Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Hepatic Encephalopathy***
-November 2020-

Background:

The IHS National Pharmacy and Therapeutics Committee (NPTC) reviewed the treatment of hepatic encephalopathy at the November 2020 meeting. "Cirrhosis and complications" was last reviewed by the NPTC in February of 2015, and lactulose was added to the National Core Formulary (NCF) at that time. After evaluating current treatment guidelines, applicable research, and procurement data, the NPTC voted to **ADD Rifaximin** to the NCF, **after failure of, or intolerance to, lactulose monotherapy as indicated for hepatic encephalopathy**.

Discussion:

Chronic liver disease is the 4th leading cause of death among American Indians and Alaska Natives, with death rates 3 times higher than non-Hispanic white populations[1]. The most common causes of cirrhosis are alcohol, chronic hepatitis C infection and non-alcoholic steatohepatitis[2]. Of those with cirrhosis, 30-45% will develop overt hepatic encephalopathy (OHE) in their lifetimes[3]. The development of OHE is associated with a poor prognosis as evidenced by 42% surviving at 1 year and 23% surviving at 3 years[2]. Hepatic encephalopathy is associated with over 111,000 hospitalizations per year and more than 7 billion dollars in hospital expenditures[4].

The pathophysiology of hepatic encephalopathy is incompletely understood. Ammonia levels are elevated in 90% of those with OHE, but can be elevated in asymptomatic individuals with cirrhosis. Recent studies have identified other mediators thought to be involved, including inflammatory cytokines, benzodiazepine-like compounds, and aromatic amino acids. Treatment is still primarily focused on ammonia as this is the best characterized neurotoxin associated with OHE and therapies targeting ammonia metabolism have been shown to improve symptoms, even in the absence of elevated serum ammonia levels[5].

There is significant uniformity in published treatment guidelines. Persons with cirrhosis who present with neurologic and/or psychiatric symptoms consistent with hepatic encephalopathy are first evaluated to exclude alternative causes. The OHE is classified by cause, severity and other factors while precipitating causes, such as GI bleeding or spontaneous bacterial peritonitis, are identified and treated. Lactulose, a non-absorbable disaccharide (NAD), is initiated by oral route or enema; lactitol, another NAD, may be used as an alternative agent, but only recently became available in the U.S. and is currently off label for use in OHE. In cases of inadequate response to a NAD, or OHE recurrence, rifaximin is added. Education is recommended to maintain optimum protein intake and enforce medication adherence[6,7].

The non-absorbable disaccharides (NAD) reduce the formation of ammonia and increase its removal through several pathways. As NADs are catabolized in the GI tract, they promote a low pH environment. This favors the formation of ammonium ions which are non-absorbable. The acidic environment modifies the colonic flora supporting lactobacillus and similar species that are non-urease producing. Additionally, the laxative effect increases stool volume and decreases transit time, limiting ammonia absorption[8]. A Cochrane Review in 2016 compared NAD vs. placebo and found a significant reduction in mortality, RR 0.59 (0.40 to 0.87), hepatic encephalopathy severity, RR 0.58 (0.50 to 0.69), and serious adverse events, RR 0.47 (0.36 to 0.6), in the treatment group. Non-serious adverse events were higher in the treatment group RR 2.47 (1.24-4.93) and primarily consisted of diarrhea and abdominal pain. The authors did not find a significant difference between NADs when evaluating these same parameters[9].

Rifaximin is a minimally absorbed broad-spectrum antibiotic which exerts its effect by reducing ammonia-producing gut bacteria[8]. A meta-analysis comparing rifaximin to a NAD did not show a significant difference in clinical efficacy or episodes of diarrhea but there were fewer reports of abdominal pain in the rifaximin group, RR 0.28 (0.08-0.95)[10]. A rifaximin/NAD combination provided a 58% relative risk reduction for time to OHE recurrence vs. placebo/NAD (NNT=4 over 6 months) and a 50% relative risk reduction in time to first hospitalization (NNT=9)[11]. Similar findings were presented in a separate meta-analysis comparing rifaximin/lactulose to lactulose with regard to outcomes of efficacy (NNT=4) and mortality (NNT=9)[12].

Findings:

Lactulose continues to be the recommended first-line therapy for hepatic encephalopathy. Lactitol is an acceptable alternative, but is currently off-label for use with OHE in the U.S. Rifaximin alone does not appear to be superior to lactulose/lactitol in terms of efficacy but in combination with lactulose or lactitol does provide benefit in terms of clinical efficacy, hospitalizations and mortality. Rifaximin is a high cost medication and to support fiscal constraints, the NPTC recommends adhering to guidelines for using rifaximin only after failure of, or intolerance to, lactulose monotherapy.

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:

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