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FOR 3RD YEAR GI FELLOWS

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CLDF

Chronic Liver Disease Foundation

Complications of Cirrhosis

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Complications of Cirrhosis

- Thrombocytopenia
- Varices
- Ascites
  - Hepatorenal Syndrome
  - Spontaneous Bacterial Peritonitis (SBP)
  - Hepatic Hydrothorax
- Hepatic Encephalopathy (HE)

Thrombocytopenia

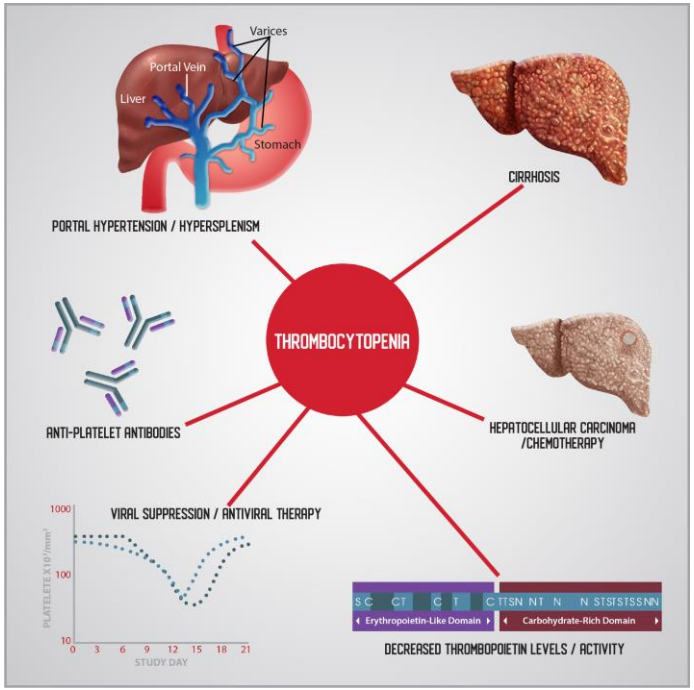
Thrombocytopenia in CLD

- Thrombocytopenia is a common problem in patients with chronic liver disease (CLD) (< 100,000)
  - Estimated to affect up to 70% of CLD patients
  - Extent worsens with severity of portal hypertension and disease
  - Patients may be ineligible for elective surgical or diagnostic procedures due to risk of bleeding
  - Increases risk of mortality
  - Increases risk of poor clinical outcomes

Mitchell O, et al. *Hepatic Medicine: Evidence and Research*. 2016;8:39-50; Maan, et al. *Drugs*. 2015;75(17):1981-92; Giannini EG. *Aliment Pharmacol Ther.* 2006;23:1055-65.

Etiologies of Thrombocytopenia in Chronic Liver Disease

- Splenic sequestration secondary to portal hypertension
- Direct bone marrow suppression secondary to viruses, alcohol, iron, or drugs
- Increased destruction secondary to anti-platelet antibodies, shear stress, infection, or increased fibrinolysis
- Decreased production of thrombopoietin (TPO) by the liver



Mitchell O, et al. *Hepatic Medicine: Evidence and Research*. 2016;8:39-50; Maan, et al. *Drugs*. 2015;75(17):1981-92; Afdhal N et al. *Journal of Hepatology*. 2008;48:1000-1007.

Guideline Recommendations for Appropriate Platelet Levels Based on Procedure

Guideline	Year	Transfusion Recommendations and Cited Evidence
American Association of Study of Liver Diseases (AASLD)	2009	• Platelet transfusion should be considered when levels are less than 50-60x10^9/L (this applies whether one is attempting **liver biopsy transcutaneously or transvenously)**
American Society of Gastrointestinal Endoscopy (ASGE) [Gastroenterologist]	2012	• Platelet threshold 20x10^9/L for **diagnostic endoscopy**; 50x10^9/L if biopsies performed

Rockey et al. *Hepatology*. 2009;49(3):1017-1044; Ben-Menachem et al. *Gastrointest Endosc.* 2012.

Platelet Transfusions: Benefits and Considerations

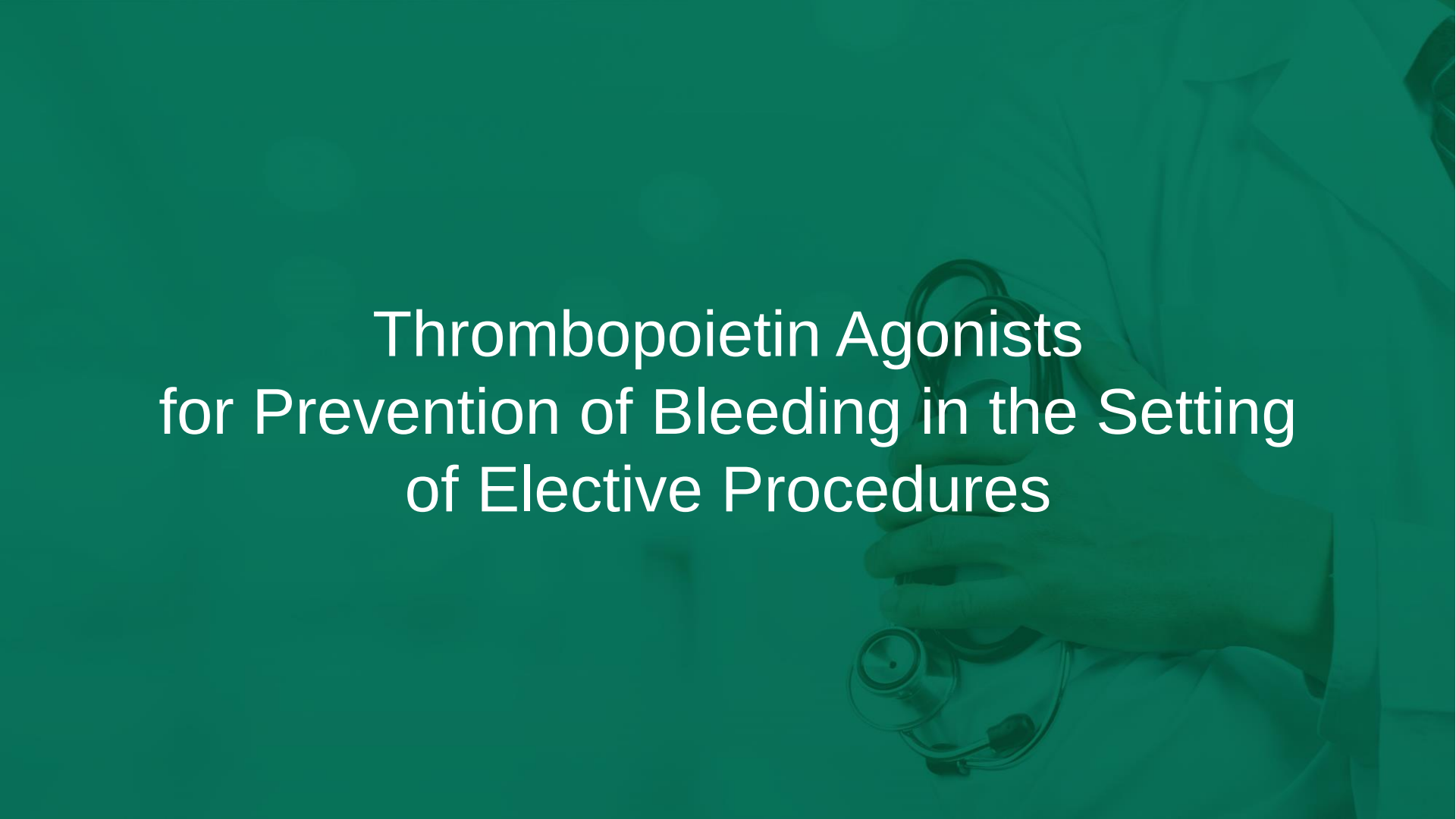
Benefits:

- Prevent the risk of bleeding:
  - Thrombocytopenic patients
  - Patients with platelet dysfunction
- Control bleeding in patients with active bleed

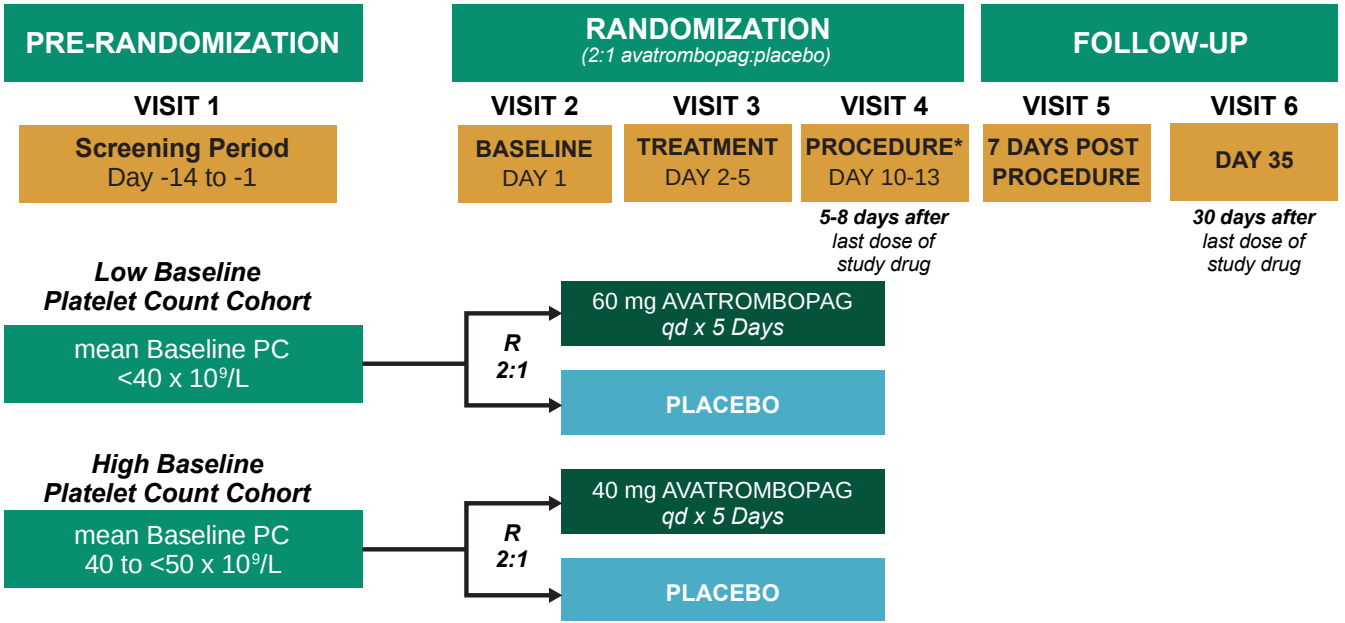
Considerations:

- Risk of infections
- Hemolytic/Febrile non-hemolytic/Allergic/ Anaphylactic Reactions
- Refractoriness (immune vs nonimmune)
- Storage logistics
- Patient scheduling logistics
- Limited shelf life
- Cost
- Supply vs demand

Thrombopoietin Agonists for Prevention of Bleeding in the Setting of Elective Procedures



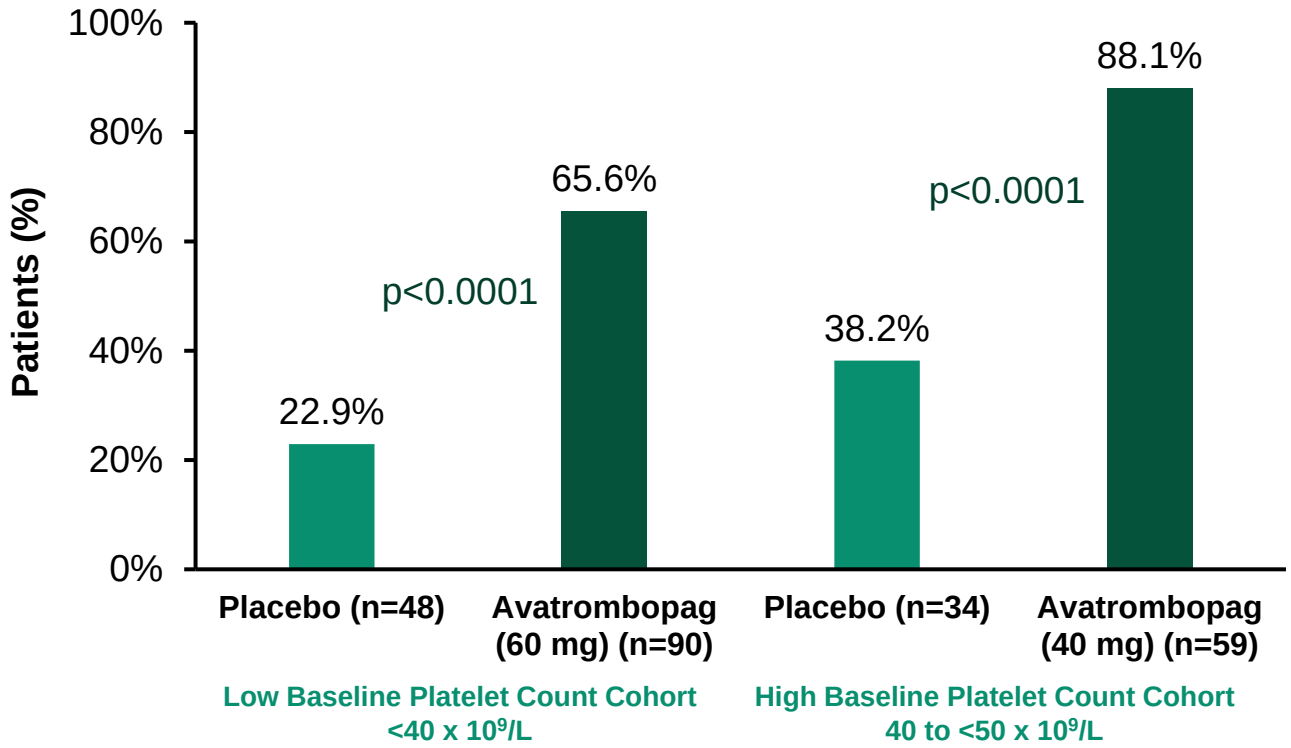
Avatrombopag Phase 3 Study Design ADAPT-1 & ADAPT-2



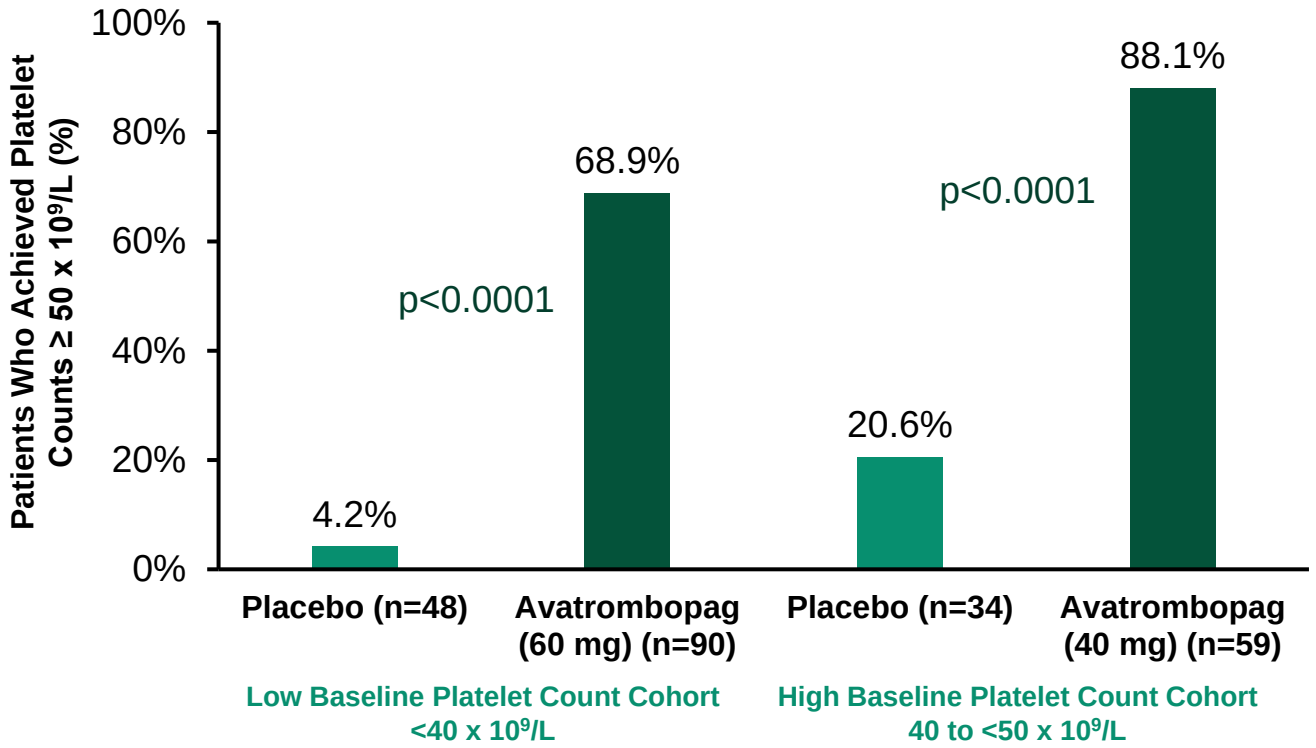
*Platelet transfusions were not mandatory

AASLD 2017

Proportion of Patients Who Did NOT Require Platelet Transfusion or Any Rescue Procedure for Bleeding

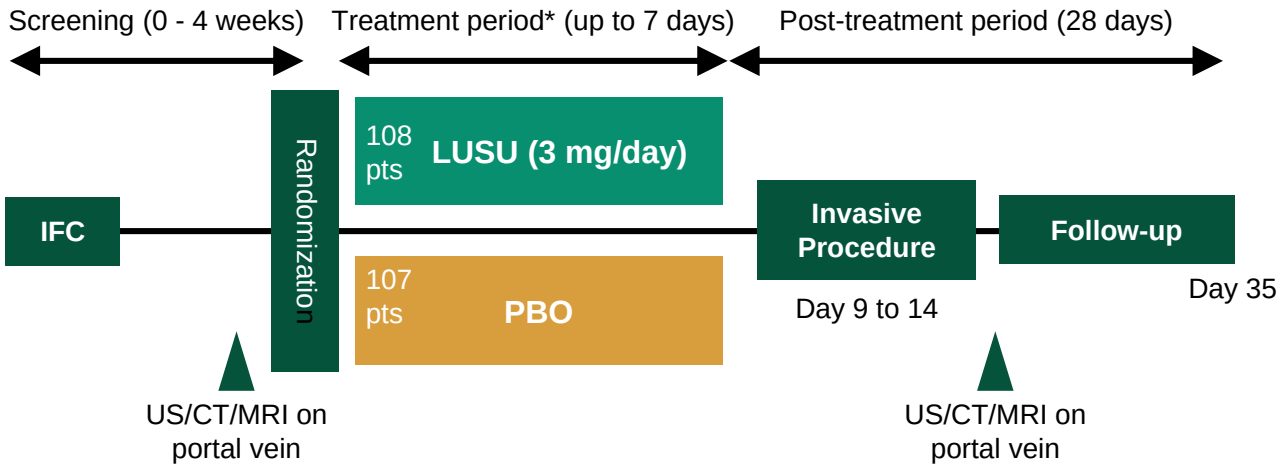


Proportion of Patients Who Achieved Platelets Counts ≥ 50 x 10^9/L on Procedure Day



Lusutrombopag Study Design

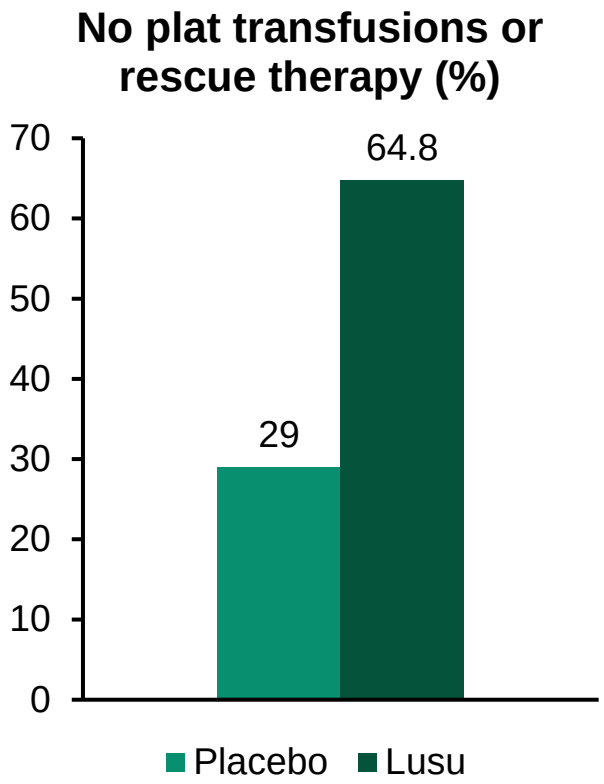
- Phase 3, multinational, randomized, double-blind, placebo-controlled study
  - Conducted at 138 study sites in 22 countries
- Platelet transfusion was required by the protocol if a patient's post treatment pre-procedural platelet count was below 50 x 10^9/L

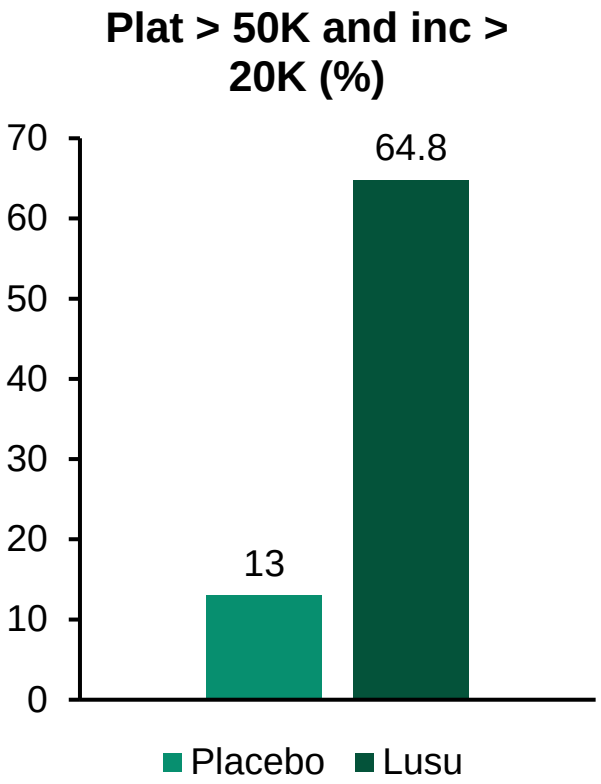


*If a patient met the stopping criterion on Day 5, 6 and 7 (platelet count ≥ 50 x 10^9/L with an increase of ≥ 20 x 10^9/L from baseline), no additional dose of study drug was administered.

CT, computed tomography; ICF, informed consent form; LUSU, lusutrombopag; MRI, magnetic resonance imaging; PBO, placebo; US, ultrasonography.

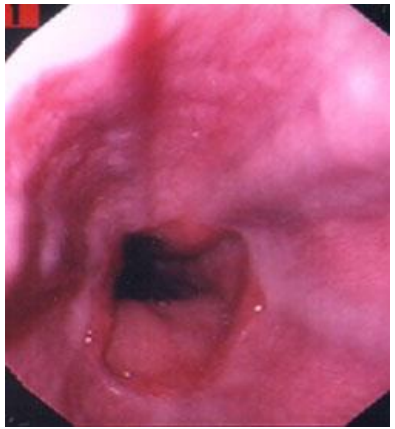
Lusutrombopag



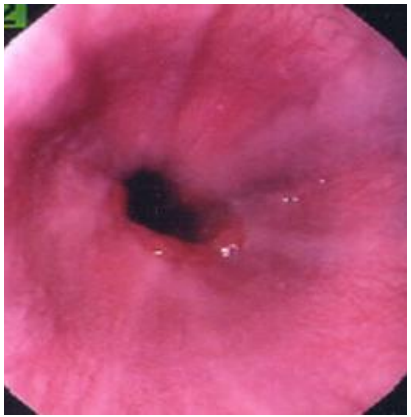


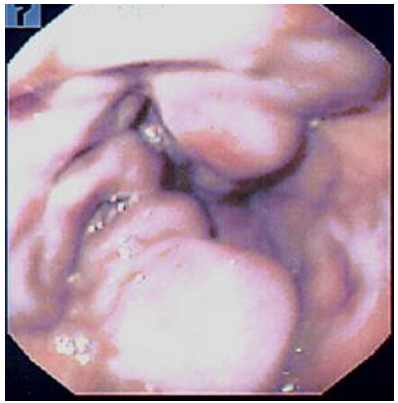
Varices

Esophageal Varices

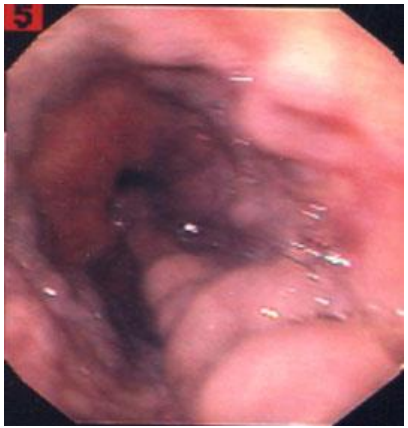


Small

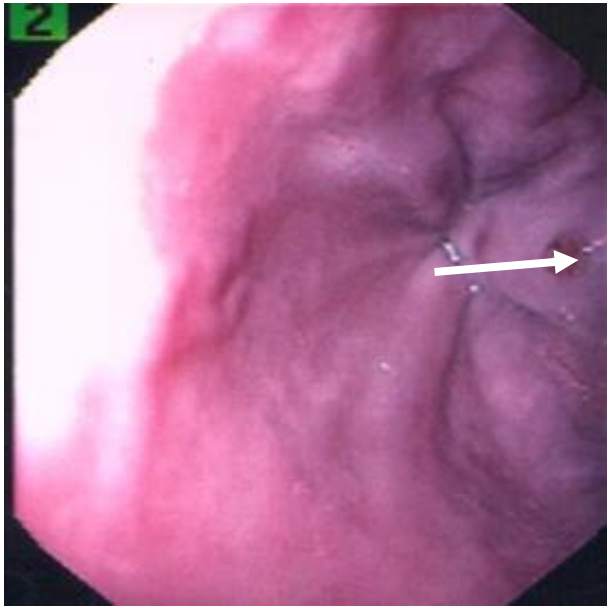


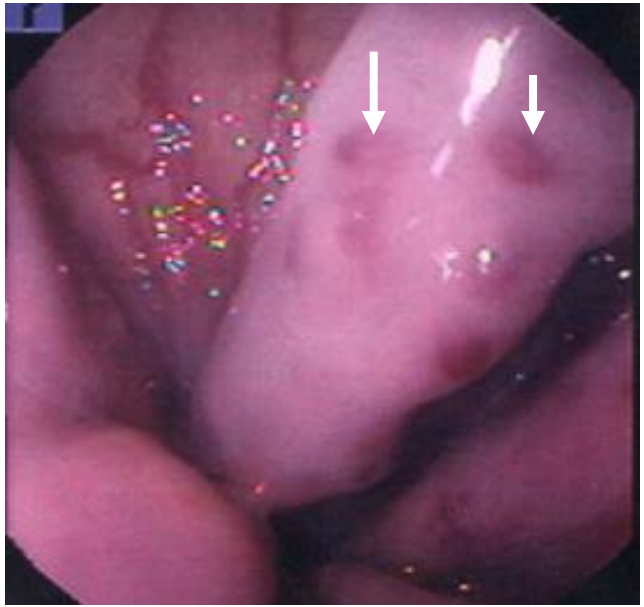


Large

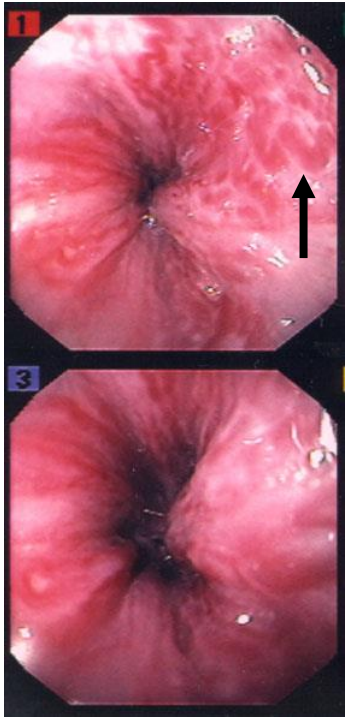


“Cherry Red” Spots

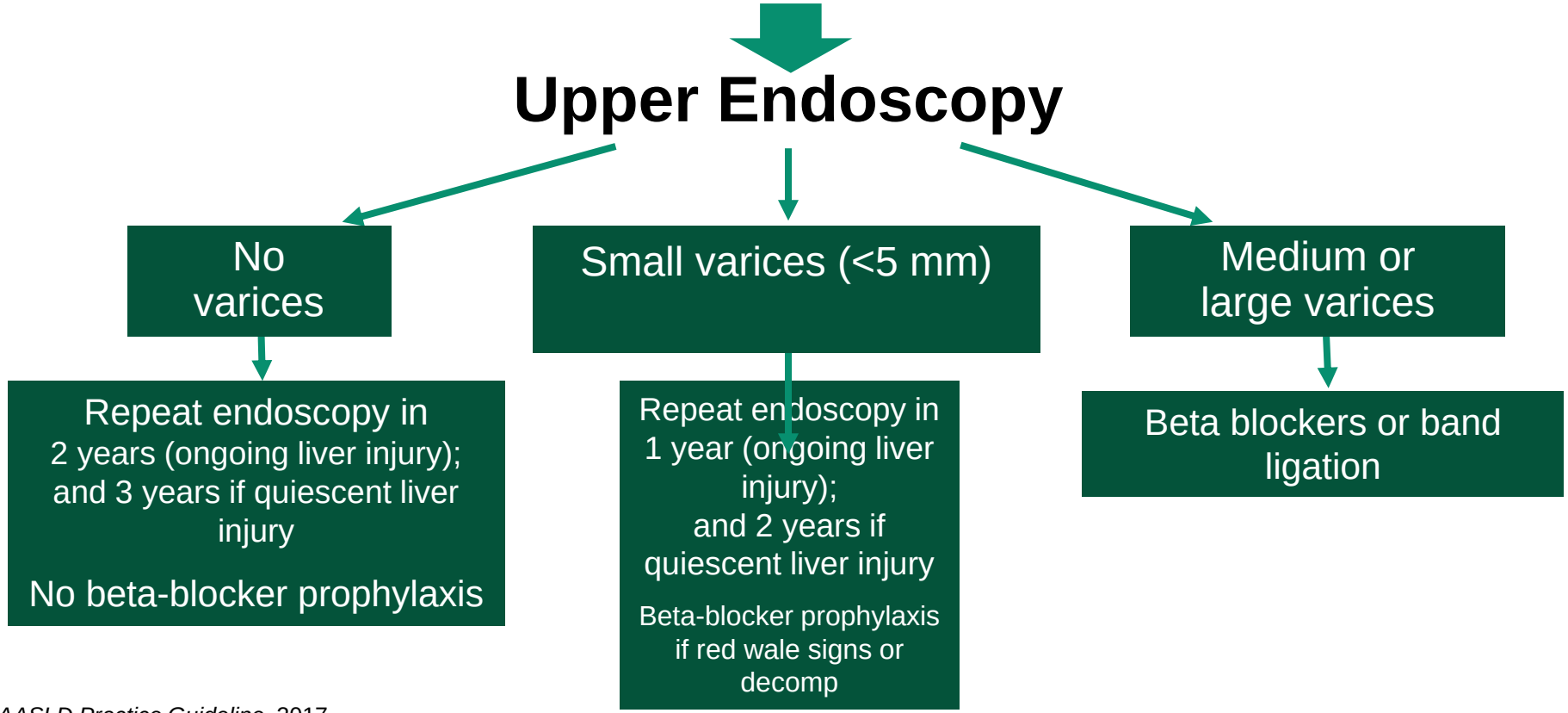




“Red Wales”



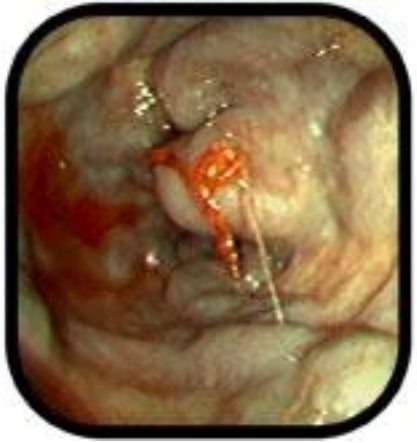
Management: Cirrhosis Screening and Surveillance



AASLD Practice Guideline. 2017

Management of Acute Hemorrhage

- Band ligation is effective and the ideal option in the acute setting
- Somatostatin or its analog (octreotide) should be initiated and maintained for 2-5 days
- TIPS may be useful as preemptive therapy in some patients, although in general it is reserved as salvage therapy
- Beta blockers should be initiated when vasoactive therapy is discontinued



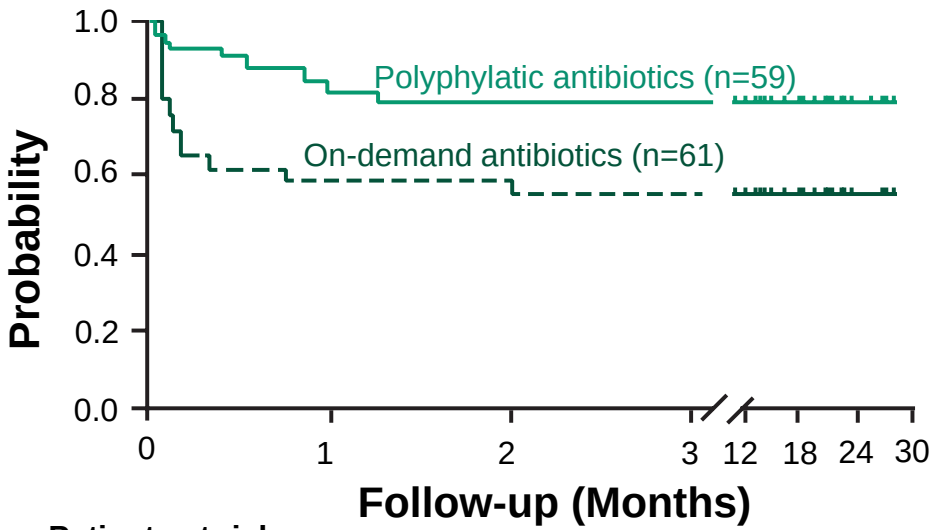
Bacterial Infection and Variceal Bleeding

- Increased risk of bacterial infection
  - (SBP or bacteremia without obvious source)
- Develops in 20% of patients within 48 hours and 35-66% within 2 weeks
- More common in hospitalized patients with variceal bleeding than other complications
- Compared to patients without infection presence of infection is associated with
  - Failure to control bleeding (65% vs 15%)
  - Early rebleeding
  - Mortality (40% vs 3%)

Vivas et al. *Dig Dis Sci*. 2001.

Antibiotic Prophylaxis During/After Acute Variceal Bleeding

- Prophylatic ofloxacin vs antibiotics only at diagnosis of infection
- ↓ infections (2/59 vs 16/61)
- Less rebleeding within 7 days
- ↓ blood transfusions for rebleeding
- IV ceftriaxone for a maximum of 7 days is recommended in management of acute variceal hemorrhage



Patients at risk

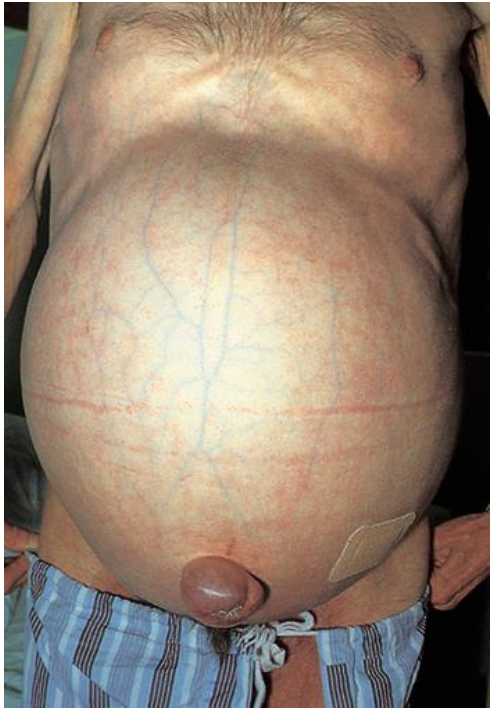
Prophylactic:	59	48	42	38	17	8	2			
On demand:	51		36		34		30	19	9	2

Hepatology. 2004;39:746; AASLD Practice Guidelines 2017.

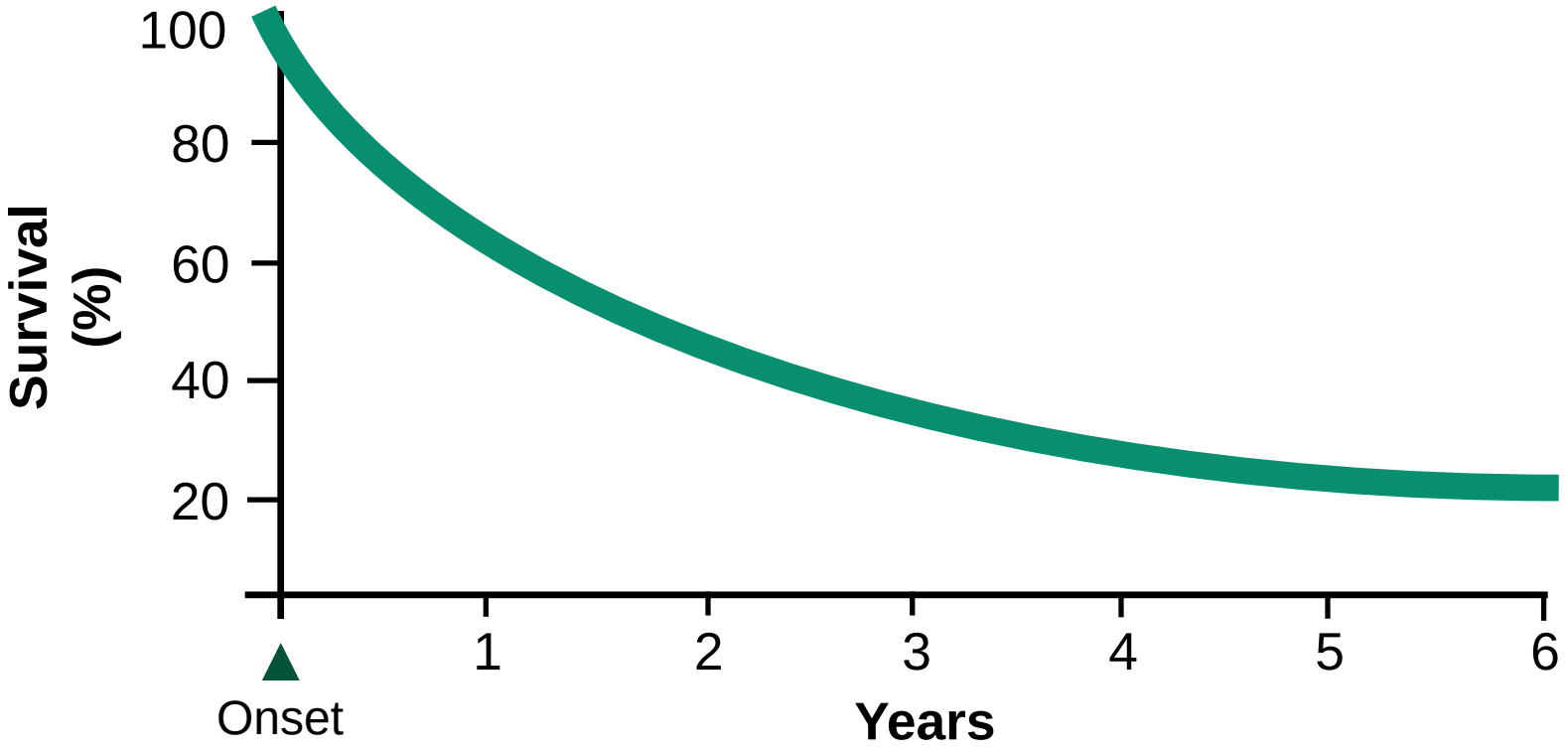
Ascites

Ascites

- Fatigue
- Poor quality of life
- Muscle wasting/catabolism
- Umbilical hernia with risk of rupture
- Hydrothorax
- SBP
- Hepatorenal Syndrome
- Pain
- Respiratory difficulties



Cirrhotic Ascites – Survival



Ascites Due to Cirrhosis: Diagnosis

- Physical Examination and Ultrasonography
  - 1.5-3.0 liters: Shifting dullness
  - 10 liters: Fluid wave
- Paracentesis
  - <1% risk of Hematoma or hemoperitoneum
  - No need for FFP or platelets for paracentesis
  - Helps in differential diagnosis
  - 20% prevalence of SBP/infection at time of admission
  - Indication:
    - Ascites!
    - New diagnosis
    - Fevers
    - Deterioration of liver disease during hospitalization

Management of Ascites

First Line Therapy

Tense ascites

→ Paracentesis

→ Sodium restriction (<2 Gm/24 Hrs) and diuretics

Non-tense ascites → Sodium restriction (<2 Gm/24 Hrs) and diuretics

Refractory Ascites 10%

Second Line Therapy

Repeated Large volume paracentesis (LVP)

TIPS

Liver Transplantation

- Diuretics: Spironolactone 100 mg/day, +/- furosemide 40 mg/day or bumetanide 1 mg a day.
- Uptitrate stepwise to spironolactone 400 mg/day, furosemide 160 mg/day or bumetanide 4 mg/day as long as it is tolerated

- Post paracentesis albumin infusion may not be necessary for < 5 liters removed
- Albumin infusion of 6-8 gm/liter of fluid removed is a consideration for repeated LVP

Other Recommendations for Patients with Refractory Ascites

- High dose beta blockers are not recommended
- Angiotensin Converting Enzymes Inhibitors and Angiotensin Receptor Blockers should be avoided
- Midodrine should be considered

Ascitic Fluid Analysis

Routine	Optional	Unusual
Cell count	Cytology	Glucose
Albumin	Amylase	LDH
Culture (in blood-culture bottles)	TB smear/culture	CEA
Total Protein		

Ascitic Fluid Infection

- Spontaneous bacterial peritonitis
- Monomicrobial non-neutrocytic bacterascites
- Culture negative neutrocytic ascites

Spontaneous Bacterial Peritonitis

- Polymorphonuclear leukocytes > 250 /mL
- Positive ascites culture (in blood culture bottles)
- Absence of intra-abdominal source of infection

Antibiotics in Cirrhosis for the Management of Known or Suspected SBP

- Spontaneous Bacterial Peritonitis
  - Cefotaxime – minimal dose 2 grams IV every 12 hours for a minimal duration of 5 days
  - Zosyn – dose 2 grams IV every 8 hours for a minimal duration of 5 days
  - Alternatives: Ceftizoxime, Ceftriaxone, Ceftazidine, Amoxicillin-Clavulanic acid
    - If patient has beta-lactam hypersensitivity – Quinolones (e.g. Ciprofloxacin)
- Albumin
  - Albumin infusion-dose of 1.5 grams/kg body weight within 6 hours of SBP diagnosis followed by 1 gram/kg BW on day 3 to reduce the risk of HRS
  - Albumin reduced mortality (29% to 10%)

Antibiotics for SBP Prophylaxis

- SBP prophylaxis
  - Secondary prophylaxis
    - Ciprofloxacin 500 mg per day
    - Double-strength trimethoprim/sulfamethoxazole daily by mouth
    - Intermittent dosing of prophylactic antibiotics may select resistant flora; daily dosing is preferred
  - Primary prophylaxis
    - High ascitic fluid protein (i.e. >1 gram/dL) – no prophylaxis indicated
    - Low ascitic fluid protein (i.e. <1 gram/dL) – no consensus but could consider for antibiotic prophylaxis

Renal Dysfunction

Differential Diagnosis of AKI in Cirrhosis

- Hepatorenal syndrome
  - Associated with bacterial infections
  - Not associated with bacterial infections
- Hypovolemia: diuretics, GI bleeding, diarrhea
- Acute tubular necrosis: shock, nephrotoxic drugs, other
- Nephrotoxicity: NSAIDs
- Intrinsic renal disease
- Miscellaneous, unknown

- Medical history
  - Physical examination
  - Blood tests
  - Urine tests
  - Abdominal ultrasound

Graupera I, et al. *Clin Liver Dis.* 2013;2:128-131.

Prevention of Acute Renal Injury in Cirrhotics

- Avoid aminoglycoside antibiotic
  - 10-fold increase renal toxicity
- Avoid NSAIDs
- Avoid I.V. contrast if possible or hydrate and use NAC
- Frequent monitoring of renal function in cirrhotic patient with ascites is essential
- Patient instruction on use of diuretics, lactulose, antibiotics, NSAID
- Early transfer of patients

Hepatorenal Syndrome

Hepatorenal Syndrome

- Functional renal failure without histological renal lesions
- Intense renal vasoconstriction
- Decreased renal perfusion and GFR associated with activation of renin-angiotensin system, ADH, SNS to maintain arterial pressure

Hepatorenal Syndrome: Diagnostic Criteria

- Cirrhosis with ascites
- Serum creatinine >133 μmol/L (1.5 mg/dL)
- No improvement of serum creatinine (↓ to a level of ≤ 133 μmol/L (1.5 mg/dL)) after at least 2 days with diuretic withdrawal and volume expansion with albumin; the recommended dose of albumin is 1 g/kg of body weight per day up to a maximum of 100 g/day
- Absence of shock
- No current or recent treatment with nephrotoxic drugs
- Absence of parenchymal kidney disease as indicated by proteinuria >500 mg/day, microhematuria (>50 red blood cells per high power field), and/or abnormal renal ultrasonography

Arroyo V et al. *Semin Liver Dis*. 2008;28:81-95.

Classification

- Two types
  - Type 1 – rapidly progressive, oliguria, very low urine Na, hyponatremia, precipitating event (SBP or other bacterial infection, surgery, GI bleed)
    - See death within 2-3 weeks
    - Dialysis is unhelpful unless transplantation planned
  - Type 2 – moderate renal insufficiency (Cr 1.5-2.5 mg/dl), steady for months, can degenerate into Type 1 with precipitant

Prevention

- Volume expansion therapy with diagnosed SBP
  - Albumin 1.5 gm/kg at diagnosis then 1.0 gm/kg at day
  - Significant decrease in subsequent HRS and hospital mortality
- Primary SBP prophylaxis in high risk patients with refractory ascites

Pharmacological Therapy for HRS

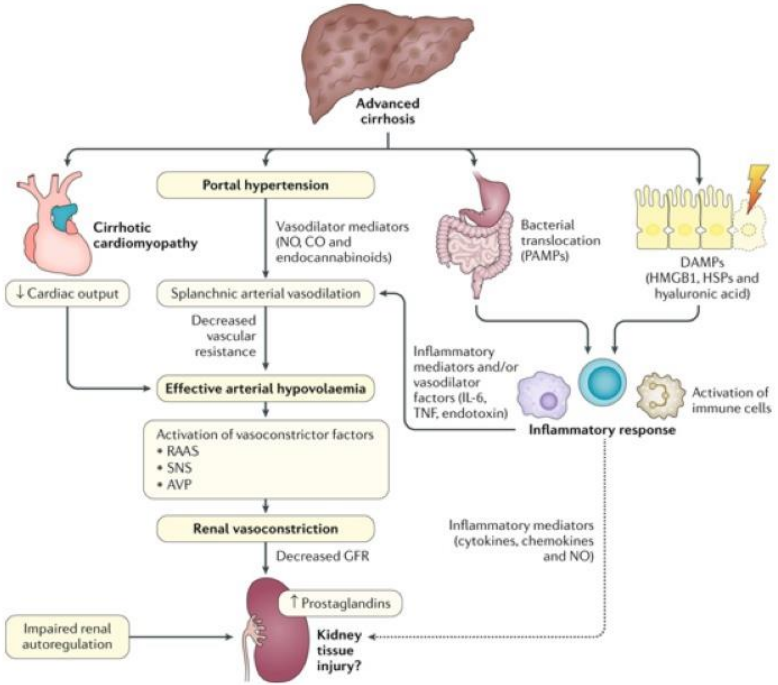
IV Albumin

- 20 to 40 g/day

Plus

Vasoconstrictors

- Midodrine + octreotide
- Norepinephrine



Nature Reviews Disease Primers. Ginès P, et al. *Nat Rev Dis Primers.* 2018;4:23;
Rheumatoid arthritis. Ginès P, et al. *Nat Rev Dis Primers.* 2018;4:23.

Midodrine Plus Octreotide: Dosing

Midodrine: initially 7.5 mg oral 3 times daily

- Titrate to maximum of 12.5 mg 3 times daily

Octreotide: 100 µg SC 3 times daily

- Target dose 200 µg SC 3 times daily
- Titrate to achieve increase of MAP by 15 mmHg

Runyon BA. *Hepatology.* 2013;57:1651-1653.

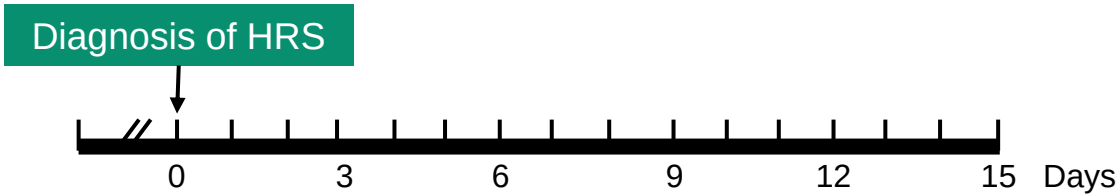
Norepinephrine

Catecholamine with α-adrenergic activity

- Administered as a continuous IV infusion at 0.5 to 3 mg/hour via central venous access, usually requires ICU-level care[1]
- Limited data
  - Systematic review: HRS reversal, mortality rates, and recurrence rates similar when comparing norepinephrine and terlipressin[2]
  - 12 patients showed 83% reversal of HRS with improvements in urine output, sodium excretion, serum sodium concentration, CrCL, MAP[3]
  - 22/30 patients achieved SCr < 1.5 mg/dL; at baseline, responders and nonresponders differed only regarding initial bilirubin levels and INR values[4]

1. EASL website. Hepatorenal Syndrome; 2. Nassar Junior AP, et al. *PLOS One.* 2014;9:e107466;
3. Davenport A, et al. *Nephrol Dial Transplant.* 2012;27:34-41; 4. Gupta K, et al. *Clin Exper Gastroenterol.* 2018;11:317-324.

Treatment with Terlipressin and Albumin



Terlipressin bolus IV 1 mg/4 to 6 hours or continuous IV infusion (2 to 12 mg/day)

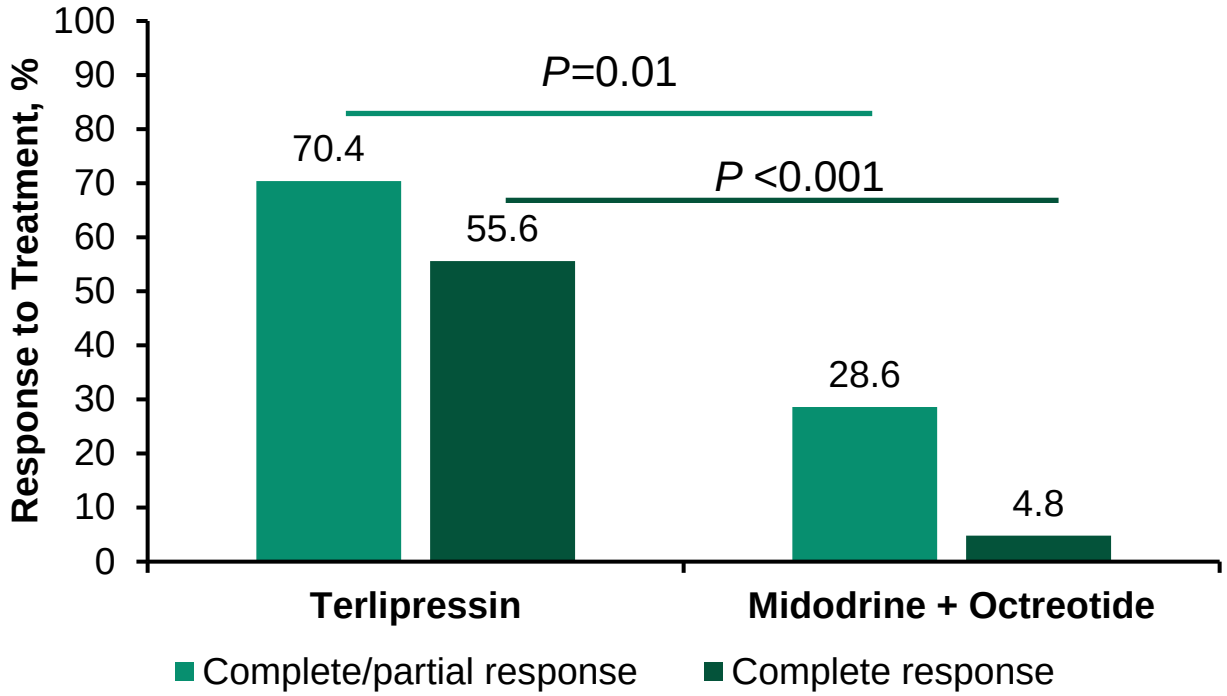
Albumin IV
1 g/kg

Albumin 20 to 40 g/day

Increase terlipressin dose if creatinine
does not decrease by 25% on day 3

Solà E, et al. *Curr Opin Organ Transplant.* 2013;18:265-270.

Improvement in Renal Function: TERLI vs MID/OCT



Cavallin M, et al. *Hepatology.* 2015;62:567-574.

TERLI vs MID/OCT: Cumulative 3-month Survival

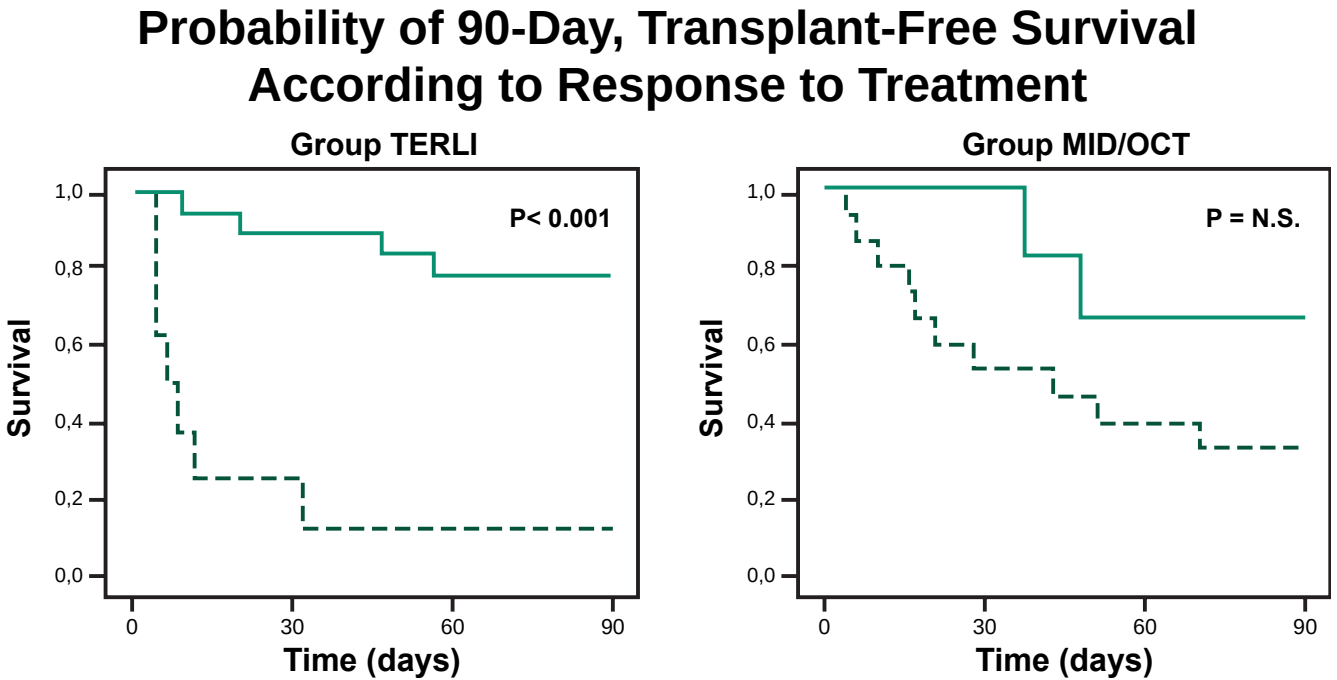


Fig. 4. Cumulative 3-month survival in patients who were randomized to terlipressin plus albumin (TERLI group) or to midodrine and octreotide plus albumin (MID/OCT group) according to the response: solid line represents responders; dotted line represents nonresponders.
Abbreviation: N.S., nonsignificant.
Cavallin M, et al. *Hepatology.* 2015;62:567-574.

Response Rates: Terlipressin vs Noradrenaline in Patients with ACLF and HRS-AKI

	Response Rate, n/N (%)		
	Noradrenaline	Terlipressin	P Value
Day 4	7/60 (11.7%)	16/60 (26.7%)	0.03
Day 7	12/60 (20%)	25/60 (41.7%)	0.01
Reversal of HRS-AKI (Day 14)	10/60 (16.7%)	24/60 (40%)	0.004

Continuous IV infusion of terlipressin (2 to 12 mg/day) vs noradrenaline (0.5 to 3 mg/hour)

Arora V, et al. *Hepatology.* 2019; 0:1-11.

Hepatorenal Syndrome

- Devastating complication of decompensated cirrhosis.
- Early recognition essential to improve outcomes; new diagnostic tools offer promise.
- Currently available treatment in the United States has limited efficacy.
- Terlipressin is superior to other vasoconstrictors in reversing HRS.
- In suitable patients, liver transplantation is the best treatment option.
- Improving renal function reduces short-term mortality and need for RRT and improves post-liver transplant outcomes.

Hepatic Encephalopathy (HE)

Importance of Overt Hepatic Encephalopathy

- Associated with a poor prognosis
- Retrospective review of 111 cirrhotic patients for 12-17 months following first episode of acute OHE:
  - 82 (74%) died during follow-up period
  - Survival probability
    - 42% at 1 year
    - 23% at 3 years

Bustamante J et al. *J Hepatol.* 1999;30(5):890-895.

Diagnosis of Overt HE

- Clinical recognition of the distinctive neurologic features of HE
- Knowledge that underlying cirrhosis is present
- Exclusion of all other etiologies of neurologic and/or metabolic abnormalities
- Identification of precipitating factors
- Generally no role for serum ammonia levels
- Grading systems to evaluate mental status
- Portal-systemic encephalopathy score (PSE score; Conn score) to evaluate overall severity

Adapted from: Mullen KD. *Semin Liver Dis*. 2007;27(suppl 2):3-9; Lawrence KR, Klee JA. *Pharmacotherapy*. 2008;28(8):1019-1032.

Neurologic Manifestations of OHE

Common	Less Common
• Confusion or coma • Asterixis • Loss of fine motor skills • Hyper-reflexia	• Cognitive deficits detected by special testing 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.

Treatment of OHE

General Principles of Management of OHE

- Acute HE in patients with cirrhosis is reversible in the majority of patients
- A precipitating cause of OHE, rather than worsening of hepatocellular function can be identified in most episodes
- Management of the precipitating events typically leads to prompt improvement
- Clinicians should simultaneously identify and resolve precipitating events while instituting pharmacologic therapy

Ferenci P. *Semin Liver Dis*. 2007;27(suppl 2):10-17.

Treatment Goals for OHE

- Provision for supportive care
- Identification and removal of precipitating factors
  - Infection, GI bleed, dehydration
- Reduction of nitrogenous load from the gut
- Correct electrolyte abnormalities
- Assessment of the need for long-term therapy
  - Control of potential precipitating factors
  - Higher likelihood of recurrent encephalopathy
  - Assessment of the need for liver transplantation

Blei AT et al. *Am J Gastroenterol.* 2001;96(7):1968-1976.

Treatment Options for OHE

- Reduction in the nitrogenous load arising from the gut
  - Bowel cleansing
  - Non-absorbable disaccharides (lactulose)
  - Antibiotics (rifaximin, metronidazole)*
  - Agents that bind NH3 in the gut and increase activity of the urea cycle
    - Na benzoate
    - Na phenylacetate
    - Na hydroxybutyrate
- Drugs that affect neurotransmission (flumazenil, bromocriptine)
- Manipulation of the splanchnic circulation (occlusion of portal-systemic collaterals)
  - Occlude TIPS shunt if present

*Neomycin (historical interest)
Adapted from Blei AT et al. *Am J Gastroenterol*. 2001;96(7):1968-1976.

Treatment Options for OHE
Lactulose

- Metabolism of lactulose by the bacterial flora in the colon to short chain fatty acids (lactic acid) lowers the colonic pH to about 5.0. The acid pH favors formation of non-absorbable NH4 from NH3.
  - Also hastens colonic transit and may lead to modification of colonic flora.
- Dose (45-90 g/d) should be titrated to achieve 2 to 3 soft stools per day, associated with a pH below 6.
- Principal side effects include abdominal distension, cramping, diarrhea, electrolyte changes, and flatulence.

Ferenci P. *Semin Liver Dis*. 2007;27(suppl 2):10-17.

Treatment Options for Overt HE
Older Oral Antibiotics

- Potential for adverse effects often precludes their use as first-line therapy for HE
  - Neomycin: Ototoxicity and nephrotoxicity
  - Metronidazole: Peripheral neurotoxicity
  - Vancomycin: Increased risk of bacterial resistance and renal toxicity
- Increased risk of serious adverse events limits use in prolonged therapy

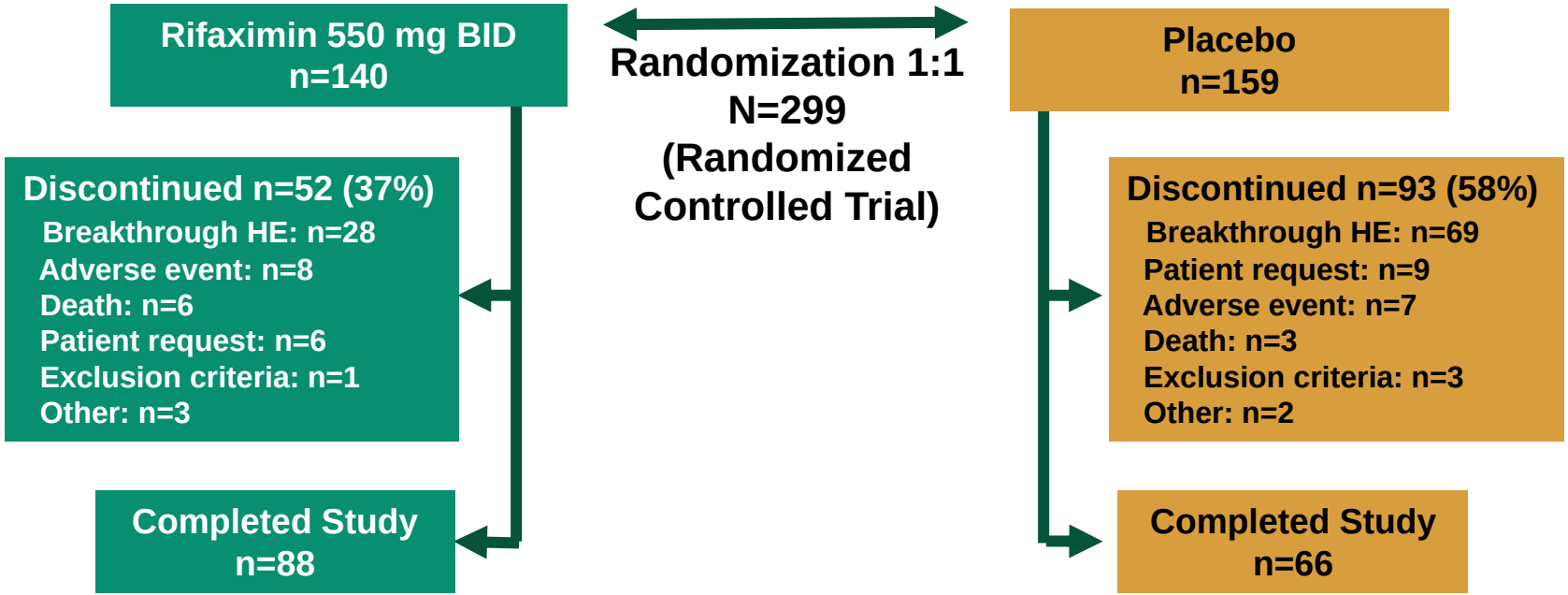
Mullen KD et al. *Semin Liver Dis*. 2007;27(suppl 2):32-47.

Treatment Options for OHE
Rifaximin

- Oral minimally absorbed (<0.4%) antibiotic
- Broad-spectrum in vitro activity against aerobic and anaerobic enteric bacteria
- No clinical drug interactions reported
- No dosing adjustment required in patients with liver disease or renal insufficiency
- Approval of 550 mg tablets was granted March 24, 2010 for reduction in risk of HE recurrence
- HE approval was based on a large, double-blind, placebo-controlled, multinational, Phase 3 clinical trial published in *The New England Journal of Medicine* on March 25, 2010

Bass NM. *Semin Liver Dis*. 2007;27(suppl 2):18-25; Mullen KD et al. *Semin Liver Dis*. 2007;27(suppl 2):32-47.

Rifaximin Treatment in HE: Randomization and Follow-up



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

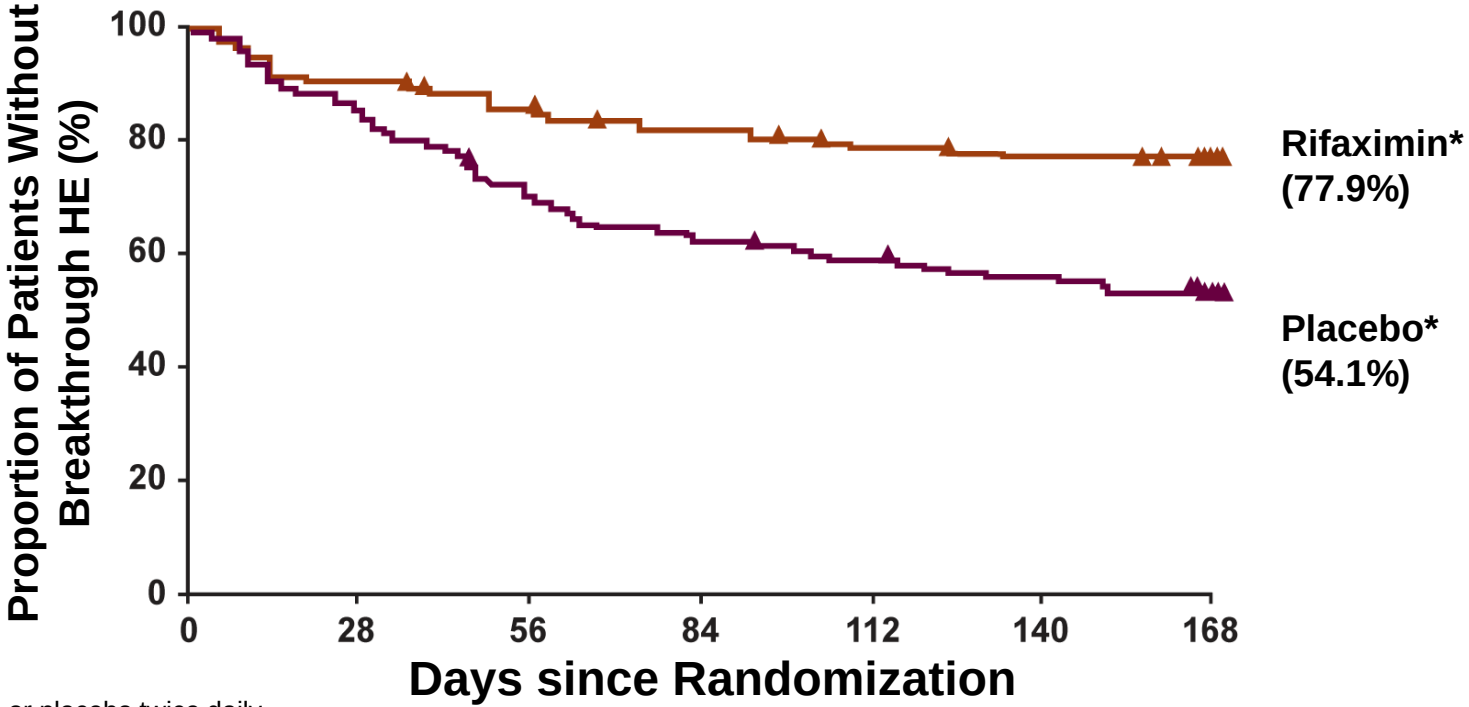
Rifaximin Treatment in HE: Lactulose Use at Baseline and During Study

	Rifaximin (n=140)	Placebo (n=159)
Lactulose use at baseline—no (%)*	**128 (91.4%)**	**145 (91.2%)**
Lactulose use during study—no (%)*	**128 (91.4%)**	**145 (91.2%)**

*During the study, 3 patients who had been receiving lactulose discontinued the therapy and another three patients started lactulose (1 in the rifaximin group and 2 in the placebo group).

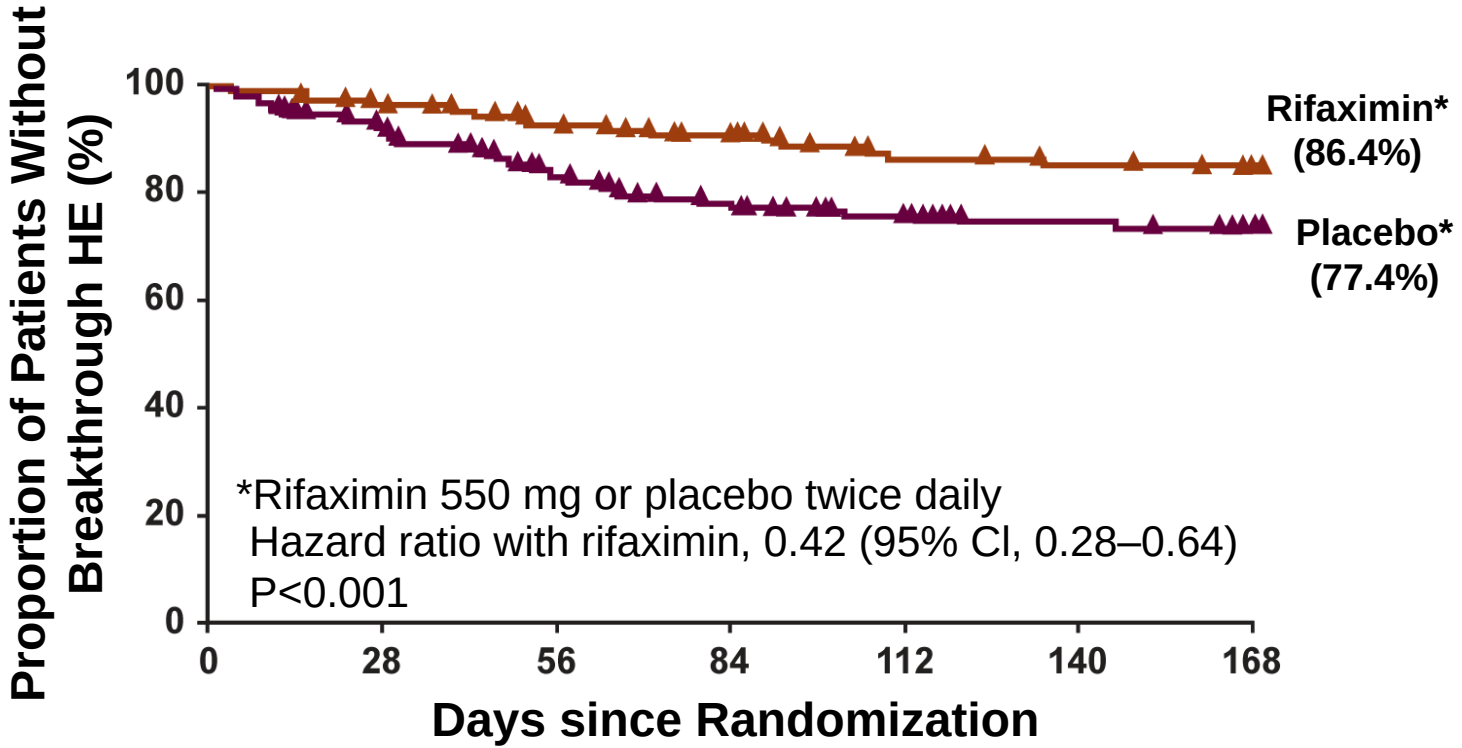
Bass NM et al. *N Engl J Med.* 2010;362:1071-1081.

Rifaximin Treatment in HE: Time to First Breakthrough HE Episode (Primary End Point)



*Rifaximin 550 mg or placebo twice daily
Hazard ratio with rifaximin, 0.42 (95% CI, 0.28–0.64)
P<0.001
Bass NM et al. *N Engl J Med.* 2010;362:1071-1081.

Rifaximin Treatment in HE: Time to First HE Related Hospitalization (Key Secondary End Point)



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

Summary

- Complications of ESLD are common and vary in different individuals
- Proper management and prophylactic strategies can improve morbidity and (sometimes) survival

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