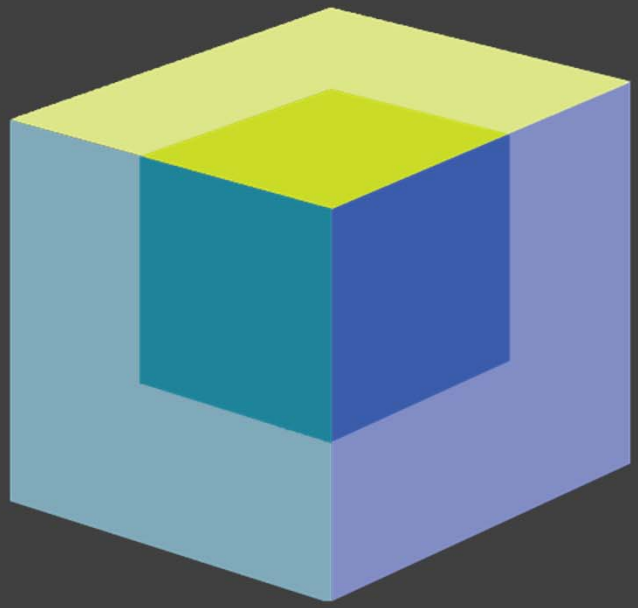

NEW INSIGHTS INTO HE

This educational programme is funded by a grant from Norgine.
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Disclaimers

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Use of medicinal products according to approved indications

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West-Haven Grading of HE

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- (also known as Conn Score)

Grade 0	Normal examination; if impaired psychometric test; minimal HE
Grade 1	Mild lack of awareness Shortened attention span Impaired performance of addition / subtraction Mild asterixis or tremor
Grade 2	Lethargy Disorientation Inappropriate behaviour Obvious asterixis; slurred speech
Grade 3	Somnolence but responsive to stimuli Gross disorientation; bizarre behaviour Muscular rigidity and clonus; hyper-reflexia
Grade 4	Coma (unresponsive to verbal or noxious stimuli) Decerebrate posturing

After: Conn HO, et al. Gastroenterology. 1977;72(4 pt 1):573–83
Ferenci P, et al. Hepatology. 2002;35:716–21

Burden of Hepatic Encephalopathy

NEW INSIGHTS INTO HE

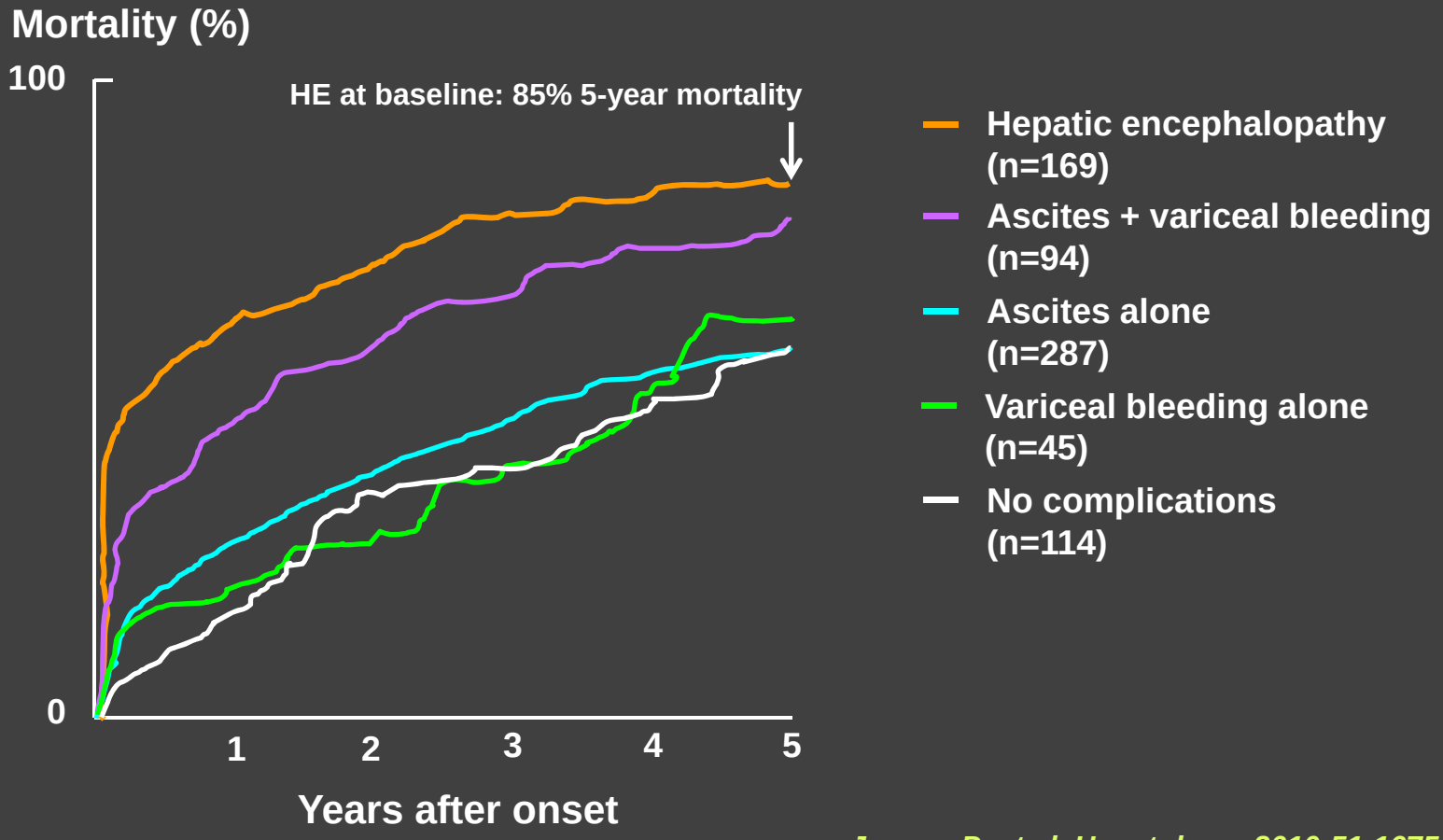
- Overt HE occurs in 30–45% of patients[1]
- 45–80% of patients with cirrhosis may suffer from minimal HE[2,3]
- HE is a criterion for decompensation and associated with poor prognosis[1,4]
  - Barcelona cohort : Mortality at 1 year 58% and 77% at 3 years[5]
  - Denmark population: Mortality at 1 year 64% and 85% at 5 years[6]
- HE is associated with a reduced quality-of-life and has a significant burden on health economics and caregivers / family[1,7]

[1]*Poordad FF. Aliment Pharmacol Ther. 2007;25(Suppl 1):3–9*
[2]*Ortiz M, et al. J Hepatol. 2005;42(Suppl 1):S45–53*
[3]*Bass NM. Aliment Pharmacol Ther. 2007;25(Suppl 1):23–31*
[4]*Amodio P, et al. J Hepatol. 2001;35:37–45*
[5]*Bustamante J, et al. J Hepatol. 1999;30:890–5*
[6]*Jepsen P, et al. Hepatology. 2010;51:1675–82*
[7]*Bajaj JS, et al. Am J Gastroenterol. 2011;106:1646–53*

Prognosis and Outcomes in Patients with HE

NEW INSIGHTS INTO HE

- 466 Danish patients with alcoholic liver disease; 1993-2005
  At diagnosis 55% had ascites and 11% HE



Jepsen P, et al. Hepatology. 2010;51:1675–82

HE Can Have Long-term Effects on Cognition and Learning

- Comparison of 54 patients after an acute episode of HE vs 52 controls[1]
  - Significantly impaired psychometric tests ($p<0.001$)
  - Significantly reduced learning capacity ($p=0.0001$)
- Effect of an acute HE episode on learning confirmed in a small prospective confirmatory study ($n=15$)[1]
- Long-term effect on cognition assessed 1.5 years after transplantation in 25 patients who had overt HE prior to transplant (14 controls without HE prior to transplant)[2]
  - Significant impairment in 4/5 domains vs 1/5 domains in controls

[1]*Bajaj JS, et al. Gastroenterology. 2010;138:2332–40*
[2]*Sotil EU, et al. Liver Transpl. 2009;15:184–92*

Diagnosis

NEW INSIGHTS INTO HE

- Overt HE is a clinical diagnosis; signs / symptoms include
  - Personality changes
  - Sleep disturbances
  - Confusion
  - Depression
  - Slurred speech
  - Lethargy
  - Coma
  - Asterixis
  - Ataxia
  - Foetor hepaticus;
    Sweet or musty odour of breath and urine believed to be due to mercaptans
- Minimal HE requires psychometric testing to identify / diagnose

Bass NM. Aliment Pharmacol Ther. 2007;25(Suppl 1):23–31
Harrison, Internal Medicine. 15th Ed:p1765
Ferenci P, et al. Hepatology. 2002;35:716–21

Diagnostic Tools for Minimal HE

NEW INSIGHTS INTO HE

Tools for detecting HE

Psychometric testing	Neurophysiologic testing	Neuroimaging	Blood ammonia levels
Neuro-psychological assessments Computerised Tests (e.g. Vienna Determination Test, Vienna Reaction Test) Paper and Pencil Tests (e.g. Number Connection Test, Serial Dotting Test, Line Tracing Test)	EEG (Specialised analysis may be necessary) Critical Flicker Evoked potentials Inhibitory control test	CT scan (for exclusion of other causes) MRI MRS (mainly for research) PET scan (research tool)	Helpful in evaluation and for planning management

Bajaj JS. Expert Rev Gastroenterol Hepatol. 2008;2:785–90
Blei AT, et al. Am J Gastroenterol. 2001;96:1968–76
Morgan MY. In Sherlock's Disease of the Liver and Biliary System, 12th ed: Blackwell Publishing Ltd; 2011

Pathogenesis of HE

NEW INSIGHTS INTO HE

- Ammonia is central to the pathogenesis of HE
  - Bacterial synthesis from amino acids is the major source
- Liver dysfunction results in a reduced capacity to detoxify ammonia
- Portal-systemic shunting results in increased levels in circulation
  - Ammonia readily crosses the blood brain barrier
  - Saturation of glutamine synthetase in astrocytes leads to increased intracellular levels and osmotic changes / cerebral oedema
- Oxidative stress / inflammation (cytokines) exacerbate astrocyte dysfunction

Williams R. Aliment Pharmacol Ther. 2007;25(Suppl 1):17–22
Häussinger D. Acta Gastro-Enterologica Belgica. 2010;73:457–64

Common Precipitating Factors for HE

NEW INSIGHTS INTO HE

- 50-80% of patients with episodic HE have identifiable precipitant

Hypovolaemia/ diuretics	Hypokalaemia and alkalosis facilitates ammonia production Dehydration may precipitate worsening mental function in previously controlled HE
Renal failure	Reduced clearance of ammonia, acid-base imbalance and other nitrogenous products
Upper GI bleed	Blood in GI tract leads to increased ammonia and nitrogen absorption
Infection	Tissue catabolism Impaired renal function Inflammation ➡increased blood ammonia
Constipation	Increases ammonia
Psychoactive medication	Worsen symptoms of HE
TIPS	HE is the most common complication of TIPS Related to portal hypoperfusion and increased availability of ammonia and toxins
Hyponatraemia	Contributes to astrocyte swelling
Additional liver injury	Worsens hepatic function and reduces ammonia metabolism

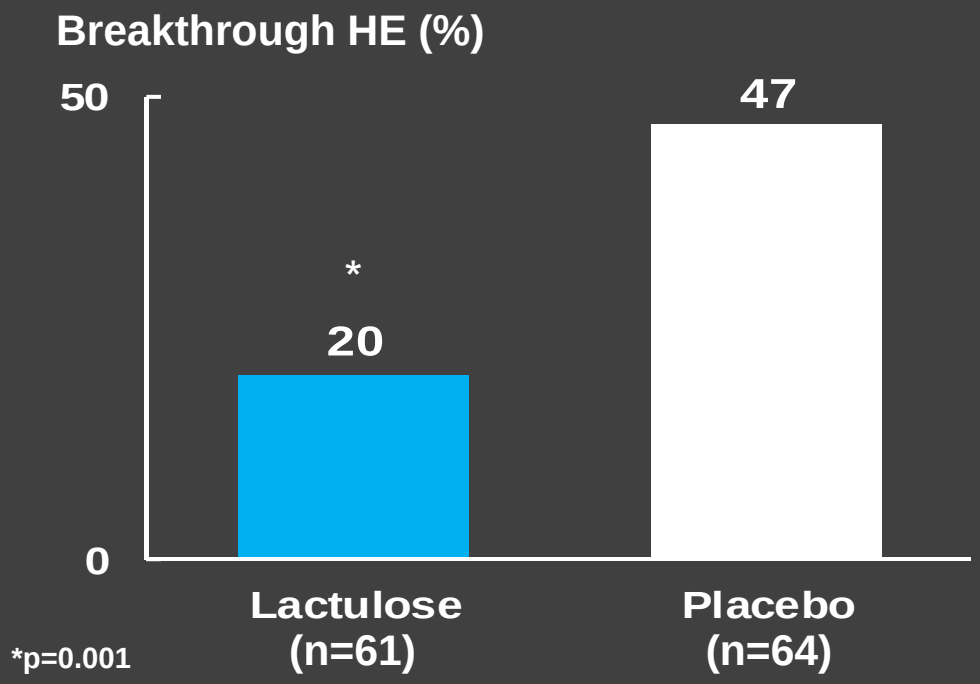
After: Morgan MY. In Sherlock's Disease of the Liver and Biliary System, 12th ed: Blackwell Publishing Ltd; 2011

After: Bajaj JS. Aliment Pharmacol Ther. 2010;31:537–47

Lactulose for Secondary Prophylaxis

NEW INSIGHTS INTO HE

- Patients recovering from HE; existing therapy continued and randomised to lactulose or placebo
  - Mean MELD score 21.8 and 20.6 respectively at baseline.
  - Median 14 (1–20) months' follow-up (n=140 entered – 15 lost to follow-up)



Sharma BC, et al. Gastroenterology. 2009;137:885–91

Lactulose Tolerability

NEW INSIGHTS INTO HE

- Patients taking lactulose / lactitol require education regarding adverse events:
  - Excessive sweet taste
  - Flatulence and bloating
  - Electrolyte imbalance
    - Hypernatraemia which can deteriorate the patient's mental status
  - Lactitol better tolerated than lactulose
  - Abdominal cramping
  - Diarrhoea
    - May worsen HE and risk of hypovolaemia and hypernatraemia
- Dose should be carefully titrated to maintain 2–3 stools/day without diarrhoea
- In patients with acute liver failure caution due to risk of colonic distension, particularly if surgery planned

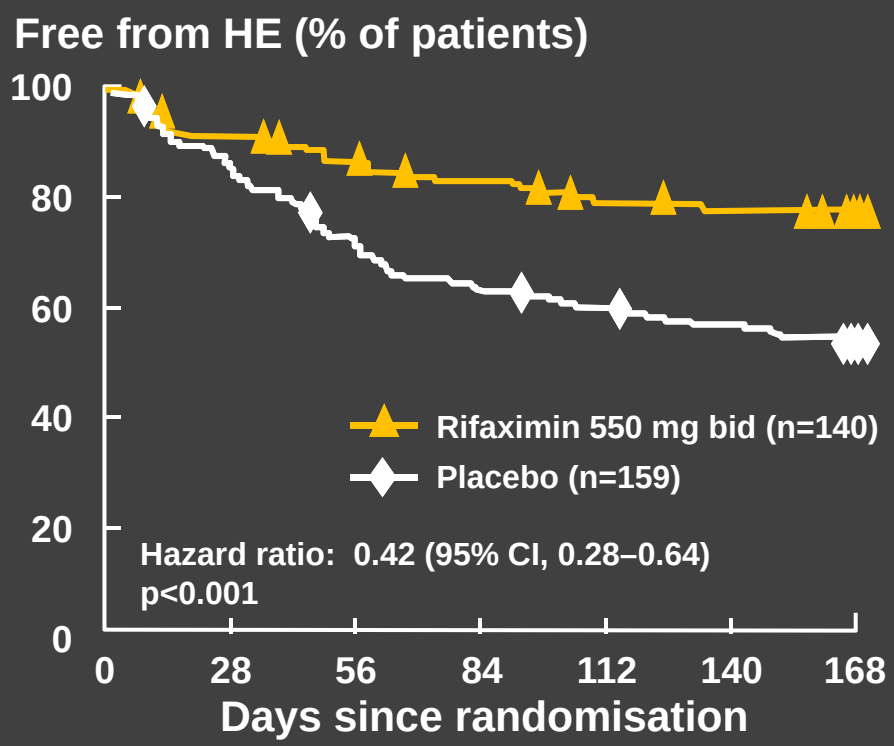
Al Sibae MR, McGuire BM. Ther Clin Risk Manag. 2009;5:617–26
Blanc P, et al. Hepatology. 1992;15:222–8
Garcia-Tsao G, et al. Am J Gastroenterol. 2009;104:1802–29
McDowell Torres D, et al. Gastroenterol Hepatol (NY) 2010;6:444–50
Morgan MY. In Sherlock's Disease of the Liver and Biliary System, 12th ed: Blackwell Publishing Ltd; 2011

Rifaximin for Secondary Prophylaxis of HE: Results

NEW INSIGHTS INTO HE

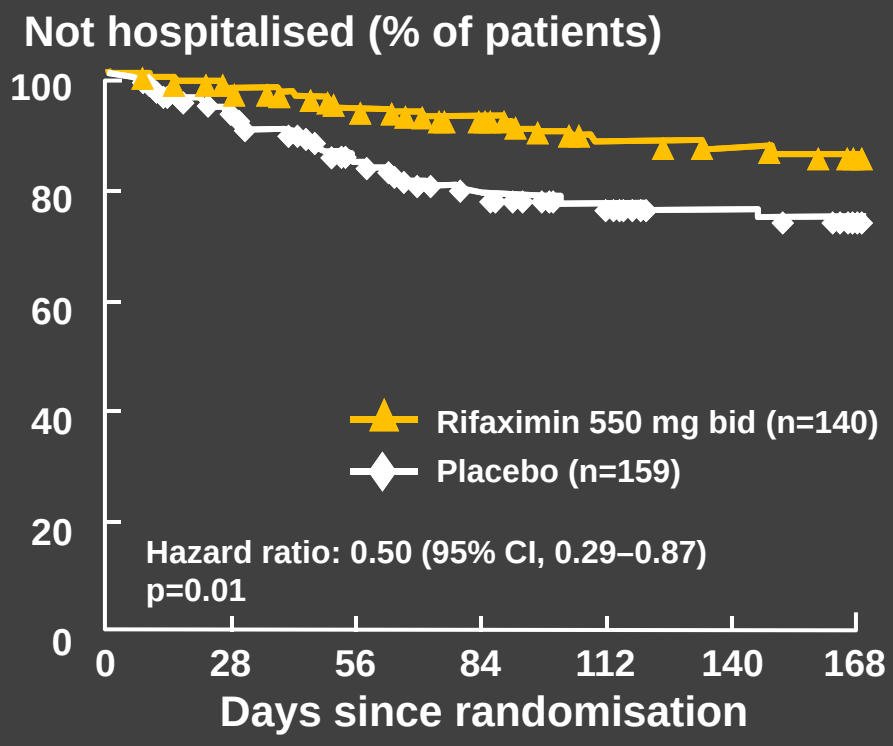
- 91% of study patients were receiving lactulose

Time to HE breakthrough



- 23.8% absolute risk reduction (NNT = 4 over 6 months)

Time to HE-related hospitalisation



- 9% absolute risk reduction (NNT = 9 over 6 months)

HE: Hepatic encephalopathy

Adapated from; Bass NM, et al. N Engl J Med. 2010;362:1071–81

Rifaximin for Secondary Prophylaxis of HE: Most Common Events

Event	Rifaximin (n=140)	Control (n=159)
Nausea	20 (14.3)	21 (13.2)
Diarrhoea	15 (10.7)	21 (13.2)
Fatigue	17 (12.1)	18 (11.3)
Peripheral oedema	21 (15.0)	13 (8.2)
Ascites	16 (11.4)	15 (9.4)
Dizziness	18 (12.9)	13 (8.2)
Headache	14 (10.0)	17 (10.7)
Muscle spasms	13 (9.3)	11 (6.9)
Pruritus	13 (9.3)	10 (6.3)
Abdominal pain	12 (8.6)	13 (8.2)

- *Clostridium difficile* infection reported in 2 patients
  - Multiple risk factors for *C. difficile* (advanced age, frequent recent hospitalisations with multiple courses of antibiotics, PPI therapy)
  - Resolved with treatment (rifaximin continued)
- 9 deaths in rifaximin group and 11 in placebo, most attributed to conditions associated with disease progression

Bass NM, et al. N Engl J Med. 2010;362:1071–81

Nutritional Advice in Patients with Cirrhosis: Protein Intake

NEW INSIGHTS INTO HE

- Maintain protein intake 1.2–1.5g/kg
- Protein restricted diets seldom have any place in management / prevention of HE
  - Vegetable or casein protein may be better tolerated
- Frequent meals (6 or more a day)
  - Complex, not simple, carbohydrate
  - Nocturnal feeding
- Balanced diet of 30 kcal/kg body weight
  - Corrected or ideal body weight in patients with ascites
  - 30–35% of calories consumed as fat
  - 50–55% of calories consumed as carbohydrate

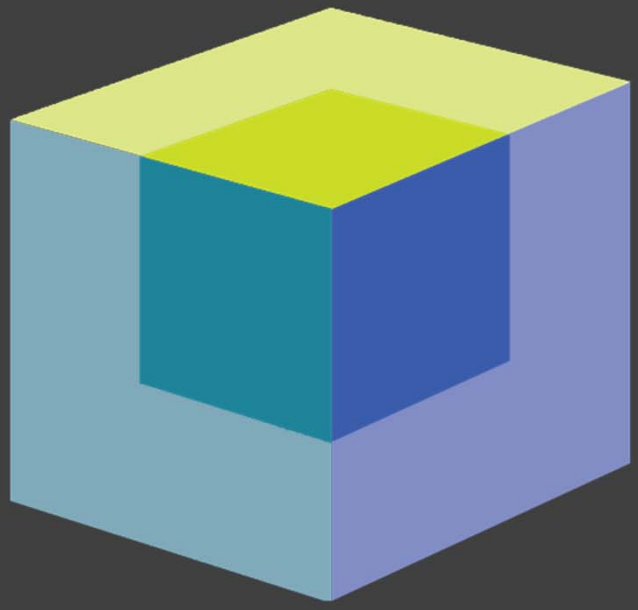
Adapted from;
Chadalavada R, et al. Nutr Clin Pract. 2010;25:257–64
Verslype C, Cassiman D. Acta Gastroenterol Belg. 2010;73:510–3
O'Brien A, Williams R. Gastroenterology. 2008;134:1729-40

HE: General Considerations

NEW INSIGHTS INTO HE

- HE is common in patients with cirrhosis[1]
- Identification of lower grades of HE allows early intervention to be initiated[1]
- Options for treatment include lactulose and traditional antibiotics[1]
- To prevent recurrence, lactulose and rifaximin are recommended[1]
- Patient follow-up is important[1]
  - Ensure on-going compliance with therapy
  - Patient and family / caregiver education
- HE is a decompensation event
  - Consider evaluation for transplantation

[1]EASL/AASLD, J Hepatol 2014; 61: 642-59.



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