

Cirrhosis

Pharmacotherapy I

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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

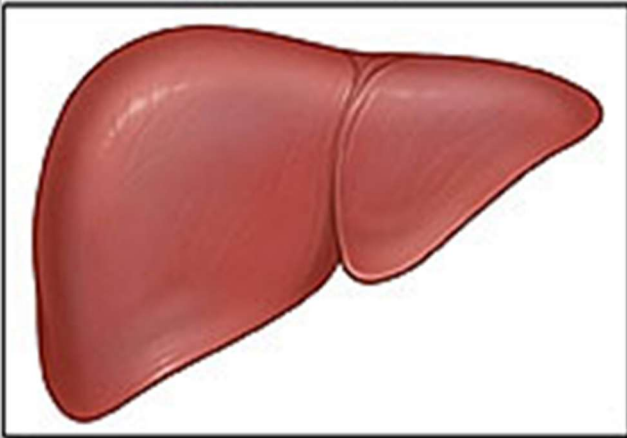


The main function(s) of the liver include which of the following?

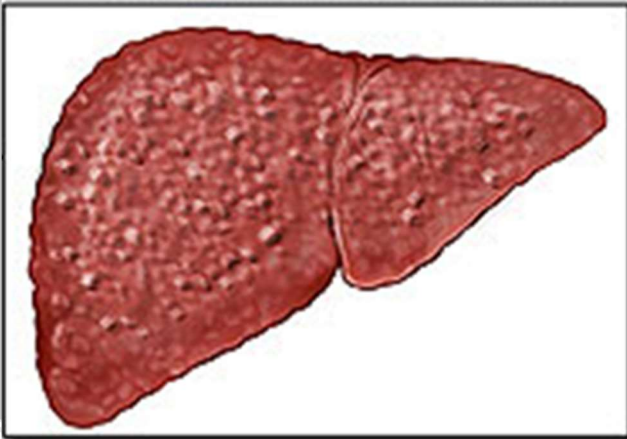
- Purification
- Synthesis
- Storage
- Transformation
- All of the above

What is cirrhosis?

Normal liver



Liver with 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

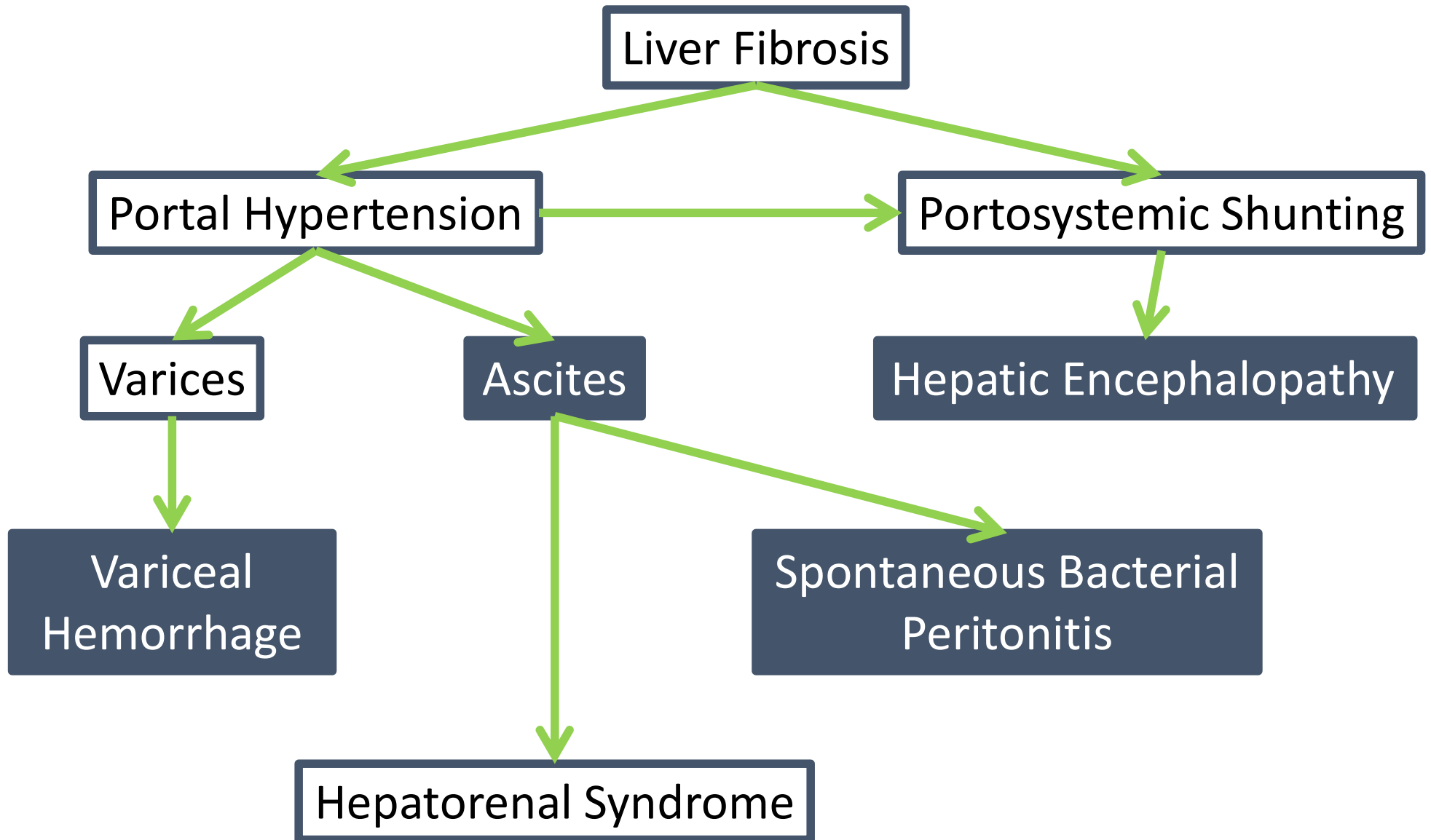
Gastroesophageal varices

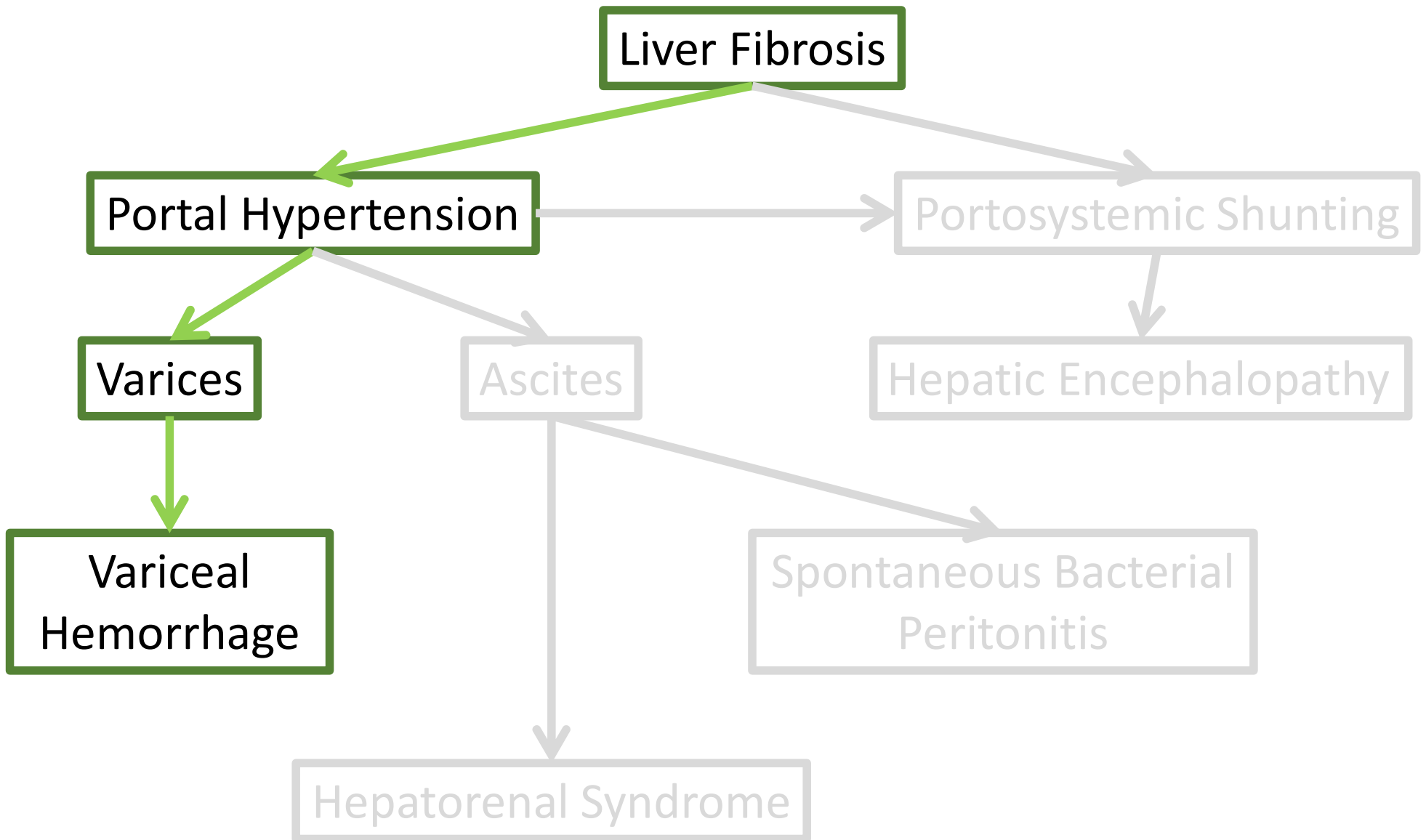
Hepatic encephalopathy (HE)

Spontaneous bacterial peritonitis (SBP)

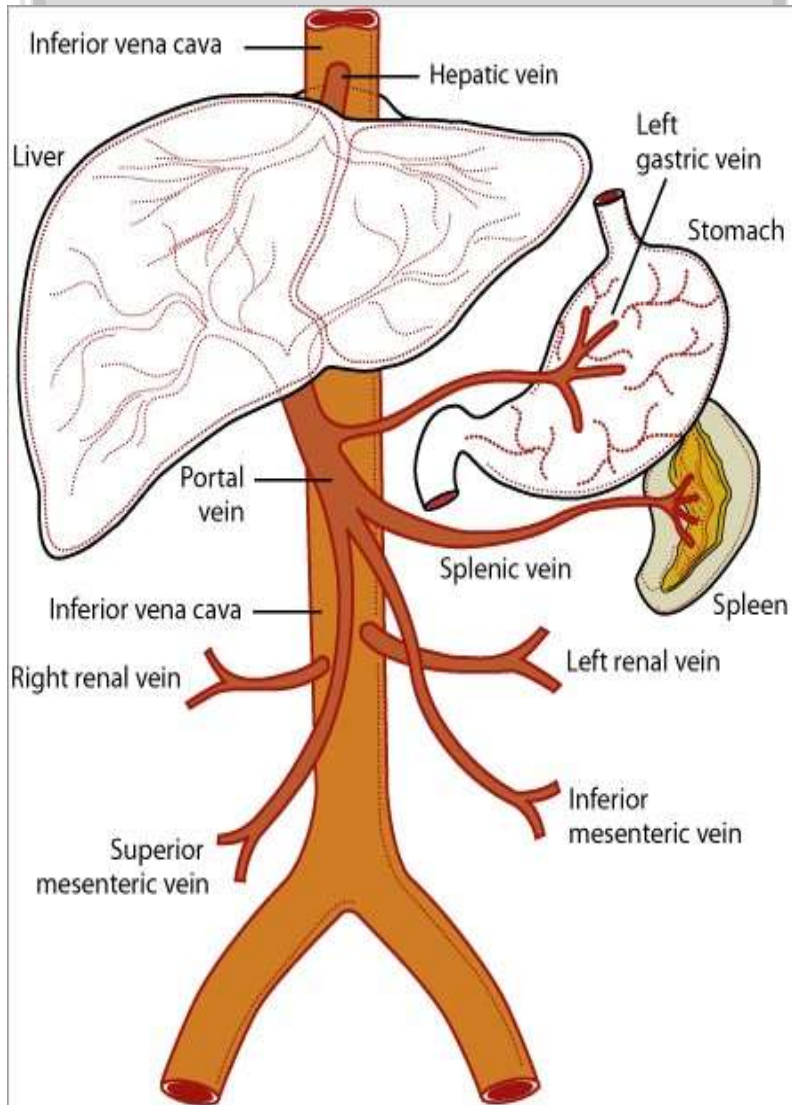
Coagulation disorders

Complications of Cirrhosis





Pathophysiology

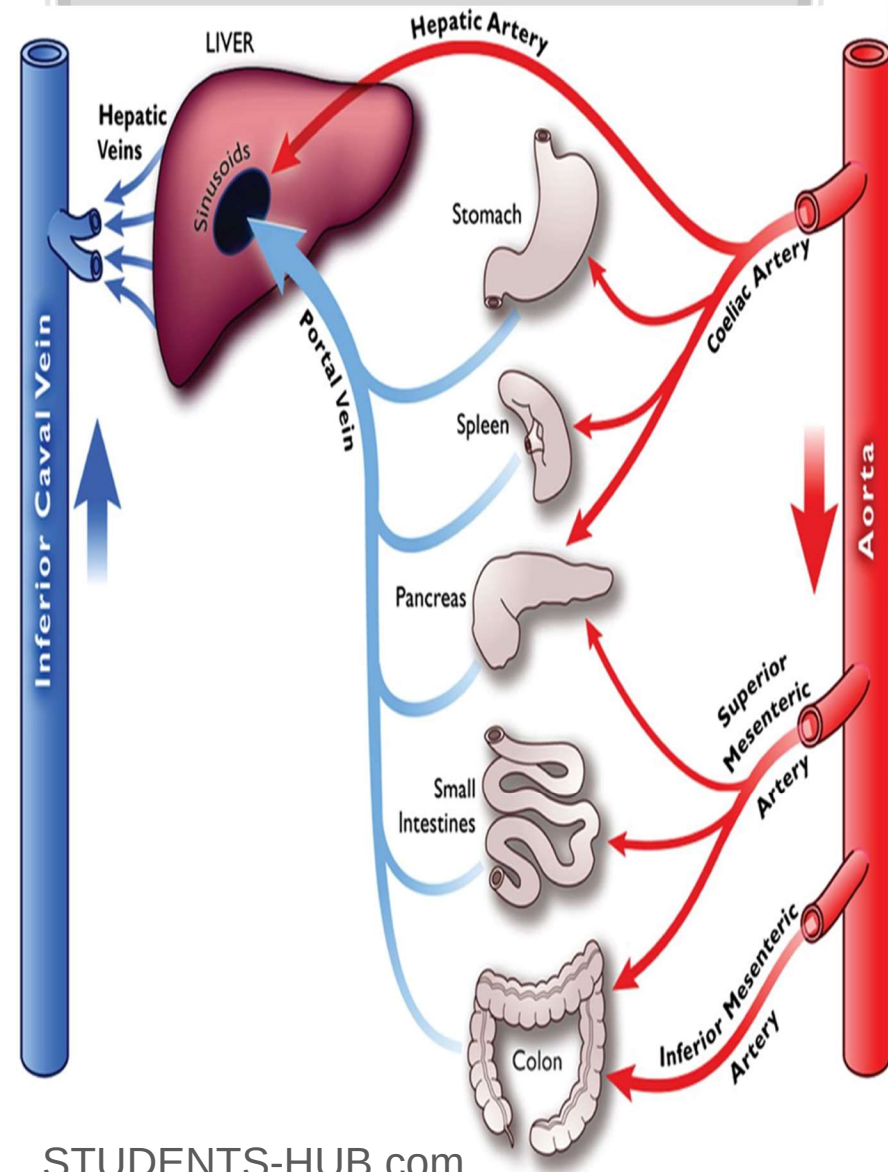


Liver receives blood from the hepatic artery and portal vein

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 $\geq$ 10 mmHg

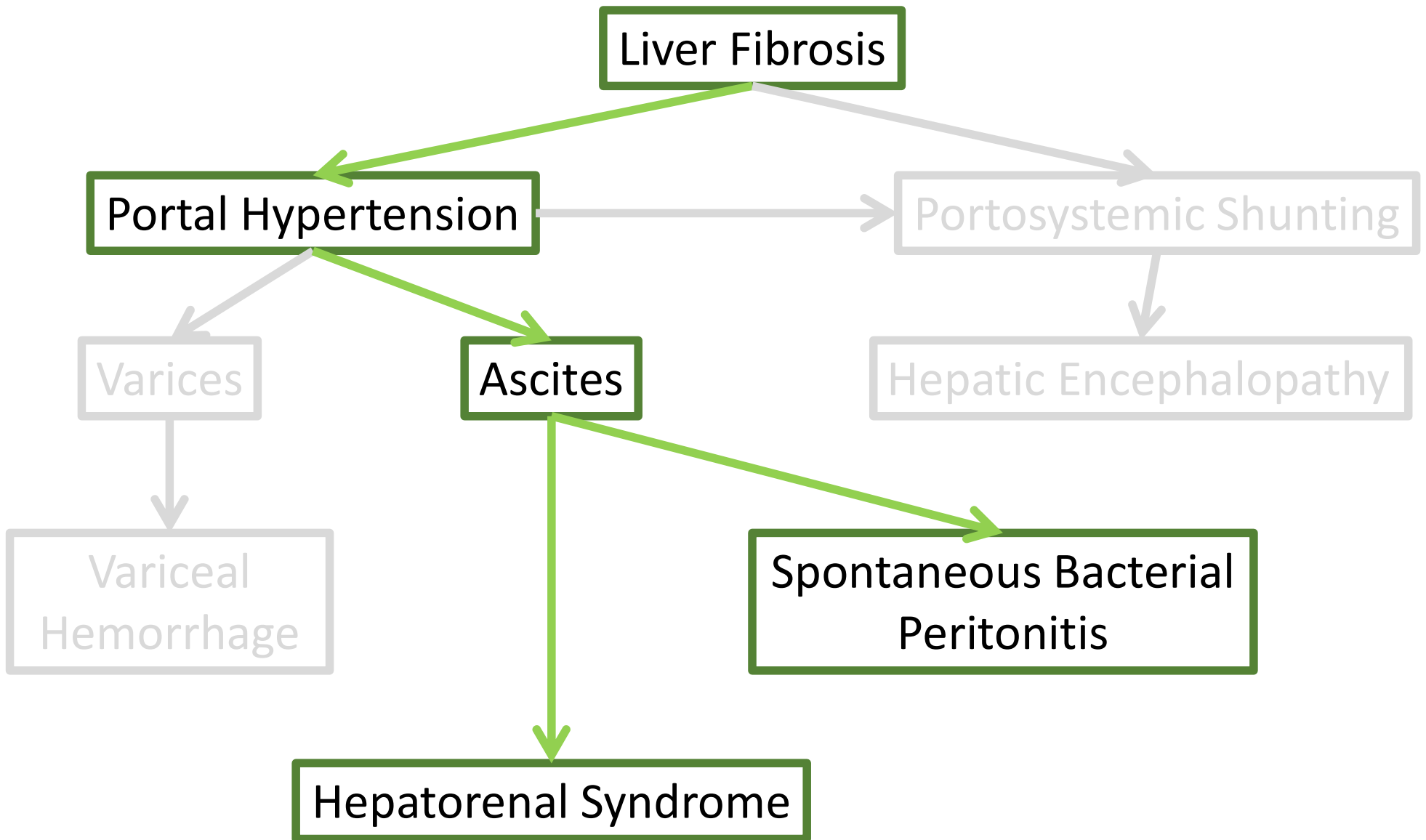
“Clinically significant portal hypertension”

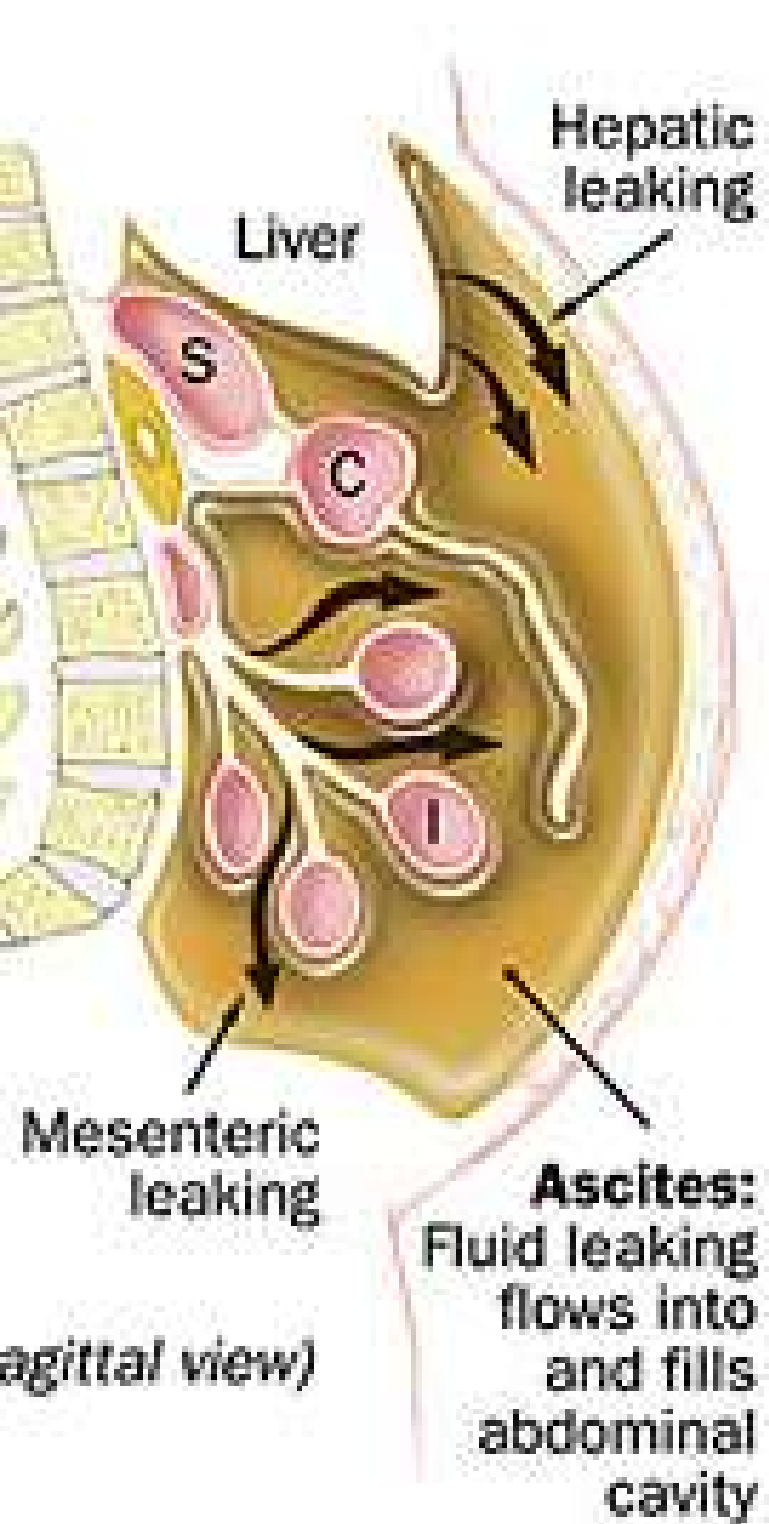
Patient Case

TH is a 53-year-old male recently discharged from the hospital. He was admitted 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





Ascites

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

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	

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)

7	13	79
	38	

AST 108 IU/L (5-30)
ALT 120 IU/L (5-40)
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<u>Paracentesis</u>
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

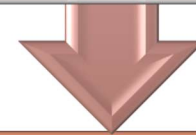


Most common complication



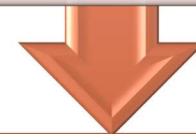
Accumulation of fluid within the peritoneal cavity

Renal sodium and water retention



Increased splanchnic vascular permeability

Lymph leakage into peritoneal cavity

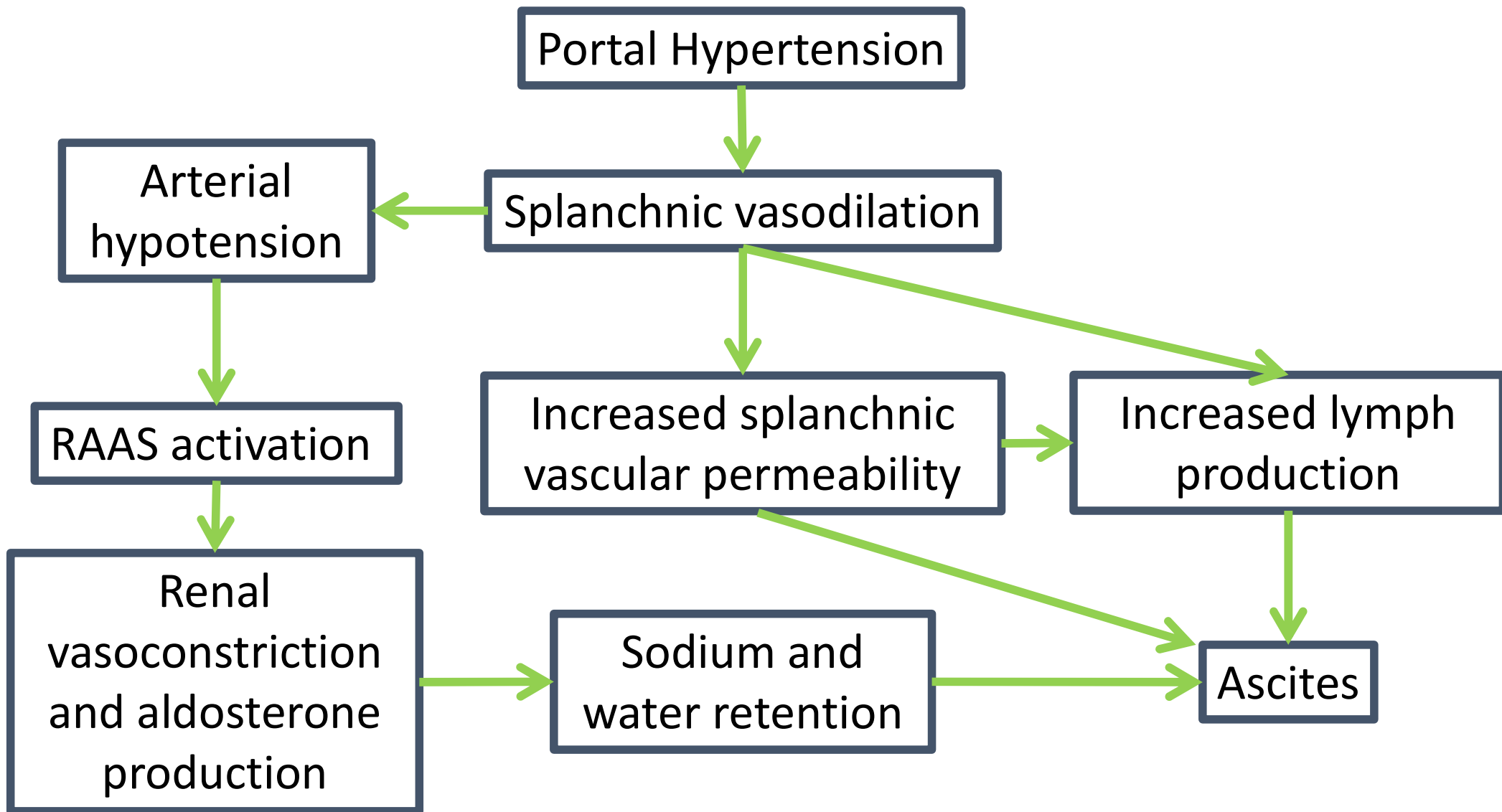


Treatment goals

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

Recur 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

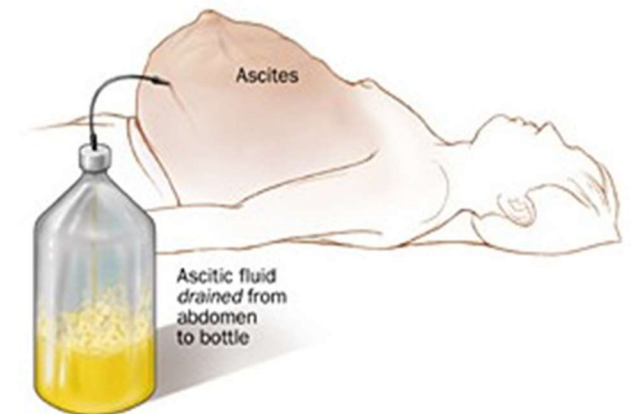
Management of Refractory Ascites

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.

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propranolol LA 80 mg PO daily
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Paracentesis

SAAG 1.5 g/dL

Protein 0.8 g/dL

PMN 333 cells/mm³

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.

<u>Paracentesis</u>
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

<u>Risk Factors</u>	<u>Ascitic Fluid Analysis</u>
Ascitic protein <1 g/dL	PMN $\geq$ 250 cells/mm ³
Variceal hemorrhage	Positive cultures
Prior episode of SBP	

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/mm³ 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 $\geq 250/\text{mm}^3$) 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/mm³ **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 ceftriaxone 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 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:

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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

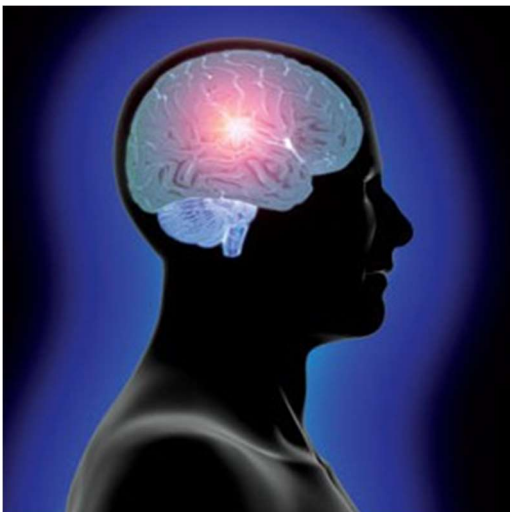
Impaired renal function secondary to cirrhosis

- 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

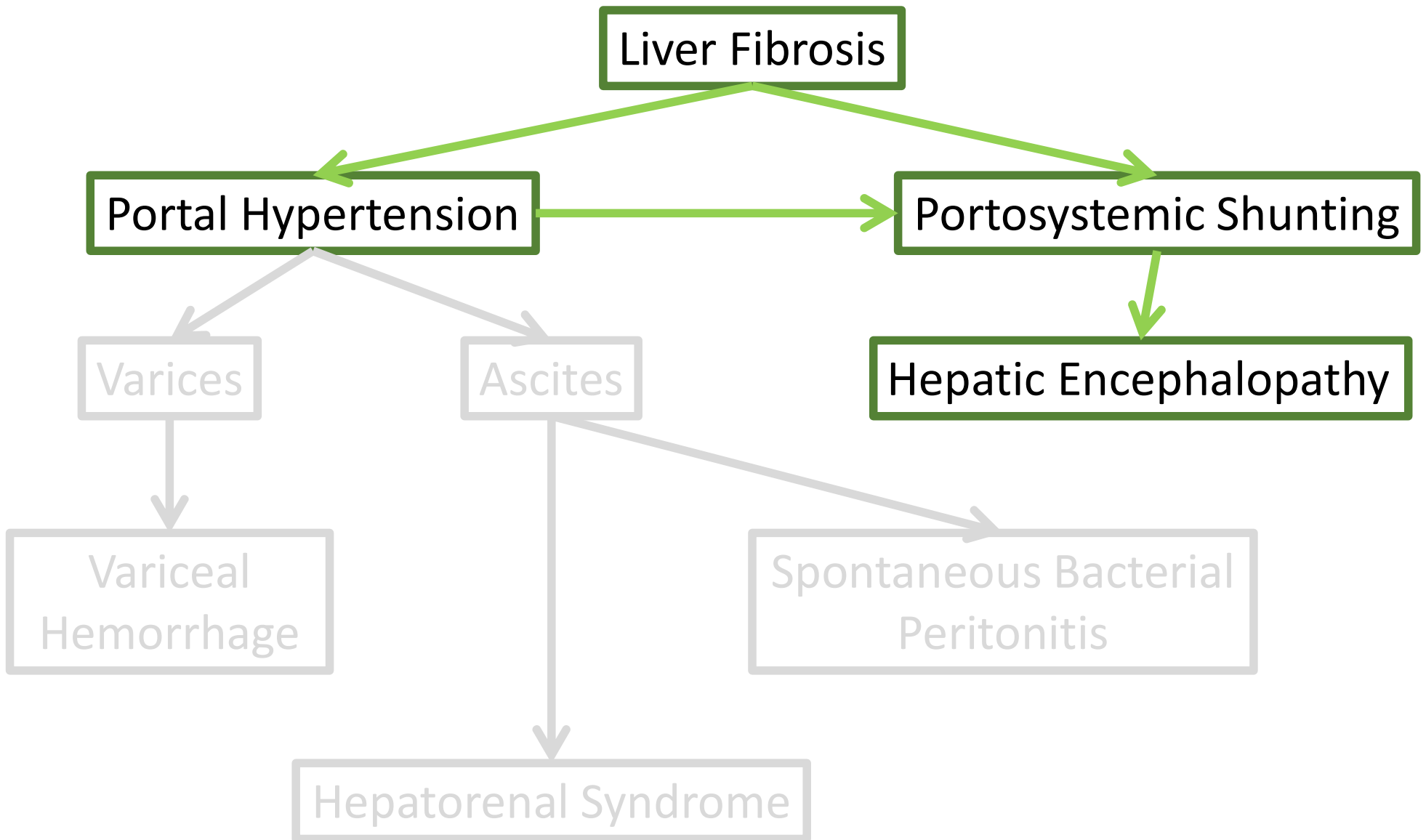
Treatment goals

- Control precipitating factors

Reverse encephalopathy

Reduce ammonia levels

- Avoid recurrence



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

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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:

- 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

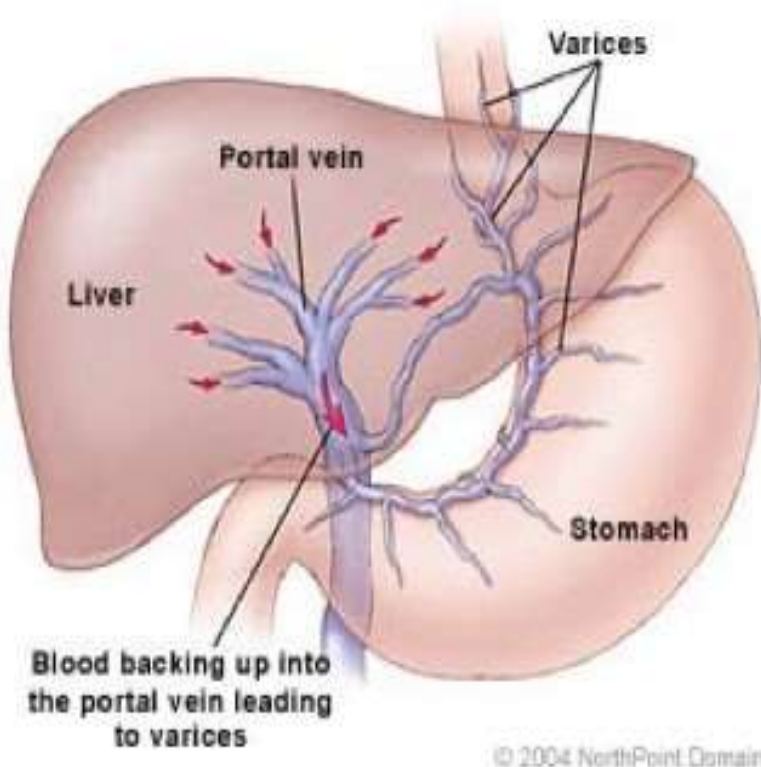
Can be life-threatening

Treatment

- Protein restriction
- Lactulose
- Rifaximin

Alternatives: metronidazole,
neomycin, zinc supplementation

Gastroesophageal Varices



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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

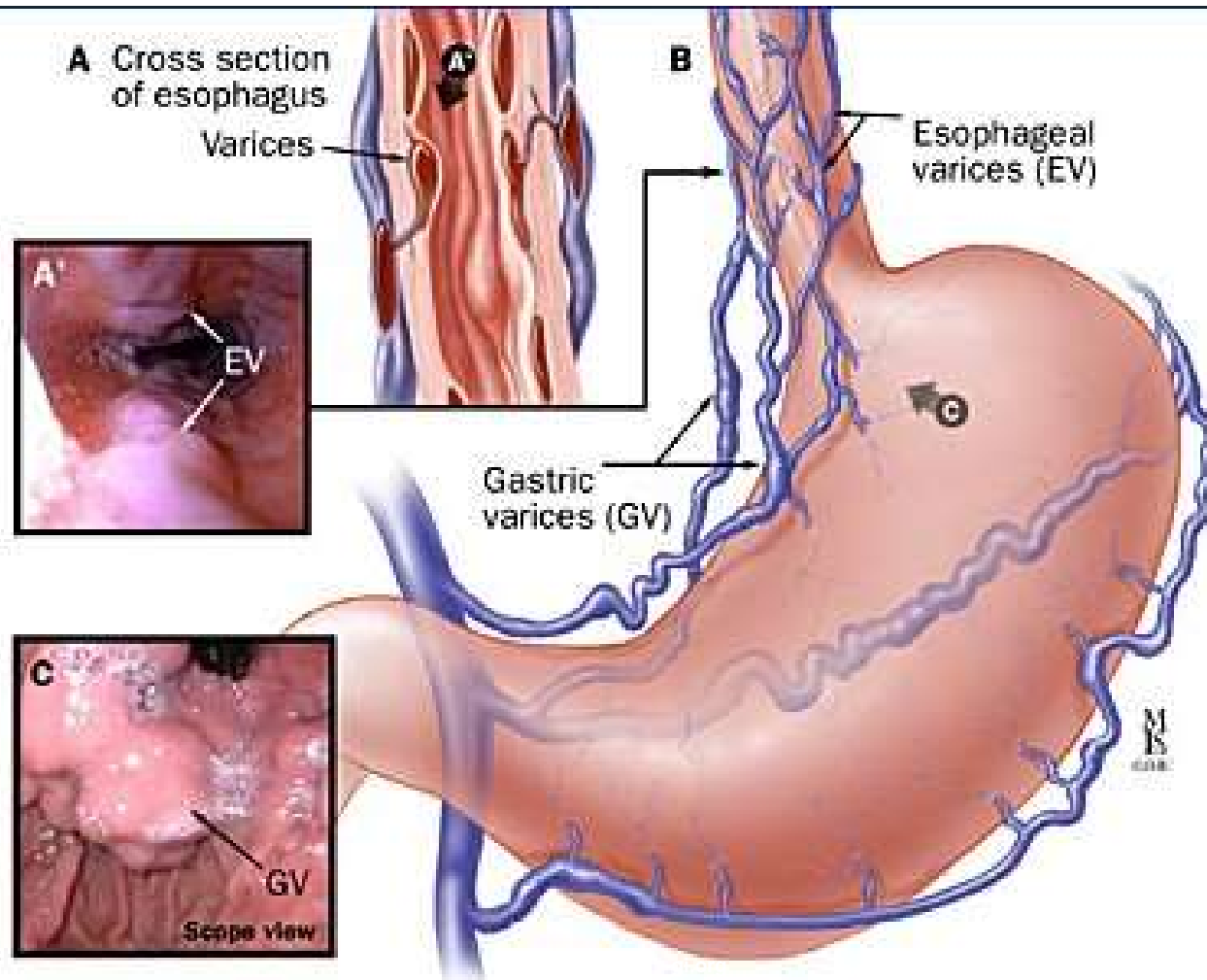
Screening

- 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
- Ceorixone 1 gm IV Q24H

Management of Gastroesophageal Varices

Secondary prophylaxis

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

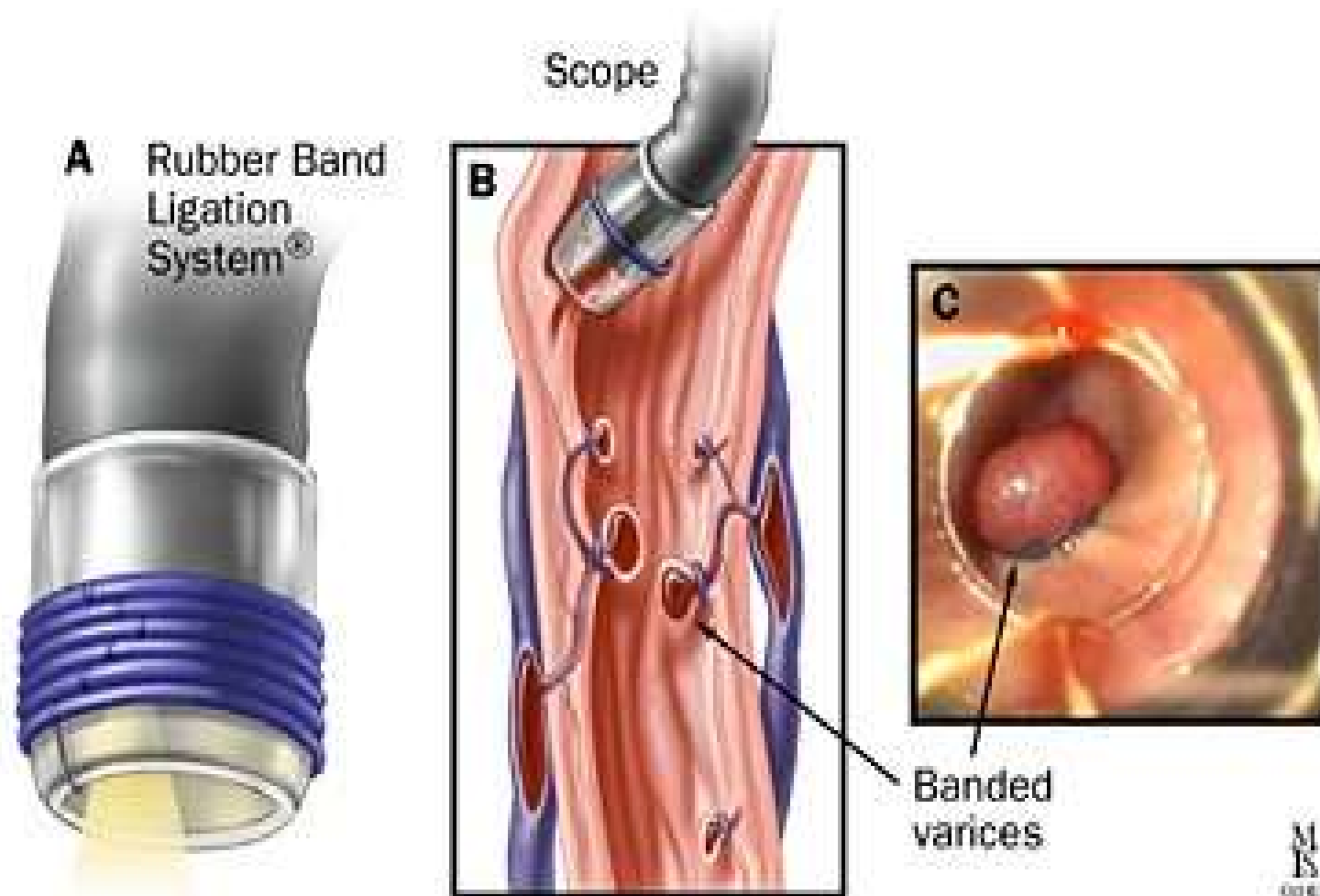
- Nadolol 40 PO daily
- Propranolol 20 mg PO BID
- Titrate to maximum tolerated dose or HR of 55-60 bpm

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 Hemorrha ge

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

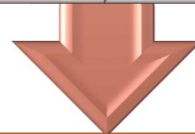
Initiate as soon as vasoactive therapy is discontinued



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

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PMN 333 cells/mm ³
10 L removed
Culture – E. coli

*From hospitalization

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

<u>Score</u>	<u>Grade</u>
<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,