Complications in Liver Cirrhosis Leading to Liver Transplant

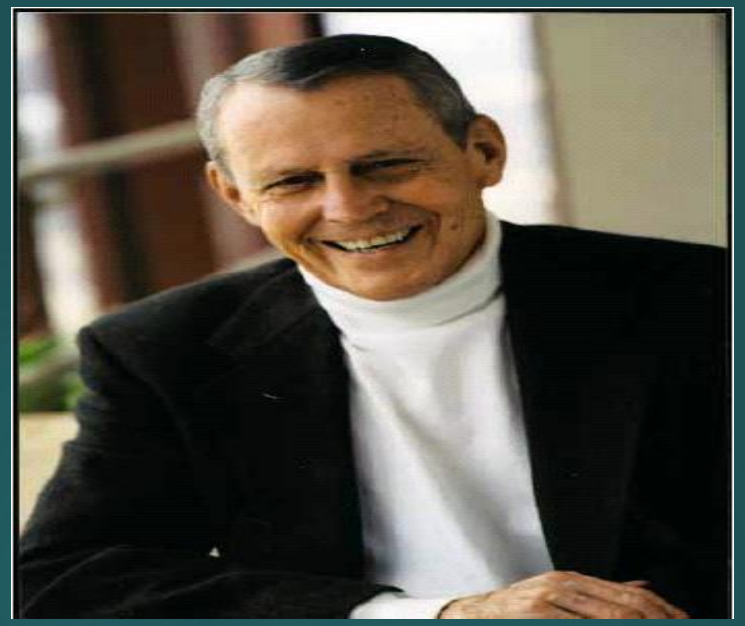
RAFAEL J. PASTRANA, MD.

ASSISTANT PROFESSOR

UNIVERSITY OF PUERTO RICO SCHOOL OF MEDICINE

AUXILIO MUTUO LIVER TRANSPLANT PROGRAM
GASTROENTEROLOGIST

Father of Modern Transplantation



Thomas Starzl

No sense of accomplishment can exceed that of seeing a robust LT recipient who, a few weeks earlier, was seemingly near death from ESLD.

First successful human liver transplant in 1967 (Denver, U.S.A.)

Liver Transplant Statistics

- Over 30 million Americans live with Liver Disease.
- 17,000 Patients currently waiting for liver transplant in 2018.
- 1,200 patients died awaiting a liver transplant in 2018.
- Nearly 8,000 liver transplants occur in USA every year.
- One year survival rate of 90%.
- Five year survival rate of 75 %.

www.optn.org

NOTICIA QUE HACE HISTORIA
Marzo de 2012

SE REALIZA EXITOSO 1ER TRASPLANTE DE HÍGADO EN PUERTO RICO

El Hospital Español Auxilio Mutuo le invita

a conocer los detalles de este importante evento

Post-Transplantation Quality of Life

- Full rehabilitation is achieved in the majority
  - in those with manageable complications
- Goal: Resumption of usual pre-end-stage liver disease activities
- Pregnancy is possible

Indications for Liver Transplant

- Hepatocellular disease
  - Viral Hepatitis
  - Etoh
  - NAFLD
  - AIH
- Cholestatic disease
  - PBC
  - PSC
- Metabolic disease
  - Wilson
  - HFE
- Vasculopathies
  - SOS
  - Budd Chiari Syndrome
- Malignancies
- Post transplant complications
- Acute liver failure

Etiologies of Cirrhosis

- 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

Indications for Liver Transplant

- Acute Liver Failure (ALF)
  - Viral etiology
  - Acute Hep B: 10%
  - Acute Hep A: 7%
- Drug Toxicity
  - Acetaminophen Overdose: 20%
- Toxins
  - Mushrooms
- Metabolic decompensation
  - Wilsons disease
- Fatty Liver of Pregnancy
  - 1:16,000

Liver Transplantation: *Absolute* Contraindications

- Significant cardiac and pulmonary dysfunction
  - e.g. severe hypoxia
  - RSVP above 35 mm Hg
  - Intubated patients: 90-95% in-patient mortality
- Uncontrolled sepsis
- Extra-hepatic malignancy
- Active drug/alcohol use
- Inability to comply with post-transplant treatment
- FHF: (+) irreversible brain injury
- Predictors of decreased chance of peri-operative survival

Liver Transplantation: *Relative* Contraindications

* Factor: expertise/experience of transplant team
- Portal vein thrombosis
- Advanced age
- HIV infection
- HCC
  - if guidelines are exceeded
* Metastatic neuroendocrine tumors

  - 5-year actuarial survival rates ~ 50%

Indications for Referral to Transplant Center

- Progressive synthetic dysfunction
  - PT/INR, albumin, bilirubin
- Malnutrition from end-stage liver disease
- First complication of cirrhosis
  - ascites, variceal bleed, PSE
- Cirrhosis (including compensated form)
- HCC
- Fulminant hepatic failure

Model for End-Stage Liver Disease (MELD)

$$[0.957\ (\log_{\text{creatinine}}) + 0.378\ (\log_{\text{total bilirubin}}) + 1.12\ (\log_{\text{INR}}) + 0.643] \times 10$$

Minimum value 6; maximum capped at 40

Creatinine capped at 4.0 mg/dl for patients on HD

MELD Score

- Used by United Network for Organ Sharing (UNOS) since early 2002
- Uses criterion of medical urgency
- Predicts pre-liver transplant mortality
- Poor predictor of post-liver transplant survival

Complications of Cirrhosis and Portal Hypertension

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

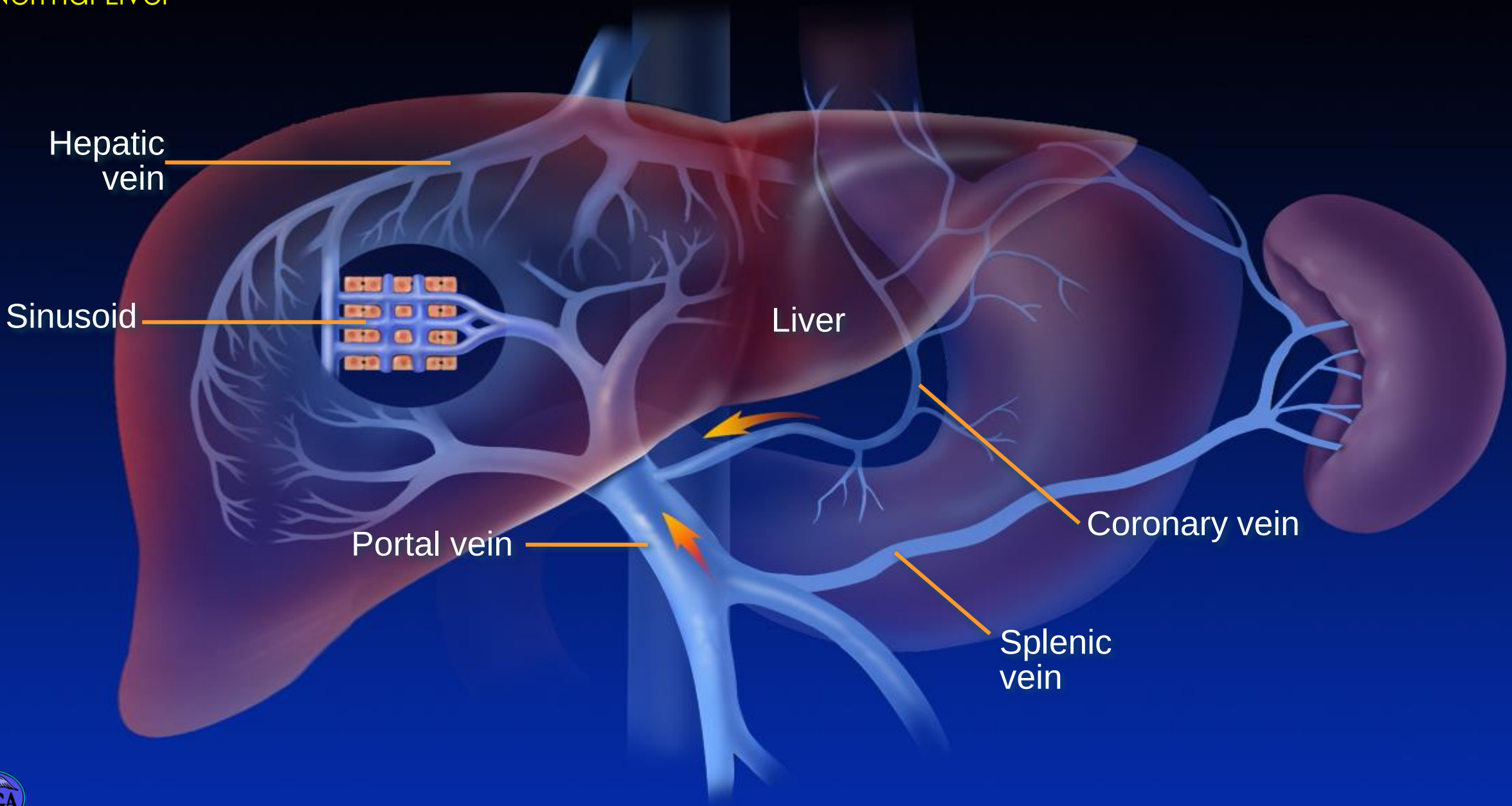
* 5-year survival with onset of any of the above: 20-50% compared to compensated cirrhotics

Cirrhosis

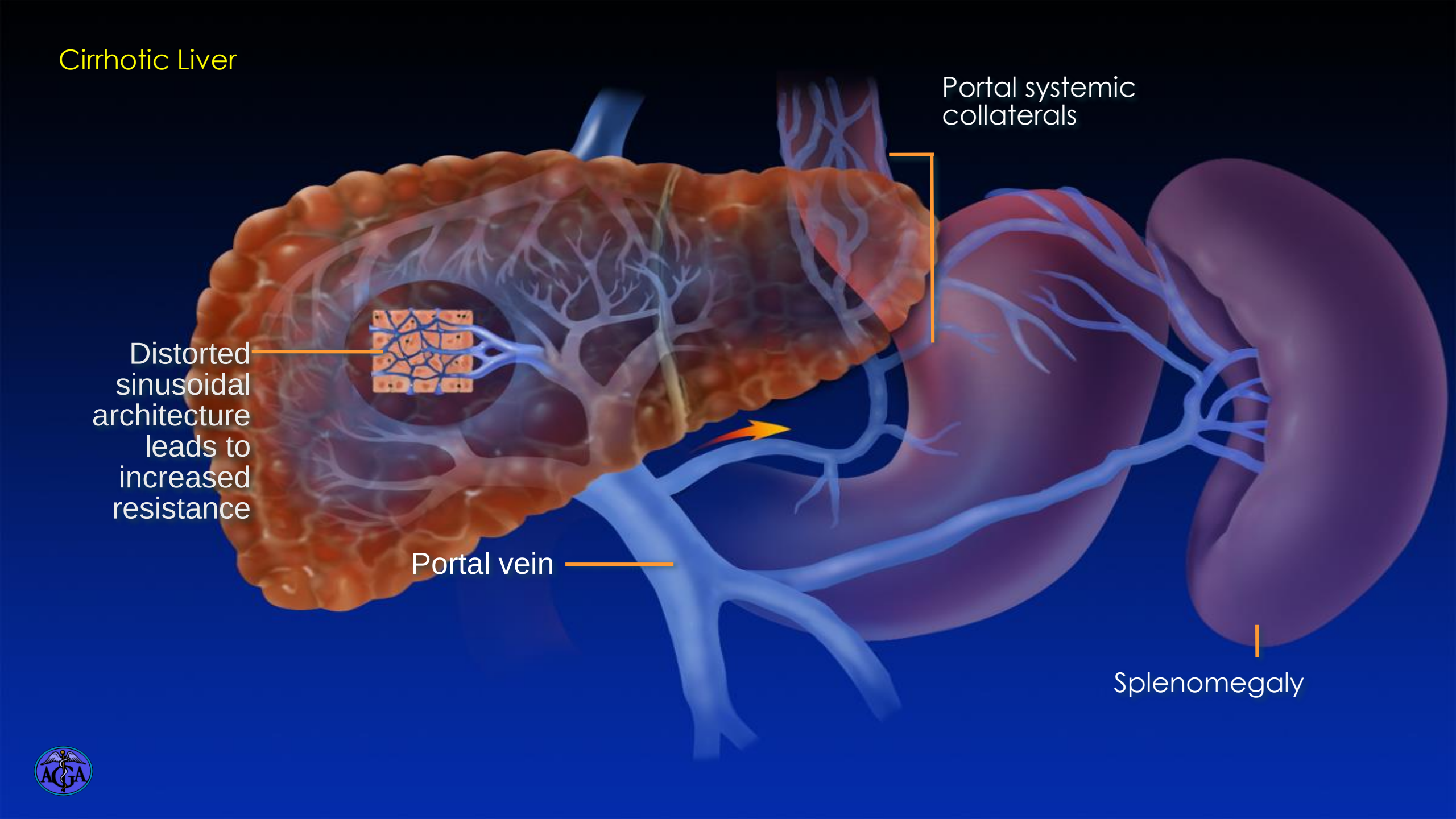
- Cirrhosis →the end stage of any chronic liver disease
- Two major syndromes result
  - Portal hypertension
  - Hepatic insufficiency
- Many definitions but common theme is injury, repair, regeneration and scarring

- Epidemiology:
  - Cirrhosis causes more than 49,500 deaths in 2010 and was the 8th leading cause of mortality[1]

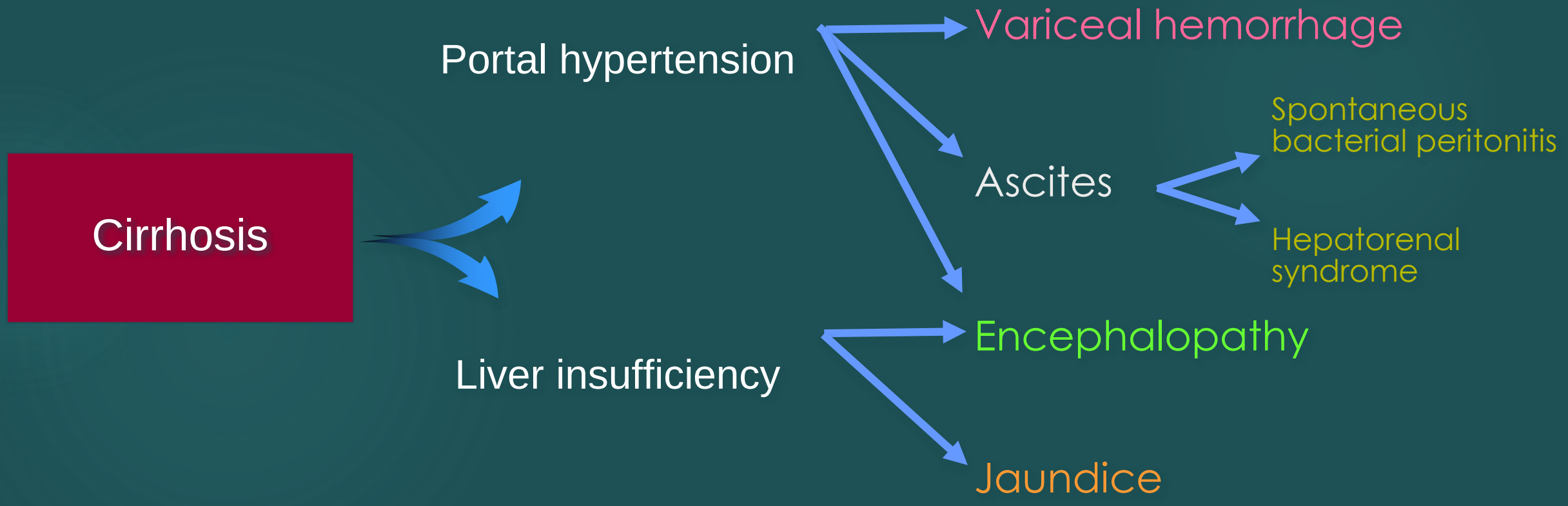
Normal Liver



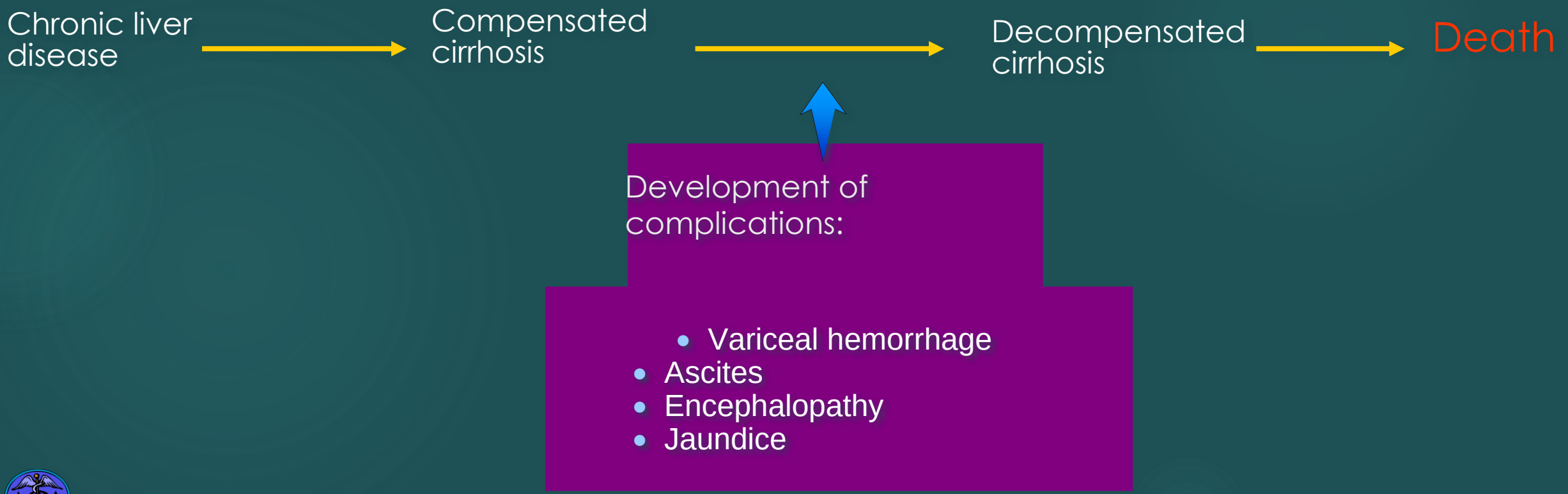
Cirrhotic Liver



Complications of Cirrhosis Result from Portal Hypertension or Liver Insufficiency



Natural History of Chronic Liver Disease



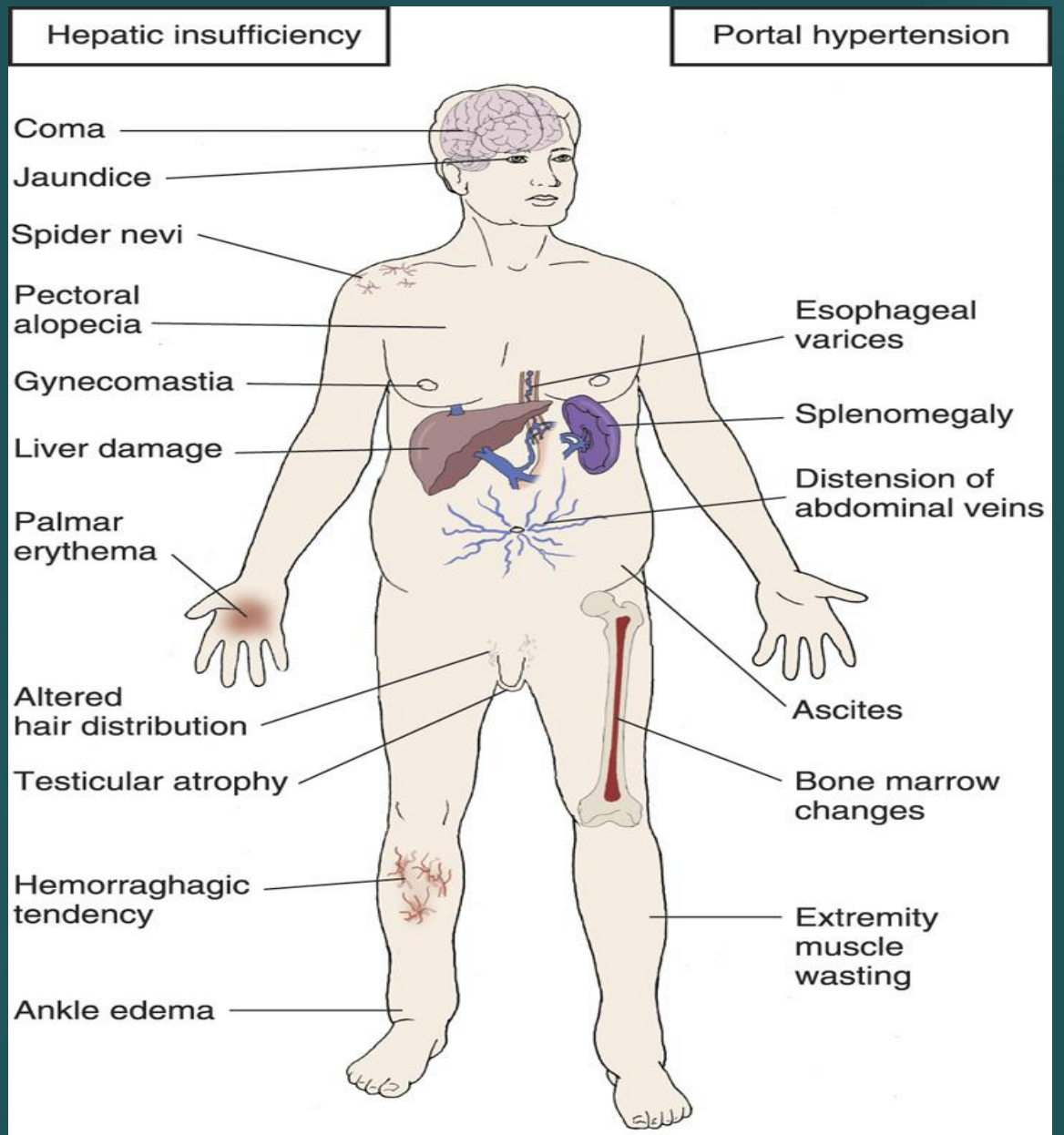


Figure 41-6 Clinical effects of cirrhosis of the liver. (From Bullock BL: Pathophysiology: Adaptations and Alterations in Function [4th Ed]. Philadelphia, Lippincott-Raven, 1996.)

Clinical Manifestation of Chronic Liver Disease
of Chronic Liver Disease

Jaundice

Spider Angiomata

Palmar Erythema

Dupuytren's Contracture

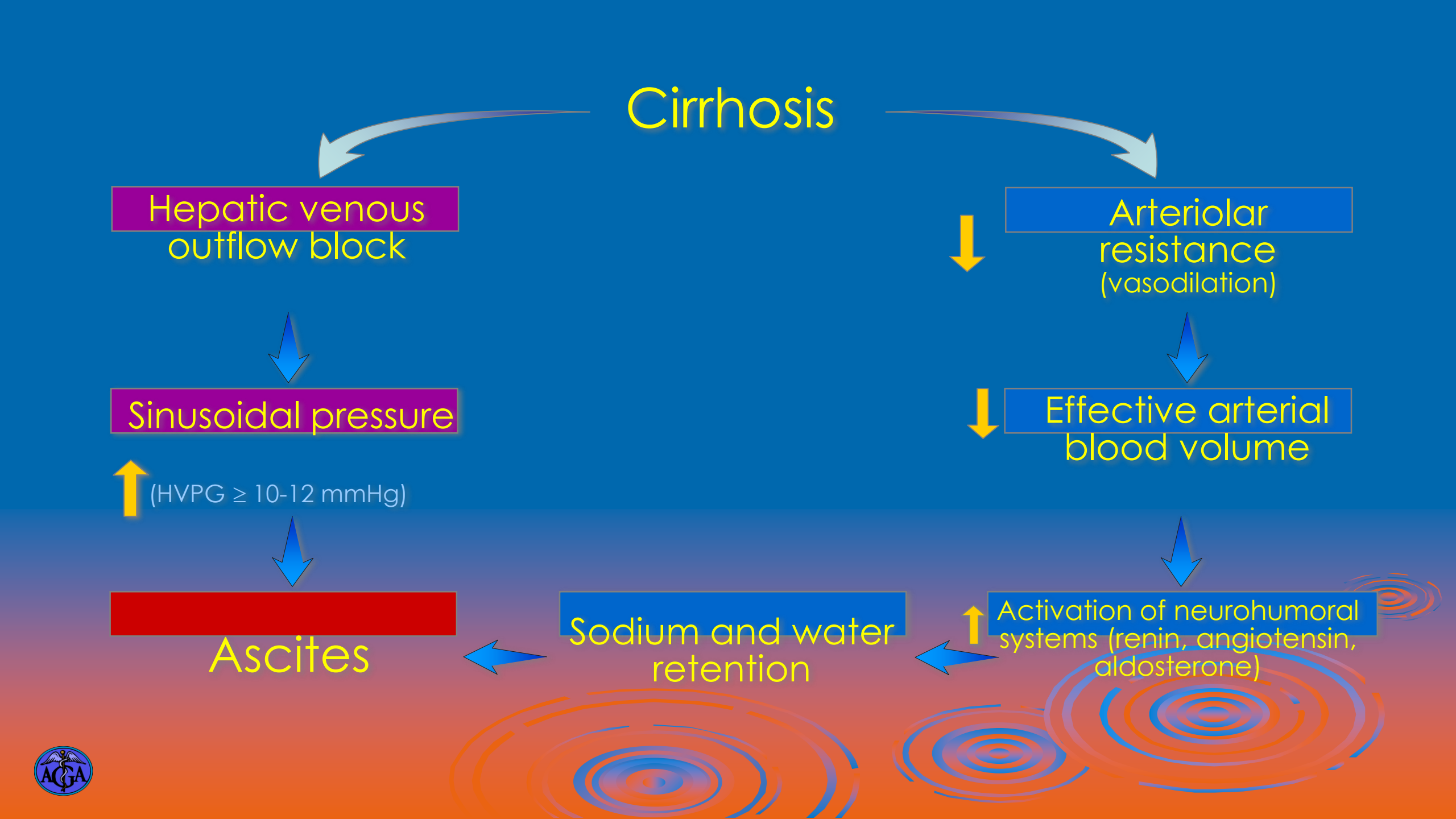
Muehrcke's Lines

Terry's Nails

Gynecomastia

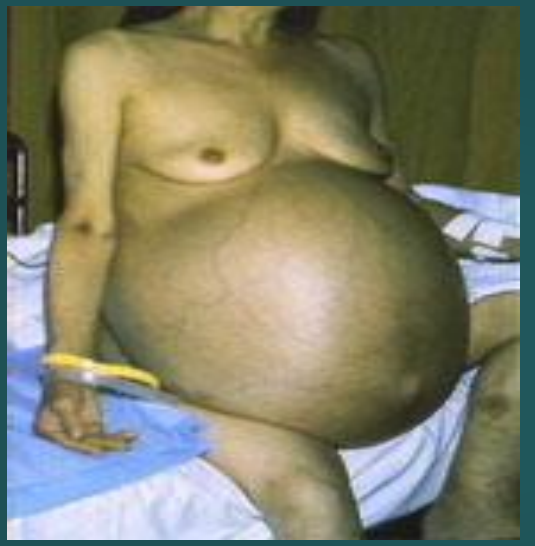
Ascites

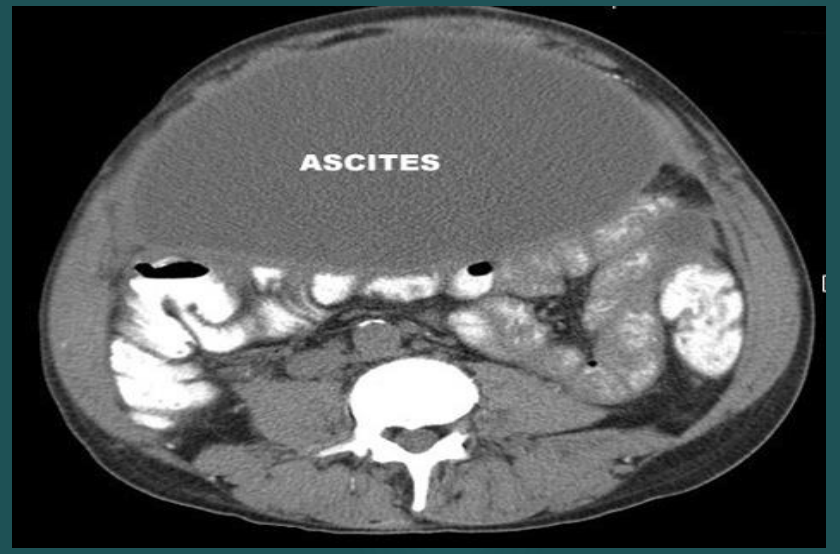
- Develops in the cirrhotic patient as the PH worsens and there is transudation of fluid from the liver to the peritoneal cavity
- Development of hyperdynamic circulation marked by splanchnic and peripheral vasodilatation and increased cardiac output
- Blood flow to other organs reduced due to vasoconstriction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


Cirrhosis
Hepatic venous outflow block
Arteriolar resistance (vasodilation)
Sinusoidal pressure
Effective arterial blood volume
(HVPG ≥ 10-12 mmHg)
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

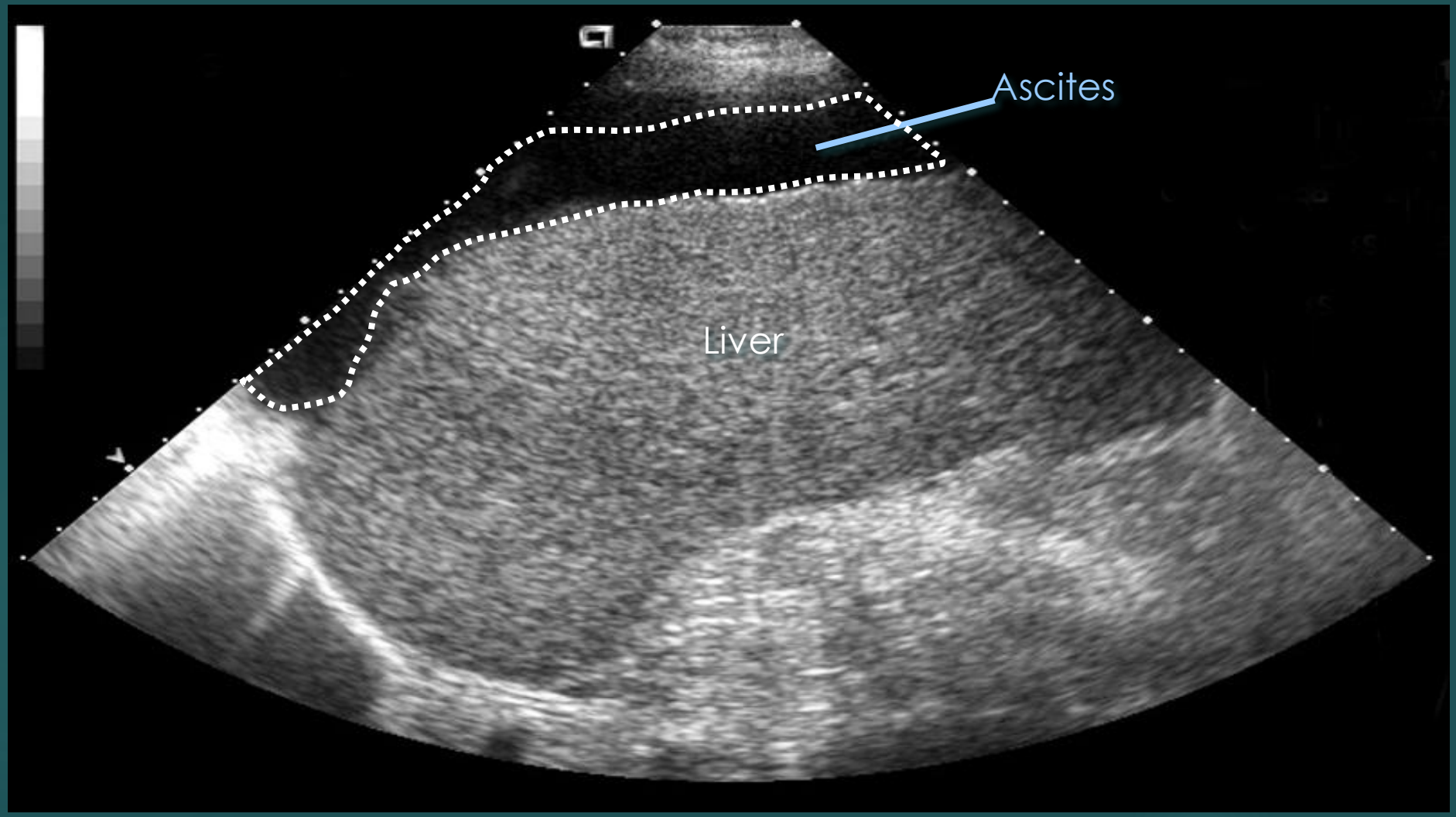




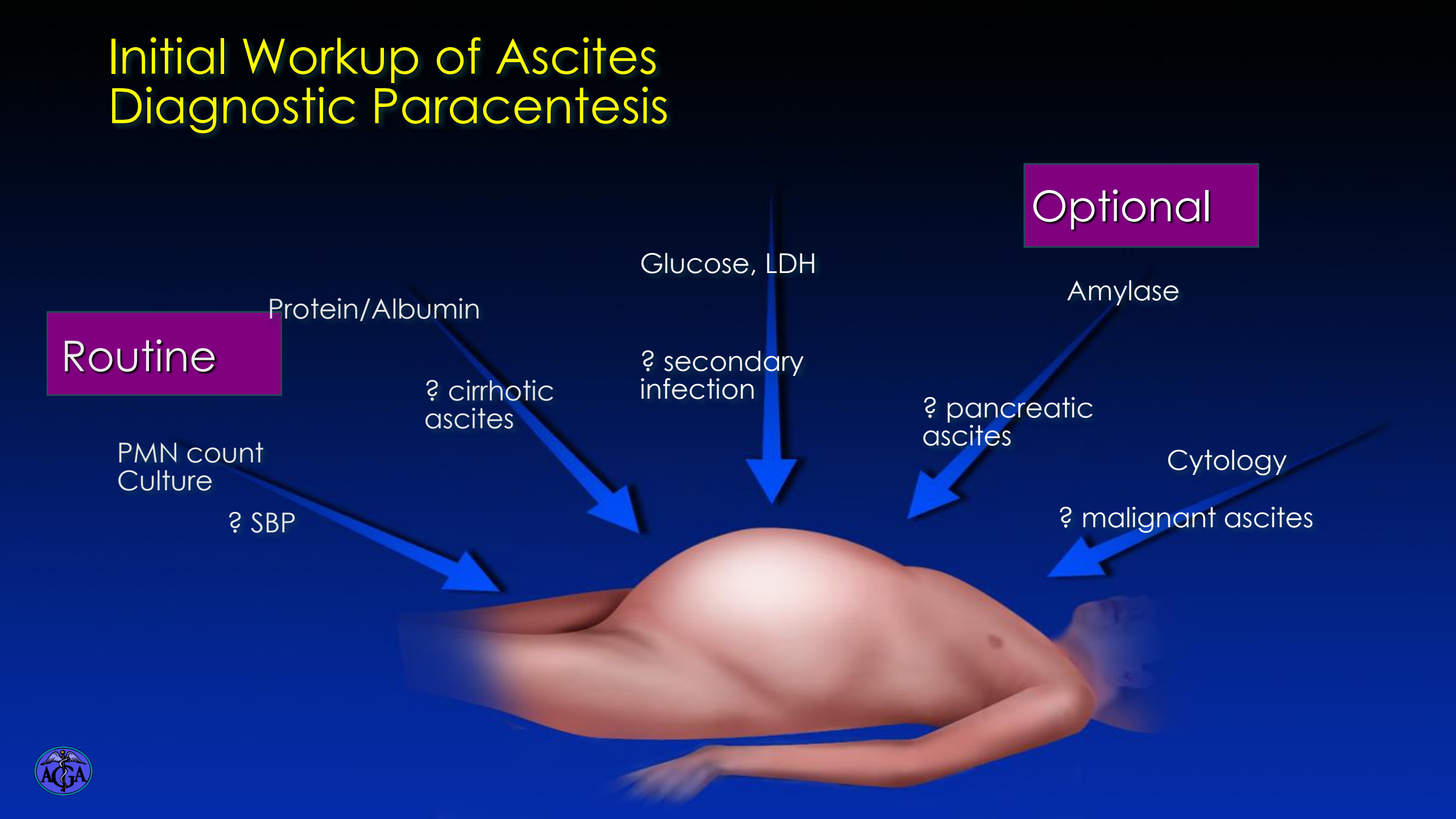
Ascites

- 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



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

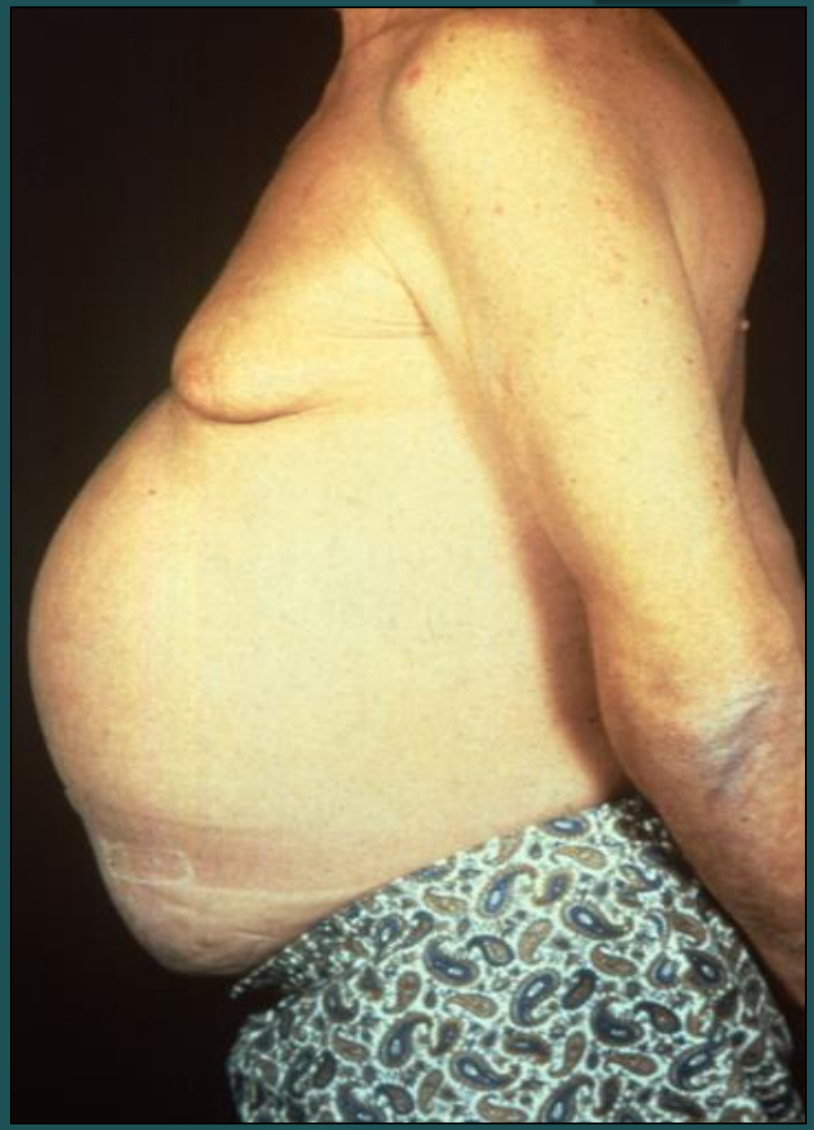
Diagnostic Paracentesis

Indications

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

Contraindications

- None



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

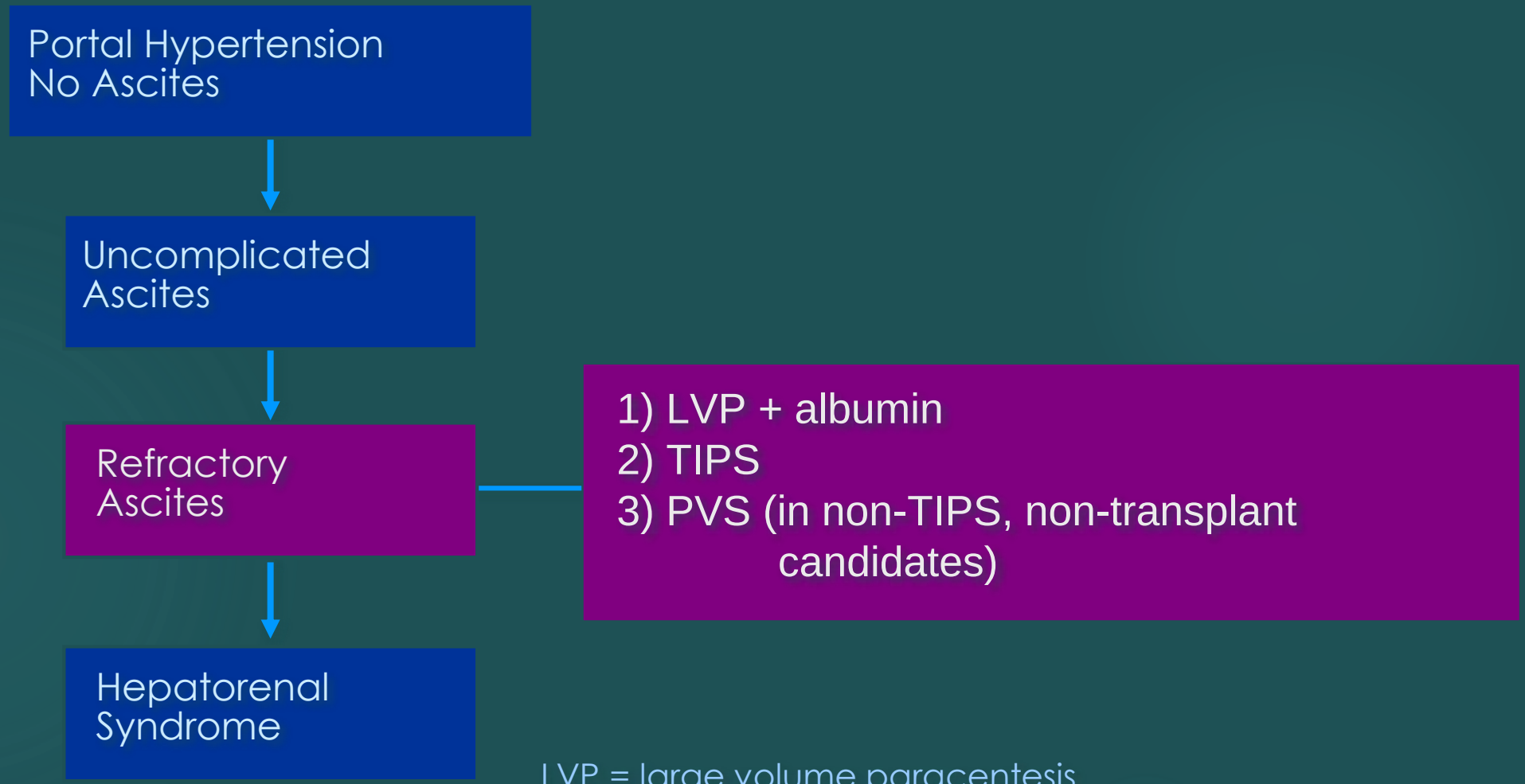
- Side effects
  - Renal dysfunction, hyponatremia, hyperkalemia, encephalopathy, gynecomastia

Difficult to Treat Ascites
Occurs in ~10% of cirrhotic patients

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

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

Treatment of Ascites



LVP = large volume paracentesis
TIPS = transjugular intrahepatic portosystemic shunt

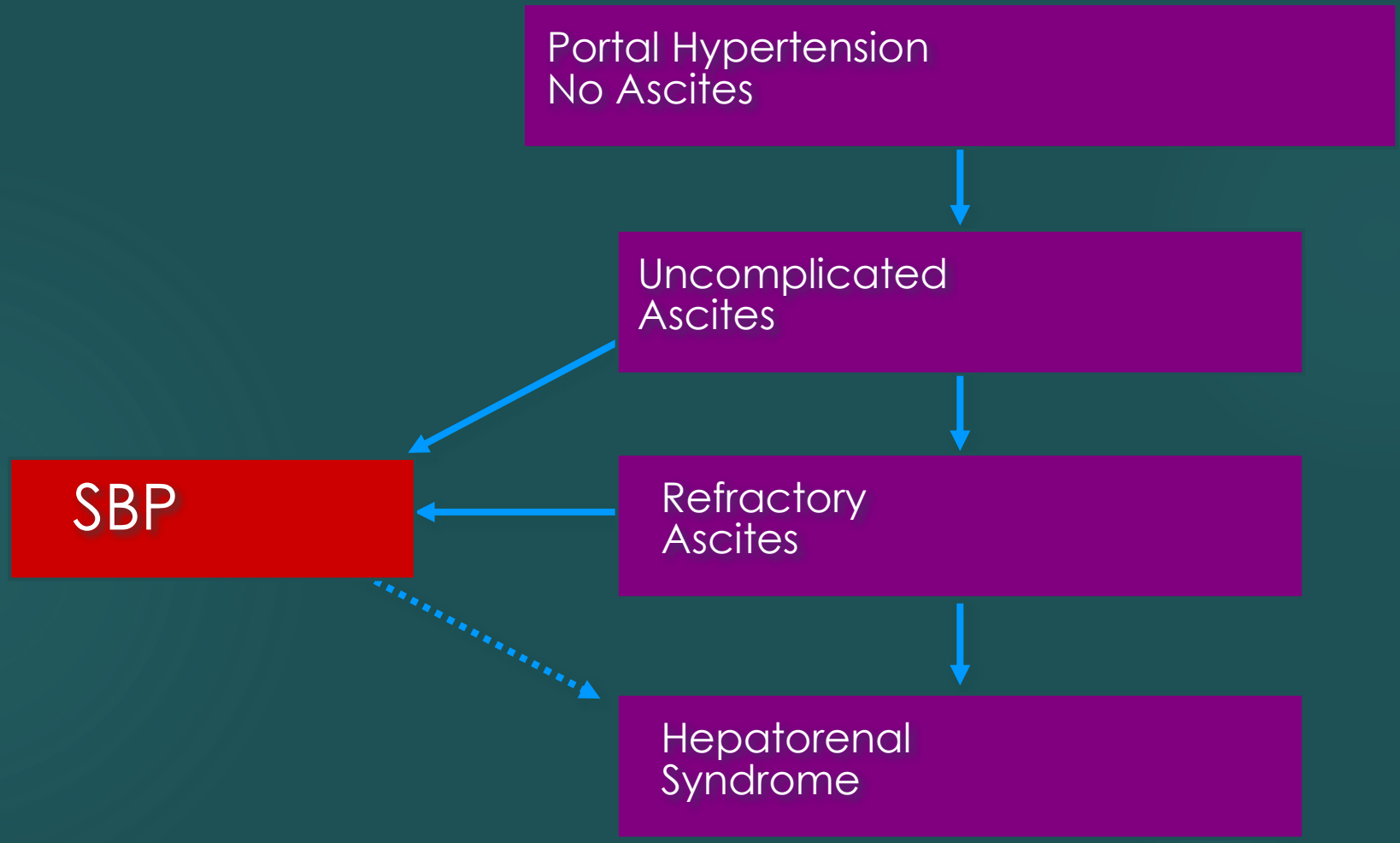
Ascites Related Complications

- Spontaneous Bacterial Peritonitis
- Hepatorenal Syndrome
- Hepatic Hydrothorax

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. cefotaxime, amoxicillin-clavulanic acid
  - oral nofloxacin (uncomplicated SBP)
  - 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

Hepatorenal Syndrome

- Development of acute renal failure in a patient with cirrhosis or fulminant hepatic failure
  - End stage of a sequence of events that reduces perfusion of kidneys
- Clinical presentation
  - Oliguiria
  - Low urine sodium (often undetectable)
  - Bland urine sediment
  - Systemic hypotension
  - Absence of another cause of renal failure

Characteristics of Hepatorenal Syndrome

- Renal failure in patients with cirrhosis, advanced liver failure and severe sinusoidal portal hypertension
- Absence of significant histological changes in the kidney ("functional" renal failure)
- Marked arteriolar vasodilation in the extra-renal circulation
- Marked renal vasoconstriction leading to reduced glomerular filtration rate

Two Types of Hepatorenal Syndrome

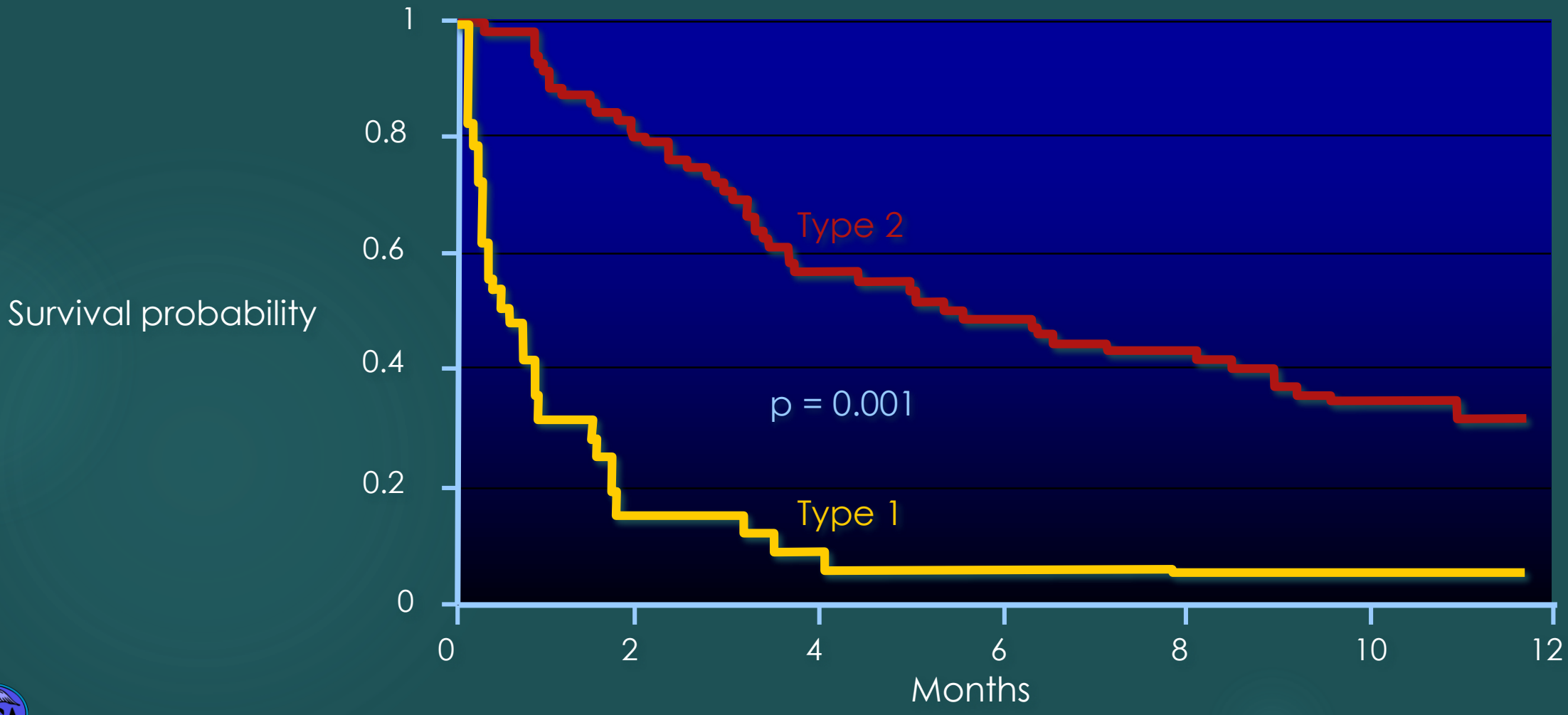
Type 1

- Rapidly progressive renal failure (2 weeks)
- Doubling of creatinine to >2.5 decrease of creatinine clearance (CrCl) to <20 ml/min

Type 2

- More slowly progressive
- Creatinine >1.5 mg/dL or CrCl < 40 ml/min
- Associated with refractory ascites

Survival in Different Types of Hepatorenal Syndrome (HRS)



Major Criteria in the Diagnosis of Hepatorenal Syndrome

- Advanced hepatic failure and portal hypertension
- Creatinine > 1.5 mg/dL or creatinine clearance < 40 ml/min
- Absence of shock, bacterial infection, or nephrotoxic drugs
- Absence of excessive gastrointestinal or renal fluid loss
- No improvement in renal function after plasma volume expansion with 1.5 L of isotonic saline
- Urinary protein < 500 mg/dL and normal renal ultrasound

Management of Hepatorenal Syndrome

Proven efficacy

- Liver transplantation

Under investigation

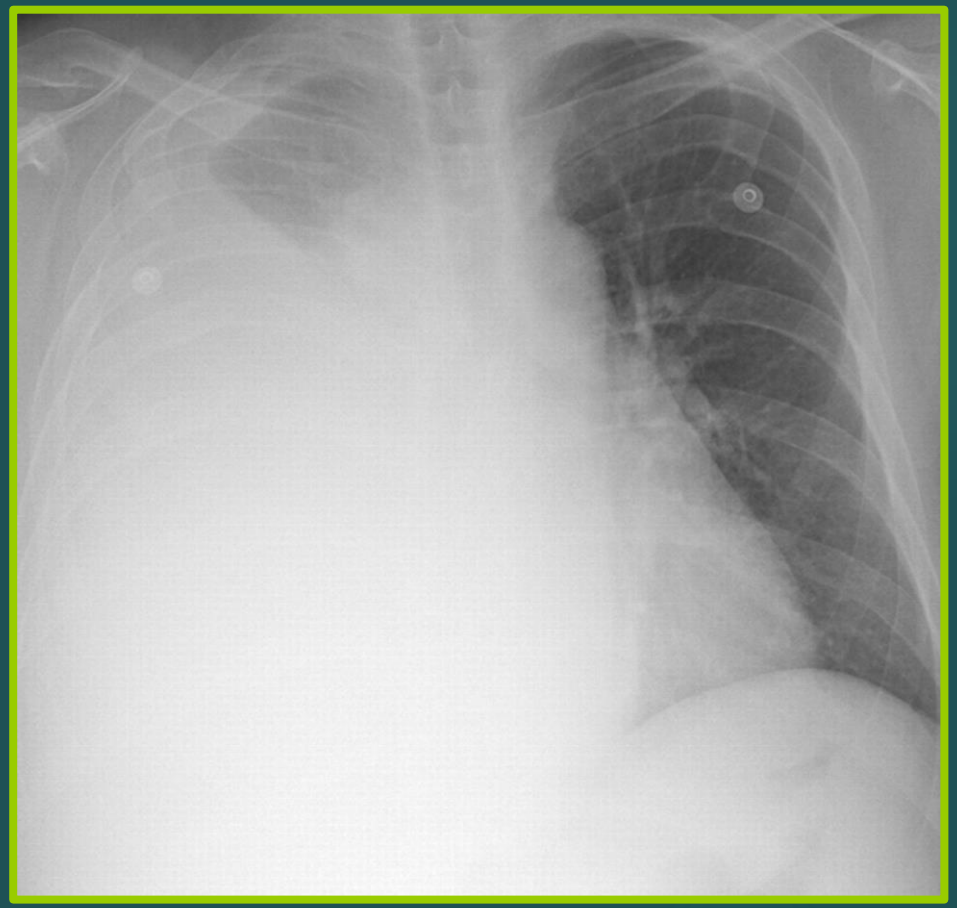
- Vasoconstrictor + albumin
- Transjugular intrahepatic portosystemic shunt (TIPS)
- Vasoconstrictor + TIPS
- Extracorporeal albumin dialysis (ECAD)

Ineffective

- Renal vasodilators (prostaglandin, dopamine)
- Hemodialysis

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.



Hepatic Hydrothorax

- Treatment:
  - Diuretics
  - Sodium restriction
  - TIPS
  - Avoid chest tubes
  - Avoid pleurodesis

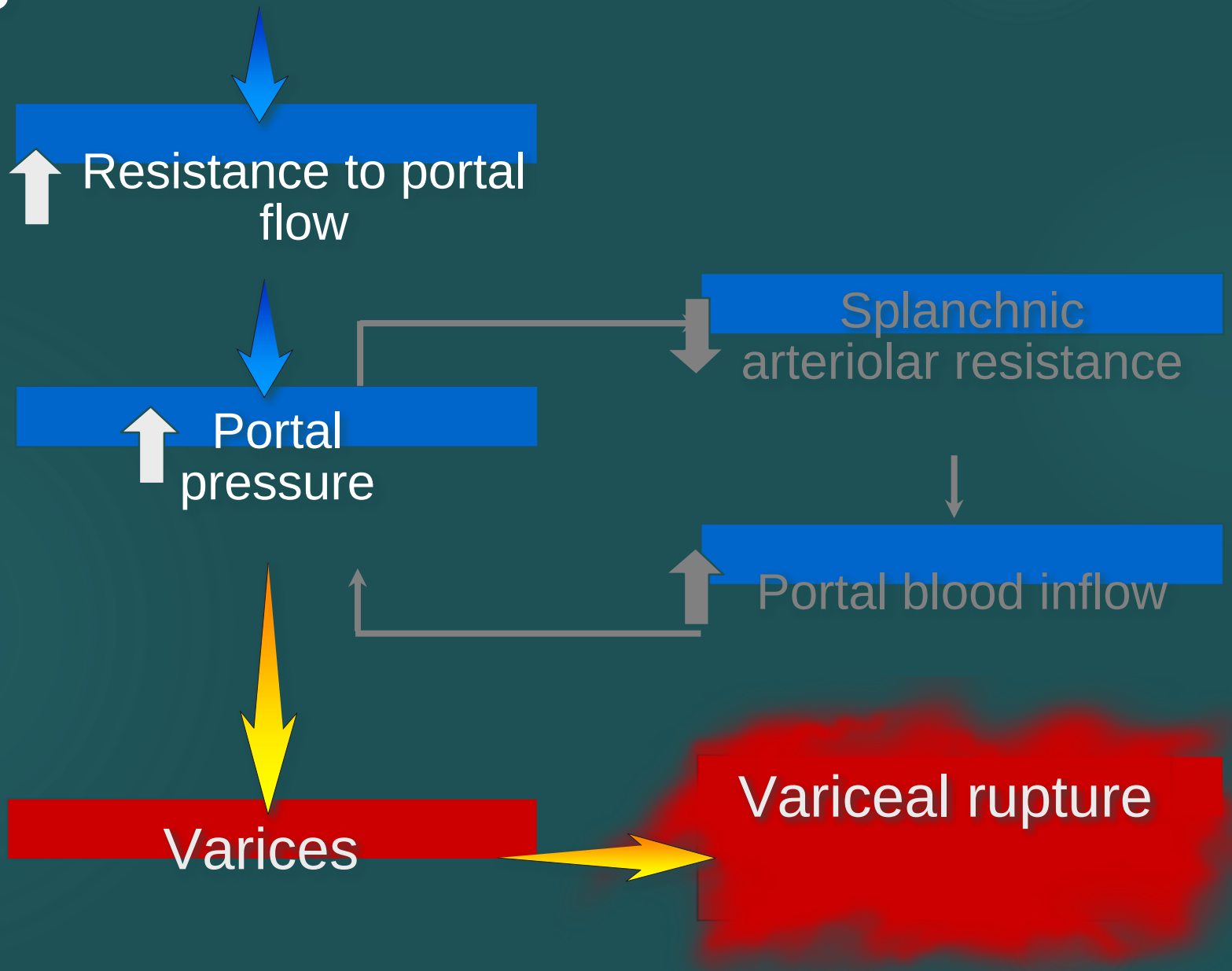
Variceal Hemorrhage

- 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

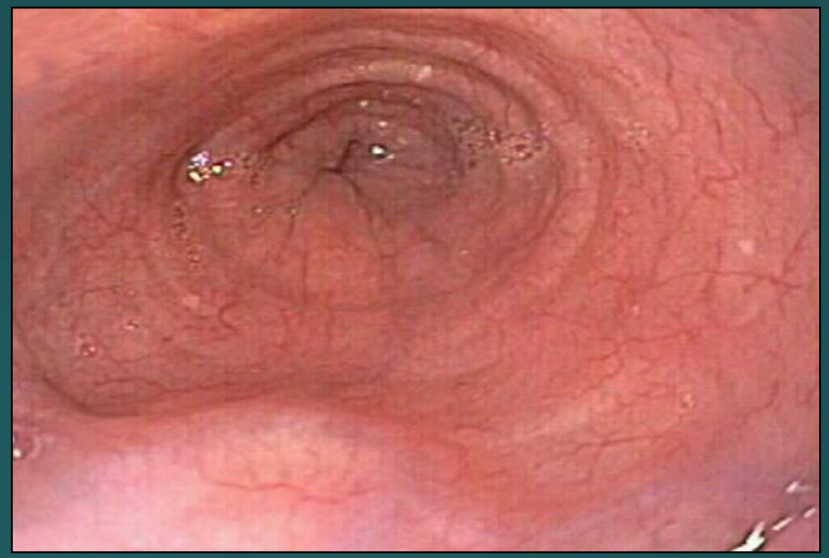
Variceal Hemorrhage

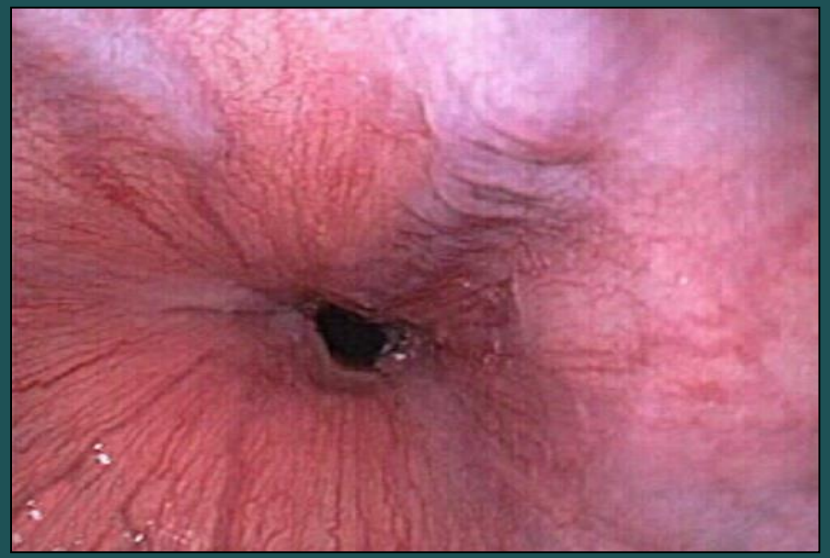
- Increase in portal pressure
  - Hepatic vein pressure gradient HVPG has to be above 10 mmHg for the formation of varices
- With time varices grow and their walls become thinner, until they finally break and bleed (wall tension)
- Most common site is gastro-esophageal junction area

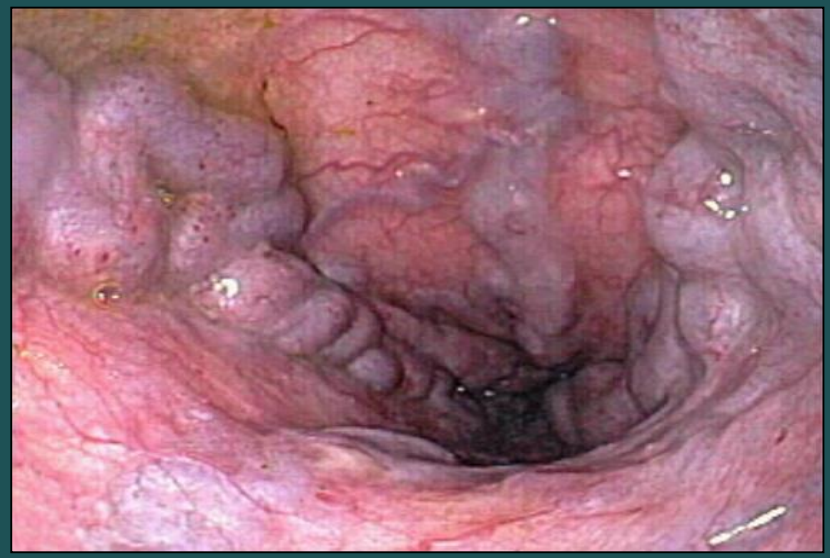
Cirrhosis


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

Varices Increase in Diameter Progressively







No varices

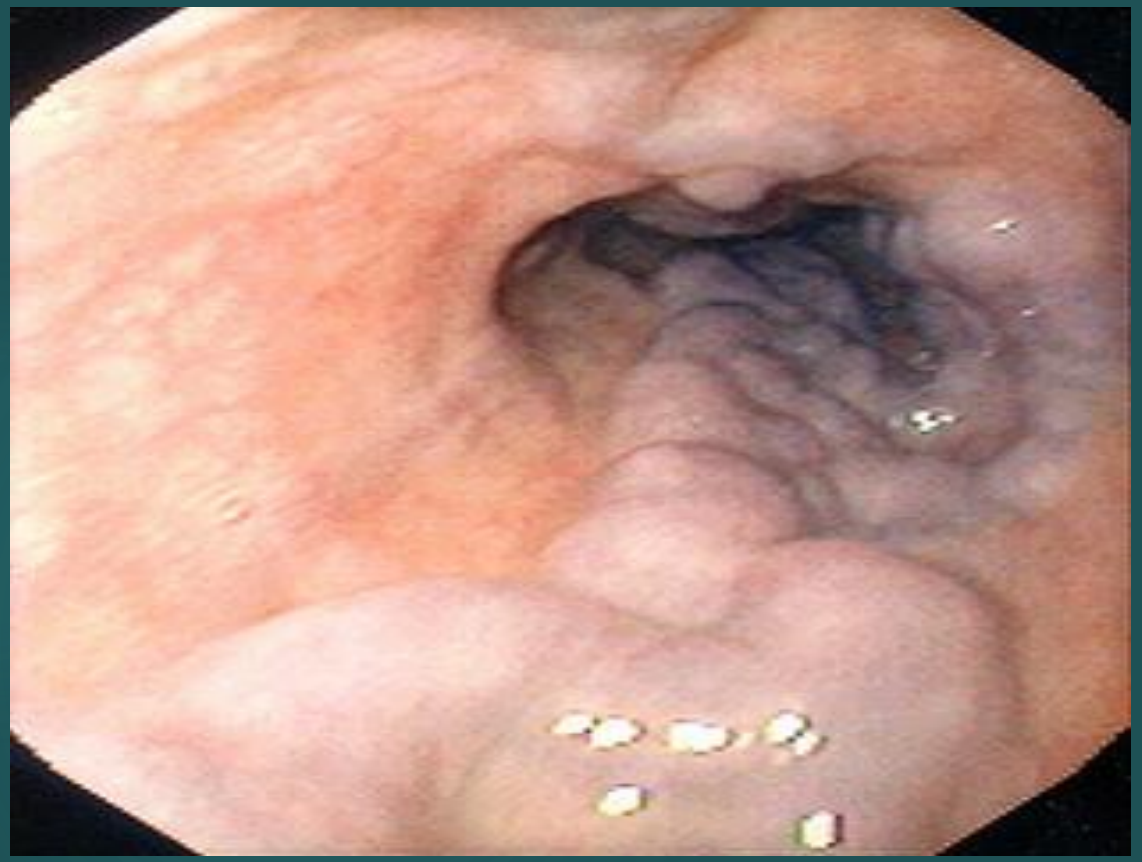
Small varices

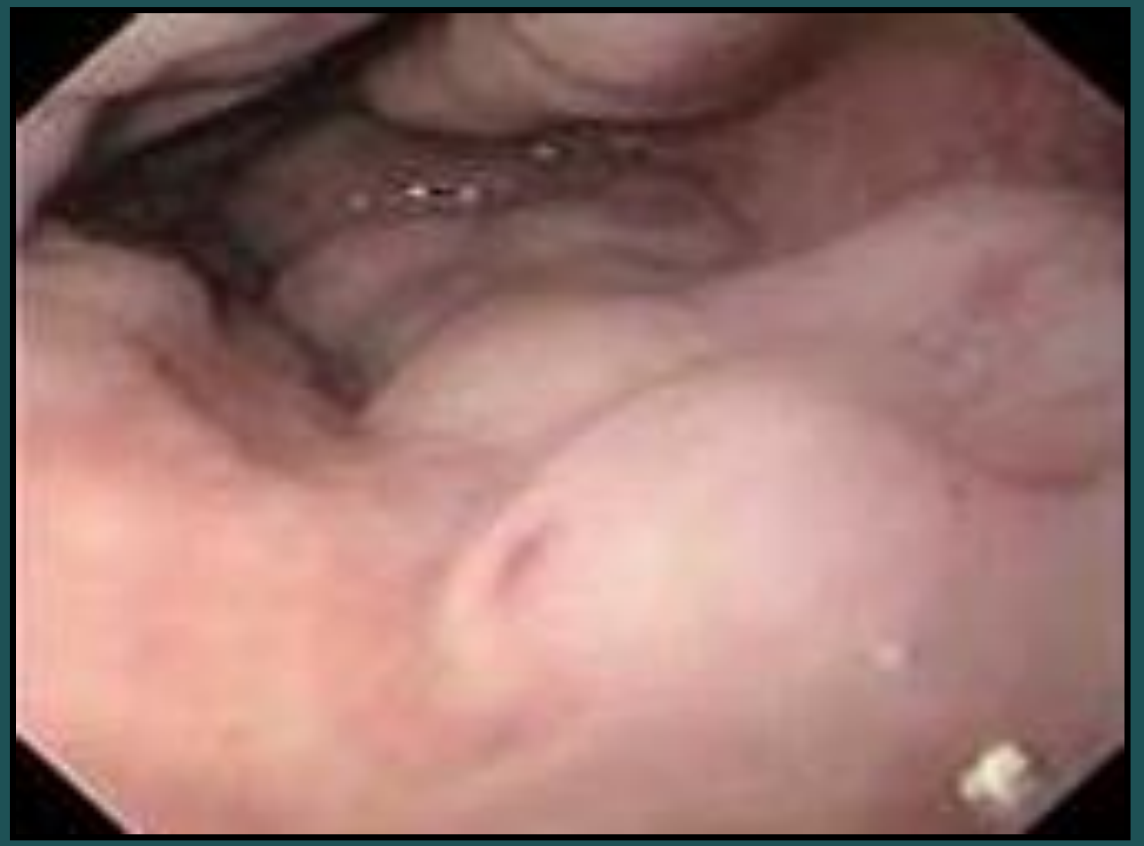
Large varices

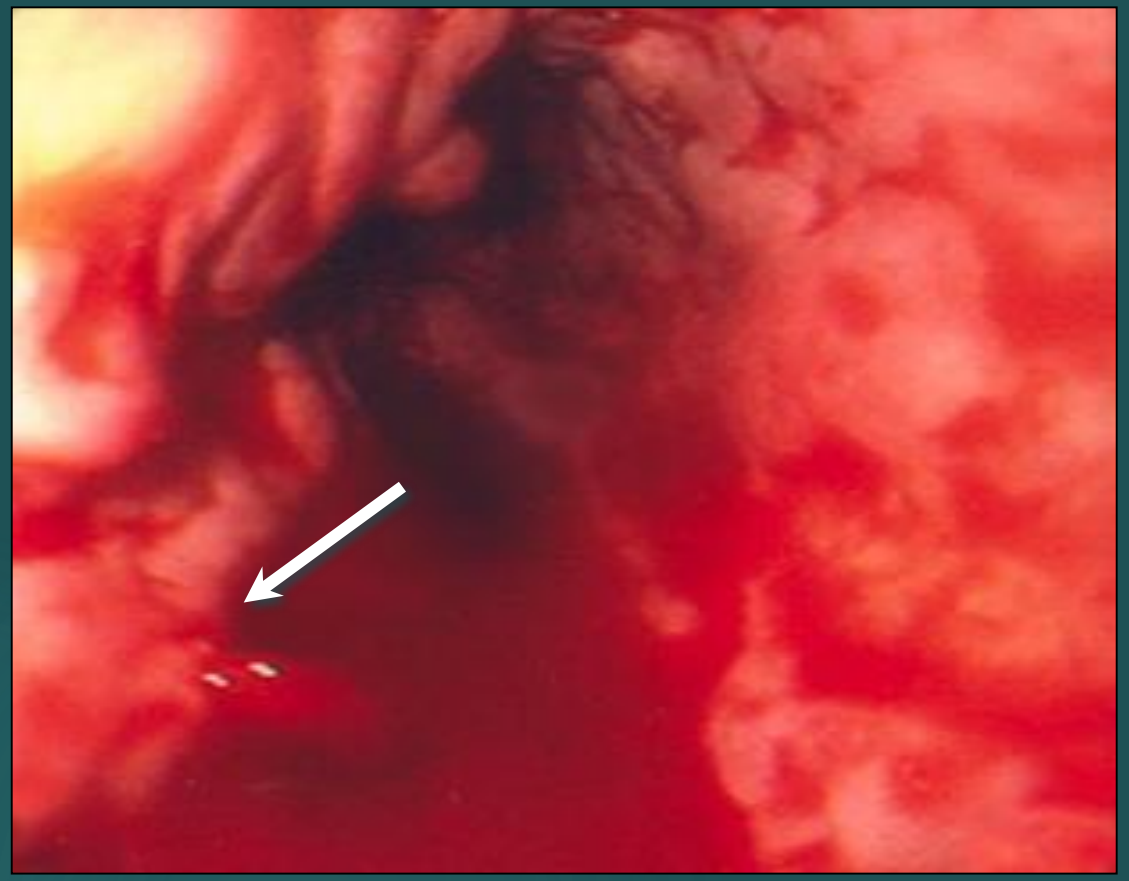
7-8%/year

7-8%/year

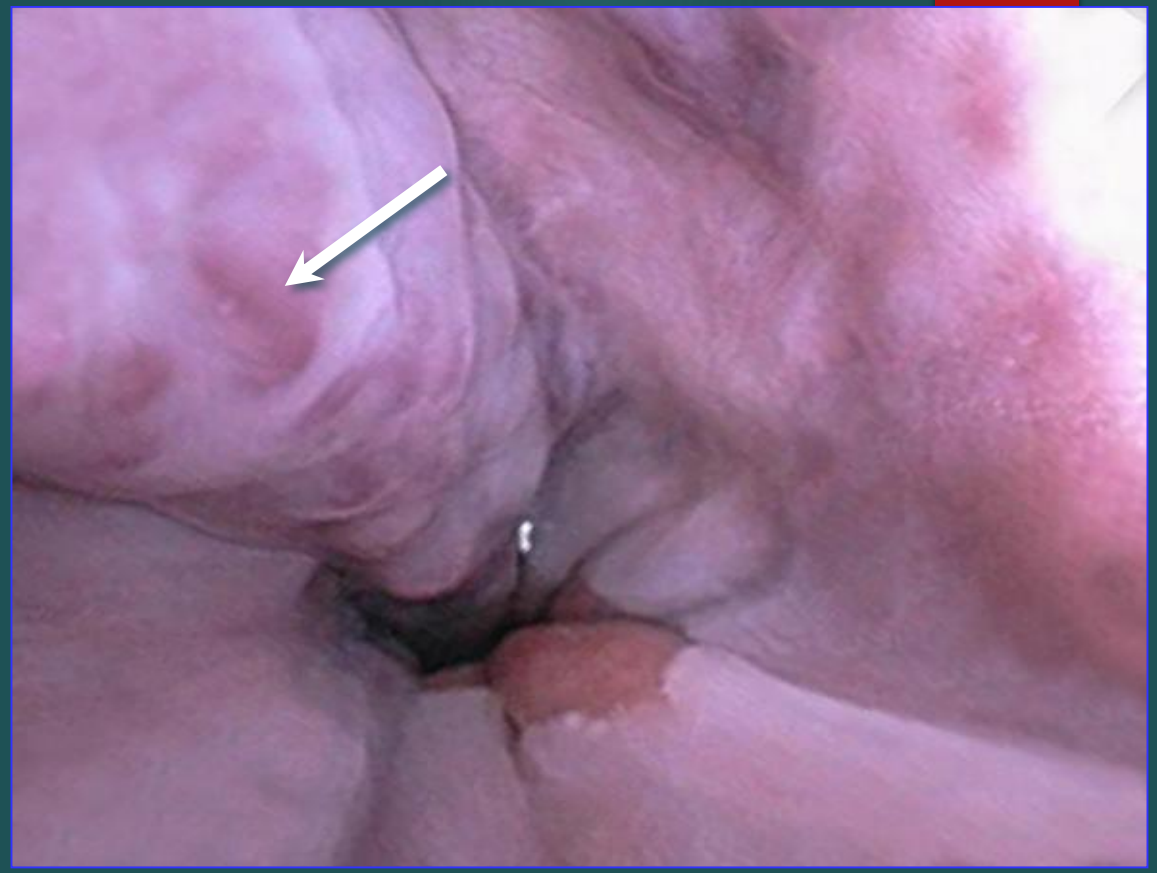
Variceal Hemorrhage







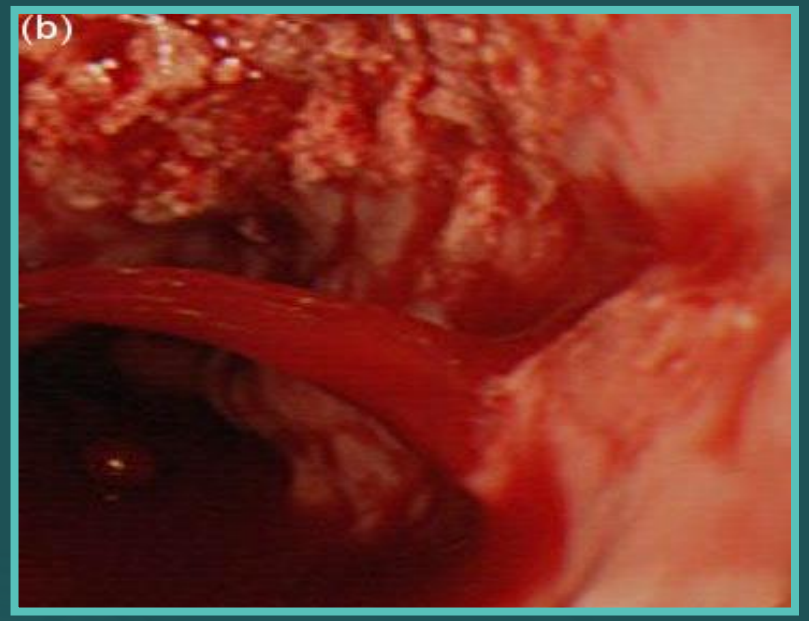
Variceal hemorrhage



Varix with red signs

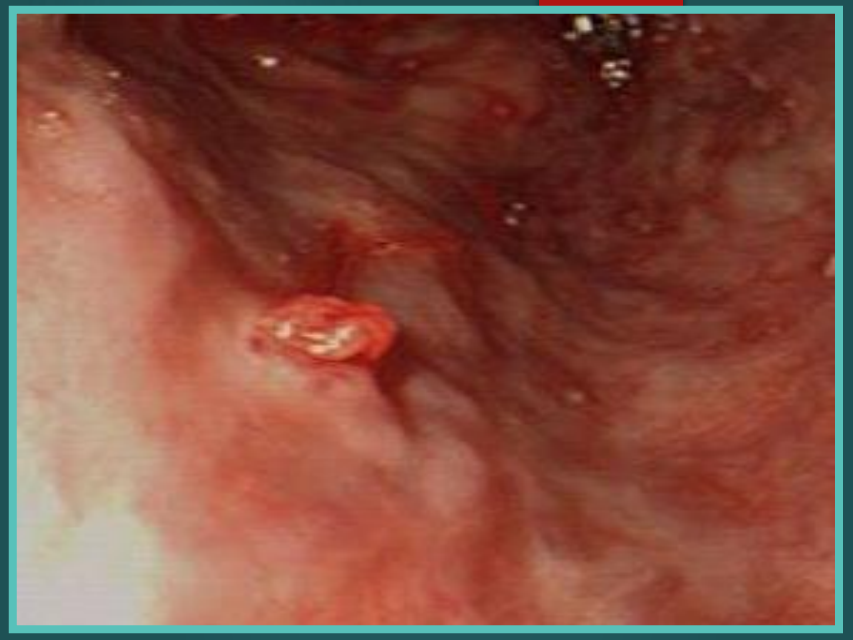
Predictors of hemorrhage:

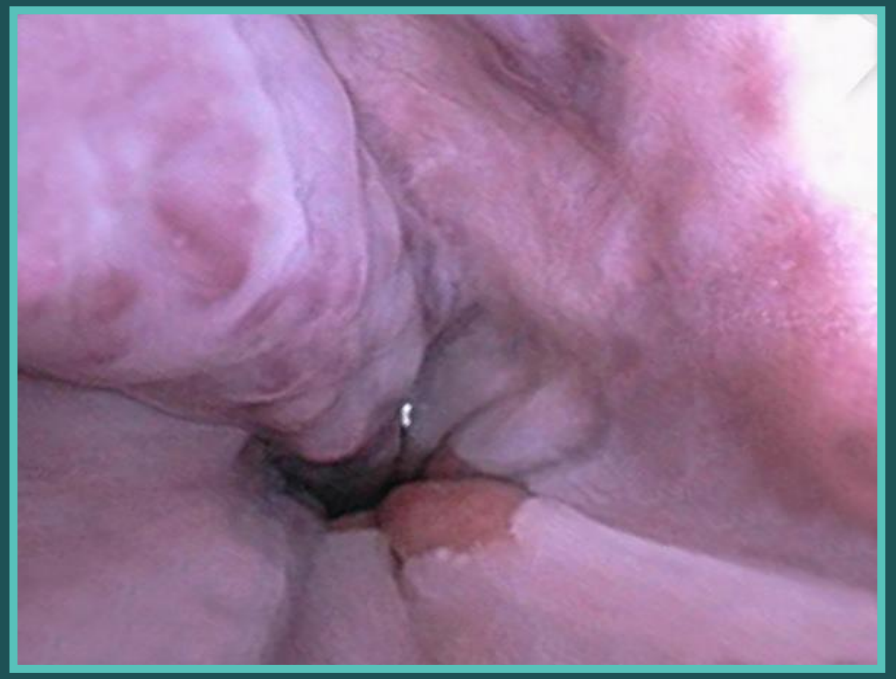
- Variceal size
- Red signs
- Child B/C



Variceal hemorrhage

Punctum





Varix with red wale sign

Variceal Hemorrhage

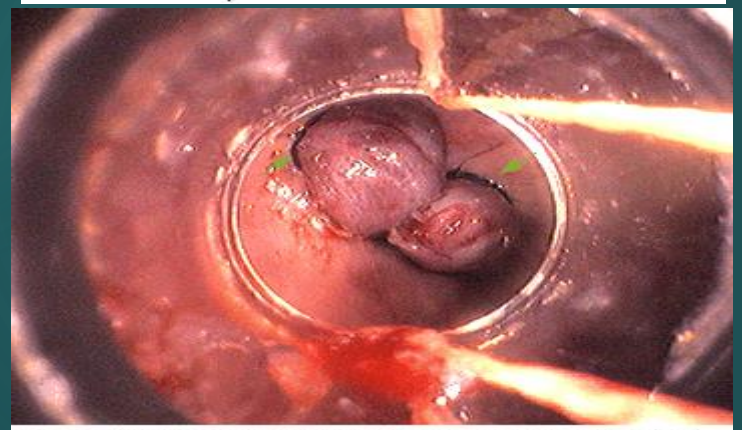
- Management of acute variceal bleeding
  - Control of bleeding
  - Prevent early re-bleeding
  - Correct and avoid concomitant complications
- Initial Management:
  - Airway, Breathing and Circulation
  - Intensive care unit setting
  - Placement of large bore IV lines
  - Blood products

Variceal Hemorrhage

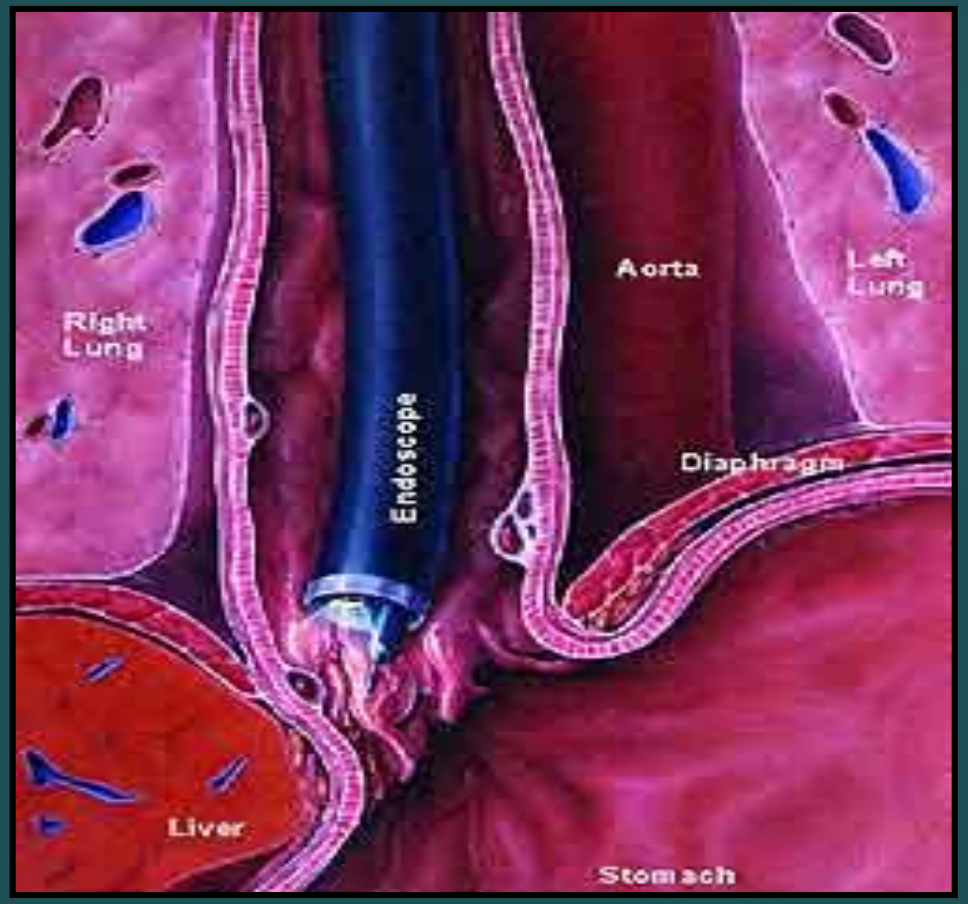
- Therapy for control of bleeding
  - Vasoactive drug therapy
    - Selection of drug mainly depends on availability
    - Octreotide, somatostatin, telipressin
- Endoscopic band ligation is the endoscopic therapy of choice over sclerotherapy in acute variceal bleeding
- Rescue therapies
  - Balloon 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.



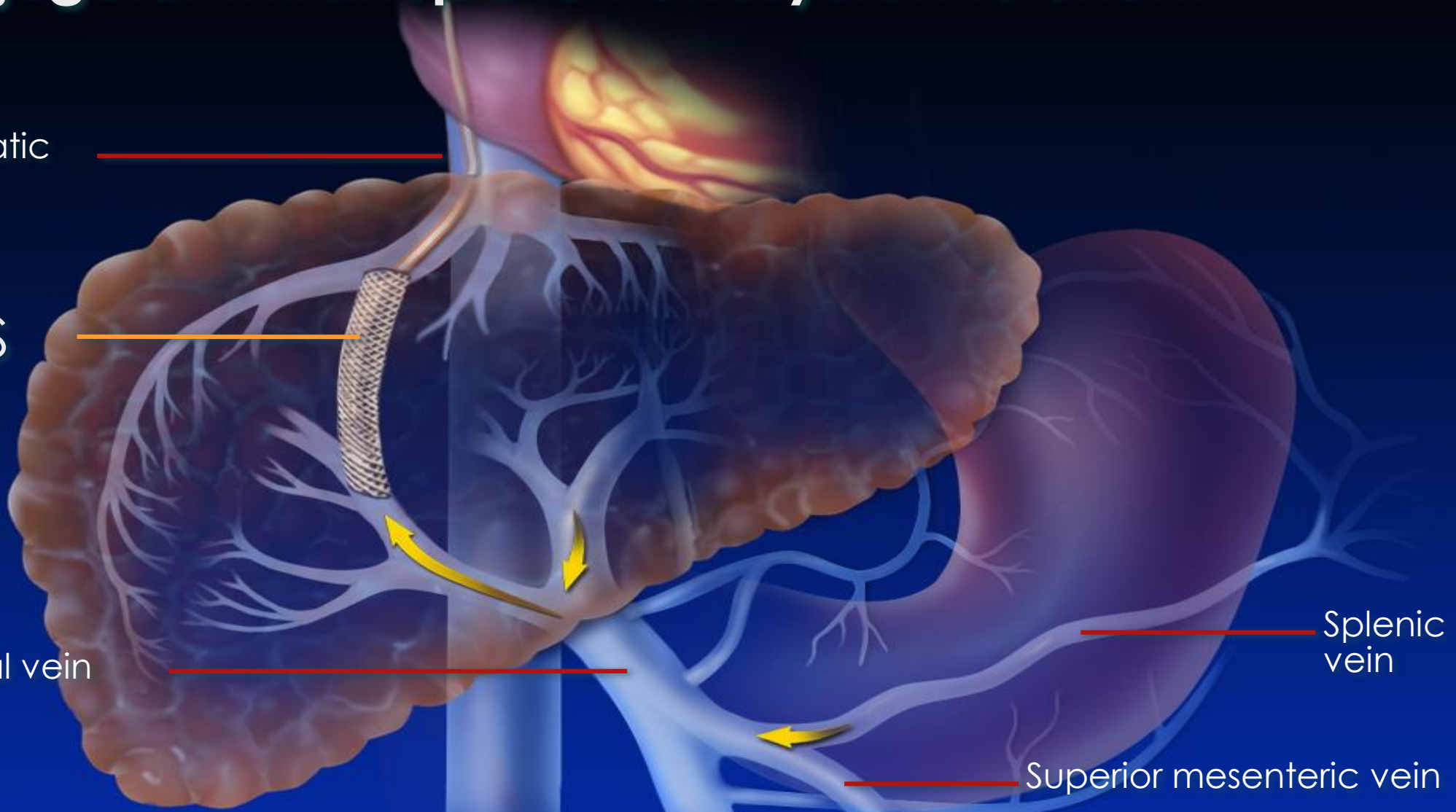
Esophageal varix band ligation Endoscopy shows two varices in the distal esophagus that have been banded. The bands are indicated with the green arrows. The two strings in the right of the field control the trigger device used to deploy the bands. Courtesy of Laurence Bailen, MD.



Endoscopic Variceal Band Ligation

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

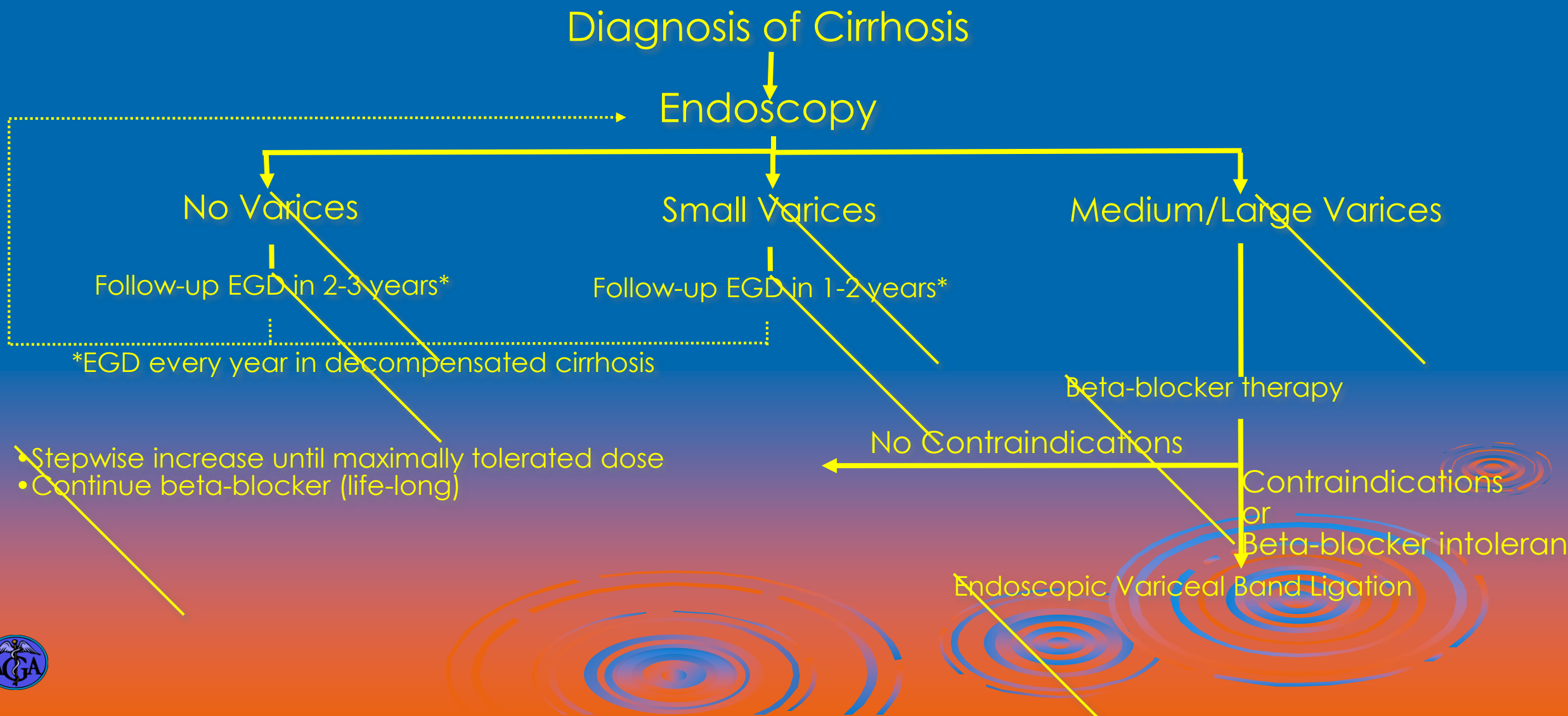
Transjugular Intrahepatic Portosystemic Shunt



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

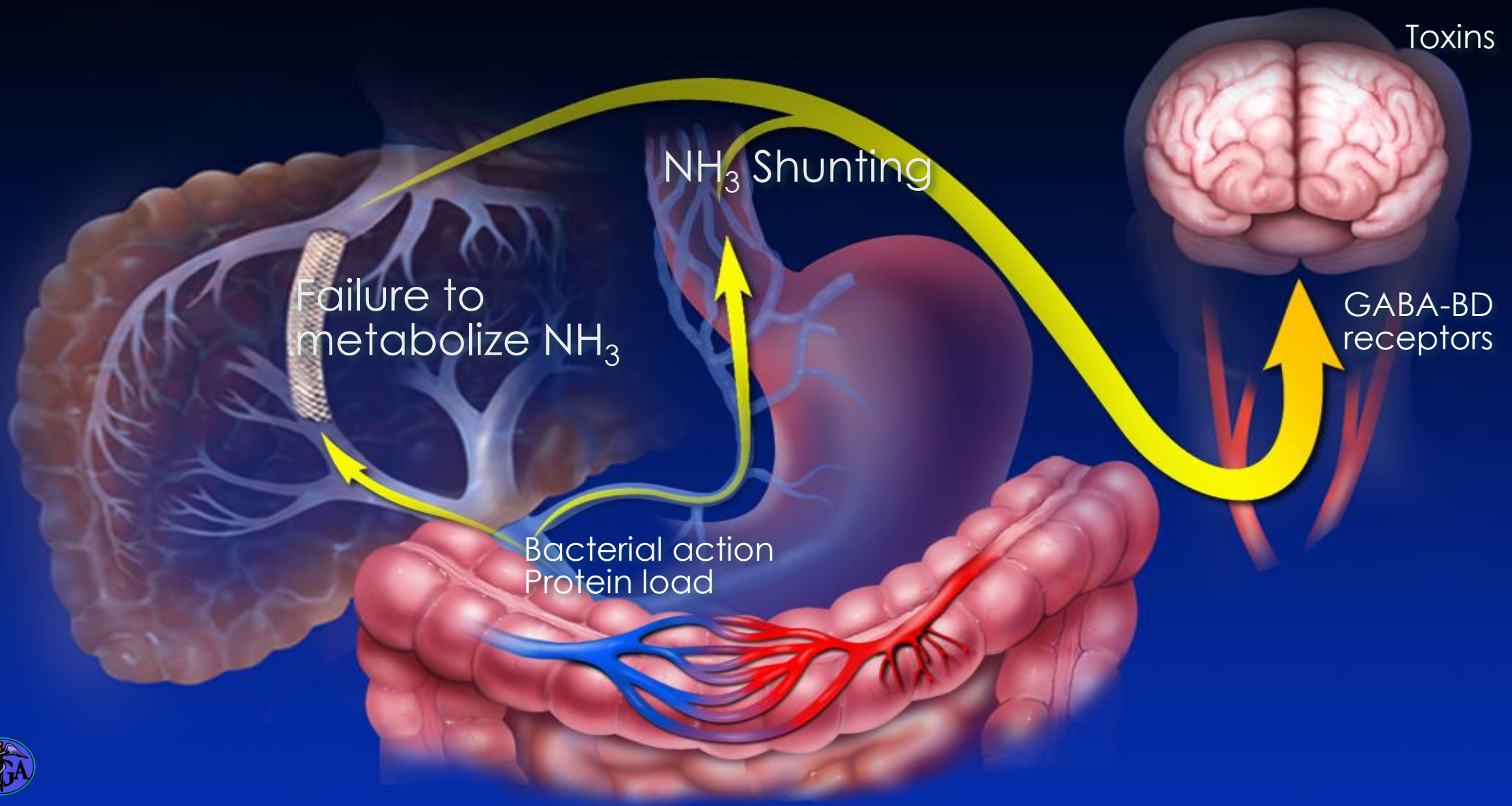
Hepatic Encephalopathy

- 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

- Failure of liver to detoxify noxious agents
- Stages:

  I Mental status changes

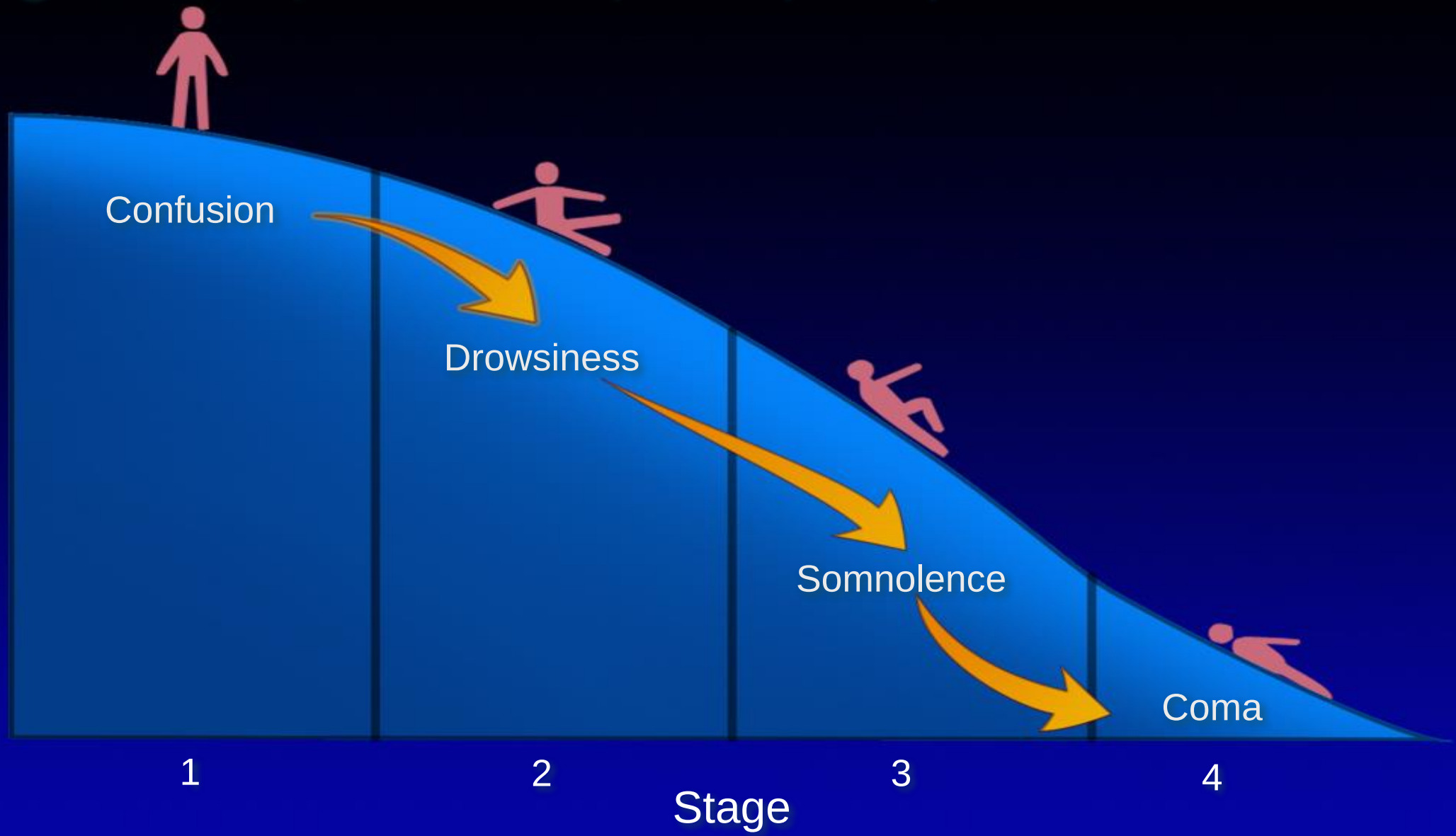
  II Lethargy and confusion

  III Stupor, but arousable

  IV Coma

- Symptoms and Signs
  - Fetor hepaticus
  - Asterixis
  - ↑ deep tendon reflexes
  - Unilateral or bilateral Babinski sign
  - Ataxia
  - Dysarthria
  - Tremors
  - Coma

Stages of Hepatic Encephalopathy



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

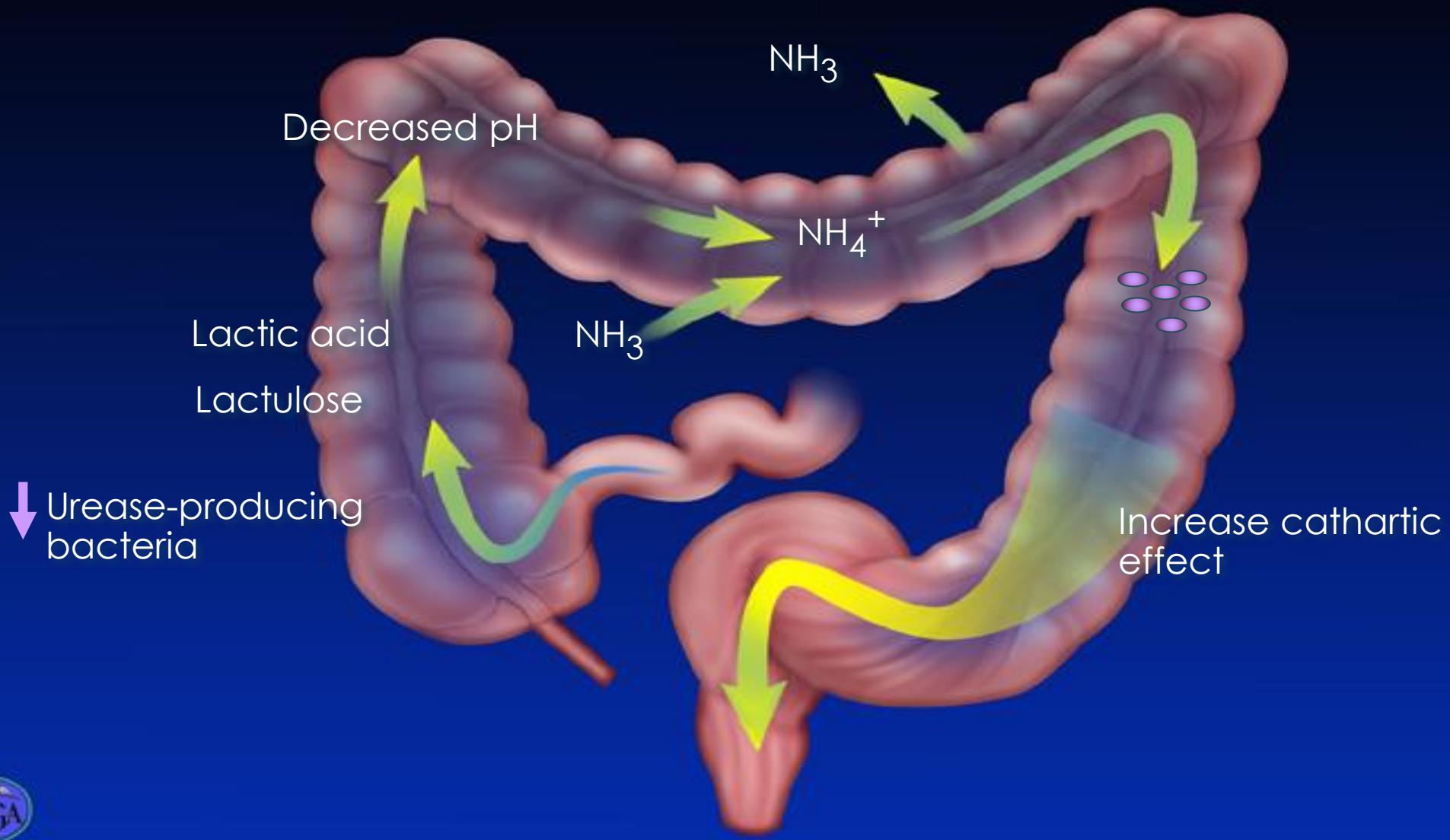
Treatment of Hepatic Encephalopathy

- 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

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

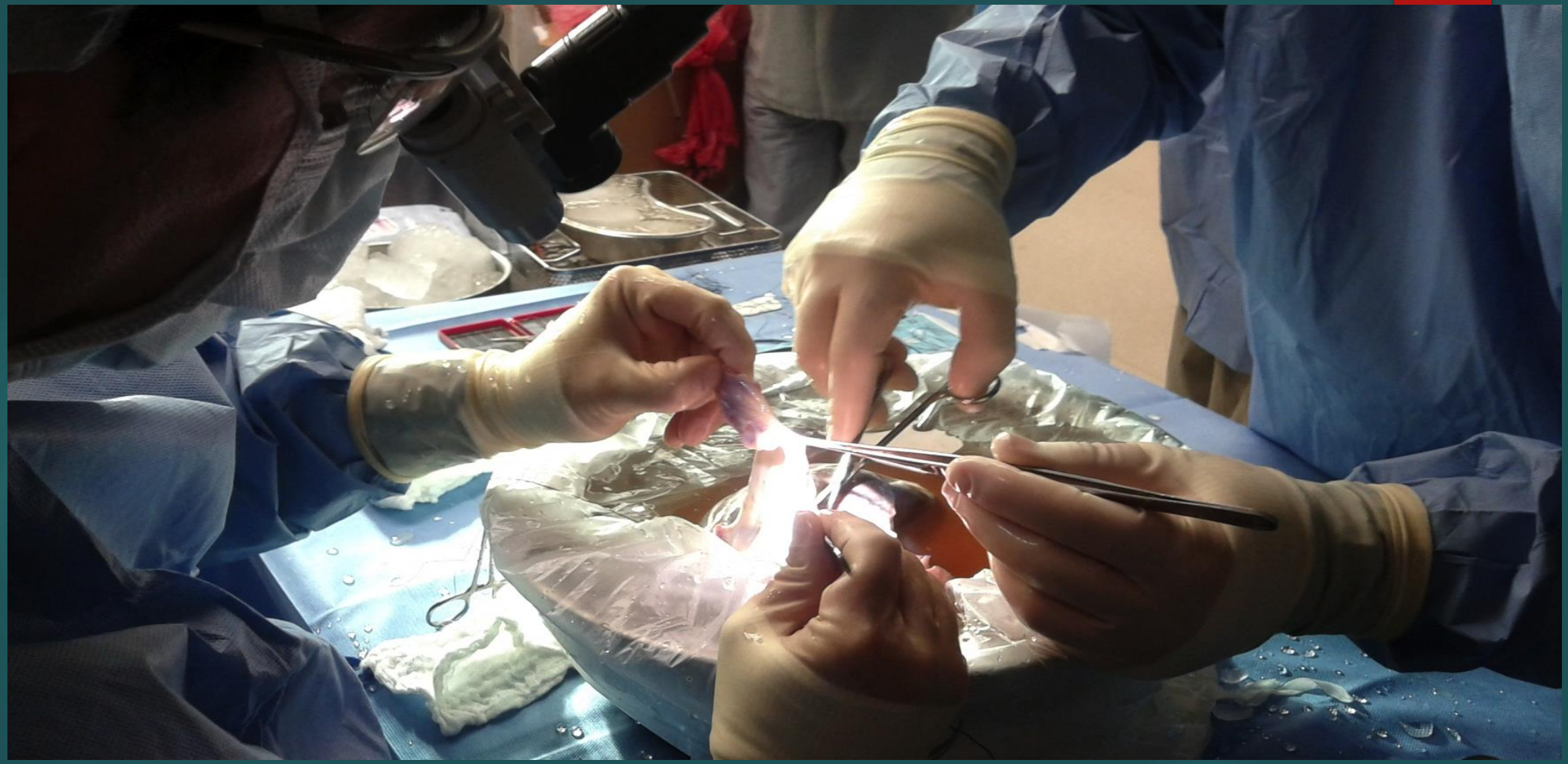
Actions of Lactulose

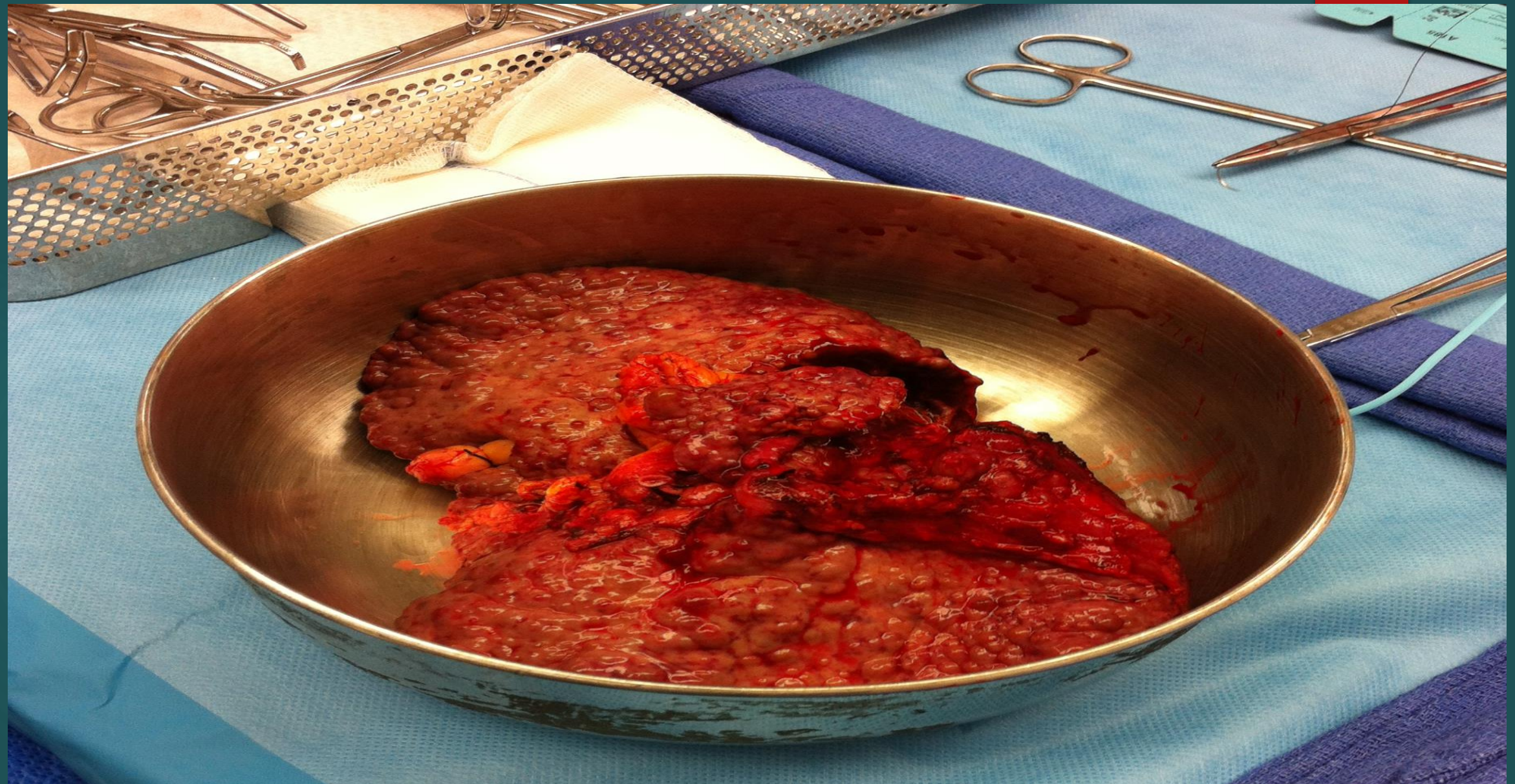


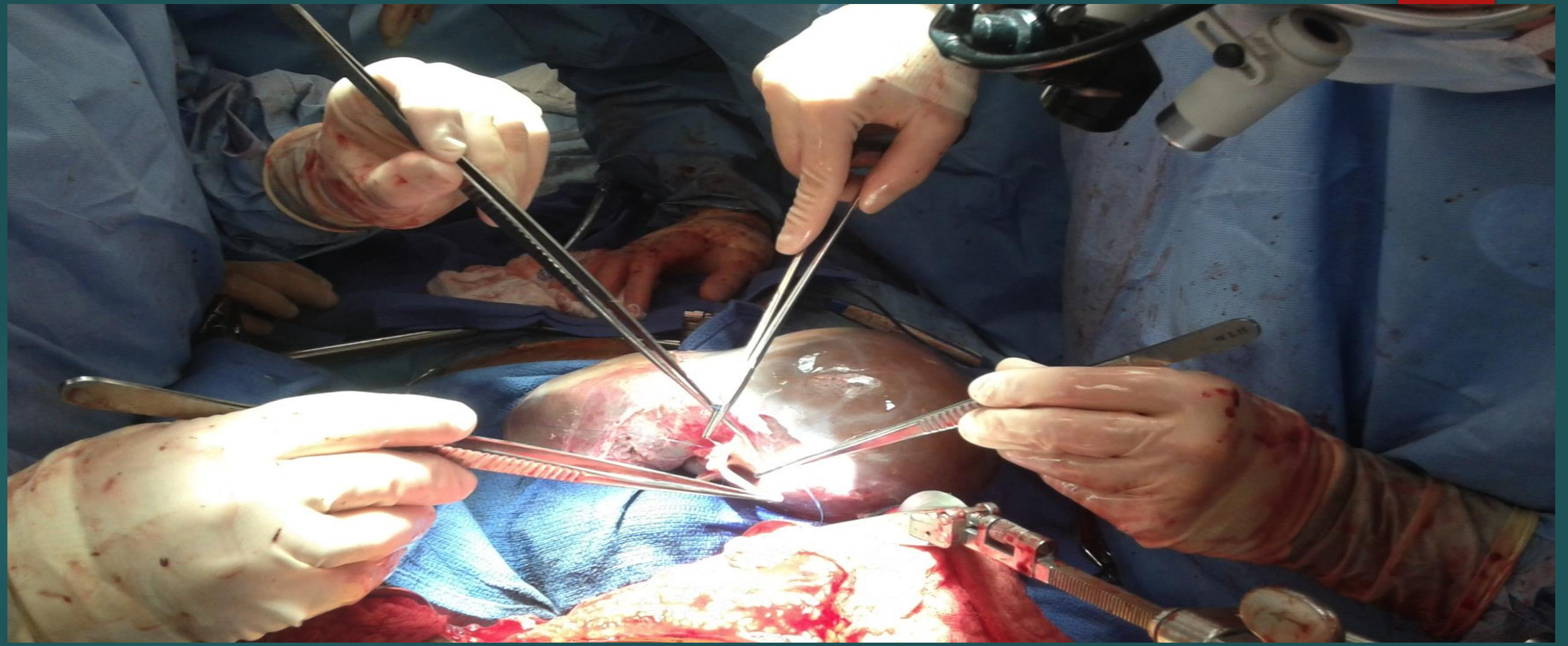
Multidisciplinary approach

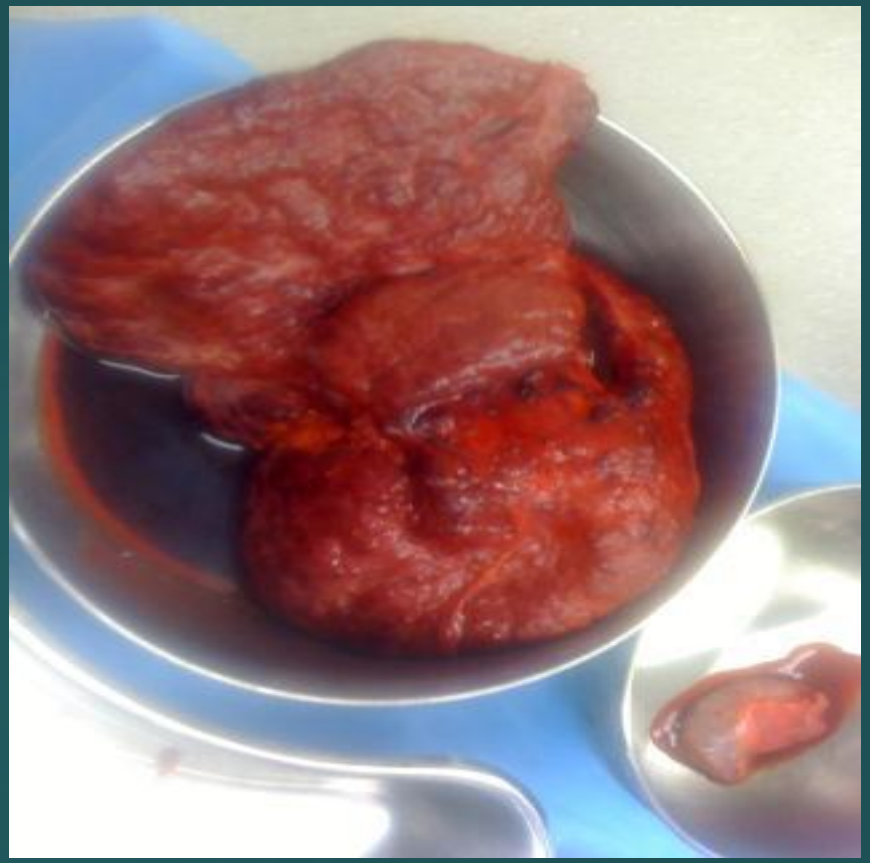
- Liver Transplantation Multidisciplinary Team
  - Surgeons
  - Hepatologists
  - Radiologists
  - Interventional Radiologists
  - Pathologist
  - Coordinators
  - Pharmacists
  - Nutritionists
  - Social Workers

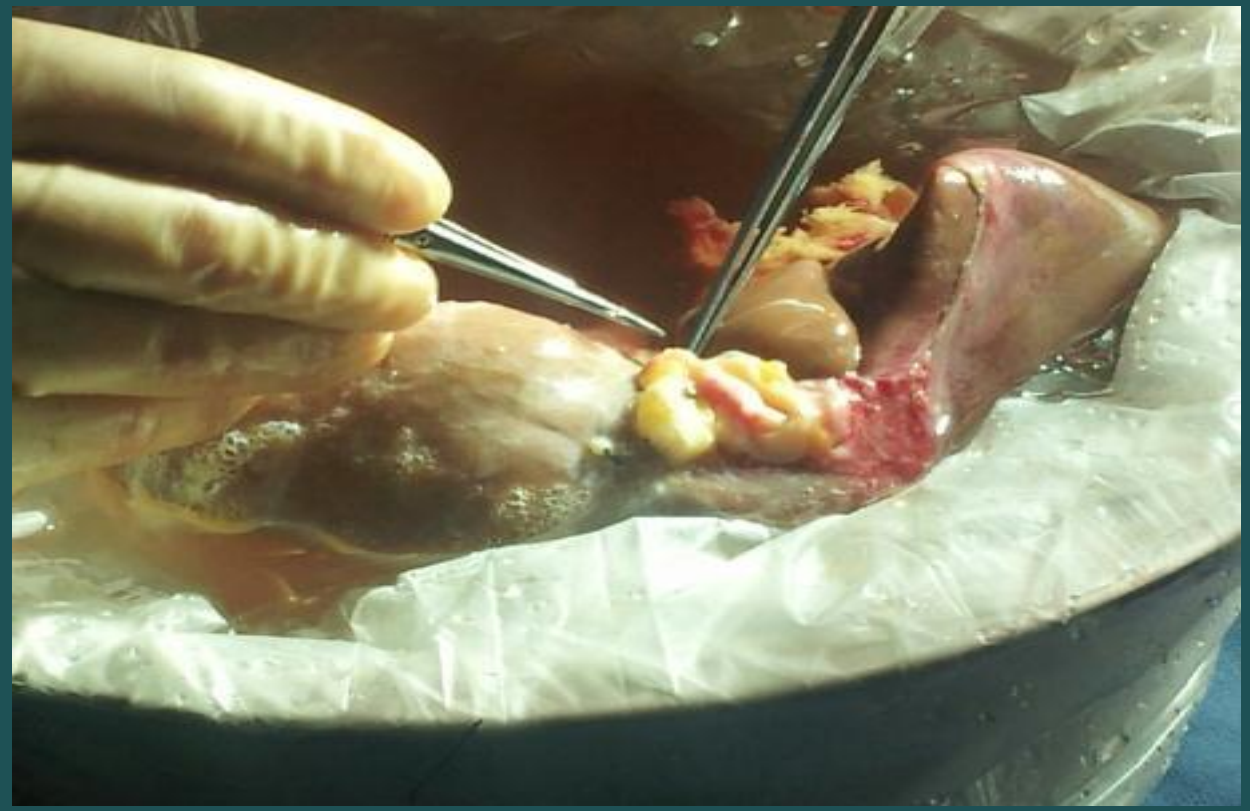
Liver Transplant Multidisciplinary team

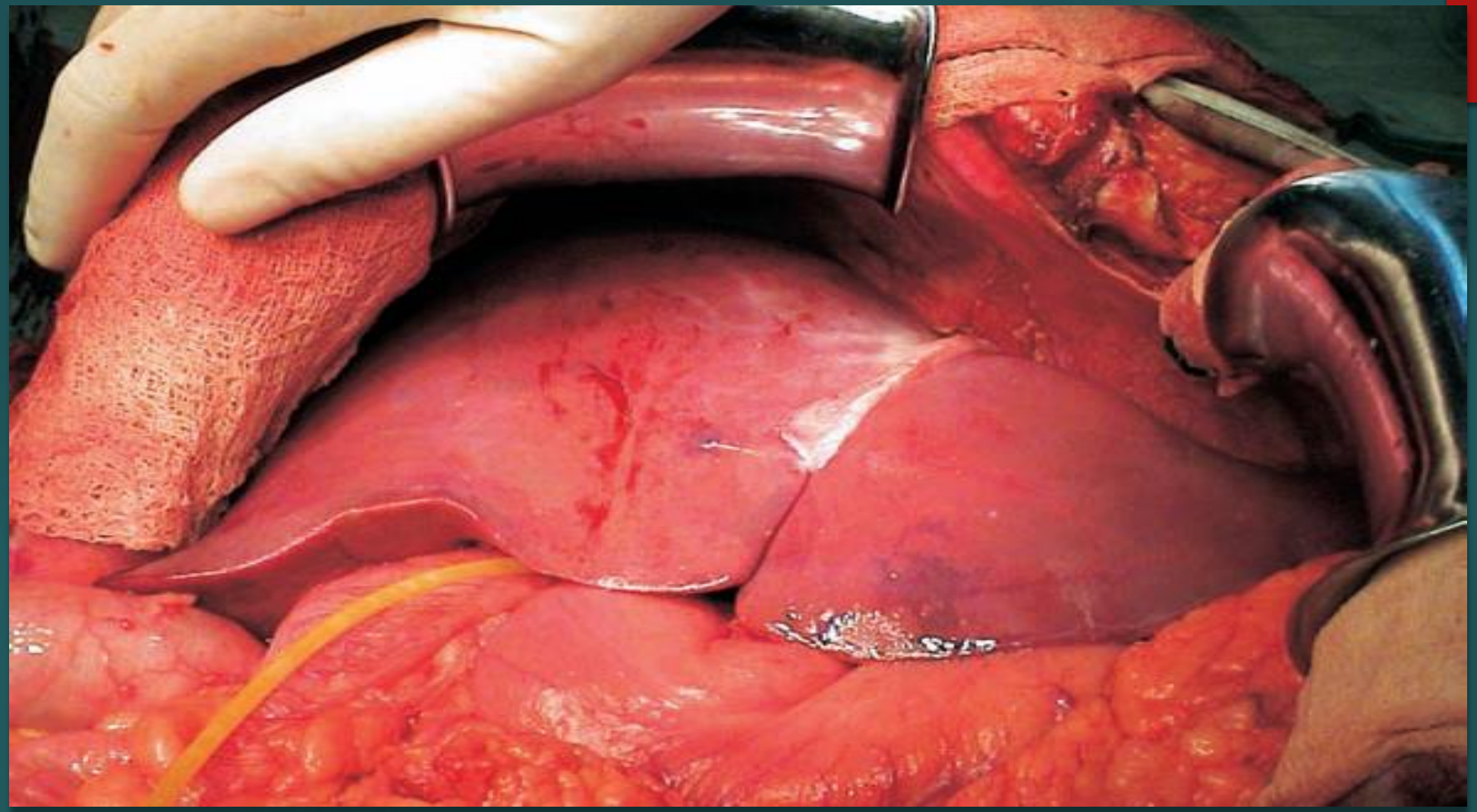


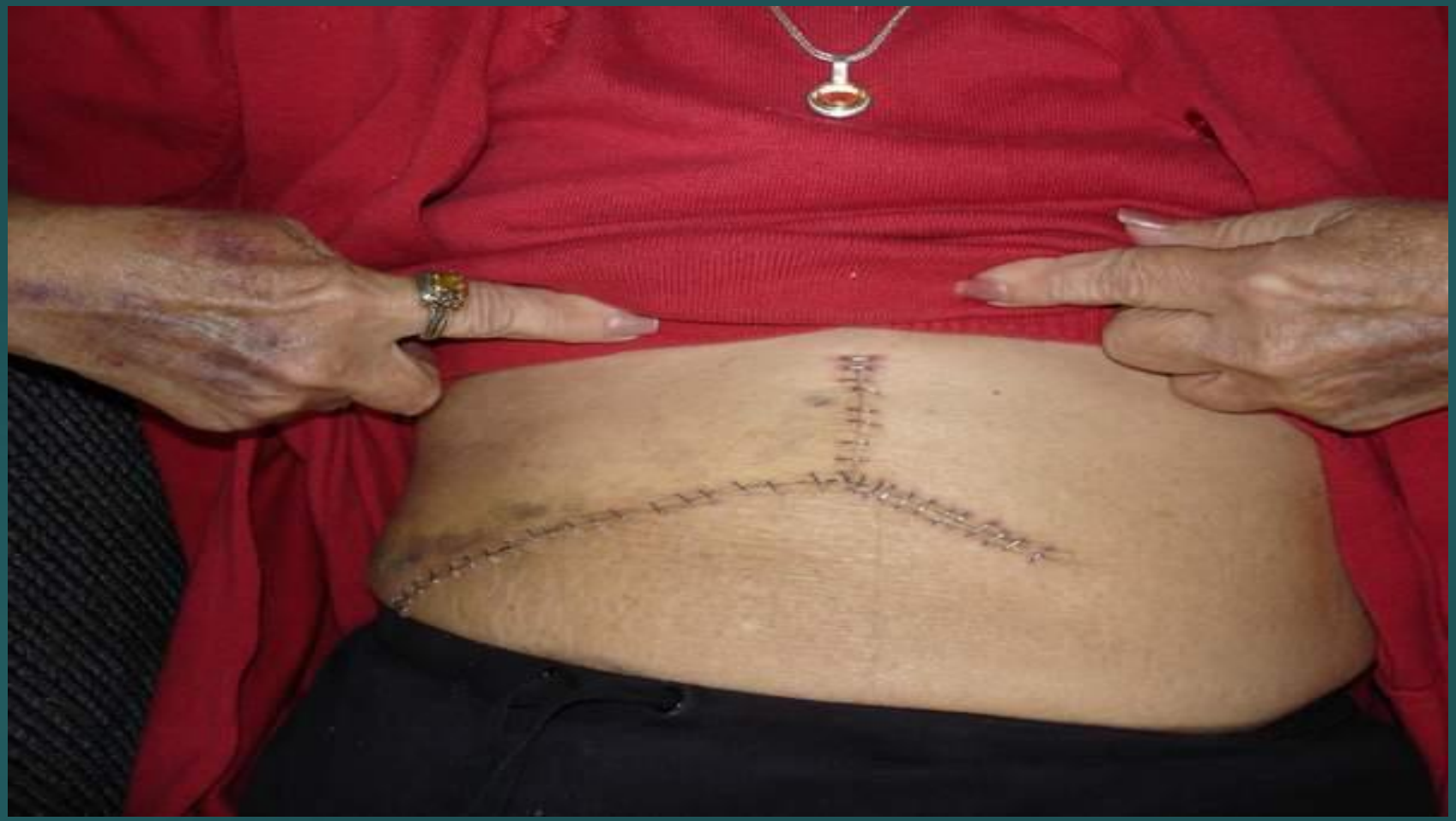


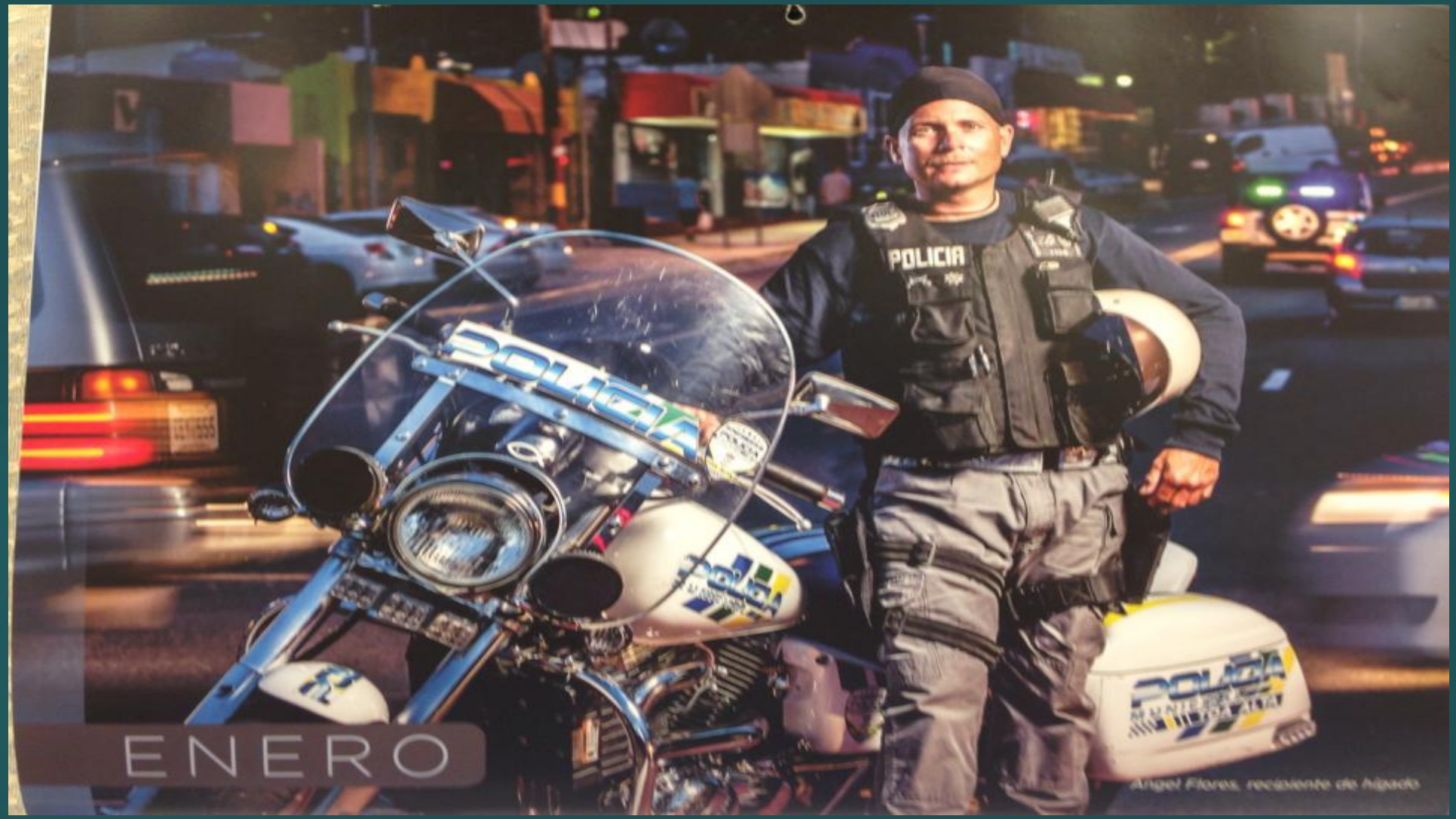








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