The Role of Probiotic in
Patient with Minimal Hepatic Encephalopathy:
An Evidence Based Case Report

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INTRODUCTION

Cirrhosis and chronic liver disease affect approximately 5.5 million patients in the United States. With increasing patient survival, the neuro-cognitive complications of cirrhosis such as overt and minimal hepatic encephalopathy (OHE and MHE, respectively) are being increasingly recognized.\(^1\)\(^2\) MHE is a neuro-cognitive dysfunction which occurs in an epidemic proportion of cirrhotic patients, estimated ranges from 30 to 84% in patients with chronic liver diseases. It is characterized by a specific, complex cognitive dysfunction which is independent of sleep dysfunction or problems with overall intelligence. Although named “minimal”, minimal hepatic encephalopathy (MHE) can have a far-reaching impact on quality of life, ability to function in daily life and progression to overt hepatic encephalopathy (OHE).\(^2\)\(^3\)

Since its first description in the 1970s, MHE has been diagnosed in several countries around the world at a rate of 30%-80%. The European experience has shown a high prevalence of MHE in patients who are predominantly non-alcoholic and without any psychoactive drug use. The diagnostic methodologies were a combination of neuropsychometric and neuro-physiologic testing strategies. In the United States, the rate of MHE in several research series has been reported to be 60%-80%, again using a combination of psychometric.\(^3\)\(^4\)

The diagnosis of MHE rests on the confirmation of a disease that can cause MHE, such as, cirrhosis or presence of portosystemic shunt, exclusion of normal mental status on clinical examination, demonstration of abnormalities of cognition and/or neurophysiological variables and exclusion of concomitant neurological disorders. There is no ideal test for the diagnosis of MHE. However, the Working Party recommends that the diagnosis of MHE requires a normal mental status examination and impairment in the performance of at least two of the following tests: number connection test-A (NCT-A), number connection test-B (NCT-B), block design test (BDT) and digit symbol test (DST).\(^2\)

A proposed mechanism for hepatic encephalopathy pathogenesis is the production of ammonia and benzodiazepine like compounds by the intestinal flora. Pathophysiology of MHE is considered to be similar to that of HE, and high intracerebral ammonia is postulated
to have a central role. Therefore, the major treatment modalities for MHE have been similar to that of overt hepatic encephalopathy (OHE): targeting ammonia production and absorption.

At present, an algorithm for MHE treatment remains undefined, but a recent consensus statement advocated lactulose as a first-line therapy while acknowledging palatability and adherence concerns. Similarly, a survey of U.S.-based hepatologists demonstrated that the majority believed that MHE should be treated and the preferred therapeutic agent for most respondents was lactulose.

As the gut microbiota play an important role in the generation of ammonia, its modulation using prebiotics, probiotics and synbiotics have been evaluated by several small studies as a therapeutic option for MHE. Prebiotics such as lactulose, are defined as a nondigestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improves host health. Probiotics are ‘live microbial feed supplement which beneficially affects the host animal by improving its intestinal microbial balance’. The combination of prebiotics and probiotics is known as a synbiotic.

At present, lactulose is the mainstay of treatment for MHE. Lactulose is a nonabsorbable, synthetic disaccharide that has multiple effects on gut flora and lowers ammonia levels by decreased production and absorption. Liu et al reported an alternative and novel approach to modulating the gut microecology and acidifying the gut lumen for therapeutic benefit in cirrhotic patients with MHE by treatment with synbiotics. We therefore try to perform critical appraisal to assess role probiotics in management of minimal hepatic encephalopathy.

**CASE RESUME**

A 57 years old female came to hepatology outpatient clinic with Cirrhotic Hepatic for routine control without any significant complaints. Her baseline disease was Hepatitis C, diabetes mellitus type 2 with controlled blood glucose. There was no sleep disorders or mental disturbances. From the physical examination revealed splenomegaly Schufner I, without ascites or jaundice. On laboratory findings there was anemia (9.7 mg/dL), leucopenia (3600/μL), hypoalbuminemia (2.7 mg/dL), no abnormality of liver enzymes (AST/ALT
34/37) with total bilirubin 1,32; direct 0,8 and indirect 0,5; PT 14 seconds with control 11,3 seconds. According to this result, the Child-Turcotte-Pugh scoring was 7 (score B). Her abdominal ultrasound showed decompensated cirrhotic hepatic. The esofago-gastro-duodenoscopy showed gastropathy portal hypertension. On examination with number-connecting test (NCT) A and B, she didn’t get any problems. Her diagnosis was cirrhotic hepatic with CTP-B due to chronic hepatitis C, bisitopenia due to treatment of hepatitis C, and diabetes mellitus. Her therapy was Pegassys 180µg per week, ribavirin 600mg per day, furosemide 1 x40 mg, aldacon 1x100mg, propranolol 2x10mg, and lactulose 3 x 1.

**CLINICAL QUESTION**
The clinical question in this appraisal is: “Does probiotic has benefit in managing minimal hepatic encephalopathy?”

**METHODS**
We searched Pubmed to identify all published studies using various terms within the domain (minimal hepatic encephalopathy) and determinant (probiotic) with narrow filter using Pubmed tool: Clinical queries. There was nine articles were retrieved initially. We then use the selection by using text availability (abstract text available), publication dates (5 years), species of the research (humans), article types (systematic review and clinical trial) and the languages (English). Six clinical-trial articles relevant to our clinical question then. From these six articles, we only can found four articles with full-access. Figure 1 below shows the schematic literature searching in this appraisal.

Of the four left studies, two trials compared a probiotic with placebo only and two others compared probiotics with lactulose. Four trials were:
1. An open-label randomized controlled trial of lactulose and probiotics in the treatment of minimal hepatic encephalopathy (Sharma et al, 2008).
2. Probiotic yogurt for the treatment of minimal hepatic encephalopathy (Bajaj et al, 2008).
4. A randomized controlled trial comparing lactulose, probiotics, and L-ornithine L-aspartate
in treatment of minimal hepatic encephalopathy (Mittal et al, 2011).

**Figure 1.** Schematic literature searching

**RESULTS**

**Probiotic yogurt for the treatment of minimal hepatic encephalopathy**

Bajaj et al conducted the study in 2008 to determine the effect of probiotic supplementation in the form of a food item, probiotic yogurt, on MHE reversal and adherence. Twenty five non-alcoholic participants with minimal hepatic encephalopathy were randomized unblinded allocation two groups. One group (n=17) received probiotic yogurt (with proven culture stability) and other (n=8) received no treatment for 60 days. They also measured quality of life (short form [SF]-36), adherence, venous ammonia, model of end-stage liver disease (MELD) scores, and inflammatory markers (tumor necrosis factor (TNF)-α, interleukin (IL-6) were also measured. The outcomes of this study were MHE reversal using blinded scoring, OHE development, and adherence. Bajaj et al found 84% of patients with Child class A. A significantly higher percentage of yogurt patients reversed MHE compared to group with no treatment. Yogurt patients demonstrated a significant improvement in number connection test-A (NCT-A), block design test (BDT), and digit symbol test (DST) compared to baseline/no
Rx group. Twenty-five percent of no Rx versus 0% of yogurt patients developed OHE during the trial. Eighty-eight percent of yogurt patients were adherent. No adverse effects or change in covariates were observed. All patients who completed the yogurt arm were agreeable to continue yogurt for 6 months if needed. For the conclusion, this trial demonstrated a significant rate of MHE reversal and excellent adherence in cirrhotics after probiotic yogurt supplementation with potential for long-term adherence.1

An open-label randomized controlled trial of lactulose and probiotics in the treatment of minimal hepatic encephalopathy

Sharma et al conducted the study in 2008 to investigate the benefit lactulose and probiotics in the treatment of MHE. By using randomized controlled trial design, this study performed in 169 cirrhotic patients without overt encephalopathy (CTP A/B/). These patients were evaluated by psychometry (number connection tests A and B or figure connection tests A and B) and P300 auditory event-related potential (P300ERP). MHE was diagnosed by abnormal psychometry and/or P300ERP. One hundred and five patients were randomized to three groups (n in each group=35). Group A received lactulose with dose 30–60 ml/day; group B got probiotics with dose 1 capsule three times/day. Each capsule that given in group B contained *Streptococcus faecalis* 60 million, *Clostridium butyricum* 4 million, *Bacillus mesentricus* 2 million, *lactic acid bacillus* 100 million]; and group C got lactulose plus probiotics for 1 month. There were not significant differences in clinical and demographic characteristic of patients. This study defined response as normalization of the abnormal test parameters. MHE was diagnosed in 105 (55.2%) patients. Of the 105 patients, 71% had both abnormal psychometry and P300ERP, whereas others 86% had abnormal psychometry alone, and 89 patients (85%) had abnormal P300ERP alone. Significant improvement was seen in abnormal psychometry tests (group A: n= 31 before treatment and n= 12 after treatment; group B: n =29 vs. n= 14, group C: n= 30 vs. n= 10), P300ERP (group A: 376.8 ± 22.3 vs. 344.3 ±30.6 ms, group B: 385.4 ± 28.5 vs. 355.5 ± 27.9 ms, group C: 387.7± 27.5 vs.347.7± 31.5 ms) and venous ammonia levels (group A: 102.3 ± 63.1 vs. 69.3 ±33.3 lmol/l, group B: 108.2 ± 37.5 vs. 75.7±33.0 lmol/l, group C: 96.3±27.7 vs. 68.7±28.4 lmol/l) in lactulose, probiotics and a combination of lactulose plus probiotics groups after treatment.
Normalization of abnormal psychometry and P300ERP was seen in 54.8, 51.6 and 56.6% of patients treated with lactulose, probiotics and lactulose plus probiotics groups, respectively. Sharma et al found that lactulose or probiotics or combinations of both are equally effective in the treatment of MHE.\(^9\)

**Probiotics for patients with compensated liver cirrhosis: a double-blind placebo-controlled study**

Pereg et al conducted the randomized blinding controlled trial in 2011 to study the effect of probiotics on clinical and laboratory parameters of patients with compensated cirrhosis. They included patients with liver cirrhosis and at least one major complication of cirrhosis in the past, clinical evidence of portal hypertension, or decreased hepatic synthetic function. Participants were randomly assigned to receive probiotic capsules containing *Lactobacillus acidophilus*, *Lactobacillus bulgaricus*, *Bifidobacterium lactis*, and *Streptococcus thermophiles* or placebo for a period of 6 mo. A total of 36 patients were available for final analysis (distributed equally between the probiotic and placebo groups). The administration of probiotics was not associated with significant differences in either clinical or laboratory parameters between the two groups. Because the lack of a beneficial effect may be related to the compensated liver disease of patients, Pereg et al conducted a subanalysis of patients with baseline ammonia levels >50 mmol/L. In this subgroup, they found that administration of probiotics appeared to significantly reduce the ammonia levels starting after 1 month of treatment. However, this effect diminished and lost its significance following comparison to the placebo group. As the conclusion, they study didn’t show a significant beneficial effect of probiotic supplementation in patients with compensated liver cirrhosis. Nevertheless, it points toward a possible positive effect of probiotics in patients with above normal baseline ammonia levels.\(^{10}\)

**A randomized controlled trial comparing lactulose, probiotics, and L-ornithine L-aspartate in treatment of minimal hepatic encephalopathy**

Mittal et al conducted a randomized controlled trial in 2011 to compare lactulose, probiotics, and L-ornithine L-aspartate in treatment of MHE and effect on health-related quality of life
(HRQoL) by using Sickness Impact Profile questionnaire. Patients with cirrhosis were screened consecutively for MHE. MHE was diagnosed by two or more abnormal psychometric tests (number/figure connection tests A and B, block design test, picture completion test). Thus, patients were randomized to four groups. Group A that received no treatment. Group B received lactulose 30–60 ml/twice per day. Group C received probiotics 110 billion colony forming units twice in a day, meanwhile group D received LOLA 6 g three times per day. All groups performed this intervention for 3 months. Arterial ammonia and HRQoL assessment using The Sickness Impact Profile (SIP) questionnaire – that often-used instrument that assesses the influence of disease and treatment on daily functioning – was done at baseline and at 3 months.

Mittal found that one hundred and sixty (49.69%) of 322 patients with cirrhosis had MHE. After 3 months, there were four patients with MHE recovered in group A (10%), 19 pts in group B (47.5%), 14 pts in group C 14 (35%), and 14 pts in group D (35%). MHE improved significantly in all three treatment groups (group B, C, and D) compared with no treatment (GpA) with p value 0.006. Mittal also found nine patients developed overt hepatic encephalopathy of 160 patients (5.6%) which were four in group A, one in group B, two in group C and D, respectively. There was significant improvement in SIP score in group B, C and D if compared to group A with p value less than 0.001. The decrease in SIP score correlated with an improvement in MHE on multivariate analysis but there was no correlation with the type of intervention offered. There was no significant change in arterial ammonia level after therapy in group A. Arterial ammonia level in group B (−8.47 ± 5.8 lmol/l), group C (−7.31± 7.9 lmol/l), and group D (−9.61± 9.3 lmol/l) were significantly more than group A with p value less than 0.0001. At last, Mittal et al concluded that lactulose, probiotics, and LOLA significantly improve MHE and HRQoL in patients with chronic liver disease.11

Table 1 below shows the characteristic of each study according to study design, inclusion criteria, interventions, and outcomes.
<table>
<thead>
<tr>
<th>Author</th>
<th>Inclusion Criteria</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Study Design</th>
</tr>
</thead>
</table>
| Sharma et al (2008) | Cirrhotic with MHE without overt encephalopathy                                      | Control group (A): 30-60 ml lactulose in 1 month  
Treatment group (B): Probiotic 3x/day in 1 month  
Treatment group (C): Lactulose plus Probiotic/day in 1 month | 1. Venous ammonia level  
2. Child-Pugh score  
3. MHE recovery | Open-label randomized trial |
| Bajaj et al (2009) | Non-alcoholic cirrhosis with minimal hepatic encephalopathy                         | Treatment group (A): Probiotic yogurt for 60 days  
Control group (B): no treatment (only standard therapy to cirrhotic) | 1. MHE reversal  
2. OHE development  
3. Adherence  
4. Child-Pugh score  
5. Meld score  
6. SF-36 score  
7. Venous ammonia  
8. IL-6 and TNF-alpha levels | A prospective randomized trial with open allocation |
| Pereg et al (2011) | Cirrhotic hepatic and at least one major complication of cirrhosis in the past, clinical evidence of portal hypertension, or decreased hepatic synthetic function. | Control group (A): Wheat-based non-fermentable fiber placebo  
Treatment group (B): Probiotic daily dose of $2 \times 10^{10}$ colony forming units | 1. Plasma ammonia  
2. Adverse events | A parallel randomized trial |
| Mittal et al (2011) | Cirrhotic hepatic with minimal hepatic encephalopathy.                               | Control group (A): No treatment (only standard therapy to cirrhotic)  
Treatment group (B): 30-60 ml lactulose, 2x1 for 3 months  
Treatment group (C): Probiotic 2x1 for 3 months  
Treatment group (D): 6g (LOLA) L-ornithine L-aspartate 3x1 for 3 months | 1. MHE recovery  
2. MHE improvement  
3. Arterial ammonia level  
4. Development of OHE  
5. Sickness impact profile score (quality of life) | A parallel randomized trial |
**Internal Validity**

**Table 2. Internal Validity**

<table>
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<tr>
<th>Author</th>
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<th>Baseline characteristic</th>
<th>Equal treatment</th>
<th>Outcome</th>
<th>Blinding</th>
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<td>Sharma et al (2008)</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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</tr>
<tr>
<td>Bajaj et al (2009)</td>
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<td>Not explained</td>
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<tr>
<td>Mittal et al (2011)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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</table>

**DISCUSSION**

Hepatic encephalopathy pathogenesis is thought because of the production of ammonia and benzodiazepine-like compounds by the intestinal flora. Pathophysiology of MHE is considered to be similar to that of HE, and high intracerebral ammonia is postulated to have a central role. Therefore, the major treatment modalities for MHE is targeting ammonia production and absorption.\(^1\)

MHE is a neuro-cognitive dysfunction which occurs in an epidemic proportion of cirrhotic patients, estimated ranges from 30 to 84% in patients with chronic liver diseases. Average prevalence of MHE in four studies was not quite different from this data. Differences criteria being used to make diagnosis of MHE, could be made the wide variation in prevalence of MHE in various studies.

As we know, the goals of MHE treatment include improvements in quality of life, driving performance, and decreased progression to OHE. The duration of MHE treatment could last for months to multiple years. Therefore, an ideal treatment for MHE should be palatable, without adverse effects, and efficacious to encourage long-term adherence. A recent consensus statement identified lactulose as a first-line therapy of MHE while acknowledging difficulties with its palatability and adherence. Eventhough treatment of MHE with lactulose has been previously in many studies associated with improvement in psychometric tests and quality of life, unfortunately, long-term adherence is often affected by the accompanying bloating, diarrhea, and nausea.\(^5\) Short-term lactulose adherence in MHE trials is approximately
80%; the actual clinical experience shows a lower rate of adherence. Therefore, alternatives to lactulose for potential long-term MHE therapy may represent an unmet need.1

Probiotics are defined as live microbiological dietary supplements that have beneficial effects to the host beyond their nutritive value. As bacterial intestinal flora-derived ammonia and neurotoxic substances have been proposed as leading culprits in the development of hepatic encephalopathy, manipulation of the intestinal bacterial flora is the mainstay of treatment. The mechanism of probiotic action is believed to be related to substrate deprivation for potentially pathogenic bacteria and the provision of fermentation end products as a substrate for potentially beneficial ones. Stool studies in MHE patients by Liu et al. demonstrated that symbiotic supplementation was associated with a decrease in pathogenic \textit{Escherichia coli, Fusobacterium} and \textit{staphylococci} with an increase in nonurease-producing \textit{Lactobacillus}.

There are many previous reports of improvement in MHE status and NP scores with lactulose but there are only few trials have investigated the administration of probiotics to patients with cirrhosis, including these four studies.10

Bajaj et al conducted the study to determine the effect of probiotic yogurt on MHE reversal. They compared administration of probiotic yogurt to group without any intervention, in mean, both of these group still received the standard therapy for cirrhosis. Bajaj et al found a significantly higher percentage of yogurt patients reversed MHE compared to no intervention patients. Yogurt patients demonstrated a significant improvement in number connection test-A (NCT-A), block design test (BDT), and digit symbol test (DST) compared to no intervention group. Bajaj also found that a significant excellent adherence in cirrhotics after probiotic yogurt supplementation with potential for long-term adherence besides rate of MHE reversal.1

Sharma et al conducted the study in 2008 to investigate the benefit lactulose and probiotics in the treatment of MHE. They compared administration of lactulose with probiotic and combination of probiotic and lactulose. Sharma found that total of 56% patients had a complete reversal of MHE, which is not statistically different in treatment than the lactulose or probiotics group patients. Possible mechanisms could be owing to the cathartic effect of lactulose, which may cause a washout of probiotics before it can have its effects or there is
acidification of the gut lumen by lactulose, which interferes with the probiotics effect. They concluded that treatment with lactulose, probiotics or lactulose plus probiotics was equally efficacious in the treatment of MHE.⁹

Pereg et al conducted the randomized blinding controlled trial in 2011 to study the effect of probiotics on clinical and laboratory parameters of patients with compensated cirrhosis. Although their study did not show any significant clinical or laboratory effect of probiotic administration in patients with compensated liver cirrhosis but from the subgroup analysis among the patients with high baseline levels of ammonia, the administration of probiotics appeared to significantly reduce the ammonia levels, especially after 1 mo of treatment.¹⁰ It is possible that the negative results of their study may be due to the relatively small population.

And the last study in this review, Mittal et al conducted a RCT study in 2011 to compare lactulose, probiotic, and LOLA. Their study emphasizes the prevalence of MHE in patients with cirrhosis, and they found that patients with MHE have poor HRQoL. Treatment with lactulose, probiotics, or LOLA leads to improvement in not only cognitive functions as assessed by NP tests, but also HRQoL. Therefore, patients with cirrhosis and MHE who are either at occupational risk or have poor QoL may benefit from treatment of MHE. Treatment may be carried out using either lactulose, probiotics, or LOLA.

A controversial point common to all studies on probiotics is the duration of treatment required to achieve the optimal effect. While several reports have shown a positive effect after a few days of treatment, others speculated that a beneficial prophylactic effect can only be expected with regular consumption of the probiotic agent. Regarding patients with liver cirrhosis, the existing evidence demonstrated a beneficial effect after 1 mo of treatment even though in Pereg’s study, the patients were treated for 6 mo without any apparent effect.

**CONCLUSION**

These studies show us that administration of probiotic is equally effective with lactulose in the treatment of MHE. And from these studies, we can see most of the patients can tolerate lactulose without any significant diarrhea or abdominal pain. Probiotics treatment also had no side effect.
REFERENCES


