INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: *Cirrhosis and Complications*
-January 2023-

Background:

The Indian Health Service National Pharmacy and Therapeutics Committee (NPTC) provided a review of cirrhosis and complications, specifically portal hypertension (PH), gastroesophageal varices (GEV), ascites, and spontaneous bacterial peritonitis (SBP). The NPTC last reviewed this topic in February 2015. Current medications listed on the National Core Formulary relevant to these conditions include carvedilol, ceftriaxone, ciprofloxacin, furosemide, lactulose, propranolol, rifaximin, and spironolactone. Ultimately, **the NPTC made no modifications to the National Core Formulary**.

Cirrhosis and chronic liver disease were the 4th leading cause of death, accounting for 6% of total deaths in American Indian/Alaskan Natives in 2019.[1] Alcoholic liver disease accounts for 48% of cirrhosis-associated deaths in the United States. There are multiple complications related to cirrhosis, the most common of which are variceal hemorrhage, ascites and hepatic encephalopathy. Compensated cirrhosis is the asymptomatic stage. Increased portal pressure leads to decompensated cirrhosis in which other complications develop.

Discussion:

PORTAL HYPERTENSION: PH is the initial and main consequence of cirrhosis and is responsible for the majority of complications from cirrhosis. Hepatic venous pressure gradient (HVPG), the gold standard to assess for the presence of clinically significant portal hypertension (CSPH) (HVPG of 10mm Hg or greater) is invasive, expensive, and not readily available. CSPH can be identified using noninvasive tests. The presence of portosystemic collaterals on imaging is sufficient to diagnose CSPH. The objective of treatment of CSPH without varices is to prevent clinical decompensation. At present, there is no evidence to recommend nonselective beta blockers (NSBBs) to prevent the formation of varices.[2]

Carvedilol, which also has anti-α-adrenergic activity, may have greater portal pressure-decreasing effect than classical NSBBs. A meta-analysis of 4 trials comparing carvedilol to no treatment or endoscopic variceal ligation found significantly lower rates of decompensation in the carvedilol group (11%) vs. 20% in the control group (HR 0.51; 95% CI: 0.29-0.89; p=0.017, I^2=0.0%). Liver-related death risk was also lower in the carvedilol group (HR 0.32; 95% CI: 0.13-0.76; p=0.01).[3] Carvedilol use to prevent decompensation in patients with compensated cirrhosis may be a recommendation in the future after larger randomized, controlled trials (RCTs) are conducted.[3]

GASTROESOPHAGEAL VARICES: GEV are present in approximately 50% of patients with cirrhosis. In compensated cirrhosis, they are found in 30-40% and develop at a rate of 7-8% per year. In decompensated cirrhosis, presence may be seen in up to 85%. Severity of disease, size of varices and presence of red wale marks are predictors of variceal hemorrhage (VH) which occurs at a rate of 10-15% per year. VH spontaneously ceases in about 40% of cases. If left untreated, there is 60% recurrence with 1-2 years of the initial bleed.[2] Prophylaxis of VH is indicated in compensated cirrhosis at high risk of bleeding. NSBBs or carvedilol are used for preventing decompensation. Endoscopic variceal ligation (EVL) treats varices but does not prevent decompensation. Combining NSBB and EVL is not recommended for primary prophylaxis against VH. Anyone with an episode of acute esophageal VH is considered decompensated. For secondary prophylaxis and prevention of rebleed if the first VH occurred while on primary prophylaxis, the combination of NSBB plus EVL is recommended. The current guidelines do not recommend carvedilol as it was not compared to NSBB and EVL at the time the guidelines were reviewed in 2016.[2]

A network meta-analysis of 60 RCTs looked at primary prevention of variceal bleeding. This compared many active treatments with NSBBs or no intervention. Mortality was lower for NSBBs vs. no intervention (HR 0.49, 95% CI: 0.36 to 0.67) as well as EVL compared with no intervention (HR 0.51, 95% CI: 0.35-0.74). NSBBs versus EVL was not studied and the authors concluded that it remains unknown which approach is better for primary prophylaxis of VH.[4]

A systematic review and meta-analysis of 7 RCTs compared carvedilol with EVL for primary and secondary prevention of VH. Benefit for the carvedilol group was seen in primary prevention (RR 0.38, 95% CI: 0.15-0.93) and for all-cause mortality in secondary prevention (RR 0.51, 95% CI: 0.33-0.79). The EVL group showed benefit with less side effects in primary prevention (RR 4.18, 95% CI: 2.19-7.95). The treatments had similar outcomes in all-cause mortality in primary prevention, bleeding-related mortality in primary prevention, compliance in primary prevention, and rebleeding events in secondary prevention. The authors concluded that carvedilol has similar efficacy to EVL in preventing first bleed in patients with GEV and is a reasonable option if EVL is unavailable or too costly.[5]

A Cochrane review provided a meta-analysis of 11 trials evaluating carvedilol vs. traditional NSBBs. No differences were observed in mortality, upper GI bleeding, serious adverse events, or non-serious adverse events. Carvedilol appears to be as safe and efficacious as propranolol and nadolol in the treatment of portal hypertension with GEV.[6]

ASCITES: Cirrhosis is the most common cause of ascites in the Western Hemisphere. Ascites is often the first defining event for decompensation, occurring in 5-10% of compensated cirrhosis patients per year. Five-year survival is decreased from 80 to 30% with ascites. Ascites is initially managed with dietary sodium restriction and diuretic therapy. Aldosterone antagonists, specifically spironolactone, may be adequate monotherapy for a first episode. Loop diuretics may be added to improve response. A ratio of 100 mg spironolactone to 40 mg furosemide is recommended for titration of these agents. Refractory ascites requires treatment with large volume paracentesis (LVP) combined with hyperoncotic human albumin and may require transjugular intrahepatic portosystemic shunt if diuretics and LVP are not effective.[7]

A 2021 systematic review and meta-analysis of 8 observational studies reviewed the safety of beta-blockers in cirrhosis patients with ascites. Overall pooled all-cause mortality showed no significant benefit or harm associated with beta-blocker use in ascites, including refractory ascites[8].

The use of plasma expanders treated with LVP for ascites showed some advantage over no plasma expanders (RR 0.52, 95% CI: 0.06-4.83). There was no significant difference in serious/non-serious adverse events or liver-related complications in this systematic review. Although evidence exists of very low certainty, it suggests that plasma expanders make little or no difference in mortality, adverse events, or other liver-related complications when used with LVP.[9]

SPONTANEOUS BACTERIAL PERITONITIS: Bacterial infections, including SBP, occur in 1/3 of hospitalized patients with cirrhosis. If a patient deteriorates, clinicians should suspect a bacterial infection as typical symptoms may be absent. Mortality increases by 10% for every hour delayed in starting antibiotics. Diagnostic paracentesis, including ascitic fluid culture, should be obtained as soon as the ascetic patient is hospitalized for any reason. SBP is typically monobacterial, and 60% are gram negative. There has been a recent shift towards gram positive and multidrug resistant organisms. Empiric treatment includes 3rd generation cephalosporins unless multidrug resistance organisms or nosocomial infection are suspected. Secondary prophylaxis with ciprofloxacin should be considered as there is a high risk of recurrence.[7]

A 2020 network meta-analysis comparing 6 treatments, including ciprofloxacin, to no intervention and showed that all but 1 treatment (rufloxacin) favored the active treatment arm. However, based on very low certainty evidence, authors concluded that there is uncertainty about whether prophylaxis is beneficial, and if so, which antibiotic is most beneficial[10].

A network meta-analysis of 13 RCTs compared norfloxacin, ciprofloxacin, rifaximin, trimethoprim-sulfamethoxazole, and placebo. The rank probability model indicated rifaximin was the most effective in preventing SBP, followed by ciprofloxacin. Authors suggest that further comparative studies with larger power are needed to confirm the findings[11].

Findings:

Cirrhosis has many complications. Current guidelines do not recommend any treatment for portal hypertension to prevent development of GEV. NSBBs or carvedilol are recommended in preventing decompensation in GEV. NSBB plus EVL is recommended for secondary prevention of VH. Ascites is managed with dietary sodium restriction plus diuretics, spironolactone and furosemide. LVP is necessary in the treatment of refractory ascites. Ciprofloxacin is recommended for secondary prophylaxis of spontaneous bacterial peritonitis.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the NPTC website.

References:

1. Heron M. Deaths: Leading causes for 2019. National Vital Statistics Reports; Vol 70 No 9.: National Center for Health Statistics. July 26, 2021.
2. Garcia-Tsao G, Abraldes JG, Berzigotti A, et al. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management. *Hepatology* 2017; 65(1):310-35.
3. Villanueva C, Torres F, Sarin S, et al. Carvedilol reduces the risk of decompensation and mortality in patients with compensated cirrhosis in competing-risk meta-analysis. *J Hepatol* 2022; 77:1014-25.
4. Roccarina D, Best L, Freeman S, et al. Primary prevention of variceal bleeding in people with esophageal varices due to liver cirrhosis: a network meta-analysis. *Cochrane Database Syst Rev* 2021, Issue 4. Art. No.: CD013121.
5. Dwinata M, Putera D, Adda'I F, et al. Carvedilol vs endoscopic variceal ligation for primary and secondary prevention of variceal bleeding: Systematic review and meta-analysis. *World J Hepatol* 2019; 11(5):464-76.
6. Zacharias AP, Jeyaraj R, Hobolth L et al. Carvedilol versus traditional, non-selective beta-blockers for adults with cirrhosis and gastroesophageal varices. *Cochrane Database Syst Rev* 2018, Issue 10. Art. No.: CD011510.
7. Biggins, SW, Angeli, P, Garcia-Tsao, G et al. Diagnosis, Evaluation, and Management of Ascites, Spontaneous Bacterial Peritonitis and Hepatorenal Syndrome: 2021 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology 2021; 74(2):1014-48.
8. Wong RJ, Robinson A, Ginzberg D et al. Assessing the safety of beta-blocker therapy in cirrhosis patients with ascites: A meta-analysis. *Liver International* 2019; 39:1080-8.
9. Simonetti RG, Perricone G, Nikolova D et al. Plasma expanders for people with cirrhosis and large ascites treated with abdominal paracentesis. *Cochrane Database Syst Rev* 2019, Issue 6. Art. No.: CD004039.
10. Komolafe O, Roberts D, Freeman S, et al. Antibiotic prophylaxis to prevent spontaneous bacterial peritonitis in people with liver cirrhosis: a network meta-analysis. *Cochrane Database Syst Rev* 2020, Issue 1. Art. No.: CD013125.
11. Faust N, Yamada A, Haider H, et al. Systematic review and network meta-analysis: Prophylactic antibiotic therapy for spontaneous bacterial peritonitis. *W J Hepatol* 2020; 12(5):239-52.