Terlipressin and albumin in HRS-AKI Risks / Benefits

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Introduction

- HRS-AKI is a devastating complication of advanced cirrhosis occurring in approximately 17% of AKI cases
- High 90-day mortality rate of 45% to 51%.
- Key points:
  - *Securing the correct diagnosis*
  - *Early management*
  - *Administration of vasoconstrictors and albumin*
  - *Monitor side effects*
  - *End goal → reach LT (best therapy)*

N Engl J Med. 2023 Feb 23;388(8):733-745
Crit Care Med 2022;50:1419-1429

Acute Kidney Injury in Cirrhosis

Definition

↑ in SCr ≥ 0.3 mg/dL (≥ 26.5 mmol/L) within 48 hours
or ≥1.5 times baseline level or urinary output <0.5 ml/kg/hr in 6 hr

Increase in mortality

- SCr > 1.5 mg/dL
- With increasing stage and progression

Up to 50% patients hospitalized with advanced cirrhosis have AKI

- AKI, acute kidney injury; SCr, serum creatinine.

Nadim MK, Garcia-Tsao G. Acute Kidney Injury in Patients with Cirrhosis. N Engl J Med. 2023 Feb 23;388(8):733-745.

AKI in Cirrhosis

Hypovolemia:
diuretics, GI bleeding, diarrhea

Nephrotoxicity:
NSAIDs, others

AKI-HRS
often associated with bacterial infections

Intrinsic renal disease

Acute tubular necrosis:
shock, nephrotoxic drugs, other (eg, obstruction)

Miscellaneous, unknown

- ☑ Medical history
- ☑ Physical examination
- ☑ Blood tests
- ☑ Urine tests
- ☑ Abdominal US

- US, ultrasound.

Graupera I, Cardenas A. Clin Liver Dis. 2013;2:128-131.

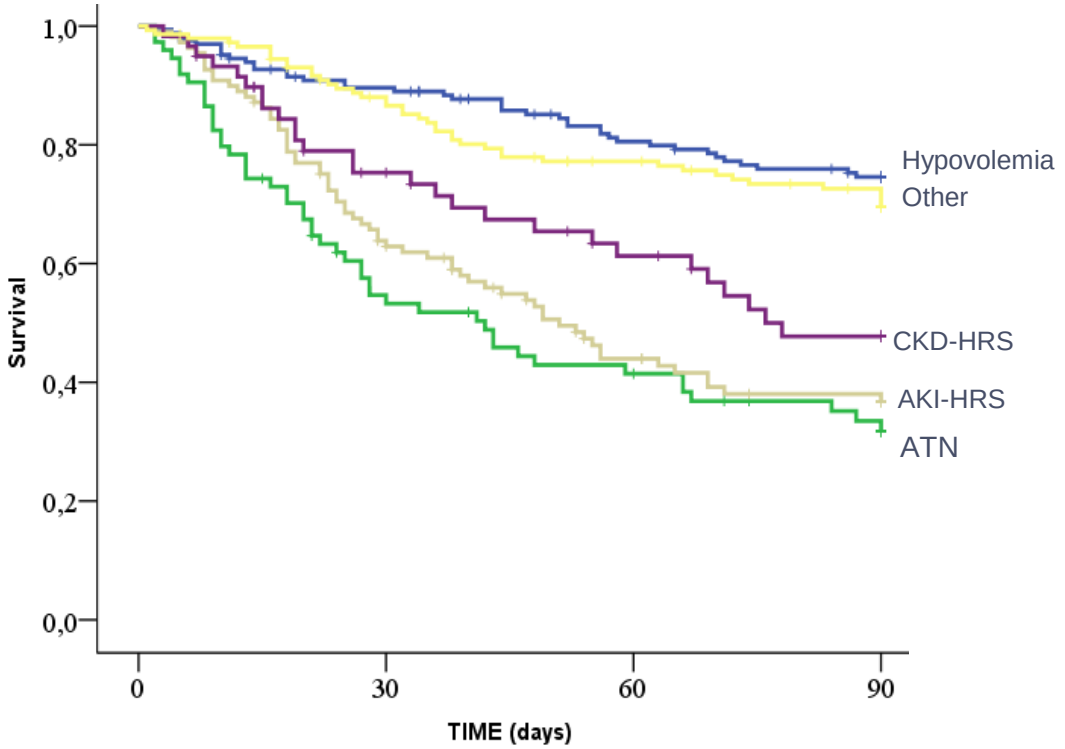
Prevalence and Causes of AKI in Patients With Cirrhosis

Prevalence and causes of AKI in patients with cirrhosis

Study	*n*	AKI prevalence (%)	Causes of AKI		
			Hypovolaemia (%)	ATN (%)	HRS (%)
Fagundes et al., 2013	375	47	35	ND	18
Piano et al., 2013	233	27	36	ND	43
Belcher et al., 2014	110[a]	ND	50	35	15
Alegretti et al., 2015	120[a]	ND	33	29	30
Tandon et al., 2017	4,733	36	ND	ND	ND
Huelin et al., 2017	547	53	27	14	32

All patients with cirrhosis had been hospitalized for complications of the disease. AKI, acute kidney injury; ATN, acute tubular necrosis; HRS, hepatorenal syndrome; ND, not determined.
[a]Studies included only patients with cirrhosis and AKI.

Probability of Survival Based on Diagnosis



Ginès P, et al. Nat Rev Dis Primers. 2018;4:23;

Stages of AKI

Stage 1

- Increase in sCr ≥ 0.3 mg/dL (≥ 26.5 mmol/L) or an increase in sCr ≥ 1.5-fold to 2-fold from baseline
- 1A vs 1B is based on absolute sCr level of 1.5 mg/dL

Stage 2

- Increase in sCr > 2-fold to 3-fold from baseline

Stage 3

- Increase of sCr > 3-fold from baseline or sCr ≥ 4.0 mg/dL (≥ 353.6 mmol/L) with an acute increase ≥ 0.3 mg/dL (≥ 26.5 mmol/L) or initiation of RRT

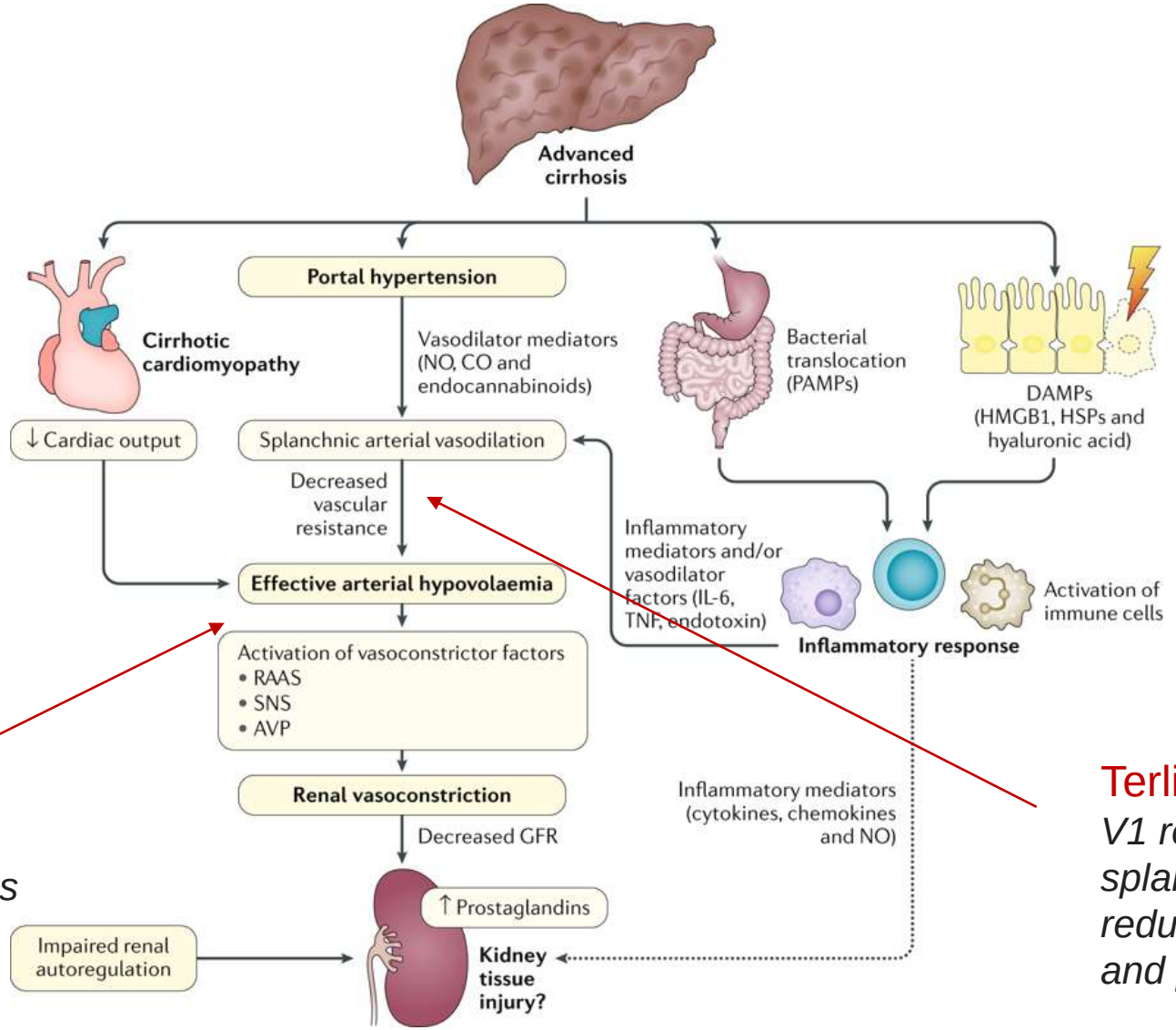
- RRT, renal replacement therapy.
- European Association for the Study of the Liver. J Hepatol. 2018;69:406-460.

Categorization of AKI-Stage 1
SCr Value at Diagnosis of AKI

Variable	AKI-1A (SCr <1.5 mg/dL), n = 58	AKI-1B (SCr ≥1.5 mg/dL), n = 139	*P* Value
Frequency (of all AKI cases), %	29.4	70.6	NA
AKI resolution, %	90	52	*P* <.001
AKI progression, %	15	31	*P* =.017
Associated ACLF, %	22	76	*P* <.001
3-month survival, %	84	58	*P* =.001

- ACLF, acute-on-chronic liver failure.
  Huelin P, et al. Clin Gastroenterol Hepatol. 2017;15:438-445.e5.

Pathogenesis of HRS



Albumin

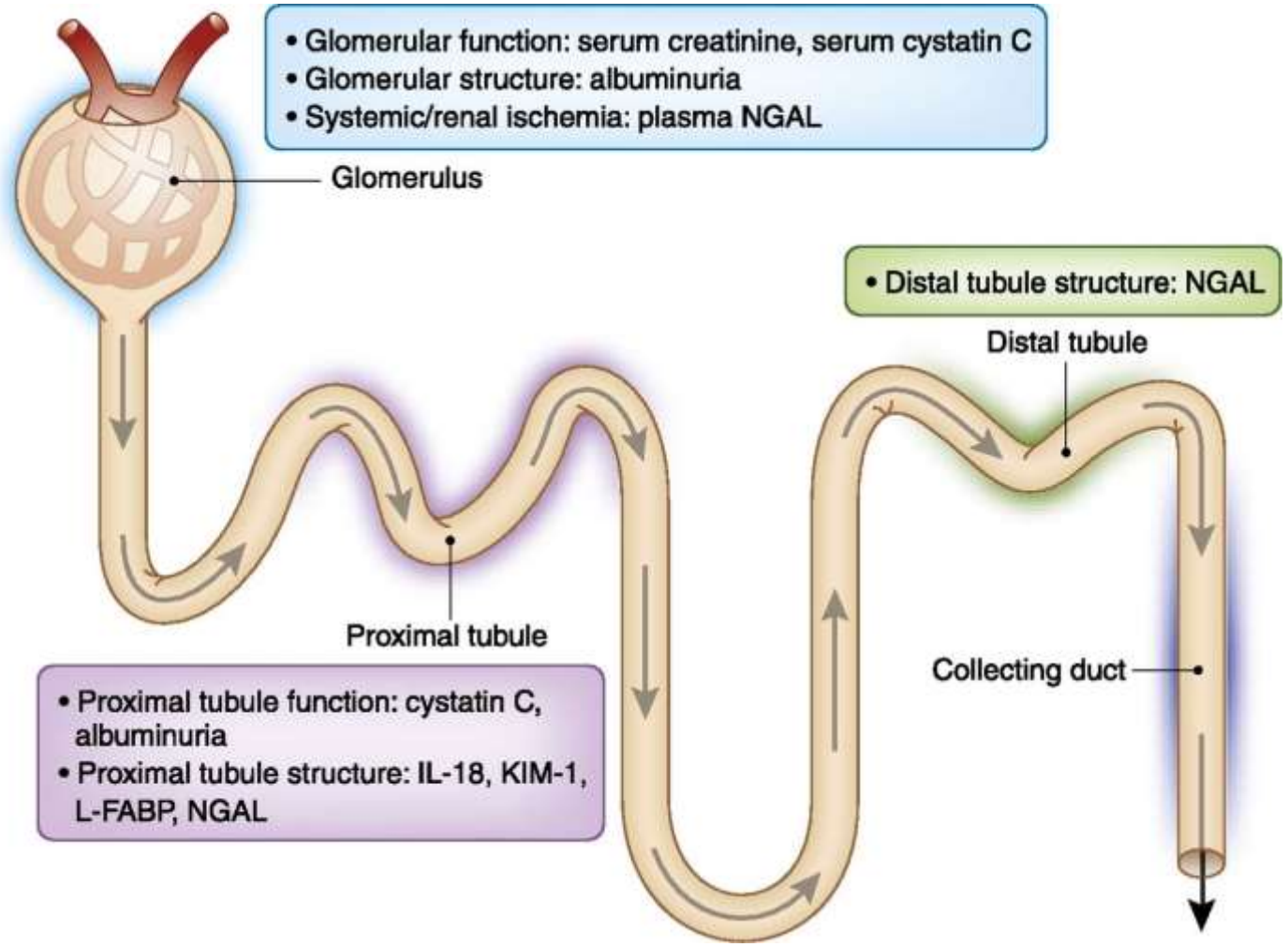
increase intravascular volume & may also have anti-inflammatory properties

Terlipressin

V1 receptor agonist → splanchnic vasoconstriction reducing splanchnic blood flow and portal pressure, and ↑ MAP

- Ginès P, et al. Nat Rev Dis Primers. 2018;4:23.

Biomarkers of Tubular Damage / uNGAL



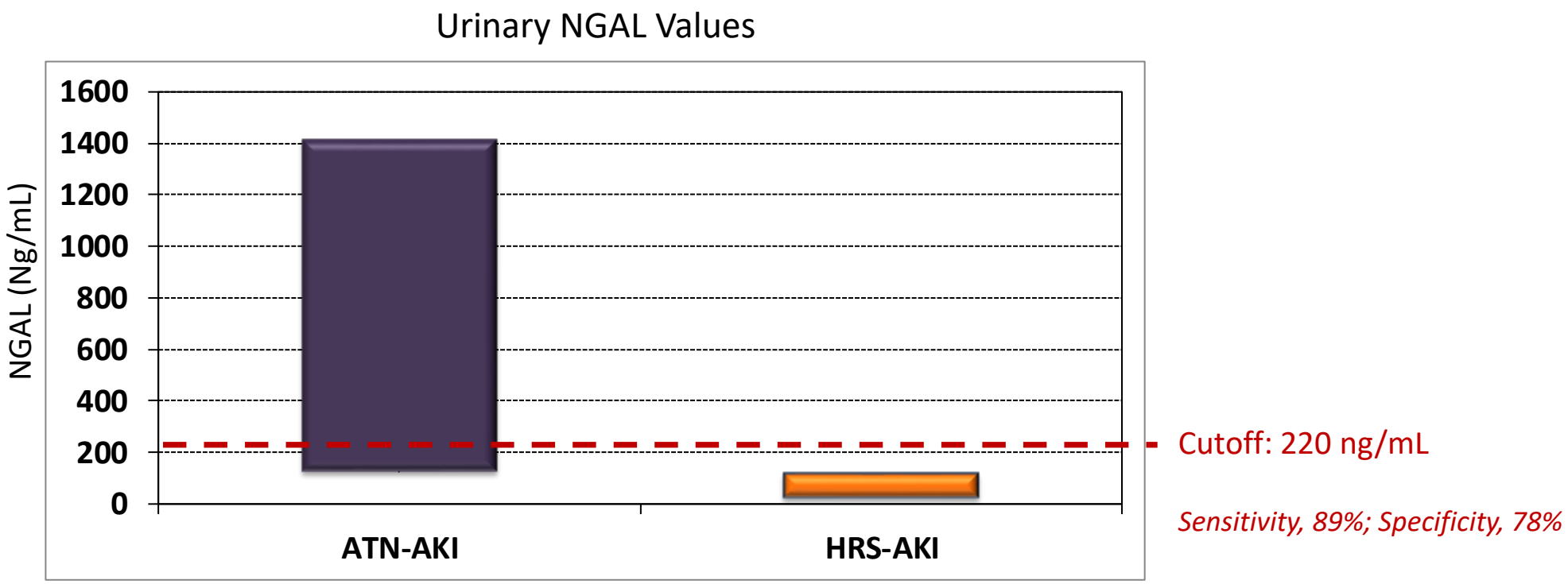
Neutrophil gelatinase-associated lipocalin (NGAL) – protein from lipocalin superfamily.

Acute-phase reactant released from neutrophils, macrophages, and other immune cells in response to inflammation or epithelial injury

- Adapted from Koyner et al, Clin J Am Soc Nephrol. 2013;8:1034-1042.

Urinary NGAL Values in Patients With Cirrhosis and HRS and ATN

- **NGAL has high accuracy in the differential diagnosis between ATN and other types of AKI, including HRS-AKI and hypovolemia-induced AKI.**
- **Useful in predicting the response to terlipressin and albumin (*Hepatology. 2023 May 1;77(5):1630-1638*)**



uNGAL is currently used in clinical trials, but is not widely available

- ATN, acute tubular necrosis; AUC, area under the curve; NGAL, Neutrophil gelatinase-associated lipocalin..
  Huelin P et al. Hepatology. 2019;70:319-333. Gambino et al. Hepatology. 2023 May 1;77(5):1630-1638.

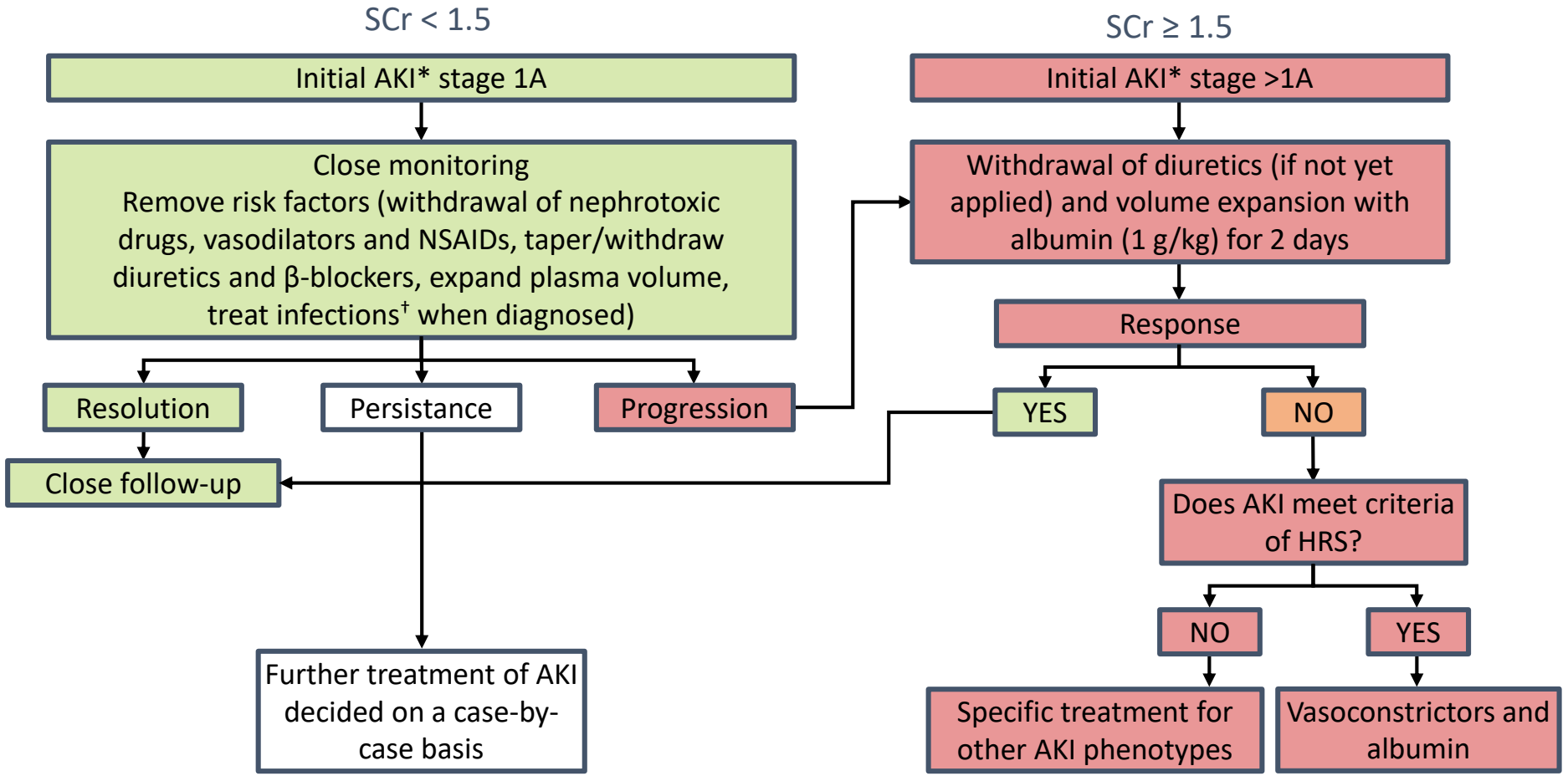
HRS-AKI Diagnostic Criteria

OLD NAME	NEW NAME
HRS type 1	**HRS-AKI**
■ Doubling of serum creatinine to a concentration ≥2.5 mg/dL within 2 weeks	■ Increase in serum creatinine of ≥0.3 mg/dL within 48 hours OR Increase in serum creatinine ≥1.5 times from baseline (creatinine value within previous 3 months, when available, may be used as baseline, and value closest to presentation should be used)
■ No response to diuretic withdrawal and 2 day fluid challenge with 1 g/kg/day of albumin 20-25%	■ No response to diuretic withdrawal and 2 day fluid challenge with 1 g/kg/day of albumin 20-25%
■ Cirrhosis with ascites	■ Cirrhosis with ascites
■ Absence of shock	■ Absence of shock
■ No current or recent use of nephrotoxic drugs (NSAIDs, contrast dye, etc)	■ No current or recent use of nephrotoxic drugs (NSAIDs, contrast dye, etc)
■ No signs of structural kidney injury – Absence of proteinuria (>500 mg/day) – Absence of hematuria (>50 RBCs per high power field) – Normal findings on renal ultrasonography	■ No signs of structural kidney injury – Absence of proteinuria (>500 mg/day) – Absence of hematuria (>50 RBCs per high power field) – Normal findings on renal ultrasound

- Simonetto DA, et al. BMJ. 2020;370:m2687 / European Association for the Study of the Liver. J Hepatol. 2018;69:406-460.

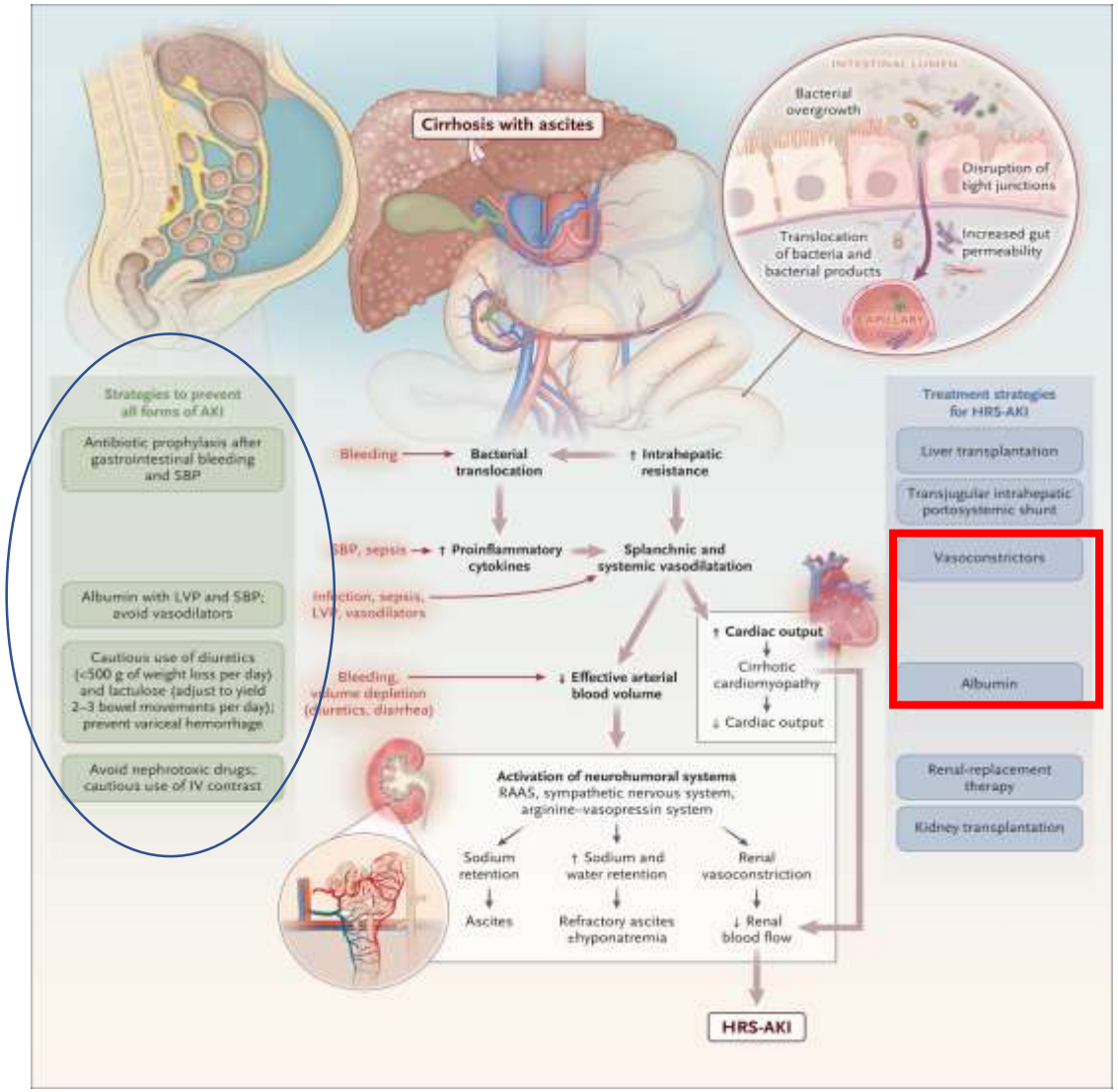
Management Algorithm for AKI in Cirrhosis

- **Investigation and management should begin immediately**



- *Initial AKI stage is defined as AKI stage at the time of first fulfilment of the AKI criteria.
  †Treatment of spontaneous bacterial peritonitis should include albumin infusion according to current guidelines.
  Adapted from Angeli P, et al. J Hepatol 2015;62:968-974.
  European Association for the Study of the Liver. J Hepatol. 2018;69:406-460.

Prevention and treatment of HRS-AKI



MK Nadim, G Garcia-Tsao. N Engl J Med 2023;388:733-745

Terlipressin effect on hepatorenal syndrome: Updated meta-analysis

8 RCT (n = 974) 534 patients with terlipressin vs 440 patients with placebo

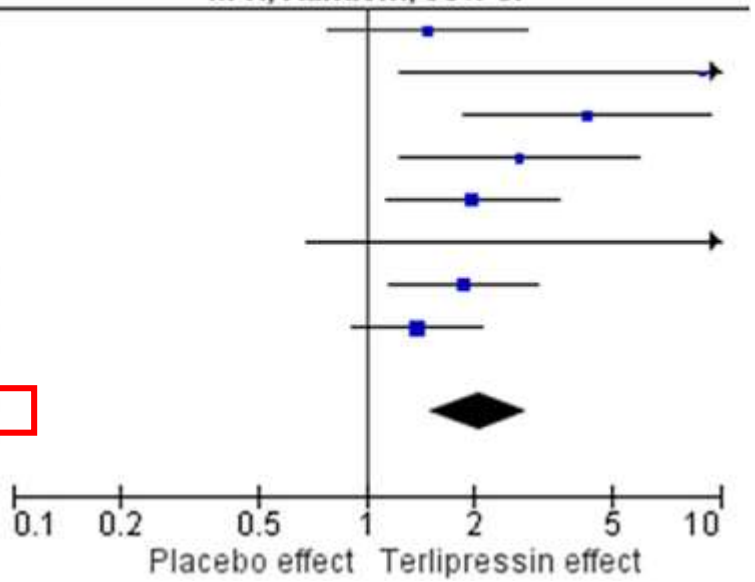
No difference in survival at 90 days between groups (RR 1.09; 95% CI (0.84,1.43),P=0.52

Reversal of hepatorenal syndrome

Study or Subgroup	Terlipressin Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Boyer et at (REVERSE)2016	19	97	13	99	14.6%	1.49 [0.78, 2.85]
Martin-Ilahi et al 2008	9	23	1	23	2.4%	9.00 [1.24, 65.41]
Neri et al 2007	21	26	5	26	10.9%	4.20 [1.87, 9.44]
Sanyal et al 2008	19	56	7	56	11.4%	2.71 [1.24, 5.94]
Silawat et al 2011	20	30	10	30	17.1%	2.00 [1.14, 3.52]
Solanki et al 2003	5	12	0	12	1.3%	11.00 [0.67, 179.29]
Wong et al (CONFIRM) 2021	63	199	17	101	20.1%	1.88 [1.16, 3.04]
Wong et al (REVERSE 2) 2019	34	91	25	93	22.1%	1.39 [0.91, 2.13]
Total (95% CI)		**534**		**440**	**100.0%**	**2.08 [1.51, 2.86]**
Total events	190		78			

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 11.21$, df = 7 (P = 0.13); $I^2 = 38\%$

Test for overall effect: Z = 4.49 (P < 0.00001)



JGH Open. 2021 Jul 1;5(8):896-901

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Terlipressin plus Albumin for the Treatment of Type 1 Hepatorenal Syndrome

F. Wong, S.C. Pappas, M.P. Curry, K.R. Reddy, R.A. Rubin, M.K. Porayko, S.A. Gonzalez, K. Mumtaz, N. Lim, D.A. Simonetto, P. Sharma, A.J. Sanyal, M.J. Mayo, R.T. Frederick, S. Escalante, and K. Jamil, for the CONFIRM Study Investigators*

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*A complete list of investigators in the CONFIRM Study are listed in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2021;384:818-28.
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ABSTRACT

BACKGROUND

The vasoconstrictor terlipressin is used for type 1 hepatorenal syndrome (HRS-1) in many parts of the world and is part of the clinical practice guidelines in Europe.

METHODS

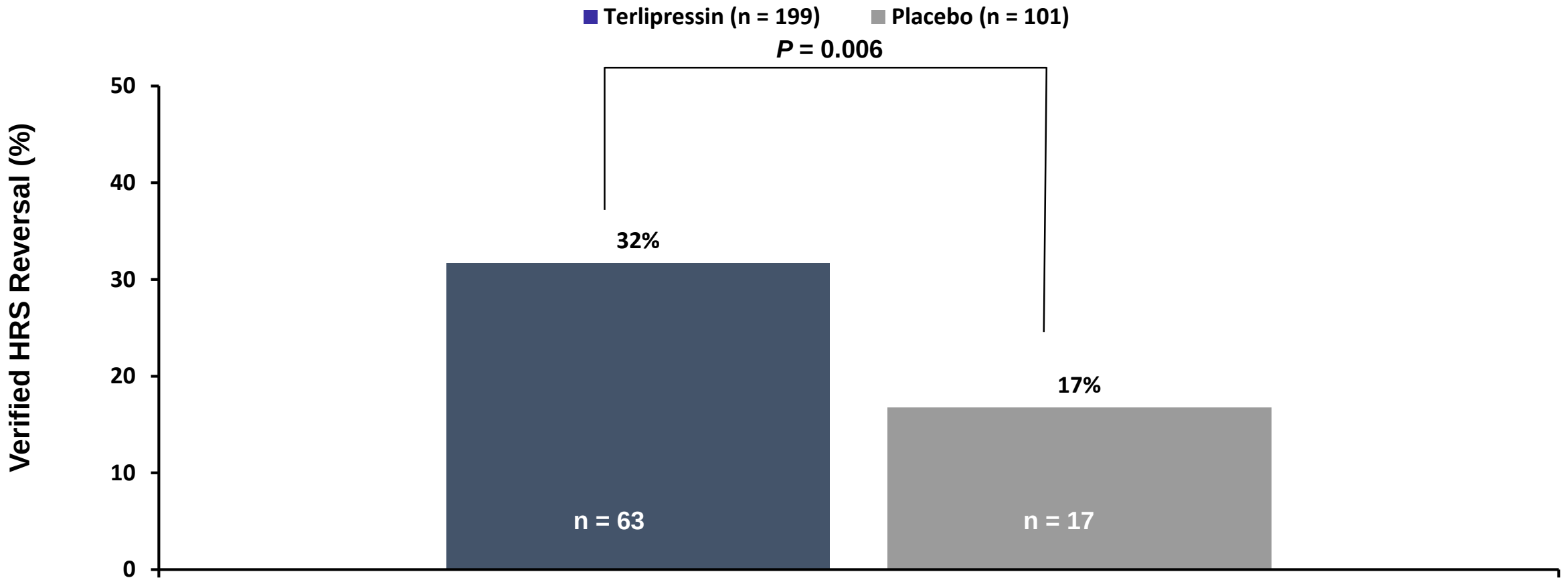
We conducted a phase 3 trial to confirm the efficacy and safety of terlipressin plus albumin in adults with HRS-1. The patients were randomly assigned in a 2:1 ratio to receive terlipressin or placebo for up to 14 days; in both groups, concomitant use of albumin was strongly recommended. The primary end point was verified reversal of HRS, defined as two consecutive serum creatinine measurements of 1.5 mg per deciliter or less at least 2 hours apart and survival without renal-replacement therapy for at least 10 days after the completion of treatment. Four prespecified secondary end points were analyzed with the Hochberg procedure to account for multiple comparisons.

- N Engl J Med. 2021 Mar 4;384(9):818-828

Terlipressin and Albumin for HRS: CONFIRM STUDY

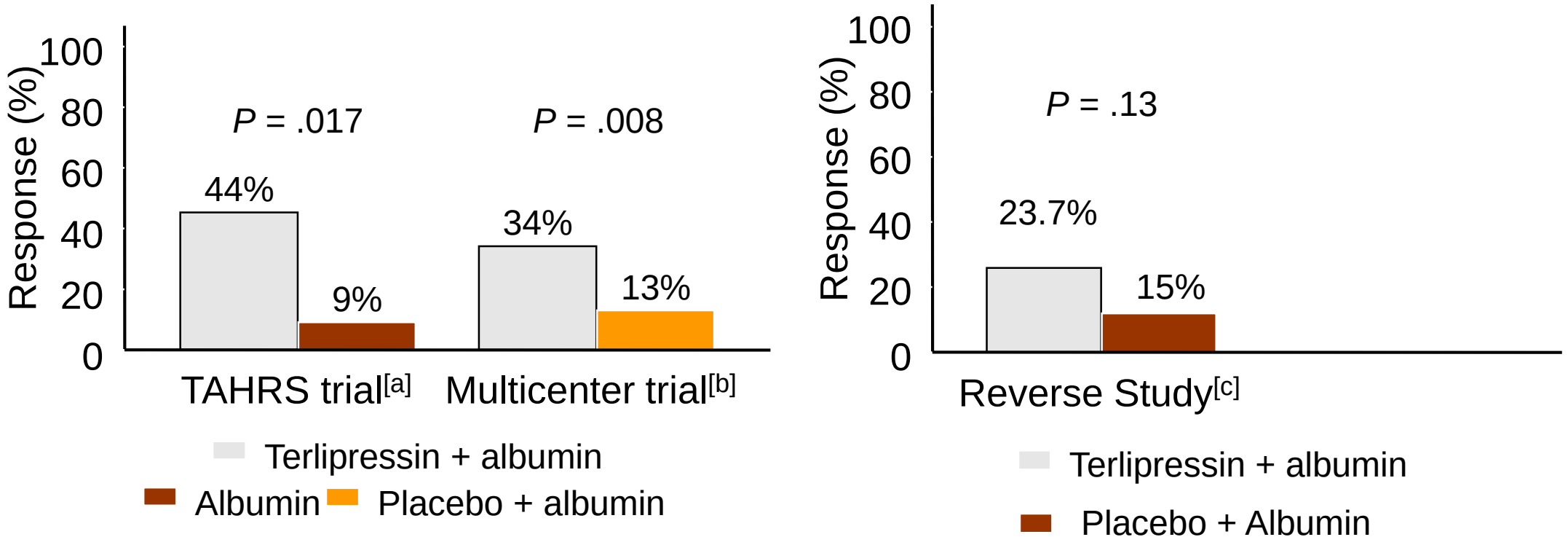
Primary Endpoint: Verified HRS reversal:
Two Scr levels of 1.5 mg/dl or less up to 2 weeks and survival without RRT for 10 days

- **Outcome / Given IV bolus**



- Z score = 2.52618.
- CONFIRM study.Wong F, et al. N Engl J Med. 2021 Mar 4;384(9):818-828.

Terlipressin and Albumin: Response to Treatment (bolus dosing)

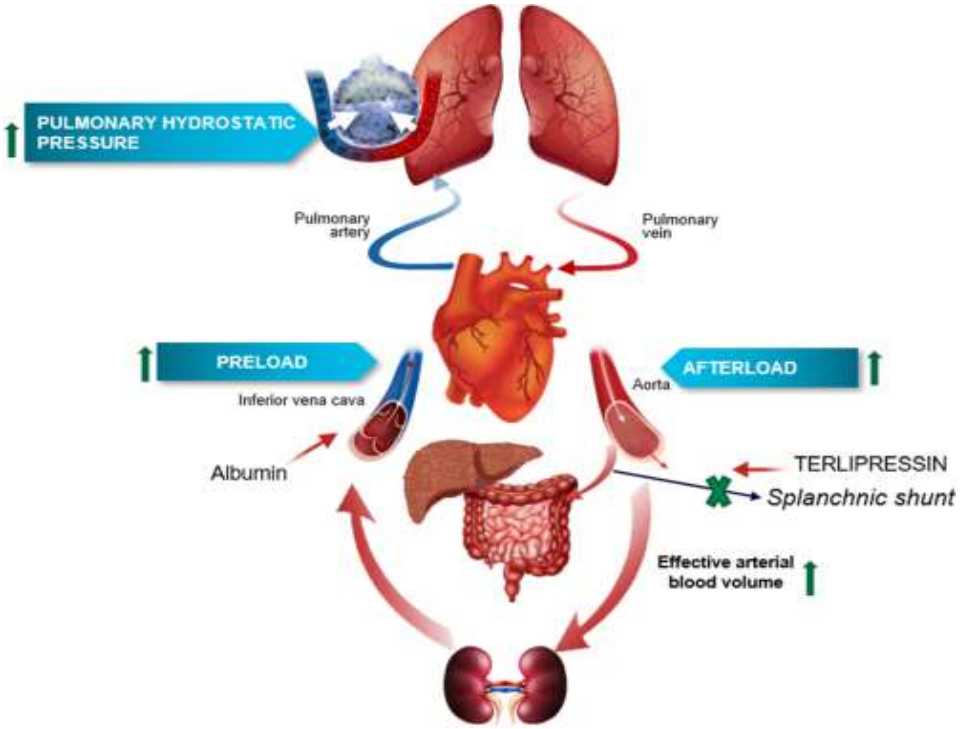


Terlipresin IV continous infusion response rate 75% (Cavallin, Hepatology 2016)

- a. Martín-Llahí M, et al. Gastroenterology. 2008;134:1352-1359; b. Sanyal AJ, et al. Gastroenterology. 2008;134:1360-1368.c Boyer T, et al.. Gastroenterology. 2016;150(7):1579-1589

Adverse Events - CONFIRM

- <u>Respiratory failure:</u>
- 13.5% terlipressin vs 5% placebo
- Not reported in previous trials.
- Possible contributing factor → high doses of albumin pre and post randomization
  - *Mean total doses of 500-600g* .
- Other AE's-
  - abdominal pain, nausea, diarrhea- 10%
  - Ischemic events (heart, extremities, tongue, nose, scrotum) – 5%



Terlipressin - ↑ hydrostatic pressure due shunting & ↑ SVR

Albumin- ↑ in plasma volume in combination with the effects of increased pre- and afterload

N Engl Med. 2021 Mar 4;384(9):818-828
Liver Int. 2022 Oct;42(10):2124-2130.

Risk / Benefit

Risk

- Not securing the diagnosis
- Adverse events
- Volume overload
- Administration in patients :
  - *Ischemic heart disease*
  - *ACLF 3*
  - *Serum Cr > 5mg /dl*

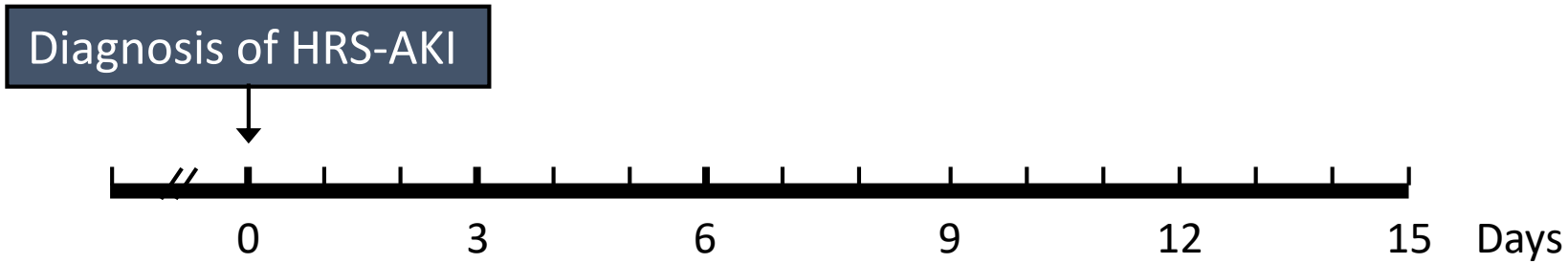
Benefit

- HRS reversal
- ↑ urinary output and serum Na
- Better ascites control
- Less ICU / hospital stay
- Less RRT
- Reach LT with low GFR

Kidney360. 2023 May 5. doi: 10.34067
N Engl Med. 2021 Mar 4;384(9):818-828
Liver Transpl. 2021 Aug;27(8):1191-1202

HEPATORENAL SYNDROME

Treatment with terlipressin and albumin



Terlipressin, 2mg/day continous infusion

Albumin i.v.
1 g/Kg

Albumin 20-40 g/day (slow infusion)

Increase terlipressin dose if creatinine
does not decrease by 25% on day 2

Solà E, Cárdenas A, Ginès P. Curr Opin Organ Transplant. 2013 Jun;18(3):265-70
European Association for the Study of the Liver. J Hepatol. 2018;69:406-460

Clinical Points- Talk to your nurses!

CARDIAC MONITOR FOR 1ST 24 HOURS

VITAL SIGNS EVERY 6-8 HOURS, INCLUDING URINE OUTPUT

CENTRAL VENOUS PRESSURE MONITORING IF POSSIBLE

TERLIPRESSIN CONTINUOUS INFUSION STARTING AT 2MG/ 24 AND TITRATE UP TO MAX DOSE OF 12 MG / DAY

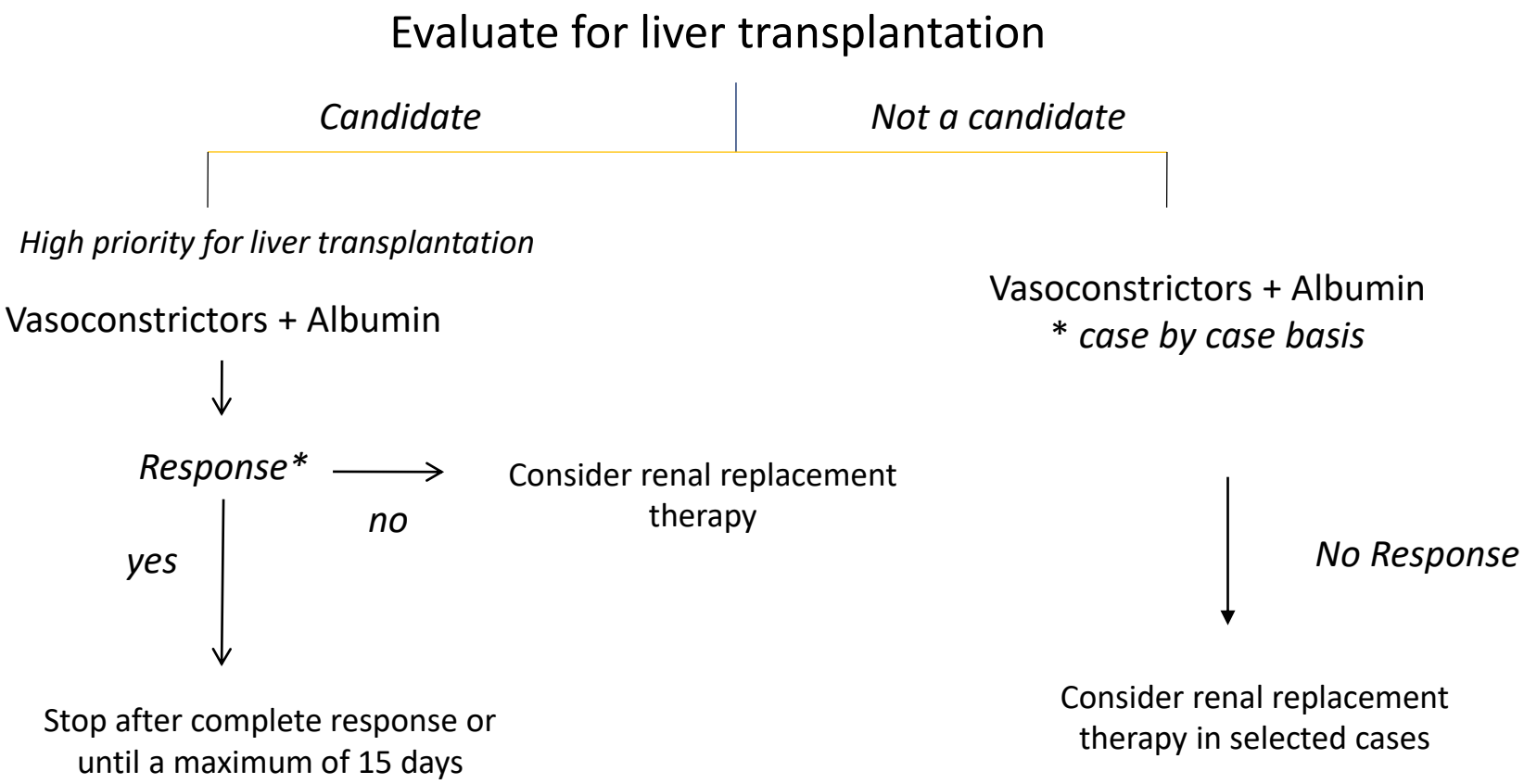
ALBUMIN INFUSION AT SLOW RATE OF 10 GM IN 2-3 HOURS

Nurses' workflow at Hospital Clinic / Hepatology Ward (courtesy of Ana Alonso, RN) with guidance of Dr Pere Gines and team

1. Baseline assessment	-Before terlipressin: detailed history and exam with vital sign assessment (including urine output) -Consider: ACLF grade, pulse oximetry, chest x-ray, echocardiography, and volume status. - Terlipressin should only be initiated if: - Patient has a clear indication for therapy - Risk/benefit ratio favors initiation - No risk factors for worsening respiratory status (ACLF grade 3, pulse oximetry <90% or >2L oxygen requirement, abnormal ejection fraction, pulmonary edema on CXR)
2. Ongoing assessment	Regularly monitor vital signs, pulse oximetry, volume status and urine output. If the patient: - has stable respiratory function and volume status, **continue terlipressin** - demonstrates worsening hypoxia, consider **stopping or holding terlipressin**
3. Stop terlipressin	Stop terlipressin if: - SCr is <1.5 mg/dL (2 consecutive tests) or within 0.3 mg/dL of baseline (**treatment success**) - SCr is at or above pre-treatment value 72 hours after terlipressin (**treatment failure**) - Patient treated for 2 weeks (**maximum recommended treatment course**) - Serious adverse events, including respiratory compromise

Allegretti AS… Cardenas A. Liver Int. 2022 Oct;42(10):2124-2130.

Hepatorenal Syndrome



Cárdenas A, Gines P Gut 2011

Muchas Gracias

Management of HRS-AKI: treatment

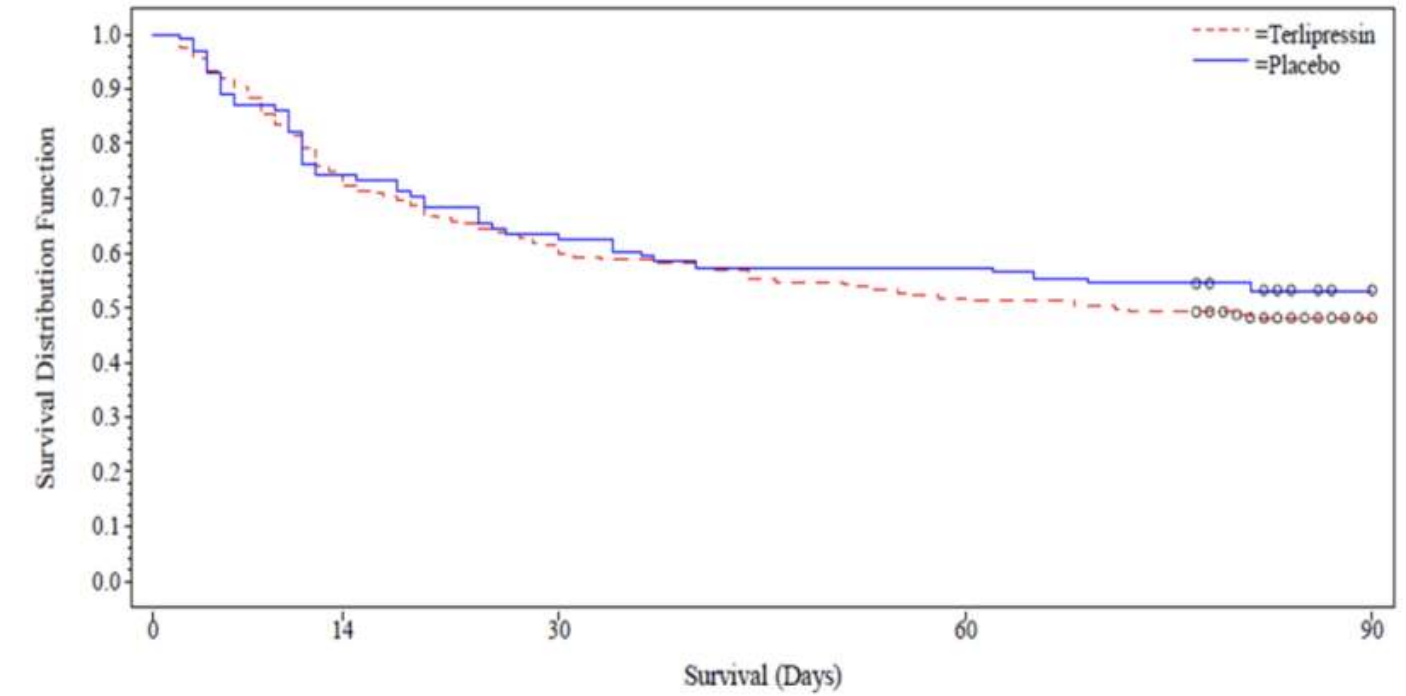
- First-line therapy is terlipressin plus albumin*

Recommendation	Grade of evidence	Grade of recommendation
All patients meeting the current definition of **HRS-AKI stage >1A** should be expeditiously treated with **vasoconstrictors and albumin**	III	1
Terlipressin can be administered by IV boluses (1 mg every 4–6 hours) or by continuous IV infusion (2 mg/day)† • In case of **non-response** (decrease in SCr <25% from the peak value) after 2 days, the dose of **terlipressin should be increased** in a stepwise manner to a **maximum of 12 mg/day**	I	1
Albumin solution (20%) should be used at 20–40 g/day • Serial measures assessing central blood volume can help to titrate the dose of albumin to prevent circulatory overload	II-2	1
Noradrenaline can be an alternative to terlipressin‡ • Requires a central venous line often in an ICU Midodrine + octreotide can be an option when terlipressin or noradrenaline are unavailable (but efficacy is much lower)	I I I	2 1 1

*Grade of evidence I, grade of recommendation 1;
†Continuous IV infusion allows for dose reduction to reduced adverse effects; ‡ Limited data are available
EASL CPG decompensated cirrhosis. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.024

CONFIRM Study- Overall Survival

At day 90, liver transplantations had been performed in 46 patients (23%) in the terlipressin group and 29 patients (29%) in the placebo group, and death occurred in 101 (51%) and 45 (45%), respectively (p=ns)



- N Engl Med. 2021 Mar 4;384(9):818-828

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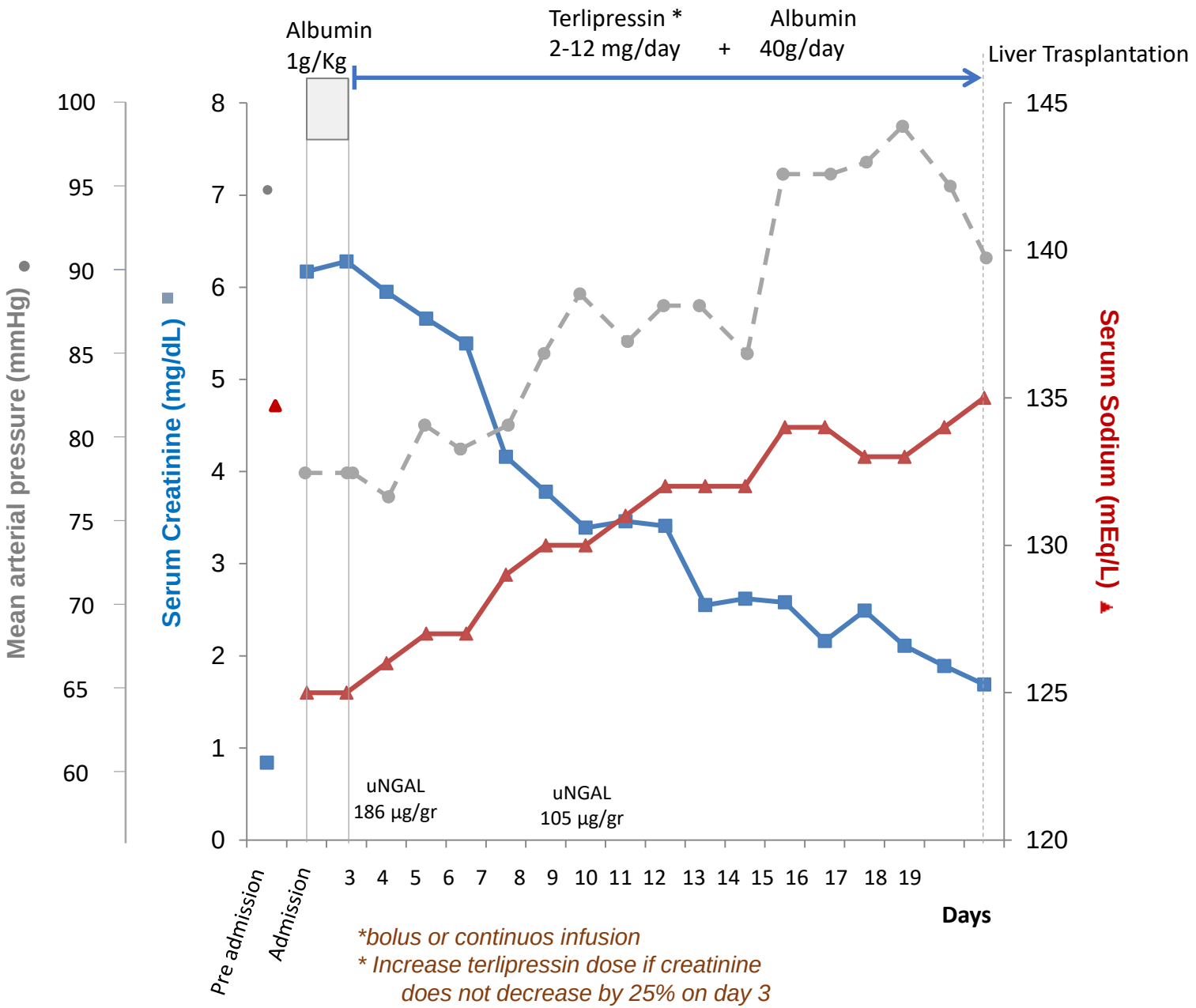
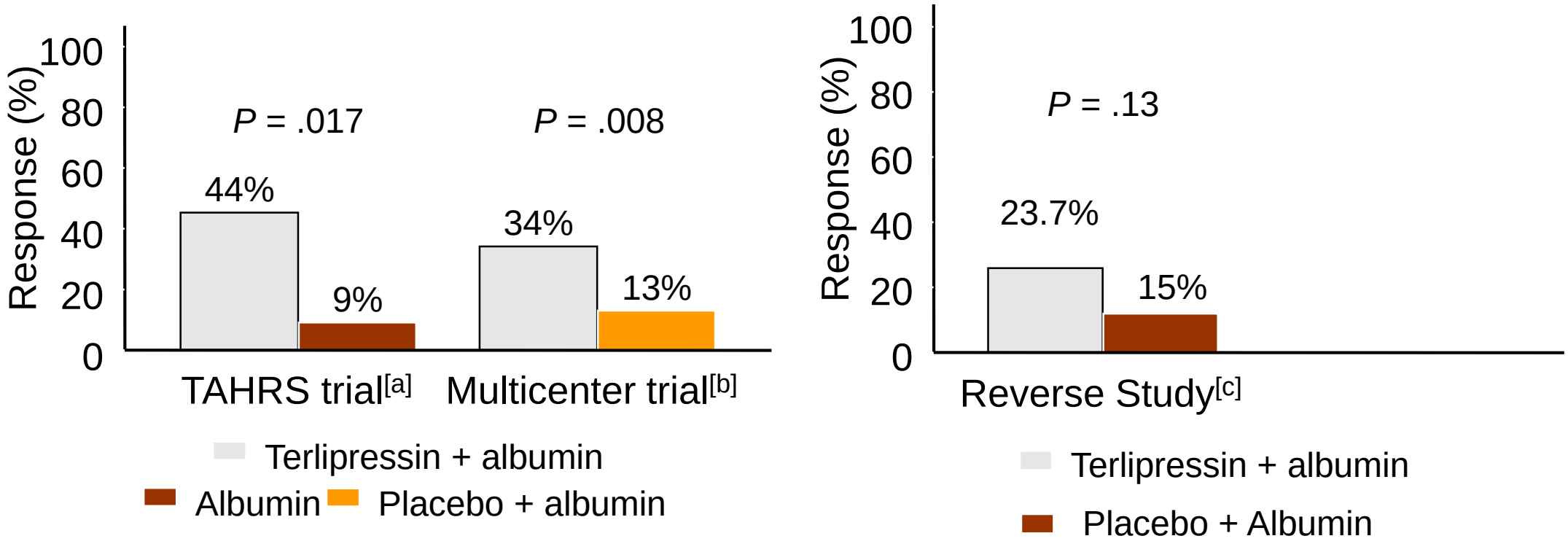
HRS AKI. EFFECTS OF TERLIPRESSIN AND ALBUMIN

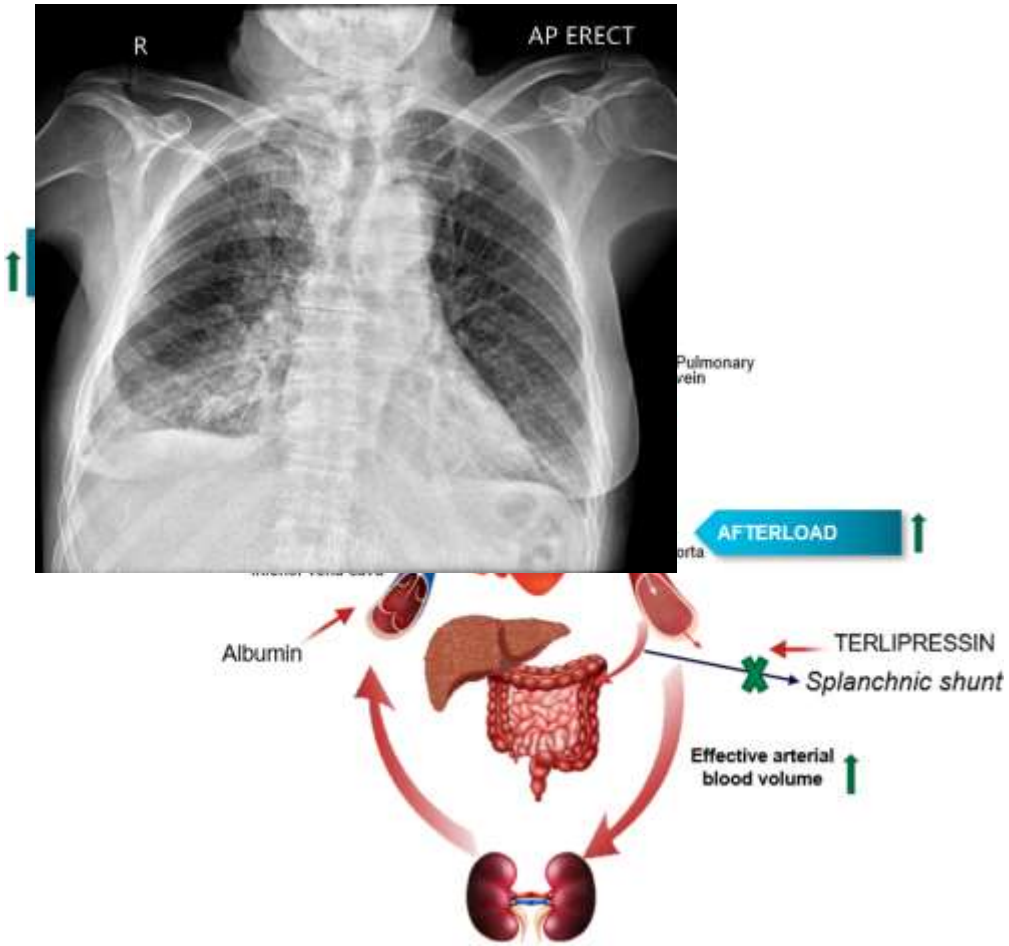


Terlipressin and Albumin: Response to Treatment



- a. Martín-Llahí M, et al. Gastroenterology. 2008;134:1352-1359; b. Sanyal AJ, et al. Gastroenterology. 2008;134:1360-1368.c. *Gastroenterology*. 2016;**150**(7):1579-1589

1. Terlipressin increases hydrostatic pressure within vessels by:
2. Shunting blood from the dilated splanchnic vascular beds and into central circulation (increasing cardiac preload)
3. Increasing systemic vascular resistance (increasing cardiac afterload).
4. IV albumin increases plasma oncotic pressure (decreasing fluid movement out of the vascular space) and the increase in plasma volume in combination with the effects of increased pre- and afterload likely contributes more to increased hydrostatic pressures

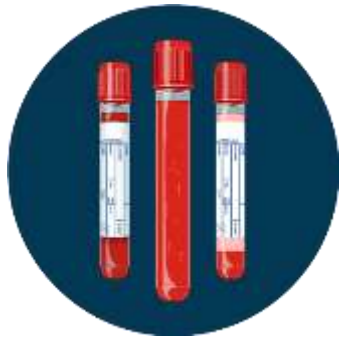


Points for Clinical Practice

1. Hospital admission
Patient with cirrhosis and ascites develops ↑SCr

2. Management
- Stop diuretics, nephrotoxic drugs
- Evaluate for sepsis ± treat with antibiotics (40% SIRS)
- IV albumin (1g/kg max) and crystalloids as appropriate

3. Diagnose with HRS-AKI
If no significant ↓SCr by 24 to 48 h

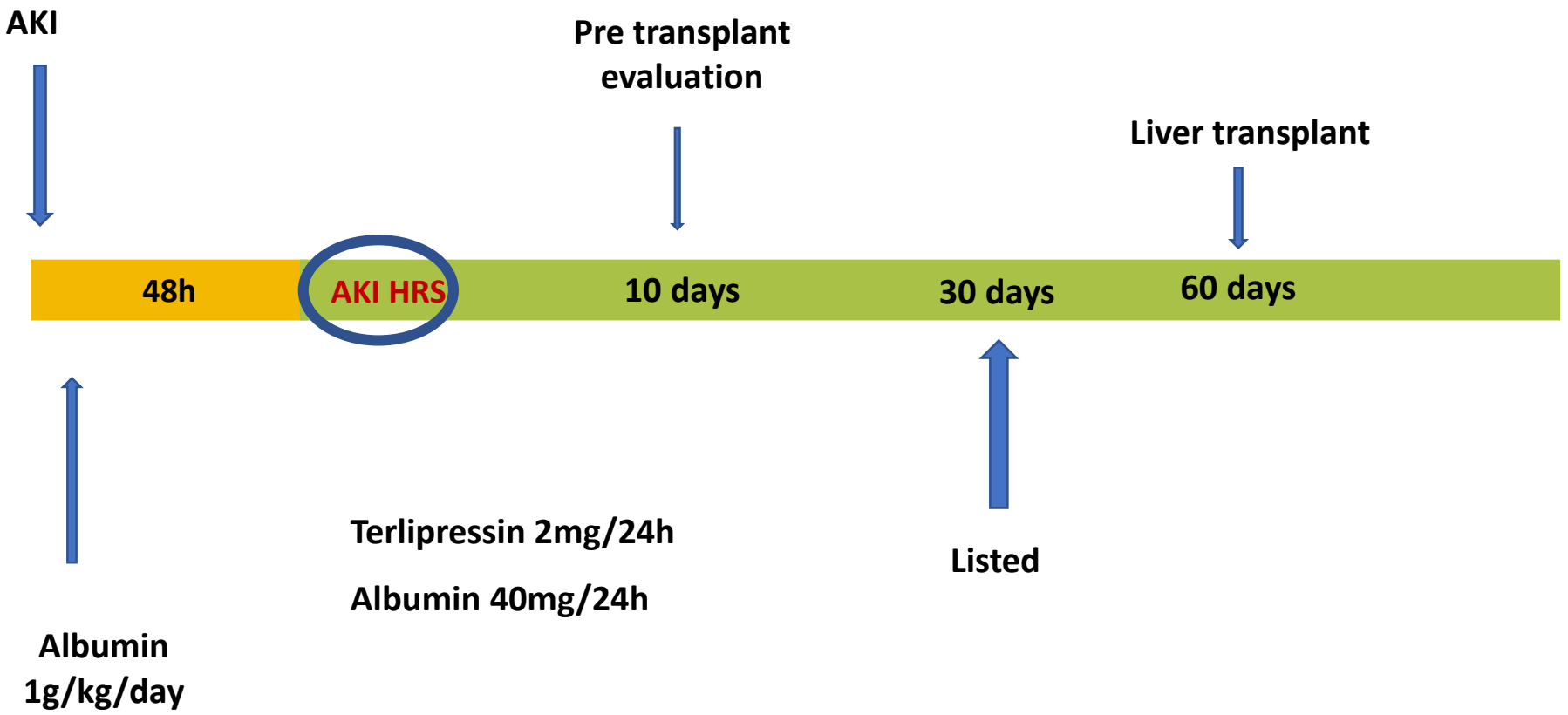


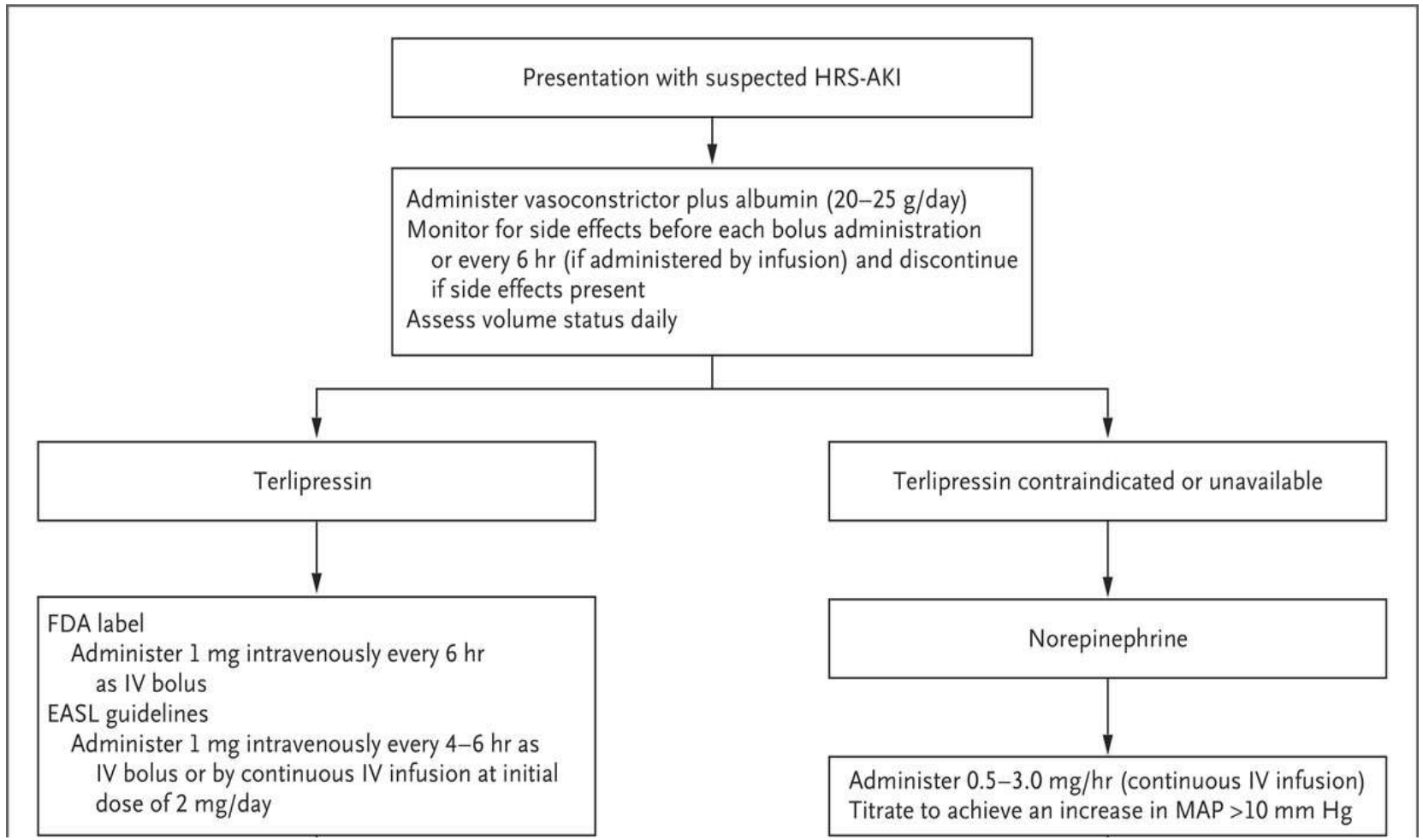
4. Administer terlipressin
Bolus injection 0.5 mg to 1 mg x 4/day on a general ward, or continuous infusion

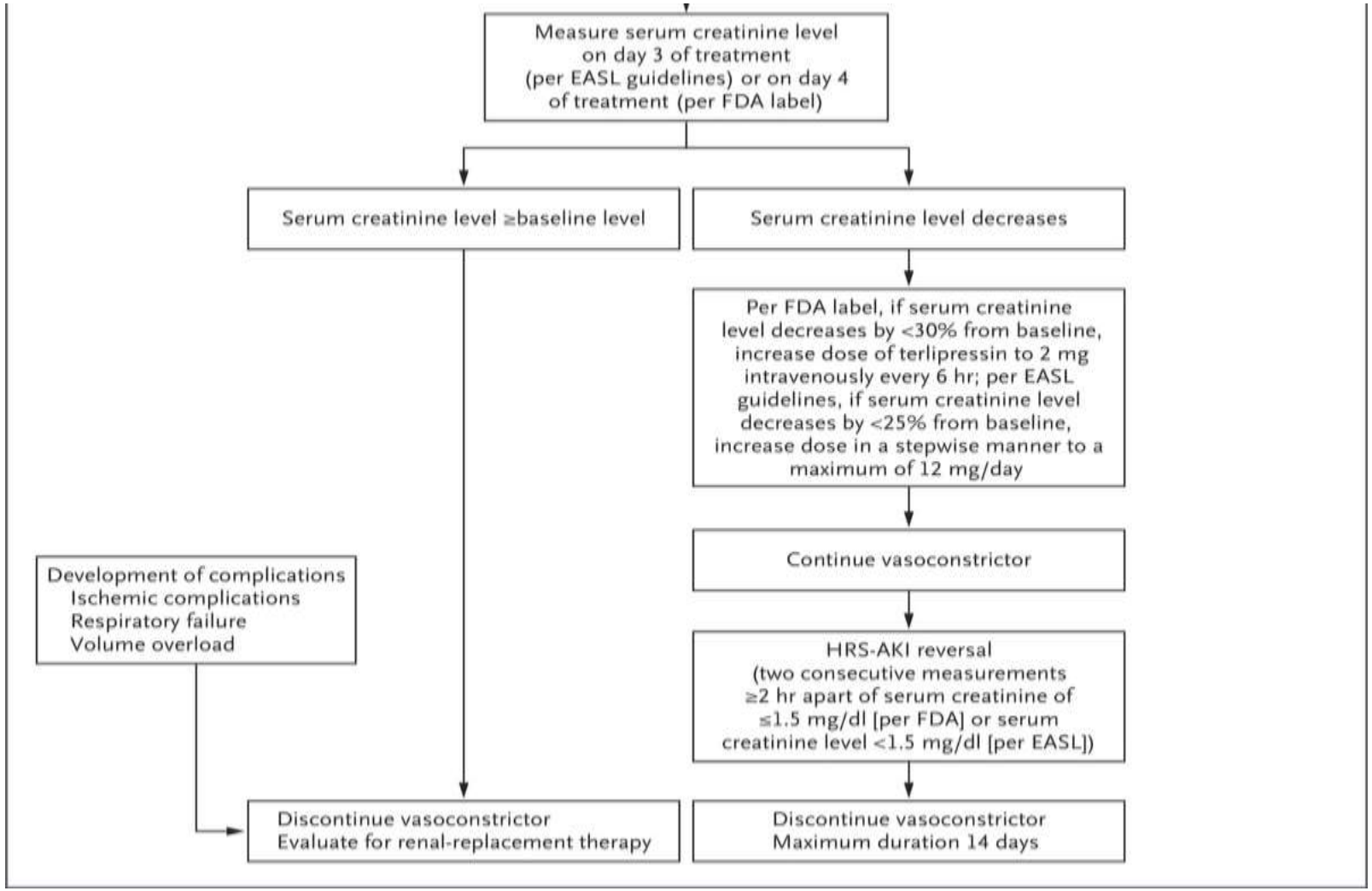
5. Monitor patient
- Change in BP, urine output
- ↓SCr (12 to 24 h)
- Kidney function improves (2 to 3 d)

Treatment response is usually evident within 12-24 h

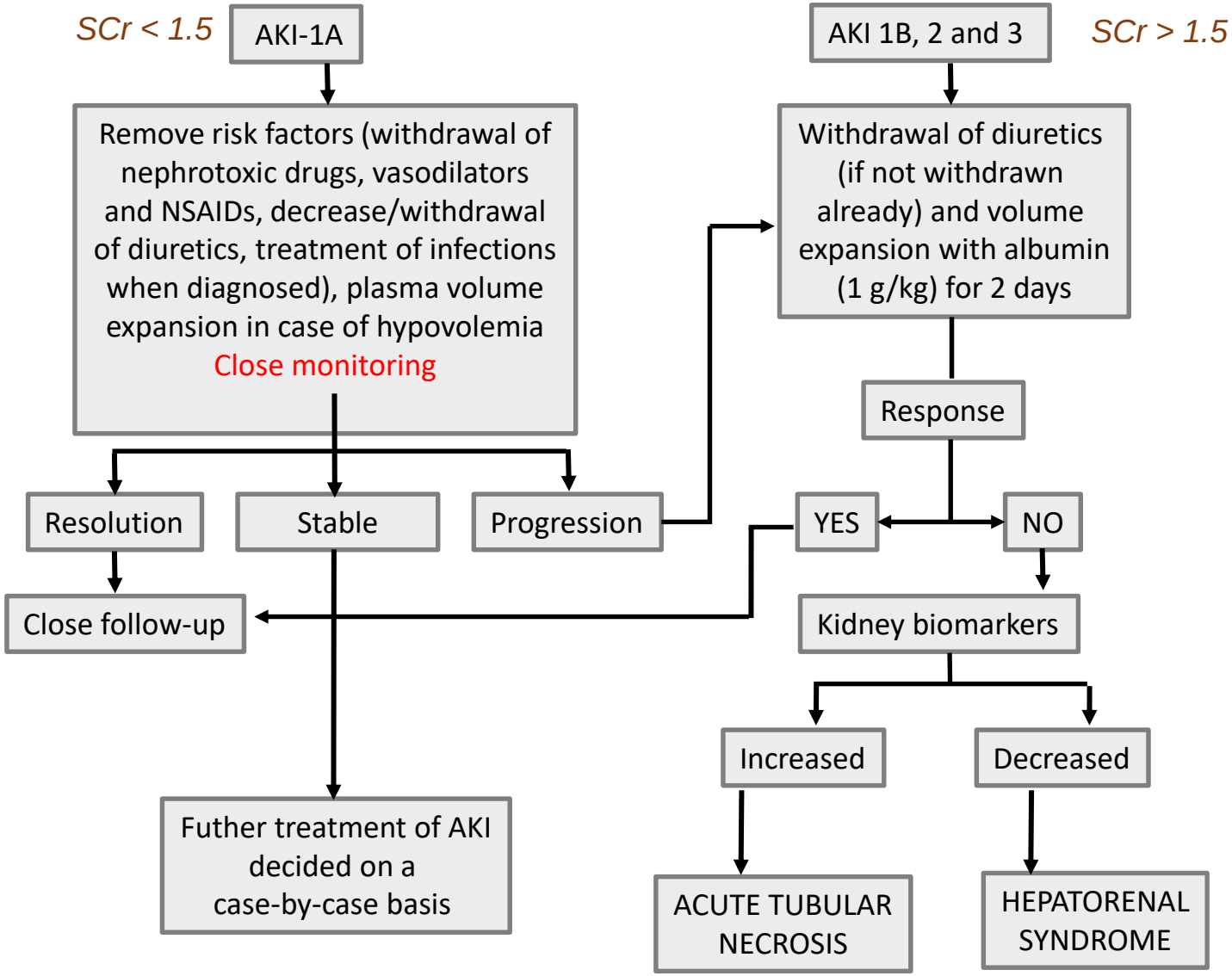
The aim of terlipressin is to buy time to enable recovery of liver and kidney function in a patient with a reversible deterioration of liver function


AKI
Pre transplant evaluation
Liver transplant
48h
AKI HRS
10 days
30 days
60 days
Albumin 1g/kg/day
Terlipressin 2mg/24h
Albumin 40mg/24h
Listed


Presentation with suspected HRS-AKI
Administer vasoconstrictor plus albumin (20–25 g/day)
Monitor for side effects before each bolus administration or every 6 hr (if administered by infusion) and discontinue if side effects present
Assess volume status daily
Terlipressin
Terlipressin contraindicated or unavailable
FDA label
Administer 1 mg intravenously every 6 hr as IV bolus
EASL guidelines
Administer 1 mg intravenously every 4–6 hr as IV bolus or by continuous IV infusion at initial dose of 2 mg/day
Norepinephrine
Administer 0.5–3.0 mg/hr (continuous IV infusion)
Titrate to achieve an increase in MAP >10 mm Hg


Measure serum creatinine level on day 3 of treatment (per EASL guidelines) or on day 4 of treatment (per FDA label)
Serum creatinine level ≥baseline level
Serum creatinine level decreases
Per FDA label, if serum creatinine level decreases by <30% from baseline, increase dose of terlipressin to 2 mg intravenously every 6 hr; per EASL guidelines, if serum creatinine level decreases by <25% from baseline, increase dose in a stepwise manner to a maximum of 12 mg/day
Continue vasoconstrictor
HRS-AKI reversal (two consecutive measurements ≥2 hr apart of serum creatinine of ≤1.5 mg/dl [per FDA] or serum creatinine level <1.5 mg/dl [per EASL])
Development of complications
Ischemic complications
Respiratory failure
Volume overload
Discontinue vasoconstrictor
Evaluate for renal-replacement therapy
Discontinue vasoconstrictor
Maximum duration 14 days

MANAGEMENT OF AKI IN PATIENTS WITH CIRRHOSIS



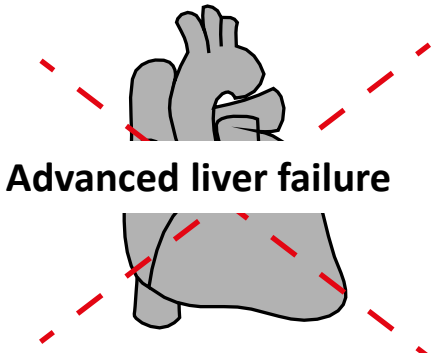
Ginès et al, Nat Rev Dis Primers. 2018 / EASL CPG 2018

Initial Steps

- Stop nephrotoxic drugs, vasodilators, (NSAIDs) and diuretics
- Culture for bacterial infections
- Rule out hypovolemia
- Prerenal AKI – IV albumin 1gr/kg
- Urine microscopy and urine sodium excretion
- Neutrophil gelatinase associated lipocalin (NGAL) if available
- Renal ultrasound

- Simonetto DA, et al. BMJ. 2020;370:m2687 / Nadim M, Garcia-Tsao G. N Engl J Med. 2023 Feb 23;388(8):733-745

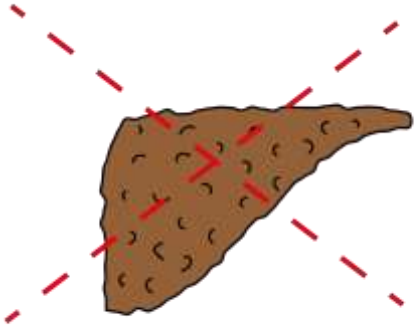
When to Be Cautious With Terlipressin



Advanced liver failure

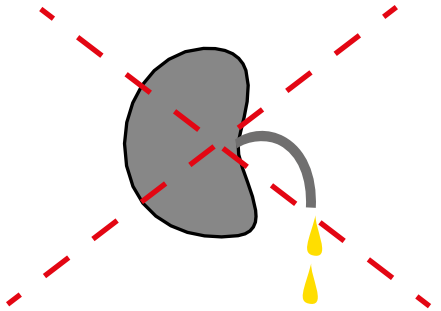
Ischemic heart disease

Baseline ECG

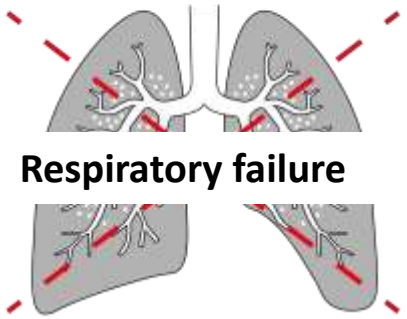


ACLF Stage 3

Calculate ACLF score



Severe HR
SCr > 5 mg/dL



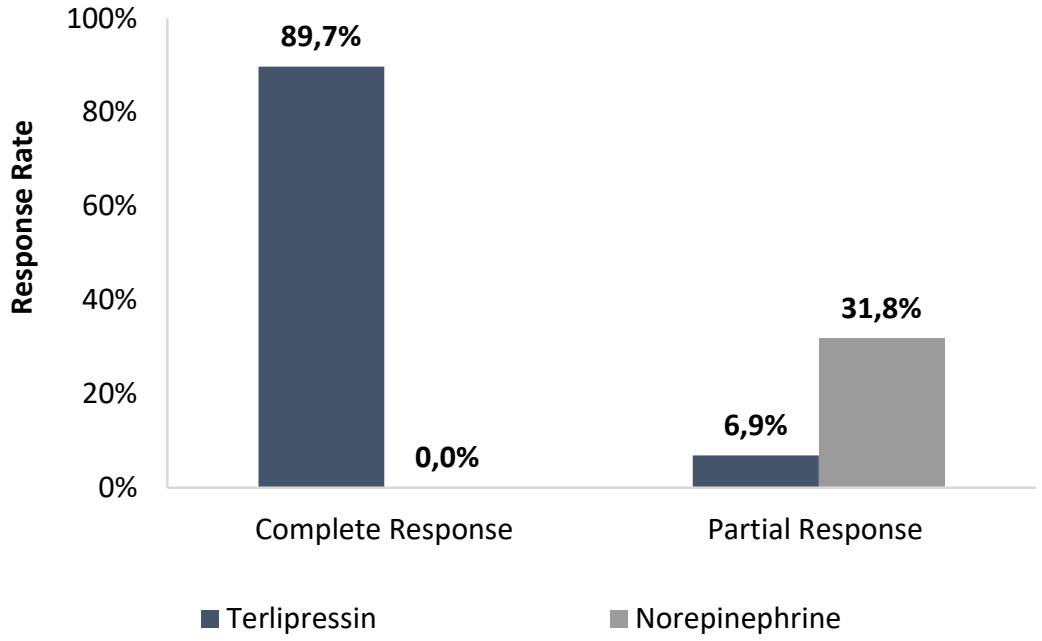
Respiratory failure

Extreme caution for patients with pulmonary edema

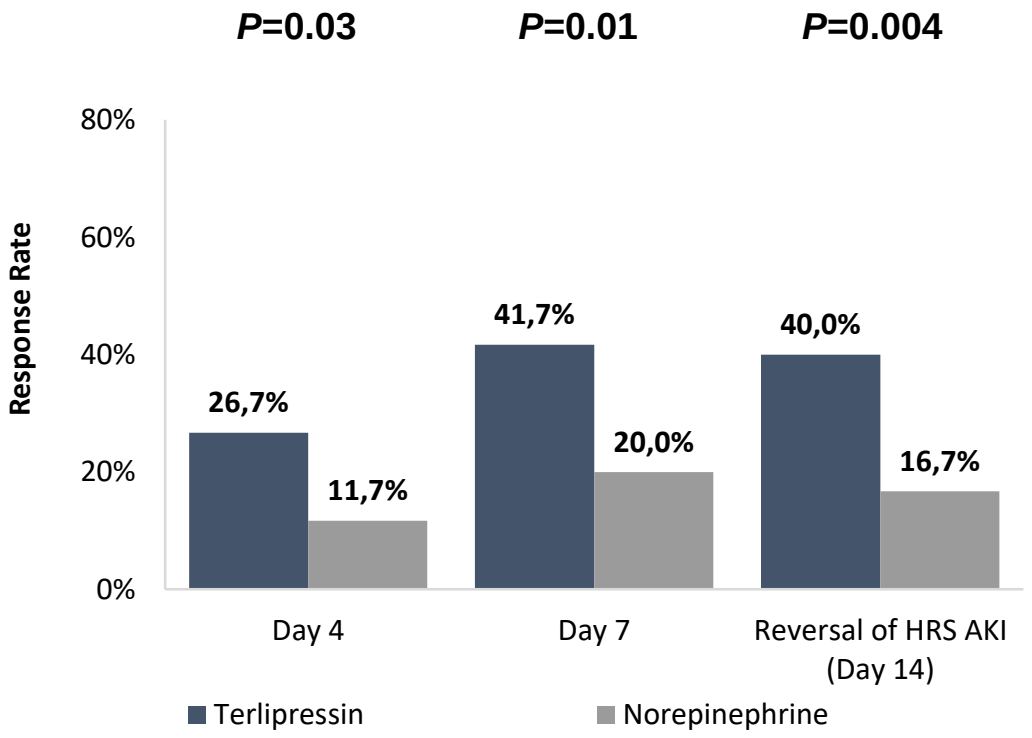
Listen to chest, CXR, FiO2/SpO2 ratio

Response Rate
Terlipressin vs Norepinephrine

Nayyar, et al 2021[a]



Arora, et al 2018[b]

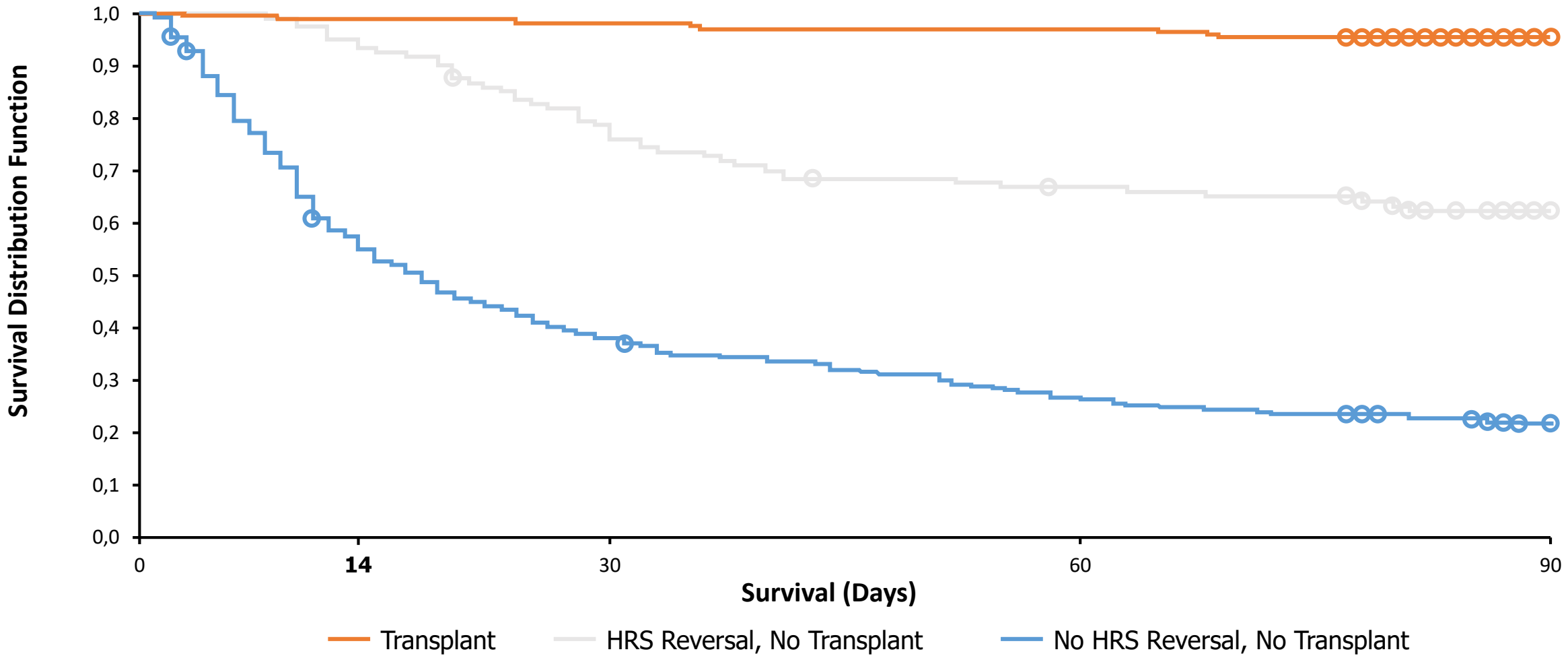


Norepinephrine is widely available and an affordable option.

a. Nayyar S et al. *Int J Adv Med.* 2021;8(9):1312-1318; b. Arora V et al. *Hepatology.* 2018;71(2):600-610.

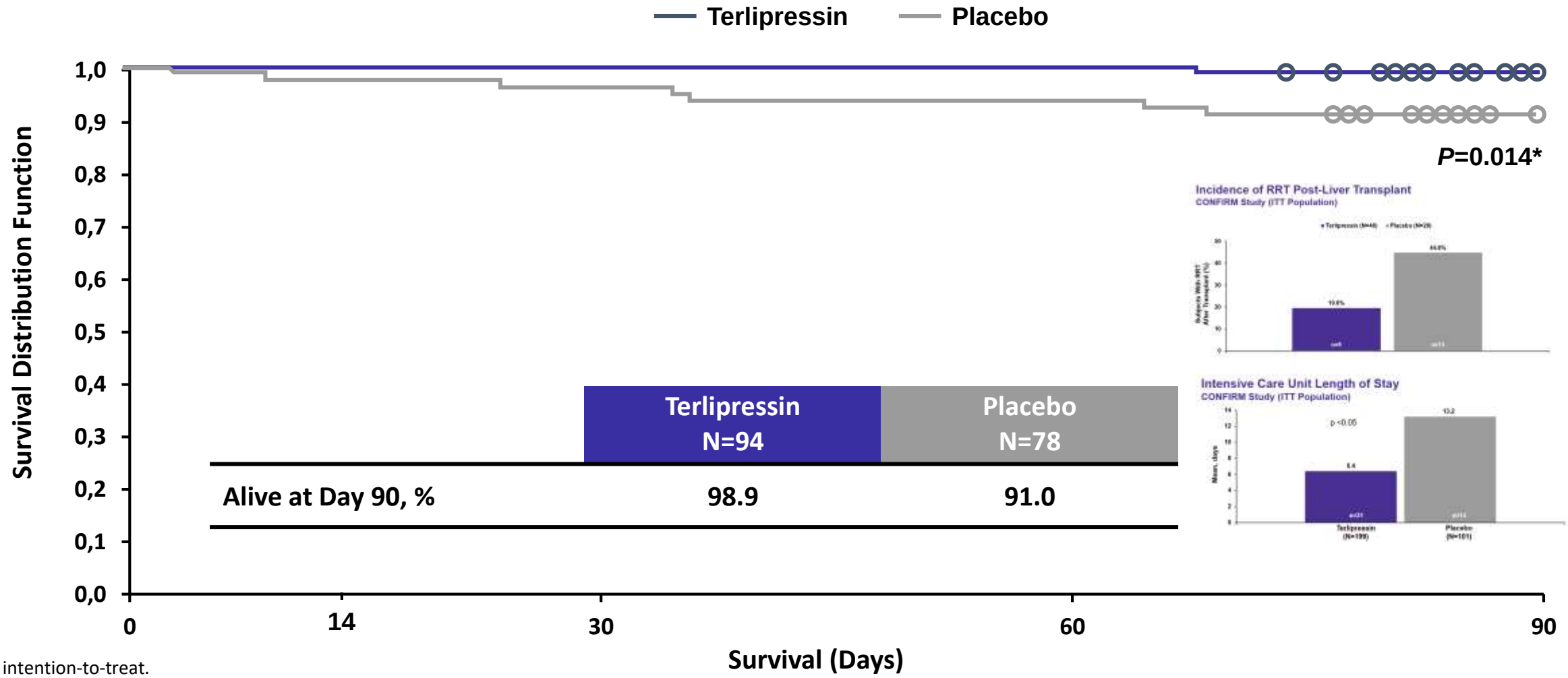
CONFIRM Study (Pooled ITT Population)

Overall Survival up to 90 Days by Transplant and HRS Reversal Status



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

CONFIRM Study (Pooled ITT Population)
Survival of Transplanted Subjects Through Day 90

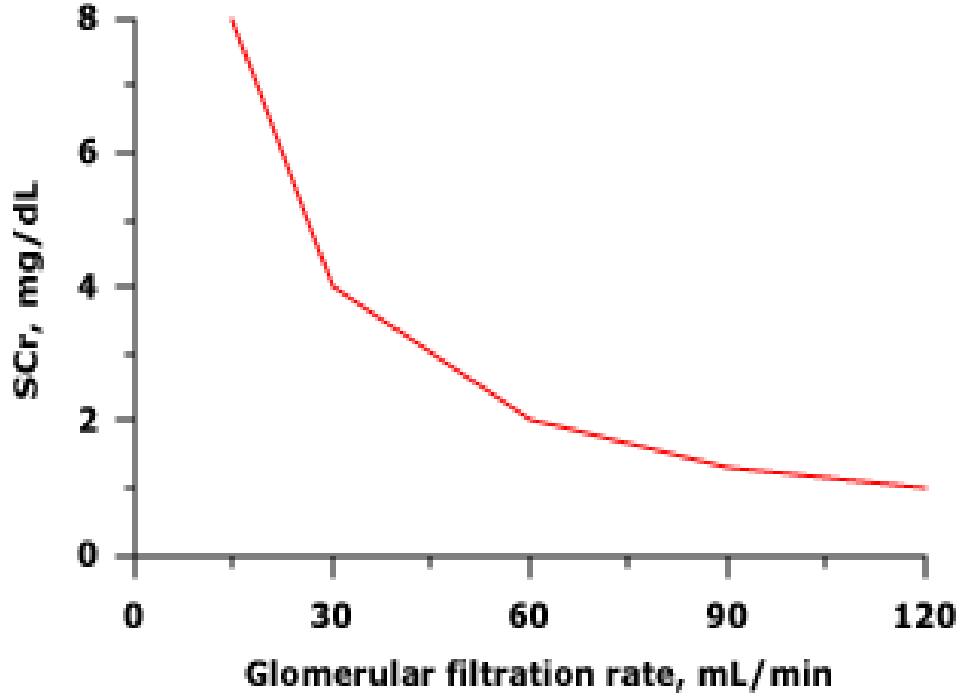


- ITT, intention-to-treat.
- *The P-value comparing the survival estimates is from a 2-sample log-rank test.
  Wong F, et al. N Engl J Med. 2021;384:818-828.; Lee BP, et al. JAMA Intern Med. 2019;179:340-348.

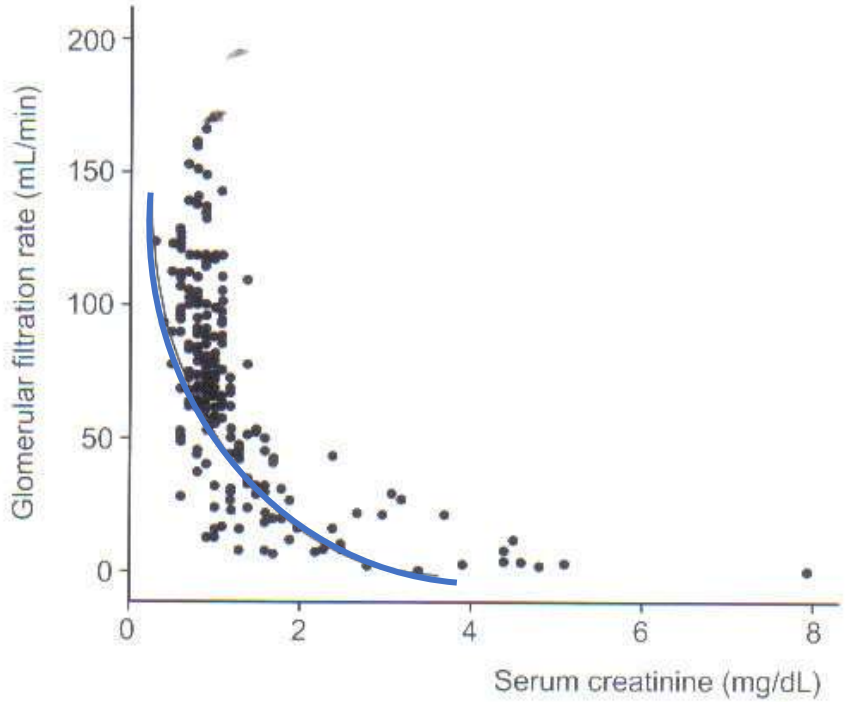
Relationship Between SCr and GFR in Patients With Cirrhosis

- SCr historically lags behind renal function whether getting worse or better
- SCr 1.5 g/dL corresponds to GFR of ~30 mL/min

Patients with Normal Renal Function[a]



Patients with Cirrhosis & Ascites[b]



- GFR, g
  Courte

- a. Inker LA, Perrone R. Assessment of kidney function. In Sterns RH, ed. UpToDate; 2022. Accessed June 18, 2022. https://www.uptodate.com/contents/assessment-of-kidney-function.
  b. Arroyo V, et al. J Hepatol. 2007 May;46:935-46.

Using SCr to Measure Renal Function

Pros

- Easily obtainable[a]
- Inexpensive[a]
- Repeated measurements seem to be reliable
- Included in MELD score[a]

Cons

- Overestimates GFR[a-c]
  - Decreased creatine
  - Low muscle mass
  - Poor protein diet
  - High urine secretion
- Low sensitivity
- Interlaboratory variability

- MELD, model for end-stage liver disease.

a. Piano S, et al. Liver Int. 2017; 37(Suppl. 1):116-122; b. Cárdenas A, Ginès P. Curr Opin Crit. Care. 2011;17:184-189; c. Francoz C, et al. J Hepatol. 2016;65:809-824.

AKI in Patients With Cirrhosis: IAC Definitions

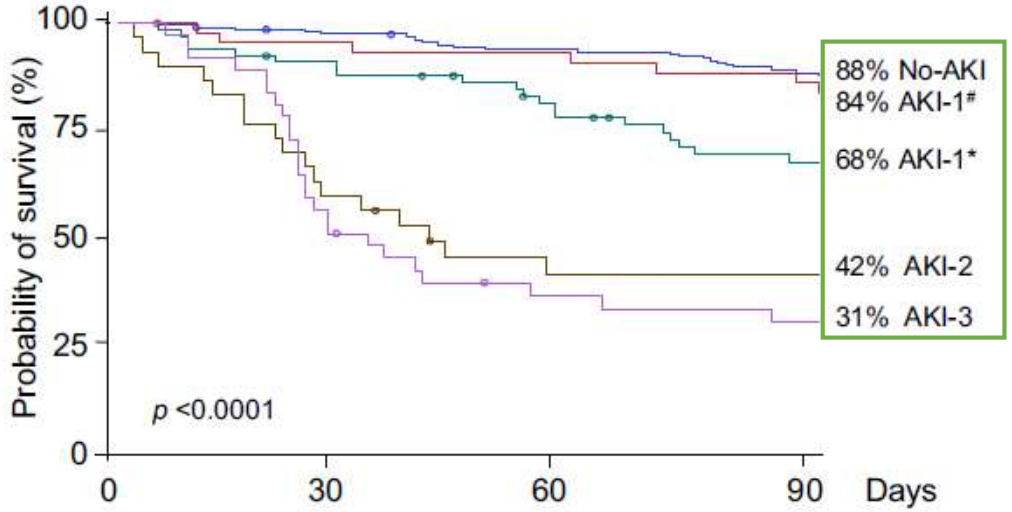
Criteria	Definition		
Baseline SCr	SCr obtained within 3 months prior to admission If > 1 value within the previous 3 mo, the value closest to the admission If no previous SCr, the SCr on admission should be used		
Progression of AKI	Progression of AKI to a higher stage and/or need for RRT	Regression of AKI to a lower stage	
Response to treatment	No response No regression of AKI	Partial response Regression of AKI stage with a decrease in SCr to ≥ 0.3 mg/dL (≥ 26.5 µmol/L) above baseline	Full response Return of SCr to a value within 0.3 mg/dL (≥ 26.5 µmol/L) of baseline

- Angeli P, et al. J Hepatol. 2015;62:968-974.

Assessment of AKI Classification in Cirrhosis

Prospective Studies in Nonselected Hospitalized Patients

Survival according to AKI stage[a]

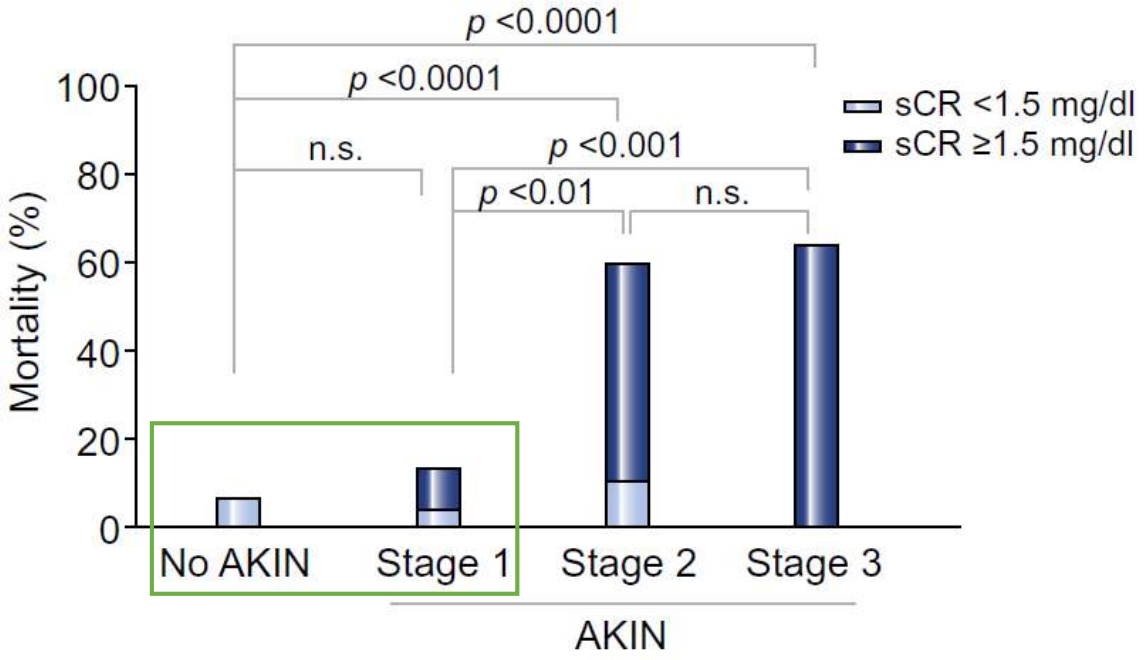


No AKI (n = 198)	191	182	172
AKI-1#(n = 44)	41	39	37
AKI-1*(n = 66)	57	48	40
AKI-2 (n = 30)	18	11	11
AKI-3 (n = 37)	18	12	10

AKI 1A: peak creatinine ≤ 1.5 mg/dL

AKI 1B: peak creatinine > 1.5 mg/dL

Peak Acute Kidney Injury Network (AKIN) stage and in-hospital mortality[b]



- a. Fagundes C, et al. J Hepatol. 2013;59:474-481; b. Piano S, et al. J Hepatol. 2013;59:482-489.

HRS non-AKI (NAKI)

HRS type 2

- Gradual increase in serum creatinine, not meeting criteria above

HRS-NAKI

HRS-AKD

- Estimated glomerular filtration rate <60 mL/min/1.73 m^2 for <3 months in absence of other potential causes of kidney disease
- Percentage increase in serum creatinine <50% using last available value of outpatient serum creatinine within 3 months as baseline value

HRS-CKD

- Estimated glomerular filtration rate <60 mL/min/1.73 m^2 for ≥3 months in absence of other potential causes of kidney disease

- NAKI, non acute kidney injury.
  Simonetto DA, et al. BMJ. 2020;370:m2687.

Main Types of AKI in Cirrhosis

Differential Diagnosis

Hypovolemia:
diuretics, GI bleeding, diarrhea

Nephrotoxicity:
NSAIDs, others

AKI-HRS
often associated with bacterial infections

Intrinsic renal disease

Acute tubular necrosis:
shock, nephrotoxic drugs, other (eg, obstruction)

Miscellaneous, unknown

- GI, gastrointestinal; HRS, hepatorenal syndrome; NSAID, nonsteroidal anti-inflammatory drug.
Graupera I, Cardenas A. Clin Liver Dis. 2013;2:128-131.

Pathogenic Mechanisms of HRS

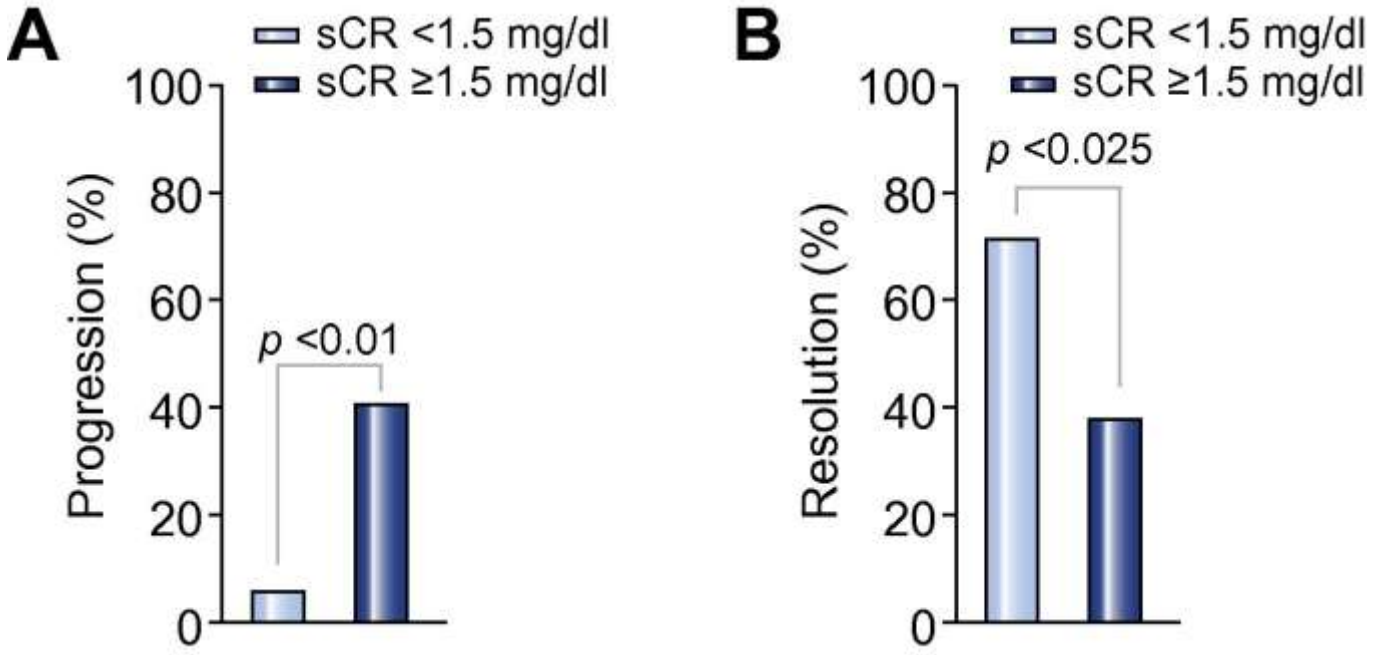
- ✓ Systemic hemodynamics
- ✓ Systemic inflammation/immune dysfunction
- ✓ Bacterial infection
- ✓ Volume loss secondary to gastrointestinal bleed, diuretics, diarrhea, large volume paracentesis
- ✓ Bile cast nephropathy
- ✓ Nephrotoxicity/tubular damage

Maiwall et al. Hepatol Int 2016 Mar;10(2):245-57; Simonetto DA, Gines P, Kamath PS. BMJ. 2020;370:m2687.

AKI and Cirrhosis

- *AKI is associated with high morbidity and mortality and an increased incidence of CKD after liver transplantation*
- *Progression through stages strongly correlates with increased mortality*
- *Cut-off of 1.5 mg/dL identifies patients at risk*

Evolution of AKIN stage 1 according to SCr[a]



- AKIN, Acute Kidney Injury Network.
- a. Piano S, et al. J Hepatol. 2013;59:482-9; b. Fagundes C, et al. J Hepatol. 2013;59:474-481.

Acute Impairment of Kidney Function in Cirrhosis

Traditional criteria

(IAC criteria)

- 50% increase in SCr over baseline
- Cut-off value of SCr: 1.5 mg/dL (133 µmoL/L)

Current definition

AKI

- ↑ in SCr ≥ 0.3 mg/dL (≥ 26.5 mmol/L) within 48 hours
  or ≥1.5 times baseline level or
  urinary output <0.5 ml/kg/hr
  in 6 hr

- IAC, International Ascites Club.
  a. Angeli P. J Hepatol 2019;71:811-822; b. European Association for the Study of the Liver. J Hepatol. 2018;69:406-460.