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**Review Article**

# Pakistan Society of Hepatology Guidelines on the Management of Hepatic Encephalopathy

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## ABSTRACT

Hepatic Encephalopathy (HE) is one of the major complications in patients with liver cirrhosis. Cirrhosis is a significant health burden worldwide, and due to the increasing population and aging, the burden has increased since 1990. The pathogenesis of HE has been explained by different hypotheses, like astrocyte dysfunction, the ammonia hypothesis, and the GABA hypothesis. Hyperammonemia is the most likely cause of MHE. The breakdown of amines, amino acids, and purines by bacteria in the gastrointestinal tract leads to the production of ammonia. Ammonia is converted to urea in the liver by the Krebs-Henseleit cycle. Guidelines are made to help physicians and gastroenterologists diagnose patients at an early stage of hepatic encephalopathy, and a prompt diagnosis can prevent overt hepatic encephalopathy. Since no previous national guidelines regarding PSE are available, the aim here is to create a unifying guideline regarding the treatment of both overt and covert encephalopathy in a cost-effective manner. The management plan given in these guidelines is flexible and can be changed with more authentic data. We recommended that these guidelines provide a valuable source of information regarding HE in the Pakistani population, its current diagnosis, and its treatment. There is a high cost of treatment for liver diseases, and according to the current available data, we must follow the guidelines of PSH.

## INTRODUCTION

Hepatic Encephalopathy (HE) is one of the major complications in patients with liver cirrhosis. Cirrhosis puts out a significant health burden worldwide and due to the increasing population and aging, the burden has increased since 1990 [1]. The entire number of patients with chronic liver disease is estimated at 1.5 billion [2]. Amongst the Pakistani population, cirrhosis is the leading cause of mortality and the most common cause of hospital admission [3]. A study conducted in a tertiary care hospital in Rawalpindi revealed that the highest burden in health care centers, that is reaching an epidemic level, is cirrhosis [4]. Approximately 30% of patients dying of end-stage chronic liver disease have had at least one event of significant hepatic encephalopathy [5]. The most common reason for readmission in patients with decompensated chronic liver disease is HE [6]. Prevalence of clinically evident HE is approximately 30–45% in cirrhotic patients and 10–50% in patients with a Trans-jugular Intrahepatic Portosystemic Shunt (TIPS) [6]. Prevalence appeared to be between 30 to 84% of Minimal Hepatic Encephalopathy (MHE), increases in patients with advanced liver disease and in one study reported being 55 % [5-7]. A study conducted in tertiary care hospital revealed that 91 patients out of 150 had MHE [5]. However, due to the non-

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availability of the central registry system, exact local prevalence of disease is difficult to find. Once hepatic encephalopathy is treated, most patients remain in MHE which affects the health-related quality of life. Such patients have increased frequency of falls and are prone to accidents [8-10]. Guidelines are made to help physicians and gastroenterologists to diagnose patients at an early stage of hepatic encephalopathy, as a prompt diagnosis can prevent overt hepatic encephalopathy. Since no previous national guidelines regarding PSE are available yet, the aim here is to create a unifying guideline regarding treatment of both overt and covert encephalopathy in a cost-effective manner. The management plan given in these guidelines is flexible and can be changed with more authentic data. These guidelines will be reviewed after a certain period when more data will be available. Consensus is drawn with Delphi panel. Guidelines have been based on international guidelines, literature and local data on the diagnosis and management of hepatic encephalopathy and include low-cost but internationally acceptable investigations and treatment options. For compilation of these guidelines, all recommendations were discussed and approved by panel of expert. Data was scrutinized and made simplified for primary and secondary health care level. Hepatic Encephalopathy (HE) is one of the complications of chronic liver disease. It is a syndrome that includes a wide range of neurobehavioral abnormalities observed in patients with liver disease after extrahepatic causes.

The guidelines under review were made in September 2022 and Pakistan Society of Hepatology approve these guidelines in September 2023.

The study was conducted to compare lipid peroxidation byproducts levels in patients of oral sub mucous fibrosis and control group.

## CLASSIFICATION

Hepatic encephalopathy is graded according to: West Haven classification system, according to cause (type A: in patients with acute liver failure, type B: patients with portosystemic shunt, type C: patients with cirrhosis), according to timeline (episodic, recurrent, and persistent) and according to precipitating factors.

### Minimal HE (MHE)

It is the mildest form of HE, is characterized by neurocognitive dysfunction and impairs health-related quality of life (HRQOL) despite nonappearance of appreciable clinical symptoms and signs of HE [7, 16, 17]. Patients with MHE have decreased decision making power, decreased attention and fine motor skills rendering them at a high risk of falls and difficulty in performing tasks requiring hand eye coordination such as operating motor vehicle [18, 19].

### Pathogenesis of Hepatic Encephalopathy

The pathogenesis of HE has been explained by different hypotheses like astrocyte dysfunction, ammonia hypothesis and GABA hypothesis. Hyperammonemia is the most likely cause of MHE. Breakdown of amines, amino acids, and purines by bacteria in gastrointestinal tract leads to production of ammonia. Ammonia is converted to urea in liver by Krebs Henseleit cycle. Ammonia is also used in conversion of glutamate to glutamine-by-glutamine synthetase. In cirrhosis, due to the decreased number of functioning hepatocytes ammonia is not converted to urea. Secondly due to portosystemic shunt there is ammonia rich blood in systemic circulation without hepatic detoxification. Skeletal muscles contain glutamine synthetase which converts glutamate to glutamine, helping in ammonia metabolism. Muscle wasting in patients with chronic liver disease potentiates hyperammonemia. Kidneys have both glutaminase and glutamine synthetase so helps in ammonia production and metabolism respectively. Ammonia crosses the blood brain barrier and metabolizes in astrocytes by glutamine synthetase. Increased glutamine levels in astrocytes lead to shift of water into astrocytes resulting in edema, hence causing cerebral dysfunction.

### Diagnosis of Overt Hepatic Encephalopathy

The diagnosis of Overt Hepatic Encephalopathy (OHE) is clinical and the West Haven Classification (WHC) system is considered the gold standard [13]. In stuporous and comatose patients with WHC 3 and 4, Glasgow Coma Scale (GCS) is widely used [11, 13]. Both the west haven classification system and the GCS can be applied to patients at all levels i.e., primary, secondary, and tertiary care to stage disease severity. Diagnostic modalities are broadly classified into four groups i.e. psychometric, neurophysiological, neuroimaging, and laboratory tests [16]. Two different testing modalities should be performed and at least one should be a Psychometric Hepatic Encephalopathy Test Score (PHES) and one should be selected from neurophysiological and computerized tests [7, 16]. The Psychometric tests include Psychometric Hepatic Encephalopathy Test Score (PHES), animal naming test, Continuous Reaction Test (CRT), Inhibitory Control Test (ICT), and Stroop Test. Neurophysiological tests include Critical Flicker Frequency (CFF), Electroencephalogram (EEG), evoked potential, neuroimaging modalities include CT, MRI, and PET scan and laboratory tests include serum ammonia level and IL-6 level. MHE can be diagnosed with PHES [7, 16]. PHES includes five paper-pencil tests i.e., Number Connection Test-A (NCT-A) Number Connection Test-B (NCT-B), Line Tracing Time (LTT), Digit Symbol Test (DST), and Serial-Dotting Test (SDOT).

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**PSH RECOMMENDATIONS**

**For Overt Hepatic Encephalopathy**

All patients with overt HE should be evaluated by West Haven Criteria. For grade 3 and 4 hepatic encephalopathy, GCS should be used. Serum ammonia levels can be considered in doubtful cases to rule out the diagnosis. CT/MRI brain should be done when clinical suspicion of cerebral lesion, hemorrhage, focal neurological deficit or the patient is not responding after appropriate recommended treatment of 48 to 72 hours.

**For Minimal Hepatic Encephalopathy:**

All cirrhotic patients should be evaluated for minimal hepatic encephalopathy in each OPD visit. PHES should be done to make a diagnosis depending upon availability. Animal naming test is easy to perform at all levels, so can be done whenever there is suspicion of impairment of cognition.

**TREATMENT**

After excluding all other causes of altered sensorium [29-30], precipitating factors [13, 15] leading to encephalopathy should be corrected. Management options should focus on reducing hyperammonemia as it is the most common cause of hepatic encephalopathy.

Patients with grade 3, 4 encephalopathy with GCS less than 7 can be considered for intubation to reduce the risk of aspiration and managed in intensive care unit [21]. It is helpful for selected patients listed for liver transplant with grade 3 or 4 hepatic encephalopathy.

**Treatment Options**

**Lactulose**

Lactulose is non absorbable disaccharide which leads to acidification of lumen of gut which leads to impaired replication of ammonia producing bacteria. Lactulose is given as oral (30ml every 2 to 4 hours) or through nasogastric tube till passage of 2-3 loose stools. It can also be given as retention enema where indicated [24, 33]. In patients with cirrhosis, lactulose is given to prevent recurrence of overt hepatic encephalopathy [33-36]. In patients with minimal hepatic encephalopathy lactulose can be given to prevent overt HE [21, 27].

**Lactitol**

Lactilol is an osmotic laxative. For acute hepatic encephalopathy 45 to 90 ml per day in three divided doses along with meal is given.

**Rifaximin**

Rifaximin inhibits the ammonia producing bacteria in gut lumen. It is used in acute hepatic encephalopathy alone or with lactulose [38].

Dose is 10-15 mg/kg/day either cyclical (every month for 2 weeks) for 3 to 6 months or continuous maximum dose is 1100mg/day [39]. It should be given in patients with recurrent hepatic encephalopathy [40, 41]. It is recommended to add rifaximin to lactulose in patients with more than one episode of overt HE within 6 months of 1st episode [21, 42, 43].

**L-Ornithine, L-Aspartate (LOLA)**

20 to 30 grams of injectable LOLA is given in 4 hours for 3 to 7 days has proved beneficial in patients with HE for a minimum duration of 3 days [47, 49]. Injectable LOLA proves to be more beneficial than oral in patients with HE while, in MHE, oral administration has showed relative improvement in psychometric test [13, 16].

**Branched Chain Amino Acids (BCAA)**

BCAA taken orally have been found to improve hepatic encephalopathy [11, 50, 51]. However, there was no effect on the quality of life, nutritional status and mortality of patient [50, 51]. In various studies improvement in MHE and muscle mass has been noted [52, 53]. No beneficial effect has been noted with injectable use of BCAA [50, 53].

**Probiotics**

Probiotics help in reducing urease producing activity of gut bacteria by changing intestinal microflora [19]. Beneficial role in grade 1 and 2 of hepatic encephalopathy is better than grade 3 and 4 [55]. Analysis of 9 RCT revealed beneficial role of probiotics in MHE [13, 16, 56].

**Neomycin**

Neomycin is a glutaminase inhibitor which converts glutamine to glutamate and ammonia. It had been widely used in past but due to ototoxicity, nephrotoxicity and equivocal evidence, it is not used now a days [13, 57].

**Metronidazole**

Metronidazole reduces urease producing anerobic gram negative bacteria in the gut. Metronidazole can be used for a short period of time for hepatic encephalopathy in dosage of 200mg four times a day [51]. Adverse effects like metallic taste, nephrotoxicity and peripheral neuropathy has limited its long term use [13, 53]. It has same efficacy as rifaximin for short time in acute HE [56].

**Zinc**

Zinc is used as a cofactor in urea cycle enzymes. Zinc supplementation in HE has conflicting results in different studies so cannot be routinely recommended [21].

**Liver Transplantation**

Liver transplant should be considered in patients with recurrent or persistent HE not responding to all possible treatment options [21].

**PSH RECOMMENDATIONS**

**Overt Hepatic Encephalopathy**

The extrahepatic causes of altered sensorium/ acute confusion should be ruled out before establishing the diagnosis of hepatic encephalopathy. Precipitating factors leading to hepatic encephalopathy should be treated. Lactulose should be given in all patients either orally, through a nasogastric tube, or through enema if no

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absolute contraindication with dose titration targeting 2-3 loose stools per day.

**Secondary Prevention**

Lactulose should be given with dose modification with the target of 2-3 bowel movements per day. Rifaximin 550 mg twice a day long term until LT, nutritional status improves, or liver function improves. Deficiency of multivitamins, macronutrients, micronutrients, and minerals should be clinically assessed and treated with supplements. Adequate protein intake should be encouraged. BCAA can be substituted to maintain adequate protein intake. BCAA, IV LOLA, and metronidazole will be used as alternative agents if the patient is nonresponsive to the above treatment.

**Minimal Hepatic Encephalopathy**

All cirrhotic patients should be assessed for minimal hepatic encephalopathy/covert hepatic encephalopathy. Lactulose can be given to prevent covert hepatic encephalopathy.

**Liver Transplantation in Pakistan**

Overt hepatic encephalopathy is an indication of liver transplant. All patients with one episode of overt hepatic encephalopathy should be assessed for liver transplant.

## CONCLUSIONS

We recommended that these guidelines provide a valuable source of information regarding HE in Pakistani population, its current diagnosis and treatment.

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## Authors Contribution

Conceptualization: MUN, KM
Writing, review and editing: AF, RK, AH, DG, HSR

All authors have read and agreed to the published version of the manuscript.

## Conflicts of Interest

The authors declare no conflict of interest.

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## REFERENCES

[1] Sepanlou SG, Safiri S, Bisignano C, Ikuta KS, Merat S, Saberifiroozi M *et al*. The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet Gastroenterology and Hepatology. 2020 Mar; 5(3): 245-66. doi: 10.1016/S2468-1253(19)30349-8.

[2] Cheemerla S and Balakrishnan M. Global epidemiology of chronic liver disease. Clinical Liver Disease. 2021 May; 17(5): 365-70. doi: 10.1002/cld.1061.

[3] Iqbal M, Clement-Pervaiz MV, Ansari MJ, Pervaiz S, Sheikh S, Katpar S, *et al.* Proceedings of the 1st Liaquat University of Medical & Health Sciences (LUMHS) International Medical Research Conference. Eur J Med Res. 2017;22:1-20.

[4] Shah SM, Mashia SA, Younus MF, Ghauri A, Ejaz R, Alshalabi H *et al.* Hepatic cirrhosis-disease burden. Journal of Rawalpindi Medical College Student Supplement. 2015; 19(1): 17-20.

[5] Yousaf S, Farhan S, Nadeem MA. Frequency of Minimal Hepatic Encephalopathy in Cirrhotic Patients with Normal Neurological Examination. Age (Years). 2016 Apr; 20(40): 22.

[6] Elwir S and Rahimi RS. Hepatic encephalopathy: an update on the pathophysiology and therapeutic options. Journal of Clinical and Translational Hepatology. 2017 Jun; 5(2): 142. doi: 10.14218/JCTH.2016.00069.

[7] Shiha G and Mousa N. Minimal hepatic encephalopathy: Silent tragedy. In: Georgios Tsoulfas, Luis Rodrigo editors. Liver Diseases Surgery. 2019. doi: 10.5772/intechopen.88231.

[8] Bibi M, Ali A, Sahar U, Sajid A, Kumar S, Palh ZA, Naqvi SH, Baloch SK. A CLINICAL MANIFESTATION OF HEPATITIS C AMONG THE POPULATION OF HYDERABAD, PAKISTAN. Pakistan Journal of Biotechnology. 2023 Jun 11;20(02):193-207.

[9] Khan RT, Hussain SZ, Shahzad S, Majid Z, Naeem MU, Harjani R, Lail G, Khalid MA, Laeeq SM, Luck NH. Frequency of Non-Alcoholic Fatty Liver Disease Among the Non-Obese Population Presenting to the Gastrointestinal Outpatient Clinic. J Liaquat Natl Hosp. 2024;1:117-21.

[10] Ali B, Salim A, Alam A, Zuberi BF, Ali Z, Azam Z, Kamani L, Farooqi JI, Salih M, Nawaz AA, Chaudhry AA. HEP-Net opinion on the management of ascites and its complications in the setting of decompensated cirrhosis in the resource constrained environment of Pakistan. Pakistan Journal of Medical Sciences. 2020 Jul;36(5):1117.

**DOI:** https://doi.org/10.54393/pjhs.v5i05.1499

[11] Tamzaourte M, Rokhsi S, Berrag S, Adioui T. Minimal Hepatic Encephalopathy: Prevalence and Associated Factors. Asian Journal of Research and Reports in Hepatology. 2022 Jan 25;4(1):43-51.

[12] Ghosh J, Ghosh J. Current Management of Hepatic Encephalopathy: A Review Article. Journal for Research in Applied Sciences and Biotechnology. 2023 Sep 23;2(4):170-5.

[13] Dharel N and Bajaj JS. Definition and nomenclature of hepatic encephalopathy. Journal of Clinical and Experimental Hepatology. 2015 Mar; 5(1): S37-41. doi: 10.1016/j.jceh.2014.10.001.

[14] Rafiq Q, Zeeshan M, Mustafa G, Irfan M. Tracheobronchial aspiration affects the outcome of hospitalization among Hepatic Encephalopathy patients. Pakistan Journal of Medical Sciences. 2022 Mar;38(4Part-II):928.

[15] Pisarek, W.J.G.R.P.G., Minimal hepatic encephalopathy–diagnosis and treatment. 2021 Dec; 16(4): 311-317. doi: 10.5114/pg.2021.111389.

[16] Dhiman RK, Saraswat VA, Sharma BK, Sarin SK, Chawla YK, Butterworth R *et al.* Minimal hepatic encephalopathy: consensus statement of a working party of the Indian National Association for Study of the Liver. Journal of Gastroenterology and Hepatology. 2010 Jun; 25(6): 1029-41. doi: 10.1111/j.1440-1746.2010.06318.x.

[17] Pessidjo Djomatcho L, Kowo MP, Ndam AN, Njonnou SR, Kenfack GU, Andoulo FA et al. Normalisation of the psychometric encephalopathy score within the Cameroonian population. Baseboard Management Controller gastroenterology. 2021 Dec; 21: 1-7. doi: 10.1186/s12876-021-01858-7.

[18] Ridola L, Cardinale V, Riggio O. The burden of minimal hepatic encephalopathy: from diagnosis to therapeutic strategies. Annals of Gastroenterology. 2018 Mar; 31(2): 151. doi: 10.20524/aog.2018.0232.

[19] Gou LB, Zhang W, Guo DJ, Zhong WJ, Wu XJ, Zhou ZM. Aberrant brain structural network and altered topological organization in minimal hepatic encephalopathy. Diagnostic and Interventional Radiology. 2020 May;26(3):255.

[20] European Association for the Study of the Liver. EASL Clinical Practice Guidelines on the management of hepatic encephalopathy. Journal of Hepatology. 2022 Sep; 77(3): 807-824. doi: 10.1016/j.jhep.2022.06.001.

[21] Campagna F, Montagnese S, Ridola L, Senzolo M, Schiff S, De Rui M *et al.* The animal naming test: an easy tool for the assessment of hepatic encephalopathy. Hepatology. 2017 Jul; 66(1): 198-208. doi: 10.1002/hep.29146.

[22] Lauridsen MM, Mikkelsen S, Svensson T, Holm J, Klüver C, Gram J *et al.* The continuous reaction time test for minimal hepatic encephalopathy validated by a randomized controlled multi-modal intervention-a pilot study. PLOS One. 2017 Oct; 12(10): e0185412. doi: 10.1371/journal.pone.0185412.

[23] Thomas S, Fiebig JE, Kuhn EM, Mayer DS, Filbeck S, Schmitz W, Krischke M, Gropp R, Mueller TD. Design of glycoengineered IL-4 antagonists employing chemical and biosynthetic glycosylation. ACS Omega. 2023;8(28).

[24] Luo M, Ma P, Li L, Cao WK. Advances in psychometric tests for screening minimal hepatic encephalopathy: From paper-and-pencil to computer-aided assessment. The Turkish Journal of Gastroenterology. 2019 May; 30(5): 398. doi: 10.5152/tjg.2019.18226.

[25] Mehreen N, Aziz B, Taj MK, Saleem M, Taj G, Zafar U. Hepatic encephalopathy and its management. 2022 June; 20(6): 45-64. doi:10.12692/ijb/20.6.45-64.

[26] Edward Ukamaka C, Nwanjo Harrison U, Nwosu Dennis C. Studies on Acute Phase Inflamatory Proteins of Type 2 Diabetics in Owerri. 2019 Oct; 4(10): 324-332. doi: 10.36348/SJBR.2019.v04i10.002.

[27] Gairing SJ, Anders J, Kaps L, Nagel M, Michel M, Kremer WM *et al.* Evaluation of IL-6 for Stepwise Diagnosis of Minimal Hepatic Encephalopathy in Patients with Liver Cirrhosis. Hepatology Communications. 2022 May; 6(5): 1113-22. doi: 10.1002/hep4.1883.

[28] Akhtar AJ, Alamy ME, Yoshikawa TT. Extrahepatic conditions and hepatic encephalopathy in elderly patients. The American Journal of the Medical Sciences. 2002 Jul; 324(1): 1-4. doi: 10.1097/00000441-200207000-00001.

[29] Amodio P. Hepatic encephalopathy: Diagnosis and management. Liver International. 2018 Jun; 38(6): 966-75. doi: 10.1111/liv.13752.

[30] Weissenborn K. Challenges in diagnosing hepatic encephalopathy. Neurochemical Research. 2015 Feb; 40: 265-73. doi: 10.1007/s11064-014-1416-x.

[31] Díaz-Fontenla F, Castillo-Pradillo M, Díaz-Gómez A, Ibañez-Samaniego L, Gancedo P, Guzmán-de-Villoria JA *et al.* Refractory hepatic encephalopathy in a patient with hypothyroidism: Another element in ammonia metabolism. World Journal of Gastroenterology. 2017 Jul; 23(28): 5246. doi: 10.3748/wjg.v23.i28.5246.

[32] Wijdicks EF. Hepatic Encephalopathy. The New England Journal of Medicine. 2016 Oct; 375(17): 1660-1670. doi: 10.1056/NEJMra1600561.

**DOI:** https://doi.org/10.54393/pjhs.v5i05.1499

[33] Gluud LL, Vilstrup H, Morgan MY. Non-absorbable disaccharides versus placebo/no intervention and lactulose versus lactitol for the prevention and treatment of hepatic encephalopathy in people with cirrhosis. Cochrane Database of Systematic Reviews. 2016; 5: CD003044. doi:10.1002/14651858.CD003044.

[34] Butt NI, Butt UI, Kakar AA, Malik T, Siddiqui AM. Is lactulose plus rifaximin better than lactulose alone in the management of hepatic encephalopathy? Journal of College of Physicians and Surgeons Pakistan. 2018 Feb; 28(2): 115-7. doi: 10.29271/jcpsp.2018.02.115.

[35] Acharya C and Bajaj JS. Current management of hepatic encephalopathy. Official Journal of the American College of Gastroenterology. 2018 Nov; 113(11): 1600-12. doi: 10.1038/s41395-018-0179-4.

[36] Sharma P, Sharma BC, Puri V, Sarin SK. An open-label randomized controlled trial of lactulose and probiotics in the treatment of minimal hepatic encephalopathy. European Journal of Gastroenterology and Hepatology. 2008 Jun; 20(6): 506-11. doi: 10.1097/MEG.0b013e3282f3e6f5.

[37] Cash WJ, McConville P, McDermott E, McCormick PA, Callender ME, McDougall NI. Current concepts in the assessment and treatment of hepatic encephalopathy. QJM: An International Journal of Medicine. 2010 Jan; 103(1): 9-16. doi: 10.1093/qjmed/hcp152.

[38] Iadevaia MD, Prete AD, Cesaro C, Gaeta L, Zulli C, Loguercio C. Rifaximin in the treatment of hepatic encephalopathy. Hepatic Medicine: Evidence and Research. 2011 Dec; 22(3): 109-17. doi: 10.2147/HMER.S11988.

[39] Flamm SL. Rifaximin treatment for reduction of risk of overt hepatic encephalopathy recurrence. Therapeutic Advances in Gastroenterology. 2011 May; 4(3): 199-206. doi: 10.1177/1756283X11401774.

[40] Bass NM, Mullen KD, Sanyal A, Poordad F, Neff G, Leevy CB *et al.* Rifaximin treatment in hepatic encephalopathy. New England Journal of Medicine. 2010 Mar; 362(12): 1071-81. doi: 10.1056/NEJMoa0907893.

[41] Kimer N, Krag A, Møller S, Bendtsen F, Gluud LL. Systematic review with meta-analysis: the effects of rifaximin in hepatic encephalopathy. Alimentary Pharmacology and Therapeutics. 2014 Jul; 40(2): 123-32. doi: 10.1111/apt.12803.

[42] Saleem MZ, Saleem MH, Saleem H, Aasil MA. Rifaximin Effectiveness in Preventing the Recurrence Of Hepatic Encephalopathy Among Patients With Liver Cirrhosis. Pakistan Armed Forces Medical Journal. 2021 Aug; 71(4): 1296-99. doi: 10.51253/pafmj.v71i4.2481.

[43] Ali B, Zaidi YA, Alam A, Anjum HS. Efficacy of Rifaximin in prevention of recurrence of hepatic encephalopathy in patients with cirrhosis of liver. Journal of College of Physicians and Surgeons Pakistan. 2014 Apr; 24(4): 269-73.

[44] Mittal VV, Sharma BC, Sharma P, Sarin SK. A randomized controlled trial comparing lactulose, probiotics, and L-ornithine L-aspartate in treatment of minimal hepatic encephalopathy. European Journal of Gastroenterology and Hepatology. 2011 Aug; 23(8): 725-32. doi: 10.1097/MEG.0b013e32834696f5.

[45] Sidhu SS, Sharma BC, Goyal O, Kishore H, Kaur N. L-ornithine L-aspartate in bouts of overt hepatic encephalopathy. Hepatology. 2018 Feb; 67(2): 700-10. doi: 10.1002/hep.29410.

[46] Jain A, Sharma BC, Mahajan B, Srivastava S, Kumar A, Sachdeva S *et al.* l-ornithine l-aspartate in acute treatment of severe hepatic encephalopathy: a double-blind randomized controlled trial. Hepatology. 2022 May; 75(5): 1194-203. doi: 10.1002/hep.32255.

[47] Aidrus F, Razzaque S, Siddiqui A, Kumar A, Ghaur MI. Therapeutic efficacy of l-ornithine l-aspartate in patients with hepatic encephalopathy. Pakistan Journal of Neurological Sciences. 2015; 10(3): 37-41.

[48] Merli M, Berzigotti A, Zelber-Sagi S, Dasarathy S, Montagnese S, Genton L *et al.* EASL Clinical Practice Guidelines on nutrition in chronic liver disease. Journal of Hepatology. 2019 Jan; 70(1): 172-93. doi: 10.1016/j.jhep.2018.06.024.

[49] Gluud LL, Dam G, Les I, Marchesini G, Borre M, Aagaard NK *et al.* Branched-chain amino acids for people with hepatic encephalopathy. Cochrane Database of Systematic Reviews. 2017 May; 2015(9). doi: 10.1002/14651858.CD001939.pub3.

[50] Ferenci, P.J.G.r., Hepatic encephalopathy. Gastroenterol Report. 2017 May; 5(2): 138-147. doi: 10.1093/gastro/gox013.

[51] Chandio SH, Fatima T, Hassan B, Jabeen S, Mumtaz H, Owais M *et al.* Role of probiotics in decreasing ammonia levels. Can they be used as a treatment of hepatic encephalopathy? 2020 Aug; 9(10): 1328-1337. doi: 10.20959/wjpr202010-18629.

[52] Dalal R, McGee RG, Riordan SM, Webster AC. Probiotics for people with hepatic encephalopathy. Cochrane Database of Systematic Reviews. 2017 Feb; (2): CD008716. doi: 10.1002/14651858.CD008716.pub3.

**DOI:** https://doi.org/10.54393/pjhs.v5i05.1499

[53] Patidar KR and Bajaj JS. Antibiotics for the treatment of hepatic encephalopathy. Metabolic Brain Disease. 2013 Jun; 28: 307-12. doi: 10.1007/s11011-013-9383-5.
[54] Morgan MH, Read AE, Speller DC. Treatment of hepatic encephalopathy with metronidazole. Gut. 1982 Jan; 23(1): 1-7. doi: 10.1136/gut.23.1.1.
[55] Mekky MA, Riad AR, Gaber MA, Abdel-Malek MO, Swifee YM. Rifaximin versus metronidazole in management of acute episode of hepatic encephalopathy: An open labeled randomized clinical trial. Arab Journal of Gastroenterology. 2018 Jun; 19(2): 76-9. doi: 10.1016/j.ajg.2018.06.001.
[56] Rehman S, Fatima QU, Rehman S, Sami Z, Ali H, Saddiqa I. Comparison of current and emerging strategies for treating hepatic encephalopathy. The Professional Medical Journal. 2021 Nov; 28(12): 1705-10. doi: 10.29309/TPMJ/2021.28.12.6644.