

Complications of Cirrhosis

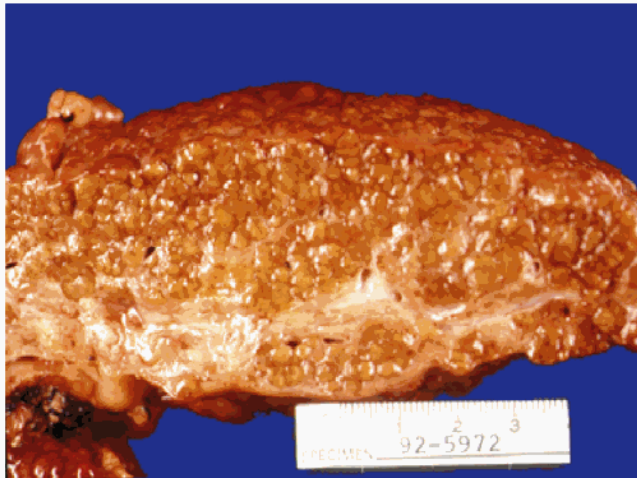
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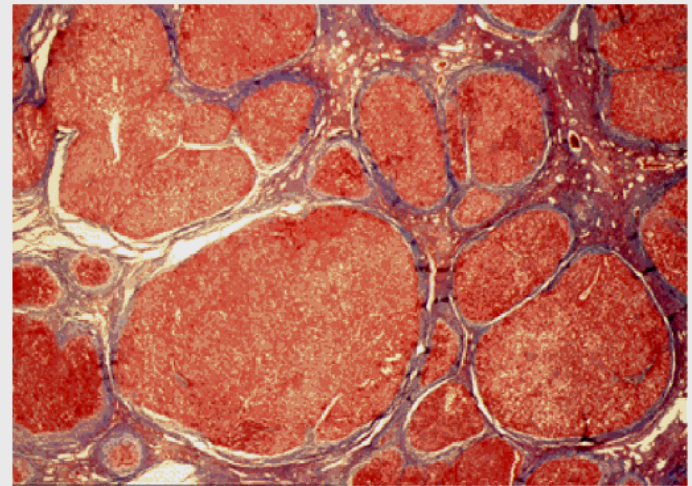
What is Cirrhosis?

- The end result of chronic liver disease
- Histologically defined as regenerative nodules surrounded by fibrous septa
- Eventually disrupts architecture of entire liver
- Etiologies in Western countries: alcohol > viral
NAFLD > biliary > genetic hemochromatosis > Wilson's, A1AT; ? cause in 10-15%
- Cirrhosis may lead to liver failure, portal hypertension, or development of hepatocellular carcinoma

CIRRHOTIC LIVER

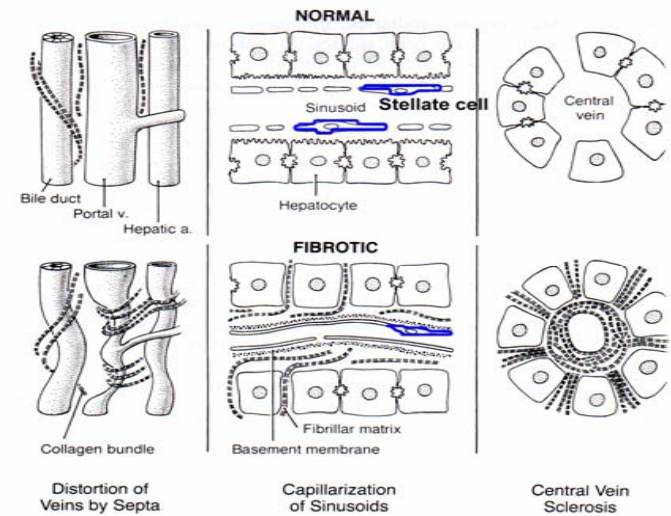


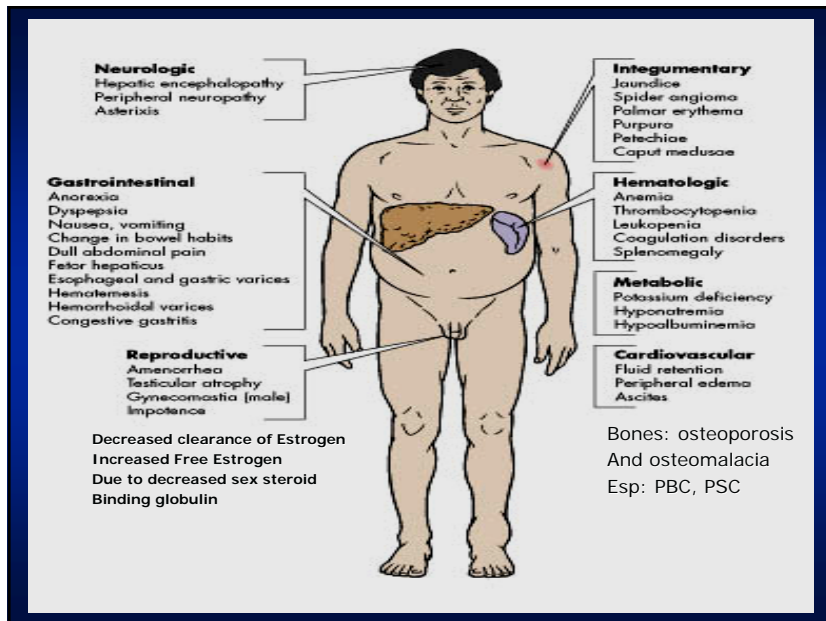
CIRRHOTIC LIVER



Cirrhosis-pathogenesis

- Stellate cell or Ito cell: normally, sit in Space of Disse and store Vit. A; during cirrhosis, transform into myofibroblasts that make and deposit collagen
- Probably stimulated by inflammation, cytokines, and toxins
- Collagen types I and III are deposited in all portions of lobule
- Ultimately, architecture and vasculature are disrupted and diffusion of solutes is impaired





LIVER: Blood Flow

- High Flow
 - Mesenteric vessels
- Low pressure
 - Vast network of sinusoids

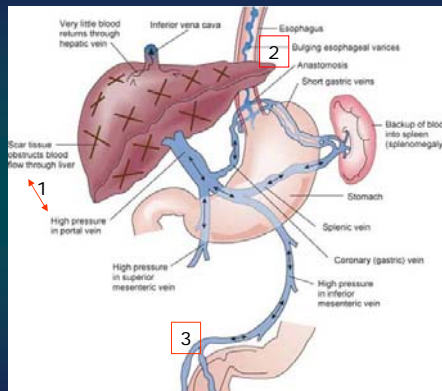
(a) Blood flow between the liver and GI tract mucosa.

(c) Hepatocytes are arranged in sheets, or 'cords', sandwiched between vascular (sinusoid) and biliary conduits (canaliculi).

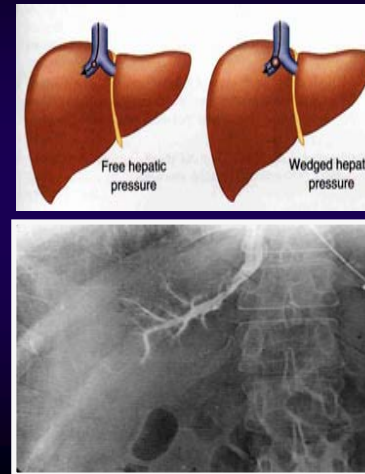
Cirrhosis: Portal Hypertension

Effects on blood flow

1. Fibrosis restricts blood flow; increased portal vein pressure
2. Collaterals acquire increased pressure, affecting spleen, esophagus, stomach (varices), gastropathy
3. Ascites due to fluid shift into peritoneum
4. Shunting of blood from liver decreases metabolism of "toxins"
5. Portal bacteremia not cleared induces peritonitis



What Pressure Defines Portal HTN? Portal Vein-Hepatic Vein Pressure Gradient



- Catheter (with deflated balloon) in Hepatic Vein measures "free HV pressure"
- Inflate Balloon in Hepatic Vein measures Portal Vein Pressure
- PV-HV pressure > 12 mmHG = portal HTN

Portal Hypertension Pathophysiology

- **Increased Resistance to inflow/outflow**
 - Fixed scarring of the liver
 - ? reversible elements: sinusoidal blood vessels
- **Increased Flow to portal system**
 - Increased splanchnic flow (vasodilatation/NO)
 - Increased cardiac output
 - » Low SVR
 - Increased blood volume
- **Decreased Albumin: hepatic synthetic dysfx**
 - » Decreased oncotic pressure, fluid leaks out of vascular space

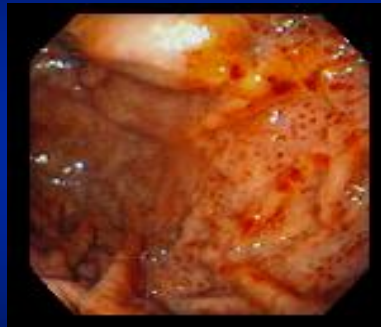
Esophageal Varices

- Risk of bleeding proportional to size and degree of portal hypertension
- Even with optimal therapy, death from initial bleed may be greater than 20%
- Bleeding, hypotension may induce SBP, MI, sepsis, hepatorenal syndrome

Portal Gastropathy



Normal



Gastropathy

Esophageal Varices

- Bleeding Control: Acute
 - Stabilize hemodynamics
 - Decrease portal Pressure
 - » Octreotide, Somatostatin
 - Antibiotics
 - Endoscopy
 - » Sclerotherapy
 - » Banding
 - TIPS
 - Surgical Shunt
 - Chronic therapy
 - » Beta Blockers/Nitrates
 - Transplantation

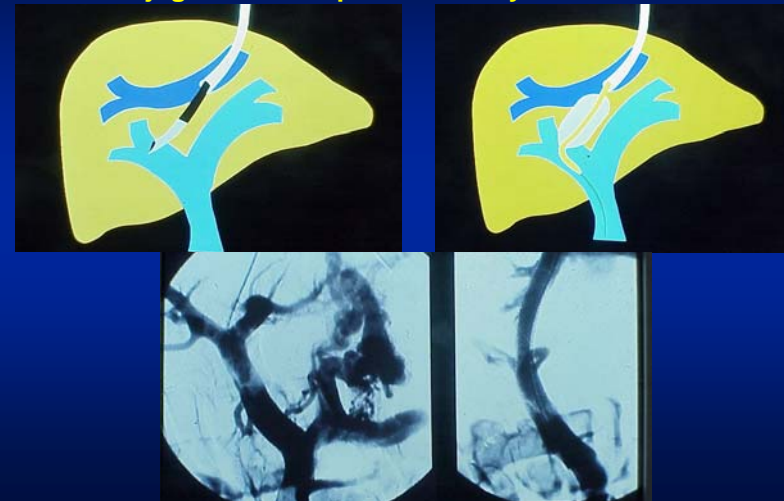
Esophageal Varices: Banding

- Used to treat bleeding
- For Acute and Chronic Therapy
- As part of variceal eradication program
- Usually combined with Beta Blockade

QuickTime™ and a
H.263 decompressor
are needed to see this picture.

TIPS

Transjugular Intrahepatic Porto-Systemic Shunt



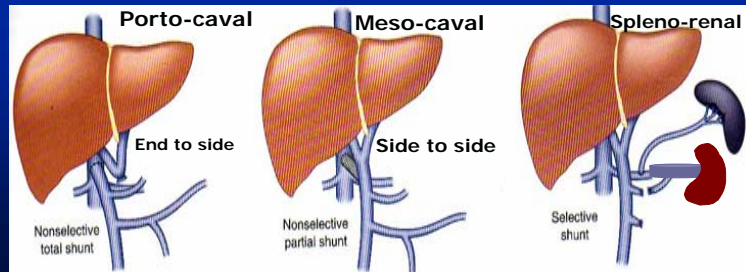
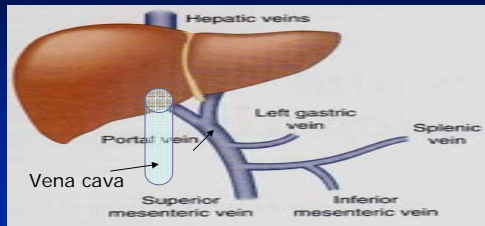
TIPS

- **Functional side to side shunt**
- **Produces connection from Portal Vein to Hepatic Vein**
 - Increase Hepatic vein pressure, RV volume
 - Decrease Portal pressure, hepatic perfusion
- **TIPS improves sodium and water handling**
 - Hepatic hydrothorax
 - Refractory ascites
- **Caution:**
 - CHF, Bili > 4, Inc Creat, PSE, Older pt

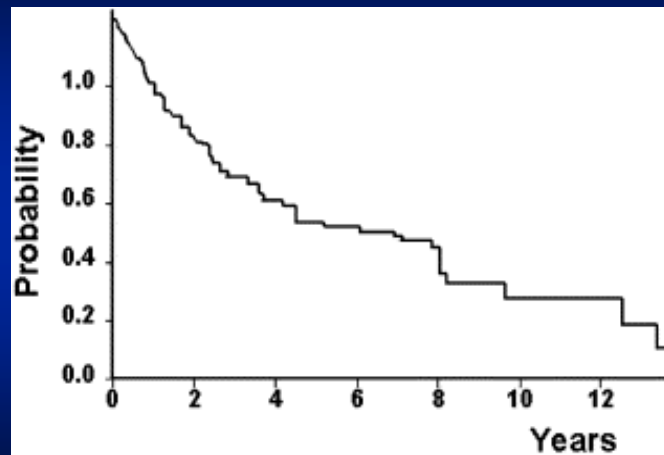
Surgical shunts

- **Limited indications: for endoscopic, medical failure, not OLT candidates**
 - **Cirrhosis: Child's A**
 - **Budd Chiari syndrome**
 - **Non-cirrhotic portal hypertension**
- **Selective vs non-selective**
 - **Goal is to preserve portal perfusion**

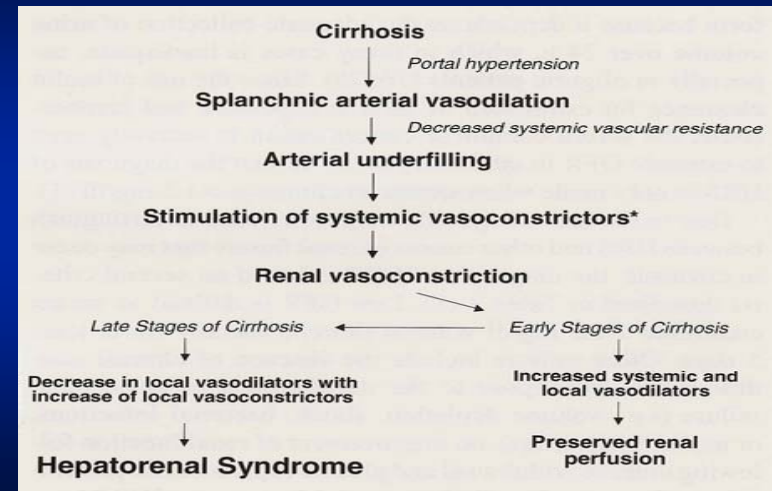
Surgical Shunts



Probability of Survival After Ascites Diagnosed

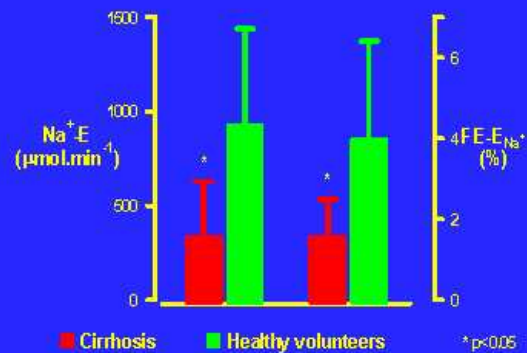


Portal HTN and Ascites



Renal Na⁺ handling after a Na⁺ challenge (2 l NaCl 0.9 %/3 h) in compensated cirrhosis

Caregari *et al.* (1985). *Eur. J. Clin. Invest.* 15: 360-364

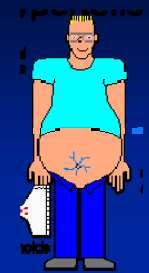


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Ascites

Clinical Diagnosis

- **History:** increasing abdominal girth
- **Physical Examination:**
 - shifting dullness, fluid wave
 - very poor in detecting modest amounts of ascites
- **Radiology:** ultrasound, CT scan more sensitive



Ascites

- Differential dx:
 - Portal hypertension
 - Hepatic (or portal vein) occlusion
 - Heart failure
 - Peritoneal inflammation
 - » TB peritonitis
 - » Carcinomatosis (sometimes chylous ascites)
 - Ovarian Cancer
 - Nephrogenic ascites (nephrotic syndrome)
 - Pancreatic ascites
 - “Other” (Schistosomiasis, non-cirrhotic portal HTN, polycystic liver disease,

Ascites

- 26 year old woman
- Presents with abdominal pain, fever and ascites
- Born in Africa

QuickTime™ and a
DVD/VIDEO - NTSC decompressor
are needed to see this picture.

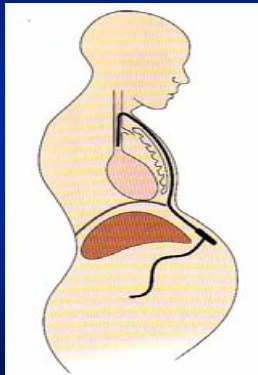
Characteristics of Ascites due to Portal Hypertension

- Transudate; i.e., ascites protein < 3 g/dl; most < 1 g/dl
- WBC < 50 cc/mm³; mostly mononuclear
- Normal ascitic fluid amylase
- Serum - ascites Albumin gradient (SAG) > 1.1 g/dl due to portal HTN

Ascites: Treatment

- **Bedrest**
 - Na⁺ restriction; 1.5-2 gms/day
 - fluid restriction: 1.5 liters
- **Diuretics (maximum doses):**
 - Spironolactone 400mg , Furosemide (200 mg)
 - Amiloride, HCTZ, Metolazone, Zaroxyn
- **Large-volume paracentesis**
- **TIPS**
- **Surgery: Liver transplantation**
 - Leveen or Denver Shunt (historical value, ?
If valuable now, radiologists now place these

LeVeen/Denver peritoneo-venous shunt

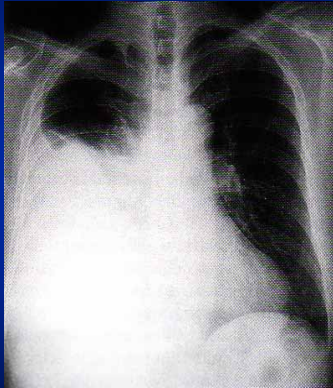


- **Coagulopathy:**
 - DIC almost universal
 - severity can be limited by replacing ascites with saline
- **Infection**
 - generally requires removal of shunt
- **Occlusion**
 - Venous side of shunt
- **Heart failure**
 - Volume overload

Large-Volume Paracentesis

- **Advantages: Fast, ↓ hospital time, less expensive**
 - Patients should have normal creatinine
 - Better if volume overloaded (peripheral edema)
- **Disadvantages:**
 - Precipitate renal insufficiency
 - Removes proteins (e.g., opsonins)
- **Use of volume expansion**
 - Albumin: 6 gms/liter of ascites removed

Hepatic Hydrothorax



- Ascites leaks through rents in the diaphragm
- Diagnosis: Fluid should have characteristics similar to ascites
- Treatment: AVOID CHEST TUBES. Surgical repair not usually effective
- TIPS is treatment of choice for diuretic-refractory cases
- Liver transplantation

SBP

Spontaneous Bacterial Peritonitis

- Infection independent of another intra-abdominal source
- Monomicrobial
- Enteric flora enters portal circulation, not cleared
- Ascites WBC > 500 or 250 with greater than 50% polys
- Culture negative neutrocytic ascites
- Culture positive neutrocytic ascites
- Culture positive non-neutrocytic ascites
 - If gm negative : treat
 - If gm positive: likely contaminant

Spontaneous Bacterial Peritonitis: Prevention

- **Risks:**
 - GI bleeding/hypotension
 - Advanced liver disease
 - Previous history !
- **Early treatment of other infections**
- **Prophylactic antibiotics to GI bleeders**
- **Volume expand with Albumin**
 - Effective to reduce hepato-renal syndrome
- **Oral Quinolones, Bactrim can prevent recurrence**
- **Liver transplantation**

Spontaneous Bacterial Peritonitis: Treatment

- **Most common organisms are E. coli, Klebsiella, Pneumococcus, Enterococcus**
- **Drug of choice for therapy:**
 - **Board exam: Cefotaxime**
 - **Real life: extended penicillin, Zosyn, Unasyn**
- **AVOID AMINOGLYCOSIDES**
- **Narrow antibiotic spectrum if culture results are known**
- **? re-tap after 48 hours to confirm response to therapy**

Hepato-Renal Syndrome

- **Etiology:** Unclear, but likely an exaggeration of mechanisms involved in ascites formation
- **Precipitants:**
 - Gi Bleed
 - Nephrotoxins (NSAID's, Aminoglycosides, sepsis)
 - Iatrogenic (diuresis, paracentesis)
- **Diagnosis:**
 - Euvolemic patient
 - Urine output < 800 cc/day, $U_{Na} < 10$ mEq/l,
 - "clean urine sediment"
- **Treatment: TIPS, MARS, Glypressin, Terlipressin, Transplantation**
 - **Midodrine 5-15mg po tid**
 - **Octrotide sq100-200 mcg sq tid**

Portal Systemic Encephalopathy: Hepatic Encephalopathy

- **Inability to clear "encephalopathogenic agents"** (Ammonia, Gaba, Mercaptans, endogenous Benzos)
 - Cirrhosis
 - Portal Hypertension
 - Shunting (TIPS, surgical shunt)
 - Protein load
 - » Usually GI bleed, Gastropathy, less common PO proteins
 - **Acute Liver Failure:**
 - PSE defines fulminant Hepatic Failure
 - Cerebral Edema (not in chronic!!)
 - Emergency Liver Transplantation is therapy

Stages of Hepatic Encephalopathy

STAGE	MENTAL STATUS	PHYSICAL EXAM
I	Euphoria/Depression, Day-Night Sleep reversal, poor concentration, mild confusion, slurred speech	Mild asterixis
II	Increased drowsiness, confusion, inability to sustain concentration	Significant Asterixis, Brisk reflexes
III	Marked confusion, arousable but sleeping continuously	Asterixis, clonus
IV	Minimally responsive to painful stimuli	Patient may "posture" Asterixis absent

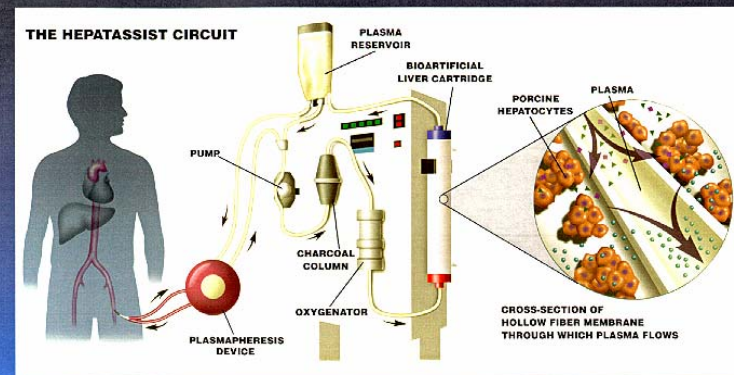
TX PSE

- **Decrease encephalopathic agent:**
 - Lactulose 30cc po q 2 until effect (traps NH3 in colon or NH3 incorporated into bacterial proteins)
 - Rectal Tube
 - » Tap water Enema
 - » Lactulose 200 cc in 300 cc tap water
 - Turning and positioning patient
- **Cathartic:**
 - Mg Citrate, Miralax, Go-lytely
- **Decrease production/block of EA:**
 - Neomycin 500 mg po q 6 (watch Creatinine and hearing)
 - Flagyl 500 mg po q 8 (neuropathy, antabuse effect)
- **"Brain Stabilizers"**
 - Zinc and/or L-Carnitene
- **Rifaximin**
 - Poorly absorbed antibiotic
 - 200-400 mg po tid
 - Not FDA approved

“PSE tx of the future”

- Enhance clearance of “EA”
 - MARS, BAL, ELAD
 - Hepatocyte transplantation
- Block receptor of EA
 - Benzodiazepene antagonist Romazicon/Flumazinel
 - 0.4 mg IV over 30 seconds
 - 5 mg/hr IV

HepatAssist® Bioartificial Liver Support System



BAL



Indications for Liver Transplantation

- Manifestations of Portal HTN not controlled by alternative measures
 - » Esophageal and/or gastric variceal bleeding
 - » Bleeding from portal hypertensive gastropathy.
 - » Hepatic encephalopathy
 - » Spontaneous Bacterial Peritonitis
 - » Significant Ascites, hydrothorax
- Patients with HCC can be transplanted if:
 - No evidence of extrahepatic disease
 - No macroscopic vascular invasion
 - One lesion < 5 cm or
 - Three lesions, each < 3 cm