الجامعة السورية الخاصة
SYRIAN PRIVATE UNIVERSITY

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Complication of cirrhosis

- Ascites
- Varices
- Encephalopathy
- Hepatocellular carcinoma
- HRS

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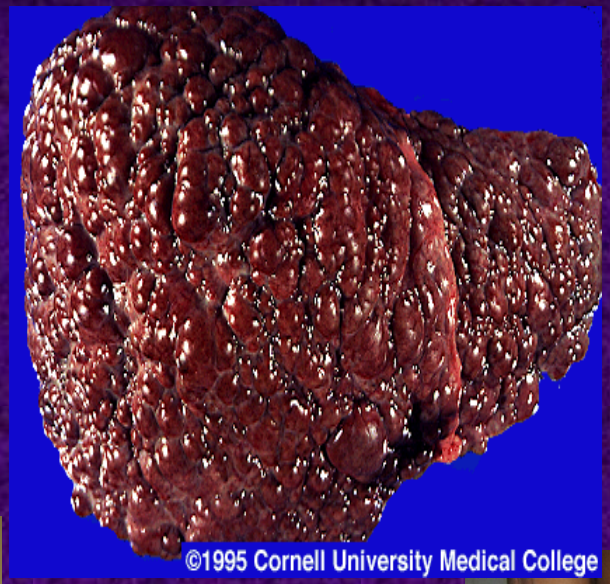
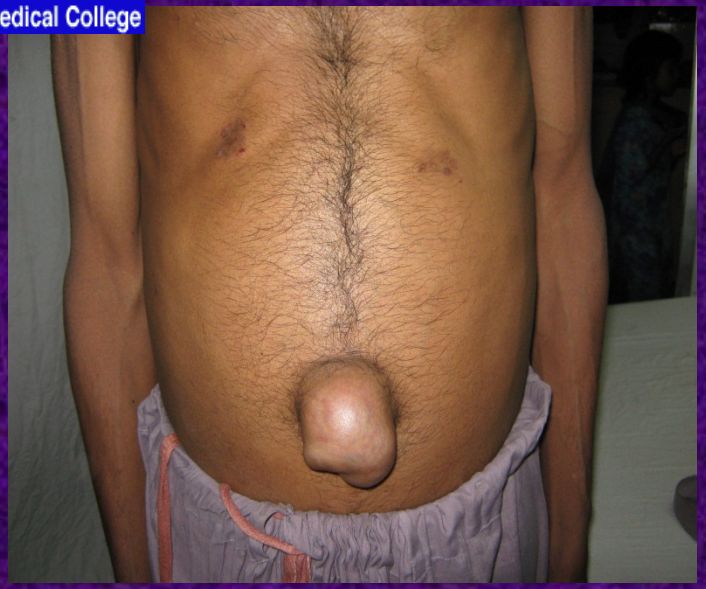
Outline





- Ascites is the most common of the major complications of liver cirrhosis

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Etymology

- Ascites
- Greek askiEs : “Dropsy”
- Meaning leather bag , sack

- 80% due to Cirrhosis (USA)

Ascites

occurs when there is a disruption in the pressure forces between intravascular and extravascular fluid spaces, which allows extravascular fluid to accumulate in the anterior peritoneal cavity.

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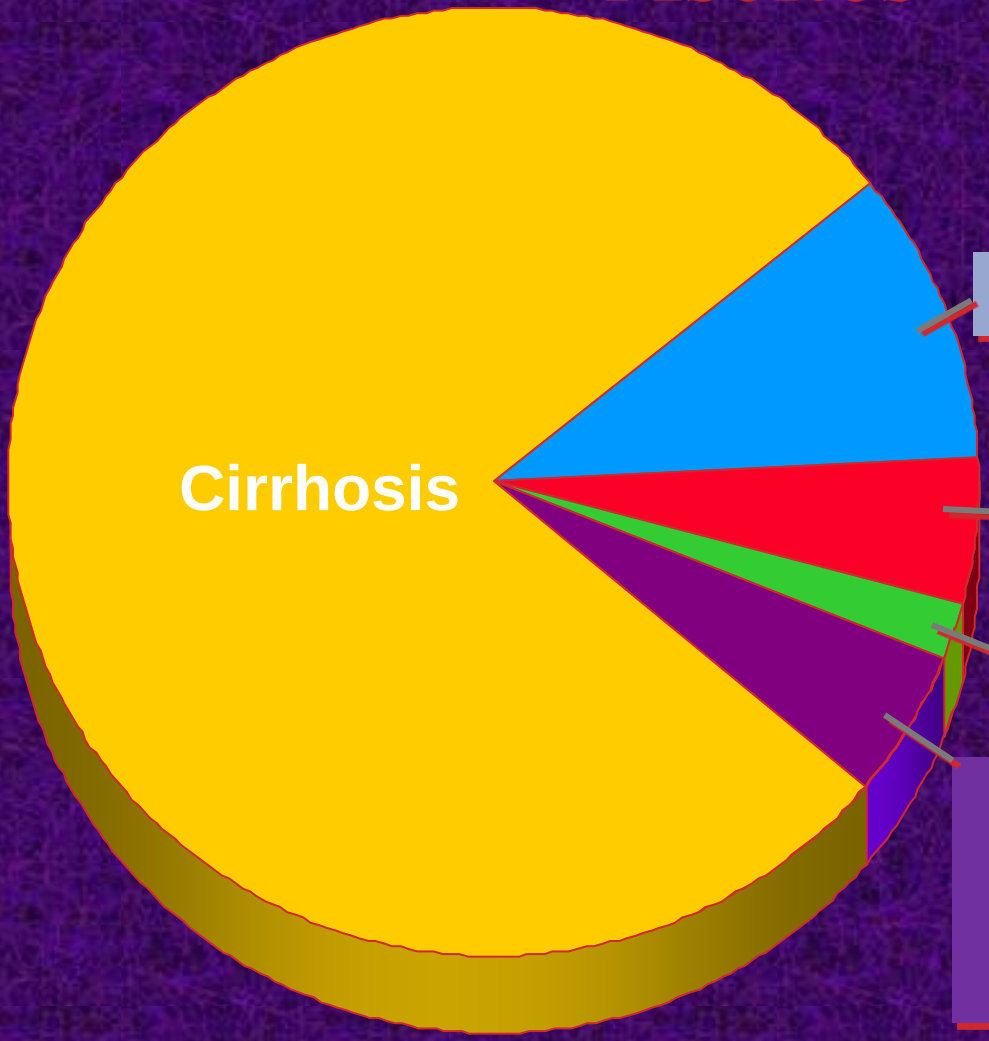
Cirrhosis is the Most Common Cause of Ascites



Peritoneal malignancy

Heart failure

Peritoneal tuberculosis

Others
- Pancreatic
- Budd-Chiari syndrome
- Nephrogenic ascites

Portal Hypertensive SAAG≥1.1	Nonportal Hypertensive SAAG<1.1
Cirrhosis	Peritoneal Carcinomatosis
Heart Failure	Heart Failure
Cancer (nonperitoneal)	Pancreatic Ascites
Budd-Chiari,	Nephrotic Syndrome
Portal Vein thrombosis	Chylous
Alcoholic hepatitis	Serositis (CVD)
Acute liver failure	TB
Sinusoidal obstructive	Myxedema
syndrome (VOD)	Biliary ascites

- **Although Ascites is not the root of all evil,**

many of the catastrophic complications of cirrhosis are rooted in ascites

Harold Conn

Statistics

- 50% of cirrhotics will develop Ascites within 10 years of diagnosis.
- -
- 50% die within 5 years of onset

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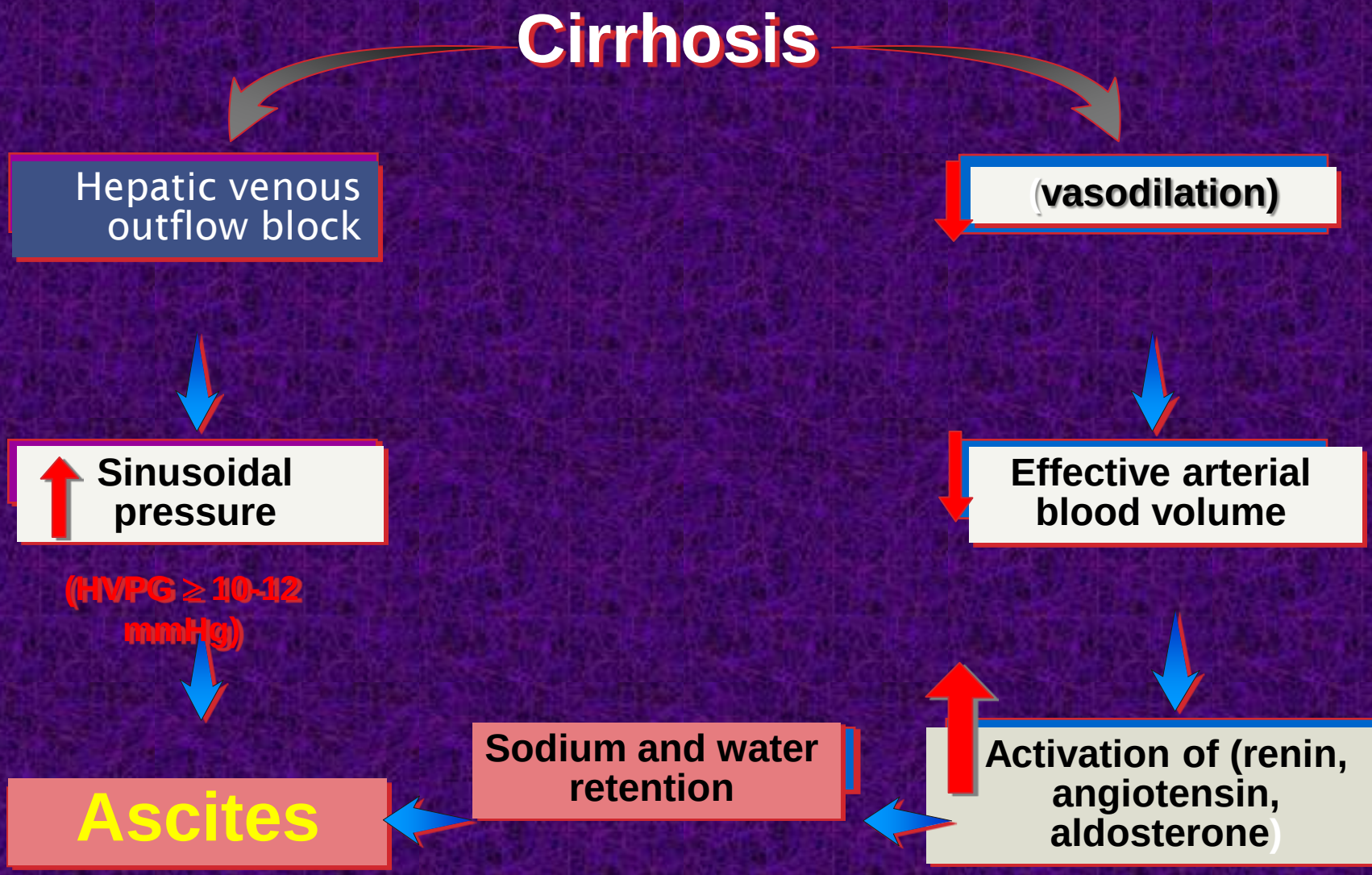
Decreased osmotic pressure :

- A- Hypoalbuminemia:
  - ++ Nephrotic syndrome
  - ++Protein-losing enteropathy
  - ++Malnutrition
  -
- B- Cirrhosis or hepatic insufficiency

PATHOGENESIS OF ASCITES



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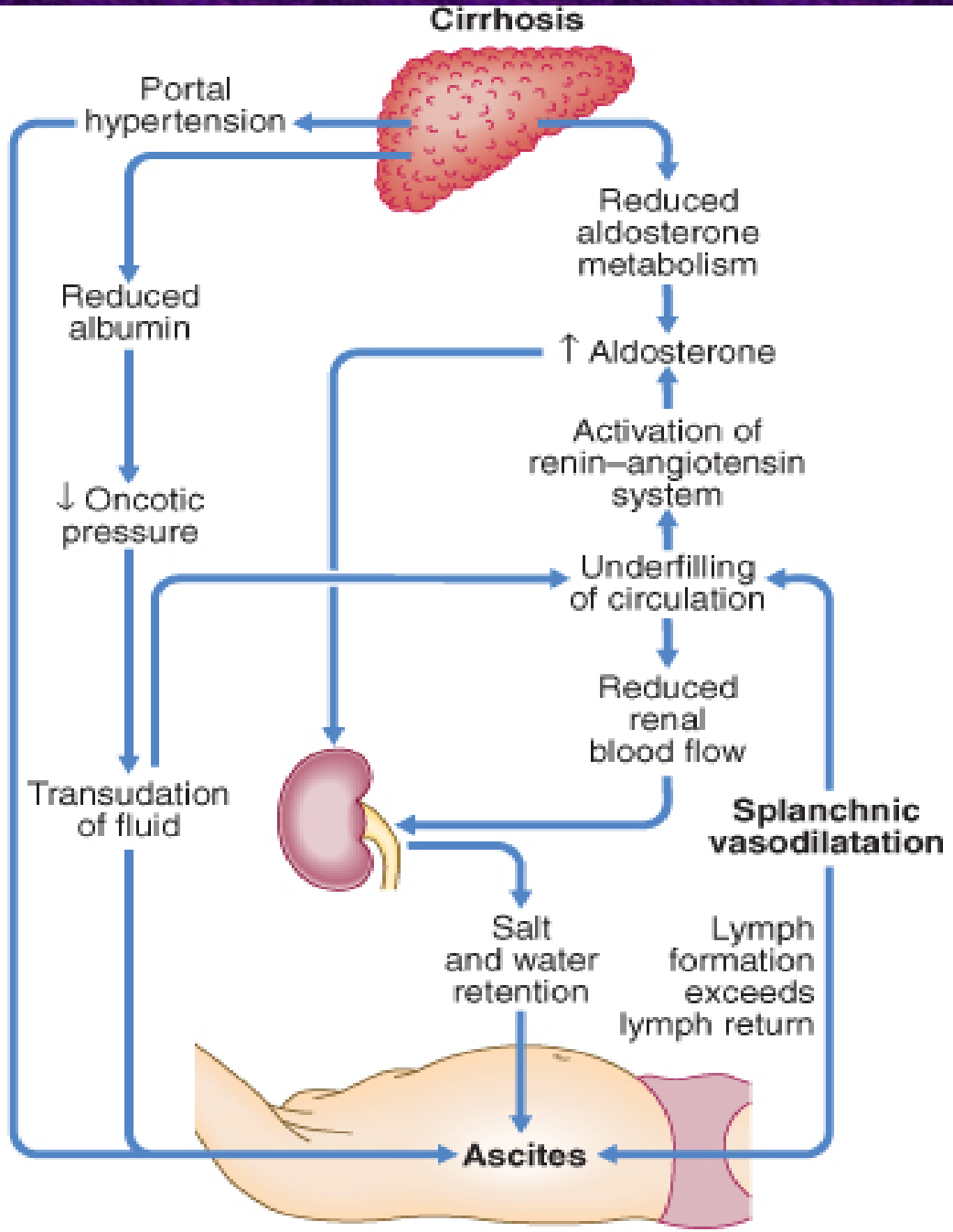
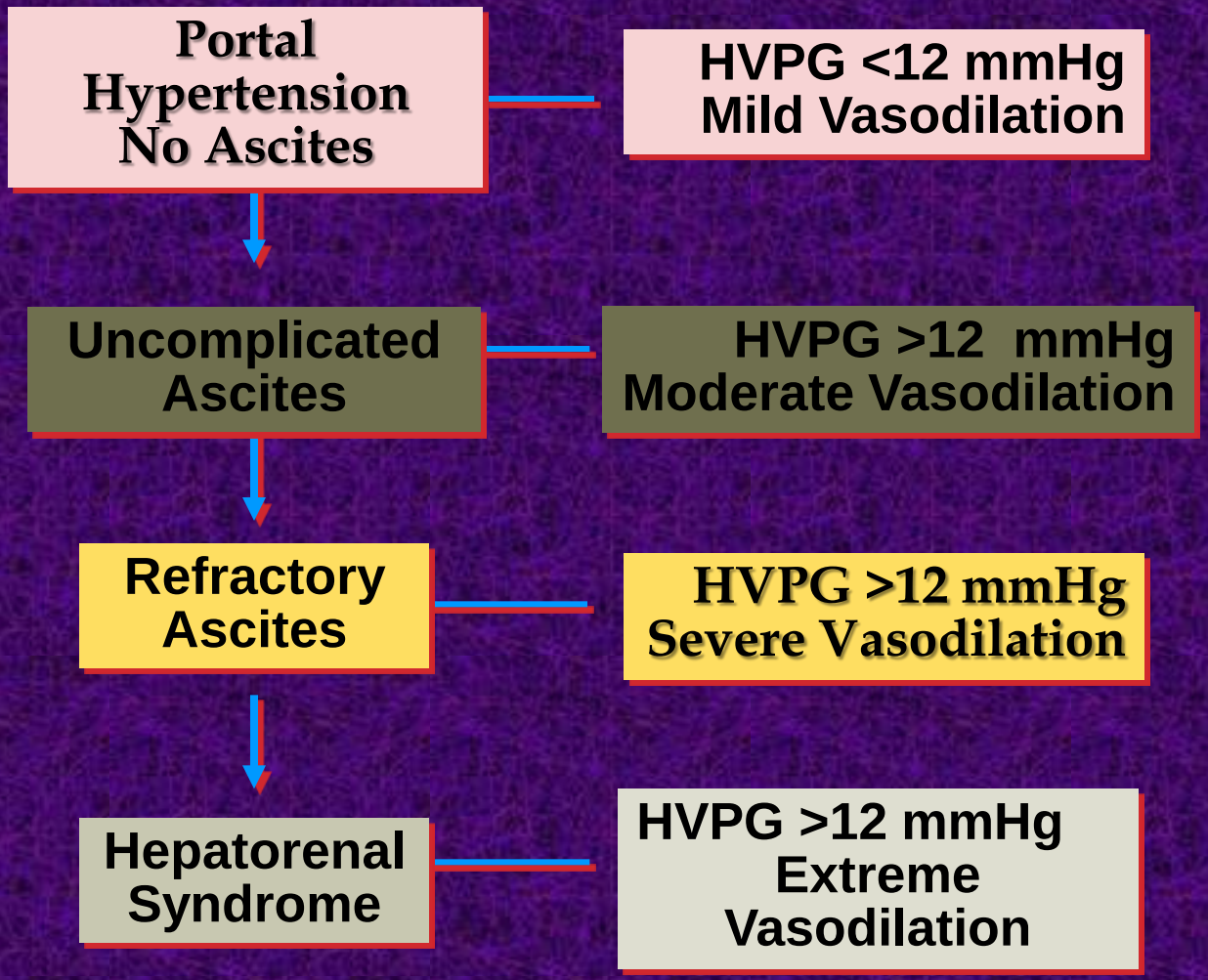


Natural History of Ascites



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Complications of ascites Cirrhosis

- - - **SBP**
- Abd. Hernia
- Impairment of respiratory function
- HRS **rare without ascites**

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In liver cirrhosis

- لا يتشكل الحبن عادة إلا بتوفر شرطين :
  1- فرط توتر وريد الباب
  2- إحتباس الصوديوم والماء بسبب قصور الخلية الكبدية.

Diagnosis of Ascites/Typical

- **Cell count**
- **Total protein**
- **Albumin**

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Diagnosis of Ascites/optional
initial tests

Culture Glucose

LDH

Amylase
Gram stain

SAAG	Testing	Diagnosis	Confirm
≥1.1	TP<2.5	cirrhosis	Imaging, liver biopsy
≥1.1	Glucose<50, LDH<225 +culture,GS	SBP	
≥1.1	+cytology	Carcinomatosis+ portal htn	Cancer workup
<1.1	TP≥2.5	Cardiac ascites	ECHO
<1.1	TP>1.1, glucose<50 Polymicrobial LDH<225	2ndary peritonitis	Abd imaging/CT abd
<1.1	Amylase>100	Pancreatic ascites	Imaging, ERCP

Is it common?

- 1/3 of admitted cirrhotic pts will have ascites
- either
- On admission
- Developed during Hospital stay

Treatment of Ascities

Patience is the key to ascities therapy

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Management of Ascites

Diuretic Therapy

Dosage

- Spironolactone or /with
- Furosemide

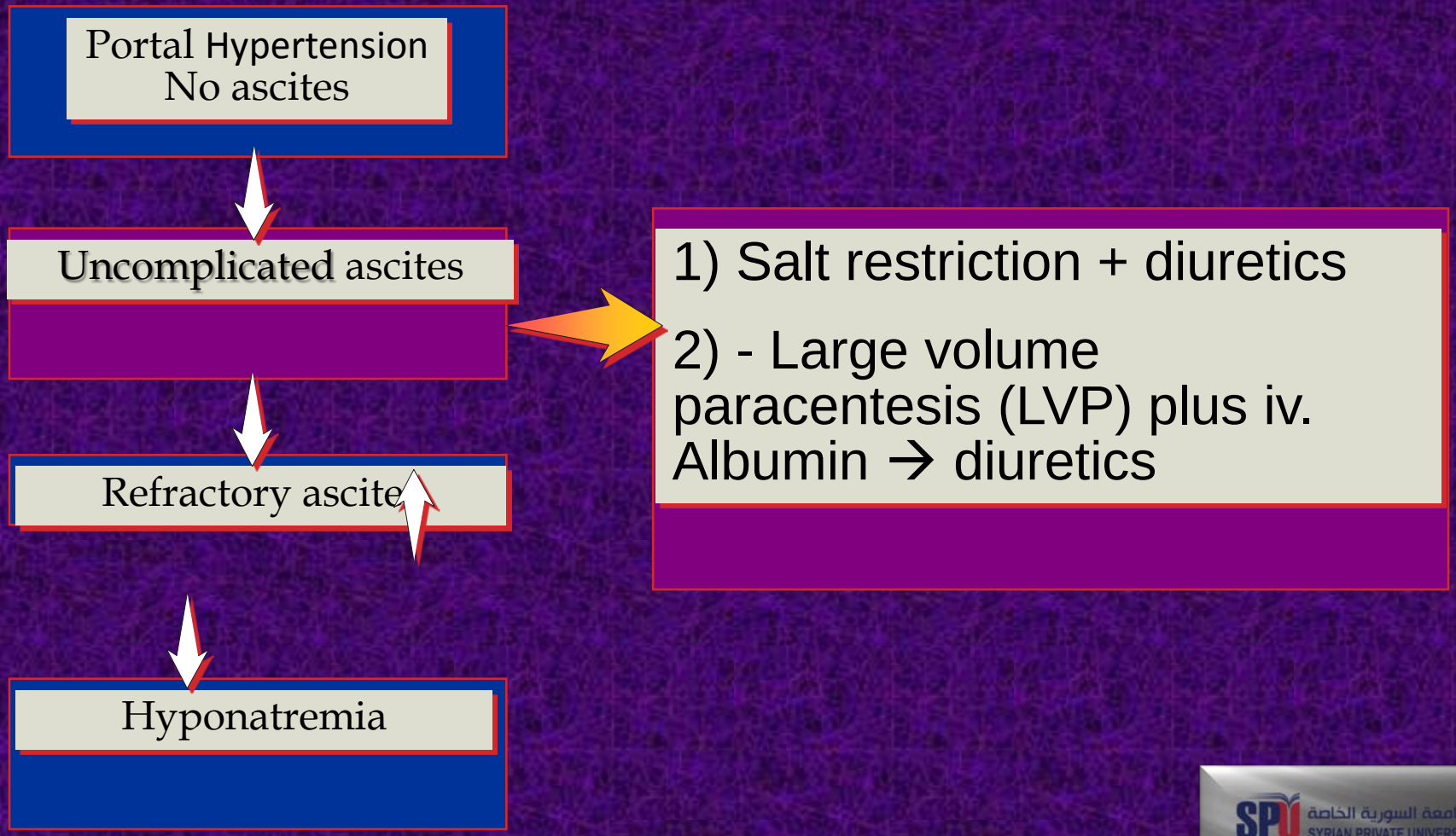
- Low sodium diet
- TIPPS
- Large paracentesis
- Fluid restriction if Na is low

Diuretic Therapy

Low sodium diet

Large para-centesis

Treatment of Ascites



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Key concepts

Spironolactone is the mainstay of ascites therapy.

Key concepts

- Loop and Thiazide diuretics should not be used as either primary or monotherapy, they are adjuncts to sodium restriction and Spironolactone.

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Bacterial infection in cirrhotic

- **20% SBP**
- 20% UTI
- 15% pneumonia
- 12% Bacteremia

Fernandez et al Hepatology 2002

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factors ?
Developing Bacterial infection

2 main factors :

1-Severity of liver disease

2-GI bleed: 50% cirrhotic admitted with bleed will develop SBP

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SBP

20% of cirrhotic with ascites

15% mortality

50% are bactermic

BP
Spontaneous?

Absence of:

- Intra abdominal inflammatory Focus

  pancreatitis ,cholicystitis, abscess

- Hollow viscus perforation

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SBP

Diagnosis >250 PMN

>500 WBC or gram stain

peritonitis

- Infected Ascites

>250 PMN

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Early recognition of SBP

- Fever
- Abdominal Pain
- **Worsening of renal failure**

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SBP

- 70% of patients present with fever,
-60% with abdominal pain,
- 50% of with changes in mental status,
- 40% of with abdominal tenderness

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Spontaneous Bacterial Peritonitis (SBP)

- **Initial Assessment and Diagnosis**
- History
- Physical examination
- Abdominal ultrasound
- Abdominal paracentesis
- Ascetic fluid analysis including a wcc and differential, ascetic fluid total protein,
- serum-ascites albumin gradient
- Culture of ascetic fluid at bedside in blood culture bottles

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Deterioration of cirrhotic patient

- A frequent cause of sudden deterioration is the development of (SBP).

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Bacterial

- E coli is main bacteria in SBP

  Not the only one

-

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Treatment SBP

- **Antibiotics : cefotaxime , amoxicillin/clavulanic acid**
- **IV albumin**
- Avoid therapeutic paracentesis

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THE KIDNEY IN CIRRHOSIS

Abnormality	**Clinical consequence**
Sodium retention	Ascites and edema
Water retention	Dilutional hyponatremia
Renal vasoconstriction	Hepatorenal syndrome

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Complication of cirrhosis

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Esophageal varices

- While most patients with cirrhosis form varices
- only 1/3 will bleed from them

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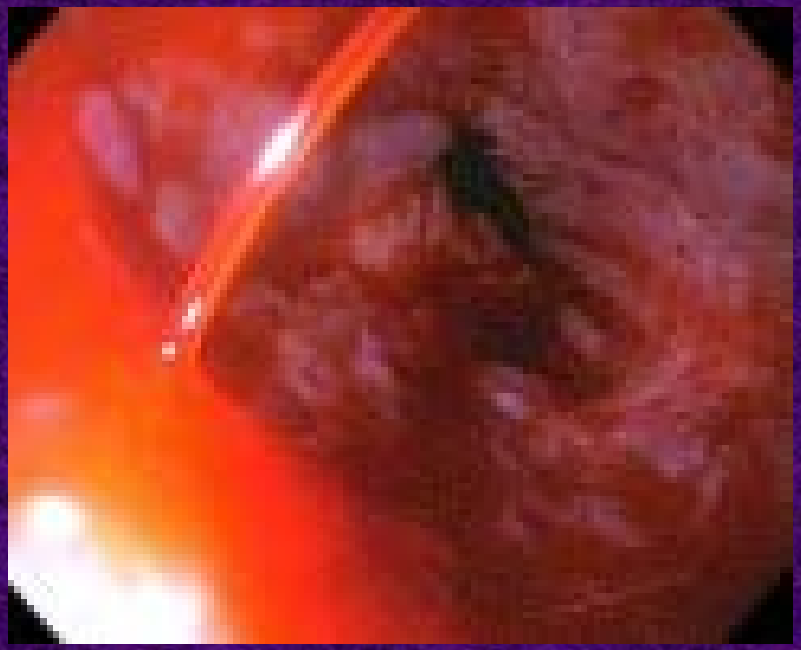

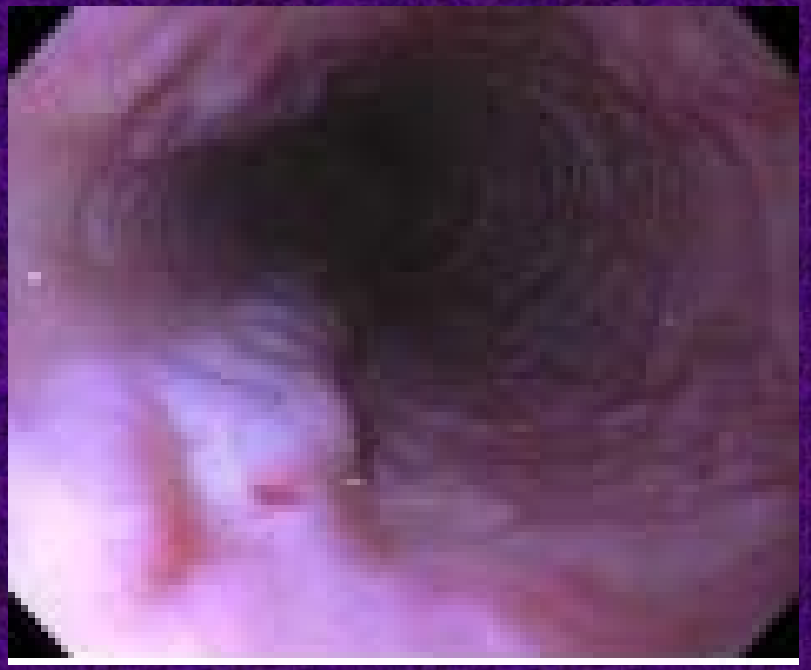

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Esophageal varices
predicted first bleed

- 1-Child-Pugh class
  2-the size of
- -presence of red color signs on, EV at endoscopy

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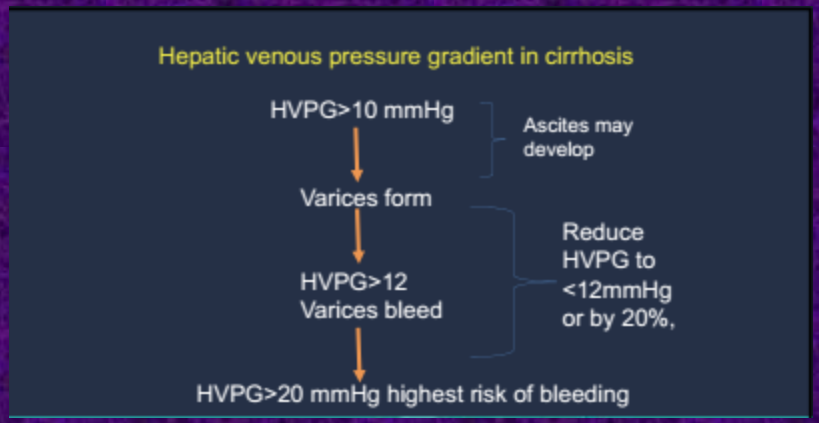

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Management of acute variceal bleeding

- General supportive measures
- -RBC transfusions if HG <8
  -IV **octreotide** infusion is recommended on first suspicion of variceal bleeding
- -Prophylactic antibiotic
- -endotracheal intubation
- Ligation or Sclerotherapy
- Management after the acute bleed from EV.

(EVL) or (EVS)

- **Both are equally effective in stopping bleeding**
- **complications after EVL (eg., bleeding from esophageal ulcers) are fewer than after EVS**

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Endoscopic Variceal Band Ligation

Technique and follow-up

Technique

Start at GEJ

↓

Apply suction
1-2 seconds

↓

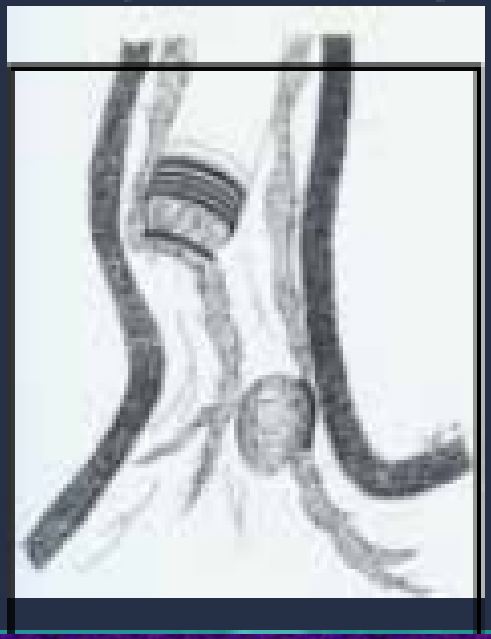
Deploy band

↓

Continue suction
1-2 seconds

↓

Progress upward:
-helically
-4-6 bands
-lower 5 cm



Follow-up

Re-band
Q 2 weeks

↓

Obliteration

↓

Re-screen
Q 3 months

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TIPS for variceal bleeding

- (1)failure of medical and endoscopic management in an acute bleed setting

- (2) recurrent EV bleeding despite NSBB and EVL with intent to obliterate.

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General Management of Acute Variceal Bleeding

Recommended	Consider
Early endoscopy (within 12 hours)	Platelets
Transfuse to Hb 7-8 gm/dL	Early TIPS
Prophylactic antibiotics (ceftriaxone)	FFP; *NOT* rFVIIa
Octreotide IV 72 hours	Lactulose
	Endotracheal intubation

Adapted from: Bosch, et al. Semin Liver Dis. 2008; 28: 3.

Garcia-Tsao, et al. AASLD Practice Guidelines. Hepatology. 2007; 46: 922.

Gastric varices.

- GV are found less commonly than EV in patients with cirrhosis (20%).

  Such bleeds are clinically more dramatic than from EV (higher transfusion requirements, higher mortality).

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Complication of cirrhosis

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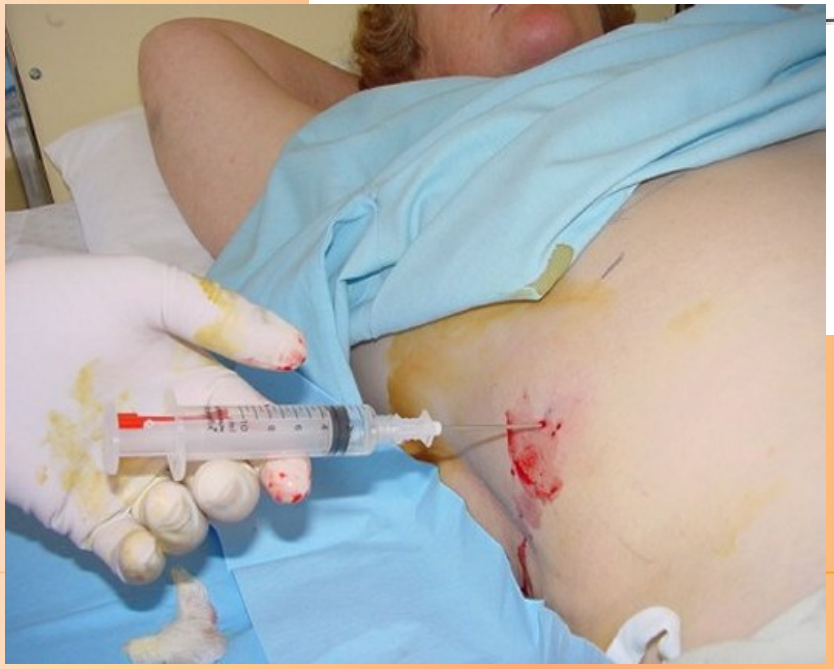
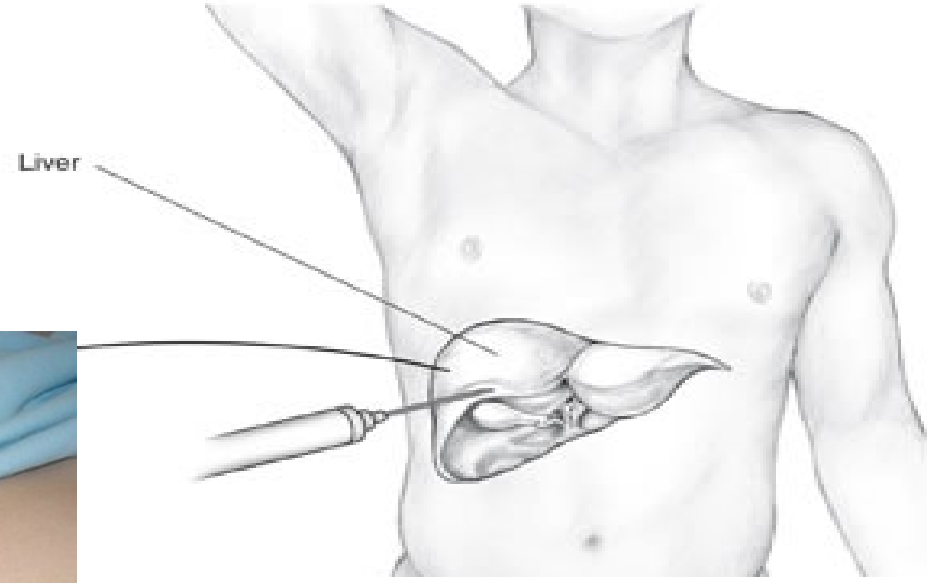
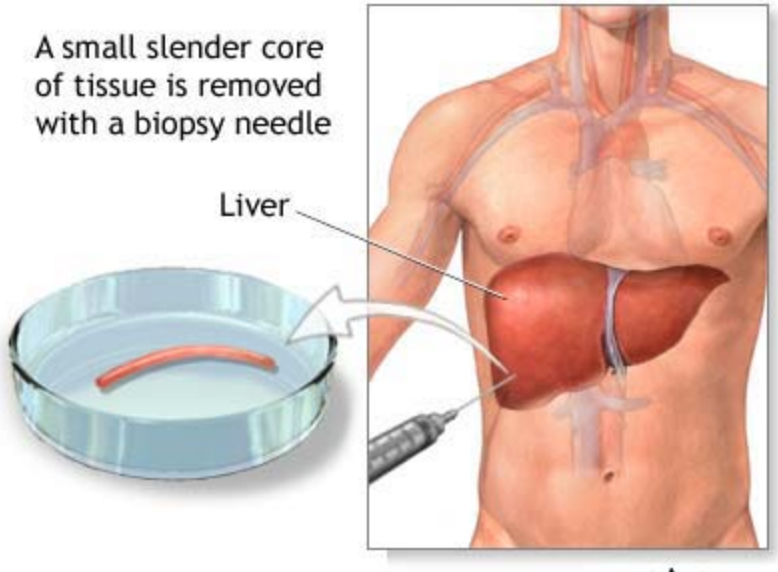
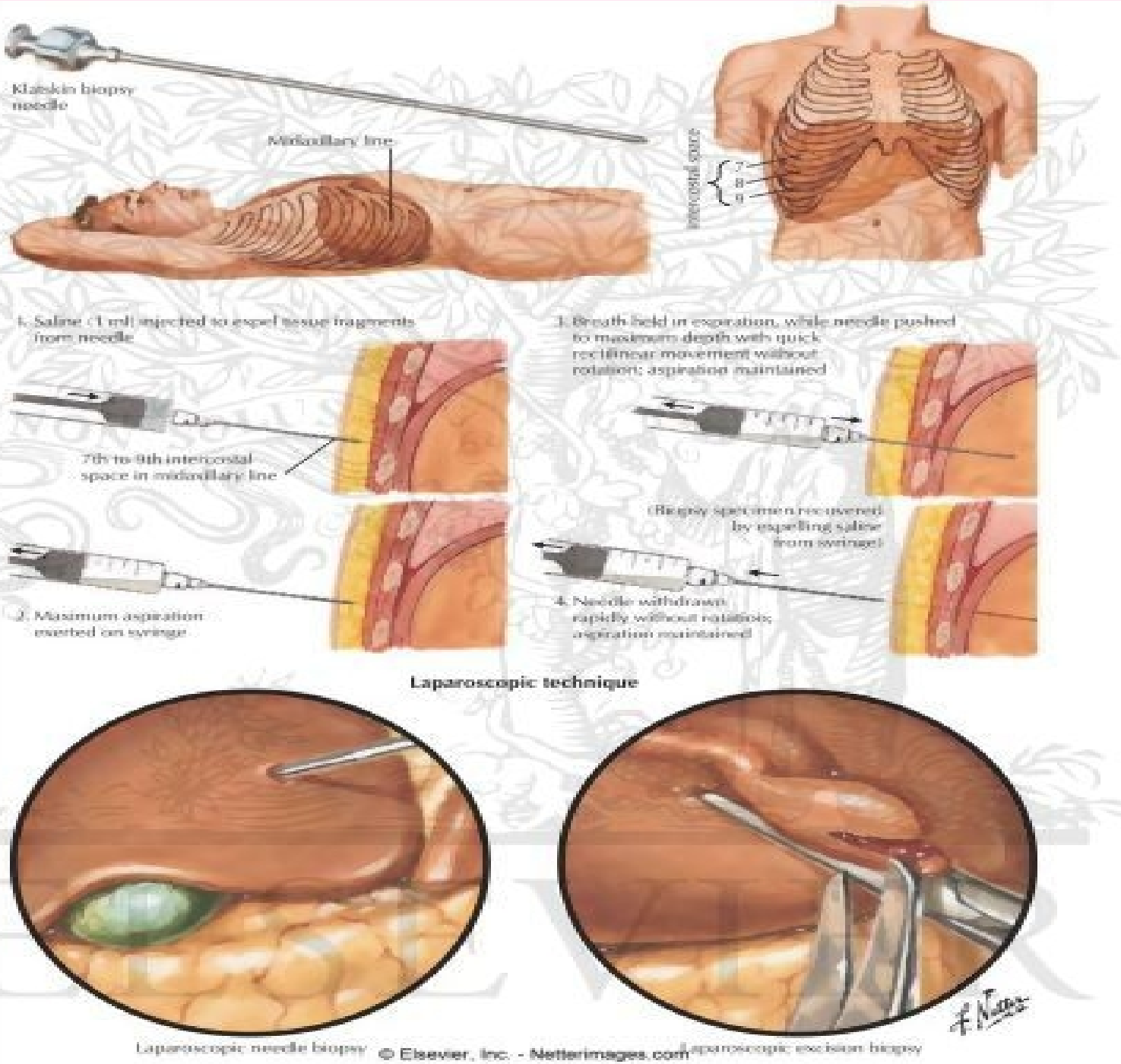
WHAT IS A LIVER BIOPSY?









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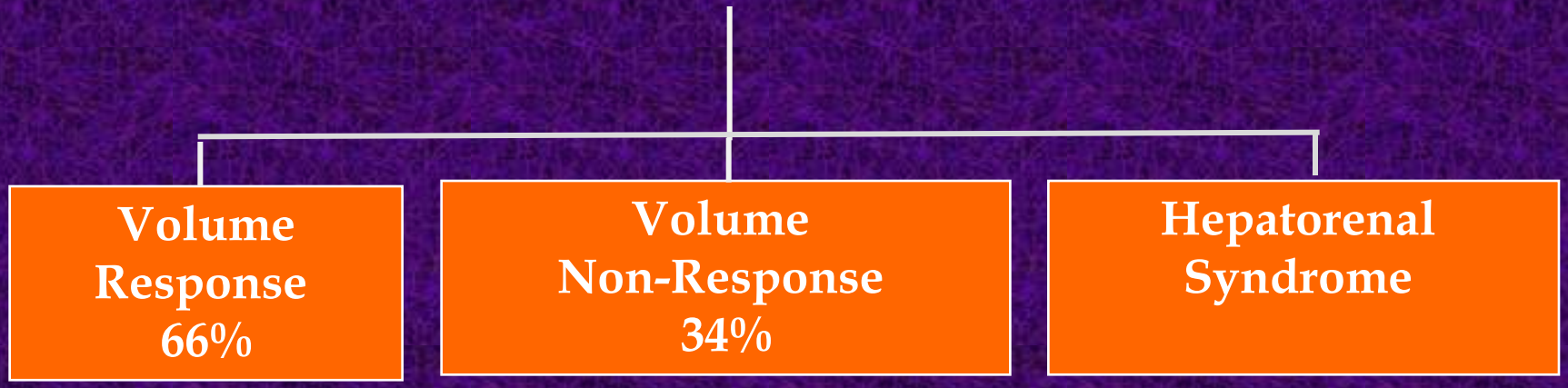
RENAL INJURY IN CIRRHOSIS



Most common causes

1) Sepsis
2) GI hemorrhage
3) Diarrhea
4) Aggressive use of diuretics

1) NSAIDS
2) Contrast dye
3) Intrinsic renal disease

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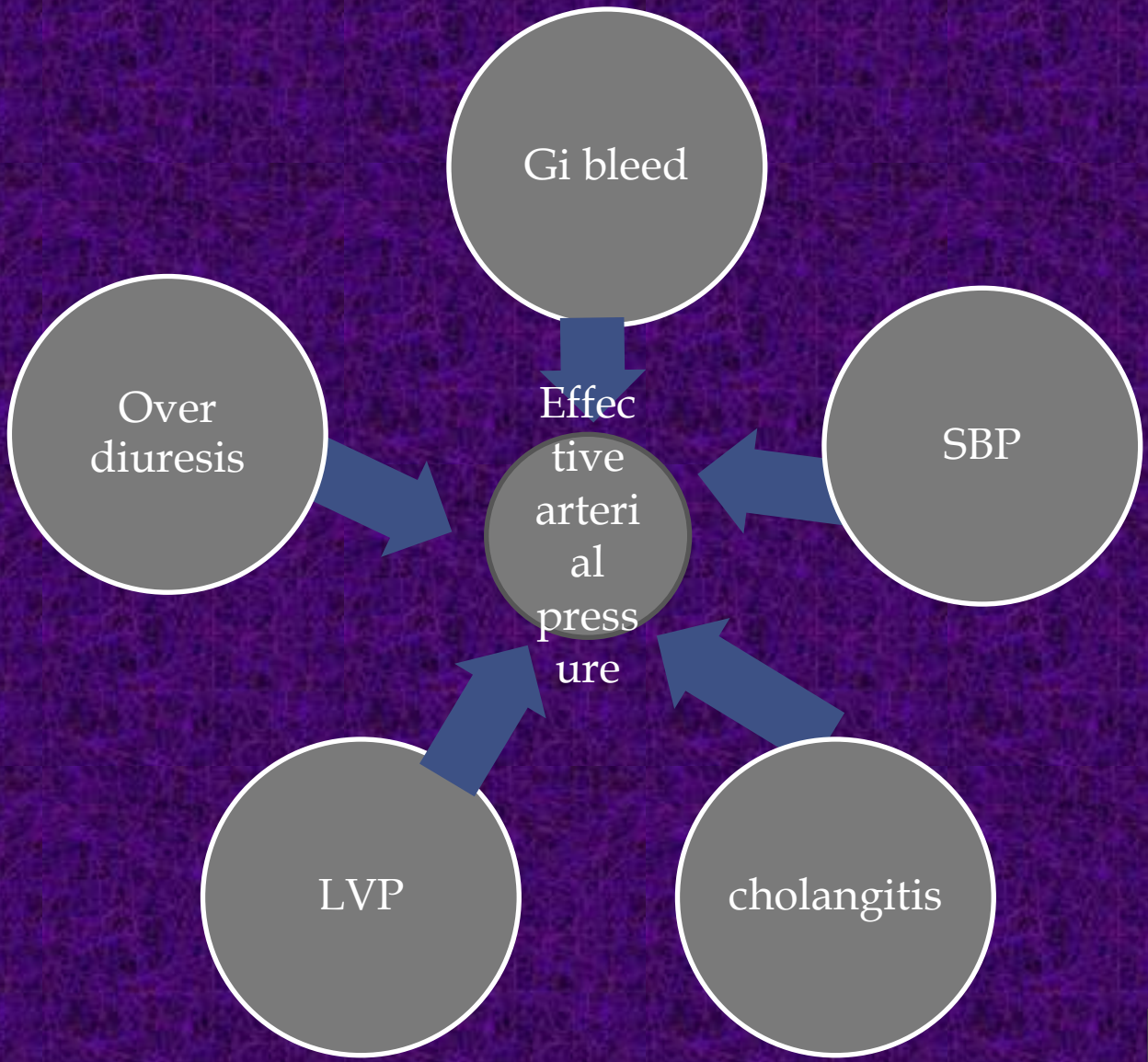

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Hepatorenal syndrome

- Low urine sodium in the absence of renal pathology
- Type 1 doubling of serum creatinine >2.5 mg/dl <2 weeks
- Median survival 2 weeks

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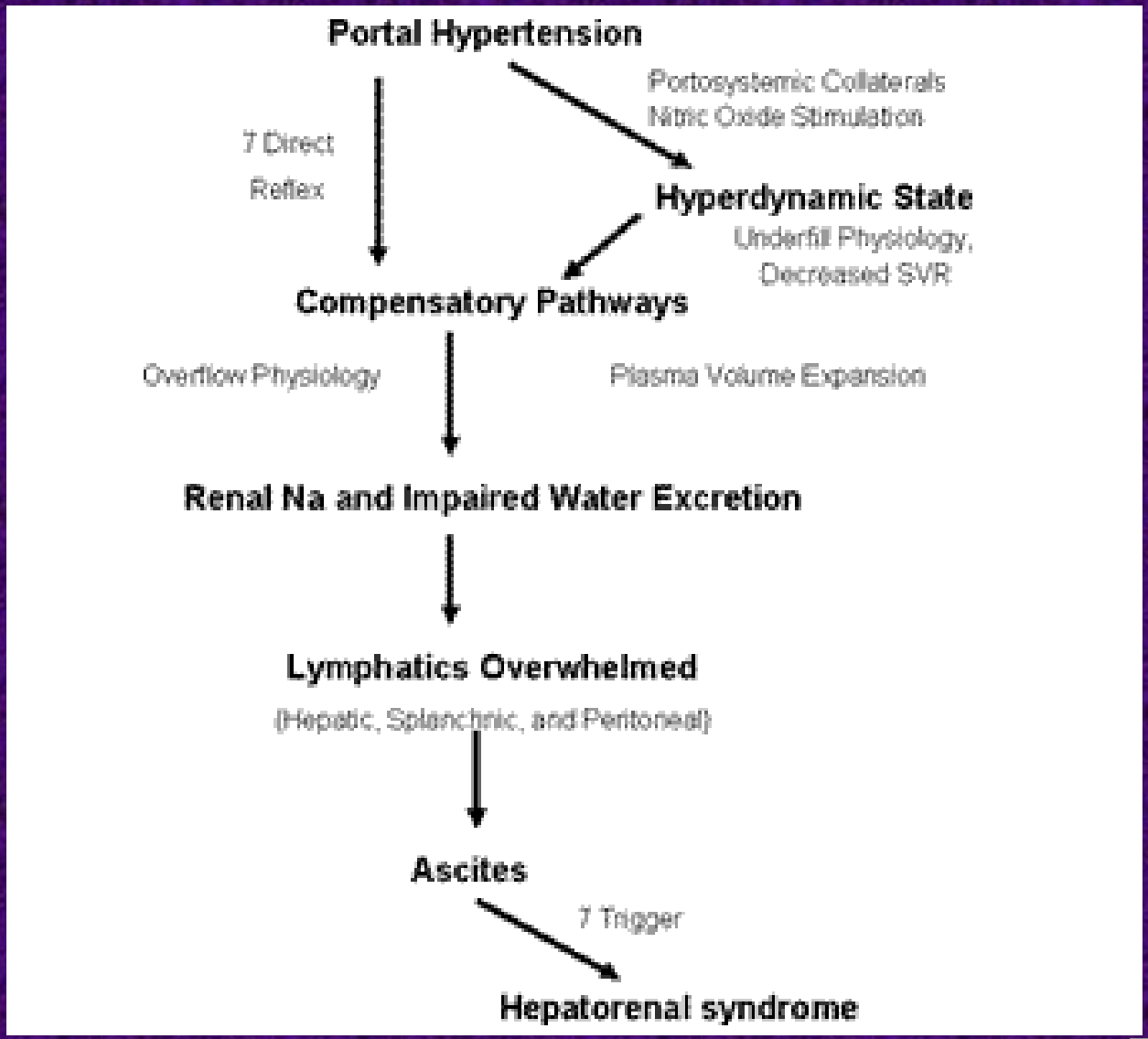
Hepatorenal syndrome

- Low urine sodium in the absence of renal pathology
- Type 2 doubling of serum creatinine >1.5 mg/dl over time
- Median survival 6 months



Hepatic Encephalopathy

Precipitating Events

Event	Mechanism
	↑ gut ammonia production
Constipation	•
GI bleed	•
Porto-systemic shunting	↓ neurotoxin clearance
Fever, infection	•
Dehydration, azotemia	↓ renal excretion of ammonium
Hypokalemia	•
Sedatives (BDZ)	↑ inhibitory neurotransmission (GABA)

Management of Hepatic Encephalopathy

1º Therapy

Remove Precipitant

↓

Lactulose

(PO dose to achieve 2-3 soft stools/d; enema in comatose patients)

↓

Antibiotics

-rifaximin

-(neomycin-no)

-(metronidazole-no)

↓

Search for spontaneous porto-systemic shunts

2º Considerations

Correct hyponatremia

↓

Dietary Modification

-fiber

-dairy/vegetable protein

-(protein restrict-no)

↓

Raise serum K^+ to 5-5.5

↓

Supplement Zinc

Probiotics?

Complication of cirrhosis

- Ascites
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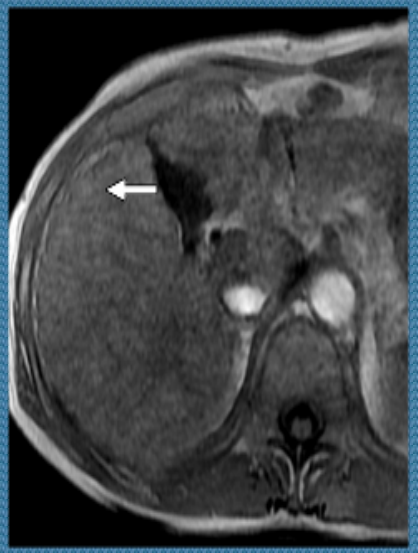
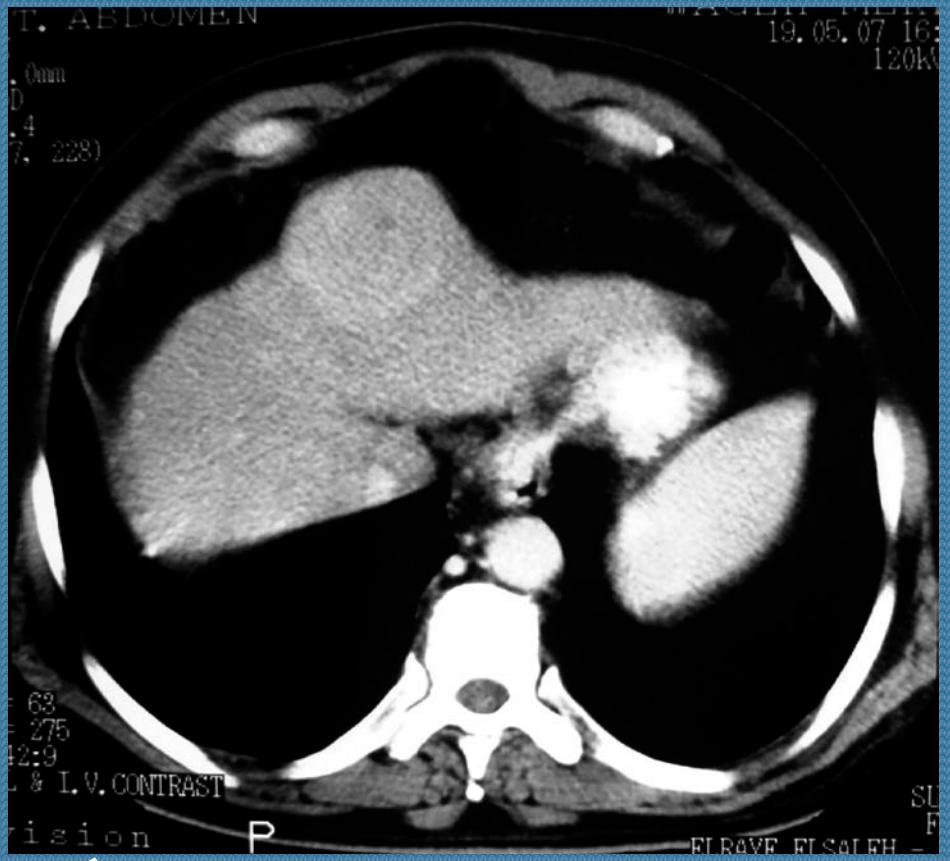
HCC

- The most common form of liver cancer in adults
- 4/5 cancers that start in the liver are this type

- Single tumor
- Many small cancer through the liver (liver cirhosis)

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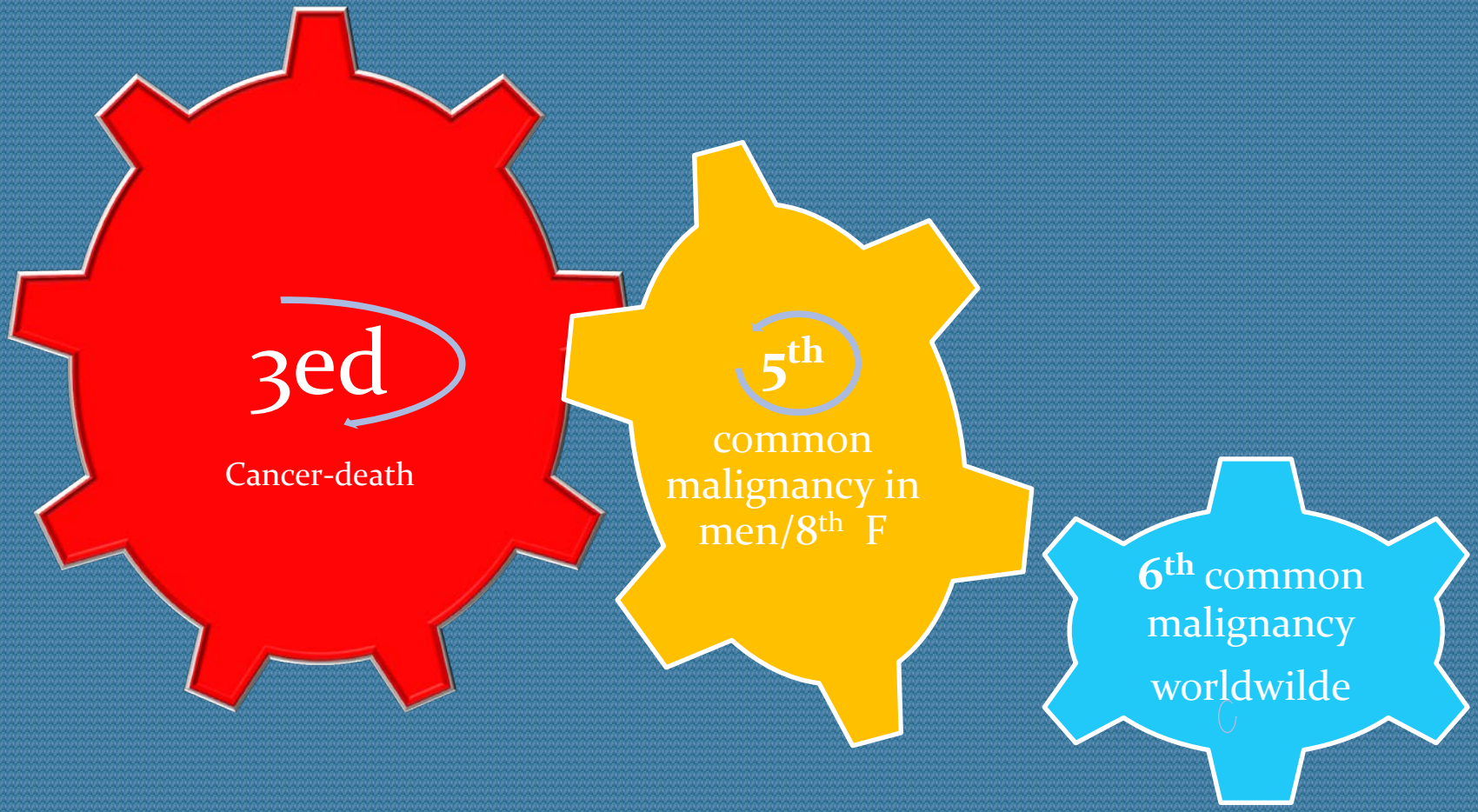
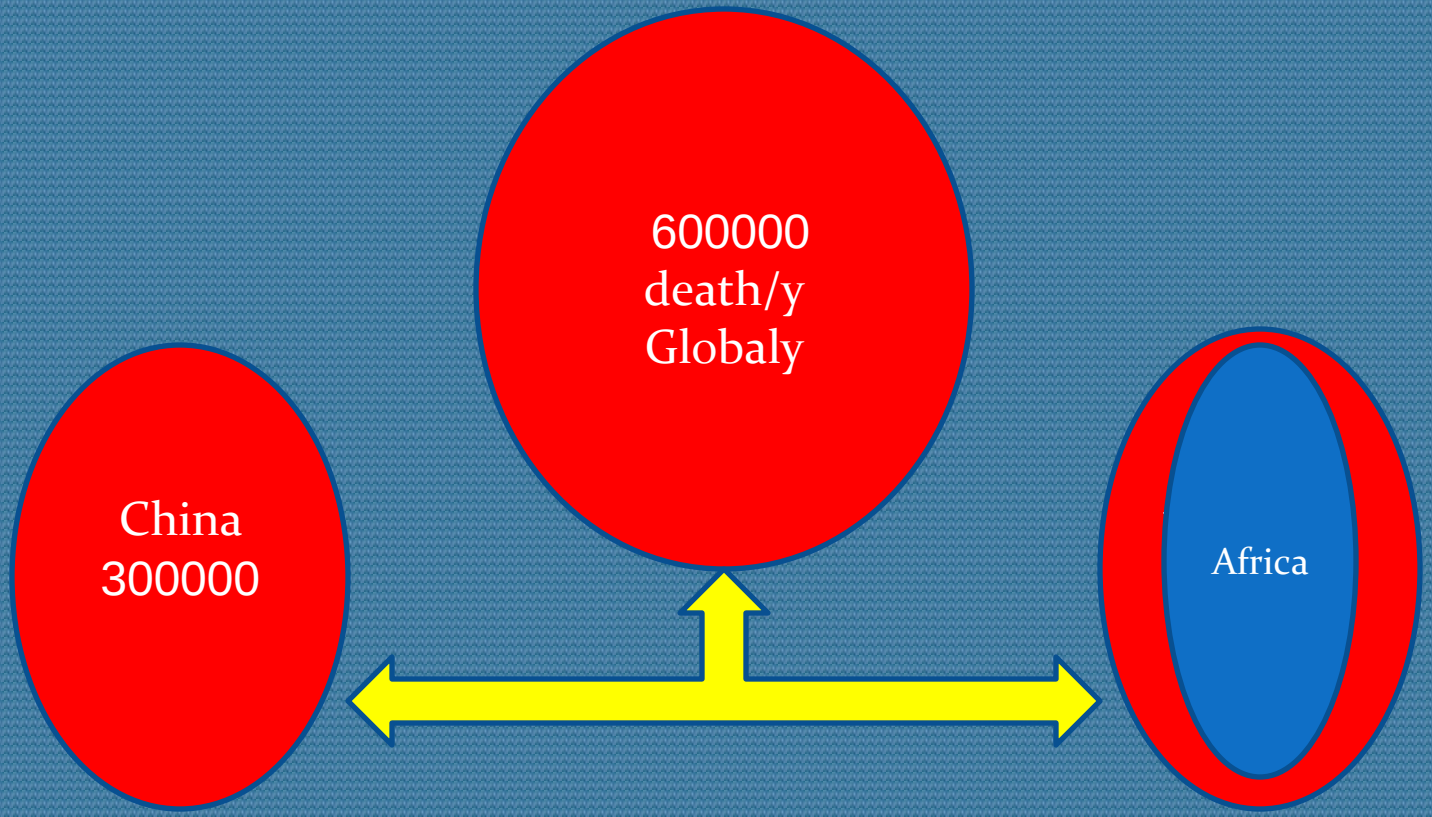
Why HCC ?

Global prevalence and incidence



HCC related death per year



Most cases of HCC are secondary to either

1-Viral hepatitis

2-Cirhosis

Table 1. Phases of chronic HBV as proposed by the EASL Guidelines [2].

	HBeAg positive		HBeAg negative	
	Chronic infection	Chronic hepatitis	Chronic infection	Chronic hepatitis
HBsAg	High	High/intermediate	Low	Intermediate
HBeAg	Positive	Positive	Negative	Negative
HBV DNA	$>10^7$ IU/ml	10^4-10^7 IU/ml	<2,000 IU/ml°°	>2,000 IU/ml
ALT	Normal	Elevated	Normal	Elevated*
Liver disease	None/minimal	Moderate/severe	None	Moderate/severe
Old terminology	Immune tolerant	Immune reactive HBeAg positive	Inactive carrier	HBeAg negative chronic hepatitis

*Persistently or °°intermittently HBV DNA levels can be between 2,000 and 20,000 IU/ml in

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HCC related death per year

HCC

600000 death/y Globaly

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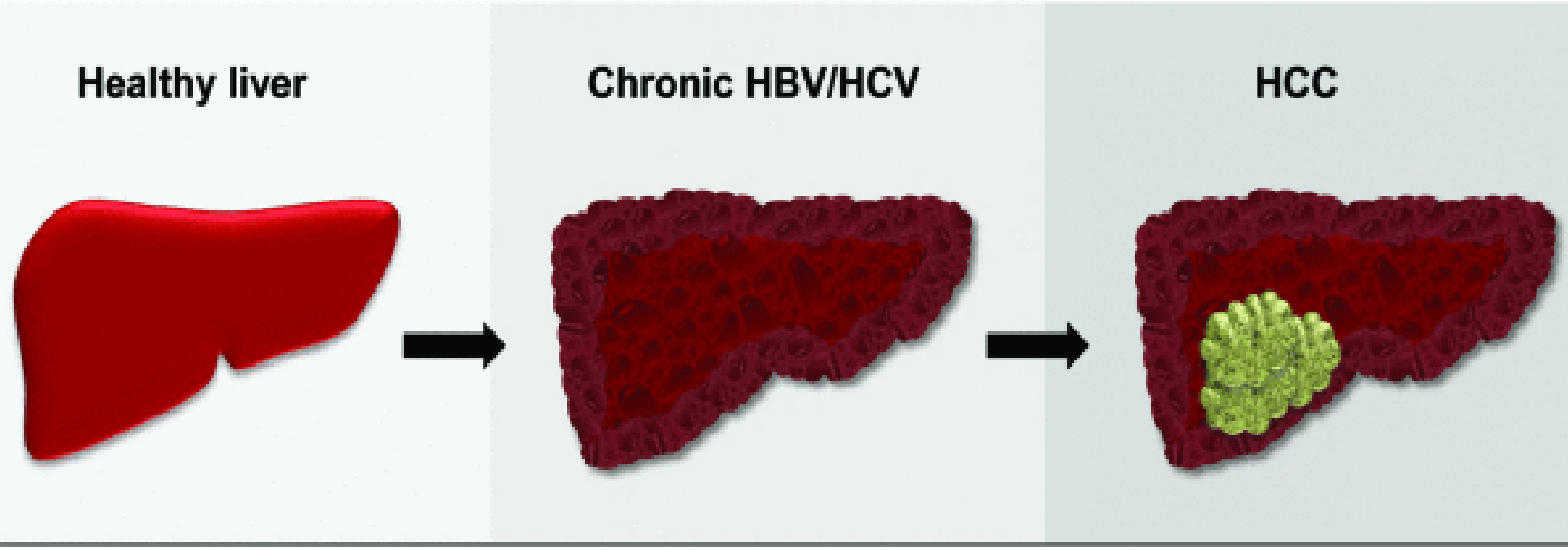

TOLEROGENIC FACTORS:

Healthy liver	Chronic HBV/HCV	HCC
1. Suboptimal T cell priming	1. Suboptimal T cell priming	1. Suboptimal T cell priming
2. PD-1-B7-H1 interactions	2. PD-1-B7-H1 interactions	2. PD-1-B7-H1 interactions
3. Regulatory DC	3. Tim-3-Gal-9 interactions	3. Low DC frequencies
4. CD8+ T cell apoptosis	4. Immature DC	4. Low NK cell frequencies
5. Th2 polarization	5. Hyporesponsive NK cells	5. MDSC, Treg enrichment
6. TGF-β, IL-10 production	6. Treg accumulation	6. Th2 polarization

The incidence of HCC is rising

Over the last few years evidence has been accumulating in different countries that the incidence of HCC is rising

Once diagnosed, HCC has a dismal prognosis.

Small, localized tumors are potentially curable with surgery (resection and liver transplantation).

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Tests used to Diagnose HCC

To establish the diagnosis	• Ultrasonography • AFP serology (negative in one-third of cases)
To confirm the diagnosis and assess the disease stage	Where available and with technical expertise available: • Ultrasound-guided biopsy and/or • CT /MRI

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Cirrhosis

For patients with cirrhosis of varying etiologies surveillance (AFP+USS)should be offered when the risk of HCC is 1.5%/year

AASLD Practice guidelines

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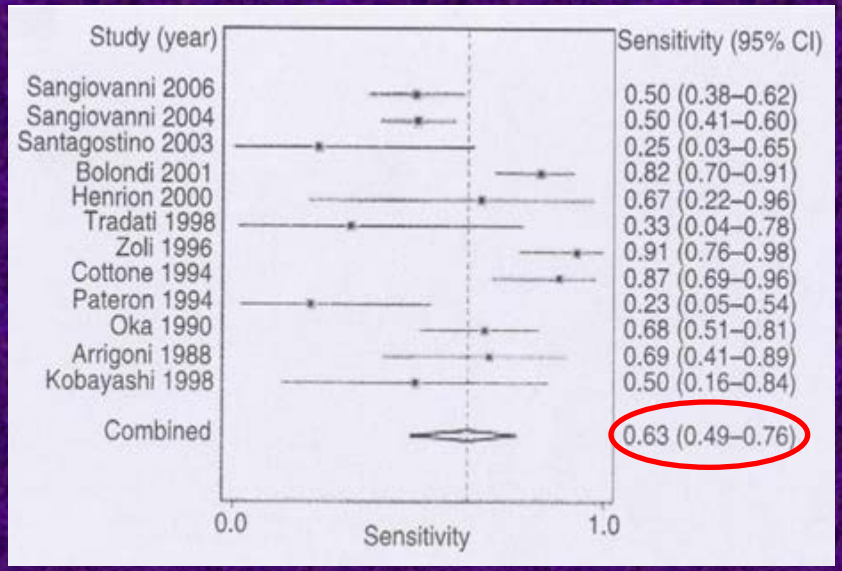
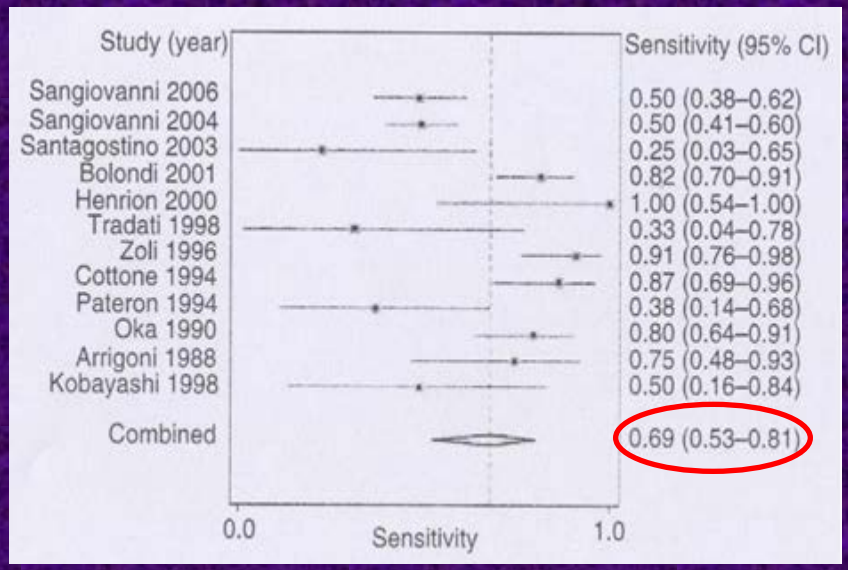
Ultrasound Diagnosis of Early-stage HCC in Patients with Cirrhosis. Meta-analysis

Ultrasound alone



Ultrasound + AFP



Singal et al Aliment Pharmacol Ther 2009;30:37-47

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- Hepatitis E virus (HEV) infection should be included early in the differential diagnosis of acute hepatitis, neuralgic amyotrophy and other neurological manifestations, drug-induced liver injury, as well as chronic hepatitis in immunocompromised patients.
- A combination of serological and molecular testing (anti-HEV IgM and PCR for HEV RNA) is best used to diagnose acute hepatitis E.
- PCR for HEV RNA should be used to diagnose chronic hepatitis E in immunocompromised patients.

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