CCHCS Care Guide: Advanced Liver Disease

SUMMARY | **DECISION SUPPORT** | **PATIENT EDUCATION/SELF MANAGEMENT**

GOALS

- ✓**Diagnose F4 Cirrhosis early and screen for HCC***
- ✓**Diagnose and treat complications**
- ✓**Delay decompensation**
- ✓**Early identification of patients who are appropriate for Palliative Care/Hospice – Ensure POLST done**

ALERTS

- **Abdominal Pain: Consider Spontaneous Bacterial Peritonitis (SBP)**
- **Mental status changes – consider encephalopathy**
- **Hematemesis/Melena**
- **Fever- Consider SBP**
- **Oliguria/Anuria**
- **Rapid weight gain or loss – fluid gain/loss**

DIAGNOSTIC CRITERIA FOR CIRRHOSIS AND DECOMPENSATED CIRRHOSIS

Cirrhosis is best **predicted** by these findings[1]:
- Ascites (likelihood ratio for cirrhosis [LR] 7.2)
- Platelet count < 160,000/mm^3 (LR 6.3) **severe thrombocytopenia often precedes other manifestations
- Spider angiomata on physical exam (LR 4.3)

Cirrhosis (liver fibrosis stage 4) is **diagnosed** with one or more of the following:
- Imaging: hepatic ultrasound, CT, MRI
- Calculations: FIB4 online calculator
- Procedure: liver biopsy, transient elastography (FibroScan™)
- Physical exam

Decompensated Cirrhosis is defined by the presence of:
- Ascites
- Hepatic encephalopathy (HE)
- *Hepatocellular carcinoma (HCC)
- Hepatorenal syndrome (HRS)
- Hepatopulmonary syndrome (HPS)
- Child-Pugh class B and C (*See page 5)*
- 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)
- Physical Exam: Particularly mental status changes, skin changes, hepatosplenomegaly, spider angiomata, 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 varices, hepatic encephalopathy, SBP) indicative of decompensated cirrhosis

Medication List Review
- Avoid hepatotoxins and chronic NSAID use
- Multiple drugs have altered kinetics in patients with severe liver disease; dose alterations frequently required

Lab/Diagnostics
- CBC, CMP, PT/INR, hepatitis serologies, HIV testing
- Cirrhosis/F4: Esophagogastroduodenoscopy (EGD) (baseline) to screen for esophageal varices, follow-up based on clinical findings
- F4 fibrosis: US to screen for HCC every 6 months (AFP not recommended as the only tool to screen for HCC)

TREATMENT (SEE PAGES 6-11)

Vaccinations**:** influenza annually, pneumococcal vaccines, if not immune, consider vaccinating for: HAV, HBV
Medications or other therapies based on specific patient findings (See below and pages 6-11)
- 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
- Hepatocellular carcinoma diagnosed: obtain consultation
- Hepatic encephalopathy: optimize lactulose and minimize potential for exacerbation
- Hepatitis C: consider treatment if no HCC and prognosis > 1 year – See CCHCS Hepatitis C Care Guide
- Liver transplantation: consult with CME or Regional DME for potential transplant candidates
- SBP: antibiotic therapy and prophylaxis

MONITORING (SEE PAGES 6-11)

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 (see algorithm on page 2)
EGD	• EGD (F4 only) at baseline, then as recommended by Gastroenterologist (GI), generally within 2-3 years (see page 9 for more details)

[1]Udell, J.A., et al. Does this patient with liver disease have cirrhosis? JAMA, 2012 Feb 22;307(8):832-42.

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LIVER DISEASE ALGORITHM

Patient Presents with Liver Disease

1. Complete a thorough History/Physical Evaluation Examination
2. Review medications (avoid hepatotoxins and chronic NSAIDs)
3. Order baseline labs and HCV, HBV, HIV
4. Update vaccinations

Determine existence and staging of liver fibrosis/ cirrhosis by determining FIB4 Score.

If FIB4 score < 1.45:
- Not likely cirrhotic
- Patient Education: no ETOH use, weight management
- Labs and Chronic Care F/U annually or as clinically indicated

FIB4 score > 3.25:

Cirrhosis present
- EGD baseline for varices (See page 9 for info on varices)
- Abd US for HCC q 6 months
- Consider Serial AFP q 6 months with Abd US
- Consider POLST

If FIB4 score 1.45-3.25:
- Fibroscan (or liver biopsy) needed to determine fibrosis level

Fibroscan results*: F4

Fibroscan results*: F3

Severe fibrosis present
- Labs and Chronic Care F/U annually or as clinically indicated
- Patient Education: avoid ETOH use, weight management; avoid chronic NSAIDs

Decompensated Cirrhosis?**

NO
- Patient Education: no ETOH use, weight management
- Labs and Chronic Care F/U as clinically indicated based on associated complications

YES

Poor 6 mos Prognosis?***

NO
- Complete/Update POLST
- Patient Education: no ETOH use, weight management, avoid NSAIDs
- Close Chronic Care F/U with labs as clinically indicated

YES
- Discuss goals of care and code status with patient;
- Complete/Update POLST
- Patient Education: no ETOH use, weight management, avoid NSAIDs
- Close Chronic Care F/U with labs as clinically indicated

***Interpreting FibroScan Results**

FibroScan Result (kpa)	≤ 7.0	> 7.0	≥ 9.5	≥ 12.0
Equivalent Stage of Fibrosis (HCV)	F0-F1	F2	F3	F4

F0-F1	Absent or mild fibrosis
F2	Significant fibrosis
F3	Severe fibrosis
F4	Cirrhosis

Above table refers to HCV only

****Decompensated Cirrhosis**
- Child-Pugh ≥ 7 (≥ 6 for HIV/HCV co-infection)
- Encephalopathy present
- Ascites
- H/O SBP
- Variceal Hemorrhage
- Hepatopulmonary/Hepatorenal Syndrome (HPS/HRS)

*****Poor 6 month prognosis, if any of the following are present**
- Recurrent SBP
- Recurrent Variceal Bleed
- Refractory Ascites
- MELD ≥ 20
- Child-Pugh C
- Poor functional status
- HCC/other cancer
- HPS/HRS
- Dialysis patient
- Heart failure (or other significant co-morbid condition)
- Any hospitalization within 30 days or > 2 within 60 days

EVALUATION

General Approach

During the initial evaluation (and subsequent evaluations), it is important 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, 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.
- If cirrhosis is present, it is important to identify patients with decompensated cirrhosis early.
- The overall prognosis, surveillance plan, and management of patients with decompensated cirrhosis is vastly different.
- Obesity has been shown to predict worsening of liver fibrosis, and cirrhosis decompensation.

History, Physical Exam and Medication Review

History: Especially noting risk factors for hepatitis (alcohol, substance abuse, and tattoos); symptoms of significant liver disease (see below). Obtain vaccination history (for HAV, HBV) and family history.

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 angiomata, jaundice, edema, and distended abdomen with shifting dullness and/or positive fluid wave.

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

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

- Ascites: likelihood ratio for cirrhosis (LR 7.2)
- Spider Angiomata: (LR 4.3)

Review Medication List: Review on a continuing basis. Be aware of hepatotoxic medications. Avoid hepatotoxins and chronic NSAIDs if liver disease is present. Discontinue or dose adjust medications as clinically indicated. Discontinue beta-blockers in patients with decompensated disease.

Laboratory Evaluation

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, anti-hepatitis B core IgM, 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** is a strong predictor for the presence of cirrhosis: Platelet count < 160,000/mm^3 (LR 6.3)
- **Annually: Calculate Fibrosis-4 (FIB4):** Based on age, AST, ALT, and platelets. (Can use online calculator, value is on Quality Management HCV Registry)
- **Treat the patient with FIB4 > 3.25 as cirrhotic**

FIB4 = [Age(y) x AST(U/L)] / [PLT(10^9/L) x ALT(U/L)$^{1/2}$] [1]	
FIB4	**Interpretation**
< 1.45	unlikely to have significant fibrosis
1.45-3.25	not accurate at this range; other staging method required
> 3.25	likely to have advanced fibrosis/cirrhosis (Fibrosis stage 3–4)

- Online calculator: http://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4

[1] Vallet-Pichard, A., et al., FIB-4: an Inexpensive and Accurate Marker of Fibrosis in HCV Infection. Comparison with Liver Biopsy and FibroTest. Hepatology 2007; 46:32-36.

EVALUATION CONTINUED

Imaging and Diagnostic Tests

For Patients with FIB4 scores of 1.45 to 3.25: Obtain FIBROSCAN™

FibroScan™ uses transient elastography to measure liver stiffness.[2] The shear wave velocity has been correlated with stages of fibrosis in HCV patients in the following manner*:

FibroScan Result (kpa)	≤ 7.0	> 7.0	≥ 9.5	≥ 12.0
Equivalent Stage of Fibrosis	F0-F1	F2	F3	F4

Metavir Fibrosis: Score:

F0-F1	Absent or mild fibrosis
F2	Significant fibrosis
F3	Severe fibrosis
F4	Cirrhosis

*For non-HCV causes of liver disease, there are different correlations between the FibroScan result and Metavir Fibrosis.

Screening:

F4 Fibrosis Patients: Ultrasound every 6 mos to screen for HCC (AFP alone is not recommended for HCC screening).

F4 Fibrosis/cirrhosis Patients: EGD (baseline) to screen for esophageal varices.

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 hepatitis C, alcoholic liver disease, and cryptogenic causes.

Other Causes of Liver Disease:

- **Nonalcoholic Fatty Liver Disease**: Diagnosis of exclusion and associated with obesity, HTN, DM, and dyslipidemia. Fatty liver on imaging.
- **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 (**45% of deaths due to HCC).** Check transferrin saturation.
- **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
  - 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 was ≤ 6 months (and a Child-Pugh score ≥ 12 or a MELD score ≥ 21)
  - 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 ≥ 18.
  - Tools to help assess severity of disease (and therefore prognosis) include the Child-Pugh and MELD score (see page 5).
- **Risk Factors for Poor 6 Month Prognosis:** Recurrent SBP, recurrent variceal hemorrhage, refractory ascites, MELD ≥ 20**,** 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).

[2] Ziol, M., et al., Noninvasive Assessment of Liver Fibrosis by Measurement of Stiffness in Patients With Chronic Hepatitis C. Hepatology 2005; 48-54.
[3] Goldberg, E. Cirrhosis in adults: Overview of complications, general management, and prognosis, Up to Date June 2018.

EVALUATION CONTINUED

Severity of Cirrhosis/Prognosis Continued

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.
Obtain a 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.

CHILD-PUGH POINTS			
	1	**2**	**3**
Encephalopathy	None	Grade 1-2	Grade 3-4 (or chronic)
Ascites	None	Mild/Moderate (diuretic-responsive)	Severe (diuretic-refractory)
Bilirubin (mg/dl)	< 2	2-3	> 3
Albumin (g/dl)	> 3.5	2.8-3.5	< 2.8
INR	< 1.7	1.7-2.3	> 2.3

CHILD-PUGH CIRRHOSIS SCORING			
Class	**Points**	**One year survival (%)**	**Two year survival (%)**
Class A	5-6	95	90
Class B	7-9	80	70
Class C	10-15	45	38

Encephalopathy Grading:

Grade 1	Mild confusion, anxiety, restlessness, fine tremor, slowed coordination
Grade 2	Drowsiness, disorientation, asterixis
Grade 3	Somnolent but arousable, marked confusion, incomprehensible speech, incontinence, hyperventilation
Grade 4	Coma, decerebrate posturing, flaccidity

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
- MELD Score Three Month Mortality:

MELD Score	3 Month Mortality
40 or more	71.3% mortality
30-39	52.6% mortality
20-29	19.6% mortality
10-19	6.0% mortality
< 9	1.9% mortality

- Online Calculator: https://optn.transplant.hrsa.gov/resources/

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
Prevent superimposed insults to the liver and minimize risks for acute exacerbations	• Vaccinations: influenza, pneumococcal vaccines, and HAV and HBV if not immune • HCV, HBV infections • Alcohol cessation
Identify medications that require dose adjustments, discontinuation, or should be avoided entirely	• Avoidance of hepatotoxins • Continued review of medication lists
Manage symptoms and laboratory abnormalities (for ascites, encephalopathy and variceal bleeding; see pages 7 and 9)	• 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 • 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 7-11 for treatment of the complications of cirrhosis
Determine the appropriateness and optimal timing for liver transplantation	• Consult with CME or Regional CME
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 • 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 • This discussion should be continued on a regular basis and include (but not limited to): Code Status, goals/end of life care, and completion of the POLST form

SUMMARY | DECISION SUPPORT | PATIENT EDUCATION/SELF MANAGEMENT

MANAGING 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 non-selective beta-blockers or esophageal variceal ligation is indicated.

The use of medications, and in particular non-selective beta-blockers, should be regularly reassessed with dose adjustments (or discontinuation) as clinically 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
- 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[1]

Major complications of cirrhosis include:

- Ascites, Hepatic Encephalopathy, Hepatocellular Carcinoma, Hepatopulmonary Syndrome, Hepatorenal Syndrome, Spontaneous Bacterial Peritonitis
- 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.

ASCITES[1]

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

EVALUATION/ TREATMENT AND PROPHYLAXIS

- Evaluation of ascitic fluid[2]:

Routine tests on ascitic fluid	Optional tests	Unusual tests
Cell count and differential Albumin level Total protein level Culture in blood culture bottles	Glucose level LDH level Gram stain Amylase level	Tuberculosis smear and culture Cytology Triglyceride level Bilirubin level

- 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 can be used as substitute for spironolactone if side effects (e.g., gynecomastia) noted

Dietary sodium restriction: 2 gm/day (consider dietary consult or handout)

- 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)
- Obtain CMP every one to two months or as indicated for patients on diuretics; adjust treatment as indicated

[1]Runyon, B.A., et al., Management of adult patients with ascites due to cirrhosis: Update 2012. Hepatology 2013 April; 57(4)

MANAGING COMPLICATIONS (CONTINUED)

REFRACTORY ASCITES[1]	
DIAGNOSIS	• Presence of ascites (See previous page) • 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	• **Discontinue beta-blockers** • Consider oral midodrine starting at 5 mg three times daily; recommended dosing is 7.5 mg three times daily • Serial paracentesis • TIPS (may precipitate encephalopathy) • 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 beta-blocker prophylaxis indefinitely if history of SBP • Empiric IV antibiotic with Cefotaxime while waiting for lab results if clinical suspicion present (fever, abdominal pain, and/or altered mental status) • Usually in hospital with IV Cefotaxime. Use Quinolone for patients with allergy to β-lactamase antibiotics, unless Quinolone 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 Cefotaxime (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

[1]Runyon, B.A., et al., Management of adult patients with ascites due to cirrhosis: Update 2012. Hepatology 2013 April; 57(4)

MANAGING COMPLICATIONS (CONTINUED)

HEPATIC ENCEPHALOPATHY (HE)[1]

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), blood transfusion, HCC, excess protein intake, constipation, dehydration, drugs, poor adherence to medications, and portohepatic shunts Treatment overt 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 e.g., nonadherence. Titrate dose to no more than three to four bowel movements per day • Rifaximin - only after optimized lactulose treatment. Recommended dose: rifaximin 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[3]
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[2]

DIAGNOSIS	• Baseline EGD to screen for varices indicated when cirrhosis is first diagnosed • EGD to diagnose when varices suspected

TREATMENT / PROPHYLAXIS	No varices seen on EGD: beta-blockers not recommended for "pre-primary prophylaxis" (i.e., to prevent EV)
	All "beta-blockers" recommendations are for **Non-Selective Beta-Blockers** (propranolol and nadolol)
	Primary Prophylaxis:
	• Small varices that haven't bled:
	  • If Child-Pugh class A and no red wales on EGD - can use surveillance EGD in place of beta-blockers
	  • If Child-Pugh class B/C or red wales on EGD - consider beta-blockers
	  • With beta-blockers: Do not lower systolic BP < 90 or heart rate < 55
	• Medium/large varices that haven't bled:
	  • Non-selective beta-blockers or esophageal variceal ligation (EVL)
	  • If bleeding risk is not high, beta-blockers preferred over EVL
	  • With large varices, EVL preferred
	• These agents are not recommended for primary prophylaxis: nitrates, combination beta-blockers and EVL, shunt therapy, or sclerotherapy
	Secondary Prophylaxis:
	• Patients who survive an EV bleed should receive both beta-blockers and EVL
	  • Repeat EGD every 1-2 weeks until varices obliterated, then every 1-3 months, then every 6-12 months for surveillance
	• Consider TIPS in the following circumstances:
	  – if bleeding recurs despite combination beta-blockers and EVL
	  – in Child-Pugh class A/B patients with recurrent bleeding despite beta-blockers and EVL
	• Sclerotherapy is not recommended for secondary prophylaxis

MONITORING	• Cirrhosis without varices on EGD → repeat EGD within 3 years • Small varices and no beta-blocker used → repeat EGD within 2 years • Small/medium/large varices and beta-blockers maximized: consider EGD within 2-3 years • Medium/large varices and EVL used: → repeat EGD every 1-2 weeks until varices obliterated, then every 1-3 months, then every 6-12 months • Decompensated cirrhosis: → repeat EGD at time of diagnosis and annually or more often as indicated

[1] American Association for the Study of Liver Diseases; European Association for the Study of the Liver. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. J Hepatology 2014 Sep;61(3):642-59.
[2] Garcia-Tsao G., et al., Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. Am J Gastroenterology 2007 Sep;102(9) :2086-102.

MANAGING COMPLICATIONS (CONTINUED)

HEPATOCELLULAR CARCINOMA (HCC)[1]	
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 (See liver mass evaluation page 11) • Biopsy, as indicated (See liver mass evaluation page 11) • Consultation recommended with a specialist knowledgeable in the diagnosis and management of HCC
TREATMENT / PROPHYLAXIS	Classification and diagnosis complements 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 - sorafenib (trade name NexAVAR®) • Terminal stage - Child-Pugh C with liver biopsy evidence of stage 3-4 disease - initiate supportive care, discuss end of life goals, comfort focused care indicated, POLST
MONITORING	• Monitor change in tumor size with imaging, new symptoms

HEPATOPULMONARY SYNDROME (HPS)[2]	
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 • 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)[3]	
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
TREATMENT / PROPHYLAXIS	There are two forms of HRS based on the speed of onset of renal failure: • Type I HRS 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 is less severe renal insufficiency associated with diuretic resistant ascites. Serum creatinine level increases over days to weeks Hepatorenal syndrome is usually treated in a hospital setting as it has high mortality rate and requires specialty care.
MONITORING	• Serum creatinine, urine output

[1]Forner A., et al., Seminar Liver Disease Current Strategy for Staging and Treatment: The BCLC Update and Future Prospects 2010 Feb;30(1):61-74. Bruix J, M. Management of Hepatocellular Carcinoma: an Update. Hepatology Vol 53, No. 3, 2011 pp 1020-1035. Rodriguez de Lope, C., et al., J. Management of HCC. Journal of Hepatology. 2012/s75-87.
[2]Lange, P.A., Hepatopulmonary syndrome: Natural history, treatment, and outcomes. UpToDate: March 2015. Lange, P.A., UpToDate: Hepatopulmonary syndrome: Prevalence causes, clinical manifestations and diagnosis March 2015.
[3]Runyon, BA, Hepatorenal syndrome. UpToDate: March 2015. [2]Adapted from Bruix J, M., Management of Hepatocellular Carcinoma: an Update, Hepatology Vol 53, No. 3, 2011 pp 1020-1035. [3]Runyon, B.A., Management of adult patients with ascites due to cirrhosis: Update 2012. Hepatology 2013 Apr; 57(4).

SUMMARY	DECISION SUPPORT	PATIENT EDUCATION/SELF MANAGEMENT

MANAGING COMPLICATIONS (CONTINUED)

LIVER MASS EVALUATION[1]

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 (See HCC page 10) • If CT/MRI is not typical for HCC, a biopsy is needed to diagnose HCC Multiple masses, all < 1cm • Refer to a specialist knowledgeable in the diagnosis of HCC
TREATMENT / PROPHYLAXIS	Treatment of HCC: (See page 10)
MONITORING	Imaging

[1]Lange, PA. Hepatopulmonary syndrome: Natural history, treatment, and outcomes. UpToDate: March 2015. Lange, PA. UpToDate: Hepatopulmonary syndrome: Prevalence, causes, clinical manifestations and diagnosis March 2015.

REFERENCES

1. Udell, J.A., et al., Does this patient with liver disease have cirrhosis? JAMA 2012 Feb 22; 307(8):832-42.
2. From UpToDate: Goldberg, Eric and Chopra, Sanjiv. Cirrhosis in adults: Overview of complications, general management, and prognosis. November 2018.
3. Vallet-Pichard, A., et al., FIB-4: an Inexpensive and Accurate Marker of Fibrosis in HCV Infection. Comparison with Liver Biopsy and FibroTest. Hepatology 2007; 46:32-36.
4. Ziol, M., et al., Noninvasive Assessment of Liver Fibrosis by Measurement of Stiffness in Patients With Chronic Hepatitis C. Hepatology 2005; 48-54.
5. Runyon, B.A., et al., Management of adult patients with ascites due to cirrhosis: Update 2012. Hepatology 2013 Apr; 57(4).
6. From UpToDate: Runyon, B.A., et al., Evaluation of the adult with ascites. April 2015.
7. Garcia-Tsao, G., et al., Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. AM J Gastroenterology 2007 Sep;102(9):2086-102.
8. American Association for the Study of Liver Diseases; European Association for the Study of the Liver. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. J Hepatology 2014 Sept; 61(3):642-59.
9. Forner A., et al., Semin Liver Dis. Current Strategy for Staging and Treatment: The BCLC Update and Future Prospects 2010 February 30(1):61-74. Bruix J, M. Management of Hepatocellular Carcinoma: an Update. Hepatology Vol 53, No. 3, 2011 pp 1020-1035. Rodriguez de Lope, C., et al., J. Management of HCC. Journal of Hepatology. 2012/s75-87.
10. Lange, P.A., Hepatopulmonary syndrome: Natural history, treatment, and outcomes. UpToDate: March 2015. Lange, P.A., UpToDate: Hepatopulmonary syndrome: Prevalence, causes, clinical manifestations and diagnosis March 2015.
11. Runyon, B.A., Hepatorenal syndrome. UpToDate: March 2015, Adapted from Bruix J. M., Management of Hepatocellular Carcinoma: an Update, Hepatology Vol 53, No. 3, 2011 pp 1020-1035. [3]Runyon, B.A., Management of adult patients with ascites due to cirrhosis: Update 2012, Hepatology. 2013 Apr; 57(4).
12. Chandok, N., Watt, K. Pain Management in Cirrhotic Patient: The Clinical Challenge. Mayo Clinic Proc 2010 May 85(5):451-458.

MEDICATIONS

DRUG CLASS / MEDICATION	DOSING	ADVERSE EFFECTS*/ INTERACTIONS	COMMENTS
INDICATION: ASCITES			
Furosemide (Lasix®) Tablet: 20 mg, 40 mg $	• Recommended starting dose: 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: 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	• 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
Spironolactone (Aldactone®) Tablet: 25 mg, 50 mg, 100 mg $-$$	• 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: 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	• 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

Bold = Formulary

The cost scale $-$$$$$ represents the relative cost of acquisition of medication only. Frequency and complexity of medication administration (institution workload, effect on adherence) should be considered when determining overall cost-effectiveness of treatment.

*See prescribing information for complete description of dosing, adverse effects and drug interactions. Hypersensitivity to the medication, medication class or a component of the formulation is a contraindication to use of the drug.

MEDICATIONS

DRUG CLASS / MEDICATION	DOSING	ADVERSE EFFECTS*/ INTERACTIONS	COMMENTS
INDICATION: ASCITES			
Amiloride (Midamor®) Tablet: 5 mg $	• 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: 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	• 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			
Midodrine Tablet: 2.5 mg, 5 mg, 10 mg $$	• 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 at 2.5mg 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	• 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	• 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

Bold = Formulary

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MEDICATIONS

DRUG CLASS / MEDICATION	DOSING	ADVERSE EFFECTS*/ INTERACTIONS	COMMENTS
INDICATION: HEPATIC ENCEPHALOPATHY (HE)			
Lactulose (Enulose®) Soln: 10 g/15ml $$$-$$$$	• Recommended dose: 30-45 mL orally two to three times daily • Titrate dose to achieve two to three soft bowel movements per day • Hepatic Impairment: No specific dose adjustments available, adjust dosage according to clinical response and indication for use • Renal Impairment: guidelines for dose adjustments not available, it appears no dose adjustment needed	• Adverse Effects: abdominal discomfort, cramping, flatulence, nausea, vomiting, electrolyte imbalance, diarrhea, metabolic acidosis • Drug interactions: droperidol, warfarin, other laxatives, antacids, sodium bicarbonate, lithium	• Patients with cirrhosis are often malnourished and protein restrictions are associated with increased mortality, so patients with hepatic encephalopathy should generally not have their protein intake restricted • For patients who have not improved within 48 hours or who can not take lactulose consider treatment with rifaximin • Contraindications: Patients who require a galactose-free or low-galactose diet • Caution in the following: use with other laxatives, diabetes, the elderly or debilitated treated for more than 6 months, electrocautery procedures during proctoscopy or colonoscopy
Rifaximin (Xifaxan®) Tablet: 550 mg $$$$$	• Recommended dose: 550 mg orally twice daily • Indicated for breakthrough HE despite optimized lactulose dosing • Hepatic Impairment: Use with caution in severe hepatic impairment (Child-Pugh Class C) • Renal Impairment: guidelines for dose adjustments not available, it appears no dose adjustment needed	• Adverse Effects: bacterial or fungal superinfection may occur with prolonged use, including C. difficile-associated diarrhea, abdominal pain, nausea, ascites, headache, fatigue, peripheral edema, angioedema, pruritus, rash • Drug interactions: warfarin, amiodarone, voxilaprevir, cyclosporine	• Avoid use in patients with diarrhea and fever or blood in stool • Use with caution in patients with severe hepatic impairment (Child-Pugh C) • Contraindications: diarrhea complicated by fever or blood in stool, hypersensitivity to rifaximin or rifamycin or any other component of the product • Caution in the following: severe hepatic impairment, pregnancy, breast-feeding
INDICATION: UNRESECTABLE HEPATOCELLULAR CARCINOMA (HCC)			
Sorafenib (Nexavar®) Tablet: 200 mg $$$$$	• 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: 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	• 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

Bold = Formulary

*See prescribing information for complete description of dosing, adverse effects and drug interactions. Hypersensitivity to the medication, medication

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MEDICATIONS

DRUG CLASS / MEDICATION	DOSING	ADVERSE EFFECTS*/ INTERACTIONS	COMMENTS
INDICATION: PORTAL HYPERTENSION (ESOPHAGEAL VARICES NON-SELECTIVE BETA-BLOCKERS)			
Nadolol (Corgard®) Tablet: 20 mg, 40 mg, 80 mg $$$-$$$$	• Recommended starting dose: 40 mg daily • Titrate to reduce resting heart rate by 25%, but not below 55 beats/min, and to reduce systolic BP, but not below 90 mmHg • Hepatic Impairment: no dose adjustment needed • Renal Impairment: CrCl 31-50 mL/min dose Q24-36h 10-30 mL/min dose Q24-48h < 10 mL/min dose Q40-60h	• Adverse Effects: heart block, hypotension, CHF, bradycardia, impaired myocardial contractility, angina exacerbation or MI with abrupt d/c, bronchospasm, fatigue, dizziness, Raynaud's phenomenon, pruritus, diarrhea, constipation, nausea, hypersensitivity reaction, rash including SJS • Drug interactions: amiodarone, dronedarone, verapamil, diltiazem, lidocaine, epinephrine, thioridazine, clozapine, fluoxetine, haloperidol, warfarin, digoxin, clonidine, antidiabetic agents, NSAIDs, α-blockers	• Approximately half of patients with cirrhosis have esophageal varices, and one-third of all patients with varices will develop variceal hemorrhage • The risk of hemorrhage has been related to the size and appearance of the varices, as well as the degree of hepatic dysfunction • Non-selective beta-blockers lower portal pressure and reduce the risk of first bleeding in patients with esophageal varices • D/C with refractory ascites • Contraindications: bronchial asthma, overt cardiac failure, cardiogenic shock, sinus bradycardia and greater than first degree conduction block (except in patients with a functioning artificial pacemaker), hypersensitivity to nadolol or any component of the formulation • Caution in the following: hepatic or renal impairment, bronchospastic disease, conduction abnormality, diabetes, heart failure, myasthenia gravis, PVD, psoriasis, pheochromocytoma, thyroid disease, elderly, avoid abrupt withdrawal and pregnancy • May mask symptoms of hypoglycemia and hyperthyroidism
Propranolol (Inderal®) Tablet: 10 mg, 20 mg, 40 mg, 60 mg $$-$$$$	• Recommended starting dose: 20 mg twice daily • 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: 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	• 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 • D/C with refractory ascites • 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

Bold = Formulary

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SUMMARY | DECISION SUPPORT | PATIENT EDUCATION/SELF MANAGEMENT

END STAGE LIVER DISEASE – CIRRHOSIS: WHAT YOU SHOULD KNOW

WHAT IS CIRRHOSIS? (SIR-O-SIS)

- Cirrhosis is when a healthy liver becomes damaged by scars and lumps
- Cirrhosis is usually caused by viral infections (like hepatitis B and C), alcoholism, or fatty liver disease
- You can live several years with cirrhosis if you get medical care

HOW DO YOU KNOW IF YOU HAVE CIRRHOSIS?

You may not know if you have cirrhosis because you may not have any symptoms.

Your doctor will determine if you have cirrhosis by examining you and performing tests if needed.

You could have cirrhosis if you have:

- Swollen legs or belly
- Yellow colored skin
- Frequent nosebleeds
- Red palms
- A tendency to bruise easily
- Unexplained weight loss or weight gain
- Belly pain
- Frequent infections
- Trouble thinking clearly or confusion

END STAGE LIVER DISEASE – CIRRHOSIS: WHAT YOU SHOULD DO

- Eat from the CDCR "heart healthy" diet
- Stay away from high salt, high fat food from the canteen, and/or packages
- Get regular exercise unless your health care provider tells you not to
- Get vaccinated for Hepatitis A and B and pneumonia
- Get a yearly flu shot
- Do not drink any alcohol, including pruno, while you are in prison or after release
- Discuss all medications with your health care provider
- Take your medication as directed by your health care provider
- Do not take more than 2000 milligrams a day of acetaminophen (brand name Tylenol®)
- Stay away from NSAID medication like Advil®, Motrin®, or Aleve® unless recommended by your health care provider
- Avoid protein and amino acid supplements
- Avoid iron supplements
- Do not take more than the recommended dose of Vitamins A, D, E, or K

TELL YOUR HEALTH CARE PROVIDER IF YOU HAVE ANY OF THESE SYMPTOMS

- Vomiting blood or what looks like "coffee grounds"
- Feeling sleepy for long periods of time
- Trouble thinking or increasing confusion
- Black tarry stools
- You don't pee as much as you used to
- Fever
- Problems breathing

ENFERMEDAD HEPÁTICA EN ETAPA TERMINAL – CIRROSIS: LO QUE USTED DEBE SABER

¿QUÉ ES LA CIRROSIS?

- La cirrosis es cuando se daña un hígado sano a causa de cicatrices y nódulos
- Es causada principalmente por infecciones virales (como hepatitis B y C), alcoholismo o la enfermedad del hígado graso
- Usted puede vivir varios años con cirrosis si recibe atención médica

¿CÓMO SABER SI TIENE CIRROSIS?

Puede que no sepa que tiene cirrosis porque no presenta ningún síntoma.

Su médico determinará si usted tiene cirrosis al examinarlo y practicarle algunos exámenes, de ser necesario.

Usted podría tener cirrosis si presenta:

- Hinchazón en las piernas o el vientre
- Piel amarillenta
- Hemorragias nasales frecuentes
- Palmas de las manos rojas
- Tendencia a sufrir de hematomas
- Pérdida o aumento de peso sin razón aparente
- Dolor abdominal
- Infecciones recurrentes
- Dificultad para pensar con claridad o confusión

ENFERMEDAD HEPÁTICA EN ETAPA TERMINAL – CIRROSIS: LO QUE DEBE HACER

- Base su alimentación en la dieta “corazón sano” del CDCR
- Evite los alimentos altos en sal y en grasas de la cantina y/o comidas que recibe en los paquetes aprobados para los presos
- Practique ejercicio de manera regular a menos que su proveedor de cuidados de la salud le indique que no lo haga

- Vacúnese contra la Hepatitis A y B y contra la neumonía
- Vacúnese anualmente contra la gripe
- No ingiera nada de alcohol, incluyendo pruno, mientras esté en prisión ni cuando sea puesto en libertad

- Consulte cualquier medicación con su proveedor de cuidados de la salud
- Tome sus medicamentos como se los recetó su proveedor de cuidados de la salud
- No tome más de 2 gramos de acetaminofén al día (la marca Tylenol®)
- Evite los medicamentos antiinflamatorios no esteroideos (NSAID) como el Advil®, Motrin® o Aleve® a menos que se lo recomiende su proveedor de cuidados de la salud
- Evite los suplementos de proteínas y aminoácidos
- Evite los suplementos de hierro
- No tome más de la dosis recomendada de vitaminas A, D, E, o K

AVISE A SU PROVEEDOR DE CUIDADOS DE LA SALUD SI PRESENTA ALGUNO DE ESTOS SÍNTOMAS

- Vomita sangre o lo que parece ser deshechos de café
- Se siente somnoliento durante largos períodos de tiempo
- Dificultad para pensar o confusión creciente
- Deposiciones negro alquitrandado
- No orina tan seguido como antes
- Fiebre
- Dificultad para respirar