Complications of Portal Hypertension: Ascites, GI bleeding and Hepatic Encephalopathy

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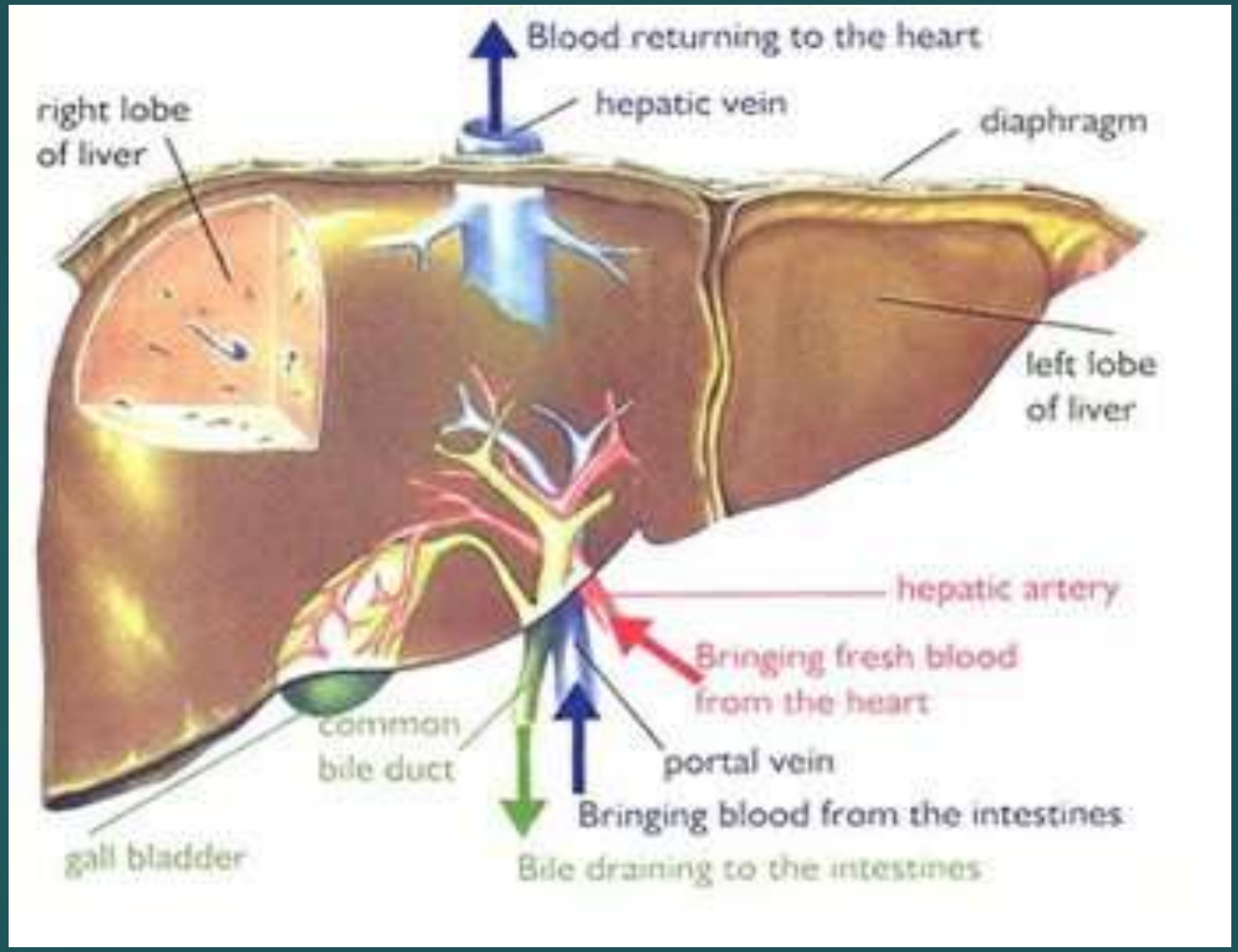
AUXILIO MUTUO LIVER TRANSPLANT PROGRAM
GASTROENTEROLOGIST

Liver Anatomy

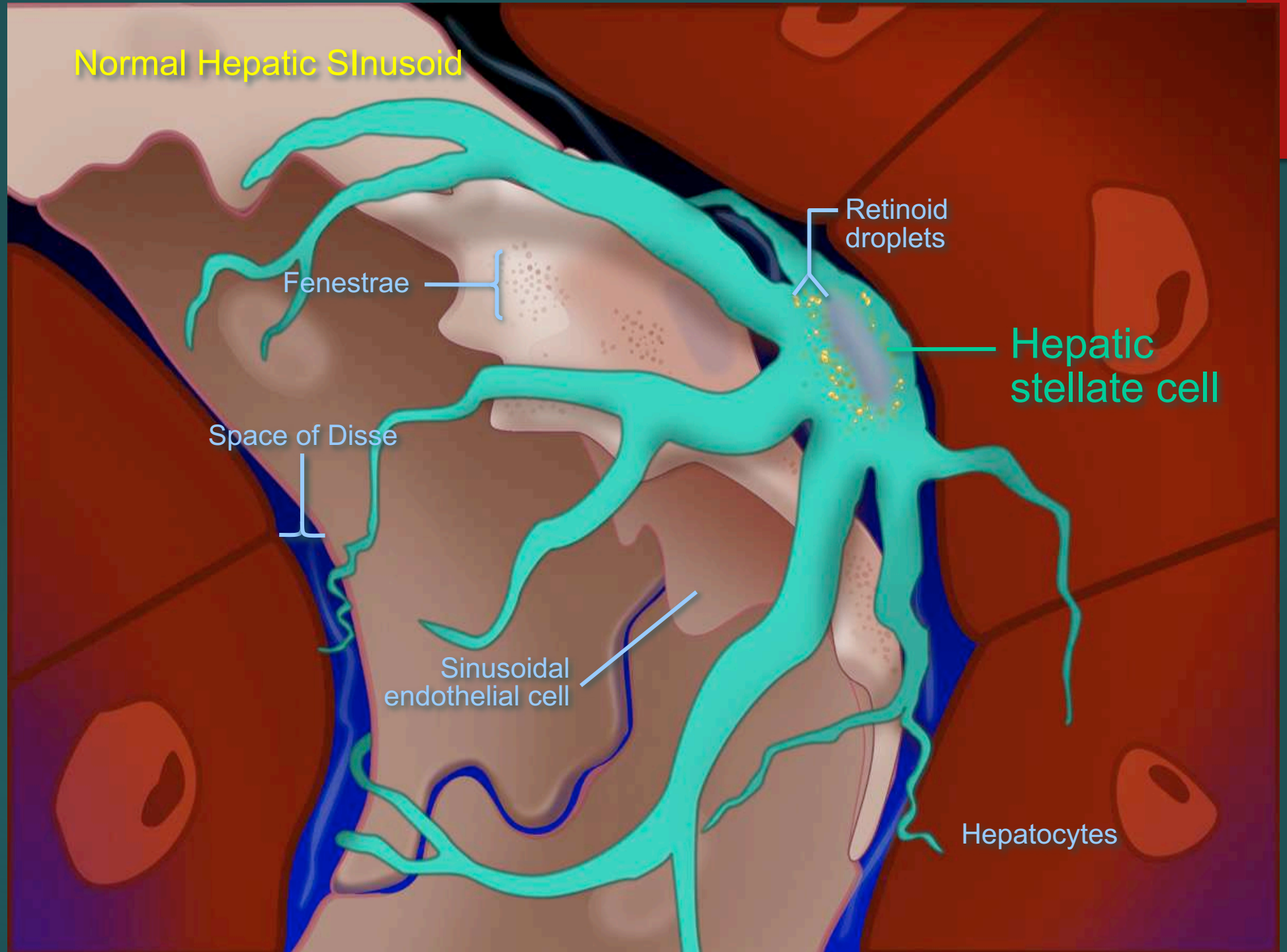
- Blood Supply
  - Portal Vein
    - Formed from the splenic vein and superior mesenteric vein
    - Brings nutrient rich blood from the gut
    - Comprises 60-80% of the blood flow to the liver
  - Hepatic Artery
    - Arterial blood supply
    - Carries oxygen rich blood to the liver
    - Comprises 25% of the blood flow to the liver
  - Hepatic Vein
    - Drains blood from the liver to the inferior vena cava then to the heart

Liver Anatomy

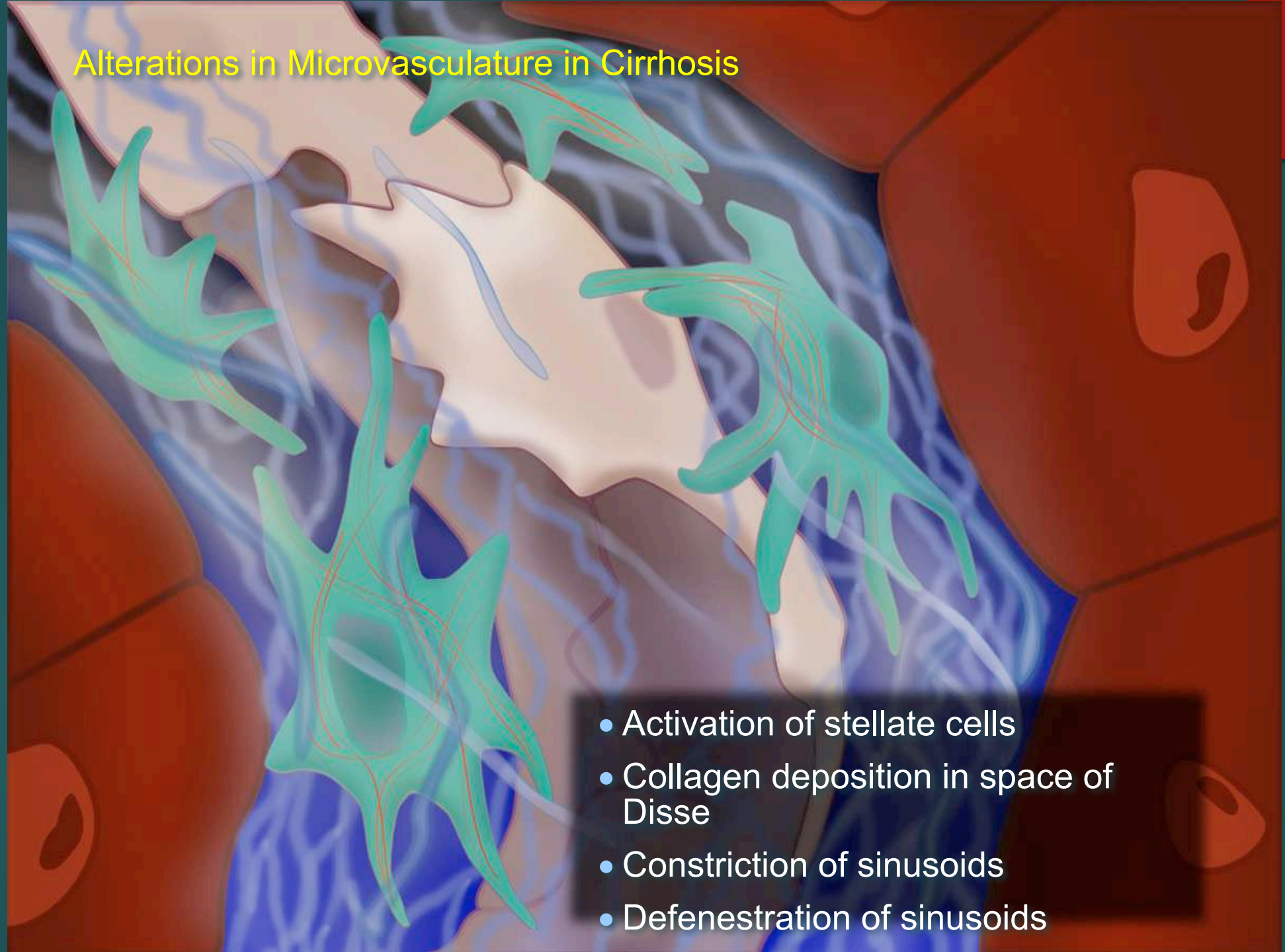


Cirrhosis

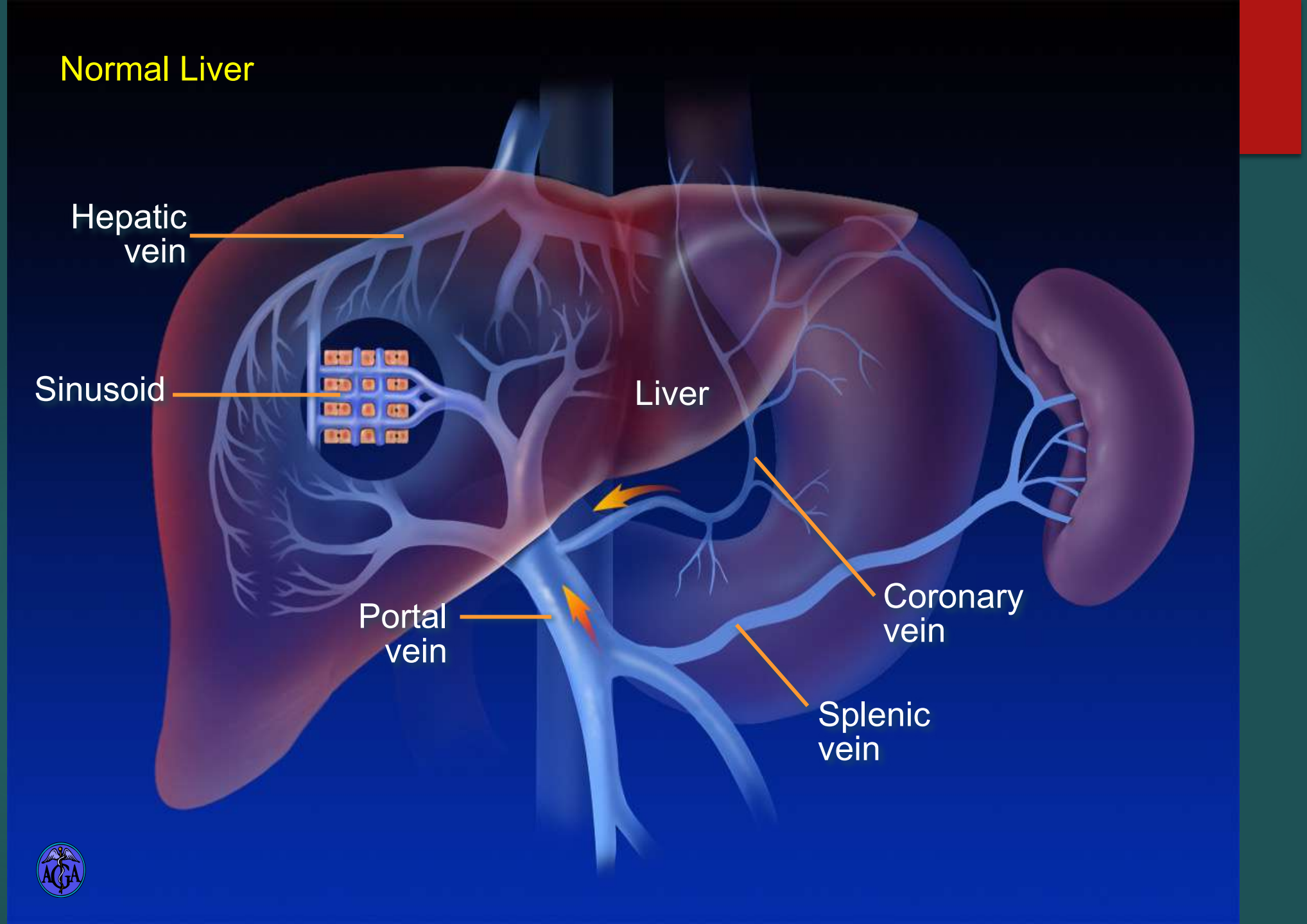
- Cirrhosis →the end stage of any chronic liver disease
- Two major syndromes result
  - Portal hypertension
  - Hepatic insufficiency
- Many definitions but common theme is injury, repair, regeneration and scarring

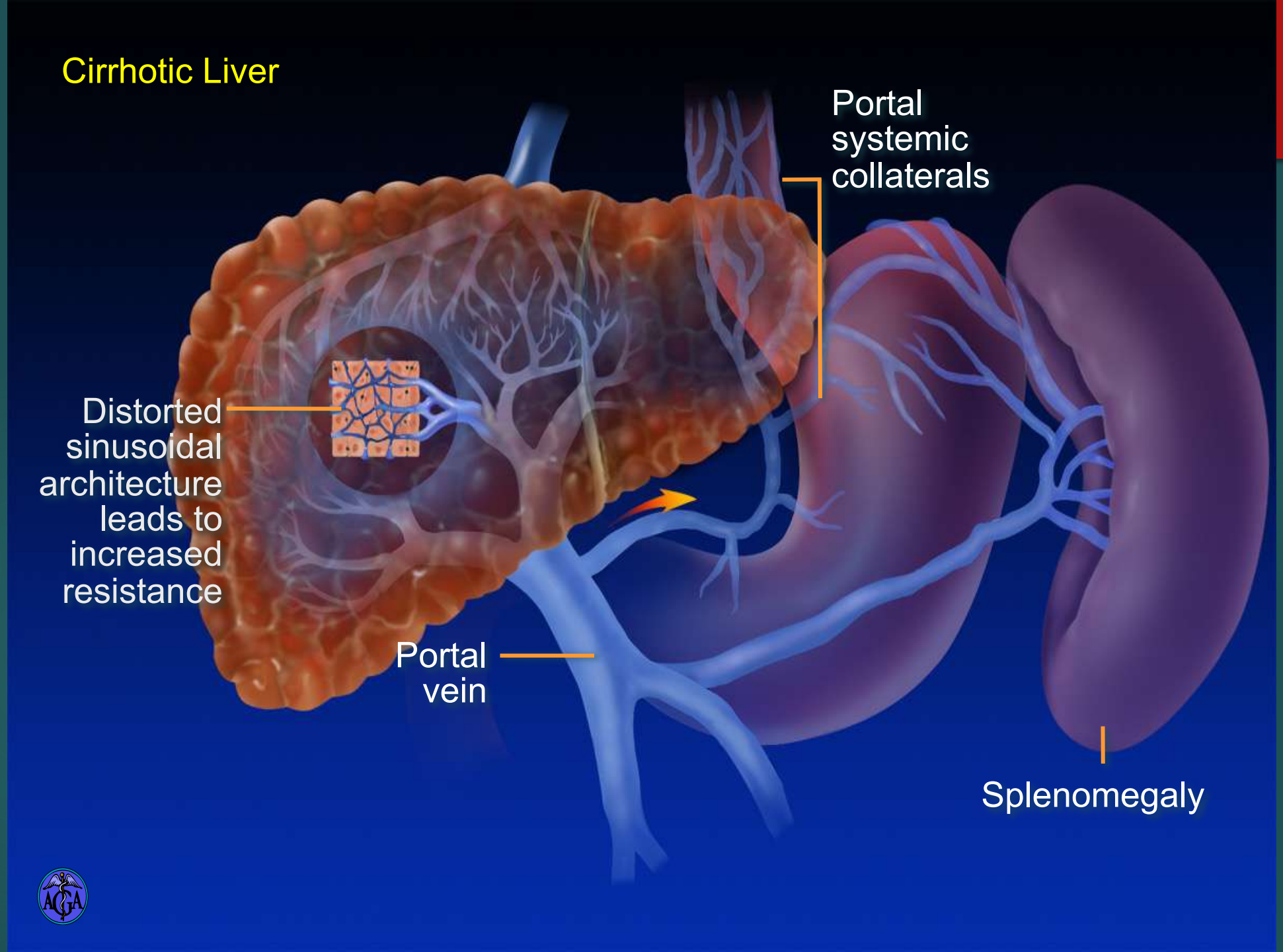

Normal Hepatic SInusoid
Retinoid droplets
Fenestrae
Hepatic stellate cell
Space of Disse
Sinusoidal endothelial cell
Hepatocytes

Alterations in Microvasculature in Cirrhosis



- Activation of stellate cells
- Collagen deposition in space of Disse
- Constriction of sinusoids
- Defenestration of sinusoids

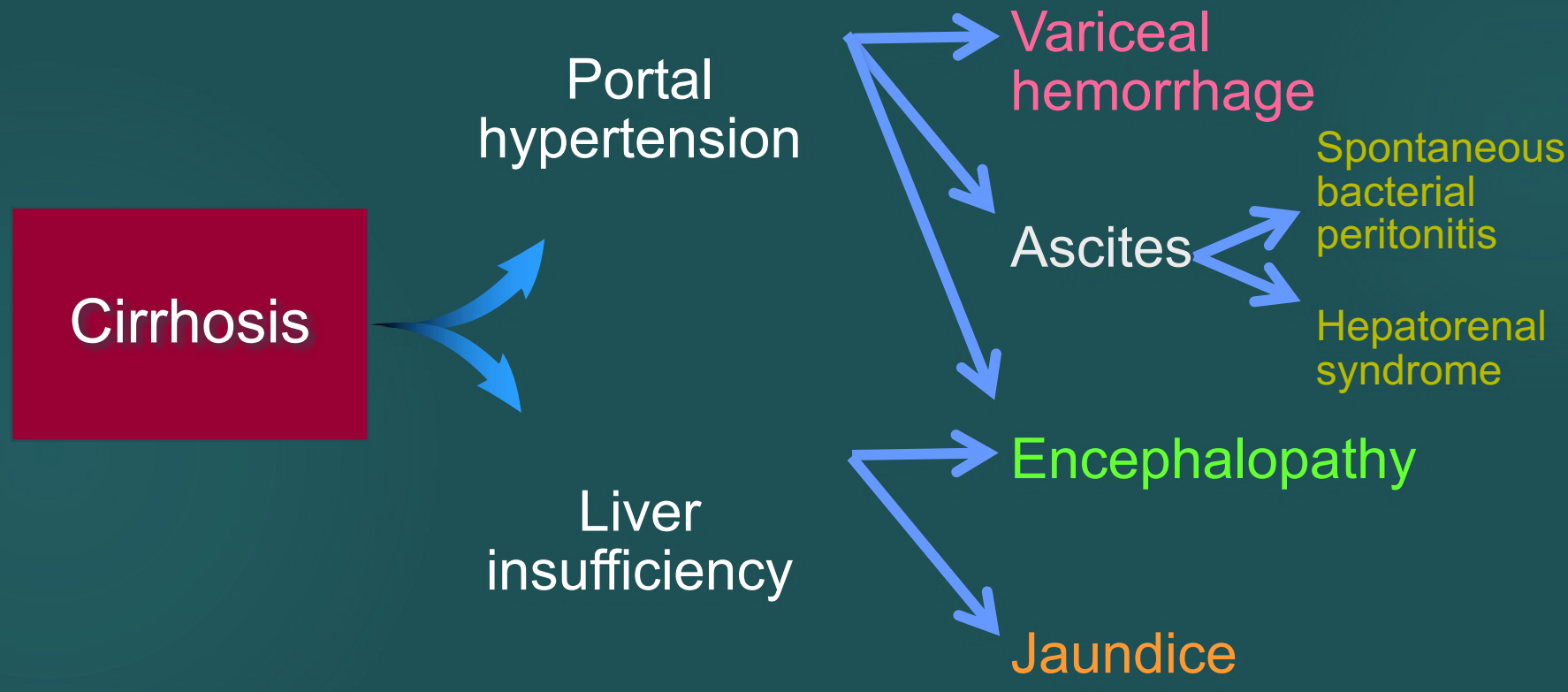

Normal Liver
Hepatic vein
Sinusoid
Liver
Portal vein
Coronary vein
Splenic vein


Cirrhotic Liver
Portal systemic collaterals
Distorted sinusoidal architecture leads to increased resistance
Portal vein
Splenomegaly

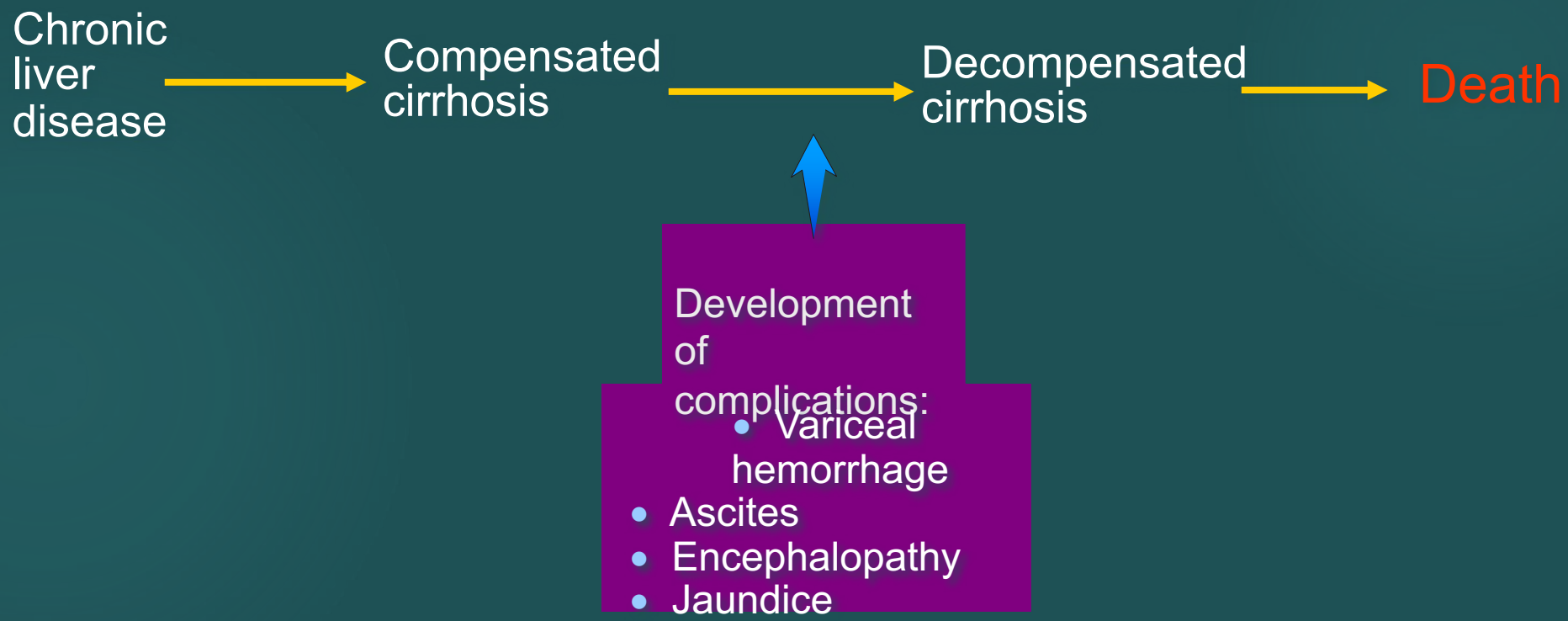
Etiologies of Chronic Liver Disease

- Viral
  - Hepatitis B
  - Hepatitis C
- Toxic
  - Alcohol, MTX
- Metabolic
  - Non Alcoholic Fatty Liver disease (NAFLD)
- Biliary
  - PSC
  - PBC
- Genetic/Hereditary
  - Hemochromatosis
  - Wilson's Disease
  - Alpha 1 Antitrypsin
  - Inborn errors of metabolism
- Others
  - Autoimmune Hepatitis
  - Congestive hepatopathy (aka Cardiac Cirrhosis)
  - Cystic Fibrosis

Complications of Cirrhosis Result from Portal Hypertension or Liver Insufficiency



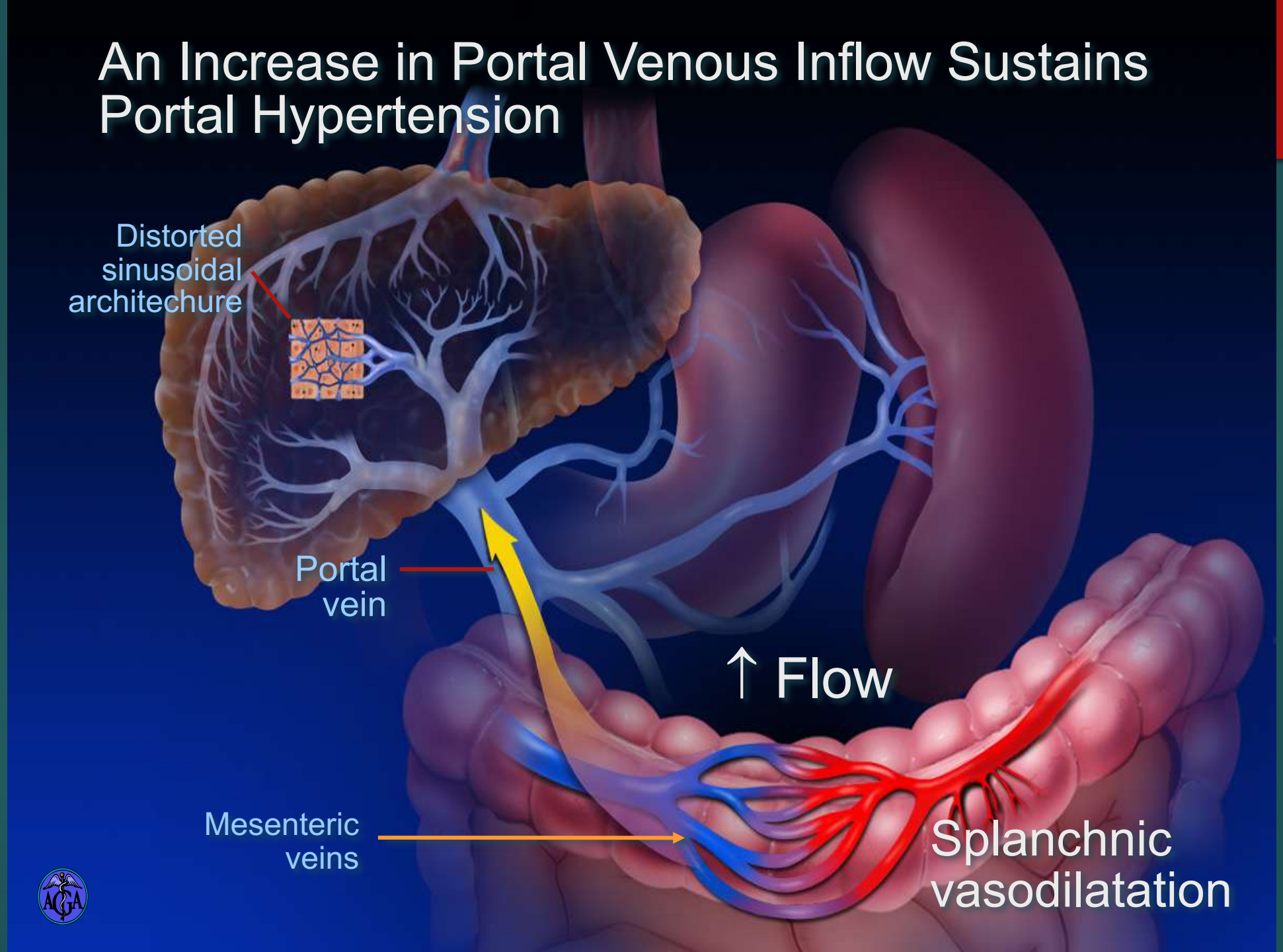
Natural History of Chronic Liver Disease



Portal Hypertension

- As pressure increases, blood flow decreases and the pressure in the portal system is transmitted to its branches
- Results in dilation of venous tributaries
- Increased blood flow through collaterals and subsequently increased venous return cause an increase in cardiac output and total blood volume and a decrease in systemic vascular resistance
- With progression of disease, blood pressure usually falls

An Increase in Portal Venous Inflow Sustains Portal Hypertension



Portal Hypertension

Compression

↓

Portal vein,hepatic veins, sinusoids

↓

Obstruction of portal blood flow

↓

Portal Hypertension

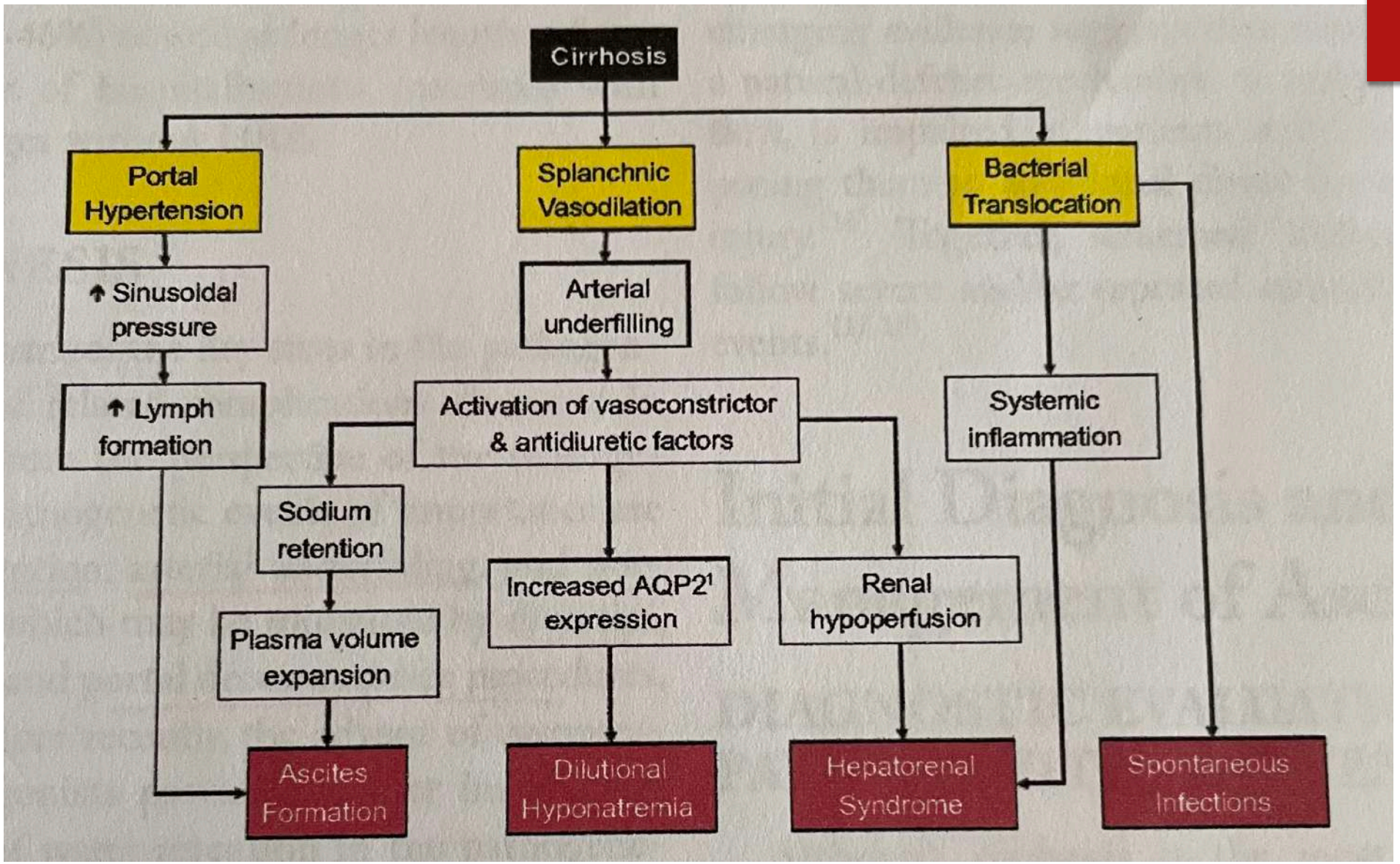
↓

Venous pressure, splenomegaly, collateral circulation, ascites, systemic hypertension, esophageal varices

Complications of Cirrhosis and Portal Hypertension

- Ascites
- Variceal bleeding
- Hepatic encephalopathy
- Spontaneous bacterial peritonitis
- Hepatorenal syndrome

* 5-year survival with onset of any of the above: 20-50% compared to compensated cirrhotics


Cirrhosis
Portal Hypertension
Splanchnic Vasodilation
Bacterial Translocation
↑ Sinusoidal pressure
Arterial underfilling
↑ Lymph formation
Activation of vasoconstrictor & antidiuretic factors
Systemic inflammation
Sodium retention
Increased AQP2[1] expression
Renal hypoperfusion
Plasma volume expansion
Ascites Formation
Dilutional Hyponatremia
Hepatorenal Syndrome
Spontaneous Infections

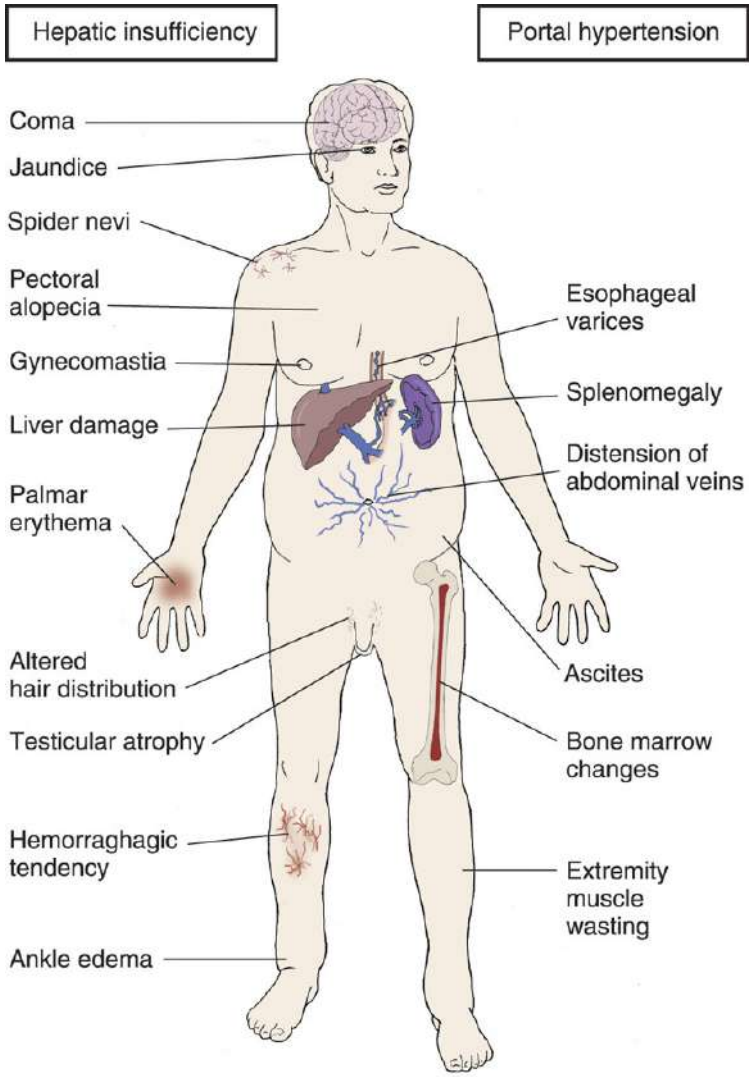


Figure 41-8 Clinical effects of cirrhosis of the liver. (From Bullock BL: Pathophysiology: Adaptations and Alterations in Function [4th Ed]. Philadelphia, Lippincott-Raven, 1996.)

Clinical Manifestation of Chronic Liver Disease

of Chronic Liver Disease

Jaundice

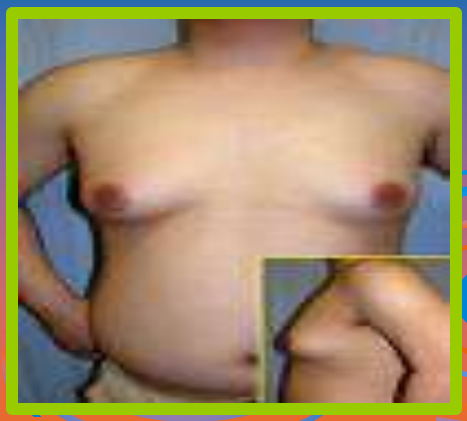
Spider Angiomata

Palmar Erythema

Dupuytren's Contracture

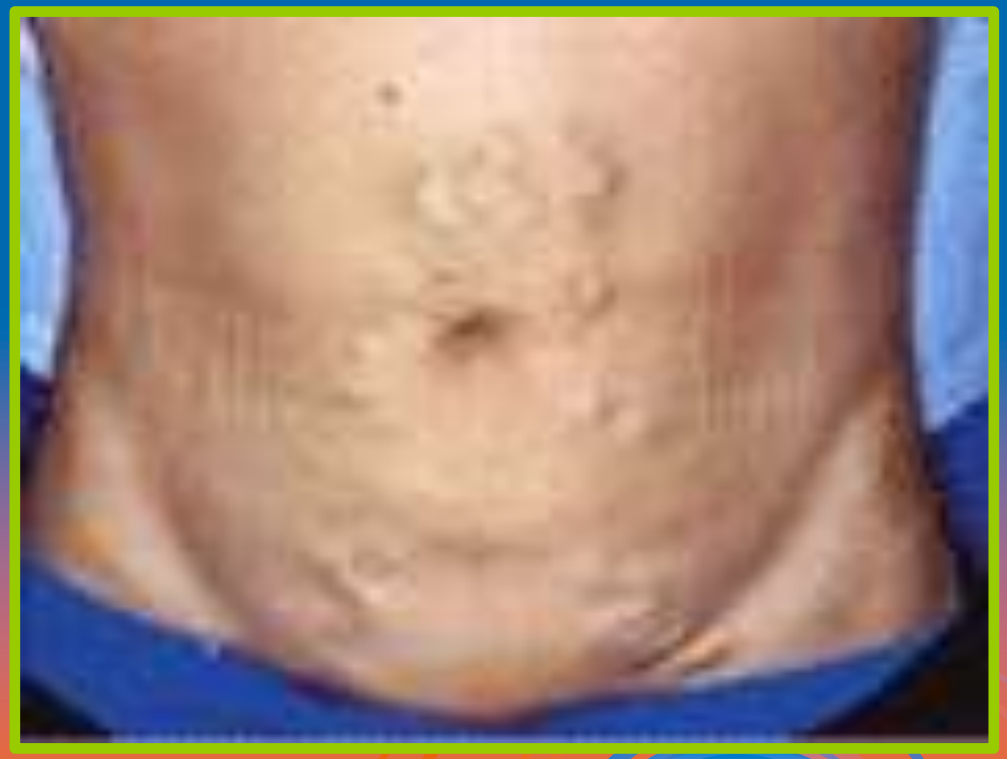
Muehrcke's Lines

Terry's Nails



Gynecomastia

Clinical Manifestations of Portal Hypertension



Clinical Manifestations of Chronic Liver Disease

Bitemporal Wasting

Parotid Enlargement

- Others:
  - Testicular atrophy
  - Asterixis
  - Fetor hepaticus
  - Encephalopathy

Ascites

- Develops in the cirrhotic patient as the PH worsens and there is transudation of fluid from the liver to the peritoneal cavity
- Development of hyperdynamic circulation marked by splanchnic and peripheral vasodilatation and increased cardiac output
- Blood flow to other organs reduced due to vasoconstriction (kidneys, muscles, brain)
- Renal perfusion falls and there is release of renin and aldosterone leading to renal sodium retention

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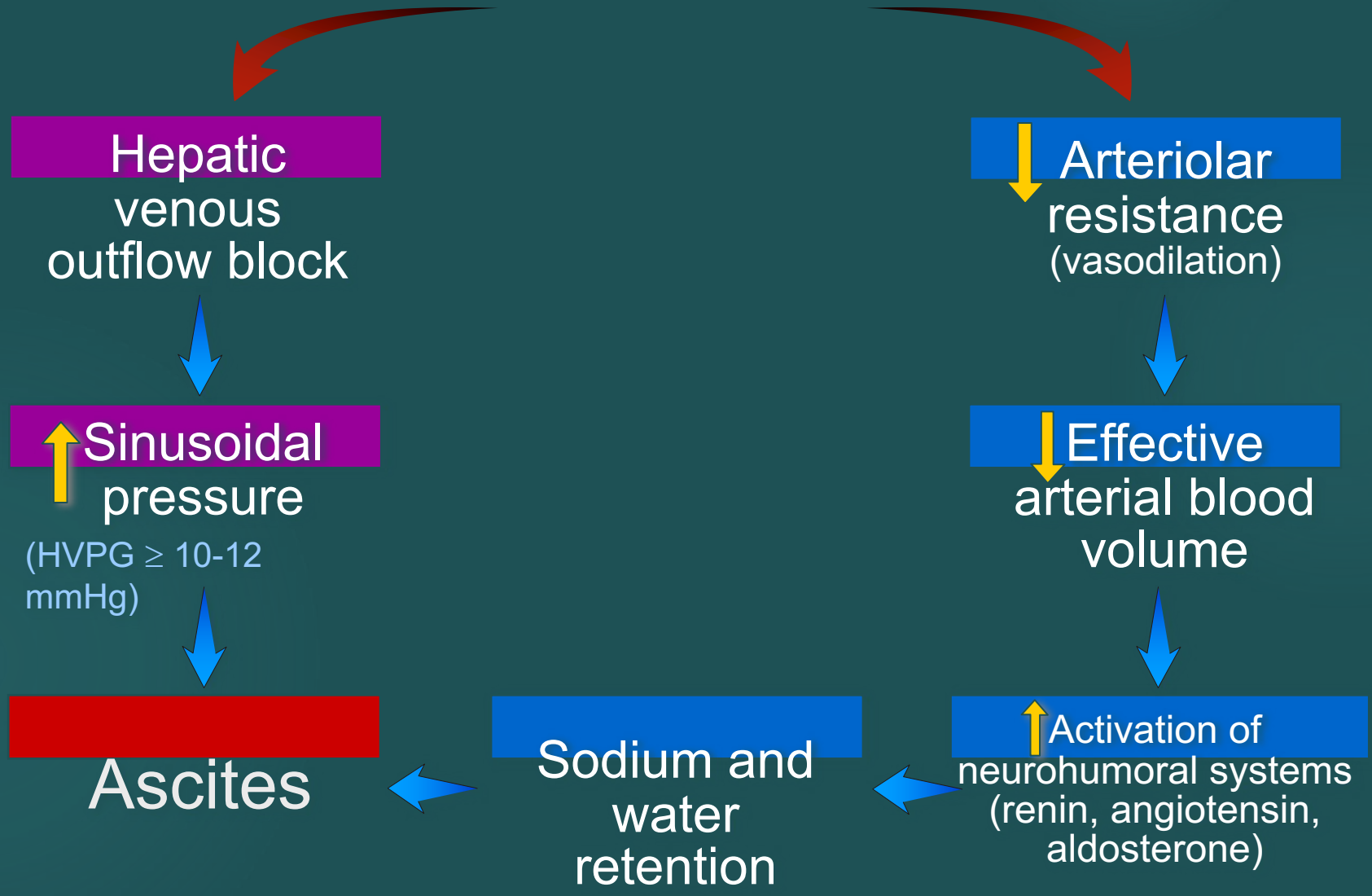
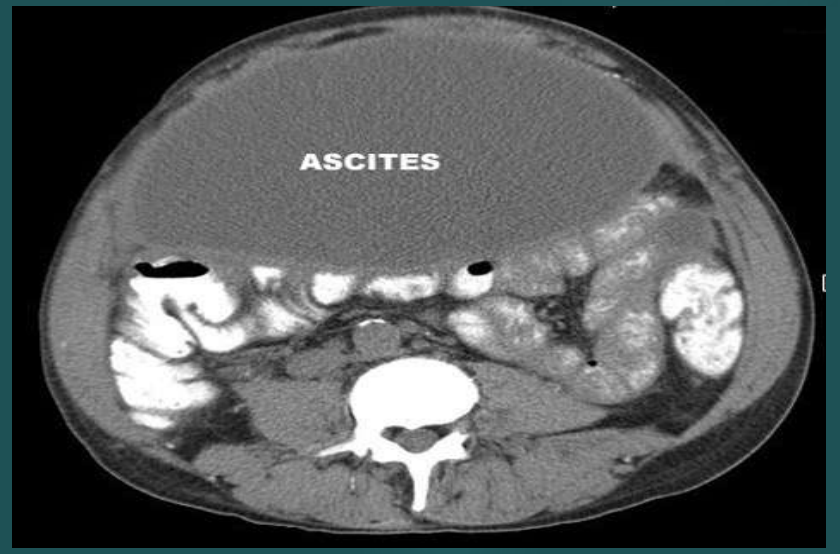
Cirrhosis


Hepatic venous outflow block
Arteriolar resistance (vasodilation)
Sinusoidal pressure
(HVPG ≥ 10-12 mmHg)
Effective arterial blood volume
Ascites
Sodium and water retention
Activation of neurohumoral systems (renin, angiotensin, aldosterone)

Ascites

- Cirrhosis (85%)
  - Most common cause of ascites
  - Most common complication of cirrhosis
- Survival 5 years after the developement of ascites is 50%
- Difficult to treat ascites survival 40-60% in two years



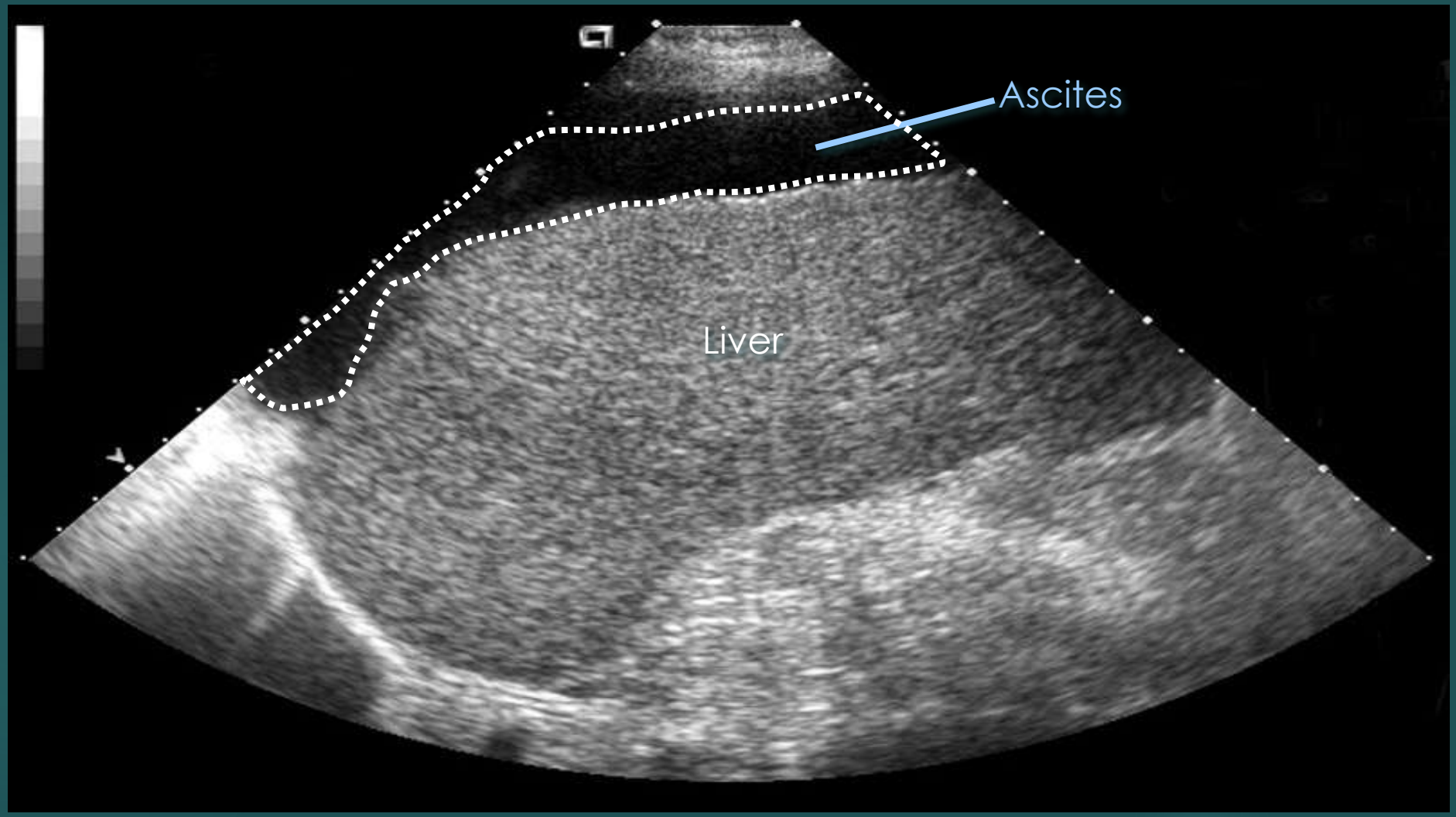
Ascites

- Other causes of ascites
  - Malignancy (10%)
  - Cardiac (3%)
  - TB (2%)
  - Pancreatic Ascites(1%)
  - Kidney disease (nephrotic syndrome)

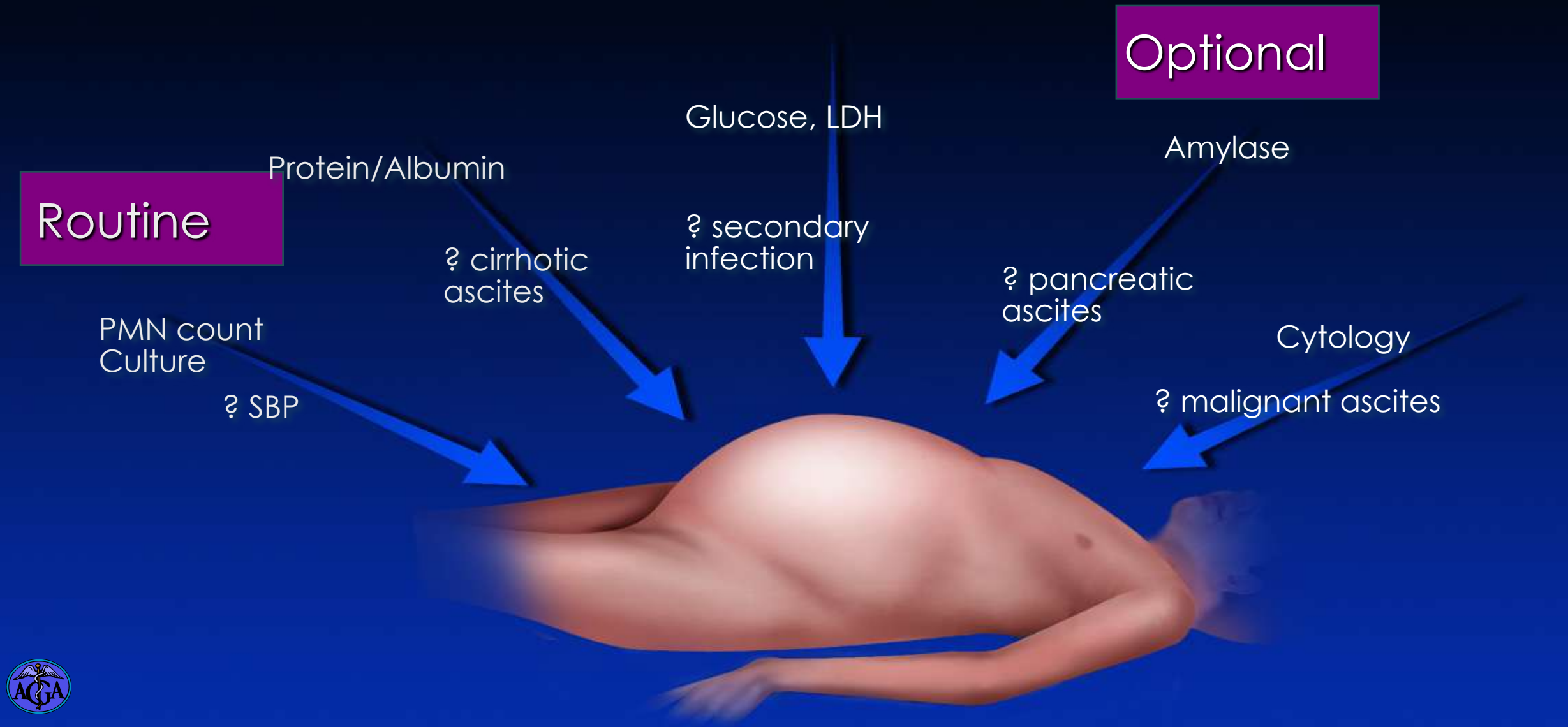
Ascites

- Diagnosis:
  - Physical examination
    - Bulging flanks
    - Shifting dullness
    - Fluid wave
  - Ultrasound
  - Diagnostic Paracentesis
  - SAAG (serum albumin-ascitic fluid albumin gradient)

Ultrasound is the Most Sensitive Method to Detect Ascites



Initial Workup of Ascites
Diagnostic Paracentesis



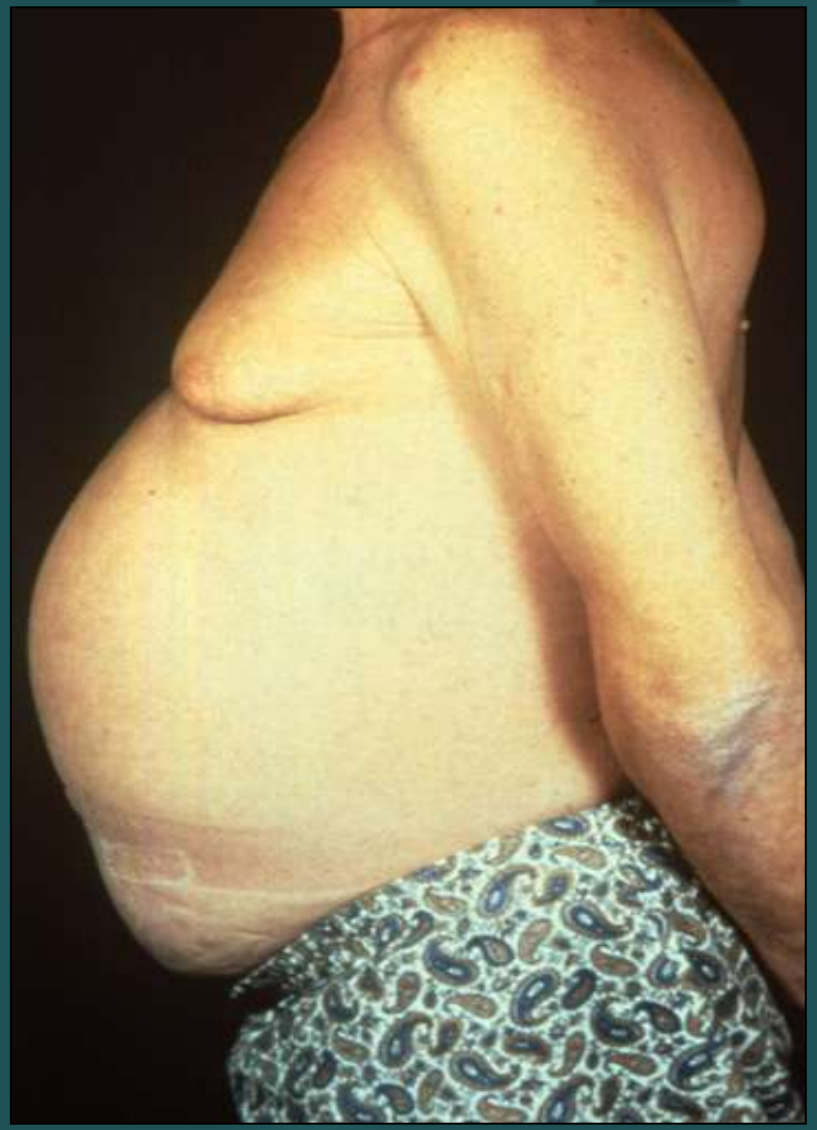
Diagnostic Paracentesis

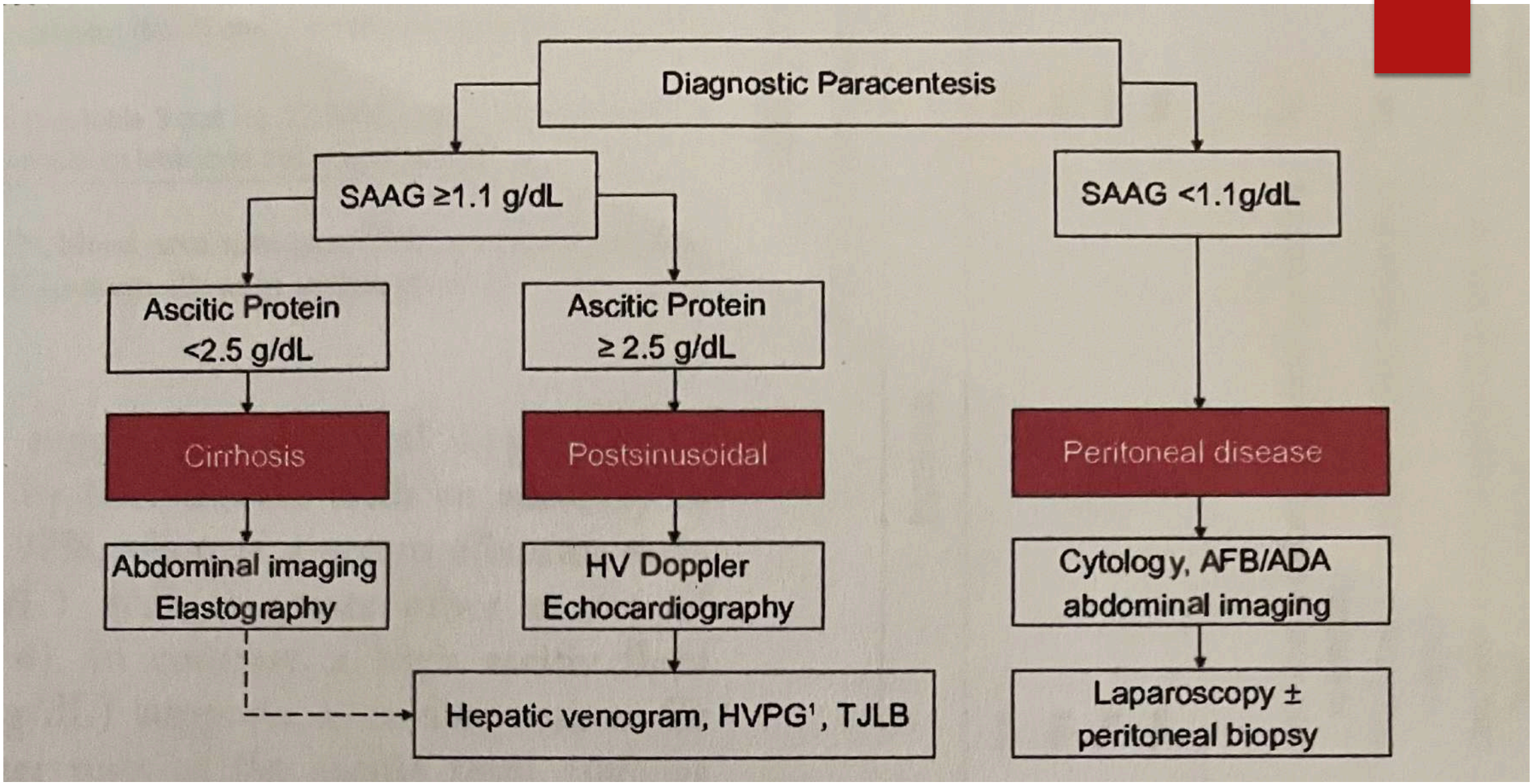
Indications

- New-onset ascites
- Admission to hospital
- Symptoms/signs of SBP
- Renal dysfunction
- Unexplained encephalopathy

Contraindications

- None




Diagnostic Paracentesis
SAAG ≥1.1 g/dL
SAAG <1.1g/dL
Ascitic Protein <2.5 g/dL
Ascitic Protein ≥ 2.5 g/dL
Cirrhosis
Postsinusoidal
Peritoneal disease
Abdominal imaging Elastography
HV Doppler Echocardiography
Cytology, AFB/ADA abdominal imaging
Hepatic venogram, HVPG[1], TJLB
Laparoscopy ± peritoneal biopsy

High albumin gradient (SAAG ≥1.1 g/dL)
Cirrhosis
Alcoholic hepatitis
Congestive heart failure
Massive hepatic metastases
Congestive heart failure/constrictive pericarditis
Budd-Chiari syndrome
Low albumin gradient (SAAG <1.1 g/dL)
Peritoneal carcinomatosis
Peritoneal tuberculosis
Pancreatitis
Serositis
Nephrotic syndrome

Management of Uncomplicated Ascites

Definition: Ascites responsive to diuretics in the absence of infection and renal dysfunction

Sodium restriction

- Effective in 10-20% of cases
- Predictors of response: mild or moderate ascites, Urine Na excretion > 50 mEq/day

Diuretics

- Should be spironolactone-based
- A progressive schedule (spironolactone → furosemide) requires fewer dose adjustments than a combined therapy (spironolactone + furosemide)

Management of Uncomplicated Ascites

Sodium Restriction

- 2 g (or 5.2 g of dietary salt) a day
- Fluid restriction is not necessary unless there is hyponatremia (<125 mmol/L)
- Goal: negative sodium balance
- Side effect: unpalatability may compromise nutritional status

Management of Uncomplicated Ascites

Diuretic Therapy

Dosage

- Spironolactone 100-400 mg/day
- Furosemide (40-160 mg/d) for inadequate weight loss or if hyperkalemia develops

- Increase diuretics if weight loss <1 kg in the first week and < 2 kg/week thereafter
- Decrease diuretics if weight loss >0.5 kg/day in patients without edema and >1 kg/day in those with edema

- Side effects
  - Renal dysfunction, hyponatremia, hyperkalemia, encephalopathy, gynecomastia

Definition and Types of Refractory Ascites

Occurs in ~10% of cirrhotic patients

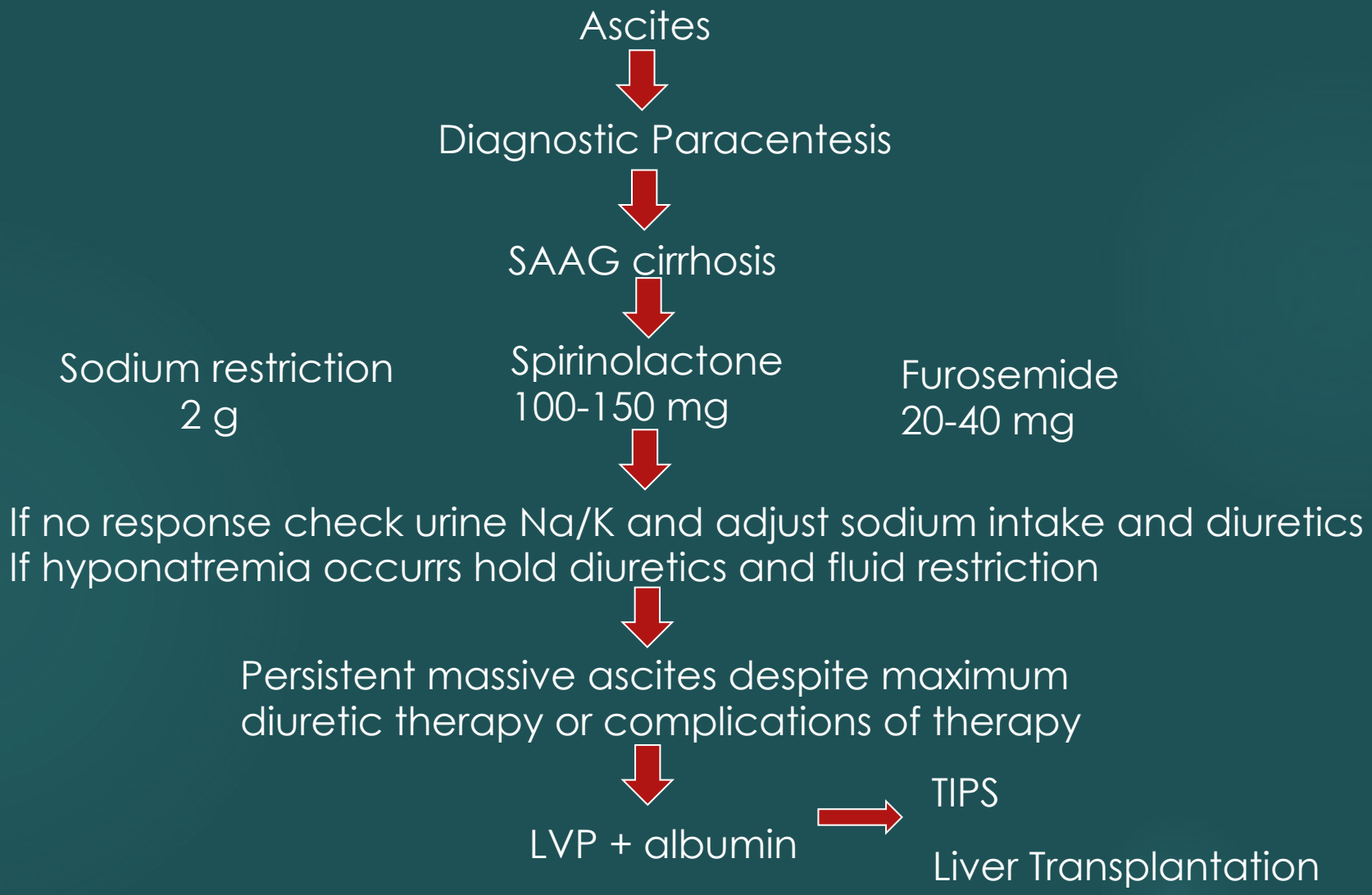
- Diuretic-intractable ascites 80%

  Therapeutic doses of diuretics cannot be achieved because of diuretic-induced complications

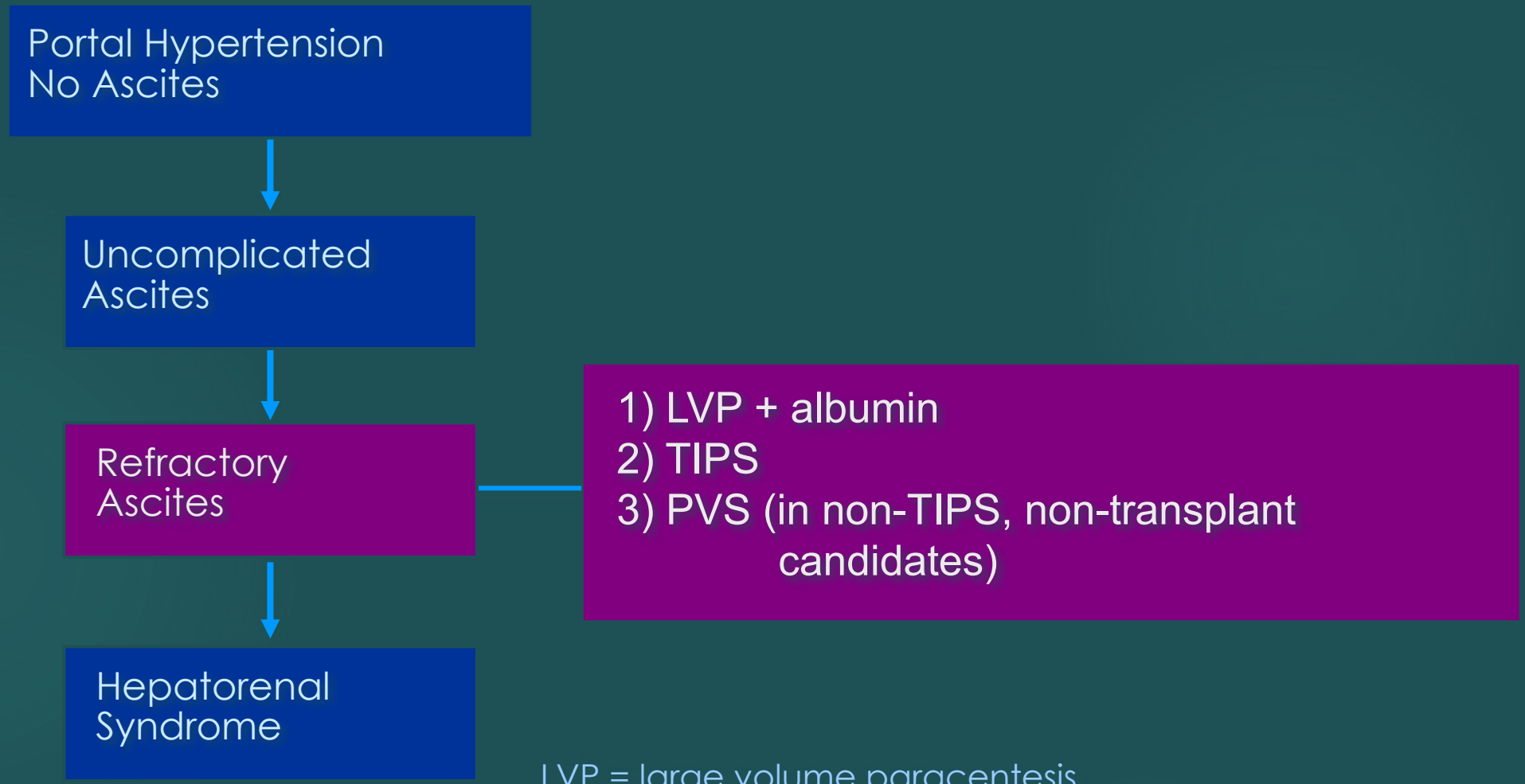
- Diuretic-resistant ascites 20%

  No response to maximal diuretic therapy (400 mg spironolactone + 160 mg furosemide/day)

Ascites

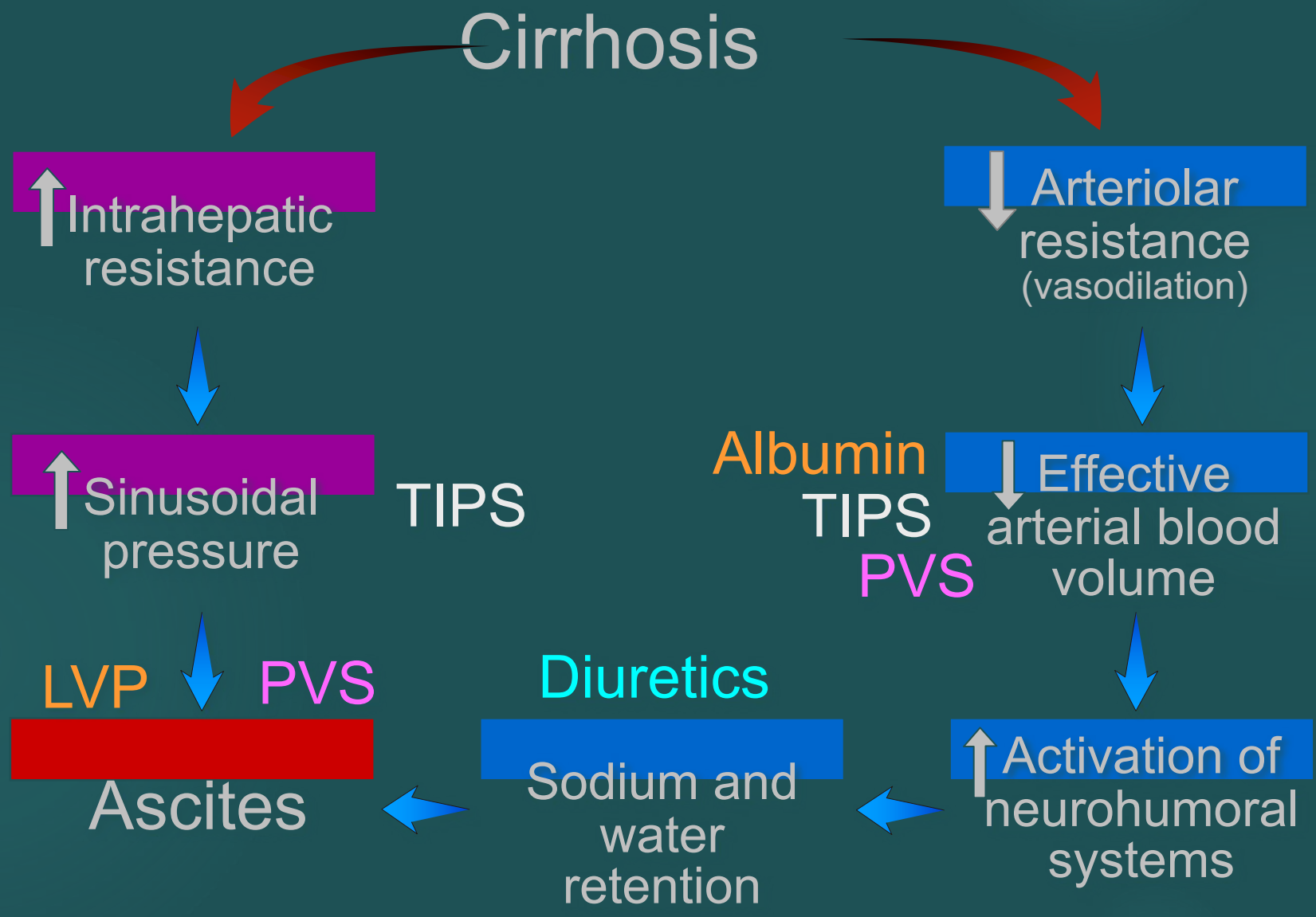

Ascites
Diagnostic Paracentesis
SAAG cirrhosis
Sodium restriction
2 g
Spirinolactone
100-150 mg
Furosemide
20-40 mg
If no response check urine Na/K and adjust sodium intake and diuretics
If hyponatremia occurrs hold diuretics and fluid restriction
Persistent massive ascites despite maximum
diuretic therapy or complications of therapy
LVP + albumin
TIPS
Liver Transplantation

Treatment of Ascites



LVP = large volume paracentesis
TIPS = transjugular intrahepatic portosystemic shunt

Site of Action of Different Therapies for Ascites



Ascites Related Complications

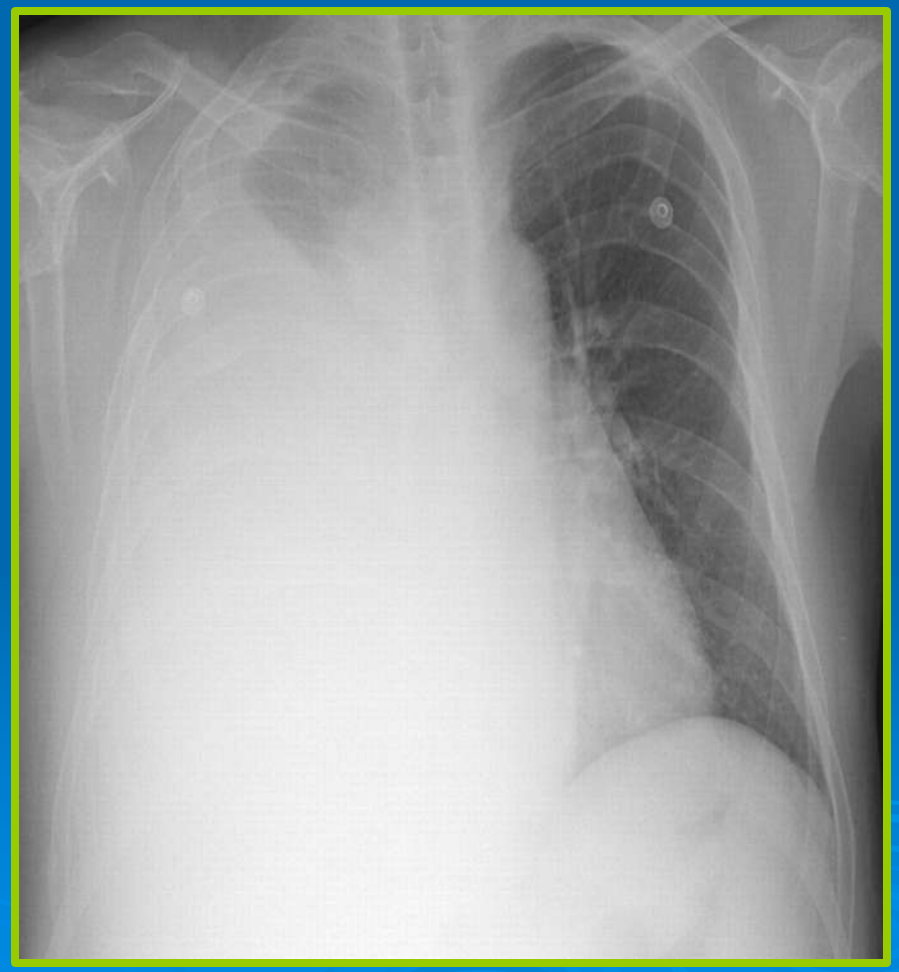
- Spontaneous Bacterial Peritonitis
- Hepatorenal Syndrome
- Hepatic Hydrothorax
- Abdominal Hernias

Hepatic Hydrothorax

- May occur in up to 12 % of patients with cirrhosis
- Most at right side and unilateral
- 9% may not have clinical ascites
- Fluid originates in the peritoneal cavity and is drawn through diaphragm defects by the negative intrathoracic pressure at inspiration
- Serum to pleural fluid albumin gradient > 1.1 is suggestive of HH
- Patients with HH have poor prognosis and should be considered for OLT
- Refractory HH is best treated with TIPS or OLT
- Chest tubes are associated with high mortality and should be avoided

Hepatic Hydrothorax

- Accumulation of fluid within the pleural space in association with cirrhosis and in the absence of 1ry pulmonary or cardiac disease.
- Usually right-sided
- Typically associated with clinically apparent ascites, but can be found in patients without ascites.



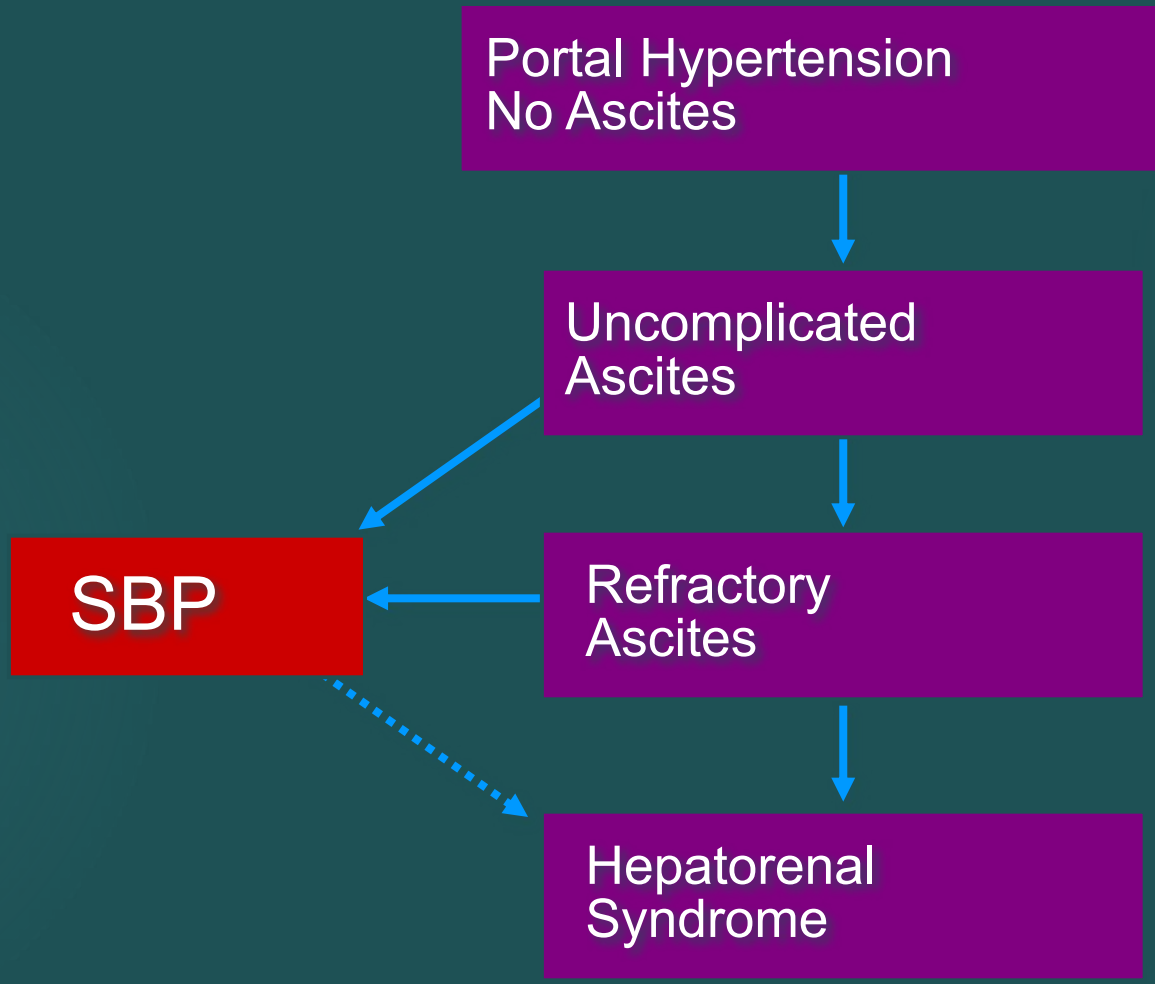
Abdominal Hernias

- Umbilical hernias develop in approximately 20% of patients with cirrhosis
- Increased abdominal pressure, weakened abdominal muscles and poor nutrition can lead to rapid enlarging hernias
- Patients who are candidates for OLT in the near future should defer hernia repair until during or after transplantation.
- If elective herniography is considered, clinically apparent ascites should be controlled
- Emergent surgery for ruptured or strangulated hernia in a patient with cirrhosis should be performed by a surgeon who is experienced in the care of patient with cirrhosis in consultation with a hepatologist for post operative care and management.

Spontaneous Bacterial Peritonitis (SBP)

- Infection of previously sterile ascitic fluid without an apparent intra-abdominal infection.
- Epidemiology:
  - Occurs in 10-30% of inpatient cirrhotics and <4% of outpatient cirrhotics.
- Pathophysiology:
  - Suspected bacterial translocation via gut

Spontaneous Bacterial Peritonitis (SBP) Complicates Ascites and Can Lead to Renal Dysfunction



Early Diagnosis of SBP

- Diagnostic paracentesis:
  - If symptoms / signs of SBP occur
  - Unexplained encephalopathy and / or renal dysfunction
  - At any hospital admission

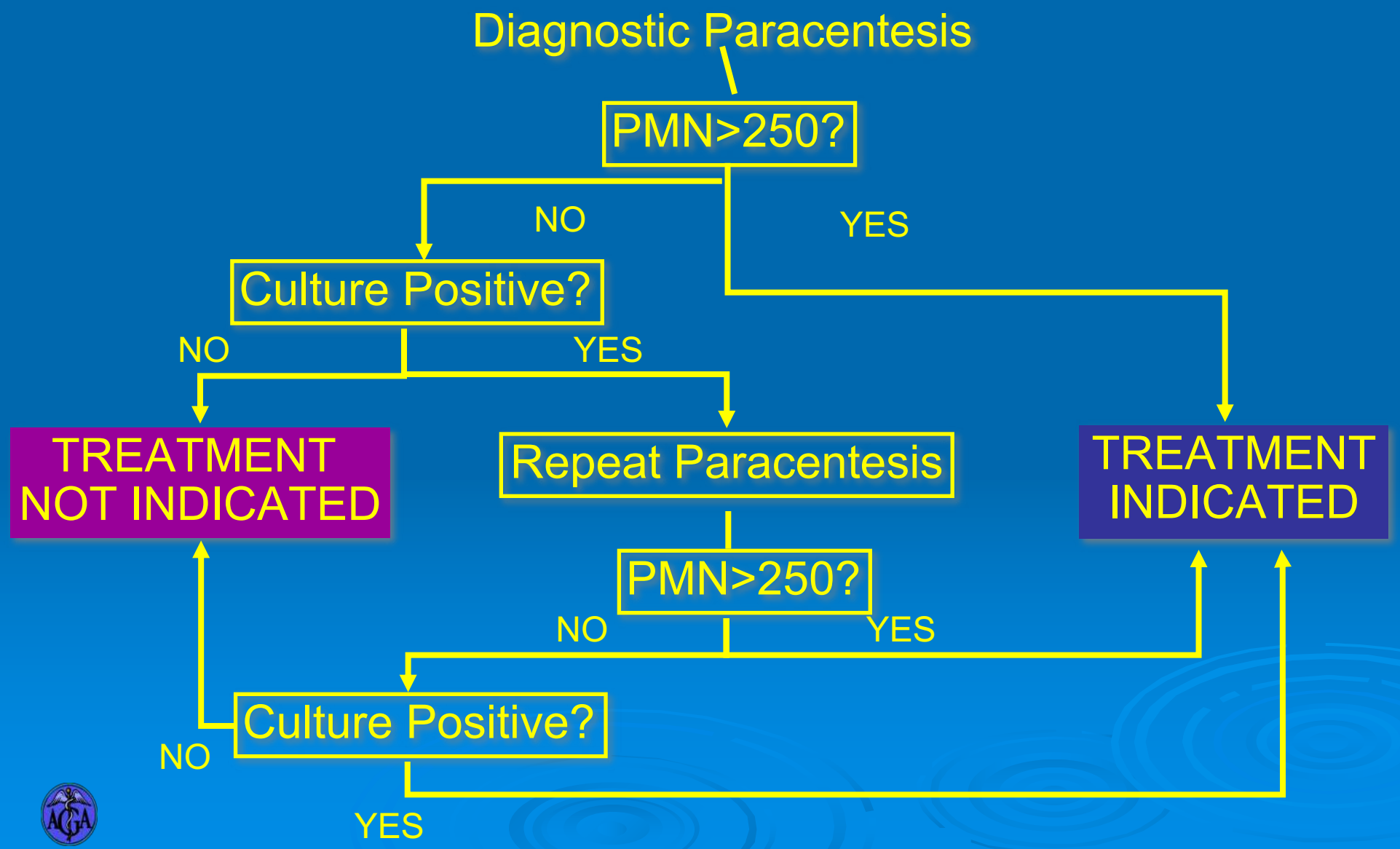
- Diagnosis based on ascitic fluid

  PMN count >250/mm^3

Treatment of Spontaneous Bacterial Peritonitis

- Recommended antibiotics for initial empiric therapy
  - i.v. cefthriaxone or cefotaxime
  - If MDRO are prevalent consider carbapenems
  - avoid aminoglycosides
- Minimum duration: 5 days
- Re-evaluation if ascitic fluid PMN count has not decreased by at least 25% after 2 days of treatment
- Phrophylaxis for prevention of recurrence????

Diagnosis and Management of Spontaneous Bacterial Peritonitis



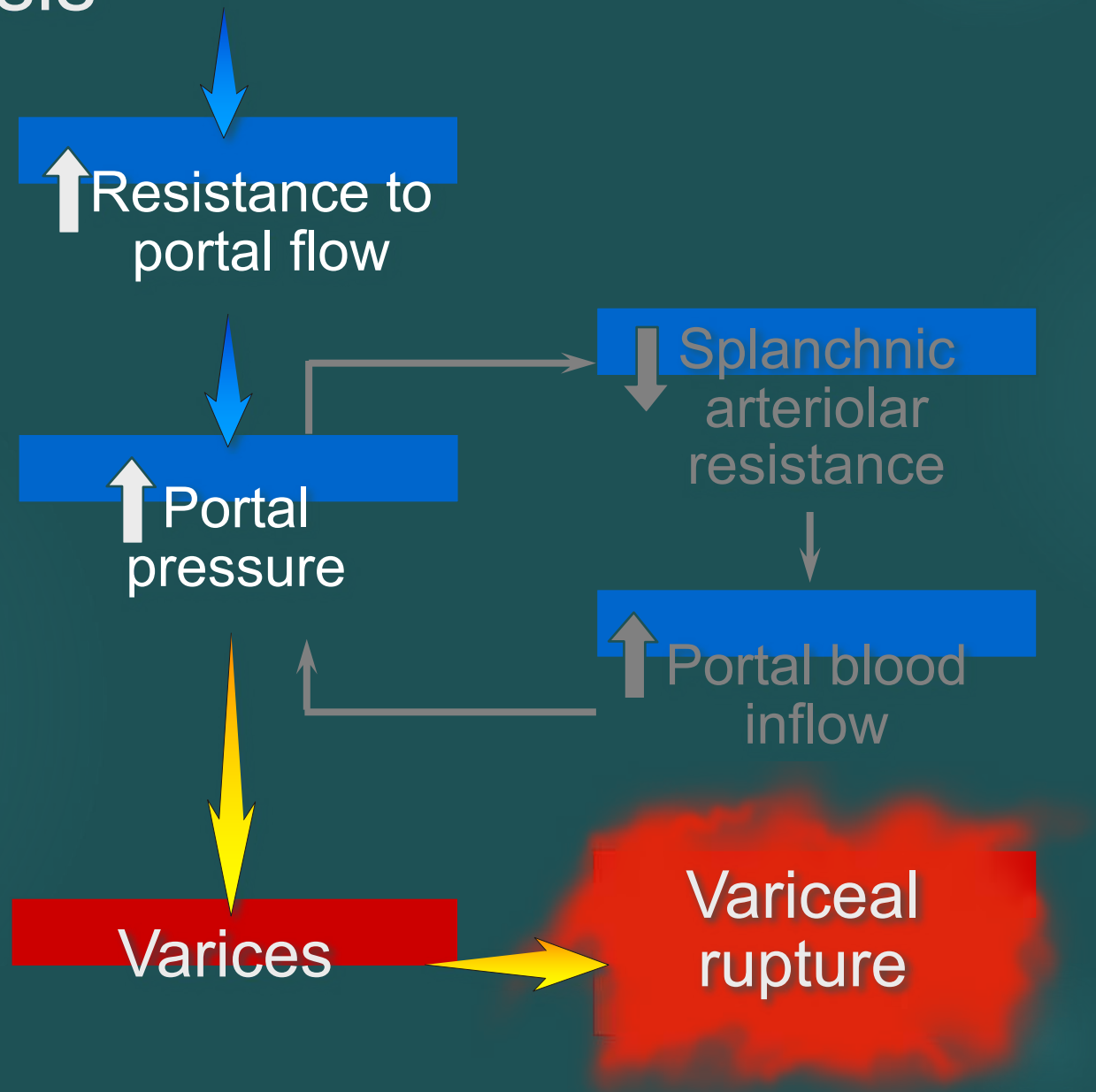
Variceal Hemorrhage

- Most devastating complication of cirrhosis and portal hypertension
- Common complication of cirrhosis and PH
  - 30-50% of patients develop varices
- High mortality 15-20% at six weeks
- High risk of recurrent bleeding 62% at two years
- Severity and prognosis associated to several factors
  - Extreme elevation of HVPG > 20 mmHg
  - Degree of liver failure
  - Prognosis worse with massive bleeding

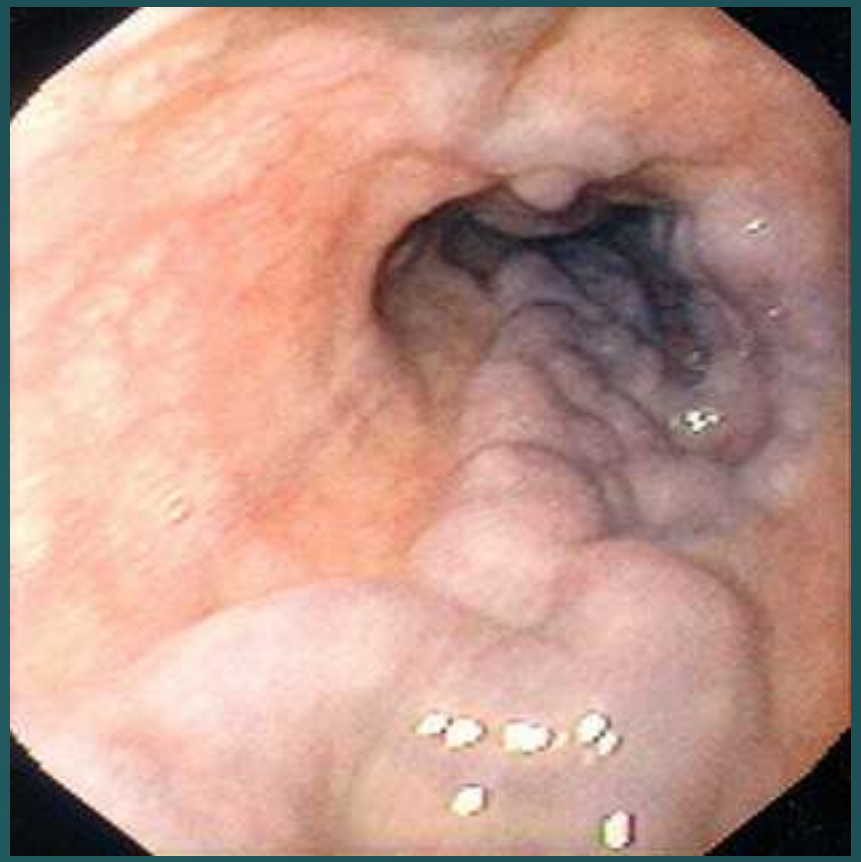
Variceal Hemorrhage

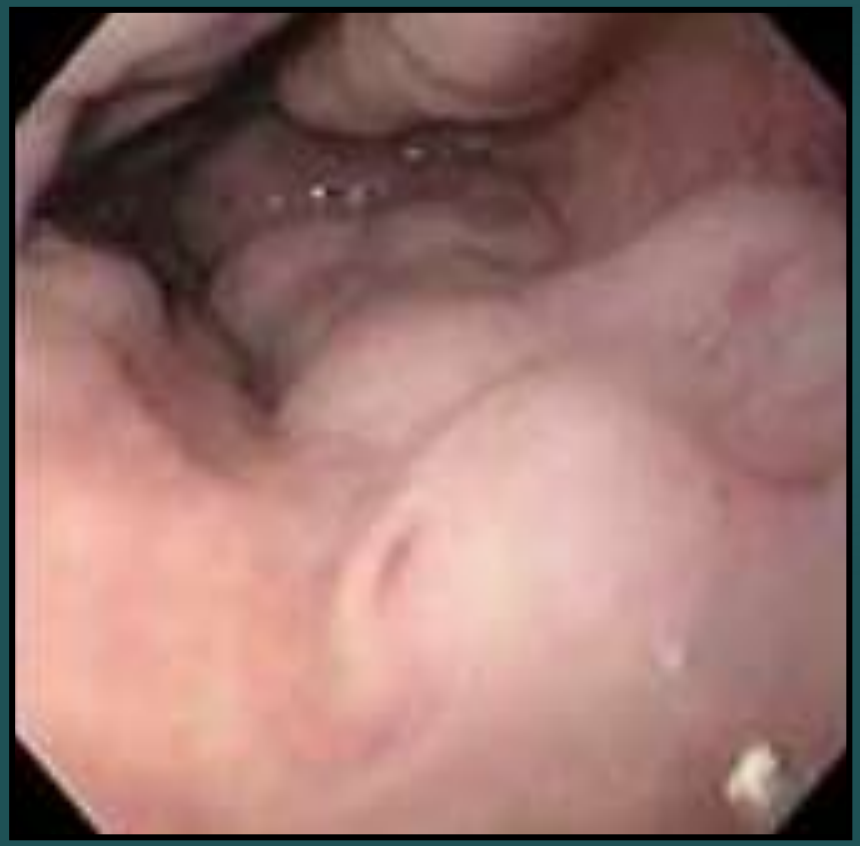
- Increase in portal pressure
  - Hepatic vein pressure gradient HVPG has to be above 10 mmHg for the formation of varices
- With time varices grow and their walls become thinner, until they finally break and bleed (wall tension)
- Most common site is gastro-esophageal junction area

Cirrhosis

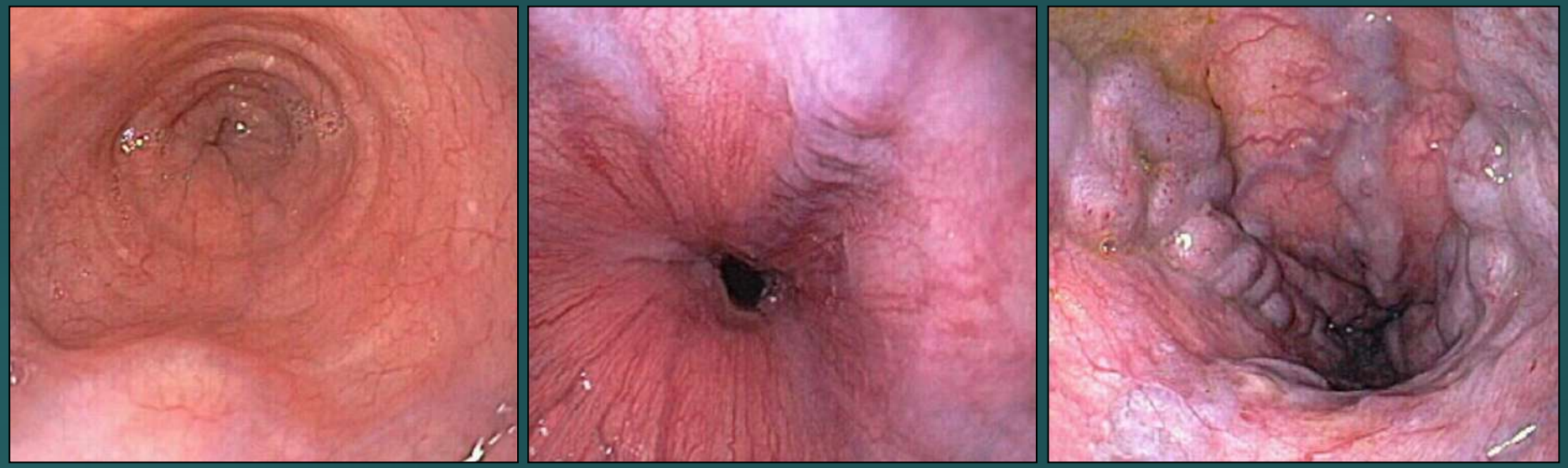

Resistance to portal flow
Splanchnic arteriolar resistance
Portal pressure
Portal blood inflow
Varices
Variceal rupture

Variceal Hemorrhage



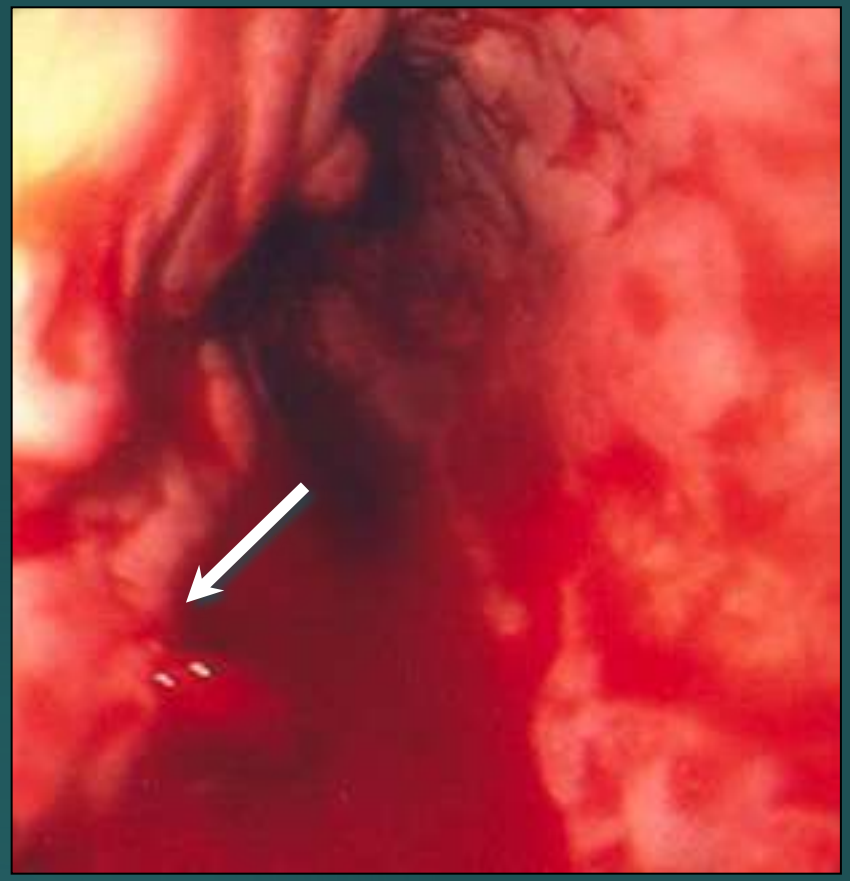


Varices Increase in Diameter Progressively

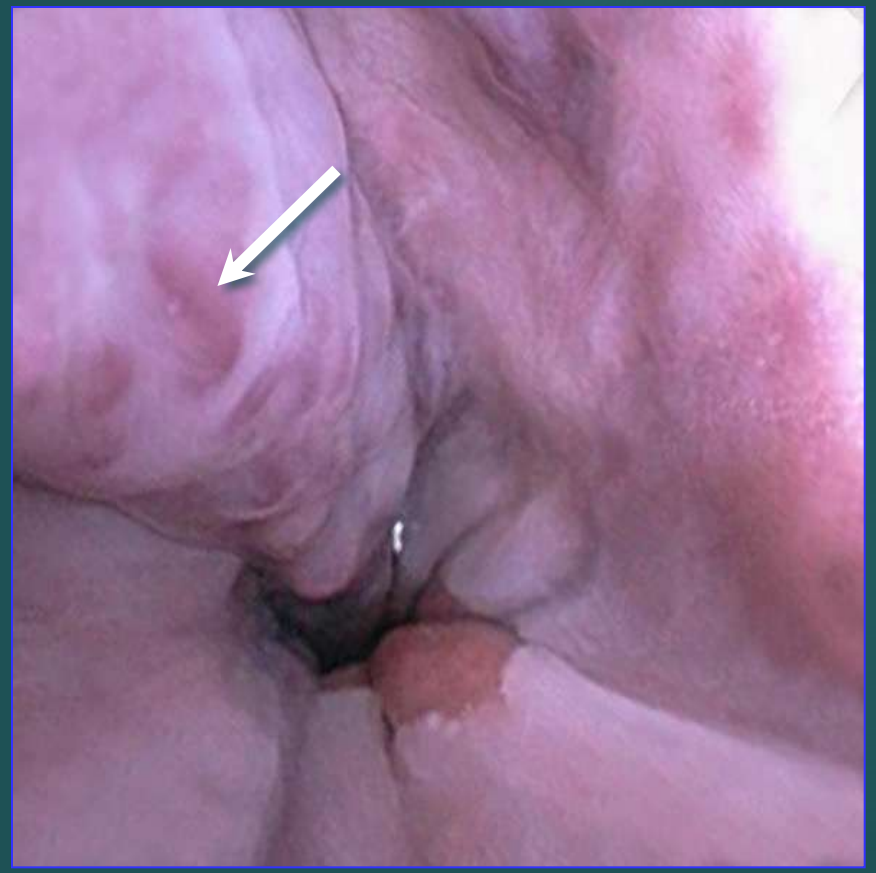


No varices | Small varices | Large varices

7-8%/year | 7-8%/year



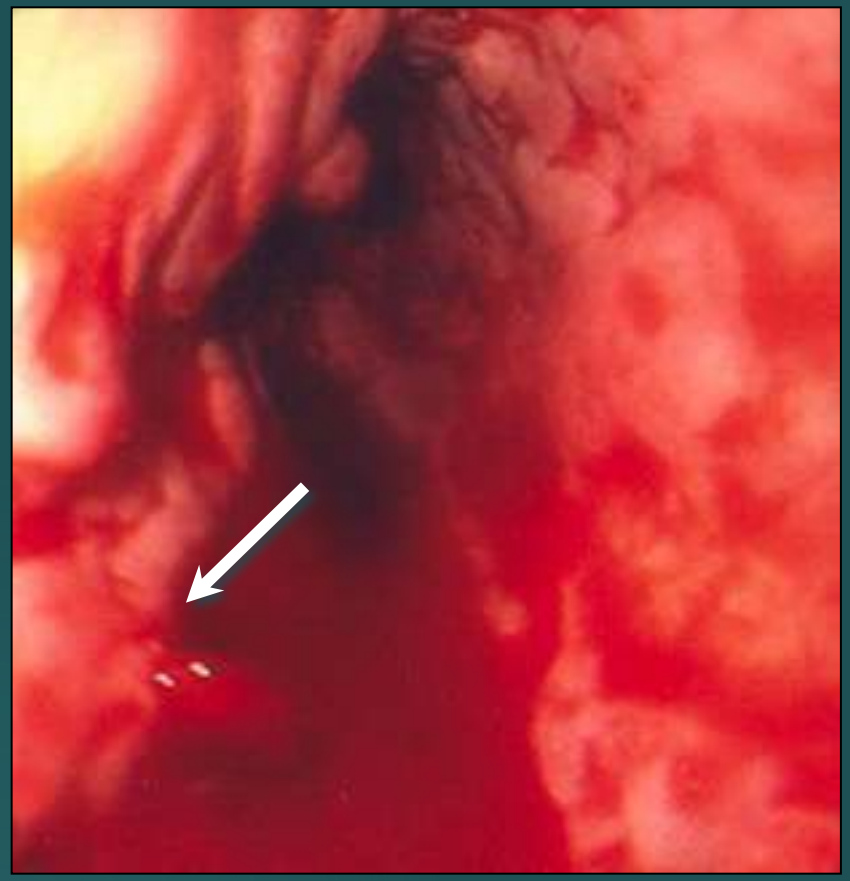
Variceal hemorrhage



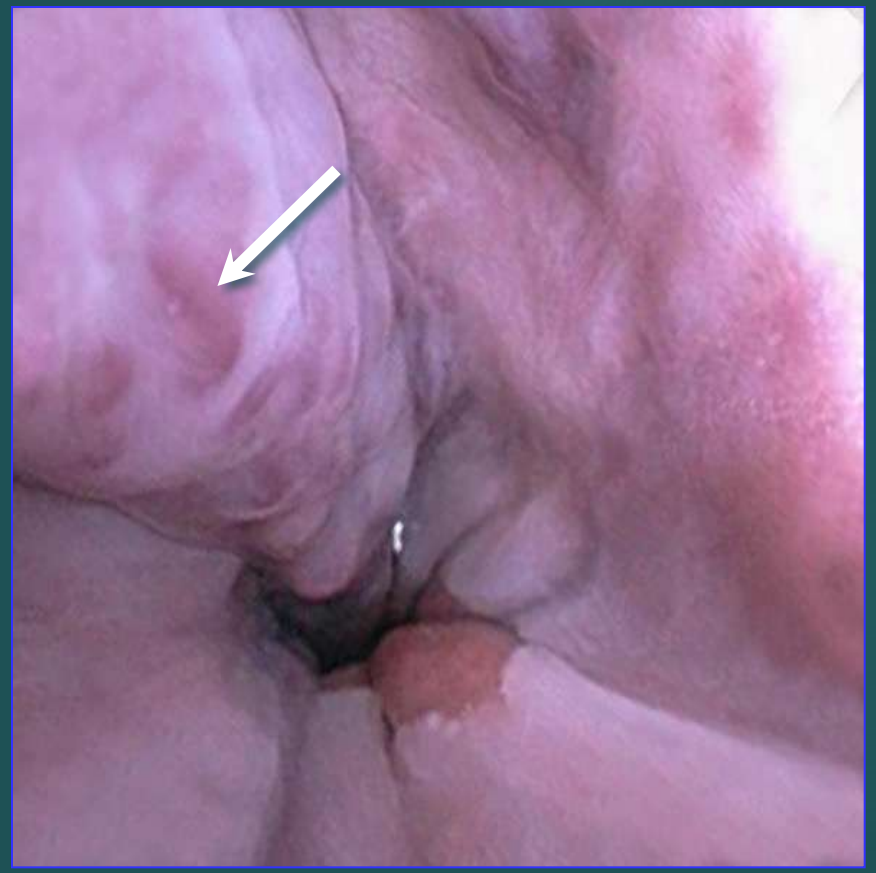
Varix with red signs

Predictors of hemorrhage:

- Variceal size
- Red signs
- Child B/C



Variceal hemorrhage



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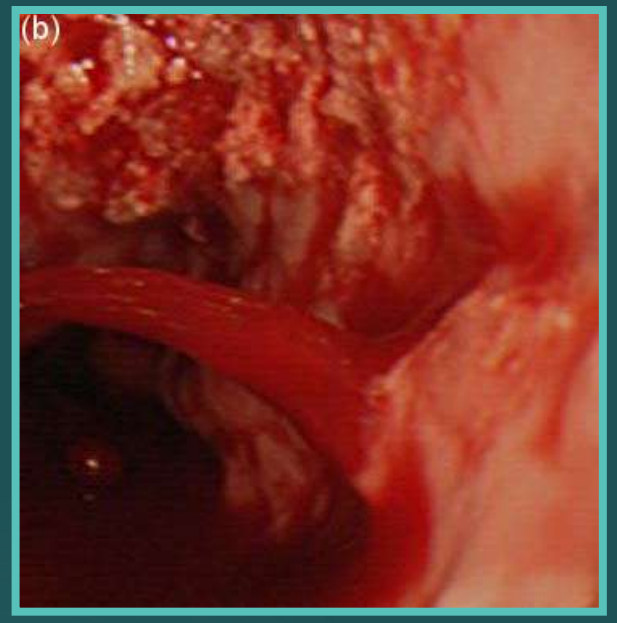
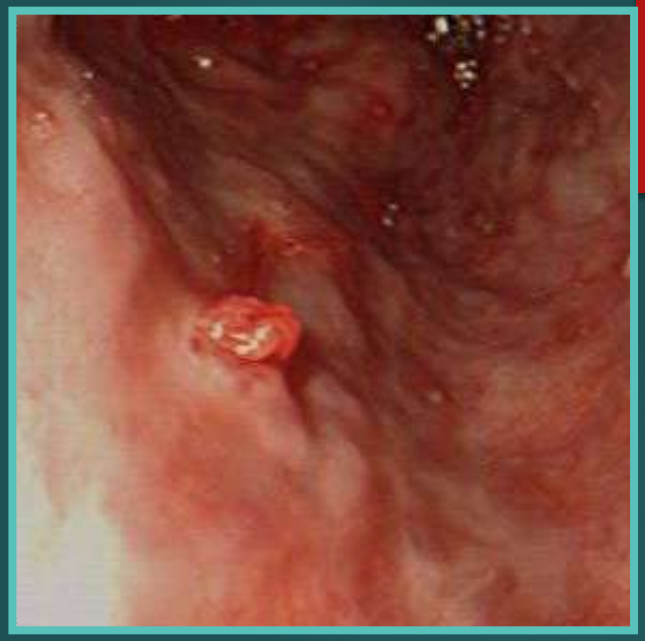
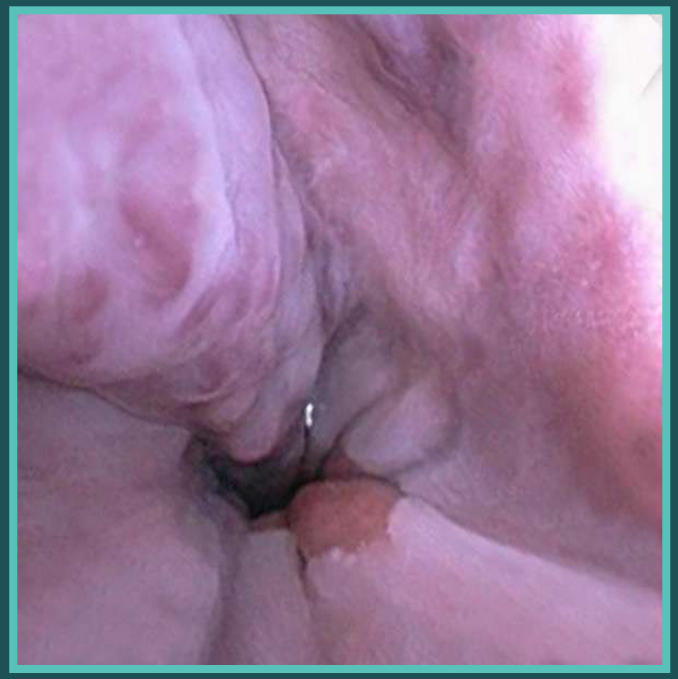


Variceal hemorrhage

Punctum





Varix with red wale sign

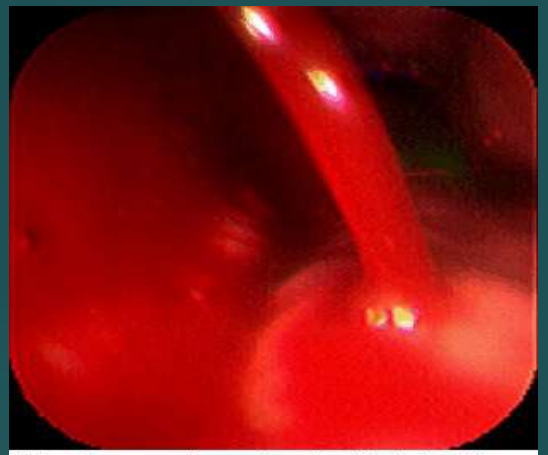
Variceal Hemorrhage

- Management of acute variceal bleeding
  - Control of bleeding
  - Prevent early re-bleeding
  - Correct and avoid concomitant complications
- Initial Management:
  - Airway, Breathing and Circulation
  - Intensive care unit setting
  - Placement of large bore IV lines
  - Blood products

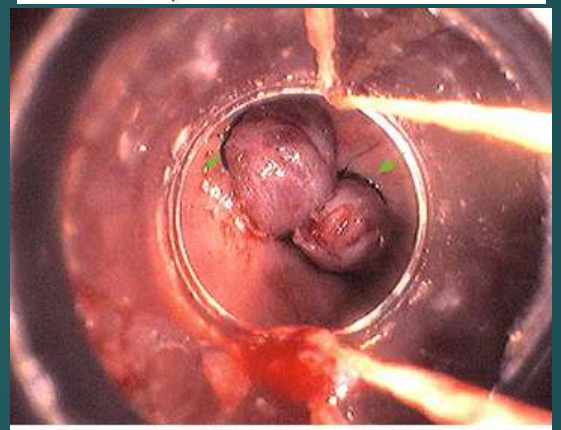
Variceal Hemorrhage

- Therapy for control of bleeding
  - Vasoactive drug therapy
    - Selection of drug mainly depends on availability
    - Octreotide, somatostatin, telipressin
- Endoscopic band ligation is the endoscopic therapy of choice over sclerotherapy in acute variceal bleeding
- Rescue therapies
  - Balloon tamponade
  - TIPS (Transjugular intra-hepatic porto-systemic shunt)
  - Surgical shunts

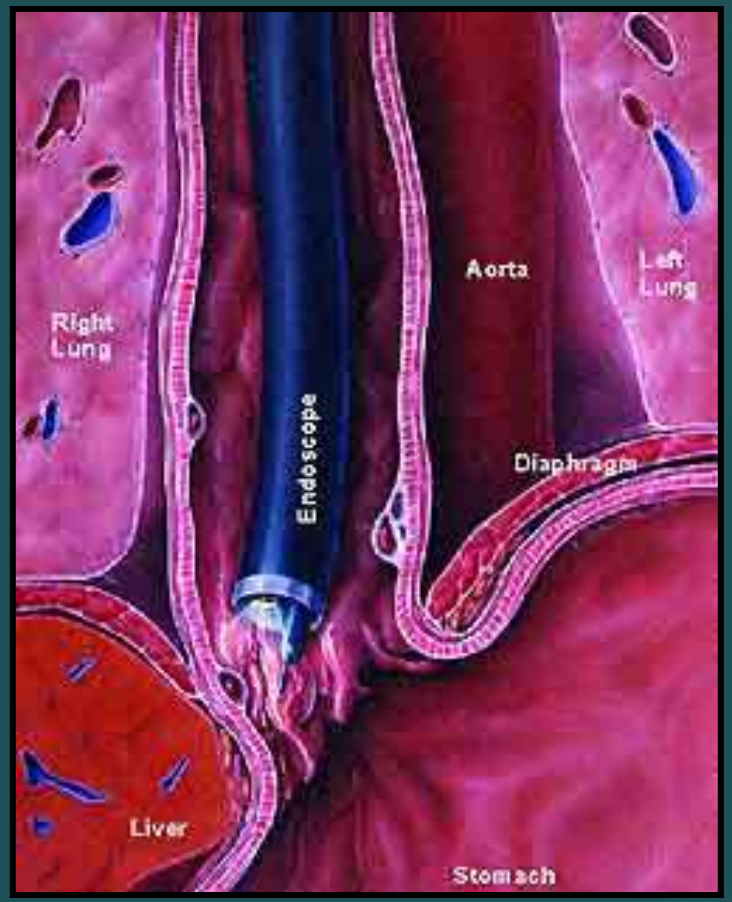
Variceal Hemorrhage



Bleeding esophageal varix A jet of active bleeding is visible from an esophageal varix in a patient with cirrhosis. Bleeding from esophageal varices can be massive. Courtesy of Rome Jutabha, MD.



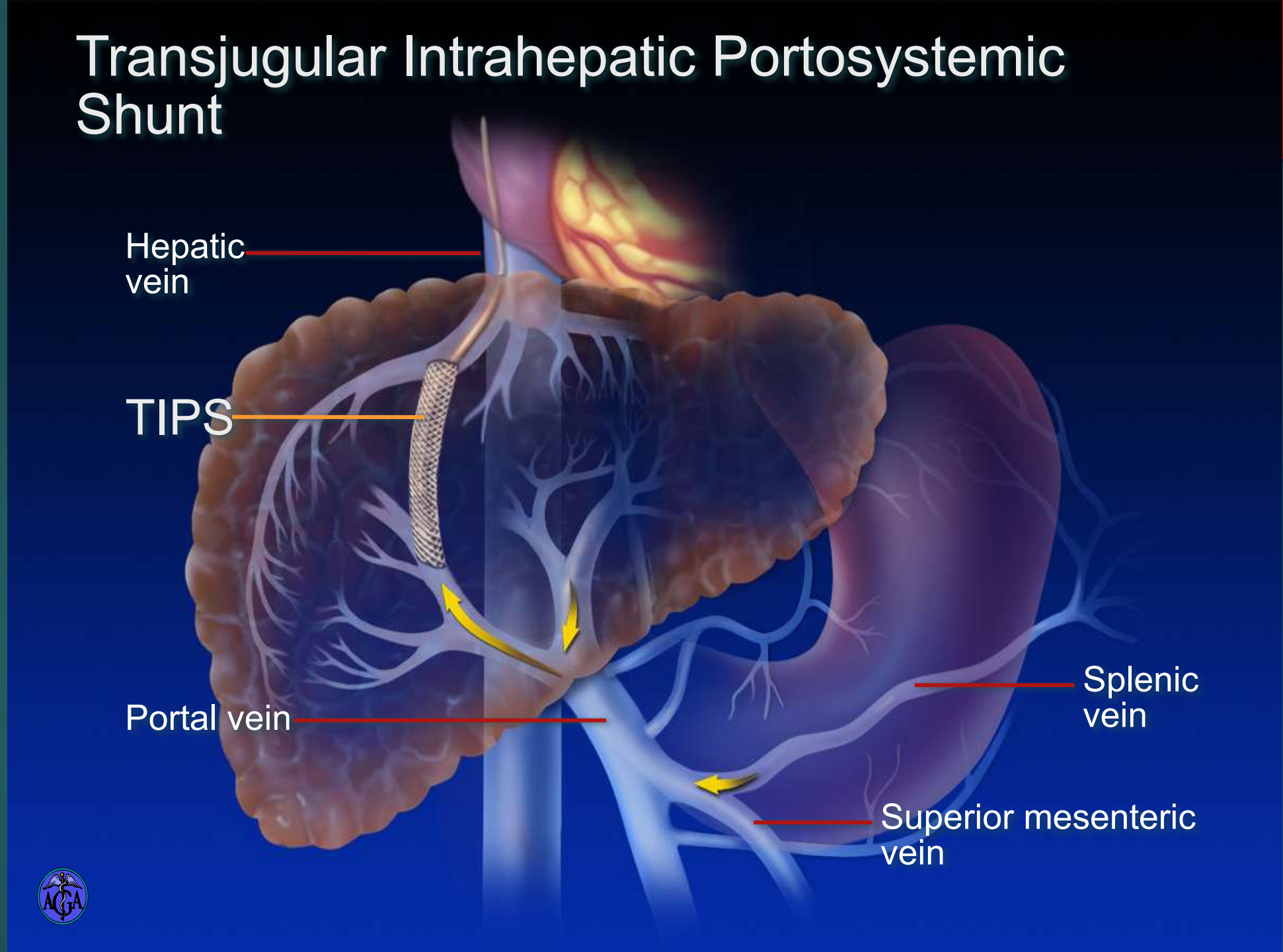
Esophageal varix band ligation Endoscopy shows two varices in the distal esophagus that have been banded. The bands are indicated with the green arrows. The two strings in the right of the field control the trigger device used to deploy the bands. Courtesy of Laurence Bailen, MD.



Endoscopic Variceal Band Ligation

- Bleeding controlled in 90%
- Rebleeding rate 30%
- Compared with sclerotherapy:
  - Less rebleeding
  - Lower mortality
  - Fewer complications
  - Fewer treatment sessions

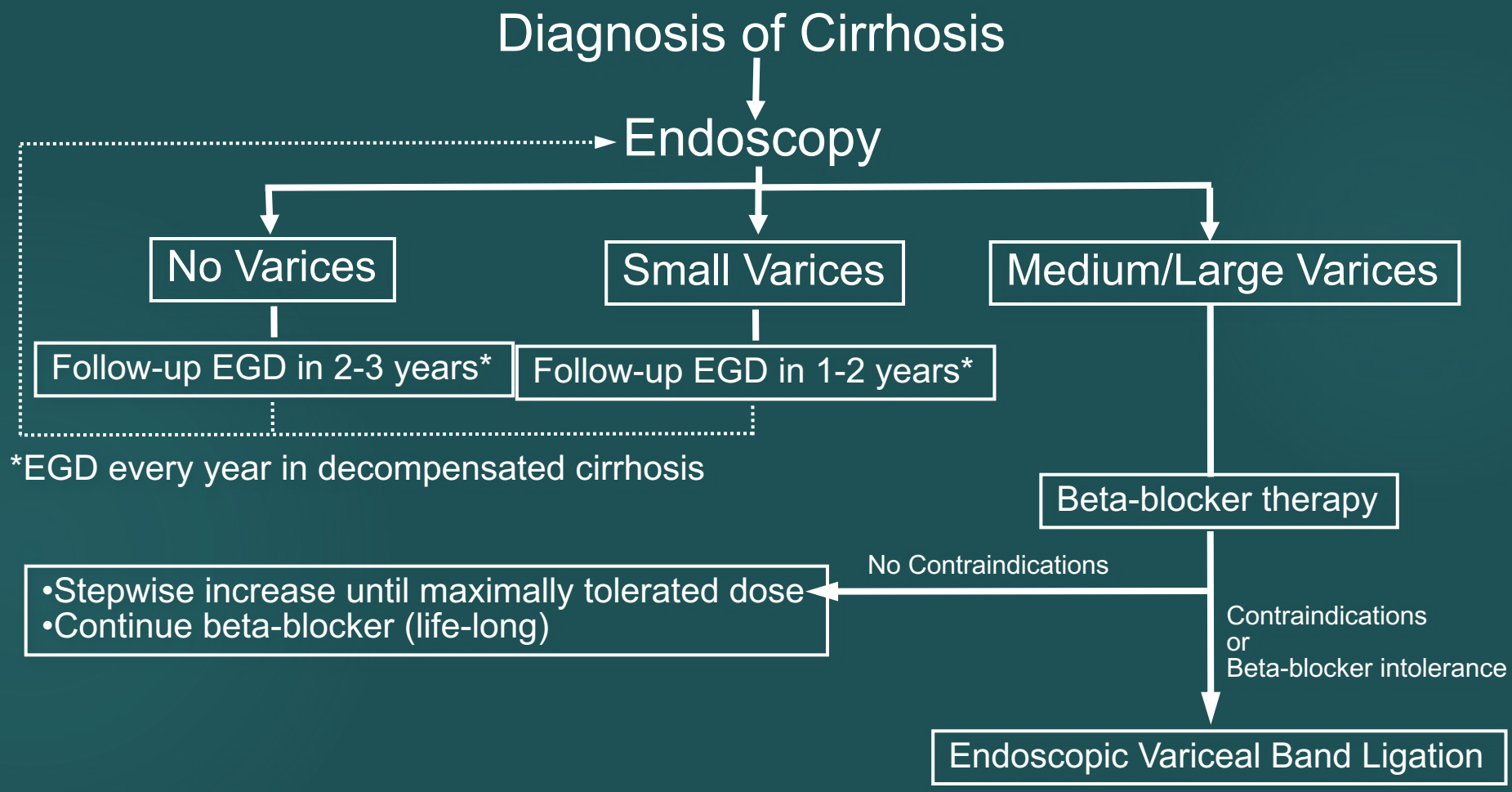
Transjugular Intrahepatic Portosystemic Shunt



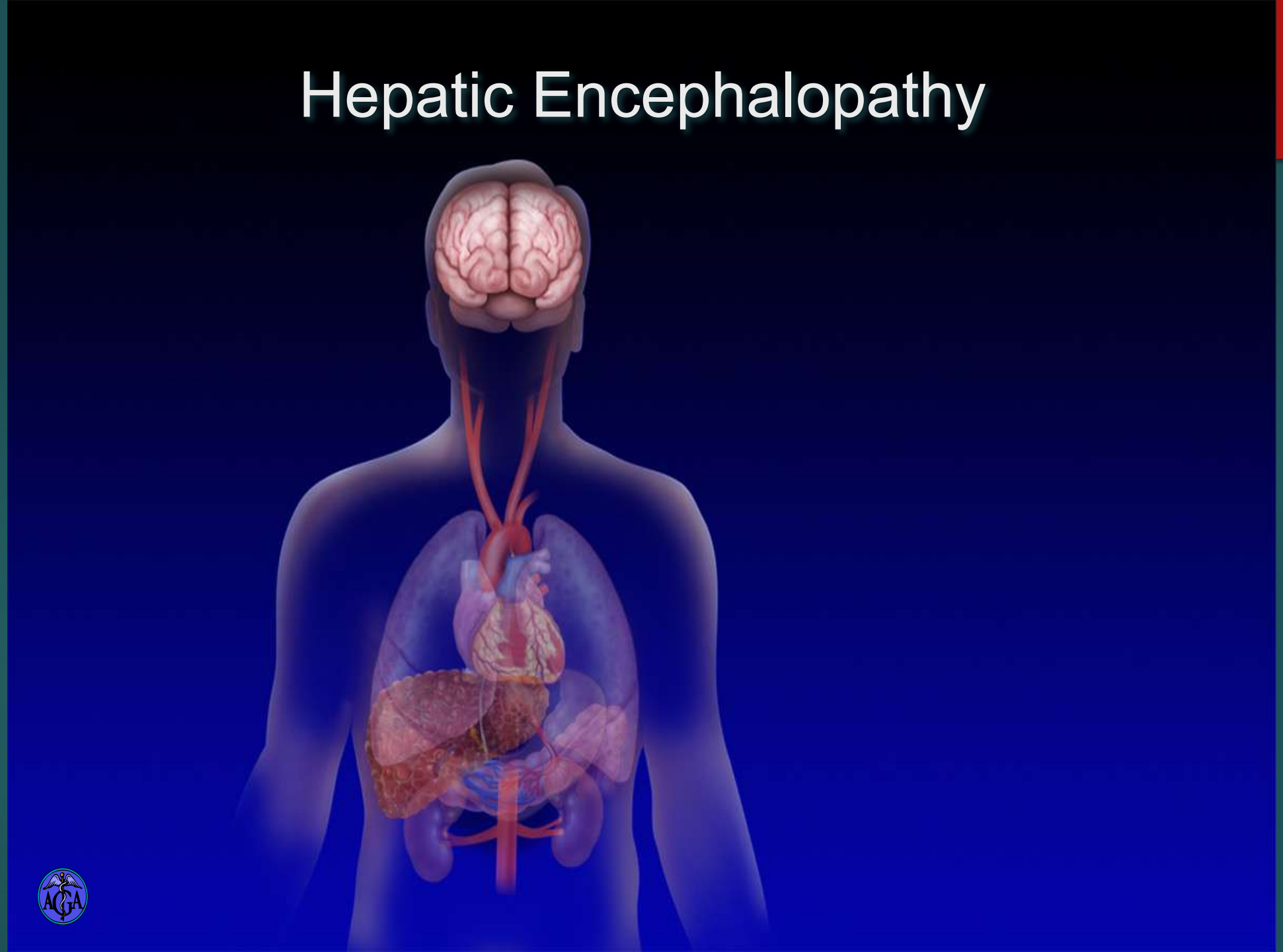
Variceal Hemorrhage

- Prevention of other complications
  - Antibiotic prophylaxis to avoid frequent infections
    - SBP (50%), UTI (25%), pneumonia (25%)
    - Antibiotics should be given to ***all*** patients from admission
    - Quinolones are frequently used
  - Watch for signs of hepatic encephalopathy
  - Renal failure is frequent and carries poor prognosis
- Primary prophylaxis:
  - Diagnostic endoscopy in all patients with cirrhosis
  - Band ligation vs. B-blockers therapy

Prophylaxis of Variceal Hemorrhage



Hepatic Encephalopathy



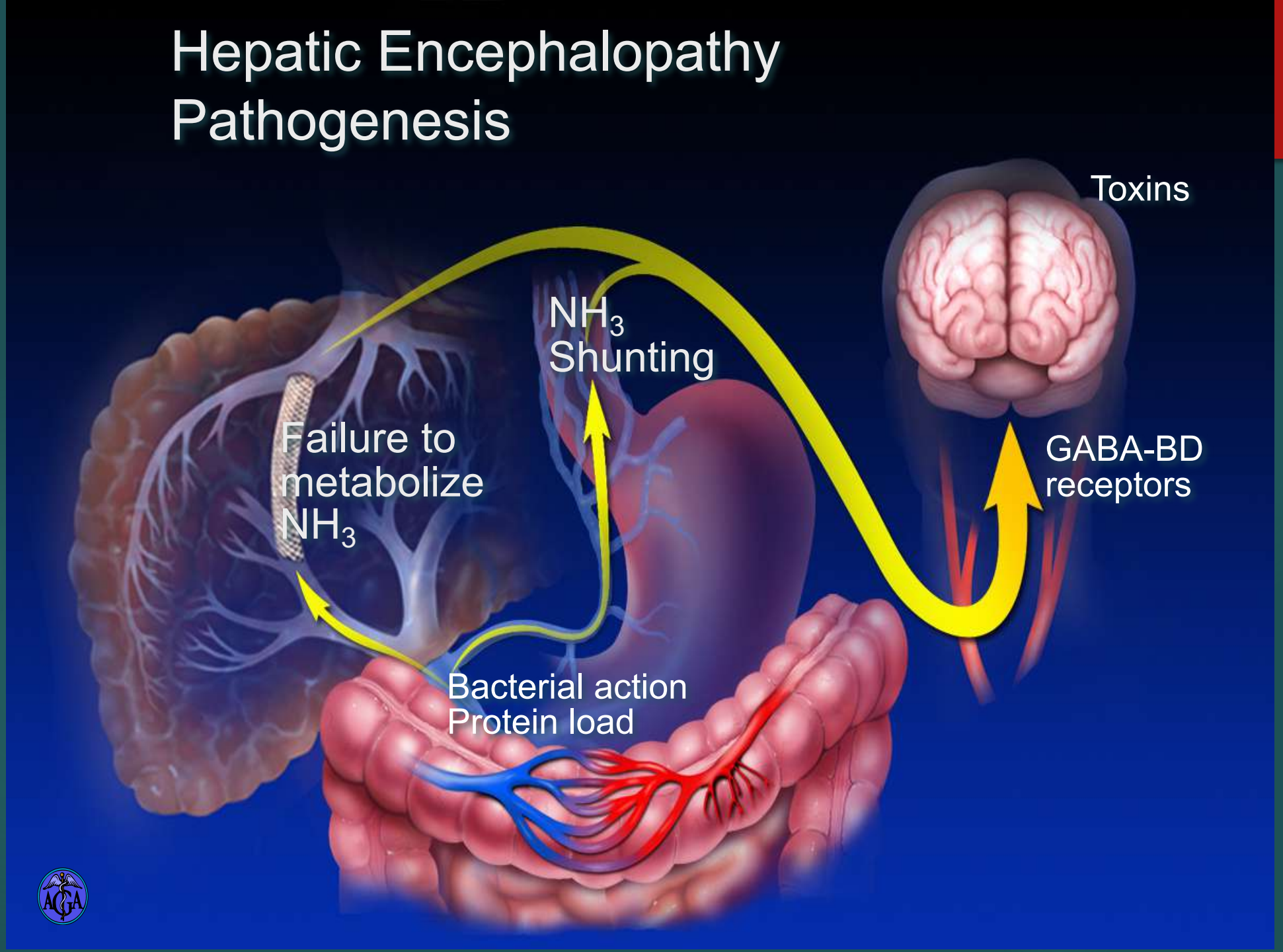
Hepatic Encephalopathy

- Reversible decrease in neurologic function
  - May be subtle from sleep disturbance to outright coma with focal neurologic signs
- Common complication of end stage chronic liver disease
- Minimal hepatic encephalopathy MHE affects 50-80% of those tested
  - Requires specialized psychometric and neuro-physiological tests

Pathophysiology of Hepatic Encephalopathy

- Nitrogenous substances derived from the gut adversely affect brain function
- Ammonia is the best known metabolite associated with HE
- Compounds gain access to the systemic circulation via decreased metabolism in liver and/or portosystemic shunts
- Experimental models describe derangements in glutamine, serotonin, GABA, and catecholamine metabolism.

Hepatic Encephalopathy Pathogenesis



Hepatic Encephalopathy

- History and physical exam
  - Exclude other etiologies for symptoms
  - Confirm chronic liver disease
  - Focal neurological deficits
- Often a precipitating factor
  - Gastrointestinal bleeding
  - Infection
  - Volume depletion/dehydration
  - Hyponatremia
  - TIPS or surgical procedures
  - Drugs: sedatives and narcotics

TABLE 3. PRECIPITATING FACTORS FOR OHE BY DECREASING FREQUENCY

EPISODIC	RECURRENT
Infections*	Electrolyte disorder
GI bleeding	Infections
Diuretic overdose	Unidentified
Electrolyte disorder	Constipation
Constipation	Diuretic overdose
Unidentified	GI bleeding

Modified from Strauss E, da Costa MF. The importance of bacterial infections as precipitating factors of chronic hepatic encephalopathy in cirrhosis. Hepatogastroenterology 1998;45:900-904.
**More recent unpublished case series confirm the dominant role of infections.*

TABLE 4. DIFFERENTIAL DIAGNOSIS OF HE

Overt HE or acute confusional state
Diabetic (hypoglycemia, ketoacidosis, hyperosmolar, lactate acidosis)
Alcohol (intoxication, withdrawal, Wernicke)
Drugs (benzodiazepines, neuroleptics, opioids)
Neuroinfections
Electrolyte disorders (hyponatremia and hypercalcemia)
Nonconvulsive epilepsy
Psychiatric disorders
Intracranial bleeding and stroke
Severe medical stress (organ failure and inflammation)
Other presentations
Dementia (primary and secondary)
Brain lesions (traumatic, neoplasms, normal pressure hydrocephalus)
Obstructive sleep apnea
Hyponatremia and sepsis can both produce encephalopathy per se and precipitate HE by interactions with the pathophysiological mechanisms. In end-stage liver disease, uremic encephalopathy and HE may overlap.

Hepatic Encephalopathy Is A Clinical Diagnosis

- Clinical findings and history important
- Ammonia levels are unreliable
- Ammonia has poor correlation with diagnosis
- Measurement of ammonia not necessary
- Number connection test
- Slow dominant rhythm on EEG

Hepatic Encephalopathy Clinical features

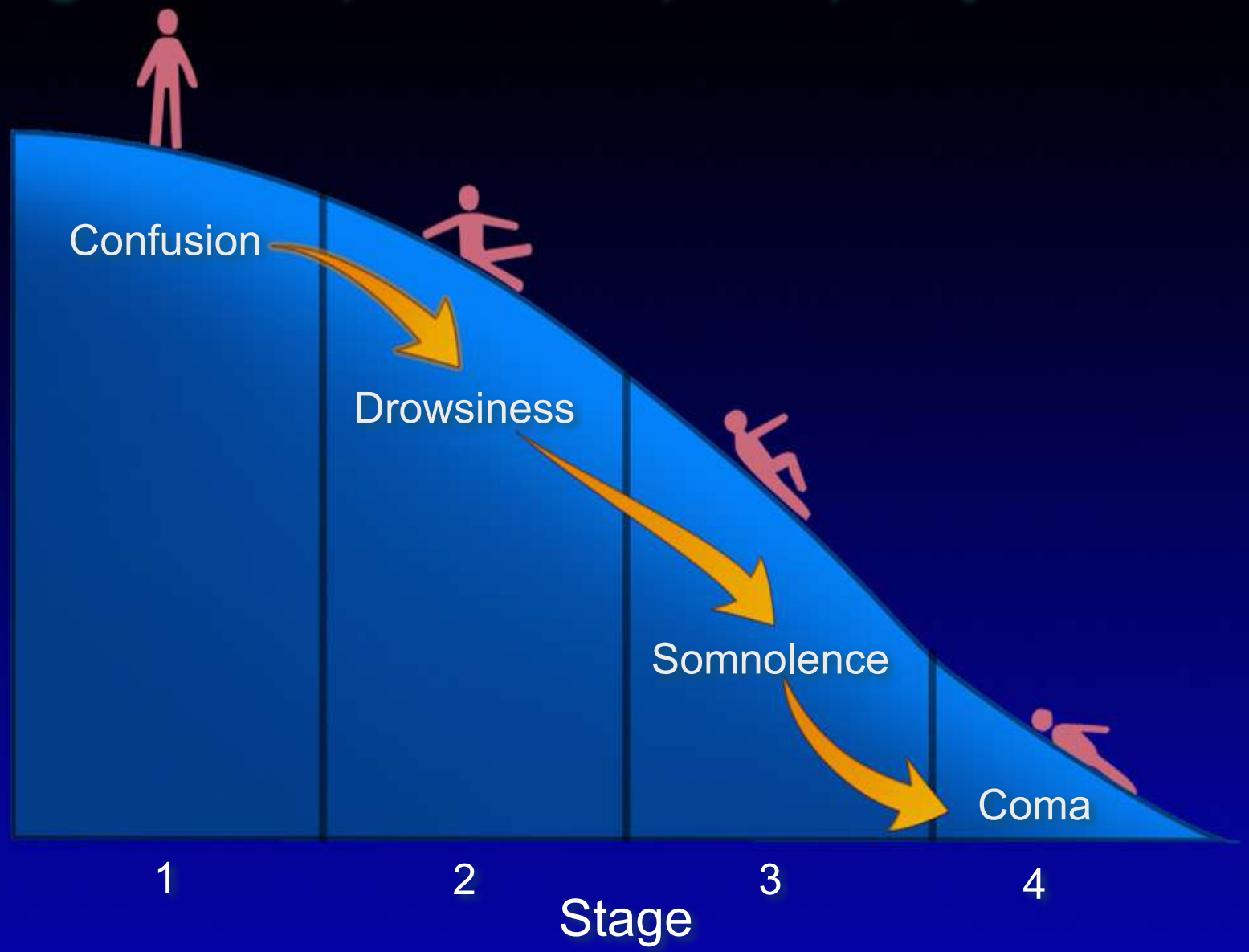
- Reversal of sleep pattern
- Disturbed consciousness
- Personality changes
- Intellectual deterioration
- Fetor hepaticus
- Astrexis
- Fluctuating

Asterixis

Stages of Hepatic Encephalopathy

Stage	Mental state	Neurologic signs
1	Mild confusion: limited attention span, irritability, inverted sleep pattern	Incoordination, tremor, impaired handwriting
2	Drowsiness, personality changes, intermittent disorientation	Asterixis, ataxia, dysarthria
3	Somnolent, gross disorientation, marked confusion, slurred speech	Hyperreflexia, muscle rigidity, Babinski sign
4	Coma	No response to pain, decerebrate posture

Stages of Hepatic Encephalopathy



Treatment of Hepatic Encephalopathy

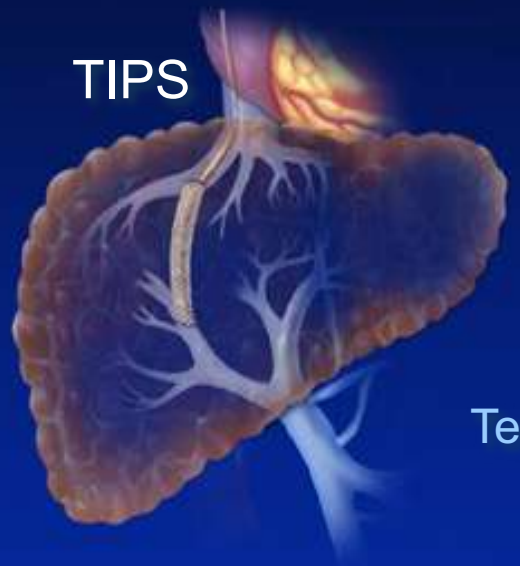
- Identify and treat precipitating factor
  - Infection
  - GI hemorrhage
  - Pre-renal azotemia
  - Sedatives
  - Constipation
- Lactulose (adjust to 2-3 bowel movements/day)
- Protein restriction, short-term (if at all)

Hepatic Encephalopathy Precipitants

Excess protein

GI bleeding

Sedatives / hypnotics



TIPS

Temp

Infections

Diuretics

Serum K^+

Plasma volume

Azotemia

Hepatic Encephalopathy

- First line therapy is lactulose/bowel catharsis
  - Theoretically lactulose acidifies bowel and prevents NH3 absorption
- Non absorbable ABX
  - Rifaximin
    - Non-absorbable antibiotic
    - Slowly becoming mainstream therapy
  - Metronidazole and neomycin
    - No significant role has been proven in clinical trials

Hepatic Encephalopathy Treatment: Summary