Mx of Hepatic Encephalopathy in Hospital

Yee Mon Htun

MAYO CLINIC

REVIEW

Management of Hepatic Encephalopathy in the Hospital

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Abstract

Hepatic encephalopathy (HE) develops in up to 50% of patients with cirrhosis and is a feature of decompensated cirrhosis. With the goal of reviewing the evidence for treatment and prevention of overt hepatic encephalopathy, pubmed was searched using search terms *hepatic encephalopathy* AND *treatment*, limited to human studies from January 1, 2003, through December 1, 2013, and supplemented by key references. The inpatient incidence of HE is approximately 23,000 annually, and management of these patients is common for internists and subspecialists. Treatment of the hospitalized patient with HE has changed in recent years. Treatment entails 2 phases: induction and maintenance of remission. Most cases of significant HE are precipitated by infection, gastrointestinal bleeding, medications, or other culprits. All patients should be evaluated for secondary triggers of HE, and treatment should be initiated with a nonabsorbable disaccharide (ie, lactulose) in most patients. Rifaximin (off label) can be added in patients not responding to lactulose. Neomycin is a less preferred alternative to rifaximin owing to its adverse effect profile. Other therapies, including zinc, L-ornithine—L-aspartate, and branched-chain amino acids, can be considered for patients not responding to disaccharides and nonabsorbable antibiotics. Large portosystemic shunts may be embolized in patients with medically refractory recurrent or severe HE with otherwise well-compensated cirrhosis. Molecular Adsorbent Recirculating System is now available for patients with severe HE who do not respond to medical therapy. It is critically important that patients hospitalized with significant HE continue maintenance therapy at the time of dismissal to prevent further episodes. Patients with a first-time episode of HE can be administered lactulose, and careful instructions should be provided to patients and caregivers about dose titration to achieve 3 bowel movements daily. Patients with recurrent HE episodes despite lactulose use benefit from the addition of rifaximin, which decreases the frequency of recurrent HE episodes and related hospitalizations. Last, patients and their families should be counseled about the risk of motor vehicle accidents, which require mandatory reporting to the Department of Motor Vehicles in some states.

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- HE develop in up to 50% of patient with cirrhosis
- Features of decompensated cirrhosis
- Treatment of hospitalized patient with HE has change in recent years

- Treatment entails 2 phases :
  - ✓ induction and
  - ✓ maintenance of remission

- Most cases of significant HE are precipitated by
  - ✓Infection
  - ✓GI Bleeding
  - ✓Medicaitons or other culprits

Hepatic Encephalopathy

- A significant neuropsychiatric syndrome that mostly occur in decompensated cirrhosis

Clinical features are range

from

- Minimal HE (MHE) which require neuropsychometric testing to identity

to

- comatose cases in worse cases

- Severity of HE is graded using WestHaven Criteria grade 1-4

- New lexicon, called SONIC (Spectrum of neurocognitive impairement in Cirrhosis)

Covert and Overt HE

TABLE 1. Hepatic Encephalopathy Grades

Grade	Impairment		SONIC criteria
	Intellectual	Neuromuscular	
0	Normal	Normal	Normal
MHE	Normal examination findings; subtle changes in work or driving	Minor abnormalities of visual perception or on psychometric or number tests	Covert
1	Personality changes, attention deficits, irritability, depressed state	Tremor and incoordination	Covert
2	Changes in sleep-wake cycle, lethargy, mood and behavioral changes, cognitive dysfunction	Asterixis, ataxic gait, speech abnormalities (slow and slurred)	Overt
3	Altered level of consciousness (somnolence), confusion, disorientation, amnesia	Muscular rigidity, nystagmus, clonus, Babinski sign, hyporeflexia	Overt
4	Stupor and coma	Oculocephalic reflex, unresponsiveness to noxious stimuli	Overt

MHE = minimal hepatic encephalopathy; SONIC = spectrum of neurocognitive impairment in cirrhosis.

- Episodic HE develops over short time frame and can fluctate
- Persistent HE impairs day to day executive function
- Most patient with episodic OHE (grade 2 or higher) will require management in hospital
- Development of HE merits consideration of liver transplantation

- Hospitalization for episodic OHE

  OR

- Development of OHE during hospitalization

- 80% of OHE episodes are precipitated by an event such as infection or GI bleeding
- Management of hospitalized patient with episodic OHE is directed at correcting underlying treatment and providing pharmacologic treatment that reduces ammoniagenesis
- Most patients require maintenance medication at the time of hospital dismissal as secondary prophylaxis

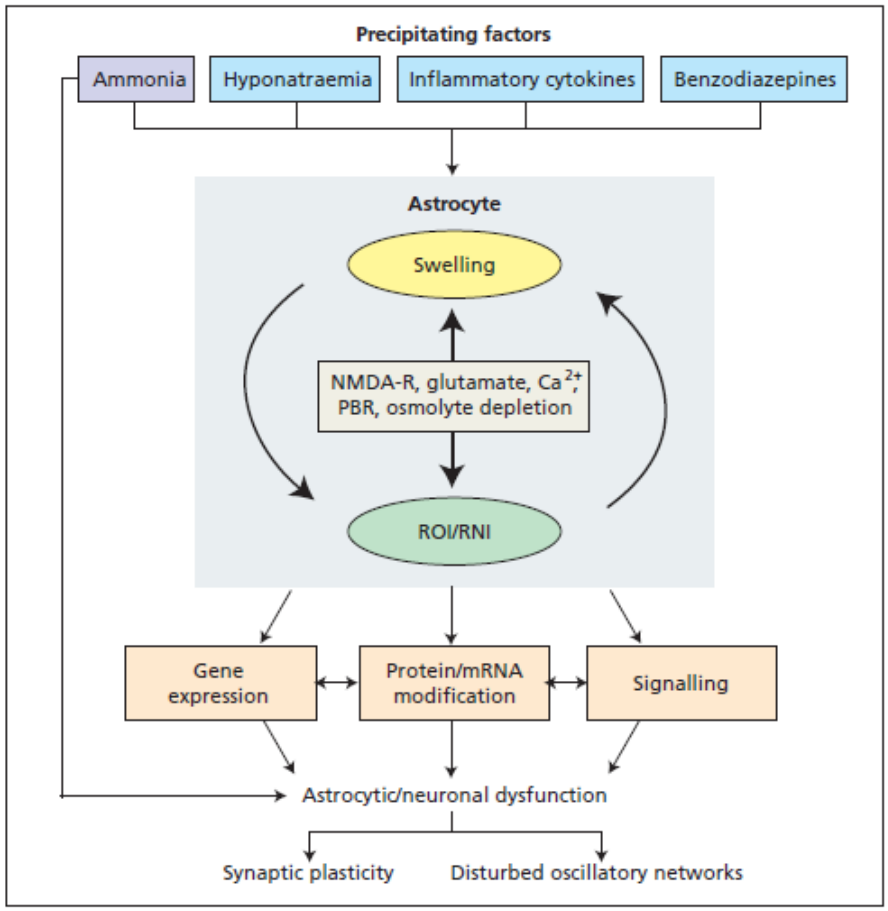
- One of the most common reasons for preventable readmission was recurrent HE due to lack of education or inappropriate use of lactulose

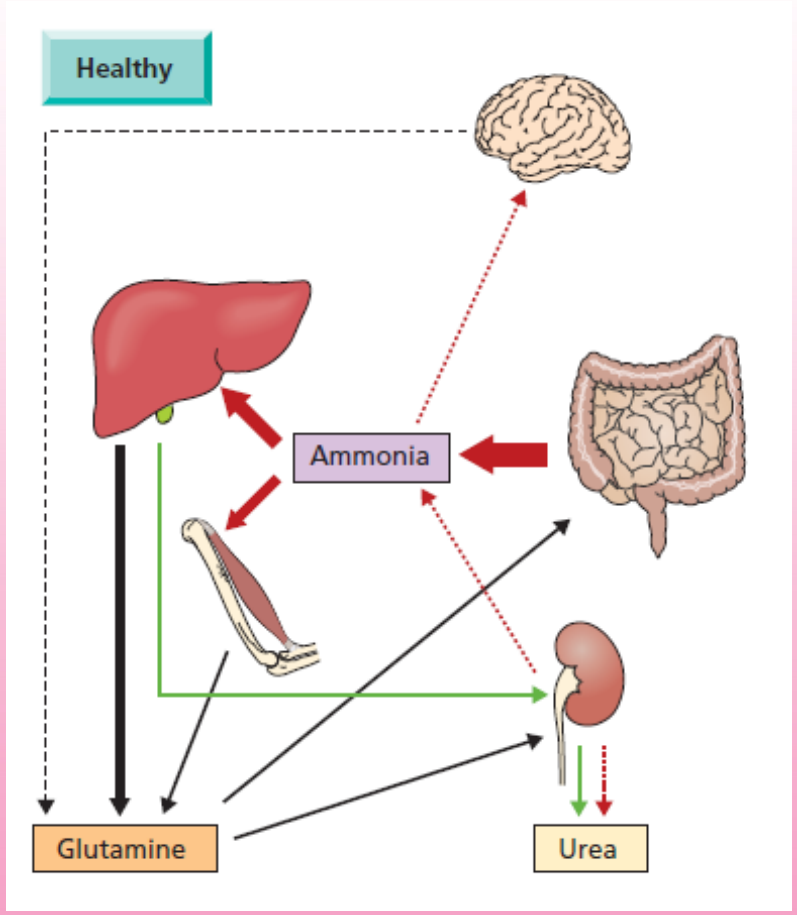
- Focused on ensuring that patients are prescribed and educated about maintenance medication therapy for 2^0 prevention of OHE at the time of hospital dismissal

Pathophysiology of HE

- **Key factors**
  - ✓ Gut - derived neurotoxins
  - ✓ Brain water homeostasis
  - ✓ Oxidative/ nitrosative stress
  - ✓ Astrocyte dysfunction
  - ✓ Neurotransmitter dysfunction
  - ✓ Infection and inflammation
- **Unified theory**

Unified Theory




Healthy
Ammonia
Glutamine
Urea

Evidence for Induction Therapies to treat Episodic OHE

1. Nonabsorbable Disaccharides
2. Neomycin, Metronidazole and other Antibiotics
3. Rifaximin
4. Zinc
5. L-Ornithine – L-Aspartate
6. Branched Chain Amino Acids
7. Percutaneous Embolization of Large Portosystemic Shunts
8. Molecular Adsorbent Recirculating System

1.Nonabsorbable Disaccharides

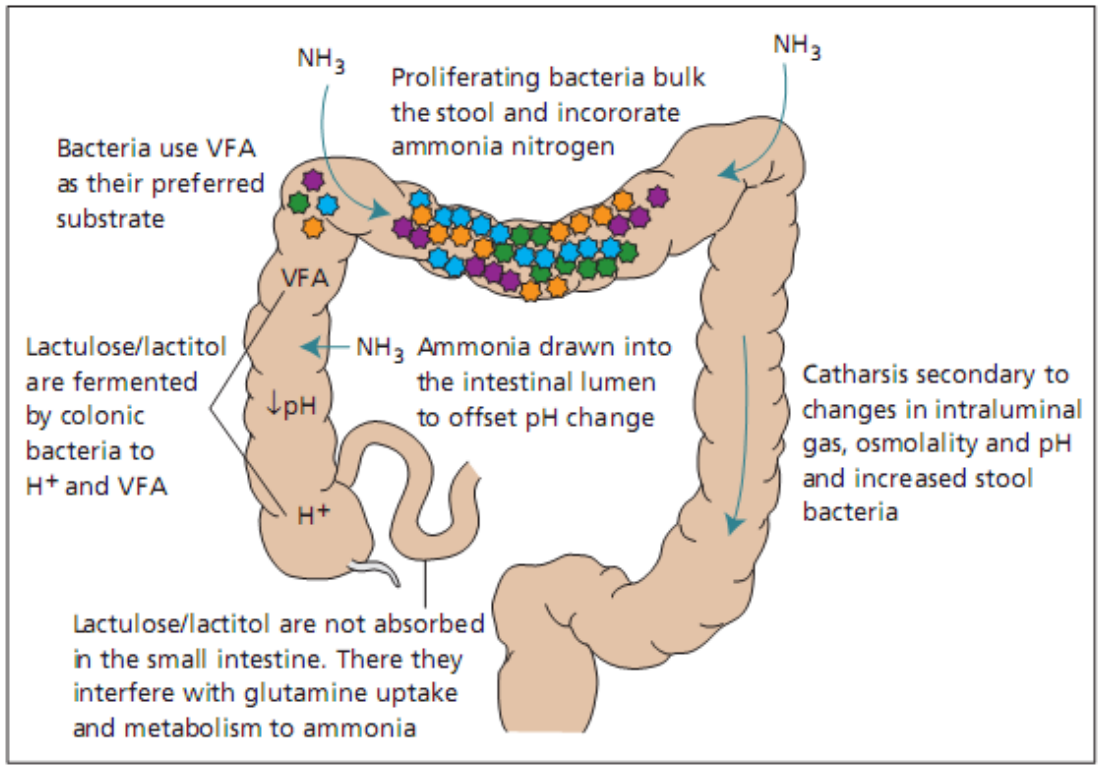
- Lactulose (beta-galactosidofructose)
- Lactitol (beta – galactosidosorbitol)

- Reduce ammonia levels by acidification of the colon with resultant conversion of ammonia to ammonium

- Shifting the colonic flora from urease to non-urease producing bacterial species

- Lactulose still remains first line therapy for acute episodic OHE

Mechanism of action of Lactulose



Mechanism ofaction of Lactulose

(1) A laxative effect:

the colonic metabolism of these sugars results in an increase in intraluminal gas formation, an increase in intraluminal osmolality, a reduction in intraluminal pH and an overall decrease in transit time

Mechanism of action of Lactulose

(2) Uptake of ammonia by bacteria:

- the intraluminal changes in pH result in a leaching of ammonia from the circulation into the colon
- The colonic bacteria use the released volatile fatty acids as substrate and proliferate
- In doing so they use the trapped colonic ammonia as a nitrogen source for protein synthesis
- The increase in bacterial numbers additionally ‘ bulks ’ the stool and contributes
- to the cathartic effect

Mechanism of action of Lactulose

(3) Reduction in intestinal ammonia production:

non -absorbable disaccharides inhibit glutaminase activity and interfere with the uptake of glutamine by the intestinal wall and its subsequent metabolism to ammonia

2.Neomycin,Metronidazole and other Antibiotics

- Neomycin is a poorly absorbed aminoglycoside used to decrease gut bacteria-derived ammonia
- It is FDA approved for use in acute episodic OHE but not chronic HE
- Complicated by the risk of ototoxicity and nephrotoxicity
- Other small trials have evaluated Metronidazole and Vancomycin – some benefit

3.Rifaximin

- Role of Rifaximin in treatment of episodic OHE is contentious
- RCT of Rifaximin Vs Placebo for acute HE grades 1-3 found improvement in a composite outcome (including mental status, neuropsychometric test results, EEG findings and ammonia level) at doses of 1200 and 2400 mg/day

3.Rifaximin

- FDA do not approve for treatment of episodic OHE, only for secondary prevention of OHE

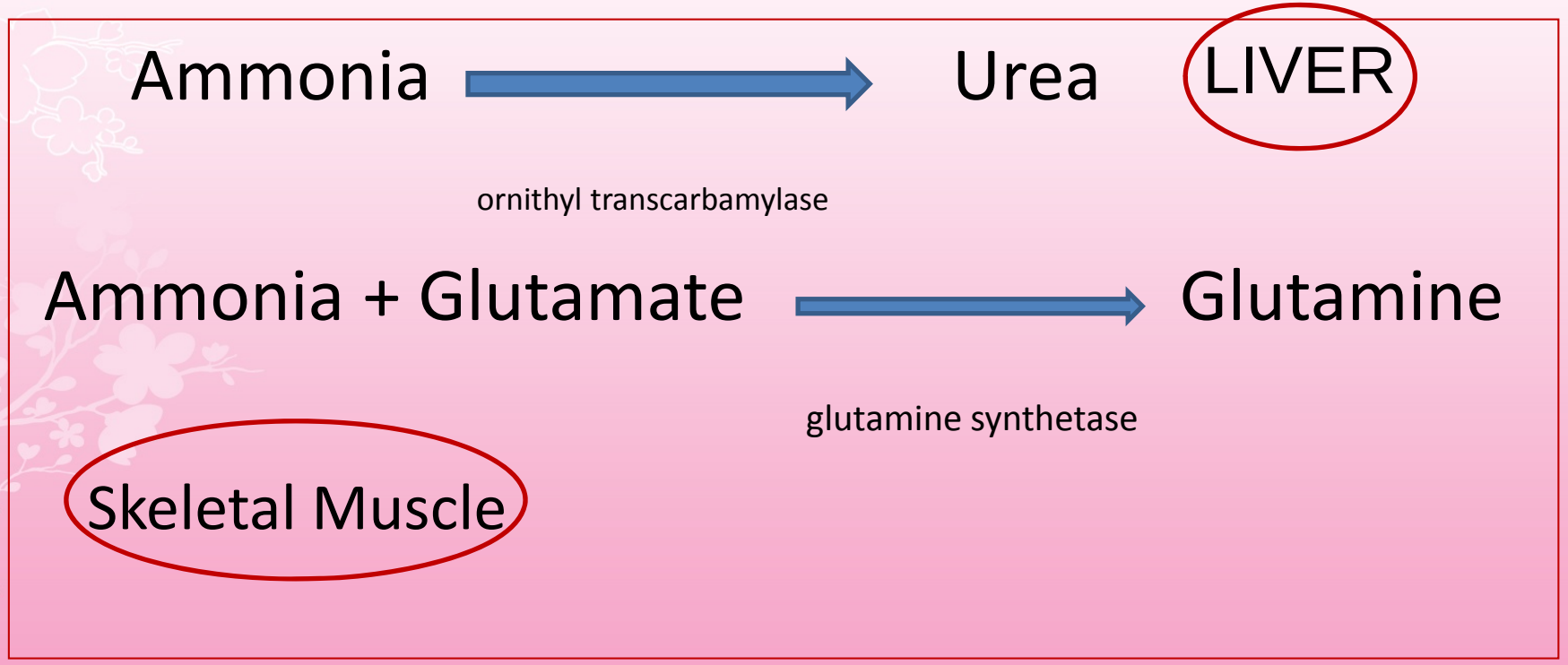
3.Rifaximin

- A recent RCT (n=120)was conducted by Sharma et al
- Comparing Rifaximin+lactulose with lactulose+placebo
- Rifaximin+lactulose had a higher proportion of complete reversal of HE

4.Zinc

- Zinc deficiency is common in cirrhosis
- Recent clinical trial, Zinc deficiency prevalence was 96% in patients with a median MELD score of 12

4.Zinc


Ammonia
Urea
LIVER
ornithyl transcarbamylase
Ammonia + Glutamate
Glutamine
glutamine synthetase
Skeletal Muscle

4.Zinc

- Both pathways are impaired by Zinc deficiency
- Treatment with Zinc has been found to enhance the formation of urea from ammonia and amino acid
- No enough data to define the optimal dose of Zinc

4.Zinc

- Zinc is relatively well tolerated, with rare adverse effects of dyspepsia and copper deficiency and

- Can decrease the effectiveness of Ciprofloxacin if taken at the same time (take zinc 2 hours before and 6hours after taking ciprofloxacin

5.L-Ornithine – L –Aspartate (LOLA)

- A compound salt that stimulates ornithine transcarbamolyase and carbamoyl phosphate synthetase
- Substrate for the formation of urea
- Works by stimulating glutamine syntheis in skeletal muscale and consequently lowering ammonia

5.L-Ornithine – L –Aspartate (LOLA)

- In Germany , 2 Randomized, placebo – controlled, Double blind studies

  - ✓ Using IV and oral forms of LOLA in patients with chronic HE
  - ✓ Both of which found improvement in no, connection tests, ammonia level and HE parameters (mental state gradation and Portosystemic Encephalopathy Index

5.L-Ornithine – L –Aspartate (LOLA)

- One study from Pakistan

LOLA + SMT Vs SMT + placebo

- ✓ significant result in patient with grade 2 HE or above had improvement in HE grade

6. Branched – Chain Amino Acids

- In a patient with cirrhosis

<u>Plasma aminoacid profile is altered</u>

- ↓ BCAAs
- ↑ Aromatic Amino acids

6. Branched – Chain Amino Acids

- BCAAs are a source of glutamate , which helps to metabolize ammonia in skeletal muscle

- Supplementation with BCAAs may
  - ✓ improve albumin synthesis
  - ✓ Decrease insulin resistance
  - ✓ decrease hepatocellular carcinoma
  - ✓ Improve immune function

6. Branched – Chain Amino Acids

- Currently, the European Society for Clinical Nutrition and Metabolism recommends
  - ✓ use of 1.2 g/kg/day of protein for compensated cirrhosis
  - ✓ use of 1.5 g/kg/day fro decompensated cirrhois

This recommendation was based on the results of RCT ofa normal protein diet (1.2g/kg per day) Vs restricted diet reporting no effect on the outcome of episodic HE but increased muscle breakdown in low- protein-diet group

6. Branched – Chain Amino Acids

- Inaddition,

<u>European Society for Clinical Nutrition and European Society</u>

- ✓ Grade A recommendation for the use of standard protein supplementation in patient with HE grade 2 or less
- ✓ BCAA prepation for HE 3 and 4

7. Percutaneous Embolization of Large Portosystemic Shunt

- Two large retrospective series have been published reporting the efficacy and safety of embolization of large portosystemic shunts i medically refractory HE

7. Percutaneous Embolization of Large Portosystemic Shunt

- In the largest US series (n=15) , 90% of patients with cirrhosisimproved 2months after the procedure
  - ✓ one developed infected hepatic cyst 2 week after procedure
  - ✓ Otherwise no significant complications

7. Percutaneous Embolization of Large Portosystemic Shunt

In a Europeanmulti-center cohort study (n=37)

- ✓ 59% of patient free of HE within 100 days and
- ✓ 48% were HE free an average of 2 years after embolization

7. Percutaneous Embolization of Large Portosystemic Shunt

- Median MELD score in both study was 13

- European Study suggets that patients wiht MELD score greater than 11 were at risk for HE recurrence after shunt embolization

8.Molecular Adsorbent Recirculating System

- Introduced in 1999
- Based on the concept of albumin dialysis
- Designed to remove protein and albumin bound toxins such as bilirubin, bile acids, nitrous oxide and endogenous benzodiazepines
- It also removes non protein bound ammonia that accumulates in liver failure

8.Molecular Adsorbent Recirculating System

- Most Recent and largest trial (RELIEF Trial)

✓ 189 patients with acute on chronic liver failure and evaluated MARS + SMT Vs SMT alone on primary end points of 28 and 90 days liver transplantation – free survival

✓ Survival end points were not met but safety was demonstrated

8.Molecular Adsorbent Recirculating System

- FDA has approved the use of MARS for HE related to decompensation of chronic liver disease
- MARS may reduce the bioavailability of certains antbiotics
- Cost is also a major concern with this modality
- MARS seemsto be a viable option fro patientswith severe HE unresponsvie to SMT

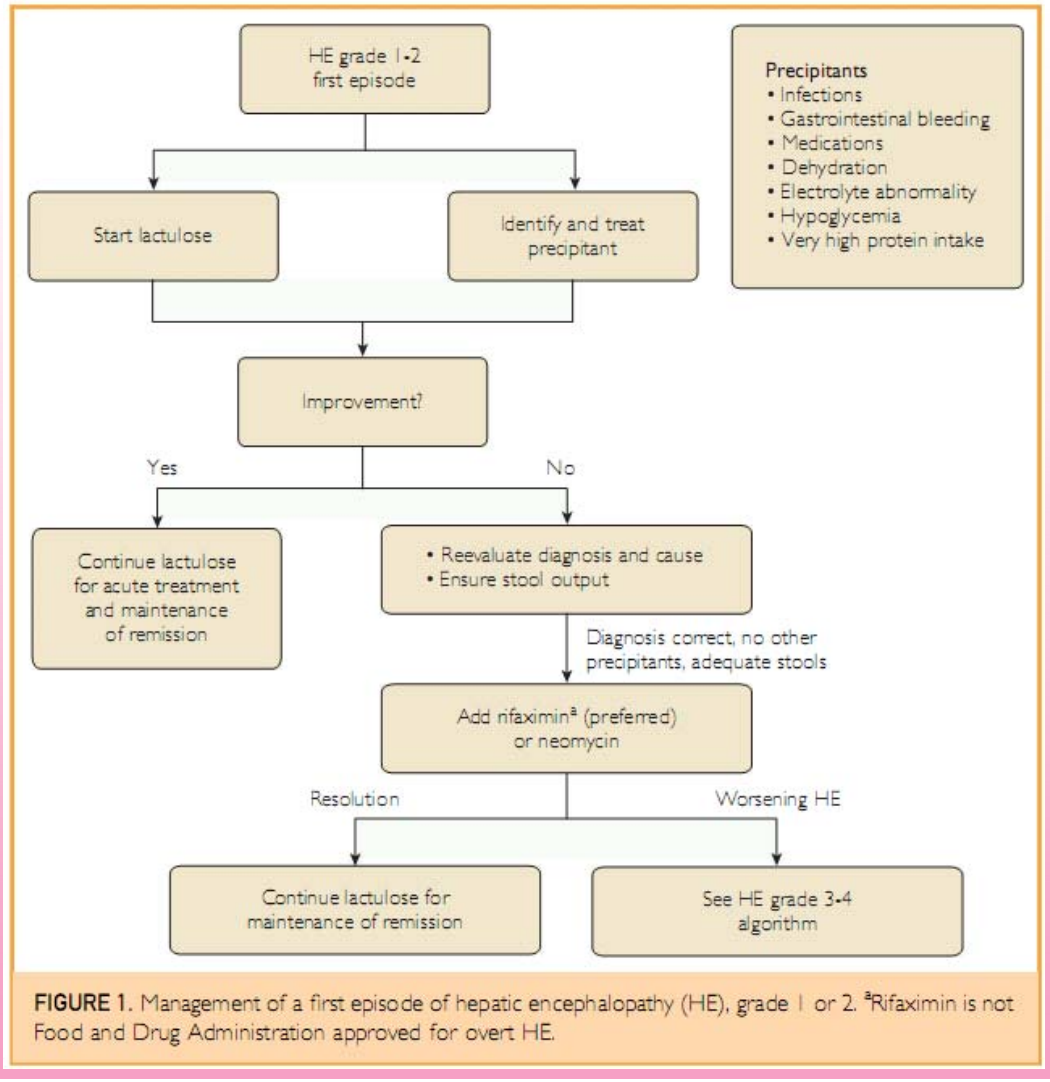


FIGURE 1. Management of a first episode of hepatic encephalopathy (HE), grade 1 or 2. [a]Rifaximin is not Food and Drug Administration approved for overt HE.

Management of Severe HE
West Haven Criteria Grade 3 or 4

Management of Severe HE

- Grade 3 or 4 is a serious complication that requires intensive care unit monitoring

- Patient who cannot protect their airway owing to decreased conciousness require endotraccheal intubation and mechanical ventilation

Management of Severe HE

- After a thorough evaluation fro precipitants, patient should be given lactulose via nasogastric NG tube = 15 to 30cc every 1 -2 hours until 3 stools are achieved
- If NG tube or orogastric access is not allowed then 300 cc of lactulose can be given in 1L of water as an enema (300cc of lactulose / 10g/15ml in 700cc of sterile water)
- Can be repeated as necessary, although care should be taken to avoid excessively loose or voluminous stool

Management of Severe HE

- Rifaximin should be administered with lactulose in patient with grade 3 or 4

- Not response to lactulose and nonabsorbable antibiotics should be reevaluated to make sure that the diagnosis is accurate

Management of Severe HE

- If diagnosis is in question, a head CT scan and EEG may be helpful to rule out the possibility of a CNS bleeding and nonconclusive status epilepticus respectively

- If Dx of HE is accurate, then patient should be evaluated for a large protosystemic shunt

Management of Severe HE

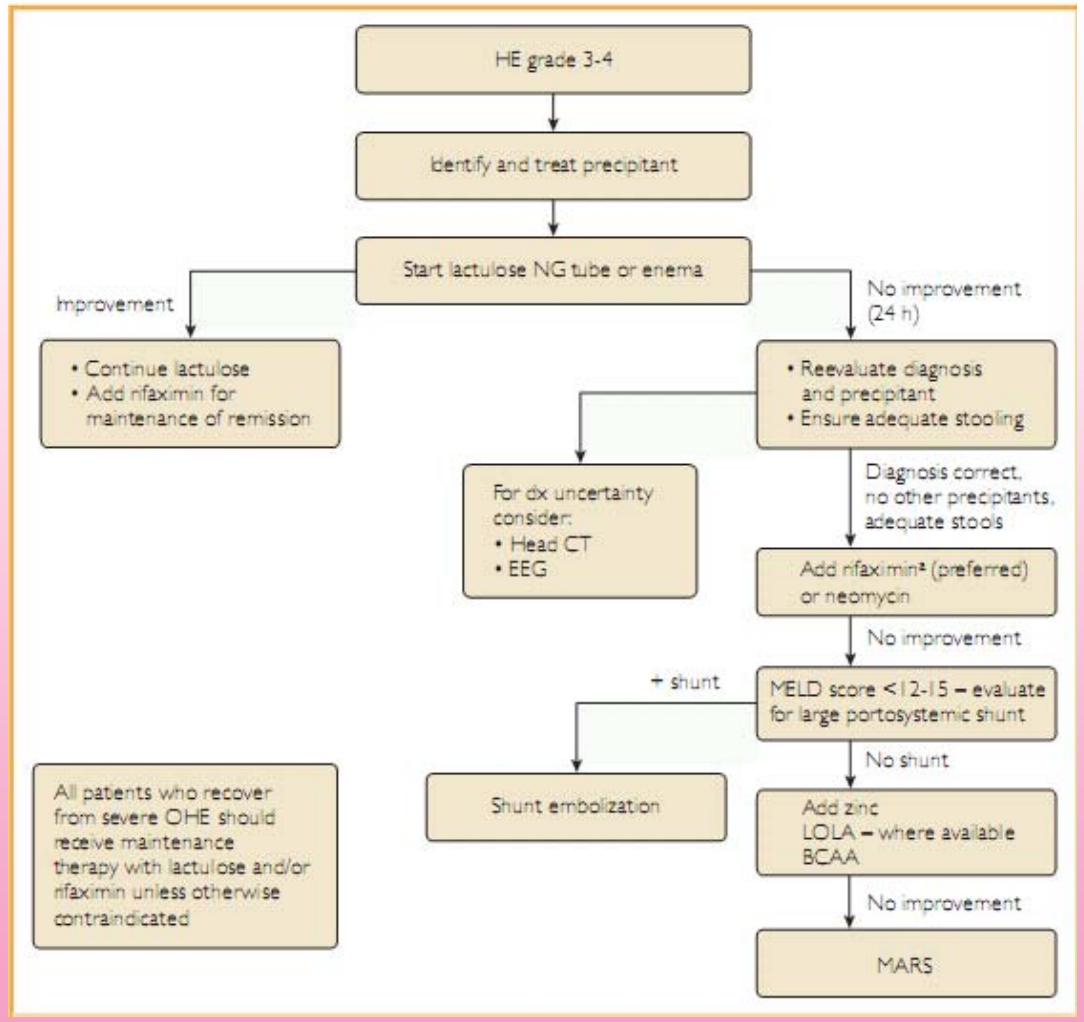
- Large shunt should be treated in the presence of refractory HE and relatively loe MELD scores < 12-15

- Most initial medication nonresponders will not have a large shunt and can be treated with BCAAs, Zinc, and LOLA where available

Management of Severe HE

- Last, for patients not responsive to the a forementioned approach, MARS should be considered

- Patient recovering from severe HE should be kept on a maintainence program of lactulose and rifaximin


HE grade 3-4
Identify and treat precipitant
Start lactulose NG tube or enema
Improvement
No improvement (24 h)
• Continue lactulose
• Add rifaximin for maintenance of remission
• Reevaluate diagnosis and precipitant
• Ensure adequate stooling
For dx uncertainty consider:
• Head CT
• EEG
Diagnosis correct, no other precipitants, adequate stools
Add rifaximin[a] (preferred) or neomycin
No improvement
+ shunt
MELD score <12-15 – evaluate for large portosystemic shunt
No shunt
Shunt embolization
Add zinc
LOLA – where available
BCAA
No improvement
MARS
All patents who recover from severe OHE should receive maintenance therapy with lactulose and/or rifaximin unless otherwise contraindicated

Evidence for secondary prophylactic/maintenance strategies for HE

Lactulose

- The results of two recent trials provided that solid evidence for practice of secondary prevention with lactulose alone or lactulose and rifaximin

- Sharma et al - open-label randomized study
  - Recurrent OHE 19.7% in lactulose treated pts and 46.9% in placebo arm

Evidence for secondary prophylactic/maintenance strategies for HE

- Agrawal et al - study
  - Recurrent OHE - 37.5 % with Lactulose , 45.4 % with probiotics, 64.1 % with no treatment

Evidence for secondary prophylactic/maintenance strategies for HE

Rifaximin

- In 2010 ,Bass et al - study
  - Recurrent OHE - 31 of 140 in rifaximin group and 73 of 159 in placebo group

Approach to Induction and Maintenance Treatment of HE

For First Episode of Episodic OHE

- Evaluation for the typical precipitants of OHE
- Up to 80% of patients may have precipitants
- Mx of Precipitants along with lactulose
- If no other precipitants are found, and bowel movements are adequate, then neomycin or rifaximin could be added to lactulose
- Neomycin id FDA approved fro this indication but there are obviousconcerns regarding nephrotoxicity and ototoxicity

For First Episode of Episodic OHE

- Patients who recover from first episode of OHE generally require lactulose maintenance theray, esp if Child-Turcotte-Pugh class B/C

For Recurrent more than 2 times episodic OHE

- Careful evaluation for precipitants
- Inappropriate lactulose dose or Non compliance are common
- For well compensated patients with Child class A cirrhosis or low MELD scores percutaneous shunt embolization should be considered
- If shunt is not foundor high MELD score precludes embolization,then additinal treatments such as zinc, LOLA and BCAA should be considered

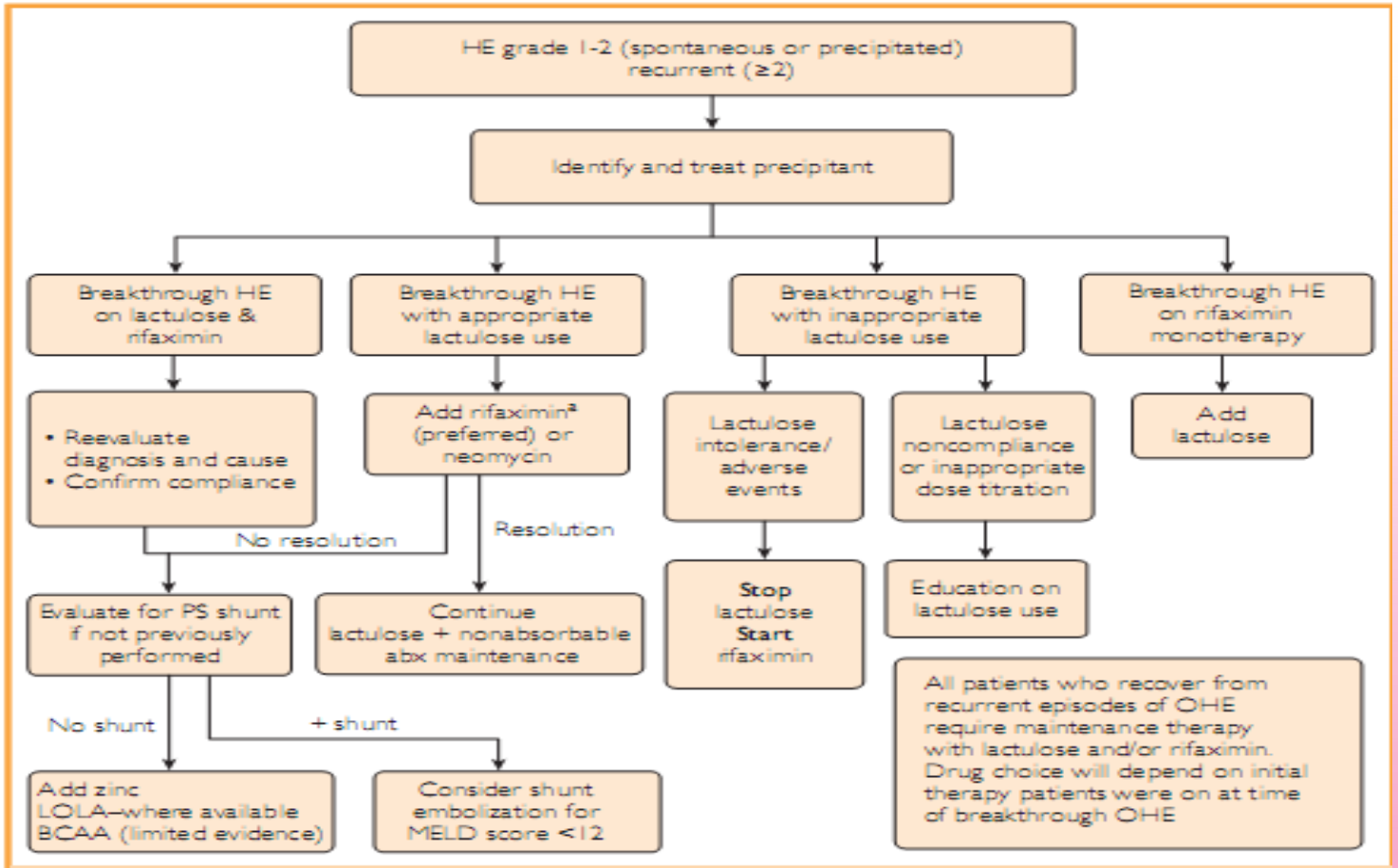


FIGURE 2. Management of recurrent episodes of hepatic encephalopathy (HE), grade 1 or 2. [a]Rifaximin is not Food and Drug Administration approved for overt HE (OHE). abx = antibiotic; BCAA = branched-chain amino acid; LOLA = L-ornithine–L-aspartate; MELD = Model for End-Stage Liver Disease; PS = portosystemic.

Conclusion

- In summary, HE eventually occurs in upto 50% of cirrhosis patients and heralds a poorprognosis
- Patients with episodic OHE are primarily cared fro in the hospital
- Treatment of the hospitalized patient with episodic OHE can be compartmentalized into induction adnmaintenance of remission

Conclusion

- Lactulose remainsthe cornerstone of treatmene for induction and maintenance of remission
- Mostpatients require maintenance medicaiton when dismissed from the hospital, and patient/caregiver education about role of those medications and appropriate dose titration for lactulose is crucial

Thank You