September 2016

RCHC Care Guide: End Stage Liver Disease (Cirrhosis)

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

GOALS

- ✓ **Diagnose Cirrhosis Early**
- ✓ **Diagnose Complications**
- ✓ **Delay Decompensation**

ALERTS

- **Abdominal Pain: Consider Spontaneous Bacterial Peritonitis (SBP)**
- **Mental Status Changes/Coma**
- **Hematemesis/Melena**
- **Fever**
- **Oliguria/Anuria**
- **Rapid Weight Gain or Loss**

DIAGNOSTIC CRITERIA

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)
- Bonacini cirrhosis discriminant score greater than 7 (LR 9.4) (*see page 2)*

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

- Imaging: hepatic ultrasound, CT, MRI
- Calculations: FIB4, Bonacini Cirrhosis Discriminant Score
- 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
- Hepatopulmonary syndrome
- Child-Pugh class C (*see page 2)*
- Spontaneous bacterial peritonitis (SBP)
- Variceal bleeding

EVALUATION

Complete clinical history and physical exam

- HX**:** Especially risk factors for hepatitis; symptoms of significant liver disease: hematochezia, melena, hematemesis, edema, weight gain
- PE: Particularly mental status changes, skin changes, hepatosplenomegaly, spider angiomata

Lab/Diagnostics

- CBC, CMP, PT/INR, hepatitis serologies, HIV testing
- EGD (baseline) to screen for esophageal varices
- Ultrasound to screen for HCC (AFP not recommended for HCC screening)

TREATMENT (SEE PAGES 3-5)

Vaccinations**:** influenza, HAV, pneumococcal vaccines
Review medication list: avoid hepatotoxins and chronic NSAIDs
Medications or other therapies based on specific patient findings (see below and pages 3-5)

- Ascites: optimize diuretics
- Esophageal varices: determine if nonselective beta-blocker indicated and EGD follow-up interval
- Hepatocellular carcinoma: obtain consultation
- Hepatic encephalopathy: optimize lactulose
- Hepatitis C: determine treatment eligibility
- Liver transplantation: consult with the CME or regional DME for potential transplant candidates
- Spontaneous bacterial peritonitis: antibiotic prophylaxis

MONITORING (SEE PAGES 3-5)

Follow-up visit	• Every 90 days if stable, more frequently if indicated • Monitor: mental status, weight, VS, abdominal girth, skin changes
Labs	• CMP every 1-2 months for ascites patients on diuretics • Consider CBC, CMP, PT/INR annually or more frequently as indicated
Ultrasound	• Every 6 months (HCC screening)
EGD	• EGD at baseline, then as recommended by GI, generally within 2-3 years (see page 3 for more details)

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

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NONINVASIVE CALCULATORS TO DIAGNOSE CIRRHOSIS

BONACINI CIRRHOSIS DISCRIMINANT SCORE (CDS)[1] *

	BONACINI CIRRHOSIS CDS POINTS						
	0	1	2	3	4	5	6
PLT	>340	280 to 339	220 to 279	160 to 219	100 to 159	40 to 99	<40
ALT/AST ratio	>1.7	1.2 to 1.7	0.6 to 1.19	<0.6			
INR	<1.1	1.1 to 1.4	>1.4				

*Alternative use of AST to Platelet Ratio Index (APRI) is acceptable

Based on platelets (PLT), ALT/AST ratio, INR
Possible score = between 0 and 11. Higher score increases the likelihood of cirrhosis

- Bonacini CDS < 3: cirrhosis unlikely
- Bonacini CDS > 7: cirrhosis likely (LR 9.4)*

*Likelihood ratio: LR >1 indicates that a test is associated with disease

FIBROSIS-4 (FIB-4) CALCULATOR[2]

FIB4 = [Age(y) x AST(U/L)] / [PLT(10^9/L) x ALT(U/L)$^{1/2}$]	
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)**

Based on age, AST, ALT, platelets
Online calculator: **http://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4**

CHILD PUGH CLASSIFICATION OF SEVERITY OF CIRRHOSIS

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
PT (seconds prolonged)	< 4	4-6	> 6
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

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.

[1] Bonacini M, et al. Utility of a discriminant score for diagnosing advanced fibrosis or cirrhosis in patients with chronic hepatitis C virus infection. Am J Gastroenterol. 1997 Aug;92(8):1302-4.

[2] 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.

ESLD COMPLICATIONS—DIAGNOSIS / MANAGEMENT

ASCITES[1]

DIAGNOSIS

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

TREATMENT / 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
- Patient may require large volume paracentesis

Diuretics: Start at low dose and titrate up. Optimal ratio 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, up to 400 mg spironolactone with 160 mg furosemide
- 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)
Avoid: alcohol, ACE inhibitors, ARBs, NSAIDs
Refractory ascites: discontinue beta blockers; serial paracentesis; TIPS (may precipitate encephalopathy)

MONITORING

Monitor patient weight and abdominal girth.
Obtain CMP every one to two months or as indicated for patients on diuretics.

ESOPHAGEAL VARICES[3]

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 are not recommended for "pre-primary prophylaxis"
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 B/C or red wales on EGD - consider nonselective beta blockers (propranolol, nadolol). 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 if bleeding recurs despite combination beta blockers and EVL.
- Sclerotherapy is not recommended for secondary prophylaxis.
- Consider TIPS in Child class A/B patients with recurrent bleeding despite beta blockers and EVL.

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 and beta blockers maximized (see page 9): consider EGD within 2-3 years
- Medium/large 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]Runyon, BA et al. Management of adult patients with ascites due to cirrhosis: Update 2012. Hepatology. 2013 Apr;57(4);
[2]From UpToDate: Runyon, BA. et al. Evaluation of the adult with ascites. April 2015;
[3]Garcia-Tsao G et al. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis.Am J Gastroenterol. 2007 Sep;102(9):2086-102.

ESLD COMPLICATIONS—DIAGNOSIS / MANAGEMENT

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 po BID -TID. Consider NA or DOT administration for recurrent symptoms in selected cases, e.g., nonadherence. Titrate dose to no more than three to four BMs/day • Rifaximin-(NF) only after optimized lactulose treatment. Recommended dose: rifaximin 550 mg two times daily • 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 (NF) to lactulose[3]
MONITORING	Medication adherence, bowel movement frequency, mental status, functional status
HEPATOCELLULAR CARCINOMA (HCC)[2]	
DIAGNOSIS	• Screen for HCC with ultrasound every 6 months. • Evaluate mass on ultrasound with contrast enhanced imaging study imaging (dynamic triphasic or quadriphasic CT or MRI with gadolinium). • Hepatic mass identified on contrast enhanced imaging (see liver mass evaluation page 5). • Biopsy, as indicated. • Consultation recommended with a specialist knowledgeable in the diagnosis and management of HCC.
TREATMENT / PROPHYLAXIS	Classification and diagnosis complements the Barcelona Clinic Liver Cancer (BCLC) 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
MONITORING	Monitor change in tumor size with imaging, new symptoms.
HEPATOPULMONARY SYNDROME (HPS)[3]	
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 DME.
MONITORING	Breathing symptoms as described Pulse oximetry 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 Hepatol. 2014 Sep;61(3):642-59.
[2] Forner A, at al Semin Liver Dis. 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.
[3] 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.

ESLD COMPLICATIONS—DIAGNOSIS / MANAGEMENT

HEPATORENAL SYNDROME (HRS)[1]	
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 Hepatorenal Syndrome (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 Clcr 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
LIVER MASS EVALUATION [2]	
DIAGNOSIS	Lesions < 1 cm • Repeat ultrasound every three months for 24 months • If lesion remains < 1 cm, resume every six month US screening • Not feasible to definitively diagnose liver lesions < 1cm Lesions > 1 cm or multiple masses and at least 1 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 4) • 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 4
MONITORING	Imaging
SPONTANEOUS BACTERIAL PERITONITIS (SBP)[3]	
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 (Most often E. coli, or klebsiella; can be streptococcus or rarely staphylococcus)
TREATMENT / PROPHYLAXIS	Treatment • Stop beta blocker prophylaxis indefinitely • Empiric IV antibiotic while awaiting culture results if patient has temp >100, ascitic PMN ≥250 cells/ml, abdominal pain, 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 usually 5 days, unless unusual organism or presentation Prophylaxis All patients with history of prior SBP, significant ascites, or impaired renal function should be treated indefinitely with: • Ciprofloxacin 500 mg daily or sulfamethoxazole/trimethoprim DS one tablet daily. (Weekly dosing is not recommended.) • Patients with cirrhosis who are hospitalized with GI bleed should receive antibiotic prophylaxis: either IV cefotaxime or sulfamethoxazole/trimethoprim DS for seven days Prophylaxis also recommended during GI bleed
MONITORING	Fever, abdominal pain, change in mental status

[1]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, BA. Management of adult patients with ascites due to cirrhosis: Update 2012. Hepatology. 2013 Apr;57(4)

MEDICATIONS

MEDICATION	DOSING	ADVERSE EFFECTS*/ INTERACTIONS/ COMMENTS
INDICATION: ASCITES		
furosemide (Lasix®) Tablet: 20 mg, 40 mg $	• Recommended starting dose: 40 mg by mouth daily (with 100 mg spironolactone) • Recommended starting dose for patients ≤ 50 kg: 20 mg/day • Increase every 3-5 days as needed up to 160 mg furosemide with 400 mg spironolactone	• Electrolyte imbalances: hypokalemia, possibly 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
spironolactone (Aldactone®) Tablet: 25 mg, 50 mg, 100 mg $	• Recommended starting dose: 100 mg by mouth daily with food with 40 mg furosemide • Recommended starting dose for smaller patient ≤ 50 kg: 50 mg/day • Increase every 3-5 days as needed up to 400 mg spironolactone with 160 mg furosemide	• Hyperkalemia, possibly severe • Renal failure • Rash including: DRESS, SJS, TENS, vasculitis • Agranulocytosis, leucopenia, thrombocytopenia • Gynecomastia • Nausea, vomiting, abdominal cramping, diarrhea • Headache, dizziness, lethargy • Pruritus, hyperuricemia
amiloride (Midamor®) Tablet: 5 mg $$	• Recommended starting dose: 5-10 mg/day • Max dose: 40 mg	Can be used in place of spironolactone in cases of painful gynecomastia; less effective for ascites • Hyperkalemia • Aplastic anemia, neutropenia, hyperuricemia • Headache, weakness, nausea, vomiting, diarrhea, dizziness
INDICATION: HEPATIC ENCEPHALOPATHY (HE)		
lactulose (Constulose®, Enulose®) Soln: 10 g/15ml $$	• Recommended dose: 30-45 ml by mouth, two to three times daily • Titrate dose to no more than three to four bowel movements per day	• Abdominal discomfort, cramping, flatulence, nausea, vomiting • With excessive dosing: electrolyte imbalance, diarrhea, metabolic acidosis
rifaximin (Xifaxan®) Tablet: 550 mg $$$$$	• Recommended dose: 550 mg by mouth, twice daily • Indicated for breakthrough HE despite optimized lactulose dosing	• Bacterial or fungal superinfection may occur with prolonged use, including C difficile-associated diarrhea • Headache, fatigue, angioedema, pruritus, rash • Avoid use in patients with diarrhea and fever or blood in stool
INDICATION: HEPATOCELLULAR CARCINOMA (HCC)		
sorafenib (Nexavar®) Tablet: 200 mg $$$$$	• Recommended dose: 400 mg (200 mg x 2) by mouth, twice daily without food (at least 1 hour before or 2 hours after a meal)	• Hand-foot syndrome, severe • Hypersensitivity reaction, SJS, TENS, erythema multiforme • GI perforation, pancreatitis, renal failure • MI, CHF, hypertensive crisis, QT prolongation, HTN • Rhabdomyolysis • Interstitial lung disease • Skin carcinoma • Hypokalemia, hypoalbuminemia, AST/ALT elevations, hypocalcemia, hypophosphatemia, anemia, lymphopenia, thrombocytopenia, prolonged INR • Headache, fatigue • Diarrhea, constipation, abdominal pain, nausea, vomiting • Anorexia, stomatitis, weight loss, sensory neuropathy • Alopecia, desquamating rash

Bold = Formulary

*See prescribing information for complete description of 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 (CONTINUED)

MEDICATION	DOSING	ADVERSE EFFECTS*/ INTERACTIONS/ COMMENTS
INDICATION: PAIN MANAGEMENT: NONOPIOID		
acetaminophen (Tylenol®) Tablets: 325 mg Suspension: 160 mg/ml $	Hepatic impairment: Do not exceed 2 grams per day in cirrhosis Recommended dose in cirrhosis: 650 mg every 8 hours (not more than 2 grams daily) Renal impairment: Cl_{cr} 10-50 ml/min: Administer every 6 hours Cl_{cr} <10 ml/min: Administer every 8 hours	• No significant anti-inflammatory effect or GI toxicity • May be hepatotoxic in acute or chronic overdosage • Interacts with warfarin to prolong INR
NSAIDs	♦ NSAIDs (including aspirin and COX-2 inhibitors) should generally be **avoided** in cirrhosis ♦ Associated with increased risk of variceal hemorrhage, impaired renal function, hepatorenal syndrome, and the development of diuretic resistant ascites	
INDICATION: PAIN MANAGEMENT: OPIOIDS (AVOID OR USE SPARINGLY IN CIRRHOSIS[1])		
morphine sulfate Morphine (MSIR®, MS Contin®) IR: 15mg, 30 mg tab SR:15 mg, 30 mg, 60 mg tab Soln: 10 mg/5 ml **DOT/NA only** **Crush and float** **Cannot crush SR formulation** $$	Hepatic impairment: Start with lower initial doses and titrate slowly OR increase dosing interval by 1.5-2 times normal dose Cirrhosis: avoid or use sparingly Initial dose in cirrhosis: IR: 15 mg every 6-8 hours as needed SR: 15 mg once daily at bedtime Titration: 15 mg SR twice daily Titrate by 15 mg every 7 days Time to max effect: varies Renal impairment: Start with lower initial doses and titrate slowly. **Black Box Warning (BBW)** Life-threatening respiratory depression: Monitor for respiratory depression during initiation or following a dose increase.	Side effects common in long acting opiates: • **Potentiation of drug effect** (including mental obtundation) may be observed in cirrhosis • Respiratory depression, apnea, respiratory arrest • Hypotension, severe; shock, bradycardia • Intracranial pressure (ICP) increase • Seizures • Paralytic ileus • Dependency, abuse • Withdrawal symptoms with abrupt discontinuation • Opioid induced androgen deficiency • Sedation • Nausea, vomiting, constipation, diaphoresis, dizziness More common with morphine: • Pruritus, flushing • Urinary retention • Headache • Edema **Significant Drug Interactions** • Barbiturates • Benzodiazepines • Chlorpromazine • Cimetidine • Cyclosporine • Gabapentin • Monoamine oxidase inhibitors • Opioid Agonists/Antagonists (e.g., tramadol) • Rifampin • Tricyclic antidepressants **Contraindications/Precautions** • Significant pulmonary disorder • Paralytic ileus/bleeding diathesis • Head Injury • Severe renal or hepatic insufficiency • Elderly • Pregnancy

Bold = Formulary

[1]Chandok, N, Watt, K.Pain Management in Cirrhotic Patient: The Clinical Challenge. Mayo Clin Proc.2010 May:85(5):451-458

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MEDICATIONS (CONTINUED)

MEDICATION	DOSING	ADVERSE EFFECTS*/ INTERACTIONS/ COMMENTS
INDICATION: PAIN MANAGEMENT: OPIOIDS (AVOID OR USE SPARINGLY IN CIRRHOSIS[1])		

methadone
 	
Tablet: 5 mg, 10 mg
Soln: 10 mg/ml
 	
DOT/NA only crush & float
 	
$
	Hepatic impairment: Lower initial doses and slower dose titration recommended
	
	Cirrhosis: avoid or use sparingly
	
	Initial dose in cirrhosis: 2.5 mg at bedtime
	
	Titration:
	2.5 mg twice daily for 7 days
	5 mg twice daily for 7 days
	7.5 mg twice daily for 7 days
	10 mg twice daily for 7 days
	10 mg three times daily for 7 days
	20 mg twice daily
	Max effect: 2-4 weeks
	
	Should not be used for PRN supplemental opioid therapy
	
	Renal impairment: Lower initial dose, longer dosing intervals, slower dose titration recommended
	
	Black Box Warning (BBW)
	Life-threatening respiratory depression: Monitor for respiratory depression especially during initiation or following dose increase.
	Life-threatening QT prolongation: Closely monitor patients for changes in cardiac rhythm during initiation and titration.
		Methadone use associated with more frequent deaths than other opioids
		Side effects common in long acting opiates:
		• **Potentiation of drug effects (including mental obtundation) may be observed in cirrhosis**
		• Respiratory depression, apnea, respiratory arrest
		• Hypotension, severe; shock, bradycardia
		• Intracranial pressure (ICP) increase
		• Seizures
		• Paralytic ileus
		• Dependency, abuse
		• Withdrawal symptoms with abrupt discontinuation
		• Opioid induced androgen deficiency
		• Sedation
		• Nausea, vomiting, constipation, diaphoresis, dizziness
		Unique to methadone:
		• QT prolongation, torsades de pointes
		• Pulmonary edema
		
		Significant Drug Interactions
		• Azole antifungals • Cyclobenzaprine • Phenobarbital
		• Antiarrhythmics • Fluoroquinolones • Phenytoin
		• Antipsychotics • Many HIV Meds • Rifampin
		• Benzodiazepines • Macrolides • Risperidone
		• Carbamazepine • Pentamidine • SSRIs/TCA's
		• Cimetidine
		
		Contraindications/Precautions
		• QT prolongation: obtain EKG at baseline, 1 month & annually
		  ▪ Increase EKG monitoring frequency if patient receiving >100 mg/day or if unexplained syncope or seizure occurs while on methadone
		  ▪ If QTc is >450 ms but <500 ms; consider risk vs. benefit- monitor EKG more frequently
		  ▪ If QTC is >500 ms consider alternative therapy, dose reduction, or elimination of contributing factors (e.g., other medications)
		• BPH, urethral stricture
		• Significant pulmonary disorder
		• Severe hepatic or renal insufficiency
		• Elderly
		• Pregnancy
		• Avoidance recommended in patients with severe liver disease (especially patients with portal hypertension and encephalopathy)

Statements from the FDA regarding methadone: see the CCHCS Care Guide: Chronic Pain or http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm142841.htm for more information		

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[1]Chandok, N, Watt, K.Pain Management in the Cirrhotic Patient: The Clinical Challenge. Mayo Clin Proc.2010 May:85(5):451-458

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MEDICATIONS (CONTINUED)

MEDICATION	DOSING	ADVERSE EFFECTS*/ INTERACTIONS/ COMMENTS
INDICATION: PORTAL HYPERTENSION (ESOPHAGEAL VARICES)		
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	<u>Side effects common to non-selective beta blockers:</u> • Cardiac: CHF, heart block, bradycardia, hypotension, impaired myocardial contractility, angina exacerbation or MI with abrupt d/c • Pulmonary: bronchospasm • Other: fatigue, dizziness, Raynaud's phenomenon, pruritus, diarrhea, constipation, nausea • Hypersensitivity reaction • Rash including SJS, TENS (propranolol)
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	

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