Leeds Teaching Hospitals Prescribing Protocol for Rifaximin Use in the management of Chronic Hepatic Encephalopathy.

Brief Description of medicine:
Rifaximin is a non-absorbed semi-synthetic derivative of Rifamycin with a wide spectrum of antibacterial activity against aerobic and anaerobic gram-positive and gram-negative organisms. It acts by binding to the β-subunit of bacterial DNA-dependent RNA polymerase resulting in inhibition of bacterial RNA synthesis. In hepatic encephalopathy (HE) it is thought to reduce the colony count of ammonia producing gut flora and to decrease the systemic absorption of ammonia from the intestinal lumen.

Trust Approved Indications:
- Rifaximin should only be initiated by a Consultant Hepatologist or Consultant Gastroenterologist.
- Treatment of chronic low grade hepatic encephalopathy (impairing quality of life) and/or the secondary prevention of recurrent overt hepatic encephalopathy in patients with cirrhosis who have failed standard therapy.
- Standard therapy is defined as:
  - removal/correction of precipitating factors
  - Laxatives (any) titrated to produce two soft stools daily
- It should not be used for patients with:
  - Acute hepatic encephalopathy
  - Hepatic encephalopathy secondary to GI bleeding
  - A history of Clostridium difficile infection within the last 6 months

Therapy should initially be for one month. The patient should then be reviewed and if there is a demonstrable improvement in symptoms then therapy can be continued. Improvement would be considered as a reduction in one grade or more of encephalopathy, a reduction in admissions for encephalopathy, an improvement in neuropsychological function tests and/or an improvement in overall quality of life.

Place in Therapy:

In-patients:
The use of Rifaximin is not indicated in the acute setting in a patient, with chronic liver disease, admitted with hepatic encephalopathy (HE) or developing HE during their hospital stay.

The cause for the development of HE should be investigated (ie underlying GI bleed, infection, metabolic disturbance) and treated appropriately. There will be a small number of patients with spontaneous HE with no obvious precipitant.

Patients will receive the current standard treatment for HE consisting of:
- Lactulose 15-20mls tds to ensure that the patient is opening their bowels 2-3 x / day
- Daily or twice daily enemas initially to ensure bowels being opened regularly.
If with the above treatment, correction of any identifiable causes and despite a stool frequency of 2-3 times daily for one week the encephalopathy persists, Rifaximin will be initiated at 550mg bd. Rifaximin will only be initiated by a Consultant Hepatologist or Consultant Gastroenterologist.

Neomycin or Metronidazole may be considered if appropriate (not for long-term use >6months, or in patients with leukopenia, neuropathy or renal impairment).

**Out patients:**
In the out-patient setting Rifaximin 550mg bd will be prescribed for:

- Patients with chronic liver disease who have a history of recurrent spontaneous encephalopathy, despite taking regular lactulose and opening their bowels two to three times a day. Rifaximin being effective in preventing hospital admissions therefore allowing significant cost savings.
- Patients who describe minimal HE: altered sleep pattern; difficulty concentrating; struggling to do simple tasks and a reduced attention span, without an obvious precipitant and despite standard lactulose therapy.

Unfortunately in minimal HE secondary to liver cirrhosis there are no standardised guidelines for assessing patients. The neuropsychometric tests typically used can be time consuming, cumbersome to perform and with widely variable results. A thorough history needs to be taken from the patient in clinic and, where possible corroborated by a family member or close friend. Patients should be reviewed after one month of Rifaximin therapy to assess whether there has been any improvement in symptoms. If there has been no improvement in quality of life the Rifaximin will be discontinued. If there has been an improvement the Rifaximin will be continued.

HE is an indication for liver transplantation and if appropriate patients will be referred for assessment for this.

**Prescriber Restrictions:** Consultant Hepatologist or Consultant Gastroenterologist

**Dosage Regimen:** 550mg twice daily (to be taken concomitantly with lactulose)

**Side Effects and Contraindications:**
- Rifaximin may cause allergic reactions, rashes, and itching or more general side effects such as nausea, abdominal pain, dizziness, fatigue, headaches, muscle cramps and joint pain.
- Rifaximin can alter the normal bacteria in the colon and encourage overgrowth of certain bacteria such as *Clostridium difficile*, which can cause inflammation of the colon (pseudomembranous colitis). Patients who develop signs of pseudomembranous colitis after starting Rifaximin (diarrhea, fever and abdominal pain) will be advised to contact their physician immediately.
- Contraindicated in patients with Rifamycin hypersensitivity

**Interactions:**
Due to the negligible gastrointestinal absorption of orally administered Rifaximin (less than 1%), the systemic drug interaction potential is low.

**Advice to Patients:**
If patients develop diarrhoea, fever and abdominal pain they will be advised to contact the on-call Hepatology Doctor (available 24/7) via switchboard (0113 243 3144). If their symptoms persist then the patient should contact the out of hours GP service or attend Accident and Emergency. There will be a letter given to patients with these contact details when they are prescribed rifaximin.
Monitoring including Criteria for Stopping:

- Liver function tests – baseline, month one and 3 monthly thereafter.
- Hepatic encephalopathy symptoms
  - Westhaven Grade
  - Admissions for encephalopathy
  - Improvement in quality of life

If there is no improvement in the level of encephalopathy or failure to prevent hospital admissions with hepatic encephalopathy then the Rifaximin will be stopped. The onset of encephalopathy is an indication for liver transplant so patients who are considered suitable candidates will be assessed. At transplantation Rifaximin will be stopped. In those patients who are not suitable for transplant but have responded to Rifaximin, the drug will be continued and it’s use reviewed at clinic visits. Please note that this latter group of patients have a significantly reduced mortality, with those patients with advanced liver disease having an expected 2 year survival of 35% (Childs Pugh C).

The use of Rifaximin will be audited to assess impact on hospital admissions for hepatic encephalopathy.

West Haven Criteria

The severity of hepatic encephalopathy is graded with the West Haven Criteria; this is based on the level of impairment of autonomy, changes in consciousness, intellectual function, behavior, and the dependence on therapy.

- Grade 1 - Trivial lack of awareness; euphoria or anxiety; shortened attention span; impaired performance of addition or subtraction
- Grade 2 - Lethargy or apathy; minimal disorientation for time or place; subtle personality change; inappropriate behaviour
- Grade 3 - Somnolence to semistupor, but responsive to verbal stimuli; confusion; gross disorientation
- Grade 4 - Coma (unresponsive to verbal or noxious stimuli)

Primary Care Prescribing:

It is anticipated that GPs will continue the prescription of rifaximin following the first month of treatment. The need for continuation of rifaximin will have been assessed in the general liver and gastroenterology clinics at one month post initiation of rifaximin. Rifaximin is licensed for HE in the UK and has few side effects, there being no on-going monitoring required by the GP. The patient will continue to be reviewed regularly in the Hepatology and Gastroenterology clinics, being followed up at least every 3 months after commencing rifaximin.

GPs will be advised to ensure that if patients develop diarrhoea, that a stool sample is sent for culture and clostridium difficile toxin.

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