Protocol for the use of Rifaximin in Treatment and Prevention of Chronic Hepatic encephalopathy in NHS Lanarkshire.

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Background

Hepatic encephalopathy (HE) is a condition where confusion, drowsiness, or coma is caused by chronic liver disease. It is due to the effects on the brain of an accumulation of toxins, rather than a physical problem with the brain itself. It is caused by an inability of the liver to metabolise toxins in the normal way, either because of a loss of liver function, or because of a change in the pattern of blood flow through the liver. HE will often relapse and remit, and there are a number of well recognised conditions which will precipitate an episode of encephalopathy, such as constipation, GI haemorrhage, infection (especially infection of abdominal fluid (ascites)- spontaneous bacterial peritonitis), dehydration, malnutrition, electrolyte disturbance, and drugs- especially opiates and benzodiazepines. HE is reversible with liver transplantation. The toxins which cause HE probably originate from naturally- occurring bacteria in the large intestine, and hence medication which either alters the transit of stool through the large intestine, or which changes intestinal bacteria, can improve encephalopathy.

Standard Treatment

The standard treatment for HE is lactulose, a non- absorbable carbohydrate which causes increased stool frequency, and also alters the intestinal pH, changing the pattern of bacterial growth. The dose is adjusted on an individual patient basis to produce two semi- formed stools per day, but a typical dose would be lactulose 20mls three times daily, taken orally. In the past lactulose was often effectively combined with the poorly absorbed oral antibiotic neomycin in cases where encephalopathy did not respond to lactulose alone. Although this treatment was effective, neomycin is now virtually never used, because of problems with hearing loss and renal toxicity, which probably related to small amounts of the antibiotic being systemically absorbed in subjects with cirrhosis.

Rifaximin

Rifaximin is a novel non- absorbable antibiotic, licensed initially for treatment of travellers' diarrhoea, which was subsequently licensed for the treatment of hepatic encephalopathy and approved for this indication by the SMC in 2013. The research which best characterised its clinical usefulness and defined the patient population was published in NEJM in 2010 (vol 362, no 12, 1071- 81).

In summary the findings of this study were:

- Rifaximin reduces both the occurrence of HE and hospitalisations for HE when given over a 6 month period, and improves quality of life (QOL)
    - NNT 4 to prevent one HE.
    - Improved QOL in treated group
    - NNT 10 to prevent hospitalisation

- Subjects did not have HE at time of initiation

- 90% of subjects were on lactulose. No benefit was seen in subjects not taking lactulose.
- Liver disease was mostly mild
    - all had MELD score (model of end stage liver disease) <25.
    - 90% had MELD<18.
    - No benefit in highest MELD group
    - ((As a rough rule of thumb, MELD >25 equates to Child's grade C cirrhosis or creatinine >100, BR >150, INR >2.5))
- No significant increased AE's or deaths in treated group.
- 2 in 140 treated patients developed c diff vs none in controls

Protocol:

Indication	• Adult patients with Hepatic encephalopathy • Treatment aim is to reduce frequency and severity of episodes, decrease hospitalisations, and improve QOL.
Eligibility criteria	• Inclusion criteria are: two or more episodes of unprecipitated chronic hepatic encephalopathy in Child's grade A or B cirrhosis, (and with extreme caution Child's C), after lack of response to lactulose, including patients with TIPPS (trans-jugular intra-hepatic porto- systemic) shunt. • Exclusion criteria- Unable or unwilling to continue concomitant lactulose therapy. Clear precipitating event for episode of encephalopathy. Ongoing excessive alcohol or drug use. Severe chronic confusion due to causes other than HE (e.g. alcohol related brain injury such as Korsakoff's psychosis). • Withdrawal criteria- withdraw after three months if there is no improvement in the major desired treatment outcomes (reduced hospitalisations, reduced frequency of HE, improved QOL) • Significant side effects are minimal, but include a rate of C Diff of approximately 1 in 70 in published series (vs none in controls).
Pre-Treatment Evaluation/Investigations	• Investigation for and treatment of possible precipitating causes of encephalopathy (as detailed in "Background" above). • Assessment of compliance with prior treatment with lactulose (dose titrated to produce two stools per day), and willingness to continue lactulose whilst on rifaximin. • Initiation should be by a consultant gastroenterologist only.
Treatment Requirements	• 550mg tablet taken orally twice daily • Patients will usually self- administer at home. • Patients should continue on lactulose, in a dose titrated to produce two semi- formed stools per day
Precautions, contraindications and adverse effects	• Caution in patients with severely decompensated liver disease. • It has not been evaluated in pregnancy
Investigations prior to subsequent treatment	• Exclusion of precipitating conditions as outlined in "Background"- this should already form part of the standard of care of patients with hepatic encephalopathy.

Dose modifications e.g.	• Use with extreme caution only in Child's C cirrhotic patients
Audit / Evaluation of Response to Treatment	• Follow up arrangements should be in place to assess response to treatment (most often by out- patient assessment). • Treatment should be withdrawn after three months if there is no improvement in the major desired treatment outcomes (reduced hospitalisations, reduced frequency of HE, improved QOL) • If treatment is effective, it should be continued long term, until death or liver transplantation (note the high transplantation and mortality rates in this group of patients) • If treatment is used in those with the most severe liver disease, weekly follow- up and blood testing is recommended at least initially, with an earlier threshold for treatment withdrawal.

Checklist prior to initiating Rifaximin of Chronic Hepatic Encephalopathy

(the answer should be yes to all these questions, with the exception that Child's C patients can be treated with extreme caution in special circumstances).

- Willing to continue lactulose in an appropriate dose to produce at least two stools per day.
- Child's A or B cirrhosis (+/- TIPSS)
- Two or more unprecipitated episodes of HE preceding initiation of therapy.
- No ongoing chaotic drug or alcohol use
- No other causes of severe confusion or cognitive impairment (e.g. Korsakoff's psychosis, cerebro-vascular disease, traumatic brain injury, etc.)
- Willingness to return for further assessments
- Acute precipitants of HE have been excluded by appropriate clinical testing (e.g. dehydration, infection, electrolyte disturbance).

Useful Tables:

Child – Pugh Score and Implications			
Parameter	**Points Allocated**		
	1	**2**	**3**
INR	1.4	1.4 - 2	>2
Alb	>35	28-34	<28
Br	<35	35-52	53+
Ascites	None	Mild	Mod+
Encephalopathy	None	1-2	3-4

Notes:

Stages of hepatic encephalopathy:

Stage 1: Euphoria, depression, mild confusion, slurred speech, disordered sleep

Stage 2: Lethargy, moderate confusion

Stage 3: Marked confusion, incoherent speech, sleeping but arousable

Stage 4: Coma, initially responsive to noxious Stimuli but later unresponsive.

Survival	**Score**	**1yr**	**2yrs**	**5yr**	**10yr**
Child's A	<7	>85%	85%	44%	27%
Child's B	7-9	62-80%	60%	20%	10%
Child's C	10+	45%	35%	21%	0%

NB. Other important factors will influence prognosis negatively independently of the Child-Pugh Score (and are therefore indications to consider transplant referral, irrespective of the Child-Pugh Score).

Diuretic – Resistant Ascites: **1 year survival 60% overall**

Prior Spontaneous Bacterial Peritonitis: **1 year survival 50% overall**

http://egret.psychol.cam.ac.uk/medicine/index.html