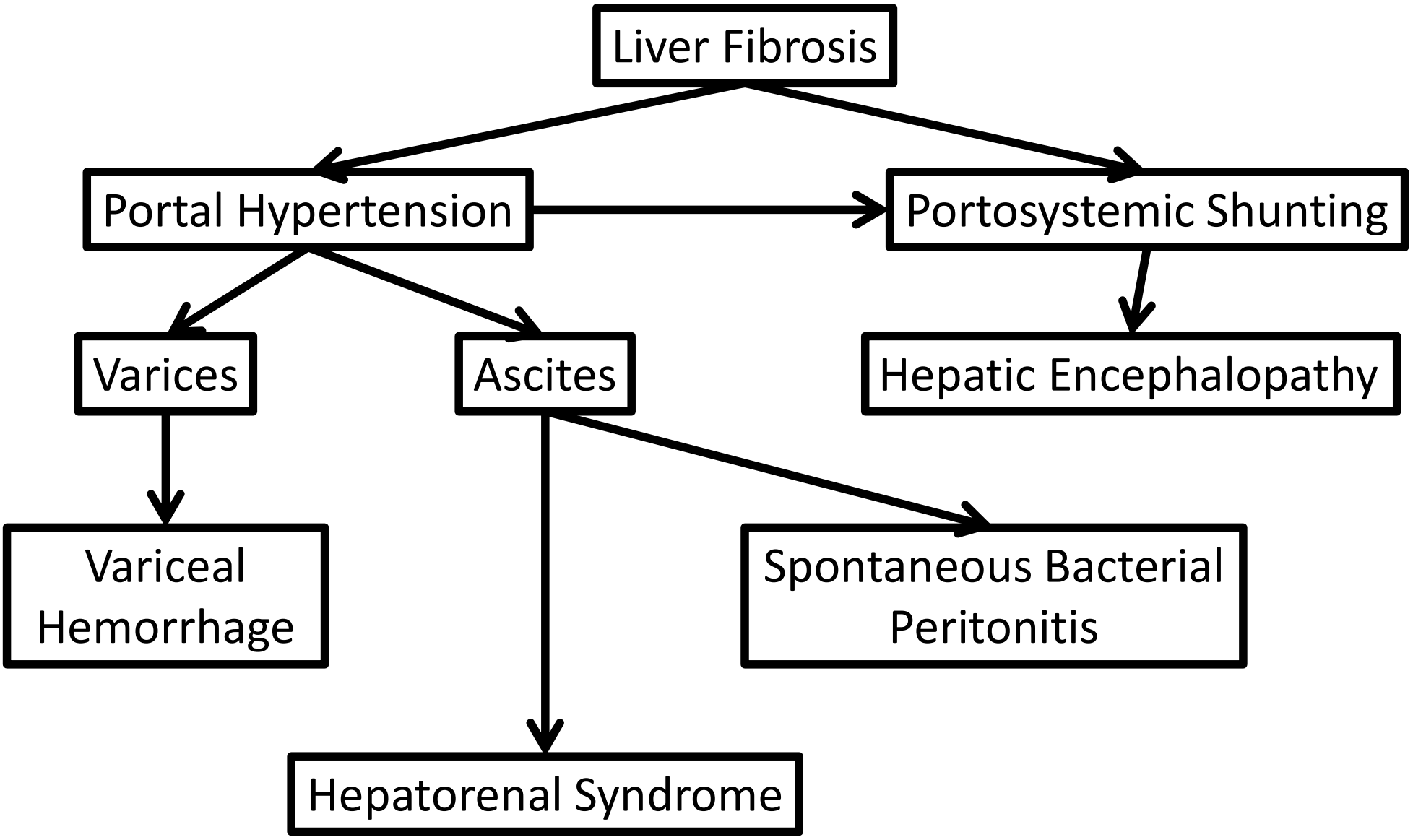
It is the final phase of chronic liver disease.

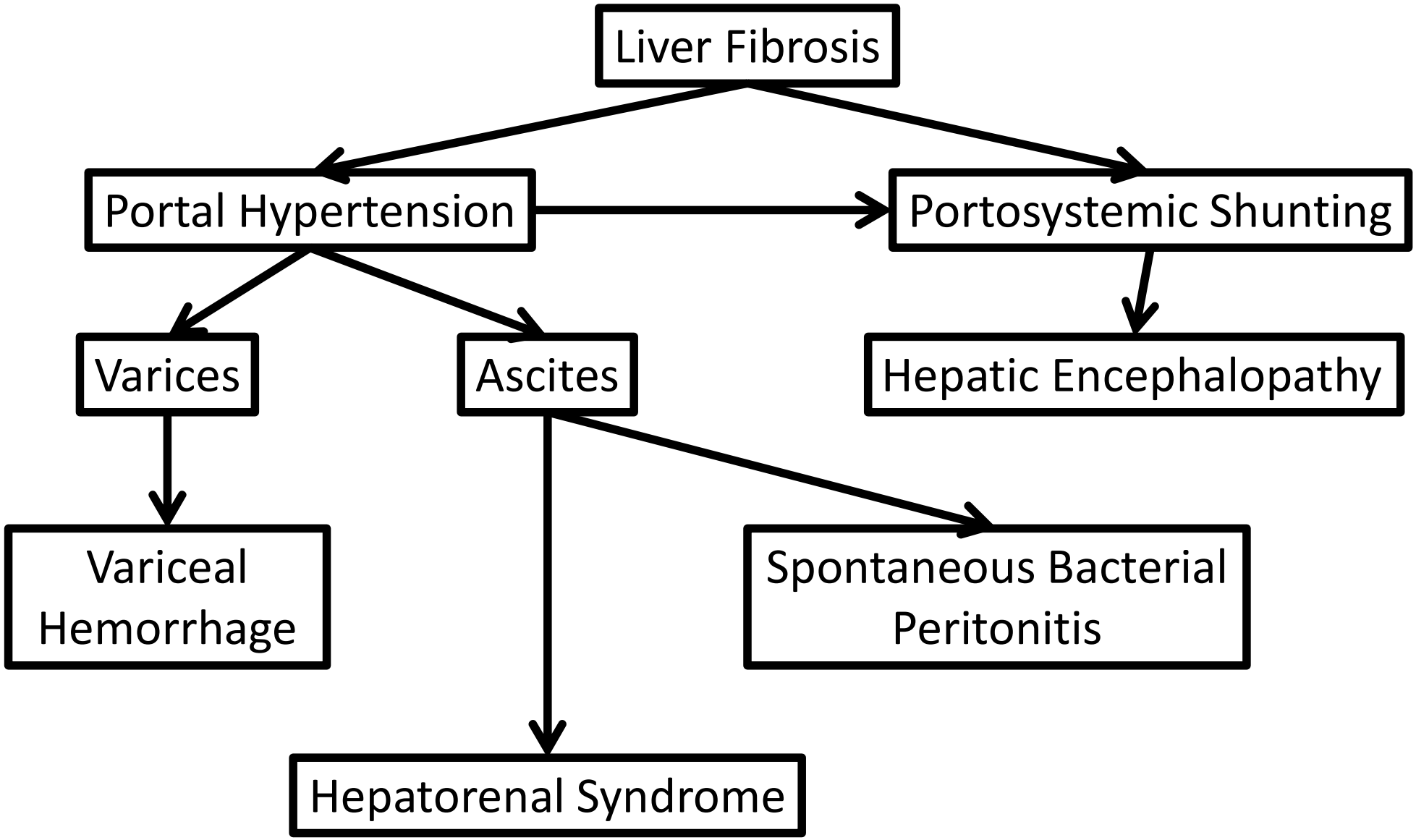
- Common causes
  - Chronic alcohol abuse
  - Chronic hepatitis B or C
- Other causes
  - Metabolic liver disease
  - Cholestatic liver disease
  - Autoimmune hepatitis
  - Drug-induced

Complications

- Ascites
- Portal hypertension
- Gastroesophageal varices
- Hepatic encephalopathy (HE)
- Spontaneous bacterial peritonitis (SBP)
- Coagulation disorders

Complications of Cirrhosis




Liver Fibrosis
Portal Hypertension
Portosystemic Shunting
Varices
Ascites
Hepatic Encephalopathy
Variceal Hemorrhage
Spontaneous Bacterial Peritonitis
Hepatorenal Syndrome

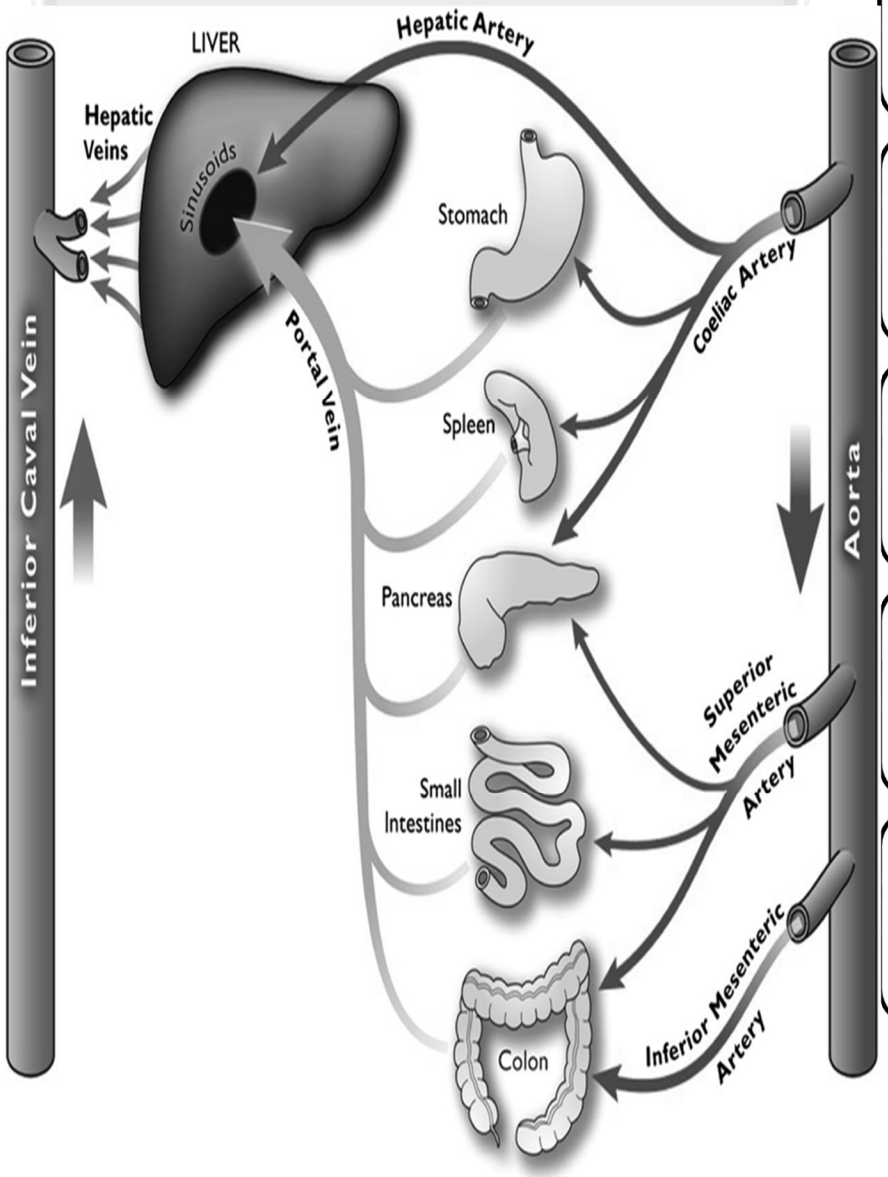
Pathophysiology

Liver receives blood from the hepatic artery and portal vein

Portal blood originates from the mesenteric, gastric, splenic, and pancreatic veins

Liver filters blood before it exits through the hepatic vein into the inferior vena cava

Pathophysiology



Increased intrahepatic resistance

Portal hypertension

Increased splanchnic blood flow

Formation of new blood vessels

Hypotension and decreased systemic vascular resistance

Activation of vasoactive factors

Portal Hypertension

Defined as: hepatic venous pressure gradient (HVPG) > 5 mmHg

Caused by:

↑ resistance to blood flow through the liver

↑ blood flow to the liver

Varices may form and bleeding may occur if HVPG ≥ 10 mmHg

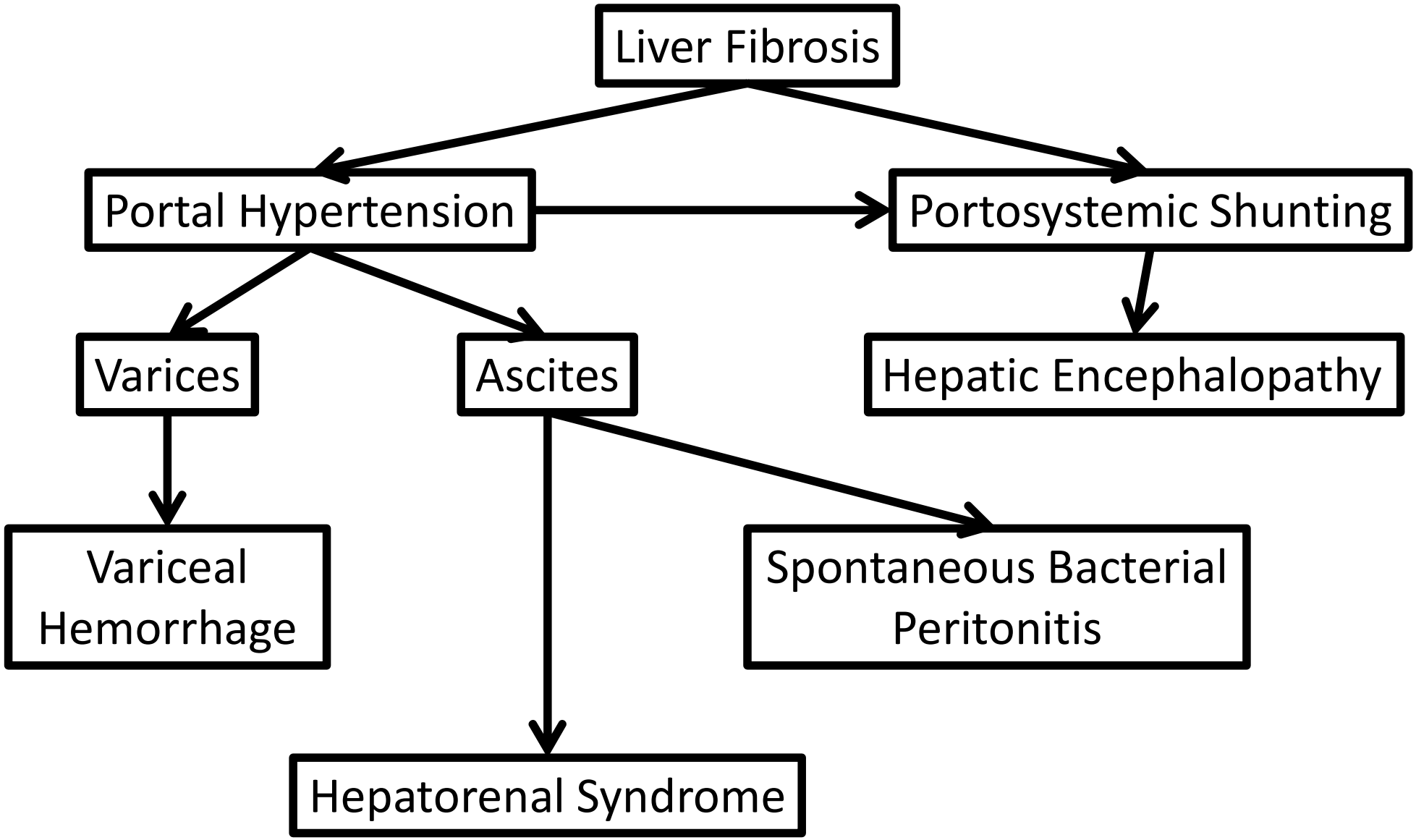
"Clinically significant portal hypertension"

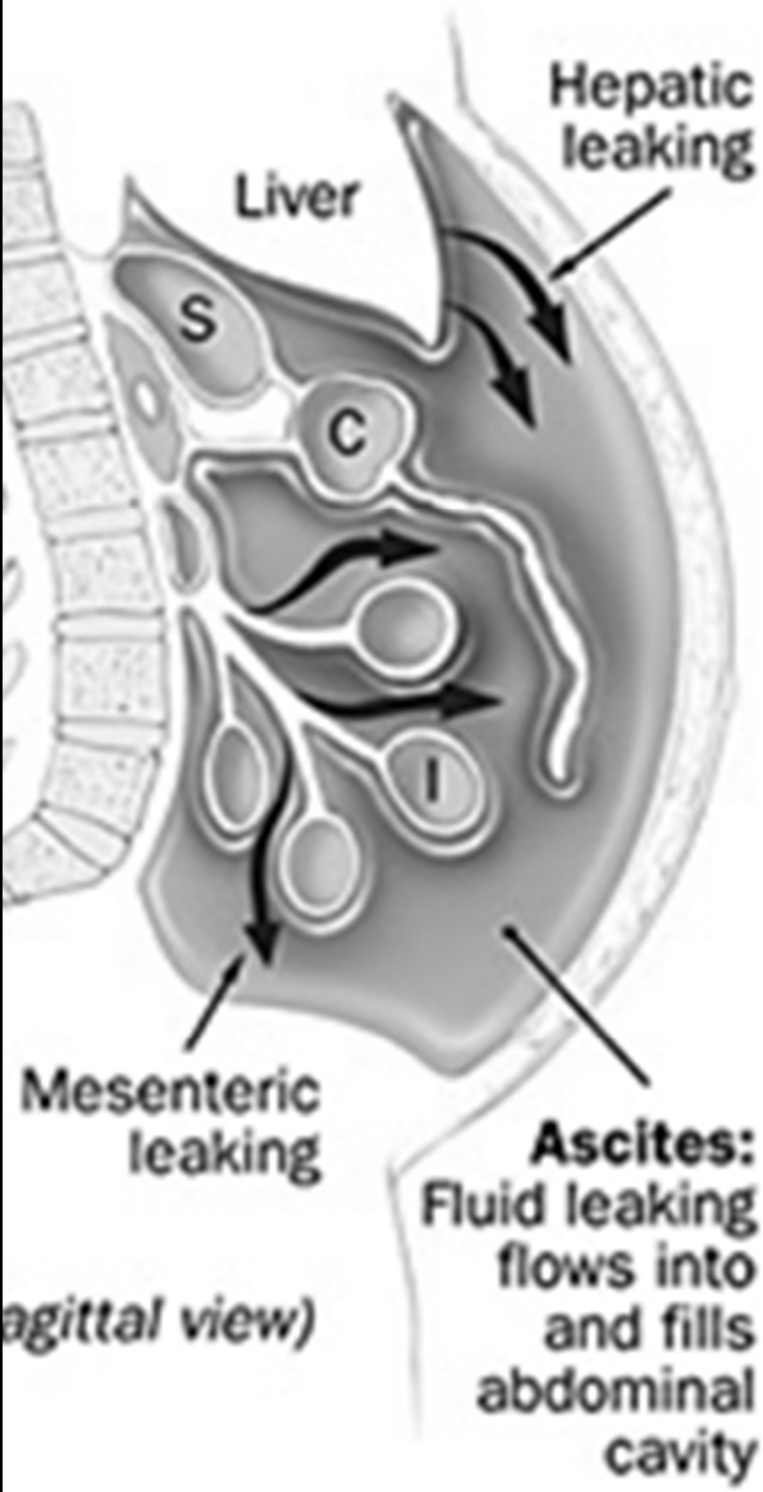
Patient Case

TH is a 53-year-old male recently discharged from the hospital. He was admited due to a 5 kg weight gain over the week prior to admission, abdominal swelling and pain, shortness of breath, and mild confusion. His discharge diagnoses were ascites and SBP.

PMH: alcoholic cirrhosis – diagnosed 6 years ago bleeding esophageal varices – last episode 6 months ago multiple occurrences of ascites hepatic encephalopathy chronic sinusitis hypothyroidism

lives alone, divorced, history of alcohol abuse quit 6 years ago, admits to heavy alcohol use over the last month with a binge one week ago


Liver Fibrosis
Portal Hypertension
Portosystemic Shunting
Varices
Ascites
Hepatic Encephalopathy
Variceal Hemorrhage
Spontaneous Bacterial Peritonitis
Hepatorenal Syndrome



Ascites

- Accumulation of fluid in the peritoneal space
- Clinical presentation:
  - Abdominal bulging
  - Shifting flank dullness > 3 cm
  - Positive fluid wave
- Poor prognostic indicator

https://gi.jhsps.org/GDL_Disease.aspx?CurrentUDV=31&GDL_Cat_ID=AF793A59-B736-42CB-9E1F-E79D2B9FC358&GDL_Disease_ID=E19DBE4A-EE02-4BDE-9FF9-A8371834DE4A

Patient Case Continued

Medications:

triamcinolone acetonide – 2 sprays each nostril daily
propranolol LA 80 mg PO daily
levothyroxine 25 mcg PO daily
lactulose 15 mL PO BID

Allergies:
NKDA

Vitals:
BP 121/74, P 82, T 36.9°C

Labs:

133	103	22	85
3.9	26	0.8	

	13	
7		79
	38	

PT 14.9 sec (10-12)
INR 1.42 (0.9-1.1)
NH3 102 mcg/dL (<30)
TSH 2.5 mIU/L (0.5-5)

AST 108 IU/L (5-30)
ALT 120 IU/L (5-40)
Tbili 2.9 mg/dL (0.3-1)
Alb 2.8 g/dL (3.5-4.5)

Paracentesis
SAAG 1.5 g/dL
Protein 0.8 g/dL
PMN 333 cells/mm^3
10 L removed
Culture – E. coli

PMN – polymorphonuclear leukocyte

Ascites

Most common complication

Accumulation of fluid within the peritoneal cavity

Renal sodium and water retention

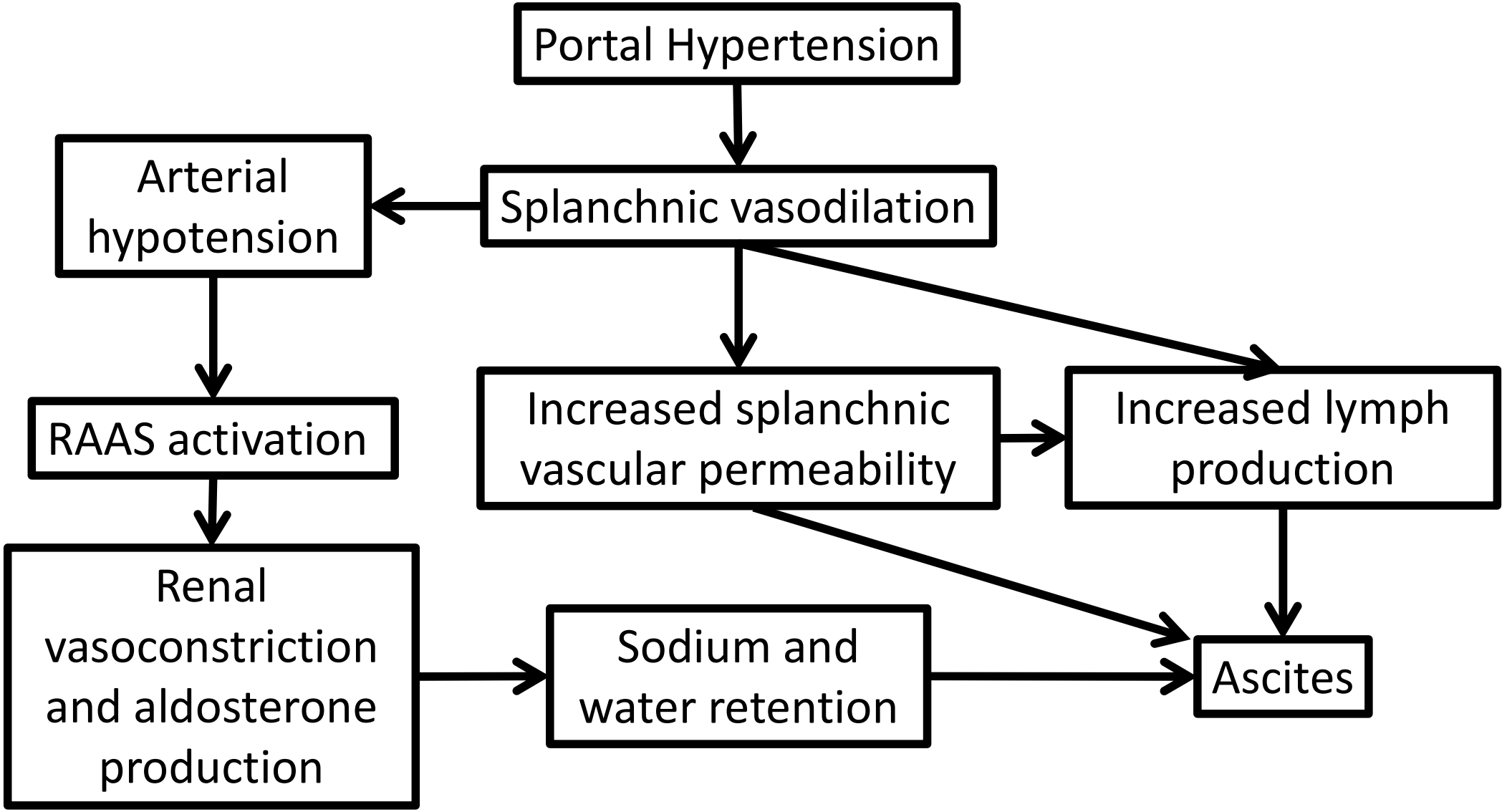
Increased splanchnic vascular permeability

Lymph leakage into peritoneal cavity

Treatment goals

Prevent/relieve symptoms	Prevent more serious complications

How Does Portal Hypertension Lead to Ascites?



Management of Ascites

Goals:

- Control ascites
- Relieve symptoms, such as dyspnea, abdominal pain and distention
- Prevent SBP and hepatorenal syndrome

Non-pharmacologic:

- Abstain from alcohol
- Restrict salt intake

Pharmacologic:

- Diuretics
- Discontinue drugs that cause sodium/water retention

Diuretic Therapy for Ascites

Mechanism:

- Spironolactone – antagonizes aldosterone receptor leading to sodium and water excretion without potassium loss
- Furosemide – inhibits sodium reabsorption leading to sodium and water excretion

Dosing:

- Spironolactone 100 mg : furosemide 40 mg ratio recommended
- May titrate up Q3-5 days if needed to max dose of spironolactone 400 mg/day and furosemide 160 mg/day

Adverse effects: electrolyte imbalance, dehydration, renal dysfunction, hypotension

Refractory Ascites	Ascites that : Is not responsive to maximized diuretic therapy along with compliance to low-sodium diet Recurs quickly after paracentesis

Management of Refractory Ascites

Discontinue drugs that decrease renal perfusion:

- NSAIDs, ACE-inhibitors, ARBs

Consider:

- Discontinuation of beta blocker
- Addition of midodrine to diuretic therapy:
  - Mechanism: alpha-1 agonist – increases BP and may increase response to diuretics
  - Dosing: 7.5 mg PO TID
- Discontinuation of diuretics if still resistant after addition of midodrine

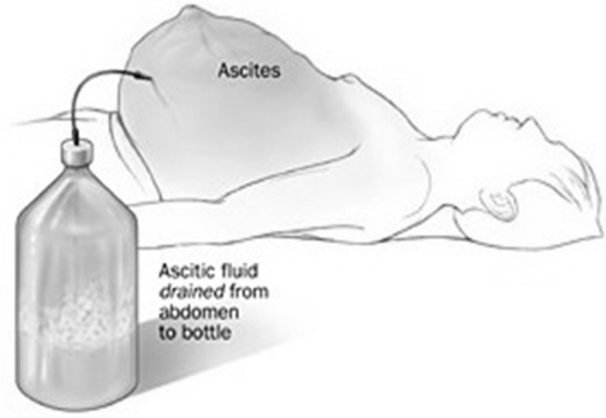
Management of Refractory Ascites

Serial therapeutic paracentesis Q2 weeks

- For large volume paracentesis (>5 L), give 25% albumin IV:
  - Mechanism: increases oncotic pressure to prevent hypovolemia
  - Dosing: 6-8 g per liter of fluid removed

Last line:

- TIPS, peritoneovenous shunt
- Consider transplant



Patient Case Continued

TH is a 53-year-old male recently discharged after hospitalization for ascites and development of SBP; a paracentesis was performed during hospitalization.

Medications:

triamcinolone acetonide – 2 sprays each nostril daily
propranolol LA 80 mg PO daily
levothyroxine 25 mcg PO daily
lactulose 15 mL PO BID

Labs:

133	103	22	85
3.9	26	0.8	

7	13	79
	38	

PT 14.9 sec (10-12)
INR 1.42 (0.9-1.1)
NH3 102 mcg/dL (<30)
TSH 2.5 mIU/L (0.5-5)

AST 108 IU/L (5-30)
ALT 120 IU/L (5-40)
Tbili 2.9 mg/dL (0.3-1)
Alb 2.8 g/dL (3.5-4.5)

Paracentesis
SAAG 1.5 g/dL
Protein 0.8 g/dL
PMN 333 cells/mm^3
10 L removed
Culture – E. coli

Patient Case Continued

Procedure: Therapeutic Paracentesis

Diagnosis: Ascites/cirrhosis

Anesthesia/sedation: 1% lidocaine subcutaneously into peritoneum

Notes:

Site accessed and marked under ultrasound guidance, site prepped/ draped in sterile fashion, scalpel used to make small incision prior to catheter introduction, 10 L of clear, yellow fluid removed. Specimen sent.

Paracentesis
SAAG 1.5 g/dL
Protein 0.8 g/dL
PMN 333 cells/mm^3
10 L removed
Culture – E. coli

Patient Case Continued

Recommendation:

- Albumin 75 gm IV infusion post-paracentesis Start spironolactone 100 mg PO daily
- Start furosemide 40 mg PO daily Titrate every 3-5 days
- Monitor electrolytes and BUN/SCr, I/O, BP

Education:

- Avoid alcohol and toxic medications Record daily weights
- Sodium restricted diet

Ascites Summary

- Not a life-threatening complication, unless SBP
- Treat with sodium restriction and diuretics first
- Paracentesis for initial tense or refractory ascites
- Consider albumin after paracentesis

Spontaneous Bacterial Peritonitis

- Infection of ascitic fluid that occurs in the absence of any evidence of an intra-abdominal, surgically treatable source of infection

Spontaneous Bacterial Peritonitis

Develops in 25-30% of patients with cirrhosis and ascites

Mechanism

- Hematogenous seeding
- translocation of bacteria from the gut
- Transmural migration of bacteria

Symptoms

- Fever, abdominal pain, ascites, leukocytosis, Altered mental status

Spontaneous Bacterial Peritonitis

Common pathogens:

- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Streptococcus pneumoniae*

Ascitic fluid PMN ≥ 250 cells/mm^3 is diagnostic for SBP

- Empiric antibiotic treatment should be initiated
- Ascitic fluid culture/sensitivity should be obtained

Treatment of SBP

Antibiotics:

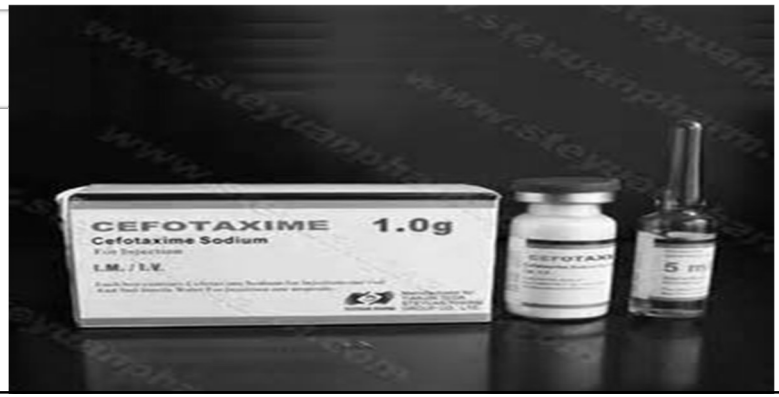
Give to all patients with confirmed (ascitic fluid PMN ≥ 250/mm^3) or suspected SBP

Empiric antibiotic therapy:

- First Lined Cefotaxime (*Claforan*) 2 g IV Q8h
- Alternative
  - Ceftriaxone (*Rocephin*) 2 g IV Q24h
  - Ciprofloxacin (*Cipro*) 400 mg IV Q12h

Adjust antibiotic choice based on culture results (targeted antibiotic therapy)

Duration: 5 days



Treatment of SBP

Albumin 25%:

- Mechanism: expansion of intravascular volume may prevent renal failure
- Indication:
  - Ascitic fluid PMN ≥ 250 cells/mm^3 ***and***
    - SCr > 1 mg/dL ***or***
    - BUN >30 mg/dL ***or***
    - Total bilirubin > 4 mg/dL
- Dosing: 1.5 g/kg IV on day 1 followed by 1 g/kg IV on day 3
- Give in addition to antibiotics

Spontaneous Bacterial Peritonitis

Long-term prophylaxis for all survivors of SBP

Antibiotic options:

- Fluoroquinolones Ciprofloxacin (Cipro) 500 mg PO daily
- Sulfamethoxazole/trimethoprim (Bactrim) 1 double-strength tablet (800/160 mg) PO daily

Prevention of SBP in patients with GI bleed

- IV ceforiaxone or fluoroquinolone x 7 days

Primary SBP Prophylaxis

Short term:

- Indication: any patient presenting with acute variceal bleeding
- Preferred antibiotic: Ceftriaxone (*Rocephin*)
- Duration: up to 7 days

Long term:

- Indication: patients who did not have a prior SBP episode, but meet the following criteria:
  - Ascitic fluid albumin < 1.5 g/dL ***and***
    - SCr ≥ 1.2 mg/dL, BUN ≥ 25 mg/dL *or* Na ≤ 130 mEq/L ***or***
    - Child-Pugh score ≥ 9 with bilirubin ≥ 3 mg/dL
- Antibiotic options: same as previous slide
- Duration: indefinite

Patient Case Continued

TH is a 53 year-old male recently discharged aoer hospitalization for ascites and development of SBP; a paracentesis was performed during hospitalization.

Medications:

triamcinolone acetonide – 2 sprays each nostril daily

propranolol LA 80 mg PO daily

levothyroxine 25 mcg PO daily

lactulose 15 mL PO BID

Labs:

Paracentesis
SAAG 1.5 g/dL
Protein 0.8 g/dL
PMN 333 cells/mm^3
10 L removed
Culture – E. coli

Patient Case Continued

Recommendation:

- Cefotaxime 2 gm IV Q8H
- SMX-TMP 1DS PO daily for secondary prevention of SBP

SBP Summary

- Infection of ascitic fluid
- Can be life-threatening
- Must treat with broad-spectrum antibiotics
- Consider albumin
- Start prophylactic antibiotics in select patients

Hepatorenal Syndrome

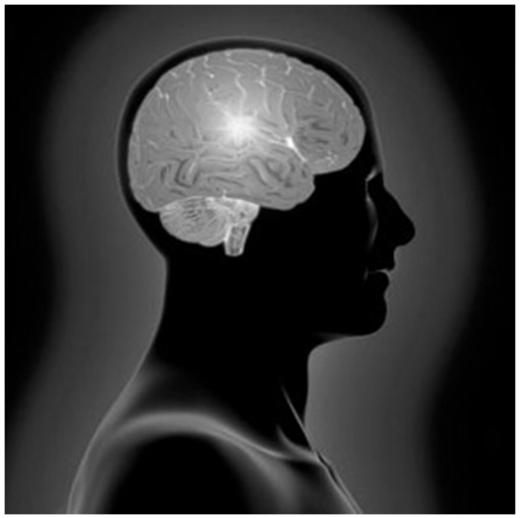
Impaired renal function secondary to cirrhosis

- Caused by renal vasoconstriction
- Leads to reduced sodium and water excretion

End-stage complication of cirrhosis

- Liver transplantation needed for survival

Hepatic Encephalopathy (HE)



Disturbance in CNS function because of hepatic insufficiency

70% of cirrhotic patients

NH_3 is key factor

- Blood levels do not correlate to mental state

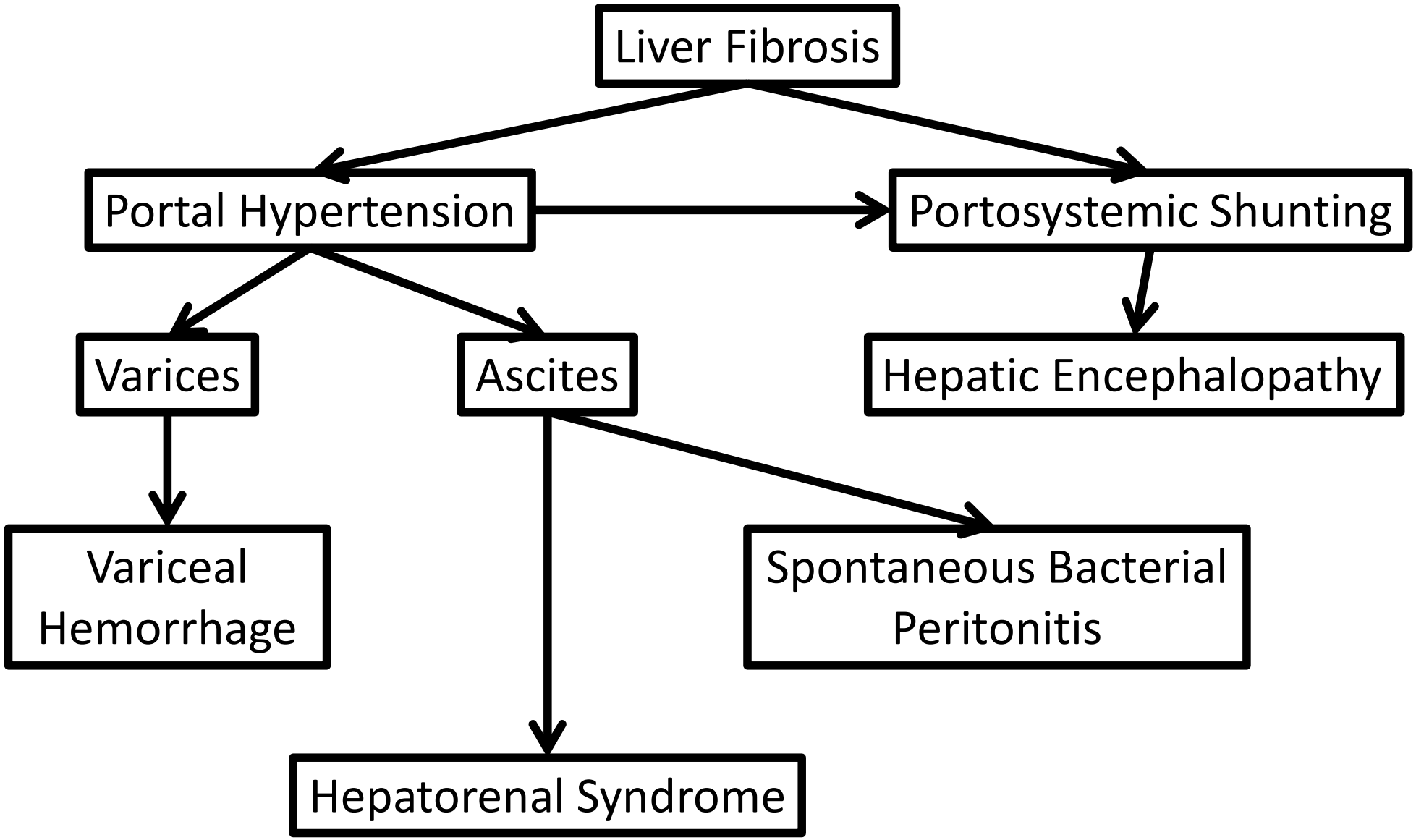
Treatment goals

- Control precipitating factors

Reverse encephalopathy

Reduce ammonia levels

- Avoid recurrence


Liver Fibrosis
Portal Hypertension
Portosystemic Shunting
Varices
Ascites
Hepatic Encephalopathy
Variceal Hemorrhage
Spontaneous Bacterial Peritonitis
Hepatorenal Syndrome

Precipitating Factors of HE

Some episodes may be spontaneous

Common causes of precipitated episodes:

- GI bleeding
- Infection
- Electrolyte abnormalities
- Sedatives
- Excessive dietary protein
- Constipation
- Renal dysfunction

Management of Hepatic Encephalopathy

Goals:

- Resolution of acute HE episode
- Prevention of recurrent HE episodes

Must identify and correct any precipitating factors

Management of Hepatic Encephalopathy

Non-pharmacologic:

- Appropriate consumption of dietary protein
  - May be initially restricted in acute HE, but titrate back to goal of 1.2-1.5 g/kg/day
  - Vegetable or dairy protein sources preferred over meat sources

Pharmacologic:

- Lactulose
- Antibiotics
- Zinc

Pharmacologic Therapies for HE: Lactulose

First line therapy for HE

Mechanism: acidifies the colon, creating catharsis

- Reduces ammonia absorption from the colon to circulation
- Increases ammonia uptake from circulation into the colon

Pharmacologic Therapies for HE: Lactulose

- Dosing: (available as a 10 g/15 mL solution)
  - Episodic HE: initiate 16.7 g (25 mL) PO Q1-2h until BM, then reduce to 10-30 g (15-45 mL) PO Q8-12h and titrate to 2-3 soft BM per day
    - May also give as enema: 200 g (300 mL) lactulose in total of 1000 mL sterile water retained for 1 hour
  - Persistent HE: 10-30 g (15-45 mL) PO q8-12h and titrate to 2-3 soft BM per day
- Adverse effects: electrolyte imbalance, diarrhea, dehydration

Pharmacologic Therapies for HE: Antibiotics

Use in combination with lactulose

Mechanism:

- Reduction of urease-producing bacteria in the colon leads to decreased production of ammonia

Pharmacologic Therapies for HE: Antibiotics

Rifaximin (*Xifaxin*): 550 mg PO BID

- Preferred over neomycin or metronidazole
- Add on to lactulose after second HE occurrence
- Adverse effects: nausea, diarrhea

Neomycin: 3-6 g/day PO in acute HE or 1-2 g/day for persistent HE

- Adverse effects: ototoxicity, nephrotoxicity

Metronidazole (*Flagyl*): 250 mg PO BID

- Adverse effect: neurotoxicity

Pharmacologic Therapies for HE: Zinc Supplementation

Zinc is a cofactor in the urea cycle (conversion of ammonia to urea)

Consider supplementation if patient has zinc deficiency

- Males: 11 mg/day
- Females: 8 mg/day

Secondary Prevention of HE

Lactulose should be used for prevention of recurrent HE

After a second episode of HE, rifaximin is recommended as an add-on therapy to lactulose

Prophylactic therapy may be discontinued if recurrent precipitating factors are fully controlled

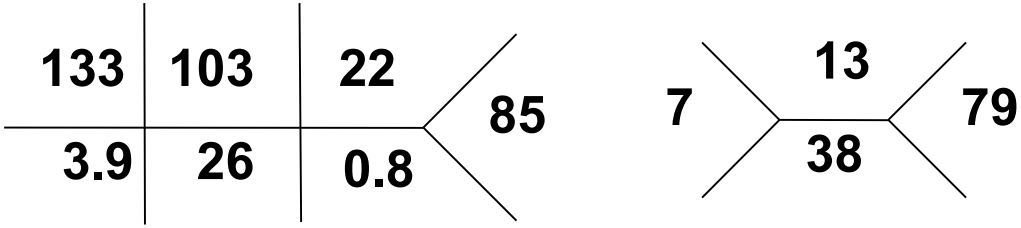
Patient Case Continued

- TH is a 53-year-old male recently discharged after hospitalization for ascites and development of SBP; a paracentesis was performed during hospitalization.

- Medications:
  - triamcinolone acetonide – 2 sprays each nostril daily propranolol LA 80 mg PO daily
  - levothyroxine 25 mcg PO daily lactulose 15 mL PO BID

Paracentesis
SAAG 1.5 g/dL
Protein 0.8 g/dL
PMN 333 cells/mm^3
10 L removed
Culture – E. coli

Labs:



PT 14.9 sec (10-12)	AST 108 IU/L (5-30)
INR 1.42 (0.9-1.1)	ALT 120 IU/L (5-40)
NH_3 102 mcg/dL (<30)	Tbili 2.9 mg/dL (0.3-1)
TSH 2.5 mIU/L (0.5-5)	Alb 2.8 g/dL (3.5-4.5)

Patient Case Continued

Recommendation:

- Start lactulose 45 mL PO Q1H Increase lactulose to 30 mL PO Q12H Titrate to achieve 2-3 BM/day

Education:

- Protein restriction Protein sources

HE Summary

Neurological symptoms

Can be life-threatening

Treatment

- Protein restriction
- Lactulose
- Rifaximin

Alternatives: metronidazole, neomycin, zinc supplementation

Gastroesophageal Varices

Increased portal pressure gradient

- Increased resistance to blood flow
- Formation of collateral blood flow

Occurrence

- Present in 50% of patients with cirrhosis
- 5% develop varices within 1 year; 28% within 3 years

Treatment goals

- Prevent initial bleed
- Prevent rebleeding

Gastroesophageal Varices

Progression to bleeding

- Child-Pugh score
- Red wale markings
  - Alcoholic or decompensated cirrhosis

Rebleeding is common

Management of varices

- Primary prophylaxis
- Treatment of acute variceal hemorrhage
- Secondary prophylaxis

Management of Gastroesophageal Varices

Screening

- EGD when diagnosed with cirrhosis
  - Every 2-3 years if no evidence of varices
  - Every 1-2 years if small varices
  - Annually if decompensated liver disease

Primary prophylaxis

- Nonselective β-adrenergic blocking agents
  - Nadolol 40 mg PO daily
  - Propranolol 20 mg PO BID
- Titrate to maximum tolerated dose (55-60 bpm)

Management of Gastroesophageal Varices

Management of Gastroesophageal Varices

Acute variceal bleed

- Medical emergency!!!

Acute bleeding

- Hematemesis
- Hematochezia
- Hypotension
- Shock

Splanchnic vasoconstriction

- Octreotide
  - 50 mcg IV bolus, 50 mcg/hr IV continuous infusion for 3-5 days
  - 1st line therapy for acute bleeding

Antibiotic prophylaxis (7 days)

- Ciprofloxacin 400 mg IV Q12H
- Ceoriaxone 1 gm IV Q24H

Management of Gastroesophageal Varices

Secondary prophylaxis

Non-selective β-blocker and chronic endoscopic variceal ligation (EVL)

- Nadolol 40 PO daily
- Propranolol 20 mg PO BID
- Titrate to maximum tolerated dose or HR of 55-60 bpm

Non-selective β-blocker + nitrate

- Isosorbide mononitrate (ISMN) 10-20 mg PO BID

Not required if shunt surgery/procedure

Management of Gastroesophageal Varices

Vasoactive Therapy for Acute Variceal Hemorrhage

Initiate as soon as variceal hemorrhage is suspected to stop or slow bleeding

- May initiate before EGD

Options:

- Octreotide (preferred)
- Vasopressin + nitroglycerin (only if octreotide unavailable)

Octreotide (*Sandostatin*)

Preferred pharmacologic therapy for acute variceal bleed

Mechanism:

- Selective splanchnic vasoconstriction leads to decreased portal pressure and blood flow

Dosing: 50 mcg IV bolus followed by 50 mcg/hr continuous IV infusion x 2-5 days

Adverse effects: bradycardia, hypertension, arrhythmias, abdominal pain, hyperglycemia

Vasopressin

Second line choice for acute variceal bleed

Mechanism:

- Non-selective vasoconstrictor
- Potent splanchnic vasoconstrictor

Dosing: 0.2-0.4 units/min continuous IV infusion, may be titrated up to 0.8 units/min

Adverse effects: myocardial ischemia, mesenteric ischemia, ischemia of the limbs, CVA, arrhythmias

Vasopressin

Must give nitroglycerin concurrently with vasopressin to decrease effects related to systemic vasoconstriction

- Initiate nitroglycerin 40 mcg/min continuous IV infusion and titrate to systolic BP > 90 mmHg (max 400 mcg/min)

May be used for up to maximum of 24 hours

Antibiotics in Setting of Acute Variceal Hemorrhage

Patients with cirrhosis and acute variceal bleeding are at higher risk of spontaneous bacterial peritonitis (SBP)

Short-term (up to 7 days) prophylaxis for SBP is recommended for all patients with cirrhosis and acute variceal bleeding

- May consider discontinuation of antibiotic after vasoactive drug discontinued and bleeding ceased

Preferred antibiotic:

- Ceftriaxone (*Rocephin*) 1 g IV Q24h

Secondary Prophylaxis of Variceal Hemorrhage

Goal: prevent rebleeding

A combination of EVL every 1-4 weeks ***plus*** pharmacologic therapy is recommended

- Required for all patients who have experienced variceal bleeding unless TIPS performed

Pharmacologic Secondary Prophylaxis

Initiate as soon as vasoactive therapy is discontinued

Traditional NSBB (propranolol or nadolol) is preferred

Same dosing and goals as primary pharmacologic prophylaxis	Continue indefinitely

Pharmacologic therapies that have been studied, but not recommended at this time:

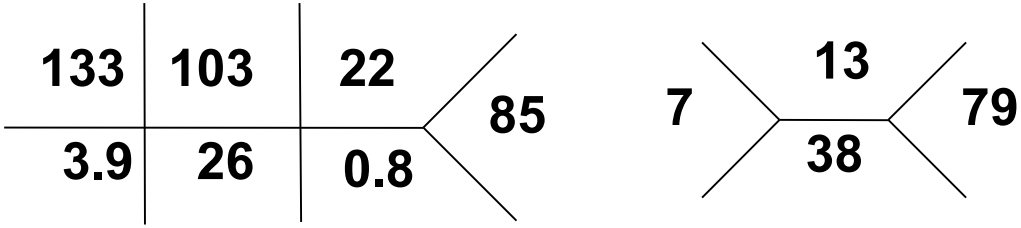
Non-selective beta blocker + isosorbide mononitrate	Carvedilol

Patient Case Continued

- TH is a 53 year-old male recently discharged aoer hospitalization for ascites and development of SBP; a paracentesis was performed during hospitalization.

- Medications:
  - triamcinolone acetonide – 2 sprays each nostril daily propranolol LA 80 mg PO daily
  - levothyroxine 25 mcg PO daily lactulose 15 mL PO BID

Labs:



Paracentesis
SAAG 1.5 g/dL
Protein 0.8 g/dL
PMN 333 cells/mm^3
10 L removed
Culture – E. coli

*From hospitalization

PT 14.9 sec (10-12)
INR 1.42 (0.9-1.1)
NH_3 102 mcg/dL (<30)
TSH 2.5 mIU/L (0.5-5)

AST 108 IU/L (5-30)
ALT 120 IU/L (5-40)
Tbili 2.9 mg/dL (0.3-1)
Alb 2.8 g/dL (3.5-4.5)

Patient Case Continued

Recommendation:

- Increase propranolol LA to 160 mg PO daily Ensure EVL therapy completed after last bleed If unable to have EVL, add ISMN 20 mg PO BID Follow-up EGD every 6-12 months

Education:

- Monitor for dizziness, bronchospasm, glucose intolerance Monitor BP and HR
- Notify physician immediately of any symptoms of bleeding

Esophageal Varices Summary

Active bleeding – life threatening

Treatment of choice:

- Pharmacological: octreotide
- Non-pharmacological: band ligation, sclerotherapy

Prophylaxis

- Non-selective β-blocker therapy

Child-Pugh Grading

- Basis for recommended drug dosing adjustments

Score	**1**	**2**	**3**
Total bilirubin (mg/dL)	1-2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
Ascites	None	Mild	Moderate
Encephalopathy (grade)	None	1 and 2	3 and 4
Prothrombin time (seconds)	1-4	4-6	>6

Score	**Grade**
<7 points	A
7-9 points	B
10-15 points	C

Summary

- Cirrhosis is a chronic disease and is characterized by fibrosis of the liver
- Portal hypertension can lead to the development of multiple additional complications of cirrhosis
- Patients should be screened for varices after cirrhosis diagnosis and primary prophylaxis for variceal bleeding should be initiated if indicated
- Variceal bleeding is a medical emergency that should be managed with vasoactive therapy, as well as antibiotics for prophylaxis of SBP and non-pharmacologic treatment
- Non-pharmacologic and pharmacologic secondary prophylaxis should be initiated following a variceal bleeding event

Summary

Pharmacists and drug therapy play a large role in the management and prevention of complications of cirrhosis.

Dual diuretic therapy with spironolactone and furosemide is the mainstay of pharmacologic treatment for ascites

Antimicrobial prophylaxis for survivors of SBP

Lactulose and/or antimicrobial therapy for prevention of hepatic encephalopathy

Non-selective β-blockers + EVL or ISMN for secondary prophylaxis of variceal hemorrhage

Reference

- Sease, Julie M., and Jennifer N. Clements.. "Portal Hypertension and Cirrhosis." Pharmacotherapy: A Pathophysiologic Approach, 10e Eds. Joseph T. DiPiro, et al. New York, NY: McGraw-Hill,