End organ stage of liver disease.

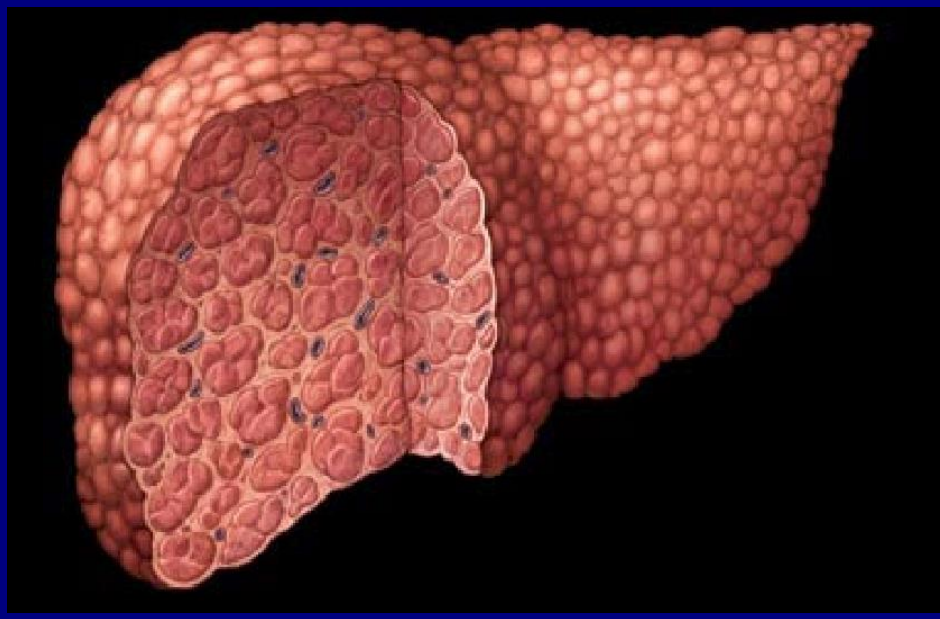
Liver Cirrhosis

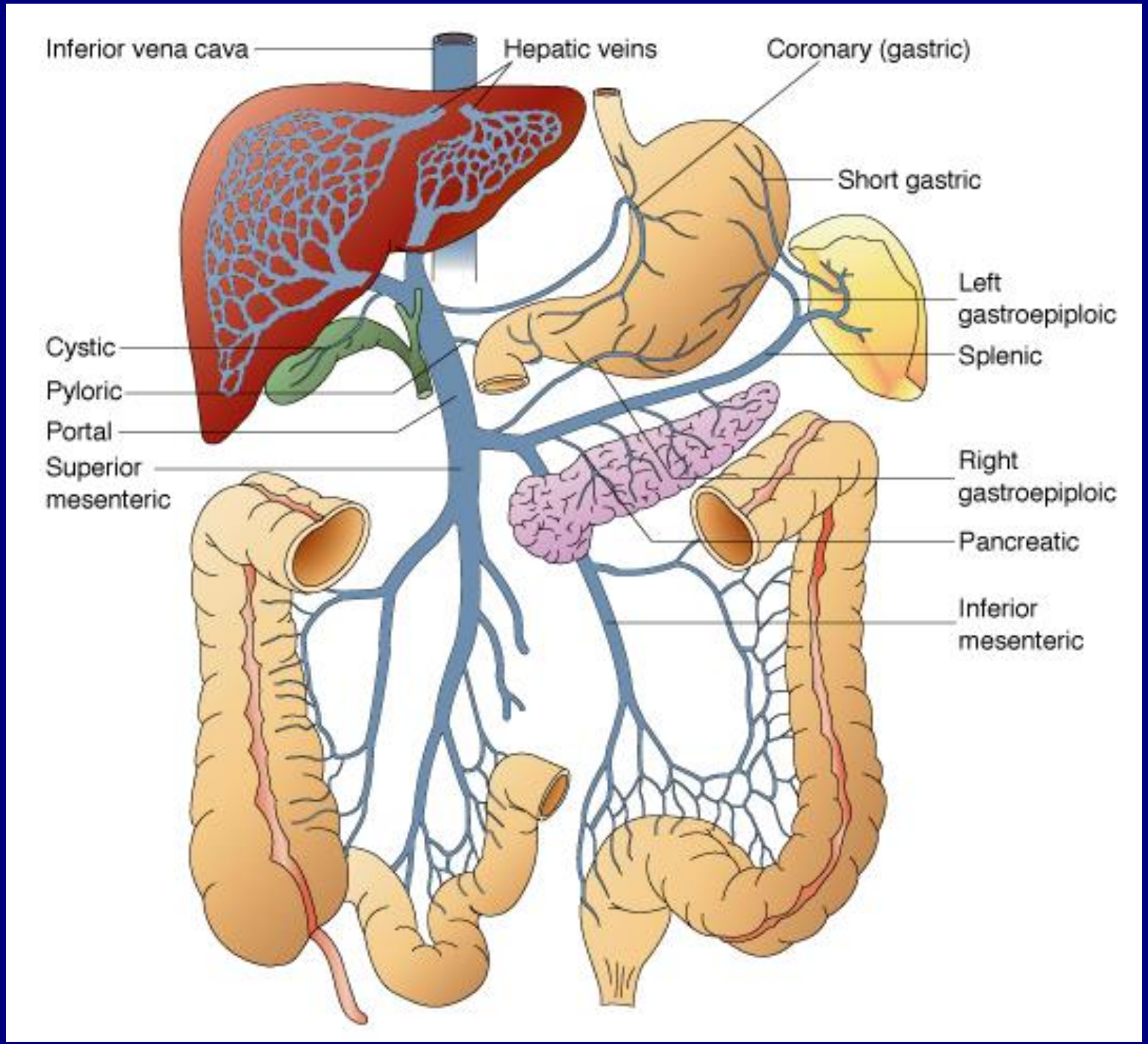
- Irriversible late stage of progressive hepatic fibrosis. (1)
  - Distortion of the hepatic architecture (2)
  - Formation of regenerative nodules. (3)

- Treatment :
- Liver Transplantation

The only cure.

↳ Living Donor or not





Dual Blood supply for liver: 80% portal vein 20% hepatic artery

- portal vein: All Gut supply to the liver
- processed blood to hepatic vein then IVC

Function of the Liver

Synthesis

- Protein and Amino Acid Synthesis
- Carbohydate metabolism
  - *Gluconeogenesis*
  - *Glycogenolysis*
  - *Glycogenesis*
- lipid metabolism:
  - *Cholesterol synthesis*
  - *Lipogenesis*,
  - The liver produces coagulation factors I (fibrinogen), II (prothrombin), V, VII, IX, X and XI, as well as protein C, protein S and antithrombin. all in liver except for vWF which happens in endothelium
- The liver produces and excretes bile required for emulsifying fats.
- The liver also produces insulin-like growth factor 1 (IGF-1), a polypeptide protein hormone that plays an important role in childhood growth and continues to have anabolic effects in adults.
- The liver is a major site of thrombopoietin production. Thrombopoietin is a glycoprotein hormone that regulates the production of platelets by the bone marrow.

Breakdown

- The breakdown of insulin and other hormones
- The liver breaks down hemoglobin, creating metabolites that are added to bile as pigment (bilirubin and biliverdin).
- The liver breaks down or modifies toxic substances (e.g., methylation) and most medicinal products in a process called drug metabolism. This sometimes results in toxication, when the metabolite is more toxic than its precursor. Preferably, the toxins are conjugated to avail excretion in bile or urine.
- The liver converts ammonia to urea.

Other functions

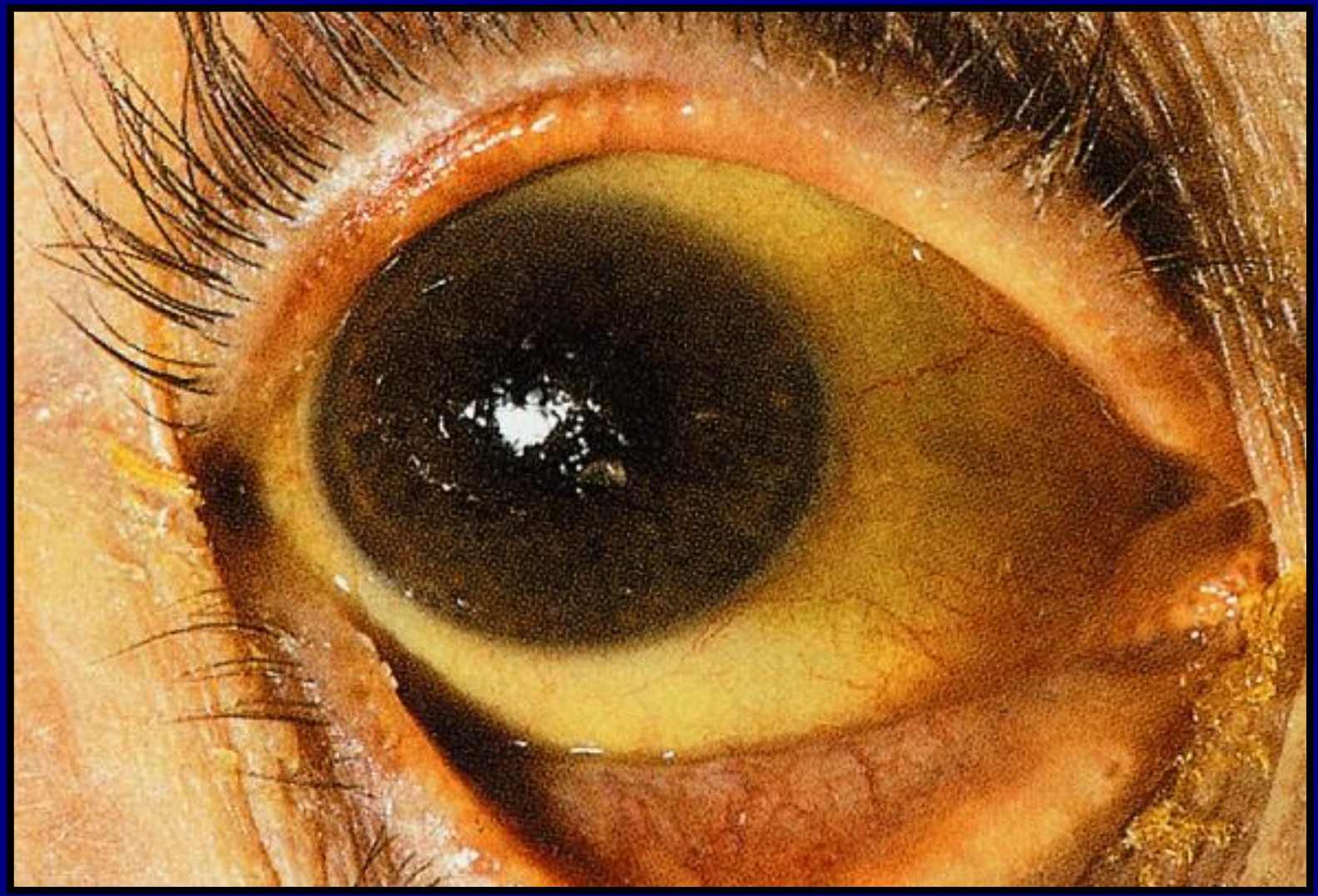
- The liver stores a multitude of substances, including glucose (in the form of glycogen), vitamin A (1–2 years' supply), vitamin D (1–4 months' supply), vitamin B12, iron, and copper.
- The liver is responsible for immunological effects- the reticuloendothelial system of the liver contains many immunologically active cells, acting as a 'sieve' for antigens carried to it via the portal system.
- The liver produces albumin, the major osmolar component of blood serum.
- The liver synthesizes angiotensinogen, a hormone that is responsible for raising the blood pressure when activated by renin, an enzyme that is released when the kidney senses low blood pressure.

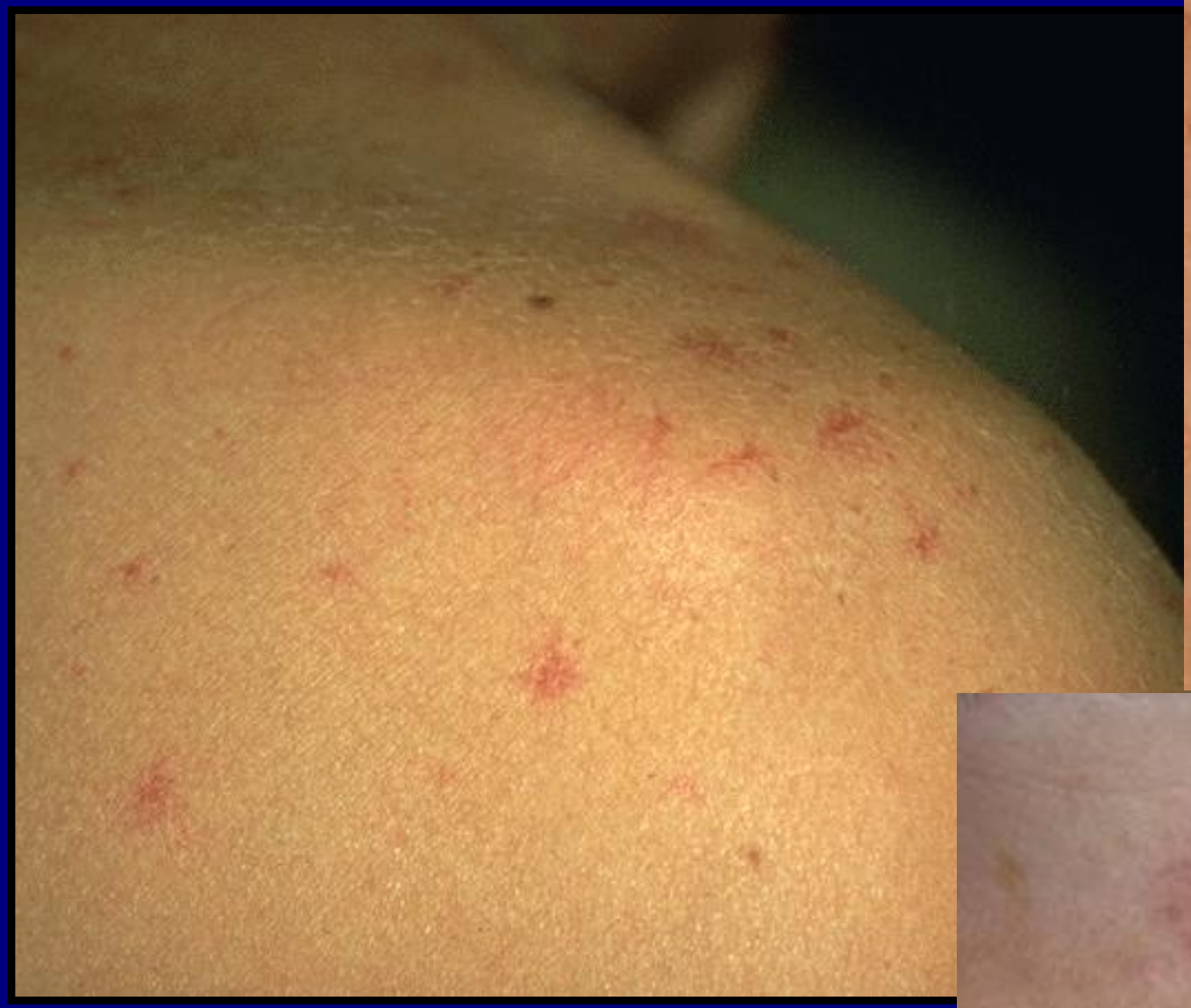
Clinical Presentation

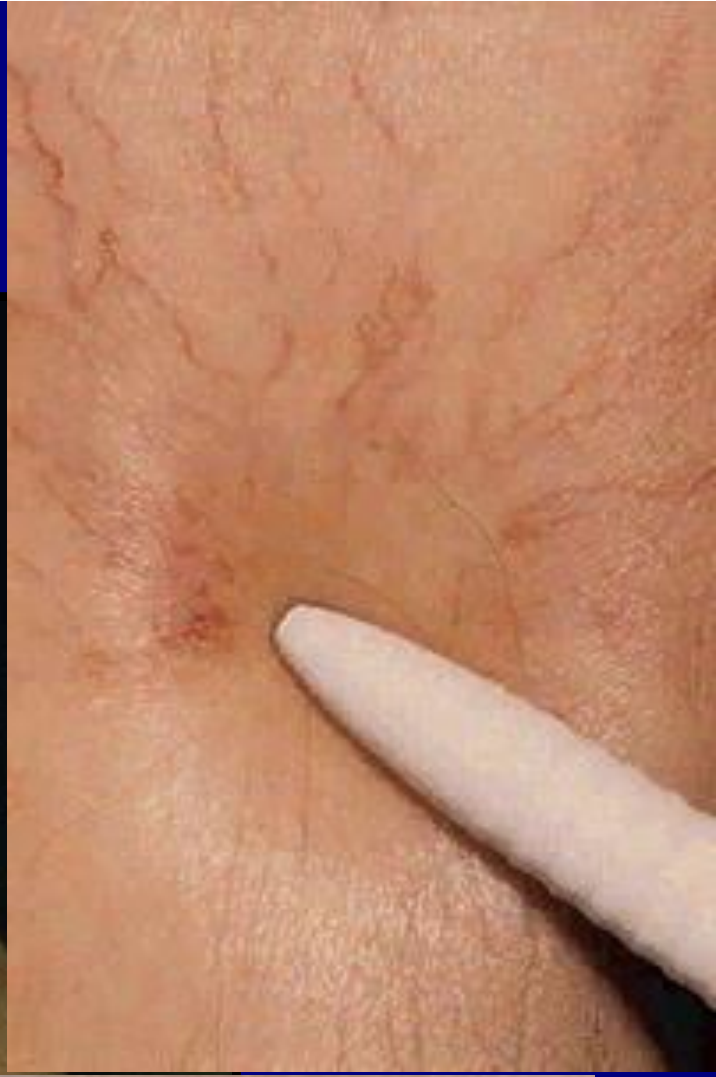
- Asymptomatic:
  - They may have stigmata of chronic liver disease discovered on routine physical examination.
  - They may have undergone laboratory or radiologic testing or an unrelated surgical procedure that incidentally uncovered the presence of cirrhosis.
- Decompensated cirrhosis (Complications)
- Some patients never come to clinical attention. (cirrhosis was diagnosed at autopsy in up to 30 – 40 %)

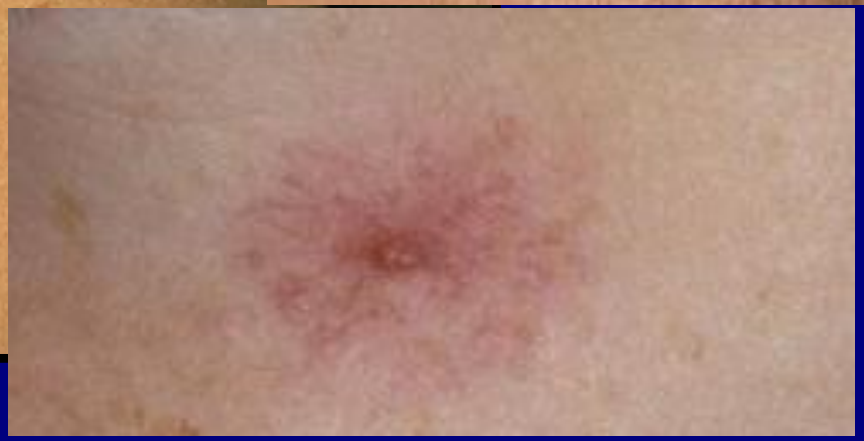
Physical Findings

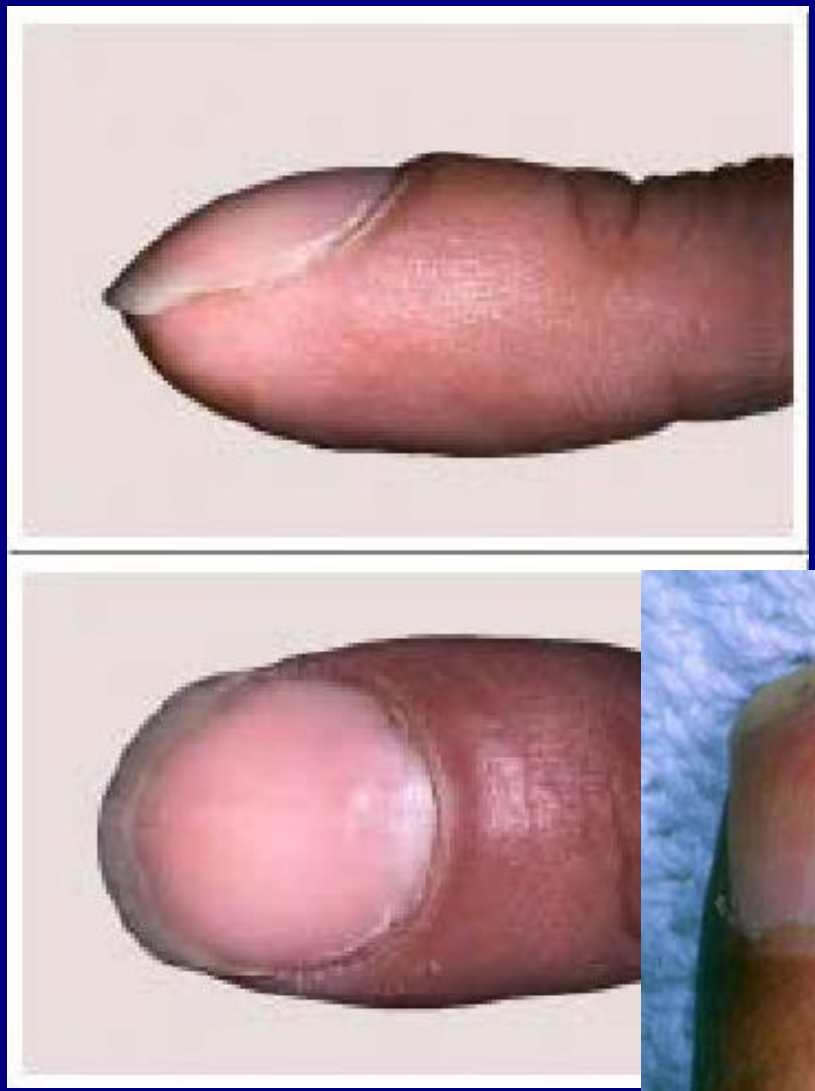
- Spider angiomata
- Palmar erythema
- Nail changes: Terry's nails
- Clubbing and hypertrophic osteoarthropathy
- Dupuytren's contracture
- Gynecomastia
- Testicular atrophy
- Hepatomegaly
- Splenomegaly
- Caput medusae
- Fetor hepaticus

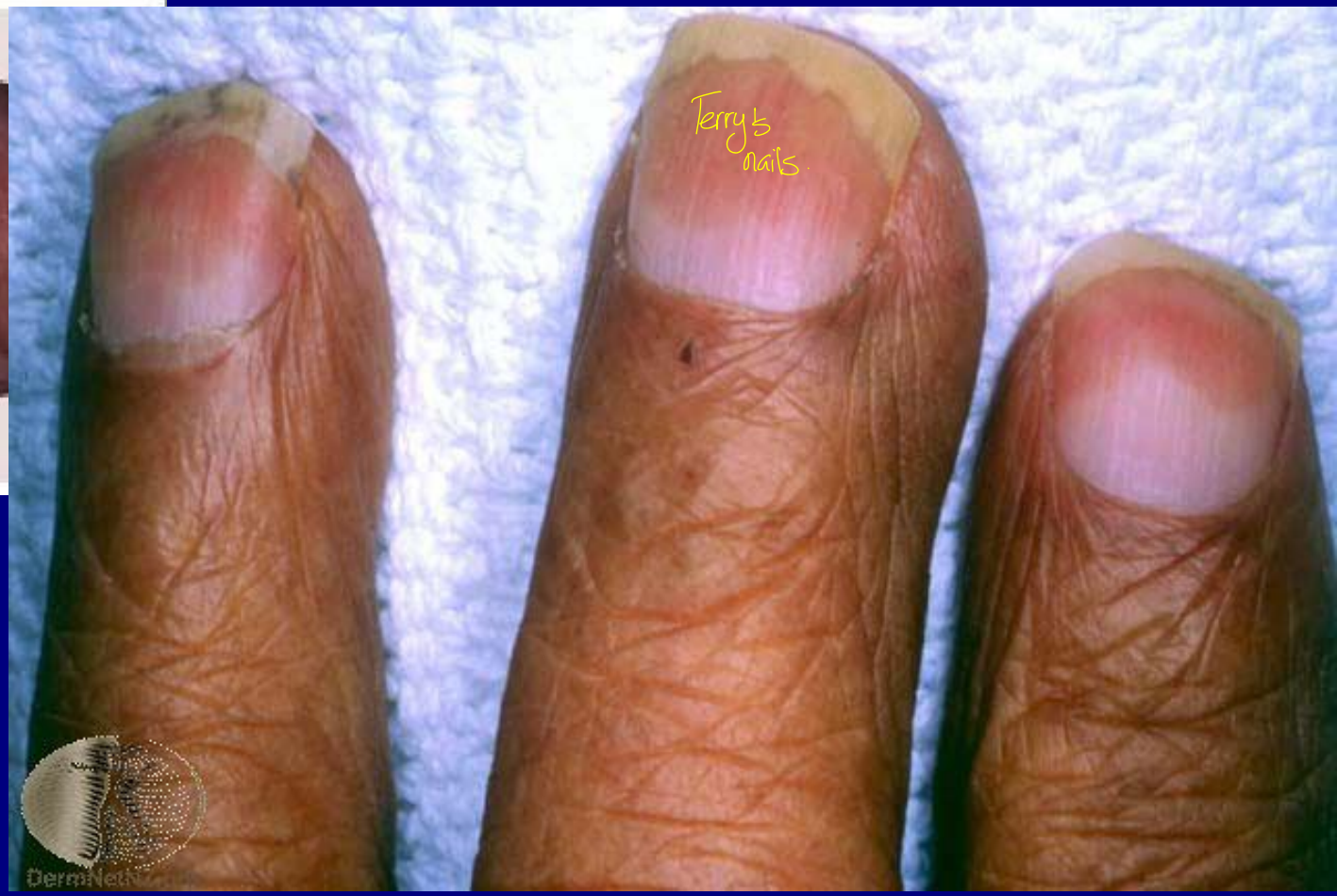


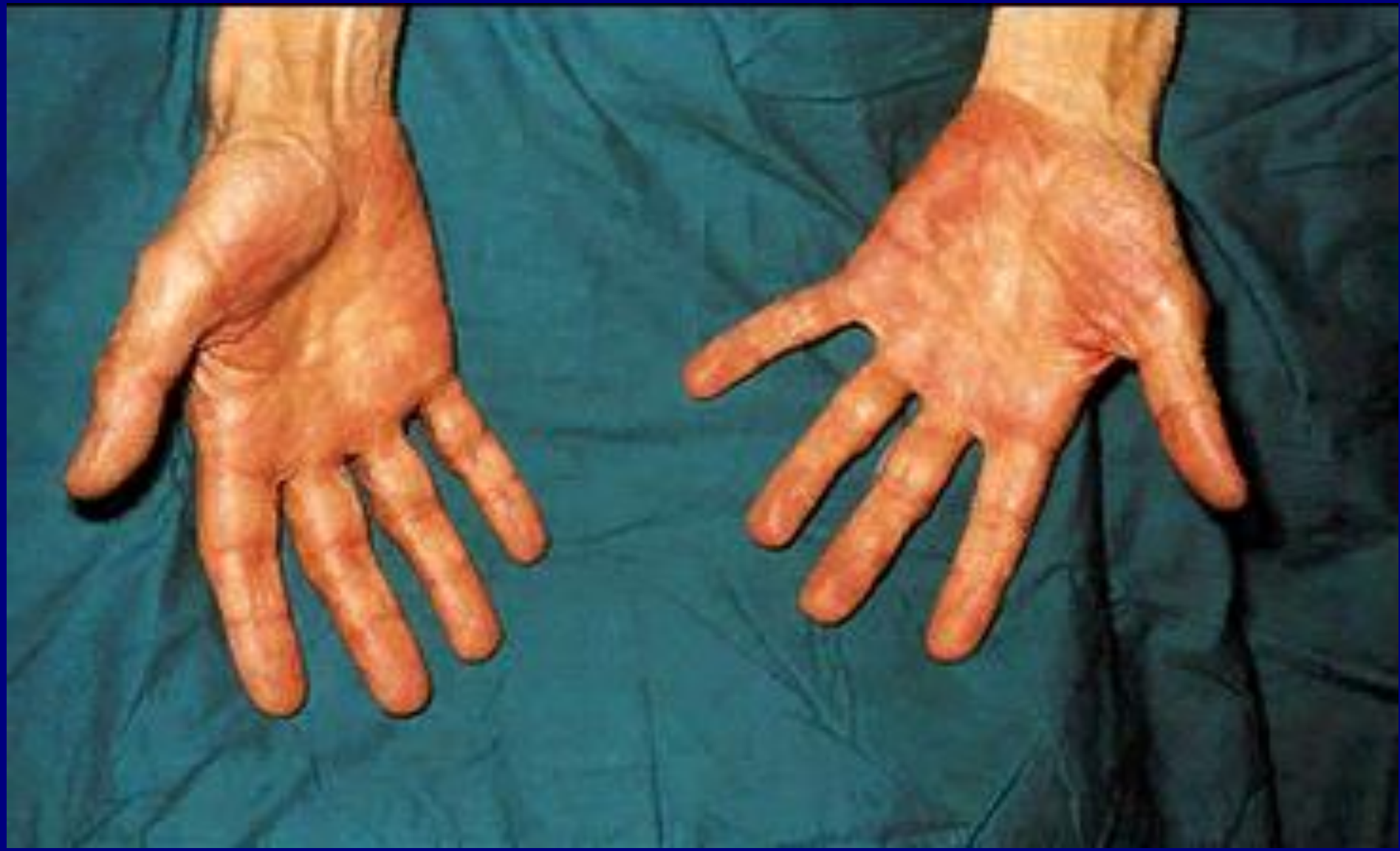


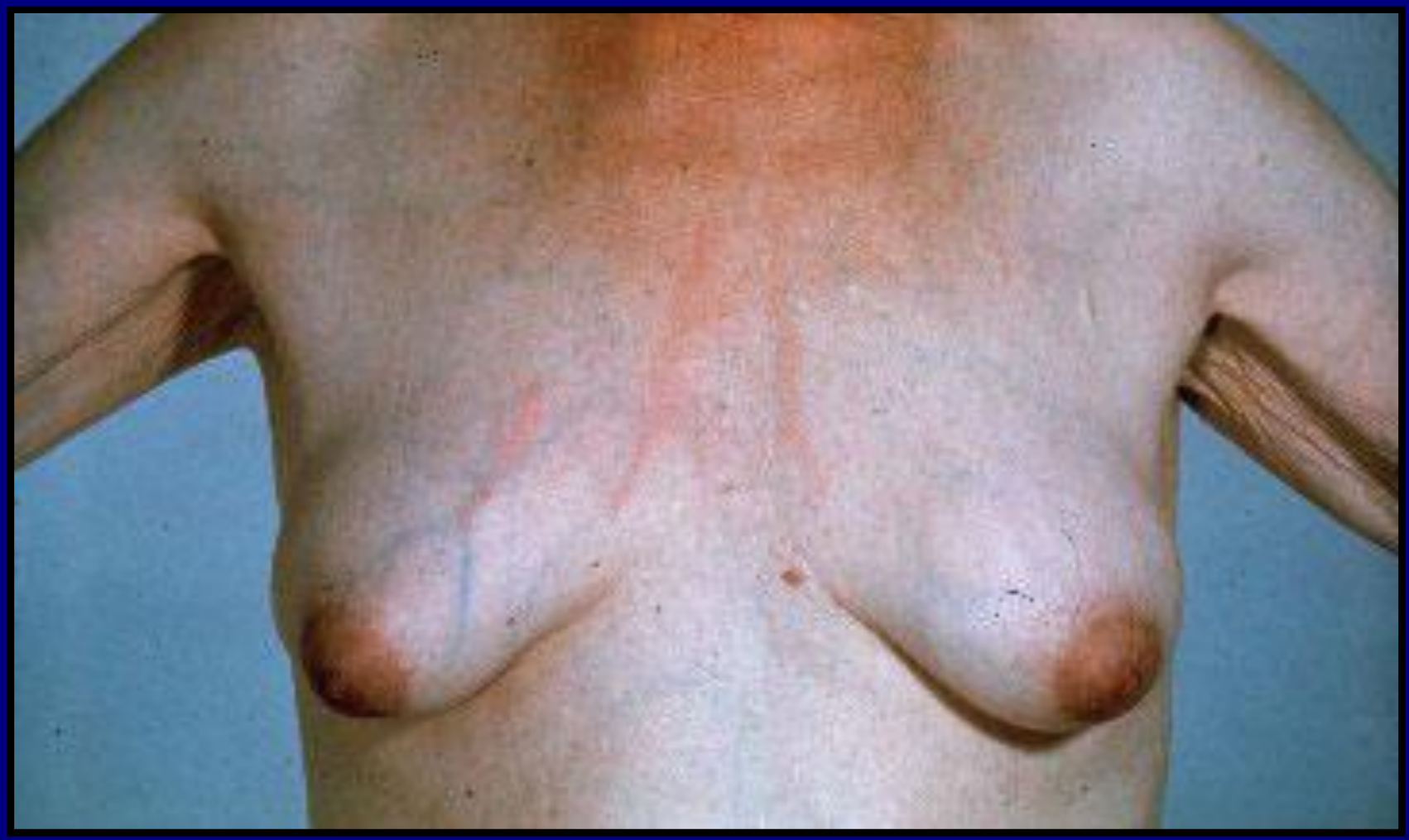


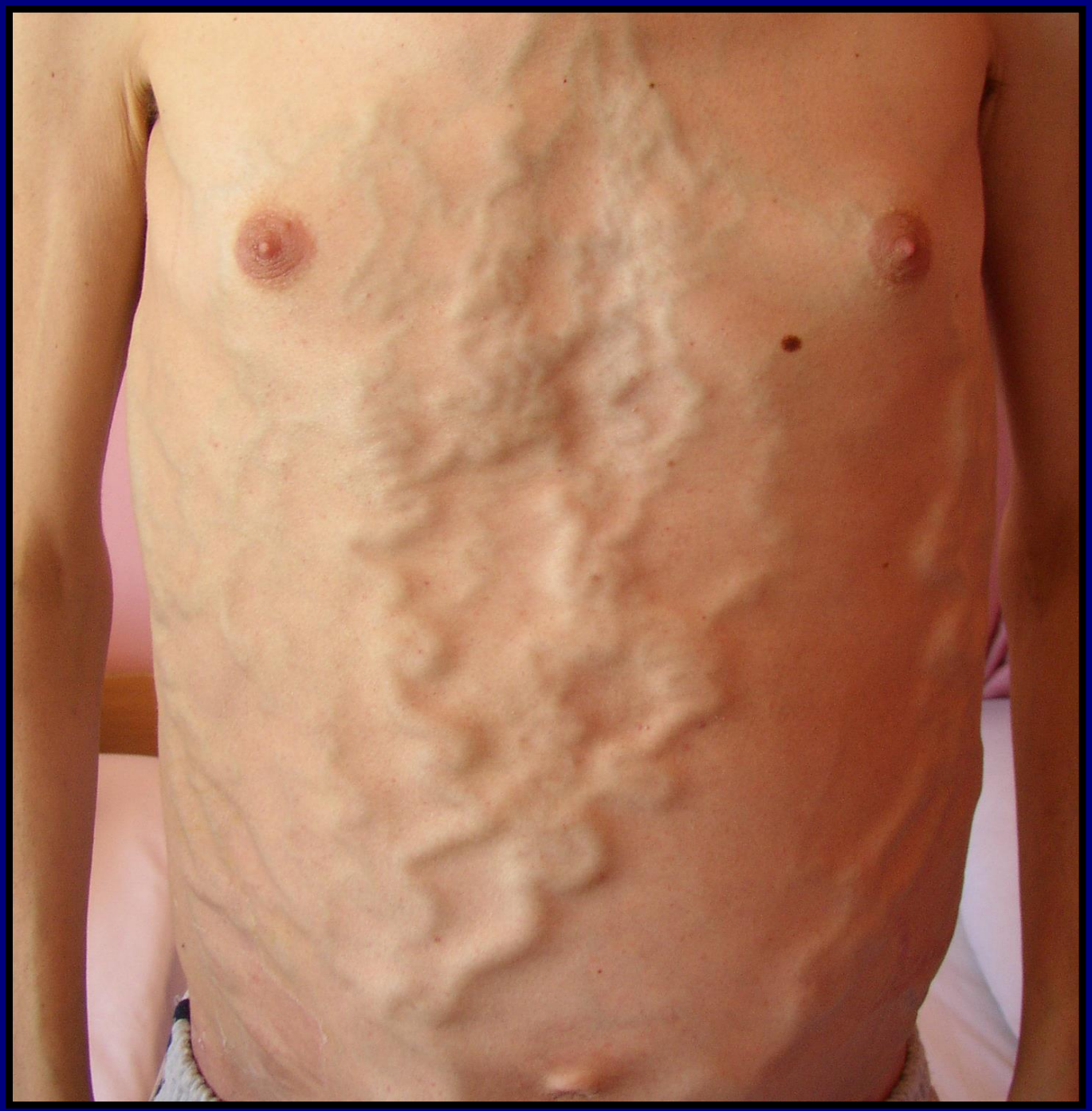





Terry's
nails.







Laboratory Findings

- **Aminotransferases**

AST / ALT → normal or slightly elevated, since they are liver enzymes, leak from injured hepatocyte but they will return to normal since hepatocytes are burned out

Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)

- Usually moderately elevated.
- AST is more often elevated than ALT.
- Normal aminotransferases do not preclude a diagnosis of cirrhosis .

- **Alkaline phosphatase**
  - Usually elevated but less than two to three times the upper normal limit.
  - Higher levels may be seen in patients with primary sclerosing cholangitis and primary biliary cirrhosis. high if lead to PBC or PSC.

- **Gamma-glutamyl transpeptidase** — GGTP
  - levels correlate reasonably well with alkaline phosphatase in liver disease .
  - Levels of GGT are typically much higher in chronic liver disease from alcohol than other causes (may be the result of alcohol inducing hepatic microsomal GGTP or alcohol causing GGT to leak from hepatocytes).

Laboratory Findings

- Bilirubin normal early / high with progression.
  - may be normal in well compensated cirrhosis then rise progressively.
- Albumin (Low)
  - Synthesized exclusively in the liver.
  - Levels fall as the synthetic function of the liver declines with worsening cirrhosis.
  - Hypoalbuminemia is not specific for liver disease since it may be seen in many other medical conditions such as congestive heart failure, the nephrotic syndrome, protein losing enteropathy, or malnutrition.
- Prothrombin time longer time.
  - The liver is involved in the synthesis of many of the proteins required for normal clotting.
  - Prothrombin time reflects the degree of hepatic synthetic dysfunction.
- Globulins Slightly elevated not know why
  - Globulins tend to be increased in patients with cirrhosis. This may be secondary to shunting of bacterial antigens in portal venous blood away from the liver to lymphoid tissue which induces immunoglobulin production .
  - Marked elevations of IgG may be a clue to the presence of autoimmune hepatitis. Increased levels of IgM are present in 90 to 95 percent of patients with primary biliary cirrhosis.

Laboratory Findings

* The lower the sodium → the more advanced the disease is.

- **Serum sodium** Advanced → Hypervolemic hyponatremia (trick of the body).
  - Hyponatremia is common in patients with cirrhosis with ascites and is related to an inability to excrete free water. This results primarily from high levels of anti-diuretic hormone secretion

- **Anemia** Multifactorial.
  - Multifactorial in origin; acute and chronic gastrointestinal blood loss, folate deficiency, direct toxicity due to alcohol, hypersplenism, bone marrow suppression (as in hepatitis-associated aplastic anemia), the anemia of chronic disease (inflammation), and hemolysis may all contribute.

- **Thrombocytopenia** → caused by PTH; Spleen tries to compensate to the high BP = enlarged spleen = more blood product
  - caused by portal hypertension with attendant congestive splenomegaly. An enlarged spleen can result in temporary sequestration of up to 90 percent of the circulating platelet mass. use.

- **Leukopenia and neutropenia**
  - Leukopenia and neutropenia are due to hypersplenism

Radiographic findings

- Suggestive of cirrhosis but they are not adequately sensitive or specific for use as a primary diagnostic modality
- Ultrasonography → Shrinkage of Liver / Nodular surface and irregular / heterogeneo Liver → Suggestive but not diagnostic bc other causes could mimic Liver cirrhosis.
  - The fastest test.
  - Routinely used during the evaluation of the cirrhotic patient.
  - It is noninvasive, well tolerated, widely available, and provides valuable information.
  - In advanced cirrhosis, the liver may appear small and nodular.
  - Findings of portal hypertension include an increased diameter of the portal vein and the presence of collateral veins.
- Fibroscan → To asses the degree of Liver Stiffness (According to the velocity of wave : ↑↑)
  - A vibration of mild amplitude and low frequency is transmitted through the liver inducing an elastic shear wave that propagates through the tissue. A pulse-echo ultrasound follows the propagation of the wave; the harder the tissue (and hence the more dense the fibrosis) the faster the wave propagates.

→ Pressure is given in kilo-pascal.

- CT Scan and MRI → Shrink / Granular

⊕ Gold Standard → Liver Biopsy

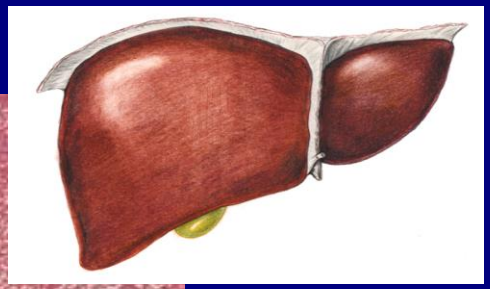
Liver Histology

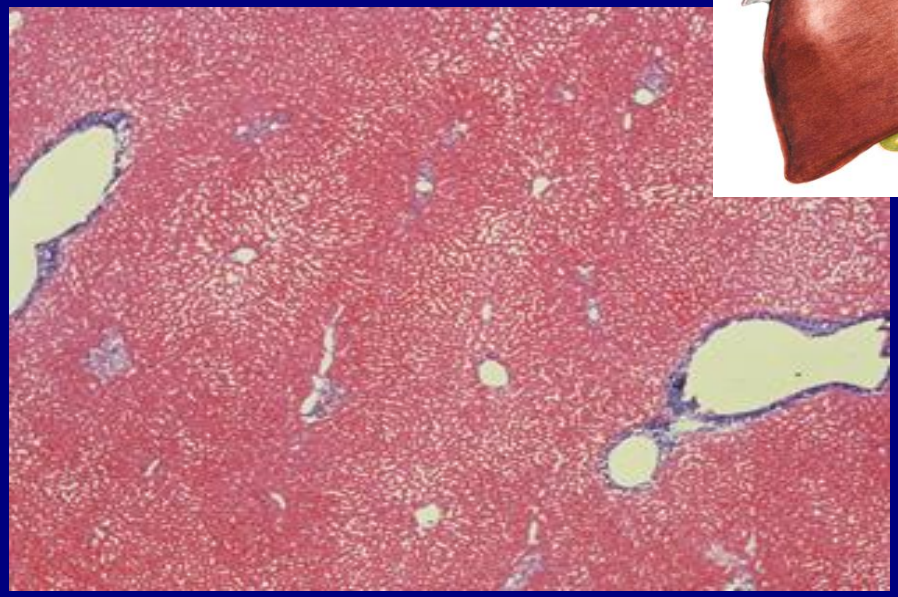
- The gold standard for diagnosis of cirrhosis is examination of an explanted liver at autopsy or following liver transplantation during which the architecture of the entire liver can be appreciated

- liver biopsy ⟶ we prefer transJugular cath to avoid bleeding, since they have high bleeding Tendency
  - Sample of the liver is obtained by either a percutaneous, transjugular, laparoscopic, or radiographically-guided fine-needle approach depending upon the clinical setting
  - The sensitivity is 80 – 100 % depending upon the method used, and the size and number of specimens obtained
  - Can suggest the cause. This is especially true for metabolic causes of cirrhosis

- Shows etiology / Degree of fibrosis.

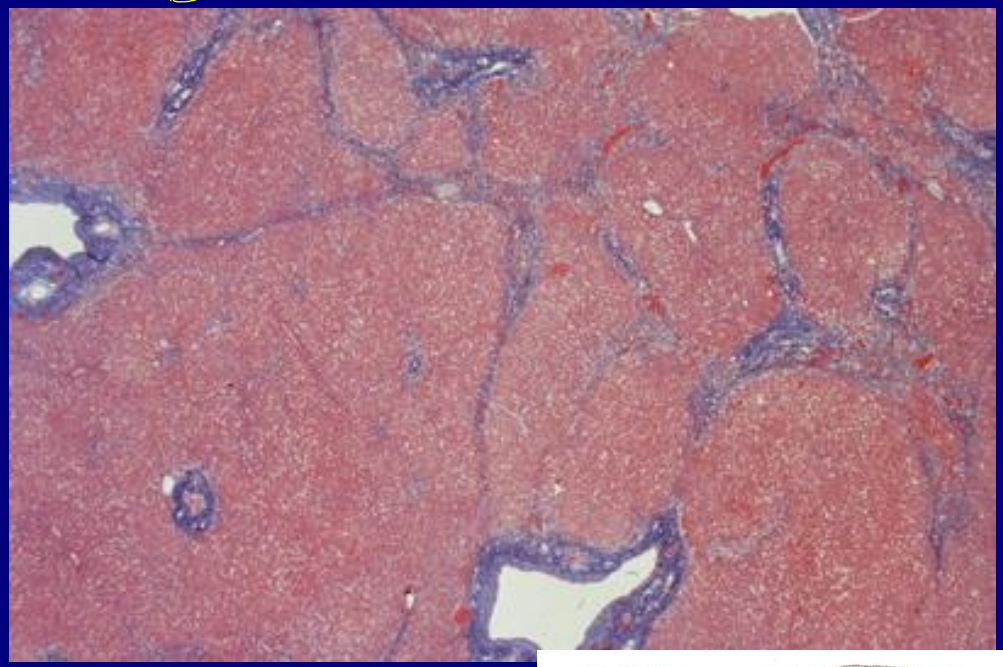
Healthy Liver





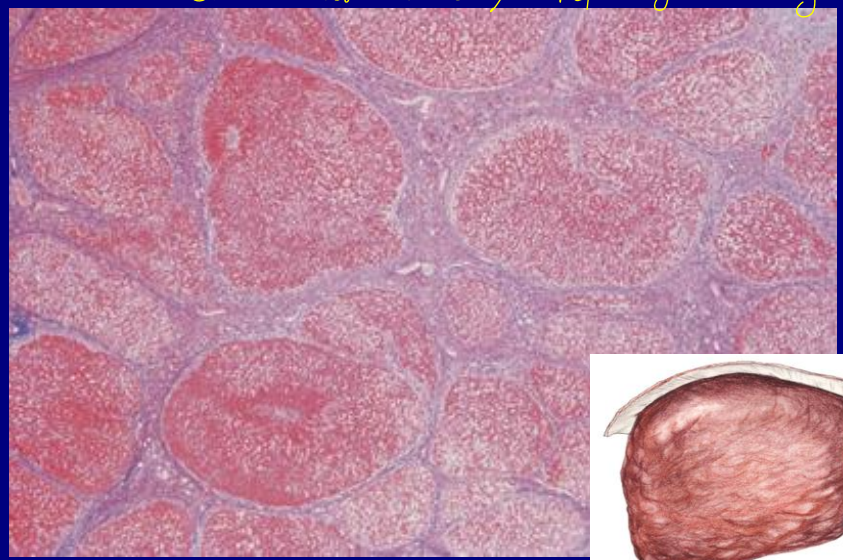
Liver Fibrosis

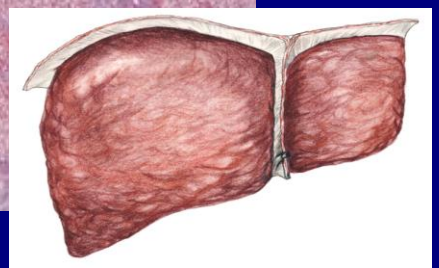
Blue bands ⟹ Fibrous bands.

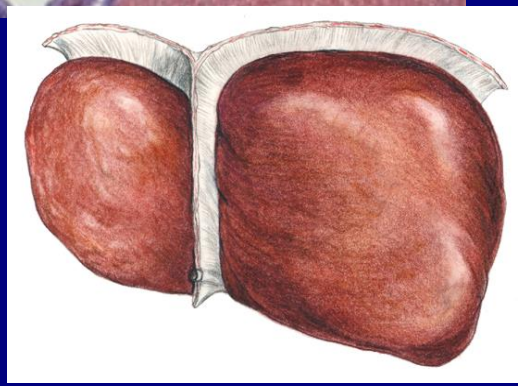


Cirrhosis

More clear fibrous band / Hepatocytes in regenerative cells which Gives the nodular appearance







Child Classification

For severity of Liver Disease.

	1	2	3
Bilirubin (mg/dl)	<2.0	2-3	>3.0
INR	<1.7	1.7-2.3	>2.3
Albumin (mg/dl)	> 3.5	2.8-3.5	<2.8
Encephalopathy	None	I-II	III-IV
Ascites	None	Slight	Tense
		Moderate	

the higher = severe

lower = severe

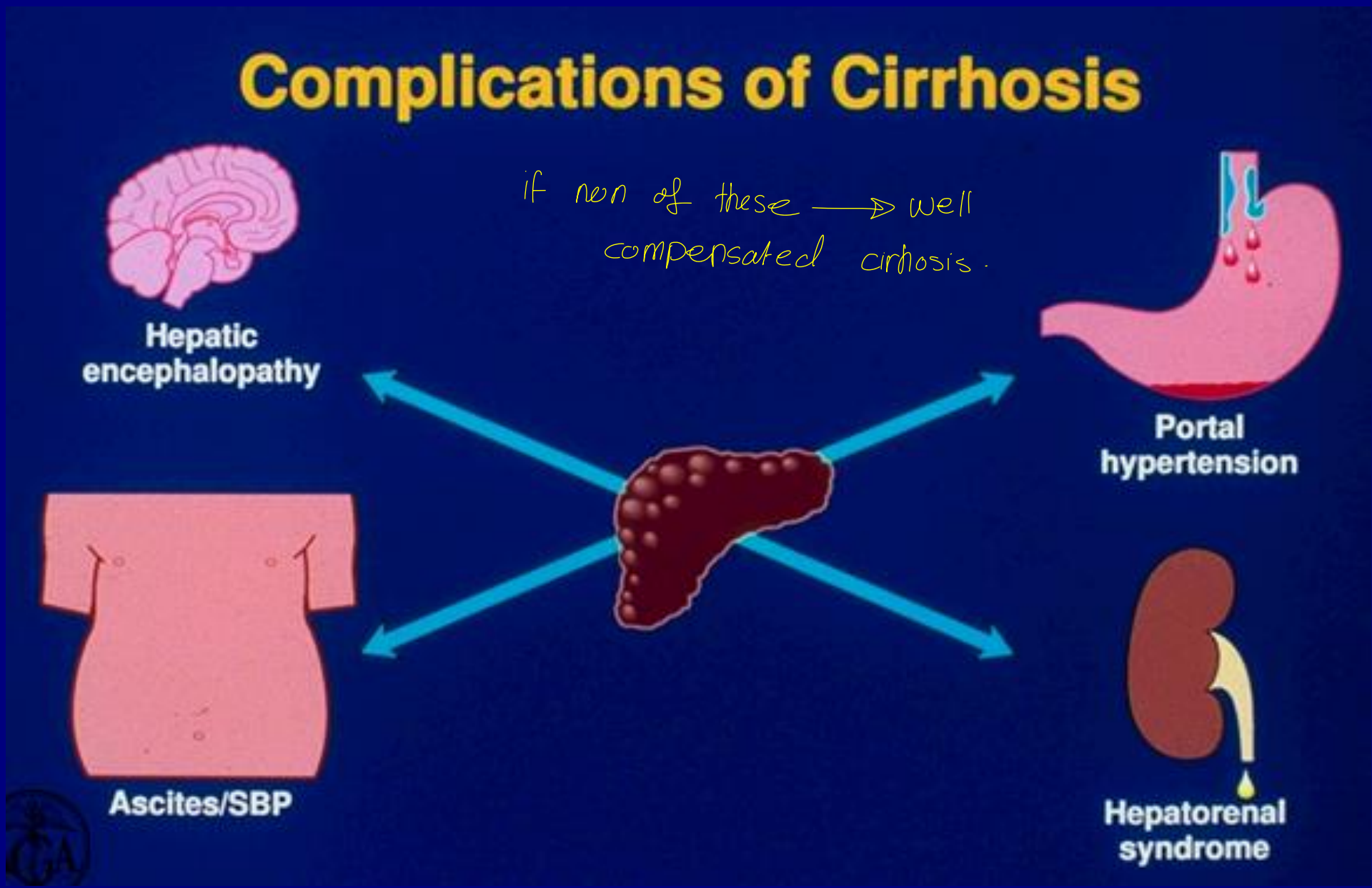
Bio-chemical

clinical

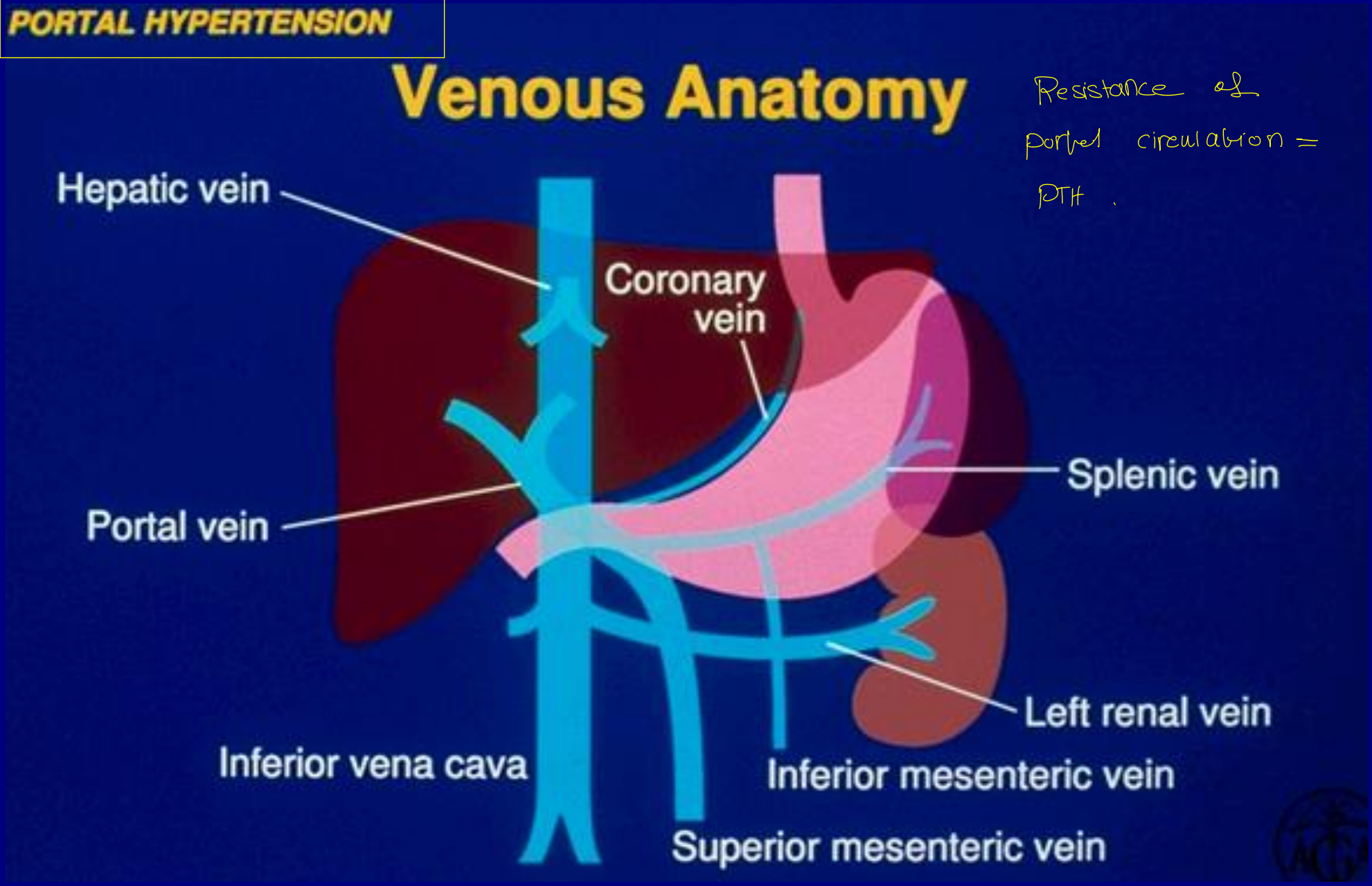
Cirrhosis
Child Classification

Score	Stage
< 7	A 5-6
7 - 10	B 7-10
> 10	C 11-15 highest score.

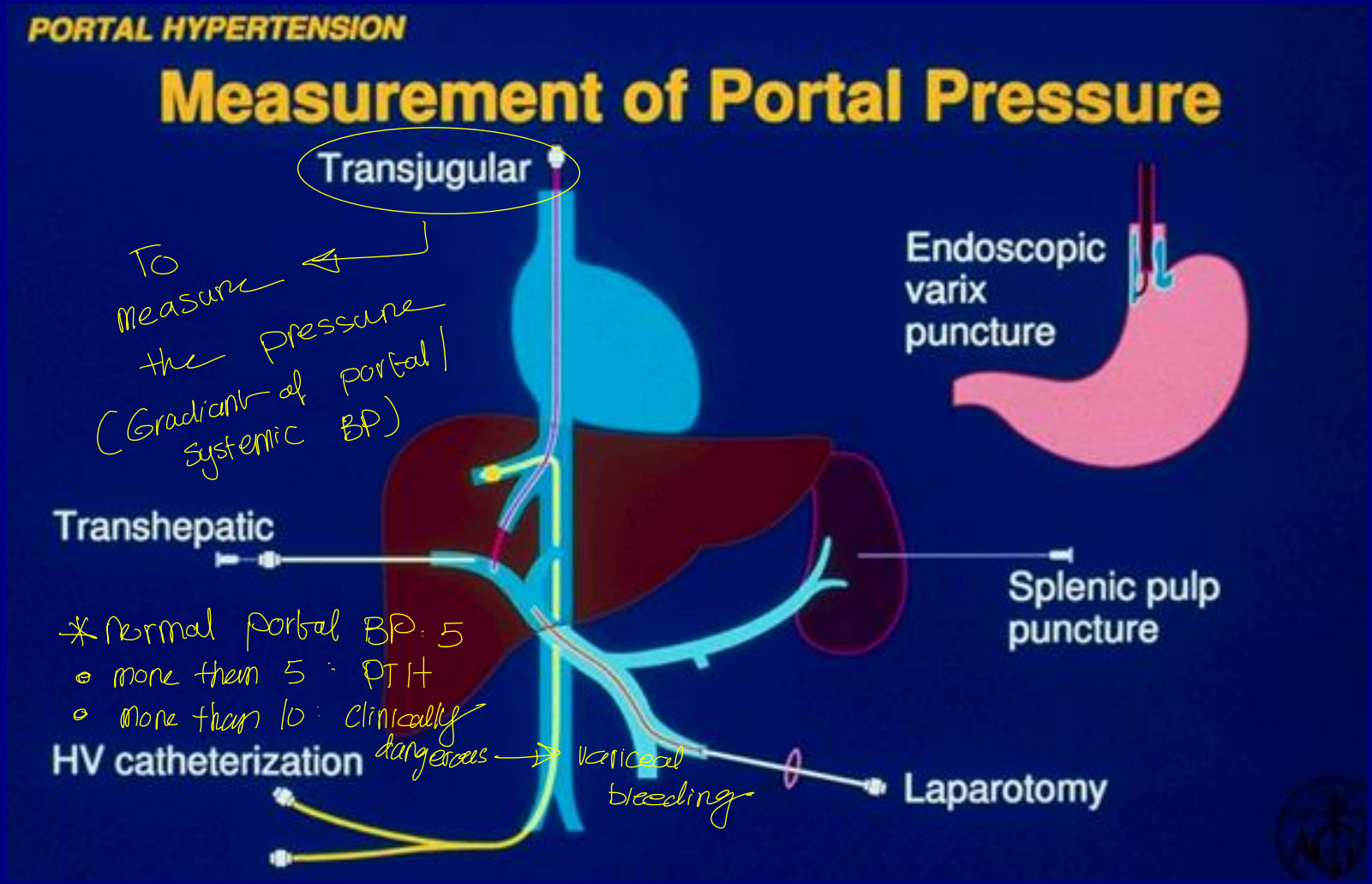
Complications of Cirrhosis



PORTAL HYPERTENSION



Resistance of portal circulation = PTH.

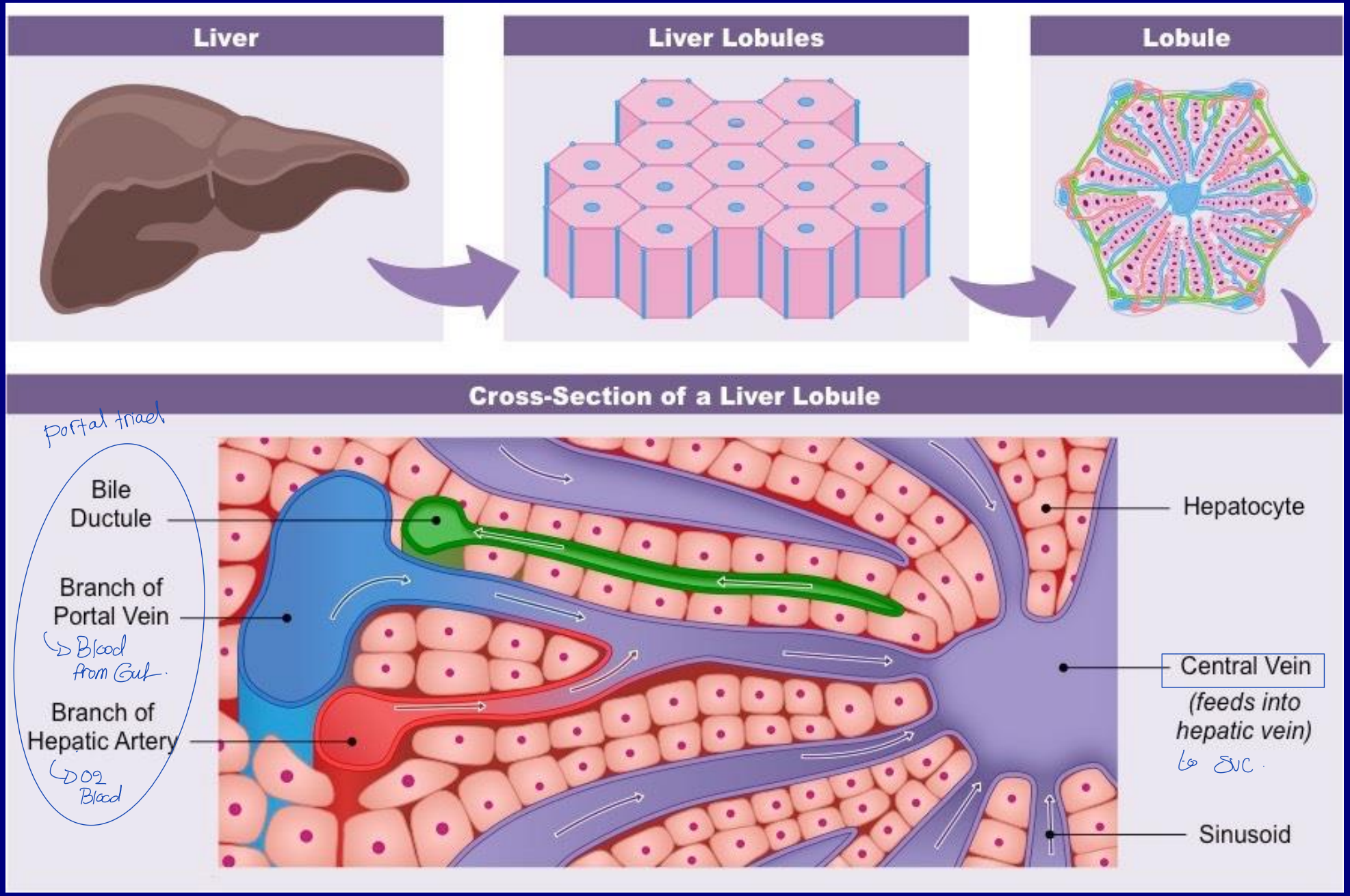

PORTAL HYPERTENSION
Measurement of Portal Pressure
Transjugular
To measure the Pressure (Gradient of portal / systemic BP)
Endoscopic varix puncture
Transhepatic
Splenic pulp puncture
* Normal portal BP: 5
• more than 5 : PTH
• more than 10 : clinically dangerous → variceal bleeding
HV catheterization
Laparotomy

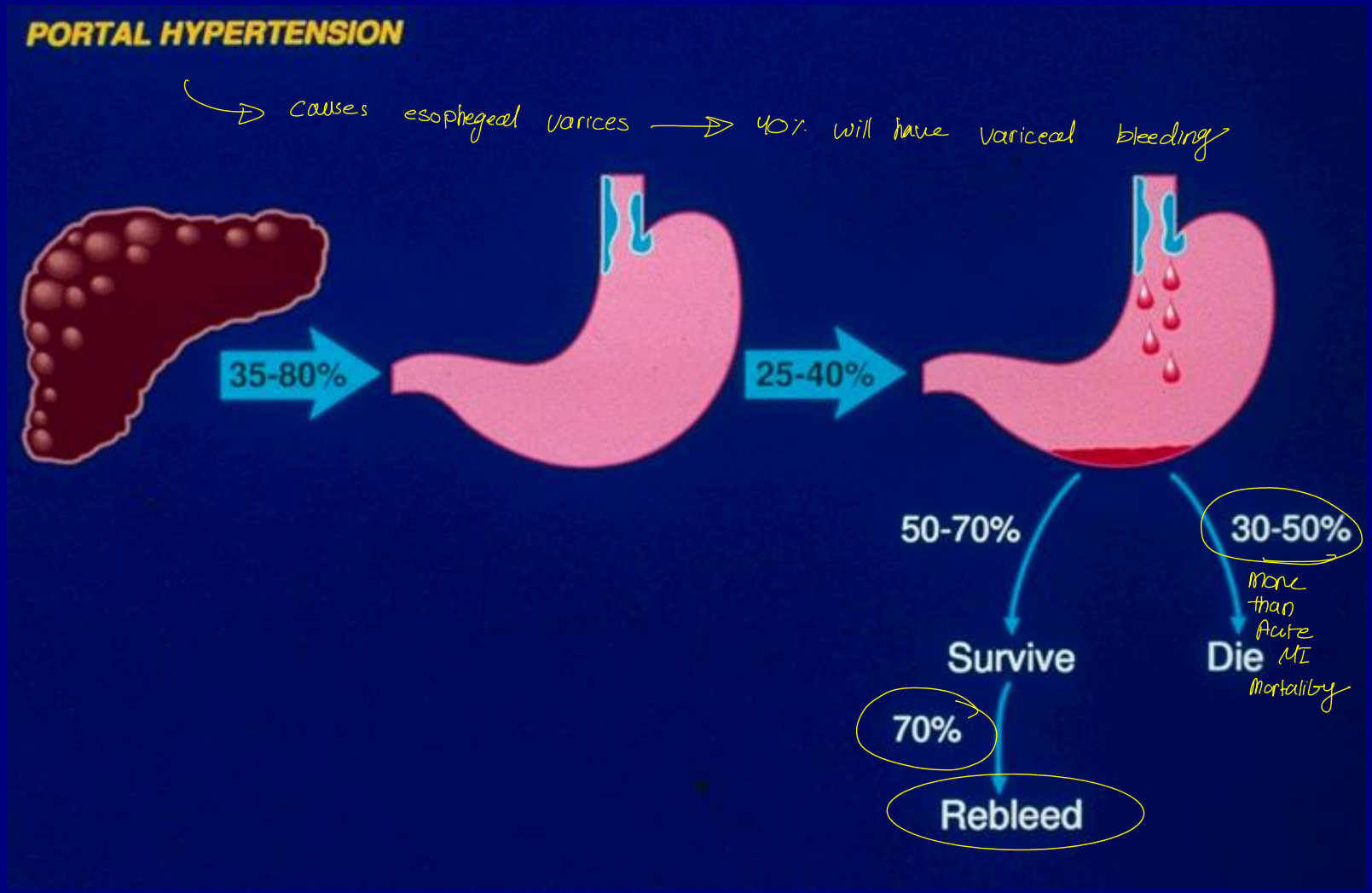
PORTAL HYPERTENSION

* imp

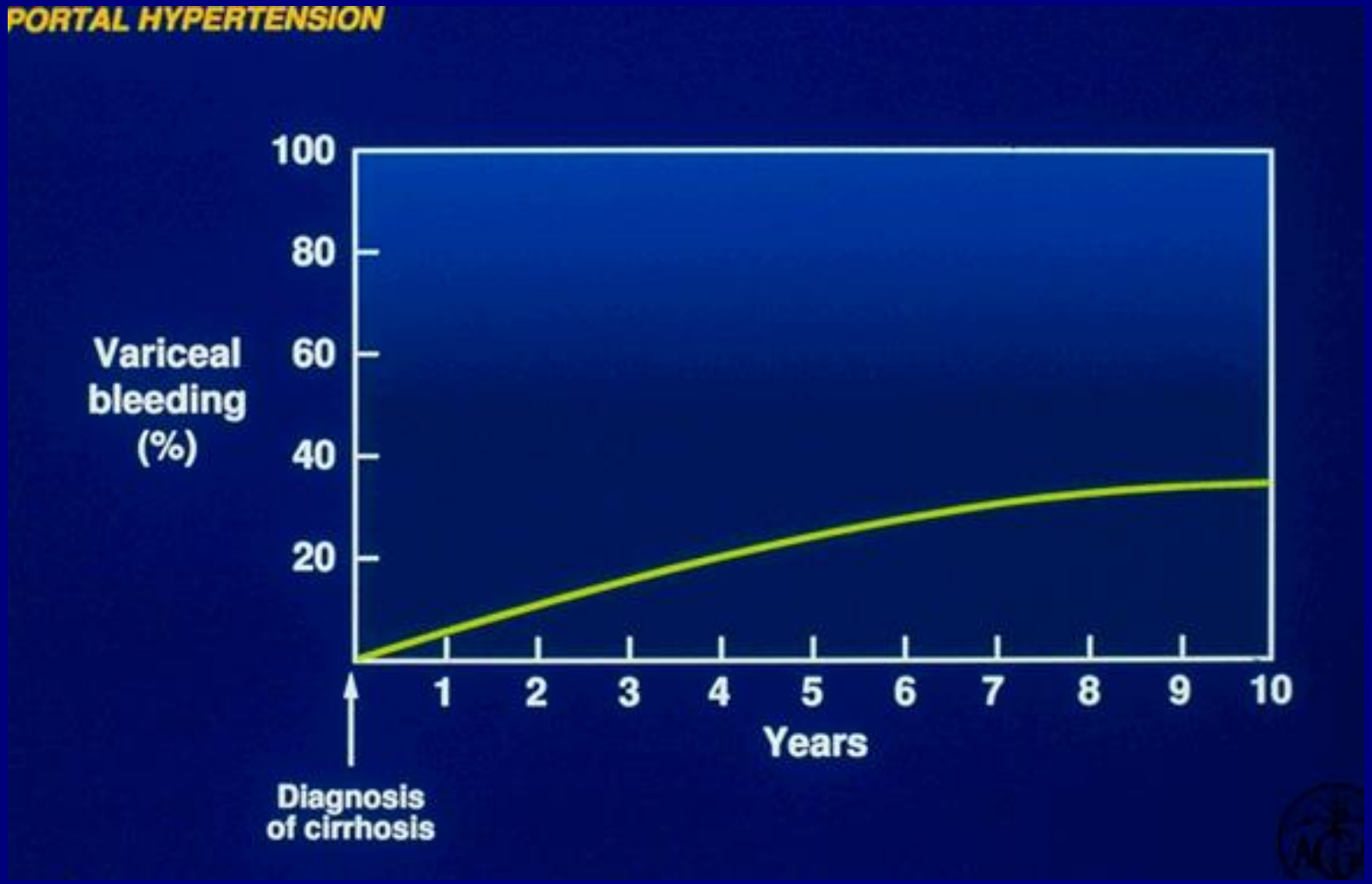
Classification

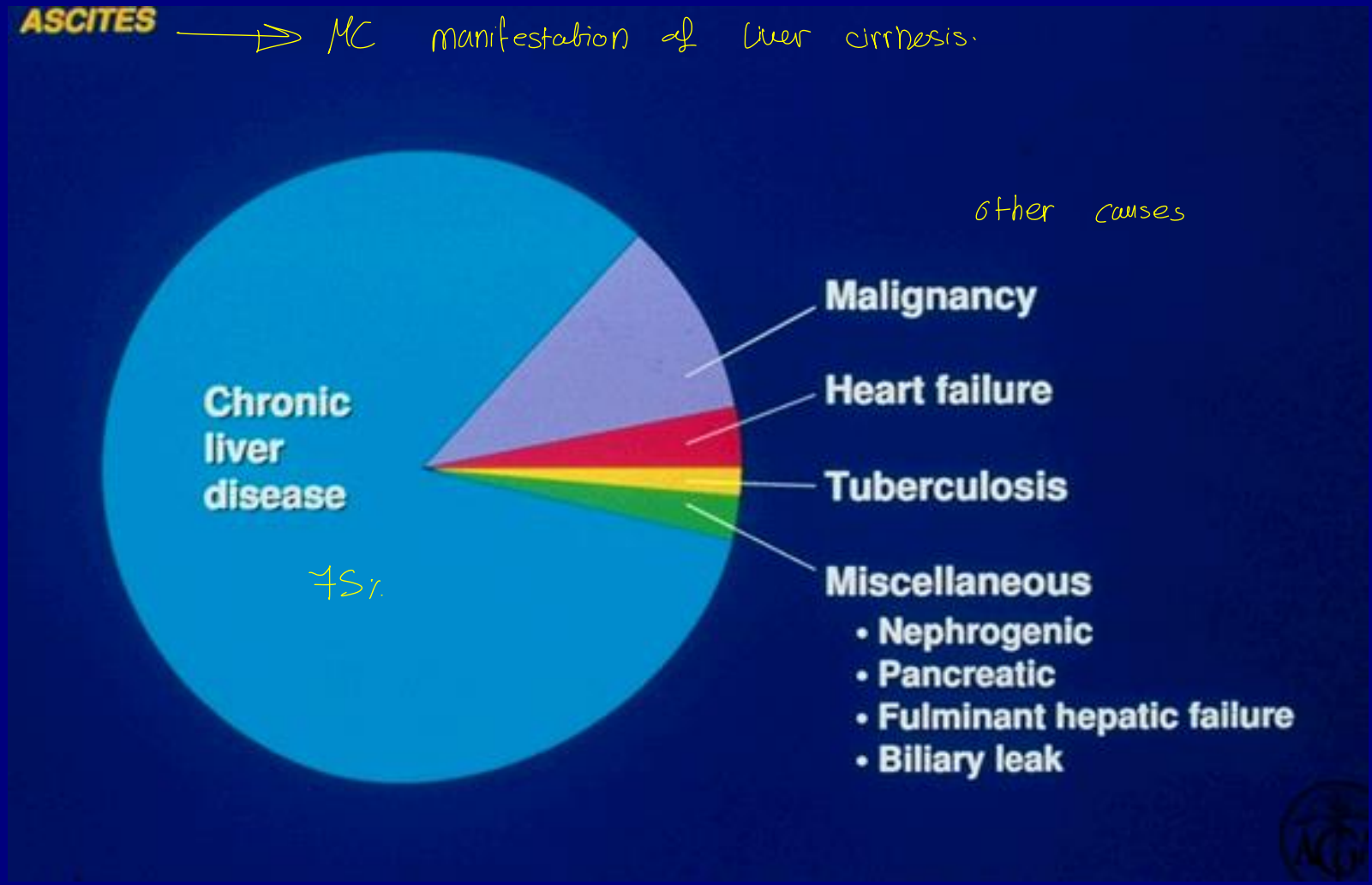
Type		Examples
Prehepatic (intact liver)		Portal or splenic vein thrombosis
Intrahepatic	Presinusoidal	Schistosomiasis
	Sinusoidal	Alcoholic cirrhosis
	Postsinusoidal	Veno-occlusive disease → Malignancy or BM transplant
Posthepatic (intact liver)	(Budd chiari)	Hepatic vein thrombosis
		Constrictive pericarditis


Liver
Liver Lobules
Lobule
Cross-Section of a Liver Lobule
Portal triad
Bile Ductule
Branch of Portal Vein
Blood from Gut
Branch of Hepatic Artery
O2 Blood
Hepatocyte
Central Vein
(feeds into hepatic vein)
to SVC
Sinusoid


PORTAL HYPERTENSION
Causes esophegeal varices → 40% will have variceal bleeding
35-80%
25-40%
50-70%
30-50%
more than Acute MI Mortality
Survive
Die
70%
Rebleed

PORTAL HYPERTENSION




ASCITES
MC manifestation of liver cirrhesis.
Other causes
Chronic liver disease
75%
Malignancy
Heart failure
Tuberculosis
Miscellaneous
• Nephrogenic
• Pancreatic
• Fulminant hepatic failure
• Biliary leak

ASCITES

Pathophysiologic Mechanisms

Elevated Hydrostatic Pressure

leakage of fluid.

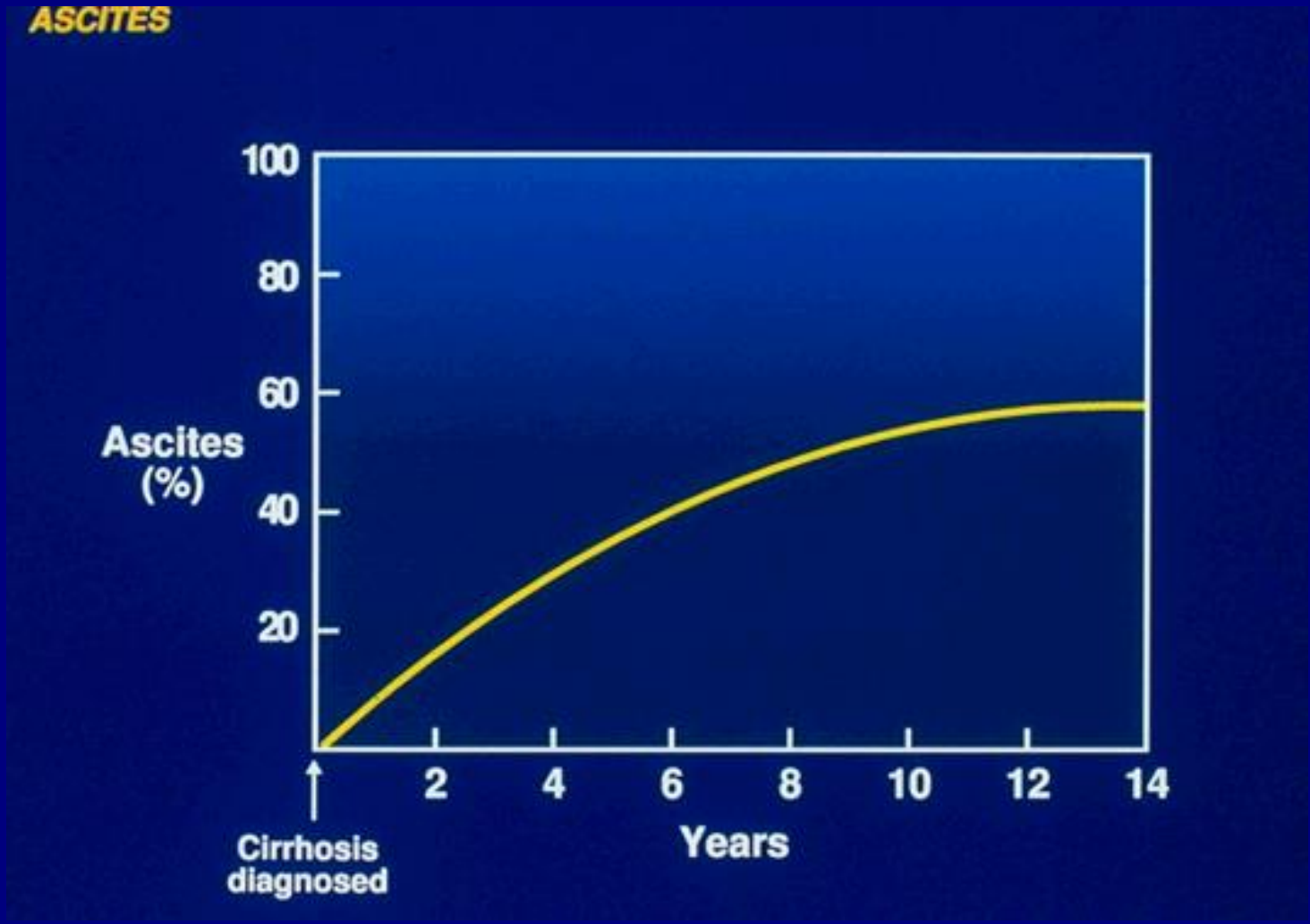
- Cirrhosis
- Congestive heart failure
- Constrictive pericarditis
- Hepatic outflow block

Decreased Oncotic Pressure

- Nephrotic syndrome
- Protein-losing enteropathy
- Malnutrition
- Cirrhosis

Peritoneal Fluid Production > Resorption

- Infections (bacterial, tuberculosis, fungal)
- Neoplasms


ASCITES
100
80
60
40
20
Ascites (%)
2
4
6
8
10
12
14
Years
Cirrhosis diagnosed

ASCITES

Diagnostic Paracentesis

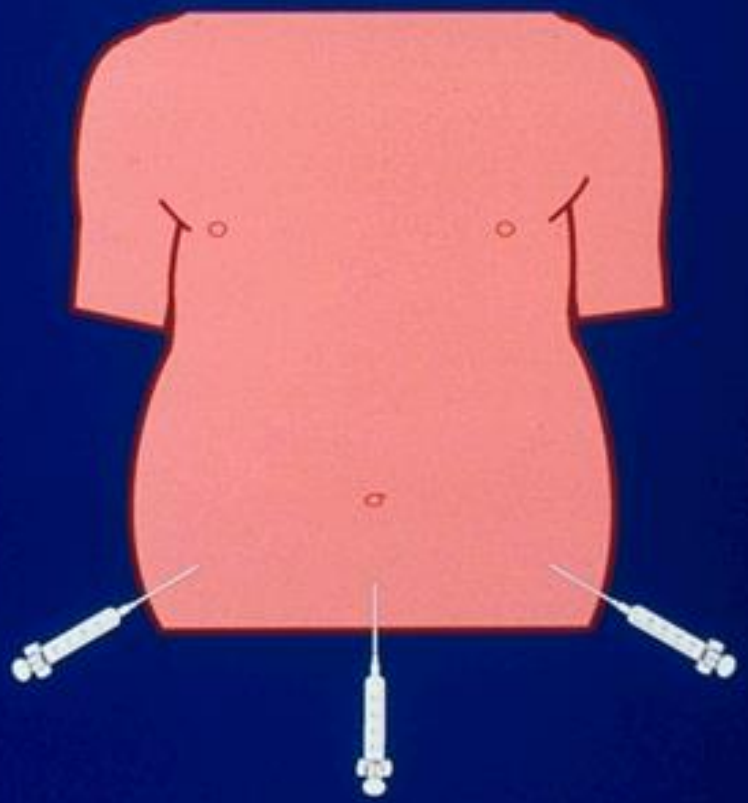
Indications

- New-onset ascites (1)
- Admission to hospital (2)
- Clinical deterioration (3)
- Fever (4)

Contraindications

- None

Presence of DIC



ASCITES

Fluid Analysis

Routine	Optional	
Cell count ①	Glucose	TB smear and culture
Culture ②	LDH	
Albumin ③	Amylase	Cytology
Protein ④	Gram stain	Triglyceride

→ Go check for presence of SBP

very imp.

	SAAG (g/dL)	
	≥ 1.1 indicates PTH	< 1.1 not PTH
Total protein (g/dL)		
< 2.5 Liver related etiology	Cirrhosis	Nephrotic syndrome
	Acute liver failure	
≥ 2.5 non liver	CHF	Peritoneal carcinomatosis
	Constrictive pericarditis	TB peritonitis
	Budd-Chiari syndrome	Pancreatic ascites
	Veno-occlusive disease	Chylous ascites

ASCITES

Initial Therapy

Sodium restriction — Less than 2 grams (88 meq) daily

Diuretics

- Spironolactone +/- furosemide
- Stepwise increase as needed to maximal doses

Large volume paracentesis (for tense ascites)

100/90 Ratio

- Spironolacton (100……400 mg daily)
  +/- furosemide (40…...160 mg)

Max doses

corner stone.

- Always monitor KFT AND electrolytes during diuretic therapy

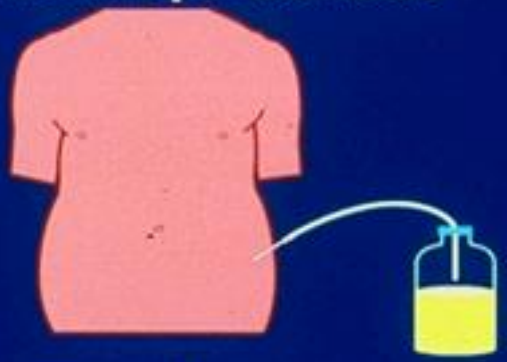
- BUT in selected patients (border line kidney function or K level you have to adjust your doses , IT IS NOT A BIBLE

not responding to diuritics

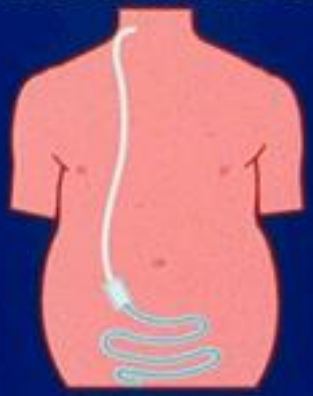
ASCITES

Therapy of Refractory Ascites

1. Large volume paracentesis



2. Peritoneovenous shunt



TIPS

Connection between portal and hepatic veins to reduce pressure

↳ But increases risk of encaphalopathy.

3. Liver transplantation → Best cure

- **LARGE VOLUME PARACENTESIS**

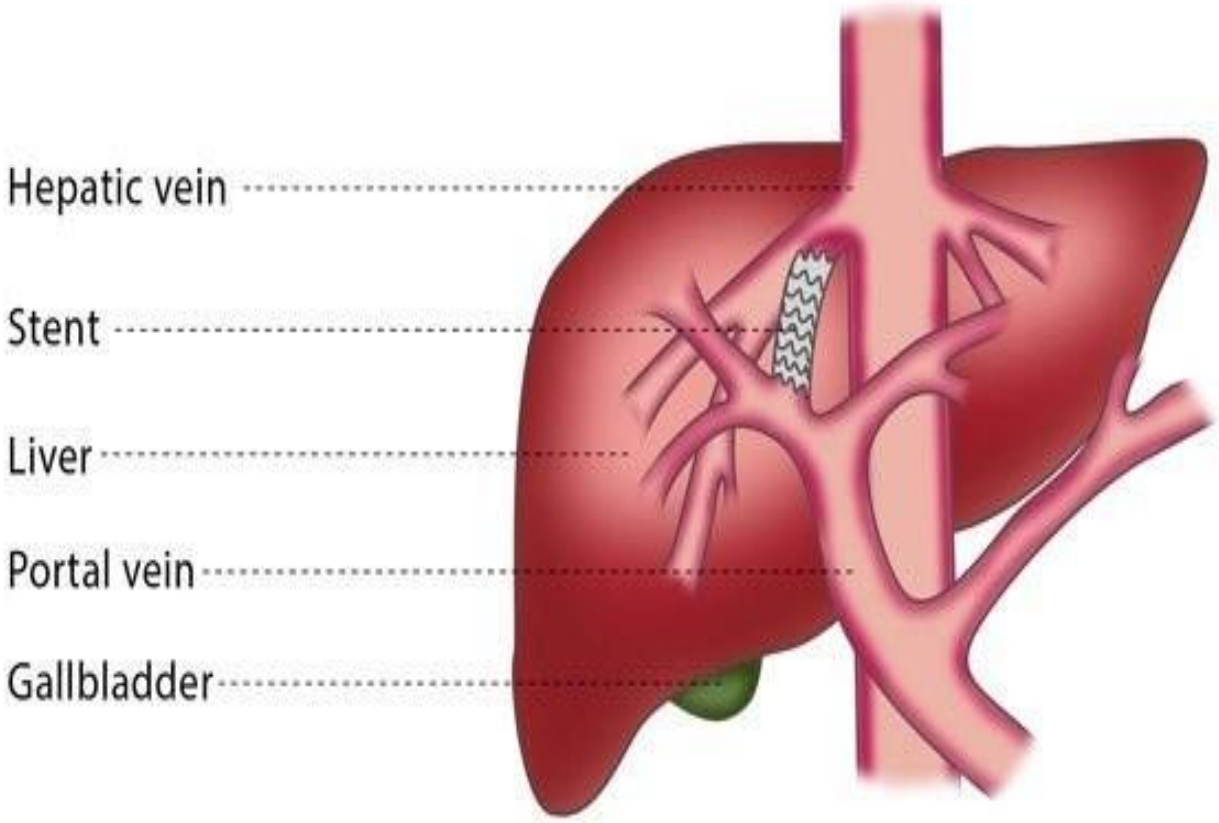
- **Albumin replacement rule:**

more than third loss space

↳ Starts after the 4th liter of paracentesis.

- **8 grams of 25 % albumin for each litre removed.**

Transjugular intrahepatic portosystemic shunt (TIPS)



ASCITES

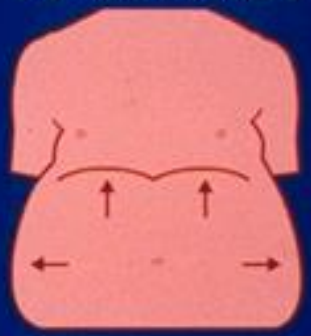
Complications

Infection (SBP)

PMN >250

WBC >500

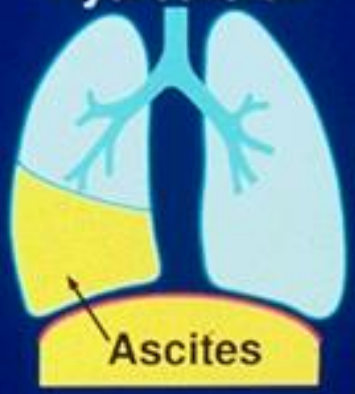
Tense ascites



Umbilical hernia

Hydrothorax

Rt sided



ASCITES

Hepatic Hydrothorax

Characteristics

Location

- right-sided (66%)
- bilateral (17%)
- left-sided (17%)

Fluid similar to ascites

Treatment

Medical therapy

- diuretics
- thoracentesis

TIPS

no chest tube

Liver transplantation

Umbilical Hernia

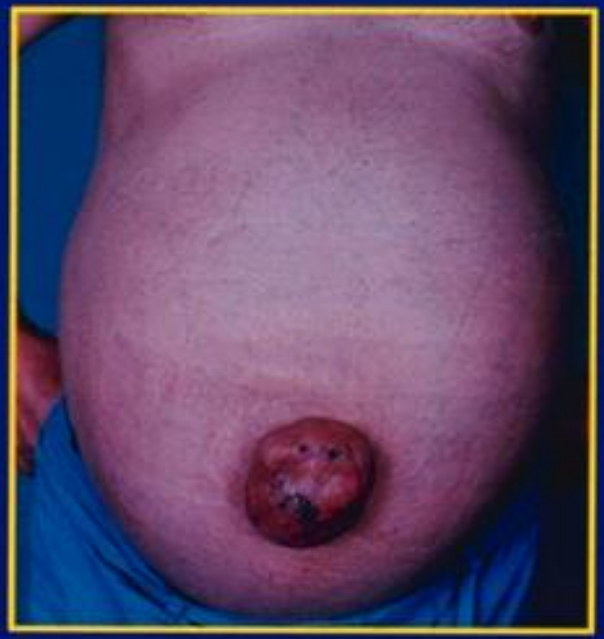
Complications

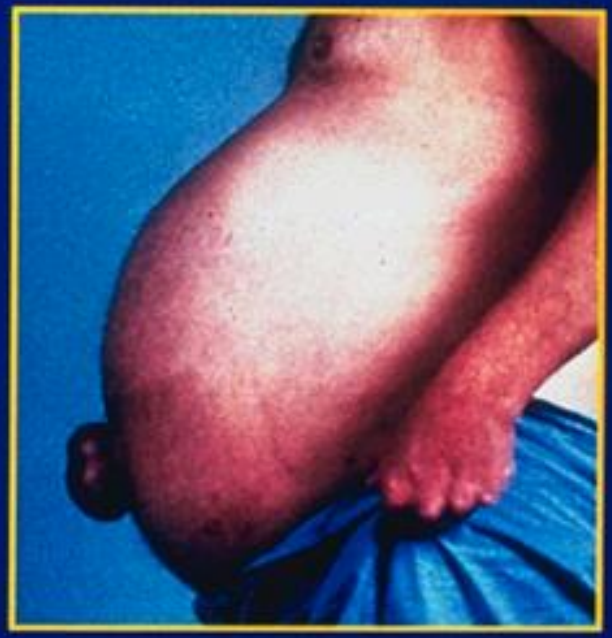
- Incarceration - 14%
- Ulceration - 35%
- Rupture - 7%

Treatment

- Control ascites
- Elective surgical repair if ascites controlled
- Urgent repair for rupture

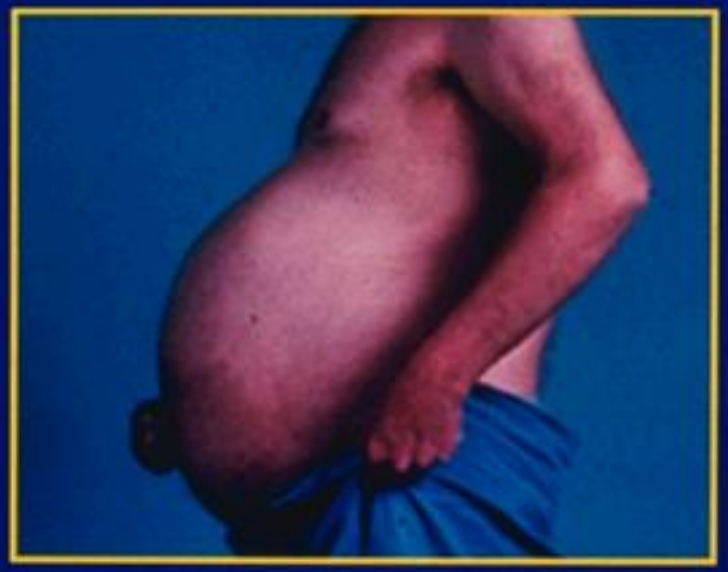
ASCITES



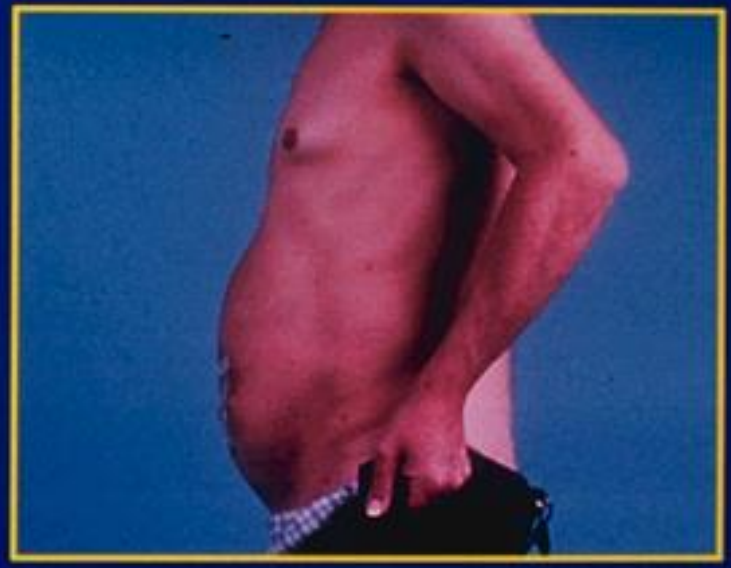


ASCITES

Peritoneovenous Shunt



Before



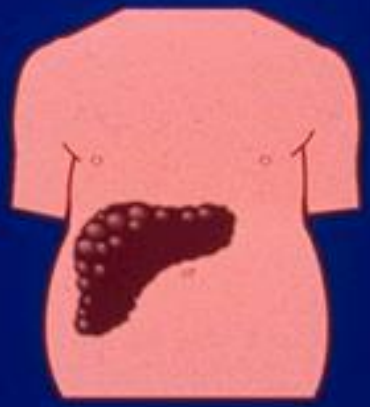
After

SBP

Clinical Setting

Advanced cirrhosis:

- ↑ serum bilirubin
- ↑ prothrombin time



Ascites, usually large volume

50% of cases detected on hospital admission

- often asymptomatic

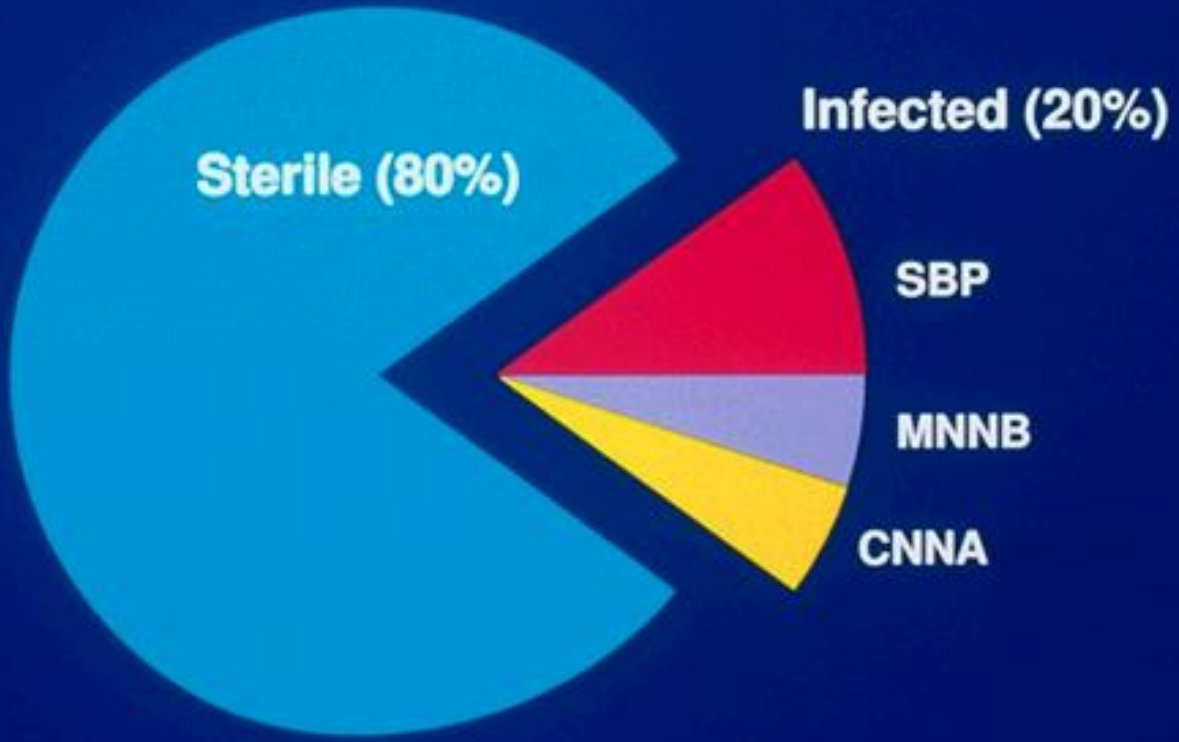
(SBP) should be suspected in a patient with ascites and any of the following:

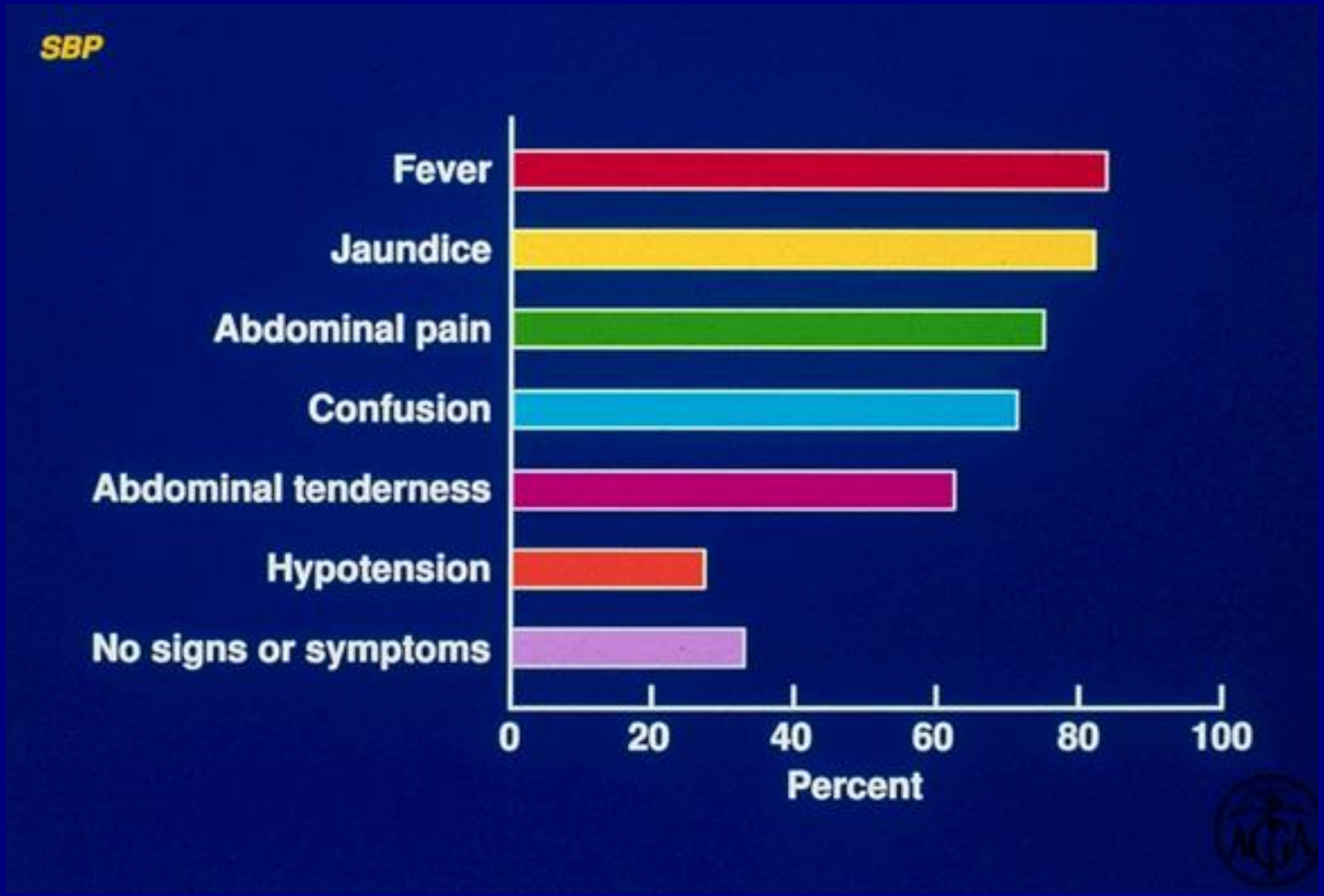
- Temperature greater than 37.8°C (100°F)
- Abdominal pain and/or tenderness
- A change in mental status
- Ascitic fluid PMN count ≥250 cells/mm^3

Also Gob SBP without symptoms.

ASCITES

Initial Paracentesis




SBP
Fever
Jaundice
Abdominal pain
Confusion
Abdominal tenderness
Hypotension
No signs or symptoms
0
20
40
60
80
100
Percent

SBP

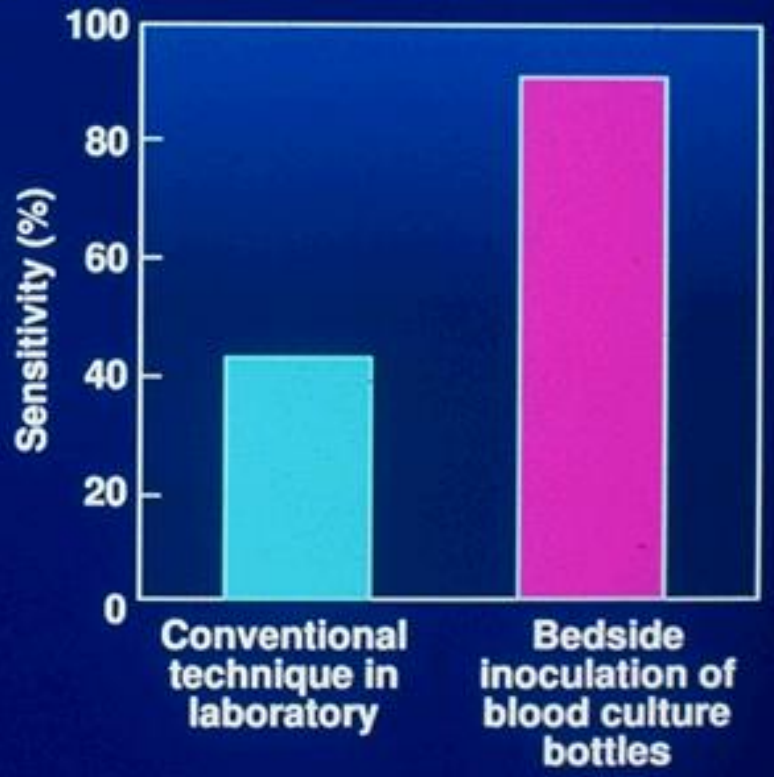
ORGANISM	%
Escherichia coli	43
Klebsiella pneumoniae	8
Streptococcus pneumoniae	8
Alpha-hemolytic streptococcus	5
Group D streptococcus	5
Other streptococcus	8
Miscellaneous Enterobacteriaceae	3
Miscellaneous	20

MC

SBP

Ascitic Fluid Culture Technique

Blood culture bottles



Neb in normal Jars since this will increase the chance of catching the micro organism.

SBP

Antibiotic Treatment

- Initiate for ascitic fluid PMN ≥250/mm^3
- Administer broad spectrum bactericidal drug intravenously
- Avoid aminoglycosides
- Treat for 5 days

In patients receiving a nonselective beta blocker, we permanently discontinue the medication once SBP has developed

Patients at high risk for SBP include:

- •Patients with cirrhosis and gastrointestinal bleeding.
- •Patients who have had one or more episodes of SBP
- •Patients with cirrhosis and ascites if the ascitic fluid protein is <1.5 g/dL along with either impaired renal function or liver failure.

Impaired renal function is defined as a creatinine ≥1.2 mg/dL ,a blood urea nitrogen level ≥25 mg/dL, or a serum sodium ≤130 mEq/L .

Liver failure is defined as a Child-Pugh score ≥9 and a bilirubin ≥3 mg/dL.

SBP

Prevention

Eliminate or reduce ascites

- diuresis
- paracentesis
- TIPS

No Ascites, no SBP

Antibiotic prophylaxis

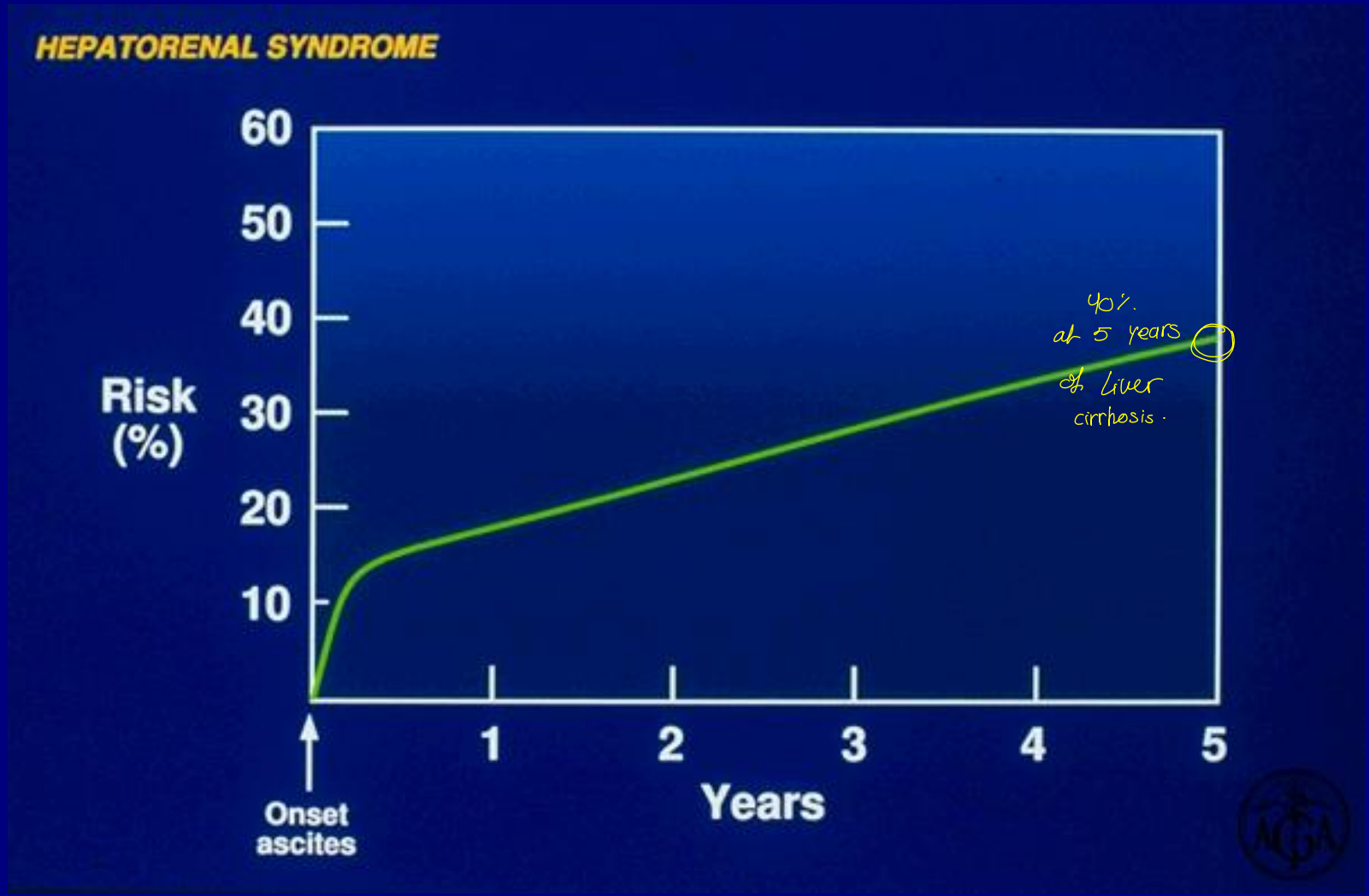
- prevention of initial episode
- prevention of recurrence

HEPATORENAL SYNDROME

- Progressive renal failure associated with advanced cirrhosis and ascites
- No other cause of renal failure
- No previous renal disease

Cirrhotic

Normal


HEPATORENAL SYNDROME
60
50
40
30
20
10
Risk (%)
40% at 5 years of liver cirrhosis.
1
2
3
4
5
Years
Onset ascites

HEPATORENAL SYNDROME

Setting

- Advanced liver disease: cirrhosis, alcoholic hepatitis, fulminant hepatitis
- Usually occurs after hospitalization
- Often no precipitating factor

Clinical Features

- Ascites
- Hypotension
- Oliguria
- Jaundice

Course

- Typically death within weeks

Laboratory Features

- Azotemia
- Hyponatremia

- Urine sodium <10 mEq/L
- Urine sediment unremarkable

very very imp

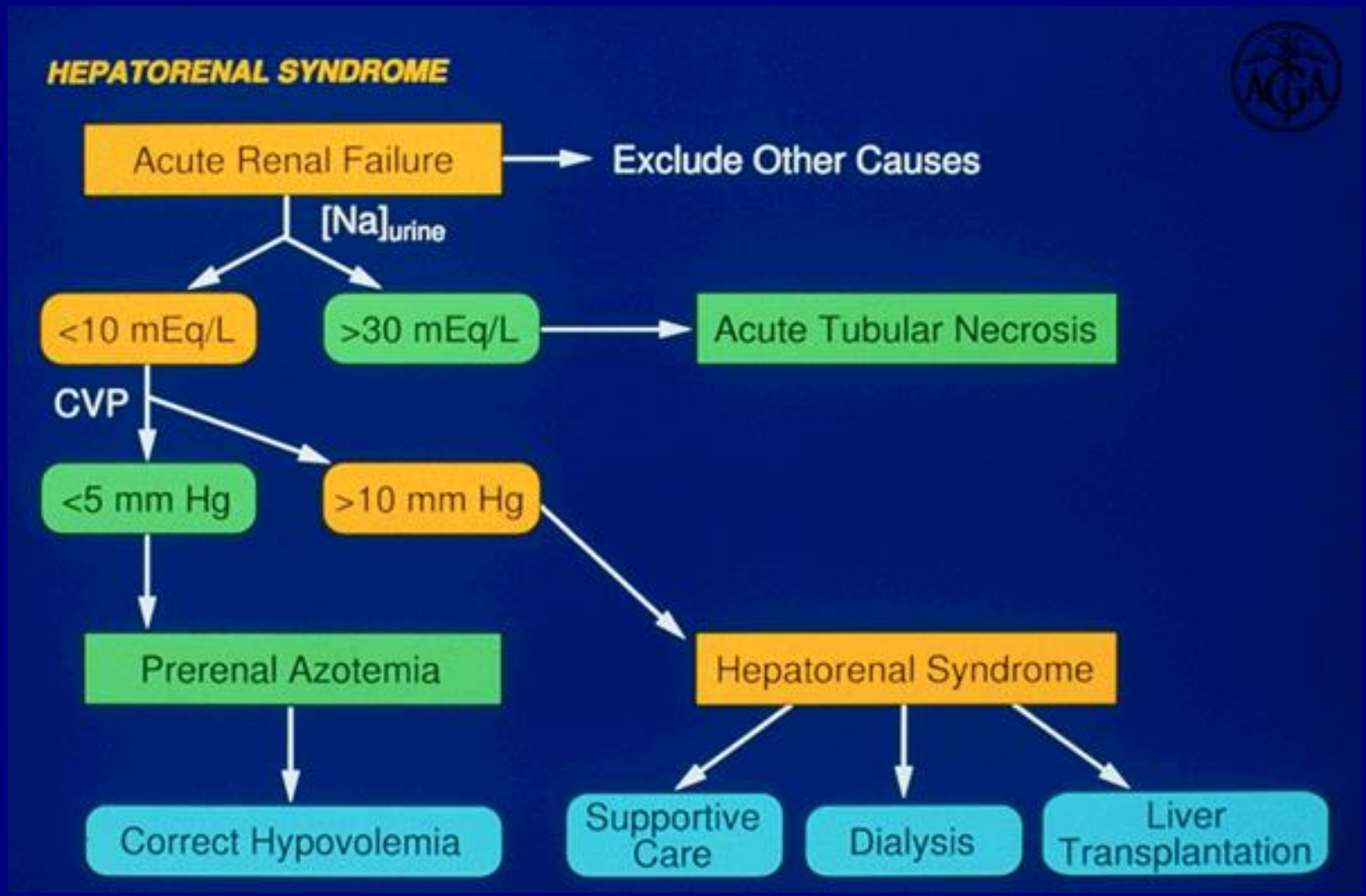
- Urine/plasma creatinine ratio >30
- Urine/plasma osmolality ratio >1

HEPATORENAL SYNDROME

Azotemia in Patients with Liver Disease

	HRS	Prerenal Azotemia	Acute Tubular Necrosis
Urine sodium (mEq/L)	< 10	< 10	>30
Urine/plasma creatinine	> 30	> 30	< 30
Urine/plasma osmolality	> 1	> 1	1
Urine sediment	Normal	Normal	Casts, cellular debris
Response to sustained plasma expansion	Absent	Good	Absent

the most imp difference.

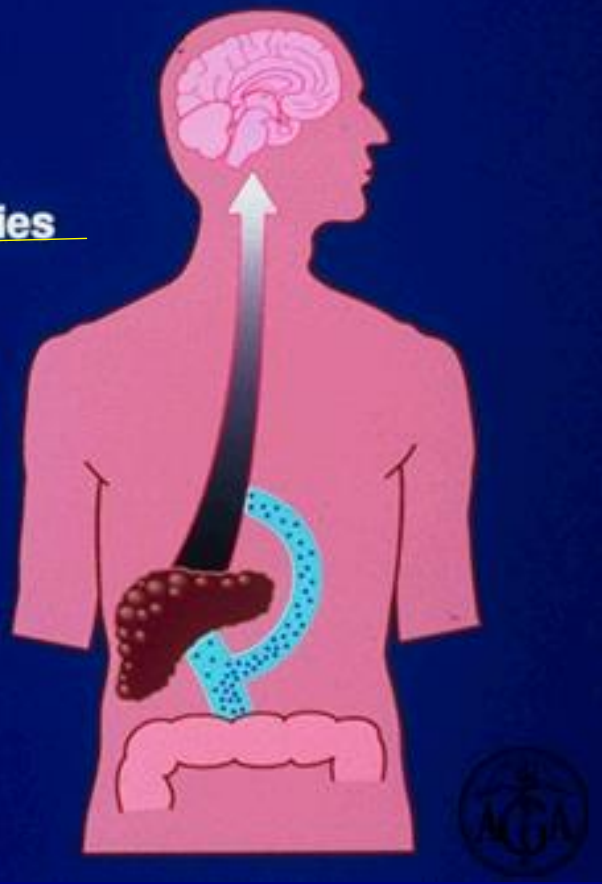

HEPATORENAL SYNDROME
Acute Renal Failure
Exclude Other Causes
[Na]urine
<10 mEq/L
>30 mEq/L
Acute Tubular Necrosis
CVP
<5 mm Hg
>10 mm Hg
Prerenal Azotemia
Hepatorenal Syndrome
Correct Hypovolemia
Supportive Care
Dialysis
Liver Transplantation

HEPATORENAL SYNDROME

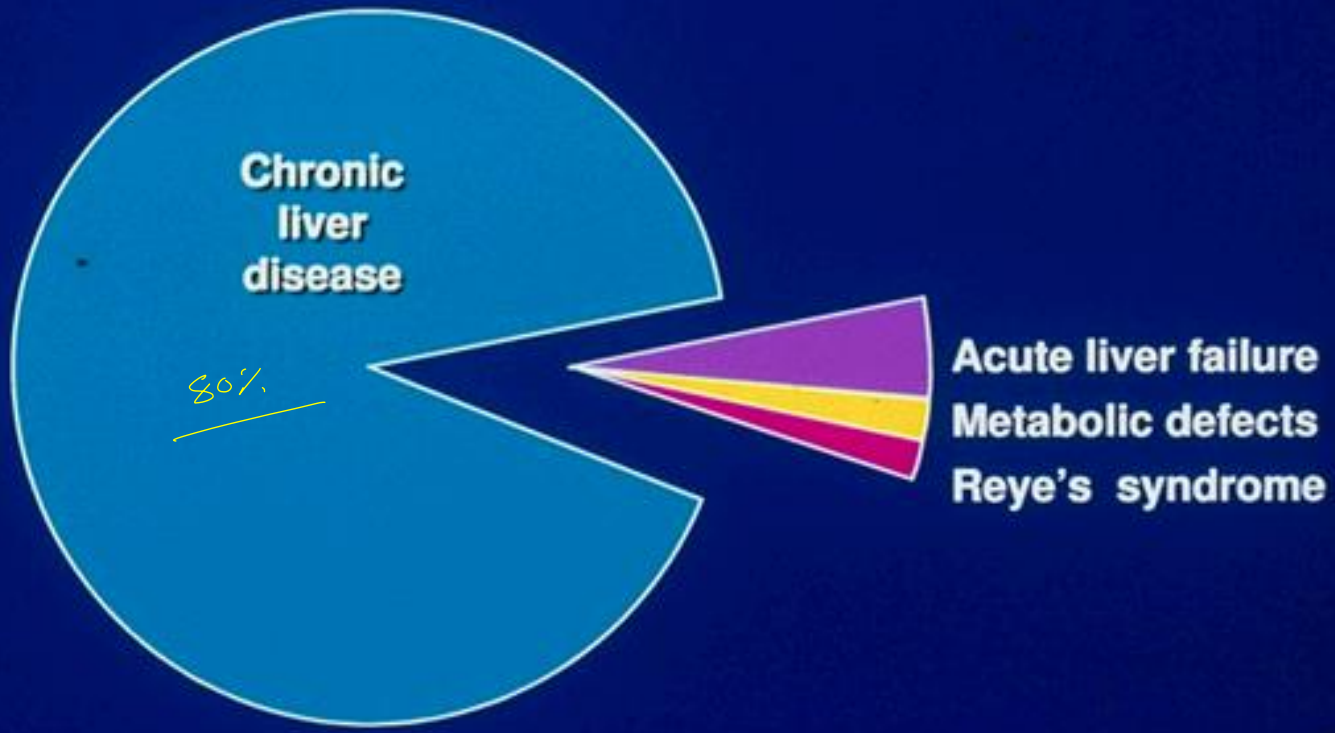
- Identify other causes
- Establish circulatory volume
- Restrict sodium and water
- Avoid nephrotoxic agents
- Consider hemodialysis
- Evaluate for liver transplantation

HEPATIC ENCEPHALOPATHY

- Reversible neuropsychiatric abnormalities
- Asterixis and abnormal EEG
- Hepatic failure and/or portosystemic shunting



HEPATIC ENCEPHALOPATHY



HEPATIC ENCEPHALOPHATHY

Doesn't show symptoms. ←

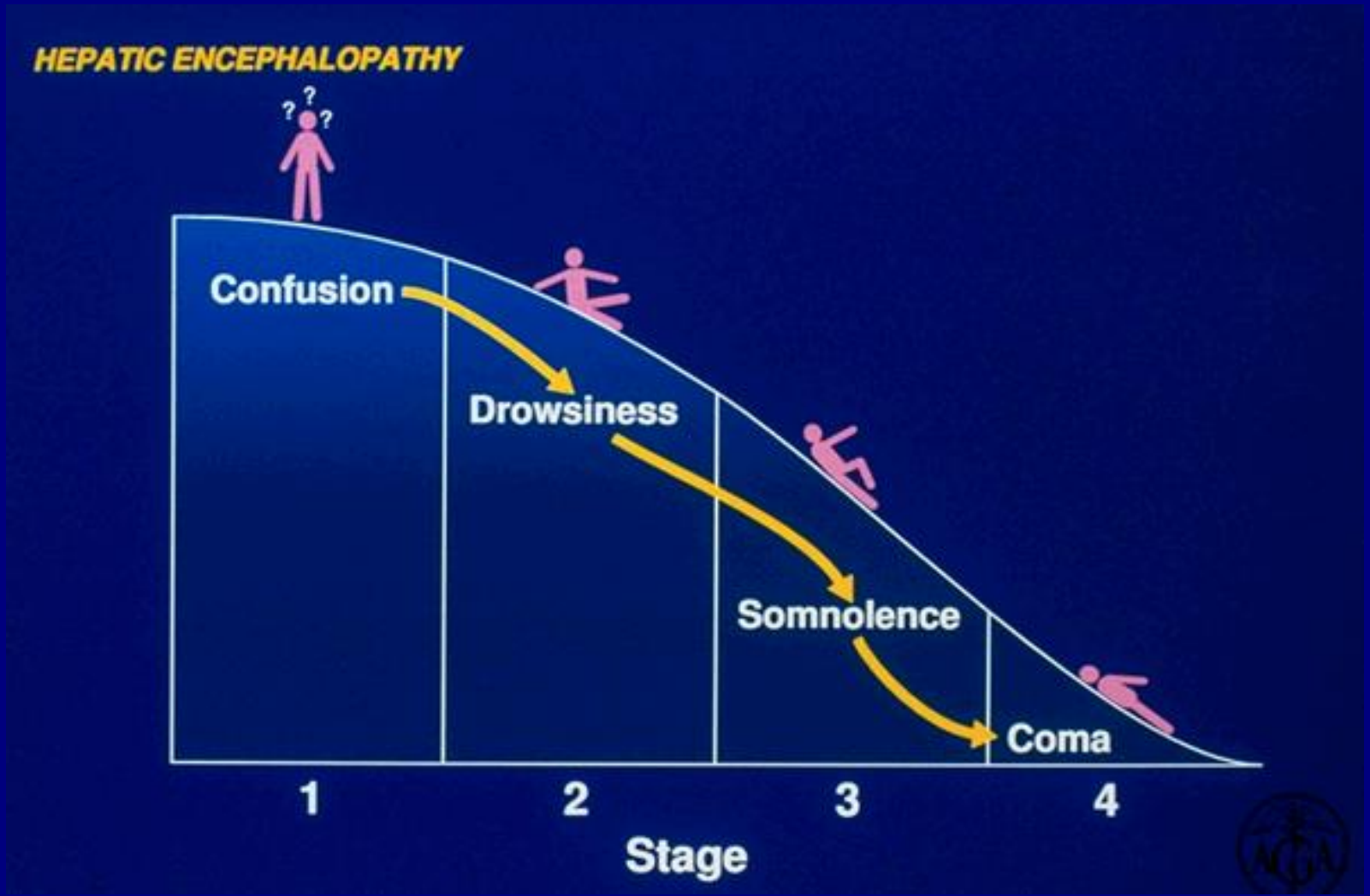
Subclinical

- Present in 50-85% of cirrhotics
- Subtle neuropsychological changes
- Normal EEG
- Diagnosed by psychomotor testing
- Reversible with empiric treatment

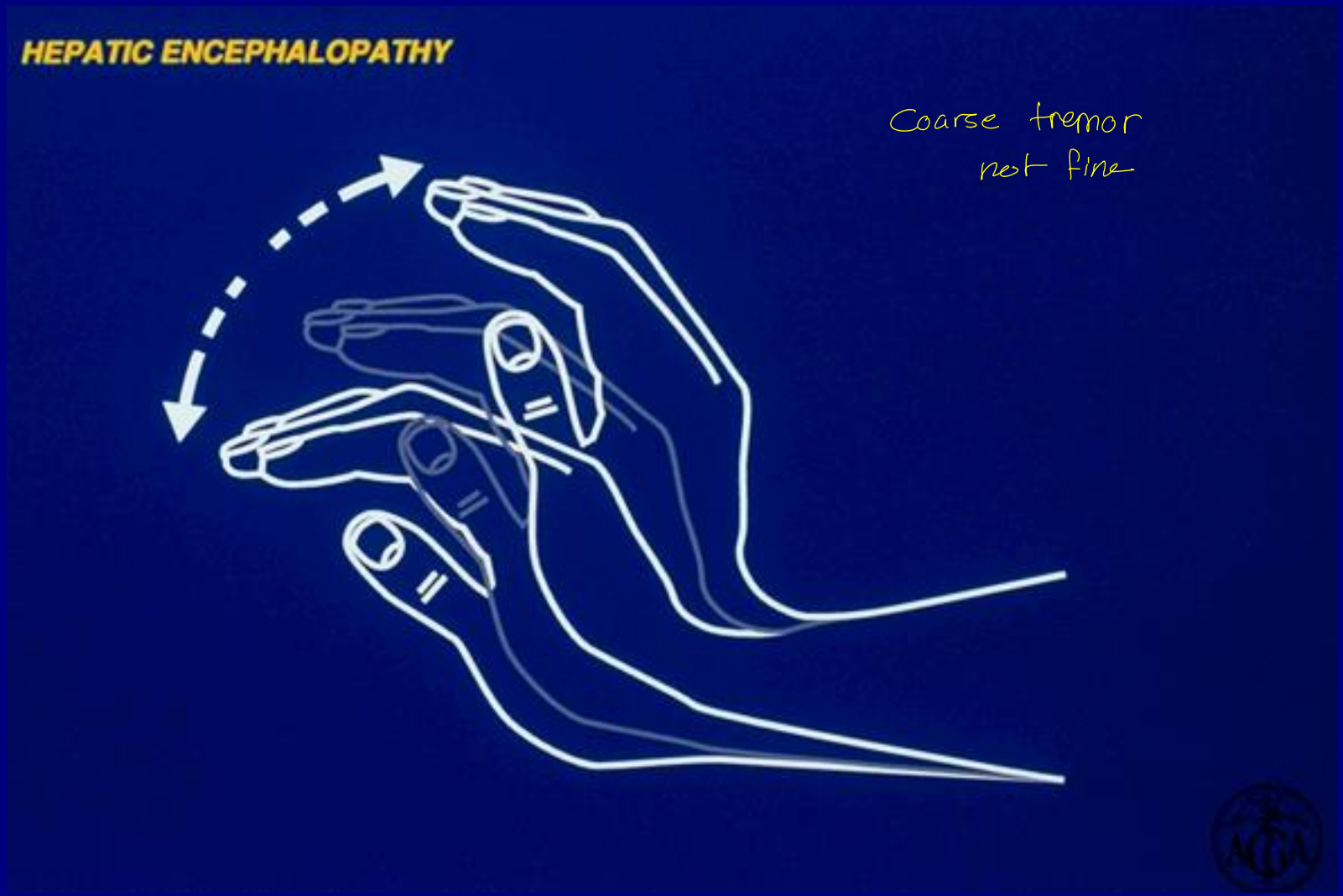
HEPATIC ENCEPHALOPHATHY

imp to know.

Stage	Mental State	Neurologic Signs
1	Mild confusion; ↓ attention; 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


HEPATIC ENCEPHALOPATHY
Confusion
Drowsiness
Somnolence
Coma
1
2
3
4
Stage

HEPATIC ENCEPHALOPATHY

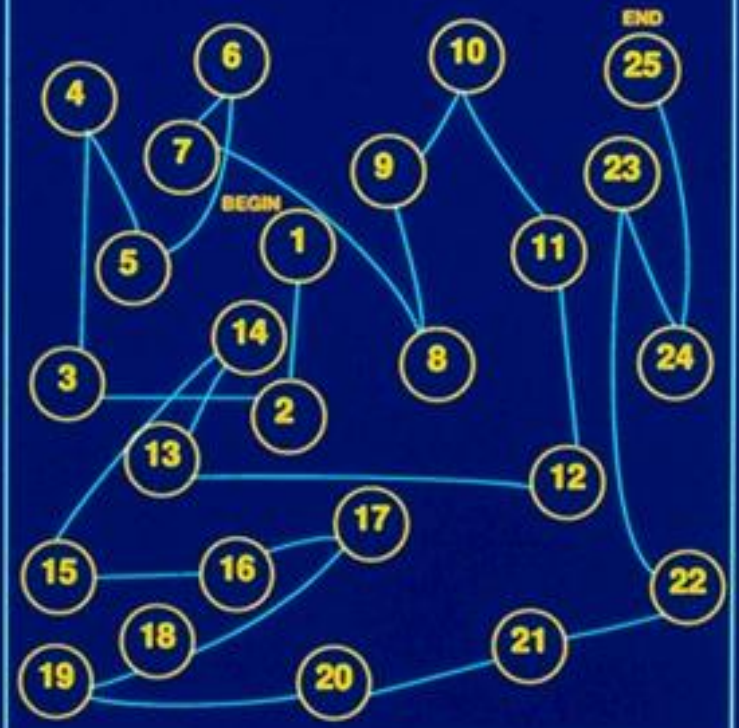


HEPATIC ENCEPHALOPATHY

they can't do any of these.

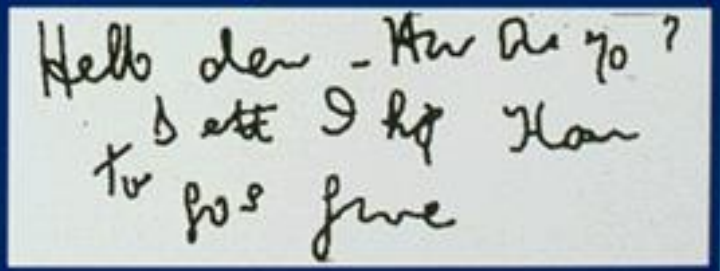
Number Connection Test

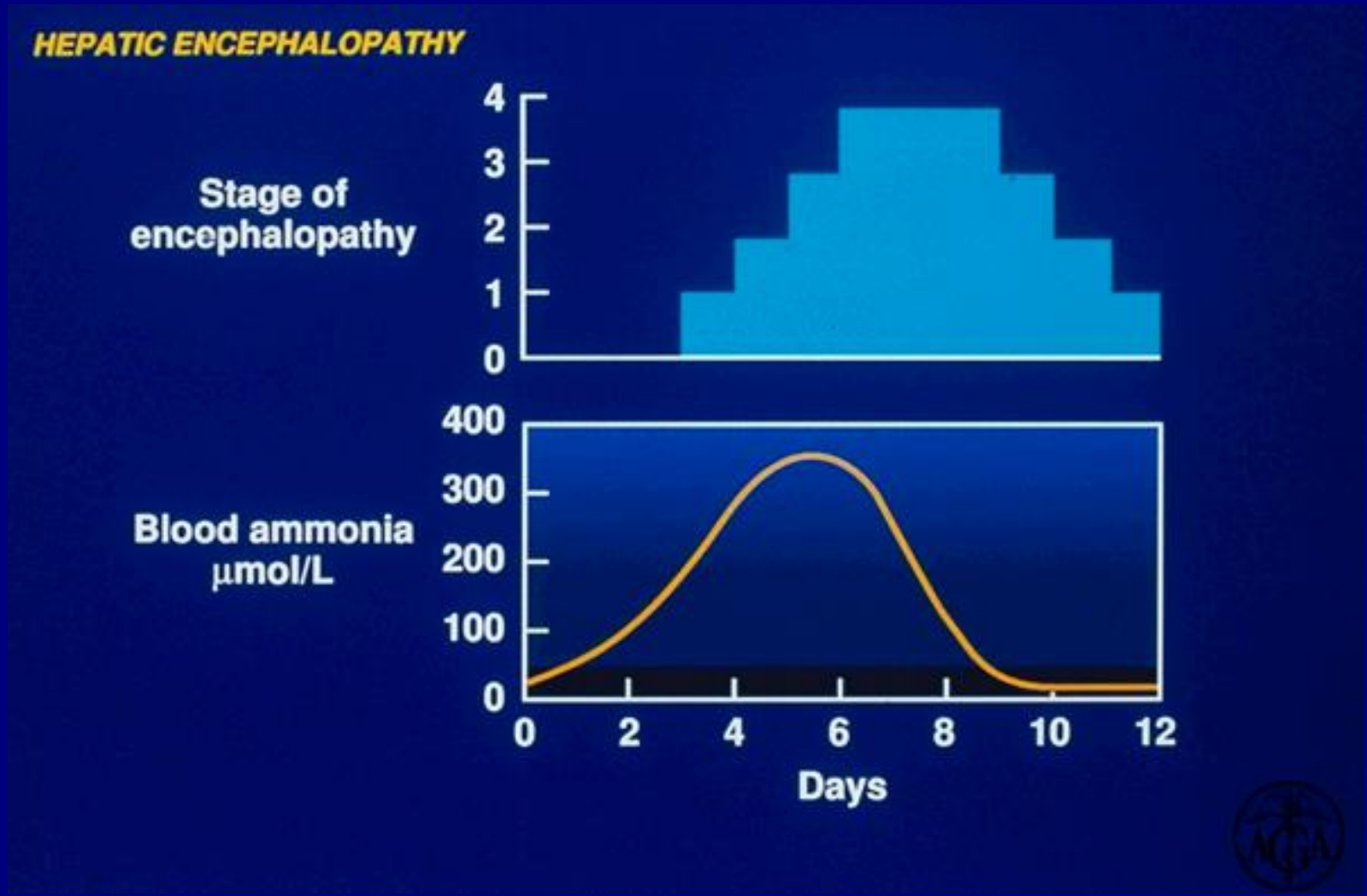
Time to complete _____



Draw a Star

Sample Handwriting




HEPATIC ENCEPHALOPATHY
Stage of encephalopathy
4
3
2
1
0
Blood ammonia μmol/L
400
300
200
100
0
0
2
4
6
8
10
12
Days

High blood-ammonia levels alone do not add any diagnostic, staging, or prognostic value in HE patients

with CLD.

However, in case an ammonia level is checked in a patient with HE and it is normal, the diagnosis of HE is in question.

HEPATIC ENCEPHALOPHATHY

Differential Diagnosis

Intracranial lesions
Hematoma, infarct,
tumor, abscess

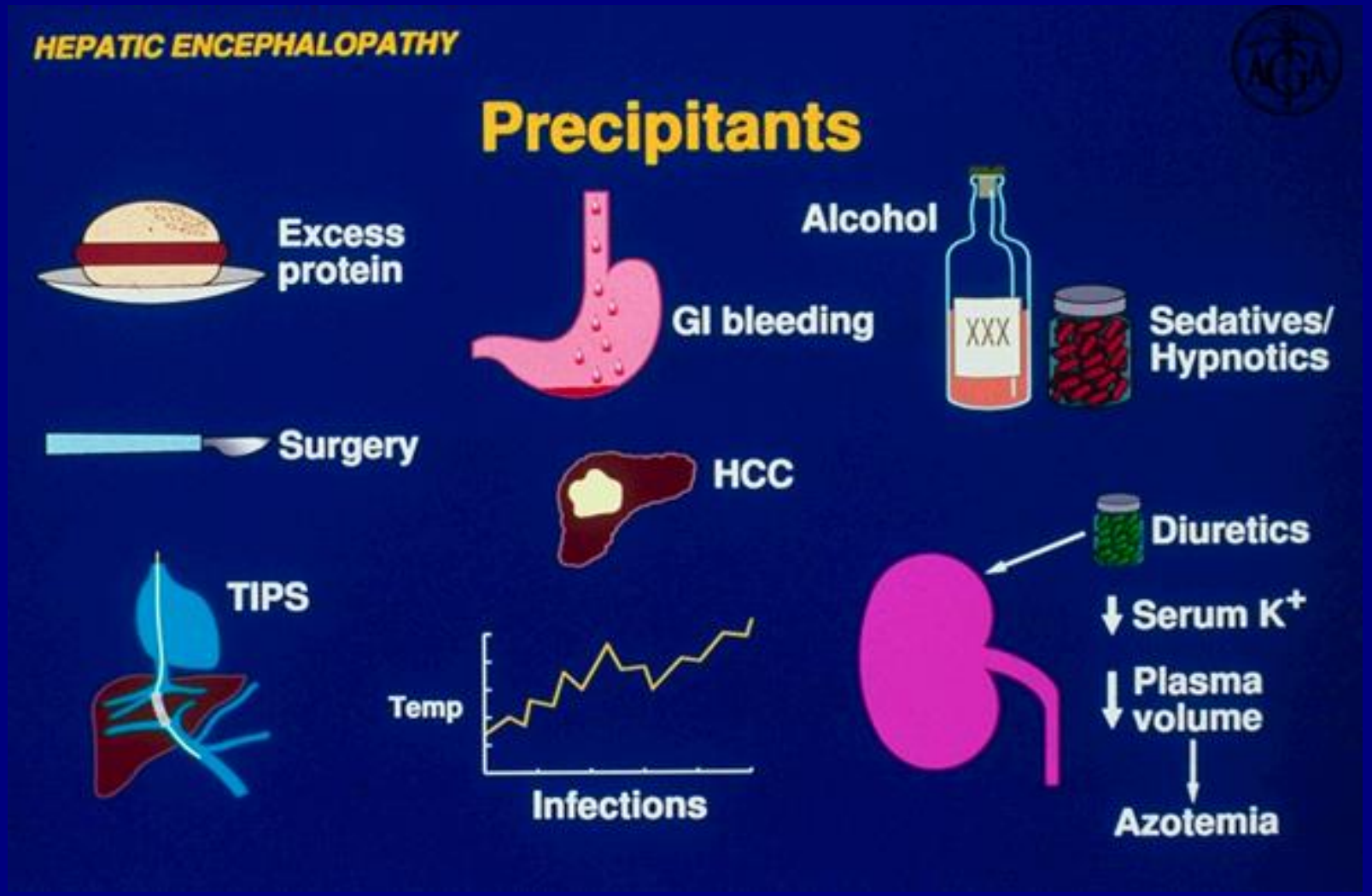
Metabolic
Electrolyte imbalance,
uremia, ↑/↓ glucose,
hypercapnea, hypoxia

Infections
Meningitis, sepsis

Alcohol
Intoxication, withdrawal

Miscellaneous
Psychiatric, post-seizure

Drugs
Sedatives, tranquilizers


HEPATIC ENCEPHALOPATHY
Precipitants
Excess protein
GI bleeding
Alcohol
XXX
Sedatives/ Hypnotics
Surgery
HCC
Diuretics
TIPS
Serum K+
Plasma volume
Temp
Infections
Azotemia

Lactulose is the first choice for treatment of episodic HE.

The dose of lactulose (30 to 45 mL [20 to 30 g] two to four times per day) should be titrated to achieve two to three soft stools per day.

Lactulose enemas can be given if the patient cannot take lactulose orally

For patients who have not improved within 48 hours of starting lactulose , rifaximin is used.

Rifaximin is an effective add-on therapy to lactulose for prevention of OHE recurrence

HEPATIC ENCEPHALOPATHY

Actions of Lactulose