Liver Cirrhosis Care Guide

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CALIFORNIA CORRECTIONAL HEALTH CARE SERVICES

Information contained in the Care Guide is not a substitute for a health care professional's clinical judgment. Evaluation and treatment should be tailored to the individual patient and the clinical circumstances. Furthermore, using this information will not guarantee a specific outcome for each patient. Refer to "Disclaimer Regarding Care Guides" for further clarification.

https://cchcs.ca.gov/clinical-resources/

Summary

GOALS

- Screen patients at risk for advanced fibrosis and cirrhosis
- Screen patients at risk for HCC (Hepatocellular Carcinoma)
- Diagnose and manage cirrhosis and its complications.
- Delay cirrhosis decompensation
- Early referral of eligible patients for palliative care and hospice care and ensure POLST is done.

ALERTS

- Abdominal Pain - Consider Spontaneous Bacterial Peritonitis (SBP)
- Mental status changes – Consider Hepatic Encephalopathy.
- Hematemesis/Melena – Consider variceal bleeding.
- Fever - Consider SBP
- Oliguria/Anuria – Consider hepato-renal syndrome.
- Rapid weight gain or loss – Consider fluid gain/loss, HCC

DIAGNOSTIC CRITERIA FOR CIRRHOSIS AND DECOMPENSATED CIRRHOSIS

Cirrhosis is best **predicted** by these findings:

- Ascites (likelihood ratio (LR) for cirrhosis [LR] 7.2)
- Platelet count < 160,000/microL (LR 6.3) **Severe thrombocytopenia often precedes other manifestations
- Spider angioma on physical exam (LR 4.3)
- *Bonacini cirrhosis discriminant score >7 (LR9.4)*

Cirrhosis (liver fibrosis stage 4) is **diagnosed** with one or more of the following:

- Physical exam
- Lab (Fibrotest, platelets, albumin, bili, INR)
- Imaging: hepatic ultrasound, CT, MRI
- Calculations: FIB-4 online calculator
- Procedure: liver biopsy, transient elastography (FibroScan™)

Decompensated Cirrhosis is defined as cirrhosis with at least one of the following:

- Ascites
- Hepatic encephalopathy (HE)
- Hepatorenal syndrome (HRS)
- Hepatopulmonary syndrome (HPS)
- Child-Pugh class B and C
- SBP
- Variceal bleeding

EVALUATION

Complete clinical history and physical exam

- History**:** Especially risk factors for hepatitis and symptoms of significant liver disease (hematochezia, melena, abdominal distension, hematemesis, weight gain), timeline of various hepatic injury (e.g., hepatitis, alcohol, related treatment).
- Physical Exam: Particularly mental status changes, skin changes, hepatosplenomegaly, spider angioma, weight changes, hematemesis, jaundice, and edema in addition to usual review of symptoms components.
- Pay attention to the presence of complications of liver disease (i.e., ascites, esophageal variceal bleeding, hepatic encephalopathy, SBP) indicative of decompensated cirrhosis, which often need prompt intervention.

EVALUATION Cont.'d

Medication List Review

- Avoid hepatotoxins and chronic NSAID use. (Some institutions have listed NSAIDS in the allergy section to ensure the provider is alerted when NSAIDS are prescribed; it is advisable to make a comment for the real reason thus patient can have NSAIDS for acute need.)
- Multiple drugs have altered kinetics in patients with severe liver disease; dose alterations are frequently required.

Lab/Diagnostics

- CBC, CMP, PT/INR, hepatitis serologies, HIV testing. Additional testing may be needed when the likely etiology of liver disease is not explained after this evaluation.
- Cirrhosis/F4: Some patients need Esophagogastroduodenoscopy (EGD) (baseline) to screen for esophageal varices, with follow-up based on clinical findings.
- Cirrhosis/F4: US to screen for HCC every 6 months (AFP not recommended as the only tool to screen for HCC). US

TREATMENT

Vaccinations: influenza annually, pneumococcal, and COVID-19. Offer vaccination for HAV, HBV if not immune.
Medications or other therapies based on specific patient findings.

- Ascites: optimize volume management (diuretics and salt restriction); consider midodrine for refractory ascites.
- Esophageal varices: determine if nonselective beta-blocker is indicated; order baseline EGD with follow-up as needed: note that in patients with compensated cirrhosis, may use platelet count and liver stiffness measurement, such as Fibroscan, to see if EGD can be avoided.
- Hepatocellular carcinoma: screen and then, if found, obtain consultation for treatment.
- Hepatic encephalopathy: optimize lactulose and minimize potential for exacerbation.
- Hepatitis C: consider treatment if no HCC and prognosis > 1 year.
- Liver transplantation: Certain patients with HCC may be considered for liver transplantation. Consult with CME or Regional DME, HQ UM for questions.
- SBP: antibiotic therapy and prophylaxis.
- Palliative care consult and hospice care.
- Dietary consult in patients with cirrhosis and ascites or HE.

MONITORING

Follow-up visit

- Chronic Care visit as clinically indicated, typically at least every 180 days, but more frequently if unstable or decompensated cirrhosis
- Monitor changes in mental status, weight, vital signs, skin

Labs

- Consider CBC, CMP, and PT/INR annually or more frequently as indicated (especially if the patient has ascites and is on diuretics)

Ultrasound

- Every 6 months (HCC screening) for cirrhosis.

EGD

- Baseline EGD at time of cirrhosis (F4) diagnosis for certain patients. Ongoing surveillance as recommended by Gastroenterologist (GI), generally within 2-3 years.

Decision Support

EVALUATION

General Approach

During the initial evaluation (and subsequent evaluations), it is essential to recognize that liver disease is likely not the only significant chronic medical condition in your patient. Coexisting medical conditions, especially heart failure, chronic kidney disease/end stage renal disease, obesity, COPD, dementia, diabetes, HIV, and malignancy can significantly alter the treatment plan, as well as the overall prognosis of your patient.

- Patients often present late in their disease progression and can already be cirrhotic at initial diagnosis.
- It is important to carefully manage patients with compensated cirrhosis, to delay its progression to decompensated cirrhosis.
- It is also important to identify patients with decompensated cirrhosis and follow them closely, because they need prompt intervention when their conditions deteriorate.
- The overall prognosis, surveillance plan, and management of patients with decompensated cirrhosis is vastly different from compensated cirrhosis, such as early involvement of palliative care if appropriate.

History, Physical Exam and Medication Review

History: First ask if the patient is cirrhotic. It is important to note risk factors for hepatic injury (alcohol abuse, risk of viral hepatitis, such as substance abuse and tattoos); symptoms of significant liver disease (see below). Obtain vaccination history (for HAV, HBV) and family history. (Refer to ISUDT if positive for substance use disorder; refer to HCV treatment if eligible). It is important to recognize other causes besides alcohol and chronic viral hepatitis (HBV, HCV). Additionally, it is important to take note of other comorbidities that may contribute to the liver injury.

Review of systems (ROS): Ask about anorexia, weight loss, weakness, fatigue, muscle cramps, and easy bruising. Patients with decompensated liver cirrhosis can present with: jaundice, dark urine, pruritus, hematemesis/melena/hematochezia, abdominal distension, lower extremity edema, confusion, or sleep disturbances.

Physical Exam: Pay particular attention to mental status changes, skin changes, hepatosplenomegaly, spider angioma, jaundice, edema, and distended abdomen with shifting dullness and/or positive fluid wave, fever, abdominal distention, abdominal tenderness, hypotension.

- Other physical examination findings may include: gynecomastia, palmar erythema, digital clubbing, and asterixis.
- Check weight and monitor for weight changes.

Note: Ascites and spider angioma are strong predictors for the presence of cirrhosis:

- Ascites: likelihood ratio for cirrhosis (LR 7.2)
- Spider Angioma: (LR 4.3)
- Bonacini cirrhosis discriminant score greater than 7 (LR 9.4)

Review Medication List: Review on a continuing basis. Be aware of hepatotoxic medications. Since most medications are metabolized by the liver, their adjustment is often needed in patients with chronic liver disease

- Avoid hepatotoxins and chronic NSAIDs if liver disease is present. Discontinue or dose adjust medications as clinically indicated.
- Caution with using nonselective beta-blockers (NSBB) in patients with decompensated cirrhosis. There were studies showing that the use of NSBB was associated with shorter survival in decompensated cirrhosis, including patients with refractory ascites and SBP. However, other publications subsequently showed no impact of NSBB use on mortality or the development of acute kidney injury in these situations. Providers should consult hepatologist when clinically indicated.
- Proton pump inhibitor (PPI): caution the use in patients with cirrhosis and ascites because its use may be associated with HE and SBP in these patients.

History, Physical Exam and Medication Review Cont.

- Diuretics: avoid use of thiazide diuretics because of their minimal impact on ascites and their association with electrolyte abnormalities (e.g., hyponatremia, hypokalemia) which can precipitate HE.
- Angiotensin converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs): avoid use in patients with decompensated cirrhosis and/or ascites, because of the risk of renal impairment. When they are used for patients with compensated cirrhosis, start low and monitor blood pressure, electrolyte, and kidney function closely.
- Statin: avoid atorvastatin for patients with cirrhosis due to higher risk of inducing rhabdomyolysis. Avoid statin in patients with decompensated cirrhosis. Refer to UpToDate "Statins: Actions, side effects, and administration" for more details.

Diagnostic and Surveillance Tests

Lab/Diagnostics:

Laboratory abnormalities may include elevated serum bilirubin, abnormal aminotransferases, elevated alkaline phosphatase/gamma-glutamyl transpeptidase, a prolonged prothrombin time/elevated international normalized ratio (INR), hyponatremia, hypoalbuminemia, and thrombocytopenia.

- **At baseline:** Hepatitis serologies (anti-hepatitis A IgM [for acute infections], hepatitis B surface antigen, hepatitis B surface antibody, total hepatitis B core antibody, anti-hepatitis C virus antibody), HCV RNA and genotype (if infected) and HIV.
- **Generally, at least annually:** CBC, CMP, PT/INR, Test for HCV RNA, and other diagnostic labs as clinically indicated.

Note: Thrombocytopenia (TCP) is a strong predictor for the presence of cirrhosis: Platelet count < 160,000/ microL (LR 6.3). However, be aware that TCP may rise from causes other than cirrhosis such as drug-induced or autoimmune process.

- Annually: Calculate Fibrosis-4 (FIB-4): Based on age, AST, ALT, and platelets. (Can use EHRS EBMCalc, online calculator, value is on Quality Management HCV Registry).

Treat the patient with FIB-4 > 3.25 as cirrhotic.

Please note that FIB-4 score may not accurately represent the extent of liver fibrosis, when patient has old age and low platelet count, even in the absence of liver disease. Additionally, liver enzymes can be affected by a number of conditions.

Moreover, the value of AST and ALT may be markedly elevated during acute hepatic injury. Thus, it is important to monitor the lab values over time and may need to repeat the calculation to see if the FIB-4 score is consistently elevated. This FIB-4 score, prior to HCV treatment, will be used to determine the pathway for HCV treatment.

Imaging and Diagnostic Tests

For Patients with chronic HCV and FIB-4 scores of 1.45 to 3.25:

Order Fibrotest, and some patients may need FibroScan™

Who needs FibroScan™:

Indications for obtaining FIBROSCAN™ include Hepatologist request, transplant team or Hepatitis central team recommendation, patients with chronic HBV, discordant Fib-4 and FibroTest, and when Fib-4 is unhelpful due to calculation such as immune/HCV thrombocytopenia unrelated to cirrhosis. Note both Fibroscan and Fibrotest are spuriously high in acute HCV and can mislead to an incorrect diagnosis of cirrhosis. When indicated, obtain FibroScan™ only prior to HCV treatment, to determine the degree of liver fibrosis.

Screening for HCC and esophageal varices in patients with advanced liver disease:

F4 Fibrosis Patients: Need to be screened for HCC and esophageal varices. Please note that HCV pre-treatment fibrosis level is used to determine the need for ongoing HCC screening post HCV treatment, even when sustained viral response is obtained and patient's fibrosis may appear improved.

Some patients with F4 fibrosis may need to have Fibroscan to determine their liver stiffness level, to see if they need EGD screening for esophageal varices.

Who needs to be screened for HCC7:

1. Patients with cirrhosis of any etiology.
2. Patients with HCV who had pre-treatment fibrosis staging as F4, even if the cirrhotic stage of fibrosis has resolved after treatment.
3. Patients with chronic HBV and without cirrhosis, with any of the following risks:
   a) Asian men > 40 years of age/ Asian women > 50 years of age.
   b) Africans and African Americans (can develop HCC at younger age).
   c) Family history of HCC (i.e., 1st degree relative) of HCC.
   d) Patients with HDV co-infection.
4. For patients on liver transplant list before arrival at CDCR, for non-HCC causes, offer continued screening for HCC.

How to screen for HCC:

Abdominal ultrasound focused on the liver every 6 months if previous exam is normal; Alpha-fetoprotein (AFP) alone is not recommended for HCC screening.
Some specialists may add alpha-fetoprotein testing to the US to guide the management of patients in whom HCC is suspected.

Who needs to be screened for esophageal varices by EGD:

Patient who has decompensated cirrhosis, or Plt < 150,000/microL, or Liver Stiffness Measurement (LSM) on Fibroscan™ > 20kPa

Other Causes of Liver Disease

There are numerous causes of liver disease that can result in cirrhosis, either by causing chronic hepatic inflammation or cholestasis. The most common causes of cirrhosis in the United States are chronic HCV, alcoholic liver disease, and nonalcohol-associated liver diseases.

Examples of Nonalcohol- associated Liver Diseases:

- **Nonalcoholic Fatty Liver Disease:** (NAFLD): NAFLD is defined as presence of hepatic steatosis in >5% of hepatocytes in the absence of significant alcohol consumption (defined as less than 20g/day [14 drinks/week] for women and less than 30g/day [21 drinks/week] for men) and other known readily identified alternative causes of liver disease. NAFLD has been recognized for its ever-increasing global prevalence (estimated
- 25-30% in the general population) and health-related significance, such as being the second most common indication for liver transplantation in the U.S. after chronic HCV, and one of the top causes for liver cirrhosis.
- **Wilson Disease**: Young patient with a family history. Can have neurologic and psychiatric symptoms, thrombocytopenia, and anemia. Check serum ceruloplasmin level and copper concentration.
- **Hereditary Hemochromatosis:** Family history and associated with DM, cardiomyopathy, skin hyperpigmentation and high risk of developing HCC (see above for details on HCC screening). Check transferrin saturation (if ≥ 45%, raise clinical suspicion).
- **Autoimmune Hepatitis:** Initial labs: antinuclear ab, anti-smooth muscle ab, ALKM-1, AMA, and IgG level. Watch for other autoimmune liver diseases such as Primary Biliary Cirrhosis and Primary Sclerosing Cholangitis.
- **Drug Induced/Ingested Toxins:** Acetaminophen, herbal supplements, mushroom poisoning, and antibiotics (Amoxicillin-Clavulanate).

Severity of Cirrhosis/Prognosis

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.3

- **Compensated Cirrhosis:** Median survival is > 12 years. It is important to have a high index of clinical suspicion for this stage because patients often are asymptomatic. US or other imaging finding is not sensitive for diagnosing this stage.
    - 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).
- **Decompensated Cirrhosis:** (Median survival is less than 2 years. Various models have been used to predict survival length)
    - In addition, patients with decompensated cirrhosis who have been hospitalized with an acute liver-related illness (e.g., 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 ≥ 21.
    - Tools to help assess severity of disease (and therefore prognosis) include the Child-Pugh and MELD score.
- **Risk Factors for Poor 6 Month Prognosis:** Recurrent SBP, recurrent variceal hemorrhage, refractory ascites, MELD ≥ 21, heart failure and/or other significant co-morbid conditions, any hospitalization within 30 days or > 2 within 60 days, poor functional status, HCC/other cancer, HPS/HRS, dialysis patient, Child-Pugh Score > 10 (Class C).

Decompensated Cirrhosis is defined by the presence of any of the following:

- Ascites, HE, HCC, Variceal bleeding, Hepatorenal syndrome, Hepatopulmonary syndrome, Child-Pugh score ≥ 7 (and ≥ 6 in patient with HIV) and/or SBP.

Recognize the poor prognosis and discuss end of life preferences with the patient. (See page 9 for more on palliative care options.)

Obtain/update the POLST and identify/document the patient's preferred surrogate decision-makers using an Advance Directive.

Child-Pugh

Child-Pugh is a tool used to help assess prognosis in patients with liver disease. Variations in the timing and subjectivity inherent in the scoring (e.g., in grading ascites or encephalopathy) are its major limitations.

Model for End-Stage Liver Disease (MELD)

MELD: Originally derived from patients with cirrhosis undergoing elective Transjugular Intrahepatic Portosystemic Shunt (TIPS) procedures to predict 3-month mortality post procedure. Adopted by the United Network for Organ Sharing in 2002 for the prioritization of patients waiting for liver transplants.

- Note: There are some conditions associated with chronic liver disease that may result in impaired survival but are not directly accounted for in the MELD scoring system; such as HCC and Hepatopulmonary Syndrome; therefore, this should not be the only tool used for assessing overall prognosis.
- MELD formula:
- MELD = 3.78 x ln [serum bilirubin (mg/dL)] + 11.2 x ln[INR] + 9.57 x ln[serum creatinine (mg/dL)] + 6.43
- ln = natural logarithm

Palliative Care Options

As mentioned above, patients with decompensated cirrhosis have a median survival of 2 years. It is important to begin advance care planning for anyone with a diagnosis of cirrhosis and preferably before hepatic decompensation and loss of decision-making capacity. Moreover, when patient is diagnosed with decompensated cirrhosis, it is essential to discuss with patients the goals of their care and other management options, such as palliative care options, besides traditional medical management. POLST and advance directives should be completed or updated as clinically indicated, to help patients (or their surrogate decision makers if applicable) understand their medical conditions, and actively plan for their care.

It has been shown in the community that in patients with decompensated cirrhosis , outpatient palliative care is associated with improved symptoms, improved care coordination, and better anticipatory planning. Note that palliative care can be provided to patients with decompensated cirrhosis at any stage of their illness, and that palliative care does not preclude the delivery of disease-directedor even curative treatments. Consider submitting a request for compassionate release if applicable.
Hospice is a subset of palliative care in that it focuses exclusively on comfort, when disease-directed curative treatment is no longer feasible and desired, and typically includes only persons with life expectancy of less than 6 months.

Child-Pugh and MELD score are the most used models to predict patient's prognosis in survival, while it is still important to look at the overall clinical picture of the patient including functional status and loss of lean body mass. Using these care options appropriately can help improving patient's symptoms and reducing unnecessary hospitalizations.

TREATMENT: GENERAL MANAGEMENT

Major Pillars in Management

Slow or reverse the progression of liver disease

- Some chronic liver diseases respond to treatment even when the liver disease has progressed to cirrhosis.
- Specific therapies directed against the underlying cause of the cirrhosis (such as HCV) should be instituted; refer to ISUDT/MAT for patients with substance use disorder.

Prevent superimposed insults to the liver and minimize risks for acute exacerbations

- Vaccinations: influenza, pneumococcal vaccines, COVID 19; and HAV and HBV if not immune.
- Treat HCV, HBV infections (consult HCV/HBV central team for patients with advanced liver disease).
- Alcohol cessation.

Identify medications that require dose adjustments, discontinuation, or should be avoided entirely

- Avoidance of hepatotoxins.
- Continued review of medication lists.
- Check for impact on liver when starting new medications.

Manage symptoms and laboratory abnormalities

- Muscle Cramps: Patients with cirrhosis may experience muscle cramps which can be severe. It is important to confirm that the muscle cramps are related to cirrhosis, check electrolyte levels, and replace if low, treat if symptoms persist.
- 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.
- Asymptomatic hernias should be managed conservatively.
- Ruptured/incarcerated hernias should be referred for immediate repair.

Major Pillars in Management Cont'd

- Hyponatremia: 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. Free water restriction is often not necessary unless serum sodium is less than 125mmol/L.

Prevent, identify, and treat complications of cirrhosis

- Patients should be monitored for the development of complications and when possible, steps should be taken to prevent their development.
- Presence of any complication is a sign of worsening long-term prognosis.
- See pages 11-20 for treatment of the complications of cirrhosis.
- Consider dietitian consult in patients with cirrhosis.

Determine the appropriateness and optimal timing for liver transplantation (LT)

- Certain patients with HCC may be considered for LT.
- Consult with CME or Regional DME.
- Contact HQ UM team for questions.

Identify and treat/manage other chronic illnesses

- For example: diabetes, heart failure, CKD/ESRD, HCV, HIV.

Patient Education

- It is important to ensure your patient understands that there are things they can do, or refrain from doing, that can help protect their liver from further damage.
- Alcohol and other illicit substance use should be stopped; there is ISUDT/ MAT program to help address this issue.
- Healthy diet: sodium restriction 2gm daily.
- Weight Management: patients should be encouraged to participate in lifestyle modification activities to improve their health; these include eating healthy and engaging in physical activity regularly.

Early identification of patients with poor prognosis

- Develop an overarching management plan that takes into account the patient's cirrhosis, other comorbid conditions, and their wishes for care towards the last year of life.
- Complete advance care planning.
- This discussion should be continued on a regular basis and include (but not be limited to): Code Status, goals/end of life care, and completion /update of the POLST form.
- Consider palliative care consult and reduce unnecessary hospitalizations.

MANAGING COMPLICATIONS

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

NSBBs are the standard of care for the prevention of variceal bleeding in patients with cirrhosis and portal hypertension. However, its use in certain patients with cirrhosis has raised controversy over the recent years. There were studies (such as those cited in UpToDate: Patients with cirrhosis and ascites, published in 2010 through 2014) suggesting the use of NSBB was associated with shorter survival in decompensated cirrhosis, including patients with refractory ascites and SBP. Other publications subsequently showed no impact of NSBB use on mortality or the development of acute kidney injury in these situations. Based on the available data, the American Association of Study of Liver Disease (AASLD) recommended in 2021 that "NSBBs are not necessarily contraindicated in patients with refractory ascites. However, caution is recommended in patients with hypotension, hyponatremia, or acute kidney injury." Furthermore, AASLD acknowledged various studies on the use of NSBB in patients with cirrhosis and SBP and stated in its 2021 guidance that "NSBBs do not need to be discontinued in patients with SBP unless hypotensive. If stopped, restarting NSBB may be considered depending on recovery of the systemic arterial blood pressure." Therefore, the use of NSBB should be regularly reassessed with dose adjustments (or discontinuation) as clinically indicated. Providers are recommended to consult hepatologist when clinically indicated.

Another medication of particular interest, related to managing the complication of cirrhosis, is proton pump inhibitors (PPIs) which are used by as many as 46-78% patients with cirrhosis (while about 40% of them were taking PPI without a proper indication), and its use may be associated with developing HE and SBP in patients with cirrhosis and ascites. Additionally, it is not uncommon to see patients with cirrhosis be maintained on PPIs after an episode of gastrointestinal bleeding. While PPI is indicated for upper gastrointestinal bleeding due to peptic ulcer disease, it can be stopped once a non-variceal etiology is ruled out or maximally use for 10 days, after a variceal hemorrhage event.

Other measures to decrease the risk of complications include:

- Judicious diuresis
- Treating infections
- Avoiding sedatives and treating hypokalemia and hyponatremia.
- Avoiding nephrotoxic agents and aggressive diuresis.
- Only using urinary catheters, mechanical ventilation, and central lines when clearly indicated
- Monitor for protein-calorie malnutrition, which is common in patients with cirrhosis, due to multiple risk factors. Providers are recommended to consider obtaining dietitian consultation for patients with cirrhosis, especially for those who have a low body weight index (BMI<18.5), unexplained weight loss, or difficult to maintain adequate oral intake due to either fluid overload or decreased physical activity, or decompensated cirrhosis.

Major complications of cirrhosis include:

- Ascites, Hepatic Encephalopathy, Hepatopulmonary Syndrome, Hepatorenal Syndrome, Spontaneous Bacterial Peritonitis, Hepatocellular Carcinoma (opinions differ among societies if it is a complication)
- Once these complications develop, patients are very likely to have decompensated cirrhosis.

PRESENCE OF ANY COMPLICATION IS A SIGN OF WORSENING PROGNOSIS.
CONSIDER EARLY GOALS OF CARE AND CODE STATUS DISCUSSION, WITH COMPLETION OF POLST.

Managing Complications Cont'd

ASCITES

DIAGNOSIS

- Diagnose with appropriate imaging study or physical exam.
- Differential diagnosis: ascites may be caused by conditions other than liver disease (or in addition to liver disease); about 15% are due to heart failure, nephrotic syndrome, cancer, tuberculosis, or other conditions.
- Paracentesis (if indicated under ultrasound guidance) for diagnosis may be indicated; especially with new onset ascites.

ALUATION/ TREATMENT AND PROPHYLAXIS

- Serum to Ascitic Albumin Fluid Gradient (SAAG) ≥ 1.1 indicates portal hypertension with 97% accuracy; SAAG < 1.1 suggests ascites from other causes. To calculate SAAG, the serum albumin should be drawn the same day as the paracentesis. (SAAG = Serum Albumin minus Ascitic Albumin level).
- Patient may require large volume paracentesis (> 5 liters). Albumin infusion (between 6-8 g of albumin per liter of fluid removed) is recommended.

Focus should be on Diuretic and Diet Therapy

Diuretics: Start at low dose and titrate up. Optimal ratio of spironolactone to furosemide is 100 mg to 40 mg.

- Spironolactone: 100 mg/day or (50 mg/day for patients ≤ 50kg) WITH;
- Furosemide: 40 mg/day (or 20 mg/day for patients ≤ 50 kg).
- Increase doses of both agents every 3-5 days if tolerated.
- Usual Daily Max dose: Spironolactone 400 mg, furosemide 160 mg.
- Alternative agents: Amiloride starting at 5-10 mg/day, with a target range of 10-40 mg/day, can be used as substitute for spironolactone if side effects (e.g., gynecomastia) noted.
- Dietary sodium restriction: 2 gm/day (providers order in EHRS; provide patient education materials: Hepatic diet handout in English and Hepatic diet handout in Spanish).
- Free water restriction is often not necessary unless serum sodium is less than 125mmol/L.
- Avoid: alcohol, ACE inhibitors, ARBs, NSAIDs

MONITORING

- Monitor patient weight and abdominal girth.
- Monitor for other complications (i.e., encephalopathy, peritonitis, systemic or localized infections, worsening creatinine, worsening urine output, worsening respiratory status, hypotension).
- Obtain CMP every one to two months or as indicated for patients on diuretics; adjust treatment as indicated.
- Obtain dietary consult for patients with ascites.

REFRACTORY ASCITES

DIAGNOSIS

- Presence of ascites.
- Patients are considered refractory ONLY if they fail max dose (or cannot tolerate) diuretic therapy, AND if on 2gm/day sodium restriction diet.

EVALUATION/ TREATMENT AND PROPHYLAXIS

- There were studies suggesting the use of NSBB was associated with increased mortality in patients with refractory ascites, yet there is emerging evidence that these medications may be safely maintained. Consult hepatologist when clinically indicated.
- Consider oral midodrine (off label use if recommended by hepatologist, usually in the setting of hypotension) starting at 5 mg three times daily; recommended target dose dosing is 7.5 mg three times daily.
- Serial paracentesis.
- TIPS (may precipitate encephalopathy).

Managing Complications Cont'd

- Continue diuretic therapy and dietary sodium restriction.
- Refractory Ascites carries a 21% 6-month mortality rate. Recommend POLST, End of Life, and Goals of Care discussion with your patient.

MONITORING

- Monitor patient weight and abdominal girth.
- Monitor for other complications (i.e., encephalopathy, peritonitis, systemic or localized infections, worsening creatinine, worsening urine output, worsening respiratory status).
- Obtain CMP every one to two months or as indicated for patients on diuretics; adjust treatment as indicated.

SPONTANEOUS BACTERIAL PERITONITIS (SBP)

DIAGNOSIS

SBP may present without obvious symptoms or may present with fever, abdominal pain, altered mental status. Any or all symptoms may be subtle or absent.

Diagnosis: ascitic fluid with ≥ 250 PMNs/ml and/or positive culture without other obvious causes of peritonitis (such as abdominal abscess, perforated bowel, patients on peritoneal dialysis) (Most often E. coli or klebsiella; can be streptococcus or rarely staphylococcus).

TREATMENT /PROPHYLAXIS

Evaluate and transfer to a higher level of care if clinical suspicion is present.

Treatment:

- Stop NSBB in patients with active SBP20. Consult hepatologist on possibly restarting NSBB after resolution of the event; there is controversy regarding the use of NSBB in this situation.
- Empiric IV antibiotic with Cefotaxime while waiting for lab results if clinical suspicion present (fever, abdominal pain, and/or altered mental status).
- Patients with SBP would benefit from IV albumin in addition to antibiotics (1.5g/Kg at day 1 and 1g/ Kg at day 3), especially if they have acute kidney injury and/or jaundice at time of diagnosis of SBP16.
- Usually in hospital with IV Cefotaxime. Check local antimicrobial resistance data. Use Quinolone for patients with allergy to β-lactamase antibiotics unless Quinolone was used for prophylaxis. Avoid aminoglycosides (due to nephrotoxicity).
- Treatment duration is usually 5 days, unless unusual organism, unusual presentation or associated bacteremia which requires extended treatment.

Prophylaxis:

Start and continue indefinitely for the following:

- All patients with history of prior SBP.
- Ascites (ascitic fluid protein is <1.5 g/dL) with impaired renal function or liver failure.
- Ciprofloxacin 500 mg orally daily or Sulfamethoxazole/Trimethoprim DS one tablet orally daily. Weekly dosing is not recommended.

Patients with cirrhosis who are hospitalized with GI bleed should receive antibiotic prophylaxis with:

- IV Ceftriaxone (1gm IV daily) until bleeding is under control and patient is stable and eating; then switch to Sulfamethoxazole/Trimethoprim DS (1 tablet orally twice daily) for a total of seven days.

Prophylaxis use for all other potential indications:

- Development of antibiotic resistance is possible - weigh risks versus benefits.
- Referral to subspecialty is highly recommended.

MONITORING

- Observe for return of fever, abdominal pain, change in mental status.
- Follow-up on culture results.

Managing Complications Cont'd

HEPATIC ENCEPHALOPATHY (HE)
DIAGNOSIS

- Presentation may vary from mild subclinical changes in mentation to overt psychiatric symptoms to deep coma.
- Presenting symptoms can include confusion, decreased attention, mental slowing, asterixis, irritability, sleep disorder, lethargy, or unresponsiveness.

TREATMENT / PROPHYLAXIS

Correct precipitating cause(s):

- Precipitating factors: GI bleed, infection (including SBP), hypokalemia and/or metabolic alkalosis, blood transfusion, HCC, excess protein intake, constipation, dehydration, drugs, poor adherence to medications, and portohepatic shunts.
- Consider documenting a search for evidence of precipitating factors in the chart.

Treatment over HE:

- Lactulose - give lactulose when patient is able to take medications orally for treatment and prophylaxis Recommended starting dose: 30 mL orally 2 to 3 times daily.
- Consider NA or DOT administration for recurrent symptoms in selected cases, such as nonadherence. Titrate dose to no more than three to four bowel movements per day.
- Rifaximin - only after optimized lactulose treatment. Recommended dose: 550 mg BID.
- Patients with significant mental status changes should be referred to a higher level of care.
- Consider lactulose enemas when patient is comatose (inpatient setting only).

Prophylaxis:

- After 1st episode: lactulose
- After 2nd episode: add rifaximin to lactulose.

Nutritional assessment:

It is estimated that approximately 75% of patients with HE suffer from moderate-severe protein-calorie malnutrition with loss of muscle mass and energy depots. Thus, there is consensus that low-protein nutrition should be avoided for patients with HE. Providers should obtain dietitian consult for patients with HE.

MONITORING

- Medication adherence, bowel movement frequency, mental status, and functional status.
- Be aware of other causes of altered mental status (i.e., localized, and systemic infections, electrolyte imbalance, renal failure, and worsening of other chronic illnesses).

ESOPHAGEAL VARICES
DIAGNOSIS

- Baseline EGD to screen for varices is indicated when cirrhosis is first diagnosed when any of the following is present:
    - Decompensated cirrhosis;
    - Platelet <150,000/microL;
    - Liver Stiffness Measurement (LSM) >20k Pa (Note: Fibroscan may be challenging to obtain in some institutions, and only the patients who have compensated cirrhosis and Plt count ≥ 150,000/microL need to have Fibroscan to see if EGD can be circumvented.)

If not, perform ongoing variceal risk stratifications with liver stiffness measurement and platelet count once annually.

- Additionally, if patients with compensated cirrhosis are already taking a nonselective beta blocker to prevent decompensation or for other indications, there is no need to perform screening upper endoscopy because the presence of varices will not modify management.

Managing Complications Cont'd

TREATMENT / PROPHYLAXIS

For those patients who met the criteria for screening EGD, perform baseline EGD:

If no varices seen on EGD:

Use surveillance EGD in 3 years; shorter interval if there is ongoing liver inflammation (e.g., untreated viral hepatitis, active alcohol use disorder, metabolic syndrome).

Beta-blockers are not recommended for "pre-primary prophylaxis" (i.e., to prevent EV)
All "beta-blockers" recommendations are for Non-Selective Beta-Blockers.

Primary Prophylaxis (prevention of first variceal hemorrhage in patients with high-risk varices):

- High risk esophageal varices: medium/large varices [≥5 mm], or varices of any size with red signs, or varices of any size in patients with Child-Pugh class C.
  a) Consider if patient has any risk factors for adverse events with NSBB therapy.
  b) If no, initiate NSBB.
  c) If yes (see Algorithm 2 for risk factors for adverse events with NSBB therapy), perform endoscopic variceal ligation (EVL).

Either NSBB or EVL can be used to prevent first VH for varices, and choice of treatment should be based on patient preference and characteristics.
Please note that once a patient is on NSBBs for preventing decompensation or other, indications including for primary prophylaxis for variceal hemorrhage, there is no need for repeat EGD.
For those that undergo EVL, EGD usually needs to be repeated ever 2-4 weeks until esophageal varices are eradicated, then surveillance EGD is performed every 3-6 months for one year and then once annually thereafter.

The following are not recommended for primary prophylaxis: nitrates, combination beta-blockers, EVL, shunt therapy, or sclerotherapy.

- Non-high risk esophageal varices: small esophageal varices [<5mm] without red signs: surveillance EGD in 2 years; shorter interval if there is ongoing liver inflammation (e.g.; untreated viral hepatitis, active alcohol use disorder, metabolic syndrome)

Secondary Prophylaxis (prevention of recurrent variceal hemorrhage in patients who have previously bled from varices):

- Patients who survive an EV bleed should receive both NSBB (if not contraindicated or intolerant), and EVL as combination therapy has been shown to be superior to either treatment alone.
- Repeat EGD every 1 - 4 weeks until varices obliterated, then perform EGD 3 - 6 months after eradication and, then every 6-12 months.
- Consider TIPS in the following circumstances:
- If bleeding recurs despite combination beta-blockers and EVL.
- Sclerotherapy is not recommended for secondary prophylaxis.

MONITORING

- For patients with compensated cirrhosis with Plt ≥ 150,000/microL and LSM ≤ 20kPa, EGD can be safely avoided. For patients who do not meet these criteria, screening EGD is recommended when diagnosis of cirrhosis is made.
- Cirrhosis without varices on EGD → repeat EGD within 3 years (2 years if ongoing liver injury, such as alcohol, lack of sustained viral responses in HCV).
- Small varices and no beta-blocker used → repeat EGD within 2 years (1 year if ongoing liver injury).
- Any varices and on beta-blockers for: (primary prophylaxis, no need for follow up surveillance EGD or perform EGD when decompensation occurs.

Managing Complications Cont'd

- EVL for primary prophylaxis: EGD every 2-4 weeks until varices are eradicated, then EGD every 3-6 months for one year and then once annually thereafter.
- Post variceal hemorrhage: perform EVL → repeat EGD every 1 - 4 weeks until varices obliterated, then every 3-6 months, then every 6-12 months.
- Decompensated cirrhosis: → repeat EGD at time of diagnosis and annually or more often as indicated.

HEPATOCELLULAR CARCINOMA (HCC)
DIAGNOSIS

- Screen for HCC with ultrasound every 6 months for Metavir F4 patients.
- Evaluate mass on ultrasound with contrast enhanced imaging study (dynamic triphasic or quadriphasic CT or MRI with gadolinium).
- Hepatic mass identified on contrast enhanced imaging.
- Biopsy, as indicated.
- Consultation recommended with a specialist knowledgeable in the diagnosis and management
- of HCC.

TREATMENT / PROPHYLAXIS
Classification and diagnosis complement the Barcelona Clinic Liver Cancer staging and treatment criteria:

- Very early to early-stage disease - may be cured with ablation, resection, or liver transplant.
- Intermediate stage - usually treated with chemoembolization.
- Advanced stage - Specialist may consider ordering sorafenib (trade name NexAVAR®) or atezolizumab plus bevacizumab.
- Terminal stage - Child-Pugh C - or very poor performance status initiate supportive care, discuss end of life goals, comfort focused care indicated, POLS.

Process of referral for liver transplant in CCHCS: When patient with HCC is seen by the specialist and considered to be a potential candidate for liver transplant, providers need to obtain RFS/LOA for transplant hepatologist evaluation at the LLUMC.

- Contact CME/DME/HQ UM team for questions.

MONITORING

- Monitor change in tumor size with imaging regularly and when new symptoms arise.

HEPATOPULMONARY SYNDROME (HPS)
DIAGNOSIS
Symptoms:

- Platypnea: dyspnea that worsens when sitting up from supine.
- Orthodeoxia: arterial deoxyhemoglobin saturation decrease >5% when sitting up from supine.

Diagnosis:

- Contrast-enhanced echocardiography.
- Pulmonary angiography.
- Nuclear scanning to view intravascular pulmonary dilatations.

TREATMENT / PROPHYLAXIS

- There are no effective treatments for HPS.
- Long term oxygen therapy for hypoxemia, such as PaO2 < 55 mmHg or SaO2 <88%.
    - Please note that indications for oxygen supplementation are similar to those used for patients with severe hypoxemia due to chronic pulmonary disease. See CCHCS Care Guide: COPD for more details.

Managing Complications Cont'd

  - Clinicians should be aware that some pulse oximeters may perform less accurately on dark- skinned patients. Clinical correlation is recommended.
- Transplant may be a treatment option; if recommended, consult with CME or Regional DME.

MONITORING

- Breathing symptoms as described.
- Pulse oximetry as indicated.

HEPATORENAL SYNDROME (HRS)

DIAGNOSIS

- Progressive rise in serum creatinine.
- Urine sediment often normal with no or minimal proteinuria (less than 500 mg per day).
- Very low rate of sodium excretion (i.e., urine sodium concentration less than 10 mEq/L).
- Oliguria or non-oliguria.

CLASSIFICATION

Over the years, the definition and classification of HRS in patients with cirrhosis have been revised.
AKD, acute kidney disease; AKI, acute kidney injury; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HRS, hepatorenal syndrome; NAKI, non-acute kidney injury; sCr, serum creatinine.

Traditionally HRS has been categorized into two forms based on the speed of onset of renal failure:

- Type I HRS (HRS-1) is more serious and generally develops in less than two weeks with serum creatinine increasing two-fold to > 2.5 mg/dl and CrCl falling to below 20 mL/min.
- Type II HRS (HRS-2) is less severe renal insufficiency associated with diuretic resistant ascites. Serum creatinine level increases over days to weeks.

TREATMENT / PROPHYLAXIS

- Hepatorenal syndrome is usually treated in a hospital setting as it has high mortality rate and requires specialty care.
- Prevention of AKI16
- Treat or prevent possible precipitating factors, particularly gastrointestinal bleeding, and bacterial infections, and avoid large volume paracentesis without albumin administration. Additionally, IV albumin, together with antibiotics, reduces the incidence of HRS-AKI and improves survival in patients with SBP.

MONITORING

- Serum creatinine, urine output.

LIVER MASS EVALUATION

DIAGNOSIS

Lesions < 1 cm

- Repeat ultrasound every 3 months for 24 months.
- If lesion remains < 1 cm, resume every 6 months US screening.
- Not feasible to definitively diagnose liver lesions < 1cm.

Lesions > 1 cm or multiple masses and at least 1 lesion is >1cm.

- Perform contrast enhanced imaging study such as dynamic triphasic or quadriphasic CT or MRI with gadolinium.
- Look for arterial hypervascularization and venous or delayed washout as diagnostic of HCC.
- If CT/MRI is not typical for HCC, a biopsy is needed to diagnose HCC.

Managing Complications Cont'd

Multiple masses, all < 1cm

- Refer to a specialist knowledgeable in the diagnosis of HCC or other types of cancer.

TREATMENT / PROPHYLAXIS

Treatment of HCC:

Classification and diagnosis complement the Barcelona Clinic Liver Cancer staging and treatment criteria:

- Very early to early-stage disease - may be cured with ablation, resection, or liver transplant.
- Intermediate stage - usually treated with chemoembolization.
- Advanced stage - Specialist may consider ordering sorafenib (trade name NexAVAR®) or atezolizumab plus bevacizumab.
- Terminal stage - Child-Pugh C - or very poor performance status initiate supportive care, discuss end of life goals, comfort focused care indicated, POLS.

Process of referral for liver transplant in CCHCS: When patient with HCC is seen by the specialist and considered to be a potential candidate for liver transplant, providers need to obtain RFS/LOA for transplant hepatologist evaluation at the LLUMC.

- Contact CME/DME/HQ UM team for questions.

MONITORING

- Imaging

MEDICATIONS

Indication: Ascites

Drug Class / Medication

Furosemide
(Lasix®)

Dosing

- Recommended starting dose: 20-40 mg orally daily with 100 mg spironolactone.
- Recommended starting dose
- for patients ≤ 50 kg:
- 20 mg/day.
- Increase every 3 to 5 days as needed up to 160 mg furosemide with 400 mg spironolactone.
- Keep the ratio of 100 mg spironolactone and 40 mg furosemide.

Renal or Hepatic Impairment: No adjustment needed; caution advised for cirrhosis/ascites

Adverse effects*/ Interactions

- Adverse Effects: hypokalemia, potentially severe, hypomagnesemia, hypocalcemia, hyperglycemia, hyperuricemia, metabolic alkalosis, hypovolemia, dehydration, ototoxicity, tinnitus, thrombocytopenia/ thrombosis, anemia, (hemolytic/aplastic), leukopenia, agranulocytosis, eosinophilia, rash including erythema multiforme, drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens Johnson Syndrome (SJS), toxic epidermal necrolysis (TENS), pruritus, photosensitivity, SLE exacerbation, urinary frequency, dizziness, weakness, hypotension, anorexia, nausea, vomiting, diarrhea, abdominal cramps
- Drug interactions: desmopressin, cisplatin, aminoglycosides, ethacrynic acid, lithium, ARBs, ACEIs, sucralfate, chloral hydrate, phenytoin, ritonavir, cephalosporins, MAOIs, cyclosporine, NSAIDs, amikacin, lofexidine, probenecid, neomycin, foscarnet, clofarabine

Medications Cont'd

Comments

- Once a patient with cirrhosis develops clinically apparent ascites, it is unlikely to resolve without specific treatment (e.g., a sodium-restricted diet [2000 mg/day] and diuretics)
- **Black Box Warning**: If given in excessive amounts, furosemide can lead to profound diuresis resulting in fluid & electrolyte depletion.
- **Contraindications:** anuria, hypersensitivity to furosemide or any component of the product, hepatic coma, electrolyte imbalances, concomitant use of desmopressin
- Caution in the following: the elderly, patients with cirrhosis, diabetes, prostatic hyperplasia/urinary stricture/urinary retention, SLE, concomitant ototoxic drugs (e.g., aminoglycosides, ethacrynic acid), sensitivity to sulfonamides, arrhythmias, iodinated contrast dye, hepatic, and renal disease

Drug Class / Medication

Spironolactone
(Aldactone®)

Dosing

- Recommended starting dose: 100 mg orally daily with food with 40 mg furosemide.
- Recommended starting dose for patients ≤ 50 kg: 50 mg/ day.
- Increase every 3 to 5 days as needed up to 400 mg spironolactone with 160 mg furosemide.

Renal Impairment:
CrCL <10 mL/min: Avoid use Heart failure patients:
CrCl 30 to 49 mL/min:
Guidelines recommend 12.5 mg orally once daily or every other day for the first 4 weeks followed by 12.5 to 25 mg orally once daily.
CrCl <30 mL/min: Avoid use.

- Hepatic Impairment with cirrhosis and ascites: initiate spironolactone in the hospital

Adverse effects*/ Interactions

- Adverse Effects: hyperkalemia, potentially severe, hypocalcemia, hypomagnesemia, renal failure, rash including: DRESS, SJS, TENS, vasculitis, agranulocytosis, leukopenia, thrombocytopenia, gynecomastia, nausea, vomiting, abdominal cramping, diarrhea, headache, dizziness, lethargy, pruritus, hyperuricemia.

- Drug interactions: triamterene, eplerenone (contraindicated), ACEIs, ARBs, heparin, lithium, corticosteroids, NSAIDs, digoxin, trimethoprim, MAOIs, amikacin, lofexidine, warfarin

Comments

- Once a patient with cirrhosis develops clinically apparent ascites, it is unlikely to resolve without specific treatment (e.g., a sodium-restricted diet [2000 mg/day] and diuretics)
- Manufacturer recommendation: initiate spironolactone in the hospital in patients with hepatic disease with cirrhosis and ascites due to potential for sudden alterations of fluid and electrolyte balance which may lead to impaired neurological function, worsening hepatic encephalopathy, and coma.
- **Black Box Warning:** Shown to be a tumorigen in chronic toxicity animal studies. Avoid unnecessary use.
- **Contraindications:** anuria, acute renal insufficiency, CrCl <30 if over 65 years old, Addison's disease, hyperkalemia, concomitant eplerenone, amiloride, and/or triamterene use, significant renal impairment
- Caution in the following: patients with cirrhosis, heart failure, renal impairment, adrenal vein catheterization, volume depletion, diabetes, hepatic impairment, gout.

Medications Cont'd

Indication: Ascites
Drug Class /Medication
Amiloride
(Midamor®)
Dosing

- Recommended starting dose: 5-10 mg orally daily.
- Max dose: 40 mg
- Renal Impairment:
- CrCl 10-50 mL/min - reduce dose 50%; however, amiloride should generally be avoided due to risk of hyperkalemia. If use is necessary, monitor potassium closely.
- <10 mL/min - contraindicated.
- Hepatic Impairment: No specific dose adjustment given. Use with caution since minor alterations of fluid and electrolyte balance may precipitate hepatic coma

Adverse effects*/ Interactions

- Adverse Effects: hyperkalemia (black box warning), aplastic anemia, neutropenia, hyperuricemia, headache, weakness, nausea, vomiting, diarrhea, loss of appetite, dizziness
- Drug interactions: Cidofovir, eplerenone, triamterene, potassium, quinidine, sotolol, NSAIDs, tranylcypromine, valsartan, losartan, irbesartan, candesartan, telmisartan, digoxin, cyclosporine

Comments

- Can be used in place of spironolactone in cases of painful gynecomastia; less effective than spironolactone in patients with cirrhosis.
- **Black Box Warning:** amiloride may cause hyperkalemia, which, if uncorrected, is potentially fatal. Hyperkalemia occurs commonly (about 10%) when amiloride is used without a kaliuretic diuretic. This incidence is greater in patients with renal impairment, diabetes mellitus (with or without recognized renal insufficiency), and in the elderly. Monitor serum potassium levels carefully in any patient receiving amiloride.
- **Contraindications:** anuria, diabetic nephropathy, acute or chronic renal insufficiency, concomitant use with potassium-sparing agents or potassium supplementation, hyperkalemia, hypersensitivity to amiloride or any other component of the product
- Caution in the following: concomitant use with ACEIs, ARBs, cyclosporine or tacrolimus, seriously ill patients, the elderly with CrCl < 30 mL/min, patients with a predisposition to metabolic or pulmonary acidosis, severe liver disease, renal impairment

Indication: Refractory Ascites
Drug Class /Medication
Midodrine
Dosing

- Recommended dose: Start at 5 mg orally three times a day. Titrate by 2.5 mg for each dose every 24 hours (Max dose 7.5 mg orally three times a day) to achieve an increase in systolic blood pressure of approx. 10-15 mmHg.
- Last dose should be taken at least 4 hours before bedtime.
- Renal Impairment: Start at2.5mg orally three times a day
- Hepatic Impairment: Not studied in hepatic disease. Midodrine is partially metabolized by the liver, use with caution in patients with hepatic disease

Medications Cont'd

Adverse effects*/ Interactions

- Adverse Effects: decreased cardiac output, bradycardia, supine hypertension, pruritus, piloerection, rash, shivering, hot flashes, paresthesia, sleep disturbances, dizziness, headache, dysuria, urinary retention, urinary urgency, pain, abdominal pain, xerostomia, scalp paresthesia)
- Drug interactions: ergot alkaloids (ergotamine, dihydroergotamine, ergonovine, ergoloid mesylates), tranylcypromine, liothyronine, pseudoephedrine, levothyroxine, phenylephrine, thyroid, MAOIs, prazosin, doxazosin, terazosin, digoxin, empagliflozin, canagliflozin, albuterol, levalbuterol, beta-blockers

Comments

- Reserve for patients with true Refractory Ascites or patients unable to tolerate increased diuretic dosing, or on max dose of diuretics and sodium restriction at 2 g/day.
- **Black Box Warning**: Because midodrine can cause marked elevation of supine blood pressure, it should be used in patients whose lives are considerably impaired despite standard clinical care. Clinical benefits of midodrine, principally improved ability to carry out activities of daily living have not been verified.
- **Contraindications**: acute renal disease/ failure, urinary retention, persistent and excessive supine hypertension, MAOI therapy, pheochromocytoma, severe organic heart disease, thyrotoxicosis,
- Caution in the following: administration with drugs that directly or indirectly lower heart rate, orthostatic hypotensive patients with diabetes, heart failure, hepatic insufficiency, patients with history of vision disorders and receiving fludrocortisone, renal impairment, hyperthyroidism

Drug Class / Medication
Indication: Hepatic Encephalopathy (HE)
Lactulose
(Enulose®)
Dosing

- Recommended dose: 30-45 mL orally two to three times daily.
- Titrate dose to achieve two to three soft bowel movements per day.
- Hepatic Impairment: No specific dose adjustments available, adjust dosage according to clinical response and indication for use.
- Renal Impairment: guidelines for dose adjustments not available, it appears no dose adjustment needed.

Adverse effects*/ Interactions

- Adverse Effects: abdominal discomfort, cramping, flatulence, nausea, vomiting, electrolyte imbalance, diarrhea, metabolic acidosis
- Drug interactions: droperidol, warfarin, other laxatives, antacids, sodium bicarbonate, lithium

Comments

- Patients with cirrhosis are often malnourished and protein restrictions are associated with increased mortality, so patients with hepatic encephalopathy should generally not have their protein intake restricted.
- For patients who have not improved within 48 hours or who cannot take lactulose consider treatment with rifaximin
- **Contraindications:** Patients who require a galactose-free or low-galactose diet
- Caution in the following: use with other laxatives, diabetes, the elderly or debilitated treated for more than 6 months, electrocautery procedures during proctoscopy or colonoscopy

Medications Cont'd

Drug Class / Medication
Rifaximin
(Xifaxan®)
Dosing

- Recommended dose: 550 mg orally twice daily.
- Indicated for breakthrough HE despite optimized lactulose dosing.
- Hepatic Impairment: Use with caution in severe hepatic impairment (Child-Pugh Class C)
- Renal Impairment: guidelines for dose adjustments not available, it appears no dose adjustment needed

Adverse effects*/ Interactions

- Adverse Effects: bacterial or fungal superinfection may occur with prolonged use, including C. difficile-associated diarrhea, abdominal pain, nausea, ascites, headache, fatigue, peripheral edema, angioedema, pruritus, rash.
- Drug interactions: warfarin, amiodarone, voxilaprevir, cyclosporine

Comments

- Avoid use in patients with diarrhea and fever or blood in stool.
- Use with caution in patients with severe hepatic impairment (Child-Pugh C)
- **Contraindications:** diarrhea complicated by fever or blood in stool, hypersensitivity to rifaximin or rifamycin or any other component of the product
- Caution in the following: severe hepatic impairment, pregnancy, breast-feeding

Indication: Unresectable Hepatocellular Carcinoma (HCC)
Drug Class / Medication
Sorafenib (Nexavar®)
Dosing

- Recommended dose: 400 mg (200 mg x 2) orally twice daily until clinical benefit ceases or unacceptable toxicity occurs.
- Administer without food (at least 1 hour before or 2 hours after a meal)
- Hepatic Impairment: Mild or moderate (Child-Pugh A or B): No dose adjustment is necessary. Severe (Child-Pugh C): studies have not been done.
- Renal Impairment: no dose adjustment needed; has not been studied in dialysis patients

Adverse effects*/ Interactions

- Adverse Effects: hand-foot syndrome (severe), hypersensitivity reaction, SJS, TENS, erythema multiforme, GI perforation, pancreatitis, renal failure, MI, CHF, hypertensive crisis, QT prolongation, rhabdomyolysis, interstitial lung disease, skin carcinoma, hypokalemia, anemia, hypoalbuminemia, hypocalcemia, AST/ALT elevations, hypophosphatemia, lymphopenia, thrombocytopenia, prolonged INR, headache, fatigue, weight loss, diarrhea, constipation, abdominal pain, N/V, anorexia, stomatitis, sensory neuropathy, alopecia, desquamating rash
- Co-administration of certain drugs may need to be avoided or dosage adjustments may be necessary.
- Drug interactions: dronedarone, thioridazine pimozide and saquinavir are contraindicated; QT interval prolonging agents, warfarin

Medications Cont'd

Comments

- Sorafenib is a multikinase inhibitor acting on the vascular endothelial growth factor receptor (VEGFR), among others.
- Findings from the SHARP trial, showed that sorafenib significantly prolonged survival over supportive care alone in patients with advanced HCC.
- Oncology co-management required.
- Blood pressure should be monitored weekly for the first 6 weeks of sorafenib therapy, then monitored and treated as needed thereafter as clinically indicated.
- Sorafenib has not been studied in patients with severe hepatic impairment (Child-Pugh C)
- **Contraindications:** in combination with paclitaxel and carboplatin in patients with lung cancer, hypersensitivity to sorafenib or any other component of the product, pregnancy, and breast-feeding
- Caution in the following: unstable coronary artery disease or recent MI, heart failure, hypertension, avoid use in patients with congenital long QT syndrome, thyroid impairment, any condition that may increase the risk of QT prolongation

Drug Class / Medication
Indication: Portal Hypertension (Esophageal Varices Non-Selective Beta-Blockers)
Nadolol (Corgard®)
Dosing

- Recommended starting dose: 10-20 mg daily (10mg is not readily available in CCHCS).
- Titrate to reduce resting heart rate by 25%, but not below 55 beats/min, and to reduce systolic BP, but not below 90 mmHg.
- Hepatic Impairment: no dose adjustment needed.
- Renal Impairment: CrCl 31-50 mL/min dose Q24-36h 10-30 mL/min dose Q24-48h < 10 mL/min dose Q40-60h

Adverse effects*/ Interactions

- Adverse Effects: heart block, hypotension, CHF, bradycardia, impaired myocardial contractility, angina exacerbation or MI with abrupt d/c, bronchospasm, fatigue, dizziness, Raynaud's phenomenon, pruritus, diarrhea, constipation, nausea, hypersensitivity reaction, rash including SJS.
- Drug interactions: amiodarone, dronedarone, verapamil, diltiazem, lidocaine, epinephrine, thioridazine, clozapine, fluoxetine, haloperidol, warfarin, digoxin, clonidine, antidiabetic agents, NSAIDs, α-blockers

Comments

- Approximately half of patients with cirrhosis have esophageal varices, and one-third of all patients with varices will develop variceal hemorrhage.
- The risk of hemorrhage has been related to the size and appearance of the varices, as well as the degree of hepatic dysfunction.
- Non-selective beta-blockers lower portal pressure and reduce the risk of first bleeding in patients with esophageal varices.
- NSBBs are not necessarily contraindicated in patients with refractory ascites yet caution is advised
- Contraindications: bronchial asthma, overt cardiac failure, cardiogenic shock, sinus bradycardia and greater than first degree conduction block (except in patients with a functioning artificial pacemaker), hypersensitivity to nadolol or any component of the formulation
- Caution in the following: hepatic or renal impairment, bronchospastic disease, conduction abnormality, diabetes, heart failure, myasthenia gravis, PVD, psoriasis, pheochromocytoma, thyroid disease, elderly, avoid abrupt withdrawal and pregnancy.
- May mask symptoms of hypoglycemia and hyperthyroidism

Medications Cont'd
Propranolol
(Inderal®)
Dosing

- Recommended starting dose: 20-40 mg twice daily in patients without ascites, 10-20 mg twice daily in patients with ascites.
- Titrate to reduce resting heart rate by 25%, but not below 55 beats/min, and to reduce systolic BP, but not below 90 mmHg.
- Hepatic Impairment: dose adjustments not provided, use with caution.
- Renal Impairment: no dose adjustment needed

Adverse effects*/ Interactions

- Adverse Effects: heart block, hypotension, CHF, bradycardia, impaired myocardial contractility, angina exacerbation or MI with abrupt d/c, bronchospasm, fatigue, dizziness, Raynaud's phenomenon, pruritus, diarrhea, constipation, nausea, hypersensitivity reaction, rash including SJS, TENS
- Drug interactions: amiodarone, dronedarone, verapamil, diltiazem, lidocaine, epinephrine, thioridazine, clozapine, fluoxetine, haloperidol, warfarin, digoxin, clonidine, antidiabetic agents, NSAIDs, MAOIs, α-blockers

Comments

- Approximately half of patients with cirrhosis have esophageal varices, and one-third of all patients with varices will develop variceal hemorrhage.
- The risk of hemorrhage has been related to the size and appearance of the varices, as well as the degree of hepatic dysfunction.
- Non-selective beta-blockers lower portal pressure and reduce the risk of first bleeding in patients with esophageal varices.
- NSBBs are not necessarily contraindicated in patients with refractory ascites yet caution is advised (see page 11 for more details)
- **Contraindications:** severe bradycardia, decompensated heart failure, cardiogenic shock, sinus bradycardia, sick sinus syndrome, or heart block greater than 1st degree (except in patients with a functioning artificial pacemaker), bronchial asthma, pheochromocytoma, hypersensitivity to propranolol or any component of the product, concurrent use with thioridazine
- Caution in the following: hepatic or renal impairment, bronchospastic disease, conduction abnormality, diabetes, heart failure, myasthenia gravis, PVD, psoriasis, psychiatric disease, thyroid disease, elderly, avoid abrupt withdrawal and pregnancy.
- May mask symptoms of hypoglycemia and hyperthyroidism

Drug Class / Medication
Indication: Portal Hypertension (Esophageal Varices Non-Selective Beta-Blockers)
Carvedilol
(Coreg®)
Dosing

- **Initial:** 3.125 mg orally twice daily. After a minimum of 3-4 days, gradually increase to 6.25 mg orally twice daily.
- Max dose: 12.5 mg/day (except in patients with persistent arterial hypertension)
- Systolic arterial blood pressure should not decrease < 90 mmHg
- Renal impairment: No adjustment needed
- Hepatic impairment: Severe: Contraindicated

Medications Cont'd
Adverse effects*/Interactions

- Adverse effects: dizziness, fatigue, hypotension, diarrhea, hyperglycemia, asthenia, bradycardia, weight increase, vomiting, nausea, arthralgia, visual disturbances, edema, syncope, angina, anemia, pulmonary edema, elevated hepatic enzymes, CHF, asthma, increased cough, dyspnea, erectile dysfunction, depression.
- Intraoperative floppy iris syndrome has been reported during cataract surgery.
- Drug interactions: rifampin, MAOIs, clonidine, cyclosporine, digoxin, amiodarone, verapamil, diltiazem, antidiabetic agents, quinidine, fluoxetine, paroxetine, propafenone, reserpine, NSAIDs, epinephrine, dronedarone, α1-blockers

Comments

- Contraindications: patients with severe bradycardia (except in patients with a functioning artificial pacemaker), 2nd or 3rd degree AV block, decompensated heart failure, requiring IV inotropic therapy, sick sinus syndrome, cardiogenic shock, bronchial asthma, severe hepatic impairment, hypersensitivity to carvedilol or any component of the product
- Use caution in patients with PVD, Prinzmetal angina, bradycardia, bronchospastic disease, heart failure, major surgery, diabetes, thyroid disorder, WPW syndrome, psoriasis, pheochromocytoma, renal impairment, hepatic impairment, myasthenia gravis, elderly, avoid abrupt withdrawal, pregnancy, and lactation.
- May mask symptoms of hypoglycemia
- Considered as first line in patients with compensated cirrhosis, but not first line in patients with decompensated cirrhosis

Indication: Spontaneous bacterial peritonitis (SBP) prophylaxis
Ciprofloxacin
Dosing

- Dose: 500 mg orally daily
- Hepatic Dosing: Use with caution in severe impairment
- Renal Dosing: CrCl 30-50: 250-500mg q12h; CrCl 5-29: 250-500 mg q18h;
- HD/PD: 250-500 mg q24h, dose after dialysis, no supplement needed

Adverse effects*/Interactions

- Common Adverse effects: nausea, diarrhea, vomiting, abdominal pain, headache, dyspepsia, dizziness, restlessness, lightheadedness, vaginitis, insomnia, photosensitivity, pruritus, rash, anxiety, agitation, confusion, tendonitis, myalgia, impaired memory, delirium.
- Drug interactions: dronedarone, fibanserin, ketoconazole, evoketoconazole, lomitapide, lonafarnib, pimozide, thioridazine, and tizanidine are contraindicated; QT prolonging agents, theophylline, alprazolam, zolpideim, mycophenolate, erlotinib, simvastatin, olanzapine, lurasidone, sirolimus, tacrolimus.

Comments

- Black Box Warnings: Disabling, Potentially Irreversible Serious Reactions—Fluoroquinolones assoc. with tendinitis/tendon rupture, peripheral neuropathy, and CNS effects that may occur together; tendinitis/tendon rupture may occur during treatment or months after treatment is discontinued; incr. tendinitis/tendon rupture risk in all ages; risk further incr. in older pts >60 yo, pts taking corticosteroids, and pts w/ kidney, heart, or lung transplant. Avoid in Myasthenia Gravis—Fluoroquinolones may exacerbate muscle weakness in pts w/ myasthenia gravis.
- Contraindications: Concurrent use with dronedarone, fibansern, ketoconazole, levoketoconazole, lomitapide, lonafarnib, pimozide, thioridazine, tizanidine.

Medications Cont'd

- Use with caution in patients with a history of aneurysm, at risk for aortic dissection, undergoing apheresis procedures, known or suspected CNS disorder, known QT prolongation, ongoing proarrhythmic conditions that may increase risk of developing TdP, receiving concomitant corticosteroid therapy, diabetes mellitus, dehydration, hepatic disease, hypertension, peripheral atherosclerotic vascular disease, renal impairment, breast-feeding, pregnancy, and the elderly.

Drug Class / Medication

Sulfamethoxazole/Trimethoprim

Dosing

- Dose: 800mg/160mg orally daily
- Hepatic Impairment: mild-mod impairment: caution advised; significant impairment: contraindicated.
- Renal Dosing: CrCl 15-30: decr. dose 50%; CrCl <15: avoid use.
- HD: supplement with 50% of maintenance dose after dialysis; PD: no supplement needed.

Adverse effects*/ Interactions

- Common Adverse Reactions: nausea, vomiting, anorexia, rash, urticarial, hypersensitivity reaction, photosensitivity, diarrhea, dizziness, dyspepsia, headache, lethargy
- Drug Interactions: dofetilide is contraindicated, thiazide diuretics, potassium sparing diuretics, methotrexate, warfarin, digoxin, QT prolonging agents, leucovorin, amantadine, aspirin, ACE inhibitors, angiotensin II receptor antagonists, amoxicillin, ampicillin, azathioprine, benzocaine, bupivacaine, erdafitinib, tetracaine, mepivacaine, lidocaine, fluorouracil and other folate antagonists, fosphenytoin, phenytoin, ganciclovir, potassium, indomethacin, naproxen, antidiabetic agents, insulins, cyclosporin, posaconazole

Comments

- Contraindications: sulfonamide hypersensitivity, trimethoprim hypersensitivity, folate deficiency megaloblastic anemia, severe hepatic impairment, renal failure/impairment, thrombocytopenia, concomitant use with dofetilide
- Use with caution in patients with AIDS, agranulocytosis, conditions that may increase the risk of QT prolongation, bone marrow suppression, C. difficile-associated diarrhea, carbonic anhydrase inhibitor hypersensitivity, mild folate deficiency, sulfonylurea hypersensitivity, thiazide diuretic hypersensitivity, pregnancy, breast-feeding, and the elderly

END OF LIVER CIRRHOSIS CARE GUIDE SUMMARY