Cirrhosis: prevalence, etiology and treatments

Cirrhosis: A Closer Look

I. Prevalence of Cirrhosis and Risk Factors

Cirrhosis is a slowly progressing, irreversible disease of the liver where healthy liver tissue is damaged and replaced with thick scar tissue, also known as fibrosis (Snyder, Kivelhan, Collopy, 2015). Cirrhosis is the 8th leading cause of death in the United States and globally, cirrhosis has been found to be the 13 th leading cause of death. Between 1990 and 2013, researchers found the mortality rate of cirrhosis increased by 45. 6% (Phillips & Runyon, 2016). and in the United States cirrhosis results in 33, 539 deaths per year (Tsochatzis, Bosch, Burroughs, 2014). In recent studies, it has been difficult to fully assess the global burden of compensated cirrhosis versus decompensated cirrhosis. The median survival rate for individuals with compensated cirrhosis was an average of 12 years, and for decompensated cirrhosis on average approximately 2 years (Asrani, Devarbhavi, Eaton, Kamath, 2018).

The leading causes and risk factors of cirrhosis are chronic hepatitis B and hepatitis C virus infection, alcoholism, diabetes, smoking, obesity, and nonalcoholic steatohepatitis (Phillips & Runyon, 2016). Lifestyle changes are very important in the prevention of cirrhosis. “ In 161 patients with compensated cirrhosis who were followed up prospectively, obesity was independently associated with clinical decompensation, together with HVPG and serum albumin. Moreover, insulin resistance and metabolic syndrome were independently associated with liver-related mortality in a NHANES-III cohort of more than 2500 patients with chronic liver disease (Tsochatzis et

al., 2014, p. 1752).” Excessive alcohol intake can cause severe damage to the liver due to the alcohol being metabolized by the liver. “ Alcohol increases the HVPG and porto-collateral blood flow, which increases the risk for variceal bleeding (Tsochatzis et al., 2014, p. 1753).” Cigarette smoking increases vasoconstriction, which leads to a decreased blood flow to the liver and after a long period of time, can cause extreme damage to the liver and other vital organs. The hepatitis B and hepatitis C viruses can also damage the liver, causing chronic inflammation and fibrosis, which then leads to cirrhosis. It is important to vaccinate and prevent exposure to these viruses since they can be spread through blood and other bodily fluids. Often times, individuals are asymptomatic and unaware they have the disease.

II. Etiology and Pathophysiology of Cirrhosis

There are many conditions that can cause cirrhosis, but the major causes are alcoholism, chronic hepatitis B virus (HBV) and hepatitis C virus (HCV), and nonalcoholic steatohepatitis (NASH). According to Phillips & Runyon, “ the increasing prevalence of nonalcoholic fatty liver disease (NAFLD), cirrhosis related to NASH is predicted to surpass HCV-related cirrhosis as the most common indication for liver transplantation in the United States” (p. 767). Other causes of cirrhosis that are less common are autoimmune disorders such as biliary cirrhosis or cholangitis, hereditary disorders such as α1-antitrypsin deficiency, Wilsons disease, as well as hemochromatosis, and hepatic circulation obstruction from congestive heart failure and Budd Chiari syndrome (Mccance and Heuther, 2014).

The pathophysiology of liver cirrhosis is characterized by fibrosis tissue formation, development of hepatocellular regenerative nodules, and angiogenesis. The liver tissue damage in cirrhosis is a result of cellular injury from toxins such as alcohol, viruses, chemicals, and fat. In response to the cellular injury, liver macrophages known as Kupffer cells are activated. These cells reside on the wall of the liver sinusoids and when activated they release inflammatory mediators, reactive oxygen species, as well as growth factors. They also destroy hepatocytes and activate hepatic stellate cells (HSC). HSC are liver cells that reside in the space between the liver sinusoids and hepatocytes, also known as the space of Disse. These cells normally function to store vitamin A and assist in wound repair. When hepatic stellate cells are activated, they lose vitamin A and release growth factors, including transforming growth factor beta (TGF-B) which causes the cells to create more collagen, thus more fibrotic tissue. As the fibrotic tissue increases, the tissue fills the space of Disse and begins to compress the central veins and sinusoids in the liver (Ebrahimi, Naderian, Sohrabpour, 2016).

The fibrotic scar tissue in a cirrhotic liver separates regenerative nodules of hepatic cells. Regenerative nodules are formed due to hepatic hyperplasia, which is induced by growth regulators such as cytokines and hepatic growth factors as a response to injury. Insulin, glucagon, and patterns of blood flow in the liver determine how and where the regenerative nodules develop. As the process of fibrosis continues, the liver structure is replaced and begins to have a cobblestone appearance. The regenerating nodules further contribute to the compressing of the hepatic circulation, leading to decreased blood flow and portal hypertension (Civan, 2018).

Angiogenesis occurs in response to injury as well, creating new blood vessels within the scar tissue and surrounding the regenerative nodules. The new vessels begin to restore hepatic circulation by connecting the hepatic artery and portal vein to the hepatic venules. Unfortunately, the restoration of circulation is not able to accommodate the normal amount of blood volume. This increases pressure in the portal veins, thus contributing to portal hypertension (Civan, 2018).

In alcoholic cirrhosis, this cascade of events in the pathophysiology of cirrhosis is induced by chronic exposure to alcohol. Alcohol is metabolized in the liver primarily by alcohol dehydrogenase (ADH), but also by the microsomal enzyme oxidation system (MEOS) and cytochrome P-450 2E1 (CYP2E1). These metabolic pathways in the liver thus lead to increased levels of acetaldehyde, accumulation of fatty acids in the liver, and increased production of reactive oxygen species (ROS) (Ebrahimi, et al., 2016). These all contribute to the disruption of the hepatic cell membrane function and increases oxidative stress from lipid peroxidation (Mccance and Heuther, 2014). Damage to the cells initiates the inflammatory response and release of inflammatory cytokines, which begins the process of liver fibrosis. Alcohol can also increase gastrointestinal absorption of endotoxins released by bacteria in the intestine which leads to Kupffer cell release of free radicals further increasing oxidative damage and inflammation, particularly in the space of Disse (Ebrahimi, et al., 2016).

The process of cirrhosis leads to loss of hepatocytes, impaired hepatocyte regeneration, and impaired liver function due to the disruption in the hepatic blood flow, increased fibrotic tissue, and increased pressure build-up in the

liver. The impaired liver function inhibits storage and synthesis of nutrients, clearing of toxins from the blood, metabolism of bilirubin, and synthesis and secretion of plasma proteins and clotting factors. As this disease progresses, it can lead to liver failure and to the development of hepatocellular carcinoma (Snyder et al., 2015).

III. Clinical Signs and Symptoms

1. Key Signs and Symptoms

Liver cirrhosis is categorized into two types, compensated and decompensated. Individuals with compensated cirrhosis are often asymptomatic or have nonspecific symptoms such as weakness, fatigue or weight loss. Compensated cirrhosis may show evidence of portal hypertension in some cases. With decompensated liver cirrhosis, the scarring of the liver is more extensive, causing greater dysfunction of the liver. Individuals with this type of cirrhosis have symptomatic complications related to hepatic insufficiency and portal hypertension (Thornton, 2018).

Hepatic insufficiency can cause symptoms including jaundice, increased bruising, and hepatic encephalopathy in late stages. In the normal liver, bilirubin is absorbed and secreted into the small intestine as bile. In a cirrhotic liver, there is decreased bilirubin absorption, leading to increased bilirubin in the blood and decreased bile secretion. Increased bilirubin in the blood can lead to a common manifestation of cirrhosis called jaundice. This condition causes yellow discoloration of the skin, mucous membranes, and most commonly the conjunctiva of the eyes. Hyperbilirubinemia may also cause patients to develop pruritus and have increased kidney excretion of

bilirubin presenting as dark urine. Decreased bile secretion can cause feces to be a pale or gray color due to loss of stercobilin. In addition, decreased bile secretion can also cause decreased intestinal fat absorption which causes the presentation of excess fat in the feces, called steatorrhea. These feces may float, due to excess gas, and typically have an oily or greasy appearance. Decrease in the synthesis of clotting factors by the liver can lead to increased bruising and possibly even severe bleeding. Impaired clearing of toxins and metabolites from the liver can lead to increased ammonia and estrogen levels in the blood. Increased ammonia levels are known to cause hepatic encephalopathy. The severity of hepatic encephalopathy can range from altered level of consciousness to coma. Asterixis is a common manifestation of hepatic encephalopathy and is characterized by bilateral asynchronous flapping or jerking motion of the hands during dorsiflexion (Udell et al., 2012). Increased estrogen levels can lead to complications like gynecomastia, spider angiomas, and palmar erythema. Spider angiomas are most often found on the face, trunk and upper limbs (Snyder et al., 2015).

Portal hypertension is the most common complication of the liver cirrhosis and is responsible for some of the most severe clinical findings of advanced cirrhosis. Portal hypertension is due to the disruption in the blood flow from the formation of fibrotic tissue, regenerative nodules and angiogenesis. The impaired blood flow through the liver can lead to regurgitation of blood into the hepatic portal circulation. This causes blood to back up and be shunted away from the liver into the systemic circulation, leading to increased pressure in the gastric, esophageal, portal and mesenteric veins (Snyder et

al., 2015). Dilation of these anastomotic vessels causes internal hemorrhoids and varices of the stomach and esophagus. If these varices rupture, patients may vomit blood or have passage of blood through the digestive tract, producing foul smelling, black tarry stools called melena. Portal hypertension can also cause backing up of blood into the spleen or lungs, leading to congestive splenomegaly or pulmonary hypertension. The changes in portal flow have also been known to trigger renal vasoconstriction in later stages of cirrhosis, leading to decreased renal filtration, also known as hepatorenal syndrome. Hepatorenal syndrome is one of the most important causes of acute kidney injury in patients with cirrhosis. Clinical manifestations of liver cirrhosis due to portal hypertension are ascites, dilated periumbilical veins also known as caput medusae, and foul smelling breath called fetor hepaticus (Bertino et al., 2016).

Ascites is a common symptom and complication seen in advanced cirrhosis caused by portal hypertension and insufficient production of albumin from the liver. Albumin plays an important role in maintaining colloidal osmotic pressure in the blood, which helps keep fluid in the vascular system. When albumin levels are low and pressure in the portal circulation is increased, fluid flows out of the blood system into the surrounding tissues, such as the peritoneal cavity. Ascites of the abdomen is the most common manifestation of third-spacing and edema, but peripheral and pulmonary edema can also occur. A very serious complication of ascites is bacterial peritonitis (Snyder et al., 2015).

Another common clinical finding of cirrhosis is right sided abdominal pain. The swelling of the liver and stretching of the protective fibrous capsule

called Glisson’s capsule can cause pain in the upper right quadrant of the abdomen where the majority of the liver is located and also referred pain in the right shoulder. The enlarged cirrhotic liver may also be palpated well below the rib cage and will have a hard and nodular surface (Snyder et al., 2015).

B. Differential Diagnoses

There are several medical conditions that can potentially mimic liver cirrhosis in regards to the manifestations and complications of this disease. It is important to be able to differentiate the cause of liver cirrhosis not only for treatment, but also diagnostic purposes. Common diagnoses that need to be differentiated from liver cirrhosis are hepatocellular carcinoma, portal vein thrombosis, and hemochromatosis.

Hepatocellular carcinoma (HCC) is the most common type of cancer that originates in the liver and is known to have a poor prognosis once identified. Although cirrhosis is one of the main causes, exposure to carcinogens, exposure to the hepatitis virus, increased alcohol consumption, and fatty liver disease are all risk factors for this cancer. The initial symptoms are usually abdominal discomfort, a large palpable mass in the right upper quadrant, and also weight loss. Symptoms can present similar to those of liver cirrhosis and may be enhanced if liver cirrhosis is present in the individual. Diagnosis of this condition can be difficult to differentiate from liver cirrhosis, but imaging and a liver biopsy can be done to confirm diagnosis. Imaging may show tumor development which can determine the diagnosis of cancer. Treatment for both liver cirrhosis and HCC are liver

transplantation, but HCC can also be treated with cancer specific treatments such as chemotherapy and internal radiation therapy (Herrine, 2017).

Portal vein thrombosis is narrowing of the portal vein due to a blood clot. Common causes of this condition are cirrhosis, cancer of the liver, pancreas, adrenal gland or kidneys, polycythemia, or any other disorder that can make blood more likely to clot. Infection of the umbilical cord stump in newborns and appendicitis in children are also common causes of portal vein thrombosis. Individuals with this condition are often asymptomatic but when symptoms are present, they often overlap the complications of cirrhosis and portal hypertension. This includes splenomegaly, ascites, and varices of the stomach and esophagus. If the esophageal and gastric varices rupture, vomiting of blood and melena can be found and this can also be seen in liver cirrhosis. In comparison to the treatment of gastric and esophageal varices for individuals with cirrhosis, portal vein thrombosis treatment entails use of medications to dissolve clots such as tissue plasminogen activator (TPA) and prophylactic anticoagulants such as heparin (Orfanidis, 2016).

Another condition that can be mistaken for liver cirrhosis is hemochromatosis. Hemochromatosis is a hereditary disorder triggered by genetic mutations of the HFE or TFR2 gene that causes the body to absorb an excess amount of iron. The excess iron build-up in the body damages joints, organs, and can potentially be fatal. Symptoms develop gradually and may vary since the iron accumulation can damage various body organs, including the pancreas, liver, heart, and endocrine glands (Mccance and Heuther, 2014). The most common symptoms of this disorder are those seen in liver cirrhosis. As the iron accumulates in other organs, complications such

as diabetes, heart failure, hypothyroidism, arthropathies, and impotence can also be found. This condition can be difficult to diagnose based on symptoms alone. Genetic testing along with iron, ferritin, and transferrin blood levels must be completed to confirm diagnosis. In addition to management of complications, phlebotomy can be performed periodically as treatment to maintain normal iron blood levels (Douketis, 2017).

IV. Diagnostic Tests & Procedures

When patients are suspected of having cirrhosis, specific tests can help confirm or negate the diagnosis. Initially, it is important to identify the most at risk patients for the development of cirrhosis. It is important to gather a thorough history of the patient and their family to be able to identify the possible risk factors that could contribute to the development of cirrhosis. A physical examination is pertinent in identifying any signs and symptoms of cirrhosis. A firm liver, ascites, or stigmata of cirrhosis is often seen in patients with the new onset of cirrhosis. Different labs are needed to be drawn as well to detect the likelihood of cirrhosis. The primary labs include CBC, electrolytes, urea, creatinine, AST, ALT, alkaline phosphatase, PT/INR, bilirubin, albumin, glucose, cholesterol, and triglyceride levels (Udell, et al., 2012).”

In one meta-analysis of 86 studies, the conclusion was drawn stating that a platelet count less than 160, 000/mm3 had the highest diagnostic accuracy and if an individual has thrombocytopenia with the presence of ascites, it is the most useful lab test investigation for the diagnosis of cirrhosis. Also, an AST: ALT ratio higher than 1 increases the likelihood of cirrhosis. “ The

Bonacini cirrhosis discriminant score (CDS) combines the ALT: AST ratio with the platelet count and INR into a discriminant function with possible total values between 0 and 11; higher values increase the likelihood of cirrhosis (Udell, et al., 2012).”

Studies have shown that the most accurate way to stage liver disease and to determine if an individual has cirrhosis is a liver biopsy test. A liver biopsy test is considered the “ gold standard” for the diagnosis of cirrhosis. Having a liver biopsy completed is very expensive and also places the individual at risk for bleeding, which can lead to further injury due to decreased clotting factors being produced in the liver (Udell, et al., 2012).

Other than lab tests, imaging testing are important in the detection of cirrhosis, which include magnetic or transient elastography and ultrasounds. Ultrasounds are normally used to help diagnose nonalcoholic fatty liver disease and hepatocellular carcinoma. Magnetic or transient elastography is used to assess the liver for levels of stiffness. Unfortunately, in the early stages of cirrhosis, individuals are normally asymptomatic, so the detection normally happens in the later stages after the development of comorbidities, making the treatment options limited (Udell, et al., 2012).

There are two scoring systems that have been developed to help with both the diagnosis of cirrhosis and also the onset of new complications. The first diagnostic scoring system is The Child-Turcotte-Pugh (CTP) scoring system. It is based on 5 different parameters which include serum albumin, prothrombin time, ascites, grade of encephalopathy, and serum bilirubin levels. Studies have shown that this method of calculating provides

important prognostic information for the patient in their disease process (Thornton, 2018). The second scoring system is The Model for End-Stage Liver Disease (MELD). This scoring system identifies information on short-term patient prognosis. This model is known to be used for any patient with cirrhosis or with the diagnosis of advanced liver disease (Thornton, 2018). By being able to identify the different long-term and short-term prognosis for the patient, the provider will be able to identify the appropriate treatment and management.

V. Therapeutic Approaches

There have been numerous studies completed in regards to the treatment of cirrhosis once it has been detected. Once cirrhosis has been confirmed, it is important to refer the patient to a gastroenterologist or hepatologist. The next step that needs to be completed is the screening for potential reversible causes of cirrhosis and to treat the reversible causes if possible. If the cirrhosis is not reversible, then it is important to coordinate care accordingly. Reversible cirrhosis normally is seen in alcohol induced cirrhosis and if the individual stops alcohol consumption, they do have a chance of ceasing the development of cirrhosis into later stages. The most important approach is education and lifestyle modifications (Tsochatzis, Bosch, Burroughs, 2014).

The patient needs to be educated on the diagnosis of cirrhosis, the importance of lifestyle modifications, and on different ways of protecting their liver. Every 6 months, patients will need to be screened for hepatocellular carcinoma by the completion of a hepatic ultrasound. If the patient has chronic hepatitis C virus and cirrhosis, the screening should be

continued, even if the patient has sustained a virologic response (Thornton, 2018). The goal of managing patients with hepatitis B virus or hepatitis C virus is to treat the actual infection. It is important to make sure the patient is put onto an all-oral direct-acting antiviral agent. These medications should be monitored by specific liver disease specialists due to the medications being high risk. If the patient is a candidate for liver transplantation, studies have shown the benefit of these medications before and after. Hepatitis B virus can be spread from mother to fetus, so it is important to the mother to be tested to prevent the spread of the virus during childbirth (Thornton, 2018).

Patients should discontinue any unnecessary medications that are metabolized in the liver, due to the liver being unable to properly break down the medications. Patients should also monitor their blood pressure and will need to discontinue any antihypertensive medications if their MAP is less than or equal to 82mm Hg. The majority of patients on antihypertensive medications will no longer need them as the cirrhosis worsens (Phillip, 2016).

With patients who have cirrhosis associated with a Model for End-stage Liver Disease score of 15 or greater or that are struggling with additional complications of cirrhosis, need to be referred to a transplant center. If abdominal surgery or liver transplant is needed, providers need to weigh out the patient’s risk and benefits due to the patient being unable to produce the appropriate clotting factors, which could lead to bleeding and further liver damage (Tsochatzis, Bosch, Burroughs, 2014).

Due to the increased risk of ascites with patients with cirrhosis, it is important to touch upon the diagnosis and treatment of the condition. Ascites should be treated with salt restrictions and diuretics because of the buildup of fluid in the abdomen. To diagnose ascites, a paracentesis consisting of cell count, total protein test, albumin level, and a bacterial culture with sensitivity should be completed. If the cell count in the paracentesis is greater than 250 cell per mm3 should be put on antibiotics within 6 to 24 hours due to the patients increased risk of bacterial peritonitis (Starr & Raines, 2011).

Hepatic encephalopathy is another condition that is often seen in cirrhosis. Patients will be diagnosed with hepatic encephalopathy after the completion of a paracentesis within the hospital setting. If the test comes back positive, the patient should be treated with disaccharides or rifaximin. An important educational point for these patients is the importance of understanding they should not be driving due to the increased risk of ammonia, which could lead to confusion, making it unsafe to drive (Starr & Raines, 2011).

When esophageal and gastric varices are present, it is important for the patient to be screened via upper endoscopy within 12 months of the diagnosis of compensated cirrhosis and within 3 months if complicated cirrhosis. If the patient has varices that are medium to large in size, they should receive beta blockers. If needed, they can also have an endoscopic variceal ligation. Some patients will have acute episodes of GI bleeding and should be treated with somatostatin or somatostatin analogue within the first 12 hours of the detection of the bleed. These patients should also receive

prophylactic antibiotics and have an endoscopy performed within 24 hours of onset as well (Starr & Raines, 2011).

IV. Variations in Disease Across the Lifespan

Liver cirrhosis primarily affects adults, but it can also be seen in children and persist into old age. In infants, it is most often caused by biliary atresia and genetic-metabolic diseases, while in older children it is usually the result of autoimmune hepatitis, Wilson's disease, primary sclerosing cholangitis, and α1-antitrypsin deficiency. Symptoms and complications of cirrhosis are similar to those seen in adults, however the first sign of cirrhosis in the pediatric population is poor weight gain. It is important to provide special attention to the alterations in nutrition from cirrhosis because children and adolescents have higher nutritional requirements and malnutrition can have severe consequences on their growth and development. Treatment of cirrhosis in the pediatric population is primarily based on methods already established for the adult population (Pinto, Schneider & da Silveria, 2015).

Physiological changes that occur with aging affect the liver as well as the clinical characteristics and outcomes of cirrhosis. As the liver ages, the liver volume is reduced by 20-40% and hepatic blood flow is reduced by 35-50% (Tajiri & Shimizu, 2013). This in turn leads to a decline in hepatic drug metabolism and increased vulnerability to drug induced liver injury and development of adverse reactions to medications. Decrease in liver regeneration capacity and impairment in immune response also occurs, leading to alterations in the pathogenesis of liver diseases and HCC. Advanced age has been associated with a poor prognosis for individuals with

cirrhosis, and individuals with alcoholic cirrhosis have more progression in their disease state in comparison to young adults. According to Tajiri and Shimizu (2013), “ In a study conducted in the United Kingdom, 62% of subjects aged 60-92 were drinkers and half of them who developed cirrhosis, died within one year of diagnosis”(p. 8462). Individuals with alcoholic cirrhosis and HCV infection were seen to have an even faster progression of the disease. Overall, aged patients have various changes in the liver and other organs that affect the prognosis, characteristics, and management of liver cirrhosis (Tajiri & Shimizu, 2013).

References

- Asrani, S. K., Devarbhavi, H., Eaton, J., Kamath, P. S. (2018). Burden of Liver Diseases in the World, *Journal of Hepatology* , *1* (6), 1-75. doi: https://doi. org/10. 1016/j. jhep. 2018. 09. 014
- Bertino, G., Privitera, G., Purrello, F., Demma, S., Crisafulli, E., Spadaro, L., Tsochatzis, E.
- (2016). Emerging hepatic syndromes: pathophysiology, diagnosis and treatment. *Internal & Emergency Medicine, 11* (7), 905–916. doi: https://doi-org. ezproxy. csusm. edu/10. 1007/s11739-016-1478-7
- Civan, J. M. (2018, February). Cirrhosis – Hepatic and Biliary Disorders. Retrieved from https://www. merckmanuals. com/professional/hepatic-and-biliary-disorders/fibrosis-and-cirrhosis/cirrhosis
- Douketis, J. D. (2017, October). Hemochromatosis – Blood Disorders. Retrieved from https://www. merckmanuals. com/home/blood-disorders/iron-overload/hemochromatosis

- Ebrahimi, H., Naderian, M., & Sohrabpour, A. A. (2016). New Concepts on Pathogenesis and Diagnosis of Liver Fibrosis; A Review Article. *Middle East Journal of Digestive Diseases, 8* (3), 166–178. https://doi-org. ezproxy. csusm. edu/10. 15171/mejdd. 2016. 18
- Phillip S., Runyon, B. (2016). Treatment of Patients with Cirrhosis. *The New England Journal of Medicine, 375* (8), 767-777. doi: 10. 1056/NEJMra1504367
- Herrine, S. K. (2017, September). Hepatocellular Carcinoma – Liver and Gallbladder Disorders. Retrieved from https://www. merckmanuals. com/home/liver-and-gallbladder-disorders/tumors-of-the-liver/hepatocellular-carcinoma
- McCance, K. L., & Huether, S. E. (2014). *Pathophysiology: The Biological Basis for Disease in Adults and Children* (7th ed.). St. Louis, United States of America: Elsevier Mosby.
- Orfanidis, N. T. (2016, October). Portal Vein Thrombosis – Liver and Gallbladder Disorders. Retrieved from https://www. merckmanuals. com/home/liver-and-gallbladder-disorders/blood-vessel-disorders-of-the-liver/portal-vein-thrombosis
- Pinto, R. B., Schneider, A. C. R., & da Silveira, T. R. (2015). Cirrhosis in children and adolescents: An overview. *World Journal of Hepatology* , *7* (3), 392–405. http://doi. org/10. 4254/wjh. v7. i3. 392
- Snyder, S. R., Kivlehan, S. M., & Collopy, K. T. (2015). Cirrhosis and Its Complications. *EMS World, 44* (10), 32–37. Retrieved from http://ezproxy. csusm. edu/login? url= https://search. ebscohost. com/login. aspx? direct= true&db= ccm&AN= 110231594&site= ehost-live

- Starr SP, & Raines D. (2011). Cirrhosis: diagnosis, management, and prevention. *American Family Physician, 84* (12), 1353–1359. Retrieved from http://ezproxy. csusm. edu/login? url= https://search. ebscohost. com/login. aspx? direct= true&db= ccm&AN= 104351258&site= ehost-live
- Tajiri, K., & Shimizu, Y. (2013). Liver physiology and liver diseases in the elderly. *World Journal of Gastroenterology : WJG* , *19* (46), 8459–8467. http://doi. org/10. 3748/wjg. v19. i46. 8459
- Thornton, K. (2018, May 31). Evaluation and Prognosis of Patients with Cirrhosis. Retrieved from https://www. hepatitisc. uw. edu/go/evaluation-staging-monitoring/evaluation-prognosis-cirrhosis/core-concept/all
- Tsochatzis, E. A., Bosch, J., & Burroughs, A. K. (2014). Liver Cirrhosis. *The Lancet, 3383* (9930), 1749-1761. doi: https://doi. org/10. 1016/S0140-6736 (14)60121-5
- Udell JA, Wang CS, Tinmouth J, FitzGerald JM, Ayas NT, Simel DL, ... Yoshida. (2012). Does this patient with liver disease have cirrhosis? *JAMA: Journal of the American Medical Association, 307* (8), 832–842. Retrieved from https://doi org. ezproxy. csusm. edu/10. 1001/jama. 2012. 186
- Zhou, W.-C., Zhang, Q.-B., & Qiao, L. (2014). Pathogenesis of liver cirrhosis. *World Journal of Gastroenterology : WJG* , *20* (23), 7312–7324. http://doi. org/10. 3748/wjg. v20. i23. 7312