Neurological Manifestations of Chronic Liver Disease and Liver Cirrhosis

APASL Single Topic Conference

Hasmik Ghazinyan MD PHD
Head of Gastroenterology and Hepatology Service
Yerevan Scientific Medical Center
Armenia

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Neurological Manifestations of Chronic Liver Disease and Liver Cirrhosis

- Patients with CLD and LC are at increased risk for a wide spectrum of neurologic complications ranging from subtle neuropsychiatric symptoms such as behavioral changes and abnormality of movements to overt hepatic encephalopathy (HE).
- Cirrhosis-associated neurologic comorbidities also include depression, bepollar disorder, schizophrenia, substance abuse, and suicidal tendencies.

Neurological Manifestations of Chronic Liver Disease and LC

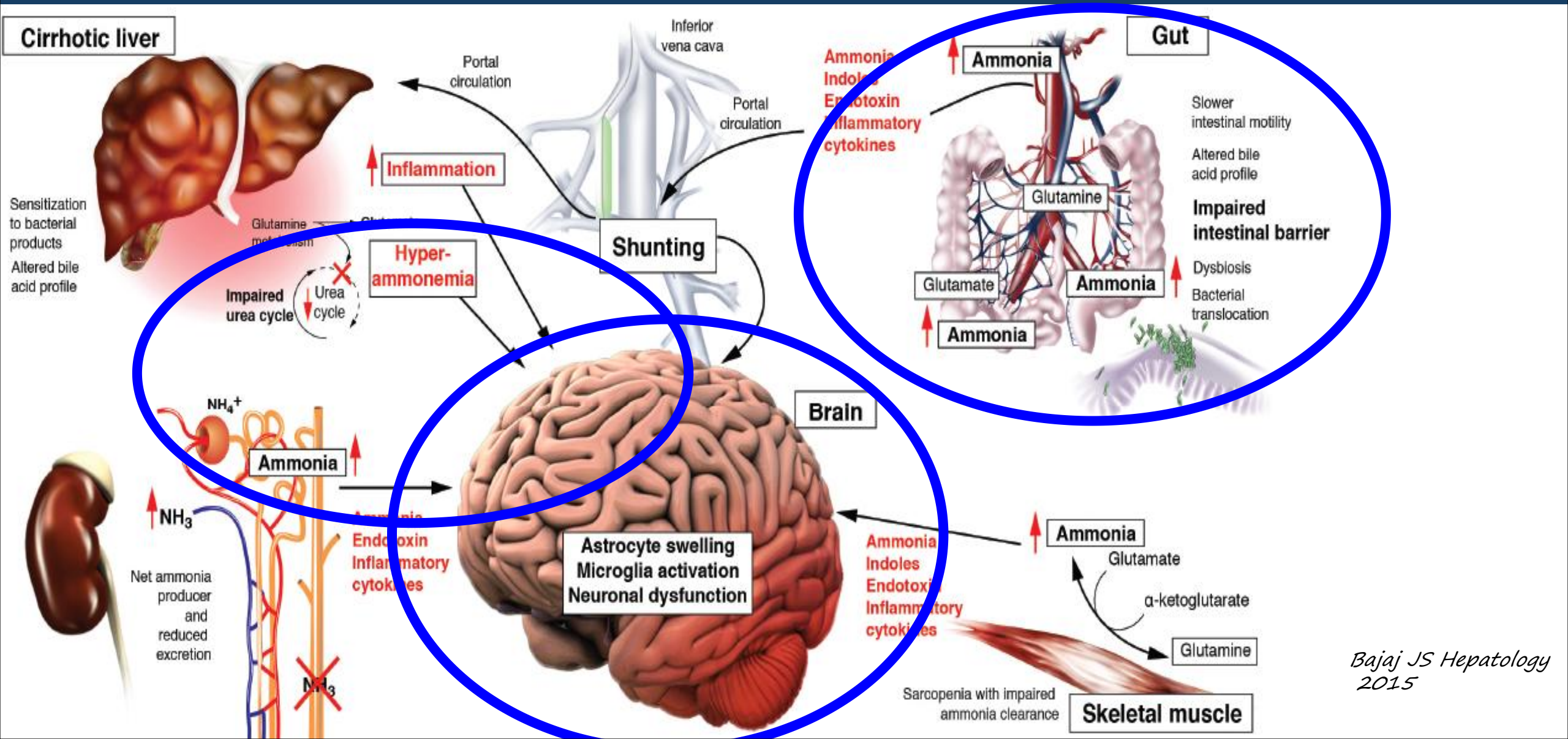
- CLD and liver cirrhosis associated neurologic complications can be divided into direct effects of cirrhosis on the nervous system
- Neurologic complications related to specific etiologies of Liver disease (alcohol, HCV, Wilson disease)

Definition of Hepatic Encephalopathy (HE)

- Hepatic encephalopathy is brain dysfunction caused by advanced liver insufficiency and/or portosystemic shunting due the build up of a variety of toxins including ammonia and exacerbated by inflammation
- The likelihood of developing HE correlates with the severity of liver disease
- It manifests as a wide spectrum of neurological/psychiatric abnormalities ranging from subclinical alterations to coma

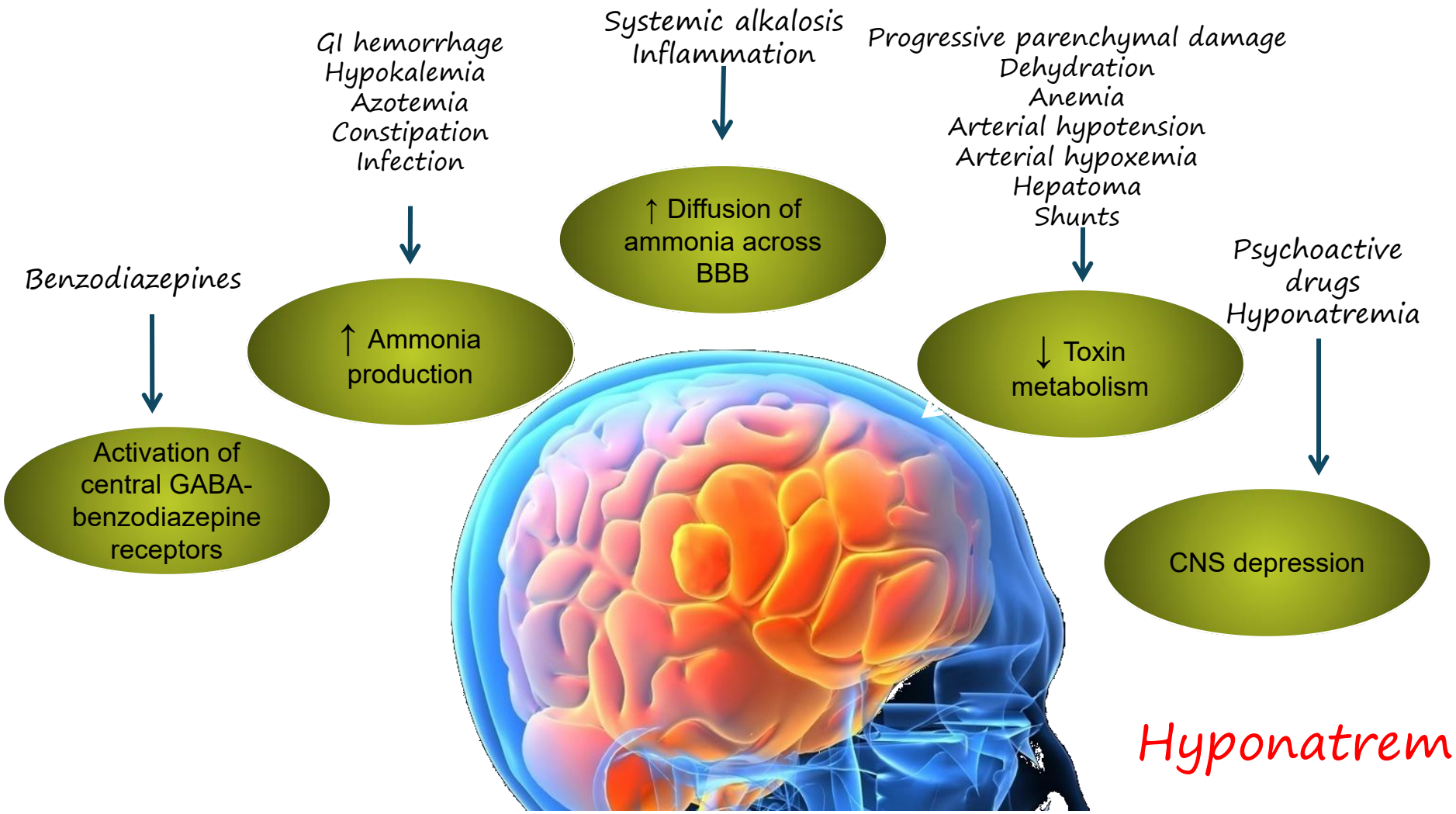
Modfied from: AASLD EASL 2014 Guidelines Hepatol/*J Hepatol*.

Pathophysiology of HE



Bajaj JS Hepatology 2015

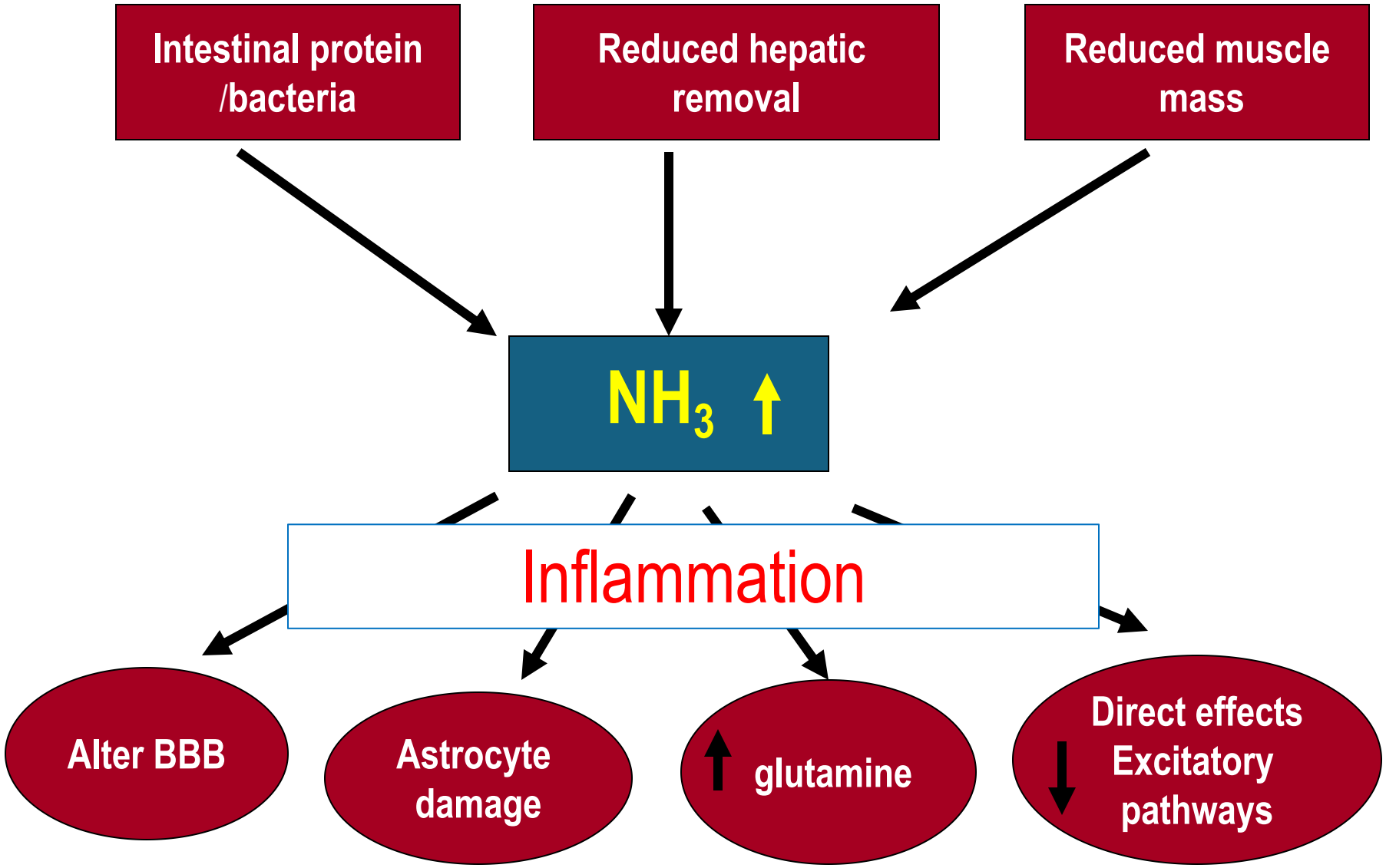
Multiple Factors Can Lead to HE Breakthrough



BBB = blood brain barrier;
CNS = central nervous system;
GABA = γ-aminobutyric acid;
GI = gastrointestinal;
HE = hepatic encephalopathy.

Riordan and Williams. N Engl J Med. 1997;337:473-479.

Sources and potential role of ammonia with inflammation

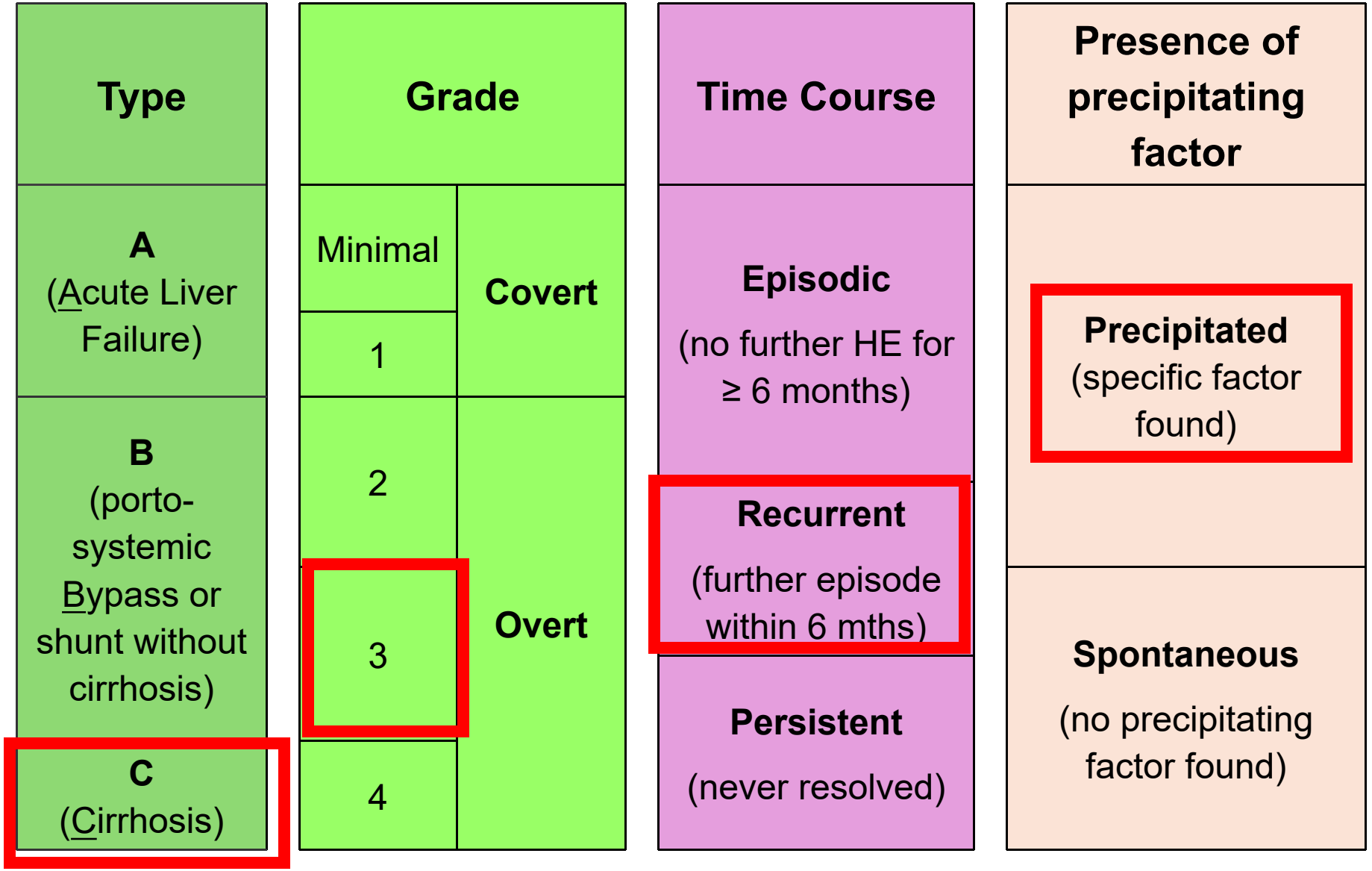


Pathogenesis

- Accumulation of neurotoxins in brain
- Impaired Astrocytes function
- Synergistic neurotoxins
- Excitatory inhibitory neurotransmitters and plasma amino acid imbalance hypothesis
- Inflammation
- Hyponatremia

1. Brusilow SW. Hyperammonemic encephalopathy. Medicine (Baltimore). May 2002;81(3):240-9

Overall Classification of HE: Four Axes



Precipitating Factors for HE

Episodic	Recurrent
– Infections	– Electrolyte disorder
– GI bleeding	– Infections
– Diuretic overdose	– Unidentified
– Electrolyte disorder	– Constipation
– Constipation	– Diuretic overdose
– Unidentified	– GI bleeding

HE = hepatic encephalopathy

AASLD EASL 2014 Guidelines Hepatol/*J Hepatol.*

What is new in HE Diagnosis and Management?

- New nomenclature and definition
- Streamlining the diagnosis for overt HE
- Potential diagnostic strategies for covert or minimal HE
- Focus on nutritional therapy for HE
- Differentiating treatment strategies regarding primary and secondary prophylaxis
- Treatments for persistent HE
- Deemphasizing ammonia testing

Key nomenclature changes

- ***Covert HE is a combination of minimal and grade 1 HE*** since grade 1 is difficult to diagnose
- ***Recurrent HE*** or >1 episode within 6 months should prompt the search for a recurrent precipitant, whose correction may prevent costly readmissions

Lactulose (4-O-beta-D-galactopyranosyl-D-fructose)

- Lactulose, a non-absorbable disaccharide, is the basis for the treatment and prevention of HE
- Proven effectiveness of lactulose:
  - Acts on the intestines and reduces the production of ammonia by bacteria
  - Acts as a laxative, preventing the absorption of ammonia by the colon

Improves QOL and survival in patients with liver cirrhosis with HE and MHE [3]

Primary prevention of SHE in patients with liver cirrhosis[4]

Secondary prevention of HE in patients with liver cirrhosis [5]

UKR1308952

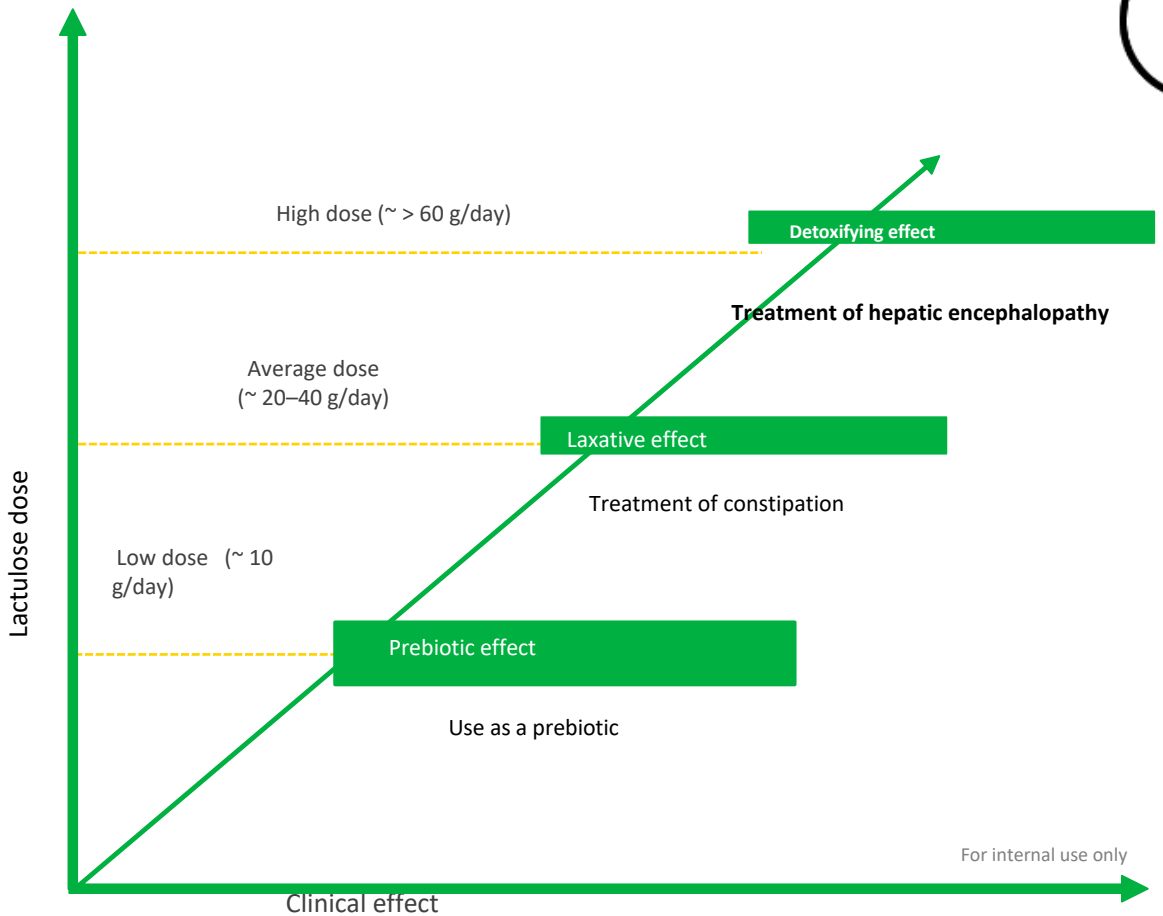
HE - hepatic encephalopathy; SHE - severe hepatic encephalopathy; QOL - quality of life; MHE - minimal hepatic encephalopathy.

1. Gupta T, Rathi S, Dhiman R. Managing encephalopathy in the outpatient setting. Euroasian J Hepato-Gastroenterol 2017;7(1):48-5; 2. Hadjihambi A, Arias N, Sheikh M, et al. Hepatic encephalopathy: a critical current review. Hepatol Int 2018;12(Suppl 1):S135–S147; 3. Xu XY, Ding HG, Li WG, et al. Chinese guidelines on management of hepatic encephalopathy in cirrhosis. World J Gastroenterol 2019; 25(36): 5403–5422; 4. Sharma P, Sharma BC, Agrawal A, Sarin SK. Primary prophylaxis of overt hepatic encephalopathy in patients with cirrhosis: An open labeled randomized controlled trial of lactulose versus no lactulose. J Gastroenterol Hepatol 2012; 27 (8): 1329-1335; 5. Agrawal A, Sharma BC, Sharma P, Sarin SK. Secondary prophylaxis of hepatic encephalopathy in cirrhosis: An open-label, randomized controlled trial of lactulose, probiotics, and no therapy. Am J Gastroenterol 2012; 107 (7): 1043–1050.

For internal use only

Dose-dependent effect of lactulose treatment

- Depending on the dose used, lactulose can act as a prebiotic, laxative, or detoxifier.[1]
- Each of these effects occurs due to the same actions of lactulose on the intestine.[2]
  - Changing intestinal microflora[2]
  - Formation of beneficial metabolites[2]
- Each effect is dose-dependent[1,2]
- Thus, the daily dose of lactulose varies depending on the type and severity of the condition for which it is to be used.[1]
- For example, the dose required to treat hepatic encephalopathy is much higher than that required to treat constipation.[1]



Adapted from Pranami *u ∂p.*(2017).

1.Pranami et al. Lactulose: a prebiotic, laxative and detoxifying agent. Drugs Ther Perspect (2017) 33:228–233. 2. Karakan T, Tuohy KM, Janssen-van Solingen G. Low-Dose Lactulose as a Prebiotic for Improved Gut Health and Enhanced Mineral Absorption. Front Nutr. 2021;8:672925. Published 2021 Jul 27. doi:10.3389/fnut.2021.672925

Dosage of Duphalac® for HE (for adults only)

- **For oral use Initial dose**

Initial dose 3-4 times a day, 30-45 ml (2-3 sachets).This dose can be adjusted until a maintenance dose is reached, which allows for soft stools to be achieved 2 to 3 times a day.

- **For rectal administration**

In severe cases (approaching coma or coma stage) Duphalac® can be administered as a retention enema (300 ml of Duphalac/700 ml® of water). The enema should be retained for 30-60 minutes, the procedure should be repeated every 4-6 hours until the medicine can be used orally.

UKR1308952

HE- Hepatic Encephalopathy

Brief description of the drug Duphalac®

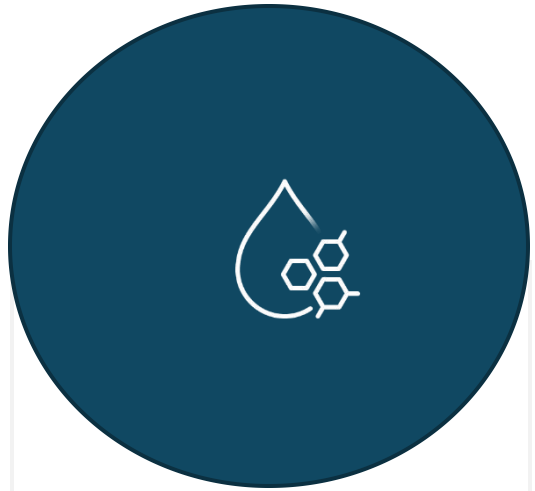
For internal use only

Resume

HE is a **common**[1] **debilitating**[2] **and rarely diagnosed**[3] complication of liver cirrhosis

If left untreated, HE is associated with **low survival** and a high risk of **recurrence**[1]

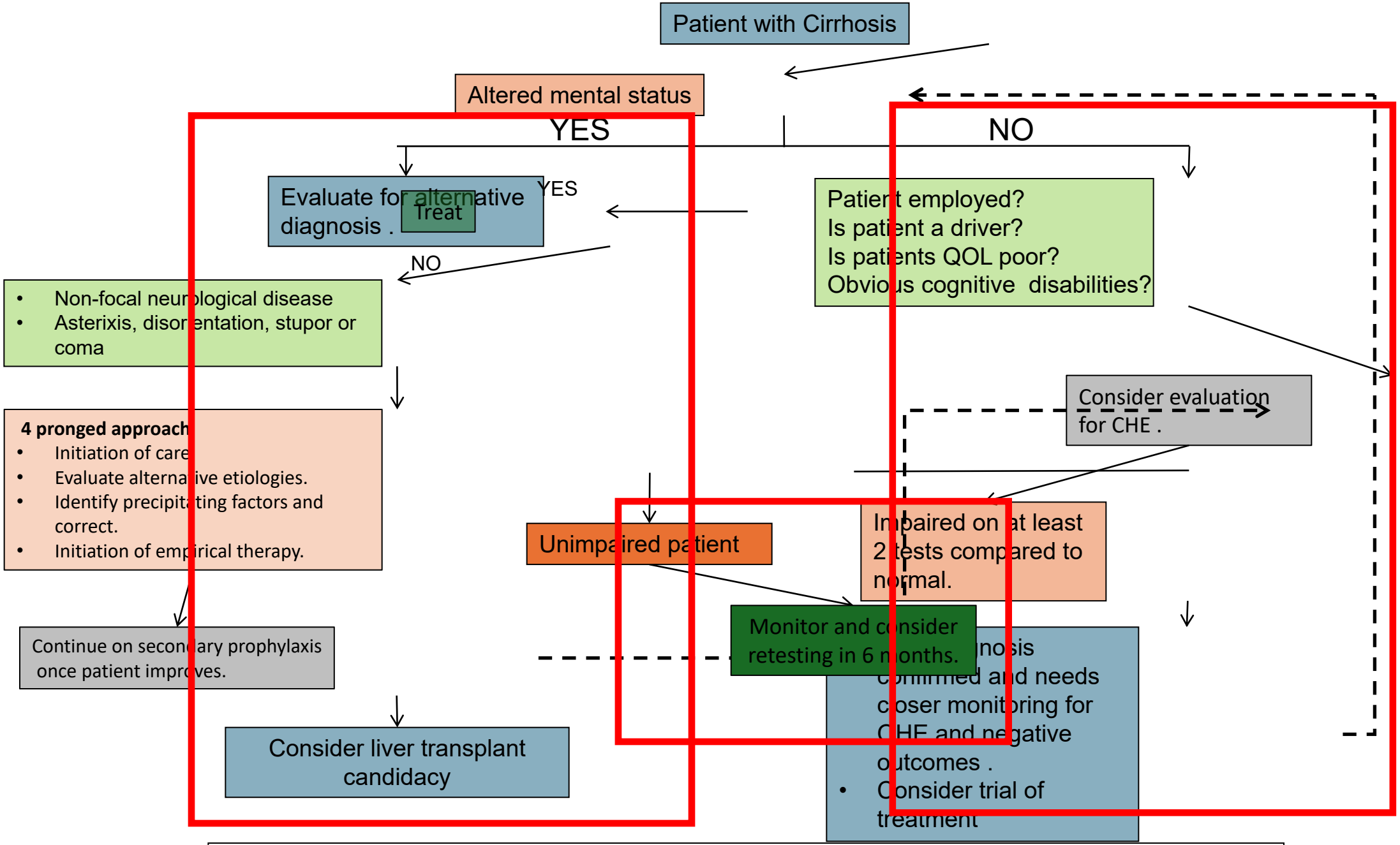
Early treatment is important, even **early stage disease** has a clinically significant impact on **QOL**[2,4]



Lactulose is recommended as first-line therapy for the treatment of HE.[5,6-8]

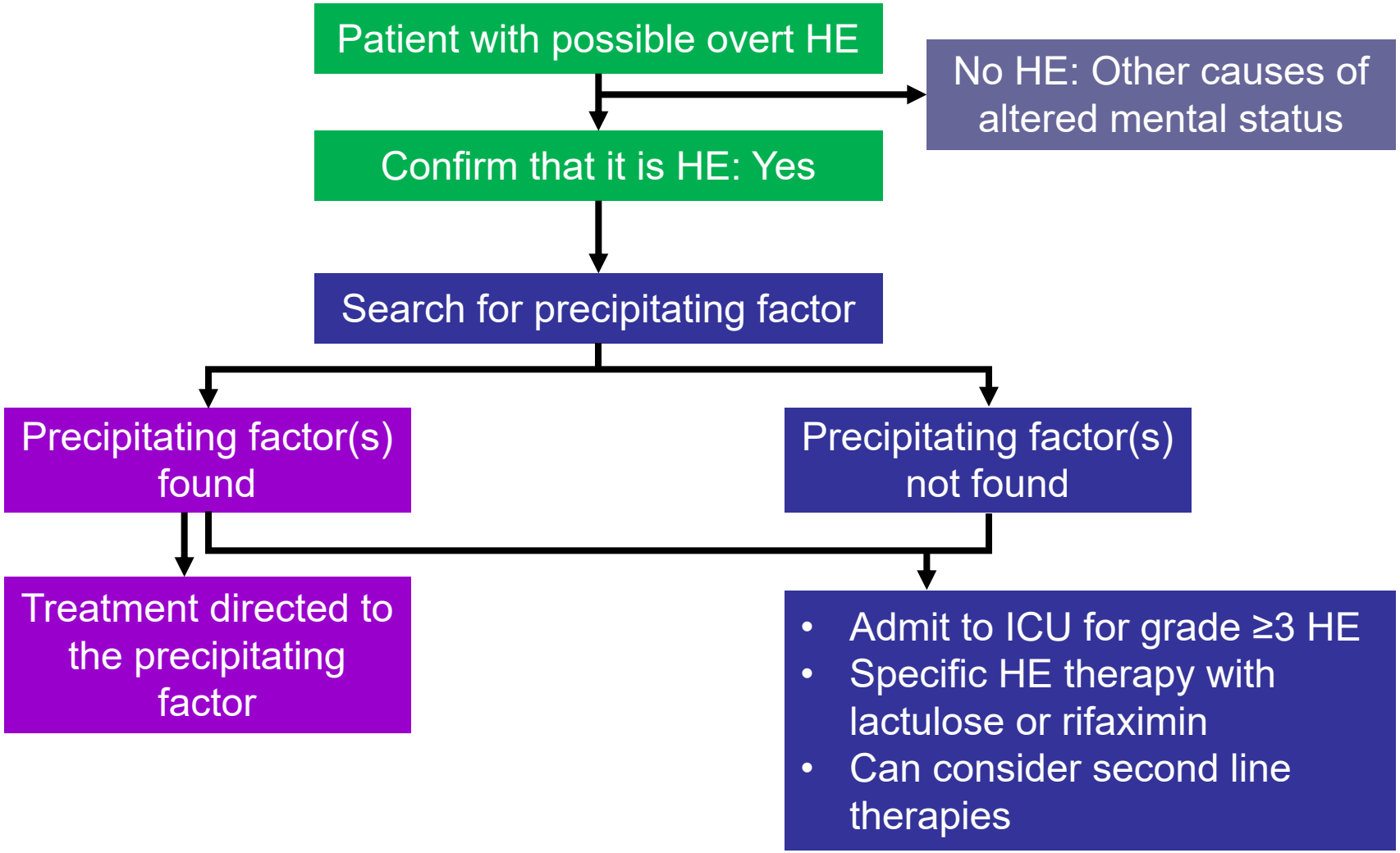
HE- Hepatic Encephalopathy; QOL- Quality of Life

1. Vilstrup H, Amodio P, Bajaj J, et al. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. *Hepatology* 2014;60(2):715–35; 2. McPherson S, Thompson A. Management of hepatic encephalopathy: beyond the acute episode. BSG 2020. Available at: https://www.bsg.org.uk/clinical-articles-list/management-of-hepatic-encephalopathy-beyond-the-acute- episode-dr-mcpherson-and-dr-thompson-provides-insight-into-the-management-of-hepatic-encephalopathy/ Accesse March 2024; 3. Stinton LM, Jayakumar S. Minimal hepatic encephalopathy. *Can J Gastroenterol* 2013;27(10):572–574 ; 4. Siddiqui AM, Farooqi J, Nasir MB, et al. Minimal hepatic encephalopathy among cirrhotics a cross sectional, clinico-epidemiological, multi-centre, study in patients of Pakistan. *SJMPS* 2019; 5(9):915–922; 5. Xu XY, Ding HG, Li WG, et al. Chinese guidelines on management of hepatic encephalopathy in cirrhosis. *World J Gastroenterol* 2019; 25(36): 5403–5422; 6. Bajaj JS, Pinkerton SC, Sanyal AJ, et al. Diagnosis and treatment of minimal hepatic encephalopathy to prevent motor vehicle accidents: A cost- effectiveness analysis. *Hepatology* 2012; 55(4):1164–1171; 7. Ming Luo, Lei Li, Chen-Zheng Lu and Wu-Kui Cao. Clinical efficacy and safety of lactulose for minimal hepatic encephalopathy: a meta-analysis. European Journal of Gastroenterology & *Hepatology* 2011; 23: 1250–1257; 8. Prasad S, Dhiman RK, Duseja A, Chawla YK, Sharma A, Agarwal R. Lactulose improves cognitive functions and health-related quality of life in patients with cirrhosis who have minimal hepatic encephalopathy. *Hepatology* 2007; 45 (3): 549–559.



Algorithm to approach OHE &CHE Patidar, Bajaj CGH 2015.

Algorithm for Inpatient HE Management



HE = hepatic encephalopathy

Bajaj JS. *Aliment Pharmacol Ther* 2010.

Cirrhosis-Related Parkinsonism

Motor dysfunction is one of the most charackteristic symptoms in patients with HE
Due to liver cirrhosis.
Acquired hepato-lenticular degeneration, also known as Parkinsonism in cirrhosis characteized by extrapyramidal symptoms including

- Progressive hypokinetic- rigid syndrome
- Progressive ataxia
- Dystonia, dysarthria, Dementia, tremor
- Choreoathetosis, spastic paraparesis (hepatic myelopathy)

and may independent of the severity of cognitive dysfunction
Estimates of the prevalence of Parkinsonism in cirrhosis have been reported as high as 21%
The possible causse of cirrhosis-related parkinsonism is pre-and post-synaptic alteration of striatal
dopaminergic neurotransmission duo to manganese deposition in basal ganglia of affected patients
Therapeutic options are limited, ammonia-lowering strategies are without substantial benefit

Neurological Manifestations Secondary to Excessive Alcohol Consuption

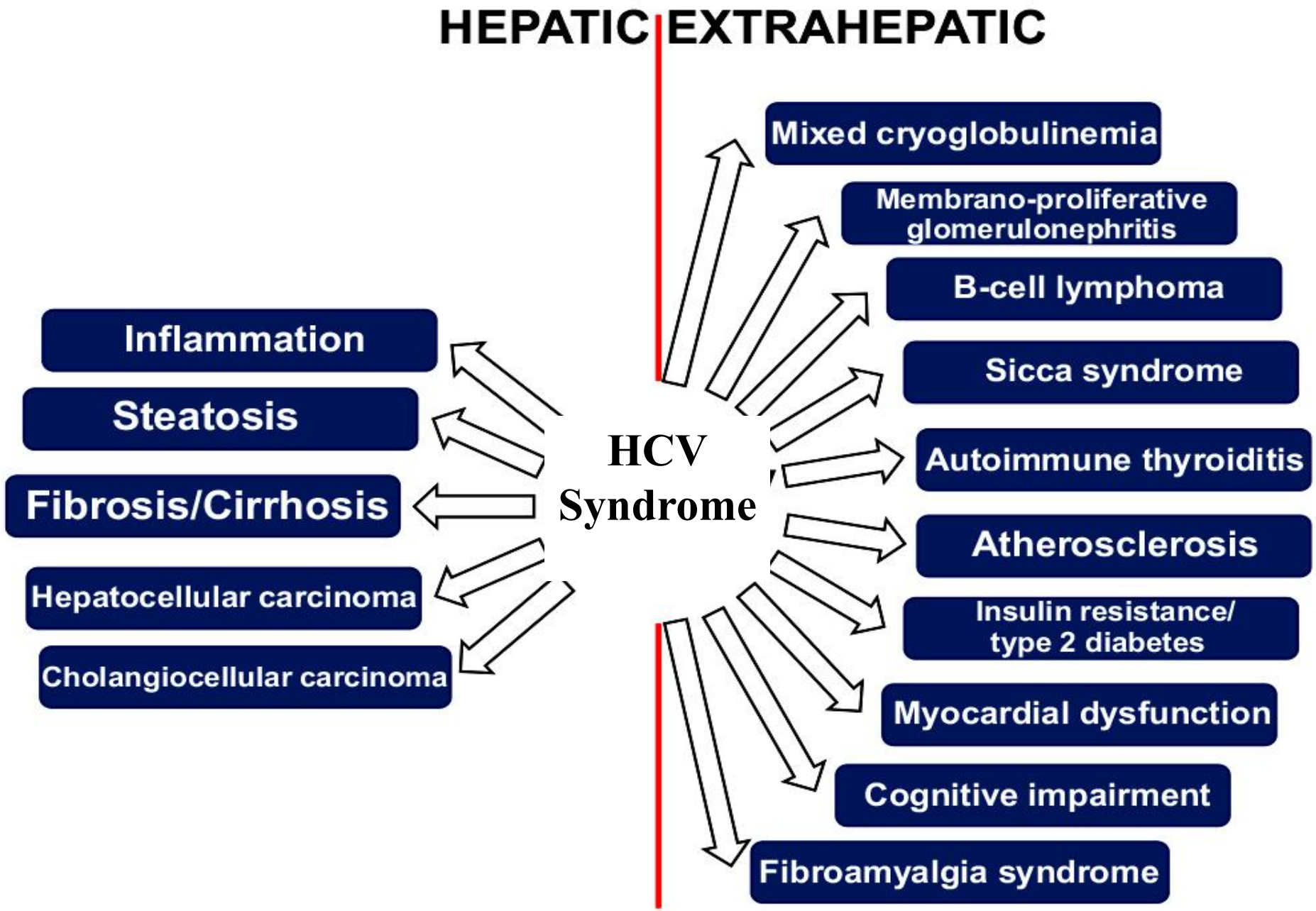
Central nervous system	Peripheral nervous system
Acute	
Acute intoxication	Acute alcoholic neuropathy
Withdrawal syndrome and delirium tremens	Alcohol-related compressive neuropathy
Wernicke's encephalopathy	
Chronic	
Korsakoff syndrome	Chronic alcoholic neuropathy
Alcohol-related dementia	Disulfiram neuropathy
Marchiafava–Bignami disease	
Cerebellar degeneration	

Wernicke Encephalopathy

- WE is neurologic emergency that occurs secondary to thiamine deficiency in chronic alcoholics with a reported incidence Of 0,8%-2% (based on autopsy series)
- Syndrome is characterized by a clinical triad of
  - Global Confusion
  - Ophthalmoplegia
  - Ataxia
- All the symptoms may not always be present
- Patient may clinically manifest nonspecific mental status changes on MRI, typical manifestations include symmetrical areas of creased T2

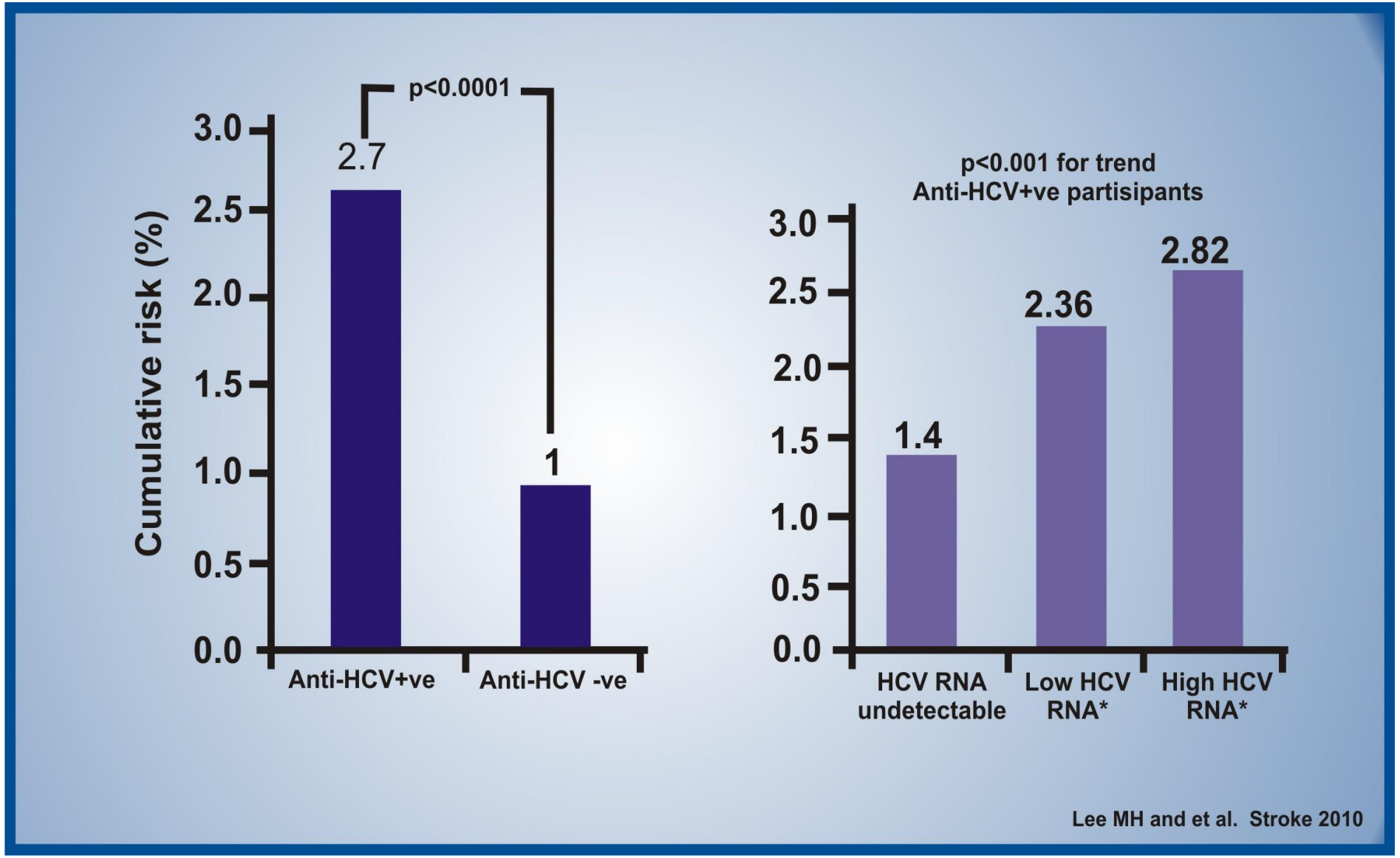
Neurologic Complications Related to Wilson Disease

- WD or Hepatolenticular degeneration is an autosomal recessive , inborn defect in ceruloplasmin metabolism characterized by abnormal accumulation of copper in various tissues , particularly in the liver and the brain
- Clinically, the patients (typically 5-35 years of age) present with
  -Weakening of hands
  -Dysarthria
  -Dystonia
- Pseudoparkinsonian and cerebellar symptoms with or without nonspecific psciathric symptoms

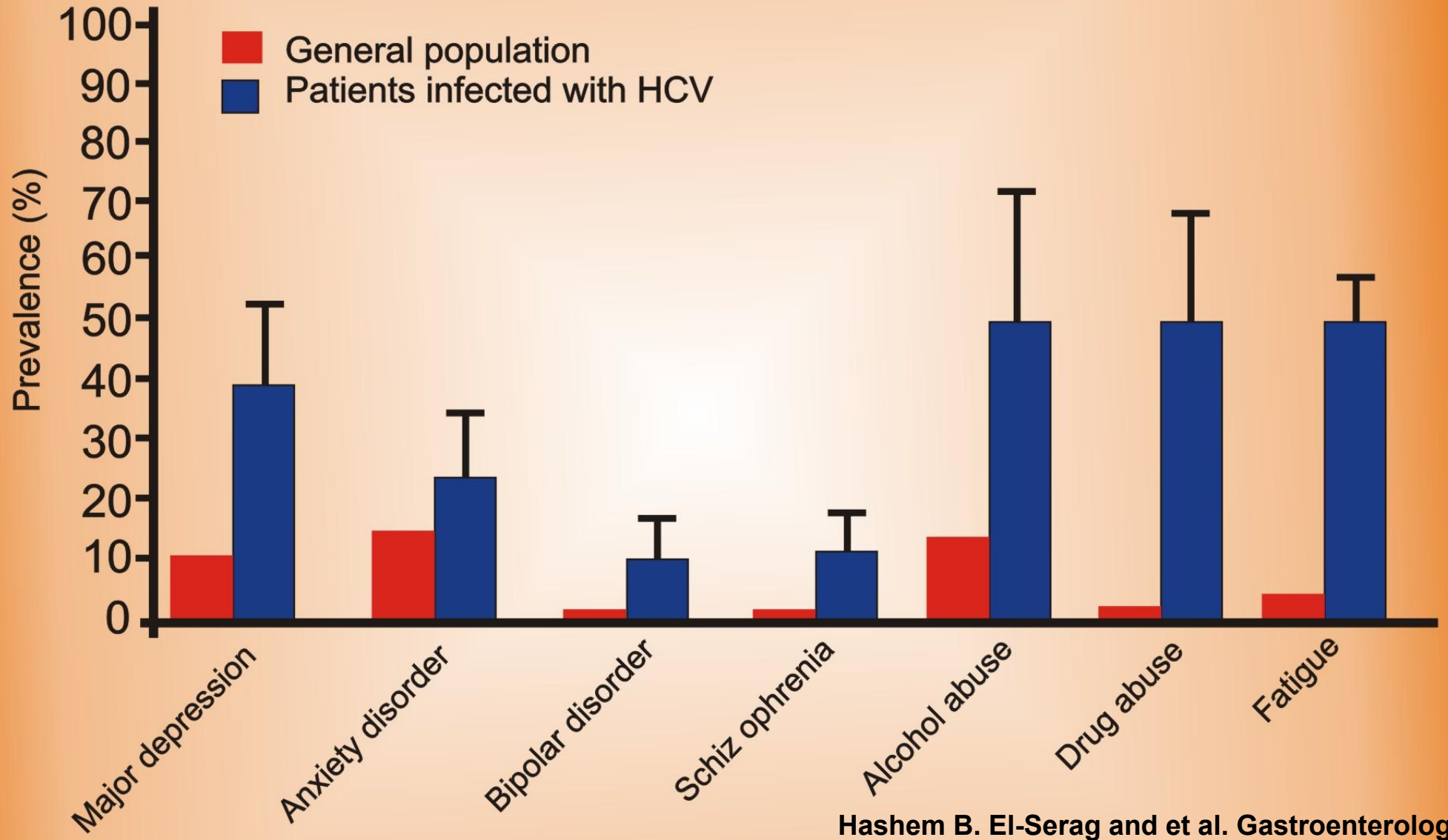


Hepatic and extrahepatic disorders associated with HCV infection.

Cerebrovascular Deaths and HCV Infection

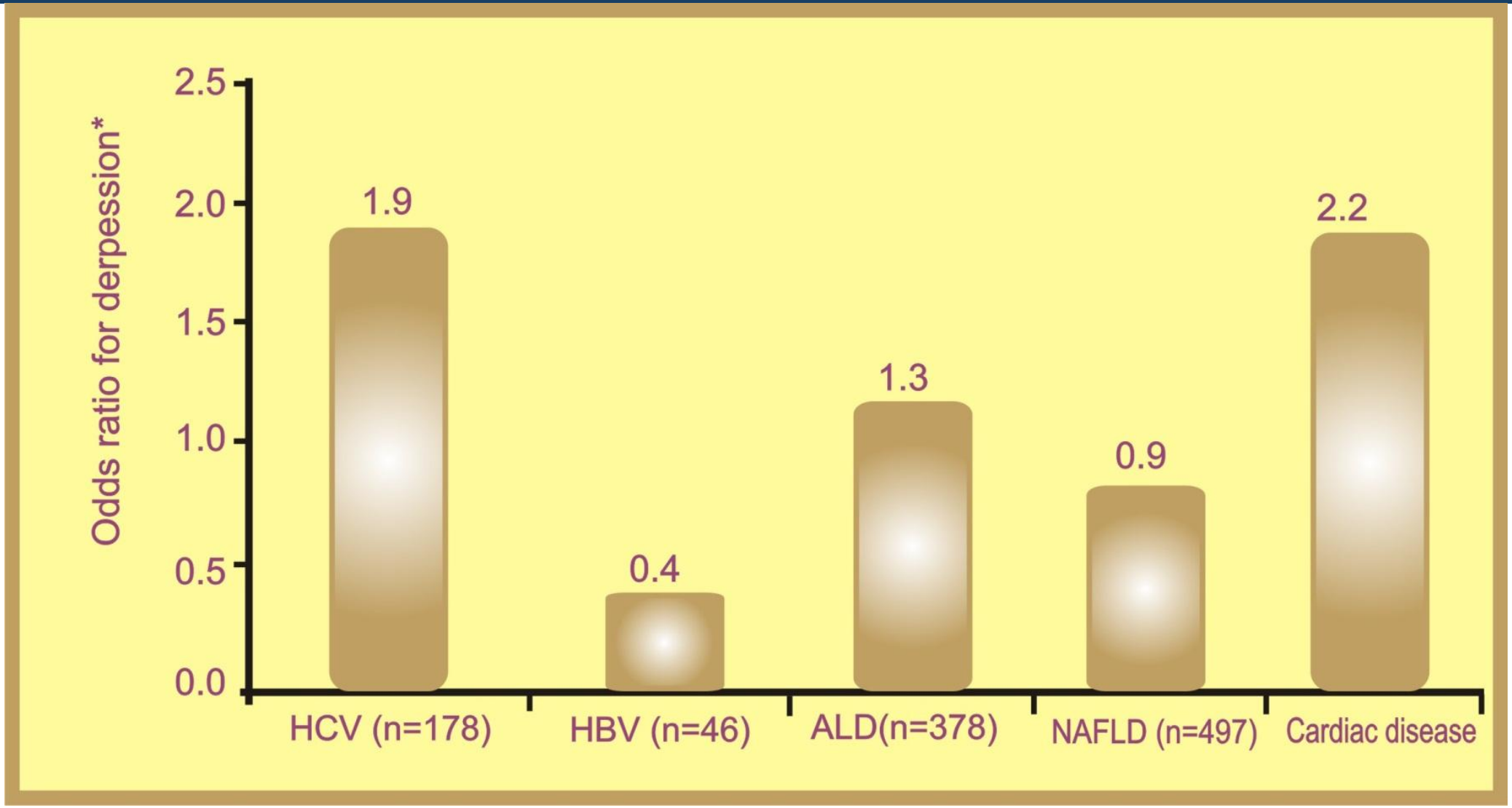


Increased Prevalence of Psychiatric Comorbidity in HCV – Infected Populations



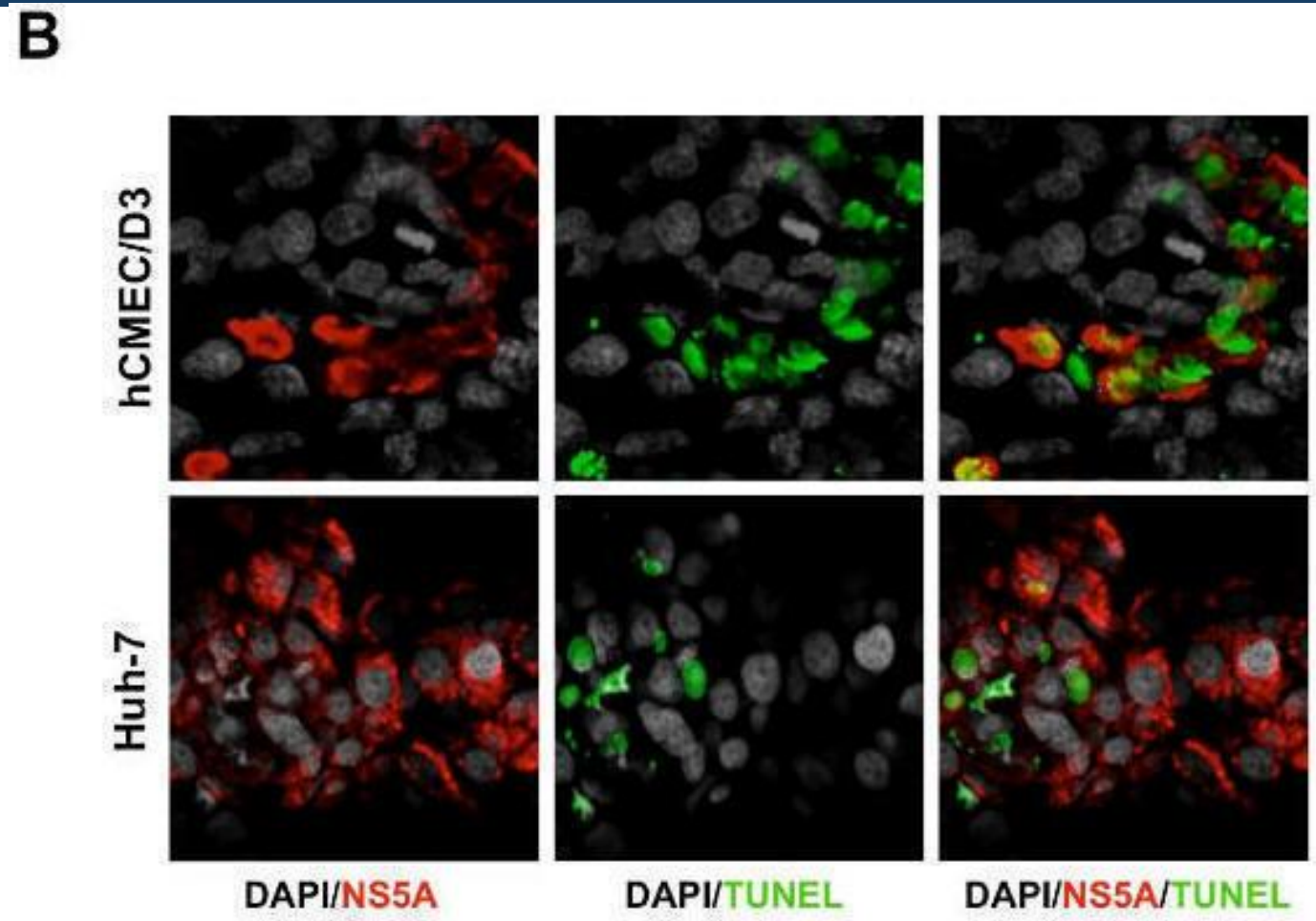
Hashem B. El-Serag and et al. Gastroenterology 2002

HCV is Strongly Associated with Depression



Forton D.M. and et al. Hepatology 2002

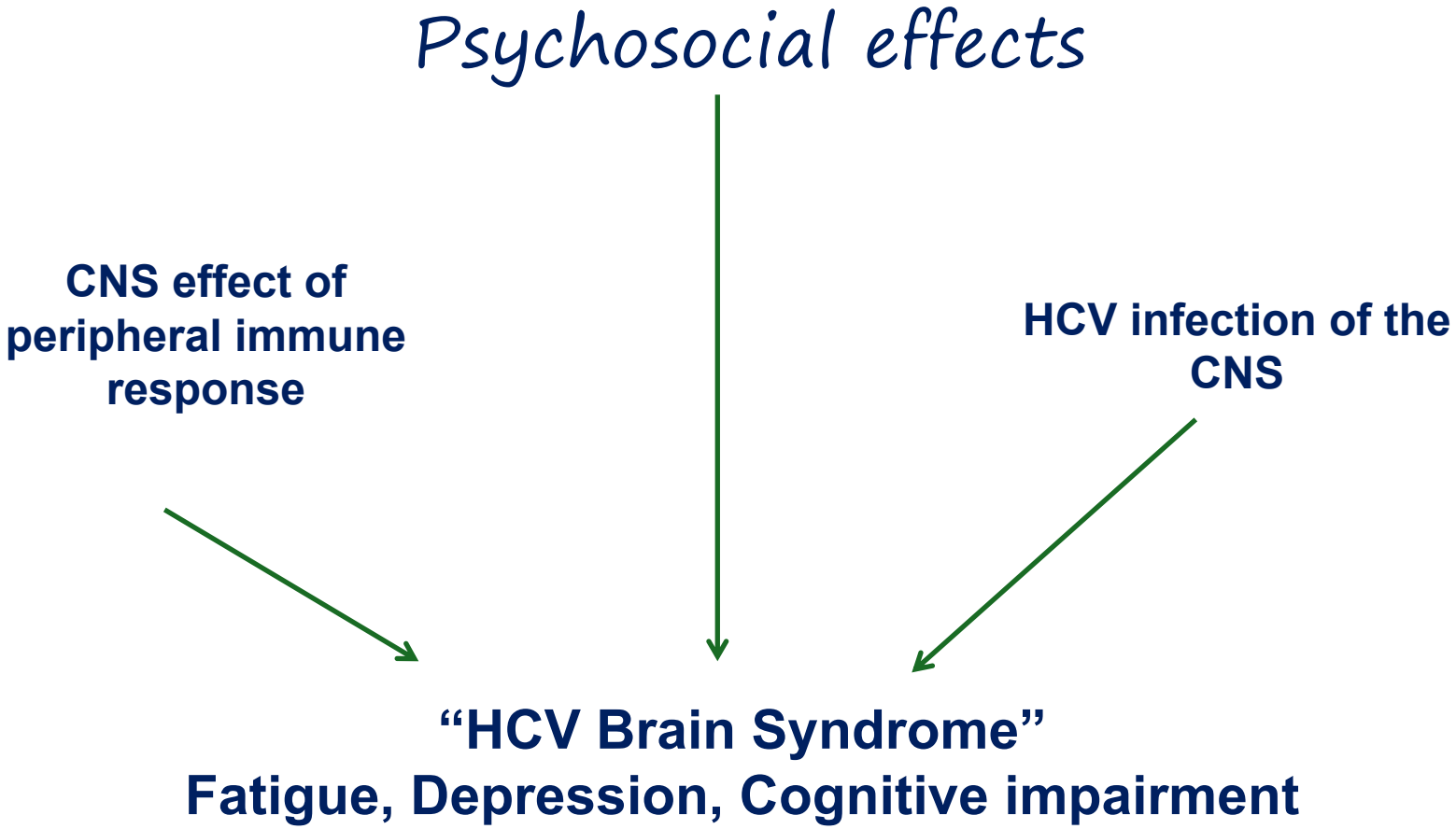
HCV Infects the Endothelial Cells of the Blood-Brain Barrier



Two brain microvascular endothelial cell lines, hCMEC/D3 and HBMEC, express all the HCV entry factors

Fletcher NF and et al Gastroentology 2012

HCV Brain Syndrome: Mechanisms



Conclusion

- CLD and Liver cirrhosis can be associated with a diverse range of neurologic manifestations, both central and peripheral, ranging in severity from subclinical changes to neurocritical conditions
- HE is the most frequently encountered and widely recognized whereas

many other conditions are rare associations, where the brain and liver are damaged by the same or similar mechanisms, Wilson`s disease being one of the best known

- Ammonia and inflammation form the patho-physiological basis for HE worsened by hyponatremia

- Treatment of overt HE as an inpatient and outpatient is largely dependent on gut milieu modification, with lactulose as the first line

THANK YOU
FOR YOUR ATTENTION