Supportive module 2 "Basics of diagnosis, treatment and prevention of major gastroenterological diseases"

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<td>The main symptoms of gastroenterological diseases and diagnostic techniques in Gastroenterology</td>
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<td>Chronic hepatitis</td>
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<td>Cirrhosis of the liver</td>
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<td>06/12</td>
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Supportive module 2: Basics of diagnosis, treatment and prevention of major gastroenterological diseases

Cirrhosis of the Liver

LECTURE IN INTERNAL MEDICINE FOR IV COURSE STUDENTS

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Plan of the Lecture

- Definition
- Epidemiology
- Risk Factors and Etiology
- Mechanisms
- Classification
- Clinical presentation
- Diagnosis
- Treatment
- Prognosis
- Prophylaxis
- Abbreviations
- Diagnostic guidelines
Definition

Cirrhosis is the final histological pathway for a wide variety of liver diseases characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules that leads to portal hypertension, hepatic encephalopathy, and liver cancer with very variable progression from over weeks to many years.
Epidemiology

- Cirrhosis is the ninth leading cause of death in the United States and is responsible for 1.2% of all US deaths
- Many patients die in their fifth or sixth decade of life
- The prevalence is higher in non-Hispanic blacks and Mexican Americans, those living below the poverty level, and those with less than a 12th grade education
- Each year, 2000 additional deaths are attributed to fulminant hepatic failure (FHF), that may be caused viral hepatitis, drugs (e.g., acetaminophen), toxins (e.g., *Amanita phalloides*, the yellow death-cap mushroom), autoimmune hepatitis, Wilson disease, or a variety of less common etiologies. Cryptogenic causes are responsible for one third of fulminant cases.
Risk Factors and Etiology

- Hepatitis C, B, B+D,
- Alcoholic liver disease
- Cryptogenic
- Autoimmune hepatitis
- Biliary cirrhosis and primary sclerosing cholangitis
- Hemochromatosis, Wilson disease, alpha-1 antitrypsin deficiency
- Granulomatous disease (e.g., sarcoidosis)
- Type IV glycogen storage disease
- Drug-induced liver disease (methotrexate, amiodarone, etc.)
- Venous outflow obstruction (Budd-Chiari syndrome, etc.)
- Congestive heart failure
- Male sex, age >50, regular (moderate) alcohol consumption
Risk Factors and Etiology

Non-alcoholic fatty liver disease (NAFLD).

http://www.mdpi.com/1422-0067/15/5/7500/htm
Mechanism

- Liver cirrhosis is the final pathological result of various chronic liver diseases, and fibrosis is the precursor of cirrhosis
- Many types of cells, cytokines and miRNAs are involved in the initiation and progression of liver fibrosis and cirrhosis
- Activation of hepatic stellate cells (HSCs) is a pivotal event in fibrosis
- Defenestration and capillarization of liver sinusoidal endothelial cells are major contributing factors to hepatic dysfunction in liver cirrhosis
- Activated Kupffer cells destroy hepatocytes and stimulate the activation of HSCs
- Repeated cycles of apoptosis and regeneration of hepatocytes contribute to pathogenesis of cirrhosis

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4064077/
Mechanism

- At the molecular level, many cytokines are involved in mediation of signaling pathways that regulate activation of HSCs and fibrogenesis.
- Recently, miRNAs as a post-transcriptional regulator have been found to play a key role in fibrosis and cirrhosis.
- Robust animal models of liver fibrosis and cirrhosis, as well as the recently identified critical cellular and molecular factors involved in the development of liver fibrosis and cirrhosis will facilitate the development of more effective therapeutic approaches for these conditions.
Formal pathogenesis of liver fibrogenesis.
Mechanism
Mechanism

Encephalopathy ↓ Liver Cell Function

Shunting

Portal vein

Cirrhotic liver

Inf. vena cava

Sup. mesenteric vein

Varices

Ascites

Spleen

Esophageal varices (EV)

Gastric varices (GV)

Portal hypertension.
Mechanism

Portosystemic anastomosis.
Classification
International Classification of Diseases

XI Diseases of the digestive
K70.3 Alcoholic cirrhosis of liver
K71.7 Toxic liver disease with fibrosis and cirrhosis of liver
K74 Fibrosis and cirrhosis of liver
K74.3 Primary biliary cirrhosis
K74.4 Secondary biliary cirrhosis
K74.5 Biliary cirrhosis, unspecified
K74.6 Other and unspecified cirrhosis of liver.
Classification


- Morphologic: macronodular, micronodular, mixed
- Histologic: portal, post-necrotic, post hepatitis, biliary, congestive
- Etiologic agents: genetic (i.e. biliary atresia, cystic fibrosis, Wilson Disease), toxic, infectious, biliary, vascular (i.e. congestive heart failure), cryptogenic (which the cause is unknown), fatty liver.
# Classification

## Child-Turcotte-Pugh Classification for Severity of Cirrhosis

<table>
<thead>
<tr>
<th>Clinical and Lab Criteria</th>
<th>Points*</th>
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<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>None</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>&lt; 2</td>
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<tr>
<td>Albumin (g/dL)</td>
<td>&gt; 3.5</td>
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<tr>
<td>Prothrombin time</td>
<td>&lt; 4</td>
</tr>
<tr>
<td></td>
<td>&lt; 1.7</td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
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<tr>
<td>Mild to moderate (grade 1 or 2)</td>
<td>2-3</td>
</tr>
<tr>
<td>Mild to moderate (diuretic responsive)</td>
<td>2.8-3.5</td>
</tr>
<tr>
<td>Severe (diuretic refractory)</td>
<td>&gt;3</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Severe (grade 3 or 4)</td>
<td></td>
</tr>
<tr>
<td>Severe (diuretic refractory)</td>
<td></td>
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</tbody>
</table>

*Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)*

- Class A = 5 to 6 points (least severe liver disease)
- Class B = 7 to 9 points (moderately severe liver disease)
- Class C = 10 to 15 points (most severe liver disease)
Symptoms

- Decreased appetite
- Edema
- Ascites
- Easy bruising
- Poor concentration and memory
- Bleeding esophageal varices
- Spontaneous bacterial peritonitis
- Weight loss
- Anorexia
- Weakness
- Impotence
- Gynecomastia.
Signs
Cutaneous Features

• Jaundice
• Scratch marks secondary to pruritus
• Spider angiomata/naevi (mainly found on the trunk and face)
• Skin telangiectasia's ('paper money skin')
• Palmar erythema
• Bruising
• Petechia or purpura
• Hair loss
• White nails (sign of hypoalbuminemia)
• Finger clubbing
• Dupuytren's contracture

http://patient.info/doctor/cirrhosis-pro
Signs
Other Features

• Hepatomegaly and a nodular liver
• Edema
• Gynecomastia and male hair loss pattern
• Hypogonadism/testicular atrophy/amenorrhoea (due to the direct toxic effect of alcohol in alcoholic cirrhosis or iron in haemochromatosis)
• Kayser-Fleischer ring (a brown-green ring of copper deposit around the cornea, pathognomonic for Wilson's disease).
Signs
Portal Hypertension

• Hepatic venous pressure gradient (HVPG) greater than or equal to 5mm Hg and is considered to be clinically significant when HVPG exceeds 10 to 12 mm Hg

• The main symptoms and complications: ascites (an accumulation of fluid in the abdomen, can be detected clinically when ≥1.5 litres of fluid is present); dilated veins in the anterior abdominal wall (caput medusae, when veins seen radiating from the umbilicus); encephalopathy or confusion and forgetfulness caused by poor liver function; splenomegaly; reduced levels of platelets or white blood cells; gastrointestinal bleeding marked by black, tarry stools or blood in the stools, or vomiting of blood due to the spontaneous rupture and hemorrhage from varices.
Signs
Hepatic Encephalopathy

• Asterixis ('flapping tremor'); suggests hepatic encephalopathy
• To detect asterixis, take the patient's hand and gently hyperextend the wrist and joints of the hand, pushing gently on the tips of the four fingers
• Ignore the thumb
• Hold that position for several seconds and you will feel a slow, clonic flexion-relaxation movement against your hand if asterixis is present.
Clinical Presentation

• Up to 40% of people with cirrhosis may be asymptomatic
• Blood testing for other reasons may reveal abnormal liver function and prompt further investigation which shows cirrhosis
• Initial clinical presentation of patients with decompensated cirrhosis is still common and is characterized by the presence of dramatic and life-threatening complications, such as variceal hemorrhage, ascites, spontaneous bacterial peritonitis, or hepatic encephalopathy.
Clinical Presentation
Activity Grades

• Inactive: no inflammation and intact limiting plates around septa which are fibrotic
• Slight: mild inflammation; segmental erosion of limiting plates
• Moderate: moderate inflammation and damage of limiting plates
• Severe: marked inflammation, extensive damage of limiting plates, piecemeal necrosis and parenchymal damage (necrosis, cholestasis, dysplasia, malignant transformation.
Clinical Presentation
Decompensation

• In patients with previously stable cirrhosis, decompensation may occur due to various causes, such as constipation, infection (of any source), increased alcohol intake, medication, bleeding from esophageal varices or dehydration.

• Patients with decompensated cirrhosis generally require admission to hospital, with close monitoring of the fluid balance, mental status, and emphasis on adequate nutrition and medical treatment.
Complications

- Anemia, thrombocytopenia and coagulopathy (folate deficiency, hemolysis, hypersplenism, cholestasis)
- Esophageal varices (portal hypertension)
- Ascites
- Spontaneous bacterial peritonitis
- Hepatocellular carcinoma
- Cirrhotic cardiomyopathy
- Hepatopulmonary syndrome
- Portopulmonary hypertension.

http://patient.info/doctor/cirrhosis-pro
Diagnosis

- The gold standard for diagnosis of cirrhosis is a liver biopsy, through a percutaneous, transjugular, laparoscopic, or fine-needle approach.
- A biopsy is not necessary if the clinical, laboratory, and radiologic data suggests cirrhosis.
- Furthermore, there is a small but significant risk to liver biopsy, and cirrhosis itself predisposes for complications caused by liver biopsy.
- The best predictors of cirrhosis are ascites, platelet count <160,000/mm³, spider angiomata, and Bonacini cirrhosis discriminant score greater than 7.

https://en.wikipedia.org/wiki/Cirrhosis#Pathophysiology
Diagnosis
Laboratory Testing

- Complete blood count and liver disease–associated blood tests (e.g., aspartate aminotransferase [AST], alanine aminotransferase [ALT], bilirubin, alkaline phosphatase [ALP])
- Coagulation tests (prothrombin time [PT], partial thromboplastin time [PTT], international normalized ratio [INR])
- Albumin: hypoalbuminemia (impaired hepatic synthetic function)
- Blood urea nitrogen, creatinine, and electrolytes
- Arterial blood gas (ABG) and pH measurements
- Hepatic and viral hepatitis serologies, antinuclear antibody, antimitochondrial antibody, antismooth muscle antibody
- Iron indices, alpha1-antitrypsin deficiency, ceruloplasmin, 24-hour urinary copper.
Diagnosis

Imaging Studies

Duplex Doppler ultrasonography of the liver and upper abdomen
Computed tomography (CT) scanning and/or magnetic resonance imaging (MRI): Can be used when ultrasonographic findings are inconclusive
Bleeding scan or angiography: Used when bleeding is obscure and the source is unclear.
Diagnosis

Procedures

- Liver biopsy and histologic examination
- Hemodynamic measurement of the hepatic venous pressure gradient (HVPG): A criterion standard for assessment of portal hypertension
- Upper GI endoscopy (or, esophagogastroduodenoscopy [EGD]): A criterion standard for assessment of portal hypertension.
Diagnosis
Histopathologic Features

Lobular architecture: No normal lobular architecture can be identified and central veins are hard to find.

High magnification micrograph of a liver with cirrhosis.

Microscopically with cirrhosis, the regenerative nodules of hepatocytes are surrounded by fibrous connective tissue that bridges between portal tracts.
Diagnosis
Morphological Type

- Micronodular < 3 mm
- Macronodular > 3 mm
- Mixed
# Diagnosis

**West Haven Criteria Grading System of Hepatic Encephalopathy**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>Trivial lack of awareness; euphoria or anxiety; shortened attention span; impaired performance of addition or subtraction</td>
</tr>
<tr>
<td>2</td>
<td>Lethargy or apathy; minimal disorientation for time or place; subtle personality change; inappropriate behavior</td>
</tr>
<tr>
<td>3</td>
<td>Somnolence to semistupor, but responsive to verbal stimuli; confusion; gross disorientation</td>
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<tr>
<td>4</td>
<td>Coma (unresponsive to verbal or noxious stimuli)</td>
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Management

• A healthy diet is encouraged, as cirrhosis may be an energy-consuming process
• Antibiotics are prescribed for infections, and various medications can help with itching
• Laxatives, such as lactulose, decrease risk of constipation
• Alcoholic cirrhosis is treated by abstaining from alcohol
• Treatment for hepatitis-related cirrhosis involves medications used to treat the different types of hepatitis
• Cirrhosis caused by Wilson's disease is treated with chelation therapy (penicillamine) to remove the copper
• Vaccination of susceptible patients should be considered for Hepatitis A and Hepatitis B.
Management

Nutrition

• Malnutrition occurs up to 60% of patients, and guidelines recommend a daily protein intake of 1.0 to 1.5 g per kilogram of dry body weight.
• High-protein diets are well tolerated and are associated with sustained improvement in mental status, whereas restriction of protein intake does not have any beneficial effect in patients with acute hepatic encephalopathy.
• Late-evening meals may improve nitrogen balance without exacerbating hepatic encephalopathy.
• A 2000-mg limit in daily sodium intake is mandatory in the treatment of ascites.
• Fluid restriction recommend only when the serum sodium concentration is less than 120 mmol per liter.

Management
Medications: Antihypertensive and Hypertensive Agents

• Nonselective beta-blockers reduce portal pressures and are used in the primary and secondary prophylaxis of variceal hemorrhage
• Antihypertensive agents should be discontinued in patients who have decompensated cirrhosis with ascites or hypotension
• In patients with stable hypotension, midodrine may improve splanchnic and systemic hemodynamic variables, renal function, and sodium excretion
• The combination of octreotide and midodrine is used for the treatment of type 1 hepatorenal syndrome; type 1 hepatorenal syndrome is defined as at least a twofold increase in serum creatinine (reflecting a 50 percent reduction in creatinine clearance) to a level greater than 2.5 mg/dL (221 micromol/L) during a period of less than two weeks.

Management
Medications: Pain Management

• Because of the risk of acute renal failure and gastrointestinal bleeding, nonsteroidal antiinflammatory drugs are contraindicated, except for low-dose aspirin in patients in whom the severity of cardiovascular disease exceeds the severity of cirrhosis.

• Opiates should be used cautiously or avoided, because they may precipitate or aggravate hepatic encephalopathy.

• Acetaminophen is effective and safe in patients with liver disease, provided that the patient does not drink alcohol.
Management
Medications: Proton-Pump Inhibitors

- Proton-pump inhibitors are vastly overprescribed in hospitalized patients with cirrhosis, often without any documented indication.
- A large study involving patients with cirrhosis who were hospitalized with an initial infection showed that the risk of subsequent infection was increased among patients taking proton-pump inhibitors and those receiving long-term antibiotic agents as prophylaxis for spontaneous bacterial peritonitis.
- Indiscriminate use without appropriate indications should be avoided.

Management
Medications: Sedatives

• Benzodiazepines should be avoided in patients with hepatic encephalopathy

• For patients with alcoholic hepatitis or cirrhosis in whom severe symptoms of acute alcohol withdrawal develop, short-acting benzodiazepines such as lorazepam and oxazepam are preferred in order to minimize the risk of oversedation

• For patients with insomnia, hydroxyzine at a dose of 25 mg at bedtime may be a reasonable alternative and has been studied in a small, randomized trial.

Management
Medications: Statins

- 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) can be safely started and continued in patients with cirrhosis.
- Statins have established cardiovascular benefits in the treatment of nonalcoholic fatty liver disease.
- The overall rate of statin-induced acute liver failure is 0.2 to 1 cases per million persons taking statins, although estimates of patients who do not receive statins because of concerns about hepatotoxicity range from 10 to 30%.
- Data from the Drug-Induced Liver Injury Network corroborated the exceedingly low likelihood of hepatic injury due to statins, with only 22 cases of drug-induced liver injury being attributed to statins over an 8-year period.

Management
Medications: Vaptans

- Selective vasopressin V$_2$–receptor antagonists (vaptans) have been evaluated for use in hyponatremia and ascites
- A large, placebo-controlled study involving patients with cirrhosis and ascites showed that although satavaptan alleviated hyponatremia, mortality was higher among patients with recurrent ascites who were receiving satavaptan than among those who were receiving placebo
- Because of these findings as well as hepatotoxicity reported with respect to tolvaptan, the use of vaptans in patients with cirrhosis and ascites is not recommended.

Management
Medications: Paracentesis

- Paracentesis is particularly helpful in all patients with new-onset ascites, in patients with existing ascites who are admitted to the hospital, and in patients with clinical deterioration (fever, abdominal pain, hepatic encephalopathy, leukocytosis, renal failure, or metabolic acidosis).
- Spontaneous bacterial peritonitis is diagnosed when the neutrophil count in ascitic fluid is at least 250 cells per cubic millimeter and secondary bacterial peritonitis is ruled out.
Management
Medications: Transplantation

• If complications cannot be controlled or when the liver ceases functioning, liver transplantation is necessary
• Survival from liver transplantation has been improving over the 1990s, and the five-year survival rate is now around 80%
• The survival rate depends largely on the severity of disease and other medical problems in the recipient
• In the United States, the MELD score is used to prioritize patients for transplantation
• Transplantation necessitates the use of immune suppressants (ciclosporin or tacrolimus).
Management
Medications: Decompensated Cirrhosis

- In patients with previously stable cirrhosis, decompensation may occur due to various causes, such as constipation, infection (of any source), increased alcohol intake, medication, bleeding from esophageal varices or dehydration.

- Patients with decompensated cirrhosis generally require admission to hospital, with close monitoring of the fluid balance, mental status, and emphasis on adequate nutrition and medical treatment - often with diuretics, antibiotics, laxatives and/or enemas, thiamine and occasionally steroids, acetylcysteine and pentoxifylline.

- Administration of saline is avoided as it would add to the already high total body sodium content that typically occurs in cirrhosis.
Management
Medications: Palliative Care

- Palliative care focuses on providing patients with relief from the symptoms, pain, and stress of a serious illness
- The goal of palliative care is to improve quality of life for both the patient and the patient's family and it is appropriate at any stage and for any type of cirrhosis
- Because the disease is not curable without a transplant, palliative care can also help with discussions regarding the person's wishes concerning health care power of attorney, Do Not Resuscitate decisions and life support, and potentially hospice
- Despite proven benefit, people with cirrhosis are rarely referred to palliative care.
Management
Medications: Care Coordination

• Patients with cirrhosis are plagued by frequent hospital readmissions for fluid overload, hepatic encephalopathy, or gastrointestinal hemorrhage

• Such readmissions are costly, moderately predictable, frequently preventable, and associated with a risk of death

• Care coordination is an increasingly popular concept to improve quality and clinical outcomes while reducing readmission rates and expenditures

• Care coordinators facilitate inpatient-to-clinic transitions, reconcile medications, call patients to prevent unnecessary visits to the emergency department, place “smart scales” in homes to monitor body weight remotely, facilitate interaction with other health care professionals, and arrange referrals to nursing facilities or hospice.

Prognosis

- Prognosis depends on the underlying cause and on the success of its treatment.
- If someone with alcoholic cirrhosis continues to drink alcohol, the rate of decompensation can be rapid.
- Patients with fulminant hepatic failure have a 50-80% mortality rate unless they receive a liver transplant.

http://patient.info/doctor/cirrhosis-pro
Prophylaxis

• Worldwide, the most important factor in prevention of cirrhosis is immunisation against hepatitis B
• There is no vaccine against hepatitis C but some treatments may delay progression and alcohol must be avoided
• Sensible drinking is essential for everyone and patients should be advised about the recommended limits
• Beware of hepatotoxic medications, including herbal remedies
• Weight reduction and exercise can improve liver function in patients with NAFLD.
Abbreviations

ALT - alanine aminotransferase
ALP - alkaline phosphatase
AST - aspartate aminotransferase
CH - Cirrhosis of the Liver
HSCs - hepatic stellate cells
HVPG - hepatic venous pressure gradient
EGD - esophagogastroduodenoscopy
FHF - fulminant hepatic failure
INR - international normalized ratio
NAFLD - non-alcoholic fatty liver disease
miRNA - a small non-coding RNA molecule
PT - prothrombin time
PTT - partial thromboplastin time
Diagnostic and treatment guidelines

Cirrhosis: Diagnosis, Management, and Prevention
NICE Guideline on Cirrhosis (2016)
Guidelines on the management of ascites in cirrhosis
Cirrhosis