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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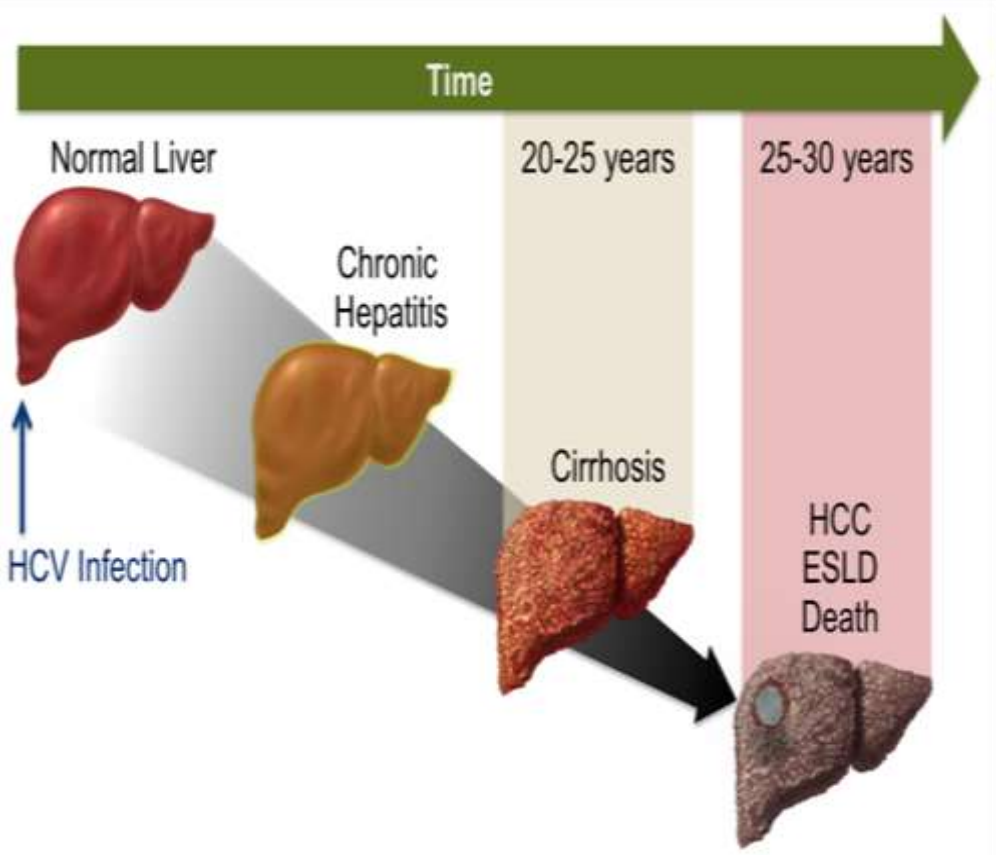
Plan of the Lecture



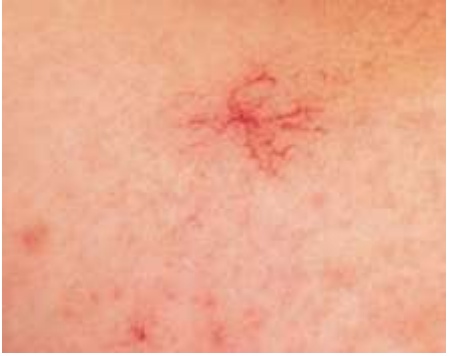
- Definition
- Epidemiology
- Risk Factors and Etiology
- Mechanisms
- Classification
- Clinical presentation
- Diagnosis
- Treatment
- Prognosis
- Prophylaxis
- Abbreviations
- Diagnostic guidelines

http://www.hepatitisc.uw.edu/process.php?action=getDoc&ID=33&name.jpg

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.

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



USMLE TEST

A 62-year-old white male presents to a primary care doctor with concern for weight gain, abdominal distension, and breast enlargement. Physical exam reveals an overweight male with bilateral gynecomastia and a distended abdomen with evidence of shifting dullness and several skin lesions as demonstrated in Image. The patient has a past medical history of recurrent gout and Wernicke encephalopathy. Which aspect of the patient's history would reveal the most-likely underlying cause of the patient's chief complaints?

1. Surgical history revealing a blood transfusion in 1984, 2. Travel history revealing time spent 20 years ago in South America, 3. Review of systems revealing constant headaches and nausea that are worse upon waking, 4. Social history revealing alcohol abuse, 5. Medical history revealing arthritis self-treated with large quantities of acetaminophen.

https://wire.ama-assn.org/education/usmle-step-2-prep-next-best-step-hypertension-and-shortness-breath

USMLE TEST

The correct answer is 4: This patient's presentation is consistent with cirrhosis, for which the most likely cause in this patient is alcohol abuse.
Incorrect answers:
1: History of a blood transfusion in 1984 puts a patient at risk for HIV and hepatitis C transmission. HIV is not a major cause of cirrhosis. Hepatitis C is less likely a cause in this patient with their history of gout and Wernicke's encephalopathy - two pathologies that are exacerbated by alcohol., 2: Such a travel history may have exposed the patient to schistosomiasis (among other possible infections), a parasite that resides in the host's liver, but is a rare cause of cirrhosis., 3: Constant morning headaches and nausea are concerning for increased intracranial pressure. This is not associated with nor a cause of cirrhosis., 5: Large doses of acetaminophen can result in acute hepatic failure, but are unlikely to cause chronic liver disease leading to cirrhosis.

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Epidemiology 1

- 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

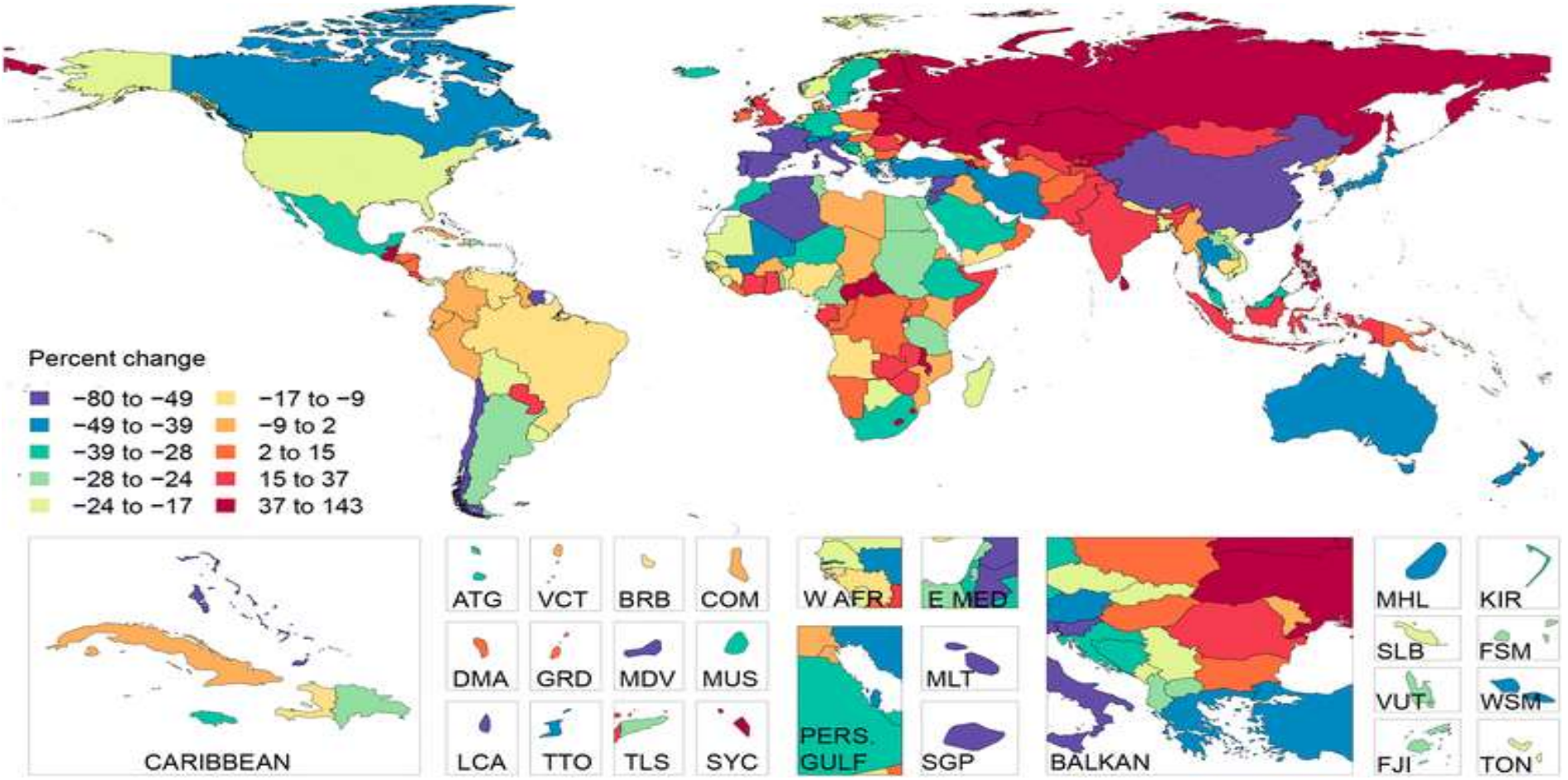
http://emedicine.medscape.com/article/185856-overview#a3

Epidemiology 2

- 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.

http://emedicine.medscape.com/article/185856-overview#a3

Epidemiology



Liver cirrhosis mortality in 187 countries between 1980 and 2010: a systematic analysis.

https://static-content.springer.com/esm/art%3A10.1186%2Fs12916-014-0145-y/MediaObjects/12916_2014_145_MOESM15_ESM.gif

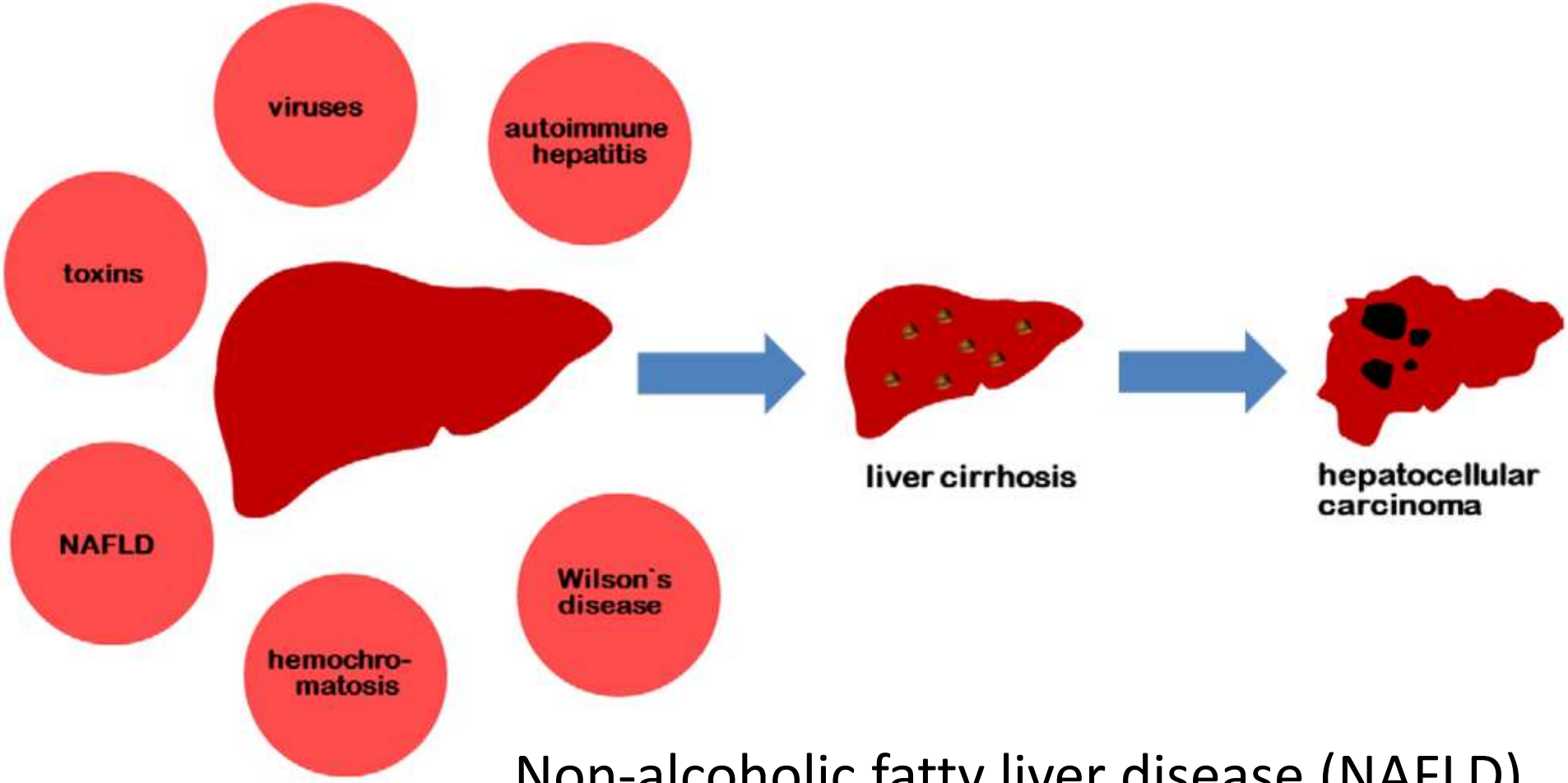
Risk Factors and Etiology 1

- 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)

Risk Factors and Etiology 2

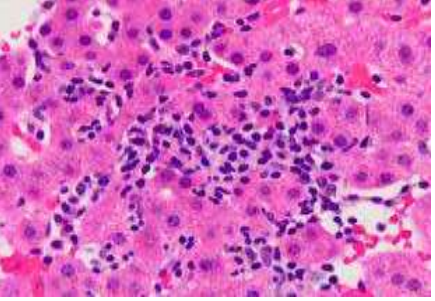
- Type IV glycogen storage disease
- Drug-induced liver disease (methotrexate, amiodarone, etc.)
- Venous outflow obstruction (Budd-Chiari syndrome, etc.)
- Congestive heart failure
- Male sex, age >50, regular (moderate) alcohol consumption.

Risk Factors and Etiology



Non-alcoholic fatty liver disease (NAFLD).

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



USMLE TEST

A 42-year-old female presents with yellowing of the skin. She also reports that her urine has been darker than normal and her stools have been lighter than normal. Vital signs are stable. Physical examination reveals hepatosplenomegaly. Initial labs are notable for increased conjugated bilirubin, increased cholesterol, and increased alkaline phosphatase. If this patient's symptoms are due to an autoimmune reaction leading to lymphocytic infitration of and granulmonatous proliferation along the biliary track, which of the following additional labs would likely be positive?

1. Antimitochondrial antibodies
2. Antiendomysial antibodies
3. Anti-Jo-1 antibodies
4. Antihistone antibodies
5. Anticentromere antibodies

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USMLE TEST

The correct answer is 1: This patient's presentation is consistent with primary biliary cirrhosis. Elevated antimitochondrial antibodies may also be found in this disease.

Incorrect answers:
2: Antiendomysial antibodies are found in Celiac disease.
3: Anti-Jo-1 antibodies are found in polymyositis and dermatomyositis.
4: Antihistone antibodies are found in drug-induced lupus.
5: Anticentromere antibodies are found in scleroderma (CREST)

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Mechanism 1

- 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 hepatocytes contribute to pathogenesis of cirrhosis

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

Mechanism 2

- 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
- At the molecular level, many cytokines are involved in mediation of signaling pathways that regulate activation of HSCs and fibrogenesis

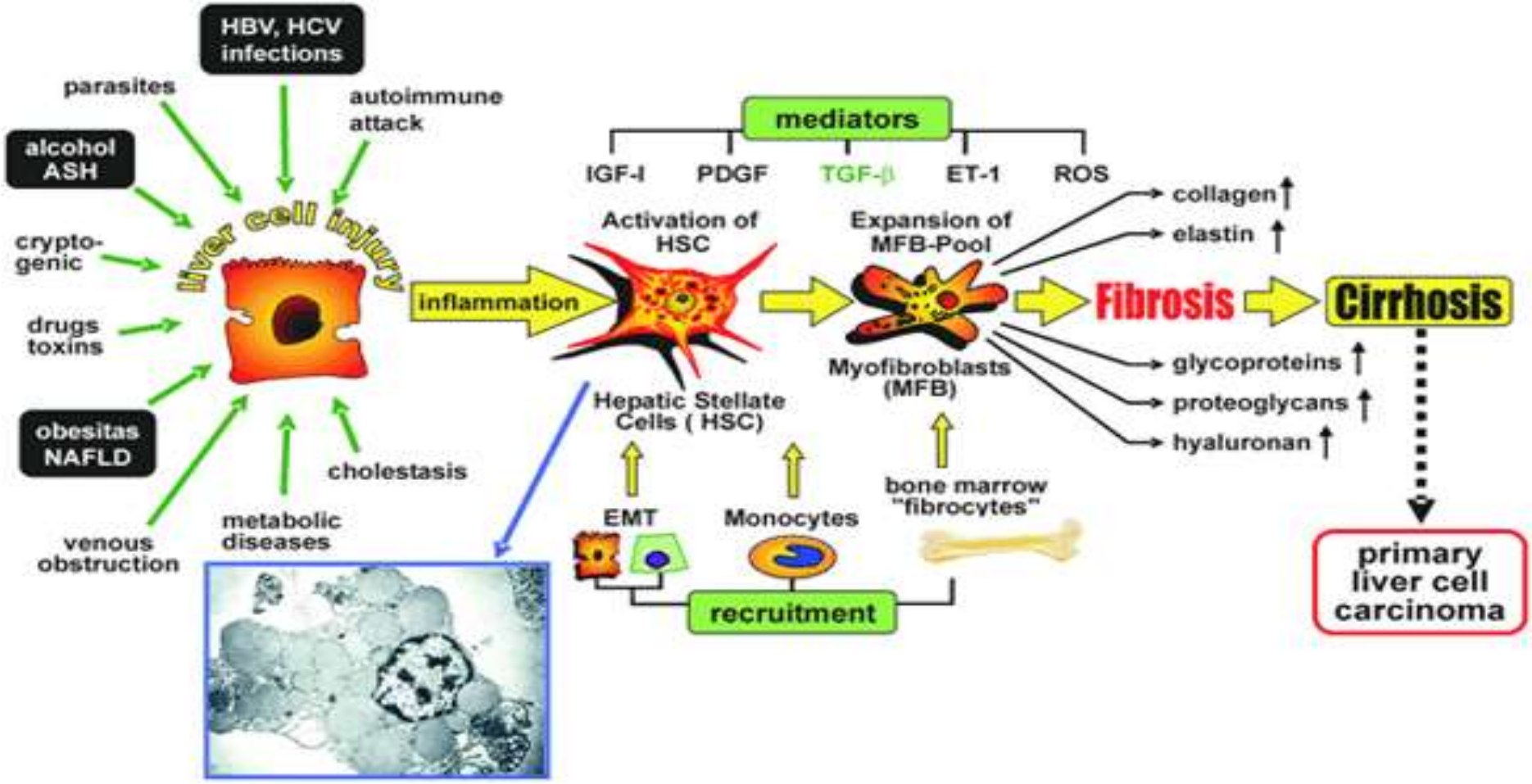
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4064077/

Mechanism 3

- 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.

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

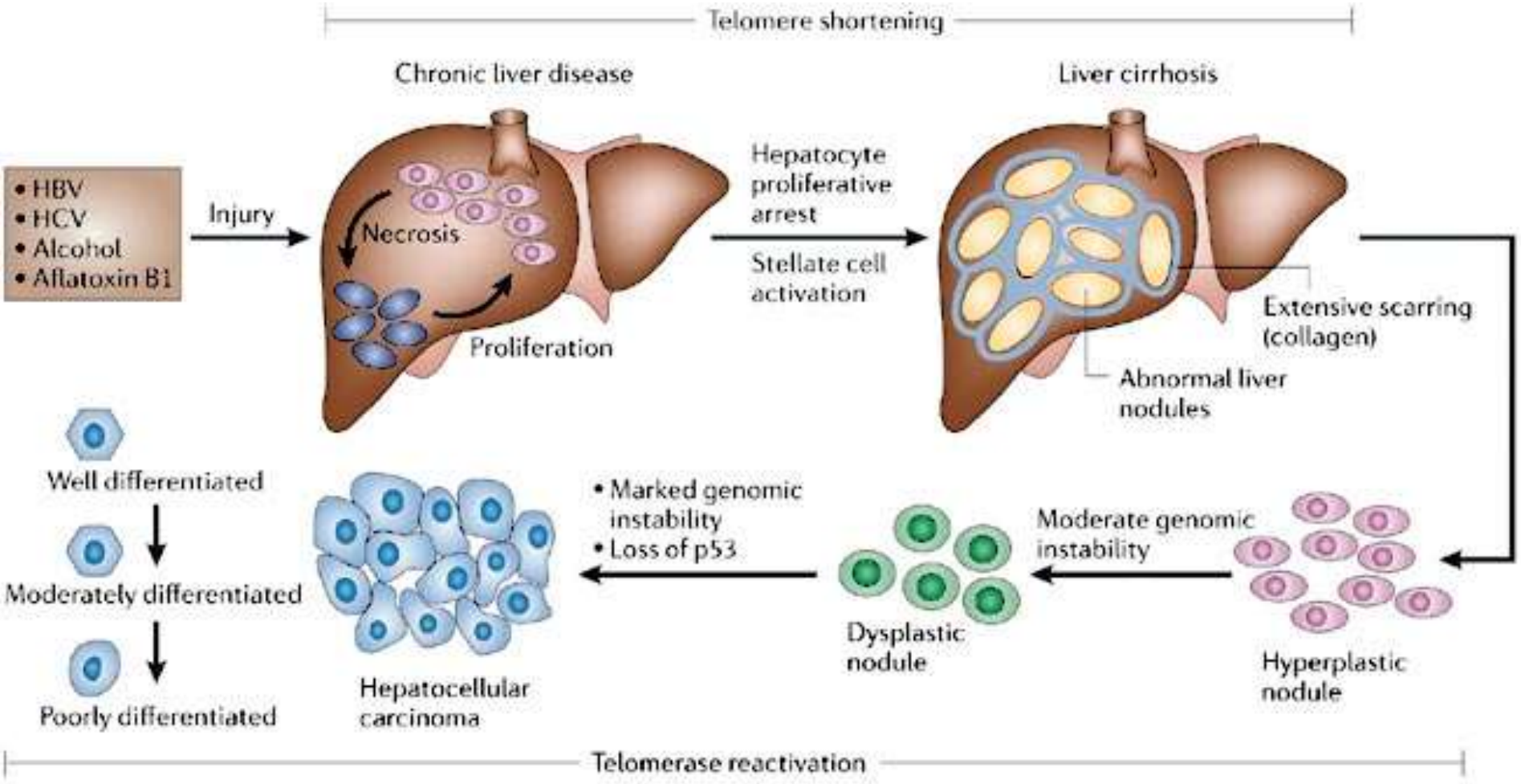
Mechanism



Formal pathogenesis of liver fibrogenesis.

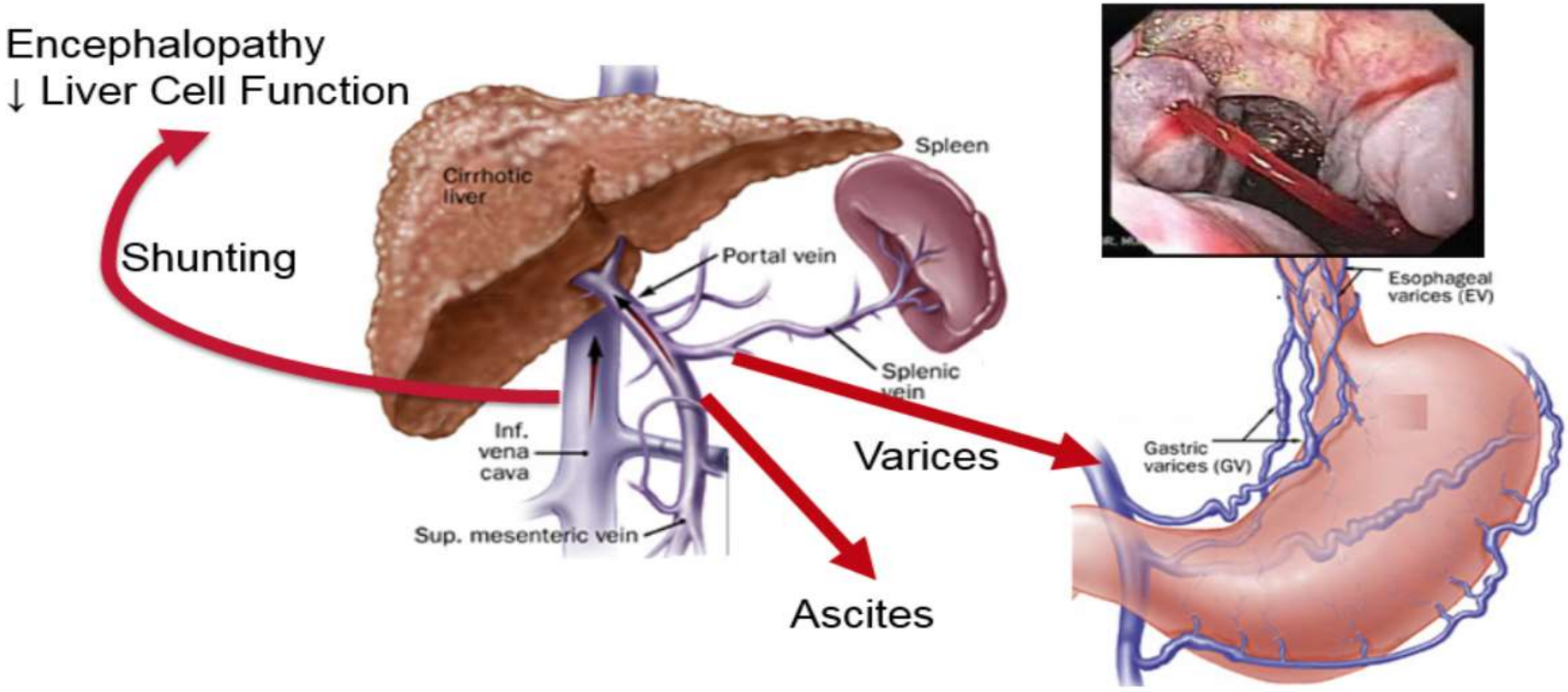
http://www.medscape.com/viewarticle/573027

Mechanism



http://www.nature.com/nrc/journal/v6/n9/images/nrc1934-f2.jpg

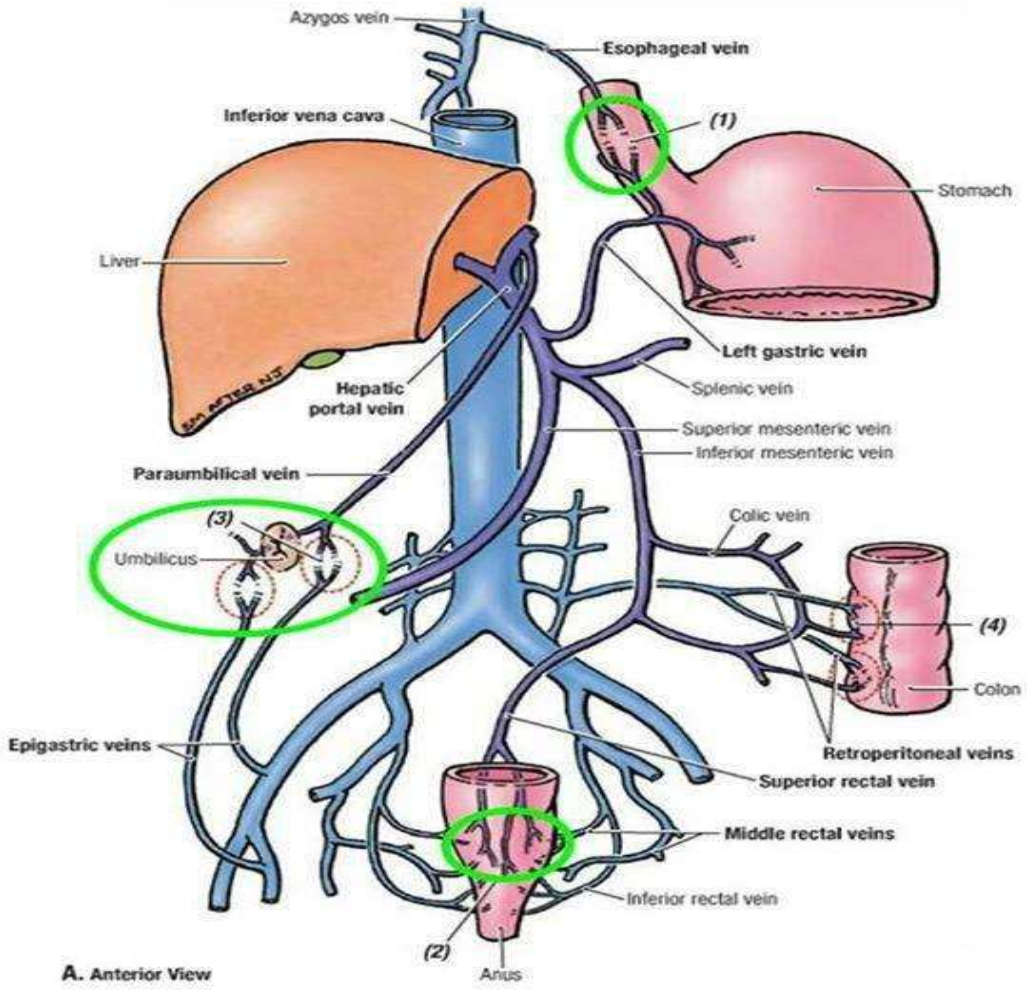
Mechanism



Portal hypertension.

http://perspectives.galectintherapeutics.com/wp-content/uploads/2016/02/Screen-Shot-2016-02-22-at-8.07.39-AM.png

Mechanism



Portosystemic anastomosis.

http://images.slideplayer.com/20/6056890/slides/slide_67.jpg

USMLE TEST

A 47-year-old woman with scleroderma is referred to the emergency department by her primary care physician. She had presented to him earlier that morning complaining of 2 weeks of fatigue and smelly, fatty bowel movements, as well as yellowing of her skin. She also notes intermittent abdominal cramping that worsens with meals. Preliminary labs reveal a total bilirubin of 4.2 mg/dL, direct 3.8 mg/dL and indirect 0.4 mg/dL. The alkaline phosphatase is elevated at 280 IU/L. She tells you she read about a liver disease that may be related to her scleroderma. Which of the following is the best initial method to address this woman's concern?

1. Serologic tests for presence of autoantibody, 2. Ultrasonography
3. Blood smear, 4. Computed tomography, 5. Biopsy.

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USMLE TEST

The correct answer is 2: In this patient with a conjugated hyperbilirubinemia and elevated alkaline phosphatase, a right upper quadrant ultrasound is the diagnostic modality of choice in distinguishing between intra- and extrahepatic biliary obstruction.

Incorrect answers:

1: If one has strong suspicion for primary biliary cirrhosis (PBC), several antibody tests can be useful. However, one must first determine if there is evidence of biliary obstruction and where the obstruction is located, using ultrasound, 3: A blood smear can be useful in patients with hyperbilirubinemia due to hemolysis, 4: A CT may be helpful in diagnosing an obstructive malignancy, but is generally reserved for use after the right upper quadrant ultrasound, 5: A biopsy is necessary for the diagnosis of PBC. However, one must first determine if there is evidence of biliary obstruction on imaging and where the obstruction is located.

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Classification

International Classification of Diseases

XI Diseases of the digestive

K70.3Alcoholic cirrhosis of liver

K71.7Toxic liver disease with fibrosis and cirrhosis of liver

K74 Fibrosis and cirrhosis of liver

K74.3Primary biliary cirrhosis

K74.4Secondary biliary cirrhosis

K74.5Biliary cirrhosis, unspecified

K74.6Other and unspecified cirrhosis of liver.

https://www.tsoshop.co.uk/productimages/default.aspx?ISBN=9789241549165&FORMAT=3 http://apps.who.int/classifications/icd10/browse/2016/en#/XI

Classification

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

- 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

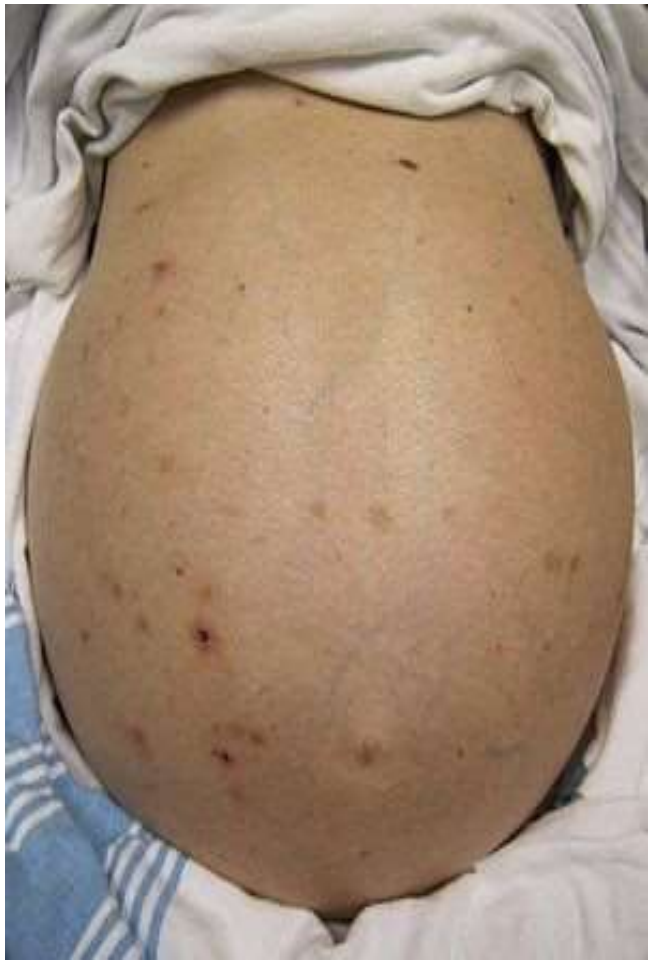
Child-Turcotte-Pugh Classification for Severity of Cirrhosis			
Clinical and Lab Criterias	**Points***		
	1	2	3
Encephalopathy	None	Mild to moderate (grade 1 or 2)	Severe (grade 3 or 4)
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/dL)	> 3.5	2.8-3.5	<2.8
Prothrombin time Seconds prolonged International normalized ratio	 <4 <1.7	 4-6 1.7-2.3	 >6 >2.3

***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)

http://depts.washington.edu/hepstudy/definitions/uploads/18/Child_Pugh_Turcotte.png

Symptoms 1

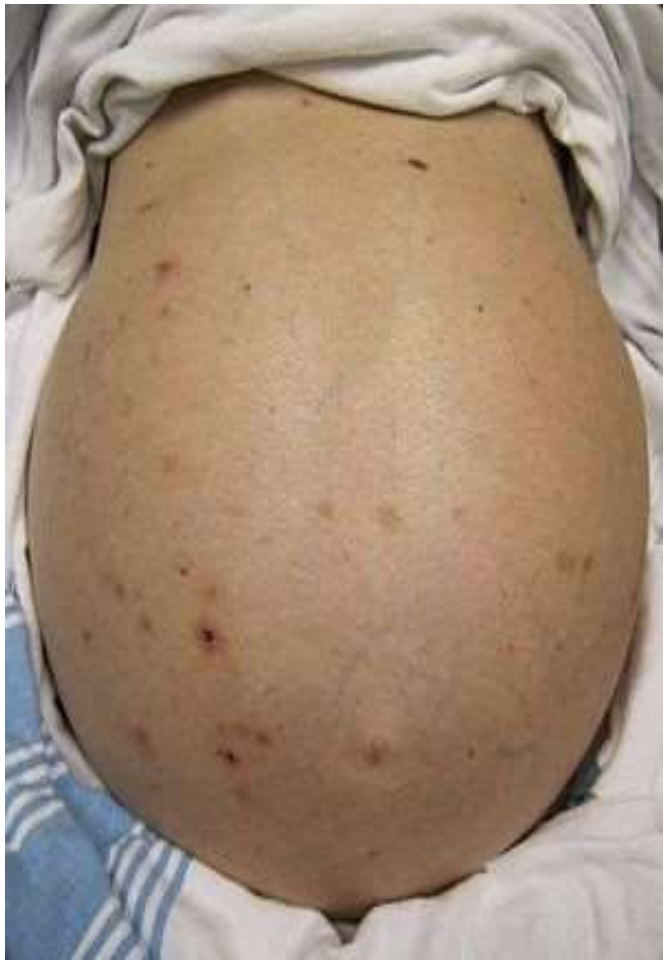
- Decreased appetite
- Edema
- Ascites
- Easy bruising
- Poor concentration and memory
- Bleeding esophageal varices
- Spontaneous bacterial peritonitis
- Weight loss



https://en.wikipedia.org/wiki/Cirrhosis healthline.com/health/cirrhosis#Symptoms4 patient.info/doctor/cirrhosis-pro

Symptoms 2

- Anorexia
- Weakness
- Impotence
- Gynecomastia.



https://en.wikipedia.org/wiki/Cirrhosis healthline.com/health/cirrhosis#Symptoms4 patient.info/doctor/cirrhosis-pro

USMLE TEST

A 32-year-old female with a history of scleroderma presents with 6 months of worsening daytime somnolence, right upper quadrant discomfort, and pruritis. Lab tests reveal an elevation of alkaline phosphatase and positive anti-mitochondrial antibody. Which of the following liver biopsy descriptions confirms the suspected diagnosis?
1. Hepatocyte swelling and necrosis with macrovesicular fat, Mallory bodies, and neutrophilic infiltration, 2. Periductal portal tract fibrosis and segmental stenosis of extrahepatic and intrahepatic bile ducts 3. Centrilobular necrosis, 4. Non-suppurative destructive cholangitis and destruction of inter-lobular bile ducts, 5. Lobular disarray, ballooning degeneration, numerous apoptotic bodies, Kupffer cell activation, and lymphocyte-predominant lobular and portal inflammation.

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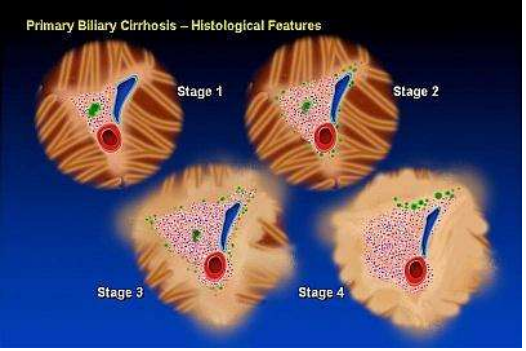
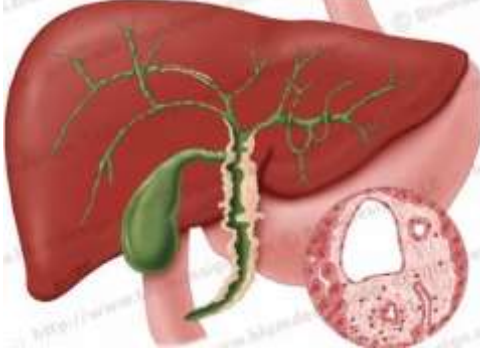


USMLE TEST



The correct answer is 4: The patient description is characteristic of primary biliary cirrhosis (PBC). Non-suppurative destructive cholangitis and progressive loss of intrahepatic bile ducts are the hallmark of PBC.

Incorrect answers:

1: This description is characteristic of alcohol-related hepatitis or nonalcoholic fatty liver disease.

2: This description is characteristic of primary sclerosing cholangitis.

3: This description is characteristic of acute acetominophen toxicity.

5: This description is characteristic of chronic hepatitis B.

https://wire.ama-assn.org/education/usmle-step-2-prep-next-best-step-hypertension-and-shortness-breath

Signs

Cutaneous Features 1

- 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

Signs

Cutaneous Features 2

- Hair loss
- White nails (sign of hypoalbuminemia)
- Finger clubbing
- Dupuytren's contracture.

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 1

- 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)

webmd.com/digestive-disorders/digestive-diseases-portalen.wikipedia.org/wiki/Portal_hypertension patient.info/doctor/cirrhosis-pro

Signs
Portal Hypertension 2

- 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.

ncbi.nlm.nih.gov/pmc/articles/PMC2271178/ patient.info/doctor/cirrhosis-pro

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.

meddean.luc.edu/lumen/MedED/orfpath/cirhosis.htm ncbi.nlm.nih.gov/pmc/articles/PMC2271178/ patient.info/doctor/cirrhosis-pro

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

USMLE TEST

A 46-year-old woman presents to her primary care provider for itching. She has dry skin but. The patient endorses fatigue and dull abdominal pain. Her past medical history includes Hashimoto's thyroiditis and osteoarthritis. She takes levothyroxine and ibuprofen for pain in her knees. The patient drinks 2-3 beers per week. On physical exam, her sclera are anicteric. Her abdomen is soft and tender to palpation in the right upper quadrant. Hepatomegaly is present. A right upper quadrant ultrasound shows no evidence of extrahepatic biliary dilation. Laboratory studies are performed which reveal the following: Aspartate aminotransferase: 76 U/L, Alanine aminotransferase: 57 U/L, Alkaline phosphatase: 574 U/L, Total bilirubin: 1.6 mg/dL. This patient is most likely to have which of the following additional findings?

1. Hyperlipidemia, 2. Skin hyperpigmentation, 3. Anti-smooth muscle antibodies, 4. Anti-neutrophil cytoplasmic antibodies, 5. Personality changes.

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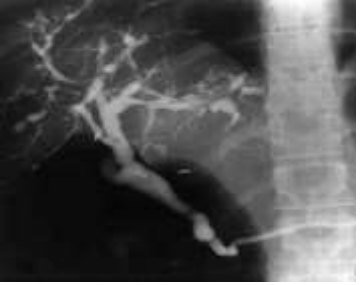


USMLE TEST

The correct answer is 1: This patient presents with fatigue, pruritus, cholestatic pattern of liver injury, and a right upper quadrant (RUQ) ultrasound without extrahepatic biliary dilation, which is consistent with a diagnosis of primary biliary cirrhosis (PBC).

Incorrect answers:

2: Skin hyperpigmentation is characteristic of hereditary hemochromatosis (HH), 3: Anti-smooth muscle antibodies would suggest a diagnosis of autoimmune hepatitis. Autoimmune hepatitis would present with elevated liver enzymes, 4: Anti-neutrophil cytoplasmic antibodies are associated with primary sclerosing cholangitis (PSC), as seen in Illustration, 5: Personality changes and other neuropsychiatric symptoms may be clinical manifestations of Wilson's disease. Patients with Wilson's disease are likely to have an elevated AST/ALT with a normal alkaline phosphatase.

https://wire.ama-assn.org/education/usmle-step-2-prep-next-best-step-hypertension-and-shortness-breath

Diagnosis 1

- 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

https://en.wikipedia.org/wiki/Cirrhosis#Pathophysiology

Diagnosis 2

- 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 1

- 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)

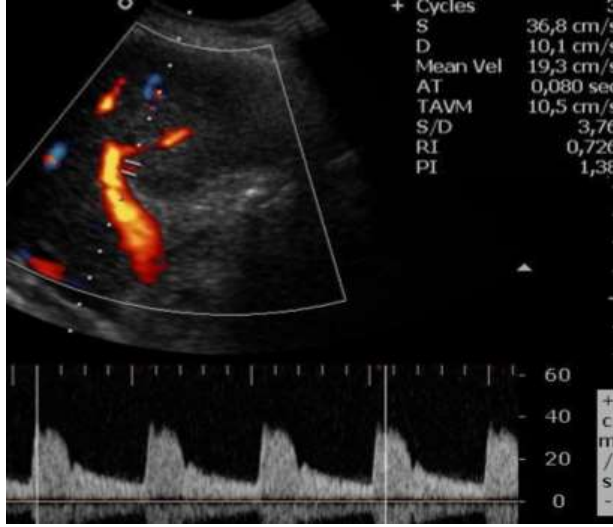
Diagnosis

Laboratory Testing 2

- 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

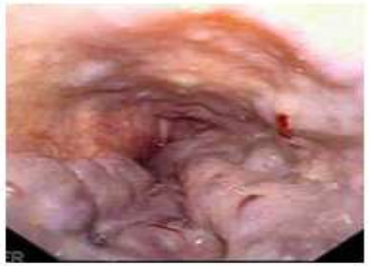


- Duplex Doppler ultrasonography of the liver and upper abdomen
- Computed tomography (CT) scanning and/or magnetic resonance imaging (MRI): can be used when ultrasonographic findings are inconclusive
- Bleeding scan or angiography: Used when bleeding is obscure and the source is uncleuar.

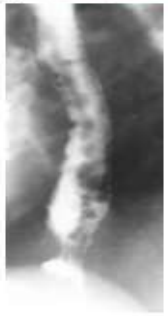
intechopen.com/source/html/18256/media/image35.jpg emedicine.medscape.com/article/182098-overview

Diagnosis

Procedures 1



Large esophageal varices with red wale signs seen on endoscopy.



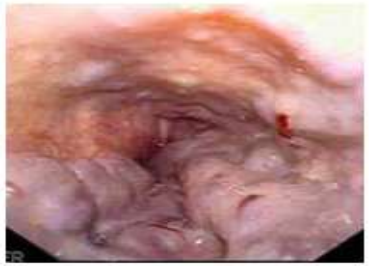
Uphill esophageal varices. Barium swallow demonstrates multiple serpiginous filling defects primarily involving the lower one third of the esophagus with striking prominence around the gastroesophageal junction. The patient had cirrhosis secondary to alcohol abuse.

- Liver biopsy and histologic examination
- Hemodynamic measurement of the hepatic venous pressure gradient (HVPG): A criterion standard for assessment of portal hypertension

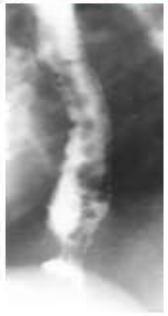
emedicine.medscape.com/article/182098-overview

Diagnosis

Procedures 2



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.

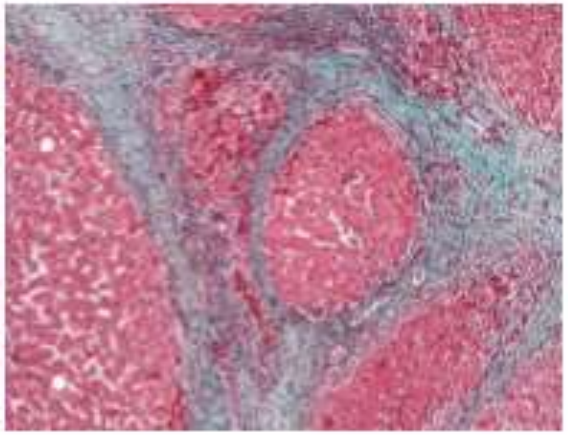
- Upper GI endoscopy (or, esophagogastroduodenoscopy [EGD]): A criterion standard for assessment of portal hypertension.

emedicine.medscape.com/article/182098-overview

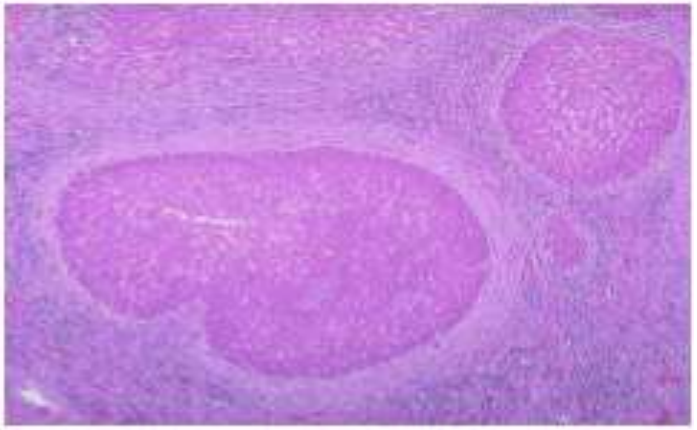
Diagnosis

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.

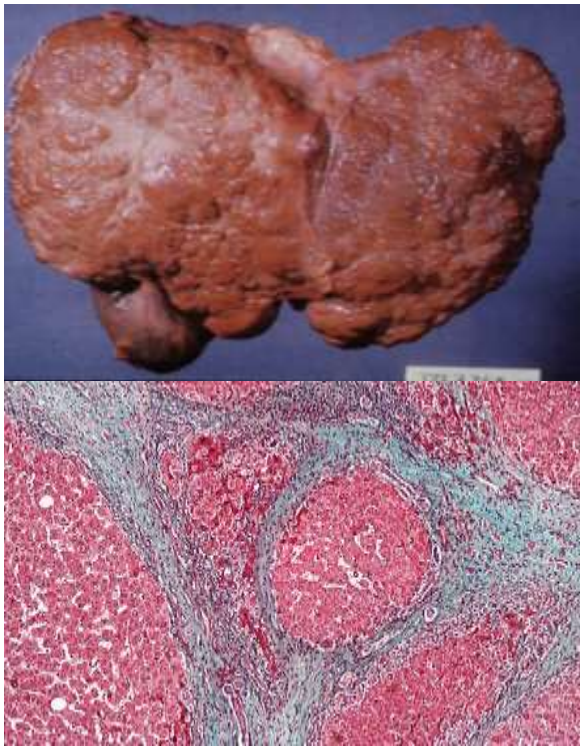


Microscopically with cirrhosis, the regenerative nodules of hepatocytes are surrounded by fibrous connective tissue that bridges between portal tracts.

https://www.pathology.med.umich.edu/greensonlab/severechronhep.jpg

Diagnosis
Morphological Type

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



https://upload.wikimedia.org/wikipedia/commons/thumb/9/94/Cirrhosis_high_mag.jpg/440px-Cirrhosis_high_mag.jpg
meddean.luc.edu/lumen/meded/orfpath/images/fig78x.jpgpathology.med.umich.edu/greensonlab/severechronhep.jpg

Diagnosis

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

USMLE TEST

Mrs. Jones is a 56-year-old female that is admitted to a general medicine floor of the local university hospital. She is noted to have new onset ascites of unknown origin. Peritoneal fluid was sent for cell count (<50 leukocytes), albumin level (4.8), culture (pending), total protein (2.0), and Gram stain (pending). Serum albumin was noted to be 4.0. Of the options below, what is the most likely cause of this patient's ascites?

1. Congestive heart failure
2. Alcoholic hepatitis
3. Cirrhosis
4. Pancreatitis
5. Vascular occlusion

https://wire.ama-assn.org/education/usmle-step-2-prep-next-best-step-hypertension-and-shortness-breath

USMLE TEST

The correct answer is 4: The patient in the above vignette has a serum albumin ascites gradient (SAAG) of -0.8 g/dL which puts it into the category of non-portal hypertensive ascites. Pancreatitis is the only cause of non-portal hypertensive ascites listed above.

Incorrect answers:
1-3,5: All of these forms of pathology represent a portal hypertensive cause of ascites and would have a SAAG >1.1 g/dL.

https://wire.ama-assn.org/education/usmle-step-2-prep-next-best-step-hypertension-and-shortness-breath

Management 1

- 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

https://en.wikipedia.org/wiki/Cirrhosis

Management 2

- 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.

https://en.wikipedia.org/wiki/Cirrhosis

Management

Nutrition 1

- 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

http://www.nejm.org/doi/full/10.1056/NEJMra1504367

Management

Nutrition 2

- 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.

http://www.nejm.org/doi/full/10.1056/NEJMra1504367

Management

Medications: Antihypertensive and Hypertensive Agents 1

- 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

http://www.nejm.org/doi/full/10.1056/NEJMra1504367

Management

Medications: Antihypertensive and Hypertensive Agents 2

- 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.

http://www.nejm.org/doi/full/10.1056/NEJMra1504367

Management

Medications: Pain Management 1

- 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

http://www.nejm.org/doi/full/10.1056/NEJMra1504367

Management

Medications: Pain Management 2

- 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.

http://www.nejm.org/doi/full/10.1056/NEJMra1504367

Management

Medications: Proton-Pump Inhibitors 1

- 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.

http://www.nejm.org/doi/full/10.1056/NEJMra1504367

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.

http://www.nejm.org/doi/full/10.1056/NEJMra1504367

Management

Medications: Statins 1

- 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%

http://www.nejm.org/doi/full/10.1056/NEJMra1504367

Management

Medications: Statins 2

- 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.

http://www.nejm.org/doi/full/10.1056/NEJMra1504367

Management

Medications: Vaptans 1

- 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

http://www.nejm.org/doi/full/10.1056/NEJMra1504367

Management

Medications: Vaptans 2

- 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.

http://www.nejm.org/doi/full/10.1056/NEJMra1504367

USMLE TEST

A 55-year-old former longtime alcoholic presents to clinic complaining of new onset increasing abdominal girth and no other complaints. He had been a Child's Class A cirrhotic for some time. His wife, who has accompanied him on this visit, reports that his mental status is unchanged and that he is eating well and attending his Alcoholics Anonymous meetings. On physical exam, his vital signs are stable. His abdomen is distended and tense without appreciable hepatomegaly. There is a fluid wave and shifting dullness. You conduct abdominal paracentesis in the office and aspirate 3L of clear fluid. If sodium and water restriction fails to control this patient's symptoms, what would be the next step in management?

1. Add nadolol, 2. Add hydrochlorothiazide, 3. Add spironolactone 4. Add acetazolamide, 5. Create a transjugular intrahepatic portosystemic shunt.

https://wire.ama-assn.org/education/usmle-step-2-prep-next-best-step-hypertension-and-shortness-breath

USMLE TEST

The correct answer is 3: Management of ascites involves sodium and water restriction followed by spironolactone, loop diuretics, and frequent abdominal paracentesis.

Incorrect answers:
1: Nadolol may be used in prophylaxis of esophageal varacies but would not be indicated in the control of this patient's ascites, 2: Hydrocholorothiazide is a first line agent for essential hypertension but is not used for ascites, 4: Acetazolamide is a carbonic anhydrase inhibitor which may be used for hypertension but is not indicated for ascites, 5: TIPS can be used as a bridge to liver transplant but would not be indicated in a patient with Child's class A or B cirrhosis who had not already tried medical management of his ascites.

https://wire.ama-assn.org/education/usmle-step-2-prep-next-best-step-hypertension-and-shortness-breath

Management

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.

http://www.nejm.org/doi/full/10.1056/NEJMra1504367

Management
Transplantation 1

- 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%

https://en.wikipedia.org/wiki/Cirrhosis

Management

Transplantation 2

- 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).

https://en.wikipedia.org/wiki/Cirrhosis

USMLE TEST

A 40-year-old man presents to the emergency department with altered mental status. He has a history of cirrhosis of the liver secondary to alcoholism. Laboratory studies show Na 140, K 2.9, Cl 100, HCO3 36, BUN 27, Cr 1.0. His home medications are lactulose and furosemide. Physical exam reveals shifting dullness consistent with ascites. Which of the following is the most appropriate treatment for this patient?

1. Dextrose
2. Potassium
3. Lactulose
4. Neomycin
5. Hydrochlorothiazide

https://wire.ama-assn.org/education/usmle-step-2-prep-next-best-step-hypertension-and-shortness-breath

USMLE TEST

The correct answer is 2: This patient is suffering from hepatic encephalopathy secondary to hypokalemia and should be treated with potassium.

Incorrect answers:

1: Dextrose is indicated for the treatment of hypoglycemia.

3: Lactulose is used to treat hepatic encephalopathy, but the underlying hypokalemia must be corrected first.

4: Neomycin, an aminoglycoside antibiotic, is used to treat hepatic encephalopathy. It kills bowel flora to reduce the production of ammonia. However, the patient's underlying hypokalemia must be treated first.

5: Hydrochlorothiazide (HCTZ) would worsen the patient's hypokalemia and is not indicated.

https://wire.ama-assn.org/education/usmle-step-2-prep-next-best-step-hypertension-and-shortness-breath

Management
Decompensated Cirrhosis 1

- 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

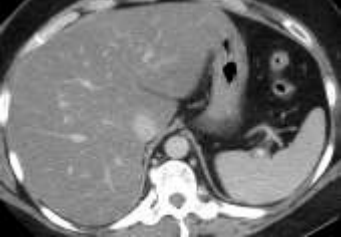
https://en.wikipedia.org/wiki/Cirrhosis

Management

Decompensated Cirrhosis 2

- 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.

https://en.wikipedia.org/wiki/Cirrhosis



USMLE TEST

A 45-year-old man with hypertension, hyperlipidemia, depression, and alcohol abuse presents to the emergency room complaining of right lower quadrant pain that started 12 hours prior. Since that time he has been unable to hold down any food or liquids. A CT scan is obtained and the report indicates acute appendicitis and early stage liver damage. AST 217, ALT 91. An uneventful laparoscopic appendectomy is performed. Upon discharge, the patient is referred to a gastroenterologist to discuss the prognosis of his liver disease. Which of the following outcomes is most likely discussed with the patient?

1. Liver disease is acute and will spontaneously resolve without intervention, 2. Liver disease is reversible if appropriate lifestyle changes are enacted, 3. Liver disease is reversible if appropriate medication is administered, 4. Liver disease is irreversible but progression can be slowed with interferon therapy, 5. Liver disease will continue to progress until man receives a liver transplant.

https://wire.ama-assn.org/education/usmle-step-2-prep-next-best-step-hypertension-and-shortness-breath

USMLE TEST

The correct answer is 2: The gentleman in the question stem has been incidentally found to have alcoholic steatosis (i.e. fatty liver disease), which is a reversible condition that has the potential to completely resolve with alcohol cessation.

Incorrect answers:
1: Fatty liver disease will not resolve without alcohol cessation.
3: The administration of medication will not resolve alcoholic fatty liver disease. Alcohol cessation is required to stop further progression of this disease.
4-5: Alcoholic fatty liver disease is a reversible condition if caught in early stages, as in this case.

https://wire.ama-assn.org/education/usmle-step-2-prep-next-best-step-hypertension-and-shortness-breath

Management

Palliative Care 1

- 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

https://en.wikipedia.org/wiki/Cirrhosis

Management

Palliative Care 2

- 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

Care Coordination 1

- 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

http://www.nejm.org/doi/full/10.1056/NEJMra1504367

Management

Care Coordination 2

- 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.

http://www.nejm.org/doi/full/10.1056/NEJMra1504367

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 1

- 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

Prophylaxis 2

- Beware of hepatotoxic medications, including herbal remedies
- Weight reduction and exercise can improve liver function in patients with NAFLD.

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

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