CIRRHOSIS AND ITS COMPLICATIONS

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Characteristic of Cirrhosis

A chronic, progressive, diffuse liver disease
Fibrosis and disorganization of the lobular and vascular architecture histologically

Normal Liver
Cirrhotic Liver

Etiologies of Cirrhosis

Drug and chemicals
DILI
Chronic viral hepatitis HBV, HCV
Inherited Wilson's disease hemochromatosis
Circulation disturbance von-Meuller disease, Budd-Chiari syndrome, schistosomiasis

Nonalcoholic steatohepatitis (NASH)
Alcoholic Steatohepatitis (ASH)
Liver Cirrhosis

Factors that contribute to the risk of developing cirrhosis

Regular (moderate) alcohol consumption
age older than 50 years
male gender
older age, obesity, insulin resistance or type 2 diabetes
hypertension, and hyperlipidaemia (all features of the metabolic syndrome)
>= factors
Genetic impact (single nucleotide polymorphisms)

Disorders and Drugs That Can Cause Hepatic Fibrosis

* Infections
  Viral (e.g., chronic hepatitis B or C)
  Bacterial (eg, brucellosis)
  Parasitic (eg, echinococcosis)
* Drugs and chemicals
  Alcohol
  Amiodarone
  Chlorpromazine
  Isoniazid
  Methotrexate
  Methyldopa
  Oxyphenisatin
  Arsenicals
  Oral contraceptives (Budd-Chiari)
  Pyrrolidine alkaloids and antineoplastic agents

Disorders and Drugs That Can Cause Hepatic Fibrosis

* Disorders affecting hepatic blood flow
  Budd-Chiari syndrome
  Heart failure
  Hepatic veno-occlusive disease
  Portal vein thrombosis (venoocclusive disease)
* Mechanical obstruction
  Biliary obstruction (chronic)
* Metabolic abnormality
  Nonalcoholic fatty liver disease
* Autoimmune
  Primary biliary cirrhosis
  Autoimmune hepatitis
  Primary sclerosing cholangitis
**Disorders and Drugs That Can Cause Hepatic Fibrosis**

- Certain storage diseases and inborn errors of metabolism
  - α 1-Antitrypsin deficiency
  - Copper storage diseases (eg, Wilson's disease)
  - Fructosemia
  - Galactosemia
  - Glycogen storage diseases (especially types III, IV, VI, IX, and X)
  - Iron-overload syndromes (hemochromatosis)
  - Lipid abnormalities (eg, Gaucher's disease)
  - Peroxisomal disorders (eg, Zellweger syndrome)
  - Tyrosinemia
- Congenital hepatic fibrosis
- Others
  - Cystic fibrosis
  - Graft-versus-host disease
  - Jejunoleal bypass
  - Sarcoidosis

**Pathogenesis of Liver Cirrhosis**

**Etiology**

- Diffuse, chronic liver injury
- Hepato-cellular necrosis, collapse of hepatic lobules
- Formation of diffuse fibrous septa
- Regenerative nodules formation

**Complications**

- Upper GI Bleeding, Hepatic coma, infections.
- Hepatocellular carcinoma; Functional renal failure

**Histopathologic Classification**

- **micronodular**
  - uniformly small nodules (< 3 mm in diameter) and regular bands of connective tissue
  - Alcoholic, stasis

- **macronodular**
  - nodules that vary in size (3 mm to 5 cm in diameter)
  - Hepatitis B, C; Hemochromatosis, Wilson's disease

- **mixed macro and micronodular**
  - (incomplete septal cirrhosis) combines elements of micronodular and macronodular cirrhosis

**2012-9-27**

This is the external surface of a normal liver. The color is brown and the surface is smooth. A normal liver is about 1200 to 1600 grams.

This is an example of a micronodular cirrhosis. The regenerative nodules are quite small, averaging less than 3 mm in size. The most common cause for this is chronic alcoholism. The process of cirrhosis develops over many years.
Histological Patterns of Fibrosis

- **Portal-based fibrosis**
  (e.g., chronic viral hepatitis, chronic cholestatic diseases, and hemochromatosis)
- **Central-based fibrosis**
  (e.g., steatohepatitis, and chronic venous outflow obstruction)

Distribution pattern of the fibrotic septae
- **Porto-portal** (e.g., cholestatic liver injuries)
- **Portal-central** (e.g., viral hepatitis)
- **Central-portal** (e.g., alcoholic liver disease)
Chronic viral hepatitis C
portal-central fibrotic septa and nodule formation (Trichrome staining)

Biliary cirrhosis
portal-portal fibrotic septa and proliferation of bile ductules (H&E)

Autoimmune hepatitis
portal-central vein bridging necrosis (Trichrome staining)

Acute alcoholic hepatitis
Deposition of extracellular matrix around hepatocytes (so called chicken wire pattern) and ballooning degeneration of hepatocytes

Nonalcoholic steatohepatitis
Macrovesicular steatosis and pericellular fibrosis (Trichrome staining)

If chronic hepatic passive congestion continues for a long time, a condition called "cardiac cirrhosis" may develop in which there is fibrosis bridging between central zonal regions, as shown below, so that the portal tracts appear to be in the center of the reorganized lobule. This process is best termed "cardiac sclerosis" because, unlike a true cirrhosis, there is minimal nodular regeneration.
**Pathogenesis**

- Fibrogenic stimuli from injured liver
- Oxidative stress; Hypoxia; Inflammation and immune responses; Apoptosis; Senescence and autophathy
- Imbalance between the accumulation and degradation of ECM
  - Tissue inhibitors of metalloproteinases (TIMPs)
- The biologic activity of ECM in fibrogenesis
  - Dramatic changes of ECM components in the quality, quantity, and distribution
  - Provides cells with positional signals and a mechanical scaffold
  - Provides “biological signals” with a resultant fibrogenic response and angiogenesis
- Cellular responses and behavior
  - Capillarization of the sinusoids, Angiogenesis
  - Vascularized fibrotic septa
  - Intrahepatic shunts between afferent (portal vein and hepatic artery) and efferent (hepatic vein) vessels of the liver
- Cirrhosis may lead to liver failure, portal hypertension, or development of hepatocellular carcinoma

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**Hepatic Stellate cell Activation - A Central Event in Liver Fibrosis**

- Normal Liver
- Activated HSC with Fibrosis

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**Pathways of Stellate cell Activation**

- Initiation
- Perpetuation
- Resolution
- Apoptosis?
- Reversion?

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**The Hepatic Perisinusoidal (Disse) Space**

- Normal
- Fibrotic

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**Guo and Friedman, Semin Liver Dis, 2007**
Metavir Scoring System for Fibrosis

- **F1**: Control vein
- **F2**: Portal tract fibrosis
- **F3**: Numerous septa
- **F4**: Cirrhosis

**Modified from Poynard**

Scoring Systems for fibrosis Progression

<table>
<thead>
<tr>
<th>Histological</th>
<th>Clinical</th>
<th>Symptoms</th>
<th>Sub-stage</th>
<th>Hemodynamic</th>
<th>Biological</th>
</tr>
</thead>
<tbody>
<tr>
<td>F3-F4</td>
<td>Non-cirrhotic</td>
<td>None (no varices)</td>
<td>Stage 1</td>
<td>&gt;6</td>
<td>Fibrogenesis and Angiogenesis</td>
</tr>
<tr>
<td>F4 (Cirrhosis)</td>
<td>Compensated</td>
<td>None (varices present)</td>
<td>Stage 2</td>
<td>&gt;10</td>
<td>Scar and x-linking</td>
</tr>
<tr>
<td></td>
<td>Decompensated</td>
<td>Acute/CH</td>
<td>Stages 3-6</td>
<td>&gt;12</td>
<td>Thick (acellular) scar and nodules</td>
</tr>
</tbody>
</table>

Classification of chronic liver disease based on histological, clinical, hemodynamic, and biological parameters.

*From Friedman SL, Gastroenterology 2009*

Pathophysiology

- **Etiology**: Alcohol abuse, Malnutrition, Infection, drugs, Fatty infiltration, biliary obstruction...
- **Liver function injury**
- **Portal hypertension**
- **Increased pressure in the venous and sinusoidal channel**
- **Obstruction of blood flow**
- **Fibrosis/scarring**
- **Destruction of hepatocytes**
- **Increased resistance** (Flow x Resistance)

Pressure = Flow x Resistance

**Increased flow**

(Fixed: Splanchnic Vasculature, Modulable: Stellate cell contraction, Organ contraction)

Portal Hypertension - Pathogenesis

**Intrahepatic resistance**
Consequences of portal hypertension

- Formation and open of portal-systemic collateral's
- Splenomegaly
- Ascites

Consequences of portal hypertension

Formation and open of portal-systemic collateral's

- Esophageal/gastric varices
  short gastric/coronary veins
- Rectal collateral's
  Suphemorrhoidal/middle & inf. Hemorrhoidal
- Caput medusae
  umbilical/epigastric
- abdominal wall varices
- Portal system and left renal

Gastro-esophageal varices bleeding

Caput medusae (umbilical)
**Consequences of portal hypertension**

**Ascites**

**Theories of ascites formation**
- Underfilling theory
- Overflow theory
- Arterial vasodilation theory

**Ascites**

- **Sodium retention**
  - Renin angiotension aldosterone system (RAAS)
  - Sympathetic nerve system, norepinephrine
  - Intrarenal factors
  - Kallikrein-kinin system, Adenosine

- **Water retention**
  - Antidiuretic hormone (ADH)
  - Impaired renal synthesis of PGs (PGE2)

- **Renal vasoconstriction**
  - RAAS, Angiotension II
  - SNS
  - ADH
  - ET

**Consequences of portal hypertension**

**Splenomegaly**

- Splenomegaly
  - Hypersplenism: anemia, leukopenia, thrombocytopenia

  Spleen: splenomegaly; congestion; blood stasis; dilation of splenic sinus; proliferation of splenic pulp; dilation of spleen artery; varicosity of splenic vein; endophlebitis

**Pathology of Liver Cirrhosis**

**Other Organs**

- **Gastrointestinal**
  - Vein varices, mucosal edema and stasis, peptic ulcer formation

- **Renal**
  - Glomerulonephritis (membranous, anti-glomerular basement membrane, mesangial proliferative glomerulonephritis)
  - Glomerulosclerosis, kidney tubules degenerative necrosis

- **Endocrine gland**
  - Atrophy and degeneration
**Endocrine system**

- Gynecomastia (男性乳房发育)
- Telangiectases (毛细血管扩张症)
- Spider nevi (蜘蛛痣)
- Palmar erythema (肝掌)
- Testicular atrophy (睾丸萎缩)
- Menstrual irregularities (月经失调)

**Pulmonary manifestations**

- Hepatic hydrothorax (肝性胸水)
- Hepatopulmonary syndrome (HPS, 肝肺综合征)
- Triad of pulmonary vascular dilatation
- Arterial hypoxemia
- In the setting of advanced liver disease

**Hepatorenal syndrome (HRS)**

- Occurred in the setting of:
  - chronic liver disease
  - advanced hepatic failure
  - portal hypertension
- Characterized by:
  - impaired renal function
  - marked abnormalities in arterial circulation
  - activation of endogenous vasoactive system
- Classified into 2 different types:
  - Type I: Rapidly progressive
  - Type II: Not rapidly progressive
  - Often results in mild renal insufficiency causing diuretic resistant ascites

**Mechanisms of HRS**

- Hypotension due to:
  - Arterial vasodilation
  - Reduced cardiac output
- Portal hypertension
- Activation of SNS, RAAS, AVP, endothelin and neuropeptide Y
- Reduced sensitivity to NO and ANP
- Increased local production of LTC4, LTD4 and F2 isoprostane
- Reduced renal production of PGI2 and PGE2

**Symptoms and Signs**

- Hepatic fibrosis itself does not cause distinct symptoms.
- Symptoms may develop secondary to the primary disorder or to portal hypertension.

- Portal hypertension with splenomegaly is often asymptomatic unless complications, such as variceal GI bleeding, ascites, or portal-systemic encephalopathy, develop. Eventually, cirrhosis supervenes.

**Clinical Features**

**Compensated cirrhosis**

- Many people experience few symptoms at the onset of cirrhosis, symptoms are typically vague and nonspecific.
  - Fatigue and loss of energy
  - Loss of appetite and nausea
  - Spider angiomas
  - Liver function is normal

** Decompensated cirrhosis**

- Hepatocellular insufficiency
  - Symptoms caused by loss of functioning liver cells
  - System:
    - Fatigue, weakness, weight loss, malnutrition
  - Digestive System:
    - Loss of appetite, nausea, diarrhea
- Portal hypertension
  - Gastro-esophageal varices, Splenomegaly, ascites...
Clinical Features

<table>
<thead>
<tr>
<th>hepatocellular insufficiency</th>
<th>portal hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaundice</td>
<td>Gastroesophageal varices</td>
</tr>
<tr>
<td>Edema</td>
<td>Splenomegaly</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>Ascites</td>
</tr>
<tr>
<td>Spider angioma</td>
<td>Hepatic encephalopathy</td>
</tr>
<tr>
<td>Palmar erythema</td>
<td>Caput medusae, Cruveilhier-Baumgarten syndrome</td>
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<table>
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<td>Yellow discoloration of skin, cornea, and mucous membranes</td>
</tr>
<tr>
<td>Compromised hepatocyte excretory function, occurs when serum bilirubin&gt;20mg/L</td>
</tr>
</tbody>
</table>

**Spider amigomata**
- Central arteriole with tiny radiating vessels, mainly on trunk and face
- Raised oestradiol, decreased oestradiol degradation in liver

**Nodular liver**
- Irregular, hard surface on palpation
- Fibrosis, irregular regeneration

**Splenomegaly**
- Enlarged on palpation or in ultrasound
- Portal hypertension, splenic congestion

**Ascites**
- Proteinaceous fluid in abdominal cavity, clinical detected when≥1.5L
- Portal hypertension

**Caput medusae**
- Prominent veins radiating from umbilicus
- Portal hypertension, reopening of umbilical vein that shunts blood from portal vein

Clinical features (I)

**Hepatocellular Insufficiency**

- **Tendency to hemorrhage and anaemia**
  - Reduced synthesis of coagulation factors (II,V,VII,IX,X)
  - Hypersplenism: low platelet count, poor absorption
  - Gastrointestinal bleeding

- **Hormonal abnormalities**
  - Gynecomastia
  - Telangiectases
  - Spider nevi
  - Palmar erythema

- **Jaundice**
Clinical Features (I)  
* Portal Hypertension

- Splenomegaly  
anemia, leukopenia, thrombocytopenia due to hypersplenism
- Development and open of collateral vessels in portal hypertension  
Esophageal varices  
Rectal collateral’s  
Caput medusae  
Abdominal wall varices  
Portal system and left renal
- Ascites, hepatic hydrothorax (right side)

Clinical Features

- Palpation of liver  
firm, hard, irregular, enlargement  
rounded or sharp edge  
below the right lower ribs
- The spleen is often palpable, and may be very large

The clinical manifestations found in cirrhosis

Laboratory Tests and Findings in Cirrhosis

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST, ALT</td>
<td>Often normal or moderately raised</td>
<td>Leakage from damaged hepatocytes; AST-to-ALT ratio often &gt;1, especially in alcoholic cirrhosis (relative vitamin B6 deficiency)</td>
</tr>
<tr>
<td>ALP</td>
<td>Increased by less than three-fold, apart from PBC and PSC</td>
<td>Cholestasis</td>
</tr>
<tr>
<td>( \gamma )-GT</td>
<td>More specific for liver than ALP; high concentrations in active alcohols</td>
<td>Cholestasis</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>Raised later than ( \gamma )-GT and ALP; important predictor or mortality</td>
<td>Cholestasis, decreased hepatocyte and renal excretory function (exacerbated by systemic inflammation)</td>
</tr>
</tbody>
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\( \gamma \)-GT = \( \gamma \)-glutamyl transpeptidase; PBC = primary biliary cirrhosis; PSC = primary sclerosing cholangitis
### Laboratory Tests and Findings in Cirrhosis

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<tr>
<td><strong>Immunoglobulins</strong></td>
<td>Increased (mainly IgG)</td>
</tr>
<tr>
<td></td>
<td>Shunting of portal venous blood carrying (intestinal) antigen stimulation of plasma cells</td>
</tr>
<tr>
<td><strong>Sodium imbalance</strong></td>
<td>Hyponatraemia</td>
</tr>
<tr>
<td></td>
<td>Inability to excrete free water via kidneys due to increased activity of antidiuretic hormone (vasopression 2 receptor effect)</td>
</tr>
<tr>
<td><strong>Anaemia</strong></td>
<td>Macrocytic, normocytic, or microcytic anemia</td>
</tr>
<tr>
<td></td>
<td>Folate deficiency, hypersplenism, direct toxicity (alcohol), gastrointestinal blood loss (eg., via oesophageal varices)</td>
</tr>
<tr>
<td><strong>Thrombocytes and leucocytes</strong></td>
<td>Thrombocytopenia (Leucopenia)</td>
</tr>
<tr>
<td></td>
<td>Hypersplenism, dysfibronogenemia, reduced hepatic thrombopoietin production</td>
</tr>
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</table>

### Diagnostic Tests in Chronic Liver Disease According to Cause

#### Laboratory findings [I]

**Blood and urine routines**
- to estimate the severity of liver dysfunction:
  - ALT, AST, AKP, GGT, serum total bilirubin, serum albumin, prothrombin time, globulin, cholesterol
- to differential diagnosis:
  - Alcoholic: AST/ALT≥2; PBC: AKP, GGT>>ALT, AST
- to reflect hepatic fibrosis: P11P, HA, laminin
- to quantify liver function

**Liver function tests**
- to estimate the severity of liver dysfunction:
  - ALT, AST, AKP, GGT, serum total bilirubin, serum albumin, prothrombin time, globulin, cholesterol
- to differential diagnosis:
  - Alcoholic: AST/ALT≥2; PBC: AKP, GGT>>ALT, AST

**Immunology**
- **Cellular immune, hormonal**
- **Immune**
  - autoimmune hepatitis: IgG, globulin, ANA(+), SMA(+)
  - PBC: IgM, AMA(+)
- **Marker of virus**
- **Alpha Fetoprotein (AFP)**
Laboratory findings [II]

- **Ascites paracentesis:**
  - routine, culture, ADA, LDH, oncology markers
  - SAAG (serum ascites albumin gradient) > 11g/L
- **Ultrasonography, CT scanning:**
  - biliary obstruction, liver masses, varices
  - splenomegaly, ascites
- **Endoscopy:**
  - the number, appearance, and size of any esophageal/gastric varix,
  - portal hypertensive gastropathy (PHG)

Laboratory findings [III]

- **Radionuclide:**
  - 99m Tc-MIBI, H/L
- **Liver biopsy:**
  - to confirm the diagnosis
- **Laparoscopy**
- **HVPG (hepatic vein pressure gradient)**
  - (肝静脉压梯度)
  - = (wedged - free) hepatic venous pressure
  - Normal: 5-6mmHg,
  - > 10mmHg: varices;
  - > 12mmHg: rupture
**Child Pugh Turcotte (CPT) Classification**

<table>
<thead>
<tr>
<th>Score</th>
<th>Variable</th>
<th>Child (A: 5-6 points), Child (B: 7-9 points), and Child (C: 10-15 points) predict a life expectancy of 15–20, 4–14, and 1–3 years, respectively, and a postoperative mortality (abdominal surgery) of 10%, 30%, and 80%, respectively. INR=international normalised ratio.</th>
</tr>
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<tbody>
<tr>
<td>1 point</td>
<td>Encephalopathy (degree)</td>
<td>Nil</td>
</tr>
<tr>
<td>2 points</td>
<td>Ascites (degree)</td>
<td>Nil</td>
</tr>
<tr>
<td>3 points</td>
<td>Bilirubin (mg/L)</td>
<td>&lt;34</td>
</tr>
<tr>
<td></td>
<td>Albumin (g/L)</td>
<td>&lt;35</td>
</tr>
<tr>
<td></td>
<td>INR</td>
<td>&lt;1.7</td>
</tr>
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**Complications of Decompensated Cirrhosis**

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<tr>
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<th>Manifestation</th>
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<td>Gastroesophageal variceal bleeding</td>
<td>Hematemesis, melena, shock</td>
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<tr>
<td>Spontaneous bacterial peritonitis</td>
<td>Abdominal pain, an acute onset of symptoms, and peritoneal irritation, fever</td>
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<tr>
<td>Primary hepatocellular carcinoma</td>
<td>Progressive hepatomegaly, firm</td>
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<td>Hepatorenal syndrome</td>
<td>Oliguria, anuria on the base of refractory ascites, nausea</td>
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<tr>
<td>Hepatopulmonary Syndrome</td>
<td>Clubbing finger or acropachy, cyanosis</td>
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<tr>
<td>Encephalopathy</td>
<td>Asterixis or &quot;flapping tremor&quot;, delirium, coma</td>
</tr>
<tr>
<td>Portal vein thrombosis</td>
<td>Chronic nonsymptomatic</td>
</tr>
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**Diagnosis of Liver Cirrhosis**

- **Etiology diagnosis**
- **Pathology diagnosis**
- **Functional diagnosis**
  - Child-Pugh classification
- **Complication(s) diagnosis**
  - Searching for complications
- **Comorbidity diagnosis**

Ex. Patient’s diagnosis:
- PBC: Liver cirrhosis; Decompensate stage, Child C; Gastric-esophageal bleeding; Dermatosclerosis

**Diagnosis [II]**

- The history of disease contributes to identifying the cause of cirrhosis
- History of viral hepatitis, blood transfusion, medication use, alcohol use, sexual practices should be carefully reviewed
- Signs and symptoms confirm to existence of portal hypertension and impaired liver function
- Liver function tests: hypoalbuminemia, hyperbilirubinemia, the prolonged prothrombin time suggest hepatic decompensation.
- Imaging study: Ultrasound and CT readily identify the lesion, but have no characteristic findings

**Differential Diagnosis**

- **Other condition of hepatomegaly or splenomegaly**
  - chronic virus hepatitis, Gaucher’s disease, lymphomas, and leukaemias, congestive splenomegaly

- **Differential diagnosis of cirrhotic ascites and other types of ascites**
  - malignant ascites, constrictive pericarditis, tuberculosis peritonitis, et al.

- **Portal hypertension**
Treatment of Cirrhosis

- Specific treatment for the underlying etiology of the liver disease
  - Antivirus therapy -- viral hepatitis
  - Abstinence from alcohol -- alcoholic
  - Ursodeoxycholic acid (UDCA) -- PBC
  - Penicillamine -- Wilson's disease

- General Treatments:
  - High calories (40 kcal/kg·d), adequate protein (1-1.5g/kg·d), vitamin
  - Hepa-protective Herbal compounds

Treatment of Cirrhosis [IV]

- Surgical treatment of portal hypertension
  - Porta-caval shunt surgery:
    - Portal-caval
    - Mesocaval
    - Distal splenorenal shunts
  - Choice of patients:
    - Child-Pugh: A, B
    - Bleeding from gastroesophageal varices, hyperplenism.

Medical Management of Ascites

- Prevention:
  - Low sodium diet

- Treatment:
  - Moderate sodium restriction
  - Diuretics (spironolactone, or furosemide)
  - Large volume paracentesis
  - Intravenous albumin replacement
  - TIPSS (LeVeen/Denver shunts)

Treatment of Ascites

- Bed rest, sodium and water restriction
  - Fluid intake: 800-1000ml/d (hyponatremia, serum sodium<130meq/L)
  - Dietary sodium intake: 88mmol/d (2.0gNacl)

- Mild patients: rest on bed, with dietary salt restriction, loss of ascites occurs in 10% to 15% of patients.

- Increasing renal sodium and water excretion:
  - Diuretics:
    - Urinary sodium / urinary potassium >1
    - Spironolactone + furosemide
    - Urinary sodium / urinary potassium <1
    - Higher doses spironolactone
Treatment of Ascites (III)

- Large-volume paracentesis associated with plasma volume expansion
- Ascites ultrafiltration and re-infusion
- Peritoneovenous (LeVeen) shunts
- TIPS (transjugular intrahepatic porto-systemic stent)
- Liver transplantation

TIPSS—stent positioned between the hepatic and portal veins

Treatment of cirrhosis[IV]

surgical treatment of portal hypertension
  - portacaval shunt surgery:
    - portacaval
    - mesocaval
    - distal splenorenal shunts

Choice of patients:
  - Child-Pugh: A, B
  - bleeding from gastroesophageal varices
  - hypersplenism

COMPLICATIONS OF LIVER CIRRHOSIS
Complication

- Gastroesophageal variceal bleeding
- Spontaneous bacterial peritonitis (SBP)
- Primary hepatocellular carcinoma (HCC)
- Hepatorenal syndrome (HRS)
- Hepatopulmonary syndrome (HPS)
- Encephalopathy
- Portal vein thrombosis

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<td></td>
<td>Acute complete occlusion: sudden onset of abdominal pain, variceal bleeding, and ascites, splenomegaly, shock</td>
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Complications [I] Gastroesophageal variceal bleeding

- Upper Gastrointestinal Bleeding
  - Hematemesis (呕血)
  - Melena (黑粪)
- Portal hypertensive gastropathy
- Peptic ulcer

Treatment of Variceal Bleeding

Reduce the hepatic venous pressure gradient (HVPG) to <12 mmHg, or by 20% from baseline

Acute:
- Resuscitation
- Vasoconstrictors (vasopressin, somatostatin, octreotide, propranolol)
- Endoscopic interventions (Sclerotherapy; Band Ligation)
- Surgical treatment (shunts)
- Transjugular intrahepatic portosystemic shunts (TIPS)

Chronic:
- Variceal Obliteration
- TIPS
- Surgical shunts
Treatment of Acute Variceal Haemorrhage

- General management:
  - abstain food
  - intensive care
  - volume and blood replacement
- Specific measures to stop the bleeding
  - Pharmacological therapy:
    - vasopressin (垂体后叶素)
    - somatostatin (生长抑素)
    - Octreotide (奥曲肽)

Treatment of acute variceal haemorrhage

Emergent endoscopy:
after Patient's hemodynamic status stabilized (usually within 2-12 hours)
- Balloon tube tamponade (if bleeding continues)
- Endoscopic variceal sclerotherapy and band ligation
- Prophylactic therapy to prevent rebleeding: Beta-adrenergic antagonists (普奈洛尔), endoscopic sclerotherapy (硬化剂)/banding (套扎) (usually 3-6 sessions), portacaval shunting, TIPS
Complications [II]
Spontaneous Bacterial Peritonitis (SBP)

Prevention:
- Treat ascites

Treatment:
- Early diagnostic paracentesis: >250 neutrophils per mL
- Intravenous antibiotics (plus albumin)
- Antibiotics: Third-generation cephalosporins
- Secondary prophylaxis with oral antibiotics such as levofloxacin

Complications [III]
Hepatic encephalopathy

- Asterixis (扑翼样振颤)
- Disoriented (定向障碍)
- Coma (昏迷)
Hepatic Encephalopathy

- Correction of precipitating factors:
  - Infection
  - Bleeding
  - Electrolyte imbalance
  - Sedatives
  - High protein intake
  - Lactose
  - Neomycin, metronidazole, rifaximin

- Supportive measures and administration of medication that decrease the production of toxins or antagonize their effects on brain

Complications [III]
Hepatorenal syndrome (HRS)

- Oliguria (少尿), azotemia (氮质血症), hypotension (低血压), dilutional hyponatremia (稀释性低钠血症), low urinary sodium (低钠尿)

Hepatorenal Syndrome

Worsening azotemia with avid sodium retention and oliguria in the absence of identifiable specific causes of renal dysfunction.

Prevention:
- Avoid hypovolaemia

Treatment:
- Discontinue diuretics
- Renal and somatostatin (octreotide)

Therapies for HRS [I]

- Avoid use of nephrotoxic drugs:
  1. Antibiotics: aminoglycosides
  2. NSAIDs: inhibit formation intrarenal prostaglandins —marked decline in renal function

- Avoid and treat factors to hypovolaemia:
  1. Active treatments of upper gastrointestinal bleeding
  2. Judicious use of diuretics (weight loss < 0.5 Kg/d)

- Rectify electrolyte and metabolic imbalance, Fluid intake restriction

Therapies for HRS [II]

- Volume expansion: with IV dextrose, plasma, albumin
  - Concomitant plasma volume expansion with albumin has been used with LVP to correct decreased effective arterial volume that leads to sodium retention, TIPS

- Vasoactive drugs: terlipressin (可利新), ornipressin, dopamine, ---increasing renal plasma flow

- Elimination of endotoxaemia and control infections

- Liver transplantation: the most effective treatment for patients with HRS

Complications [IV]
Hepatocellular Carcinoma

- Risk factors for hepatocellular carcinoma
  - Cirrhosis
  - Decompensated cirrhosis
  - Viral hepatitis B and C
  - Non-alcoholic steatohepatitis
  - Type 2 diabetes
  - Aflatoxin exposure
  - Coinfection with multiple viruses: viral hepatitis B, Viral hepatitis C, and HIV (risk 2-6-fold)
  - Increasing age
  - Male sex
  - Positive family history of hepatocellular carcinoma
  - Associated secondary alcohol abuse (risk 2-4-fold)
  - Non-alcoholic steatohepatitis as cofactor
Indications for Liver transplantation (irreversible, progressive chronic liver diseases)

- Primary biliary cirrhosis
- Sclerosing cholangitis
- Fulminant liver failure
- Metabolic liver diseases
- Alcoholic cirrhosis
- Postnecrotic cirrhosis
- Autoimmune liver disease
- Budd-Chiari syndrome
- Hepatocellular carcinoma

Indications for Liver transplantation (cirrhosis)

- Refractory ascites
- Recurrent variceal bleeding
- Hepatic encephalopathy
- Spontaneous bacterial peritonitis
- Worsening functional status, rising bilirubin, decreasing albumin, worsening coagulopathy (Child-Pugh C)

Prevention and Treatment for complications of cirrhosis

### Prevention

<table>
<thead>
<tr>
<th>Complication</th>
<th>Prevention</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variceal bleeding</td>
<td>Non-selective β blockers, Variceal band Ligation</td>
<td>Acute: Resuscitation, Vasoconstrictors, Sclerotherapy, Band Ligation, TIPS, Surgical shunts, Chronic Variceal obliteration, TIPS, Surgical shunts</td>
</tr>
<tr>
<td>Ascites</td>
<td>Low sodium diet</td>
<td>Low sodium diet, Diuretics, Large volume paracentesis, TIPSS (LeVeen/Denver shunts)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>Avoid hypovolaemia</td>
<td>Rehydration, Albumin infusion</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>Avoid precipitants</td>
<td>Infection, Bleeding, Electrolyte imbalance, Sedatives, High protein intake, Lactulose, Neomycin, metronidazole, rifaximin</td>
</tr>
</tbody>
</table>

TIPS=Transjugular intrahepatic portosystemic shunt; *Nadolol, propranolol; *Vasopressin; octreotide/somatostatin; terlipression
CIRRHOSIS AND ITS COMPLICATIONS
--Teaching Notes

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Objectives

• To master the definition, etiology, major clinical features, treatment of liver cirrhosis and the management of its complications.

• To be familiar with the pathogenesis of cirrhosis, the laboratory parameters which are associated with the etiology and severity (compensate or decompensate cirrhosis).

Teaching plan
Contents and time assignment

1) Definition of cirrhosis (5 min)
2) Pathogenesis (15 min)
   General
   Disease specific:
   viral hepatitis, alcoholic, primary and biliary cirrhosis
3) Diagnosis (25 min)
   Etiology for cirrhosis
   Compensate and decompensate cirrhosis
   The complications of cirrhosis

4) Treatment (45 min)
   Disease specific and non-specific treatment
   Major complication
   • Acute bleeding and prevention of recurrent hemorrhage
   • Encephalopathy
   • Spontaneous bacterial peritonitis
   • Encephalopathy

Key points and special difficulties

1. To understand that the early diagnosis and treatment of chronic liver diseases are important for the prevention of cirrhosis progression and improving prognosis.
2. To understand that the treatment of complications are the major management for decompensate cirrhosis

Questions for review

• What is cirrhosis? What are the etiologies of cirrhosis and why it is important to identify them?
• How to diagnosis cirrhosis? What are the common complications for advanced cirrhosis?
• The management of disease specific cirrhosis
• The management of the major complications of cirrhosis
Key words

- Cirrhosis; Portal hypertension; Ascites; Variceal bleeding; Spontaneous bacterial peritonitis; Hepatorenal syndrome; Hepatic encephalopathy; Hepatocellular carcinoma
- Alcoholic cirrhosis; posthepatitic cirrhosis; cryptogenic cirrhosis; Primary biliary cirrhosis; Secondary biliary cirrhosis; Cardiac cirrhosis; Budd-Chiari Syndrome