

## Probiotics as Alternative Therapy for Psychometric Disorders in Hepatic Encephalopathy

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### ABSTRACT

**Aim:** To identify whether probiotics have the same effectiveness as lactulose in improving the results of psychometric testing in patients with hepatic encephalopathy.

**Method:** Literature Searching were performed on Pubmed, EBSCOhost, Scopus, and Cochrane databases to obtain an randomized controlled trial (RCT) or a systematic review. Searches were made with the keywords "hepatic encephalopathy", "probiotic", "lactulose" and number connection test ("NCT"). Search is continued by excluding the literature through abstract and full text.

**Results:** Two studies were found to be relevant according to the criteria. The study by Mittal showed that probiotics were better than lactulose in improving NCT-B with a risk ratio (RR) = 0.88 (95% CI: 0.54-1.44;  $p = 0.62$ ) but not better for improving NCT- A with RR = 1.43 (95% CI: 0.62-3.24;  $p = 0.40$ ). In the Sharma study, lactulose was better in improving NCT score with the mean difference (MD) 6.7 (95% CI: 0.58-12.82) and in the Li study, there was no significant significance between MD 3.93 (95% CI: -0,72-8,58)

**Conclusion:** In conclusion, Probiotics cannot replace lactulose as a standard therapy for hepatic encephalopathy. There is not enough evidence that proves probiotics are better than lactulose.

**Keywords:** Hepatic encephalopathy, lactulose, number connection test (NCT), probiotic

### ABSTRAK

**Tujuan:** Mengetahui apakah probiotik memiliki efektivitas yang sama dengan laktulosa dalam memperbaiki hasil uji psikometri pada pasien dengan ensefalopati hepatikum.

**Metode:** Penelusuran literatur dilakukan pada database Pubmed, EBSCOhost, Scopus, dan Cochrane untuk mendapatkan uji acak terkontrol atau systematic review. Pencarian dilakukan dengan kata kunci "hepatic encephalopathy", "probiotic", "lactulose" dan number connection test ("NCT"). Penelusuran dilanjutkan dengan mengeksklusi literatur melalui abstrak dan full text.

**Hasil:** Dua studi ditemukan relevan sesuai kriteria. Studi oleh Mittal menunjukkan probiotik lebih baik dibandingkan dengan laktulosa dalam memperbaiki NCT-B dengan risk ratio (RR) = 0,88 (95% CI: 0,54-1,44;  $p = 0,62$ ) namun tidak lebih baik untuk memperbaiki NCT-A dengan RR = 1,43 (95% CI: 0,62-3,24;  $p = 0,40$ ). Pada studi Sharma, laktulosa lebih baik dalam memperbaiki skor NCT dengan mean difference (MD) 6,7 (95%

CI: 0,58-12,82) dan pada studi Li, tidak terdapat perbedaan signifikan antara keduanya dengan MD 3,93 (95% CI: -0,72-8,58).

**Simpulan:** Dapat disimpulkan bahwa probiotik belum dapat menggantikan laktulosa sebagai terapi standar ensefalopati hepatikum. Belum terdapat cukup bukti yang menyatakan probiotik lebih baik daripada laktulosa

**Kata kunci:** Ensefalopati hepatikum, laktulosa, uji acak terkontrol, probiotik

## INTRODUCTION

Hepatic encephalopathy (HE) is a brain dysfunction that is caused by liver problems or portosystemic shunt. Wijdicks said that when liver fails, brain function also changes. This phenomenon happened because of the accumulation of ammonia and urea and its derivatives on the brain. The sign of hepatic encephalopathy is decreased consciousness preceded by jaundice. Hepatic encephalopathy can progress to brain edema and making it a disease with high mortality.<sup>1-3</sup>

Diagnosis of hepatic encephalopathy is done by testing brain function and consciousness. The goal is to rule out other brain abnormalities. The screening procedure that is a gold standard for hepatic encephalopathy is West Haven scoring. However, this test is not sensitive enough to detect early stage of hepatic encephalopathy. Thus, other examinations that are more sensitive need to be done, including some neurophysiologic and psychometric test.<sup>1</sup> In the guide for the treatment of hepatic encephalopathy with chronic liver disease, lactulose is given as the first line treatment. Beside lactulose, sometimes rifaximin is given as the complement. Lactulose works by turning ammonia into unabsorbable form and rifaximin is given to decrease the side effect of lactulose. This therapy helps the body to reduce ammonia level and preventing complications.<sup>4,5</sup>

There is an alternative to lactulose as a cure for hepatic encephalopathy: probiotic. This idea comes from the fact that a big portion of ammonia that accumulated in the gut is there because of a decomposition process by gut flora.<sup>5</sup> Probiotic

helps reducing ammonia level produced by gut flora by various mechanisms such as modulation of proinflammatory response and gut permeability.<sup>5</sup> Seeing positive effects of probiotic, this evidence-based case report is done to compare the effectivity of probiotic therapy to improve psychometric test results compared to lactulose as the standard of therapy.

## CLINICAL QUESTION

Mr. X, 42 years-old, come back to a doctor due to lack of concentration and sleep problems. In the previous appointment, Mr. X is diagnosed with hepatic cirrhosis. Physical examination shows that vital sign is normal, no sign of hepatomegaly, and positive flapping tremor. Laboratory examination shows that there is a decrease in liver function. The doctor said that Mr. X had a hepatic encephalopathy.

Referring to the standard of therapy, the doctor gave Mr. X lactulose. Mr. X then told the doctor that there is an advertisement saying that probiotic is helpful for a patient with hepatic cirrhosis. Mr X wanted to know whether probiotic can be an effective solution to his problem because of the price that is relatively cheaper.

## METHOD

Literature searching was carried out using 4 databases, which are Pubmed, EBSCOhost, Scopus, and Cochrane on September 7, 2018. The keywords used were "Lactulose", "Hepatic Encephalopathy", "Probiotics", and "Repairs" along with synonyms and other terms related. Table 1. Summarize the search strategy and the number of articles we used.

**Table 1. Searching strategies and results**

Database	Search Terms	Result
Pubmed (7 <sup>th</sup> September 2018)	("lactulose"[MeSH Terms] OR "lactulose"[All Fields]) AND ("hepatic encephalopathy"[MeSH Terms] OR ("hepatic"[All Fields] AND "encephalopathy"[All Fields]) OR "hepatic encephalopathy"[All Fields]) AND ("probiotics"[MeSH Terms] OR "probiotics"[All Fields] OR "probiotic"[All Fields]) AND (("psychometrics"[MeSH Terms] OR "psychometrics"[All Fields] OR "psychometric"[All Fields]) OR ("psychometrics"[MeSH Terms] OR "psychometrics"[All Fields] OR ("psychometric"[All Fields] AND "test"[All Fields]) OR "psychometric test"[All Fields]) OR NCT[All Fields] OR NCT-A[All Fields] OR NCT-B[All Fields] OR (number[All Fields] AND connection[All Fields] AND ("research design"[MeSH Terms] OR ("research"[All Fields] AND "design"[All Fields]) OR "research design"[All Fields] OR "test"[All Fields]))	23
Ebscohost (7 <sup>th</sup> September 2018)	OR NCT-A OR NCT-B OR number connection test)	26
Scopus (7 <sup>th</sup> September 2018)	lactulose AND hepatic encephalopathy AND probiotic AND (psychometric OR psychometric test OR NCT	29
Cochrane (7 <sup>th</sup> September 2018)	OR NCT-A OR NCT-B OR number connection test) (psychometric OR "psychometric test" OR NCT* OR NCT-A OR NCT-B OR "number connection test")	23
	AND lactulose AND "hepatic encephalopathy" AND probiotic	

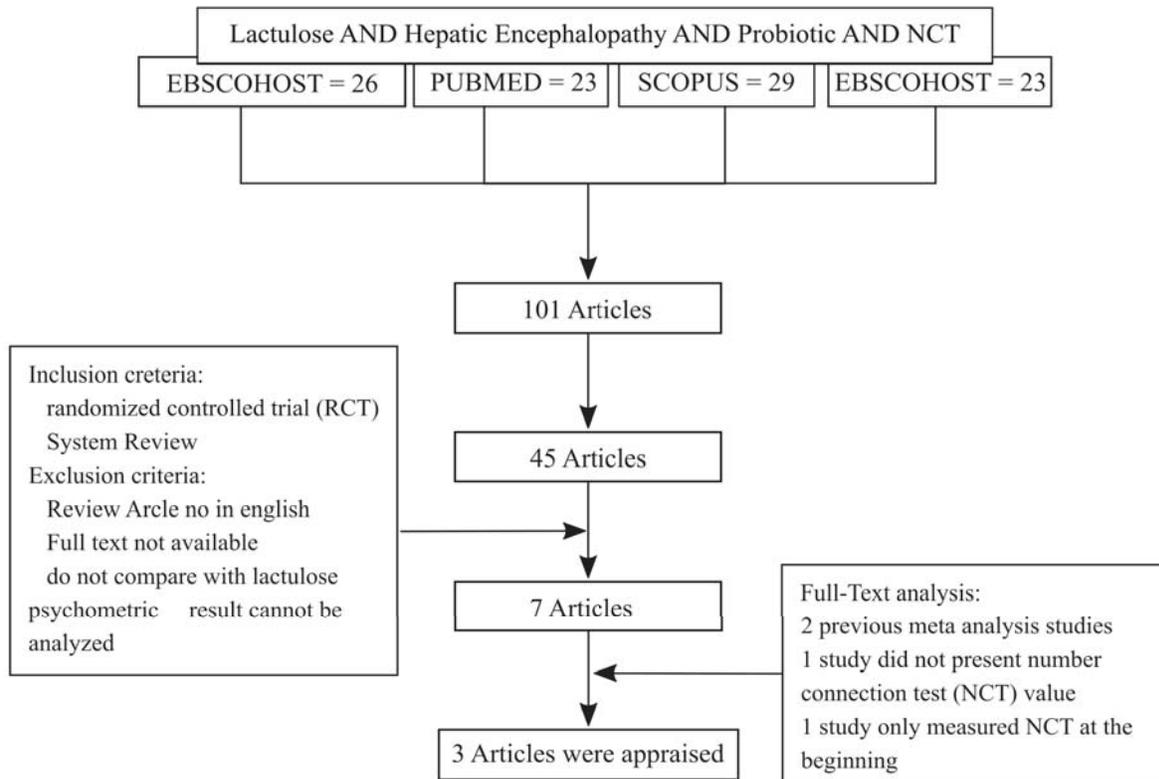


Figure 1. Flowchart of searching strategy

The result of searching strategies, inclusion and exclusion criteria were shown on flowcharts (Figure 1). Critical appraisal was conducted on related articles using critical appraisal tools for RCT (therapeutic studies) based on the Evidence-Based Medical Center, Oxford University.

## RESULTS

Based on the search, seven studies were found to meet inclusion and exclusion criteria. three of the seven studies were assessed further after full-text analysis.

The three studies were assessed for validity and two studies were concluded that it had good validity so that it was used in this evidence-based case report (EBCR). One study is a randomized controlled trial (RCT) study and one study is a meta-analysis study of RCTs with the characteristics of each study in (Table 3).

Mittal et al study looked at probiotics with 110 billion colony-forming bacterial units compared with lactulose 30-60 mL/day in 70 patients with minimal hepatic encephalopathy to differences in the results of test psychometric tests including number connection test (NCT) A and B. there were no differences

Table 2. Critical appraisal of randomized controlled trial (RCT) based on Centre of Evidence-Based Medicine (CEBM)

Article	Validity			Relevance					Result	Level of evidence*		
	Study design	Number of patients	Randomization	Similarity treatment and control	Blinding	Comparable treatment	Intention to treat	Domain			Determinant	Measurement of outcome
Mittal et al	+	80	+	+	?	+	+	+	+	+	A	18
Mouli VP et al	+	120	+	+	-	+	-	+	+	+	B	18

+ stated clearly; - not done; ? : not stated clearly ; \*Level of evidence based on The Oxford Centre of Evidence-based Medicine; A: In the administration of probiotics 110 billion colony forming units did not improve NCT-A parameters and there was an improvement in NCT-B parameters; B: Study excluded because of the high rate of dropout (39%)

Table 3. Critical appraisal of systematic review based on Centre of Evidence-Based Medicine (CEBM)

Validity						
Authors	PICO	Appropriate Searching	Relevant study included	Quality assessment of trials	Heterogeneity	Level of evidence*
Cao Q et al	+	+	-	+	?	1a

+ stated clearly; - not done; ? : not stated clearly ; \*Level of evidence based on The Oxford Centre of Evidence-based Medicine

significant between probiotic and lactulose groups ( $p > 0.05$ ).<sup>6</sup>

A meta-analysis study by Cao et al analyzed two literature related to improvement in the value of NCT, a study by Sharma et al and Li et al. The meta-analysis assesses that the two studies have a high risk of bias.<sup>7</sup> The Sharma et al study used probiotics with *Streptococcus faecalis*, *Clostridium butyricum*, *Bacillus mesentericus*, and *Lactic acid bacillus* strains for 4 weeks. While the study by Li et al used probiotics with strains of *Bifidobacterium*, *Bacterium lacticum*, and *Bacillus subtilis* for 8 weeks. The Sharma study showed that lactulose was better at improving NCT values with Mean difference: 6.7 (CI: 0.58 - 12.82) and the study of Li et al did not show significant results.

## DISCUSSION

Hepatic encephalopathy is syndrome which happens in a patient with liver cirrhosis, also can be called neuropsychiatry spectrum abnormality in a patient with liver dysfunction after excluding brain disease. Minimal hepatic encephalopathy (MHE) is a condition where the liver is already cirrhosis, but still have normal mental and neurological status, only having a minimum neuropsychiatry and neurophysiology impairment. Pathophysiology of MHE is related with a high concentration of intracerebral ammonia. Lactulose is still a standard therapy for MHE, because it's a synthetic disaccharide compound, which is as prebiotics that supports the growth of bacterial or gut flora to reduce the production and absorption of ammonia. Probiotic considered as an alternative

to reduce those bacteria which produce urease and promoting the growth of non-urease bacteria, in order to reduce ammonia in blood significantly.<sup>8-9</sup>

Mittal et al study use the intervention of probiotic with dose of 110 billion colony forming unit, while, Cao et al study use various dose of probiotics, for example, Sharma et al in their study (in Cao et al) use capsule which contains 60 millions of *Streptococcus faecalis*, 4 millions of *Clostridium butyricum*, 2 millions of *Bacillus mesentericus*, and 100 millions of *Lactic acid bacillus* 3 times a day for 4 weeks and in Li et al study, they use capsule which contains *Bifidobacterium*, *Bacterium lacticum*, and *Bacillus subtilis* for 8 weeks. From the three studies, dose and probiotic strains are various, which may end in a different result. In Mittal et al study, the NCT-A parameter worse, while the NCT-B parameter becomes better. Sharma et al study shows different result; it states that lactulose still better for improving the NCT parameter. While, Li et al shows no significant difference for the NCT parameter improvement between those 2 studies.<sup>6-7</sup> Studies outside the three studies above, stating that probiotics have a comparable result with lactulose. The research of different strains on the probiotics that they use still uncertain, but, different strains may affect the floral gut composition.<sup>8-9</sup>

As previously explained, both studies show that lactulose and probiotics have a similar efficacy in improving abnormalities of psychometric tests in patients with MHE. This can be caused by the similar mechanism of action between probiotics and lactulose in the case of HE. Lactulose works by changing the intestinal flora through acidification to reduce the

**Table 4. Summary of studies**

Author	Nation	Subject	Treatment regimen		Result
			Probiotic	Lactulose	
Mittal et al <sup>6</sup>	Iran	69 patients with minimal hepatic encephalopathy with an average age of: Probiotics: 44.25 ± 11.8 Lactulose: 43.85 ± 10.9	Probiotic consisting 110 billion colony-forming unit	Lactulose 30-60 mL/ day	NCT-A = RR: 1.4286 (0.6214 to 3.2840) ARR: -0.0937500 RRR: -0.428571 NNT: -10.667 (Harm) P: 0.4010  NCT-B = RR: 0.8824 (0.5395 to 1.4430) ARR: 0.0625000 RRR: 0.117647 NNT: 16.000 (Benefit) P: 0.6180
Cao et al <sup>7</sup>	Sharma et al (India)	70 patients with minimal hepatic encephalopathy with an average age: Probiotics: 43.5 ± 12.1 Lactulose: 39.5 ± 13.0	Capsule consisting of 60 million <i>Streptococcus faecalis</i> , 4 million <i>Clostridium butyricum</i> , 2 million <i>Bacillus mesentericus</i> , and 100 million <i>Lactic acid bacillus</i> three times a day for four weeks	Lactulose 30-60 mL/ day	Sharma et al:  Lactulose is better at improving NCT values at 4 weeks MD: 6.7 (95% CI 0.58 - 12.82) Li et al:  There was no significant difference between the two intervention MD: 3.93 (95% CI: -0.72 – 8.58)
	China	Li et al: 54 patient with hepatic encephalopathy	Li et al: Capsule consisting of <i>Bifidobacterium</i> , <i>Bacterium lacticum</i> , and <i>Bacillus subtilis</i> for 8 weeks		

production and absorption of ammonia. Several studies have shown that lactulose acts as a prebiotic material that triggers the growth of endogenous non-urease producing bacteria. Meanwhile, probiotics are thought to play a role through several mechanisms, including balancing the microbiota in the intestine, reducing inflammation and oxidative stress in hepatocytes, reducing ammonia absorption, increasing liver clearance of ammonia, and maintaining intestinal epithelial integrity.<sup>7</sup> Ammonia is the main target of both agents because it was found to play an important role in changes in blood circulation and brain glucose metabolism in MHE cases. Ammonia causes the decrease in glucose utilization in some cortical regions which results in the decrease of cognitive function.<sup>6,9</sup>

Although there are no significant differences between probiotics and lactulose, both studies showed that lactulose had a higher percentage of the effect of improving the abnormalities of psychometric tests compared to probiotics. This finding is in line with the results of several other studies which show that lactulose has better efficacy than probiotics.<sup>7</sup> Nevertheless, a study by Shavakhi et al showed that MHE therapy with probiotics showed a more stable effect on psychometric tests in long-term treatment.<sup>10</sup> Various findings of efficacy in several studies might be due to differences in the duration of therapy, as well as the dose and content of probiotics used.

Probiotic bacteria that are often used as therapeutic agents generally come from genus *Lactobacillus*, *Bifidobacterium*, *Streptococcus* and *Enterococcus*. Each of these genera has its unique probiotic mechanism. *Lactobacillus*, *Streptococcus*, and *Enterococcus* perform intraluminal acidification by converting hexose sugar to lactic acid. This acidification process aims to increase the growth of non-urease producing bacteria and inhibit the growth of harmful microorganisms that are easier to survive at high pH. *Bifidobacterium* is also often used as a probiotic agent because of its resistance mechanism to bile salts. Bile salt is known to have properties that resemble detergents so that it can interfere with the integrity and permeability of the cell wall of probiotic bacteria.<sup>11</sup> The difference in the action mechanism of each strain produces a variety of effects, both in terms of efficacy and stability.

Regarding safety, a study by Shukla et al showed that probiotics had lower side effects compared to lactulose.<sup>12</sup> Giving lactulose in MHE cases was reported to cause side effects such as diarrhea. In some patients, this effect can be overcome by adjusting the interval of lactulose administration. However, lactulose

intolerance also remains found in several other patients. Meanwhile, several studies have shown that no significant side effects were found in the administration of probiotics. Several other studies have reported the occurrence of constipation, but can be overcome by food modification.<sup>6,8</sup> Therefore, probiotics have the potential to be an alternative MHE therapy in patients with lactulose intolerance.

The limitation of this report is that there are no clear standards regarding the duration of therapy as well as dosages, regimens, and types of probiotics to produce the best efficacy. The two studies used in this report still use various dosages and types of probiotics. Therefore, further studies are needed to elaborate the comparison of the duration of therapy as well as the dosage, regimen, and bacterial strains of each probiotic specifically. This aims to determine which dosages, regimens, and strains are best for managing MHE and how long the therapy needs to be given.

## CONCLUSION

Probiotics have a similar efficacy to lactulose but produce side effects that are more tolerable than lactulose. However, there is no clear standard regarding the duration of therapy and the dosage, regimen, and type of probiotic content needed to treat MHE. In addition, the interaction between probiotics and other drugs that are also often given to patients with cirrhosis, such as rifaximine and cephalosporin for HE prophylaxis, is still unknown. The use of probiotics in clinical practice is still very limited when compared to lactulose which is currently the drug of choice for MHE patients. The results of this study can be applied in clinical practice, for example in the case given to us. 42-year-old male patient with complaints of difficulty in concentrating and sleeping. Previously, patients had been diagnosed with liver cirrhosis. Physical examination shows vital signs within normal limits, the liver is not palpable, positive tremor flapping examination. Investigation shows decreased liver function. The doctor's diagnosis is hepatic encephalopathy. Because the evidence that supports probiotics to replace lactulose as MHE therapy is not sufficient yet, the doctor decides not to give probiotics and still give lactulose.

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