Module 2: Gastroenterology
Liver Cirrhosis, 4 hours

NOTES FOR PRACTICAL LESSONS IN INTERNAL MEDICINE FOR STUDENTS OF IV COURSE OF MEDICAL SCHOOL V.N.KARAZIN KHARKOV NATIONAL UNIVERSITY FOR 2ST SEMESTER 2015-2016 STUDY YEAR

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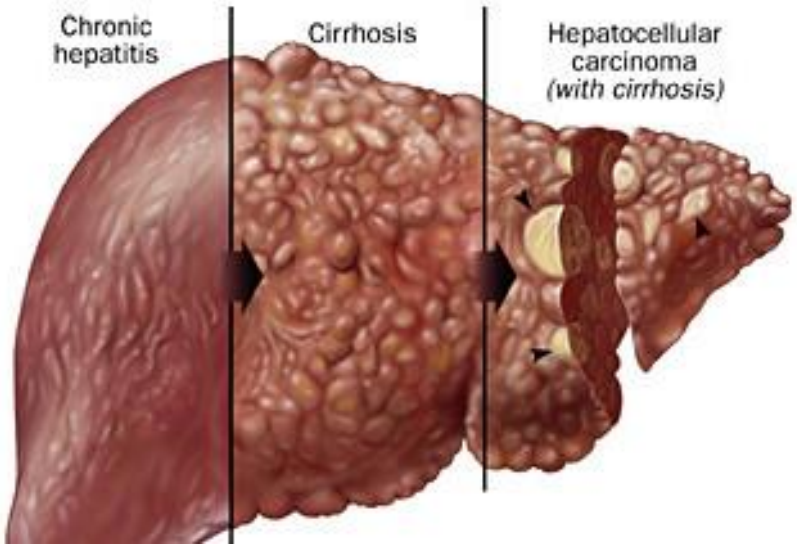
Plan of the Lesson

- Definition
- Classification
- Epidemiology
- Etiology
- Mechanisms
- History
- Clinical investigation
- Complications
- Diagnosis
- Treatment
- Prognosis
- Prophylaxis
- Clinical cases
- Abbreviations
- Diagnostic guidelines



youthincharge.org/wp-content/uploads/2014/03/hp-b.jpg

Definition

Cirrhosis is a clinical syndrome at the terminal stages of chronic hepatitis in which healthy liver tissue is replaced with scar tissue, eventually preventing the liver from functioning properly, that leads to portal hypertension, in early stages often without explicating symptoms, but later with its worsening patient become tired, weak, itchy, more and more often has swelling in the lower legs, develops yellow skin, builds up fluid in the abdomen, or develops spider-like blood vessels on the skin, bleeding from dilated (esophageal, stomachic, hemoroidal) veins, often with hepatic encephalopathy, and liver cancer.

en.wikipedia.org/wiki/Cirrhosis

Classification

World Health Organization (Anthony P.P. et al. J Clin Pathol 31:395,1978)

- Morphologic
  - Macronodular
  - Micronodular
  - Mixed
- Histologic
  - Portal
  - Post-necrotic
  - Post Hepatitic
  - 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

meddean.luc.edu/lumen/MedED/orfpath/cirhosis.htm

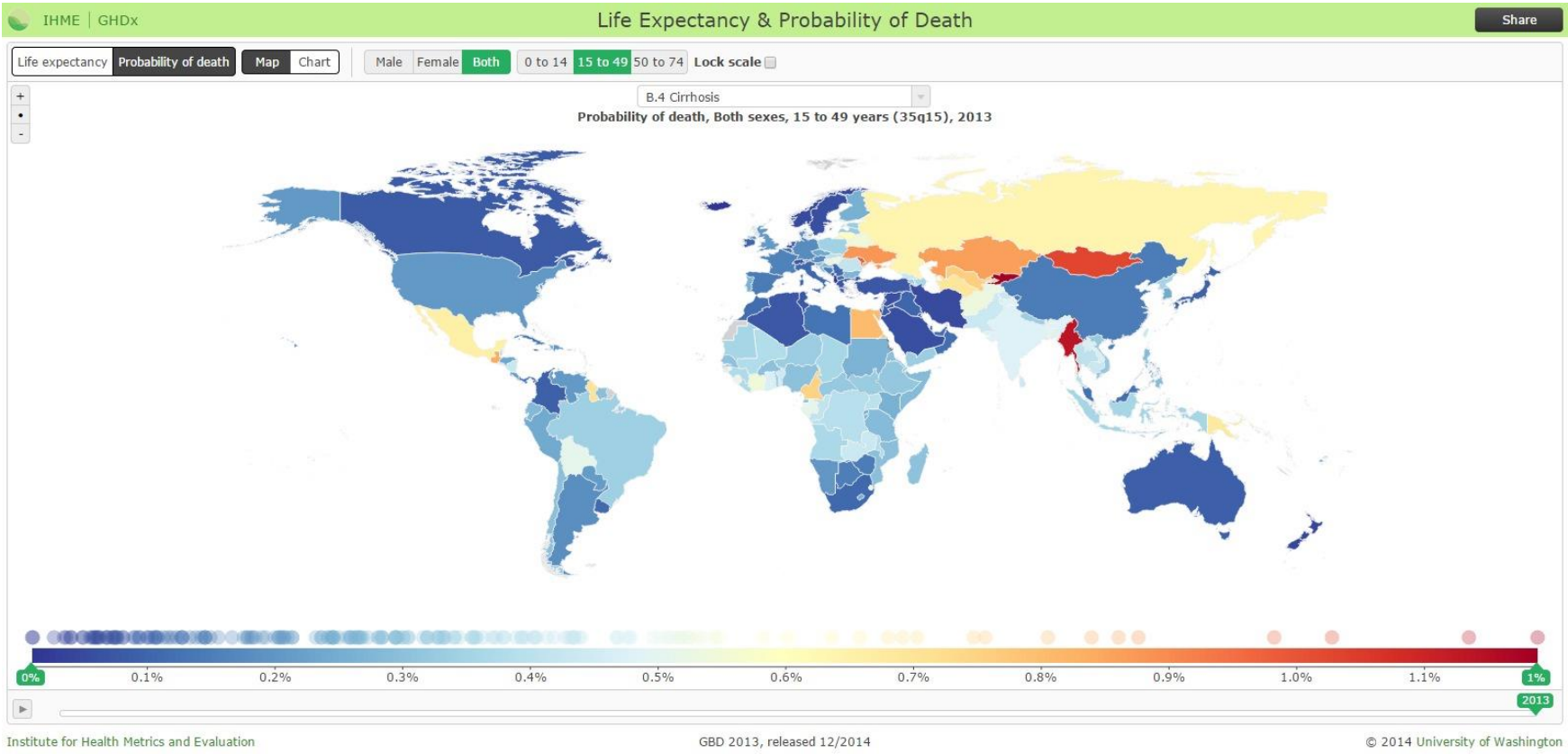
Epidemiology

The Epidemiology of Cirrhosis in the United States

- The prevalence of cirrhosis in the United States is approximately 0.27%, corresponding to 633,323 adults.
- Sixty-nine percent report that they were unaware of having liver disease.
- 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.
- Diabetes, alcohol abuse, hepatitis C and B, male sex, and older age are all independently associated with cirrhosis, with a population attributable fraction of 53.5% from viral hepatitis (mostly hepatitis C), diabetes, and alcohol abuse.
- Mortality is 26.4% per 2-year interval in cirrhosis compared with 8.4% in propensity-matched controls.
- Cirrhosis is the 12th leading cause of death in the United States.

aafp.org/afp/2011/1215/p1353.html ncbi.nlm.nih.gov/pubmed/25291348

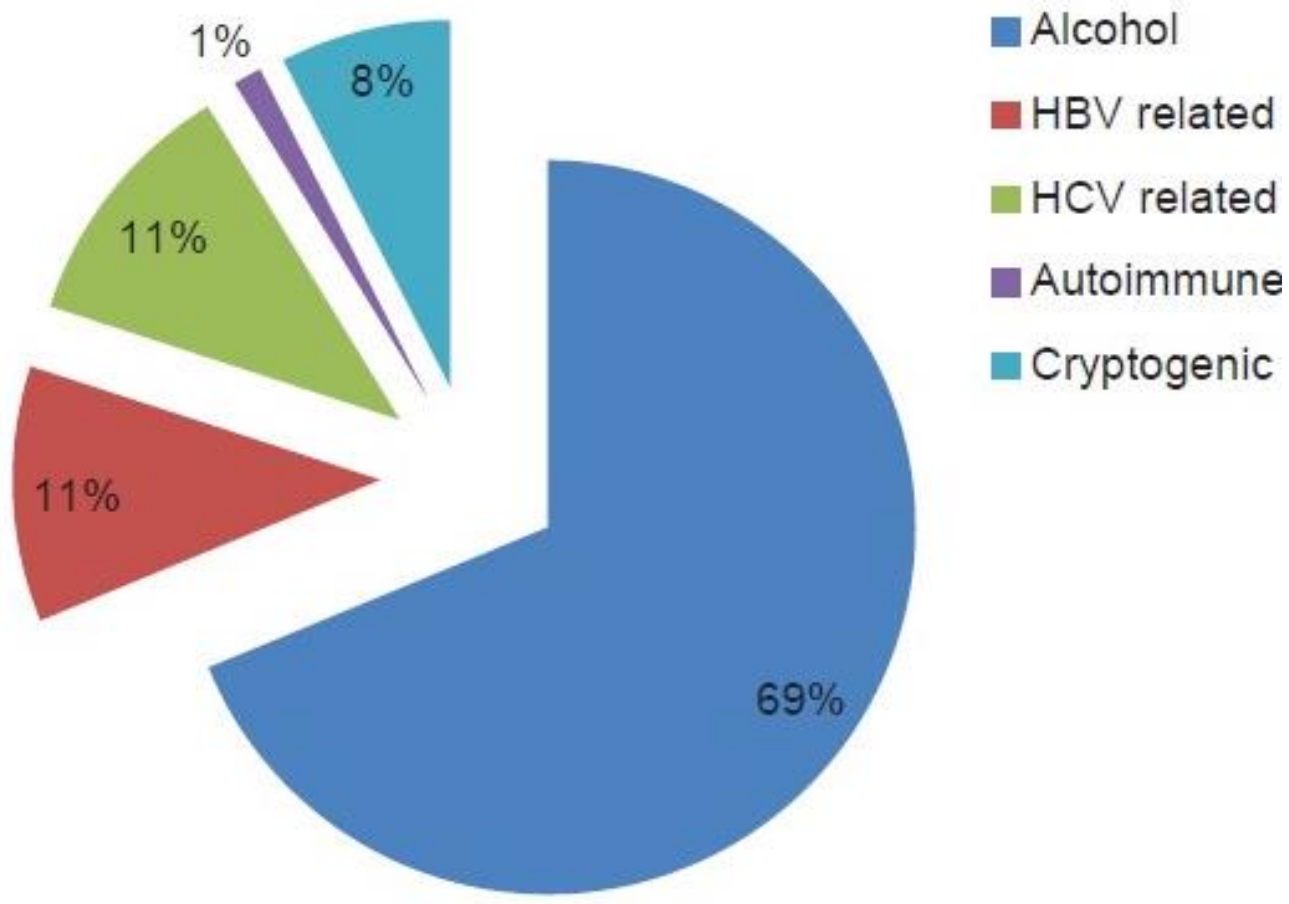
Epidemiology



Probability of death from cirrhosis among 15-49 year olds, 2013

humanosphere.org/science/2014/12/cirrhosis-its-not-just-for-heavy-drinkers-anymore/

Etiology



Etiological profile of cirrhosis of liver from North-East India.

oghr.org/articles/2015/4/1/images/OncGasHepRep_2015_4_1_8_139623_u1.jpg

Mechanisms

- Injury
- Degeneration
- Fibrosis
- Formation of fibro-vascular membranes
- Parenchymal dissection into nodules
- Rearrangement of blood circulation cirrhosis

meddean.luc.edu/lumen/MedED/orfpath/cirhosis.htm

History

- The clinical features of cirrhosis have been known since ancient times.
- The Ebbers papyrus written around 2600 BC describes ascites, which was known to be associated with a “hardness of the liver” and excessive alcohol consumption.

aafp.org/afp/2011/1215/p1353.html

Clinical investigation

- Cirrhosis is frequently indolent, asymptomatic and unsuspected until complications of liver disease present: a sizable proportion of these patients never come to clinical attention, and previously undiagnosed cirrhosis is still frequently found at autopsy.
- However, 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.

ncbi.nlm.nih.gov/pmc/articles/PMC2271178/

Clinical investigation

Portal hypertension

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).
- Dilated veins in the anterior abdominal wall.
- Splenomegaly.
- Encephalopathy or confusion and forgetfulness caused by poor liver function.
- Reduced levels of platelets, blood cells that help form blood clots, or white blood cells, the cells that fight infection.
- 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.

webmd.com/digestive-disorders/digestive-diseases-portalen.wikipedia.org/wiki/Portal_hypertension

Clinical investigation

Symptoms

- Decreased appetite
- Nose bleeds
- Jaundice (yellow discoloration)
- Small spider-shaped arteries underneath the skin
- Weight loss
- Anorexia
- Itchy skin
- Weakness
- Confusion and difficulty thinking clearly (hepatic encephalopathy)
- Abdominal swelling (ascites: free fluid in the peritoneal cavity)
- Swelling of the legs (edema)
- Impotence
- Gynecomastia (when males start to develop breast tissue)

healthline.com/health/cirrhosis#Symptoms4

Clinical investigation
Activity

Activity is assessed by extent of cell damage, inflammatory reaction within the scar tissue, piecemeal necrosis along fibrous septa, edema of the septa and changes in the parenchymal nodules such as necrosis and cholestasis.

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.

meddean.luc.edu/lumen/MedED/orfpath/cirhosis.htm

Complications

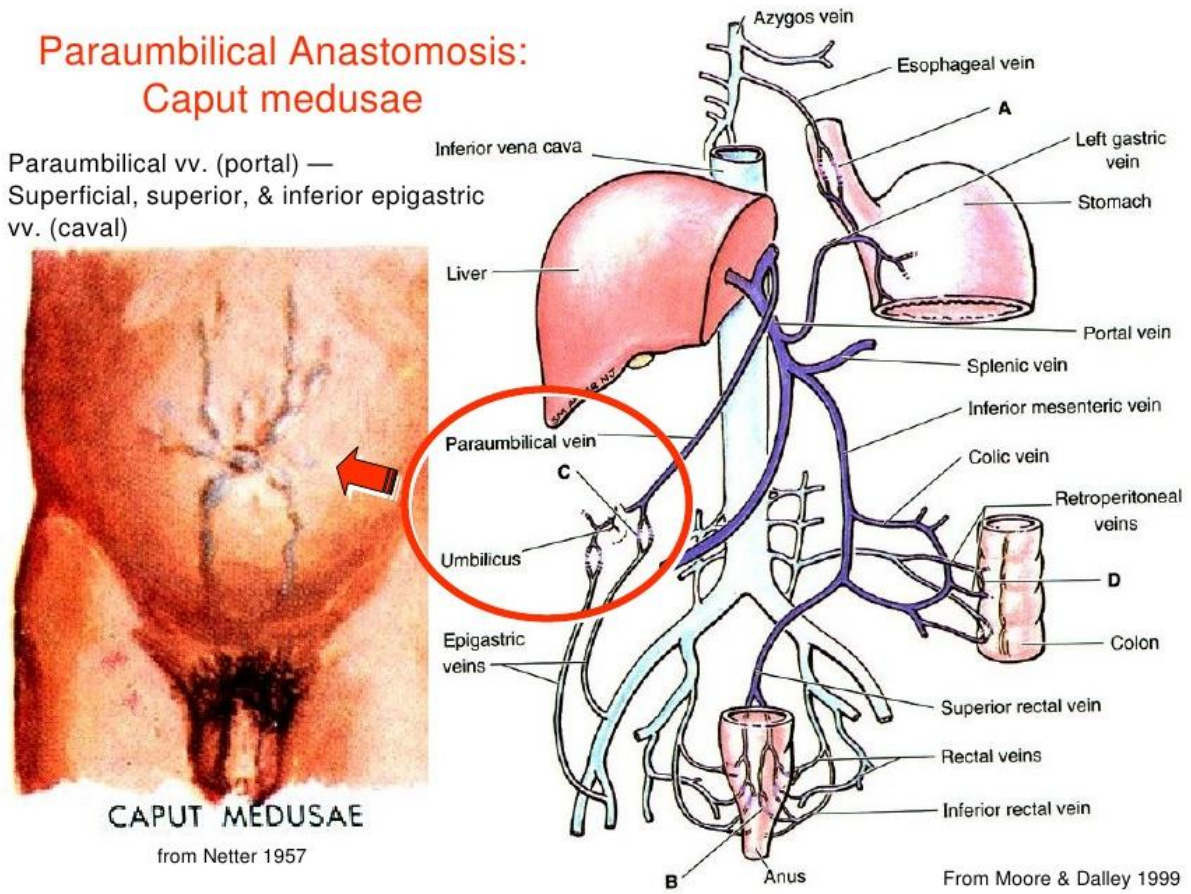
About one third of cirrhosis are compensated and, do not produce any clinical symptoms and are accidentally discovered during a medical examination or an operation or at autopsy. The rest are decompensated and produce complications mainly due to liver failure and portal hypertension.

- Edema and ascites.
- Varices (in the anterior abdominal wall, esophageal, hemorroidal).
- Portal Vein Thrombosis.
- Digestive Hemorrhages.
- Jaundice
- Hepatic encephalopathy (confusion due to the effects of blood toxins on the brain)
- Impaired Coagulation
- Anemia
- Infection
- Infarction Of Nodules
- Bruising (due to low platelet count and/or poor clotting)
- Bleeding (due to decreased clotting proteins)
- Sensitivity to medications (the liver processes medications in the body)
- Kidney failure
- Liver cancer
- Insulin resistance and type 2 diabetes
- Gallstones (interference with bile flow can cause bile to harden and form stones)
- Enlarged spleen (splenomegaly)

healthline.com/health/cirrhosis#Complications6meddean.luc.edu/lumen/MedED/orfpath/cirhosis.htm

Clinical investigation

Dilated veins in the anterior abdominal wall



Caput medusae or palm tree sign, is the appearance of distended and engorged superficial epigastric veins due to portal hypertension, which are seen radiating from the umbilicus across the abdomen.

image.slidesharecdn.com/portal-090805013712-phpapp01/95/portal-10-728.jpg?cb=1249436242 en.wikipedia.org/wiki/Caput_medusae

Clinical investigation
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.

en.wikipedia.org/wiki/Cirrhosis

Clinical investigation

West Haven Criteria Grading System of Hepatic Encephalopathy

GRADE	DESCRIPTION
1	Trivial lack of awareness; euphoria or anxiety; shortened attention span; impaired performance of addition or subtraction
2	Lethargy or apathy; minimal disorientation for time or place; subtle personality change; inappropriate behavior
3	Somnolence to semistupor, but responsive to verbal stimuli; confusion; gross disorientation
4	Coma (unresponsive to verbal or noxious stimuli)

aafp.org/afp/2011/1215/p1353.html

Clinical investigation

Liver Cirrhosis

Diagnosis

Diagnosis is made by assessing an individual's symptoms, physical exam, and medical history, in conjunction with blood tests, liver biopsy, and imaging.

Diagnosis

Laboratory testing

- Complete blood count.
- Liver disease–associated blood tests (e.g., aspartate aminotransferase [AST], alanine aminotransferase [ALT], bilirubin, alkaline phosphatase [ALP])
- Coagulation studies (prothrombin time [PT], partial thromboplastin time [PTT], international normalized ratio [INR]): Prolonged INR is suggestive of impaired hepatic synthetic function.
- Albumin: hypoalbuminemia is common (impaired hepatic synthetic function).
- Blood urea nitrogen, creatinine, and electrolytes.
- Arterial blood gas (ABG) and pH measurements.
- Hepatic and viral hepatitis serologies, particularly hepatitis B and C serologies.
- Antinuclear antibody, antimitochondrial antibody, antismooth muscle antibody.
- Iron indices.
- Alpha1-antitrypsin deficiency.
- Ceruloplasmin, 24-hour urinary copper: Consider this test only in individuals aged 3-40 years who have unexplained hepatic, neurologic, or psychiatric disease.

emedicine.medscape.com/article/182098-overview

Diagnosis

Liver chemistry test

Liver chemistry test	Clinical implication of abnormality
Alanine transaminase (ALT)	Hepatocellular damage
Aspartate transaminase (AST)	
Lactate dehydrogenase	
Bilirubin	Cholestasis
Alkaline phosphatase	
Gamma-glutamyl transpeptidase (GGT)	
Bile acids	
Prothrombin time	Impaired synthetic function
Albumin (ALB)	

en.wikipedia.org/wiki/Hepatitis

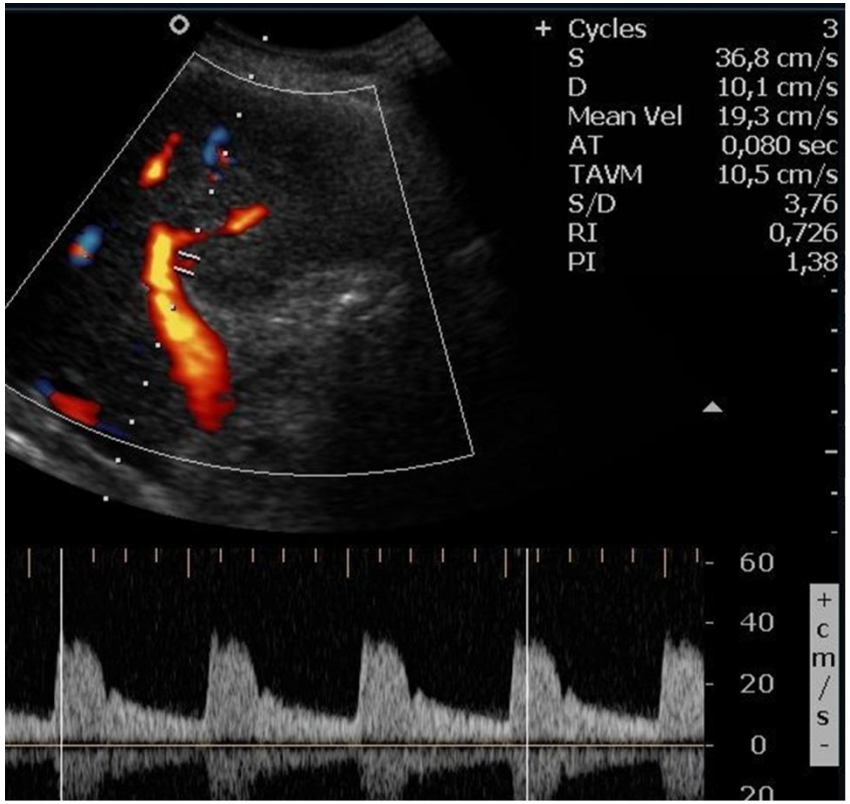
Diagnosis

Instrumental tests

- Upper endoscopy (to see if esophageal varices are present)
- Ultrasound scan of the liver
- MRI of the abdomen
- CT scan of the abdomen
- Liver biopsy (the definitive test for cirrhosis)

Diagnosis

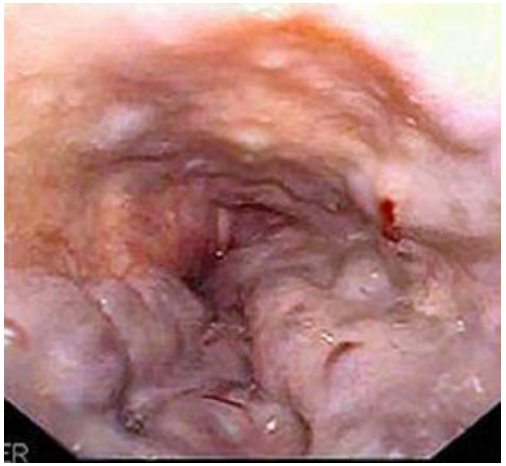
Imaging studies



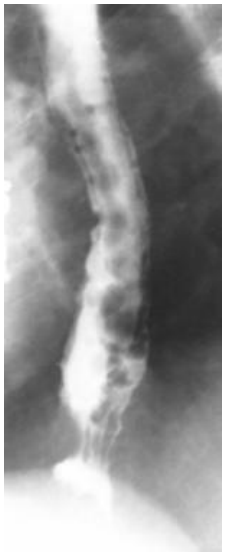
- Duplex Doppler ultrasonography of the liver and upper abdomen
- Computed tomography (CT) scanning and/or magnetic resonance imaging (MRI): Can be used when ultrasonographic findings are inconclusive
- Bleeding scan or angiography: Used when bleeding is obscure and the source is unclear

intechopen.com/source/html/18256/media/image35.jpg emedicine.medscape.com/article/182098-overview

Diagnosis
Procedures



Large esophageal varices with red wale signs seen on endoscopy.



Uphill esophageal varices. Barium swallow demonstrates multiple serpiginous filling defects primarily involving the lower one third of the esophagus with striking prominence around the gastroesophageal junction. The patient had cirrhosis secondary to alcohol abuse.

- 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.

emedicine.medscape.com/article/182098-overview

Diagnosis

Liver biopsy

- Biopsy is considered the gold standard for diagnosis of cirrhosis, and sequential histological grading of inflammation and staging of fibrosis can assess risk of progression.
- A liver biopsy is obtained by either a (radiographically-guided) percutaneous, a transjugular or laparoscopical route.
- A greater risk of bleeding following a biopsy has been observed with larger-diameter needles.
- In suspected cirrhosis a cutting is preferred over a suction needle, in order to prevent tissue fragmentation.
- Aspirin and other anti-platelet agents should be stopped at least a week before biopsy.

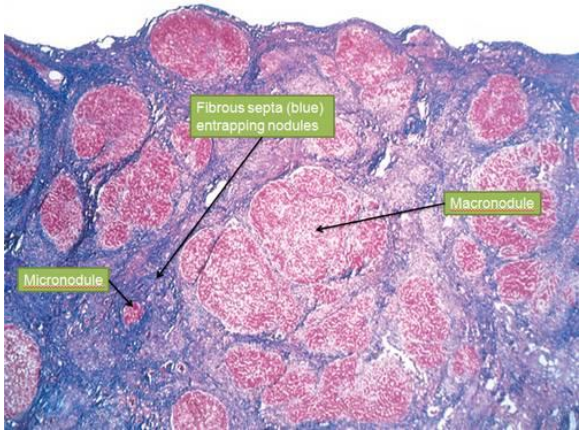
ncbi.nlm.nih.gov/pmc/articles/PMC2271178/

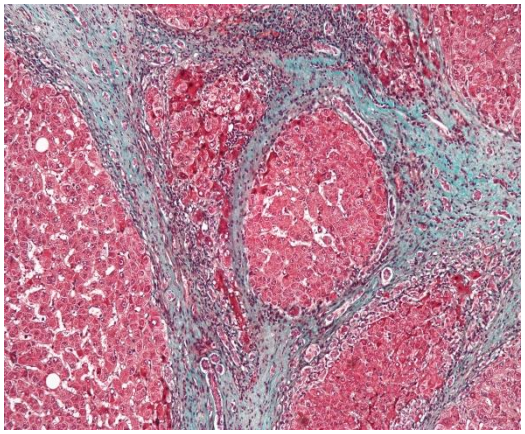
Clinical investigation

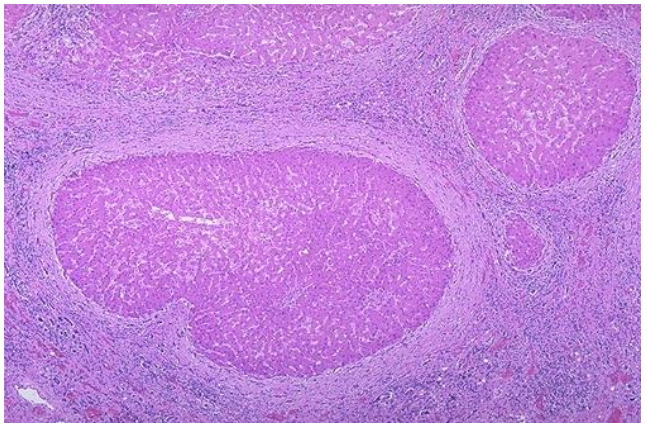
Laparoscopy of Cirrhosis and Liver Biopsies

Diagnosis

The histopathologic features







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

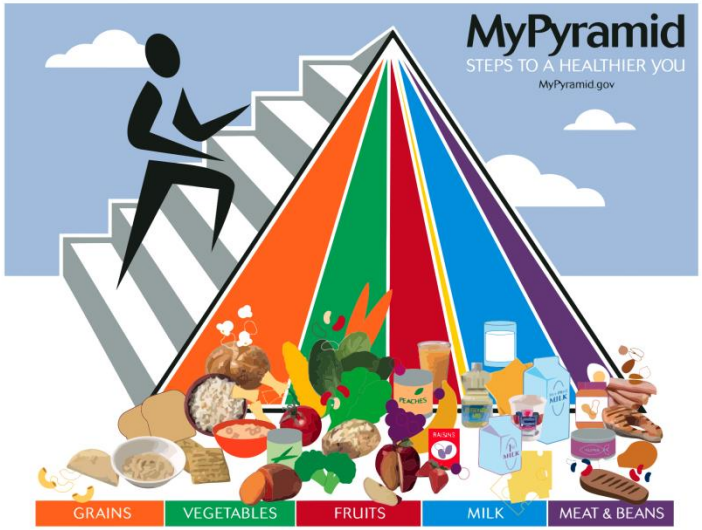
High magnification micrograph of a liver with cirrhosis.

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

library.med.utah.edu/WebPath/jpeg4/LIVER014.jpg meddean.luc.edu/lumen/MedED/orfpath/cirhosis.htm

Treatment

Lifestyle modifications



MyPyramid

- Lifestyle modifications are strongly recommended for patients with chronic hepatitis.
- Management of patients with liver cirrhosis and ascites but without hemorrhage includes a low-sodium diet and diuretics.

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Treatment

- Treatment for cirrhosis varies based on what caused it and how far the disorder has progressed.
- There is evidence that causal treatment may even reverse cirrhosis, although in some of the reports sampling variability cannot be excluded.

ncbi.nlm.nih.gov/pmc/articles/PMC2271178/

Treatment

Medications and other approaches

- Beta blockers or nitrates (for portal hypertension).
- Quitting drinking (if the cirrhosis is caused by alcohol).
- Often diuretics, antibiotics, laxatives and/or enemas, thiamine and occasionally steroids, acetylcysteine and pentoxifylline.
- Lactulose and a low protein diet (to treat encephalopathy).
- Banding procedures (used to control bleeding from esophageal varices).
- Hemodialysis (to purify the blood of those in kidney failure).
- Liver transplantation is an option of last resort, when other treatments fail.

Treatment

Variceal bleeding

PREVENTION	TREATMENT
Non selective beta blockers **Variceal band ligation**	Acute: Resuscitation Vasocontrictors Sclerotherapy Band Ligation TIPSS Surgical Shunts
	Chronic: Variceal obliteration TIPS Surgical Shunts

ncbi.nlm.nih.gov/pmc/articles/PMC2271178/

Treatment

Ascites

PREVENTION	TREATMENT
Low Na diet	Low Na diet Diuretics Large volume paracentesis TIPSS (transjugular intrahepatic porto-systemic shunt) (LeVeen / Denver shunts)

ncbi.nlm.nih.gov/pmc/articles/PMC2271178/

Treatment

Renal failure

PREVENTION	TREATMENT
Avoid hypovolemia	Discontinue diuretics Rehydration Albumin infusion *Hepatorenal syndrome* Add Terlipressin or Midodrine (Noradrenaline) and Somatostatin (Octreotide)

ncbi.nlm.nih.gov/pmc/articles/PMC2271178/

Treatment

Spontaneous bacterial peritonitis

PREVENTION	TREATMENT
Treat ascites	Early diagnosic paracentesis: Neutrophils >250/cc → antibiotics iv Secondary prophlaxis with a po antibiotic such as Levofloxacin

ncbi.nlm.nih.gov/pmc/articles/PMC2271178/

Treatment

Encephalopathy

PREVENTION	TREATMENT
Avoid precipitants	Treat precipitating factors: Infection Bleeding Electrolyte imbalance Sedatives High protein intake

ncbi.nlm.nih.gov/pmc/articles/PMC2271178/

Treatment
Palliative care

- Palliative care is specialized medical care that focuses on providing patients with relief from the symptoms, pain, and stress of a serious illness, such as cirrhosis.
- 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.
- Especially in the later stages, people with cirrhosis experience significant symptoms such as abdominal swelling, itching, leg edema, and chronic abdominal pain which would be amenable for treatment through palliative care.
- Despite proven benefit, people with cirrhosis are rarely referred to palliative care.

Prognosis

- Prognosis depends heavily on the cirrhosis or complications that are causing the symptoms.
- Serious complication of chronic hepatitis is liver cancer, specifically hepatocellular carcinoma.
- Some cases can require a liver transplant.

Prophylaxis

- Daily limit of one or two drinks and avoid drinking every day.
- Avoid uncooked shellfish.
- Never mix alcohol and drugs.
- Avoid exposure to industrial chemicals, which can enter the bloodstream and cause liver damage.
- Maintain a healthy, balanced diet.
- Avoid contracting viral hepatitis.
- Hepatitis B vaccinations and immune serum globulin shots.
- Nonselective beta-blockers (e.g., propranolol, nadolol, carvedilol).
- Vasodilators (e.g., isosorbide mononitrate [ISMN])
- Combination pharmacotherapy when a single agent fails.

webmd.com/digestive-disorders/understanding-cirrhosis-prevention

Clinical cases, 1

A case of breast cancer in a male patient with cryptogenic cirrhosis.

Breast cancer is a rare disease in men.

Shin SR with colleagues (Departments of Internal Medicine and Pathology, Hallym University Kangnam Sacred Heart Hospital, Seoul, Korea) report a case of 53-year-old obese male, with known cryptogenic cirrhosis and hepatocellular carcinoma, presenting a tender mass on left breast.

He was diagnosed with invasive intraductal carcinoma, which was consistent with a sporadic lesion.

On the basis of previous literatures, obesity can be regarded as a cause for breast cancer even in men.

However, there has been inconsistent data about link between liver cirrhosis and male breast cancer, which can be due to heterogenity in the etiology of cirrhosis.

Through this case, it can be postulated that the risk for male breast cancer may vary according to the etiology of cirrhosis.

dgcases.docguide.com/case-breast-cancer-male-patient-cryptogenic-cirrhosis

Clinical cases, 2

A case of variceal bleeding from the jejunum in liver cirrhosis.

While esophagogastric varices are common manifestations of portal hypertension, variceal bleeding from the jejunum is a rare complication of liver cirrhosis. In addition, ectopic variceal bleeding occurs in the duodenum and at sites of previous bowel surgery in most cases, including of stomas.

Park CW with colleagues (Department of Internal Medicine, Eulji University Hospital, Eulji University College of Medicine, Daejeon, Korea) report a case of obscure overt gastrointestinal bleeding from jejunal varices in a 55-year-old woman who had not previously undergone abdominal surgery, who had liver cirrhosis induced by the hepatitis C virus. Emergency endoscopy revealed the presence of esophageal varices without stigmata of recent bleeding, and no bleeding focus was found at colonoscopy. She continued to produce recurrent melena with hematochezia and received up to 21 units of packed red blood cells. CT angiography revealed the presence of jejunal varices, but no active bleeding was found. Capsule endoscopy revealed fresh blood in the jejunum. The patient submitted to embolization of the jejunal varices via the portal vein, after which she had a stable hemoglobin level and no recurrence of the melena.

Clinical cases, 3a

How can we treat a patient with liver cirrhosis (hepatitis C virus), hepatocellular carcinoma, and synchronous colon cancer?

A 46-year-old man, diagnosed incidentally during an ultrasound (US) examination with a 3.5-cm HCC in segment VII related to chronic hepatitis C virus (HCV), was referred for liver resection. He underwent a laparoscopic protocol evaluation for liver cirrhosis. Liver appearance and biopsy of the left lobe showed Child B/C liver cirrhosis. Because he fulfilled the Milan criteria, was suggested an orthotopic liver transplantation (OLT). During protocol colonoscopy, was discovered an ulcerative sigmoid colon Ca. Three weeks after completing the pre-OLT assessment he underwent an OLT and was discharged home on day 9 on an immunosuppressive regimen of Everolimus, Myfortic, and Prezolone. After transplantation, the patient underwent a sigmoidectomy and for month thereafter received chemotherapy for colon Ca (6 cycles of FOLFOX:Folinic Acid+Fluorouracil+Oxaliplatin).

Clinical cases, 3b

How can we treat a patient with liver cirrhosis (hepatitis C virus), hepatocellular carcinoma, and synchronous colon cancer?

One and a half years after OLT, patient was in good condition but presented with an increased alpha fetoprotein (a-FP) without other findings. A couple of months later we discovered a colon Ca recurrence and 3 small liver metastases. Patient underwent a bowel resection with Hartmann's procedure. Almost immediately after the last operation, he was found to suffer multiple myeloma. He underwent chemotherapy for both malignancies with good responses, but a few months later died of severe sepsis.

dgcases.docguide.com/how-can-we-treat-patient-liver-cirrhosis-hepatitis-c-virus-hepatocellular-carcinoma-and-synchronous

Clinical cases, 5

Liver transplantation followed by pulmonary resection complicated with end-stage liver cirrhosis: a case report.

With the recent popularization of living-donor liver transplantation (LDLT), it has become important to provide treatment for comorbidities in recipients. Taniguchi D (Anticancer Res.. 2015 Jun:35(6):3411-4.) report the case of a patient who was successfully treated with LDLT, followed by left upper lobectomy for lung cancer concomitant with decompensated liver cirrhosis. A 67-year-old female was admitted for treatment for severe liver cirrhosis. The lung cancer was identified preoperatively using computed tomography. The patient was discharged postoperatively on day 39 without complication. Three months after LDLT, was performed a left upper lobectomy. The patient's postoperative course was uneventful and she was discharged after 11 days. So, an aggressive and appropriate surgical strategy, including LDLT, is an effective curative treatment in patients with controllable malignancy, concomitant with severe liver dysfunction.

Clinical investigation

Endstage liver disease patient

Diagnostic and treatment guidelines

- Cirrhosis: Diagnosis, Management, and Prevention
- Liver Cirrhosis