HEPATIC ENCEPHALOPATHY
Are we doing any better?

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Practice guidelines

Hepatic encephalopathy

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HEPATIC ENCEPHALOPATHY

- DEFINITION
- PATHOGENESIS
- CLINICAL FEATURES
- TREATMENT

HEPATIC ENCEPHALOPATHY

- Spectrum of neuropsychiatric abnormalities: impairment of sleep-wake cycle, cognition, memory, consciousness, motor-sensory function.
- Patients with liver dysfunction.
- After exclusion of metabolic, infectious, intravascular or space-occupying lesion.

SUBTYPES OF HEPATIC ENCEPHALOPATHY

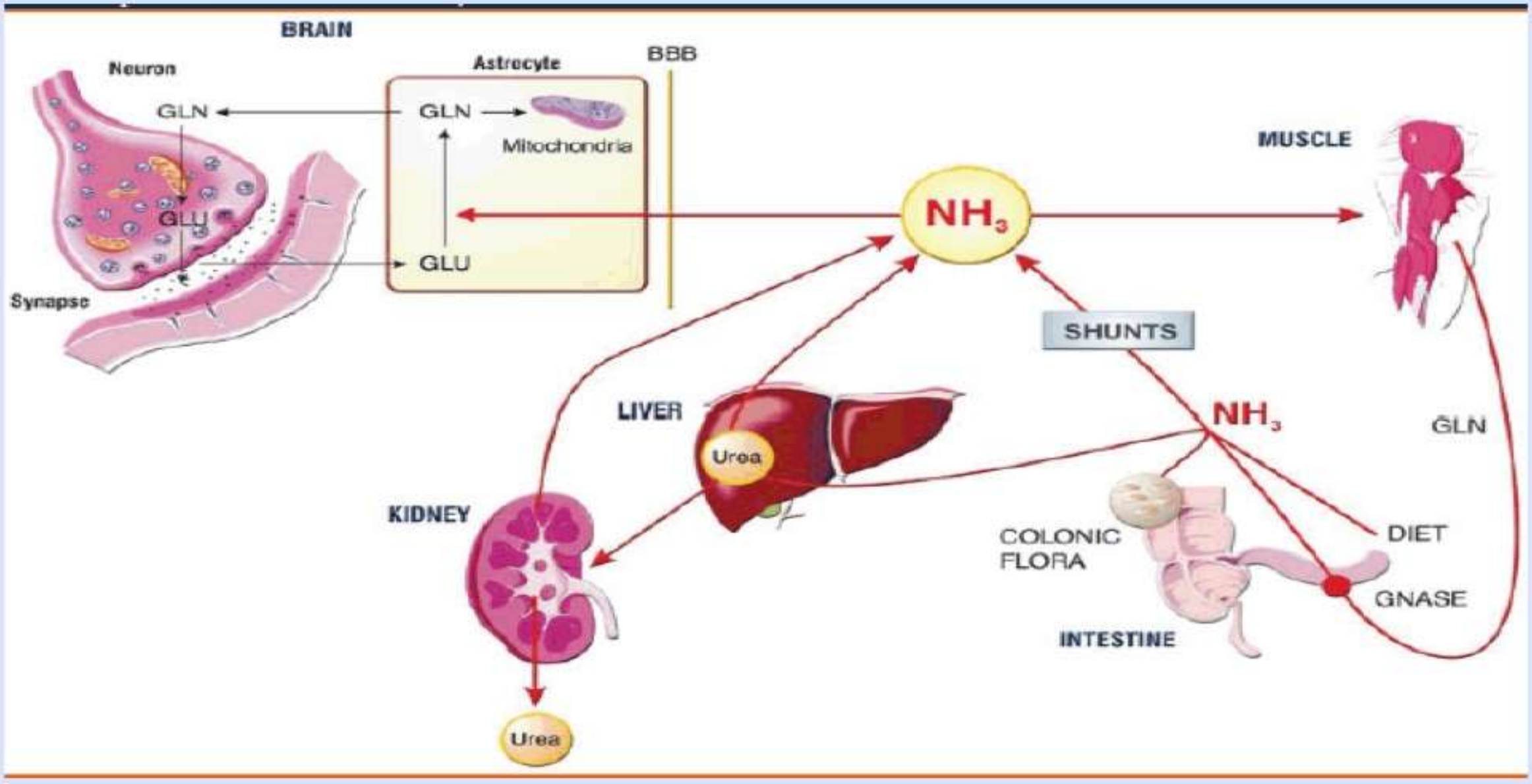
Table 1

Type	Description	Subcategory	Subdivision
A	Encephalopathy associated with acute liver failure	—	—
B	Encephalopathy associated with portal-systemic bypass and no intrinsic hepatocellular disease	—	—
C	Encephalopathy associated with cirrhosis and portal hypertension or portal-systemic shunts	Episodic	Precipitated Spontaneous Recurrent
		Persistent	Mild Severe Treatment-dependent
		Minimal	

PATHOGENESIS

- Ammonia Hypothesis
- GABA Hypothesis
- Neurotoxins
- Acetylcholinesterase
- Hyponatremia
- Astrocyte swelling and dysfunction

AMMONIA HYPOTHESIS



- NH3
  - Produced by degradation of AA amines in the GIT
  - Enterocyte convert gluatamine to glutamate and NH3 by glutaminase
- NH3 detoxified by the liver by conversion to urea Kreb's cycle

- Cirrhosis: NH3 is due to functioning of hepatocytes
  Portosystemic shunting divert NH3 to the systemic circulation

- Skeletal muscle contains glutamine synthetase which helps consume NH3 by converting glutamate to glutamine
  Temporary means of detoxifying NH3

- The kidneys can both produce ammonia thru glutamine and excrete ammonia as NH4 thru glutamine synthetase.
  - In Acidosis: NH4 is released in the urine.
  - In Alkalosis: decreased loss of NH4 in the urine.

GABA HYPOTHESIS

- Gamma Butyric Acid (GABA)
  - Neuroinhibitory substance produced in the GIT
  - GABA receptor complex contains binding sites for GABA, Benzodiazepines.

    - permit influx of chloride ions into the postsynaptic neuron generating inhibitory postsynaptic potential

NEUROTOXINS ACCUMULATION HYPOTHESIS

- Ammonia, Manganese, False transmitters, Short chain fatty acids
- ↑production of peripheral type benzodiazepine receptor (PTBR) or 18-kda translocator protein (TSPO)
- Stimulates conversion of cholesterol to pregnenolone to neurosteroids
- Binds to gamma receptor complex increasing inhibitory neurotransmissions

ACETYLCHOLINESTERAS E HYPOTHESIS

- Acetylcholinesterase results to Acetylcholine which is a neurotransmitter at the neuromuscular junction

ASTROCYTE SWELLING and DYSFUNCTION

- Astrocyte
  - Key role in the regulation of blood brain barrier
  - Maintain electrolyte homeostasis
  - Provide nutrients and neurotransmitter precursors to neurons

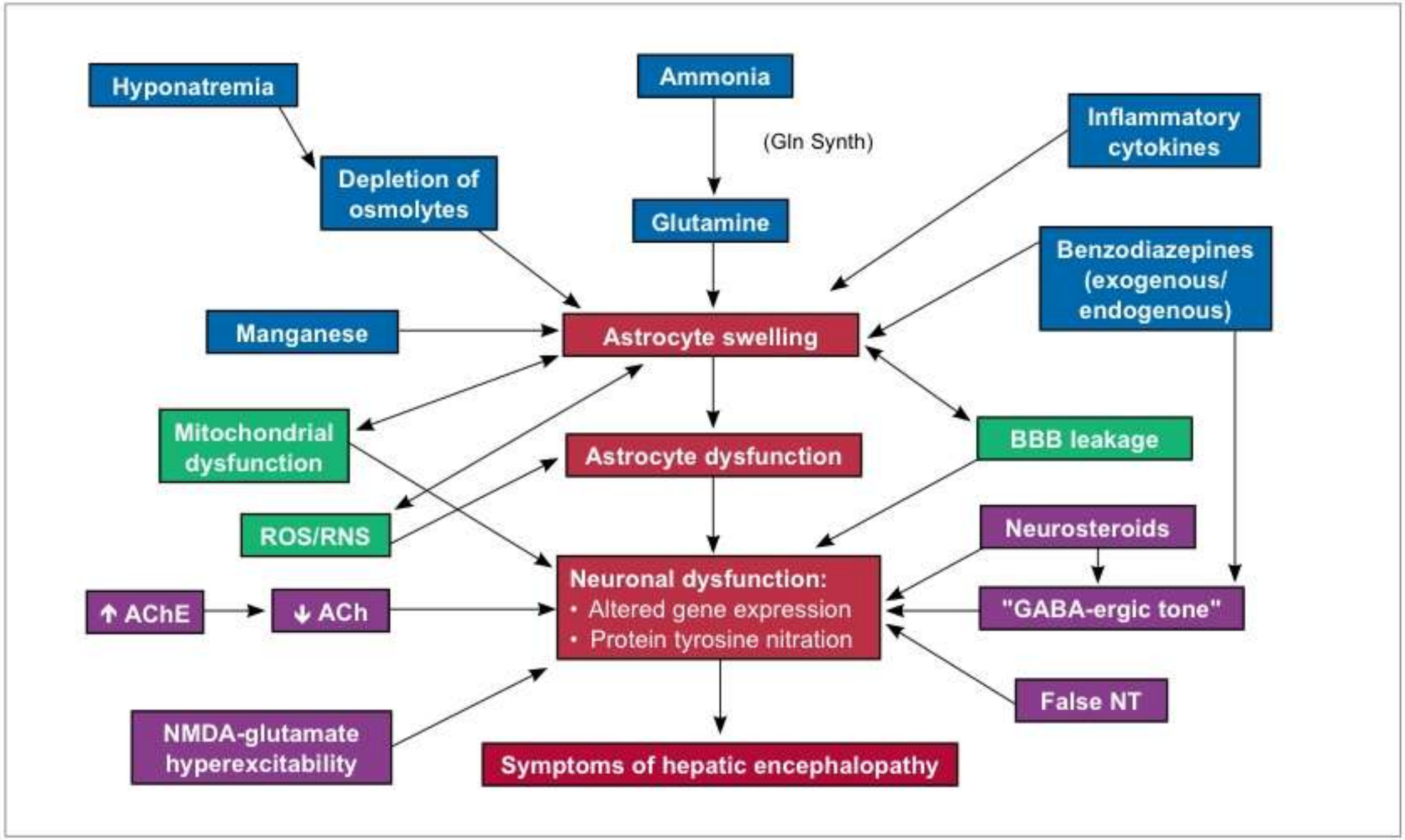
ALZHEIMER TYPE 2 ASTROCYTOSIS

- Large pale nucleus, prominent nucleolus
- Leads to neuronal edema → Neuronal dysfunction

HYPONATREMIA - "Second Hit"

- Causes depletion of astrocyte osmolytes
- Cells cannot compensate well during period of hyperammonemia or inflammation ~~—→~~ Astrocyte swelling, cerebral edema, oxidative and nitrosative and astrocyte dysfunction.

PATHOPHYSIOLOGY of HEPATIC ENCEPHALOPATHY



CLINICAL FEATURES: West- Haven Criteria

Stage	Consciousness	Intellect and behavior	Neurological findings
0	Normal	Normal	Normal examination; if impaired psychomotor testing, consider MHE
1	Mild lack of awareness	Shortened attention span	Impaired addition or subtraction Mild asterixis or tremor
2	Lethargic	Disoriented; inappropriate behaviour	Obvious asterixis; slurred speech
3	Somnolent but arousable	Gross disorientation; bizarre behaviour	Muscular rigidity and clonus; hyperreflexia
4	Coma	Coma	Decerebrate posturing

CLINICAL FEATURES

Stage 0-1	Covert hepatic encephalopathy (Minimal hepatic encephalopathy)
Stage 2-4	Overt hepatic encephalopathy

COVERT HEPATIC ENCEPHALOPATHY

- Low level cognitive dysfunction in 70% of patients with cirrhosis
- Decrease attention and executive dysfunction
- Depressed psychomotor speed and visuomotor activity
- Delayed choice reactive time
- Impaired fitness to drive

DIAGNOSIS OF COVERT HEPATIC ENCEPHALOPATHY

Methods	Advantages	Limitations
Formal neuropsychological assessment	• Established and well-recognized clinical significance	• Expensive • Time consuming
Short neuropsychological batteries	• Easy to administer in office setting • Inexpensive • Rapid results • High sensitivity for discerning CHE from other encephalopathies	• Test often copyrighted • Limited access
Computerized tests (CFF, ICT, reaction times, etc)	• Easy to apply	• Limited data on diagnostic significance • Require standardization
Neurophysiologic tests (EEG, spectral EEG, P300)	• Allows for objective repeat testing	• Equipment • Limited data on diagnostic significance

Table 1. Neuropsychological and neurophysiologic tests that have been used in the diagnosis of CHE. CFF, critical flicker frequency; ICT, inhibitory control test; EEG, electorencephalography; P300, auditory event-related evoked potential.[2]

NEW TESTS FOR DIAGNOSIS OF CHE

A.Inhibitory Control Test (ICT)

- Sensitivity 87%, specificity 77%
- http//www.hecme.tv. (HEcme TV Website)

B. CNS Vital Signs (CNSVS)

- Sensitivity 85%, specificity 64%
- http://www.cnsvs.com (CNSVS Website)
- Presented at DDW 2012

TREATMENT STRATEGIES for HEPATIC ENCEPHALOPATHY

1. Management of precipitating factors.
2. Reduction of NH3 and other toxins.
3. Modulation of fecal flora.
4. Modulation of neurotransmission.
5. Correction of nutritional deficiencies.
6. Reduction of inflammation.
7. Molecular adsorbent recirculating system (MARS Gambro) - liver dialysis

PRECIPITATING FACTORS

Precipitating Factor	Frequency per 200 Admissions	Percentage
Lactulose nonadherence	78	39
Constipation	44	22
Opioids and benzodiazepines	34	17
Dehydration	32	16
Infections	30	15
Acute renal failure	17	8.5
Hypokalemia (potassium <3.5)	14	7
Gastrointestinal bleeding	12	6
Large volume paracentesis	4	2
TIPS	4	2
Hyponatremia (sodium <130)	4	2
High protein diet	2	1
Unknown precipitants	18	9

Table 2: Factors identified as precipitants of OHE in 109 cirrhotic patients who had 200 hospital admissions with a primary diagnosis of OHE. TIPS, transjugular intrahepatic portosystemic shunt.[18]

MANAGEMENT OF PRECIPITATING FACTORS

- Hepatic encephalopathy is usually precipitated by an event.
- Careful history and physical examination are required to identify less dramatic and contributing cause.

REDUCTION of NH3 and OTHER TOXINS

1. Non-absorbable dissacharide (Lactulose)

- Mechanism of action
  - Cathartic
  - Acidification of gut lumen favors conversion of NH3 to nH4 ion
  - Reduction of urease producing bacteria (Prebiotic)

- Cirrhosis
  - 30-45% Overt HE (Annual risk 20%)
  - 60-80% Covert HE

EFFECTS of LACTULOSE vs NO TREATMENT in CIRRHOTICS WITHOUT ANY EPISODE OF OVERT HE

Number of Patients	Overt HE	Percentage
55 with Lactulose	6	11
50 w/o Lactulose	15	30

- 66% of the covert hepatic encephalopathy in the Lactulose group showed improvement.
- Followed monthly for 12 months

Agrawal et al. Primary prophylaxis of encephalopathy in patients with cirrhosis: An open-labeled randomized controlled trial of lactulose vs no lactulose. J. Hepatol 2012.

SECONDARY PROPHYLACTIC THERAPY FOR PREVENTION OF OHE IN CIRRHOTIC PATIENTS WHO HAVE EXPERIENCED AN OHE EPISODE

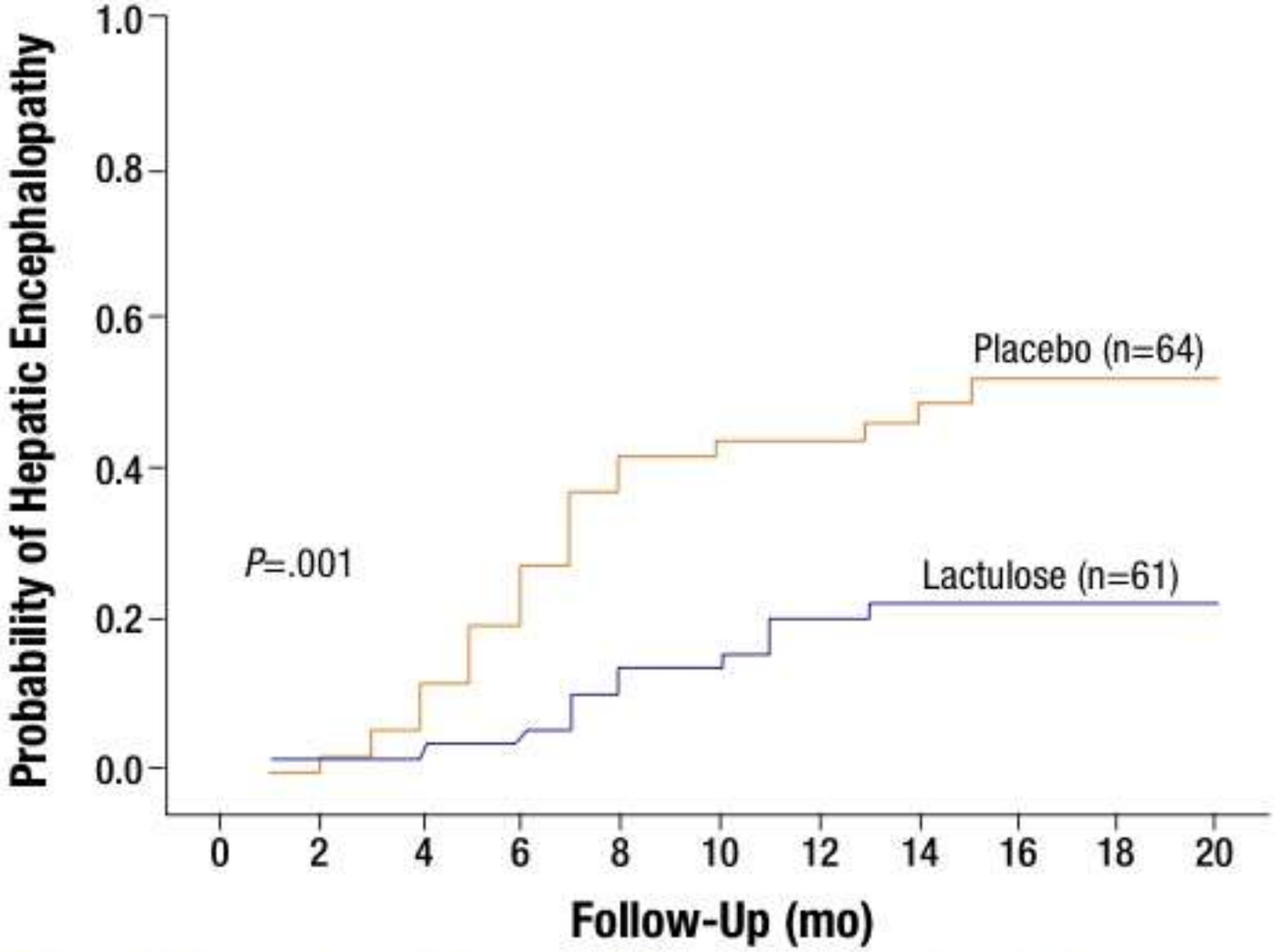


Figure 1: Probability of developing recurrent OHE in patients receiving prophylactic therapy with lactulose following an episode of OHE compared with patients receiving placebo.[7]

REDUCTION of NH3 and OTHER TOXINS

2. NH3 Scavengers

a. L-ornithine L-aspartate (LOLA)

- substrate for glutamate transaminase which results in increase glutamate levels. Glutamate with NH3 produce glutamine in the presence of glutamine synthetase.

b. L-ornithine, Phenylacetate (LOPA)

- increase supply of ornithine to the urea cycle

c. Sodium benzoate, Sodium phenylbutyrate, Sodium phenylacetate, Glycerol phenylbutyrate

- Sodium benzoate interacts with glycine to form hippurate excretion of hippurate leading to NH_3 loss.

  - limited by risk of sodium overload

- Sodium phenylbutyrate is converted to phenylacetate reacts with glutamine to form phenylacetylglutamine excreted in urine with loss of NH_3 ions

- Sodium phenylbutyrate (Buphenyl)
- IV Sodium phenylacetate (Ammonul)
- Glycerol phenylbutyrate (Ravicti)

- FDA approved for treatment of hyperammonemia associated with urea cycle disorders

d. Zinc

- Increase activity of ornithine transcarbamylase, an enzyme in urea cycle
- Zinc sulfate or Zinc acetate 600 mg/day

e. L-carnitine

- Improved HE symptoms in several studies
- Decrease brain NH3 uptake

f. AST-120 (OCERA)

- Spherical carbon adsorbent
- Adsorbs small molecules not only NH3, but also Liposaccharides, and Cytokines.
- Pilot study: Efficacy equivalent with Lactulose
- Large study recently completed.

MODULATION of FECAL FLORA

1. ANTIBIOTICS

- decrease concentration of ammoniagenic bacteria

A. Neomycin, Metronidazole, Paromomycin, Vancomycin

- limitation in safety and resistance (ototoxicity, nephrotoxicity, neurotoxicity)

B. Rifaximin

- poorly absorbed relative of Rifamycin
- broad antibacterial activity for aerobes and anaerobes
- approved by US FDA for hepatic encephalopathy

SECONDARY PROPHYLACTIC THERAPY FOR PATIENT IN REMISSION FOR OVERT HEPATIC ENCEPHALOPATHY

Randomized double blind study: Rifaximin 555 mg BID vs Placebo

	Number of Patients	Number of Patients Who Developed HE	Percentage of Patients Who Developed HE
Rifaximin	140	31	22.1%
Placebo	159	73	45.9%

2. **Prebiotics** (Lactulose, Fermentable fibers)

Probiotics (Bifidobacteria, Lactobacilli)

- Reduce urease-producing species
- Improved overall liver function
- Reduced translocation of bacteria (Endotoxemia) by ameliorating hyperdynamic circulation

3. **Acarbose** (Alpha-Glucosidase Inhibitor)

- Reduce glucose absorption, promotes primarily saccharolytic bacteria reducing NH3 generation.
- Double-blind randomized trial among DM patients with mild HE showed improvement in number connection test and HE grading.

MODULATIONS of NEUROTRANSMISSION

- Drugs Used to Target Altered Neurotransmission

Flumazenil	Used when benzodiazepine is trigger factor
Naloxone	
Bromocriptine	
Levodopa	
Rivastigmine	Acetylcholinesterase inhibitor pilot study showed some benefit

CORRECTION of NUTRITIONAL DEFICIENCIES

- Factors Involved in Poor Nutrition
  - Poor Dietary Absorption (Fat soluble vitamins)
  - Poor Intake (Weakness, ascites)
  - Baseline Hypercatabolic State
  - Zinc Deficiency
  - Skeletal Muscle Depletion

CORRECTION of NUTRITIONAL DEFICIENCIES

- Daily Protein Intake: 1.0-1.5 g/kg/day depending on the degree of hepatic decompensation
  - ESPEN Guidelines 1997
- Branched-chain Amino Acids
  - Prevents synthesis of false neurotransmitters
  - Corrects Fischer's ratio balance between AAA and BCAA
  - Reduces catabolism and muscle breakdown

- Zinc Supplementation
  - Zinc - cofactor in the urea cycle
- L-ornithine L-aspartate/L-ornithine phenylacetate
- L-carnitine or its acetylated form

REDUCTION of INFLAMMATION

- Cirrhotics are in a proinflammatory state
  - Increase levels of endotoxin, tumor necrosis factor, cytokines
- Antibiotics improved hyperdynamic circulation of cirrhosis; reduced the risk of hepatorenal syndrome

POTENTIAL DRUGS with ANTI-INFLAMMATORY ROLE

- **Pentoxyfylline**: anti-TNF alpha activity reduce complication of cirrhosis and hepatic encephalopathy
- **AST-120:** bind small molecule in the gut, TNF lipopolysaccharide and endotoxin

REVERSIBILITY of HEPATIC ENCEPHALOPATHY

" Those who recovered from an episode of overt hepatic encephalopathy appeared to improve with drug therapy with no residual neurocognitive impairment"

- This statement has been challenged.

- ***Sotil et al. 2009***

39 Patients with Liver transplantation

25 Patients who have HE before liver transplant performed worse on psychomotor test

14 Patients with no history of HE

- ***Garcia-Martinez et al. 2011***

- 52 Patients with liver transplant

  - Patients with history of HE prior to liver transplant performed worse in the global cognition function test; brain volume (MRI) was smaller.

- Episodes of hepatic encephalopathy may lead to neurologic injury that is not reversible.

- Aggressive prophylactic therapy to prevent overt hepatic encephalopathy in patients awaiting transplants.

SUMMARY

- Hepatic Encephalopathy (HE) is a spectrum of neuropsychological dysfunction in patients with liver dysfunction after exclusion of other metabolic, infectious and brain disease.
- Pathophysiology involves overproduction, reduced metabolism of various neurotoxins particularly ammonia. Recent hypothesis implicates astrocytes dysfunction, low-grade cerebral edema as a final common pathway.

SUMMARY

- Management is multifaceted.
  - Careful identification and amelioration of precipitating factors.
  - Lactulose remain the mainstay in therapy. Prophylactic use of lactulose in patients with or without previous episodes of overt hepatic encephalopathy showed encouraging results and may impact success in liver transplant candidates.

SUMMARY

- Rifaximin - a non-absorbable antibiotic replaces the more toxic antibiotics like Neomycin.
- Prebiotics/Probiotics, other potential treatment options like:

- L-ornithine L-aspartate (LOLA)

- L-ornithine phenylacetate (LOPA)

- L-carnitine

- Acarbose

- AST-120

- Rivastigmine

Needs further validation in larger trial.

SUMMARY

- Newer diagnostic tools suitable in community practice to diagnose covert hepatic encephalopathy is now available online.
  - Inhibitory Control Test (ICT)
  - CNS Vital Signs (CNSVS)

Hepatic Encephalopathy - Are We Getting Better?

- Yes.

THANK YOU