Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: Cirrhosis and complications
February 2015

Background:
The IHS National Pharmacy and Therapeutics Committee (NPTC) reviewed cirrhosis and common complications including ascites, hepatic encephalopathy, variceal hemorrhage, spontaneous bacterial peritonitis and hepatorenal syndrome at the February 2015 meeting. Cirrhosis is the eighth leading cause of death in the United States (US) and is a disease that has tremendous impact on the American Indian/Alaska Native (AI/AN) population. Data from 2006 to 2008 showed AI/AN die at a 368% higher rate than other Americans from chronic liver disease and cirrhosis. The mortality disparity rate during that time was 4.7 times higher for AI/AN than for other US ethnicities/races.

Discussion:
MEDICATIONS AND CHRONIC LIVER DISEASE:
Many medications require dosage adjustments in patients with liver disease. Patients with cirrhosis need to be educated on the use of OTC analgesics. Acetaminophen (APAP) and nonsteroidal anti-inflammatory drugs (NSAIDs) can lead to decompensation in patients with compensated cirrhosis or to further decompensation in the already decompensated patient. APAP is an intrinsic hepatotoxin and should be used at therapeutic doses for limited time in patients with cirrhosis. However, a maximum of 2 grams per day is recommended, especially in those with alcoholic cirrhosis. NSAIDs should be avoided in patients with cirrhosis. NSAIDs blunt the response to diuretics in patients with cirrhosis and ascites, as well as, promote renal vasoconstriction leading to acute kidney injury and decreased GFR.

GASTROESOPHAGEAL VARICES:
Variceal hemorrhage is the most common lethal complication of cirrhosis. Varices occur in ~ 50% of patients with cirrhosis. Variceal bleeding, which has a mortality rate of 20% at 6 weeks, ceases spontaneously in up to 40%. If left untreated, late rebleeding occurs in 60% of patients in 1-2 years with a mortality rate of 33%.

Treatment options for primary prophylaxis include nonselective beta blockers (NSBB) or endoscopic variceal ligation (EVL). NSBBs include propranolol and nadolol. Although carvedilol has shown promise in one study, further research is needed before use as primary prophylaxis for varices can be recommended. NSBBs are recommended in both low and high risk patients. EVL is a procedure that can be done at the same time as an EGD. There are few contraindications to performing EVL and a lower incidence of side effects as compared to NSBB use. A 2012 Cochrane review of banding ligation versus beta blockers for primary prevention showed that both NSBB and EVL may be considered for primary prophylaxis in adults with large esophageal varices with high risk for rebleed. NSBB and EVL appear equivalent in prevention with rebleeding rates of 32-35%. The combination of NSBB and EVL had rebleed rates of 14-23% in 2 studies.

ASCITES:
Ascites is both the most common complication of cirrhosis and the most common complication leading to hospitalization. During 10 years of observation, 50% of patients with compensated cirrhosis will develop cirrhosis. Data from 2006 shows those with ascites have a 56% survival rate at 5 years, which is an increase from previous studies.

Treatment of ascites is determined by the cause of fluid retention. First line treatment for ascites includes the following: alcohol cessation if using, sodium restricted diet (2000 mg/day) and diet education, dual diuretics, discontinue NSAIDs if using. Second line treatment includes discontinuing beta blockers, ACE inhibitors, ARBs. Midodrine may be considered if the patient is profoundly hypotensive. Serial therapeutic paracentesis and transjugular intrahepatic portasystemic stent-shunt (TIPS) are also considered second line. For patients who are not candidates for paracentesis, TIPS, or liver transplantation, peritoneovenous shunt is considered third line treatment. Dual diuretic dosing starts with 100mg spironolactone and 40mg furosemide, titrating up every 3 to 5 days maintaining a 100:40 ratio to maximum doses of 400mg/day

and 160mg/day respectively. In patients with edema, the goal maximum weight loss is 1 kg/day and in those without edema, 0.5kg/day. The ultimate goal in patients with ascites is to minimize or discontinue the diuretics. Paracentesis is reserved for those patients who do not respond to diuretics and sodium restriction.

SPONTANEOUS BACTERIAL PERITONITIS (SBP):

SBP is an ascitic fluid infection without an evident intra-abdominal surgically treatable source. The mortality rate of greater than 90% has been reduced to about 20% with early diagnosis and treatment. Diagnosis is based on diagnostic paracentesis with ascitic fluid neutrophils > 250/mm^3. Ascitic fluid culture is positive in about 40% of cases. The most common organism in SBP is *E. coli*, 30% of which are resistant to trimethoprim/sulfamethoxazole and 30% resistant to quinonolones. Of *E. coli* resistant to quinolones, 70% of those are also resistant to trimethoprim/sulfamethoxazole. Common gram positive cocci include streptococcus and enterococci. Culture negative SBP, in which the culture is negative but the neutrophils are greater than 250/mm^3, is treated as though it is culture positive.

Empirical antibiotic treatment should start immediately after diagnosis is made. The European Association for the Study of the Liver (EASL) guidelines recommend third generation cephalosporins as first line. Quinolones are an acceptable alternative provided the local susceptibility patterns are reasonable. Antibiotics may be switched from IV to oral after 48 hours if the patient is showing clinical improvement. After the neutrophil count drops below 250, typically within 5 to 10 days, the antibiotics can be discontinued.

Prophylaxis should be restricted to those at highest risk for SBP. Ceftriaxone is the antibiotic of choice for GI hemorrhage while oral norfloxacin is recommended for those with low protein count or prior history of SBP. A Cochrane review from 2009 included 13 studies that looked at antibiotics used for SBP and concluded that the current evidence does not demonstrate superiority of 3rd generation cephalosporins, but rather equal efficacy. Further research is needed to determine the efficacy of oral versus intravenous antibiotics as well as to determine length of therapy and efficacy of lower doses versus higher doses of cephalosporins.

HEPATORENAL SYNDROME (HRS):

Renal failure in cirrhosis may occur spontaneously or is triggered by events seen in advanced cirrhosis. Prognosis for those with HRS is poor with a survival rate of 50% at 1 month and 20% at 6 months. Liver transplantation provides the best outcome.

HRS treatment requires an inpatient setting for severe acute renal failure. Complications need to be treated early, i.e., screen for sepsis or continue prophylactic antibiotics. Loop diuretics likely will be ineffective, but may be used to maintain urine output and treat central volume overload. Potassium sparing diuretics (spironolactone) are contraindicated as they are high risk for causing hyperkalemia. There is no data on whether or not to continue beta blockers for variceal bleed prophylaxis in these patients. Ascites in patients with HRS should be treated with large volume paracentesis with IV albumin (8g/l of fluid removed). Oral midodrine plus octreotide and albumin has also shown some benefit. In those patients awaiting transplant or with acute, potentially reversible conditions, renal replacement therapy may be recommended.

HRS may be prevented in some patients. EASL guidelines support the use of IV albumin since this has been shown to decrease the incidence of HRS and improve survival. Additionally, norfloxacin 400mg orally daily is suggested to prevent HRS in advanced cirrhosis although further studies are needed.

HEPATIC ENCEPHALOPATHY (HE):

Hepatic encephalopathy is an event that defines decompensated cirrhosis. Within 5 years of cirrhosis diagnosis, the risk of first occurrence of HE is 5-25%. Minimal or covert HE occurs in 20-80 % of those with cirrhosis. Forty percent of patients will have recurrence of overt HE within 1 year.

Clinical diagnosis of HE is based on two concurrent types of symptoms, impaired mental status and impaired neuromotor function. Because the mental and motor signs do not progress in parallel, it is difficult to stage. HE is mostly a diagnosis of exclusion and should be treated as a continuum. It is classified according to underlying disease, severity of manifestations, time course, and existence of precipitating factors. Only overt hepatic encephalopathy (OHE) is routinely treated.

Treatment should be initiated for patient with altered consciousness. Current drug options for treating HE are nonabsorbable disaccharides (lactulose) and rifaximin. Lactulose is widely recommended for maintaining remission. Rifaximin in addition to lactulose is the best documented agent to maintain remission. Once precipitating factors are removed and liver function and nutritional status have improved, prophylaxis may be discontinued. Lactulose dosing is started with 30ml every 1-2 hours until bowel movement then titrated to achieve 2-3 soft stools per day. No dosage adjustments are required for geriatric patients or renal or hepatic impairment. Rifaximin is dosed at 550mg orally twice a day. It has not been studied in renal impairment and should be used with caution in those with severe hepatic impairment. Major drug interactions include p-glycoprotein/ $ABCB_1$ inhibitors, cyclosporine, and warfarin. It may cause *C. difficile* associated diarrhea.

A Cochrane review of 34 randomized trials in 2004 reviewed the use of nonabsorbable disaccharides (NDs) for HE. Treatment with lactulose or lactitol appeared to reduce risk of no improvement, lowered blood ammonia levels, and showed no statistically significant effect on mortality. Authors concluded there is insufficient evidence to confirm or exclude that nonabsorbable disaccharides have a significant beneficial effect on patients with HE. A meta-analysis published in 2008 compared rifaximin and NDs and found no significant difference in the primary outcome of improvement in HE between the two agents. The authors concluded that rifaximin is not superior to NDs for acute or chronic HE. An open-label trial of lactulose for secondary prevention of HE showed a statistically significant decrease in recurrent episodes of HE in the lactulose group (vs placebo), apparent after 4 months. Finally, rifaximin was studied in a randomized, double-blind, placebo controlled trial for secondary prophylaxis for 6 months. A significant reduction in risk of HE was observed with rifaximin with a NNT of 4 to prevent 1 episode of overt HE. A significant reduction in hospitalization for HE was also noted with a NNT of 9 to prevent 1 hospitalization. More than 90% of all patients in the trial took concomitant lactulose therapy and treatment effects were apparent within 28 days.

Findings:
The National Core Formulary (NCF) currently lists propranolol, spironolactone and furosemide. Following the clinical presentation and agency-specific data analyses (procurement and National Data Warehouse), the NPTC **added lactulose** to the NCF.

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.

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