Cirrhosis And Hepatic Encephalopathy: Prevalent, Complex, And Debilitating

Chronic Liver Disease Has Multiple Causes And Affects Millions of Americans

- ~10.2 million people in the United States may be at risk for chronic liver disease[1]
  - Up to 3.2 million Americans have chronic hepatitis C infection but this is considered a vast underestimate
  - Up to 2 million Americans have chronic hepatitis B infection
  - Up to 5 million Americans have NAFLD/NASH related cirrhosis[2]
- Most common causes of cirrhosis include alcohol use, hepatitis C, hepatitis B, NAFLD, and autoimmune disorders[3]
- Current US burden of NAFLD-related cirrhosis is about twice as high as cirrhosis caused by chronic hepatitis C[2]

1. CDC Website http://www.cdc.gov/hepatitis/hcv/. Accessed September 29, 2014. 2. Michelotti, A. et al. *Nat. Rev. Gastroenterol and Hep* 10, 2013 656-665 . 3. Clark et al. *Am J Gastroenterol*. 2003;98:960-967.

Portal Hypertension Has Consequences That Have a High Mortality

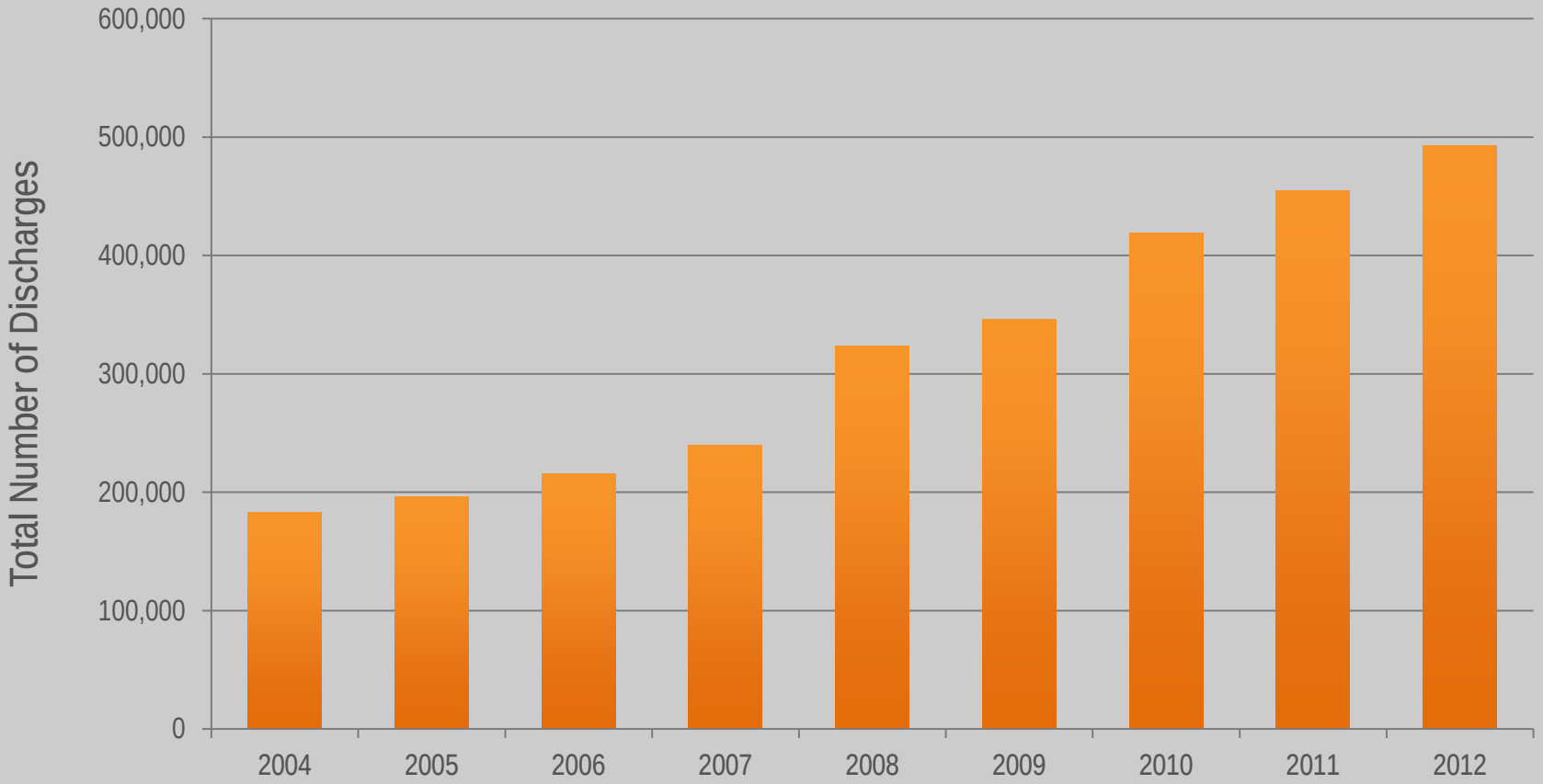
Complication	Survival at 1 year	Survival at 3 years
Varices (non-bleeding) without ascites[1]	97%	NA
Ascites ± varices[1,2]	80%	50%
Hepatic encephalopathy[3]	42%	23%
Bleeding varices ± ascites	43%	NA

- Hepatocellular Carcinoma (HCC) affects many patients with cirrhosis and is the fastest growing solid-tumor cancer in the U.S.
  - Surveillance recommended every 6 months

1. Segarra-Newnham et al. *Ann Pharmacother*. 2010;44:1946-1954. 2. Bustamante et al. *J Hepatol*. 1999;30:890-895. 3. Medscape Portal Hypertension. http://emedicine.medscape.com/article/182098-overview#a0199. Accessed December 15, 2011.

Hepatic Encephalopathy (HE): Disease Background

Hospital Discharges Associated With HE Continue to Increase



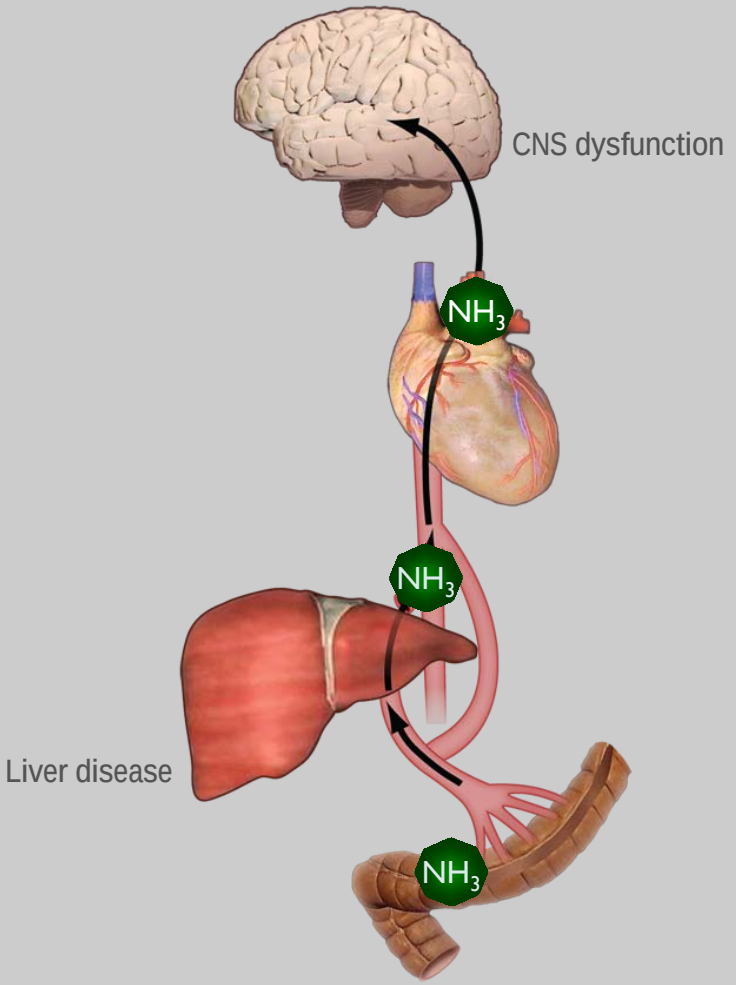
*Data calculated using ICD-9-CM codes 291.2 (alcoholic dementia, not elsewhere classified), 348.30 (encephalopathy, not otherwise specified), and 572.2 (hepatic coma).

†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 28, 2014.

HE is a Frequent And Debilitating Complication of Cirrhosis

- HE is a brain dysfunction caused by liver insufficiency and/or Portal Systemic Shunting[1]
  - Wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma
- Clinically overt HE will occur in 30%-40% of those with cirrhosis and in most patients repeatedly[1]
  - Subjects with a previous bout of overt HE were found to have a 40% cumulative risk of recurring HE at 1 year
  - Subjects with recurrent overt HE have a 40% cumulative risk of another recurrence within 6 months, despite standard treatment



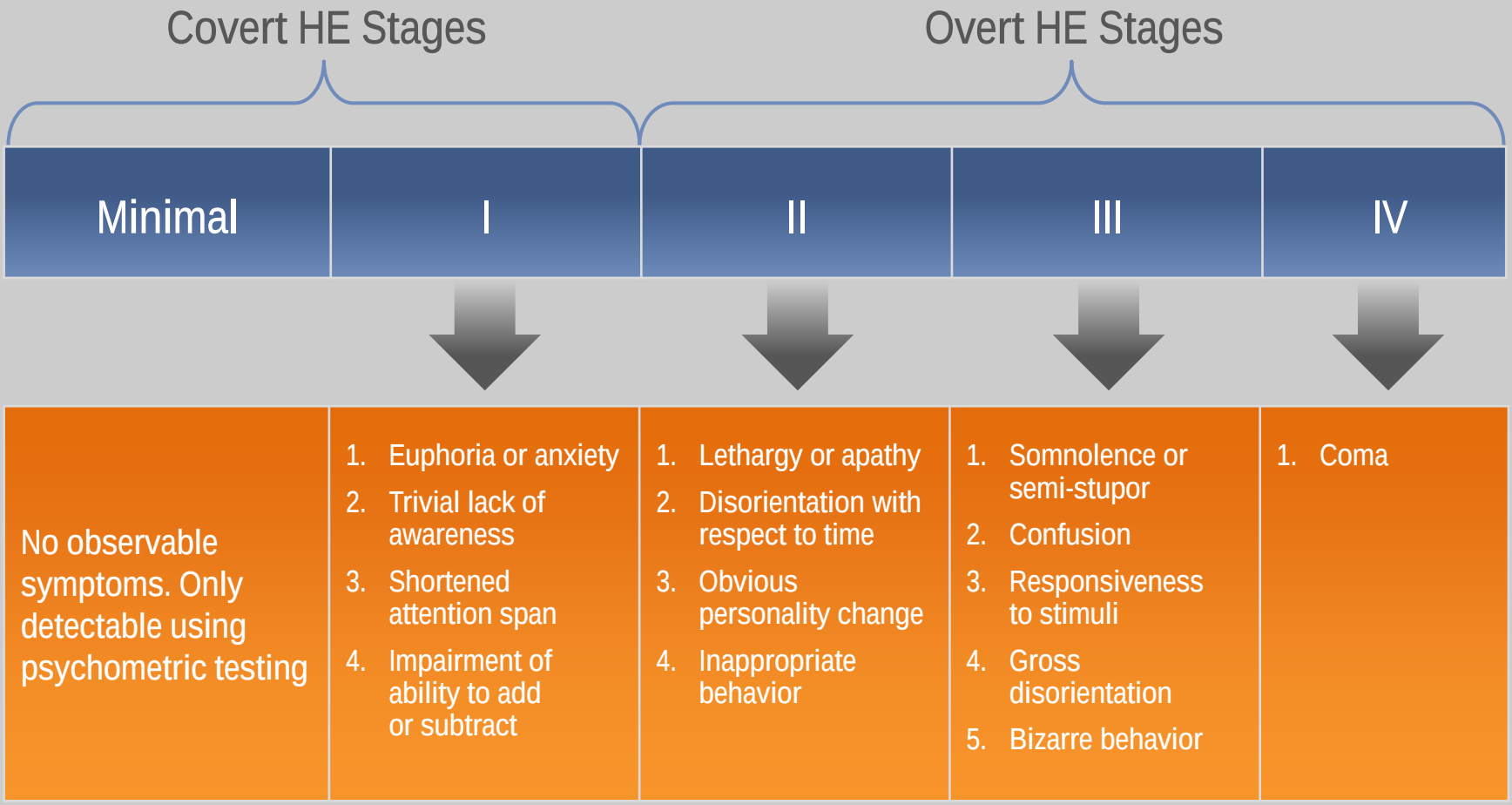
1. Vilstrup, H., et. al(2014), Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study Of Liver Diseases and the European Association for the Study of the Liver. Hepatology, 60: 715–735. doi: 10.1002/hep.27210AASLD/EASL HE Guidelines. *Hepatology*. 2014.

Diagnosis of HE is Based on Clinical Examination

- Diagnosis is based on a clinical examination and a clinical decision
  - Knowledge of existing liver disease and precipitating factors is essential
- Common signs and symptoms of HE
  - Mild: Personality changes such as apathy, irritability, confusion and uninhibited behavior
  - Moderate: Disorientation to time and place, agitation, somnolence, excessive daytime sleepiness Note: asterixis may or may not be present
  - Severe: Coma
- Patients and their family can offer insights into whether there has been a history of symptoms indicative of HE
- Ammonia (regardless of level) does not add any diagnostic, staging, or prognostic value for HE

1. Vilstrup, H., Amodio, P., Bajaj, J., Cordoba, J., Ferenci, P., Mullen, K. D., Weissenborn, K. and Wong, P. (2014), 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, 60: 715–735. doi: 10.1002/hep.27210

HE Symptoms Can be Subtle; Should be Considered in Any Patient With Cirrhosis

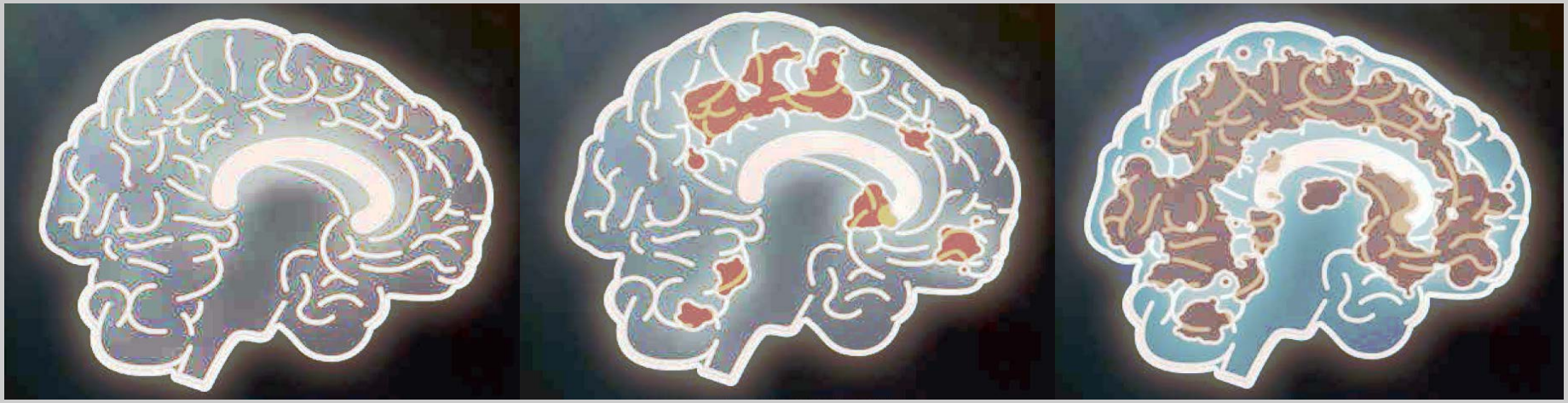


HE = hepatic encephalopathy

1. Vilstrup, H., Amodio, P., Bajaj, J., Cordoba, J., Ferenci, P., Mullen, K. D., Weissenborn, K. and Wong, P. (2014), 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, 60: 715–735. doi: 10.1002/hep.27210.

Continued HE Episodes May Cause Cognitive Damage in Patients

- Studies show that patients with a history of overt HE episodes have:
  - Significant decrease in brain tissue density compared to those with cirrhosis alone
  - Significantly smaller brain volume than other cirrhotic patients post liver transplant

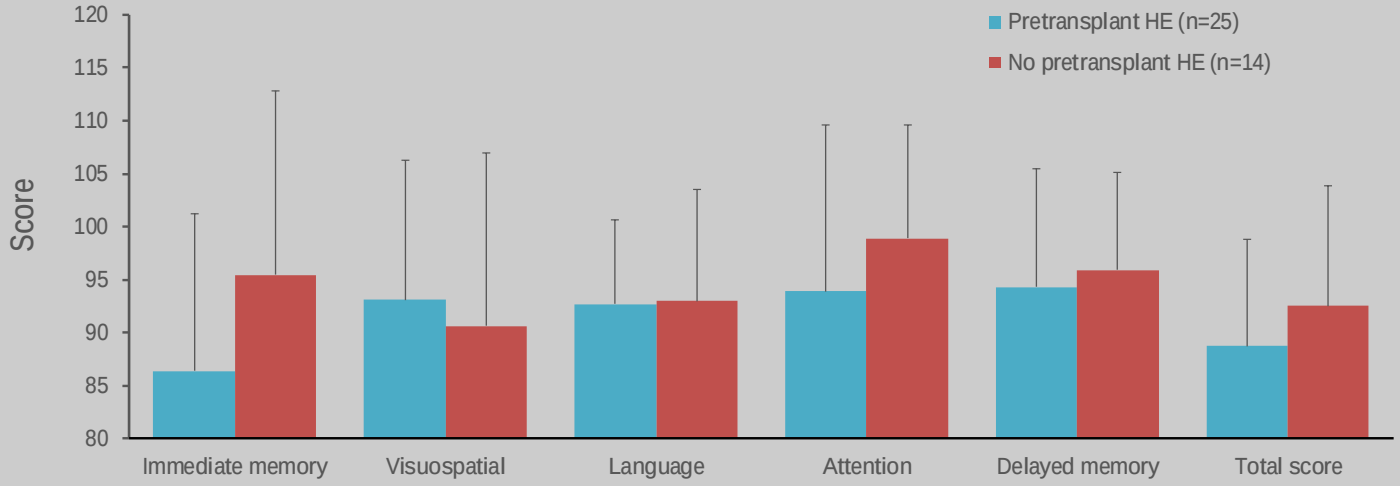


For illustrative purposes only

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

Cognitive Function May be Compromised, Even Post Liver Transplant[1]

- Study objective: evaluate the cognitive function and quality of life in a group of OLT recipients who had suffered from overt HE prior to their procedure
- Patients with cirrhosis with and without overt HE scheduled for liver transplantation (n=39) underwent 2 psychometric batteries* an average of 18 months after liver transplant



*Includes the psychometric hepatic encephalopathy score and Repeatable Battery for the Assessment of Neuropsychological Status. Error bars indicate standard deviation. †Based on results of Repeatable Battery for the Assessment of Neuropsychological Status. ‡$P<0.001$ vs normative values. §$P<0.05$ vs normative values.

1. Sotil et al. *Liver Transpl*. 2009;15:184-192. Figure adapted from Sotil et al. *Liver Transpl*. 2009;15:184-192, with permission.

HE Treatment Guidelines Recommend Prophylaxis Treatment Post HE Episode or HE Hospitalization

- HE Practice Guidelines developed by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver recommend secondary prophylaxis after an overt HE episode

- Preventative care post discharge due to an HE event is also recommended
  - Patients and relatives should be educated on side effects of medications
  - The importance of adherence to medications should be emphasized
  - Patients and caregivers should be counseled on recognizing early signs and symptoms of HE and actions to take if there is a recurrence

1. Vilstrup, H., Amodio, P., Bajaj, J., Cordoba, J., Ferenci, P., Mullen, K. D., Weissenborn, K. and Wong, P. (2014), 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, 60: 715–735. doi: 10.1002/hep.27210

Xifaxan 550 mg

A twice-daily tablet to reduce the risk of overt hepatic encephalopathy (HE) recurrences

Therapies For Reducing The Risk of HE Recurrence

Nonabsorbable Disaccharides (Lactulose)

- Products: Lactulose/Lactitol*[1]
  - Can be administered orally or via enema
- MOA
  - Works by flushing toxins out of the body by inducing diarrhea; acidifies stool
- Dose
  - 45 to 90 g/d, titrated to achieve 2 to 3 soft stools per day
- Drug to drug interactions and adverse events
  - Lactulose has been known to interact with other medications and affect absorption of those medications[2]
  - Abdominal cramping, diarrhea, nausea, vomiting and flatulence have been reported
    - Diarrhea may lead to other adverse events, including dehydration, hypernatremia, and hypokalemia[2]

*Lactitol is not currently available in the US.

1. Lactulose solution USP [package insert]. Apotex Corp, Inc; 2005. 2. Infomed.ch.Lactulose:Interactions. http://.infomed.ch/100drugs/lactadre.html Accessed September23, 2014

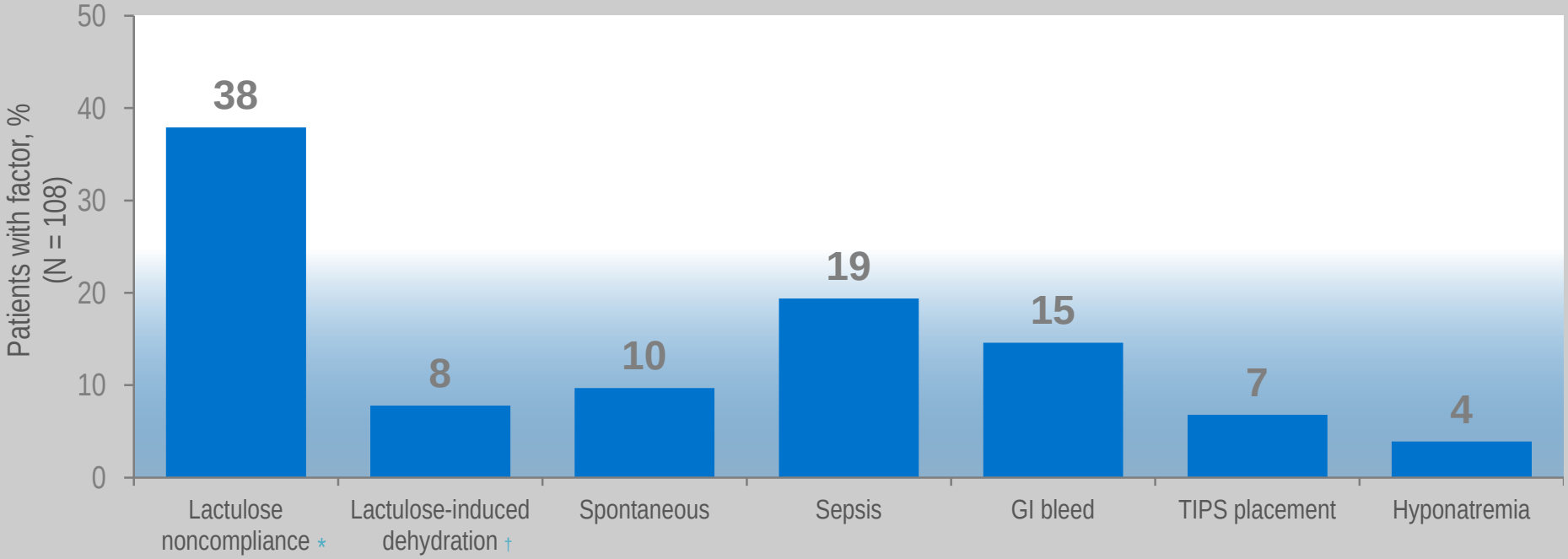
Lactulose Alone May Not Be Enough For Maintenance Therapy

- AASLD/EASL HE guidelines raise concerns over lactulose monotherapy to reduce the risk HE recurrences
  - In patients with HE, there is a 40% cumulative risk for another recurrence within 6 months despite lactulose treatment

- HE guidelines caution that overuse of lactulose may lead to complications, such as aspiration, dehydration, hypernatremia,
  - Overuse of lactulose may precipitate HE

1. Vilstrup, H., et. al(2014), 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, 60: 715–735. doi: 10.1002/hep.27210AASLD/EASL HE Guidelines. *Hepatology*. 2014

Common Factors Associated With HE Recurrence



In this study, patients with cirrhosis who were initiated on lactulose following an initial episode of HE in a liver transplant center were retrospectively followed. Recurrence of HE, precipitating factors, and adherence to lactulose were investigated using chart review and electronic pharmacy records, and predictors of HE recurrence were analyzed.

*Noncompliance inferred with evidence (as documented in patient charts) of discontinuation of lactulose as prescribed (determined by questioning patient or family members); lack of lactulose refill according to pharmacy records; and <2 bowel movements/day, for at least 1 month.

†Lactulose-induced dehydration defined as >4 bowel movements/day with dehydration and azotemia (new rise in serum creatinine >1.5 mg/dL).

Bajaj et al. *Aliment Pharmacol Ther*. 2010;31:1012-1017.

Conventional Antibiotics (Neomycin)

- Products: neomycin
  - Neomycin is indicated for adjunctive therapy in hepatic coma by reducing the ammonia-forming bacteria in the intestinal tract
- Profile
  - Potential for adverse events often precludes their use as first-line therapy for HE
  - Risk of infection by the opportunistic pathogen Clostridium difficile
  - Increased risk of serious adverse events limits use in prolonged therapy
- Adverse Events
  - Long-term use can cause ototoxicity and nephrotoxicity
- Other conventional antibiotics, such as metronidazole, are not indicated for hepatic encephalopathy

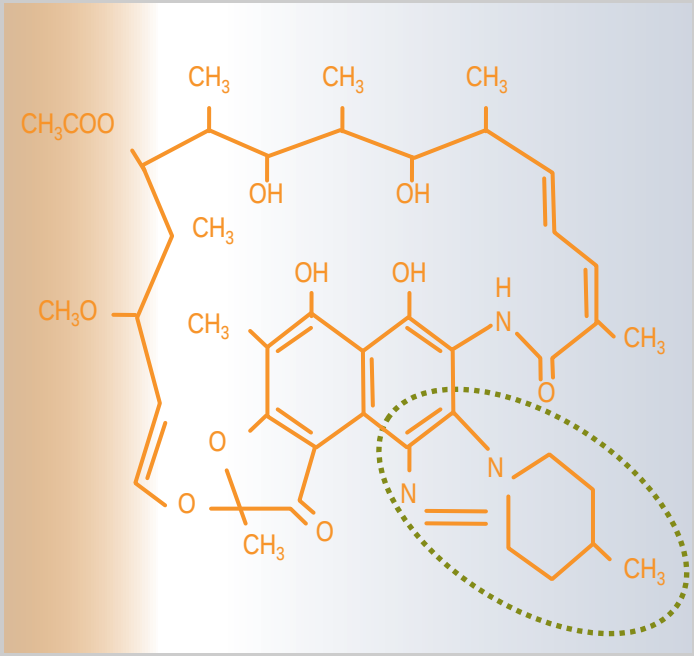
Neo-Fradin (neomycin sulfate) Prescribing Information

Xifaxan 550 mg

A twice-daily tablet to reduce the risk of overt hepatic encephalopathy (HE) recurrences

Xifaxan (rifaximin) 550 mg is a Nonsystemic Antibiotic

- Indicated for reduction in risk of overt hepatic encephalopathy (HE) recurrence in patients **≥18** years of age
- A minimally absorbed antibiotic that targets the gut
  - Low risk of bacterial resistance
- Broad-spectrum *in vitro* activity against Gram-positive and Gram-negative bacteria
- Concomitant administration of drugs that are P-glycoprotein (P-gp) inhibitors can substantially increase the systemic exposure to Xifaxan
- Caution should be exercised when administering Xifaxan to patients with severe hepatic impairment (Child-Pugh C)



1. Xifaxan [prescribing information]. Raleigh, NC: Salix Pharmaceuticals, Inc;

Phase 3 Clinical Trial of Xifaxan 550 mg For Reducing The Risk of HE Recurrence

Randomized, placebo-controlled, double-blind trial with an open-label extension

Xifaxan 550 mg is licensed by Alfa Wassermann S.p.A. to Salix Pharmaceuticals, Inc.

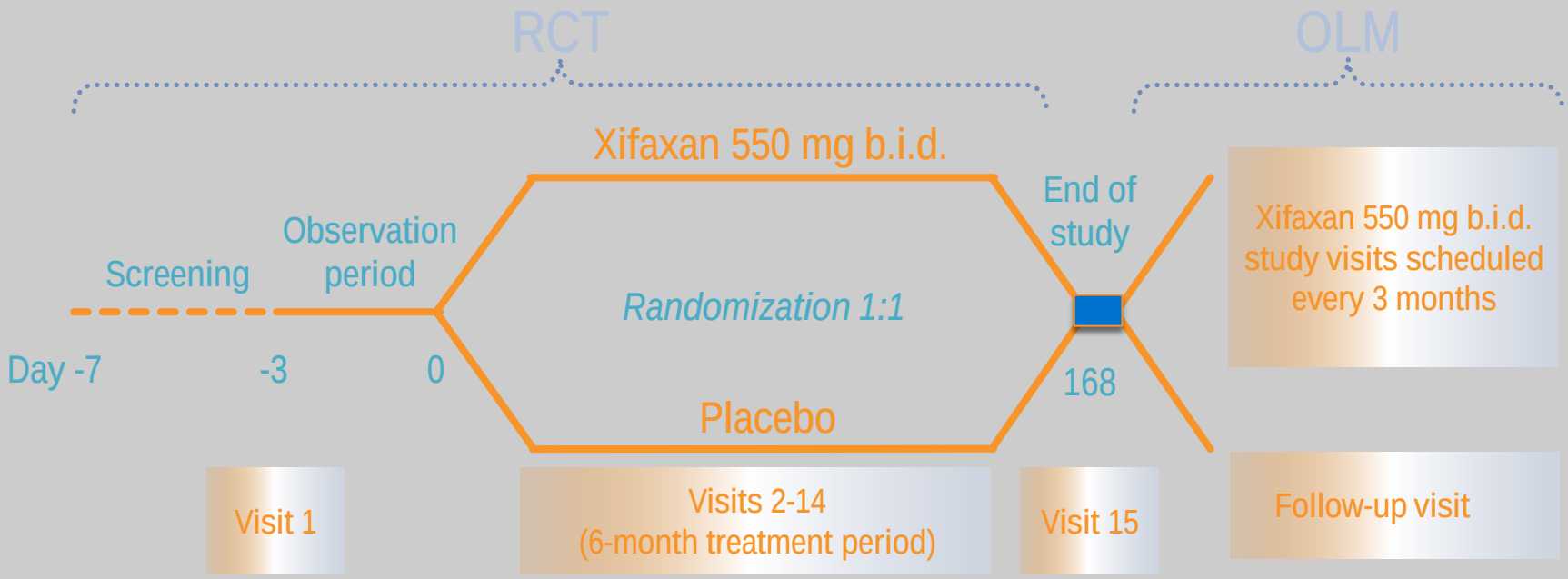
Study Objective And Key Eligibility Criteria

- Objective
  - Compare the maintenance of remission from previously demonstrated recurrent hepatic encephalopathy (HE) during 6 months of treatment with rifaximin at 550 mg twice daily (BID) or placebo
- Inclusion criteria
  - ≥2 episodes of HE (Conn score ≥2) associated with cirrhosis within 6 months of screening
  - Currently in HE remission (ie, Conn score = 0 or 1 and MELD score ≤25)
- Exclusion criteria
  - Active SBP or intercurrent infection
  - GI hemorrhage or TIPS placement within 3 months of screening
  - Chronic renal or respiratory insufficiency, anemia, or electrolyte abnormality

GI = gastrointestinal; HE = hepatic encephalopathy; MELD = model for end-stage liver disease; SBP = spontaneous bacterial peritonitis; TIPS = transjugular intrahepatic portosystemic shunt.

Bass et al. *N Engl J Med*. 2010;362:1071-1081.

Study Design[1,2]

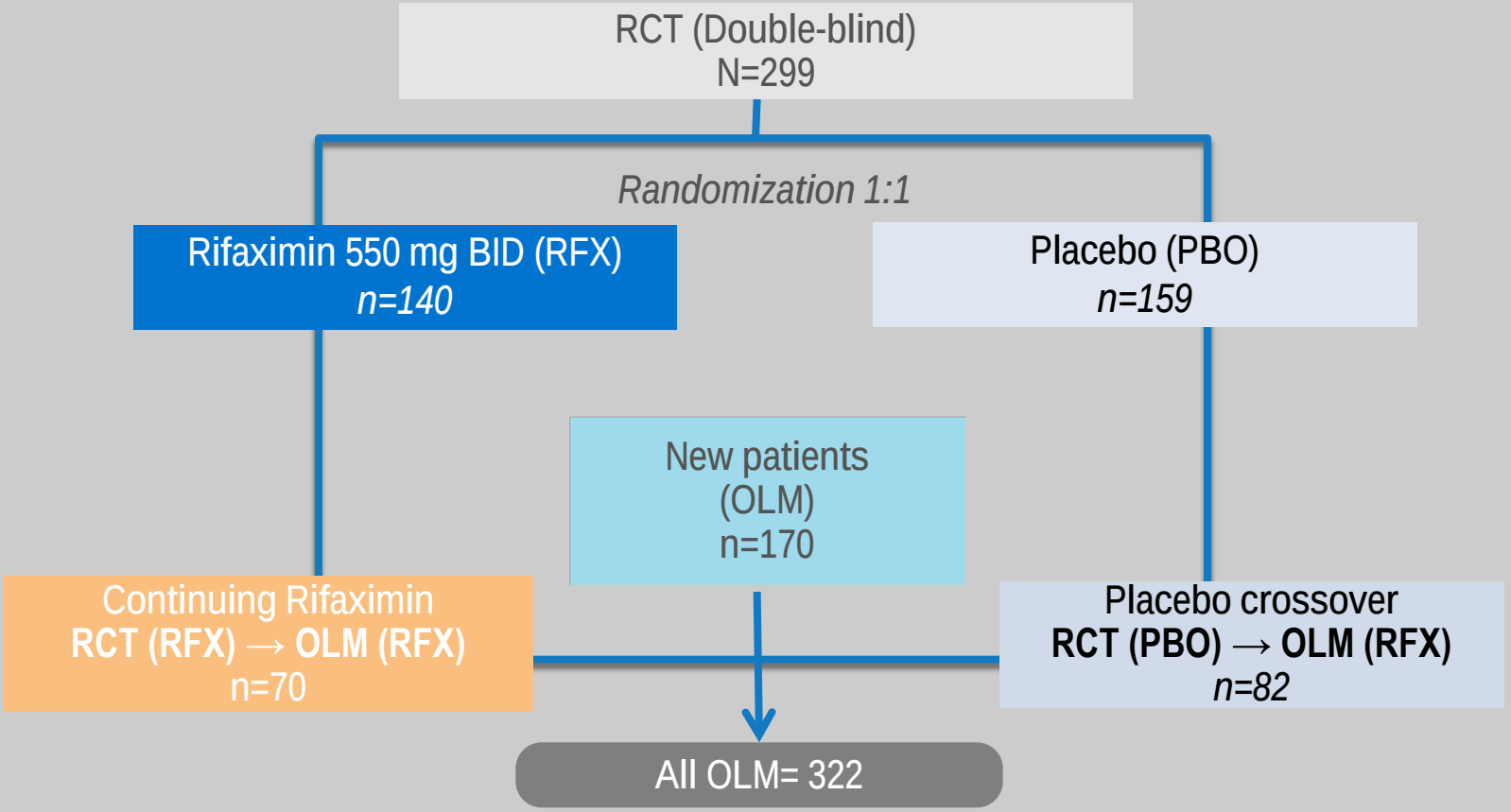


Concomitant lactulose (approximately 90% in both arms) use was permitted throughout the RCT and OLM trials.

b.i.d. = twice daily; OLM = open-label maintenance; RCT = randomized controlled trial.

1. Bass et al. *N Engl J Med*. 2010;362:1071-1081. 2. Mullen et al. *Clin Gastroenterol Hepatol.* 2013; pii: S1542-3565(13)01968-X.

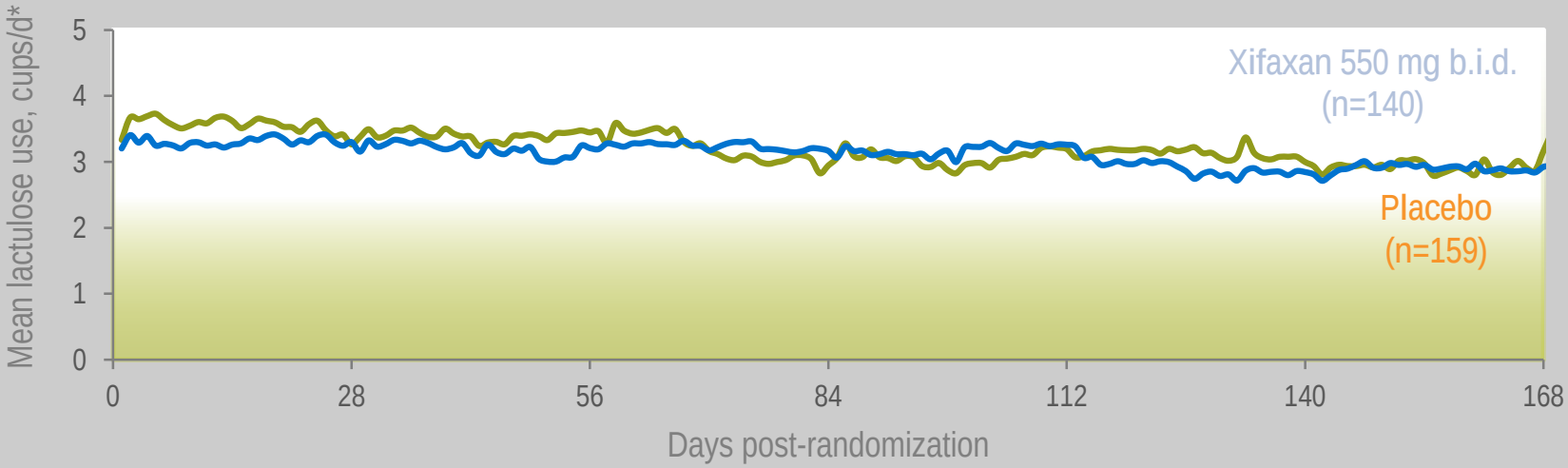
Patient Disposition



"All Rifaximin" population= 392 (140+170+82)

Bass et al. *N Engl J Med*. 2010;362:1071-1081.

Daily Lactulose Use Remained Stable Throughout Pivotal Phase III Trial



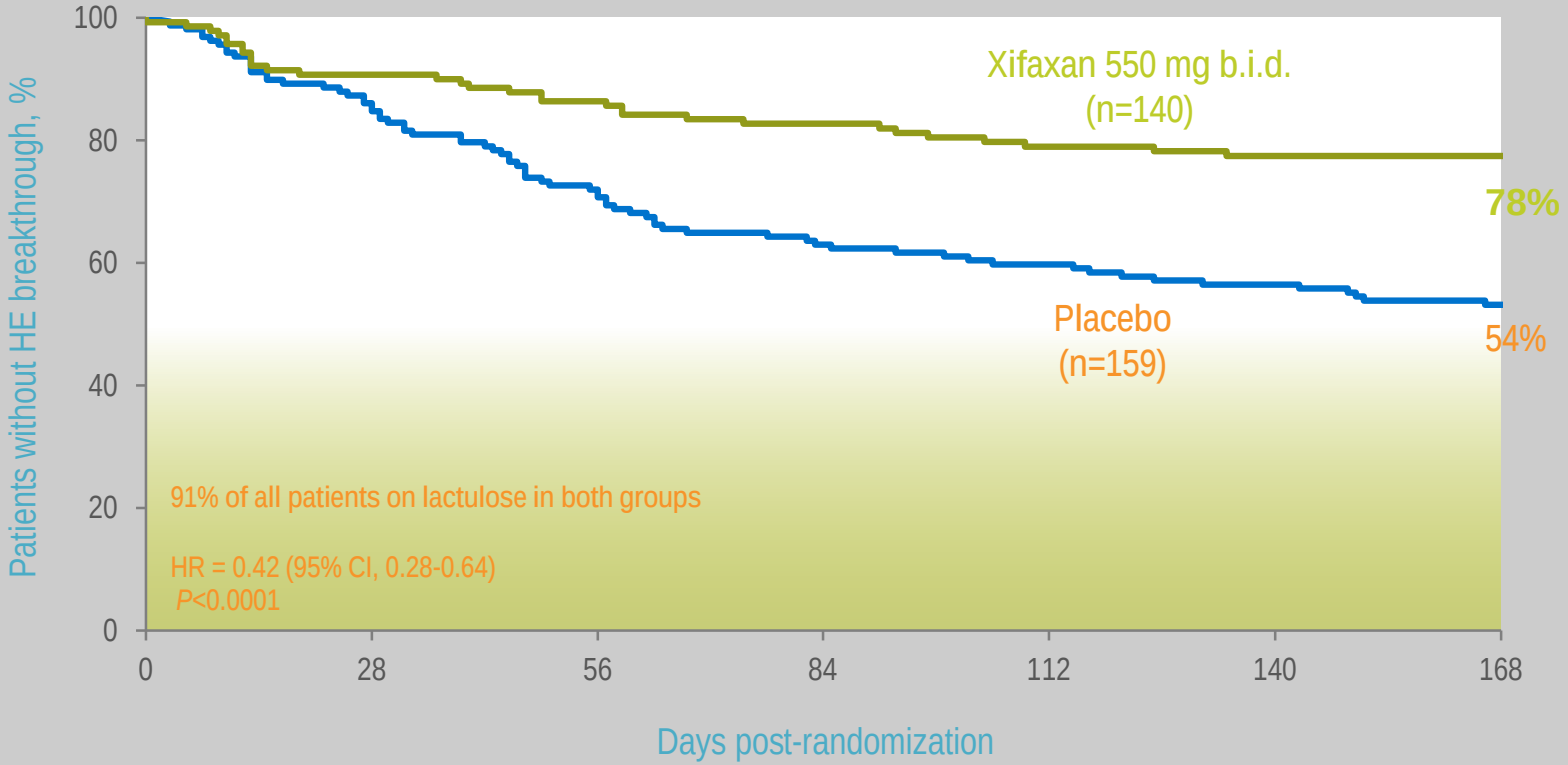
Parameter	Xifaxan 550 mg b.i.d.	Placebo
Daily lactulose use, mean ± SD, cups/d*	3.14 ± 2.10	3.51 ± 2.59
Rate of change in lactulose use, mean ± SD	0.0030 ± 0.0377	0.0076 ± 0.1060

b.i.d. = twice daily; HE = hepatic encephalopathy; SD = standard deviation.

*1 cup = 15 mL/cup at 10 g/15 mL.

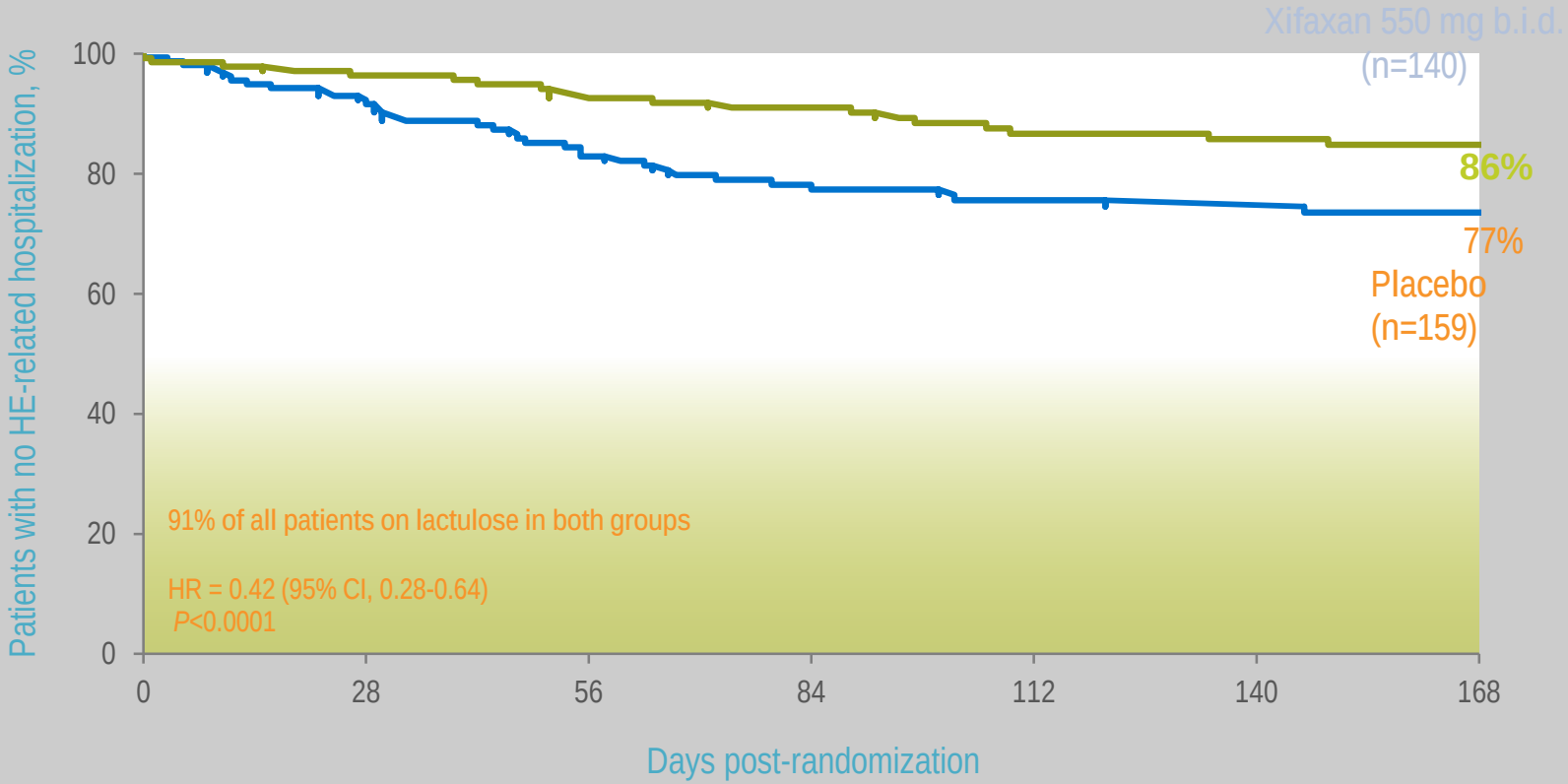
Figure and table adapted from Bass et al. *N Engl J Med.* 2010;362(12):1071-1081.

Xifaxan 550 mg Reduced the Risk of Breakthrough HE Episode by 58% vs. Placebo[1,2]



1. Bass et al. *N Engl J Med*. 2010;362:1071-1081. 2. Xifaxan [prescribing information]. Raleigh, NC: Salix Pharmaceuticals, Inc; 2011. Figure adapted from Bass et al. *N Engl J Med.* 2010;362:1071-1081. With permission.

Xifaxan 550 mg Reduced The Risk of HE-Related Hospitalization by 50% vs. Placebo[1,2]



1. Bass et al. *N Engl J Med*. 2010;362:1071-1081. 2. Xifaxan [prescribing information]. Raleigh, NC: Salix Pharmaceuticals, Inc; 2011. Figure adapted from Bass et al. *N Engl J Med.* 2010;362:1071-1081. With permission.

Xifaxan 550 mg Number Needed to Treat in Relation to Other Therapeutic Classes

Condition	Treatment	To Prevent	NNT
HE[1]	Xifaxan 550 mg + lactulose	Breakthrough HE First HE-related hospitalization	4 9
Hypertension[2]	Beta-blockers	CV event in 5 years	140
Diabetes[3]	Sulfonylurea-insulin	Diabetes-related death	29
Kidney transplant[4]	Sirolimus or everolimus	CMV disease Acute rejection	21 18-41
CV disease[5]	Statins	CV event in 10 years	12-26

The above data is not a comparison of NNT among different treatments but is intended to provide an overview of published data on NNT.

1. Bass et al. *N Engl J Med.* 2010;362:1071-1081.2. Wiysonge et al. *Cochrane Database Syst Rev.* 2007;1:CD002003. 3. Devries. *Diabetologia.* 2011;54(3):705-706. 4. Webster et al. *Cochrane Database Syst Rev.* 2006;2:CD004290. 5. Mcelduff et al. *Heart.* 2006;92:1213-1218.

Xifaxan 550 mg in HE: Rate of Adverse Events[1,2] Events

Adverse event,* % (rate†)	RCT		All Xifaxan 550 mg b.i.d. patients‡ (n=392)
	Xifaxan 550 mg b.i.d. (n=140)	Placebo (n=159)	
Nausea	14 (0.4)	13 (0.5)	22 (0.2)
Peripheral edema	15 (0.4)	8 (0.3)	21 (0.2)
Urinary tract infection	6 (0.2)	9 (0.3)	20 (0.2)
Ascites	11 (0.3)	9 (0.3)	17 (0.1)
Anemia	8 (0.2)	4 (0.1)	16 (0.1)
Abdominal pain	9 (0.2)	8 (0.3)	15 (0.1)
Fatigue	12 (0.3)	11 (0.4)	14 (0.1)
Vomiting	7 (0.2)	9 (0.3)	14 (0.1)
Diarrhea	11 (0.3)	13 (0.5)	13 (0.1)
Muscle spasms	9 (0.3)	7 (0.2)	13 (0.1)
Dizziness	13 (0.4)	8 (0.3)	12 (0.1)
Dyspnea	6 (0.2)	4 (0.2)	12 (0.1)

b.i.d. = twice daily; HE = hepatic encephalopathy; RCT = randomized controlled trial. *Adverse events other than HE reported in >12% of patients in either RCT treatment group or "all Xifaxan" patients.

†Event rate was calculated as the number of events that occurred divided by patient exposure year).

‡Consists of patients who took **≥1 dose** of rifaximin and for whom a safety assessment was conducted. Includes 140 patients from the RCT and 252 new rifaximin patients in the open-label extension trial.

1. Bass et al. *N Engl J Med.* 2010;362:1071-1081.2. Mullen et al. *Clin Gastroenterol Hepatol.* 2013; pii: S1542-3565(13)01968-X.

Xifaxan 550 mg Treatment in HE: Overall Safety

	RCT				All Xifaxan 550 mg b.i.d. patients* (n=392)	
	Xifaxan 550 mg b.i.d. (n=140)		Placebo (n=159)			
	Patients, %	Event rate†	Patients, %	Event rate†	Patients, %	Event rate†
Any AEs	80	2.2	80	2.8	92	0.7
SAEs	36	1.0	40	1.4	62	0.5
AEs causing discontinuation	21	0.6	28	1.0	33	0.2

AE = adverse event; b.i.d. = twice daily; HE = hepatic encephalopathy; RCT = randomized controlled trial; SAE = **serious AE. *Consists of patients who took ≥1dose of** rifaximin and for whom a safety assessment was conducted. Includes 140 patients from the RCT and 252 new rifaximin patients in the open-label extension trial.
†Event rate was calculated as the number of events that occurred divided by patient exposure years.

Mullen et al. *Clin Gastroenterol Hepatol.* 2013;pii: S1542-3565(13)01968-X.

Xifaxan 550 mg Does Not Have an Adverse Effect on Mortality

Analysis group	Death, n	Death rate*	Persons Years of Exposure	*P* value†
Placebo RCT (n=159)	11	0.2	46.0	—
All Xifaxan 550 mg b.i.d. (n=392)	76	0.1	510.5	0.1480

No significant difference in the occurrence or rate of mortality was observed with Xifaxan 550 mg versus placebo, indicating that Xifaxan 550 mg did not adversely affect long-term survival

b.i.d. = twice daily; CI = confidence interval; OLM = open label maintenance; RCT = randomized controlled trial.

†Obtained from parameter estimates with effect for treatment and region.

*Includes patients in the placebo group of the RCT who switched to Xifaxan 550 mg during the OLM trial and patients newly recruited into the OLM trial.

Mullen et al. *Clin Gastroenterol Hepatol.* 2014;pii: S1542-3565(13)01968-X.

In Summary, Continuous Management With Xifaxan 550 mg Can Help Reduce the Risk of HE Recurrence

- Xifaxan 550 mg tablets are indicated for reduction in risk of overt hepatic **encephalopathy (HE) recurrence in patients ≥ 18 years of** age
  - For HE, Xifaxan 550 mg is thought to have an effect on gut flora
- Xifaxan 550 mg reduced the risk of breakthrough HE episode by 58% vs. placebo
- Xifaxan 550 mg reduced the risk of HE-related hospitalization by 50% vs. placebo
- In a clinical study, nonsystemic Xifaxan 550 mg had a tolerability profile comparable to placebo for most adverse events when used as directed
  - Caution should be used in patients with severe hepatic impairment
- Long-term use of Xifaxan 550 mg (≥ 24 months) does not show an increased rate of AEs or change in survival rates[1]

1. Mullen et al. *Clin Gastroenterol Hepatol.* 2014;pii: S1542-3565(13)01968-X.

Important Safety Information

Important Safety Information about XIFAXAN 550 mg

XIFAXAN® (rifaximin) 550 mg tablets are contraindicated in patients with a hypersensitivity to rifaximin, any of the rifamycin antimicrobial agents, or any of the components in XIFAXAN. Hypersensitivity reactions have included exfoliative dermatitis, angioneurotic edema, and anaphylaxis.

Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including XIFAXAN, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon which may lead to overgrowth of C. difficile. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against C. difficile may need to be discontinued.

There is increased systemic exposure in patients with more severe hepatic dysfunction. The clinical trials were limited to patients with MELD scores < 25. Therefore, caution should be exercised when administering XIFAXAN to patients with severe hepatic impairment (Child-Pugh C).

Important Safety Information (cont.)

Concomitant administration of drugs that are P-glycoprotein (P-gp) inhibitors with XIFAXAN can substantially increase the systemic exposure to XIFAXAN. Caution should be exercised when concomitant use of XIFAXAN and a P-gp inhibitor such as cyclosporine is needed. In patients with hepatic impairment, a potential additive effect of reduced metabolism and concomitant P-gp inhibitors may further increase the systemic exposure to XIFAXAN.

Based on animal data, XIFAXAN may cause fetal harm. Discontinue in nursing mothers after taking into account the importance of the drug to the mother.

The most common adverse reactions occurring in ≥ 10% of patients and at a higher incidence than placebo in the clinical study were peripheral edema (15%), nausea (14%), dizziness (13%), fatigue (12%), and ascites (11%).

Xifaxan 550 mg is licensed by Alfa Wassermann S.p.A. to Salix Pharmaceuticals, Inc.

Please see complete Prescribing Information for XIFAXAN.