Hepatic Encephalopathy, Hepatic Myelopathy, and Acquired Hepato-Cerebral Degeneration

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2012

Hepatic Encephalopathy

Definition & Pathogenesis

- Reversible neuro-psychiatric manifestation of severe liver dysfunction.
  - One-year survival 40%.
- Decreased hepatic clearance of ammonia derived from:
  - 1) kidney,
  - 2) urease activity of gastro-intestinal bacteria, and
  - 3) deamination of glutamine in small bowel.
- Increased Gut-derived neuro-mediators:
  - 1) benzodiazepine-like substances,
  - 2) neurotoxic short- and medium-chain fatty acids,
  - 3) phenols and,
  - 4) mercaptans.

Types (by Cause)

- **Type A:** Acute Liver Failure
- **Type B:** Large Spontaneous or Post-traumatic Portal-Systemic By-pass (normal liver)
  - Uretero-Sigmoid anastomosis.
- **Type C:** Cirrhosis; Portal HTN or Shunt

- Hepatic Myelopathy: Symmetrical demyelination of lateral corticospinal tracts

Sub-Categories of Cirrhotic Hepatic Encephalopathy

- **Minimal or Covert:**
  - Detected only by psycho-metric testing.
  - Impairs concentration and ability to drive.
- **Overt Episodic:**
  - Clinically apparent (stages 1 to 4)
  - Usually precipitated after a triggering event.
  - May be spontaneous and recurrent
- **Chronic Persistent:**
  - H.E. fluctuating from “mild” to “severe”
  - Usually without apparent trigger;
  - May be treatment dependent.
  - Very rare.

Current Terminology for the Classification of HE

Type	Description	Subcategory	Subdivision
A	Encephalopathy associated with **a**cute liver failure	---	---
B	Encephalopathy with portosystemic **b**ypass and no intrinsic hepatocellular disease	---	---
C	Encephalopathy associated with **c**irrhosis or portal hypertension/portosystemic shunts	• Episodic HE	• Precipitated • Spontaneous • Recurrent
		• Persistent HE	• Mild • Severe • Treatment dependent
		• Minimal	---

Ferenci P et al. *Hepatology* 2002;35:716-721.

Neurologic Manifestations of OHE

Common

- Confusion or coma
- Asterixis
- Loss of fine motor skills
- Hyper-reflexia
- Cognitive deficits detected by special testing
- Slow speech

Less Common

- Babinski sign
- Slow, monotonous speech
- Extrapyramidal-type movement disorders
- Clonus
- Decerebrate posturing
- Decorticate posturing
- Hyperventilation
- Seizures[a]

[a]Seizures seen primarily in type A HE.

Mullen KD. *Semin Liver Dis*. 2007;27(suppl 2):3-9.

West Haven Criteria

Grade	Symptoms
0 (minimal)	• No detectable changes in behavior or personality[1]
1	• Euphoria or anxiety[2] • Impaired performance of addition[2] • Shortened attention span[2] • Trivial lack of awareness[2]
2	• Minimal disorientation to time or place[2] • Inappropriate behavior[2] • Impaired performance of subtraction[2] • Lethargy or apathy[2] • Subtle personality change[2]
3	• Confusion[2] • Gross disorientation[2] • Somnolence to semistupor (may respond to verbal stimuli)[2]
4	• Coma (no response to verbal or noxious stimuli)[2]

HE = hepatic encephalopathy.

1. Mullen et al. *Semin Liver Dis*. 2007;27(suppl 2):32-48. **2.** Ferenci et al. *Hepatology*. 2002;35:716-721.

Precipitating Factors

- Constipation
- Gastrointestinal bleed
- Infection
- Overdiuresis
- Azotemia & dehydration
- Hypokalemia
- Hypo- or hyper-natremia
- Sedative or opiate
- Hepatic injury (toxic, viral, HCC)
- Portal vein thrombosis
- Excessive protein intake.
- TIPSS
- Non-compliance with H.E. therapy

Multiple Factors Can Lead to HE Breakthrough

GI hemorrhage
Hypokalemia
Azotemia
Constipation
Excess dietary protein
Infection

↑ Ammonia production

Systemic alkalosis

↑ Diffusion of ammonia across BBB

Progressive parenchymal damage
Dehydration
Anemia
Arterial hypotension
Arterial hypoxemia
Hepatoma
Shunts

↓ Toxin metabolism

Benzodiazepines

Activation of central GABA-benzodiazepine receptors

Psychoactive drugs

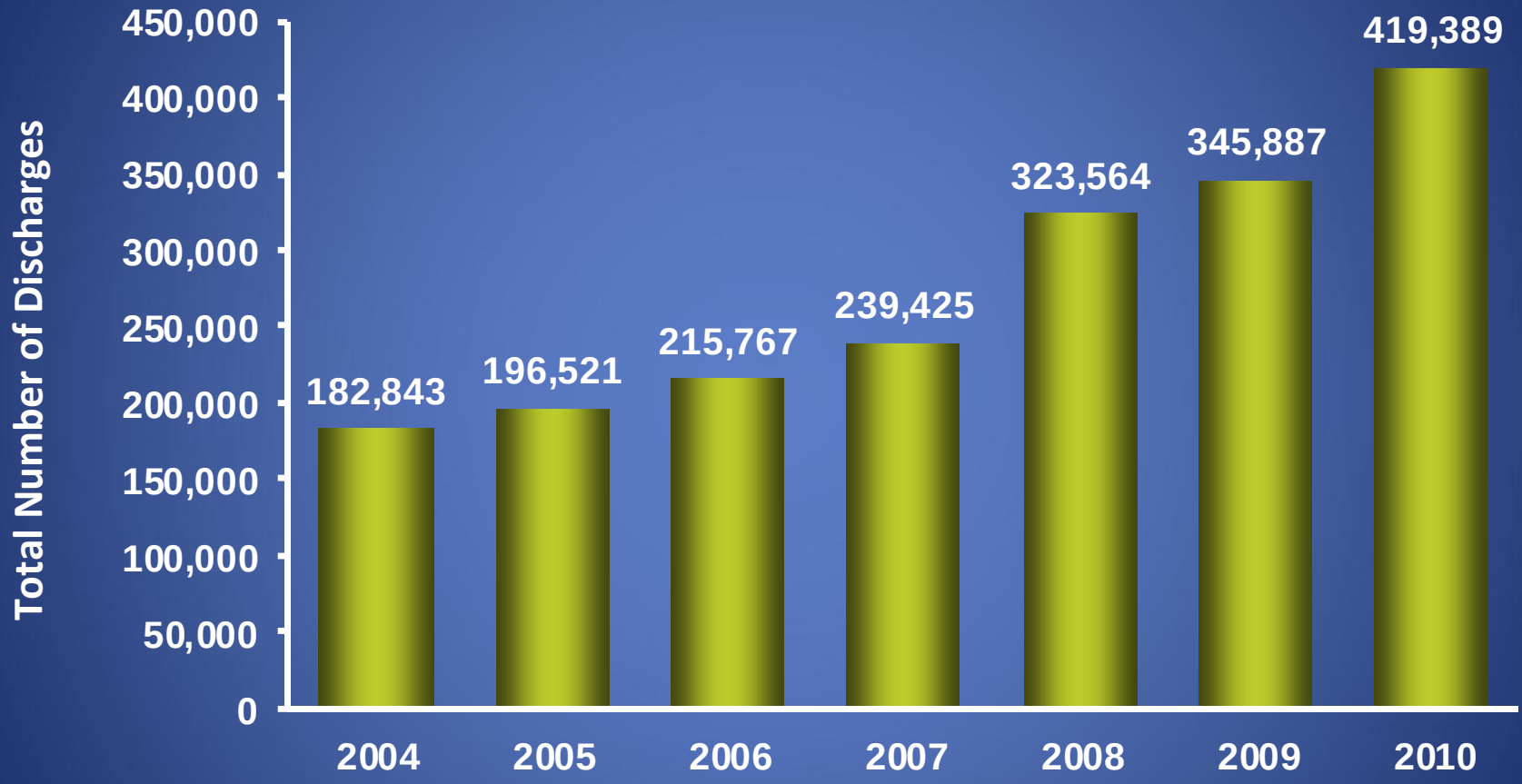
CNS depression

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.

Differential Diagnosis

- Intracranial lesion
  - bleed,
  - tumor,
  - infarct,
  - abscess
- CNS infection
- Metabolic
  - Hyper- or hypo-glycemia,
  - uremia,
  - acidosis,
  - electrolyte disorder
- Neuro-psych disorder
- Alcohol-related
  - Intoxication,
  - withdrawal,
  - Wernicke, Korsakoff
- Drug
  - sedative,
  - psychoactive,
  - heavy metal
- Post-ictal

Hospital Discharges Associated with HE Increased by 21% in 2010



HE = hepatic encephalopathy; ICD = International Classification of Diseases.

*Data calculated using ICD-9-CM codes 291.2 (alcoholic dementia, not elsewhere classified), 348.30 (encephalopathy, not otherwise specified), and 572.2 (hepatic coma). †Includes all listed discharge diagnoses.

HCUPnet, Healthcare Cost and Utilization Project. Agency for Healthcare Research and Quality, Rockville, MD. http://hcupnet.ahrq.gov. Accessed May 28th, 2012

Greater Than 50% Increase in Cost HE Discharge Since 2004

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Poor QoL and Prognosis in Patients With HE

- HE significantly diminishes physical and mental QoL[1]
  - Patient may be disabled from driving, employment, and independent care[2]
- <50% survival at 1 year after diagnosis of HE and <25% survival at 3 years[3]

  - For patients with severe HE who are hospitalized in intensive care, 1-year survival rate is <50%[4]

HE = hepatic encephalopathy; QoL = quality of life.

1. Arguedas et al. *Dig Dis Sci.* 2003;48:1622-1626. **2.** Munoz. *Med Clin N Am.* 2008;92:795-812. **3.** Bustamante et al. *J Hepatol.* 1999;30:890-895. **4.** Fichet et al. *J Crit Care.* 2009;24:364-370. Reprinted from *Journal of Hepatology*, volume 30, Bustamante et al. Prognostic significance of hepatic encephalopathy in patients with cirrhosis, Pages 890-895, Copyright 1999, with permission from Elsevier.

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Cognitive Deficits in Patients With a History of Overt HE

- 226 patients with cirrhosis and a history of overt HE, MHE,* or no HE underwent psychometric evaluation
  - 54 had prior overt HE†
  - 120 had MHE
  - 52 had normal psychometric test results

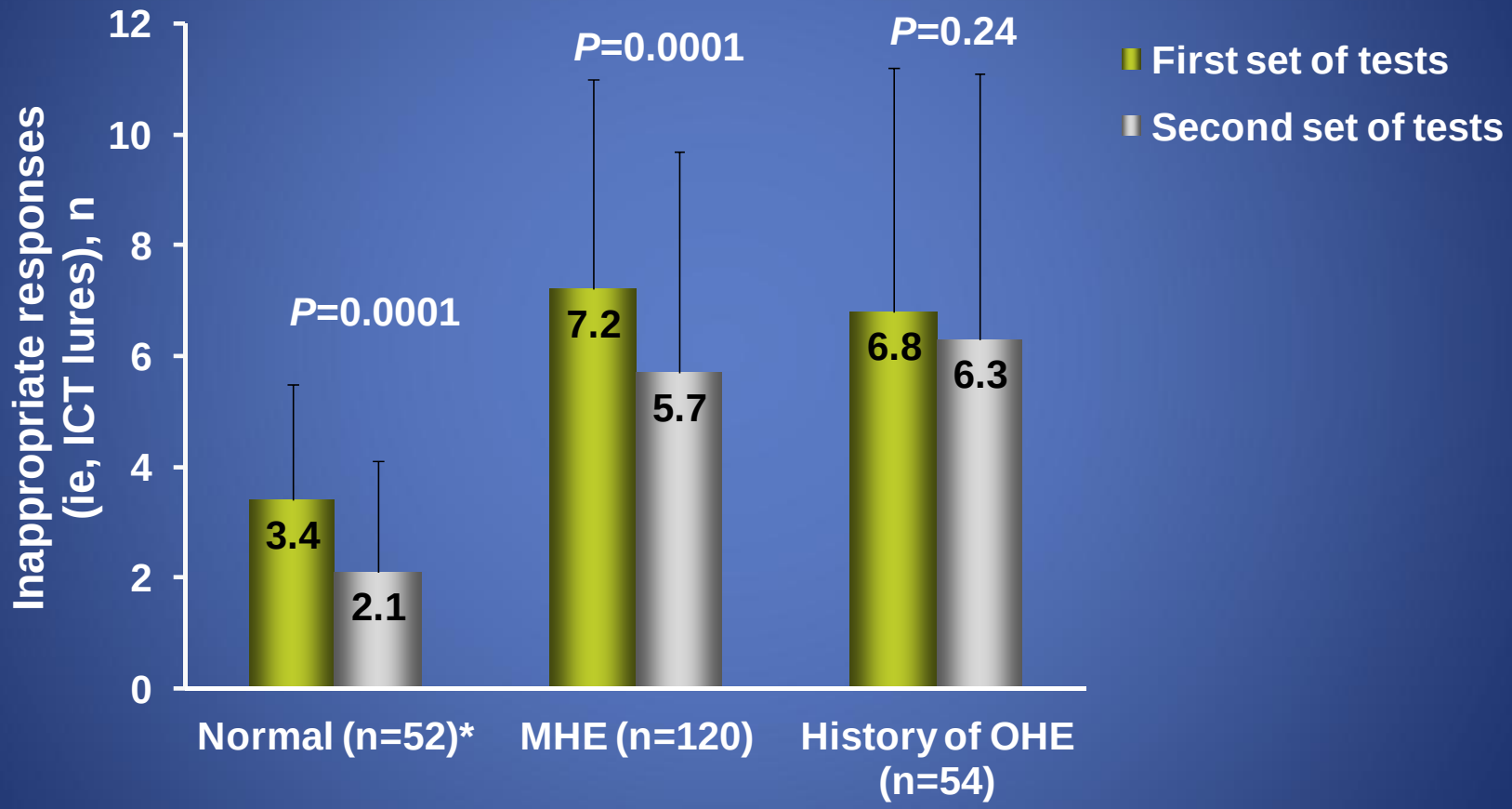
- Patients with a history of overt HE performed significantly worse than normal patients with cirrhosis ($P \leq 0.001$) and had impaired learning on the ICT

ICT = inhibitory control test; HE = hepatic encephalopathy; MHE = minimal HE.

*Patients had an impairment of 2 standard deviations from normal on 2 of the 4 following: number connection tests A or B, block design test, or digit symbol test. †Patients adherent on lactulose therapy.

Bajaj et al. *Gastroenterology*. 2010;138:2332-2340.

History of Overt HE May Cause Learning Deficit



HE = hepatic encephalopathy; ICT = inhibitory control test; MHE = minimal HE; OHE = overt HE.

*Patients with cirrhosis with normal cognitive function.

Bajaj et al. *Gastroenterology*. 2010;138:2332-2340.

Treatment Goals for Patients with HE

- Investigate precipitating factors that may have led to an HE event[1]
  - Precipitating factors may include GI bleed, sepsis, and dehydration[1]
  - In a large clinical trial, 80% of HE events at baseline were considered spontaneous[2]
- After ruling out precipitating factors, chronic management of HE should be initiated
  - The prevention of further episodes of HE is an important goal in the treatment of patients with liver disease[3]
  - After an episode of OHE, prophylactic therapy with lactulose or rifaximin is recommended for an indefinite period of time or until liver transplantation[4]

1. *The Modern Management of Hepatic Encephalopathy*, http://www.medscape.com/viewarticle/718706_6 Accessed May 15th, 2012. **2.** Data on file **3.** Bass et al. *N Engl J Med.* 2010;362:1071-1081. 4. Khungar, V ., Poordad, F. *Clinics in Liver Disease.* 2012;16 301-320.

Mechanism of Action of Therapies for HE

- **Lactulose:** (also sorbitol, fiber, and acarbose) inhibit intestinal ammonia production by a number of mechanisms:
  - Conversion of unabsorbed sugar to lactic acid results in acidification of the gut lumen. This favors conversion of NH_4^+ to NH_3 and the passage of NH_3 from tissues into the lumen.
  - Gut acidification inhibits ammoniagenic coliform bacteria, leading to increased levels of nonammoniagenic lactobacilli.
  - Unabsorbed works as a cathartic, reducing colonic bacterial load.
- **Antibiotics**: such as rifaximin, neomycin, metronidazole, oral vancomycin, paromomycin, and oral quinolones, decrease the colonic concentration of ammoniagenic bacteria.
- **Zn:** improves hyperammonemia by increasing the activity of ornithine transcarbamylase, an enzyme in the urea cycle.

Mechanism of Action of Therapies for HE

- **Sodium benzoate:** interacts with glycine to form hippurate. The renal excretion of hippurate results in the loss of ammonia ions.
- **Sodium phenylbutyrate** is converted to phenylacetate. **Phenylacetate**, reacts with glutamine to form phenylacetylglutamine, which is subsequently excreted in the urine, with loss of ammonia ions.
- **L carnitine:** is unclear if improves blood ammonia levels or if works centrally by decreasing brain ammonia uptake.
- **LOLA** is a stable salt of l-ornithine and l-aspartate:
  - L-ornithine stimulates the urea cycle, with resulting loss of ammonia.
  - Both l-ornithine and l-aspartate are substrates for glutamate transaminase. Their administration increases glutamate levels. Ammonia is subsequently used in the conversion of glutamate to glutamine by glutamine synthetase.

Treatment of Hepatic Encephalopathy

- Reduction of Ammonia load:
  - Lactulose p.o. to give 3-4 BM/day or retention enema (300 ml + 700 ml water) TID
  - Rifaximin 550 mg BID, p.o.
  - Neomycin 4-6 grams/day p.o.
  - Metronidazole 250 mg TID, p.o.
  - Others: arginine benzoate, sodium benzoate (Ammonul), L-carnitine 990 mg TID, sodium phenylbutyrate (Buphenyl), Acarbose, fiber, sorbitol, LOLA (l-ornithine and l-aspartate)

Treatment of Hepatic Encephalopathy

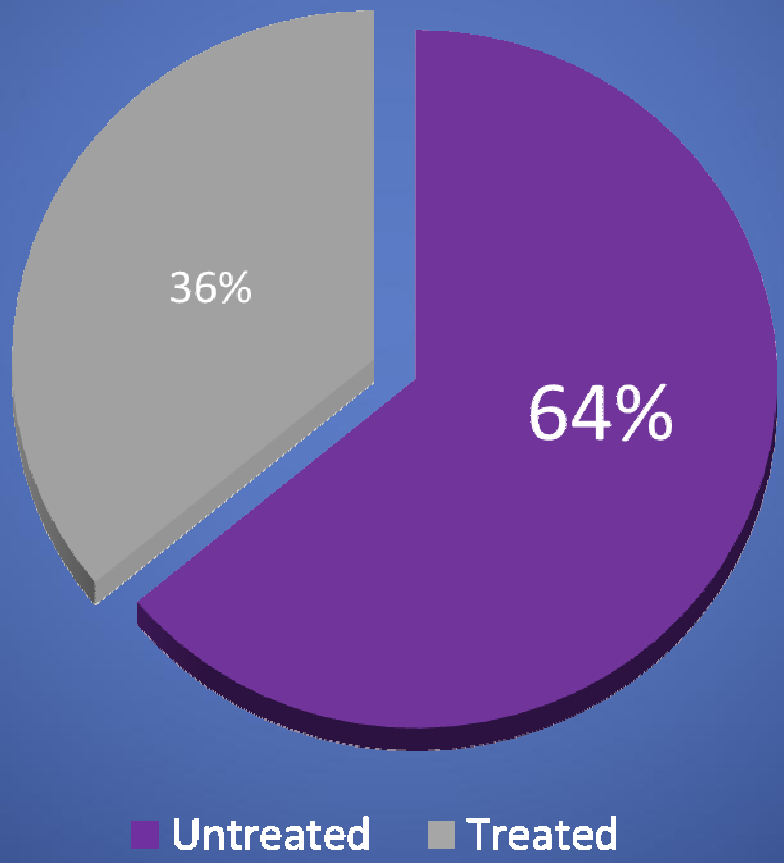
- Nutritional Management:
  - Early nutrition to cover calorie needs and 1-1.5 g protein/kg/day.
  - In Chronic Persistent PSE: branched-chain aminoacids enriched formula (Nutra-Hep)
  - Zn 50 mg QD or BID.
- Manipulation of Splanchnic Circulation:
  - Radiology-guided occlusion of shunts.
  - Reduction of TIPS with hourglass-shaped expanded polytetrafluoroethylene (ePTFE) stent-graft.

Treatment of Hepatic Encephalopathy

- Drugs affecting Neurotransmission:
  - Flumazenil: used more often in Acute Liver Failure in person without chronic benzodiazepine use.
  - Bromocryptine: may improve extra-pyramidal signs.

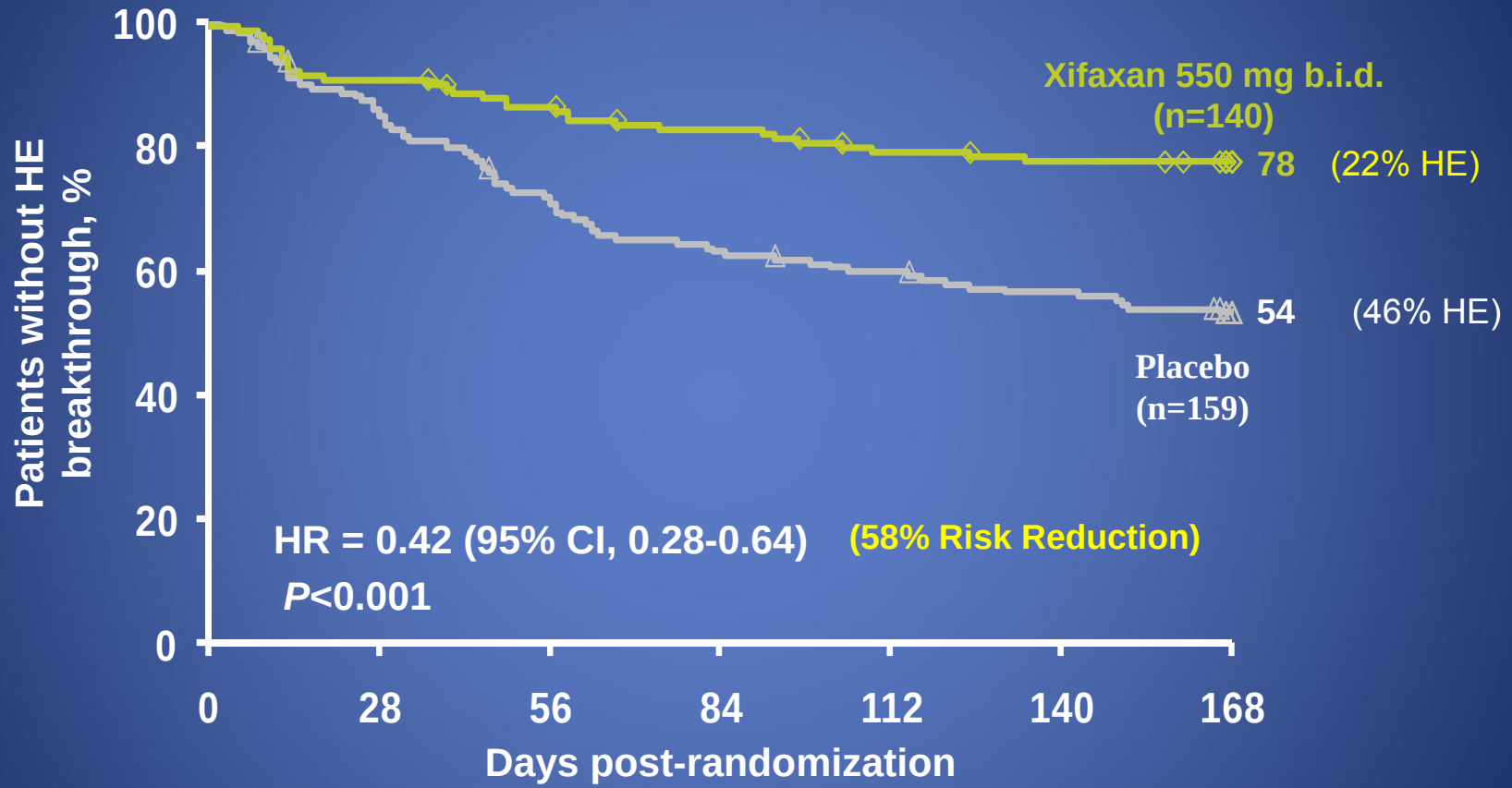
64% of Patients Did Not Receive Treatment for their HE Outside the Hospital in 2011

Percent of Patients with HE Untreated & Treated as OP



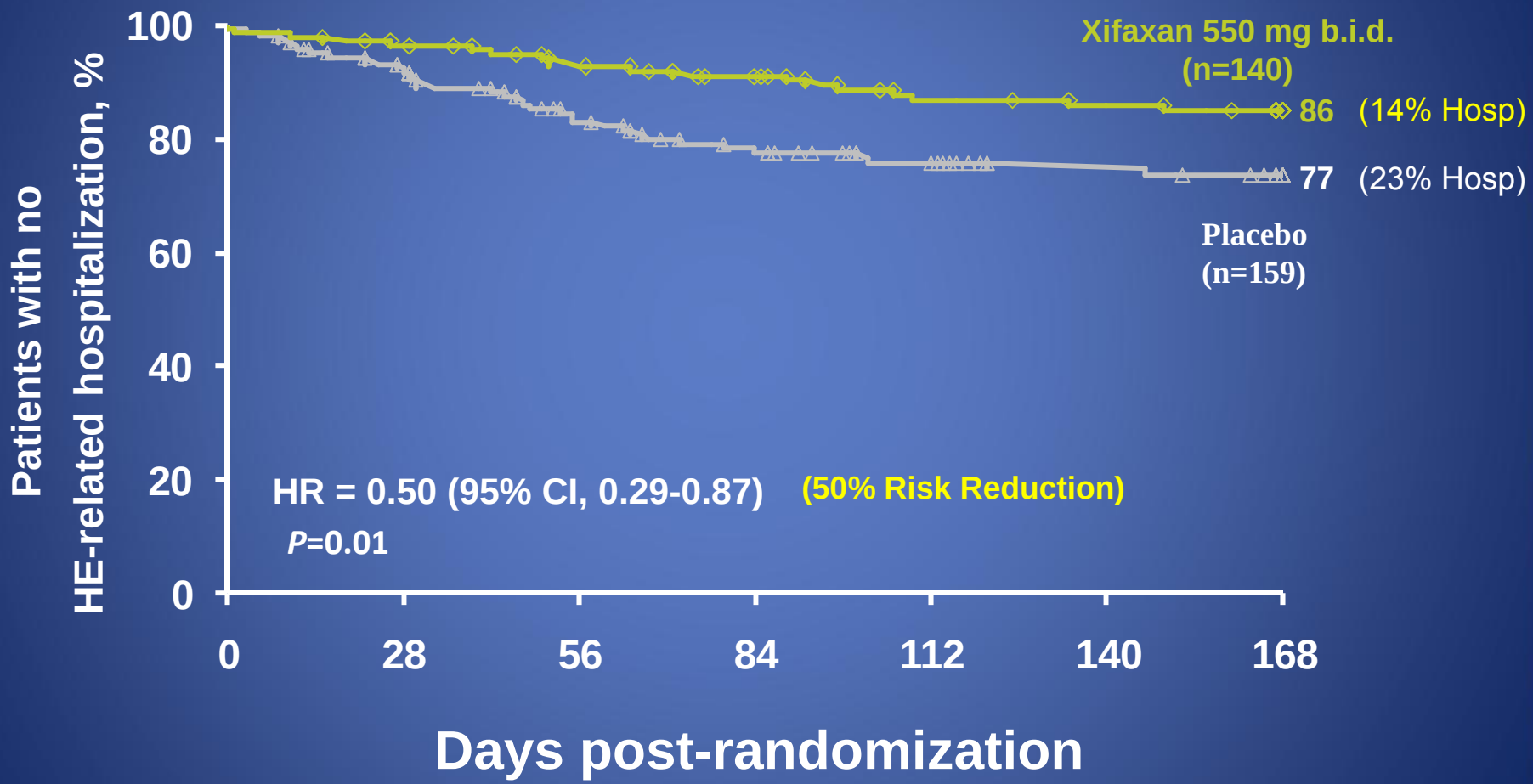
Walters Kluwer 2012
ICD-9 Code: 572.2 Hepatic Encephalopathy

Xifaxan550 Reduced the Risk of Breakthrough HE Episode* by 58% vs Placebo



b.i.d. = twice daily; CI = confidence interval; HE = hepatic encephalopathy; HR = hazard ratio.
*HE breakthrough defined as increase in Conn score to ≥2 or, if baseline Conn = 0, an increase of 1 each in Conn score and asterixis grade.

Xifaxan550 Reduced the Risk of HE-Related Hospitalization by 50% vs Placebo



b.i.d. = twice daily; CI = confidence interval; HE = hepatic encephalopathy; HR = hazard ratio.

Minimal or Covert Hepatic Encephalopathy

Minimal Hepatic Encephalopathy

- **Cirrhotic patients**
  - Without clinical signs of encephalopathy
  - Perform worse in psychometric tests when compared with healthy controls
- **Affects an estimated 60% (50% to 80%)* of patients with cirrhosis**
- **Cerebral dysfunction has a major impact on patients' daily living**
- **No consensus on diagnostic criteria or diagnostic tests has been established**

*depends on mode of diagnosis

Mullen KD. *Aliment Pharmacol Ther.* 2006;25(suppl 1):11-16.

Diagnostic Methods for Detecting Minimal HE

Methods	Advantages	Limitations
Formal neuropsychologic assessment	Established and well-recognized clinical significance	• Expensive • Time consuming
Short neuropsychologic batteries	• Easy to administer in office setting • Inexpensive • Rapid results • High sensitivity for discerning minimal HE 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

CFF, critical flicker frequency; ICT, inhibitory control test; EEG, electroencephalography; P300, auditory event-related evoked potential.

Adapted from Mullen KD et al. *Semin Liver Dis*. 2007;27(suppl 2):32-47.

Standard "Pencil-and-Paper" Psychometric Tests for the Detection of HE

- Number connection test A (NCT-A)
- Number connection test B (NCT-B)
- Digit symbol test (DST)
- Serial-dotting test (SDOT)
- Line-tracing test (LTT)
- Figure connection test
- Block design test

The Porto-systemic Encephalopathy (PSE) Syndrome Test [a]

[a]PSE psychometric test is not currently available in the United States.

Ferenci P et al. *Hepatology* 2002;35:716-721.

Recommendations for MHE Testing

- **Alternatives to psychometric hepatic encephalopathy score (PHES) in the United States**
  - Impairment in 2 of 4 tests below
    - Number connection test-A
    - Number connection test-B
    - Digit Symbol
    - Block Design tests of the Wechsler's Adult Intelligence Scale-III (Psychological Corp, San Antonio, TX)
  - Above tests need psychological expertise to order, administer, and interpret

Ferenci P et al. *Hepatology*. 2002;35(3):716-721.
Bajaj JS et al Gastroenterol 2008 135(5):1591-1600
Bajaj JS et al. *Am J Gastroenterol*. 2007;102(9):1903-1909.
Romero-Gomez M et al. *Hepatology*. 2007;45(4):879-885.

Test Studied in the U.S. for MHE

Inhibitory Control Test

- A computerized test of attention and response inhibition which consists of lures and targets.
- Does not need a psychologist for administering or interpretation
- Can be administered by a medical assistant within 15 minutes.
- ICT has a high sensitivity and specificity for MHE diagnosis and predicting overt HE.

Bajaj JS et al *Gastroenterol* 2008;135(5):1591-1600
Garavan et al *Proc Natl Sci Usa* 1999; 96(14):8301-6.
Bajaj JS et al. *Am J Gastroenterol*. 2007;102(9):1903-1909.

Inhibitory Control Test

- ICT has good reliability between 2 administrations
- ICT also has external validity, i.e. gets worse after TIPS and gets better after therapy
- ICT performance has been correlated with driving simulator performance.
- Available on the Chronic Liver Disease Foundation website (www.hecme.tv) for download with detailed instructions.

Bajaj JS et al *Gastroenterol* 2008;135(5):1591-1600
Garavan et al *Proc Natl Sci Usa* 1999; 96(14):8301-6.
Bajaj JS et al. *Am J Gastroenterol*. 2007;102(9):1903-1909.
Bajaj JS et al *Hepatol* 2008;47(2):596-604.

Probiotic Yogurt in the treatment of MHE

Bajaj JS et al. Am J Gastroenterol 2008;103:1707-1715

- Subjects: 25 nonalcoholic MHE cirrhotics (defined by a standard psychometric battery); 84% were Child A
- **Groups:** randomized with unblinded allocation to receive for 60 days in 2:1 ratio
  - **A:** probiotic yogurt (N: 18) (CC's Jersey Crème Yogurt 6 oz BID; with proven culture stability)
  - **B:** no treatment (no Rx) (N: 7).
- **Measurements:** Quality of life (short form [SF]-36), adherence, venous ammonia, model of end-stage liver disease (MELD) scores, and inflammatory markers (tumor necrosis factor [TNF]-α, interleukin [IL]-6).
- **Outcomes**:
  - MHE reversal using blinded scoring,
  - OHE development, and
  - Adherence.

Probiotic Yogurt in the treatment of MHE

Bajaj JS et al. Am J Gastroenterol 2008;103:1707-1715

- RESULTS:
  - A significantly higher percentage of yogurt patients reversed MHE compared to no Rx patients (71% *vs* 0%, *P* = 0.003, intention-to-treat).
  - Yogurt patients demonstrated a significant improvement in number connection test-A (NCT-A), block design test (BDT), and digit symbol test (DST) compared to baseline/no Rx group.
  - Overt HE: developed in 25% of no Rx *versus* 0% of yogurt patients.
  - Adherence: Eighty-eight percent of yogurt patients.
  - No adverse effects or change in covariates were observed.
  - All patients who completed the yogurt arm were agreeable to continue yogurt for 6 months if needed.

CC's Jersey Crème Yogurt
6 oz BID

Treatment of MHE

(Mittal VV et al. Eur J Gastroenterol Hepatol 2011; 23:725–732).

- 160 cirrhotics with MHE were randomized in 4 groups of 40 patients to receive for 3 months:
  - Group A: no therapy,
  - Group B: lactulose 30–60 ml b.i.d.,
  - Group C: probiotics of 110 billion colony-forming units b.i.d. or
  - Group D: L-ornithine-L-aspartate 6 g t.i.d. (LOLA).
- Parameters:
  - health-related quality of life (HRQoL) improvement, and
  - progression to overt hepatic encephalopathy.
- **RESULTS:**
  - A) Using neuropsychological assessment, recovery of MHE was seen in groups: A = 10%, B = 48%, C =35% and D = 35% (*P* = 0.006).
  - There was no significant difference in recovery from MHE or changes in ammonia levels when comparing lactulose to either probiotics or LOLA.
  - B) Nine (6%) developed overt PSE.

Culturelle has only 10 billion cells/capsule

Treatment of MHE

(Bajaj JS et al. Gastroenterology 2011; 140:478–487; e1).

- 42 cirrhotics with MHE at baseline were randomized to 8 weeks of rifaximin (*n* = 21) or placebo (*n* = 21) and tested in a driving simulator.
- RESULTS:
  - A) Rifaximin group showed improvement in avoiding total driving errors (76 vs. 31%; *P* = 0.013), speeding (81 vs. 33%; *P* = 0.005), and illegal turns (62 vs. 19%; *P* = 0.01) compared to those given placebo; however,
  - B) The number of collisions were not significantly different between groups.
  - C) In rifaximin group, the cognitive performance improved (91 vs. 61%; *P* = 0.01) compared to placebo group.

Hepatic Myelopathy

- **Symptoms:**
  - Subacute bilateral lower extremity weakness,
  - Puppet-like walk or inability to walk in setting of cirrhosis or porto-caval shunt.
  - Upper extremity involvement is very rare.
  - Disorder is progressive and irreversible.
- **Signs:** Spastic paraparesis, hyperreflexia, extensor plantar response, and no sensory level (Zieve 1960).
- **Pathogenesis:** Symmetrical demyelination of lateral corticospinal tracts, occasionally with axonal loss.

Hepatic Myelopathy

- Imagen:
  - a) Brain MRI: may show FLAIR in subcortical white matter,
  - b) MRI of spine with contrast, or CT myelogram: No evidence of compression. MRI may show FLAIR in subcortical spinal tracts.
- Central motor conduction time (CMCT): abnormal in lower lumbar spine, and normal in upper cervical spine.
- Treatment: Closure of shunt or liver transplantation.

Acquired (non-Wilsonian) hepatocerebral degeneration (AHCD)

- Clinico-pathological syndrome of brain dysfunction associated with a variety of liver diseases. (Victor *et al.* in 1965).
- Clinical features: dementia, dysarthria, ataxia of gait, intention tremor and choreoathetosis.
- Evolution: chronic and largely irreversible syndrome.
- Pathogenesis: poorly understood; may be damage accumulated from multiple episodes of hepatic encephalopathy
- Neuropathological findings: diffuse but patchy cortical necrosis, diffuse proliferation of Alzheimer type II glial cells and uneven neuronal loss in the cerebral cortex, basal ganglia and cerebellum.
- MRI: T1-weighted images hyperintensities in the globus pallidus, and 75% have extrapallidal involvement.