Cirrhosis in adults: Overview of complications, general management, and prognosis

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INTRODUCTION

Cirrhosis represents a late stage of progressive hepatic fibrosis characterized by distortion of the hepatic architecture and the formation of regenerative nodules. It is generally considered to be irreversible in its advanced stages, at which point the only option may be liver transplantation. In earlier stages, specific treatments aimed at the underlying cause of liver disease may improve or even reverse cirrhosis.

Patients with cirrhosis are susceptible to a variety of complications, and their life expectancy can be markedly reduced. Cirrhosis accounted for approximately 49,500 deaths and was the eighth leading cause of death in the United States in 2010 [1]. In addition, there were an estimated 19,500 deaths due to liver cancer, which often occurs in the setting of cirrhosis. Similarly, a study that used data from the National Death Index from the Centers for Disease Control and Prevention and the Rochester Epidemiology Project estimated that liver disease was responsible for 66,007 deaths in 2008, of which 18,175 were due to hepatobiliary cancer [2].

This topic will review the complications, general management, and prognosis of cirrhosis. An overview of the causes and diagnosis of cirrhosis is presented separately. (See "Cirrhosis in adults: Etiologies, clinical manifestations, and diagnosis".)

MAJOR COMPLICATIONS

Major complications of cirrhosis include (table 1):

- Variceal hemorrhage
- Ascites
- Spontaneous bacterial peritonitis
- Hepatic encephalopathy
- Hepatocellular carcinoma
- Hepatorenal syndrome
- Hepatopulmonary syndrome

Once these complications develop, patients are considered to have decompensated cirrhosis. Multiple factors can predispose to decompensation in a patient with cirrhosis. Risk factors for decompensation include bleeding, infection, alcohol intake, medications, dehydration, and constipation [3-5]. In addition, patients with obesity are at increased risk for decompensation [6]. Once decompensation has developed, patients should be considered for liver transplantation. (See "Liver transplantation in adults: Patient selection and pretransplantation evaluation" and "Liver transplantation in adults: Patient selection and pretransplantation evaluation", section on 'Cirrhosis'.)

Other major complications of cirrhosis include portal vein thrombosis and cardiomyopathy. However, patients with these complications alone are not considered to have decompensated cirrhosis.

This section provides an overview of the complications of cirrhosis. The individual complications are discussed in detail in their respective topic reviews.

Complications of portal hypertension — Many of the complications of cirrhosis are the result of portal hypertension (increased pressure within the portal venous system). This can lead to the formation of venous collaterals (varices) as well as circulatory, vascular, functional, and biochemical abnormalities that contribute to the pathogenesis of ascites and other complications. (See "Portal hypertension in adults" and "Pathogenesis of ascites in patients with cirrhosis", section on 'Portal hypertension'.)

Complications of portal hypertension include:

- Ascites
- Hepatic encephalopathy
- Variceal hemorrhage

- Spontaneous bacterial peritonitis
- Hepatorenal syndrome
- Portal hypertensive gastropathy
- Hepatic hydrothorax
- Hepatopulmonary syndrome
- Portopulmonary hypertension
- Cirrhotic cardiomyopathy

Variceal hemorrhage — Patients with variceal hemorrhage typically present with hematemesis and/or melena. It is typically treated with endoscopic variceal band ligation. Other treatments include endoscopic sclerotherapy and placement of a transjugular intrahepatic portosystemic shunt (TIPS). (See "Overview of the management of patients with variceal bleeding".)

Variceal hemorrhage is associated with high mortality rates. In the past, the mortality rate of a single variceal hemorrhage was 30 percent, and only one-third of patients survived for one year [7,8]. Although survival has improved with modern techniques for controlling variceal hemorrhage, mortality rates remain high (15 to 20 percent 30-day mortality) [9].

Portal hypertensive gastropathy — Portal hypertensive gastropathy (congestive gastropathy), while extremely common in patients with portal hypertension, is an uncommon cause of significant bleeding in these patients. When portal hypertensive gastropathy is the sole cause of bleeding, there is diffuse mucosal oozing with no other lesions, such as varices, to account for the GI bleeding and anemia. The mucosa is friable, and bleeding presumably occurs when the ectatic vessels rupture. The severity of gastropathy is related to the level of portal pressure, the level of hepatic vascular resistance, and the degree of reduction in hepatic blood flow (See "Portal hypertensive gastropathy".)

Ascites — Ascites is the accumulation of fluid within the peritoneal cavity. It is the most common complication of cirrhosis. The first step leading to fluid retention and ultimately ascites in patients with cirrhosis is the development of portal hypertension. Patients without portal hypertension do not develop ascites or edema. Those with ascites have several circulatory, vascular, functional, and biochemical abnormalities that contribute to the pathogenesis of fluid retention. (See "Pathogenesis of ascites in patients with cirrhosis".)

Ascites is typically treated with a combination of diuretics and sodium restriction, though some patients require repeated therapeutic paracenteses or TIPS placement. Among patients with refractory ascites or spontaneous bacterial peritonitis, the use of nonselective beta blockers may be associated with increased mortality [10,11]. This may occur because reduced mean arterial blood pressure has been correlated with reduced survival in patients with advanced cirrhosis. (See "Ascites in adults with cirrhosis: Initial therapy" and "Ascites in adults with cirrhosis: Diuretic-resistant ascites", section on 'Discontinuing beta blockers' and 'Decompensated cirrhosis' below and "Spontaneous bacterial peritonitis in adults: Treatment and prophylaxis", section on 'Discontinue nonselective beta blockers'.)

Spontaneous bacterial peritonitis — Spontaneous bacterial peritonitis (SBP) is an infection of preexisting ascitic fluid without evidence for an intra-abdominal secondary source, such as a perforated viscus. SBP is almost always seen in the setting of end-stage liver disease. Clinical manifestations of SBP include fever, abdominal pain, abdominal tenderness, and altered mental status. Some patients are asymptomatic and present with only mild laboratory abnormalities. (See "Spontaneous bacterial peritonitis in adults: Clinical manifestations".)

The index of suspicion for SBP must be high with a low threshold for diagnostic paracentesis. The diagnosis is established by a positive ascitic fluid bacterial culture and/or an elevated ascitic fluid absolute polymorphonuclear leukocyte count (≥250 cells/mm^3). Without early antibiotic treatment, mortality is high. (See "Spontaneous bacterial peritonitis in adults: Diagnosis" and "Spontaneous bacterial peritonitis in adults: Treatment and prophylaxis".)

Hepatorenal syndrome — Hepatorenal syndrome refers to the development of renal failure in a patient who has advanced liver disease due to cirrhosis, severe alcoholic hepatitis, acute liver failure, or less often, a metastatic tumor. Rather than being a new disease, hepatorenal syndrome usually represents the end-stage of a sequence of reductions in renal perfusion induced by increasingly severe hepatic injury. Arterial vasodilatation in the splanchnic circulation, which is triggered by portal hypertension, appears to play a central role in the hemodynamic changes and the decline in renal function in hepatorenal syndrome. The initial reductions in glomerular filtration rate are often masked clinically since associated decreases in muscle mass and hepatic urea production minimize elevations in the plasma creatinine concentration and blood urea nitrogen. (See "Hepatorenal syndrome", section on 'Pathogenesis'.)

Hepatorenal syndrome is characterized by a generally benign urine sediment, a very low rate of sodium excretion, and a progressive rise in the plasma creatinine concentration. There is some confusion regarding the presence or absence of oliguria. The percentage of patients with oliguria depends upon the cut-off for defining oliguria. If the cutoff is 400 mL/day, only 44 percent of patients are oliguric. If 500 mL/day is used, approximately two-thirds are oliguric. (See "Hepatorenal syndrome", section on 'Clinical presentation'.)

The diagnosis is one of exclusion, being made when other causes of renal dysfunction have been excluded. In particular, volume depletion (as with overly rapid diuresis) can mimic all of the findings of hepatorenal syndrome. The prognosis is poor unless hepatic function improves or a liver transplantation is performed. (See "Hepatorenal syndrome", section on 'Diagnosis' and "Hepatorenal syndrome", section on 'Treatment'.)

Hepatic hydrothorax — Hepatic hydrothorax is defined as the presence of a pleural effusion in a patient with cirrhosis and no evidence of underlying cardiopulmonary disease. It results from the movement of ascitic fluid into the pleural space through defects in the diaphragm, and it is usually right-sided. (See "Hepatic hydrothorax".)

The treatment for hepatic hydrothorax includes diuretics and sodium restriction. Patients who do not respond to conservative therapy may require repeated therapeutic thoracenteses or TIPS. The most important aspect of management is evaluation for liver transplantation. Chest tubes should **not** be placed in patients with hepatic hydrothorax. Placement of chest tubes in this setting can result in massive protein and electrolyte depletion, infection, renal failure, and bleeding.

Hepatopulmonary syndrome — Hepatopulmonary syndrome (HPS) is defined by the following triad (see "Hepatopulmonary syndrome in adults: Prevalence, causes, clinical manifestations, and diagnosis"):

- Liver disease
- Increased alveolar-arterial gradient while breathing room air
- Evidence for intrapulmonary vascular abnormalities, referred to as intrapulmonary vascular dilatations

Estimates of the prevalence of HPS among patients with chronic liver disease range from 4 to 47 percent, depending on the diagnostic criteria and methods used. Even in those without HPS, mild hypoxemia is common and is presumably caused by ascites, with resulting diaphragmatic elevation and ventilation/perfusion mismatch. There are no effective medical therapies for HPS. Liver transplantation offers the most promise for successful treatment. (See "Hepatopulmonary syndrome in adults: Natural history, treatment, and outcomes".)

Portopulmonary hypertension — Portal hypertension-associated pulmonary hypertension (portopulmonary hypertension) refers to the presence of pulmonary hypertension in patients with portal hypertension. The prevalence in patients with cirrhosis is approximately 2 percent [12]. Neither the prevalence nor the severity of portopulmonary hypertension appears to correlate with the degree of portal hypertension [12]. (See "Portopulmonary hypertension".)

Patients with portopulmonary hypertension may present with fatigue, dyspnea, peripheral edema, chest pain, and syncope. The diagnosis may be suggested by echocardiography and confirmed by right heart catheterization. Patients with moderate to severe portopulmonary hypertension are difficult to treat with medical therapy, and the perioperative mortality with liver transplantation is high.

Cirrhotic cardiomyopathy — Up to 50 percent of patients with advanced cirrhosis have features of cardiac dysfunction. The term "cirrhotic cardiomyopathy" has been used to describe such patients, who are characterized as having normal to increased cardiac output and contractility at rest, but a blunted response to pharmacologic, physiologic, or pathologic stress [13]. Patients may also have electrophysiologic abnormalities. It is thought to be related to both portal hypertension and cirrhosis. Cardiomyopathy can occur from any cause of cirrhosis, although patients with alcoholism or hemochromatosis may have additional contributing causes to cardiac dysfunction. (See "Definition and classification of the cardiomyopathies", section on 'Cirrhotic cardiomyopathy' and "Causes and pathophysiology of high-output heart failure", section on 'Cirrhosis'.)

Hepatic encephalopathy — Hepatic encephalopathy describes the spectrum of potentially reversible neuropsychiatric abnormalities seen in patients with liver dysfunction. Disturbance in the diurnal sleep pattern (insomnia and hypersomnia) is a common early feature that typically precedes overt neurologic signs (figure 1 and figure 2). More advanced neurologic features include the presence of asterixis, hyperactive deep tendon reflexes, and, less commonly, transient decerebrate posturing. (See "Hepatic encephalopathy in adults: Clinical manifestations and diagnosis".)

Treatments for hepatic encephalopathy include addressing any predisposing conditions (eg, infection or gastrointestinal bleeding), synthetic disaccharides (eg, lactulose), and nonabsorbable antibiotics (eg, rifaximin). (See "Hepatic encephalopathy in adults: Treatment".)

Hepatocellular carcinoma — Patients with cirrhosis have a markedly increased risk of developing hepatocellular carcinoma (HCC). Patients with most forms of chronic hepatitis are not at an increased risk until cirrhosis develops. Exceptions to this rule are patients with chronic hepatitis B virus infection, who can develop HCC in the absence of cirrhosis. (See "Epidemiology and risk factors for hepatocellular carcinoma" and "Surveillance for hepatocellular carcinoma in adults".)

Certain causes of cirrhosis appear to have a relatively increased risk for HCC. Patients with cirrhosis from hepatitis B, hepatitis C, nonalcoholic steatohepatitis, and hemochromatosis are at the highest risk, while those with cirrhosis from autoimmune hepatitis and Wilson disease appear to have a lower risk. (See "Epidemiology and risk factors for hepatocellular carcinoma", section on 'Cirrhosis'.)

Because of the large functional reserve of the liver, patients with HCC are frequently asymptomatic early in its course, and the diagnosis is often delayed. Decompensation in a patient with previously compensated cirrhosis should raise the clinical suspicion that HCC has developed. Other common signs and symptoms of HCC are usually related to mass effect from the tumor and include pain, early satiety, obstructive jaundice, and a palpable mass. HCCs can rupture, causing hemoperitoneum. Paraneoplastic manifestations include erythrocytosis, hypercalcemia, hypoglycemia, and diarrhea. (See "Clinical features and diagnosis of hepatocellular carcinoma".)

The diagnosis of HCC may be suggested by marked elevations of serum alpha-fetoprotein (AFP) or by characteristic radiographic findings. Elevated AFP is not specific for HCC since it can also be seen in patients with acute or chronic hepatitis, gonadal tumors, and pregnancy. However, rising serum AFP levels in a patient with cirrhosis should raise clinical suspicion for HCC. However, a significant proportion of patients with HCC have normal AFP levels, especially when the tumor is small. As a result, a normal AFP does not preclude a diagnosis. (See "Clinical features and diagnosis of hepatocellular carcinoma".)

Portal vein thrombosis — Portal vein thrombosis can develop in patients with cirrhosis and contribute to the development of portal hypertension. In patients with cirrhosis, the pathogenesis is likely related to unbalanced hemostasis and slowing of portal flow. Treatment often involves anticoagulation, though the decision to anticoagulate must take into account the patient's risk for bleeding, particularly if esophageal varices are present. (See "Epidemiology and pathogenesis of portal vein thrombosis in adults", section on 'Pathogenesis' and "Acute portal vein thrombosis in adults: Clinical manifestations, diagnosis, and management" and "Chronic portal vein thrombosis in adults: Clinical manifestations, diagnosis, and management".)

GENERAL MANAGEMENT

The major goals of managing patients with cirrhosis include:

- Slowing or reversing the progression of liver disease
- Preventing superimposed insults to the liver
- Identifying medications that require dose adjustments or should be avoided entirely (table 2)
- Managing symptoms and laboratory abnormalities
- Preventing, identifying, and treating the complications of cirrhosis
- Determining the appropriateness and optimal timing for liver transplantation

Slowing or reversing the progression of liver disease — Although cirrhosis is generally considered to be irreversible in its advanced stages, the exact point at which it becomes irreversible is unclear [14,15]. Some chronic liver diseases respond to treatment even when the liver disease has progressed to cirrhosis. Thus, specific therapies directed against the underlying cause of the cirrhosis should be instituted.

As examples:

- Patients with hepatitis C and advanced fibrosis or cirrhosis who achieve a sustained virologic response (SVR) with antiviral treatment have a lower risk of liver-related mortality compared with patients who do not achieve an SVR [16]. (See "Patient evaluation and selection for antiviral therapy for chronic hepatitis C virus infection", section on 'Bridging fibrosis and compensated cirrhosis'.)

- Abstinence from alcohol substantially improves survival in alcoholic cirrhosis. (See "Management of alcohol-associated steatosis and alcohol-associated cirrhosis", section on 'Abstinence'.)

- Successful treatment of chronic viral hepatitis can improve long-term outcomes and may affect fibrosis. In a study of 91 patients with chronic hepatitis C and significant fibrosis based on liver elastography, patients who achieved a sustained virologic response had a significant decrease in liver stiffness (and thus presumably fibrosis) 24 weeks after the end of treatment [17]. (See "Noninvasive assessment of hepatic fibrosis: Ultrasound-based elastography".)

Nonselective beta blockers (NSBB) have been studied for a possible role in preventing disease progression in patients with compensated cirrhosis, but the implication for clinical practice is uncertain. In a trial including 201 patients with compensated cirrhosis and portal hypertension (ie, hepatic venous pressure gradient [HVPG] ≥10 mmHg) with median follow-up of 37 months, patients treated with NSBB had lower rates of decompensated cirrhosis (defined by ascites, bleeding or encephalopathy) or death compared with placebo (16 versus 27 percent; HR 0.51, 95% 0.26-0.97) [18]. Further study is needed to establish a noninvasive method for identifying patients with portal hypertension because HVPG is not routinely measured [19]. (See "Portal hypertension in adults", section on 'Noninvasive tests'.)

In addition, long-term beta blocker use may not be tolerated by some patients due to adverse effects (fatigue, dizziness). (See "Major side effects of beta blockers".)

Preventing superimposed insults to the liver

Vaccinations — Vaccination against hepatitis A and B for those who are not already immune can help prevent superimposed insults to the liver. Other vaccinations, such a yearly influenza vaccination, are also recommended (figure 3). (See "Immunizations for patients with chronic liver disease".)

Avoidance of hepatotoxins — Patients with cirrhosis should avoid medications, supplements, and other substances that are commonly associated with liver injury. This includes abused substances, such as alcohol, hepatotoxic over-the-counter medications, prescribed drugs with hepatotoxic side effects, and certain herbal remedies. (See "Drug-induced liver injury" and "Hepatotoxicity due to herbal medications and dietary supplements" and "Management of pain in patients with advanced chronic liver disease or cirrhosis".)

Medication adjustments — Patients with cirrhosis are at increased risk of adverse events with many medications because of impaired hepatic metabolism or renal excretion. Many medications require dose adjustments or should be avoided entirely (table 2) [20]. (See "Overview of medication adjustments for adult patients with cirrhosis".)

Issues related to the use of pain medications in patients with cirrhosis are discussed in detail elsewhere. (See "Management of pain in patients with advanced chronic liver disease or cirrhosis".)

Management of symptoms and laboratory abnormalities

Muscle cramps — Patients with cirrhosis may experience muscle cramps, which can be severe [21-24]. The cause is incompletely understood, although they may be related to a reduction in effective circulating plasma volume, nerve dysfunction, and alterations in energy metabolism [25]. If other disorders are excluded, treatments that may be helpful include quinine sulfate, branched-chain amino acids, taurine, zinc repletion (for patients with low levels), and correction of electrolytes. We prefer quinine sulfate if patients are able to obtain it (200 to 300 mg at bedtime). (See "Nocturnal leg cramps", section on 'Causes and pathogenesis'.)

In patients suspected of having muscle cramps related to cirrhosis, other causes of pain should be excluded. Muscle cramping related to cirrhosis is often spontaneous, chronic, and nocturnal. If there is new onset of persistent pain, other disorders such as rhabdomyolysis, myositis, or acute kidney injury should be considered.

Quinine sulfate has been found to be beneficial for the treatment of muscle cramps in patients with cirrhosis, but it is no longer available through pharmacies for treatment of cramps because of side effects including arrhythmias and thrombocytopenia [26,27]. However, it is available through some online retailers. In a meta-analysis that included 409 patients who completed participation in randomized trials, tinnitus was the only side effect that occurred more often with quinine than with placebo. Quinine sulfate may act by reducing the excitability of the motor nerve [25]. Note that quinine sulfate is **not** the same as quinidine sulfate (the latter being an antiarrhythmic drug). (See "Nocturnal leg cramps", section on 'Management'.)

Other treatments have shown some benefit in small studies. These include branched-chain amino acids (4 g granules three times daily) [28,29], taurine (3 g once daily) [30,31], and vitamin E (200 mg three times daily) [32]. Branched-chain amino acids and taurine are thought to act by correcting alterations in energy metabolism, and vitamin E is thought to decrease circulating free radicals within cells. Correcting electrolyte abnormalities is often recommended, though it is not known whether it improves symptoms [25].

Zinc has been used in the past and may be beneficial in patients with low zinc levels, though its role as a therapeutic agent remains unclear [25,33]. When used, it has been given as 220 mg twice daily. Magnesium supplementation has not specifically been studied in patients with liver disease, but it does not appear to be beneficial in patients with skeletal muscle cramps in general [34].

One suggested approach to treatment is [25]:

- Confirm the muscle cramps are related to cirrhosis
- Check electrolyte levels and replete if low
- Treat with branched-chain amino acids if symptoms persist
- Treat with taurine if symptoms persist
- Treat with vitamin E if symptoms persist

Our approach is to treat with quinine sulfate if patients can obtain it. If not, we believe the above approach is a reasonable alternative.

Umbilical hernias — Umbilical hernias pose a management dilemma in patients with cirrhosis, since they often develop in patients with severe liver disease and ascites who are at high risk of complications with surgical repair [35]. Successful management using a variety of minimally invasive surgical techniques has been reported [36-40]. However, clinical experience has tempered our enthusiasm for elective surgical repair. We have witnessed an unacceptably high complication and recurrence rate in our patients referred for elective repair [41]. Liver transplantation surgeons prefer to repair hernias at the time of transplantation and not before because many have observed high postoperative morbidity and mortality when repair was performed before the transplantation.

We have adopted the following approach to managing umbilical hernias in patients with cirrhosis:

- Most patients with ruptured or incarcerated hernias are referred for immediate repair. However, if incarceration is detected early, it can sometimes be reduced.

- Patients with symptomatic hernias or those with marked thinning of the skin overlying the hernia sac (a sign of impending rupture), especially if there is weeping of fluid or an eschar on the apex of the hernia, are referred for elective repair.

- Patients with asymptomatic hernias are managed conservatively, with surgical correction of the hernia performed at the time of liver transplantation. The cornerstone of conservative management in asymptomatic patients with umbilical hernias is aggressive management of ascites. Elastic/Velcro

abdominal binders can also help reduce pain and minimize further enlargement of the hernia. (See "Ascites in adults with cirrhosis: Initial therapy" and "Ascites in adults with cirrhosis: Diuretic-resistant ascites".)

Hyponatremia — Hyponatremia is a common problem in patients with advanced cirrhosis. The pathogenesis of hyponatremia is directly related to the hemodynamic changes and secondary neurohumoral adaptations that occur in the setting of cirrhosis, resulting in an impaired ability to excrete ingested water. The severity of the hyponatremia is related to the severity of the cirrhosis. The management of hyponatremia is discussed elsewhere. (See "Hyponatremia in patients with cirrhosis", section on 'Management'.)

Thrombocytopenia or elevated INR — Patients with cirrhosis frequently have low platelet counts and elevated international normalized ratios (INRs). Because the liver makes coagulation factors as well as anticoagulant proteins, liver disease can lead to a hypocoagulable state or a hypercoagulable state. The relative balance or imbalance of these factors is not reflected in conventional indices of coagulation, such as the prothrombin time, activated partial thromboplastin time, or INR. (See "Hemostatic abnormalities in patients with liver disease", section on 'Physiologic effects of hepatic dysfunction'.)

Patients typically only need treatment for thrombocytopenia if an invasive procedure that is at moderate or high risk for bleeding is planned, or in the setting of active bleeding. It is reasonable to aim for platelet counts of at least 50,000/microL during moderate-risk procedures [42] or interventions and platelet counts closer to 100,000/microL in high-risk situations or in the presence of active bleeding [43]. (See "Hemostatic abnormalities in patients with liver disease", section on 'Invasive procedures'.)

Because conventional indices of coagulation are not helpful in determining a patient's bleeding risk, patients who require an invasive procedure that is at moderate or high risk for bleeding or who have active bleeding may need additional testing, such as a determination of fibrinogen levels, thromboelastography, or thromboelastometry to guide management. While plasma is commonly given to patients with chronic liver disease and an elevated INR, plasma infusion may have adverse effects on portal vein pressures and collateral vessel flow. In addition, the traditional dose of two units of plasma is unlikely to significantly alter coagulation factor levels. (See "Clinical use of plasma components", section on 'Plasma products' and "Hemostatic abnormalities in patients with liver disease", section on 'Laboratory abnormalities'.)

The management of patients with chronic liver disease who require an invasive procedure that is at moderate or high risk for bleeding, or who have active bleeding, is discussed in detail elsewhere. (See "Hemostatic abnormalities in patients with liver disease", section on 'Bleeding' and "Hemostatic abnormalities in patients with liver disease", section on 'Invasive procedures'.)

Preventing and identifying complications — Patients should be monitored for the development of complications, and when possible, steps should be taken to prevent their development. In particular, patients should be screened for esophageal varices and hepatocellular carcinoma. If varices are present, prophylactic treatment with beta blockers or esophageal variceal ligation is indicated.

Other measures to decrease the risk of complications include judicious diuresis and avoiding proton pump inhibitors in patients without clear indications for their use (spontaneous bacterial peritonitis); treating infections (spontaneous bacterial peritonitis, hepatic encephalopathy); avoiding sedatives and treating hypokalemia and hyponatremia (hepatic encephalopathy); avoiding nephrotoxic agents and aggressive diuresis (hepatorenal syndrome); and only using urinary catheters, mechanical ventilation, and central lines when clearly indicated (secondary infections). (See 'Major complications' above.)

- **Variceal bleeding** – All patients with cirrhosis should undergo screening for esophageal varices with upper endoscopy so that prophylactic therapy can be given to those with varices that are at increased risk for bleeding and to determine the risk of variceal hemorrhage. Prophylactic therapy most commonly involves treatment with a nonselective beta blocker or endoscopic variceal ligation, which reduces the risk of variceal bleeding. (See "Primary and pre-primary prophylaxis against variceal hemorrhage in patients with cirrhosis".)

- **Hepatocellular carcinoma** – Patients with cirrhosis should undergo surveillance with ultrasonography every six months. (See "Surveillance for hepatocellular carcinoma in adults", section on 'Our approach to surveillance'.)

- **Spontaneous bacterial peritonitis** – The risk of spontaneous bacterial peritonitis (SBP) can be reduced by efforts to diurese patients since diuresis concentrates ascitic fluid, thereby raising ascitic fluid opsonic activity. Early recognition and aggressive treatment of localized infections (eg, cystitis, cellulitis) can also help to prevent bacteremia and SBP. Proton pump inhibitor use has been associated with an increased risk of SBP, so proton pump inhibitors should only be given to patients who have clear indications for their use. Finally, prophylactic antibiotics aimed at decontaminating the gut have a role in specific clinical settings. (See "Spontaneous bacterial peritonitis in adults: Treatment and prophylaxis".)

- **Hepatic encephalopathy** – Patients with cirrhosis should be evaluated regularly for hepatic encephalopathy, the earliest features of which can be subtle. Events that can precipitate hepatic encephalopathy include the development of variceal bleeding, infection (such as SBP), the administration of sedatives, hypokalemia, and hyponatremia, all of which should be corrected/avoided whenever possible (table 3). (See "Hepatic encephalopathy in adults: Clinical manifestations and diagnosis" and "Hepatic encephalopathy in adults: Treatment".)

- **Portal vein thrombosis** – Enoxaparin may be effective for preventing portal vein thrombosis (PVT) in patients with cirrhosis, though it is not used routinely. If it is to be used, we suggest eradication of varices (if present) prior to initiation of anticoagulation when possible. (See "Chronic portal vein thrombosis in adults: Clinical manifestations, diagnosis, and management", section on 'Prevention in patients with cirrhosis' and "Primary and pre-primary prophylaxis against variceal hemorrhage in patients with cirrhosis", section on 'Endoscopic variceal ligation'.)

- **Hepatorenal syndrome** – Nephrotoxic agents (such as aminoglycosides) and vigorous diuresis should be avoided in patients with cirrhosis since they can precipitate renal failure. (See "Hepatorenal syndrome".)

- **Secondary infections** – Patients with cirrhosis who are hospitalized often acquire infections while in the hospital. Factors that have been associated with hospital-acquired secondary infections in patients with cirrhosis include the use of urinary catheters, mechanical ventilation, and the placement of central lines [44]. Many of these interventions are performed routinely (such as placement of urinary catheters to measure urine output). However, avoiding these interventions unless they are absolutely necessary may decrease the risk of acquiring an infection while in the hospital, and it is our practice to only use these interventions when clearly indicated.

  In a study of 207 patients with cirrhosis who were admitted with or developed an infection during hospitalization, 50 (24 percent) developed a second infection during hospitalization [44]. Respiratory infections were the most common (14 patients), followed by urinary tract infections (13 patients), and *Clostridioides* (formerly *Clostridium*) *difficile*. Of the urinary tract infections, 6 (46 percent) were related to the use of bladder catheters. Other factors associated with second infections included intensive care unit admission, the use of central lines, mechanical ventilation, shock, renal replacement therapy, and hepatic encephalopathy. Overall mortality was 39 percent, but it was 48 percent for those who developed a second infection during admission.

Treatment of complications — The treatment of the complications of cirrhosis is discussed in the respective topic reviews. (See 'Major complications' above.)

Liver transplantation — Liver transplantation is the definitive treatment for patients with decompensated cirrhosis. It is important to determine whether patients may be eligible for transplantation and to refer them to a transplant center for evaluation. Several guidelines are available which help determine when referral for liver transplantation may be beneficial. The decision to proceed to liver transplantation (either cadaveric or live donor) depends upon the severity of disease, quality of life, and the absence of contraindications. (See "Liver transplantation in adults: Patient selection and pretransplantation evaluation".)

PROGNOSIS

The prognosis of cirrhosis is highly variable since it is influenced by a number of factors, including etiology, severity, presence of complications, and comorbid diseases. Once decompensation occurs (eg, the patient develops variceal bleeding, hepatic encephalopathy, or spontaneous bacterial peritonitis), mortality rates are high. (See 'Decompensated cirrhosis' below.)

Compensated cirrhosis — Patients with cirrhosis who have not developed major complications are classified as having compensated cirrhosis. The median survival of patients with compensated cirrhosis is >12 years [45]. Patients with varices but who have not developed variceal bleeding are considered to have compensated cirrhosis, though their prognosis is worse than that of patients who have compensated cirrhosis without varices (3.4 versus 1.0 percent one-year mortality rates) [45].

Decompensated cirrhosis — Patients who have developed complications of cirrhosis, such as variceal hemorrhage, ascites, spontaneous bacterial peritonitis, hepatocellular carcinoma, hepatorenal syndrome, or hepatopulmonary syndrome, are considered to have decompensated cirrhosis and have a worse prognosis than those with compensated cirrhosis. (See 'Major complications' above.)

A systematic review found that the median survival was ≤6 months in patients with decompensated cirrhosis and a Child-Pugh score ≥12 or a Model for End-stage Liver Disease (MELD) score ≥21 [46]. In addition, patients with decompensated cirrhosis who had been hospitalized with an acute liver-related illness (eg, variceal hemorrhage or spontaneous bacterial peritonitis) had a median survival of ≤6 months if the Child-Pugh score was ≥12 or the MELD score was ≥18.

An important factor related to survival is mean arterial pressure. In a series of 139 patients with cirrhosis and ascites, a mean arterial pressure of ≤82 mmHg was an important predictor of survival [47]. Among patients with a mean arterial pressure ≤82 mmHg, survival was 20 percent at 24 months and 0 percent at 48 months (compared with 70 and 50 percent, respectively, for patients with a mean arterial pressure >82 mmHg).

Another factor that may be associated with survival is the presence of relative adrenal insufficiency [48,49]. In a study of 143 patients who were admitted to the hospital with decompensated cirrhosis, relative adrenal insufficiency was detected in 37 patients (26 percent) [48]. At the time of presentation, compared with patients who did not have relative adrenal insufficiency, patients with relative adrenal insufficiency had lower mean arterial pressures (76 versus 83 mmHg) and serum sodium levels (131 versus 135 mEq/L) and had higher blood urea nitrogen levels (32 versus 24 mg/dL). During three months of follow-up, patients with relative adrenal insufficiency were more likely to develop infection (41 versus 21 percent), severe sepsis (27 versus 9 percent), type 1 hepatorenal syndrome (16 versus 3 percent), and death (22 versus 7 percent). (See "Diagnosis of adrenal insufficiency in adults".)

Among patients with cirrhosis and severe septic shock, administration of hydrocortisone may improve outcomes [50]. (See "Treatment of adrenal insufficiency in adults", section on 'Glucocorticoid regimens'.)

Other factors associated with poor survival in patients with decompensated cirrhosis included hepatopulmonary syndrome, rapidly progressive hepatorenal syndrome, and intensive care unit admission for complications of liver disease along with hypotension requiring pressor support, serum creatinine >1.5 mg/dL, or jaundice.

Patients with decompensated cirrhosis often require liver transplantation. For those who are not candidates, hospice care can be considered for patients with predicted survival of ≤6 months. (See "Liver transplantation in adults: Patient selection and pretransplantation evaluation" and "Benefits, services, and models of subspecialty palliative care".)

Predictive models — Multiple studies have attempted to predict the prognosis of patients with cirrhosis based on clinical and laboratory information. Two commonly used models are the Child-Pugh classification and MELD.

Child-Pugh classification — The Child-Pugh classification (table 4) has been used to assess the risk of non-shunt operations in patients with cirrhosis (calculator 1 and calculator 2) [51]. It is a modification of the Child-Turcotte classification, which incorporated five variables that were designed to stratify the risk of portacaval shunt surgery in patients with cirrhosis. The variables included the serum albumin and bilirubin, ascites, encephalopathy, and nutritional status (table 5) [52]. The Child-Pugh classification replaces nutritional status with prothrombin time. The score ranges from 5 to 15. Patients with a score of 5 or 6 have Child-Pugh class A cirrhosis (well-compensated cirrhosis), those with a score of 7 to 9 have Child-Pugh class B cirrhosis (significant functional compromise), and those with a score of 10 to 15 have Child-Pugh class C cirrhosis (decompensated cirrhosis).

In a review of 92 patients with cirrhosis who underwent abdominal surgery, the mortality rate was 10 percent for patients with Child-Pugh class A cirrhosis, 30 percent for patients with Child-Pugh class B cirrhosis, and 82 percent for patients with Child-Pugh class C cirrhosis [53]. Other studies have validated the utility of the Child-Pugh classification for the assessment of surgical risk [54]. (See "Assessing surgical risk in patients with liver disease".)

The Child-Pugh classification system also correlates with survival in patients not undergoing surgery; one-year survival rates for patients with Child-Pugh class A, B, and C cirrhosis are approximately 100, 80, and 45 percent, respectively [55,56]. Child-Pugh class is also associated with the likelihood of developing of complications of cirrhosis. As an example, patients with Child-Pugh class C cirrhosis are much more likely to develop variceal hemorrhage than those with Child-Pugh class A cirrhosis [57].

MELD score — Another model to predict prognosis in patients with cirrhosis is the MELD score. It is based upon bilirubin levels, creatinine, INR, and the etiology of cirrhosis (calculator 3 and calculator 4). The MELD score has been adopted for use in prioritizing patients awaiting liver transplantation and has an expanding role in predicting outcomes in patients with liver disease in the non-transplantation setting. In January 2016, Organ Procurement and Transplantation Network Policy 9.1 (MELD Score) was updated to include serum sodium as a factor in the calculation of the MELD score [58]. The MELDNa score can be calculated online. (See "Model for End-stage Liver Disease (MELD)".)

WHEN TO REFER TO A SPECIALIST

Referral to a hepatologist is recommended if the patient develops decompensated cirrhosis or major complications of cirrhosis. Patients with a MELD score ≥10 should be referred to a liver transplantation center for evaluation. In addition, referral to a hepatologist should be considered if the patient requires treatment for the underlying cause of the cirrhosis (eg, hepatitis C, autoimmune hepatitis) or if the clinician managing the patient would like the assistance of a hepatologist in the patient's general management. (See "Liver transplantation in adults: Patient selection and pretransplantation evaluation", section on 'Cirrhosis'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Cirrhosis".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Cirrhosis (The Basics)" and "Patient education: Liver cancer (The Basics)")

- Beyond the Basics topics (see "Patient education: Cirrhosis (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- Cirrhosis represents a late stage of progressive hepatic fibrosis characterized by distortion of the hepatic architecture and the formation of regenerative nodules. It is generally considered to be irreversible in its advanced stages. In earlier stages, specific treatments aimed at the underlying cause of liver disease may improve or even reverse cirrhosis. (See 'Introduction' above.)

- Patients with cirrhosis are susceptible to a variety of complications, and their life expectancy can be markedly reduced. Major complications of cirrhosis include (see 'Major complications' above):

  - Variceal hemorrhage
  - Ascites
  - Spontaneous bacterial peritonitis
  - Hepatic encephalopathy
  - Hepatocellular carcinoma
  - Hepatorenal syndrome
  - Hepatopulmonary syndrome
  - Portal vein thrombosis
  - Cardiomyopathy

- The major goals of managing patients with cirrhosis include (see 'General management' above):

  - Slowing or reversing the progression of liver disease (see 'Slowing or reversing the progression of liver disease' above).
  - Preventing superimposed insults to the liver (see 'Preventing superimposed insults to the liver' above).
  - Identifying medications that require dose adjustments or should be avoided entirely (table 2) (see 'Medication adjustments' above and "Overview of medication adjustments for adult patients with cirrhosis").
  - Managing symptoms and laboratory abnormalities (see 'Management of symptoms and laboratory abnormalities' above).
  - Preventing and treating the complications of cirrhosis (see 'Preventing and identifying complications' above).
  - Determining the appropriateness and optimal timing for liver transplantation (see 'Liver transplantation' above).

- The prognosis of cirrhosis is highly variable since it is influenced by a number of factors, including etiology, severity, presence of complications, and comorbid diseases. Once decompensation occurs (eg, the patient develops variceal bleeding, hepatic encephalopathy, or spontaneous bacterial peritonitis), mortality rates are high. (See 'Decompensated cirrhosis' above.)

Topic 1263 Version 40.0

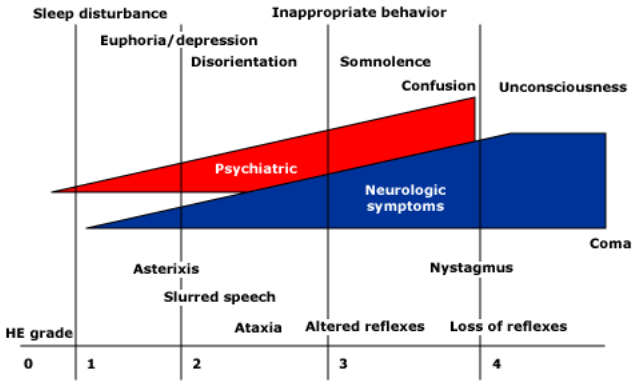
GRAPHICS

Common complications of cirrhosis

Variceal hemorrhage
Ascites
Spontaneous bacterial peritonitis
Hepatic encephalopathy
Hepatocellular carcinoma
Hepatorenal syndrome
Hepatopulmonary syndrome
Hepatic hydrothorax
Portopulmonary hypertension
Cirrhotic cardiomyopathy
Portal vein thrombosis

Graphic 65667 Version 3.0

Evolution of hepatic encephalopathy



Graphic 58163 Version 1.0

Clinical features of hepatic encephalopathy

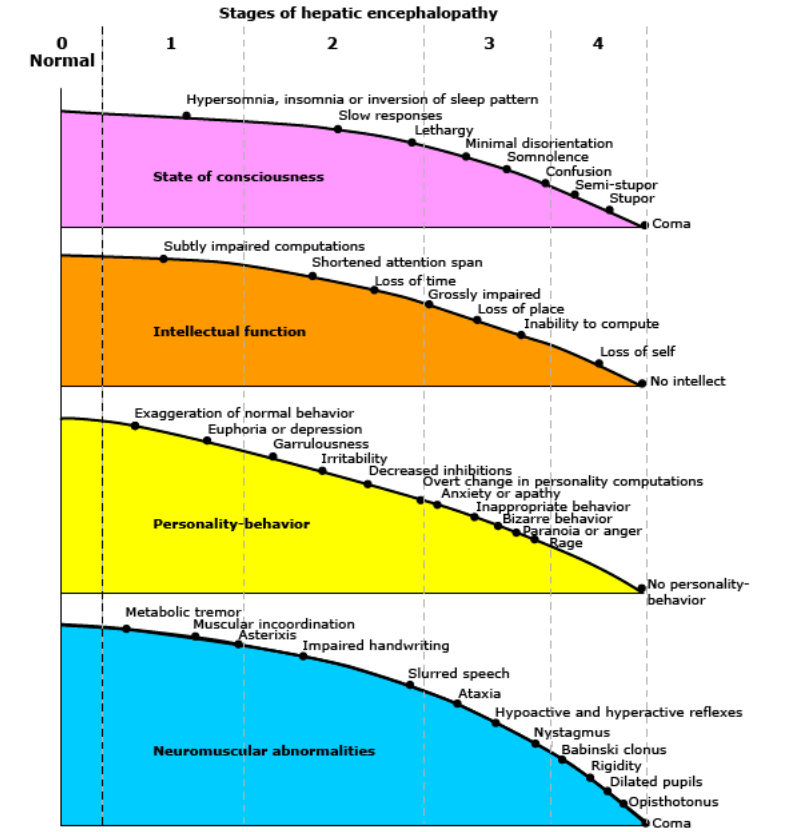


Diagram depicting the grade of hepatic encephalopathy and the clinical features associated with advancing stages.

Data from: Conn HO, Lieberthal MM. The hepatic coma syndromes and lactulose. Lippincott Williams & Wilkins, Baltimore 1979.

Graphic 70740 Version 5.0

Analgesic use in adult patients with advanced chronic liver disease or cirrhosis

	Altered response and pharmacokinetics	Management suggestions
Non-opioid analgesics		
Acetaminophen (paracetamol)	▪ Glutathione tissue stores needed to block formation of acetaminophen's toxic metabolite (NAPQI) are reduced in individuals with cirrhosis or malnutrition, thereby lowering the dose threshold of acetaminophen that can be safely administered each day. ▪ Active alcohol consumption further reduces available glutathione stores. ▪ Half-life of acetaminophen may be prolonged by up to 2-fold compared with healthy patients.	▪ Acetaminophen is generally well tolerated in patients with CLD or cirrhosis who do not consume alcohol, provided the total daily dose is limited to no more than 2 g/day. ▪ For short-term or one-time use, a maximum total acetaminophen dose of up to 4 g/day may be considered in lower risk patients who do not consume alcohol and have CLD or early stage compensated cirrhosis. ▪ Warn patients concerning acetaminophen content in combination prescription analgesics (eg, oxycodone-acetaminophen) and non-prescription (OTC) preparations. ▪ Avoid use in patients with advanced CLD or cirrhosis who are actively consuming alcohol, malnourished, not eating, receiving multiple medications that undergo hepatic biotransformations, or any co-administered medication that is a potent inducer of hepatic enzymes. ▪ A list of medications that induce hepatic enzymes is provided in a separate table.
Nonselective nonsteroidal antiinflammatory drugs (NSAIDs) including aspirin	▪ An increased risk of GI mucosal bleeding, variceal hemorrhage, impaired renal function, and development of diuretic-resistant ascites is seen with use of NSAIDs in patients with cirrhosis with portal hypertension. ▪ NSAIDs can decrease GFR and impair renal function in patients with advanced CLD or cirrhosis. ▪ Most NSAIDs are metabolized by CYP and highly bound to serum albumin, increasing drug bioavailability and potential for toxicity in patients with advanced CLD or cirrhosis. ▪ Individual NSAIDs (eg, diclofenac) have been associated with hepatotoxicity in general population.	▪ NSAIDs and aspirin should be avoided in patients with advanced CLD or cirrhosis. ▪ Low-dose acetaminophen should be used instead of NSAIDs.
Selective COX-2 inhibitors	▪ Available data are inadequate to establish the safety of selective COX-2 inhibitors in patients with advanced CLD or cirrhosis. Refer to UpToDate content for detail. ▪ Excess cardiovascular events have been observed with this class of medications when used by patients without cirrhosis.	▪ We advise against use of selective COX-2 inhibitors in patients with advanced CLD or cirrhosis, pending availability of additional safety data. ▪ If used, celecoxib product information suggests a 50% dose reduction for Child-Pugh class B cirrhosis.
Opioid analgesics (refer to important note)*		
Fentanyl	▪ Metabolized by CYP3A4 to inactive (nontoxic) metabolites. ▪ Parent drug can accumulate after repeated dosing or when administered as a continuous infusion due to tissue and protein binding. ▪ Less histamine release than other opiates. ▪ Less hemodynamic disturbance than other opiates.	▪ Generally a good choice for patients with CLD or cirrhosis when opiate treatment is indicated. ▪ Useful option in patients with renal failure in setting of cirrhosis. ▪ No dose adjustment needed for single dose. ▪ With repeated dosing, reduce dose and frequency by approximately 25 to 50%. ▪ Initiate transdermal patch at half usual dose.
Hydrocodone, oxycodone	▪ Metabolized to active metabolite by CYP2D6 and CYP3A4, which may result in a prolonged time to onset, variable analgesic efficacy, and risk of accumulation in patients with advanced CLD or cirrhosis.	▪ Due to variability of onset and analgesic efficacy in hepatic insufficiency, fentanyl or hydromorphone may be better tolerated and more safely and predictably adjusted than hydrocodone and oxycodone in patients with advanced CLD or cirrhosis. ▪ If used, reduce dose and frequency.
Hydromorphone	▪ Hepatically metabolized by non-CYP transformations (glucuronidation) to apparently inactive metabolites. ▪ Oral bioavailability in advanced CLD or cirrhosis seems to be increased relative to healthy individuals due to diminished first-pass extraction, but specific data are lacking, and wide inter-individual variability is observed.	▪ Generally a good choice for patients with advanced CLD or cirrhosis. ▪ Reduce dose and frequency by approximately 50%. ▪ Titrate dose gradually to avoid accumulation of active drug. ▪ Useful option in patients with renal failure in setting of cirrhosis. ▪ Small volume for IV preparation and non-CYP3A4 metabolism may be advantageous given clinical setting.
Meperidine (pethidine), codeine	▪ Altered oral bioavailability and elevated risk of accumulation of intermediates (codeine) or toxic metabolite (meperidine). ▪ Meperidine is highly bound to serum protein. ▪ Unpredictable analgesic efficacy and increased risk of toxicity in patients with advanced CLD or cirrhosis.	▪ Meperidine and codeine should be avoided in patients with advanced CLD or cirrhosis.
Morphine	▪ Oral bioavailability in advanced CLD or cirrhosis increased up to 100% relative to healthy individuals due to diminished first-pass extraction. Wide inter-individual variability may be seen. ▪ Hepatically metabolized by non-CYP transformations (glucuronidation). ▪ Half-life can be increased by up to 2-fold. ▪ Accumulation of metabolites with complex effects (eg, respiratory depression, analgesic tolerance, neurotoxicity) can occur in patients with cirrhosis and renal failure.	▪ Reduce dose and frequency by approximately 50% in advanced CLD or cirrhosis. ▪ Titrate dose gradually to avoid accumulation of active drug. ▪ Avoid in patients with cirrhosis and renal failure.
Naloxone-containing opioid combinations	▪ Orally administered naloxone, which is included in these combinations to deter abuse (ie, crushing, snorting) and counteract constipation by a local effect, is systemically absorbed in patients with moderate to severe hepatic impairment. ▪ Systemic absorption of naloxone will reverse analgesic efficacy and can precipitate opioid withdrawal.	▪ Oxycodone-naloxone: • Reduce starting dose by one-half to two-thirds in mild hepatic impairment. • Use in advanced CLD or cirrhosis is contraindicated. ▪ Pentazocine-naloxone: Avoid use.
Remifentanil	▪ Cleared by nonspecific plasma esterases to inactive metabolites. ▪ Does not accumulate in hepatic or renal insufficiency. ▪ Prompt reversal of analgesia and sedation upon discontinuation.	▪ No adjustment needed.
Tramadol	▪ Hepatically metabolized to active metabolite by CYP3A4, CYP2D6, and glucuronidation.	▪ Avoid use in patients with decompensated cirrhosis. ▪ Avoid use in patients at risk for seizures.

	▪ Unpredictable onset, variable analgesic efficacy, and risk of accumulation in patients with cirrhosis. ▪ Can interact with serotoninergic medications, including antidepressants.	▪ Based on limited experience, a reduced dose of 25 mg every 8 hours may be considered for treatment of pain in patients with advanced CLD or well-compensated cirrhosis.
Adjunctive agents for neuropathic pain		
Carbamazepine	▪ Carbamazepine is a potent inducer of hepatic enzymes and has been associated with hepatotoxicity and serious allergic reactions in genetically predisposed individuals. ▪ May precipitate rapid decompensation in patients with cirrhosis.	▪ Carbamazepine should be avoided as there are safer options for treatment of neuropathic pain in patients with advanced CLD or cirrhosis.
Gabapentin	▪ Not hepatically metabolized or bound to plasma proteins. ▪ Highly dependent on renal function for clearance of unchanged drug. ▪ Sedation, ataxia, dizziness, and nausea may limit usefulness in patients with advanced CLD or cirrhosis.	▪ Initiate treatment at 300 mg orally per day and gradually titrate dose if needed over weeks due to delayed onset of action and to improve tolerability. ▪ Maintenance dose is dependent on renal function. For specific adjustment, refer to Lexicomp monograph included with UpToDate. ▪ According to the product information, should not be abruptly stopped due to risk of discontinuation symptoms (eg, nausea, insomnia, anxiety) and/or rebound seizures in at-risk patients.
Lidocaine topical patch	▪ Low (3 to 5%) systemic absorption through intact skin.	▪ A good choice for local relief of pain in limited areas of intact skin in patients with advanced CLD or cirrhosis. ▪ No adjustment needed in hepatic impairment.
Nortriptyline	▪ Subject to extensive first-pass metabolism and CYP2D6 transformations, which include active and inactive metabolites. ▪ Accumulation of metabolites in hepatic impairment is less likely with nortriptyline than amitriptyline. ▪ Dose-related anticholinergic and cardiovascular side effects may be poorly tolerated in medically ill patients with advanced CLD or cirrhosis.	▪ Initiate treatment at 10 mg orally each night and gradually titrate dose if needed over weeks due to delayed onset of action and to improve tolerability. ▪ Use "low" maintenance dose for neuropathic pain (eg, 25 mg to no more than 50 mg daily) to decrease risk of accumulation.
Pregabalin	▪ Not hepatically metabolized or bound to plasma proteins. ▪ Highly dependent on renal function for clearance of unchanged drug. ▪ Sedation and dizziness may limit usefulness in patients with advanced CLD or cirrhosis.	▪ Initiate treatment at 50 mg orally twice per day and gradually titrate dose if needed over weeks due to delayed onset of action. ▪ Maintenance dose is dependent on renal function. For specific adjustment, refer to Lexicomp monograph included with UpToDate. ▪ According to the product information, should not be abruptly stopped due to risk of discontinuation symptoms (eg, nausea, insomnia, anxiety) and/or rebound seizures in at-risk patients.

For information about use and adjustment of medications other than analgesics in CLD, refer to separate table in UpToDate on non-analgesic medications used in adult patients with advanced CLD or cirrhosis.

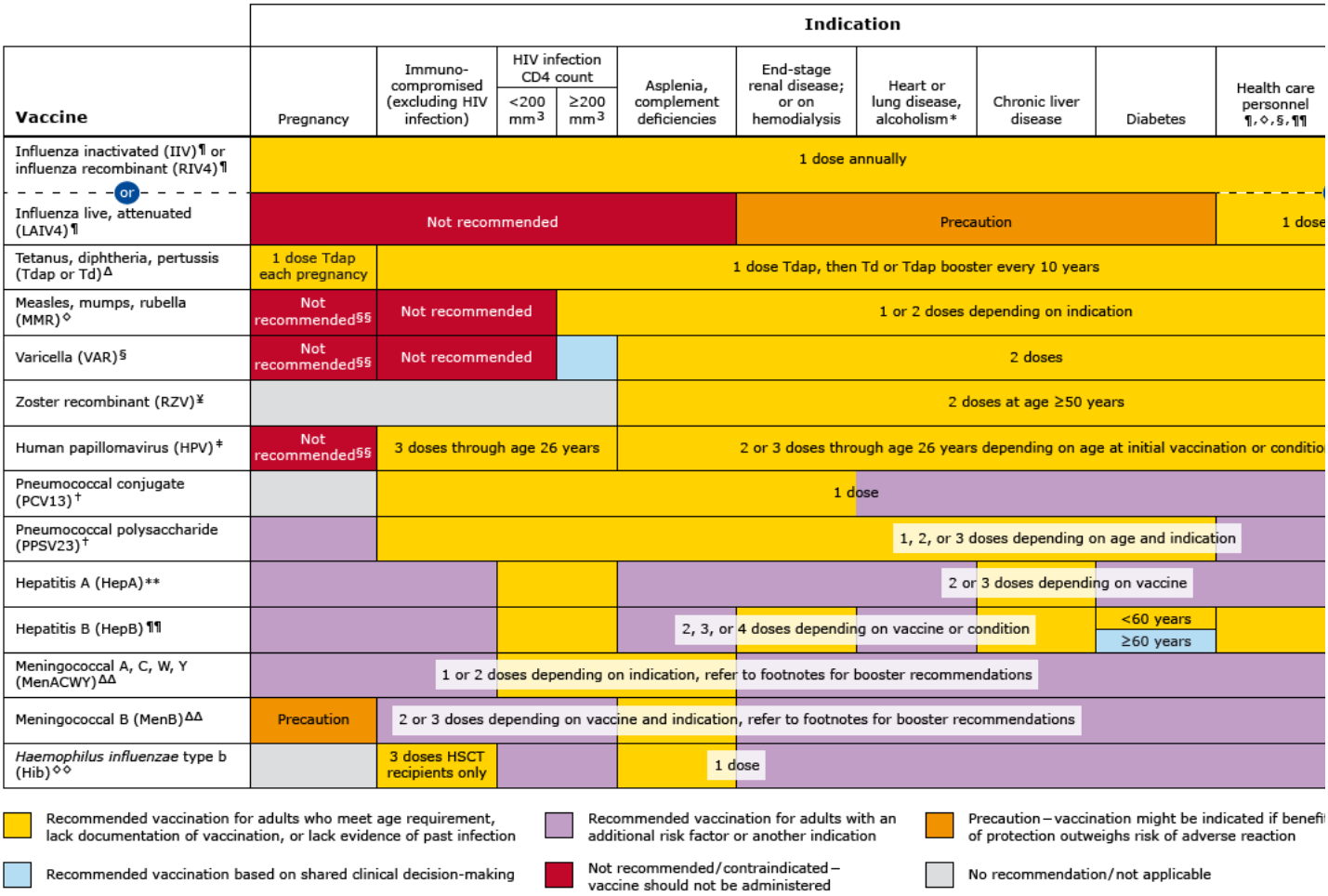
NAPQI: n-acetyl-p-benzoquinone imine; CLD: chronic liver disease; OTC: over the counter; GI: gastrointestinal; GFR: glomerular filtration rate; CYP: cytochrome P-450; COX-2: cyclooxygenase 2; IV: intravenous; HE: hepatic encephalopathy.
* **NOTE:** All opioids can worsen or precipitate HE and should be used cautiously or avoided in patients with portal hypertension and preexisting HE.

Prepared with data from:

1. Lewis JH, Stine JG. Review article: Prescribing medications in patients with cirrhosis – a practical guide. Aliment Pharmacol Ther 2013; 37:1132.
2. Chandok N, Watt KD. Pain management in the cirrhotic patient: The clinical challenge. Mayo Clin Proc 2010; 85(5):451.

Graphic 90196 Version 14.0

Recommended adult immunization schedule by medical condition and other indications - United States, 2021



COVID-19 vaccination

The Advisory Committee on Immunization Practices (ACIP) recommends use of COVID-19 vaccines within the scope of the Emergency Use Authorization or Biologics License Application fo vaccine. Interim ACIP recommendations for the use of COVID-19 vaccines can be found at www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/covid-19.html.

HSCT: hematopoietic stem cell transplant.

* Precaution for LAIV4 does not apply to alcoholism.

¶ Influenza vaccination

- **Routine vaccination:**
  - Persons age 6 months or older: 1 dose any influenza vaccine appropriate for age and health status annually.
  - For additional guidance, refer to www.cdc.gov/flu/professionals/index.htm.
- **Special situations:**
  - Egg allergy, hives only: 1 dose any influenza vaccine appropriate for age and health status annually.
  - Egg allergy - any symptom other than hives (eg, angioedema, respiratory distress): 1 dose any influenza vaccine appropriate for age and health status annually. If using an influenza vaccine ccIIV4, administer in medical setting under supervision of health care provider who can recognize and manage severe allergic reactions. Severe allergic reactions to any vaccine can occur eve history of previous allergic reaction. Therefore, all vaccine providers should be familiar with the office emergency plan and certified in cardiopulmonary resuscitation. A previous severe allergi influenza vaccine is a contraindication to future receipt of the vaccine.
  - LAIV4 should not be used in persons with the following conditions or situations:
    - History of severe allergic reaction to any vaccine component (excluding egg) or to a previous dose of any influenza vaccine.
    - Immunocompromised due to any cause (including medications and HIV infection).
    - Anatomic or functional asplenia.
    - Close contacts or caregivers of severely immunosuppressed persons who require a protected environment.
    - Pregnancy.
    - Cranial cerebrospinal fluid/oropharyngeal communications.
    - Cochlear implant.
    - Received influenza antiviral medications oseltamivir or zanamivir within the previous 48 hours, peramivir within the previous 5 days, or baloxavir within the previous 17 days.
    - Adults 50 years or older.
  - History of Guillain-Barré syndrome within 6 weeks after previous dose of influenza vaccine: Generally, should not be vaccinated unless vaccination benefits outweigh risks for those at higher r complications from influenza.

Δ Tetanus, diphtheria, and pertussis vaccination

- **Routine vaccination:**
  - Previously did not receive Tdap at or after age 11 years: 1 dose Tdap, then Td or Tdap every 10 years.
- **Special situations:**
  - Previously did not receive primary vaccination series for tetanus, diphtheria, or pertussis: At least 1 dose Tdap followed by 1 dose Td or Tdap at least 4 weeks after Tdap and another dose Td months after last Td or Tdap (Tdap can be substituted for any Td dose, but preferred as first dose), Td or Tdap every 10 years thereafter.
  - Pregnancy: 1 dose Tdap during each pregnancy, preferably in early part of gestational weeks 27 to 36.
  - Wound management: Persons with 3 or more doses of tetanus-toxoid-containing vaccine: For clean and minor wounds, administer Tdap or Td if more than 10 years since last dose of tetanus vaccine; for all other wounds, administer Tdap or Td if more than 5 years since last dose of tetanus-toxoid-containing vaccine. Tdap is preferred for persons who have not previously received history is unknown. If a tetanus-toxoid-containing vaccine is indicated for a pregnant woman, use Tdap. For detailed information, refer to www.cdc.gov/mmwr/volumes/69/wr/mm6903a5.htm

◇ Measles, mumps, and rubella vaccination

- **Routine vaccination:**
  - No evidence of immunity to measles, mumps, or rubella: 1 dose.

- Evidence of immunity: Born before 1957 (health care personnel, see below), documentation of receipt of MMR vaccine, laboratory evidence of immunity or disease (diagnosis of disease wi confirmation is not evidence of immunity).

- **Special situations:**
  - Pregnancy with no evidence of immunity to rubella: MMR contraindicated during pregnancy; after pregnancy (before discharge from health care facility), 1 dose.
  - Nonpregnant women of childbearing age with no evidence of immunity to rubella: 1 dose.
  - HIV infection with CD4 count ≥200 cells/mm^3 for at least 6 months and no evidence of immunity to measles, mumps, or rubella: 2-dose series at least 4 weeks apart; MMR contraindicated fo CD4 count <200 cells/mm^3.
  - Severe immunocompromising conditions: MMR contraindicated.
  - Students in postsecondary educational institutions, international travelers, and household or close, personal contacts of immunocompromised persons with no evidence of immunity to measle 2-dose series at least 4 weeks apart if previously did not receive any doses of MMR or 1 dose if previously received 1 dose MMR.
  - Health care personnel:
    - Born in 1957 or later with no evidence of immunity to measles, mumps, or rubella: 2-dose series at least 4 weeks apart for measles or mumps or at least 1 dose for rubella.
    - Born before 1957 with no evidence of immunity to measles, mumps, or rubella: Consider 2-dose series at least 4 weeks apart for measles or mumps or 1 dose for rubella.

§ **Varicella vaccination**

- **Routine vaccination:**
  - No evidence of immunity to varicella: 2-dose series 4 to 8 weeks apart if previously did not receive varicella-containing vaccine (VAR or MMRV [measles-mumps-rubella-varicella vaccine] for received 1 dose varicella-containing vaccine, 1 dose at least 4 weeks after first dose.
    - Evidence of immunity: United States-born before 1980 (except for pregnant women and health care personnel [see below]), documentation of 2 doses varicella-containing vaccine at least diagnosis or verification of history of varicella or herpes zoster by a health care provider, laboratory evidence of immunity or disease.
- **Special situations:**
  - Pregnancy with no evidence of immunity to varicella: VAR contraindicated during pregnancy; after pregnancy (before discharge from health care facility), 1 dose if previously received 1 dose vaccine or dose 1 of 2-dose series (dose 2: 4 to 8 weeks later) if previously did not receive any varicella-containing vaccine, regardless of whether United States-born before 1980.
  - Health care personnel with no evidence of immunity to varicella: 1 dose if previously received 1 dose varicella-containing vaccine; 2-dose series 4 to 8 weeks apart if previously did not receiv containing vaccine, regardless of whether United States-born before 1980.
  - HIV infection with CD4 count ≥200 cells/mm^3 with no evidence of immunity: Vaccination may be considered (2 doses 3 months apart); VAR contraindicated for HIV infection with CD4 count
  - Severe immunocompromising conditions: VAR contraindicated.

¥ **Zoster vaccination**

- **Routine vaccination:**
  - Age 50 years or older: 2-dose series RZV (Shingrix) 2 to 6 months apart (minimum interval: 4 weeks; repeat dose if administered too soon), regardless of previous herpes zoster or history o (ZVL, Zostavax) vaccination (administer RZV at least 2 months after ZVL).
- **Special situations:**
  - Pregnancy: Consider delaying RZV until after pregnancy if RZV is otherwise indicated.
  - Severe immunocompromising conditions (including HIV infection with CD4 count <200 cells/mm^3): Recommended use of RZV under review.

‡ **Human papillomavirus vaccination**

- **Routine vaccination:**
  - HPV vaccination recommended for all persons through age 26 years: 2- or 3-dose series depending on age at initial vaccination or condition:
    - Age 15 years or older at initial vaccination: 3-dose series at 0, 1 to 2 months, 6 months (minimum intervals: dose 1 to dose 2: 4 weeks / dose 2 to dose 3: 12 weeks / dose 1 to dose 3: 5 if administered too soon).
    - Age 9 to 14 years at initial vaccination and received 1 dose or 2 doses less than 5 months apart: 1 additional dose.
    - Age 9 to 14 years at initial vaccination and received 2 doses at least 5 months apart: HPV vaccination series complete, no additional dose needed.
  - Interrupted schedules: If vaccination schedule is interrupted, the series does not need to be restarted.
  - No additional dose recommended after completing series with recommended dosing intervals using any HPV vaccine.
- **Shared clinical decision-making:**
  - Some adults age 27 to 45 years: Based on shared clinical decision-making, 2- or 3-dose series as above.
- **Special situations:**
  - Age ranges recommended above for routine and catchup vaccination or shared clinical decision-making also apply in special situations.
    - Immunocompromising conditions, including HIV infection: 3-dose series as above, regardless of age at initial vaccination.
    - Pregnancy: HPV vaccination not recommended until after pregnancy; no intervention needed if vaccinated while pregnant; pregnancy testing not needed before vaccination.

† **Pneumococcal vaccination**

- **Routine vaccination:**
  - Age 65 years or older (immunocompetent – refer to www.cdc.gov/mmwr/volumes/68/wr/mm6846a5.htm?s_ cid=mm6846a5_w): 1 dose PPSV23.
    - If PPSV23 was administered prior to age 65 years, administer 1 dose PPSV23 at least 5 years after previous dose.
- **Shared clinical decision-making:**
  - Age 65 years or older (immunocompetent): 1 dose PCV13 based on shared clinical decision-making if previously not administered.
    - PCV13 and PPSV23 should not be administered during the same visit.
    - If both PCV13 and PPSV23 are to be administered, PCV13 should be administered first.
    - PCV13 and PPSV23 should be administered at least 1 year apart.
- **Special situations:**

  (refer to www.cdc.gov/mmwr/preview/mmwrhtml/mm6140a4)
  - Age 19 to 64 years with chronic medical conditions (chronic heart [excluding hypertension], lung, or liver disease, diabetes), alcoholism, or cigarette smoking: 1 dose PPSV23.
  - Age 19 years or older with immunocompromising conditions (congenital or acquired immunodeficiency [including B- and T-lymphocyte deficiency, complement deficiencies, phagocytic disorde chronic renal failure, nephrotic syndrome, leukemia, lymphoma, Hodgkin disease, generalized malignancy, iatrogenic immunosuppression [eg, drug or radiation therapy], solid organ transplar or anatomic or functional asplenia (including sickle cell disease and other hemoglobinopathies): 1 dose PCV13 followed by 1 dose PPSV23 at least 8 weeks later, then another dose PPSV23 at previous PPSV23; at age 65 years or older, administer 1 dose PPSV23 at least 5 years after most recent PPSV23 (NOTE: only 1 dose PPSV23 recommended at age 65 years or older).
  - Age 19 years or older with cerebrospinal fluid leak or cochlear implant: 1 dose PCV13 followed by 1 dose PPSV23 at least 8 weeks later; at age 65 years or older, administer another dose PPS after PPSV23 (NOTE: only 1 dose PPSV23 recommended at age 65 years or older).

** **Hepatitis A vaccination**

- **Routine vaccination:**
  - Not at risk but want protection from hepatitis A (identification of risk factor not required): 2-dose series HepA (Havrix 6 to 12 months apart or Vaqta 6 to 18 months apart [minimum interva dose series HepA-HepB (Twinrix at 0, 1, 6 months [minimum intervals: dose 1 to dose 2: 4 weeks / dose 2 to dose 3: 5 months]).
- **Special situations:**
  - At risk for hepatitis A virus infection: 2-dose series HepA or 3-dose series HepA-HepB as above.
    - Chronic liver disease (eg, persons with hepatitis B, hepatitis C, cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis, alanine aminotransferase [ALT] or aspartate am level greater than twice the upper limit of normal).
    - HIV infection.
    - Men who have sex with men.
    - Injection or noninjection drug use.
    - Persons experiencing homelessness.
    - Work with hepatitis A virus in research laboratory or with nonhuman primates with hepatitis A virus infection.
    - Travel in countries with high or intermediate endemic hepatitis A (HepA-HepB [Twinrix] may be administered on an accelerated schedule of 3 doses at 0, 7, and 21 to 30 days, followed b months).
    - Close, personal contact with international adoptee (eg, household or regular babysitting) in first 60 days after arrival from country with high or intermediate endemic hepatitis A (adminis adoption is planned, at least 2 weeks before adoptee's arrival).
    - Pregnancy if at risk for infection or severe outcome from infection during pregnancy.
    - Settings for exposure, including health care settings targeting services to injection or noninjection drug users or group homes and nonresidential day care facilities for developmentally di (individual risk factor screening not required).

¶¶ **Hepatitis B vaccination**

- **Routine vaccination:**
  - Not at risk but want protection from hepatitis B (identification of risk factor not required): 2- or 3-dose series (2-dose series Heplisav-B at least 4 weeks apart [2-dose series HepB only appl Heplisav-B are used at least 4 weeks apart] or 3-dose series Engerix-B or Recombivax HB at 0, 1, 6 months [minimum intervals: dose 1 to dose 2: 4 weeks / dose 2 to dose 3: 8 weeks / do weeks]) or 3-dose series HepA-HepB (Twinrix at 0, 1, 6 months [minimum intervals: dose 1 to dose 2: 4 weeks / dose 2 to dose 3: 5 months]).

- **Special situations:**
  - At risk for hepatitis B virus infection: 2-dose (Heplisav-B) or 3-dose (Engerix-B, Recombivax HB) series or 3-dose series HepA-HepB (Twinrix) as above.
    - Chronic liver disease (eg, persons with hepatitis cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis, ALT or AST level greater than twice upper limit of normal).
    - HIV infection.
    - Sexual exposure risk (eg, sex partners of hepatitis B surface antigen [HBsAg]-positive persons; sexually active persons not in mutually monogamous relationships; persons seeking evalu a sexually transmitted infection; men who have sex with men).
    - Current or recent injection drug use.
    - Percutaneous or mucosal risk for exposure to blood (eg, household contacts of HBsAg-positive persons; residents and staff of facilities for developmentally disabled persons; health care personnel with reasonably anticipated risk for exposure to blood or blood-contaminated body fluids; hemodialysis, peritoneal dialysis, home dialysis, and predialysis patients; persons wit age younger than 60 years, shared clinical decision-making for persons age 60 years or older).
    - Incarcerated persons.
    - Travel in countries with high or intermediate endemic hepatitis B.
    - Pregnancy if at risk for infection or severe outcome from infection during pregnancy (Heplisav-B not currently recommended due to lack of safety data in pregnant women).

ΔΔ **Meningococcal vaccination**

- **Special situations for MenACWY:**
  - Anatomic or functional asplenia (including sickle cell disease), HIV infection, persistent complement component deficiency, complement inhibitor (eg, eculizumab, ravulizumab) use: 2-dose s (Menactra, Menveo, or MenQuadfi) at least 8 weeks apart and revaccinate every 5 years if risk remains.
  - Travel in countries with hyperendemic or epidemic meningococcal disease, microbiologists routinely exposed to *Neisseria meningitidis*: 1 dose MenACWY (Menactra, Menveo, or MenQuadfi) a 5 years if risk remains.
  - First-year college students who live in residential housing (if not previously vaccinated at age 16 years or older) and military recruits: 1 dose MenACWY (Menactra, Menveo, or MenQuadfi).
  - For MenACWY booster dose recommendations for groups listed under "Special situations" and in an outbreak setting (eg, in community or organizational settings and among men who have additional meningococcal vaccination information, refer to www.cdc.gov/mmwr/volumes/69/rr/rr6909a1.htm.
- **Shared clinical decision-making for MenB:**
  - Adolescents and young adults age 16 to 23 years (age 16 to 18 years preferred) not at increased risk for meningococcal disease: Based on shared clinical decision-making, 2-dose series Me least 1 month apart or 2-dose series MenB-FHbp (Trumenba) at 0, 6 months (if dose 2 was administered less than 6 months after dose 1, administer dose 3 at least 4 months after dose 2); FHbp are not interchangeable (use same product for all doses in series).
- **Special situations for MenB:**
  - Anatomic or functional asplenia (including sickle cell disease), persistent complement component deficiency, complement inhibitor (eg, eculizumab, ravulizumab) use, microbiologists routine *Neisseria meningitidis*: 2-dose primary series MenB-4C (Bexsero) at least 1 month apart or MenB-4C (Bexsero) at least 1 month apart or 3-dose primary series MenB-FHbp (Trumenba) at 0, dose 2 was administered at least 6 months after dose 1, dose 3 not needed); MenB-4C and MenB-FHbp are not interchangeable (use same product for all doses in series); 1 dose MenB boos primary series and revaccinate every 2 to 3 years if risk remains.
  - Pregnancy: Delay MenB until after pregnancy unless at increased risk and vaccination benefits outweigh potential risks.
  - For MenB booster dose recommendations for groups listed under "Special situations" and in an outbreak setting (eg, in community or organizational settings and among men who have sex additional meningococcal vaccination information, refer to www.cdc.gov/mmwr/volumes/69/rr/rr6909a1.htm.

◇◇ ***Haemophilus influenzae* type b vaccination**

- **Special situations:**
  - Anatomic or functional asplenia (including sickle cell disease): 1 dose if previously did not receive Hib; if elective splenectomy, 1 dose, preferably at least 14 days before splenectomy.
  - Hematopoietic stem cell transplant (HSCT): 3-dose series 4 weeks apart starting 6 to 12 months after successful transplant, regardless of Hib vaccination history.

§§ Vaccinate after pregnancy.

Reproduced from: Advisory Committee on Immunization Practices. Recommended Adult Immunization Schedule for ages 19 years or older, United States, 2021. Centers for Disease Control and Preve https://www.cdc.gov/vaccines/schedules/hcp/imz/adult-conditions.html (Accessed on February 22, 2021).

Graphic 62130 Version 21.0

Precipitants of hepatic encephalopathy in patients with cirrhosis

Drugs
Benzodiazepines
Nonbenzodiazepine hypnotics (eg, zolpidem)
Narcotics
Alcohol
Increased ammonia production, absorption or entry into the brain
Excess dietary intake of protein
Gastrointestinal bleeding
Infection
Electrolyte disturbances such as hypokalemia
Constipation
Metabolic alkalosis
Dehydration
Vomiting
Diarrhea
Hemorrhage
Diuretics
Large volume paracentesis
Portosystemic shunting
Radiographic or surgically placed shunts
Spontaneous shunts
Vascular occlusion
Hepatic vein thrombosis
Portal vein thrombosis
Primary hepatocellular carcinoma

Graphic 50440 Version 4.0

Child-Pugh classification of severity of cirrhosis

Parameter	Points assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin	<2 mg/dL (<34.2 micromol/L)	2 to 3 mg/dL (34.2 to 51.3 micromol/L)	>3 mg/dL (>51.3 micromol/L)
Albumin	>3.5 g/dL (35 g/L)	2.8 to 3.5 g/dL (28 to 35 g/L)	<2.8 g/dL (<28 g/L)
Prothrombin time			
Seconds over control	<4	4 to 6	>6
INR	<1.7	1.7 to 2.3	>2.3
Encephalopathy	None	Grade 1 to 2	Grade 3 to 4

Modified Child-Pugh classification of the severity of liver disease according to the degree of ascites, the serum concentrations of bilirubin and albumin, the prothrombin time, and the degree of encephalopathy. A total Child-Turcotte-Pugh score of 5 to 6 is considered Child-Pugh class A (well-compensated disease); 7 to 9 is class B (significant functional compromise); and 10 to 15 is class C (decompensated disease). These classes correlate with one- and two-year patient survival: class A: 100 and 85%; class B: 80 and 60%; and class C: 45 and 35%.

INR: international normalized ratio.

Graphic 78401 Version 13.0

Child-Turcotte classification of patients with cirrhosis

Parameter	A	B	C
Ascites	None	Easily controlled	Poorly controlled
Bilirubin	<2 mg/dL (<34.2 micromol/liter)	2 to 3 mg/dL (34.2 to 51.3 micromol/liter)	>3 mg/dL (>51.3 micromol/liter)
Albumin	>3.5 g/dL (>35 g/liter)	3.0 to 3.5 g/dL (30 to 35 g/liter)	<3.0 g/dL (<30 g/liter)
Encephalopathy	None	Mild	Advanced
Nutritional status	Excellent	Good	Poor

Graphic 56436 Version 3.0

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