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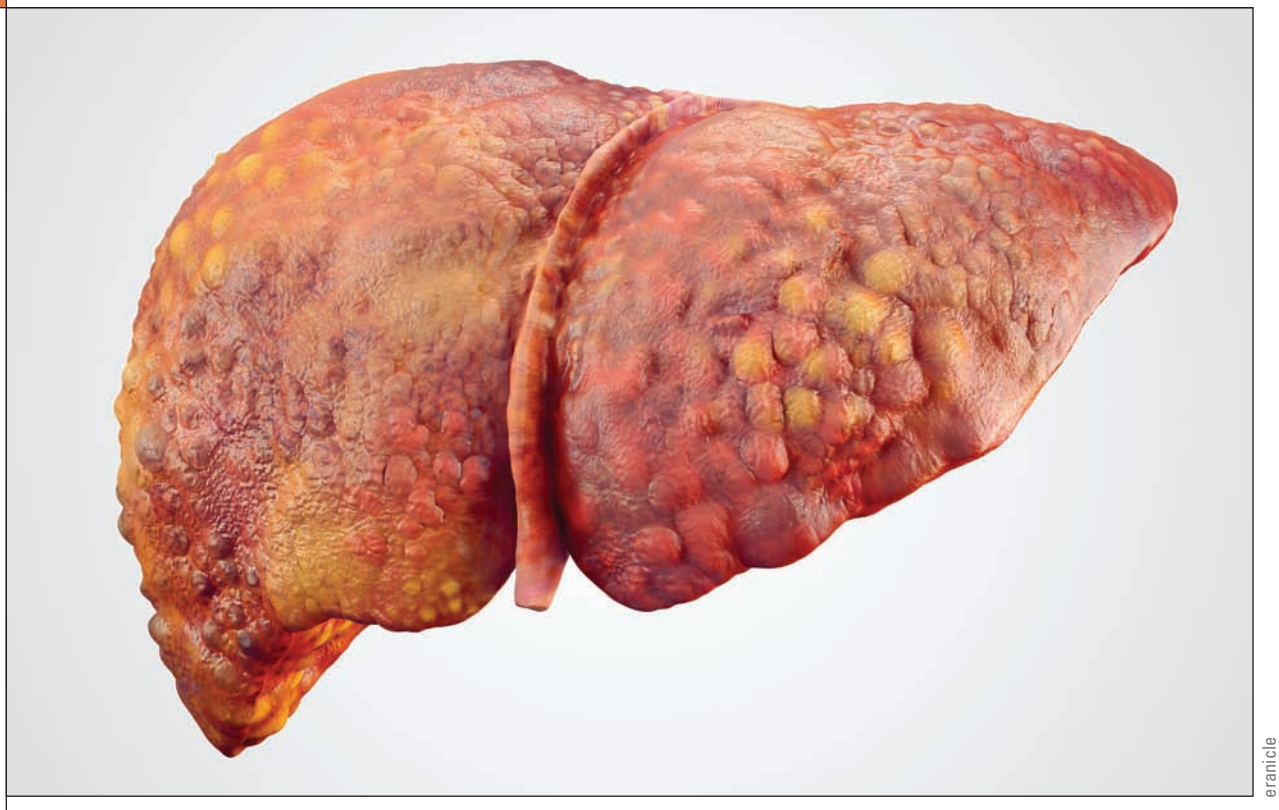

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Cirrhosis:
An evidence-based treatment approach

Abstract: The NP's role in managing cirrhosis is increasing due to the growing prevalence of the disease. The purpose of this article is to review the pathophysiology, diagnosis, and management of patients with cirrhosis with an emphasis on interdisciplinary collaboration and evidence-based practice. Cirrhosis complications are also discussed.

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Cirrhosis is reported to be one of the most challenging chronic conditions healthcare providers must manage, yet evidence suggests that primary care providers (PCPs) will take on more of the burden of care as the disease becomes more prevalent.[1] Therefore, it is imperative that NPs understand the challenges and best practices of managing this common chronic disease.

Epidemiology

Cirrhosis prevalence has increased over the last 20 years with higher disease rates seen in impoverished and Black patients.[2,4] It is the 12th leading cause of death in the US, causing at least 1 million deaths annually.[3,4] Underdiagnosis is common; over two-thirds of patients are unaware that they have liver disease. This is concerning given that cirrhosis confers a higher risk of mortality than many other chronic diseases.[1,4] Annually, 30 billion dollars are spent on care of patients with cirrhosis.[2]

Pathophysiology

Cirrhosis starts with an initial injury or inciting event to the liver that triggers an inflammatory response. The

Keywords: cirrhosis, collaboration, evidence-based practice, interdisciplinary, NP

most common inciting events in the US are viral infections (hepatitis B or C), nonalcoholic steatohepatitis (caused by excess carbohydrates and calories), and alcoholic liver disease (excess alcohol) (see *Chronic liver conditions that can lead to cirrhosis*).[5,6] In response to inflammation, new blood vessels form, extracellular matrix proliferates, and new hepatocytes migrate to the area, replicating excessively. Angiogenesis becomes abnormal and fibrosis develops. The fibrosis coalesces, causing nodules to replace normal liver tissue.[7] Fibrosis then advances from mild to severe, with the most severe fibrosis leading to cirrhosis. During this time, the liver attempts to regenerate normal functioning liver tissue in between diseased areas and these regenerative nodules give the cirrhotic liver its hallmark lumpy appearance (see *Progression to cirrhosis and its complications*). Recovery and regression of early fibrosis is usually possible if the damaging event is removed. However, liver transplant has been traditionally thought of as the only cure once cirrhosis develops.[7] But new research is exploring the reversibility of liver cirrhosis.[8,9] Since progression toward cirrhosis is slow, taking 2 to 3 decades, cirrhosis is most often diagnosed in the fourth or fifth decade of life. However, recent data reveal that diagnosis is occurring at younger ages than in past decades.[2,4]

A healthy liver performs a wide range of functions including carbohydrate and lipid metabolism; breakdown of medications, ammonia, and bilirubin; and synthesis of albumin and coagulation factors.[10] Kupffer cells help with immune system regulation and hepatocytes produce bile, which is critical for digestion and absorption of fat-soluble vitamins.[10] Cirrhosis can cause dysfunction affecting one or more of these primary liver functions. Additionally, persistent alterations in cellular homeostasis during cirrhosis can lead to increased propensity for hepatocellular neoplasm.[8]

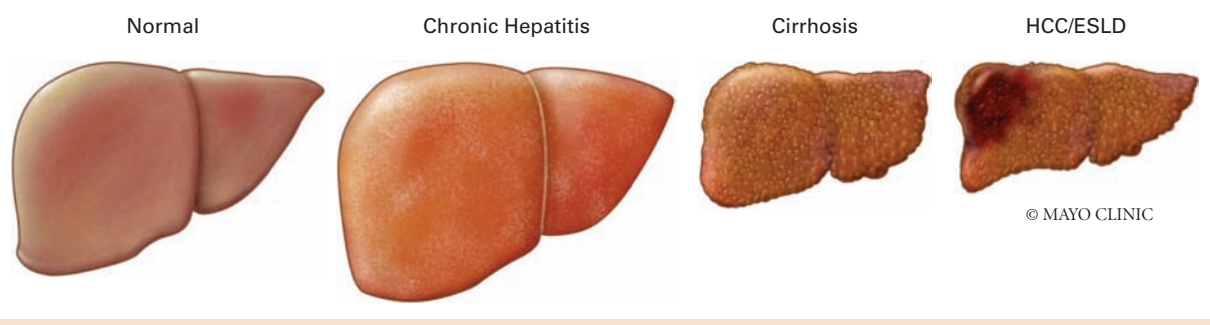
Chronic liver conditions that can lead to cirrhosis[6]

Most common	Less common
Nonalcoholic steatohepatitis	Primary sclerosing cholangitis
Infectious hepatitis	Primary biliary cholangitis
Alcoholic liver disease	Autoimmune hepatitis

Cirrhosis of the liver also alters the hepatic vasculature, which results in portal hypertension, a state of increased pressure in the portal venous system. As the pressure inside the liver increases, blood flow is restricted, and blood vessels become congested and engorged with blood. As this occurs over months to years, this pressure increase can cause damage to the vessel walls and chronic inflammation. Ultimately, portal hypertension can lead to complications of esophageal varices, portal hypertensive gastropathy, and ascites. Additionally, patients may develop portal vein thrombosis that can further complicate blood flow to and from the portal circulation.

Cirrhosis is classified as either compensated or decompensated. Compensated cirrhosis is often asymptomatic and may therefore go undetected.[1] Conversely, decompensated cirrhosis is manifested by complications; the most common are ascites, esophageal varices, and hepatic encephalopathy. Comorbidities, such as diabetes, predispose a patient to a higher likelihood of decompensation.[11] Prognosis is poor

Progression to cirrhosis and its complications

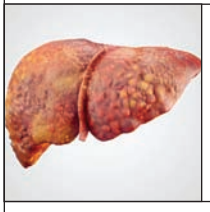


Key: HCC, hepatocellular carcinoma; ESLD, end-stage liver disease

following decompensation.[12] While life expectancy estimate for compensated cirrhosis is 12 or more years, life expectancy for decompensated cirrhosis is approximately 2 years.[12] Therefore, when a patient moves from compensated to decompensated cirrhosis, referral to a transplant center for liver transplant evaluation is warranted.

Evaluation of patients with cirrhosis

As with any chronic illness, a thorough history, physical exam, and diagnostic evaluation is important. During this time, the NP may evaluate for signs of cirrhosis, identify the underlying etiology of liver disease, and intervene for improved outcomes (see *Signs and symptoms of cirrhosis and underlying pathophysiology*). For example, treatment of hepatitis C and abstinence from alcohol can improve complication rates and life expectancy in patients with cirrhosis.[8,13]



The gold standard to diagnose fibrosis and cirrhosis is liver biopsy, but its invasiveness limits its usefulness.

Two of the most common lab tests to monitor and evaluate cirrhosis are alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Although it is frequently assumed that both AST and ALT are elevated in patients with cirrhosis, their levels can be normal during compensated cirrhosis and even sometimes, decompensated cirrhosis.[12,14] Consequently, although these tests are frequently referred to as "liver function tests," they should actually be referred to as liver enzymes or liver transaminases, since they do not reflect how well the liver is functioning.[14] True "liver function tests" include albumin, prothrombin time (PT)/international normalized ratio (INR), and bilirubin. However, even these tests may not show variation until late in decompensated cirrhosis, at which point albumin levels will be reduced and PT/INR will be elevated. Thrombocytopenia can be an early lab clue to cirrhosis, since it can occur in the early stages of portal hypertension.[12,15] Patients should be evaluated for possible cirrhosis when platelet levels fall below 160,000/mm^3.[13]

Several diagnostic tests are used in the evaluation and monitoring of cirrhosis. Ultrasound will often show splenomegaly during cirrhosis and portosystemic collateral veins with worsening cirrhosis.[15] The gold standard to diagnose fibrosis and cirrhosis is liver biopsy, but the invasiveness of the procedure limits its usefulness. Therefore, transient liver elastography is frequently used to evaluate for advanced fibrosis.[16] Other mechanisms for fibrosis and cirrhosis diagnosis, such as serum biomarkers, are being studied, but not yet FDA-approved.

Signs and symptoms of cirrhosis and underlying pathophysiology[53-55]

Sign/symptom	Underlying pathophysiology
Splenomegaly and thrombocytopenia	Splenic congestion from portal hypertension
Caput medusae, dilated abdominal wall veins, ascites, peripheral edema	Portal hypertension
Palmar erythema, spider angiomas, gynecomastia, loss of body hair	Increased estrogen levels
Jaundice	Hepatocyte damage
Sarcopenia	Increased metabolism

Evaluation and management of cirrhosis complications

Ascites, hepatic encephalopathy, and esophageal/gastric varices are the three most common complications seen in decompensated cirrhosis. However, there are several other possible complications that require monitoring (see *Monitoring for complications of cirrhosis*).

Ascites. Ascites is the most common complication of cirrhosis with almost one half of patients with compensated cirrhosis developing it over a 10-year period.[13,17] Sometimes, the diagnosis of ascites is the first clue to prompt the identification of cirrhosis. Ascites is thought to occur due to disrupted equilibrium between the intravascular and extravascular space when portal hypertension results in elevated hydrostatic pressure and hypoalbuminemia results in decreased osmotic pressure. As a consequence, fluid accumulates in the peritoneal space.[10,15]

Evaluation of patients with ascites may show a positive fluid wave test. A fluid wave test is performed by having the patient lay supine and push down on the midline of their abdomen with their hands. The NP then places one hand on each side of the patient's flank

Monitoring for complications of cirrhosis[32,54-57]

Monitor for	Methods for monitoring	Management (all complications require care coordination with hepatology or gastroenterology)
Hepatic encephalopathy	History and clinical exam - daytime sleepiness, disorientation, and asterixis Diagnostics - varies; use to rule out competing diagnoses	- Lactulose/rifaximin
Ascites	History and clinical exam - Early satiety, abdominal distension/bloating, peripheral edema - Fluid wave test (+LR = 6.0) - Edema (+LR = 3.8) Diagnostics - Abdominal ultrasound	- Sodium restriction and diuretics - Hospital admission if concern for spontaneous bacterial peritonitis (fever or abdominal pain)
Esophageal and gastric varices	History & clinical exam - May have no abnormalities Diagnostics - EGD at cirrhosis diagnosis	- No varices + compensated cirrhosis = repeat EGD every 2 to 3 years - Small varices = repeat EGD every 1 to 2 years and start nonselective beta-blocker - No varices + decompensated cirrhosis = repeat EGD yearly - Hospital admission if signs or symptoms of bleeding
Hepatocellular carcinoma	Abdominal ultrasound at time of diagnosis of cirrhosis and every 6 months	- Referral to surgical oncology
Hepatorenal syndrome	History and clinical exam - May have no abnormalities Diagnostics - Kidney ultrasound, urinalysis (hematuria and proteinuria not expected with HRS), creatinine increase > 0.3 mg/dL or 50% of baseline	- Referral to nephrology
Portopulmonary hypertension	History and clinical exam - Audible P2, BP ≥ 140/90 mm Hg, right ventricular heave Diagnostics - Pulmonary hypertension on echocardiogram or cardiac catheterization	- Referral to pulmonology - Home oxygen
Hepatopulmonary syndrome	History and clinical exam - suspect if platypnea-orthodeoxia or clubbing Diagnostics - Diagnostics vary, but may include arterial blood gas, echocardiogram, pulmonary function test	- Referral to pulmonology - Home oxygen

+LR = positive likelihood ratio, EGD = esophagogastroduodenoscopy, HRS = hepatorenal syndrome

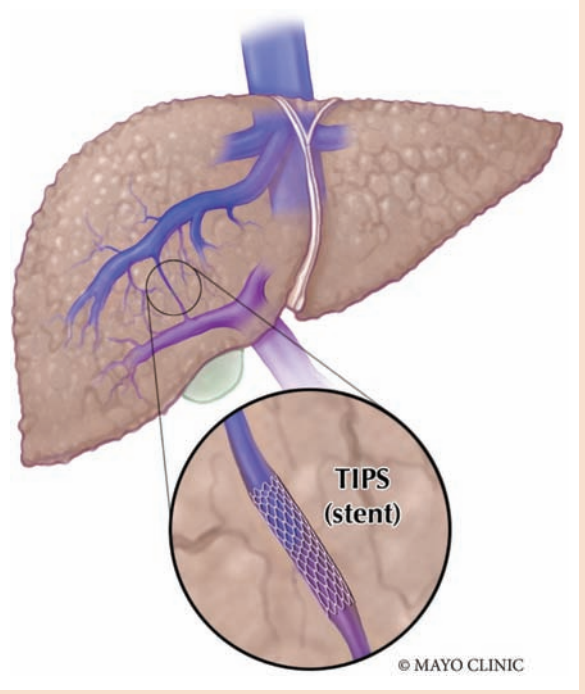
area and alternates tapping each flank, feeling for an impulse that transmits across the abdomen. However, ascites may be hard to diagnose in this manner, especially in patients with large abdominal girth or only a small amount of ascitic fluid. An ultrasound can confirm ascites.[17,18]

Diet and medication can help manage ascites. A dietary sodium restriction of 2,000 mg per day is recommended, though evidence for its success is low.[17,19,20] Two diuretics, spironolactone (a potassium-sparing diuretic) and furosemide (a loop diuretic), are often used together to manage ascites while maintaining a normal potassium level. Single morning dosing will help avoid nocturia and increase the likelihood of compliance. It is important to closely monitor kidney function and watch for hyponatremia when

initiating and titrating doses and prescribing high doses. Even a small increase in creatinine within the normal range, such as 0.3 mg/dL, can signal acute kidney injury. Diuretics should be stopped in the presence of hepatic encephalopathy, sodium level less than 120 mEq/L, or a creatinine level more than 2.0 mg/dL.[19]

Another method of ascites management is paracentesis. Current clinical guidelines suggest that patients should have a paracentesis as soon as possible (within 1 month) of the first episode of ascites in order to evaluate the fluid.[18,21] Paracentesis may also be needed for ascites that is refractory to diuretics and sodium restriction. In order to provide renal protection from volume loss, albumin infusion is suggested following paracentesis when more than 5L of fluid is removed.[17] If paracentesis is required frequently, it may be a clue to worsening decompensation or inability to adhere to sodium restriction or diuretics.[13,17] Other methods for ascites management include a transjugular intrahepatic portosystemic shunt (TIPS) (see *Transjugular intrahepatic portosystemic shunt*), which is more effective than paracentesis for severe or refractory ascites.[22]

Transjugular intrahepatic portosystemic shunt



Spontaneous bacterial peritonitis

Spontaneous bacterial peritonitis can be a complication of ascites and is usually caused by a translocation of bacteria from the gut to the ascitic fluid. It is defined by a polymorphonuclear leukocyte count of at least 250 cells/mm^3 in ascitic fluid and/or positive ascitic fluid cultures.[13] This diagnosis should be suspected when a patient develops fever, abdominal pain, and/or leukocytosis. When this happens, it is important to perform paracentesis as soon as possible (within 12 hours of first suspicion) to confirm the diagnosis and collect cultures since prompt treatment is associated with better patient outcomes.[13]

Hepatic encephalopathy

Hepatic encephalopathy (HE) is another common cirrhosis complication, and perhaps the most complex complication to identify.[13,23] Although the pathophysiology of HE is not fully understood, it is thought to develop due to excess accumulation of ammonia in the bloodstream, which then crosses the blood brain barrier and becomes neurotoxic. Normally, hepatocytes break down the ammonia produced by intestinal bacteria, a process that is impaired in cirrhosis. Portosystemic shunting can also cause HE since it hinders the delivery of ammonia to hepatocytes for detoxification.[10]

The course of HE is often unpredictable and the diagnosis is challenging.[24] This is partially due to variability and the subtle nature of symptoms.[24] HE can be categorized as covert and overt; the West Haven criteria are also used to categorize HE from Grade 0 (no symptoms) through 4 (coma).[24,25] (See *Resources for NPs caring for patients with cirrhosis.*) Symptoms may be overlooked during early stages and covert HE due to their subtle nature. These subtle symptoms include attention deficits, psychomotor slowing, insomnia, daytime sleepiness, apathy, and mild hypokinesia.[13,23,25] NPs should engage the patient's caregiver in discussions involving history to achieve accurate evaluation since patients tend to avoid specific questions and "hide" their confusion. The psychometric hepatic encephalopathy score (PHES), the critical flicker frequency (CFF), and the Trail Making test are useful objective tests to supplement the physical exam and identify covert HE.[13] Other tools, such as online applications, are available for diagnostic guidance. Patients with overt HE are more easily diagnosed as they may exhibit asterixis or hyperactive deep tendon

Resources for NPs caring for patients with cirrhosis

Resource	Used for	Where to find
West Haven Criteria	Diagnosis: Hepatic encephalopathy	www.mdcalc.com/hepatic-encephalopathy-grades-stages#use-cases
EncephalApp	Diagnosis: Encephalopathy	www.encephalapp.com
MELD-Na Score	Prognosis	www.mdcalc.com/meldna-meld-na-score-liver-cirrhosis
Child-Turcotte-Pugh Score	Prognosis and prescribing	www.hepatitisc.uw.edu/page/clinical-calculators/ctp
LiverTox	Prescribing	livertox.nih.gov
Fibrosis-4 (FIB-4) Score	Prognosis: Evaluation of degree of fibrosis in hepatitis B/C	www.mdcalc.com/fibrosis-4-fib-4-index-liver-fibrosis
AST to Platelet Ratio Index (APRI) Score	Prognosis: Hepatitis C progression	www.mdcalc.com/ast-platelet-ratio-index-apri
ALD/NAFLD Index (ANI)	Diagnosis: Differentiate between alcoholic liver disease and nonalcoholic fatty liver disease	www.mdapp.co/ald-nafld-index-ani-calculator-355/

reflexes.[13] Further complicating diagnosis, HE can be episodic, recurrent, or persistent and may either be spontaneous or precipitated by problems such as a urinary tract infection (UTI), medication noncompliance, or electrolyte imbalances.[25]

HE is a clinical diagnosis and the nonspecific signs and symptoms associated with it necessitate ruling out alternate diagnoses.[25] Diagnostic evaluation should include evaluation for a precipitating event; the most common are infection and electrolyte abnormalities. Usual workup should include electrolyte evaluation and infection evaluation (that is, lactate, two sets of blood cultures, a urinalysis if patient presents symptoms of UTI, and stool studies if there is presence of diarrhea).[13,26–28,30] Although traditionally used in the evaluation of HE, recent research shows that ammonia lacks sufficient sensitivity and specificity to be helpful in HE diagnosis and monitoring and is no longer recommended as a diagnostic tool.[26,27]

Treatment options for HE focus on intestinal elimination of ammonia before it makes its way to the bloodstream or reduction of intestinal ammonia production. Lactulose is a nonabsorbable disaccharide that alters the pH of the colon and reduces the absorption of ammonia. It causes frequent, loose stools. Once HE is resolved, doses are titrated toward a goal of two to three bowel movements per day to prevent future HE episodes. Lactulose is continued indefinitely, but there is increased risk of dehydration and hypernatremia when bowel movements exceed five per day.[27-29] Adverse reactions of lactulose include bloating, diarrhea, dehydration, electrolyte abnormalities, cramping, nausea, and/or vomiting.

Antibiotics are added to lactulose therapy in the case of continued recurrent HE episodes. Rifaximin is an antibiotic that targets bacteria in the intestines, reducing ammonia production.[25,28] Drawbacks to rifaximin include high cost and prior authorization requirements. Less commonly used antibiotics include neomycin, metronidazole, and vancomycin.

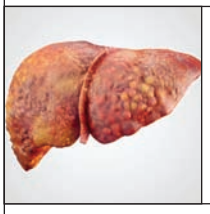
HE management includes correcting electrolyte imbalances and optimizing nutrition with a high protein diet to avoid HE exacerbation.[24,25] Additionally, NPs caring for patients with a diagnosis of HE will want to consider referral to a fitness-to-drive assessment performed by occupational therapists or state agencies to ensure that it is safe for patients to operate vehicles.[30]

Esophageal and gastric varices

Esophageal and gastric varices are concerning sequelae to the congestion of portal hypertension. They can ooze or burst causing severe blood loss, anemia, and multiorgan failure. Therefore, all patients should be screened for varices within 12 months of cirrhosis diagnosis using esophagogastroduodenoscopy (EGD).[21]

The goal in management of varices is to prevent bleeding. When bleeding does occur, patients require hospitalization, most often in the ICU where

they are administered blood products to maintain hemoglobin greater than 7 g/dL.[13,31] Beta-blockers are used to prevent bleeding from existing varices, but they are not effective at preventing the formation of varices.[13] Nonselective beta-blockers like propranolol, nadolol, and carvedilol should be chosen since optimized blood flow occurs from beta-2 effects rather than beta-1 effects.[15] Carvedilol is unique in that it also exhibits some anti-alpha-1 adrenergic effects allowing for beneficial vasodilation in intrahepatic circulation.[15] Beta-blockers should be discontinued in the presence of any of the following: mean arterial pressure (MAP) less than 80 mm Hg, systolic BP less than 100 mm Hg, sodium concentration less than 120 mEq/L, refractory ascites, hepatorenal syndrome (HRS), or episodes of spontaneous bacterial peritonitis.[13]



Care coordination between PCPs, hepatology/gastroenterology specialists, and other healthcare professionals results in improved patient outcomes.

Endoscopic variceal ligation is also used to manage varices. This procedure is completed at the time of initial EGD and involves placing rubber bands around the varices to cut off the blood supply. Unfortunately, varices often recur after banding since there is no underlying treatment of the portal hypertension. In these cases, patients can also undergo local therapies such as injection of a cyanoacrylate glue or sclerotherapy. Additionally, patients with severe decompensated cirrhosis and varices may undergo TIPS.[15]

Other complications of cirrhosis

Other complications of cirrhosis such as hepatopulmonary syndrome, hepatic hydrothorax, and portopulmonary hypertension cause respiratory dysfunction and often require supplemental oxygen. Hepatopulmonary syndrome results from intrapulmonary vascular dilation and altered alveolar-arterial oxygen exchange and is diagnosed by combined testing with arterial blood gas and echocardiogram showing a PaO_2 less than 60 to 80 mm Hg and the presence of an intrapulmonary shunt, respectively.[32] Liver transplant is the only effective treatment for hepatopulmonary syndrome. Hepatic hydrothorax occurs when ascitic fluid moves into the right pleural space from a defect in the right diaphragm. Initial treatment options are the same as those for ascites.[13] Thoracentesis is an option for those with large volume effusions and/or severe symptoms.[19] Portopulmonary hypertension is defined by cirrhosis-associated pulmonary hypertension and causes fatigue, exertional dyspnea, orthopnea, and sometimes respiratory failure. Each of these complications exhibits specific clinical signs/symptoms with distinct recommendations for management.

HRS is a consequence of splanchnic vasodilation and subsequent decreased kidney perfusion. These patients also exhibit ascites and, usually, hyponatremia.[33] Hypovolemia and acute kidney injury should be ruled out prior to diagnosing HRS.[13] HRS is prevented through avoidance of nephrotoxic medications and hypotension. Volume expansion with albumin is recommended as first-line treatment; if no response is seen after 48 hours, vasoactive medications like midodrine and octreotide may be used.[19]

Hepatocellular carcinoma (HCC) is a final complication of cirrhosis that warrants discussion. Globally, HCC is the fifth most common tumor and the fourth leading cause of cancer-related death.[34,35] Patients with cirrhosis are at high-risk for developing HCC, regardless of cirrhosis etiology; 80% of newly diagnosed HCC cases are in patients with cirrhosis. HCC prognosis is more favorable when the disease is diagnosed in early stages. HCC can be treated by resection, radiofrequency ablation, or chemoembolization. Transplant is also a potential option for those who meet criteria. Screening for HCC should be completed twice annually, although recent research has questioned whether screening improves mortality rates.[34-36]

Management of the patient with cirrhosis

Care coordination. Care coordination between PCPs, hepatology/gastroenterology specialists, and other healthcare professionals results in improved patient outcomes and reduced hospital readmission rates for patients with cirrhosis.[13] However, patients perceive that communication and coordination among healthcare professionals is poor.[37] Thus, it is important for healthcare providers to work together to achieve quality of care. The care coordination process should focus on monitoring for changes in prognosis, patient and family

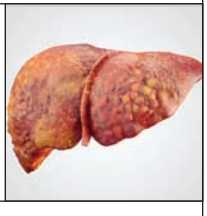
education and support, health promotion, nutrition, and medication reconciliation and monitoring. Patients should be referred to hepatology or gastroenterology specialists as soon as possible after cirrhosis is suspected. After any hospitalization for cirrhosis decompensation, patients should follow up with their PCP within a week of discharge, although this recommendation is extrapolated from heart failure research.[17]

Patients with cirrhosis should be routinely monitored for changes in prognosis. One method for monitoring prognosis and need for liver transplant is calculation of the Model for End-stage Liver Disease-Sodium (MELD-Na).[38] The MELD-Na Score uses INR, bilirubin, creatinine, serum sodium, and the need for dialysis to predict severity of disease and risk for poor outcomes.[39,40] An online calculator to determine the patient's MELD-Na score is available (see *Resources for NPs caring for patients with cirrhosis*). Specialists begin liver transplant planning once the MELD score rises above 17 or a patient develops a cirrhotic complication.[17,26] Liver transplant planning is also indicated when medical interventions for complications become ineffective.[38]

Palliative care and hospice services should be considered for patients with cirrhosis and are often underutilized.[41] All patients with cirrhosis qualify for palliative care and should be educated on its premise.[37] Palliative care can provide important interdisciplinary team members and an additional support system to reduce symptoms and improve quality of life.[41] Another important aspect of palliative care is the assistance of social workers in helping the patient and family make advanced care planning decisions. If a patient meets criteria for a liver transplant, but is unable to safely proceed, then a hospice referral is recommended. Other indications for hospice referrals are oliguria and refractory or recurrent cirrhosis complications.[41]

Communication with the patient and caregivers while supporting and educating them is essential. Caregivers of patients with cirrhosis experience significant stress and, therefore, the importance of supporting them cannot be understated.[41] Patient education is important since patients lack the knowledge needed to manage their illness successfully and specifically need education on the symptoms and how they relate to the diagnosis and its complications.[37,42] Patients also usually have inadequate knowledge to manage the special nutrition needs of cirrhosis, so involvement of a registered dietitian is beneficial especially since malnutrition occurs in over 80% of patients, including patients with an elevated body mass index.[13,20,43,44] Patients should be advised about the hypermetabolic state seen in cirrhosis, choosing high-protein foods, and consuming a high-protein diet (1.0 to 1.5 grams of protein per kilogram of body weight per day).[13] Late evening meals with protein or protein nutritional supplements may help achieve this goal. Additional nutrition education is warranted based on other complications (that is, low sodium for ascites, fluid restriction for hyponatremia, and low carbohydrate for diabetes).[13]

Some medication dosages may need to be reduced since cirrhosis results in decreased metabolism of drugs.



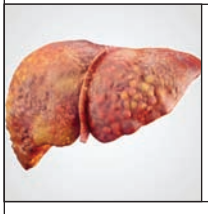
NPs should assure health promotion for patients with cirrhosis based on their age, gender, and other comorbidities. Additionally, all patients with cirrhosis should be vaccinated for hepatitis A and B to prevent new insults to the liver in the future.[21] Immunization for pneumococcal disease with pneumococcal polysaccharide vaccine (PPSV23) is also required regardless of age.[45] Alcohol avoidance is important since alcohol cessation can help stabilize cirrhosis symptoms and intake is linked to cirrhosis decompensation.[15,17]

Astute medication management is important in cirrhosis. Some medication dosages may need to be reduced since cirrhosis results in decreased metabolism of drugs.[46] Additionally, medications should be evaluated for hepatotoxicity using resources such as LiverTox.[47] Unlike chronic kidney disease, for which glomerular filtration rate guides dosage adjustment, there is no single lab value available to reflect the severity of cirrhosis for medication dose adjustments. Prescribing references often suggest dosage adjustments based on the Child-Turcotte-Pugh score.[46] Pharmacist consultation is also helpful to determine optimal dosages.

Management of comorbidities

Cardiovascular disease is a common comorbidity that poses unique patient management concerns. Despite popular belief, statins can and should be continued

during compensated cirrhosis. In fact, statins improve liver function by enhancing hepatic blood flow through intrahepatic vessel dilation.[15] Statins also partially reverse the endothelial dysfunction and fibrosis that is seen in portal hypertension.[15] The benefit of aspirin to prevent cerebrovascular accident and/or myocardial infarction should be carefully balanced with the increased risk for azotemia or gastrointestinal bleeding seen in cirrhosis. Additionally, all nonsteroidal anti-inflammatory drugs should be used with caution, and avoided if possible, due to decreased urinary sodium excretion and azotemia risks.[19] BP should be closely monitored in hypertensive patients, because patients may transition from hypertension to normotension, and possibly hypotension. As portal hypertension progresses, systemic vasodilation, increased nitric oxide release, and splenic artery vasodilation all create excessive blood vessel relaxation. Initially, the body compensates by increasing its vasoconstrictors, but over time it loses this compensatory mechanism.[17] When a patient's BP starts trending down, NPs should consider discontinuing antihypertensive medications since an MAP less than 80 mm Hg has been associated with poorer health outcomes and decreased survival in patients with cirrhosis.[13,17]



As many as 30% of patients with cirrhosis may experience depression. Anxiety and insomnia are also common.

Patients with cirrhosis may complain of pruritus; management of this complaint has mainly been studied in those with primary sclerosing cholangitis and primary biliary cholangitis.[48,49] Antihistamines are ineffective since the itch occurs from cholestasis rather than histamine release.[49] Cholestyramine is a first-line approach, but is an off-label use of the medication. Doses should be taken before or with a meal and at least 4 hours prior to other medications because of potential drug interactions.[48,49] Naltrexone and sertraline may be used if cholestyramine is ineffective, although this is an off-label use of these medications. Patients should also be counseled to use moisturizing lotion and cooling ointments (menthol, for example) twice a day and to keep nails trimmed short to prevent injury from scratching.

As many as 30% of patients with cirrhosis may experience depression.[50] Anxiety and insomnia are also common. Selective serotonin reuptake inhibitors are the safest class of medication to treat depression and anxiety in this group. Since medication clearance is reduced in cirrhosis, NPs should aim for a maintenance dose that is half of the usual dose.[50] Benzodiazepines should be avoided due to an increased risk of HE. Hydroxyzine or trazadone at bedtime may be safe, effective choices for insomnia although this is an off-label use. Refer to package inserts for guidance on appropriate dosing. Agents such as zolpidem and diphenhydramine should be avoided as they are related to increased HE risk.[13]

Pain management for patients with cirrhosis can be challenging. Acetaminophen up to 2 grams a day is safe, though some patients may need stronger pain relievers.[13,51] The risk of opioid toxicity is increased in patients with cirrhosis and caution is advised. If opioids are used, medications to prevent constipation should be coprescribed, and only immediate-release forms should be given. For neuropathic pain management, medications such as gabapentin and pregabalin may be considered since they are not metabolized in the liver.[51]

Osteoporosis occurs more frequently in patients with cirrhosis than in the normal population due to physiologic alterations of hypogonadism and poor nutrition.[38,52] Additionally, patients with autoimmune causes of cirrhosis are at increased risk for osteoporosis due to the need for daily corticosteroid use. Therefore, all patients should be counseled on adequate vitamin D and calcium intake. Further, NPs should assess the patient for other osteoporosis risk factors like postmenopausal status or smoking. Screening densitometry is warranted in these patients.[53] Patients undergoing liver transplant should also receive densitometry testing.[38] If indicated based on densitometry results, bisphosphonates, like weekly alendronate and monthly ibandronate, may be used in patients with cirrhosis.[53]

The management of patients with cirrhosis is complex and requires a team approach. Understanding pathophysiology, diagnosis, and management strategies helps NPs become more adept at caring for patients afflicted with this common chronic disease. NP

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