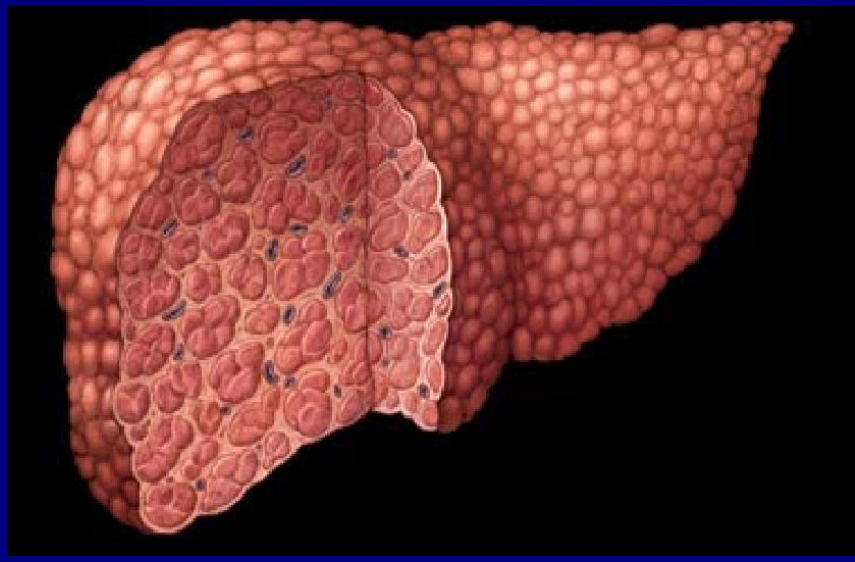
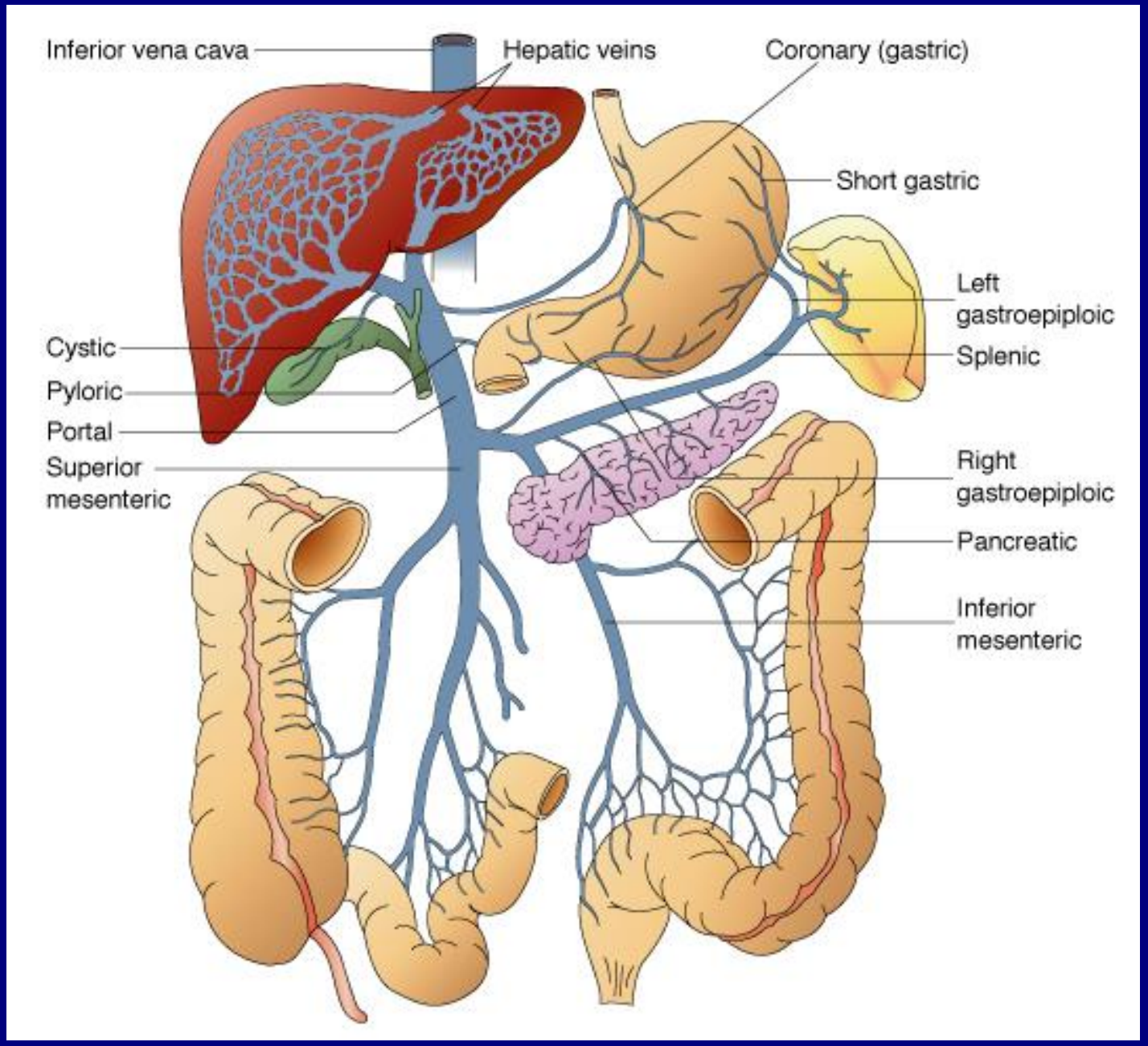
# Liver Cirrhosis

- Irriversible late stage of progressive hepatic fibrosis.
  - Distortion of the hepatic architecture
  - Formation of regenerative nodules.

- Treatment :
- Liver Transplantation




Inferior vena cava
Hepatic veins
Coronary (gastric)
Short gastric
Left gastroepiploic
Splenic
Cystic
Pyloric
Portal
Superior mesenteric
Right gastroepiploic
Pancreatic
Inferior mesenteric

# 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.
- 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

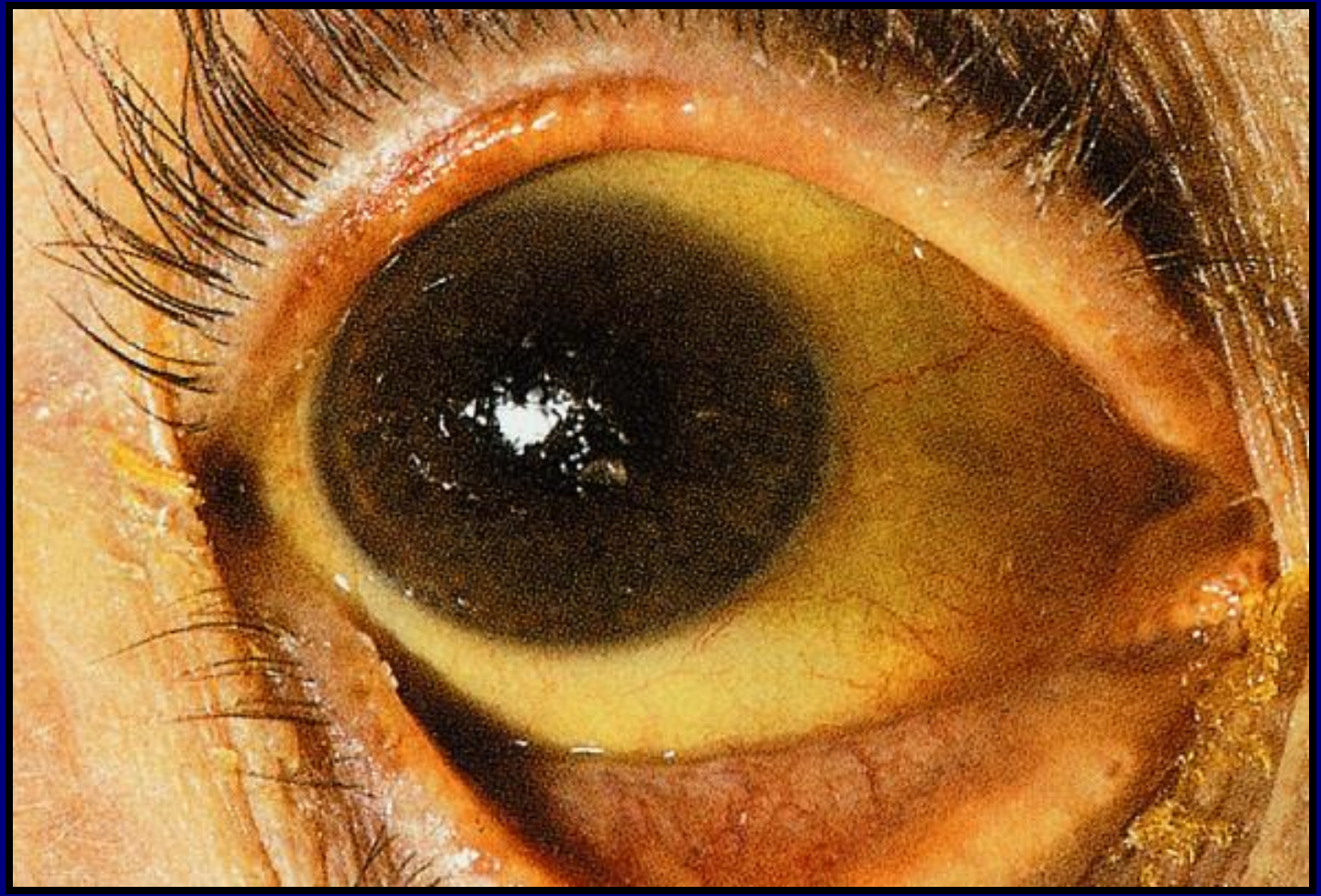
- The liver stores a multitude of substances, including glucose (in the form of glycogen), vitamin A (1–2 years' supply), vitamin D (1–4 months' supply), vitamin B12, iron, and copper.
- The liver is responsible for immunological effects- the reticuloendothelial system of the liver contains many immunologically 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.

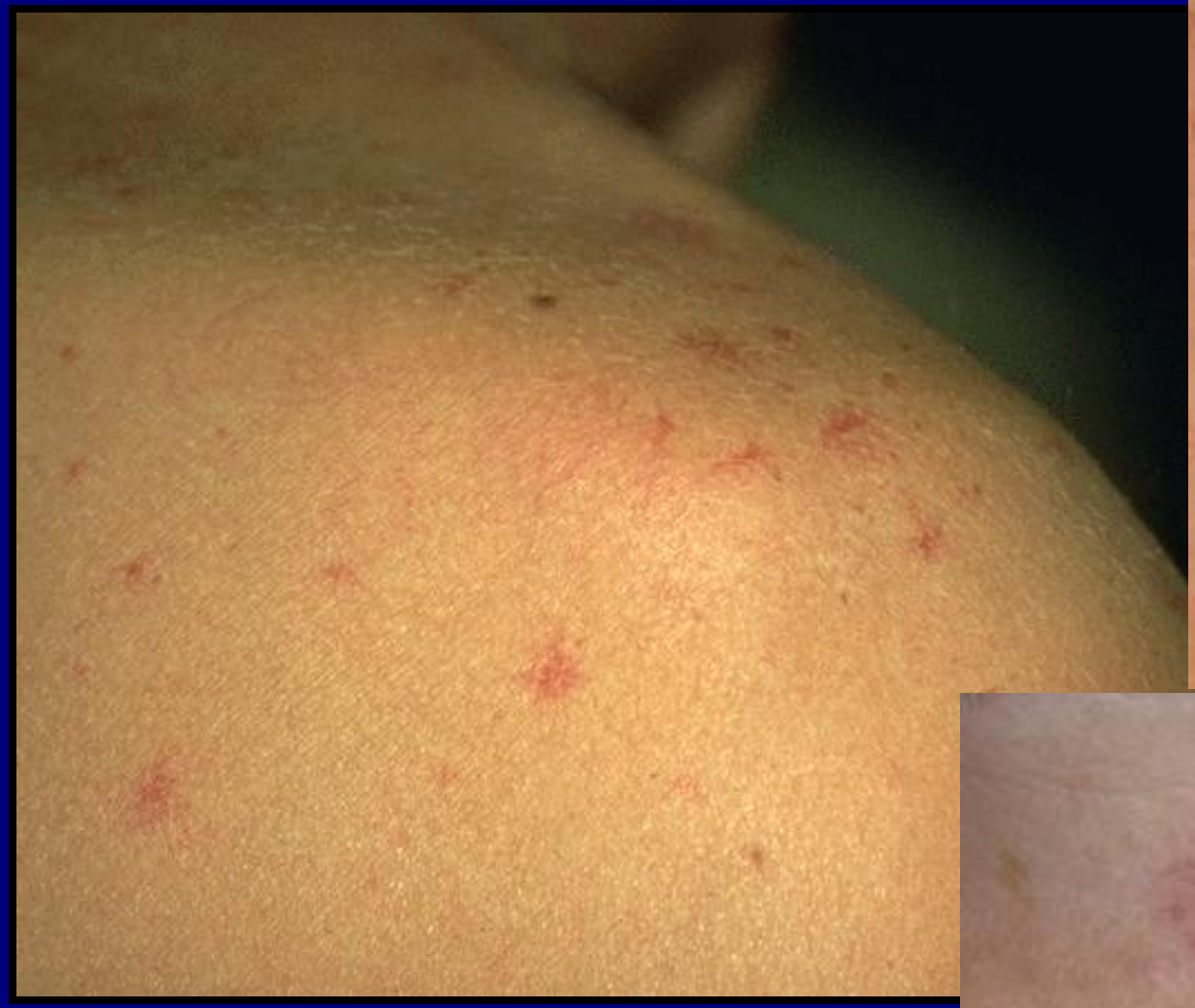
# Clinical Presentation

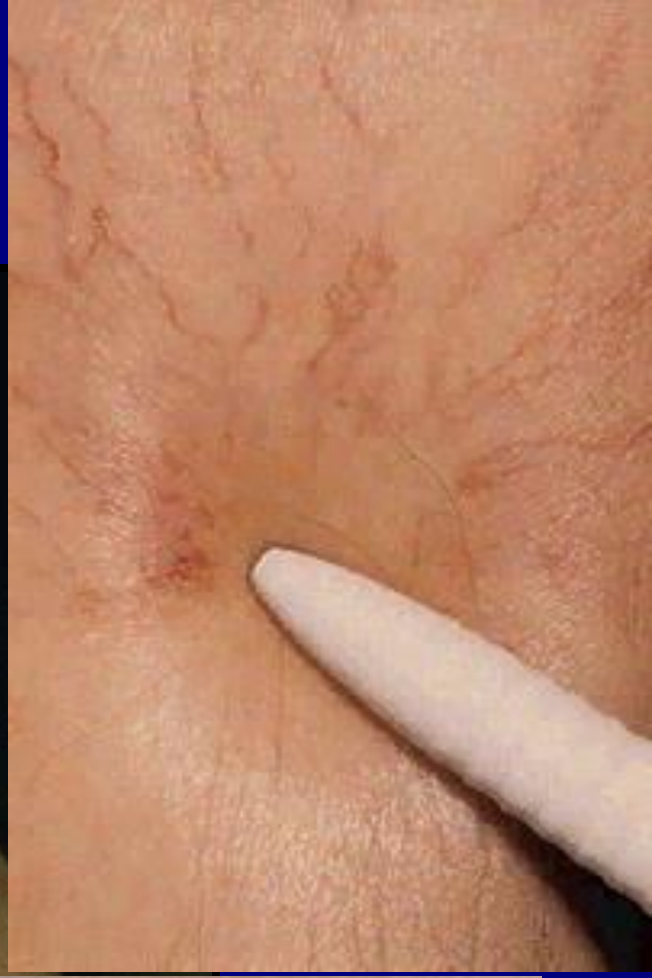
- Asymptomatic:
  - They may have stigmata of chronic liver disease discovered on routine physical examination.
  - They may have undergone laboratory or radiologic testing or an unrelated surgical procedure that incidentally uncovered the presence of cirrhosis.
- Decompensated cirrhosis (Complications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

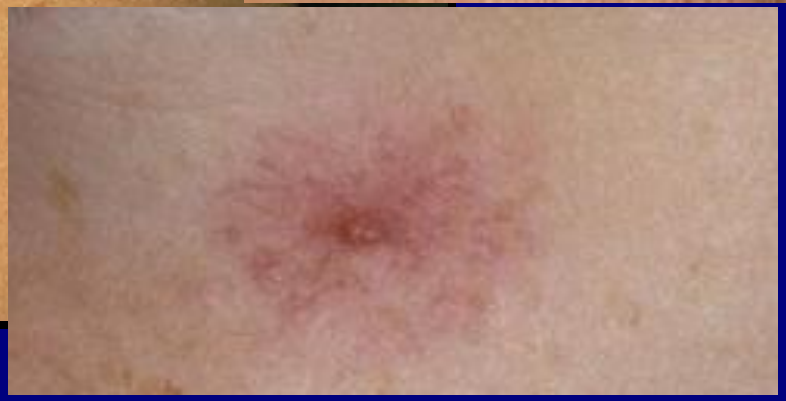
# Physical Findings

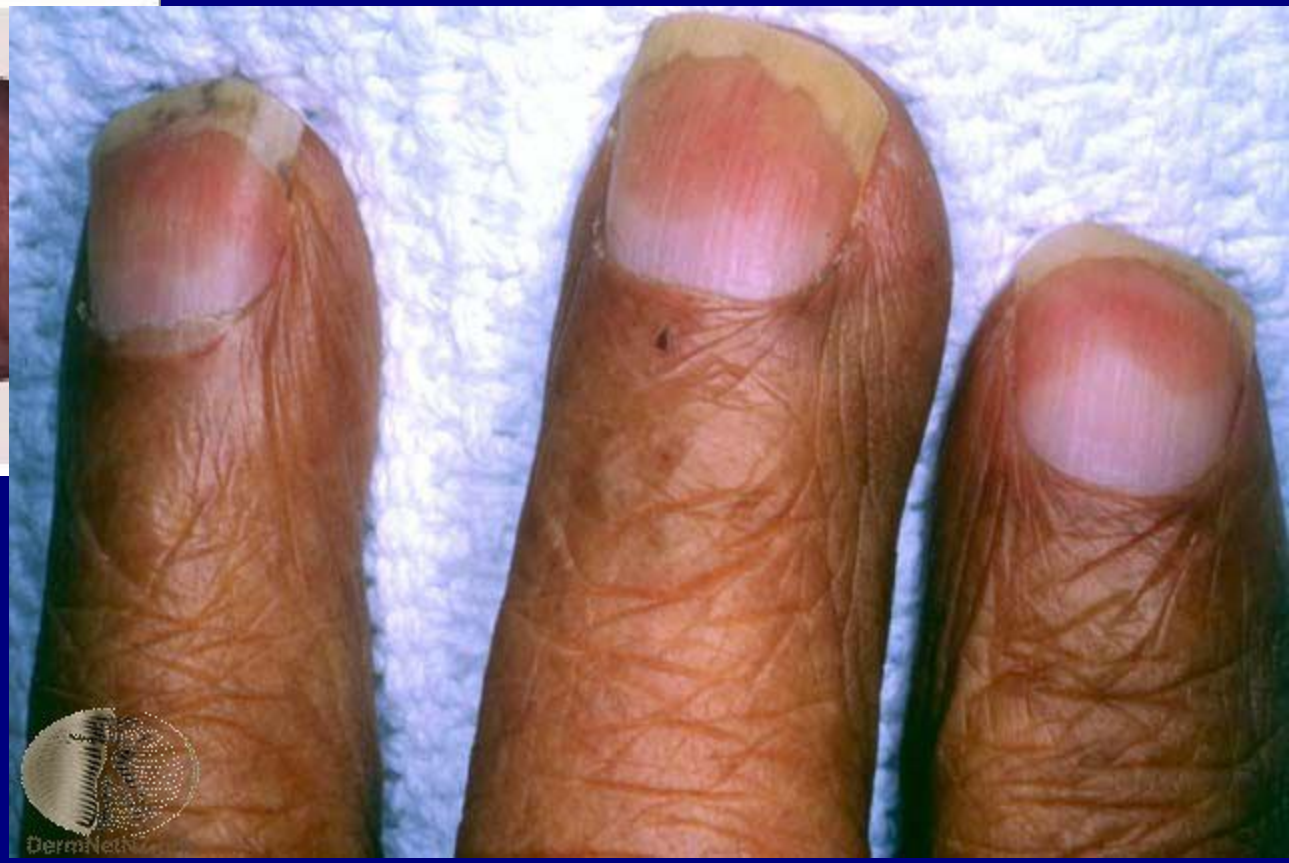
- Spider angiomata
- Palmar erythema
- Nail changes:  Terry's nails
- Clubbing and hypertrophic osteoarthropathy
- Dupuytren's contracture
- Gynecomastia
- Testicular atrophy
- Hepatomegaly
- Splenomegaly
- Caput medusae
- Fetor hepaticus

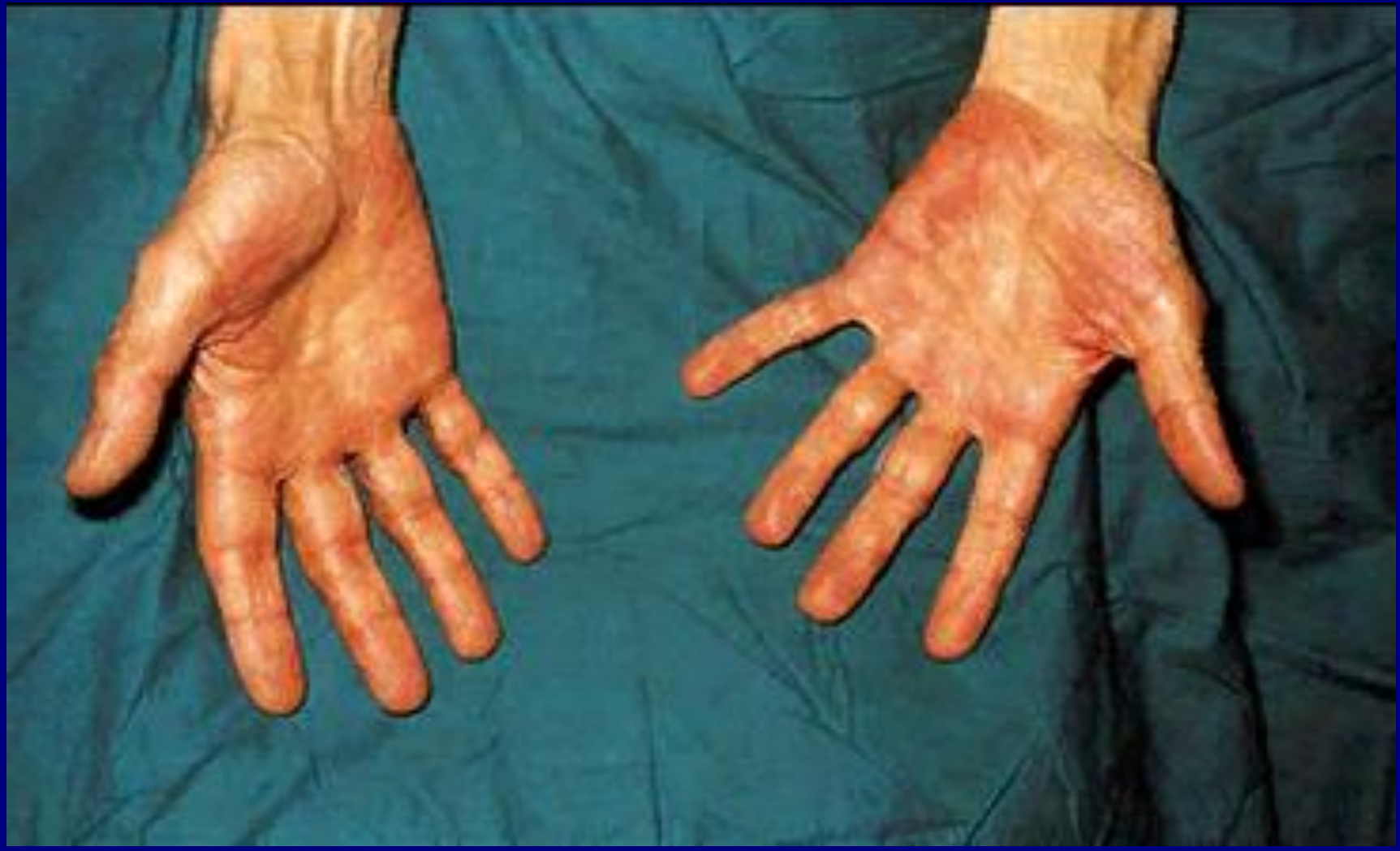


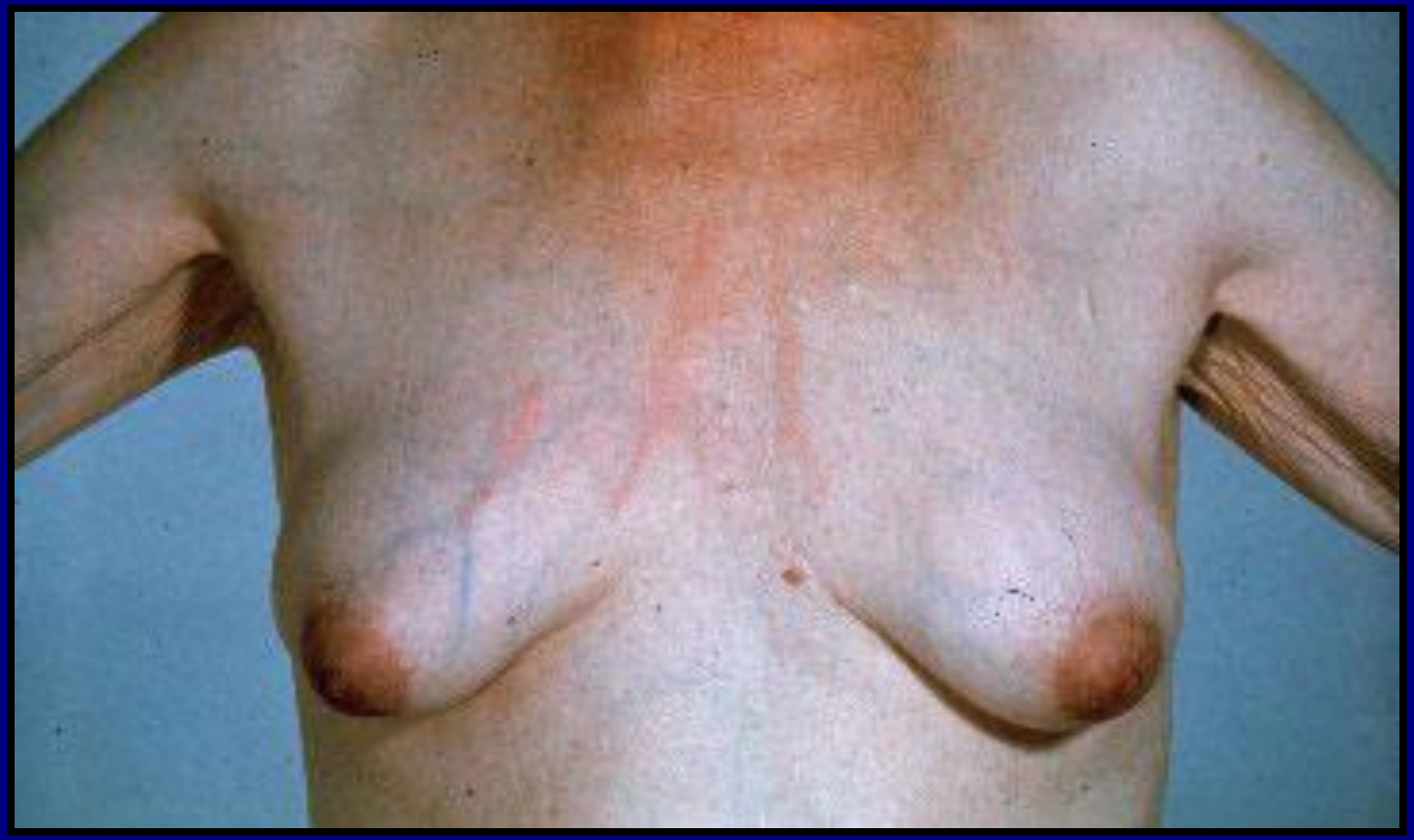


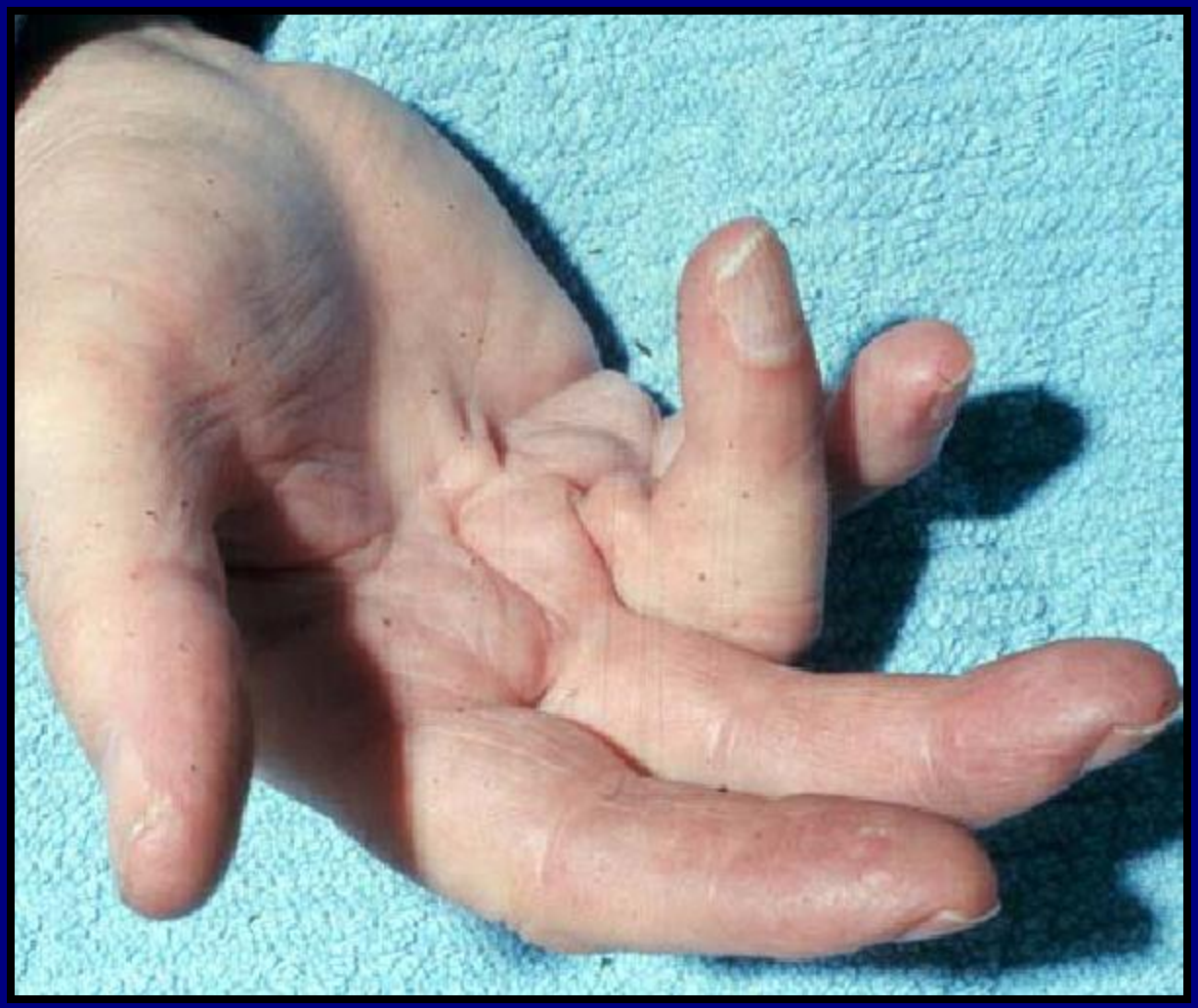


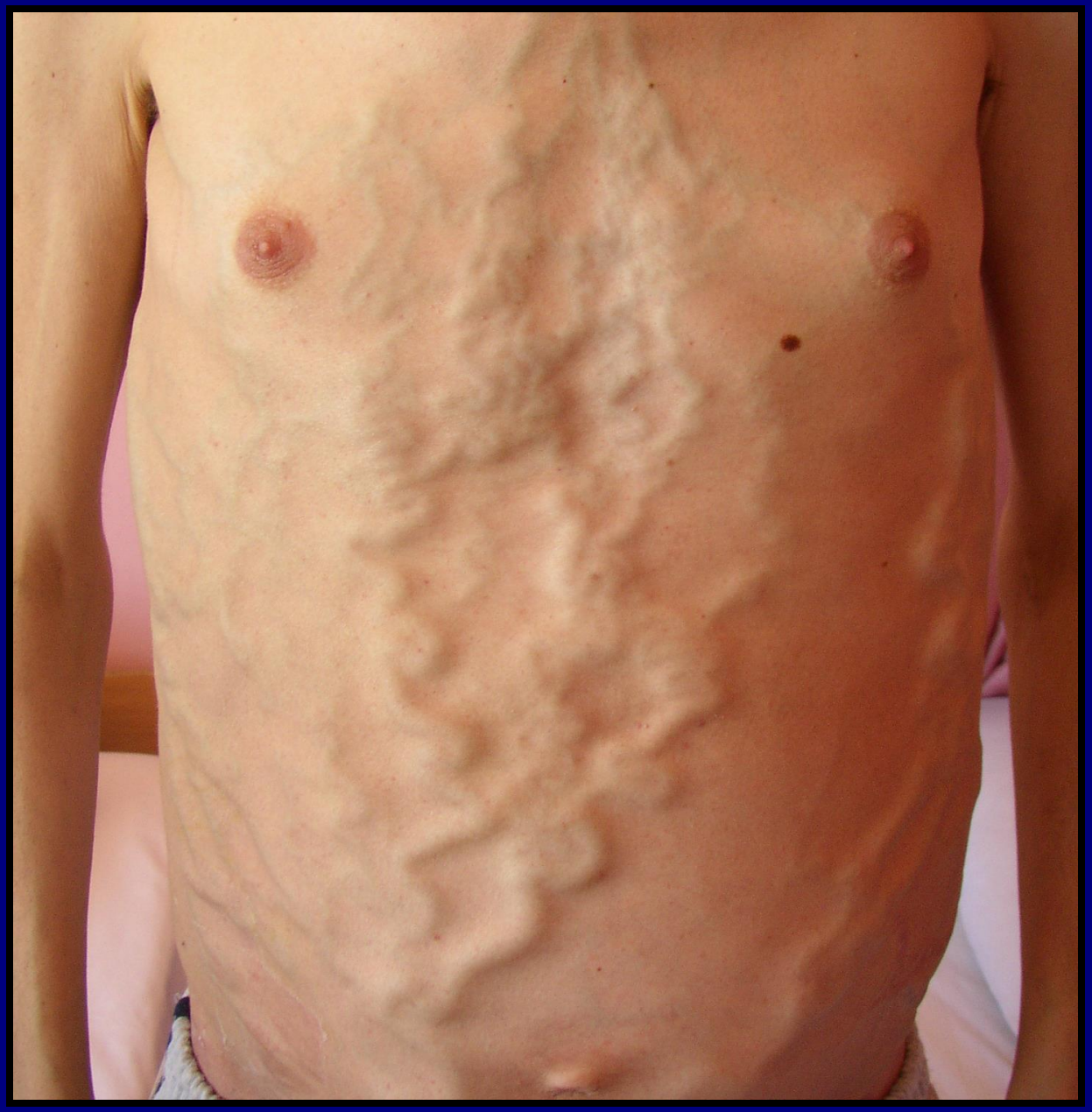












# Laboratory Findings

- Aminotransferases

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.

- 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
  - may be normal in well compensated cirrhosis then rise progressively.
- Albumin
  - 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
  - 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
  - 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

- Serum sodium
  - 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 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 portal hypertension with attendant congestive splenomegaly. An enlarged spleen can result in temporary sequestration of up to 90 percent of the circulating platelet mass.
- Leukopenia and neutropenia
  - Leukopenia and neutropenia are due to hypersplenism

# Radiographic findings

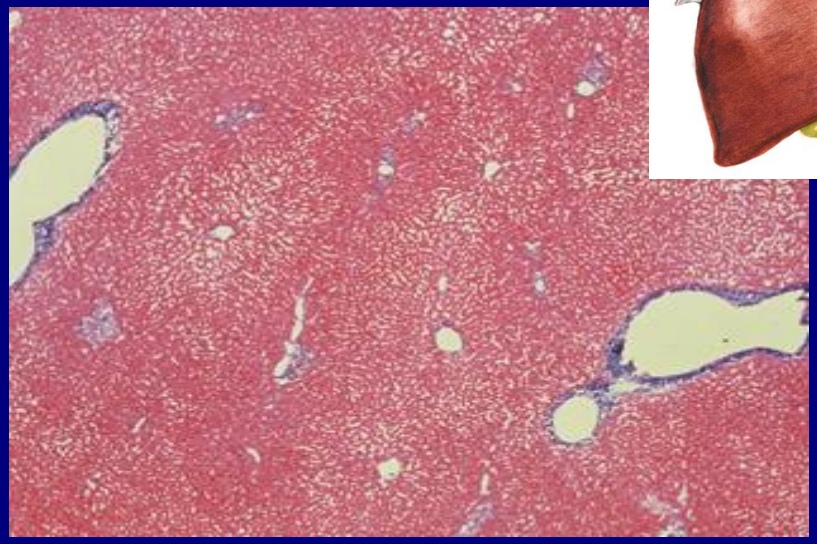
- Suggestive of cirrhosis but they are not adequately sensitive or specific for use as a primary diagnostic modality
- Ultrasonography
  - Routinely used during the evaluation of the cirrhotic patient.
  - It is noninvasive, well tolerated, widely available, and provides valuable information.
  - In 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
  - 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.
- CT Scan and MRI

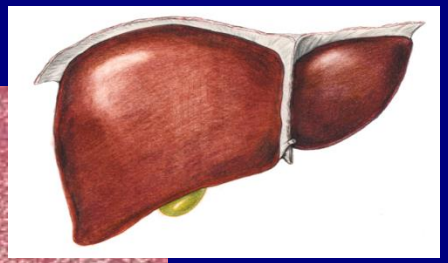
# Liver Histology

- 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

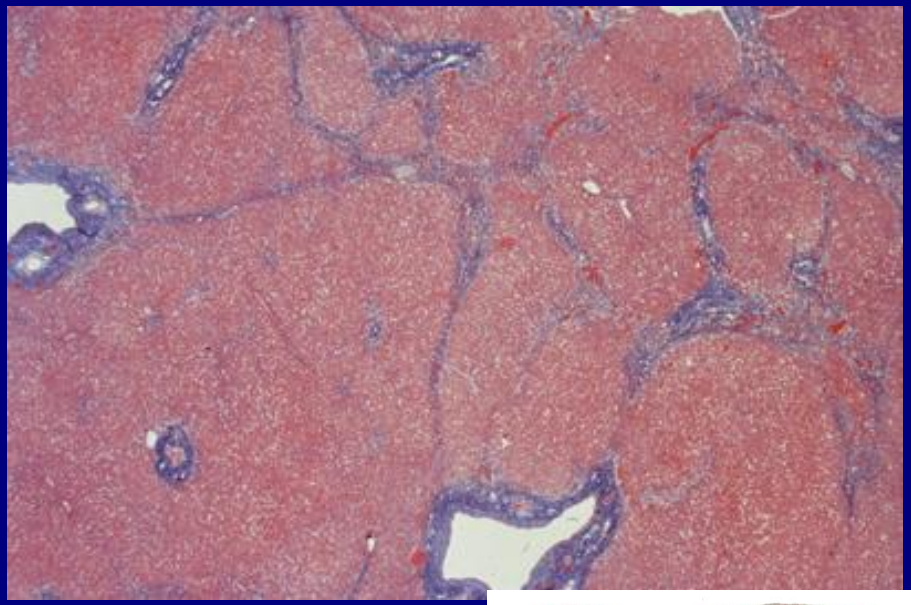
- liver biopsy
  - Sample of the liver is obtained by either a percutaneous, transjugular, laparoscopic, or radiographically-guided fine-needle approach depending upon the clinical setting
  - The sensitivity is 80 – 100 % depending upon the method used, and the size and number of specimens obtained
  - Can suggest the cause. This is especially true for metabolic causes of cirrhosis

## Healthy Liver

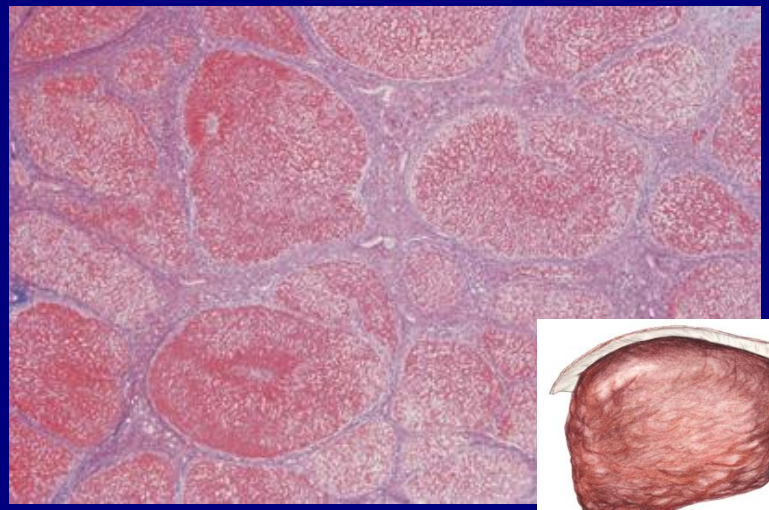


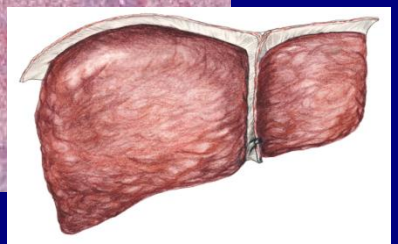


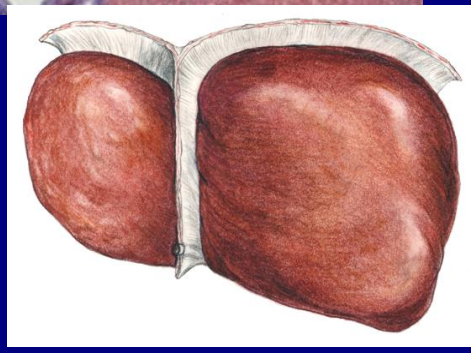
## Liver Fibrosis



## Cirrhosis





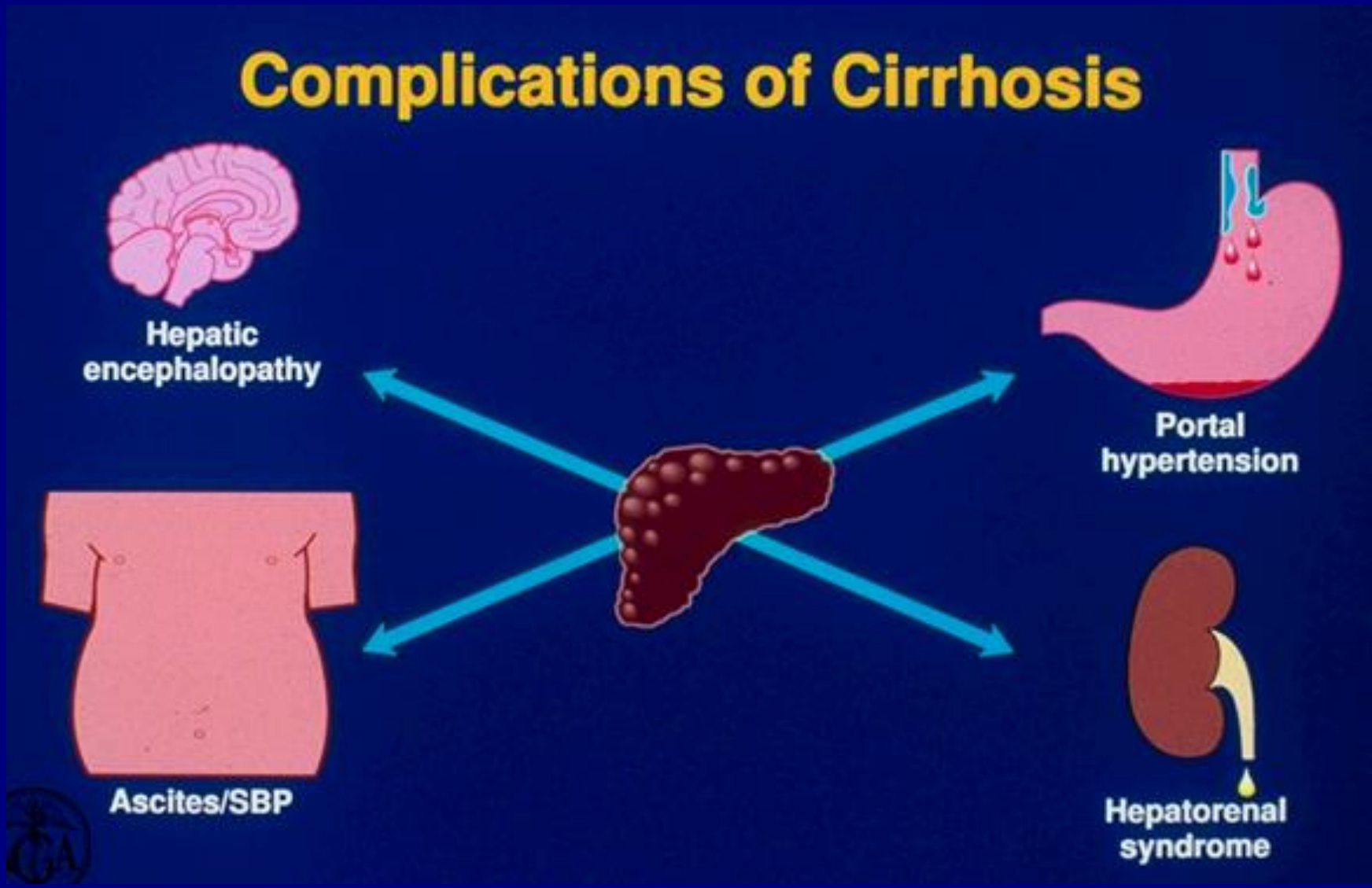


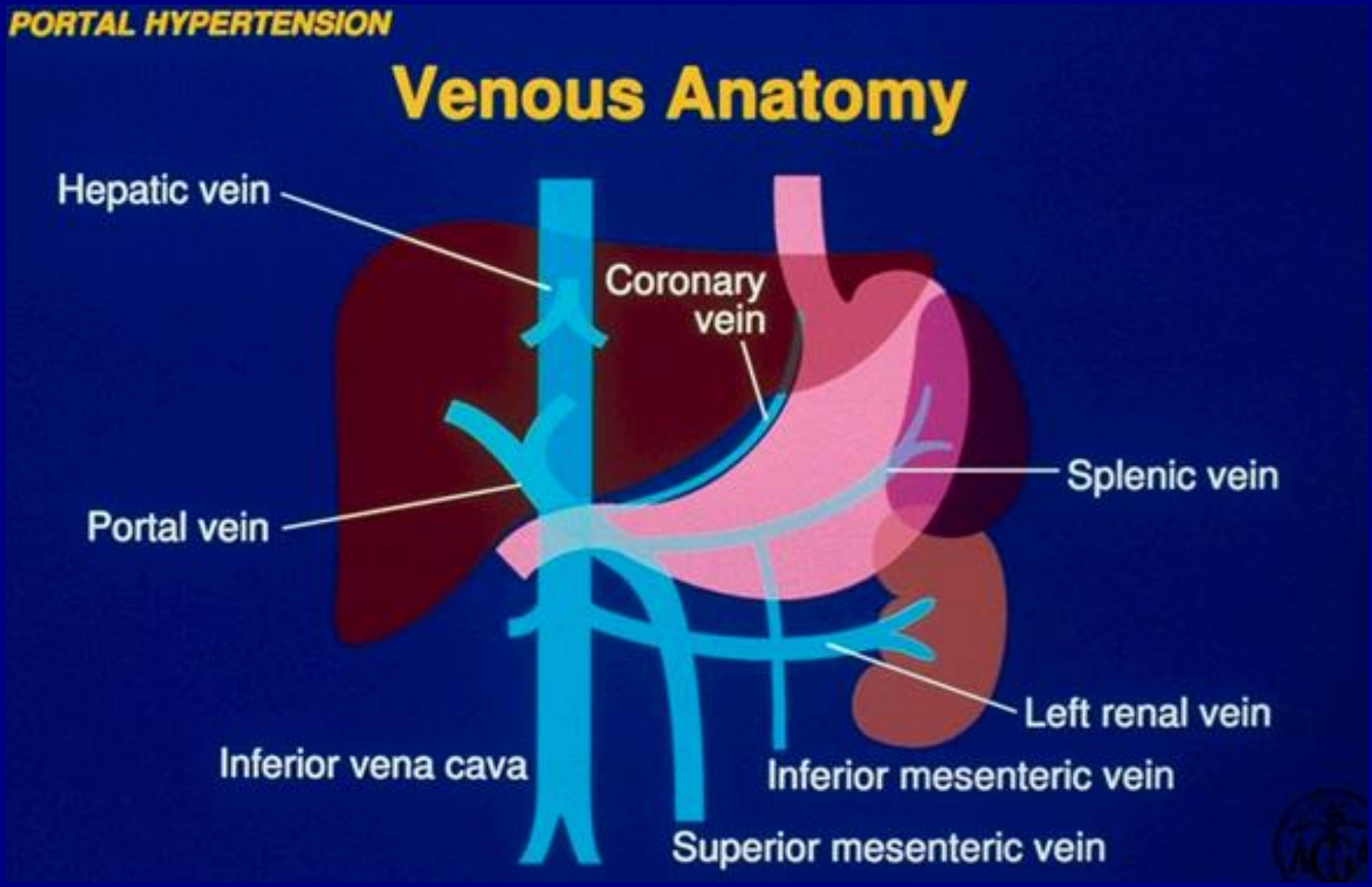
# Child Classification

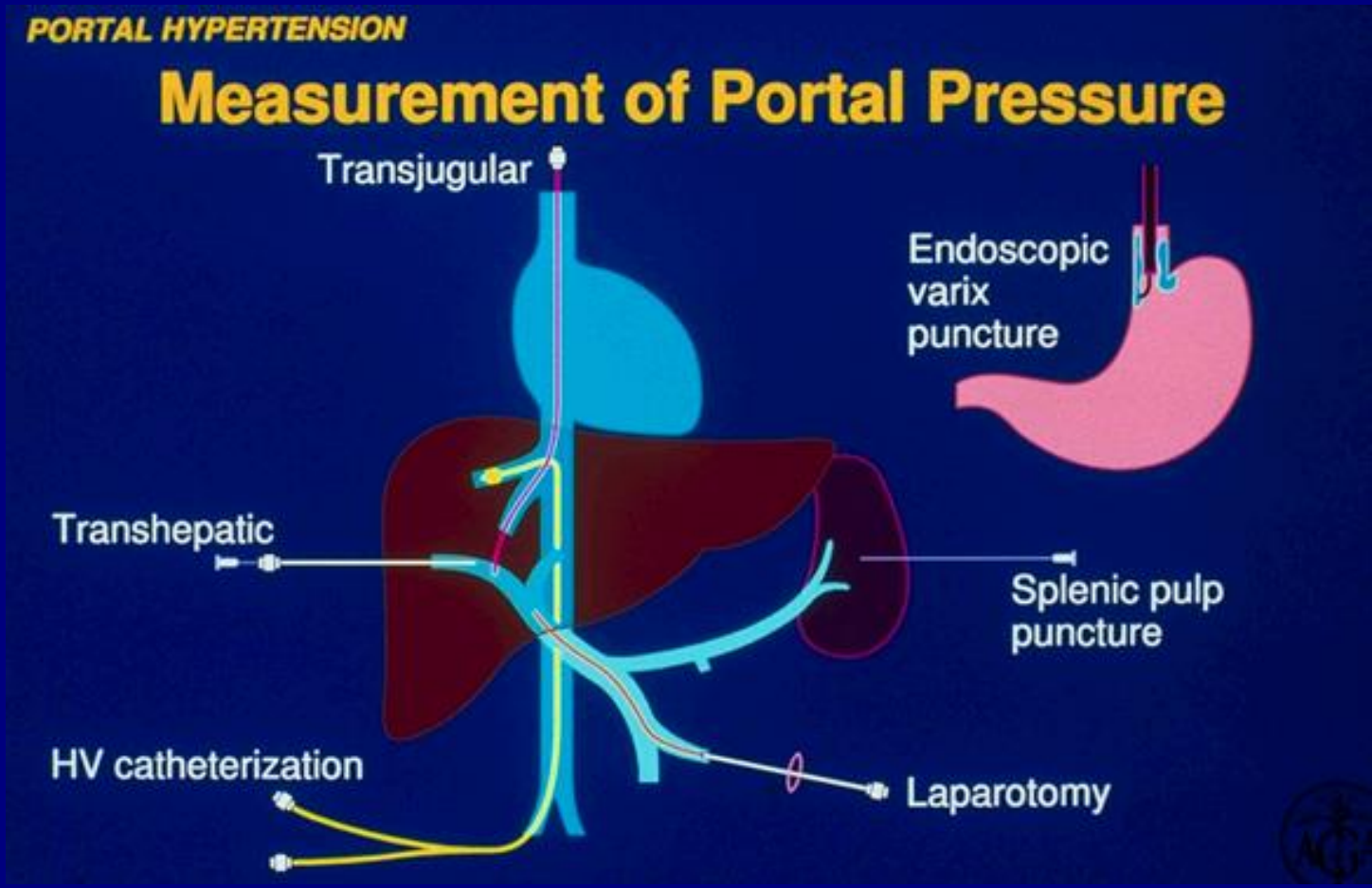
| | 1 | 2 | 3 |
|---|---|---|---|
| **Bilirubin ( mg/dl)** | <2.0 | 2-3 | >3.0 |
| **INR** | <1.7 | 1.7-2.3 | >2.3 |
| **Albumin (mg/dl)** | > 3.5 | 2.8-3.5 | <2.8 |
| **Encephalopathy** | None | I-II | III-IV |
| **Ascites** | None | Slight<br>Moderate | Tense |

# Cirrhosis
# Child Classification

| Score | Stage |
|---|---|
| < 7 | A |
| 7 - 10 | B |
| > 10 | C |


Complications of Cirrhosis
Hepatic encephalopathy
Portal hypertension
Ascites/SBP
Hepatorenal syndrome

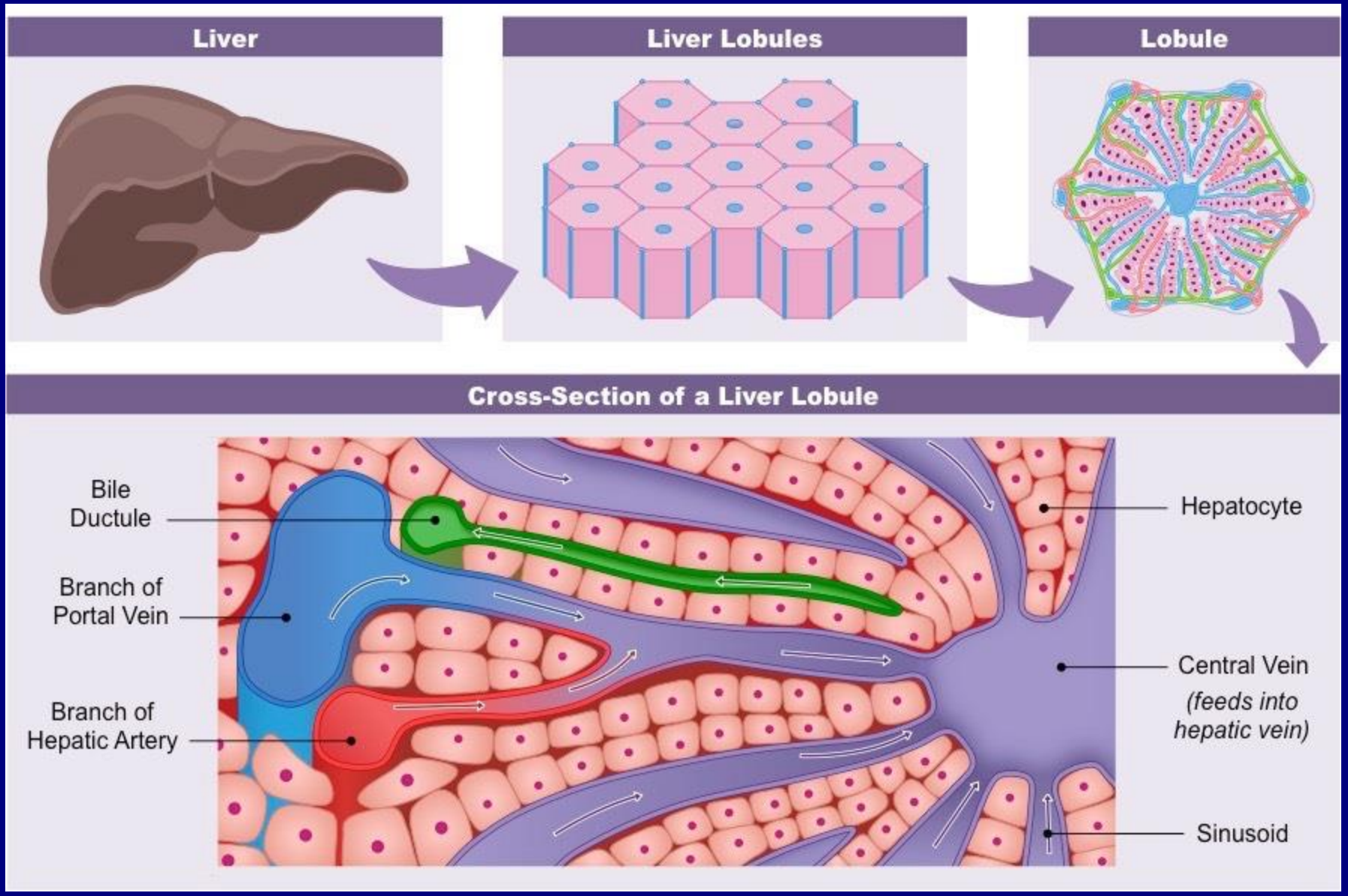

PORTAL HYPERTENSION
Venous Anatomy
Hepatic vein
Coronary vein
Splenic vein
Portal vein
Left renal vein
Inferior vena cava
Inferior mesenteric vein
Superior mesenteric vein

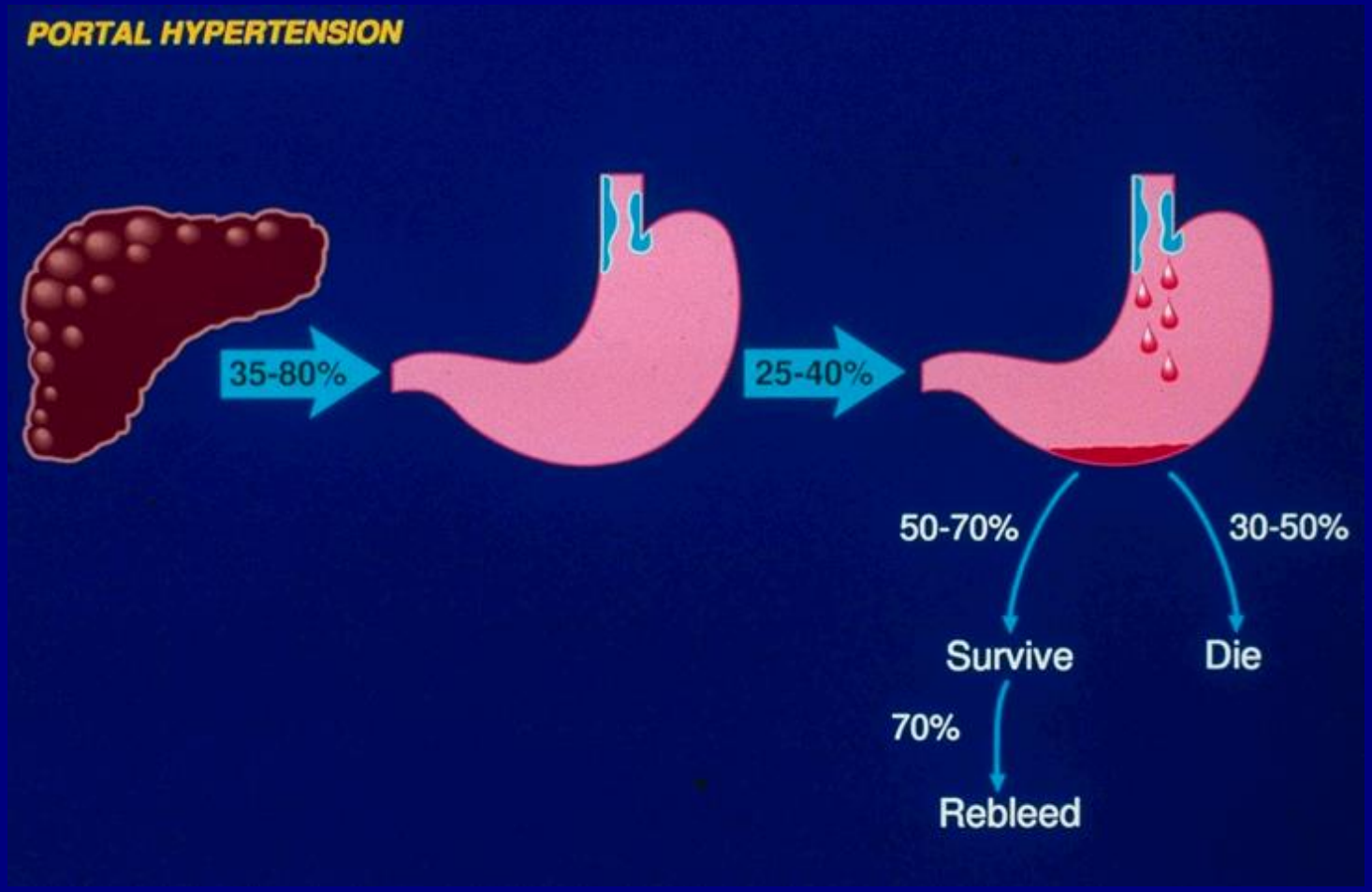

PORTAL HYPERTENSION
Measurement of Portal Pressure
Transjugular
Endoscopic varix puncture
Transhepatic
Splenic pulp puncture
HV catheterization
Laparotomy

*PORTAL HYPERTENSION*

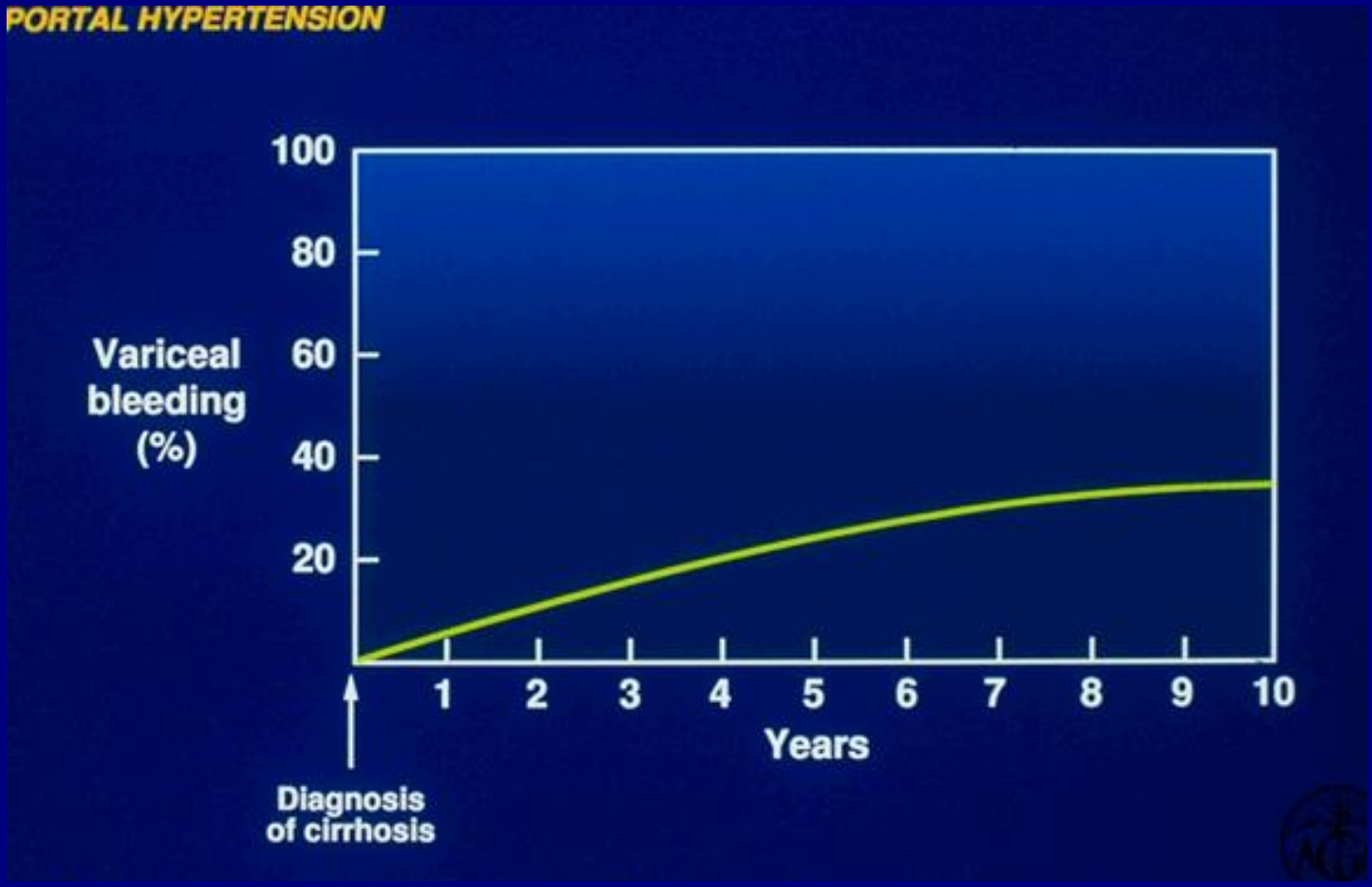
# Classification

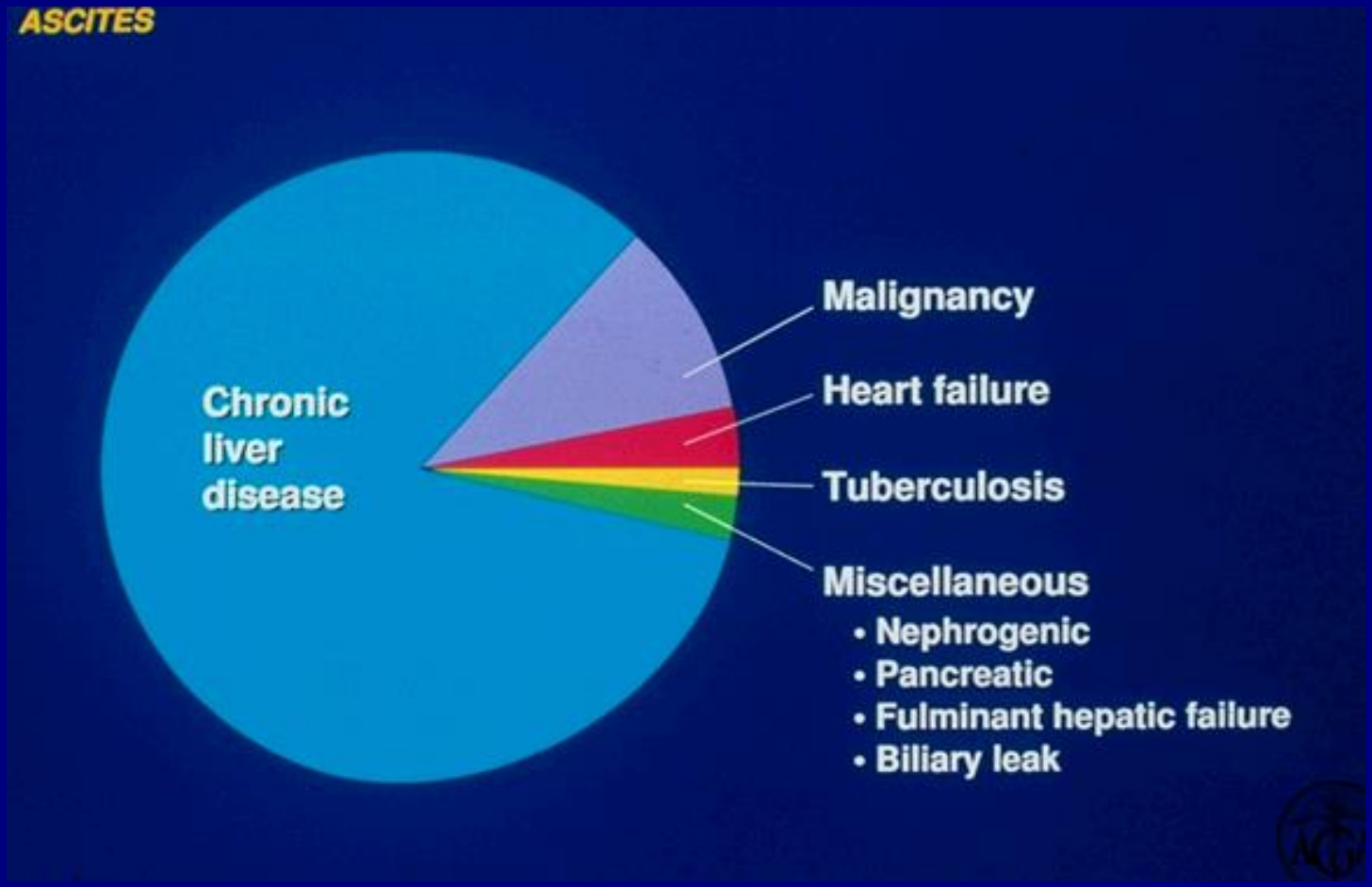
| Type | | Examples |
|---|---|---|
| Prehepatic | | Portal or splenic vein thrombosis |
| Intrahepatic | Presinusoidal | Schistosomiasis |
| | Sinusoidal | Alcoholic cirrhosis |
| | Postsinusoidal | Veno-occlusive disease |
| Posthepatic | | Hepatic vein thrombosis<br>Constrictive pericarditis |


Liver
Liver Lobules
Lobule
Cross-Section of a Liver Lobule
Bile Ductule
Branch of Portal Vein
Branch of Hepatic Artery
Hepatocyte
Central Vein
(feeds into hepatic vein)
Sinusoid


PORTAL HYPERTENSION
35-80%
25-40%
50-70%
30-50%
Survive
Die
70%
Rebleed

## PORTAL HYPERTENSION




ASCITES
Chronic liver disease
Malignancy
Heart failure
Tuberculosis
Miscellaneous
• Nephrogenic
• Pancreatic
• Fulminant hepatic failure
• Biliary leak

ASCITES

# Pathophysiologic Mechanisms

**Elevated Hydrostatic Pressure**

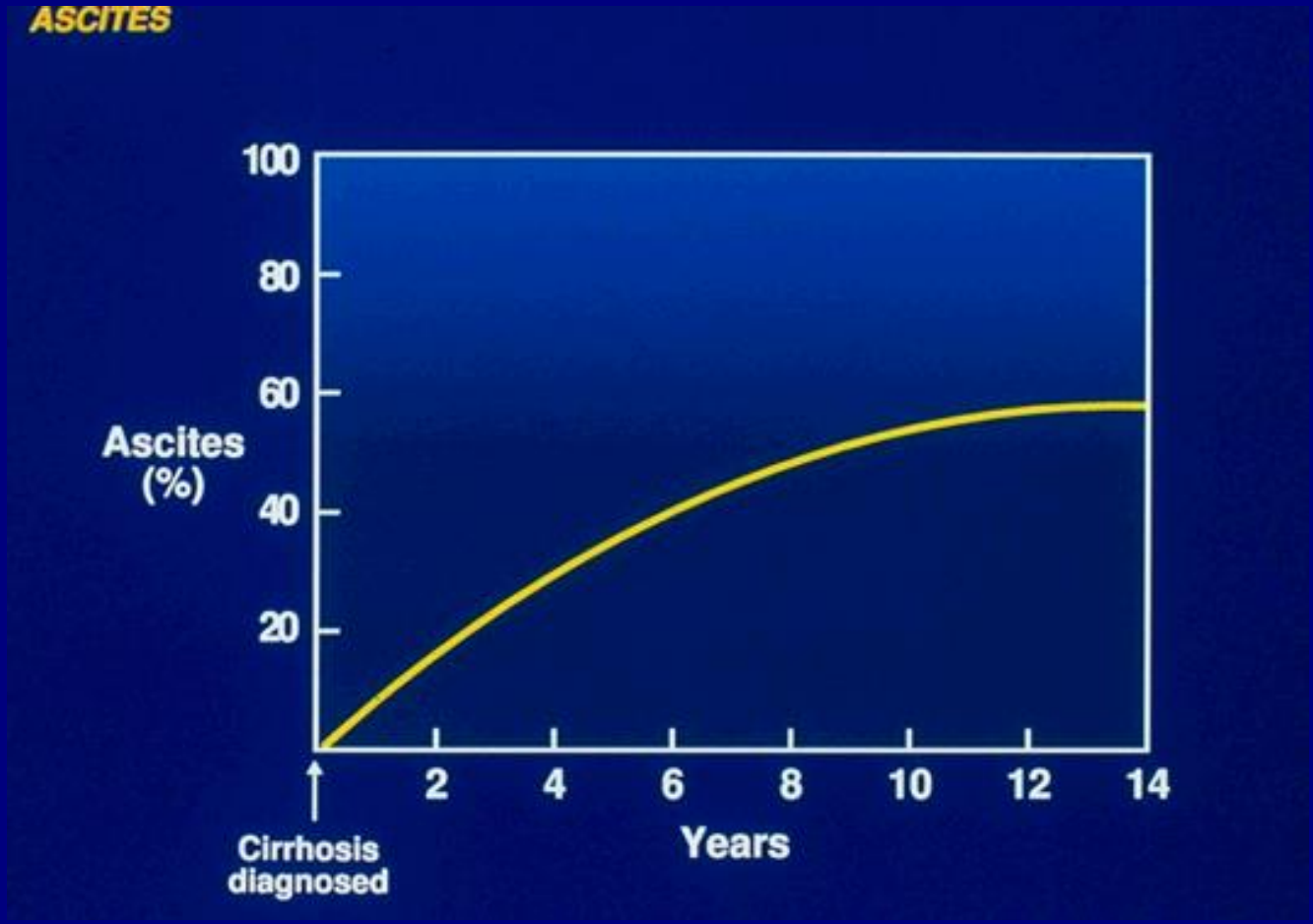
- Cirrhosis
- Congestive heart failure
- Constrictive pericarditis
- Hepatic outflow block

**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*

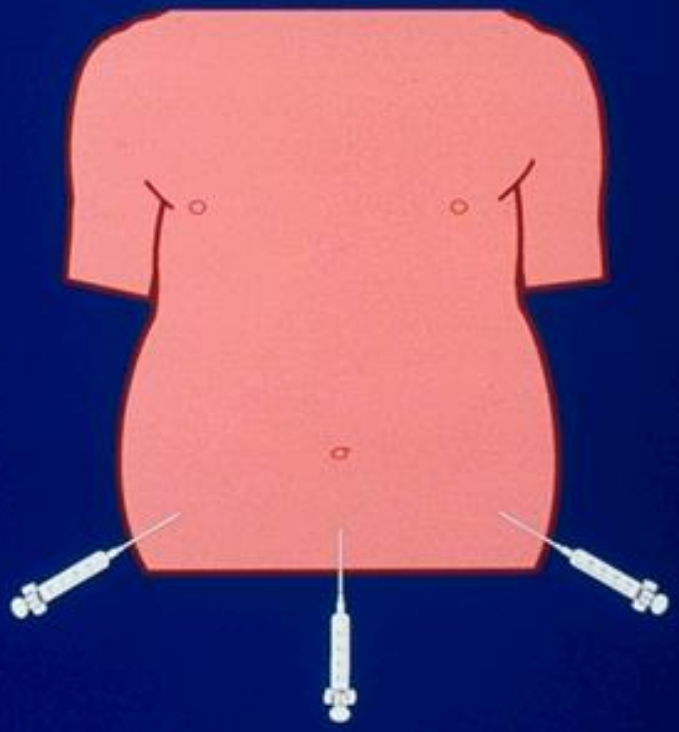
# Diagnostic Paracentesis

## Indications

- New-onset ascites
- Admission to hospital
- Clinical deterioration
- Fever

## Contraindications

- None



# Fluid Analysis

| Routine | Optional | |
|---|---|---|
| Cell count | Glucose | TB smear and culture |
| Culture | LDH | |
| Albumin | Amylase | Cytology |
| Protein | Gram stain | Triglyceride |

| | SAAG (g/dL) | |
|---|---|---|
| | ≥ 1.1 | < 1.1 |
| **Total protein (g/dL)** | | |
| < 2.5 | Cirrhosis | Nephrotic syndrome |
| | Acute liver failure | |
| ≥ 2.5 | 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

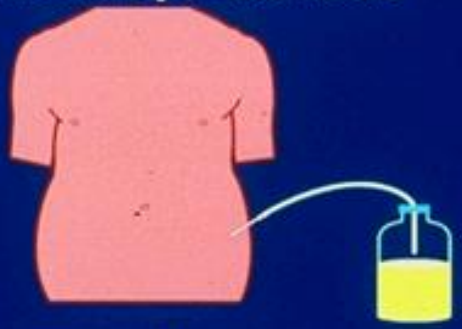
Large volume paracentesis (for tense ascites)

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

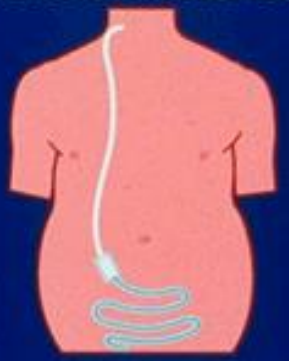
ASCITES

# Therapy of Refractory Ascites

Large volume paracentesis



Peritoneovenous shunt

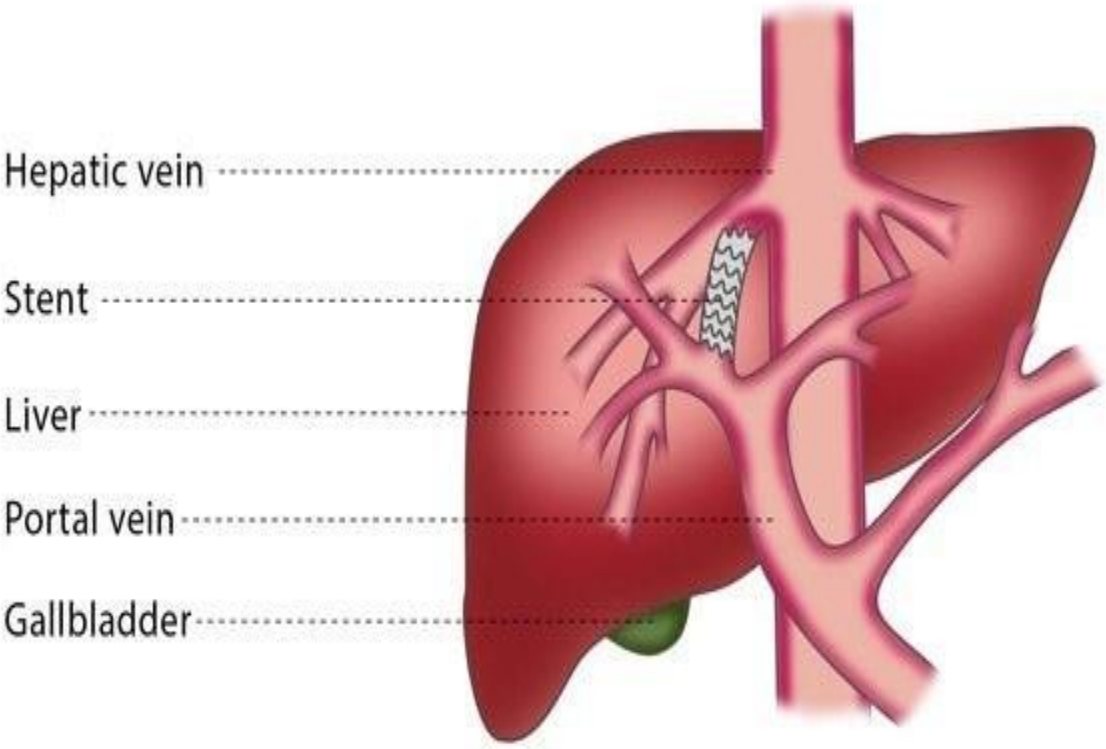


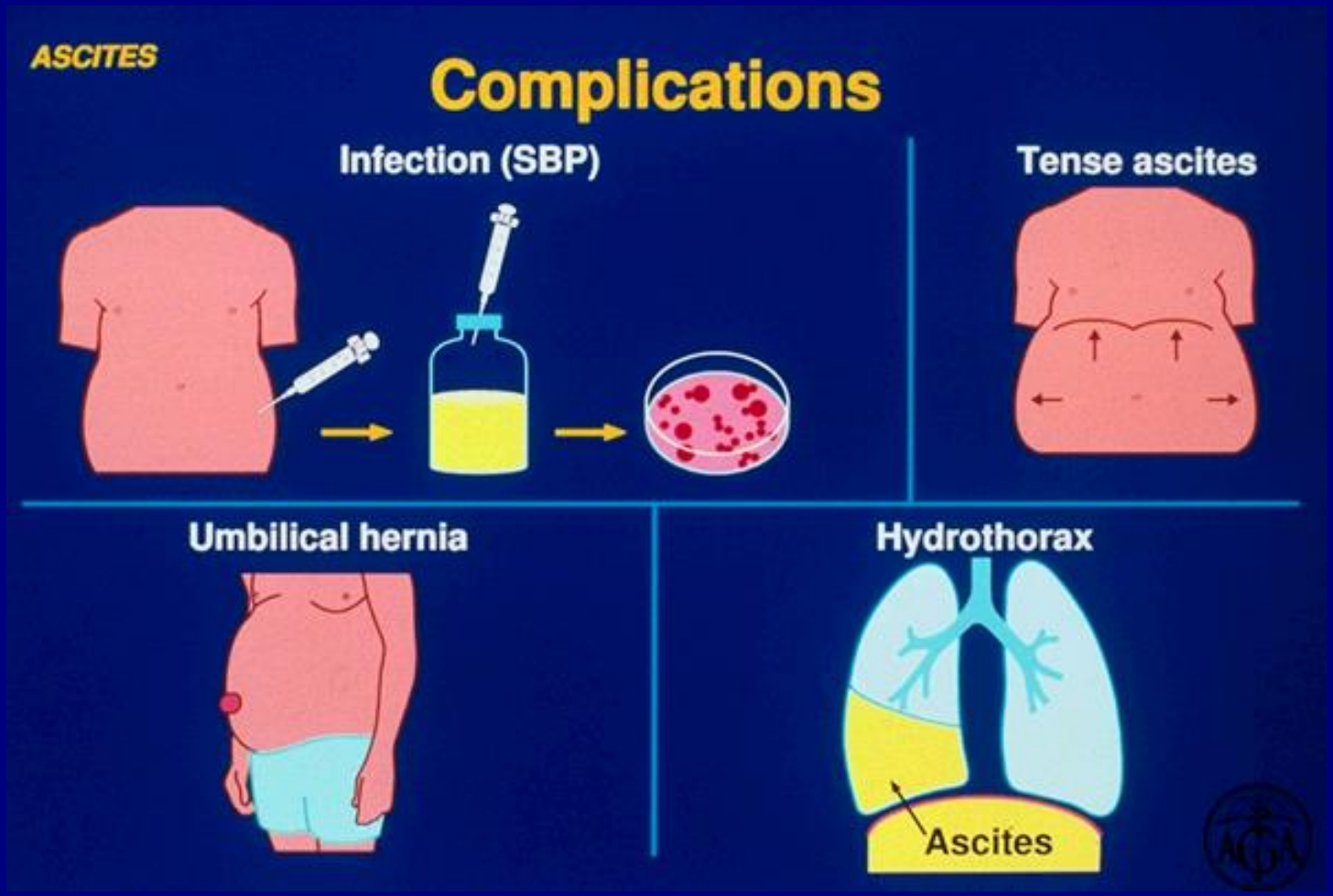
TIPS

Liver transplantation

- **LARGE VOLUME PARACENTESIS**
- **Albumin replacement rule:**
- **8 grams of 25 % albumin for each litre removed.**

## Transjugular intrahepatic portosystemic shunt (TIPS)




ASCITES
Complications
Infection (SBP)
Tense ascites
Umbilical hernia
Hydrothorax
Ascites

# Hepatic Hydrothorax

## Characteristics

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

Fluid similar to ascites

## Treatment

Medical therapy
- diuretics
- thoracentesis

TIPS

Liver transplantation

# Umbilical Hernia

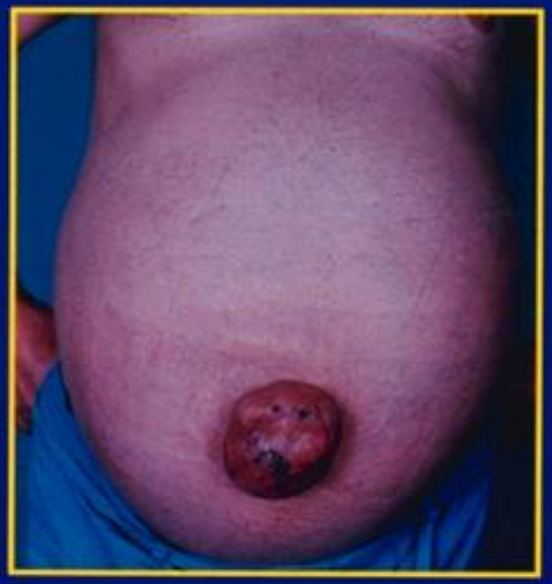
## Complications

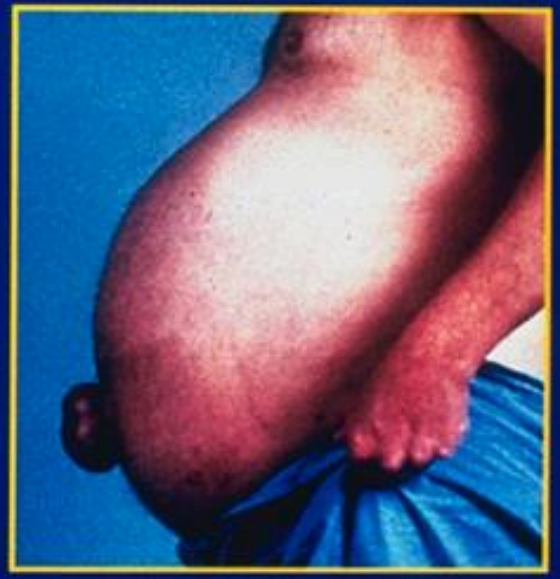
- Incarceration - 14%
- Ulceration - 35%
- Rupture - 7%

## Treatment

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

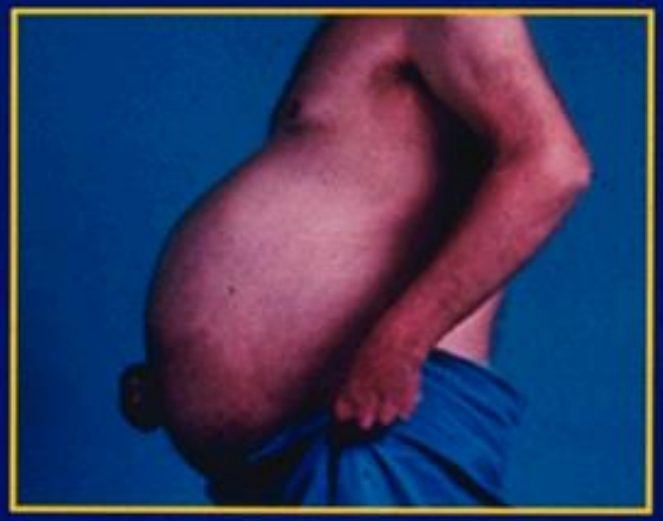
## ASCITES



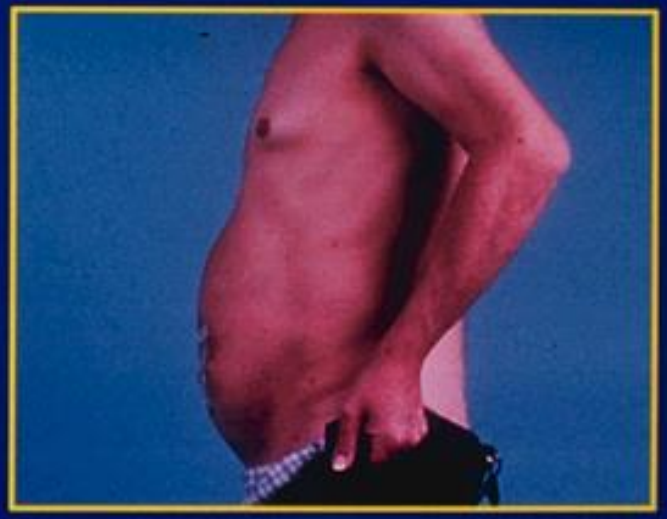


*ASCITES*

# Peritoneovenous Shunt



Before

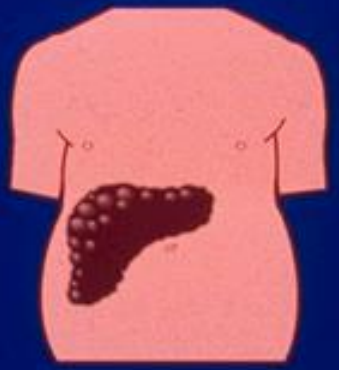


After

SBP

# Clinical Setting

Advanced cirrhosis:
- ↑ serum bilirubin
- ↑ prothrombin time



Ascites, usually large volume

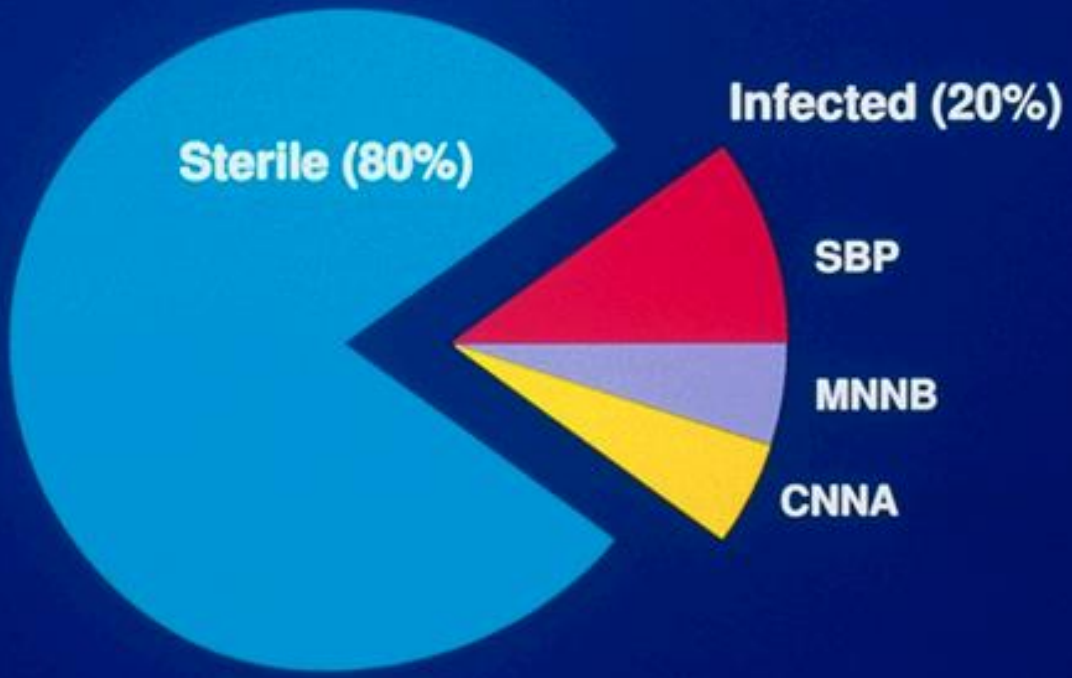
50% of cases detected on hospital admission
- often asymptomatic

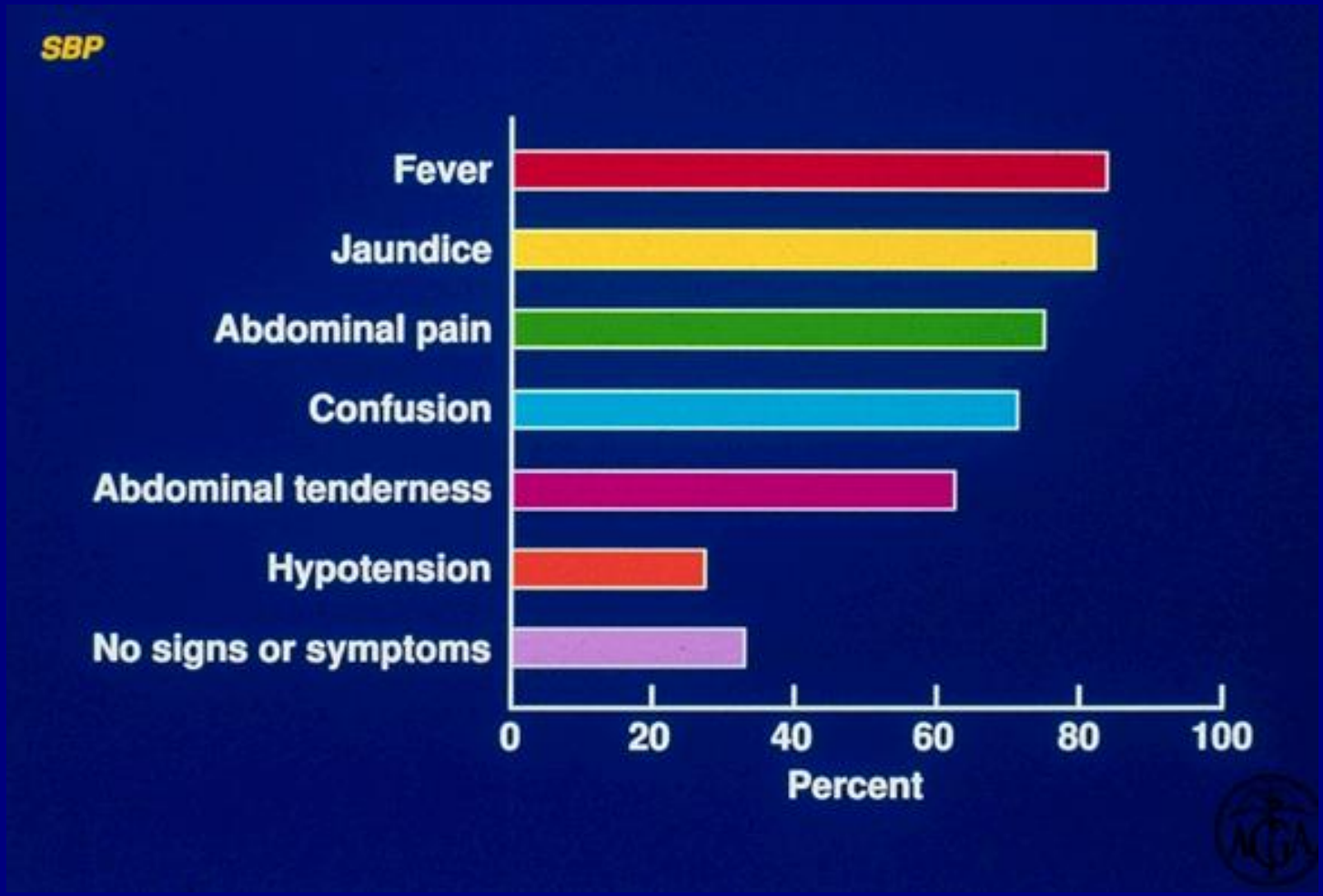
(SBP) should be suspected in a patient with ascites and any of the following:

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

*ASCITES*

# Initial Paracentesis



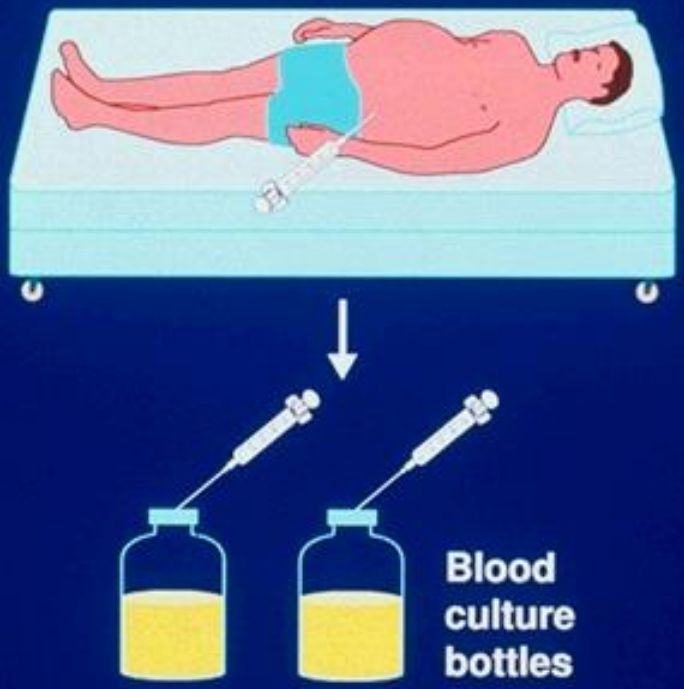

SBP
Fever
Jaundice
Abdominal pain
Confusion
Abdominal tenderness
Hypotension
No signs or symptoms
0
20
40
60
80
100
Percent

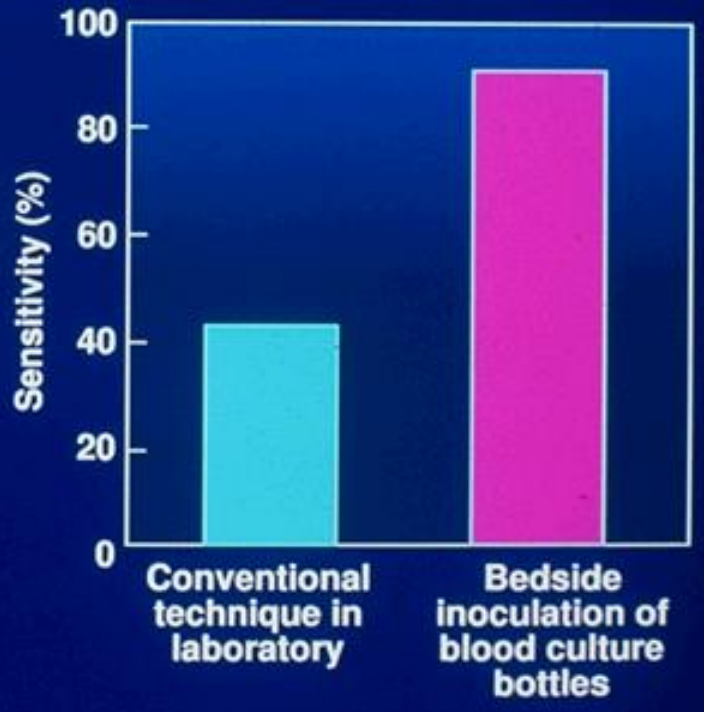
SBP

| 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 |

SBP

# Ascitic Fluid Culture Technique



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

Antibiotic prophylaxis

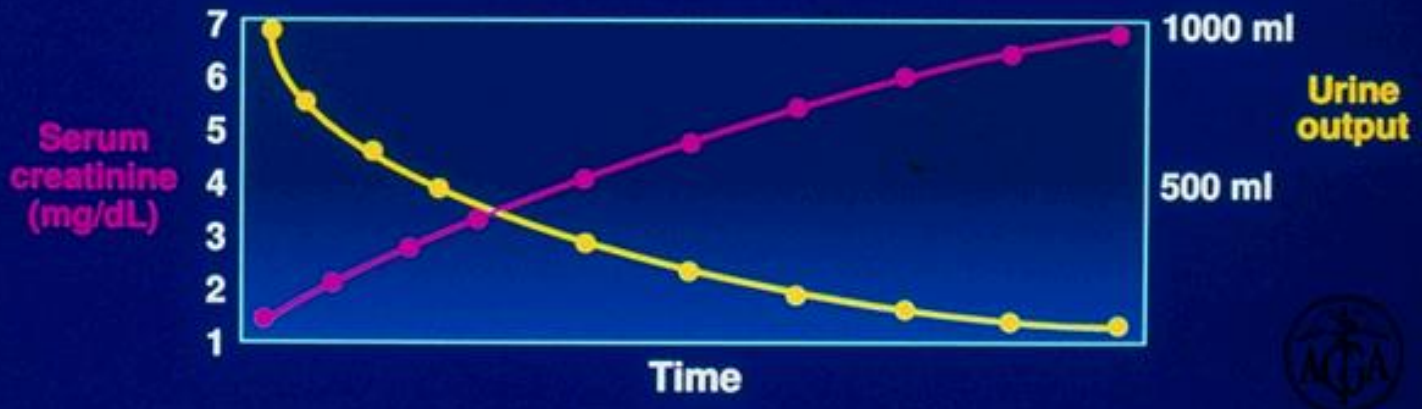
- prevention of initial episode
- prevention of recurrence

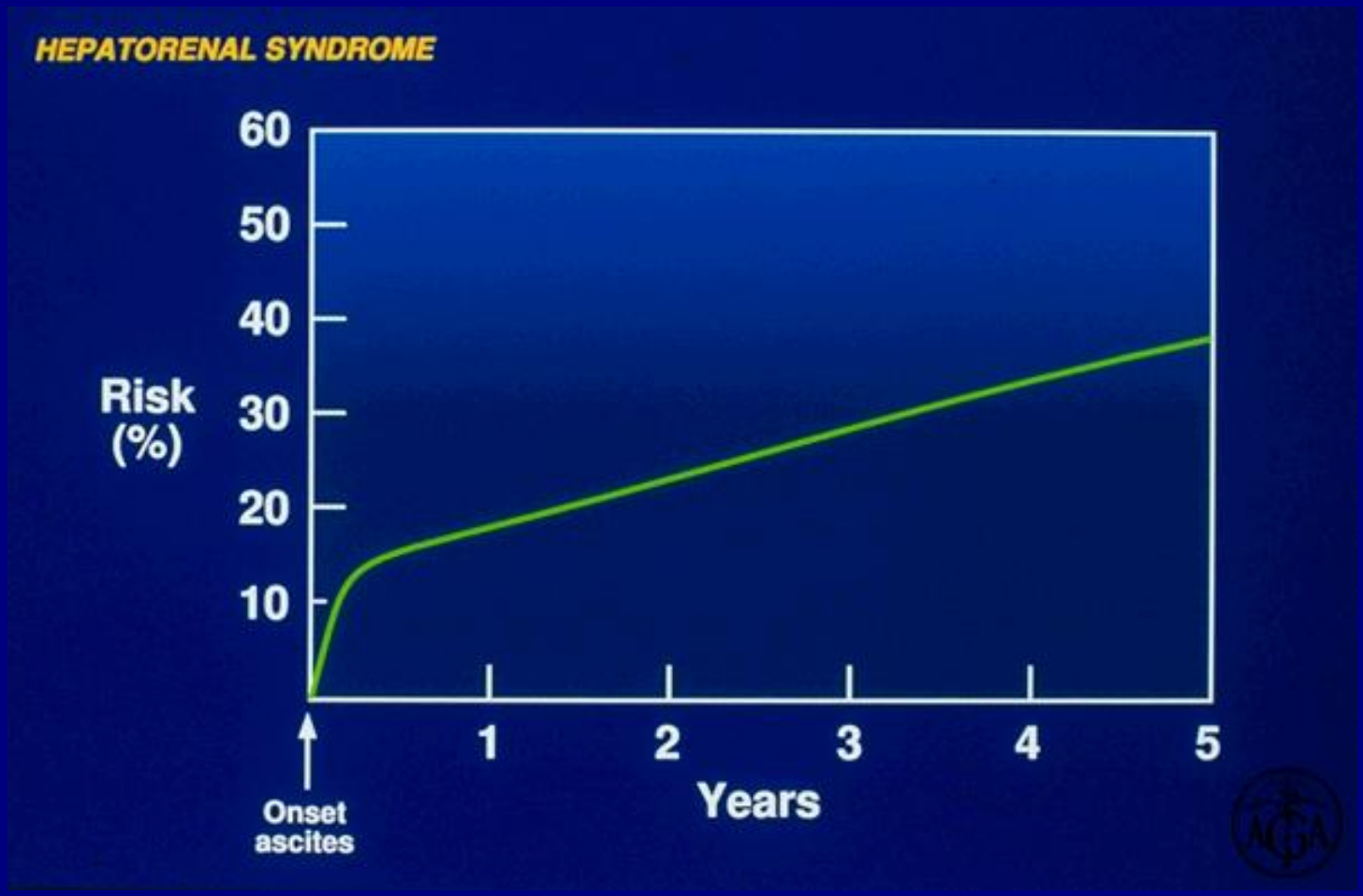
## *HEPATORENAL SYNDROME*

- 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
(%)
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

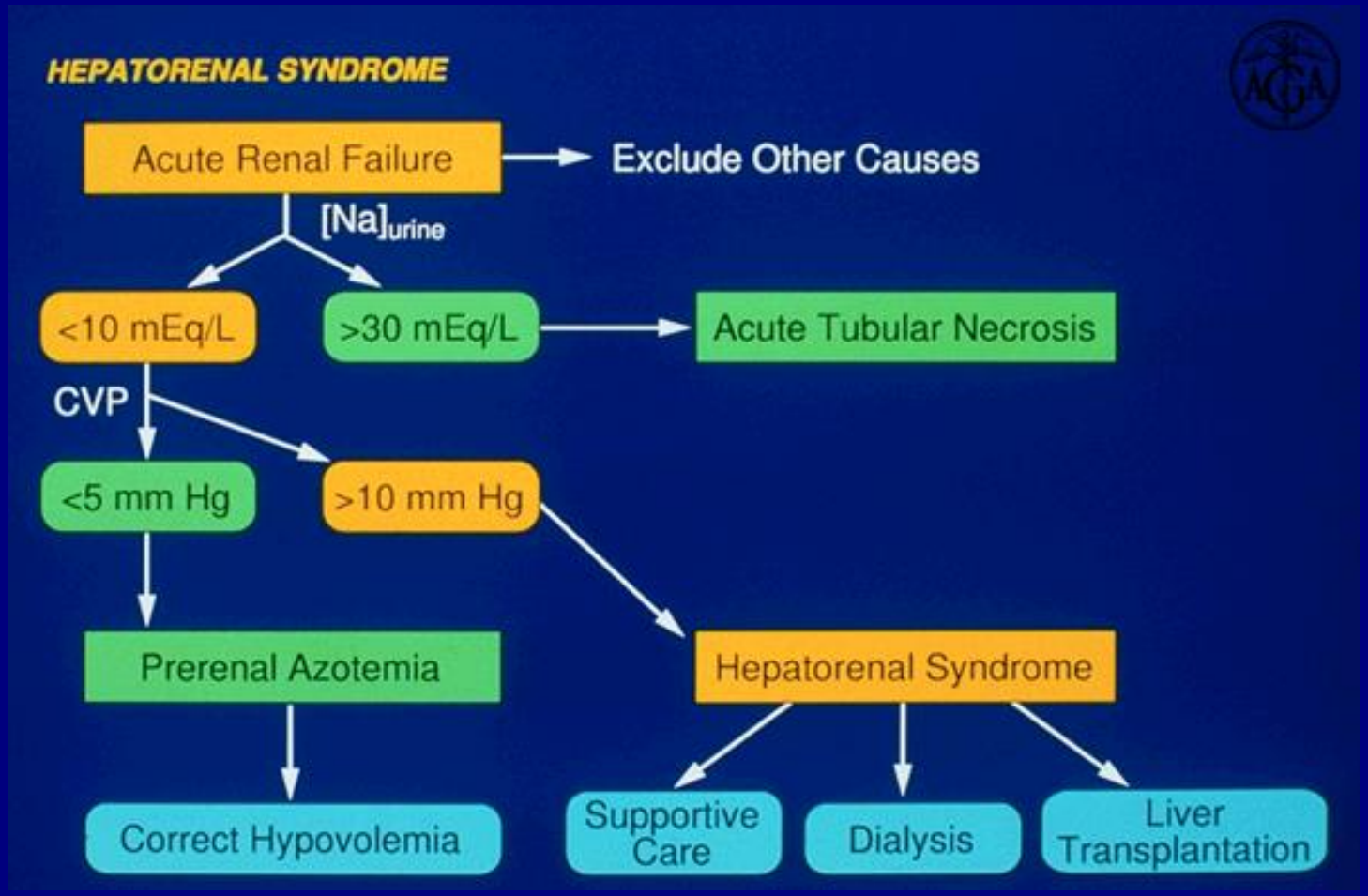
- Urine sodium <10 mEq/L
- Urine sediment unremarkable

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

*HEPATORENAL SYNDROME*

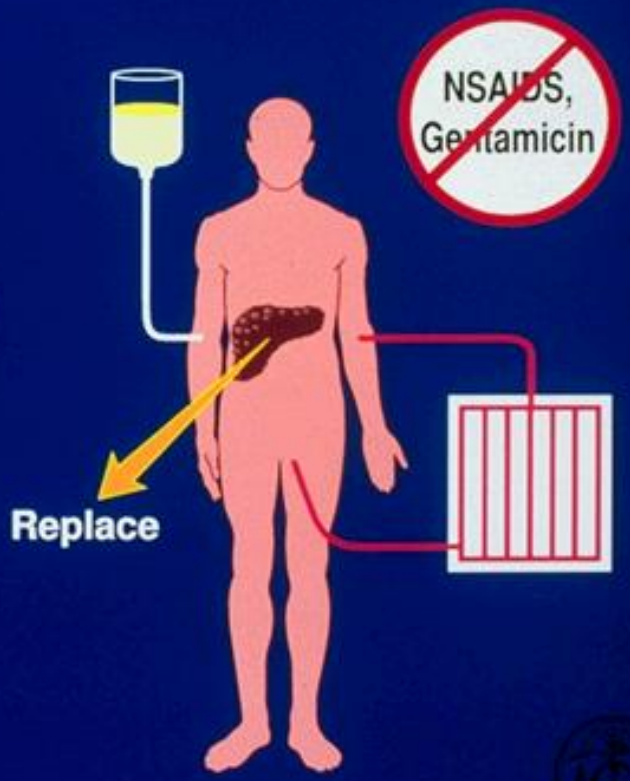
# Azotemia in Patients with Liver Disease

| | 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 |


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

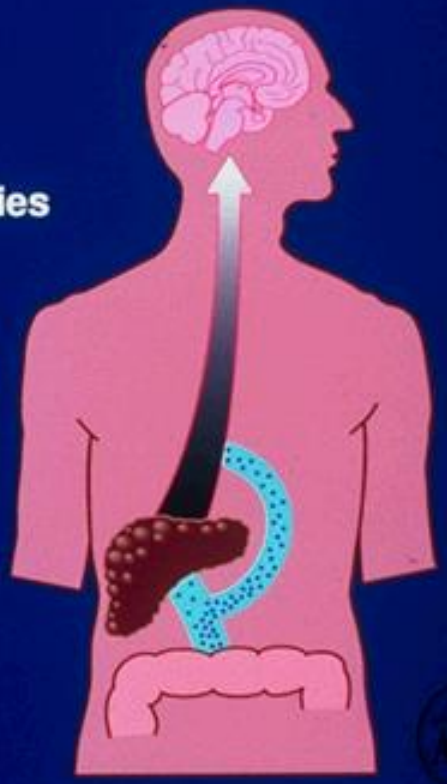
## *HEPATORENAL SYNDROME*

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

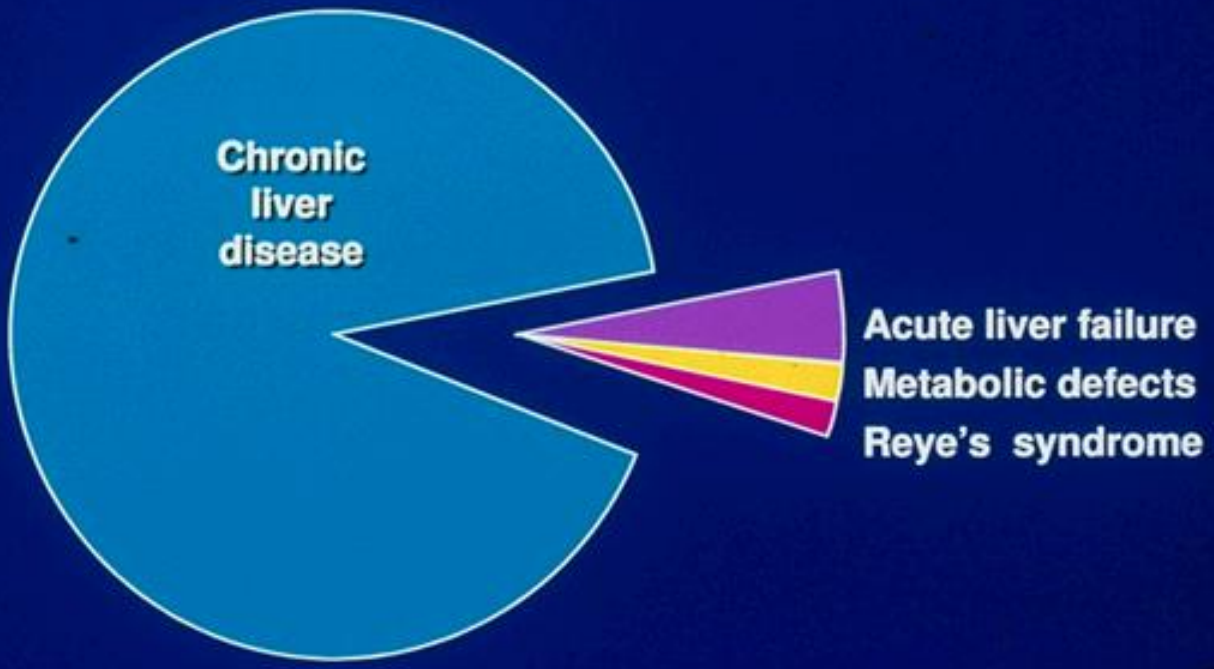


## HEPATIC ENCEPHALOPATHY

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



## HEPATIC ENCEPHALOPATHY



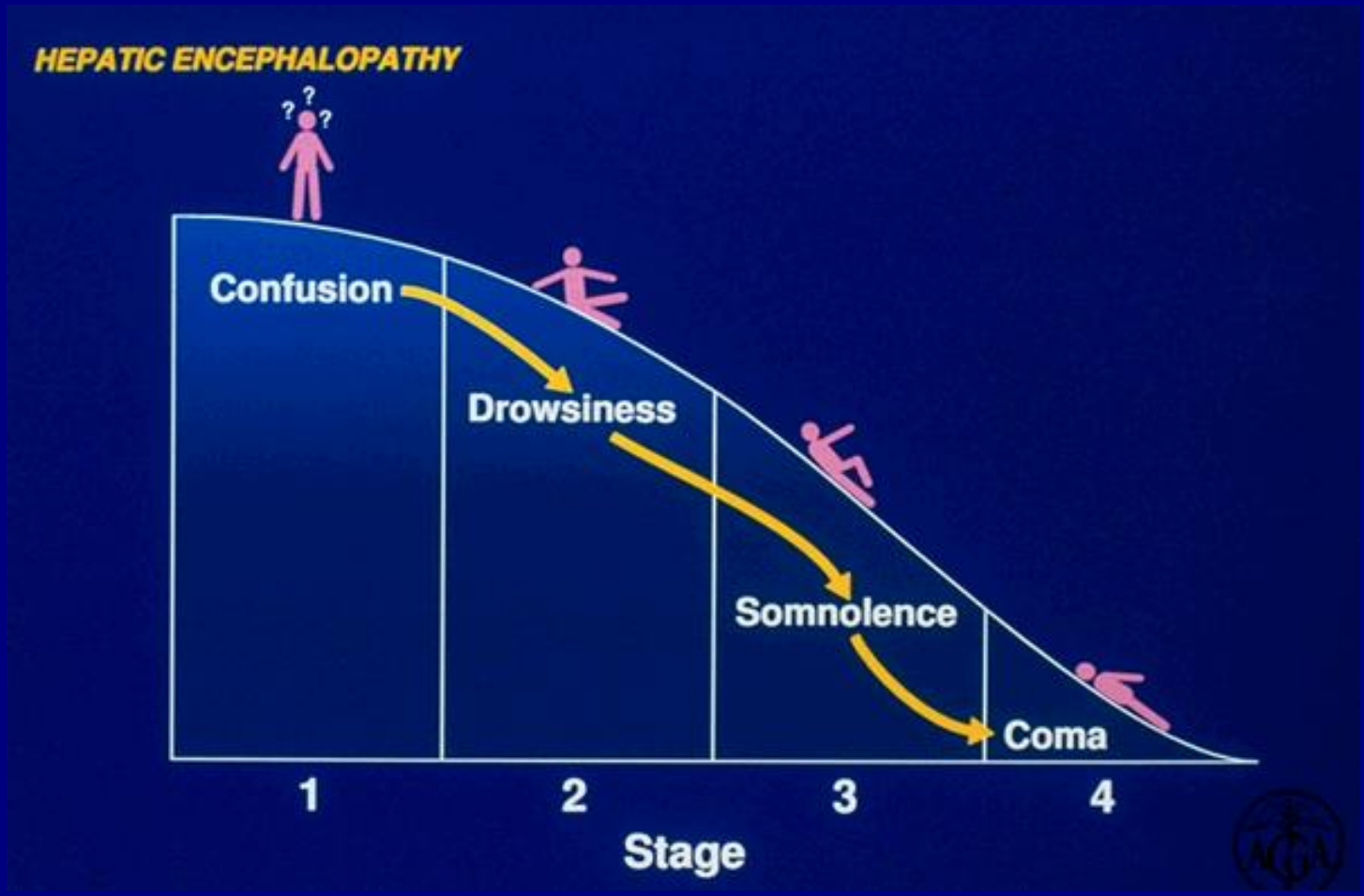
*HEPATIC ENCEPHALOPHATHY*

# Subclinical

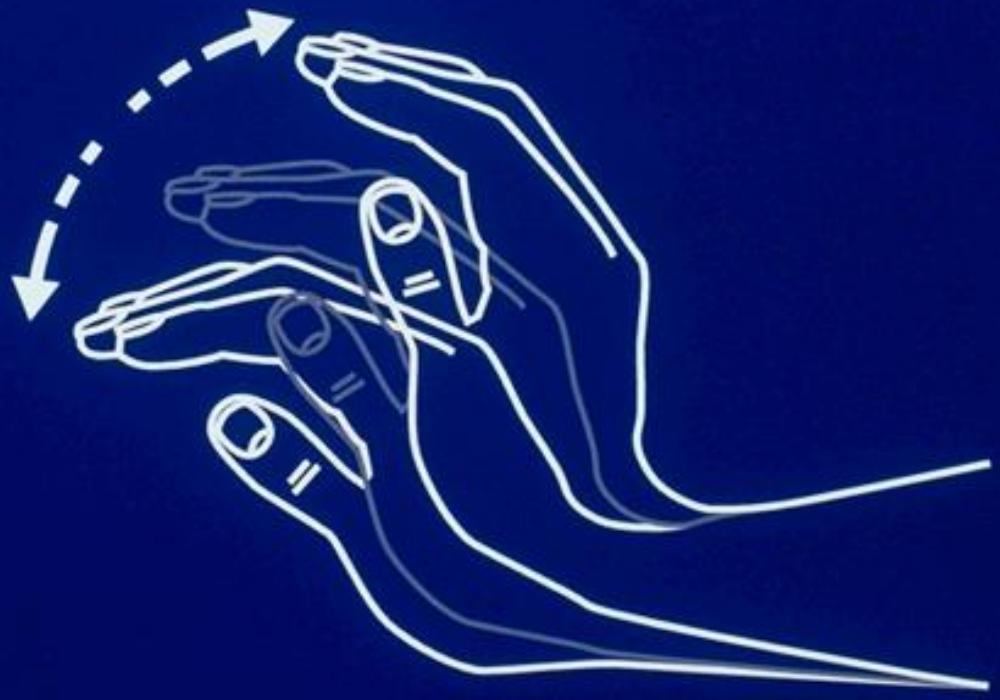
- Present in 50-85% of cirrhotics
- Subtle neuropsychological changes
- Normal EEG
- Diagnosed by psychomotor testing
- Reversible with empiric treatment

## *HEPATIC ENCEPHALOPHATHY*

| 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

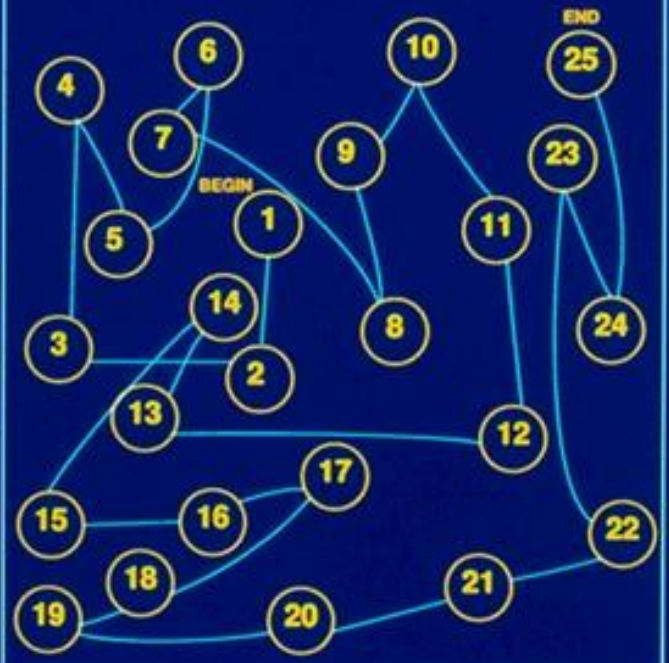
## HEPATIC ENCEPHALOPATHY



# HEPATIC ENCEPHALOPATHY

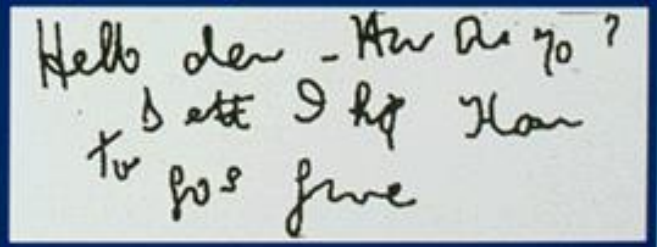
## Number Connection Test

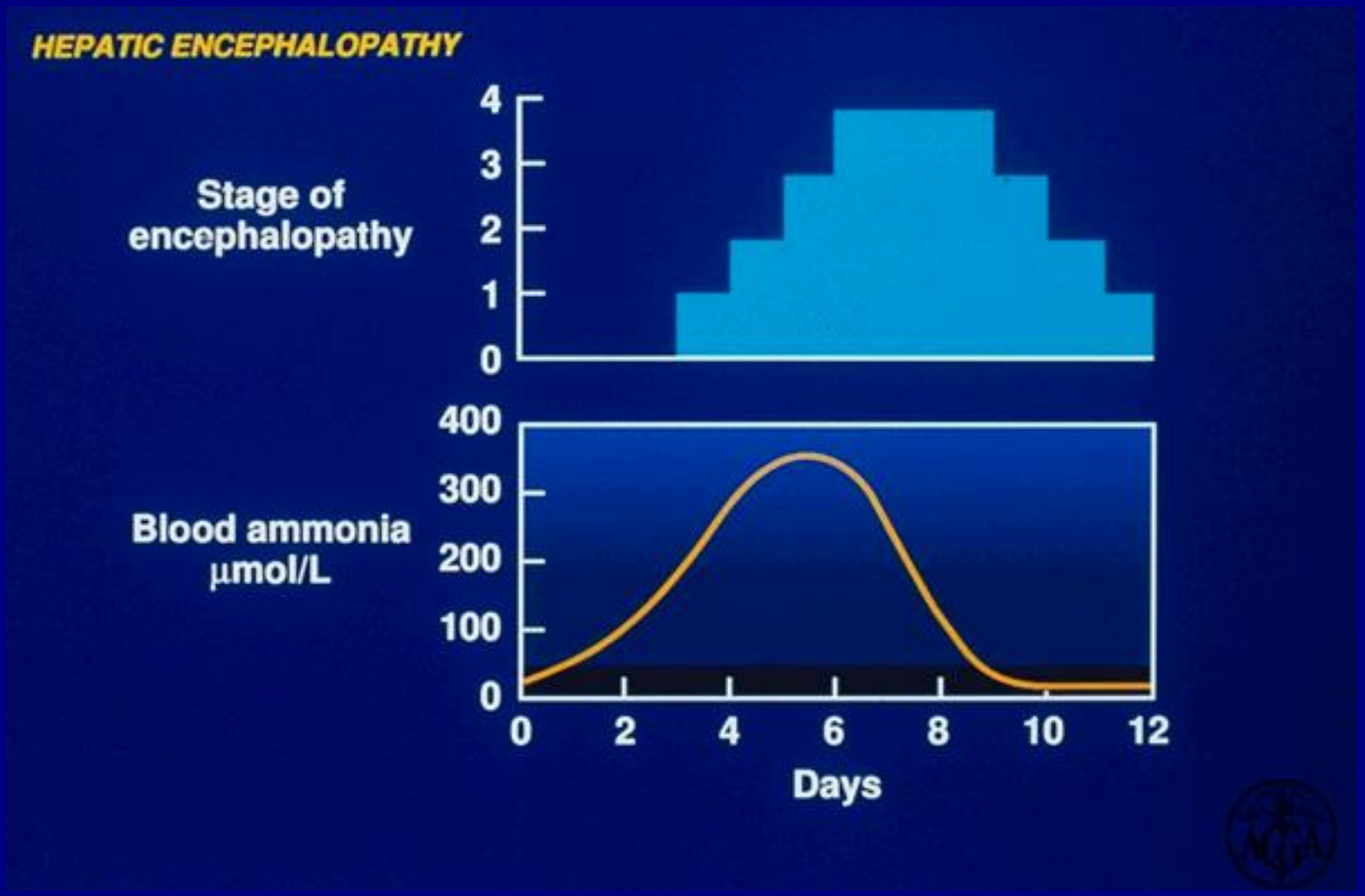
Time to complete _____




## 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

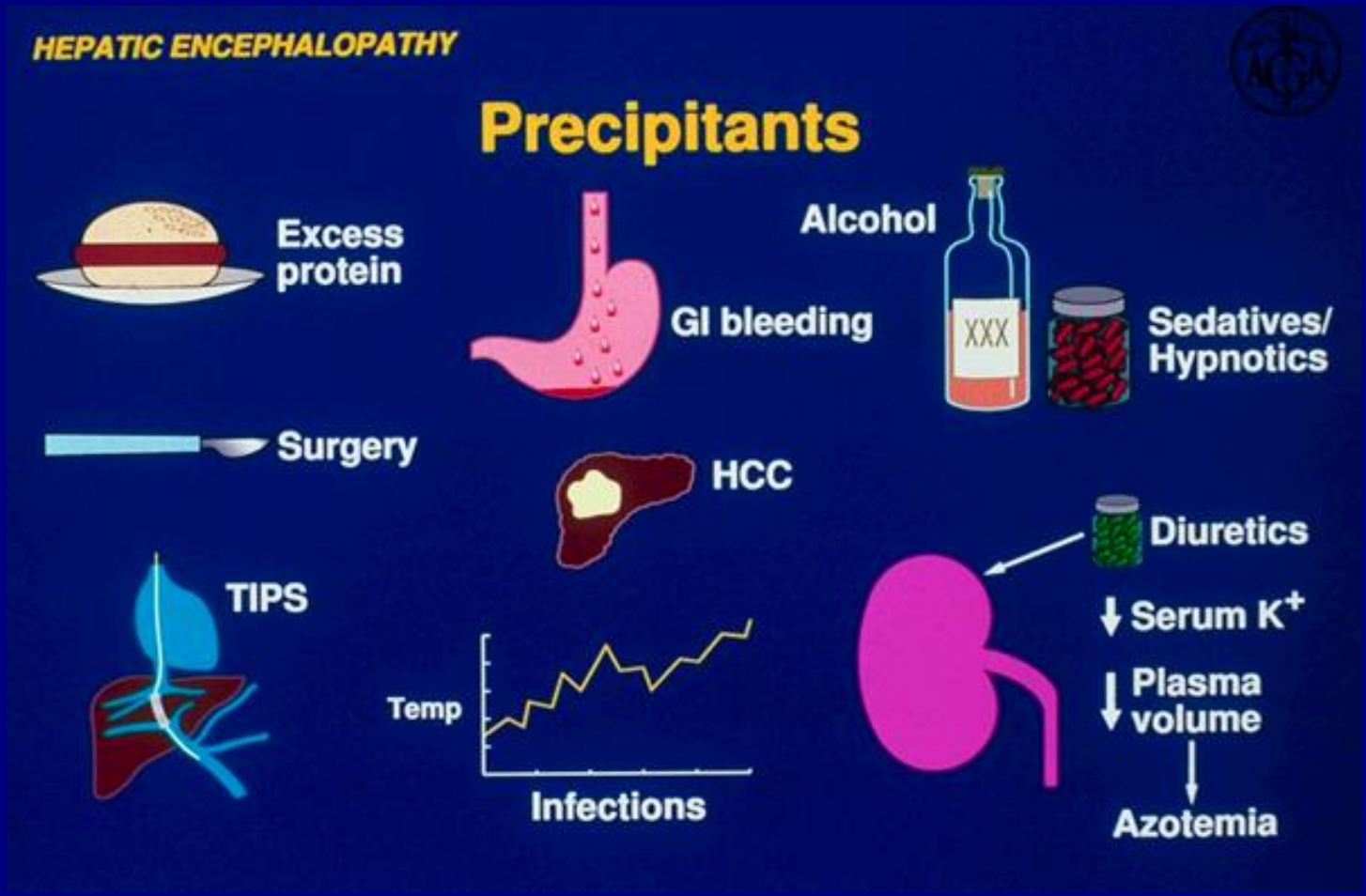
**Metabolic**
Electrolyte imbalance, uremia, ↑/↓ glucose, hypercapnea, hypoxia

**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