Liver Diseases

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Objectives

- Liver function
- Causes of acute hepatitis
- Causes of chronic hepatitis
- Cirrhosis and its complications.
- Liver Transplantation

Liver Function

- Bile metabolism and excretion.
- Protein production
  - Albumin
  - Clotting factors
- Detoxification
  - Encephalopathy

Acute Liver Disease

- Causes
  - Infectious
    - Viral (A,B,C).
  - Toxic
    - Drugs (acetaminophen, toxins)
  - Ischemic
    - Hypotension
  - Idiosyncratic
    - HELLP, AIH

Acute Liver Disease

- Patients with acute hepatitis usually present with fatigue, nausea, abdominal pain, jaundice, etc.
- Serum aminotransferases (ALT, AST) are markedly elevated.
- Prothrombin time (PT) and the presence of encephalopathy indicate liver function and possible failure.

Acute Liver Disease

- Fulminant liver failure is defined as the presence of acute liver failure and hepatic encephalopathy in someone without history of liver disease.
- Cerebral edema and metabolic derangements as lactic acidosis, renal failure and hypoglycemia are common findings.
- Patients should be referred to a transplant center for evaluation.

Chronic Hepatitis

- Causes
  - Viral
    - HBV
    - HCV
  - Alcohol induced
  - Autoimmune Hepatitis
  - Cholestatic Disorders
    - PBC
    - PSC
  - Hereditary disorders
    - Hemochromatosis
    - Wilson's
  - Cryptogenic disorders
    - NAFLD/NASH
  - Vascular
    - Budd Chiari Syndrome

Viral Hepatitis

- Hepatitis A
  - Transmission
    - fecal /oral
  - Test for diagnosis
    - IgM anti-HAV
  - Incubation
    - 15-20 days
  - Almost always self limited
  - Treatment supportive
  - Vaccine available

Viral Hepatitis

- Hepatitis B
  - Transmission
    - Parenteral
  - Incubation
    - 30-120 days
  - Vaccination available
  - Treatment available
    - pegylated interferon, lamibudine, adefovir, entecavir, tenofovir, telbivudine.

Viral Hepatitis
HBV serologic markers

HBsAg	Anti-HBs	IgM Anti HBc	IgG Anti HBc	HBeAg	Anti Hbe Ab	HBV DNA Titers	Interpretation
++++	--------	+++++	------	+++++	------	++++	Acute Infection
-------	++++++	-------	+++++++	--------	-----/+++	------	Prior infection
-----	+++++	-----	-----	-----	------	------	Vaccine
++++	----	----	++++	----	++++	<100000	Inactive carrier
++++	----	----	++++	+++++	-----	>100000	Chronic Infection
+++++	-----	----	++++	----	++++	.100000	Chronic infection

Viral Hepatitis

- Hepatitis B
  - Patients with HBV who also require cancer chemotherapy have an increased risk of exacerbation.
    - Therapy indicated.
  - High risk of hepatocellular carcinoma.
    - Even without cirrhosis.
    - Screening indicated

Viral Hepatitis

- Hepatitis C
  - Most common blood borne infection in the US.
  - Many genotypes
    - 1 (most common)
  - HCVab screening test
  - HCV RNA assay confirmatory test
  - 85% of patients develop chronic infection
  - Most common cause of cirrhosis and liver transplantation.

Viral Hepatitis
HCV

- Treatment available
  - Pegylated interferon with concomitant Ribavirin
- Sustained viral response close to 50% for all genotypes.
- No vaccine available.

Chronic Hepatitis

- Alcohol related liver disease.
  - May cause acute hepatitis or chronic hepatitis (cirrhosis)
- Acute
  - AST: ALT ration is 2:1, values <300
  - Discriminant function
  - DF=4.6[PT patient – Pt control] + serum bilirubin
  - DF > 32 identifies patients with a 50% mortality.

Alcohol related liver disease

- Acute
  - Corticosteroids may be used to treat severe alcoholic hepatitis.
- Chronic
  - Prognosis depends on whether abstinence is achieved and the complications of cirrhosis.
  - 5 year survival is 80% in those who no longer drink.
  - Liver Transplantation is an option.

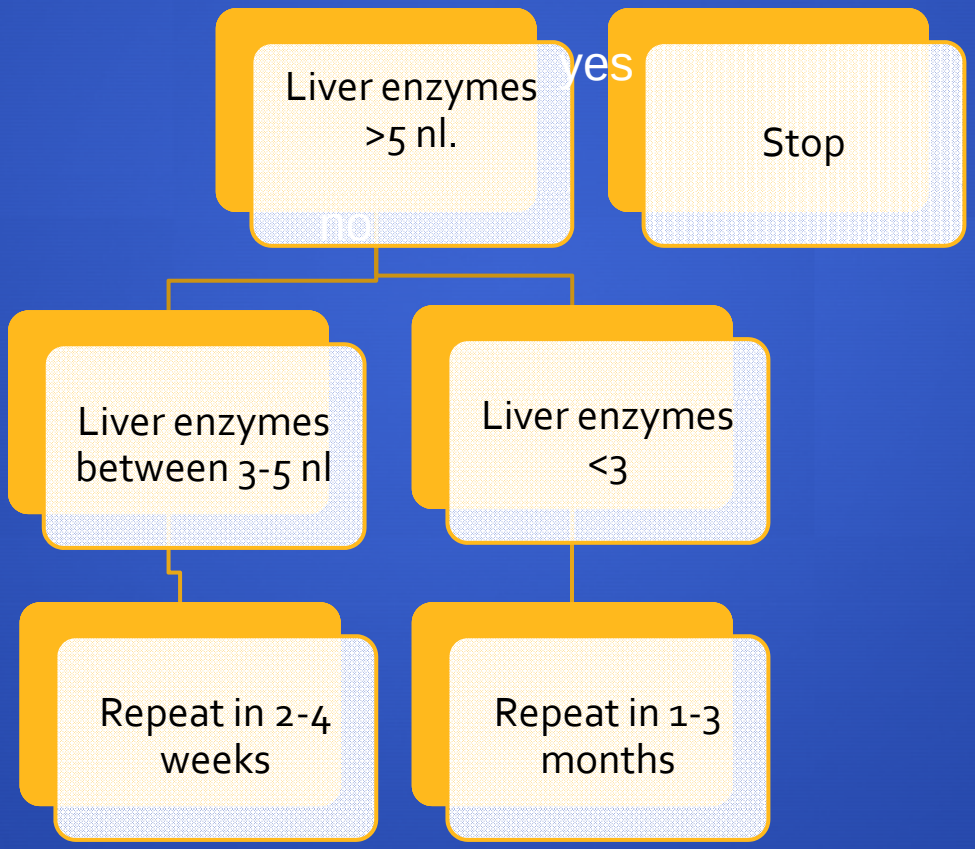
Chronic Hepatitis

- Drug Induced Liver Disease.
  - Drugs (i.e. acetaminophen) are the most common cause of fulminant hepatic failure
  - Several drugs cause chronic syndromes causing abnormal liver enzymes that deserve further evaluation.

Drug Induced Liver Disease

Clinical Syndrome	Causative Medication
Acute Hepatitis	Acetaminophen Halothane Isoniazid Statins Venlafaxime
Chronic Hepatitis	Methyldopa Ntrofurantoin
Cholestasis	Estrogen Sulfa's
Steatosis	Amiodarone Tamoxifen Valproic Acid
Fibrosis	MTX Vitamin A
Ischemia	Amphetamines Cocaine

Drug Induced Liver Disease



Chronic Hepatitis

- Autoimmune Hepatitis
  - Inflammatory condition of the liver of unknown etiology.
  - More common in women between 20-40 years of age.
  - 40% may have an acute presentation.
  - Symptoms include fatigue, jaundice, anorexia, myalgias, diarrheas.

Autoimmune Hepatitis

- Laboratories
  - Abnormal liver function tests, hypergammaglobulinemia,hyperbilirubinemia, presence of auto antibodies.
  - ANA, ASMA, Anti LK-M1 are present in 87% of pts.
- Liver biopsy usually needed to establish diagnosis and prognosis.

Autoimmune Hepatitis

- Treatment with prednisone alone or prednisone plus azathioprine is associated with remission in 80% of pts. at 3 years.
- Liver transplantation is an option for those who do not respond to treatment and/or develop complications from cirrhosis.

Chronic Hepatitis

- Metabolic Liver Disease
  - Non Alcoholic Liver Disease
  - Hereditary Hemochromatosis
  - Wilson's Disease

- Refers to the spectrum of histologic changes in the liver initiated by steatosis in the absence of excess alcohol consumption.
- Steatosis causes oxidative stress, lading to cell death and necroinflammatory hepatic changes.
- Associated to patients with metabolic syndrome(obesity, dyslipidemia, and diabetes mellitus or glucose intolerance.)

NASH

- Usually increased AST/ ALT levels 2 to 5 times normal.
- Ratio AST:ALT is usuallu,1 initially but tends to to rise as the degree of fibrosis increases.
- Imaging usually consistent with fatty infiltration.
- Liver biopsy usually indicated for pts most likely to have advanced fibrosis. (older age, DM, Increased AST:ALT ratio).

NASH

- Weight loss is the cornerstone of treatment.
- Hypoglycemic agents to be considered for select pts.
- Prognosis-
  - 1/3 will develop progressive fibrosis or cirrhosis.
- Liver Transplantation is a good option.

Hereditary Hemochromatosis

- An autosomal recessive disorder characterized by increased intestinal absorption of iron and iron deposition in multiple organs, including the liver pancreas, heart, joints, thyroid and hypothalamus.
- "Classic" description of cirrhosis, DM 1, and skin hyperpigmentation ("bronze diabetes").
- Presenting symptoms include fatigue, impotence, arthropathy.

Hereditary Hemochromatosis

- Many pts. are asymptomatic and are diagnosed after abnormal lab tests.
- Screening test of choice is % of iron saturation on fasting labs and ferritin levels.
- Confirmatory tests is the hemochromatosis gene testing (HFE gene test) for C282Y and H63D mutations.
- Liver biopsy with deposition of hemosiderin in the hepatocytes is also diagnostic.

Hereditary Hemochromatosis

- Phlebotomy is the preferred treatment.
- Goal of therapy is to keep ferritin levels below 50 and low % saturation.
- Cirrhosis highly prevalent upon diagnosis.
- Liver transplantation is an option, but outcomes are not the best.

Wilson's Disease

- Autosomal recessive disorder of copper metabolism caused by abnormal bile excretion of copper and deposition throughout the body including the liver, brain, corneas, and kidneys.
- Isolated to the ATP7B gene on chromosome 13.
- 50% of pts present with liver disease ranging from mild abnormal liver tests to progressive cirrhosis, and/or fulminant liver failure.
- Findings include neurologic symptoms, psychiatric findings, hemolytic anemia, cardiomyopathy and, endocrine dysfunction.

Wilson's Disease

- Physical exam may disclose Kayser-Fleischer rings on slit lamp examination.
- Labs may present with low alk. phos., low ceruloplasmin levels and, elevated urine copper concentration.
- Liver biopsy is the confirmatory test for diagnosis.
- Penicillamine is the initial treatment of choice. Trientine and zinc acetate are alternatives.
- Liver transplantation is indicated for those with fulminant failure or with end stage liver disease.

Cholestatic Liver Diseases

- Primary Biliary Cirrhosis (PBC).
- Primary Sclerosing Cholangitis (PSC).

Primary Biliary Cirrhosis

- Autoimmune disorder that occurs predominantly in women between 40 and 60 years of age.
- Symptoms include fatigue, pruritus, jaundice, sicca syndrome, and abdominal pain.
- Physical exam may include skin thickening, hyperpigmentation, excoriations, xanthomas and xanthelasmas.
- Autoimmune disorders are usually present as metabolic bone disease, hypercholesteronemia, and fat soluble vitamin deficiencies.

Primary Biliary Cirrhosis

- Lab findings include cholestatic pattern (increased on alk. phos. and GGT levels (10x)).
- + anti mitochondrial antibodies are present in 95% of cases.
- Serum bilirubin levels increases as the disease progresses .
- Liver biopsy confirms diagnosis.

Primary Biliary Cirrhosis

- Ursodeoxycholic acid is the treatment of choice.
- Improves biochemical profile, reduces pruritus, and retards disease progression.
- Liver transplantation is a good option with excellent outcomes.

Primary Sclerosing Cholangitis

- Characterized by progressive bile duct destruction.
- More common in men ages between 20 and 39 years of age.
- 80 % of pts. with PSC have concomitant inflammatory bowel disease.
- Most common symptoms are pruritus, jaundice, fatigue, but most are asymptomatic.

Primary Sclerosing Cholangitis

- Labs demonstrate cholestatic pattern (alk phos 3x normal and mild hyperbilirubinemia).
- Diagnosis confirmed by ERCP or MRCP.
- Pts have higher risk of developing cholangiocarcinoma.
- Management include assessment of dominant strictures and treatment of superimposed bacterial cholangitis.
- Liver transplantation is associated with improved quality of life and overall survival.

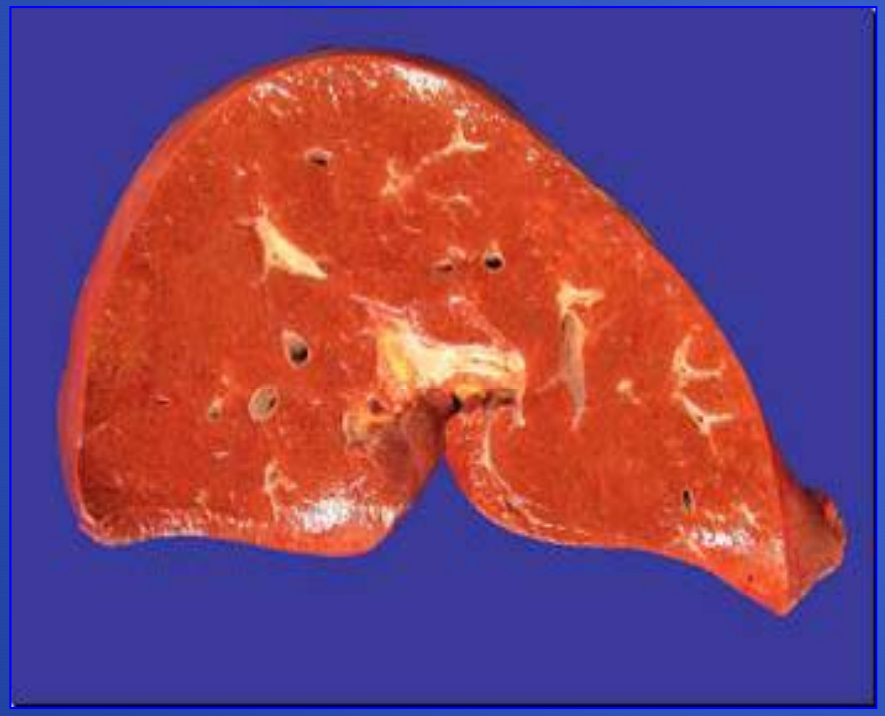
Complications of Chronic Liver Disease

Cirrhosis

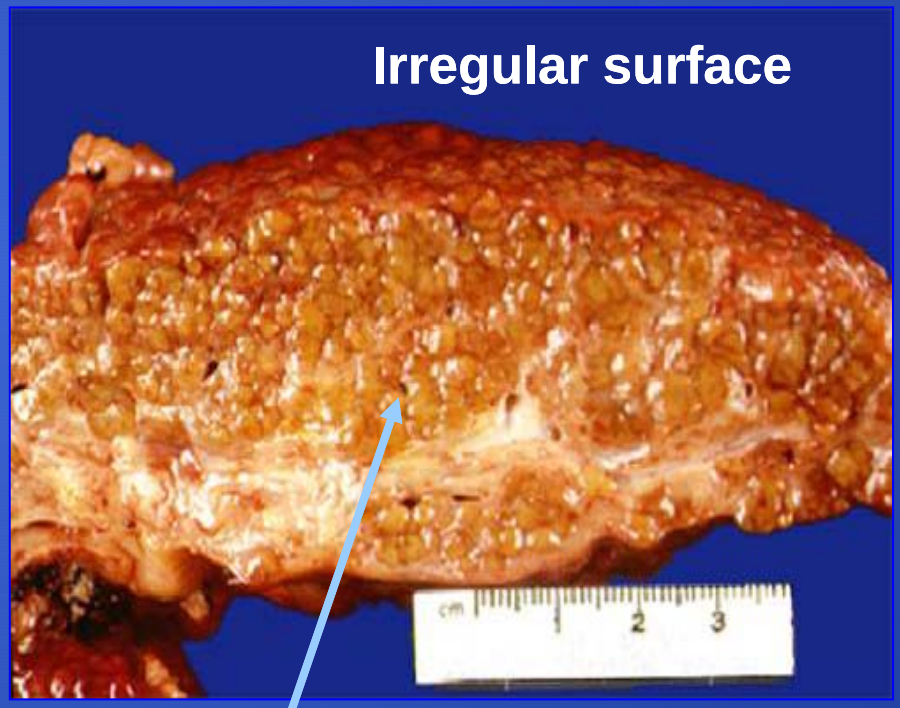
- End stage of any chronic liver disease
- Characterized histologically by regenerative nodules surrounded by fibrous tissue
- Clinically there are two types of cirrhosis:
  - Compensated
  - Decompensated

GROSS IMAGE OF A NORMAL AND A CIRRHOTIC LIVER

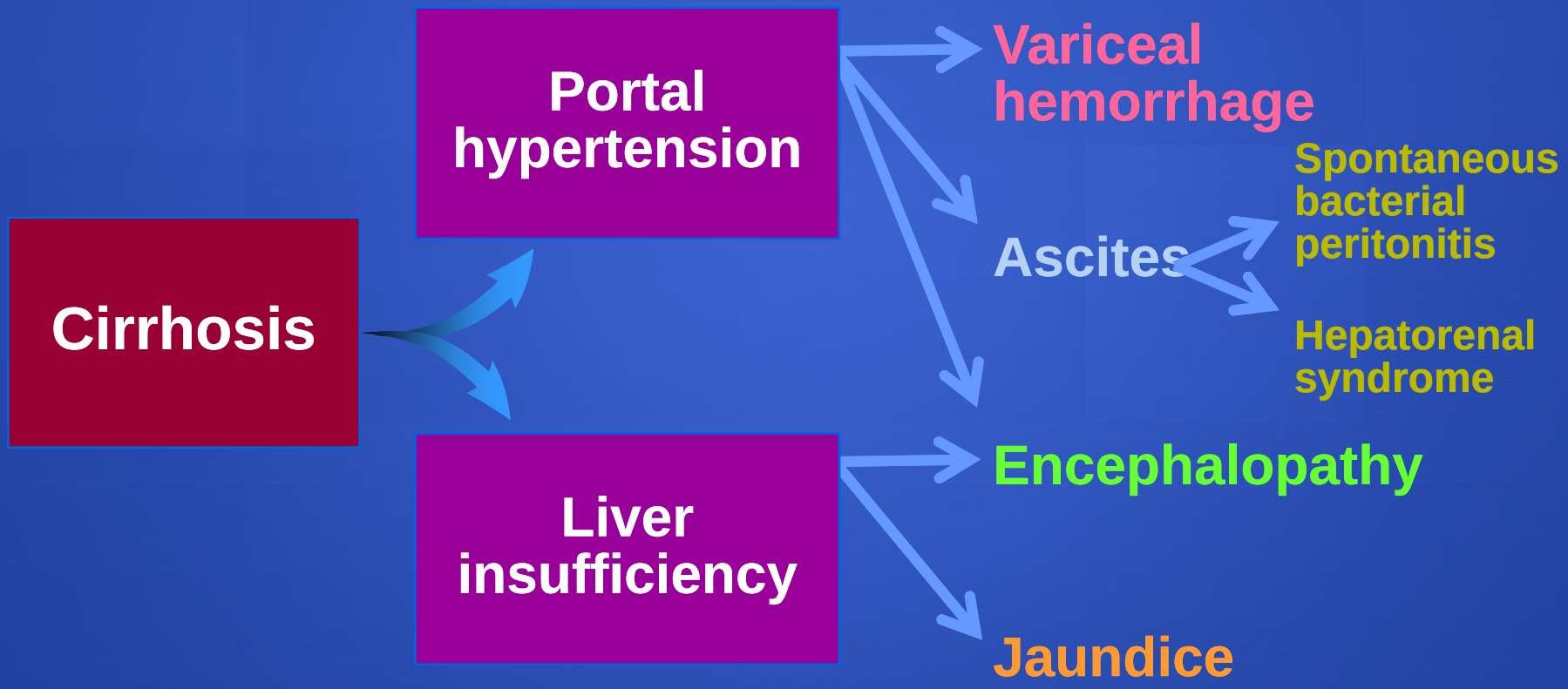
Normal



Cirrhosis



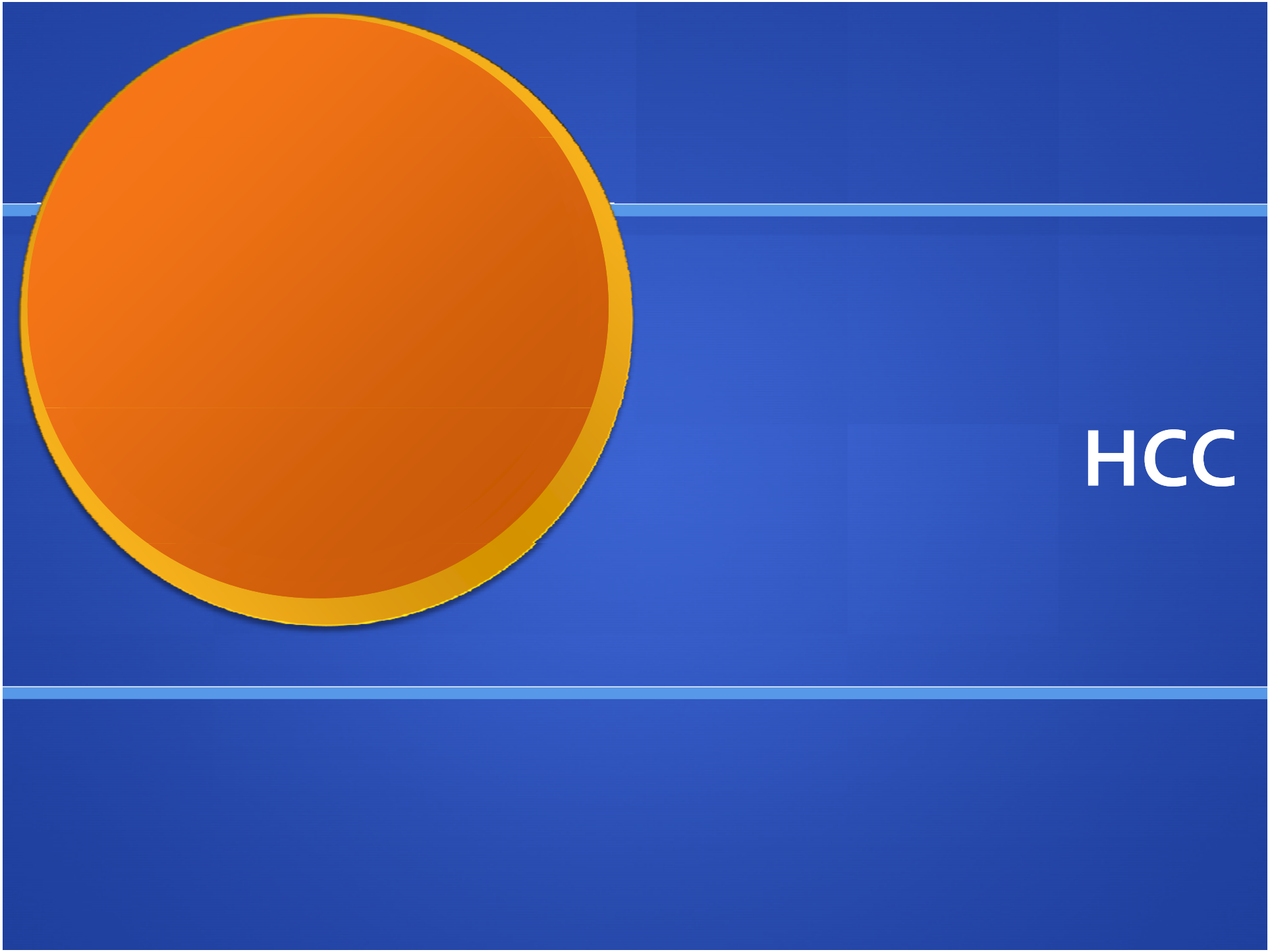
Complications of Cirrhosis Result from Portal Hypertension or Liver Insufficiency



Twelve-year Follow-up of 154 Patients with HCV Compensated Cirrhosis

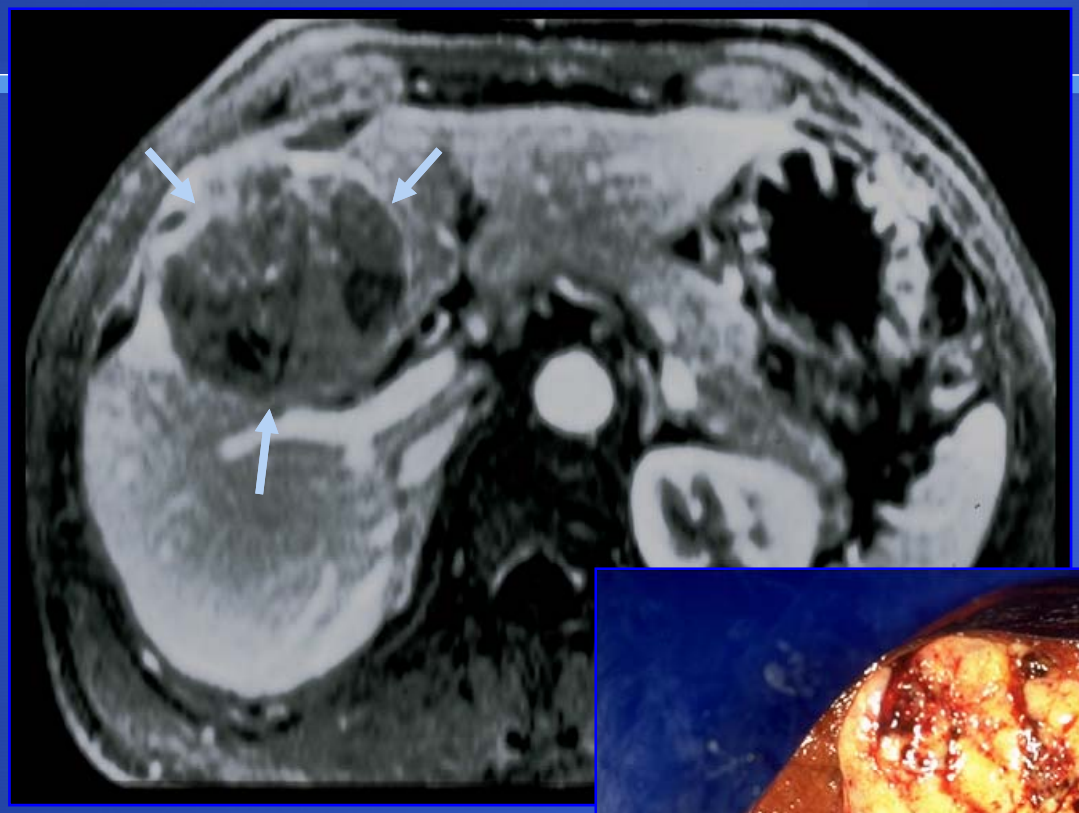
	Patients	Mean Incidence
Clinical decompensation	51 (33%)	3.7%
Ascites	39 (25%)	2.7%
Jaundice	21 (14%)	1.4%
GI bleeding	15 (10%)	1.0%
Hepatocellular carcinoma	48 (31%)	3.3%
Death	44 (28%)	3.0%

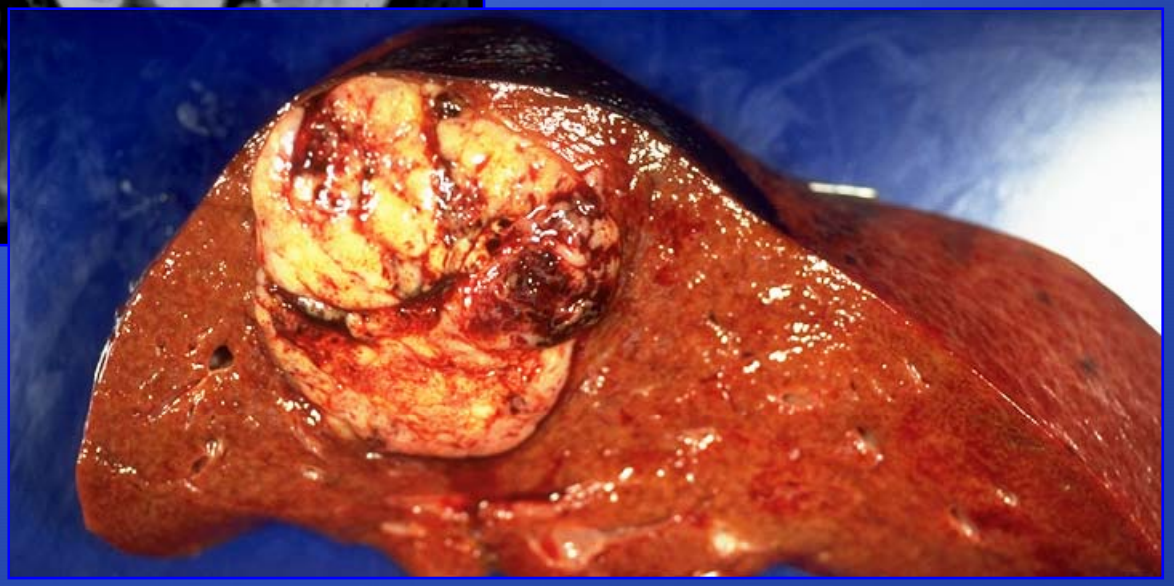
Sangiovanni et al. EASL Meeting, Madrid 18-21 April 2002


HCC

HCC - MRI and Surgical Resection

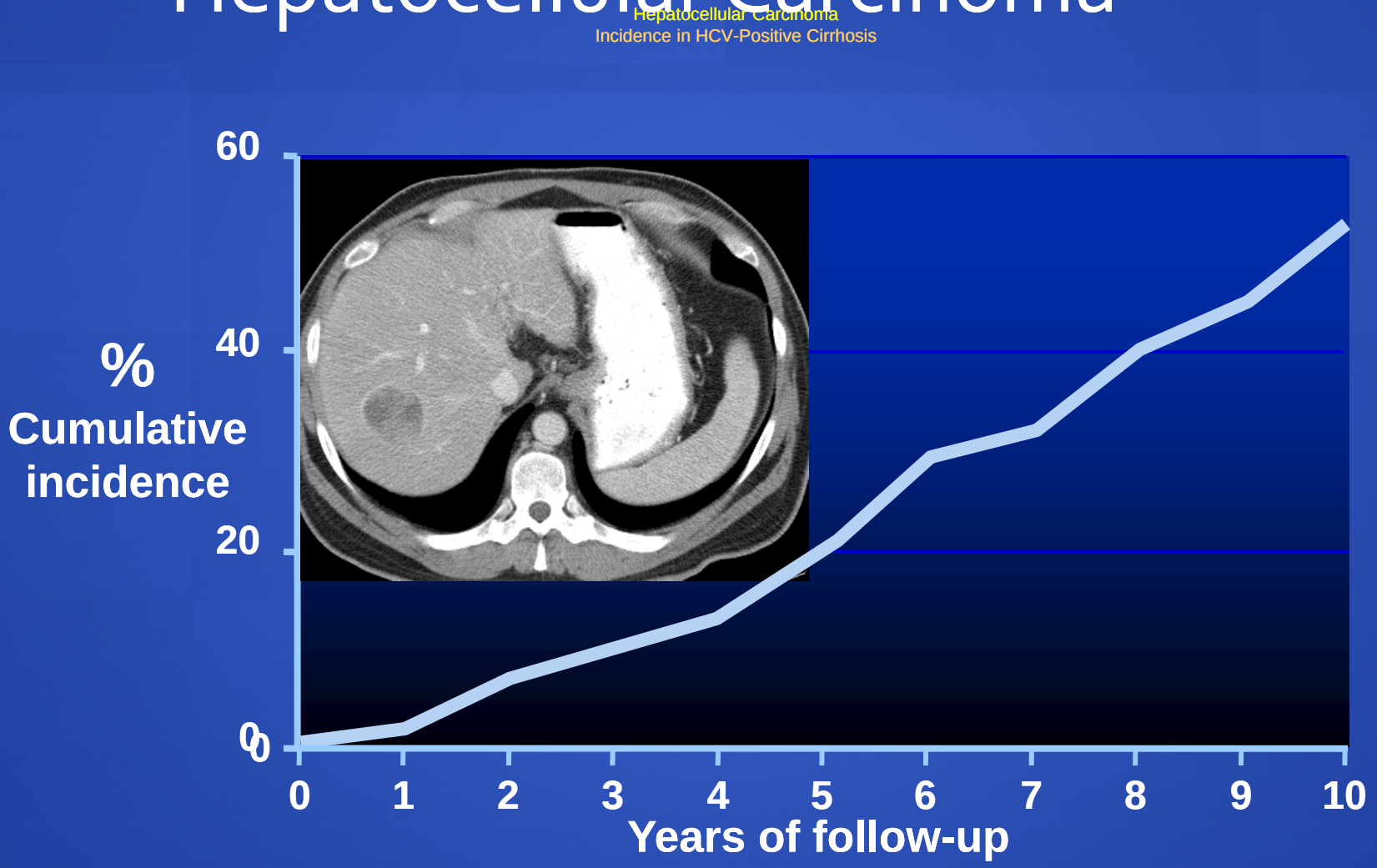
HCC: MRI and Surgical Resection



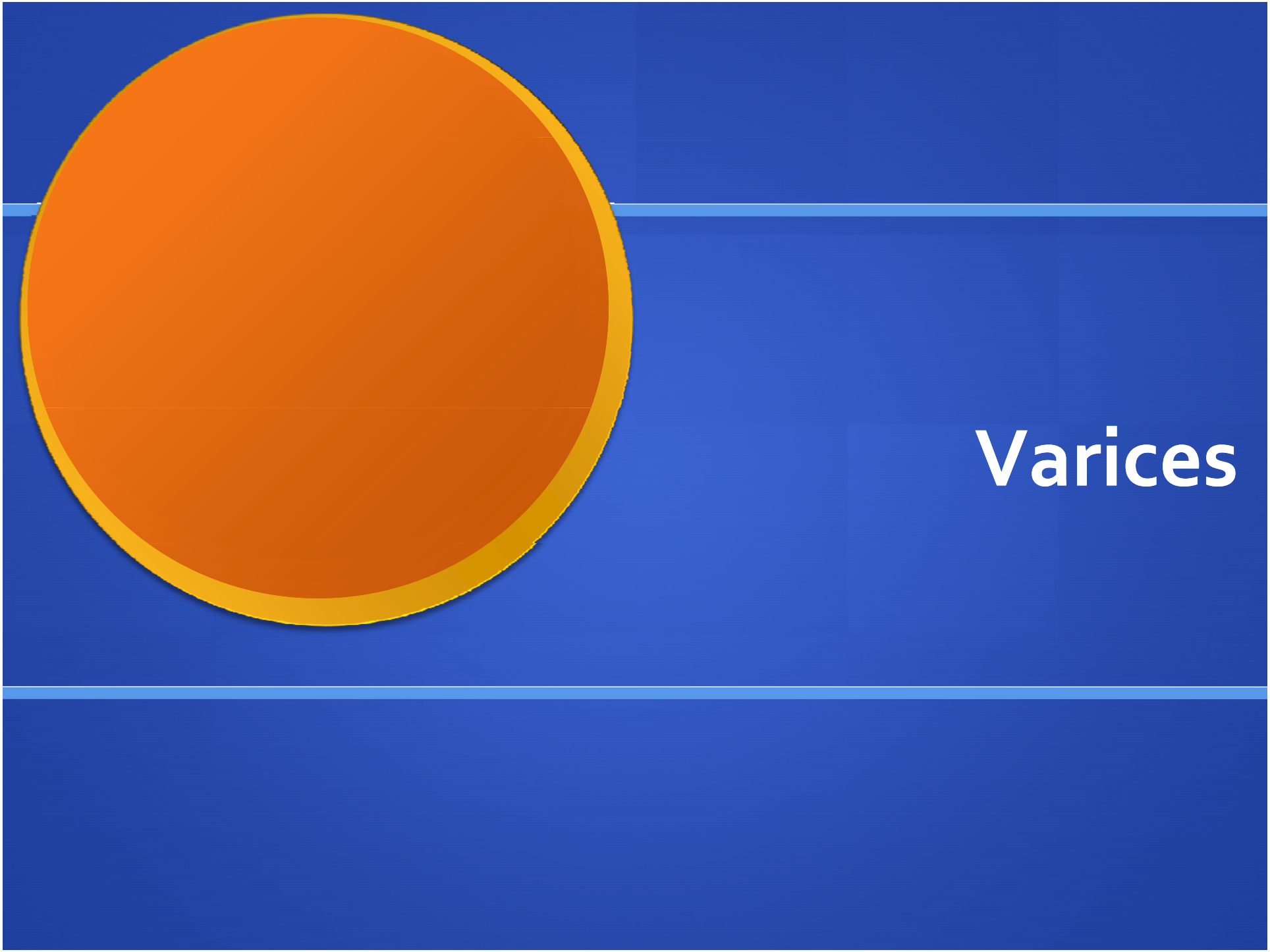


HCV - Natural History

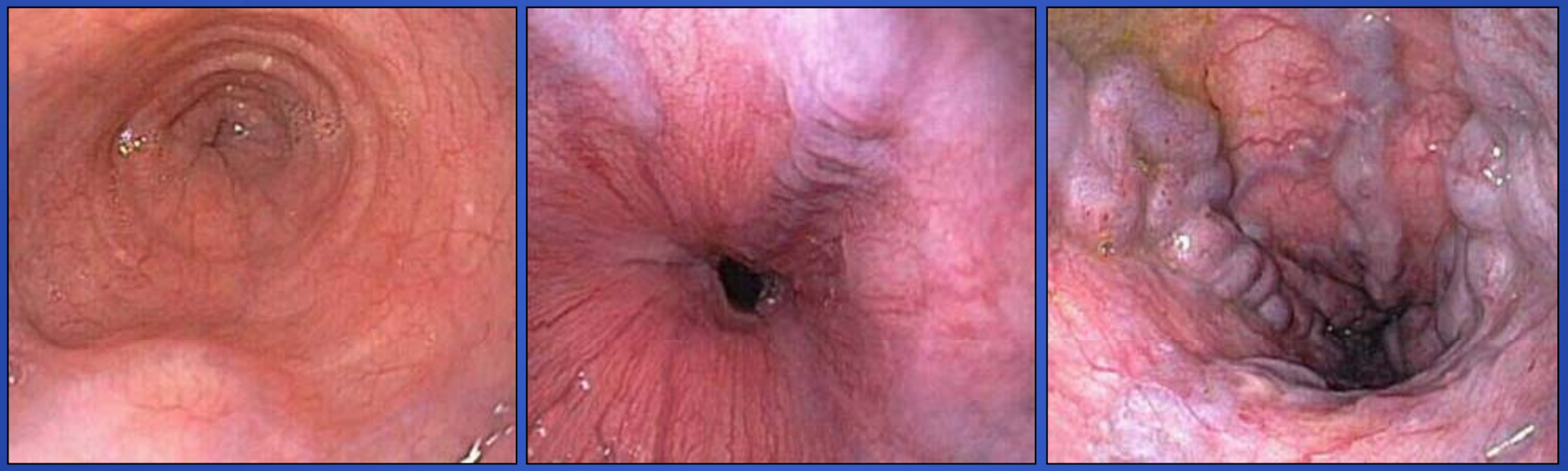
Hepatocellular Carcinoma



Adapted from Ikeda K et al, Hepatology 1993;18:47


Varices

Varices Increase in Diameter Progressively

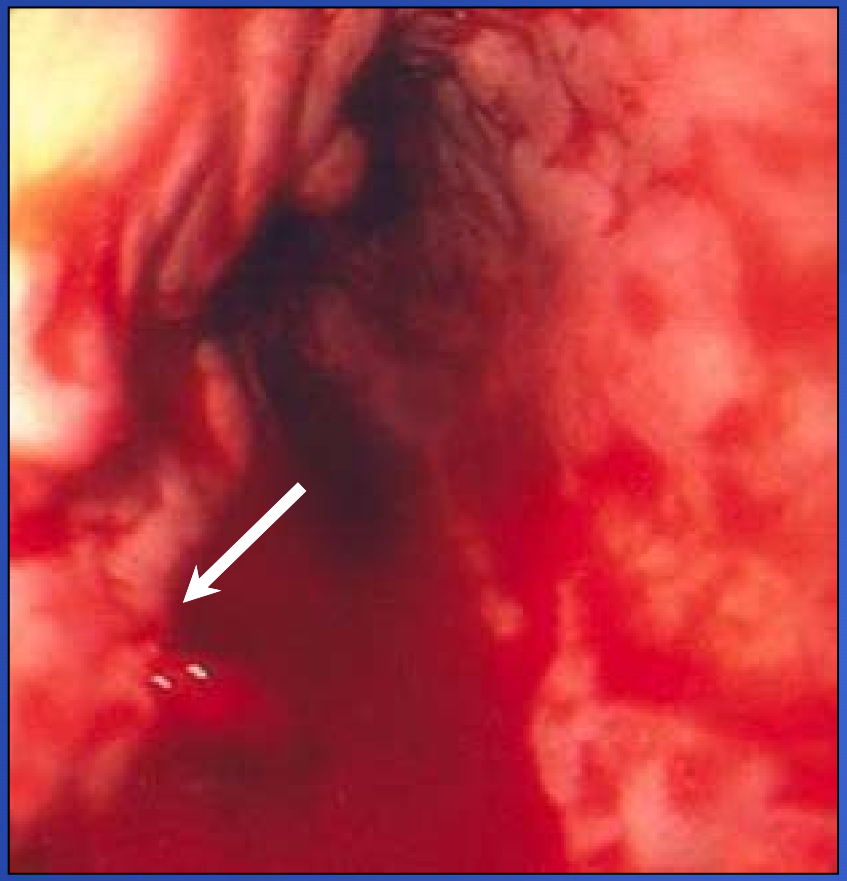


No varices | Small varices | Large varices

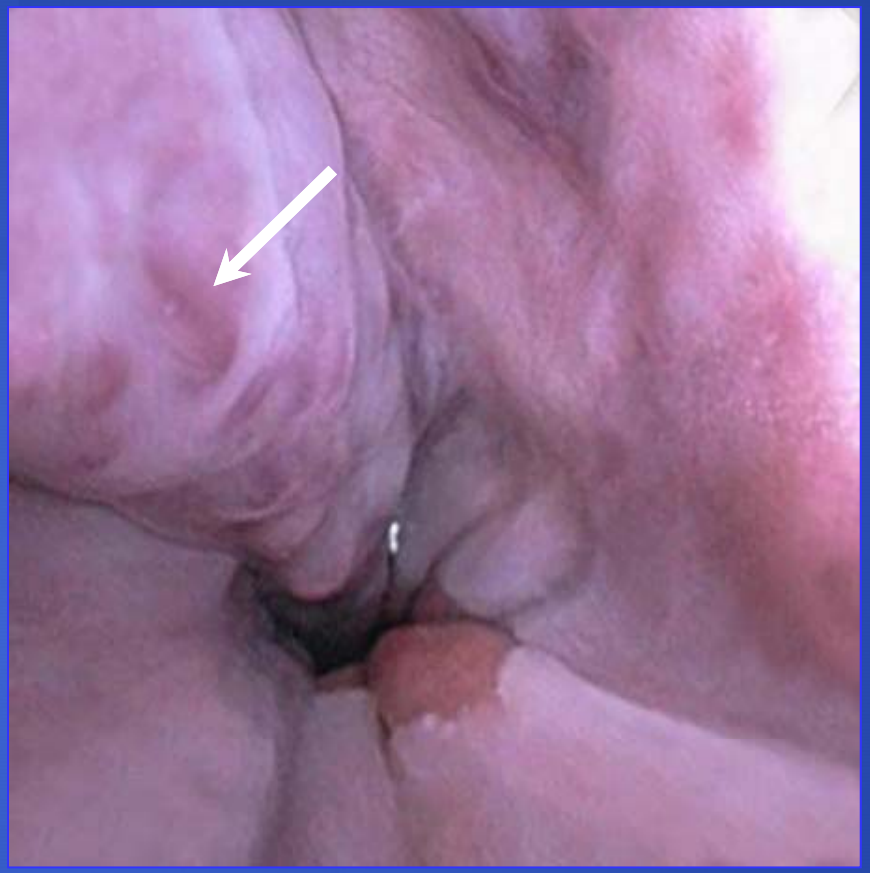
7-8%/year | 7-8%/year

Merli et al. J Hepatol 2003;38:266

PROGNOSTIC INDICATORS OF FIRST VARICEAL HEMORRHAGE



Variceal hemorrhage



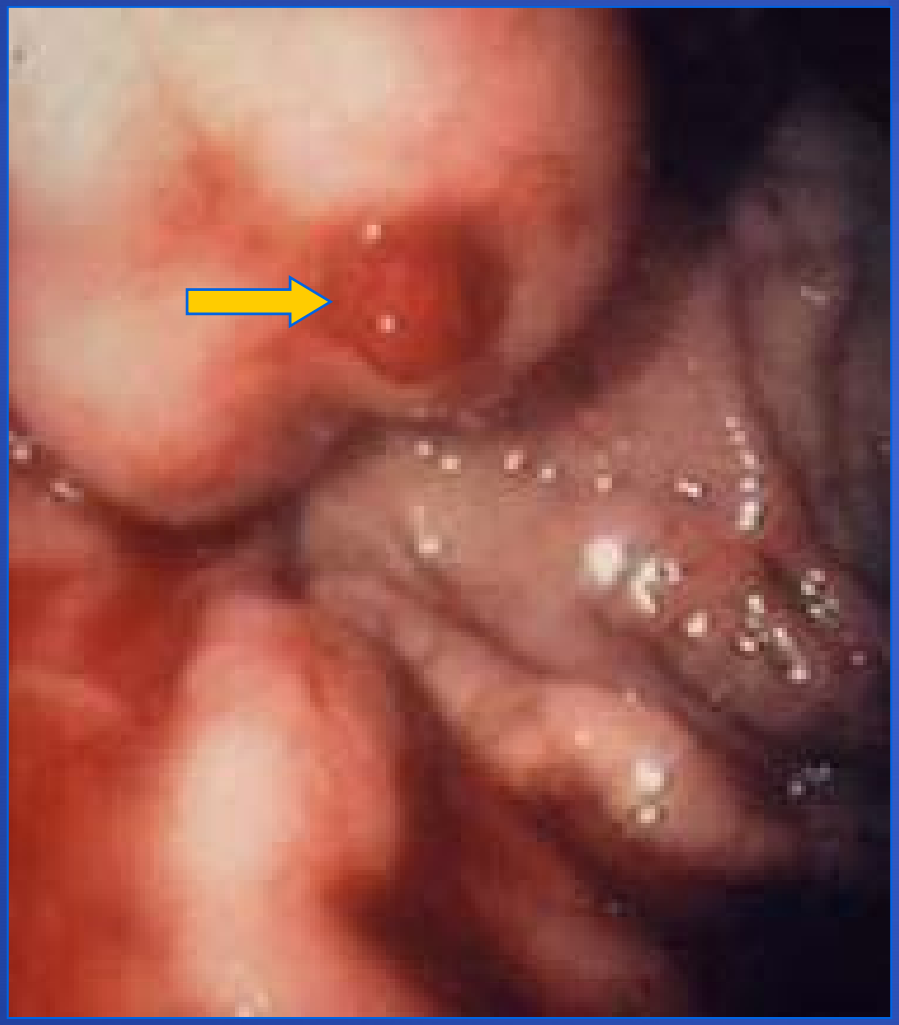
Varix with red signs

Predictors of hemorrhage:

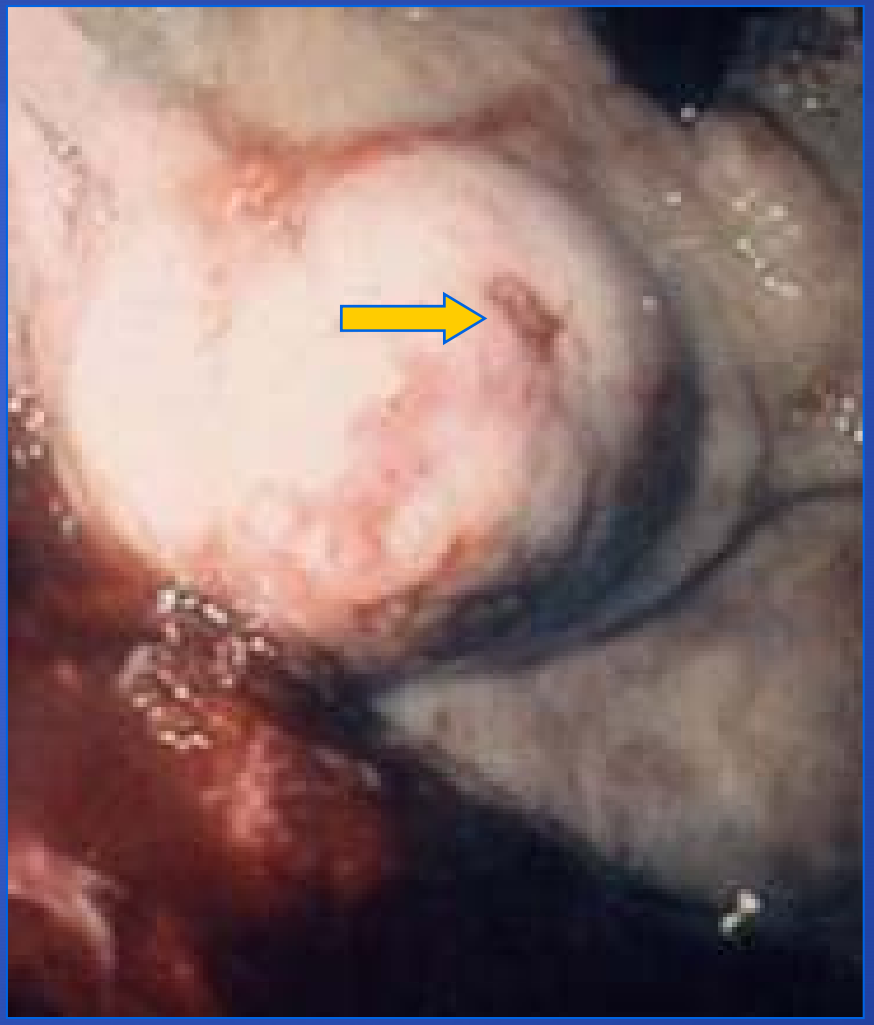
- **Variceal size**
- **Red signs**
- **Child B/C**

NIEC. N Engl J Med 1988; 319:983

Gastric Varices



Pretreatment cyanoacrylate



Post-treatment cyanoacrylate

Ascites

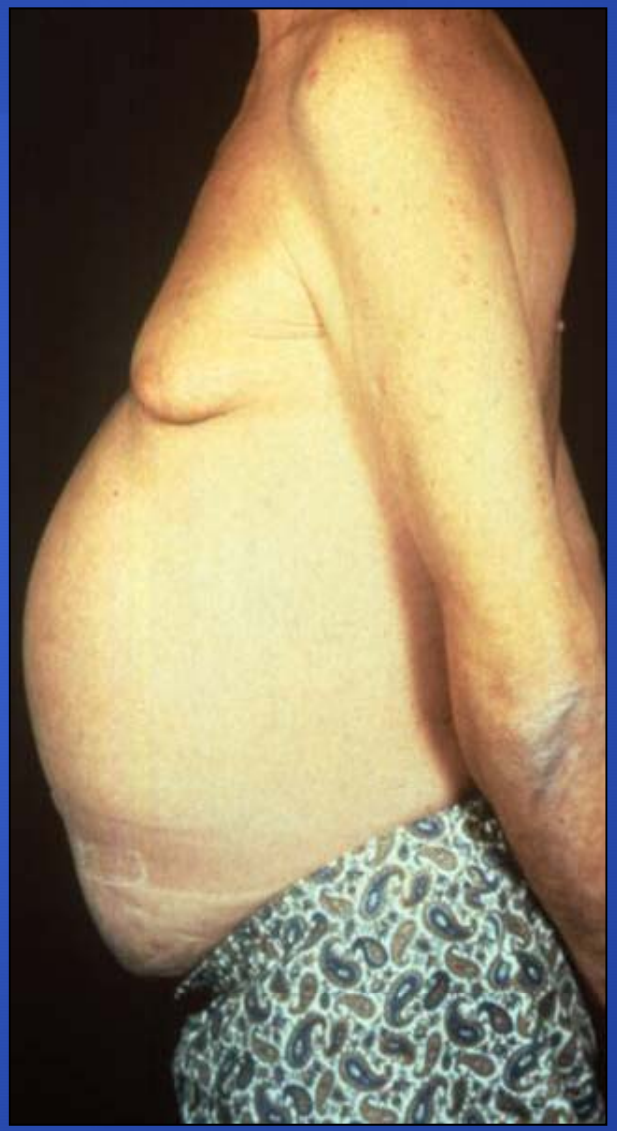
Diagnostic Paracentesis

Indications

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

Contraindications

- None



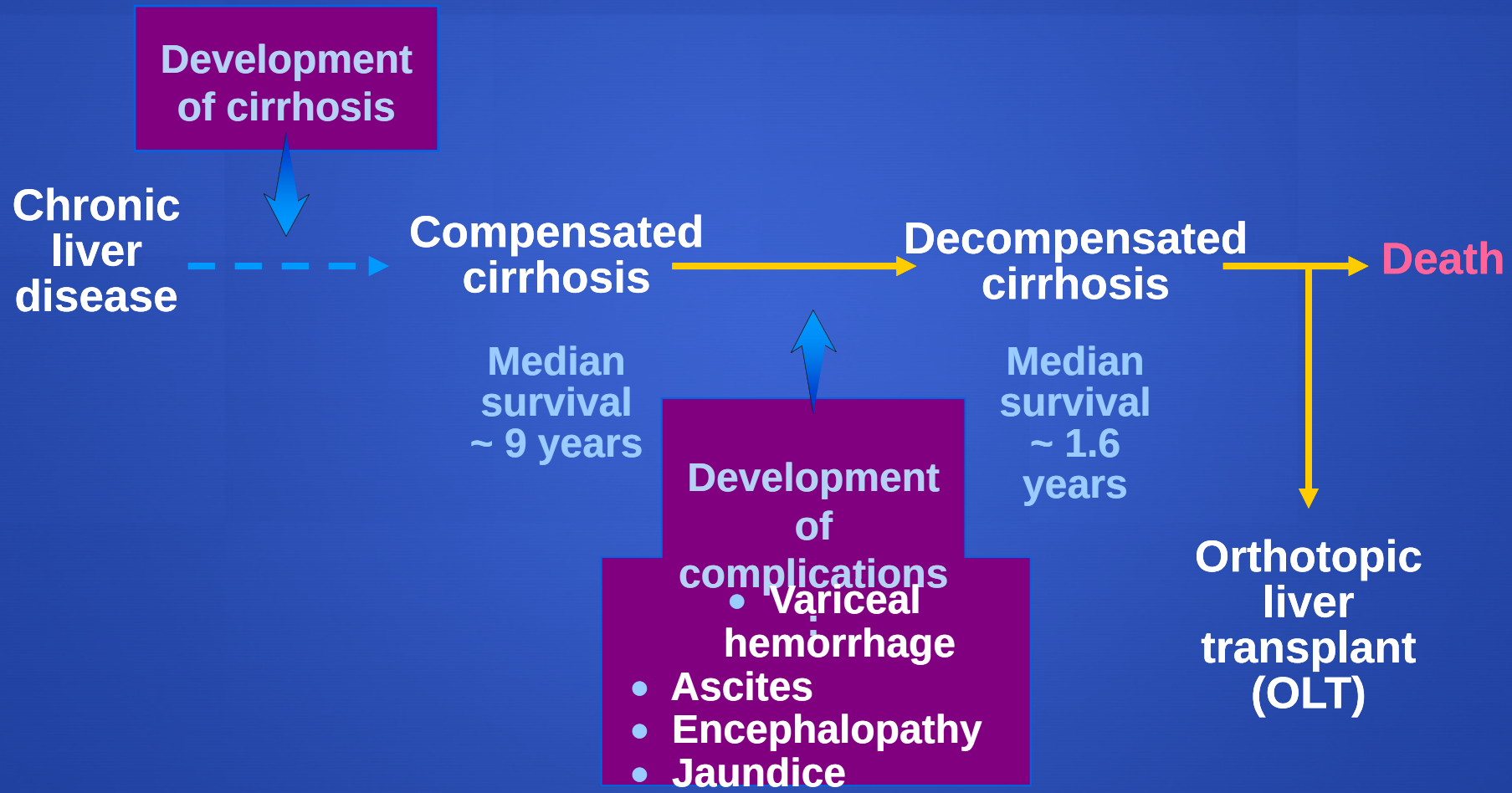
Hepatic Encephalopathy

Stages of Hepatic Encephalopathy

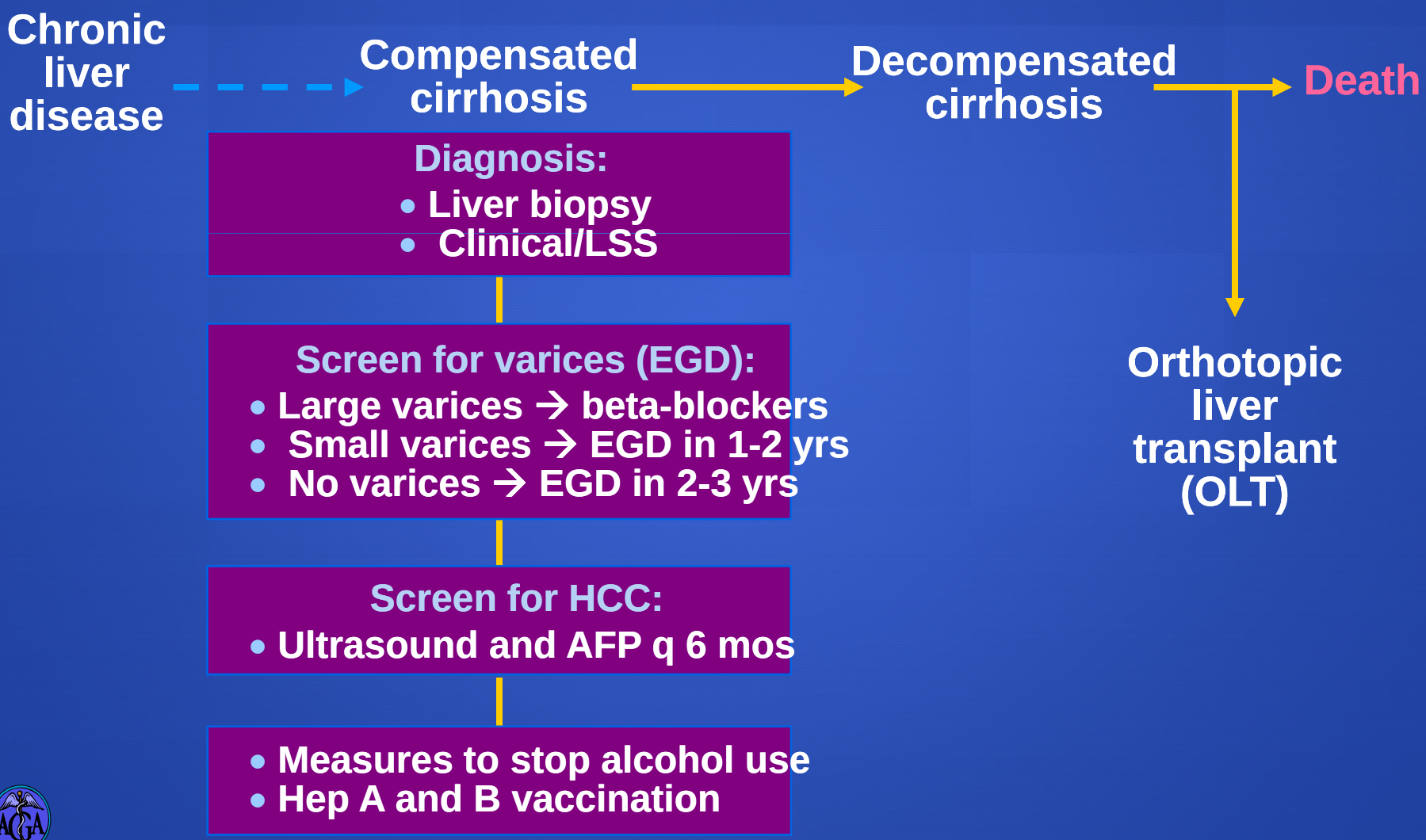
Stage	Mental state	Neurologic signs
1	Mild confusion: limited attention span, irritability, inverted sleep pattern	Incoordination, tremor, impaired handwriting
2	Drowsiness, personality changes, intermittent disorientation	Asterixis, ataxia
3	Somnolent, gross disorientation, marked confusion, slurred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

Asterixis

Natural History of Chronic Liver Disease



Management of Compensated Cirrhosis



Liver Transplantation

- Is the treatment of choice for suitable candidates with end stage liver disease, fulminant hepatic failure and certain metabolic disorders.
- The Model for End-stage Liver Disease (MELD) scoring system is used to allocate cadaveric livers for transplant so that the sickest pts. receive transplants first.
- The most common complications in liver transplant recipients are hypertension, DM, osteoporosis, and renal insufficiency.

Thanks!