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. The entire number of patients with chronic liver disease is estimated at 1.5 billion. Amongst the Pakistani population, cirrhosis is the leading cause of mortality and the most common cause of hospital admission. 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. Approximately 30% of patients dying of end-stage chronic liver disease have had at least one event of significant hepatic encephalopathy. The most common reason for readmission in patients with decompensated chronic liver disease is HE. 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). 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%. A study conducted in tertiary care hospital revealed that 91 patients out of 150 had MHE. However, due to the non-
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) 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 psychophysiological 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).
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
Lactitol 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].
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**

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**References**


