

Complications of Cirrhosis – HE and HRS

Robert S. Brown Jr., MD, MPH
Vincent Astor Distinguished Professor of Medicine
Chief, Division of Gastroenterology and Hepatology
Weill Cornell Medical College,
New York-Presbyterian Hospital

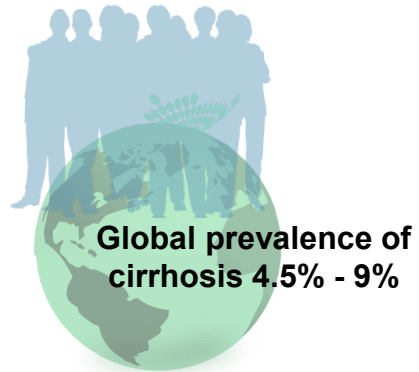
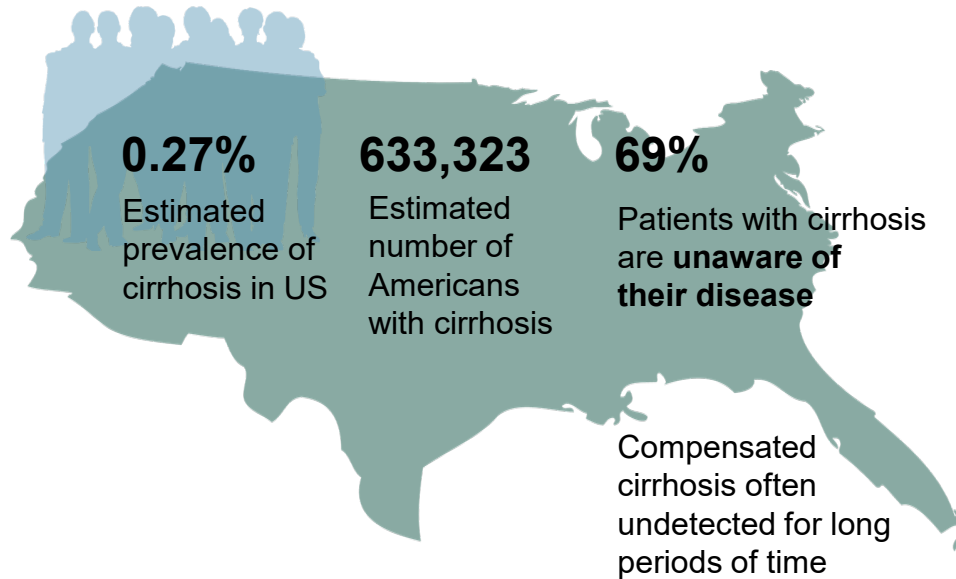
Med.cornell.edu/rsbrownjr
Robert.Brown@med.cornell.edu
[@drboobybrown](https://twitter.com/drboobybrown)

Disclosure

- Robert S. Brown Jr., MD, MPH
 - Consultant: Mallinckrodt, AbbVie, Salix, Gilead, Antios, Ambys, Miram, Intercept
 - Research: AbbVie, Salix, Intercept



Prevalence of Cirrhosis



Compensated Cirrhosis May Be Difficult to Recognize^{1,2}

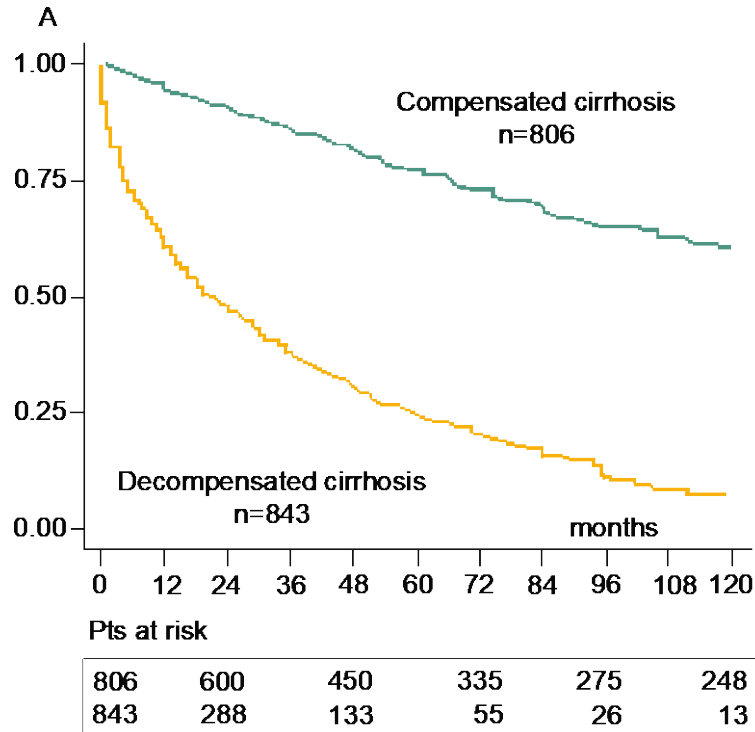
- Most patients remain asymptomatic until decompensation occurs
- Subtle clues may be overlooked
 - Thrombocytopenia
 - Muscle wasting
 - AST>ALT without alcohol consumption
 - Liver enzymes may not be abnormal
- Etiology may not be obvious
 - Prior alcohol use
 - Uncontrolled diabetes mellitus and obesity

Compensated vs Decompensated Cirrhosis

- Compensated: Patients with cirrhosis that have not developed major complications of cirrhosis
- Decompensated: Patients with cirrhosis who have developed major complications:
 - Variceal hemorrhage
 - Ascites
 - Hepatic encephalopathy
 - Spontaneous bacterial peritonitis
 - Hepatocellular carcinoma
 - Hepatorenal syndrome

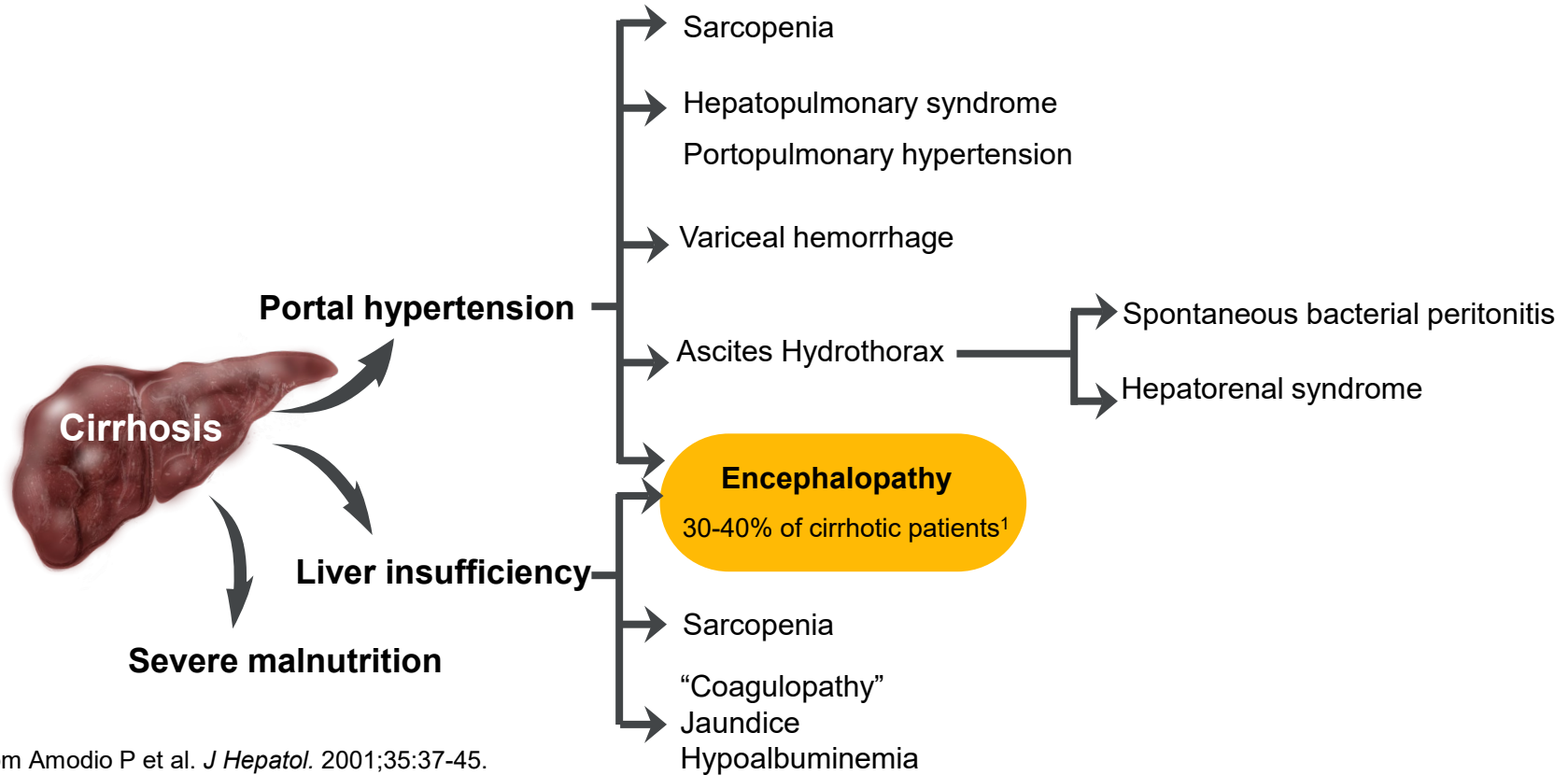
Survival Is Significantly Longer in Compensated Cirrhosis Compared With Decompensated Cirrhosis

Survival According to Decompensation at Diagnosis



>12 year median survival
in patients with compensated cirrhosis

Complications of Cirrhosis: Distinguish Portal Hypertension From Liver Insufficiency



Definition of Hepatic Encephalopathy

HEPATOLOGY

Official Journal of the American Association for the Study of Liver Diseases



AASLD PRACTICE GUIDELINE

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

Hendrik Vilstrup,¹ Piero Amadori,² Jazmohan Bajaj,^{3,4} Juan Cordoba,^{5†} Peter Ferenci,⁶ Kevin D. Mullen,⁷
Karin Weissenborn,⁸ and Philip Wong⁹

The AASLD/EASL Practice Guideline Subcommittee on Hepatic Encephalopathy are: Jayant A. Talwalkar (Chair, AASLD), Hans S. Conjeevaram, Michael Borzak, Raphael B. Merriman, Peter L.M. Jansen, and Fabien Zoulim. This guideline has been approved by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver and represents the position of both associations.

Preamble

These recommendations provide a data-supported approach. They are based on the following: (1) formal review and analysis of the recently published world literature on the topic; (2) guideline policies covered by the American Association for the Study of Liver Diseases/European Association for the Study of the Liver (AASLD/EASL) Policy on the Joint Development and Use of Practice Guidelines; and (3) the experience of the authors in the specified topic.

Intended for use by physicians, these recommendations suggest preferred approaches to the diagnosis,

therapeutic, and preventive aspects of care. They are intended to be flexible, in contrast to standards of care, which are inflexible policies to be followed in every case. Specific recommendations are based on relevant published information.

To more fully characterize the available evidence supporting the recommendations, the AASLD/EASL Practice Guidelines Subcommittee has adopted the classification used by the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) workgroup, with minor modifications (Table 1). The classifications and recommendations are based on three categories: the source of evidence in levels I through III, the quality of evidence designated by high (A), moderate (B), or low quality (C), and the strength of recommendations classified as strong (1) or weak (2).

Literature Review and Analysis

The literature databases and search strategies are outlined below. The resulting literature database was available to all members of the writing group (i.e., the authors).

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ACE, angiotensin-converting enzyme inhibitor; ALD, alcoholic liver disease; AIE, acute liver failure; BCAA, branched-chain amino acids; CPE, Critical Flicker Frequency; CHE, acute HE; CLD, chronic liver disease; CRET, Cretanone Reaction Time; CT, computed tomography; DM, diabetes mellitus; EASL, European Association for the Study of the Liver; EEG, electroencephalography; GI, gastrointestinal; GRADE, the Grading of Recommendation Assessment, Development, and Evaluation; GCS, Glasgow Coma Scale; GOR, glyoxylic aciduria; HCV, hepatitis C virus; HE, hepatic encephalopathy; HEM, hepatic encephalopathy; ICT, Inhibitory Control Test; ISEHN, International Society for Hepatic Encephalopathy and Nitrogen Metabolism; IT, International IT; Lactulose; Lactulose; LE, liver encephalopathy; MHE, minimal HE; MR, magnetic resonance; OHS, oral HE; JF, jejunum bypass; PHES, Psychometric Hepatic Encephalopathy Score; IP, portal pressure; PSS, portosystemic encephalopathy; PSS, portosystemic shunting; RCT, randomized, controlled trial; TIPS, transjugular intrahepatic portosystemic shunt; VR, variceal bleeding; WHC, WHO Haven Criteria; WM, working memory.

From the ¹Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark; ²Department of Medicine, SIMEG, University of Padua, Padua, Italy; ³Division of Gastroenterology, Hepatology and Nutrition, Virginia Commonwealth University, Richmond, VA; ⁴McGill-Virginia Affairs Medical Center, Richmond, VA; ⁵Liver Unit, Hospital Vall d'Hebron, Barcelona, Spain; ⁶Department of Internal Medicine III (Gastroenterology and Hepatology), Medical University of Vienna, Vienna General Hospital (AGH), Vienna, Austria; ⁷Division of Gastroenterology, Mayo/Robt Medical Center, Cox Science Research Building, Cleveland, OH; ⁸Department of Neurology, Hannover Medical School, Hannover, Germany; ⁹Division of Gastroenterology and Hepatology, McGill University, Montreal, Quebec, Canada.

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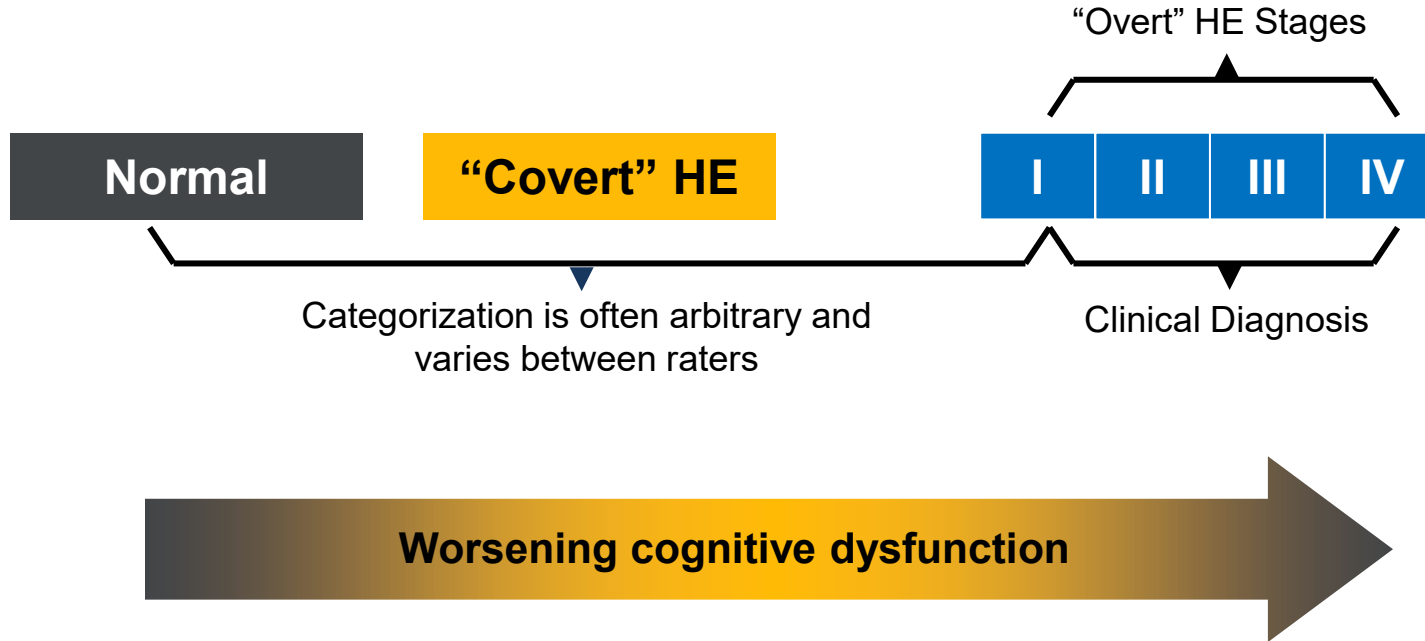
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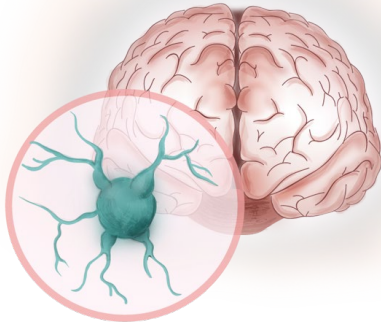
†Deceased.

Hepatic encephalopathy is a brain dysfunction caused by liver insufficiency and portal systemic shunt; it manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma

Characterization of HE Stages



Precipitating Factors for HE



Increased ammonia production

- GI hemorrhage
- Excessive dietary protein
- Blood transfusion
- Electrolyte imbalance (eg, hypokalemia)
- Constipation

Portosystemic shunts

- Spontaneous
- Iatrogenic (eg, TIPS)

Other

- Drugs (eg, opioids, benzodiazepines, beta blockers)
- Infections (eg, SBP)
- Malignancy (eg, hepatoma)

Role of Ammonia Testing in HE

- “Increased blood ammonia alone does not add any diagnostic, staging, or prognostic value for HE in patients with CLD. A normal value calls for diagnostic reevaluation (GRADE II-3, A, 1)”¹
- “Blood ammonia levels cause as much confusion in those requesting the measurements as in the patients in whom they are being measured”²
- Ammonia level >200 $\mu\text{mol/L}$ is predictive of poor outcome in acute liver failure³



AASLD Recommends 4-Pronged Approach to Treating Overt Hepatic Encephalopathy



*Grade II-2, A, 1 recommendation.

Vilstrup H et al. *Hepatology*. 2014;60(2):714-735.

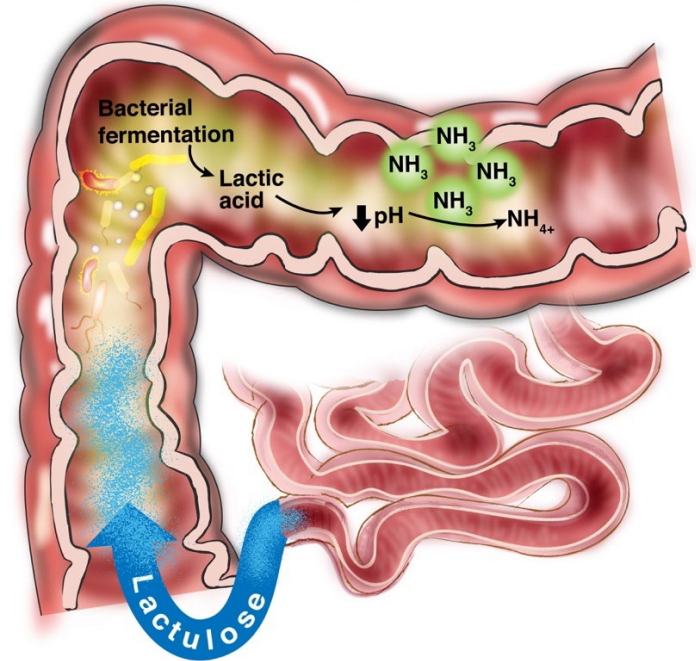
Current Therapy Options for HE

Agent	Drug Class	Indication
Lactulose ¹	Poorly absorbed disaccharide	<ul style="list-style-type: none">• Decrease blood ammonia concentration• Prevention and treatment of portal-systemic encephalopathy
Rifaximin ²	Non-aminoglycoside semi-synthetic, nonsystemic antibiotic	Reduction in risk of OHE recurrence in patients ≥18 years of age
Neomycin ³	Aminoglycoside antibiotic	Not to be used, renal and ototoxic risk
Metronidazole ¹	Synthetic antiprotozoal and antibacterial agent	Not approved for HE
Vancomycin ¹	Aminoglycoside antibiotic	Not approved for HE

1. USNLM. DailyMed. Available at <https://dailymed.nlm.nih.gov/dailymed>. Accessed March 22, 2018; 2. Xifaxan (rifaximin) [prescribing information]. Valeant Pharmaceuticals North America LLC; Bridgewater, NJ; 2018; 3. Mullen KD et al. *Semin Liver Dis.* 2007;27(Suppl 2):32-47.

Lactulose for HE

- Current mainstay of HE therapy^{1,2}
- Mechanism of action²⁻⁵
 - Non-absorbable disaccharide is fermented in the colon and metabolized by bacterial flora to lactic acid, lowering colonic pH
 - Cathartic effect can increase fecal nitrogen excretion with up to a 4-fold increase in stool volume



1. Vilstrup H et al. *Hepatology*. 2014;60(2):714-735; 2. Mullen KD et al. *Semin Liver Dis*. 2007;27(Suppl 2):32-47; 3. Conn HO et al. *Gastroenterology*. 1977;72:573-583; 4. Sharma P, Sharma BC. *J Clin Exp Hepatol*. 2015;5:S82-S87; 5. Morgan MY. *Metab Brain Dis*. 2016;31:1361-1364.

Practical Considerations for Use of Lactulose in HE

Dosage/Administration

- Administered orally, by mouth or through a nasogastric tube or via retention enemas^{1,2}
- Initiated at 25 mL every 1-2 hours to achieve ≥ 2 soft or loose stools per day²

Safety

- Key side effects include abdominal distension, cramping, diarrhea, electrolyte changes, and flatulence^{1,3}



Rifaximin

Description

- Minimally absorbed (<0.4%) oral antibiotic^{1,2}
- Broad-spectrum in vitro activity against aerobic and anaerobic enteric bacteria²

Indication

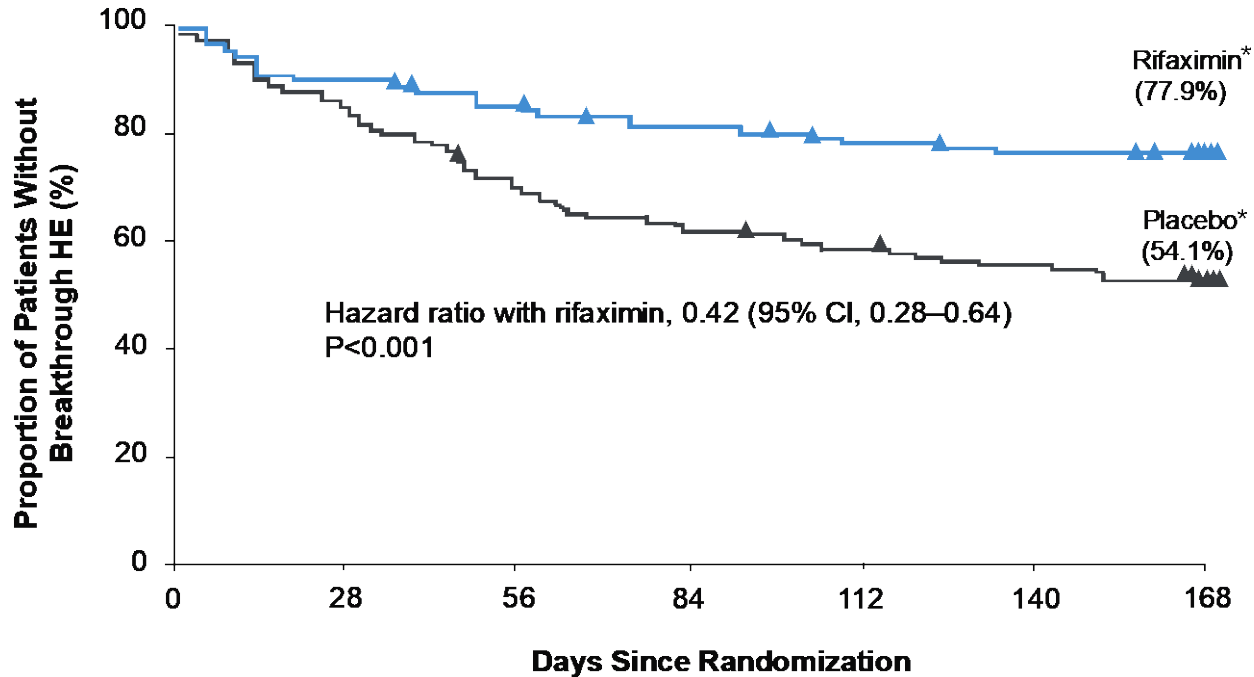
- 550 mg BID for reduction in risk of OHE in patients ≥18 years of age²

Safety

- Drug interactions²
 - Concomitant administration of drugs that are P-glycoprotein (P-gp) inhibitors with rifaximin can substantially increase the systemic exposure to rifaximin
 - Changes in INR have been reported postmarketing in patients receiving rifaximin and warfarin concomitantly
- No dosing adjustment required in patients with liver disease or renal insufficiency³



Rifaximin Randomized, Controlled Trial: Time to First Breakthrough HE Episode Primary Endpoint



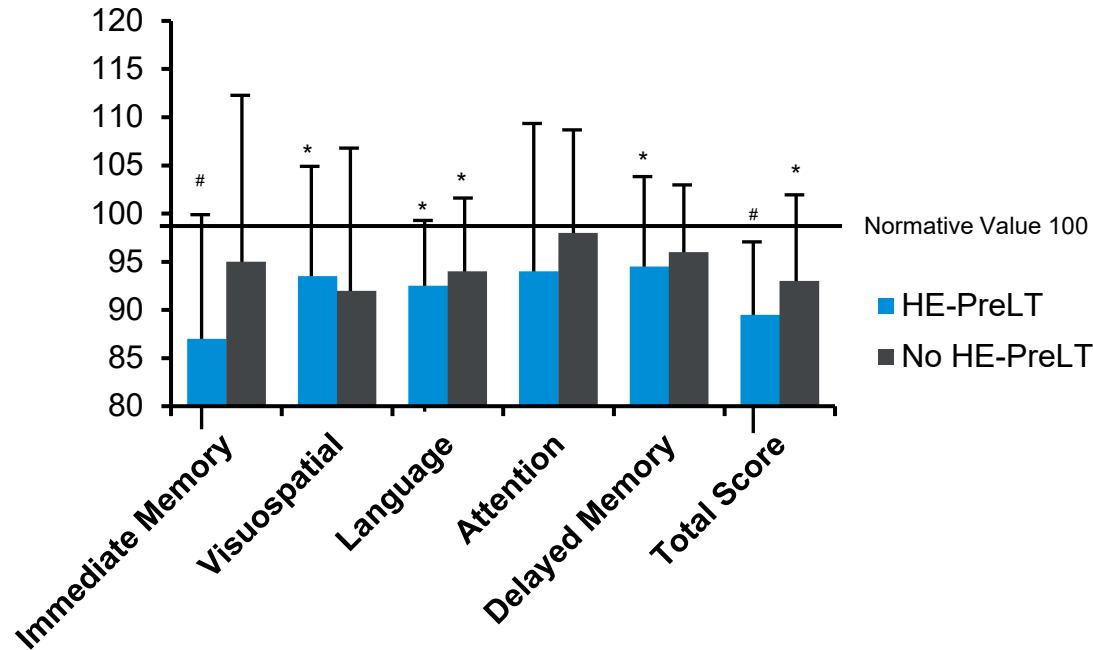
*Rifaximin 550 mg or placebo twice daily. 91% of patients in both arms received concomitant lactulose.
Bass NM et al. *N Engl J Med*. 2010;362:1071-1081.

Additional Effects of HE

- Poor quality-of-life¹
- Impaired driving ability²
- Caregiver burden is increased³
- Family daily functioning is affected due to financial burden⁴

Cognitive Function May Be Compromised, Even Post Liver Transplant

- Study objective: evaluate cognitive function and quality of life in 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



OLT, orthotopic liver transplant; LT, 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.

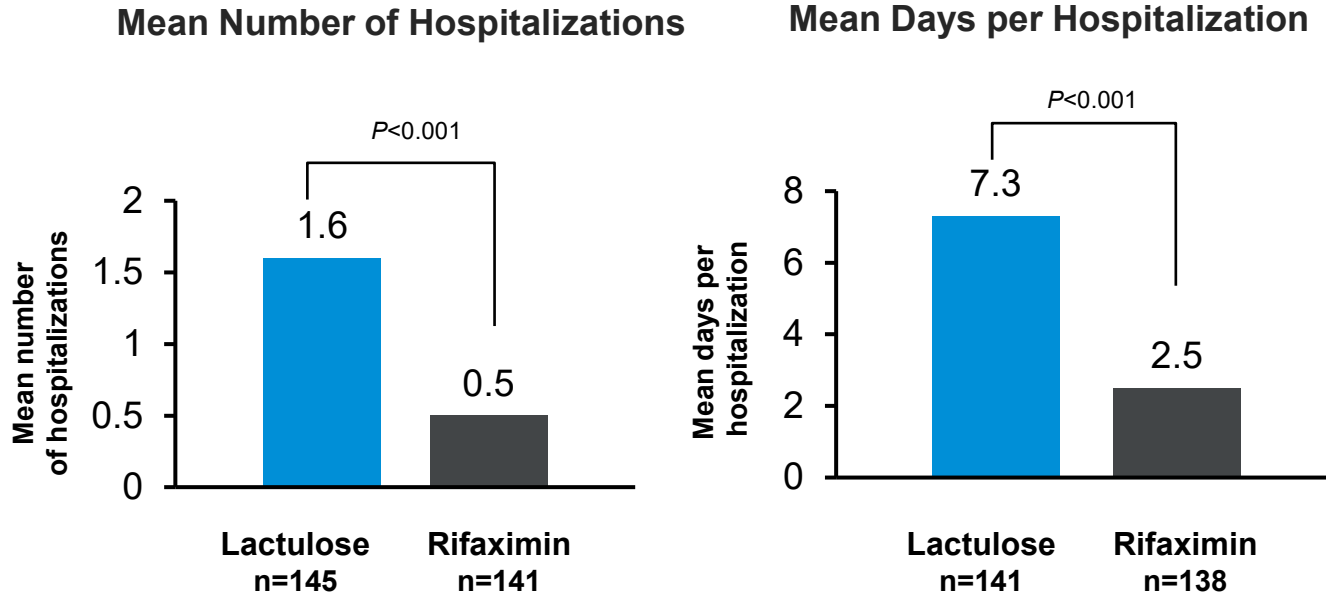
Sotil et al. *Liver Transpl.* 2009.

Unadjusted and Adjusted Odds Ratios for 30-Day Readmissions by Condition for Complications of Liver Disease

30-Day Hepatology Readmission

	Unadjusted OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)
Ascites	1.28 (1.20-1.37)	1.47 (1.37-1.58)	1.78 (1.66-1.90)
Variceal hemorrhage	1.85 (1.71-2.00)	1.69 (1.56-1.83)	1.55 (1.43-1.69)
Hepatic encephalopathy	2.62 (2.41-2.83)	2.67 (2.46-2.89)	3.23 (2.97-3.52)
Hepatorenal syndrome	2.33 (1.90-2.85)	2.46 (2.00-3.02)	1.41 (1.13-1.77)
Hepatocellular carcinoma	1.79 (1.61-2.00)	1.64 (1.45-1.84)	1.70 (1.51-1.91)

Frequency and Duration of Hospitalization Associated With Lactulose and Rifaximin in HE









* $P < 0.001$ rifaximin period versus lactulose period, paired t -test
Leevy CB, Phillips JA. *Dig Dis Sci*. 2007;52:737-741.

The Majority of Overt HE Patients Do Not Receive Proper Therapeutic Management After Discharge

- Analysis of medical and hospital claims
 - Outpatients who had ≥ 1 OHE episodes from 2009 to 2011 during a 3-year period
- **>60%** of patients did not receive ongoing prophylactic therapy to reduce risk of HE recurrence after discharge



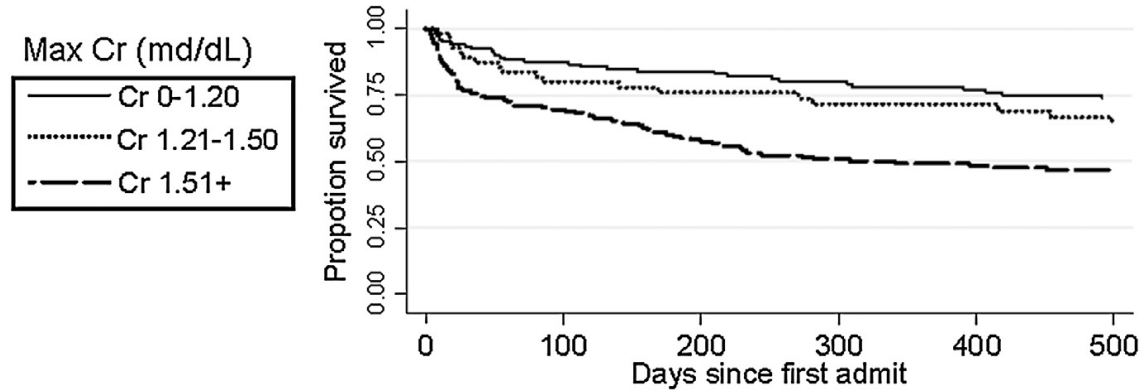
Checklist at Discharge

Topics	
Does the patient know the change in their prognosis and daily function?	
Does the patient and family know signs of recurrence and ways to get in touch?	
Do they have a scheduled appointment for follow-up?	
Do they have medications to prevent HE recurrence with instructions in hand?	
Have potential recurring precipitating factors been investigated?	
Are they candidates for transplant?	

Revised HRS Definitions and Criteria: No More Type 1 and Type 2

Old classification	New classification		Criteria
HRS-1*	HRS-AKI		<ul style="list-style-type: none"> a) Absolute increase in sCr ≥ 0.3 mg/dl within 48h and/or b) Urinary output ≤ 0.5 ml/kg B.W. $\geq 6h^*$ or c) Percent increase in sCr $\geq 50\%$ using the last available value of outpatient sCr within 3 months as the baseline value
HRS-2*	HRS-NAKI	HRS-AKD HRS-CKD	<ul style="list-style-type: none"> a) eGFR < 60 ml/min per 1.73 m² for < 3 months in the absence of other (structural) causes b) Percent increase in sCr $< 50\%$ using the last available value of outpatient sCr within 3 months as the baseline value c) eGFR < 60 ml/min per 1.73 m² for ≥ 3 months in the absence of other (structural) causes

Serum Creatinine Is an Independent Predictor of Mortality in Patients With Cirrhosis



	<u>Number at risk at time</u>					
Cr 0-1.20	119	101	91	81	75	61
Cr 1.21-1.50	56	42	37	32	30	24
Cr 1.51+	164	112	88	73	64	56

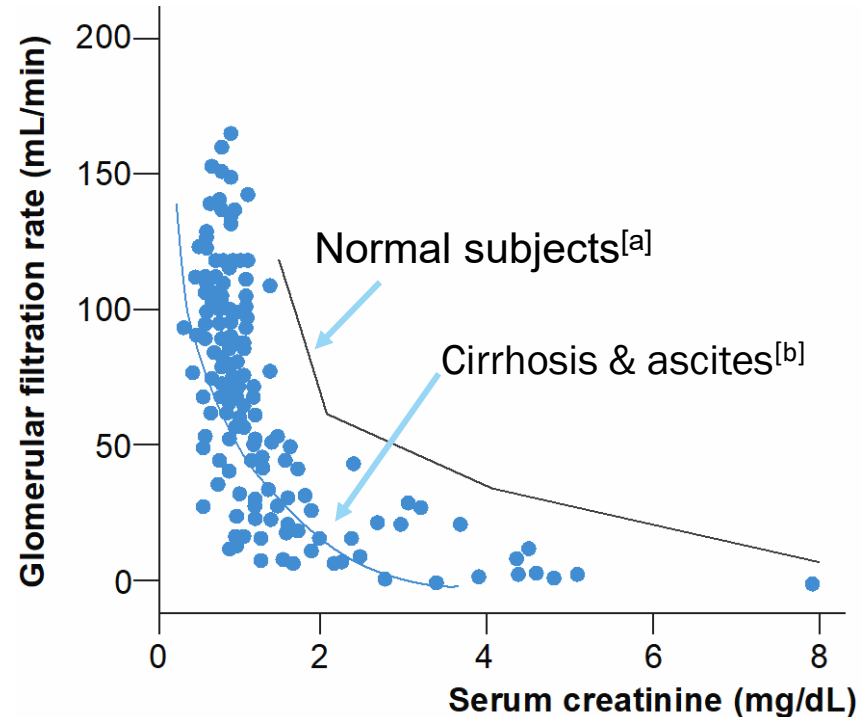
Time scale: Days since patient's first admission

Data from 636 admissions were used. Deaths were recorded for 169 out of 339 patients in this sample.

Any increment increase in SCr within 48 hours from hospitalization is associated with a higher mortality, provided the peak SCr within 48 hours is >1.2 mg/dL.

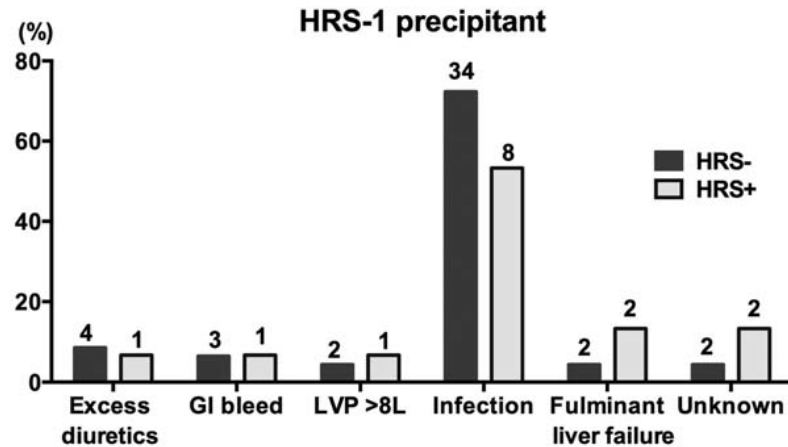
Relationship Between Serum Creatinine and GFR in Patients With Cirrhosis

- Serum creatinine of 1.5 g/dL corresponds to GFR of ~30 mL/min in cirrhosis
- Due to low muscle mass in cirrhosis, SCr overestimates renal function

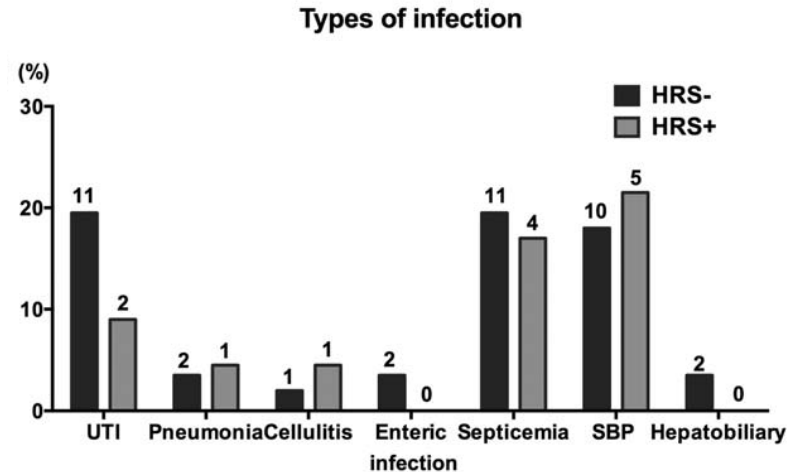


Precipitants and Types of Infection Associated With Hepatorenal Syndrome

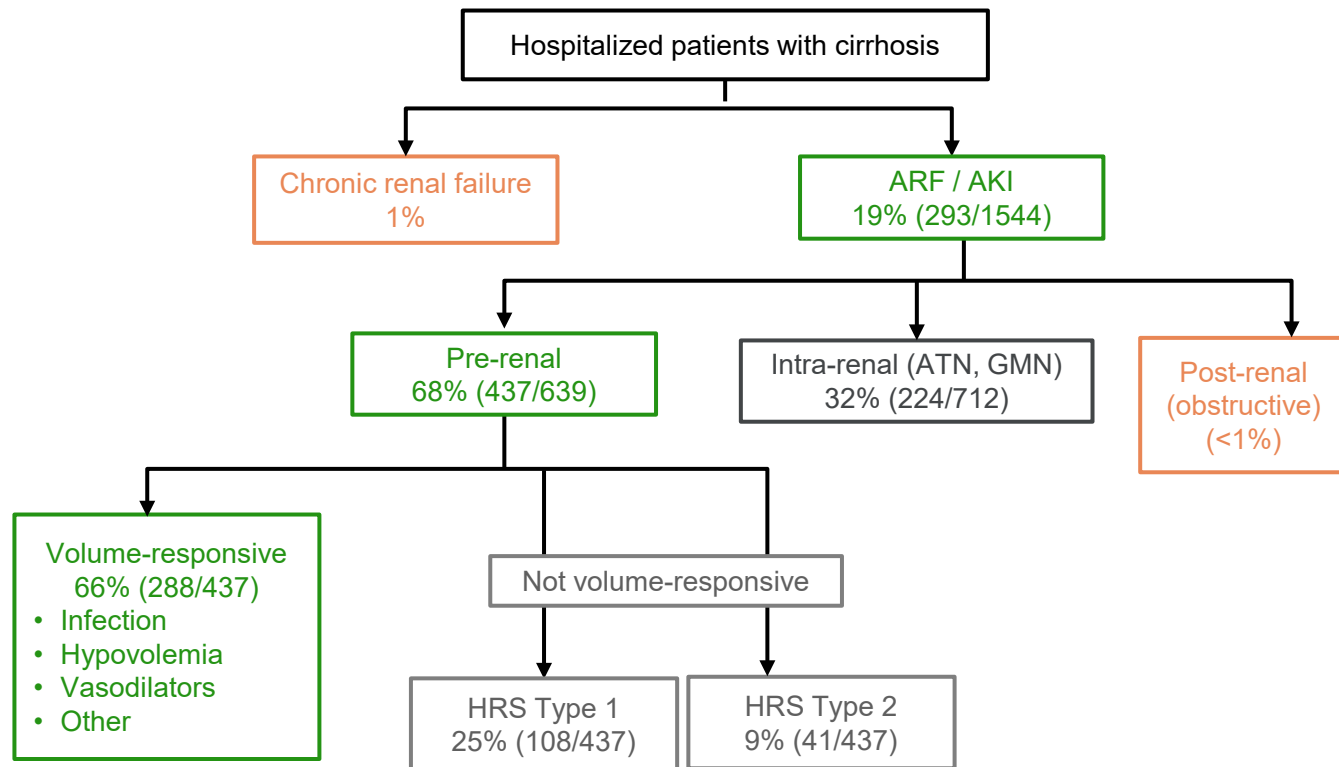
Frequencies of precipitants for HRS1 in the HRS- (reversed) and HRS+ groups



Frequencies of types of infections as precipitants for HRS1 in HRS- (reversed) and HRS+ groups



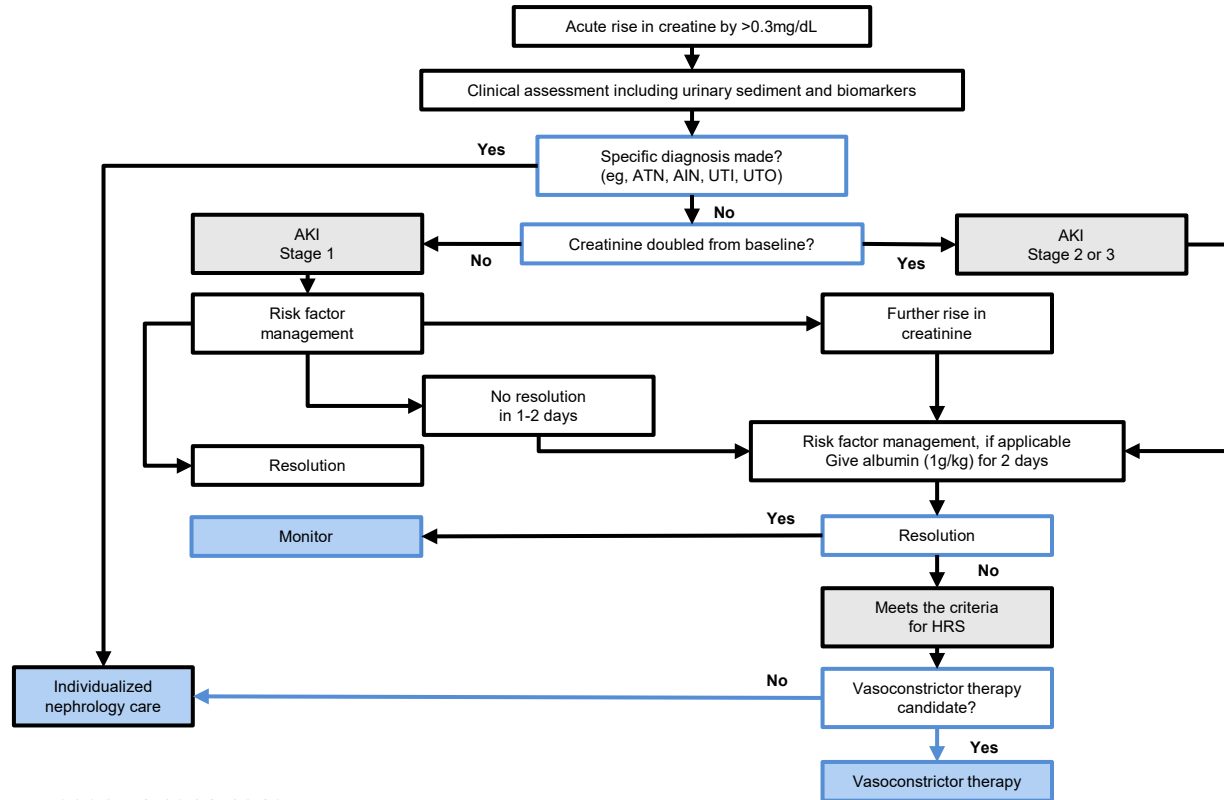
Prevalence and Etiology of HRS-AKI in Cirrhosis



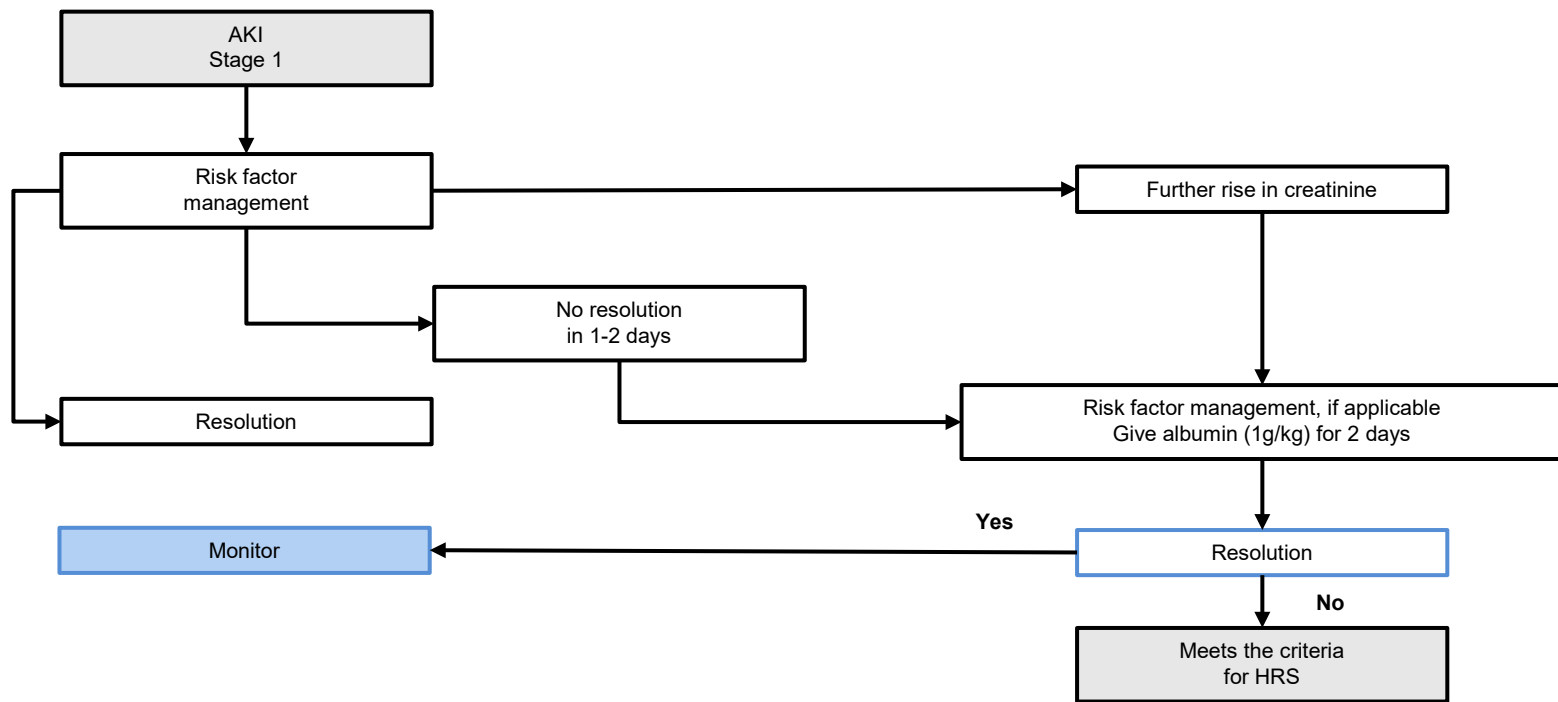
Stages of AKI

AKI Stage	Description
1	Increase of creatinine ≥ 0.3 mg/dL up to 2-fold of baseline
2	Increase in creatinine between 2-fold and 3-fold of baseline
3	Increase in creatinine > 3 -fold of baseline or creatinine > 4 mg/dL (353.6 $\mu\text{mol/L}$) with an acute increase ≥ 0.3 mg/dL (26.5 $\mu\text{mol/L}$) or initiation of RRT

AASLD Proposed Algorithm for Diagnosis and Management of AKI in Cirrhosis



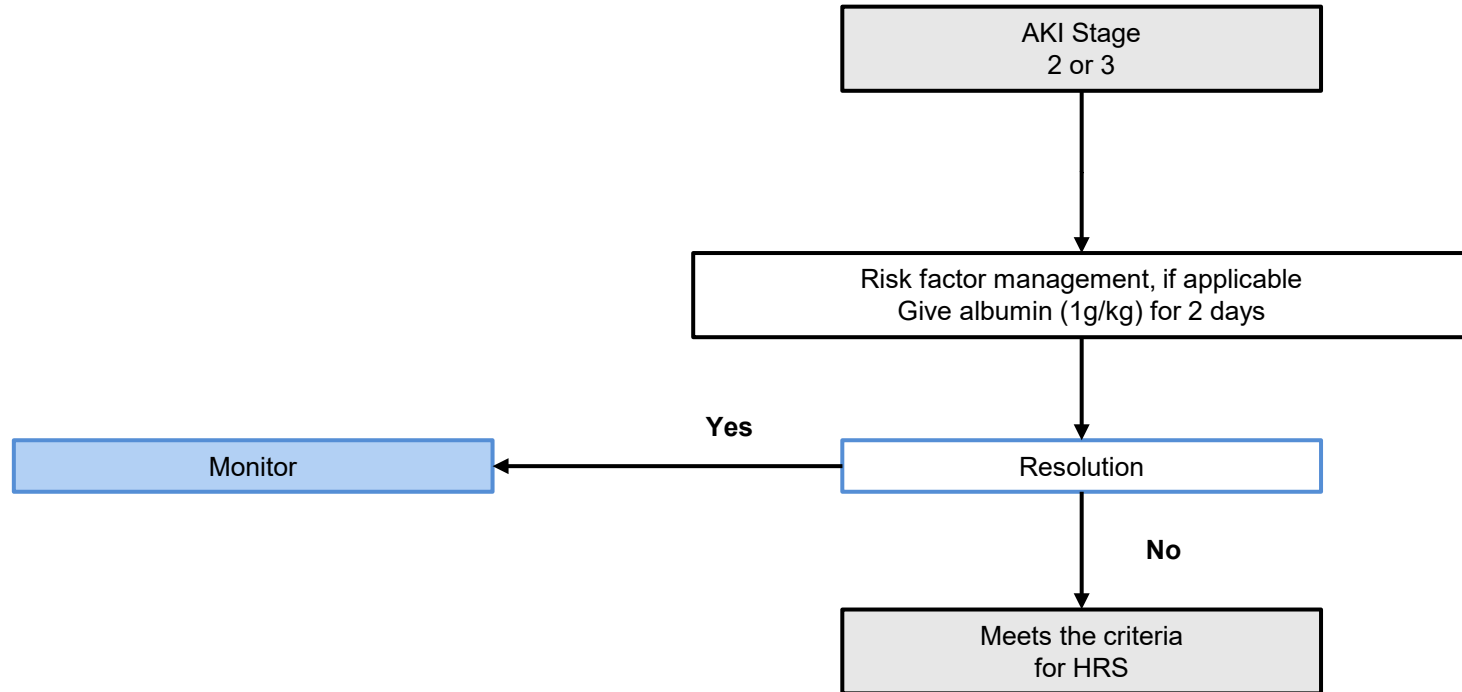
AASLD Proposed Algorithm for Diagnosis and Management of AKI in Cirrhosis



Prevention of HRS-AKI in Patients With Cirrhosis

- Avoid NSAIDs
- Avoid ACE inhibitors
- Decrease/withdraw diuretics when decompensated
- Limiting lactulose dose to accomplish 2-3 BMs per day
- Threshold at which to discontinue beta-blockers?
- Maintain mean arterial pressure (MAP)

AASLD Proposed Algorithm for Diagnosis and Management of AKI in Cirrhosis



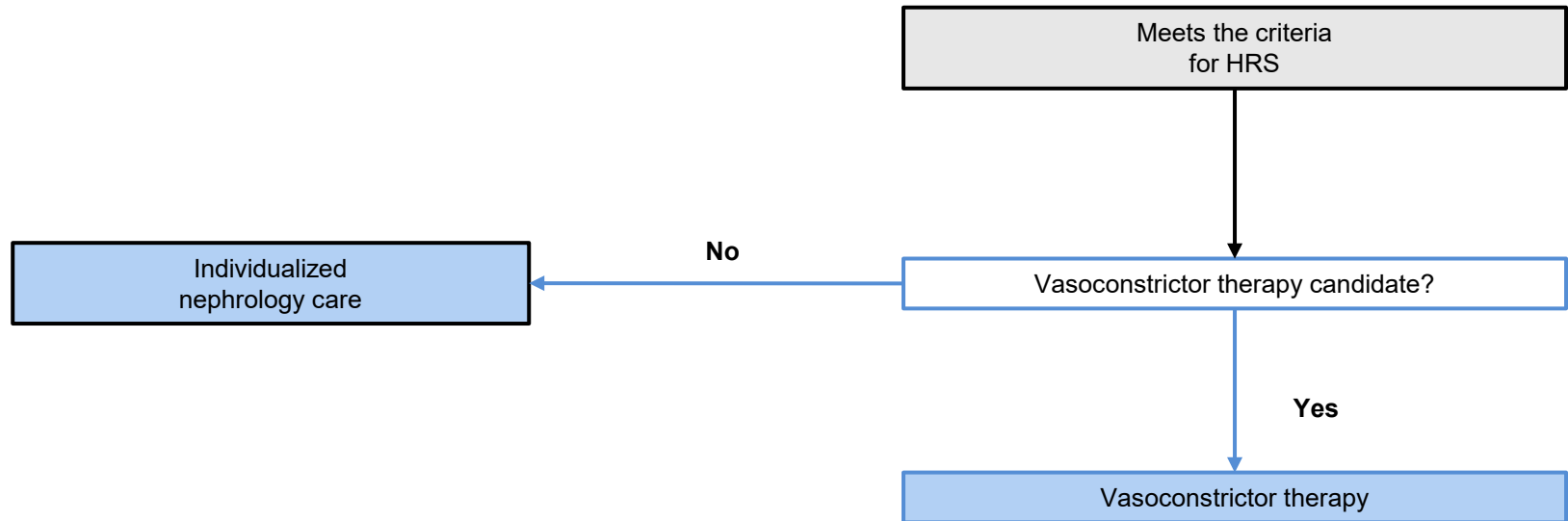
Criteria to Diagnose HRS-AKI

Cirrhosis with ascites
Diagnosis of AKI according to International Club of Ascites-Acute Kidney Injury[†] criteria
No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin infusion (1 g/kg body weight per day)
Absence of shock
No current or recent use of nephrotoxic drugs (NSAIDs, aminoglycosides, or iodinated contrast media)
No signs of structural kidney injury, as indicated by proteinuria (>500 mg per day), microhematuria (>50 red blood cells per high-power field), and/or abnormal renal ultrasonography

[†]Increase in serum creatinine ≥ 0.3 mg/dL from baseline within 48 hours or a percent increase in serum creatinine of $\geq 50\%$ which is known or presumed to have occurred within the preceding 7 days.

Biggins SW et al. *Hepatology*. 2021;74:1014-1048.

AASLD Proposed Algorithm for Diagnosis and Management of AKI in Cirrhosis



Pharmacologic Therapy for HRS-AKI

IV Albumin

Plus

Vasoconstrictors

- Midodrine + octreotide
- Norepinephrine
- Terlipressin

Midodrine and Octreotide

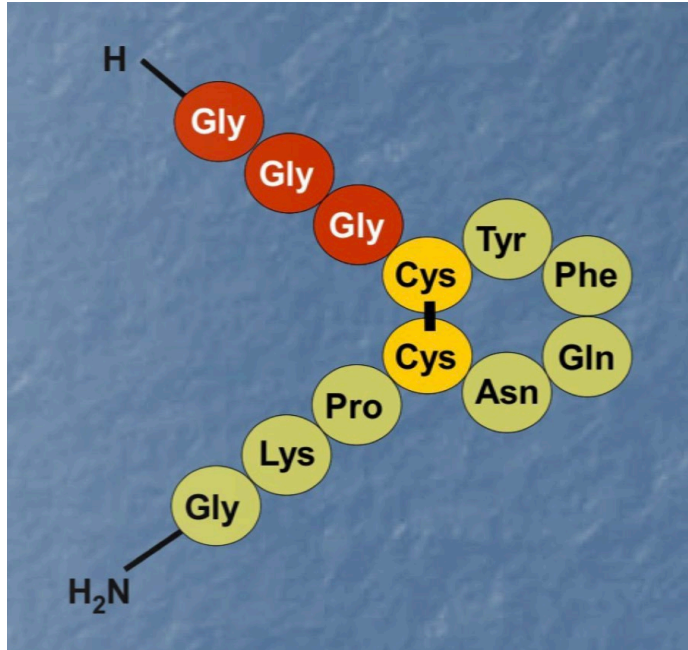
Midodrine

- Midodrine binds to alpha-1-adrenergic receptors
- Improves systemic blood pressure and hence improves renal perfusion pressure

Octreotide

- Octreotide is a splanchnic vasoconstrictor that antagonizes the action of various splanchnic vasodilators
- Not effective alone

Terlipressin: Recently Approved in the US



- Widely studied (more than 70 published manuscripts and presented abstracts on clinical data)
- Approved outside the U.S. for more than 30 years and available on five continents
- Synthetic 12 amino acid peptide, pro-drug
- Constrictive activity via V-1 receptors
 - Vascular and extra vascular smooth muscle cells
- Splanchnic vasoconstriction reduces portal blood flow and portal pressure
- Systemic vasoconstriction
 - Increases effective blood volume
 - Reduces renin and angiotensin
 - Can lead to renal vasodilation
 - Can lead to improvement in serum creatinine
- V-2 agonist activity
 - Could possibly cause hyponatremia

AASLD and ACG Guidelines: Vasoconstrictor Dosing and Administration for HRS-AKI

Drug	AASLD Dosing and Administration Recommendations ¹
Terlipressin	Vasoconstrictor of choice for treating HRS-AKI (unapproved in the US at the time this guidance was written*)
Norepinephrine	Recommended when terlipressin is not available/cannot be administered Continuous IV infusion starting at 0.5 mg/h to achieve an increase in mean arterial pressure of at least 10 mmHg or an increase in urine output of > 200 mL/4 h If at least one of these goals is not achieved, increase every 4 h in increments of 0.5 mg/h up to a maximum of 3 mg/h
Oral midodrine in combination with octreotide	Recommended when terlipressin and norepinephrine are not available/cannot be administered Midodrine 5–15 mg po every 8 h plus octreotide 100–200 µg every 8 h or 50 µg/h via IV

The **ACG** also suggests that terlipressin or norepinephrine be administered to hospitalized patients with cirrhosis and HRS-AKI without high grade of ACLF or disease.²

*Terlipressin was approved in the US on September 14, 2022.

1. Biggins SW et al. *Hepatology*. 2021;74:1014-1048; 2. Bajaj JS et al. *Am J Gastroenterol*. 2022;117:225-252.

Terlipressin: Indications, Usage and Boxed Warning

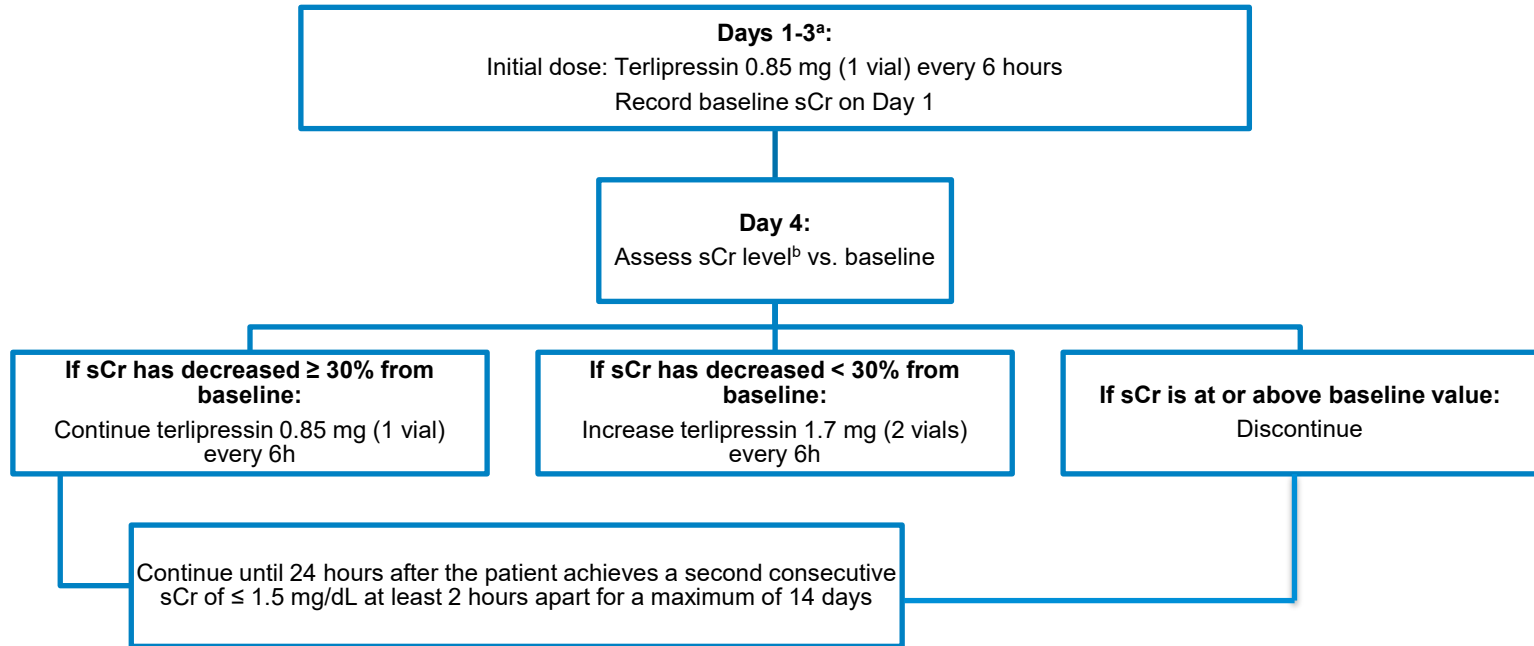
- Indicated to improve kidney function in adults with HRS with rapid reduction in kidney function
- Patients with a serum creatinine >5 mg/dL are unlikely to experience benefit

WARNING: SERIOUS OR FATAL RESPIRATORY FAILURE

Terlipressin may cause serious or fatal respiratory failure. Patients with volume overload or with ACLF Grade 3 are at increased risk. Assess oxygenation saturation (e.g., SpO₂) before initiating terlipressin.

Do not initiate terlipressin in patients experiencing hypoxia (e.g., SpO₂ <90%) until oxygenation levels improve. Monitor patients for hypoxia using continuous pulse oximetry during treatment and discontinue terlipressin if SpO₂ decreases below 90%

Terlipressin: Dosing and Administration



h, hours; sCr, serum creatinine

^aPrior to initial dosing, assess patients for ACLF Grade 3 and obtain patient baseline oxygenation level. Monitor patient oxygen saturation with pulse oximetry.

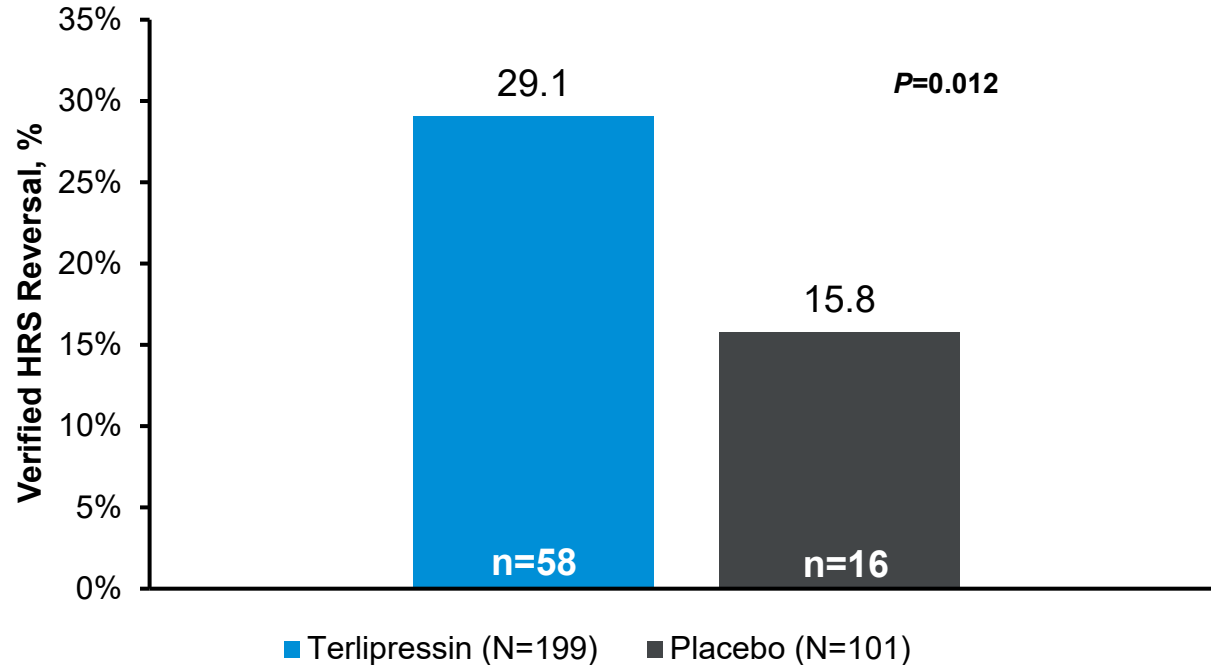
^bBaseline sCr is the last available sCr before initiating treatment

Terlivaz (terlipressin) [package insert]. Bedminster, NJ: Mallinckrodt Pharmaceuticals Inc.; 2022

Terlipressin + Albumin vs Albumin Alone for HRS-1 (CONFIRM Study)

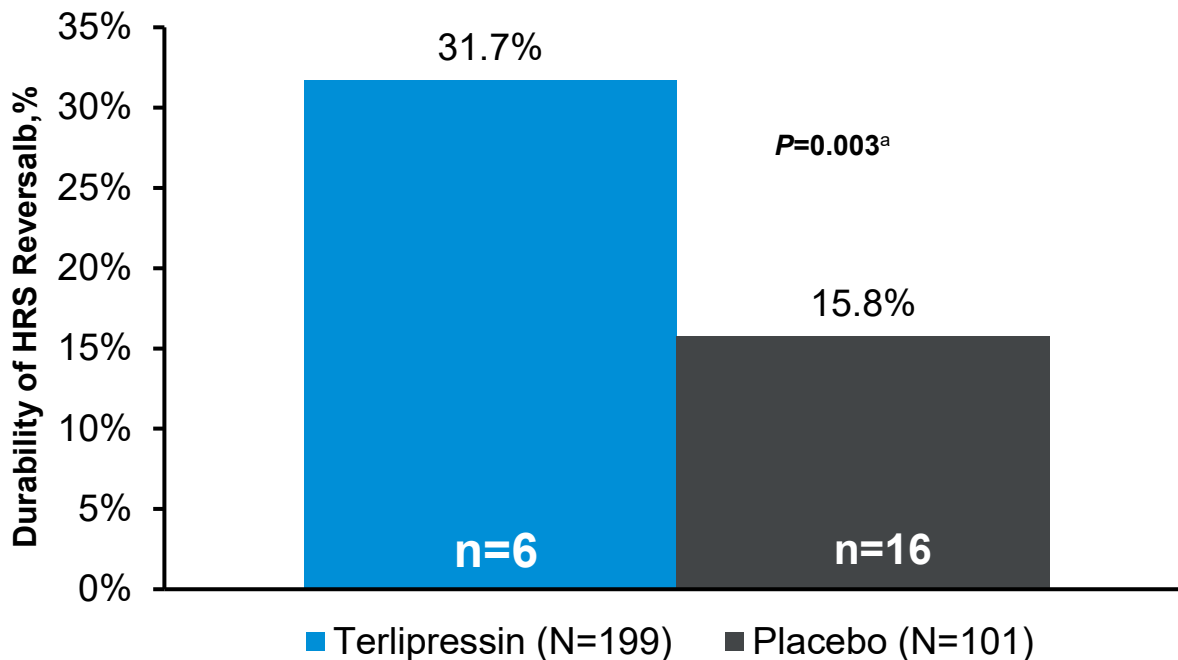
- Randomized, placebo-controlled study in 300 patients
- 2:1 to terlipressin (1 mg IV every 6 hours) or placebo, plus albumin in both groups
- Treatment for up to 14 days unless one of the following occurred:
 - Verified HRS reversal (VHRSR) (decrease in SCr to ≤ 1.5 mg/dL)
 - Renal replacement therapy (RRT)
 - Liver transplantation (LT) or
 - SCr at or above baseline (BL) at Day 4
- Primary Endpoint
 - VHRSR defined as 2 consecutive SCr values ≤ 1.5 mg/dL, at least 2 hours apart, with patient alive without RRT for ≥ 10 days after the second SCr ≤ 1.5 mg/dL

Primary Endpoint: Verified HRS Reversal (CONFIRM Study)



Z score=2.52618. The final analysis is successful if the score is >1.97743.
Wong F et al. *N Engl J Med.* 2021;384:818-828.

Secondary Endpoint: Durability of HRS Reversal (CONFIRM Study)



^aFrom a CMH Test stratified by qualifying serum creatinine (<3.4 vs ≥3.4 mg/dL) and prior LVP within 14 days of randomization (at least one single event of ≥4 vs <4 L); ^bPercentage of subjects with HRS reversal without RRT to day 30.

Wong F et al. *N Engl J Med.* 2021;384:818-828.

Incidence of Adverse Events (>10% Terlipressin Patients) (CONFIRM Study)

Preferred Term ^a	Terlipressin (N=200) ^b % (n)	Placebo (N=99) ^b % (n)
Abdominal pain	19.5 (39)	6.1 (6)
Nausea	16.0 (32)	10.1 (10)
Diarrhea	13.0 (26)	7.1 (7)
Dyspnea	12.5 (25)	5.1 (5)
Respiratory failure	10.5 (21)	5.1 (5)
Hepatic encephalopathy	10.0 (20)	13.1 (13)

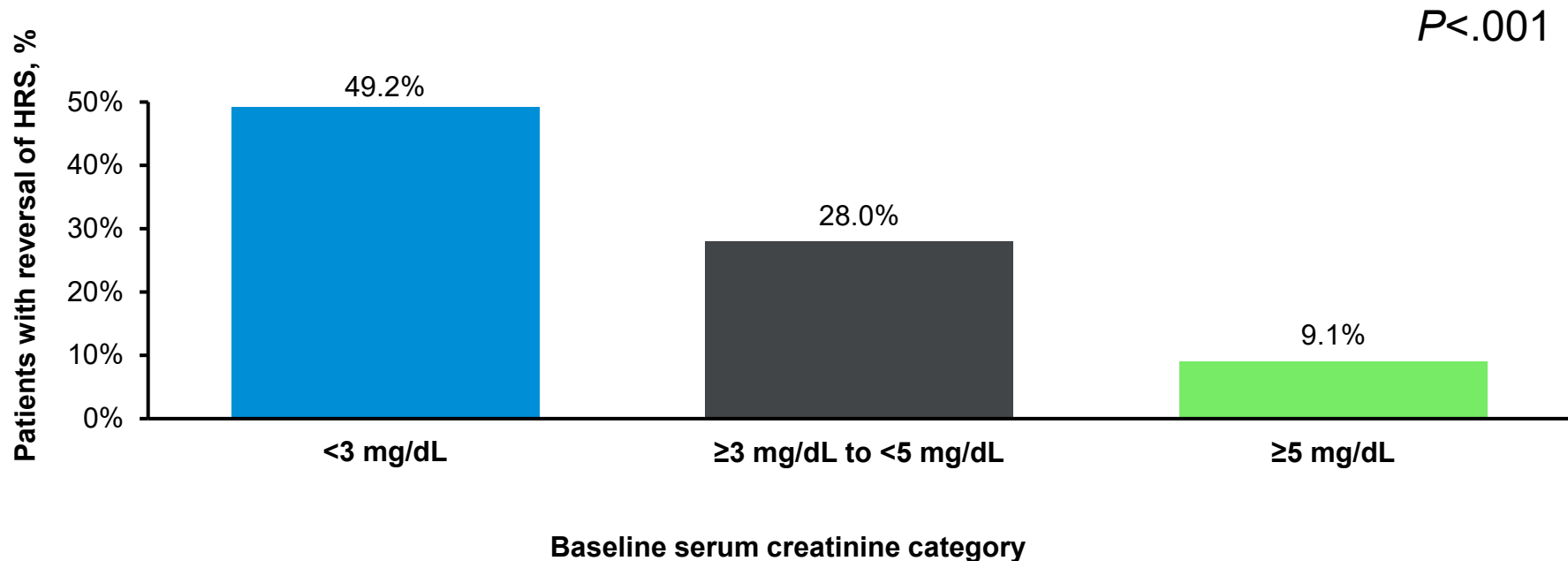
Respiratory Failure higher in both cohorts in CONFIRM than REVERSE trial;
REVERSE T 5.4% vs P 2.1%; none of the respiratory failure were reported as related to study drug.

AEs, adverse events; N, number of subjects in the treatment group; n, number of subjects in the category of subjects in the treatment group.

^aUp to 7 days posttreatment; ^bSubjects experiencing multiple episodes of a given adverse event are counted once within each preferred term.

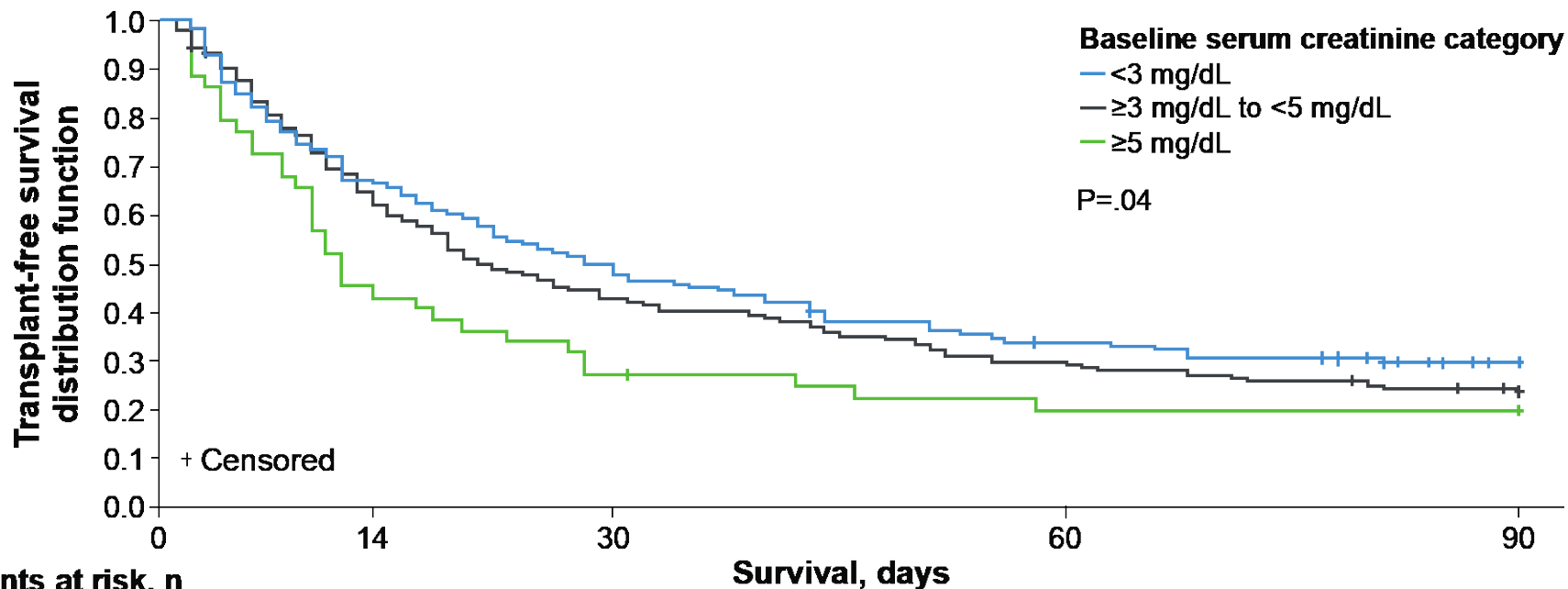
Wong F et al. *N Engl J Med.* 2021;384:818-828.

Figure 2. Percent of Patients in the Terlipressin Treatment Group Who Had HRS Reversal by Baseline Serum Creatinine Subgroup (Pooled ITT Population^a)



^aPooled data were collated from the following Phase III studies: OT-0401⁵, REVERSE², and CONFIRM⁵. The P value was calculated using a chi-square test. HRS, hepatorenal syndrome; ITT, intent-to-treat.

Transplant-free Survival by Baseline Creatinine

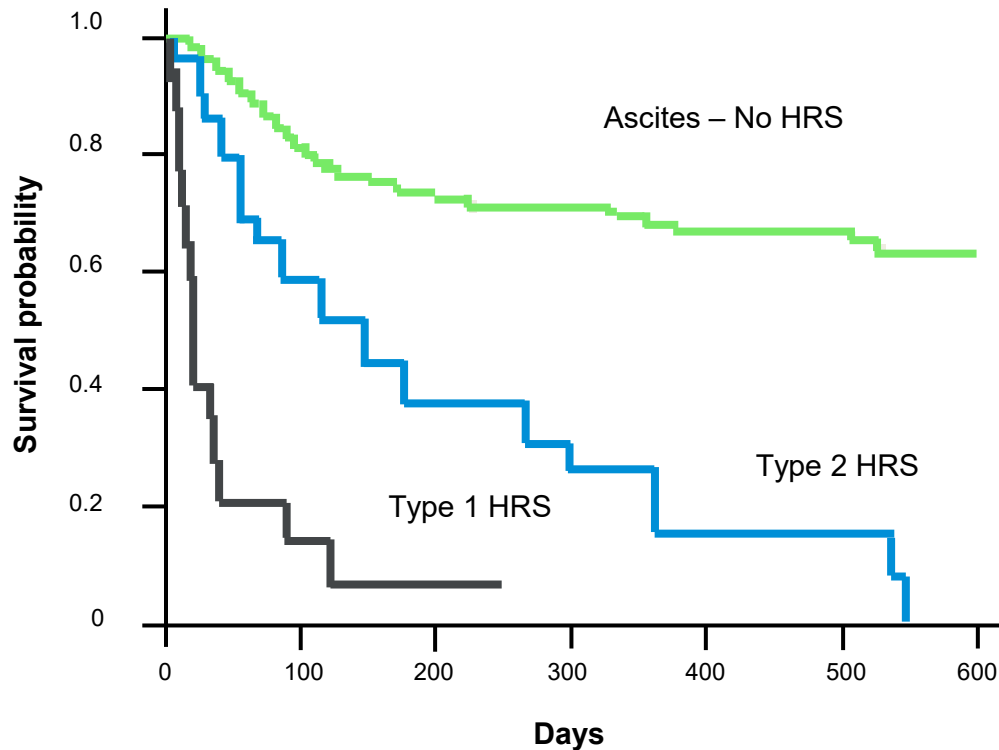


Patients at risk, n

Baseline serum creatinine

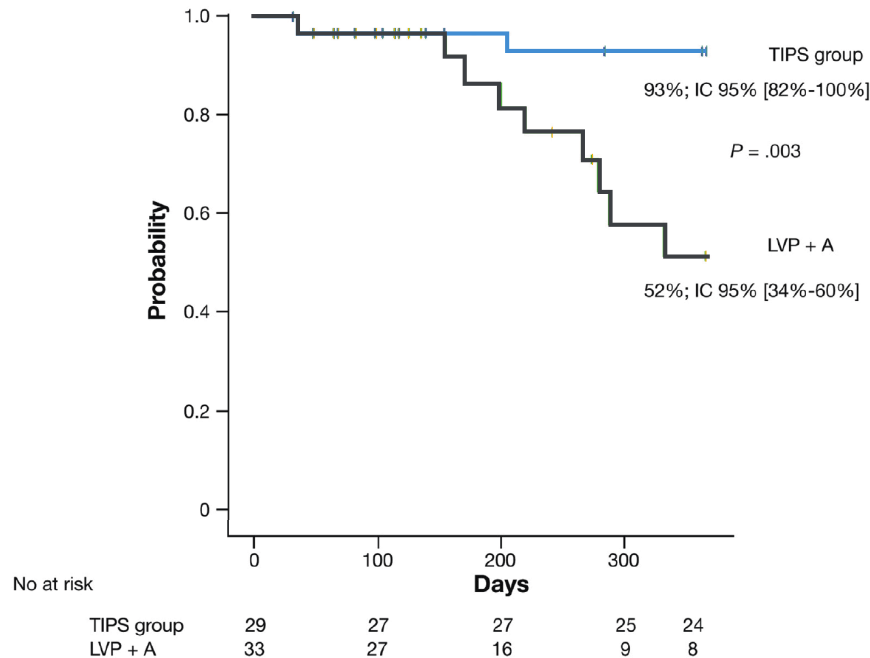
<3 mg/dL	126	85	63	41	25
≥3 to <5 mg/dL	182	117	77	54	40
≥5 mg/dL	44	20	12	8	8

Survival in Patients With Ascites and HRS

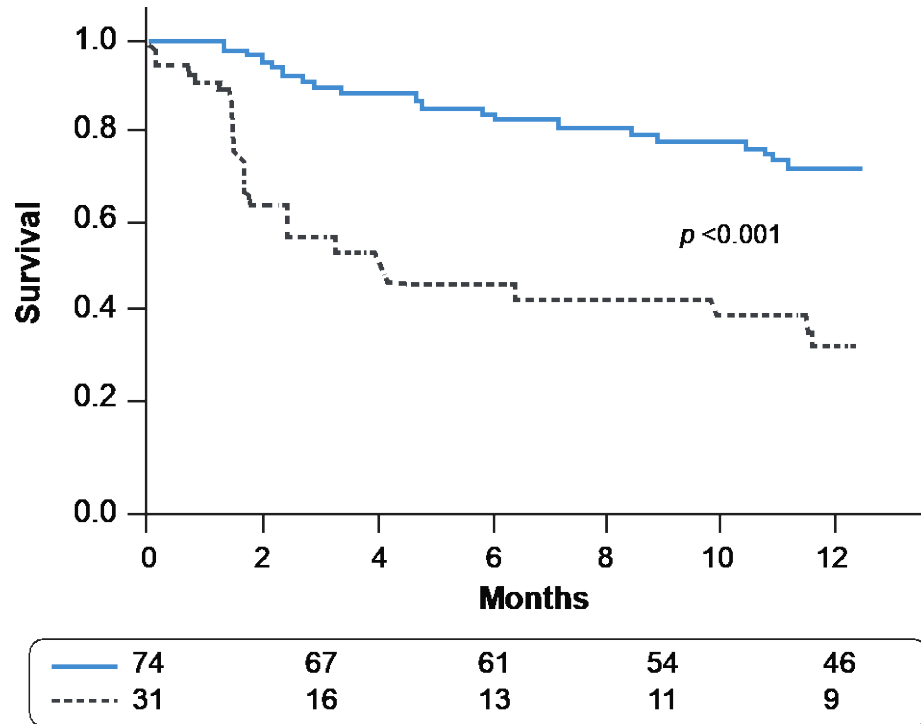


TIPS vs LVP for Refractory Ascites

- Probability of survival without liver transplantation in patients allocated to covered TIPS group and in those allocated to LVP+A group.



TIPS: Patient Selection



Perspective of Liver Transplantation in Patients With HRS

- To what extent renal failure is reversible after LT
- When should a simultaneous liver kidney transplantation (SLK) be considered in non-responders to pharmacological treatment
- How to ascribe the correct priority on the waiting list to responders to pharmacological treatment.