Lecture 7[2hrs]

Management of Cirrhotic Ascites

Successful treatment relieves discomfort but does not prolong life.
Over vigorous treatment can precipitate hepatic encephalopathy.

Non-diuretic Therapy include:-

1-Drugs must be avoided includes

* Non-steroidal anti-inflammatory drugs (NSAIDs) and nephrotoxic drugs *Antacids• Antibiotics• Phenytoin, Effervescent preparations (e.g., Aspirin, calcium, paracetamol) Sodium valproate, Carbenoxolone• Glucocorticoids• Metoclopramide, estrogens.

2-Sodium restriction of 2 gr [88mmol /day] and water restriction [o.5 –1 L /day] when serum
Na < 125mmol/L.

3-Bed rest [enhance renal perfusion].

Diuretic therapy indicated when patients do not respond well to salt and fluid restriction**]. Drugs include**

1-Potassium-sparing agents

*Spironolactone- a distal diuretic with antialdosterone activity. usually started at a dose of 100 mg/day [maximum dose is 400mg /day]. side effects are painful gynecomastia.
or
*Amiloride [The starting dose is 5 mg/day [maximum dose is 20mg/day].
Either potassium-sparing diuretic is usually combined with a loop diuretic.

2-Loop diuretic-

*Furosemide, starting at 40 mg/day[maximum dose is 160mg/day] Increase diuretics in stepwise

The goal of diuretic therapy should be to reduce a 1Kg bodyweight if there are ascites and leg edema [Because only 900 ml can be mobilized from the peritoneal cavity daily if more than 1 kg wt loss per day fluid may be removed from the rest of body]. or ½ Kg if there are only ascites without leg edema

*Monitoring of diuretic therapy is by

1. Daily weights.
2. Weekly postural symptoms/signs.
3. Twice-weekly electrolytes and renal function.
4. Symptoms/signs of encephalopathy.

5-24 hr. urine collection for quantitation of sodium the goal excretion of >78mmol/ day of sodium with wt loss.

Refractory Ascites

*Ascites that cannot be mobilized or prevented from recurring by medical therapy

Refractory Ascites Maybe

a-Diuretic Resistant. characterized by a lack of response to dietary sodium restriction and intensive diuretic therapy by a high dose of diuretics [400 mg of Spironolactone and 20 mg of Amiloride or 160 mg of furosemide daily for two weeks].

b-Diuretic intractable-characterized by the development of diuretic-induced complications like [azotemia, electrolyte disturbance, encephalopathy] that preclude the use of effective diuretic doses.

Treatment of Refractory Ascites include

1-Serial large-volume paracentesis

*First-line treatment of refractory ascites is large-volume paracentesis. If tense ascites causing cardiorespiratory discomfort a single large volume paracentesis [3-5L over 1-2 hours] with human albumin 6–8 g per liter of ascites removed.

*Paracentesis to dryness is safe, provided the circulation is Supported with an intravenous colloid such as human albumin or another plasma expander. [to minimize intravascular hypovolemia ,activation of vasoconstrictor,antinatriuretic systems and impairment of renal function].

2-TIPSS [transjugular intrahepatic portal-systemic stent- shunt]

*Relieve resistant ascites but does not prolong life. *Should not be used in a terminally ill patient. It can be used where liver function is reasonable or patient awaiting liver transplantation

3-Peritoneo-venous shunting [PVS] include

*LeVeen or Denver shunt.

A long tube with non-return value running S.C from peritoneum to internal jugular vein in the neck which allows ascitic fluid to pass directly into the systemic circulation.

Complications of LeVeen or Denver shunt include

Infection. Superior vena cava thrombosis, Pulmonary edema, Bleeding from esophageal Varices, DIC [disseminated intravascular coagulation].

4-Liver transplantation.

Complications of ascites include

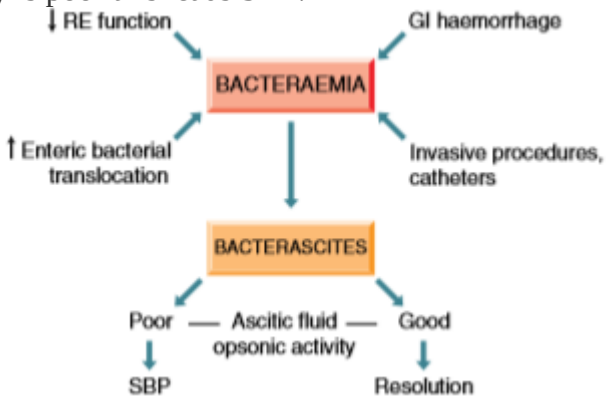
1-Spontaneous Bacterial Peritonitis[SBP]

*Spontaneous bacterial peritonitis is a common and often fatal complication of cirrhosis. *It is a clinical syndrome in which ascites becomes infected usually with a single organism and an Ascitic fluid neutrophils count >= 250 cell/ml in the absence of a recognizable cause of peritonitis.

Risk factors for the development of SBP include

1-Ascitic fluid protein < 10 gr /L. 2-GIT hemorrhages .3-Prior SBP.4-Invasive procedures.

Pathogenesis of SBP involves 1- increase bacterial translocation from the gut to the systemic circulation and then to ascitic fluid and depend on ascitic fluid opsonic activity if an opsonic activity is poor this leads SBP.



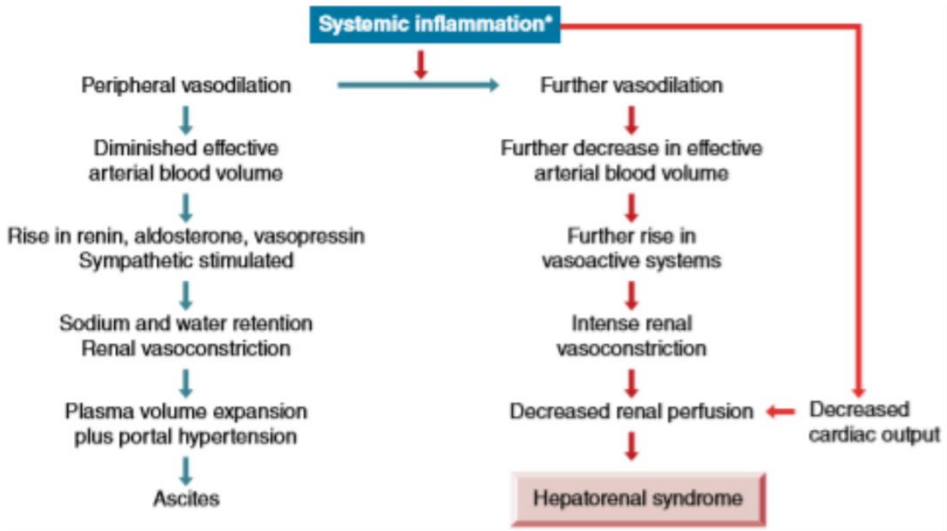
Most Common isolates Organisms are[E.coli, klebsiella, and pneumococcus].

Clinical Features of SBP includes -Abdominal Pain, rebound tenderness, Absent bowel sound, and Fever some time Abdominal signs are absent and patient presented with HEP and fever.

Radiographic examinations are required to exclude perforation of the gastrointestinal tract.

Treatment

Treatment should be started immediately with broad-spectrum antibiotics after the diagnostic PMN count rather than waiting for positive culture results.
*Aminoglycosides should not be used because cirrhotic patients are sensitive to their nephrotoxic effect.
*Cefotaxime, a broad-spectrum, third-generation cephalosporin the treatment of choice for SBP and it is not nephrotoxic in the therapeutic range. Cefotaxime 2 g intravenously every eight to 12 hours for five days.
*Piperacillin/tazobactam.*intravenous followed by oral amoxicillin/clavulinic acid
*intravenous ciprofloxacin followed by oral treatment
Prophylaxis of SBP by.
*Norfloxacin 400 mg daily is the drug of choice
*Ciprofloxacin 750 mg weekly is equally effective.*Trimethoprim/sulfamethoxazole 160/800 mg daily is an alternative and may confer greater gram-positive coverage.
2-Hepato-Renal Syndrome (HRS).
*HRS is a functional renal failure occurring in patients with advanced liver disease.
The Pathophysiology of HRS
*Peripheral vasodilatation secondary to portal hypertension and systemic inflammation both causing more decrease in effective arterial blood volume these events causing a further rise in vasoactive systems [Renin-aldosterone, Sympathetic nervous system, Vasopressin, Endothelin]. these stimuli Causing intense renal vasoconstriction.
intense renal vasoconstriction and decrease in cardiac output due to systemic inflammation both causing decrease in renal perfusion which results in HRS



The mechanism for hepatorenal syndrome

Diagnostic Criteria for HRS are:
*Cirrhosis with ascites.
*Serum creatinine >1.5 mg/dL.
*No improvement in serum creatinine (to <1.5 mg/dL) after at least 2 days of diuretic withdrawal and volume expansion with albumin (1 g/kg of body weight per day daily).
*Absence of shock.
*No current or recent treatment with nephrotoxic drugs.
*Absence of parenchymal kidney disease, as indicated by proteinuria >500 mg/day, microhematuria (>50 RBCs/high-power field), and/or abnormal renal ultrasonography.
Classifications of HRS

Type 1 HRS characterized by
*Severe and rapidly progressive renal failure, with doubling of serum creatinine to >2.5 mg/dL in <2weeks.
* Patients usually have severe liver failure [jaundice, encephalopathy, and coagulopathy].
*Frequently occurs after precipitating events, such as SBP and variceal bleed.
* Bad prognosis Median survival only 2 w.

Type 2 HRS
*More slowly progressive renal failure the serum creatinine levels are usually between 1.5 and 2.5 g/dL.
*Usually associated with refractory ascites.

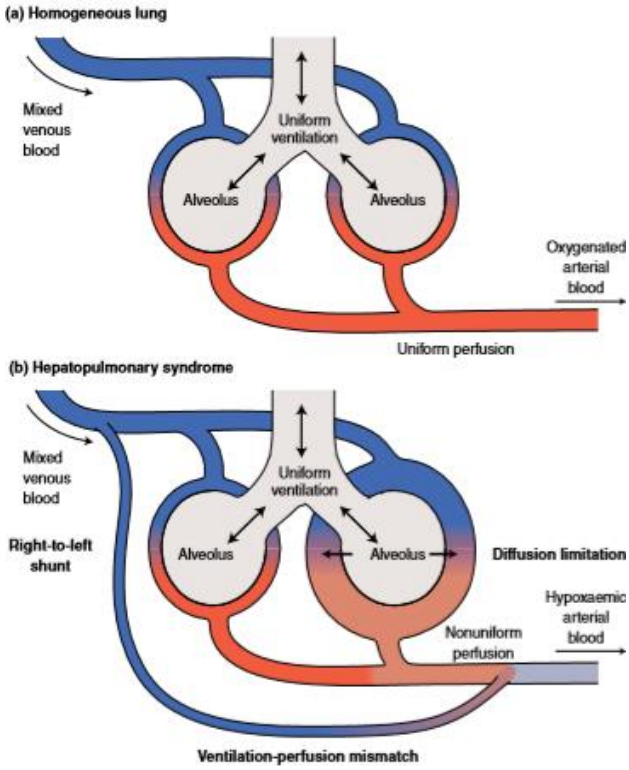
Differentiated diagnosis of HRS include
*Pre-renal causes such as over diuresis, acute tubular necrosis, and obstructive uropathy.
*Intrinsic renal diseases such as glomerulonephritis in patients with hepatitis B or C.
Drugs such as aminoglycosides, NSAIDs, and vasodilators (e.g., prazosin, nitrates) can cause renal failure and must be avoided.

Treatment
The aim of treatment in HRS is the correction of the circulatory dysfunction including Expansion of the intra-arterial volume with
1-Albumin1 g/kg body weight/day, up to 100 g/day 2-Splanchnic vasoconstrictors like *Terlipressin 1mg iv every 4 hr. or *Midodrene 2.5-5 mg orally 3 times daily and* Octreotide
3-TIPS and Liver Transplantation

3-Hepato-Pulmonary Syndrome[HPS]

*HPS defines as a disorder in pulmonary gas exchange [Mismatch of ventilation and perfusion] due to intrapulmonary vasodilatation in a patient with liver disease and or PHT.
*Intrapulmonary vascular dilation(IPVD) results in rapid shunting of mixed venous blood into the pulmonary Veins causing hypoxemia

Pathogenesis of HRS. *Nitric oxide (NO) overproduction



Mechanisms of arterial hypoxemia in the hepatopulmonary syndrome

Clinical Features of HPS

*Platypnea (dyspnea exacerbated by standing) is the pathognomonic symptom of HPS. Platypnea results from worsening of the ventilation-perfusion mismatch on standing due to *Orthodeoxia. (Decrease paO2 of >3mm Hg upon assuming upright position).

*The cause of Platypnea and Orthodeoxia is the reinforced perfusion of the dilated pulmonary vessels in the poorly ventilated basal lung area in an upright body position.

*Clubbing and cyanosis

Investigations include.

*Chest X-ray- which shows bilateral, basilar, nodular or reticulo-nodular opacities

*Arterial blood gas-shows respiratory alkalosis due to hyperventilation and hypoxemia Pa O2 <60 mm Hg.,

*Echocardiography * Brain–lung perfusion scanning

Differential diagnosis.

*Dyspnea with exertion or at rest is the most common symptom in patients with liver disease because of anemia, muscle wasting, atelectasis caused by ascites or pleural effusion,

*Porto-pulmonary hypertension

*Complications due to right-to-left pulmonary communications such as brain abscesses or polycythemia

Treatment-

*Long term supplemental oxygen 100 % *TIPS *Liver transplantation.

4-Porto Pulmonary Hypertension [PPH].

Pathophysiology

Pulmonary arterial hypertension associated with portal hypertension results from pulmonary vasoconstriction.

*Release of cytokines such as tumor necrosis factor (TNF)-β and growth factors promotes vascular Endothelial and smooth-muscle proliferation and in situ thrombosis.

*Vasoactive substances like serotonin and endothelin that escape the liver metabolism due to portosystemic shunting reach the lungs are implicated in pulmonary arterial vasoconstriction.

Clinical Features

*Dyspnea and fatigue are the most common presenting manifestations. As PPH worsens Symptoms of right heart failure develop, including

*Leg edema *Loud P2 and* Systolic murmur consistent with tricuspid regurgitation.

Investigations

*Chest x-ray- Shows prominent central pulmonary arteries.

*ECG: shows Right axis deviation, RBBB.

*Doppler echocardiography

*Right heart catheterization for direct measurement of pulmonary artey pressure, pulmonary capillary wedge pressure and calculation of systemic and pulmonary vascular resistance

*Arterial blood gas analysis shows-Respiratory alkalosis usually mild and less severe than HPS

Treatment.

*Diuretics may be used when pulmonary hypertension is secondary to volume overload.

*Prostacyclin (epoprostenol), a systemic and pulmonary vasodilator and platelet inhibitor,

* PDE5 inhibitors (sildenafil, tadalafil, and vardenafil) prevent the breakdown of cyclic guanosine monophosphate which mediates NO-induced vasodilation and reduces pulmonary artery pressure.

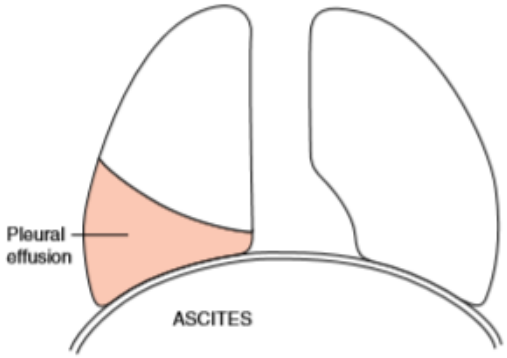
*Oral endothelin receptor antagonists [bosentan and ambrisentan].

Hepatic hydrothorax

*Hepatic hydrothorax is a complication of portal hypertension that is characterized by a transudate pleural effusion.

*It occurs in approximately 5–15% of cirrhotic patients.

*Ascites passes from the abdominal cavity into the pleural cavity due to a defect in the diaphragm occurring in the right hemidiaphragm.
*Symptoms include dyspnea, cough, and hypoxemia.
Management- is as for ascites with
*Dietary salt restriction
*Diuretics Some patients may require
*Drainage by chest drain should be avoided due to the high risk of complications.
*TIPS - indicated for refractory hepatic hydrothorax



R side hydrothorax

Hepatic Encephalopathy (HEP)

*Hepatic encephalopathy is the neuropsychiatric abnormalities that occur in a patient with chronic liver disease and portal hypertension but also seen in patients with acute liver failure.
*It results from a combination of portosystemic shunting and liver dysfunction.

Pathogenesis of HEP.

*Failure of hepatic detoxification of toxic products arising from the gut.
*Toxic products of gut origin that are usually metabolized by the liver before entering the systemic circulation and reaching the brain include

A*Nitrogenous subs. (ammonia, mercaptans).

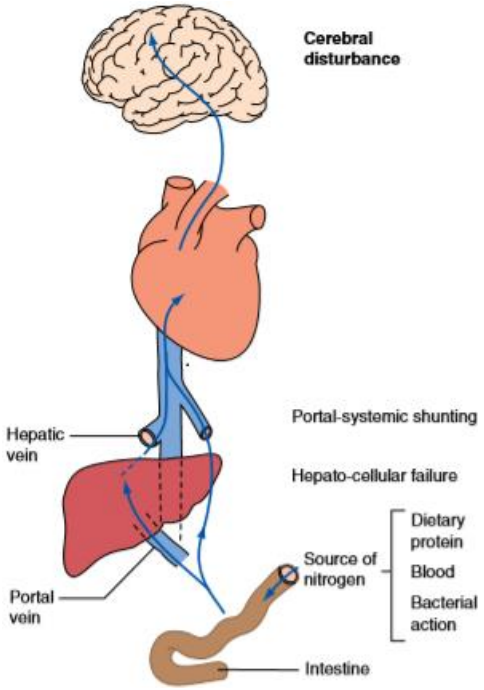
*Ammonia derived from colonic bacteria and deamination of glutamine in the small bowel is absorbed into the portal circulation.
*The intact liver clears portal vein ammonia by the urea synthesis pathway.
*Patients with liver disease ammonia reaches the systemic circulation because of vascular shunts and the inability of the liver to metabolize the ammonia.
*Ammonia exposure to cerebral structures leads to astrocyte swelling, edema, cytotoxicity, and depletion of glutamate.

B***Benzodiazepine-like compounds**

*Arising from intestinal flora, diet and medications may accumulate in the brain of cirrhotic patients due to impaired clearance.
*Benzodiazepine-like compounds bind to GABA receptors, inducing GABA release leads to neural inhibition.

C*False neurotransmitters.

*Increase Aromatic amino acid (tyrosine phenylamine, tryptophan) due to failure of hepatic deamination and decrease in branched-chain amino acid (valine, leucine, isoleucine) .
*The imbalance of plasma levels allows more aromatic amino acid to pass an abnormal blood-brain barrier leads to the formation of false neurotransmitters.



Hepatocellular failure and portal-systemic shunting are key players in the development of hepatic encephalopathy in patients with cirrhosis.

Encephalopathy associated with cirrhosis and/or portal-systemic shunts may develop as a result of specific precipitating factors include:

*****Excessive dietary protein*Gastrointestinal bleeding*Electrolyte disturbance (hypokalemia)

* Metabolic alkalosis*Constipation * Azotemia.

*****Infection: Spontaneous bacterial peritonitis, Urinary tract infection, and Pulmonary infection.

*Dehydration: Vomiting, Diarrhea, Diuretics, and large volume paracentesis.

*Drugs: Narcotics, tranquilizers, sedatives, and Alcohol.

*Portosystemic shunting: Tipss or surgically placed stents and Spontaneous shunts

*Vascular occlusion: Portal vein thrombosis, Hepatic vein thrombosis.

*Primary Hepatocellular carcinoma, Hypothyroidism, and Anemia.

Clinical Features:

The clinical presentation of a patient with HE is variable.

*Patients with HE usually has features of advanced chronic liver disease.

*Sings suggesting advanced liver disease include *Fetor hepaticus [sweet smell from the mercaptans in the breath of patients with HE]. *spider telangiectasia *gynecomastia, *loss of body hair in men, *testicular atrophy, * jaundice, *ascites,*amenorrhea, *caput medusa, *ecchymoses,

splenomegaly, edema *Muscle wasting.

*Hepatic encephalopathy is characterized by changes in personality, consciousness, behavior, and neuromuscular function.

Grading Systems of HEP.

0-Sub clinical. Normal examination but work or driving may be impaired.

1-Impaired attention, irritability, personality changes, depression reversal of sleep pattern

2-Drowsiness behavioral changes, poor memory, sleep disorder

3-Confusion, disorientation, somnolence, amnesia O/E clonus, nystagmus, muscular rigidity

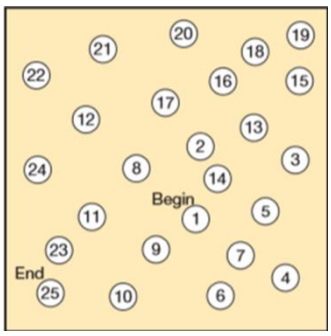
4-Stupor or coma. Dilated pupils, decerebrate posture absence of response to stimuli in an advanced stage.
*Asterixis, also called "flapping tremor," is present in stage 2 and 3 hepatic encephalopathies. Asterixis appears as a rapid flexion-extension movement at the wrist and the metacarpophalangeal joints.
*Chronic refractory encephalopathy may cause dementia, spastic Paraparesis, cerebellar degeneration, and extrapyramidal movement disorders.

Differential Diagnosis of HEP

This includes the exclusion of
*Central nervous system disease such as subdural hematoma, tumor, CVA, Infection,
*Drug overdose *Alcohol intoxication *Delirium tremens *Wernickes encephalopathy [Triad of symptoms including ophthalmoplegia, ataxia, and confusion caused by thiamine deficiency] *Primary psychiatric disorders* Hypoglycemia *Neurological Wilson's disease

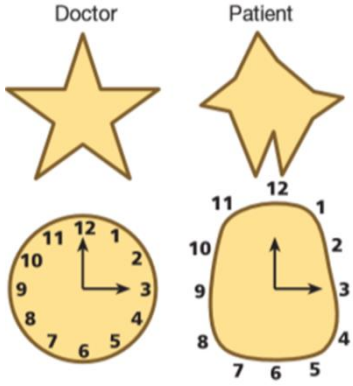
Investigation: -

Blood tests help identify precipitating factors of HE such as
*Hypoglycemia *azotemia* Electrolyte imbalance and *infection
*Elevated blood ammonia is not diagnostic of HE a normal ammonia level does not rule out HE.
*Lumbar puncture and brain imaging studies such as CT scan or MRI may be necessary to rule out other CNS pathology. The cerebrospinal fluid is usually normal and may show increased protein with increased GABA levels.
*The EEG shows slow, triphasic wave activity mainly over the frontal area.
*impaired Number connection test



Number connection test. These 25 numbered circles can normally be joined together within 30 sec.

- *Constructional apraxia: drawing stars and clocks reveal a marked abnormality



Constructional apraxia-drawing stars and clocks reveal a marked abnormality

Management: -

*The most important aspect of management is recognition and treatment of precipitating factors.
Therapeutic management is then aimed at reducing the amount of ammonia or nitrogenous products in the circulatory system.

Drug therapies for Encephalopathy Commonly used include

1-lactulose [galactosido-fructose]-

*****A synthetic disaccharide that is degraded by intestinal bacteria into lactate and acetate to produce stool acidification and osmotic diarrhea.

*The acidification of colonic contents reduces ammonia absorption by trapping nitrogenous compounds in the lumen.

*The daily Oral dosing (15–30 mL four times a day) is titrated to result in two or three soft bowel movements/day.

* Patients in a coma or with a small bowel ileus can receive lactulose by enema[300 ml of lactulose in 1 L of water every 2 -4 hrs until there is clinical improvement].

*Lactulose can be used chronically to reduce the frequency of encephalopathy.

*Common side effects of lactulose are. flatulence, diarrhea, and cramping.

2-Lactitol [galactosido-sorbitol]-can be used instead of lactulose.

Too much diarrhea can result in fluid and electrolyte depletion with renal failure and can worsen HEP.

3-Metronidazole [400-800 mg/day in divided doses] recommended for short term use because of long term toxicity.

4-Neomycin [2-4gr orally/day in divided doses for 5 days].

* Acts by inhibiting urea-splitting and deaminating bacteria, reducing the production of ammonia and other potential toxins.

*Neomycin-use is now limited due to its potential nephrotoxic and ototoxic side-effects.

5-Rifaximin [400 mg 3 times daily] for 5-10 days

*is a semi-synthetic derivative of rifampin that reduces GI ammonia absorption by inhibiting urease-producing bacteria, which decreases ammonia production and facilitate its elimination.

*Side effects include nausea, peripheral edema

6-Oral BCAA

*Improve the manifestation of encephalopathy. Produce clinical improvement in a patient with low-grade HE.

*BCAA acts by detoxification of ammonia in skeletal muscle.

*Decrease malnutrition and increase muscle bulk.

7-Zinc Replacement. The significant incidence of zinc deficiency in cirrhosis and because enzymes involved in the metabolism of ammonia to urea is zinc-dependent.

8-Benzodiazepine Receptor Antagonists such as flumazenil.

9-**Probiotics** to modify enteric bacteria population.

10-Ornithine–aspartate

*Provides substrates for both urea and glutamine synthesis.

11-Bromocriptine-at a dose of 10 mg twice a day, resulted in an improvement in extrapyramidal symptoms

12-Refractory HE complicating TIPS can be managed by implanting a reducing stent to reduce blood flow through the TIPS

13-Liver Transplantation