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# Disaccharides in the Treatment of Hepatic Encephalopathy in Patients with Cirrhosis

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## 1. Introduction

Hepatic encephalopathy (HE) is one of the major complications of liver cirrhosis. It has a considerable socioeconomic impact as it reduces the individual's quality of life and needs repeated admission in hospital for its treatment. HE is a complex neuropsychiatric syndrome, which may complicate acute or chronic liver failure and defined as a disturbance in central nervous system function because of hepatic insufficiency and after exclusion of other brain disease. Traditionally, HE is graded according to the West Haven criteria, which define HE grades I-IV based on the presence of specific clinical signs and symptoms and their severity (1,2). The Working Party proposed a nomenclature of HE and classified into three types : type A, associated with acute liver failure; type B, associated with the existence of porto-systemic communications without intrinsic liver disease; and type C, associated with cirrhosis, which, depending on the manner of presentation, is classified into episodic HE (related to precipitating factors) or spontaneous (persistent HE)(1). However, patients with cirrhosis present with a continuous severity spectrum of neuropsychological symptoms ranging from entire normality (HE 0) up to obvious deficits (3). Even in minimal HE (MHE) without obvious clinical symptoms, neuropsychological and neurophysiological testing uncovers deficits which impact on the quality of life and the fitness to drive a motor vehicle (4-7). In this article we will focus mainly on treatment of HE related to cirrhosis (type-C) using disaccharides.

## 2. Pathophysiology of HE and role of ammonia

The pathogenesis of HE in cirrhosis is complex and has multiple components, including ammonia, inflammatory cytokines, benzodiazepine-like compounds, and manganese, that cause functional impairment of neuronal cells. Numerous factors have been shown to precipitate HE including infections, sedatives, gastrointestinal bleeding, dietary protein excess, diuretics, and electrolyte imbalance (8)

There is consensus that ammonia is a key toxin in HE, which may sensitize the brain to the different precipitating factors(9,10). Ammonia is created primarily from nitrogenous products in the diet, bacterial metabolism of urea and proteins in the colon, and from deamination of glutamine in the small intestine by the enzyme glutaminase(11,12). Due to

hepatocellular dysfunction and portosystemic collaterals in cirrhosis, the ammonia concentration rises in the bloodstream and crosses the blood-brain barrier. Exposure to ammonia results in structural alterations in neurons manifested primarily as astrocyte swelling resembling Alzheimer type II astrocytosis (13,14). In chronic liver disease, urea synthesis is impaired and the brain acts as an alternative major ammonia detoxification pathway. Astrocytes have the ability to eliminate ammonia by the synthesis of glutamine through amidation of glutamate by the enzyme glutamine synthetase (15-18). Glutamine enters the mitochondria (Trojan horse hypothesis) and is subsequently cleaved by glutaminase to ammonia and glutamate, thereby increasing intracellular ammonia levels. This causes a feed-forward loop as elevation in mitochondrial ammonia causes production of reactive nitrogen and oxygen species (RNOS) leading to further edema (19-22). Studies have also examined the role of ammonia-induced potentiation of aquaporin-4, a water channel expressed copiously in astrocytes (23). Astrocyte edema also causes depletion of taurine, a molecule that serves as an antioxidant and helps to buffer ammonia-induced toxicity (24). Increased ammonia levels cause abnormal cerebral blood flow and glucose metabolism. Single photon emission computed tomographic (SPECT) studies have demonstrated altered cerebral perfusion with hyperammonemia resulting in a redistribution of blood flow from the cortex to the subcortical regions, which was associated with impaired performance on neuropsychiatric testing (25). Further support for the ammonia-glutamine-brain water hypothesis has been provided by inducing hyperammonemia in patients with cirrhosis through the oral administration of an amino acid solution. An increase in brain glutamine, reduction in magnetization transfer ratio, and significant deterioration in neuropsychological function was suggestive of an increase in brain water (26).

### 3. Treatment of HE

The most important aspect of HE management is prompt recognition and treatment of precipitating factors. Fessel and colleagues demonstrated that HE is caused by reversible factors in over 80% of patients (27). These common reversible factors include constipation, infection, hypokalemia, gastrointestinal bleeding, increased protein intake, sedatives, and tranquilizers. Thus, identifying and correcting the reversible precipitating factors can be beneficial in treating most episodes of HE. Administration of various ammonia-lowering therapies such as nonabsorbable disaccharides and **selected** antimicrobial agents and other less utilized alternative and investigational treatment options include administration of benzodiazepine receptor antagonists, branched-chain amino acids (BCAAs) and ornithine aspartate. If infection is suspected or the patient has clinical evidence of ascites, a paracentesis should be performed with analysis of cell count, gram stain, and culture to evaluate for spontaneous bacterial peritonitis. Additional investigations for infection should be performed with blood cultures, urinalysis, or chest radiographs. Broad-spectrum antibiotics should be initiated after obtaining cultures if infection is suspected, especially in patients with stage III or IV HE. Hypokalemia can be corrected with oral or intravenous potassium. Severe hyponatremia, particularly serum sodium less than 120 mEq/L, should be addressed with appropriate free-water restriction (28). Vasopressin receptor antagonists may be considered for symptomatic patients with severe hyponatremia. HE precipitated by dietary protein intake or use of sedatives often resolves gradually with supportive care (29,30).

#### 4. Non-absorbable disaccharides and mechanism of action

Non-absorbable disaccharides are recommended as first-line pharmacotherapy in current guidelines(2,28).

Current therapies for HE are based on ammonia lowering, with the hypothesis that the colon is the primary organ that generates ammonia (2,28). Lactulose is the most commonly utilized non-absorbable disaccharide for HE. Lactulose, a synthetic disaccharide, is comprised of the monosaccharides lactose and galactose, and is available as a syrup. Doses are generally titrated to achieve two to four semi-soft stools daily, with typical doses of 20 g/30mL orally three to four times per day. A second non-absorbable disaccharide, lactitol, has also been used in the treatment of HE, but it is not currently commercially available in some countries like US(31,32). Lactitol (p-galactosido-sorbitol) is a disaccharide analog of lactulose which is neither absorbed nor broken down in the small intestine, but is extensively metabolized by colonic bacteria. It is available in a highly soluble crystalline powder form and is reported to be less sweet in taste than lactulose. Clinical trials have reported lactitol dosages of 10-12 g every 6 hours, titrated to two bowel movements daily to be effective in treatment of HE (31,33). Disaccharides (both lactulose and lactitol) remain undigested until they reach the colon, where they get metabolized by the bacteria in the colon to acetic and lactic acid. This acidification of colonic lumen inhibits bacterial ammonia production and trap ammonia as non-diffusible ammonium in the intestinal lumen. Due to their cathartic effect it facilitates a 4-fold increase in faecal nitrogen excretion. Both effects result in reduced levels of ammonia in the colon and portal blood. (Figure-1)(34-36).

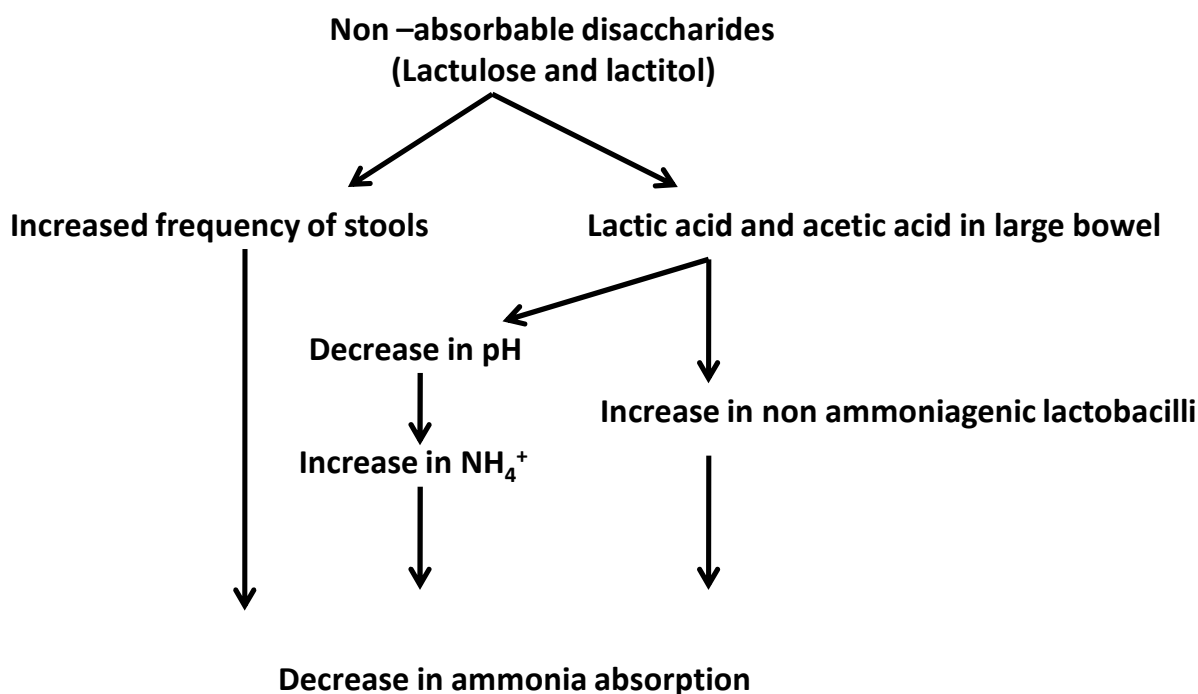


Fig. 1. Mechanism of actions of disaccharides.

## **5. Clinical efficacy of non-absorbable disaccharides**

### **5.1 Lactulose or lactitol versus placebo or no intervention**

#### **5.1.1 Overt hepatic encephalopathy**

The non-absorbable disaccharides have been a mainstay of therapy for HE for decades, and have been extensively studied in several small clinical trials since the late 1960s for this indication. In most of these trials patients had cirrhosis with acute, chronic, acute or chronic or minimal hepatic encephalopathy (37-44). Oral lactulose was used in majority of these studies though some had used lactitol and lactulose enemas also (40). In most of the studies the daily mean doses of lactulose ranged from 30 g to 80 g (median 50 g) to obtain two to three semisoft stools per day. The median duration of treatment was 15 days (range 5 to 360 days). None of the trials followed up patients after the end of treatment. Uribe M et al (40) performed a double-blind, controlled trial to study the efficacy of acidifying enemas of lactitol and lactose versus nonacidifying tap-water enemas in 45 episodes of acute portal-systemic encephalopathy. A favorable response to treatment was obtained in 19 (86%) of the patients receiving lactitol enemas and in 14 (78%) of those receiving lactose enemas. They concluded that acidifying agents like lactose and lactitol are effective and superior to tap-water enemas for the treatment of acute nitrogenous portal-systemic encephalopathy. Study by Mas et al(45) in 53 patients with acute hepatic encephalopathy which were treated with lactitol 60g/day for 5-10 days concluded lactitol to be effective in 81% of patients. A recent meta-analysis evaluated 22 clinical trials in order to better assess the utilization of non-absorbable disaccharides in the management of HE when compared with placebo, no intervention or antimicrobials. Compared with placebo or no intervention, lactulose and lactitol seemed to reduce the risk of no improvement of hepatic encephalopathy (relative risk 0.62, 95% confidence interval 0.46 to 0.84). However high quality trials found no significant effect of lactulose or lactitol on the risk of no improvement (0.92, 0.42 to 2.04), whereas low quality trials found a significant beneficial effect of lactulose or lactitol (0.57, 0.40 to 0.83)(46,47). At the present time, however, there is a lack of sufficient evidence to thoroughly refute the use of non-absorbable disaccharides for the treatment of HE. Sharma et al(48) had shown that high baseline model for end stage liver disease(MELD), high total leukocyte count, low serum sodium, low mean arterial pressure, and presence of hepatocellular carcinoma were predictors of nonresponse to lactulose.

## **6. Disaccharides in treatment of minimal hepatic encephalopathy**

Trials in patients with minimal hepatic encephalopathy (MHE) found that lactulose or lactitol significantly reduced the risk of no improvement assessed by various psychometric tests (0.61, 0.47 to 0.79). Compared with placebo or no intervention, lactulose and lactitol had no significant effect on mortality but tended to lower blood ammonia. A summary analysis of some clinical trials of non-absorbable disaccharides versus placebo/ no treatment is shown in table-1. In a recent study Prasad et al(44) found that treatment with lactulose improved both cognitive function and health-related quality of life, as measured by the Sickness Impact Profile(SIP), when compared against a 'no treatment' patient group. The mean total SIP score improved among patients in the treated group (baseline, 10.39 [95% CI 9.36-11.43]; after 3 months, 3.77 [95% CI 2.52-5.02]) compared with patients in the untreated group (baseline, 10.36 [95% CI 8.98-11.73]; after 3 months, 10.39 [95% CI 8.36-12.42]); $p=0.002$ . Improvement in health related quality of life (HRQOL) was related to the improvement in psychometry. Study

by Sharma et al had shown that on univariate and multivariate analysis, serum sodium and venous ammonia were the only two parameters associated with nonresponse to lactulose(49). Reported adverse events were not serious, and all originated from the gastrointestinal tract (diarrhoea, flatulence, abdominal pain, or nausea)(46).

Trial	Study design	Patients	No	treatment	Assessment	Efficacy
Simmons et al (1970)(37)	Parallel	AHE+CHE	26	Lactulose /glucose	Clinical grading, ammonia, stool production	Lactulose=glucose
Rodgers et al (1973)(38)	Crossover	CHE	6	Lactulose /sorbitol	Clinical grading, EEG, Ammonia	Lactulose=sorbitol
Corazza et al(1982)(39)	Parallel	CHE	32	Lactulose /placebo	Encephalopathy intensity score, ammonia	Lactulose better than placebo
Uribe et al (1987)(40)	Parallel	AHE	15	Lactulose enema	Mortality, clinical grading	Lactulose> placebo
Horsmans et al (1997)(41)	Parallel	MHE	14	Lactulose /placebo	Psychometric tests, ammonia levels	Lactulose > placebo
Wantabe et al (1997)(42)	Parallel	MHE	36	Lactulose / no treatment	Three psychometric tests, ammonia	Lactulose > placebo
Dhiman et al (2000)(43)	Parallel	MHE	26	Lactulose / no treatment	psychometric tests	Lactulose > placebo
Prasad et al (2007)(44)	Parallel	MHE	61	Lactulose / no treatment	psychometric tests and HRQOL	Lactulose > placebo

AHE: acute hepatic encephalopathy CHE: Chronic hepatic encephalopathy

MHE: Minimal hepatic encephalopathy EEG: Electroencephalography

Table 1. Comparison of non absorbable disaccharides and placebo or no treatment for hepatic encephalopathy.

## 7. Lactulose versus lactitol for the treatment of hepatic encephalopathy

Lactulose and lactitol both have been used for the treatment of HE and lactulose has been compared with lactitol in various studies (32,33,50-57)(Table-2).Morgan et al(32) enrolled twenty-five cirrhotic patients experiencing 28 episodes of acute hepatic encephalopathy which were randomized blindly to treatment with either lactitol (n = 15) or lactulose (n = 13). At the end of the trial, 67% of the patients in the lactitol group and 69% of the lactulose group were clinically normal. Metaanalysis by Blanc et al(56) studied the efficiency and tolerance of both compounds(lactulose and lactitol) by using a meta-analysis on the basis of published controlled trials. Analyzed parameters were the portosystemic encephalopathy index of Conn after treatment, the percentage of improved patients and the percentage of patients who had ill effects related to the treatment (flatulence, diarrhea). Bibliographical screening revealed five studies comparing the effects of lactitol and lactulose in chronic hepatic encephalopathy. Four crossover studies were done that included 48 patients and one parallel study that included 29 patients. The duration of the treatment ranged from 3 to 6 months. All studies found a similar efficiency with both drugs. However, they exhibited some discrepancies in the relative frequency of adverse reactions (flatulence).



Meta-analysis showed no statistical differences in the portosystemic encephalopathy index after lactitol or lactulose treatment. The percentage of improved patients after lactitol or lactulose was similar. In contrast, the analysis revealed a higher frequency ( $p$  less than 0.01) of flatulence in patients treated with lactulose compared with those treated with lactitol(56). In conclusion, this meta-analysis shows no statistical difference between therapeutic effects of lactitol and lactulose, but it does show a higher frequency of flatulence with lactulose. However another metaanalysis by Camma et al (57) showed that lactitol was as effective as other disaccharides in the treatment of encephalopathy: pooled odds ratio was 0.83, 95% confidence interval was 0.38-1.82. Patients experienced fewer side effects during treatment with lactitol, but the pooled odds ratio was not statistically significant. In all studies lactitol was considered more palatable (50,55). Clinical effectiveness of lactitol, in long-term treatment of chronic encephalopathy, is similar to those of lactulose. It seems that lactitol has lower side effects than lactulose.

Trial	Study design	Patients	No	Treatment duration	Assessment	Efficacy
Lanthier et al (1985)(50)	Crossover	CHE	5	6 months	Clinical examination, psychometric tests, ammonia levels, EEG, cerebral blood flow	Lactulose =lactitol
Morgan and Hawley et al(1987)(32)	Parallel, double blind	AHE	25	5 days	Psychometric tests, EEG, PSE index	Lactulose =lactitol
Heredia et al(1987)(51)	Parallel	AHE	40	5 days	Mortality, clinical grading, PSE grade, adverse events	Lactulose =lactitol
Heredia et al(1988)(34)	Randomized, crossover	CHE	25	6months	Psychometric tests, ammonia levels, EEG, PSE index	Lactulose =lactitol
Morgan et al(1989)(52)	Double-blind, randomized, Crossover	MHE	9	3 months	Psychometric tests, ammonia levels, EE	Lactulose =lactitol
Riggio et al 1989(53)	Parallel	CHE + MHE	31	6 months	PSE Index, new episodes of HE, adverse events	Lactulose =lactitol
Grandi 1991(54)	Cross-over	CHE	40	-	PSE Index, adverse events	Lactulose =lactitol
Pai et al 1995(55)	Parallel	AHE	45	5 days	PSE Index, adverse events	Lactitol>lactulose
Blanc P et al 1992(56)	Metaanalysis	CHE	77	3-6months	PSE Index	Lactulose =lactitol
Cammà C et al 1993(57)	Metaanalysis	CHE	-	-	PSE Index	Lactulose =lactitol

AHE: acute hepatic encephalopathy CHE: Chronic hepatic encephalopathy  
MHE: Minimal hepatic encephalopathy PSE Index: Portosystemic encephalopathy index

Table 2. Comparison of lactulose and lactitol for hepatic encephalopathy.

## 8. Comparison of lactulose and antimicrobial agents for hepatic encephalopathy

Certain oral antibiotics can reduce urease-producing bacteria in the intestines, resulting in a decrease of ammonia production and absorption through the gastrointestinal tract. Antibiotics are used generally in patients who do not tolerate nonabsorbable disaccharides or in patients who are symptomatic on nonabsorbable disaccharides and require a second agent. Antibiotics with activity against urease-producing bacteria (e.g. neomycin, metronidazole) are effective in reducing intestinal ammonia production. However, the safety and efficacy of these antibiotics in treatment of HE have not been adequately demonstrated. Neomycin and other antimicrobials are utilized as a treatment modality in HE due to their ability to inhibit ammonia production by intestinal bacteria(58). Conn et al(58) conducted a randomized double blind clinical comparison of neomycin and lactulose in 33 cirrhotic patients with chronic portal-systemic encephalopathy. Serial assessments were made in all patients regarding mental status, asterixis, trailmaking test (TMT), electroencephalograms (EEG) and arterial ammonia levels. Both neomycin-sorbitol and lactulose were effective in the majority of patients (83 and 90%, respectively). Atterbury et al (59) evaluated in double-blind, randomized study the efficacy of lactulose and compared with neomycin-sorbitol in 45 episodes of acute nitrogenous portal-systemic encephalopathy (PSE) induced by dietary protein, azotemia, or gastrointestinal hemorrhage. All patients had underlying cirrhosis, and at the time of randomization had encephalopathy of at least grade 2 severity and arterial ammonia concentrations greater than 150 microgram/100 ml. Two thirds of the patients in each group returned to normal mental status and more than 80% in each group showed at least one grade improvement in mental state. In addition, there was equivalent improvement in asterixis, in the performance of the Number Connection Test, in the electroencephalographic pattern, and in arterial ammonia concentration. The principal difference between the two groups was a greater reduction in stool pH after lactulose therapy than after neomycin-sorbitol therapy. Other antimicrobials, including metronidazole and vancomycin, have been studied to a more limited extent than neomycin(59-61)(Table-3). Orlandi et al (60) conducted a randomized

Trial	Study design	No of patients	Duration of treatment	Assessment	Efficacy
Conn et al(1977)(58)	Neomycin vs lactulose (double-blind, randomized, crossover)	29	10 days each arm before crossover	Mental status, asterixis score, EEG, ammonia levels, PSE index	Neomycin = lactulose
Atterbury et al(1978)(59)	Parallel	47	7 days	Mental status, asterixis score, EEG, ammonia levels, PSE index	Neomycin = lactulose
Orlandi et al(1981)(60)	Single blind	173	14 days	Mental status, asterixis score, EEG, ammonia levels, HE change	Neomycin = lactulose

EEG: Electroencephalography

Table 3. Comparison of lactulose and neomycin for hepatic encephalopathy.



Trial	Study design	No of patients	Duration of treatment	Assessment	Efficacy
Festi et al(1993)(64)	Lactulose (open-label)	21	21	Neurological signs of HE, asterixis score, HRNB, EEG, ammonia levels	Rifaximin =lactulose
Bucci and Palmieri (1993)(68)	Lactulose (double-blind, double-dummy)	58	15	Neurological status, asterixis score, HRNB, cancellation tasks, EEG, ammonia levels	Rifaximin >lactulose
Massa et al(1993)(70)	Lactulose (double-blind, double-dummy)	40	15	HE index severity, mental status, cancellation tasks, HRNB, EEG	Rifaximin >lactulose
Fera et al(1993)(72)	Lactulose (double-blind, double-dummy)	40	First 2 weeks of each month for 3 months	Mental status, asterixis score, cancellation tasks, HRNB, EEG, ammonia levels, PSE index	Rifaximin >lactulose
Mas et al(2003)(71)	Lactitol (double-blind, double-dummy)	103	5-10 days	Mental status, asterixis score, EEG, ammonia levels, PSE index, psychometric tests	Rifaximin = lactitol
Leevy et al(2007)(73)	Lactulose (crossover)	145	>6 months lactulose >6 months rifaximin	HE grade, asterixis score	Rifaximin >lactulose
Paik et al(2005)(74)	Lactulose (open-label)	54	7 days	Ammonia levels, flapping tremor, mental status, HE index, psychometric tests	Rifaximin = lactitol
Jiang Q et al(2008)(76)	meta-analysis	264	-	-	Rifaximin = lactitol

Table 4. Comparison of disaccharides and rifaximin for hepatic encephalopathy.

study in order to compare the course of HE in patients treated with neomycin plus magnesium sulfate or with lactulose. The treatment groups were similar in terms of clinical characteristics, fatalities, recovery rate from grade 1 encephalopathy, and disappearance rate of neuropsychiatric signs. Transitions from severe to grade 1 or 0 encephalopathy showed a 0.17 (NS) difference in favor of neomycin. Early therapy and evidence of precipitating factors showed a favorable prognostic significance. Ascites, hyperbilirubinemia, poor nutritional state, and hypoprothrombinemia showed bad prognostic significance.

A combination of disaccharides and antibiotics is generally used in difficult to treat patients with HE, but clinical data is limited. In a retrospective chart review of 213 cases, Mantry and colleagues showed that the number of hospitalizations and the duration of hospital stays were shortened for patients receiving combination therapy compared with those receiving lactulose monotherapy. Additional studies to further investigate the potential therapeutic benefit of combination therapy will be needed.(77,78)

### 9. Disaccharides versus other therapy for hepatic encephalopathy

Mittal et al(79) compared lactulose, probiotics, and L-ornithine L-aspartate (LOLA) in treatment of MHE and effect on health related quality of life by Sickness Impact Profile questionnaire. MHE improved significantly in all three treatment groups. Lactulose, probiotics, and LOLA significantly improve MHE and health related quality of life in patients with chronic liver disease. Similar results were found in other studies (80,81) Table-5

Trial	Study design	No of patients	Type of patient	Treatment	assessment	Efficacy
Loguercio et al 1987(82)	Parallel	40	CHE	Lactobacillus SF68 / lactulose	PSE parameters, adverse events	SF68=lactulose
Loguercio et al 1995(83)	Parallel	40	CHE	Lactobacillus SF68 / lactulose	PSE parameters, adverse events	SF68=lactulose
Sushma et al 1992(84)	Parallel	74	AHE	Sodium benzoate / lactulose	Mortality, PSE parameters	Sodium benzoate=lactulose
Fiaccadori 1980(86)	Parallel	23	AHE + CHE	BCAA/BCAA + lactulose / lactulose	Clinical grading	BCAA+lactulose> BCAA/lactulose
Rossi-Fanelli 1982(87)	Parallel	40	AHE	BCAA / lactulose	Clinical grading	BCAA=Lactulose

Table 5. Disaccharides versus other therapy for hepatic encephalopathy.

Loguercio et al. (82) in 40 patients with cirrhosis on a dietary protein regimen of 1 g/kg determined the effect on chronic hepatic encephalopathy of long-term administration of *Enterococcus faecium* (SF68) versus lactulose. The patients received one of the two treatments for three periods of 4 weeks, each separated by drug-free 2-week intervals. The efficacy of treatment was assessed by arterial blood ammonia concentration, mental status, number connection (Reitan's part A) test and flash-evoked visual potentials. At the end of the third period the reduction in both blood ammonia concentrations and Reitan's test times was more enhanced in patients on SF68 than in patients on lactulose. In conclusion, SF68 is at least as useful as lactulose for the chronic treatment of chronic hepatic encephalopathy; it has no adverse effects, and treatment can be interrupted for 2 weeks without losing the beneficial effects.

Sushma et al(84) conducted a prospective randomized double-blind study to evaluate the efficacy of sodium benzoate in the treatment of acute portal-systemic encephalopathy. Seventy-four consecutive patients with cirrhosis or surgical portasystemic anastomosis and hepatic encephalopathy of less than 7 days duration were randomized to receive lactulose (dose adjusted for 2 or 3 semiformal stools/day) or sodium benzoate (5 gm twice daily). Assessment of response included mental status, asterixis, arterial ammonia level, electroencephalogram and number-connection test. The incidence of side effects was similar in the two treatment groups. The cost of lactulose for one course of therapy was 30 times that of sodium benzoate. They concluded that sodium benzoate is a safe and effective alternative to lactulose in the treatment of acute portasystemic encephalopathy. However in a study by Efrati et al (85) Blood ammonia increased after the glutamine load both before (from  $66 \pm 12$  mg/dl to  $123 \pm 34$  mg/dl and  $179 \pm 53$  mg/dl after 30 and 60 min, respectively;  $p < 0.0004$ ) and after benzoate treatment (from  $102 \pm 27$  mg/dl to  $185 \pm 49$  mg/dl and  $250 \pm 39$  mg/dl after 30 and 60 min, respectively;  $p < 0.00001$ ). The Number Connection test and the Posner's test were not altered by benzoate treatment and this study suggests a note of caution in the use of sodium benzoate in cirrhotic patients.

Rossi-Fanelli F et al(87) conducted a controlled study in two groups of 20 cirrhotic patients with deep coma in order to compare the efficacy of intravenous branched-chain amino acid solutions in 20% glucose (group A) vs. lactulose plus glucose in isocaloric amount (group B). Complete mental recovery was obtained in 70% of patients in group A and in 47% in group B. They concluded that , branched-chain amino acids are at least as effective as lactulose in deep hepatic coma. However, in a meta-analysis of eleven randomised trials (556 patients) assessing BCAA versus carbohydrates, neomycin/lactulose, or isonitrogenous control. There was no significant evidence of an effect of BCAA on improvement of hepatic encephalopathy in trials with adequate generation of the allocation sequence (RR 1.01, 95% CI 0.84 to 1.23, three trials), adequate allocation concealment (RR 1.09, 95% CI 0.89 to 1.33, five trials), or adequate double-blinding (RR 1.20, 95% CI 0.83 to 1.73, three trials). So it was concluded that BCAA had no significant beneficial effect on patients with hepatic encephalopathy (88).

## 10. Disaccharides for primary prophylaxis of hepatic encephalopathy

Certain patients are at risk of development of HE like patients with minimal hepatic encephalopathy and those with advanced liver disease (89-91). Variceal bleed is an important precipitating factor for HE in patients with cirrhosis. In a randomized trial, (92)

we enrolled seventy patients with acute variceal bleed into group-1(lactulose, n = 35) and group-2 (no lactulose, n = 35). Nineteen (27%) patients developed HE, 5 patients (14%) in the lactulose and 14 patients (40%) in no lactulose,  $p = 0.03$ . On multivariate analysis, only baseline arterial ammonia, blood requirement during hospital stay and no lactulose therapy were predictors of development of HE. Hence, lactulose was effective in preventing HE in these patients. We therefore, recommend lactulose (30-60ml/day) so that patients pass two to three semi formed stools in a day in these subsets of patients.

Recently our group has shown in a randomized trial (93) involving 120(48%) patients, receiving either lactulose (n=60) or no lactulose (n=60). Twenty (19%) of 105 patients followed for 12 mo developed an episode of overt HE. Six (11%) of 55 in the lactulose group and 14(28%) of 50 in the no lactulose group ( $p=0.02$ ) developed HE. Ten (20%) of 50 patients no lactulose group and 5(9%) of 55 patients lactulose group died,  $p=0.16$ . On multivariate analysis, Child's score and presence of MHE at baseline was significantly associated with development of HE. Lactulose is effective in the primary prevention of HE.

### **11. Disaccharides for secondary prophylaxis of hepatic encephalopathy**

Hepatic encephalopathy may be a cyclic condition in which patients develop overt HE, receive treatment, enter remission, and relapse. The emergence of HE after transjugular intrahepatic portosystemic shunt (TIPS) is of major concern for patients undergoing this procedure for refractory ascites or for prevention of variceal rebleeding. This clinical complication tends to occur within the first few days post-procedure.

Although the majority of post-TIPS HE episodes are mild and responsive to pharmacological therapy, there are some cases where intractable HE develops and hospitalization is required. There are limited data on the use of drug therapy for the prophylaxis of HE after a TIPS procedure or in patients who have recovered from an episode of HE who may benefit from pharmacological prophylaxis to prevent future recurrences. Until recently, there has not been any conclusive evidence to support routine use of pharmacological prophylaxis for this purpose. Riggio and colleagues (94) conducted the first randomized controlled trial utilizing lactitol or rifaximin as pharmacological prophylaxis of post-shunt HE. Seventy-five consecutive patients with cirrhosis undergoing a TIPS procedure were randomized to receive lactitol 60mL/day, rifaximin 1200 mg/day or no treatment. Patients in the rifaximin or no-treatment groups were allowed administration of a sorbitol enema (120mL) in cases of minimal bowel movement (<1 bowel movement/day). Treatments were continued for 1 month post-TIPS or until the occurrence of an episode of HE. There was no significant difference in rate of HE occurrence among the three patient groups ( $p = 0.97$ ).

Two recent clinical trials have been conducted to evaluate the efficacy of lactulose or rifaximin used concomitantly with lactulose, as secondary prophylaxis of overt HE compared with placebo(95,96). Sharma and colleagues(95) conducted a single-centre, open-label, randomized controlled trial in 125 cirrhotic patients who had recovered from at least one previous episode of HE. Patients were randomized to receive either lactulose 30-60mL/day or placebo. Development of overt HE was the primary study endpoint. At the end of a median follow-up time of 14 months, significantly more patients in the placebo group (30 of 64 patients [46.8%]) than in the lactulose group (12 of 61 patients [19.6%]) developed HE ( $p = 0.001$ ).

In a recent multicenter double blind randomized clinical trial to assess the secondary prevention of HE Bass and colleagues(96), enrolled 299 cirrhotic patients with a history of at least two episodes of overt HE to receive either rifaximin (550 mg twice daily; n = 140) or placebo (n = 159) for a period of 6 months. All enrolled patients had Model for End-Stage Liver Disease (MELD) scores of <25. More than 90% of patients in both groups were also maintained on concomitant lactulose therapy. A significantly lower percentage of patients in the rifaximin group (22.1%) experienced a breakthrough HE episode during the study period than in the placebo group (45.9%), with a hazard ratio (HR) of 0.42 (95% CI 0.28, 0.64;p < 0.001). In addition, there was a significantly reduced risk of hospitalization due to hepatic encephalopathy in the rifaximin patient group when compared with placebo; 19 patients in the rifaximin group (13.6%) versus 36 patients in the placebo group (22.6%),(p = 0.01). No significant difference in the incidence of adverse events was found between the two groups. In a similar study by Sanyal et al(97) patients with cirrhosis in remission from HE (Conn score = 0 or 1) and a documented history of recurrent HE episodes ( $\geq 2$  within 6 months of screening) were randomised to rifaximin 550 mg twice daily (N = 101) or placebo (N = 118) for 6 months. Concomitant lactulose was permitted during the study. The Chronic Liver Disease Questionnaire (CLDQ) was administered every 4 weeks, and time for occurrence of HE breakthrough was recorded. The time-weighted averages of the overall CLDQ score and each domain score were significantly higher in the rifaximin group vs. placebo (P-values ranged from 0.0087 to 0.0436); and were significantly lower in patients who experienced HE breakthrough compared to those who remained in remission (P-values were <0.0001)(Table-6). Hence lactulose and rifaximin for the secondary prophylaxis of HE is recommended.

Trial	Study design	No of patients	Duration of treatment	assessment	Efficacy
Sharma BC et al (2009)(69)	Lactulose (open-label)	140	14months	Psychometry and CFF	Lactulose> no treatment
Bass et al (2010)(70)	Rifaximin+lactulose (randomized, double-blind, placebo-controlled)	299	6 months	HE clinical	Rifaximin >placebo

Table 6. Disaccharides for secondary prophylaxis of hepatic encephalopathy.

## 12. Conclusion

Current pharmacotherapy for the management of HE is fairly limited, mainly because of the complex and relatively limited understanding of the pathophysiology of the disorder. Although the evidence of ammonia is robust, in everyday clinical practice a consistent correlation between the concentration of ammonia in the blood and the manifest symptoms of HE is not observed. More recently the synergistic role of inflammation and infection in modulating the cerebral effects of ammonia has been shown to be important. The most commonly utilized pharmacological agents include the non-absorbable disaccharides lactulose and lactitol, and the antimicrobial agent rifaximin. Lactulose and lactitol, the synthetic compounds of lactose, are poorly absorbed from the small intestine, and both are almost exclusively metabolized by the bacterial flora of the colon. These disaccharides



shorten the small bowel transit time mechanically and lower the pH of the bowel, both by their osmotic effects and by the acidic pH of their metabolites hence diminish the absorption of ammonia. Lactulose and lactitol are the classical therapy of choice for the treatment of hepatic encephalopathy. Recent literature has questioned the clinical efficacy of disaccharides in improving morbidity and mortality in patients with HE and, although antimicrobial agents such rifaximin have had an established role in the treatment of low grade (West Haven grade 1 and 2) encephalopathy, its use in high grade HE (grade 3 and 4) needs more data. Till we have more definitive agents non-absorbable disaccharides lactulose still continues to be the first line therapy for the prevention, treatment and secondary prophylaxis of hepatic encephalopathy.

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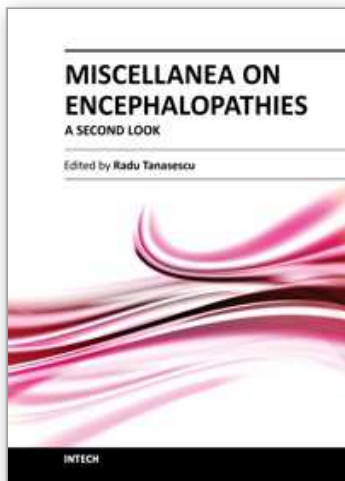
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### **Miscellanea on Encephalopathies - A Second Look**

Edited by Dr. Radu Tanasescu

ISBN 978-953-51-0558-9

Hard cover, 390 pages

**Publisher** InTech

**Published online** 25, April, 2012

**Published in print edition** April, 2012

The book project “Miscellanea on Encephalopathies-a second look” aims to cover some of the important aspects regarding metabolic, hypoxic, neoplasm- and drug-related encephalopathies, by transmitting valuable information filtered through the real life clinical and research experience of the authors.

#### **How to reference**

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Praveen Sharma (2012). Disaccharides in the Treatment of Hepatic Encephalopathy in Patients with Cirrhosis, *Miscellanea on Encephalopathies - A Second Look*, Dr. Radu Tanasescu (Ed.), ISBN: 978-953-51-0558-9, InTech, Available from: <http://www.intechopen.com/books/miscellanea-on-encephalopathies-a-second-look/disaccharides-in-the-treatment-of-hepatic-encephalopathy>

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