Brigham and Women's Hospital
Founding Member, Mass General Brigham

Liver and the Kidney

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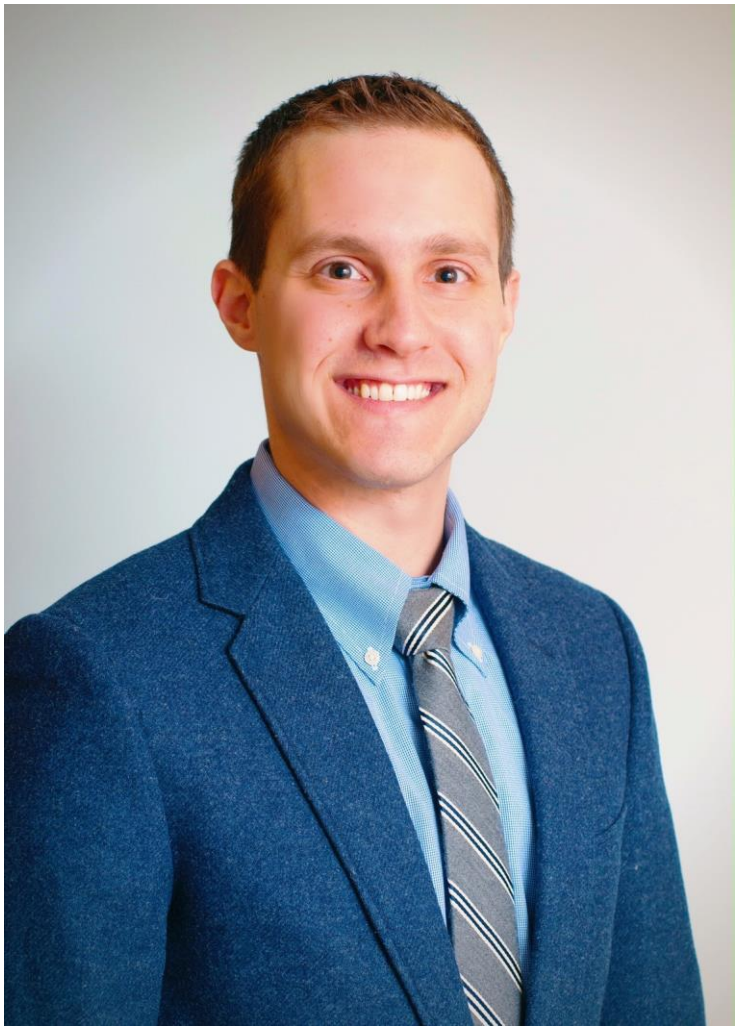

- Medical School: Brown University
- Residency: MGH
- Nephrology Fellowship: BWH/MGH
- Masters in Epidemiology: HSPH
- Current Roles:
  - Assistant Professor of Medicine, HMS
  - Director of ICU Nephrology, MGH
  - Principal Investigator, MGH Kidney Research Center
  - Co-chair, HRS-HARMONY research collaborative
- Areas of Interest
  - AKI in cirrhosis, hepatorenal syndrome
  - Critical Care Nephrology

Disclosures

Consulting: Mallinckrodt Pharmaceuticals, Ocelot Bio, Motric Bio, Sequana Medical, Acta Pharmaceuticals

Research Support: NIH K23 DK128567

Review Question 1

A 62 year old man with end stage liver disease due to hepatitis C presents to the emergency room with melena. He takes only propranolol, furosemide, and spironolactone at home. On arrival, he appears well, with a blood pressure of 109/50, heart rate 90, scleral icterus, and a mildly distended abdomen. Labs on arrival show a creatinine of 2.5 mg/dL, up from 0.8 mg/dL 3 weeks ago as an outpatient. Urinalysis and renal ultrasound are normal. He is admitted, diuretics are held, and he is given 50 g of intravenous albumin for 2 days. Repeat labs on hospital day 3 show a stable creatinine of 2.5 mg/dL.

What is the cause of his AKI?

a. Hepatorenal syndrome
b. Acute tubular necrosis
c. Pre-renal AKI due to intravascular volume loss
d. Hepatitis C related kidney disease

Review Question 1 Answer

A 62 year old man with end stage liver disease due to hepatitis C presents to the emergency room with melena. He takes only propranolol, furosemide, and spironolactone at home. On arrival, he appears well, with a blood pressure of 109/50, heart rate 90, scleral icterus, and a mildly distended abdomen. Labs on arrival show a creatinine of 2.5 mg/dL, up from 0.8 mg/dL 3 weeks ago as an outpatient. Urinalysis and renal ultrasound are normal. He is admitted, diuretics are held, and he is given 50 g of intravenous albumin for 2 days. Repeat labs on hospital day 3 show a stable creatinine of 2.5 mg/dL.

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Objectives

1. Understand how the pathophysiology of HRS/AKI in cirrhosis serves as the framework for our clinical approach to this disease.
2. Provide treatment updates for HRS.
3. Look forward to new HRS approaches.

Outline

1. Background and physiology of HRS
2. Diagnostic criteria and approach to AKI in cirrhosis
3. Pre-transplant treatment updates
   - Vasoconstrictors
   - Renal replacement therapy

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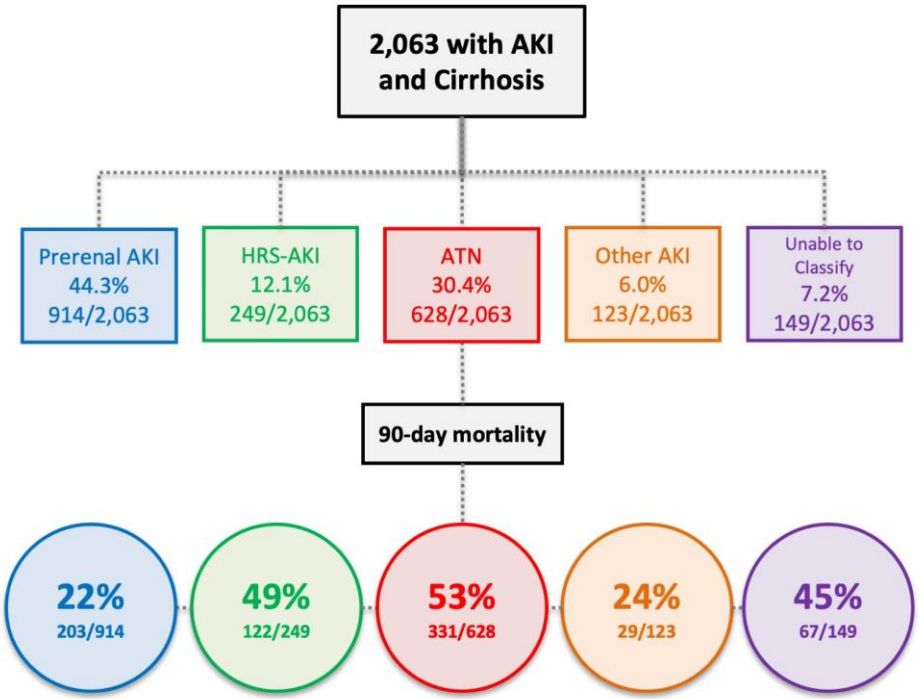
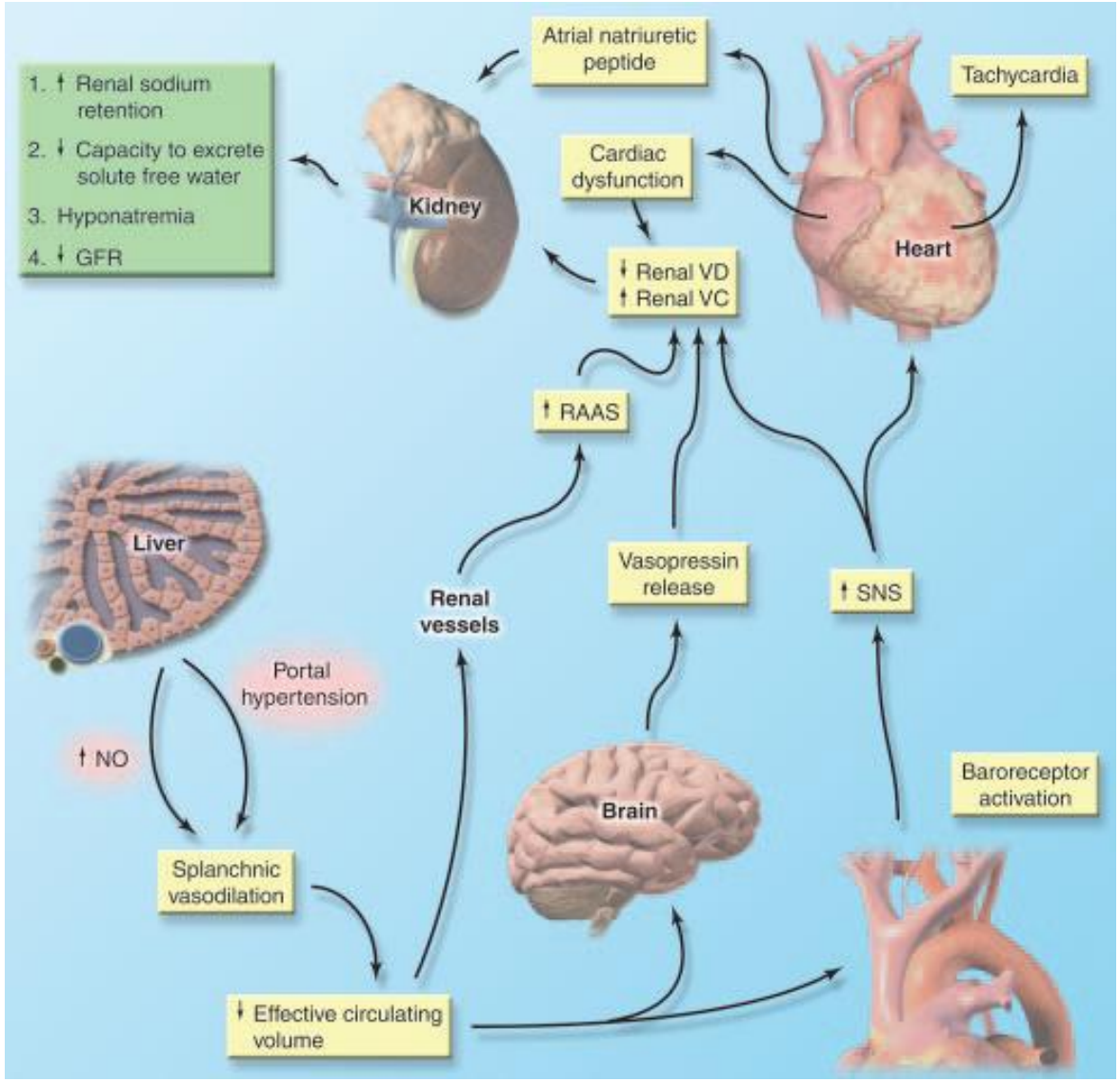
Background: AKI in Cirrhosis

- **Common:** 50% of decomp. cirrhosis
- **High mortality:**
  - Untreated HRS – ~90% mortality
  - More recent: ~50% mortality
- **Many triggers:**
  - Infection (SBP)
  - Bleeding, volume depletion (LVP)
  - Glomerulonephritis (HCV, cryos)
  - Alcoholic hepatitis (ACLF)
  - Medications (NSAIDs, antibiotics)
  - Abdominal compartment syndrome

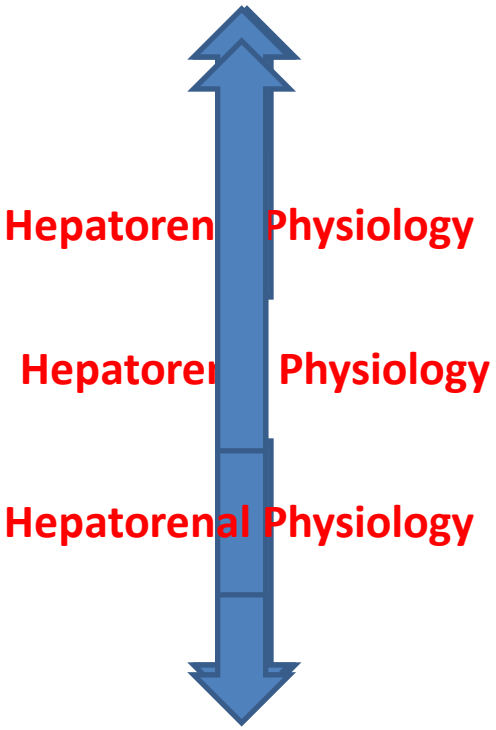


HRS HARMONY. Under Review.
Gines, et al. *Gastroenterology*. 1993

Pathophysiology of HRS (and ascites)



Normal Circulation



Hepatorenal Syndrome

Wadei et al. *CJASN.* 2006

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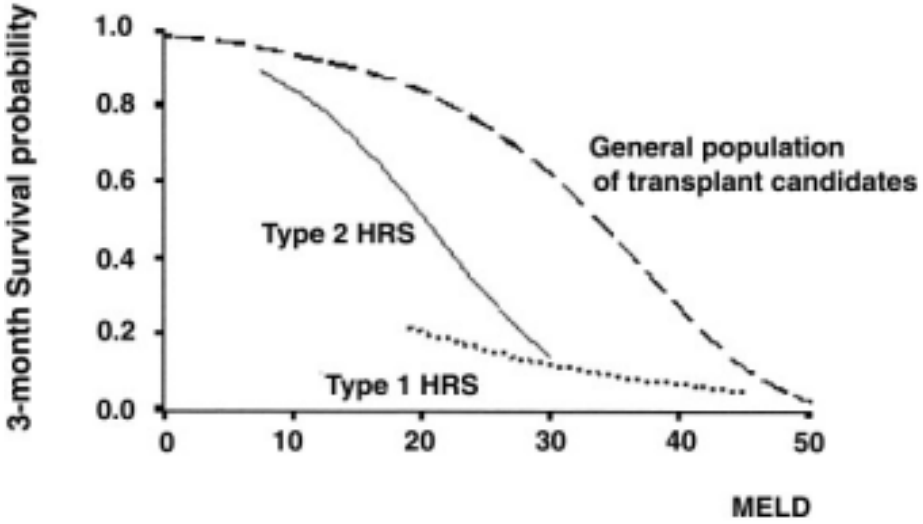
MELD does not capture acute decompensation, ACLF score emerges



A

Organ system	1 point	2 points	3 points
Liver	Bilirubin <6 mg/dl	Bilirubin 6–11.9 mg/dl	Bilirubin ≥12 mg/dl
Kidney	Creatinine <1.5 mg/dl	Creatinine 2–3.4 mg/dl	Creatinine ≥3.5 mg/dl or RRT
	Creatinine 1.5-1.9 mg/dl		
Brain (West Haven Score)	Grade 0	Grade 1–2	Grade 3–4
Coagulation	INR <2.0	INR 2.0–2.4	INR ≥2.5
Circulation respiratory	MAP ≥70 mmHg	MAP <70 mmHg	Vasopressor requirement
	PaO_2/FiO_2 >300 SpO_2/FiO_2 >357	PaO_2/FiO_2 201-300 SpO_2/FiO_2 215-357	PaO_2/FiO_2 ≤200 SpO_2/FiO_2 ≤214

B

Patient group	Prevalence over 1,287 patients (%)	28-day mortality (%)	Assigned category
Absence of OF	68.3	4.4	Absence of ACLF
Single non-kidney OF without KD or BD	9.9	6.3	
Single KF	6.7	18.6	ACLF-1
Single non-kidney OF with KD or BD	4.2	27.8	ACLF-1
Two OFs	7.5	32.0	ACLF-2
Three OFs	1.9	68.0	ACLF-3
Four to six OFs	1.4	88.9	ACLF-3

Alessandria et al. Hepatology 2005. Jalan et al. J Hepatology 2021.

2015 Ascites Club Criteria for HRS

HRS-AKI

- Diagnosis of cirrhosis and ascites
- Diagnosis of AKI according to ICA-AKI criteria
- No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin 1 g/kg bodyweight
- Absence of shock
- No current or recent use of nephrotoxic drugs (NSAIDs, aminoglycosides, iodinated contrast media, etc)
- No macroscopic signs of structural kidney injury*, defined as:
  - absence of proteinuria (>500 mg/day)
  - absence of microhaematuria (>50 RBCs per high power field)
  - normal findings on renal ultrasonography

*Patients who fulfil these criteria may still have structural damage such as tubular damage. Urine biomarkers will become an important element in making a more accurate differential diagnosis between HRS and acute tubular necrosis.

Angeli et al. *Gut.* 2015

2024 ADQI/ICA Guideline Update

Recommend following diagnostic criteria for HRS-AKI:

a) cirrhosis with ascites

b) SCr increase ≥ 0.3 mg/dL within 48h or ≥ 50% from baseline within 7 days, and/or UO ≤ 0.5 mL/kg for ≥6h

c) lack of SCr/UO improvement within **24h post volume resuscitation (if clinically indicated),** and

d) no strong alternative AKI cause

(Not graded)

Advise **against** systematic albumin administration for 48h as prerequisite for HRS-AKI diagnosis

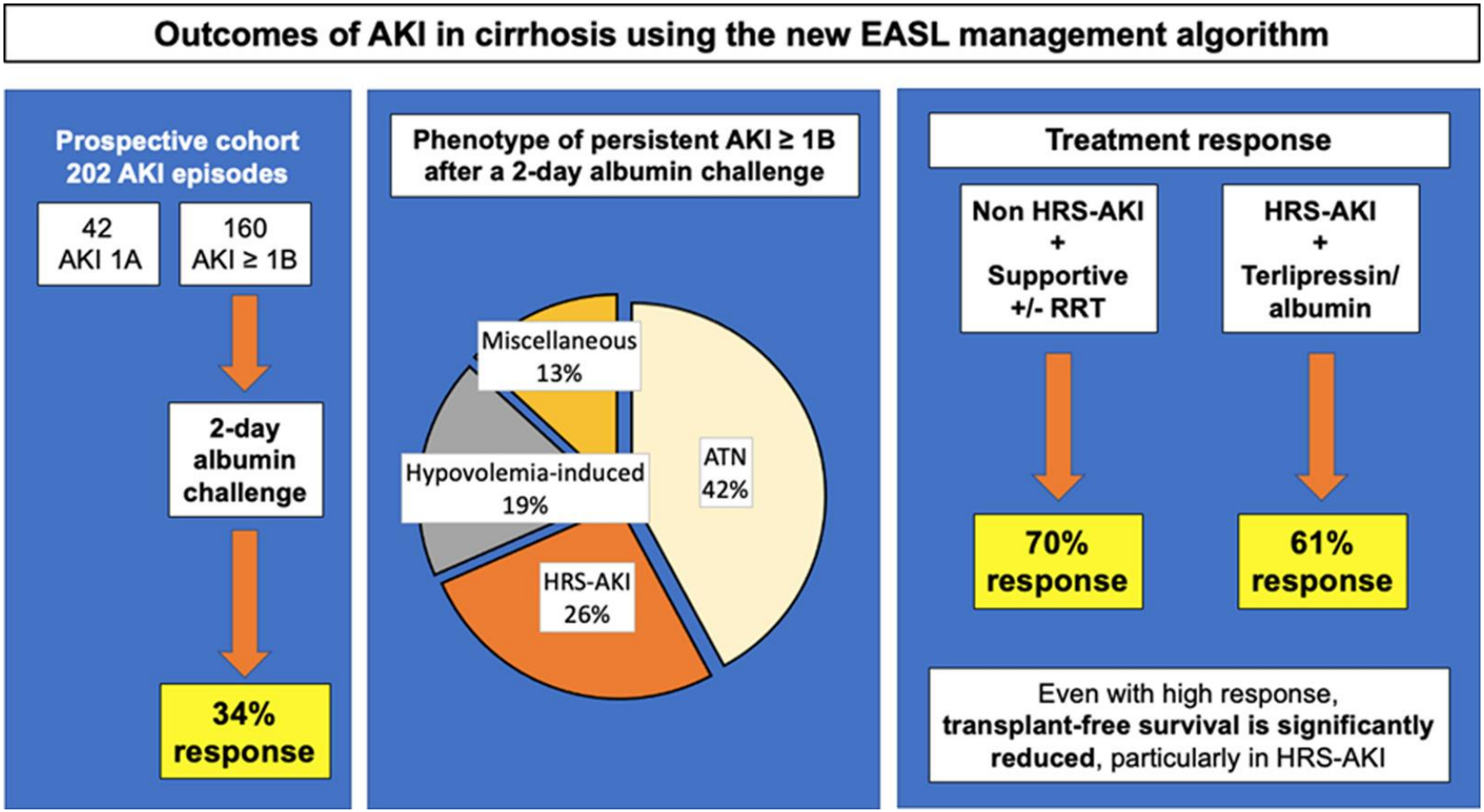
(Strong recommendation, grade D)

Suggest replacing historical terms HRS type 1 and 2 with HRS-AKI, HRS-AKD, and HRS-CKD based on kidney dysfunction timing/duration

(Strong recommendation, grade D)

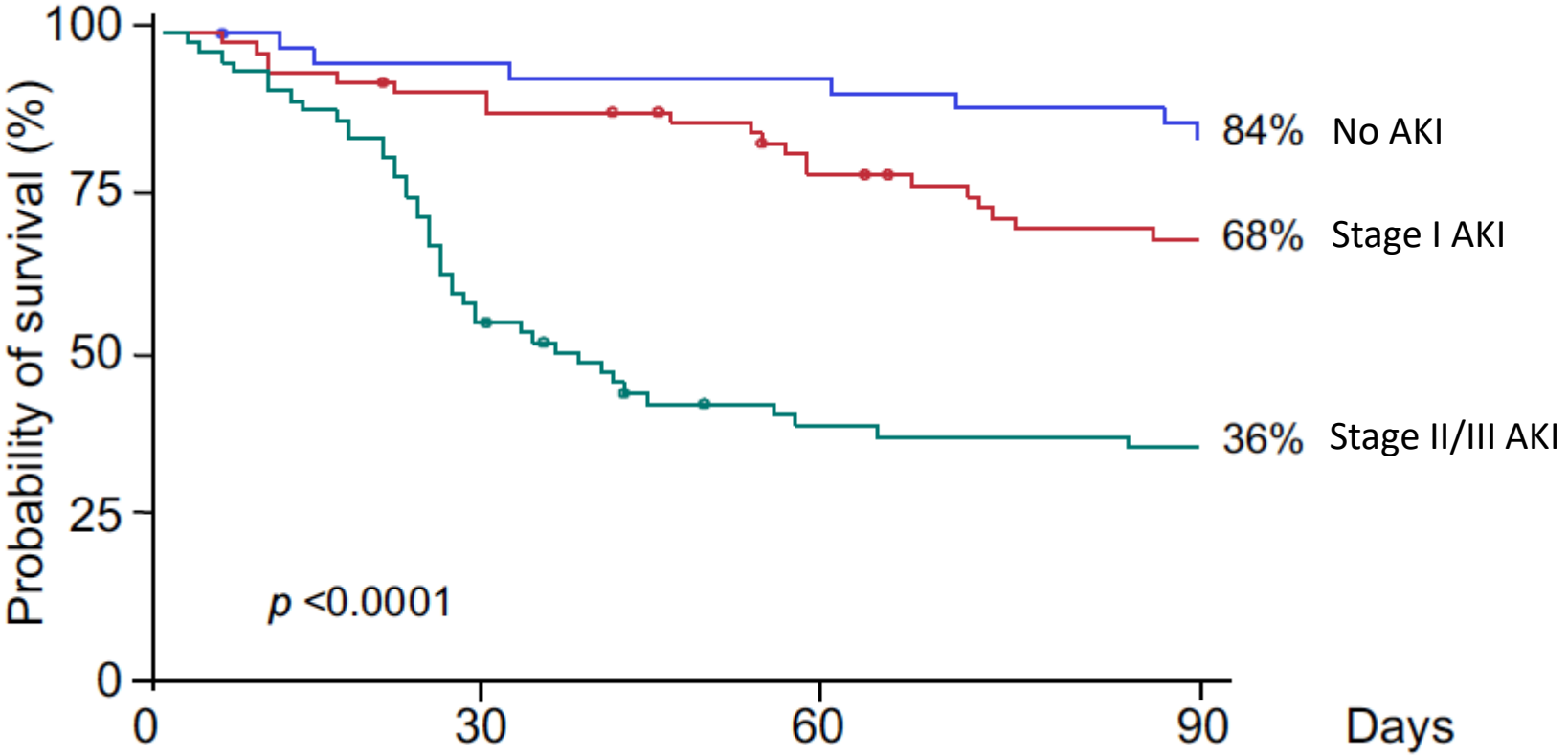
Nadim MK et al. Journal of Hepatology 2024.

2015 ICA (2018 EASL) Approach Works Fairly Well



Ma AT et al. Journal of Hepatology 2024.

AKIN Stage and Mortality



Fagundes, et al. *Journal of Hepatology* 2013.

Glomerular Disease in Cirrhosis

- **Hepatic IgA Nephropathy:** most common, may be due to impaired hepatic IgA clearance, esp. in EtOH/HCV disease
- **Hepatitis C associated MPGN**: with or without cryos
- **Hepatitis B associated Membranous*:*** usually HBeAg +
- **Hepatic glomerulosclerosis:** MPGN +/- IgA/IgM deposits
- **Rare:** HCV associated Fibrillary/Immunotactoid GN, HBV associated PAN, post-infectious GN associated with SBP
- **Complement (C3/C4) testing** is rarely useful to evaluate glomerular disease in cirrhotics as levels are often low due to reduced hepatic synthesis.

Pouria et al. NDT. 1999;14:2279 & McGuire et al. Ann Int Med 2006;144:735.

Diagnosis of HRS Summary

- HRS is a diagnosis of exclusion
  - Absence of HTN and $U_{Na} < 20$ also helpful
- Updated criteria suggested iterative evaluation of AKI in cirrhosis
  - >1 process may cause AKI
  - Volume challenge may not need to be applied universally
- Severity (AKI stage) correlates with prognosis

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Treatment of Choice for HRS

LIVER TRANSPLANT

Treatment: Supportive Liver Care

- **VIBES**
  - **V**olume: **IV albumin** 1 g/kg x 48 hr initially*
  - **I**nfection: antibiotics, SBP ppx
  - **B**leeding: endoscopy, TIPS
  - **E**ncephalopathy: lactulose/rifaxmin
  - **S**creening/Surgery: Transplant evaluation

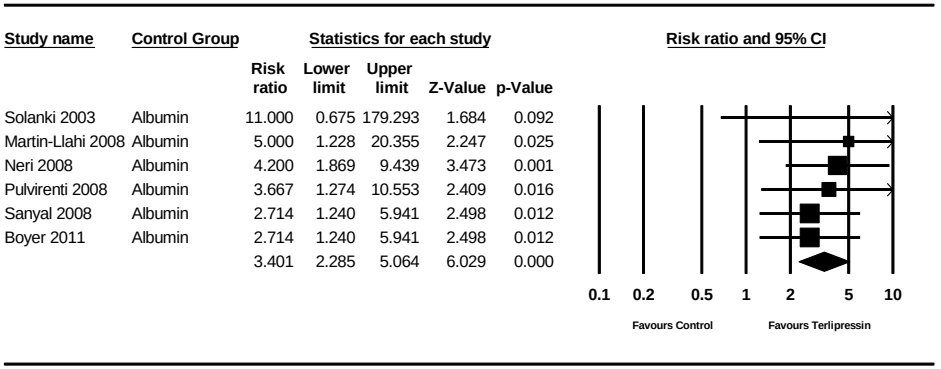
Sort, et al. *NEJM*. 1999

Vasoconstrictors for HRS

Drug	Pros	Cons	# RCTs
Midodrine Octreotide	• Can give on floor • Cheap(-ish), safe	• Doesn't work well (10-15% effective)	1
Vasopressin Terlipressin	• Effective (30-50%) • Best studied (terli)	• Ischemia (vaso>terli) • Respiratory events	0 15
Norepinephrine	• Effective at ↑ MAP	• Requires ICU	5

Meta-analysis: HRS reversal

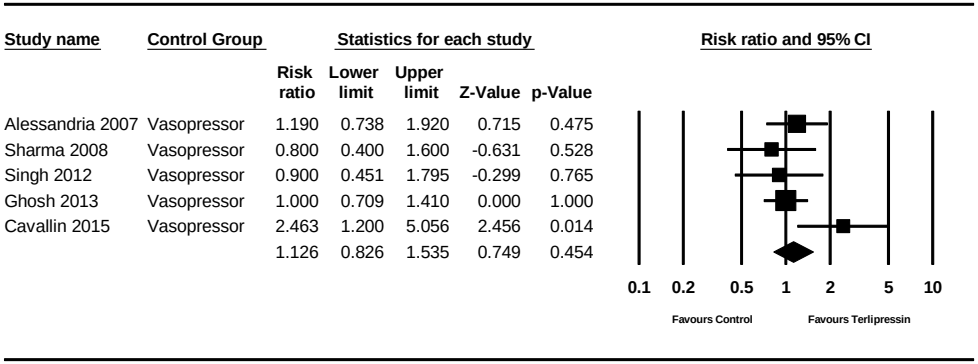
- Terli >> albumin alone



Study name	Control Group	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
Solanki 2003	Albumin	11.000	0.675	179.293	1.684	0.092
Martin-Llahi 2008	Albumin	5.000	1.228	20.355	2.247	0.025
Neri 2008	Albumin	4.200	1.869	9.439	3.473	0.001
Pulvirenti 2008	Albumin	3.667	1.274	10.553	2.409	0.016
Sanyal 2008	Albumin	2.714	1.240	5.941	2.498	0.012
Boyer 2011	Albumin	2.714	1.240	5.941	2.498	0.012
		3.401	2.285	5.064	6.029	0.000

Figure 3B

- Terli ≈ norepi
- Terli > mido/octreotide (1 study)



Study name	Control Group	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
Alessandria 2007	Vasopressor	1.190	0.738	1.920	0.715	0.475
Sharma 2008	Vasopressor	0.800	0.400	1.600	-0.631	0.528
Singh 2012	Vasopressor	0.900	0.451	1.795	-0.299	0.765
Ghosh 2013	Vasopressor	1.000	0.709	1.410	0.000	1.000
Cavallin 2015	Vasopressor	2.463	1.200	5.056	2.456	0.014
		1.126	0.826	1.535	0.749	0.454

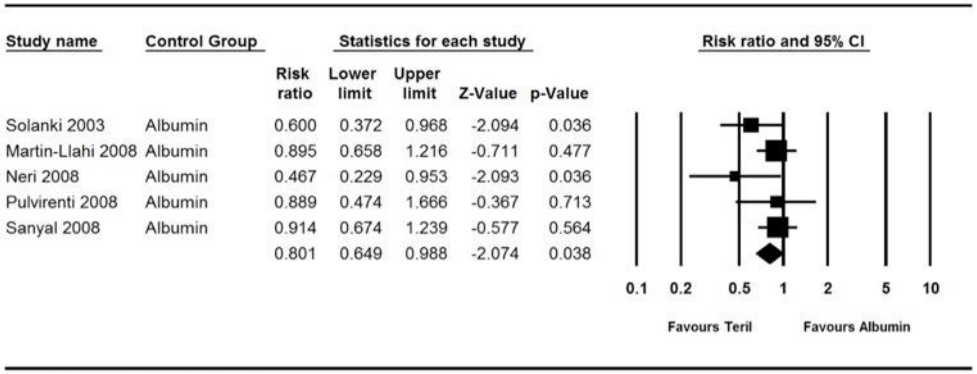
Figure 3C

Allegretti, et al. Cochrane Reviews 2017.

Meta-analysis: Mortality

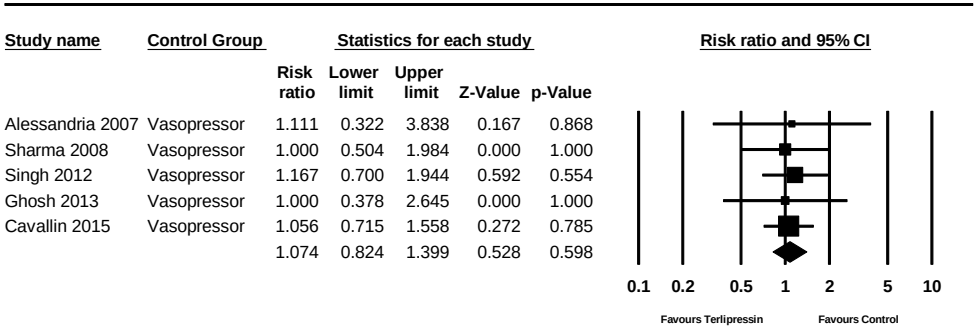
- Terli > albumin alone

- Terli ≈ norepi



Study name	Control Group	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
Solanki 2003	Albumin	0.600	0.372	0.968	-2.094	0.036
Martin-Llahi 2008	Albumin	0.895	0.658	1.216	-0.711	0.477
Neri 2008	Albumin	0.467	0.229	0.953	-2.093	0.036
Pulvirenti 2008	Albumin	0.889	0.474	1.666	-0.367	0.713
Sanyal 2008	Albumin	0.914	0.674	1.239	-0.577	0.564
		0.801	0.649	0.988	-2.074	0.038

Mortality: Terlipressin vs. Albumin

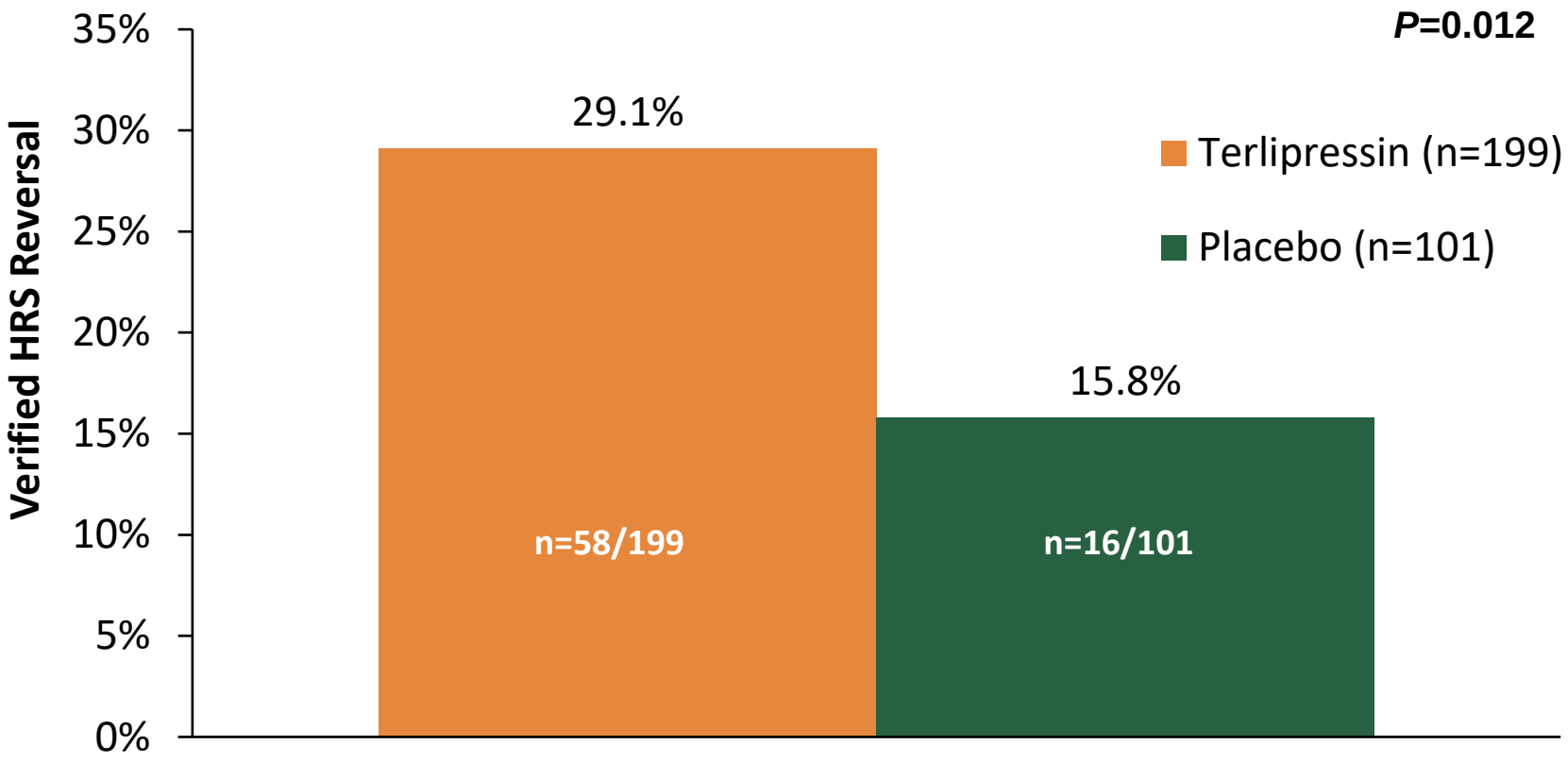


Study name	Control Group	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
Alessandria 2007	Vasopressor	1.111	0.322	3.838	0.167	0.868
Sharma 2008	Vasopressor	1.000	0.504	1.984	0.000	1.000
Singh 2012	Vasopressor	1.167	0.700	1.944	0.592	0.554
Ghosh 2013	Vasopressor	1.000	0.378	2.645	0.000	1.000
Cavallin 2015	Vasopressor	1.056	0.715	1.558	0.272	0.785
		1.074	0.824	1.399	0.528	0.598

Figure 2C

Allegretti, et al. Cochrane Reviews 2017.

CONFIRM Study: Verified HRS Reversal



Wong et al. NEJM 2021.

CONFIRM : Verified HRS-Reversal by SCr Category

SCr Category	Terlipressin (n=199)	Placebo (n=101)
<3 mg/dL	29/79 (36.7%)	13/40 (32.5%)
≥3 to <5 mg/dL	27/97 (27.8%)	3/53 (5.7%)
≥5 mg/dL	2/23 (8.7%)	0/8 (0%)

Wong et al. NEJM 2021.

Serious Adverse Events

Parameter, n (%)	Terlipressin (n=200)	Placebo (n=99)
Serious adverse events – overall	130 (65.0)	60 (60.6)
Respiratory failure	20 (10.0)	3 (3.0)
Abdominal pain	10 (5.0)	1 (1.0)
Hepatic failure	9 (4.5)	10 (10.1)
Multiple organ dysfunction syndrome	9 (4.5)	3 (3.0)
Sepsis	9 (4.5)	0 (0.0)
Intestinal ischemia	2 (1.0)	0 (0.0)

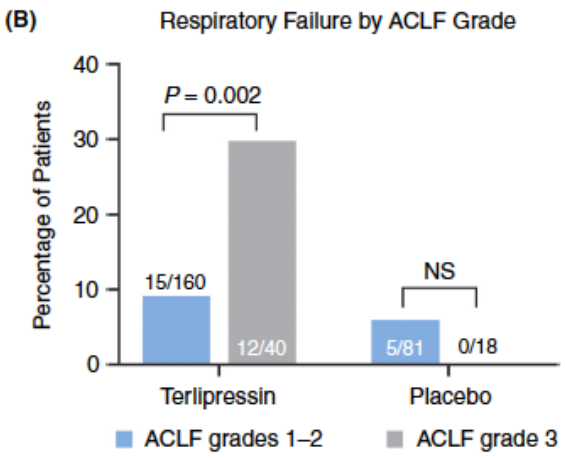
Wong et al. NEJM 2021.

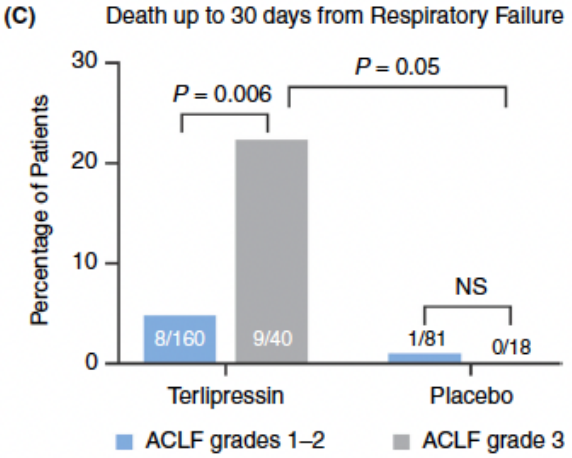
Warnings Around Terlipressin

WARNING: SERIOUS OR FATAL RESPIRATORY FAILURE

TERLIVAZ 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., SpO_2) before initiating TERLIVAZ.

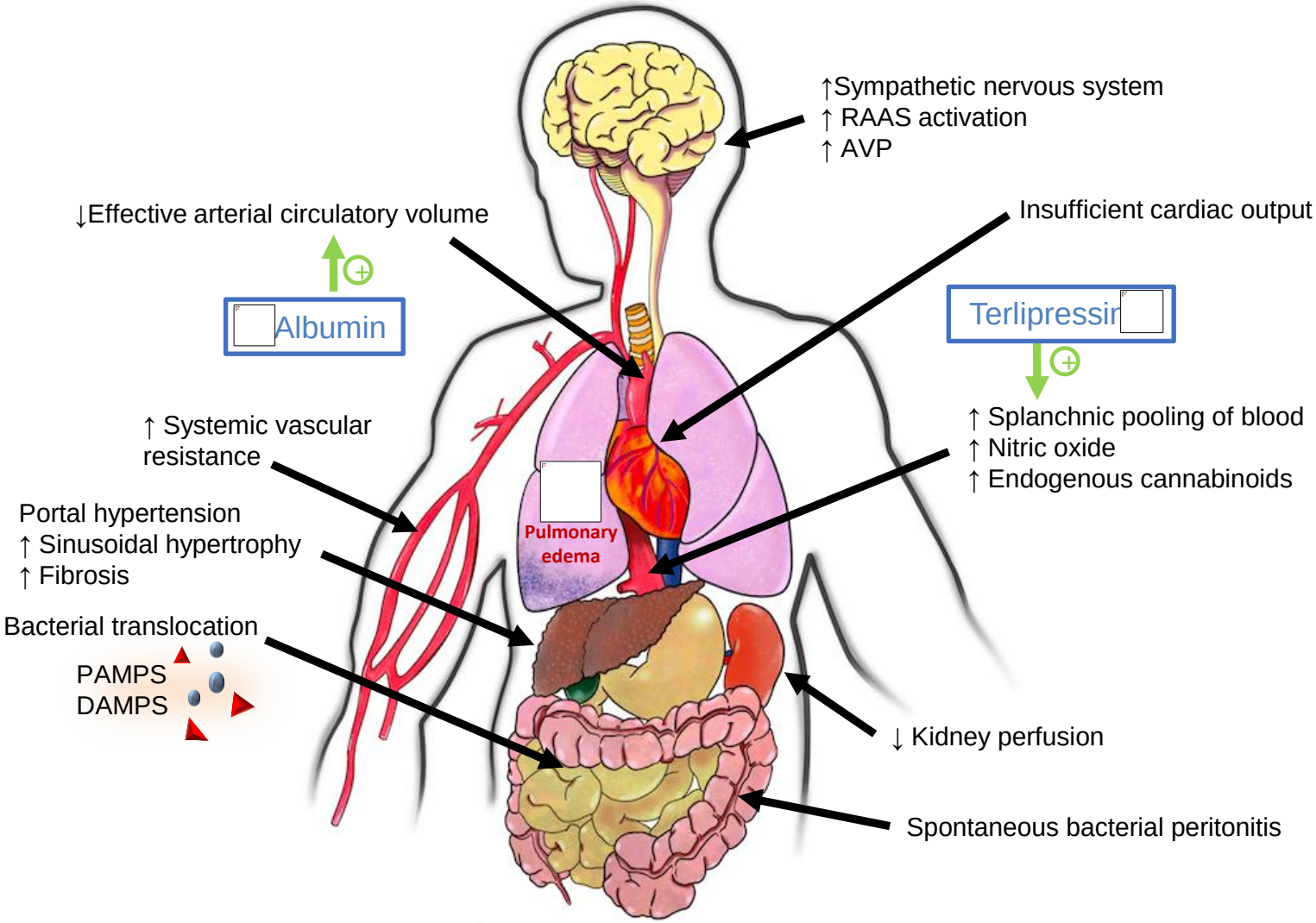
Do not initiate TERLIVAZ in patients experiencing hypoxia (e.g., SpO_2 <90%) until oxygenation levels improve. Monitor patients for hypoxia using continuous pulse oximetry during treatment and discontinue TERLIVAZ if SpO_2 decreases below 90% (2.1, 4, 5.1).





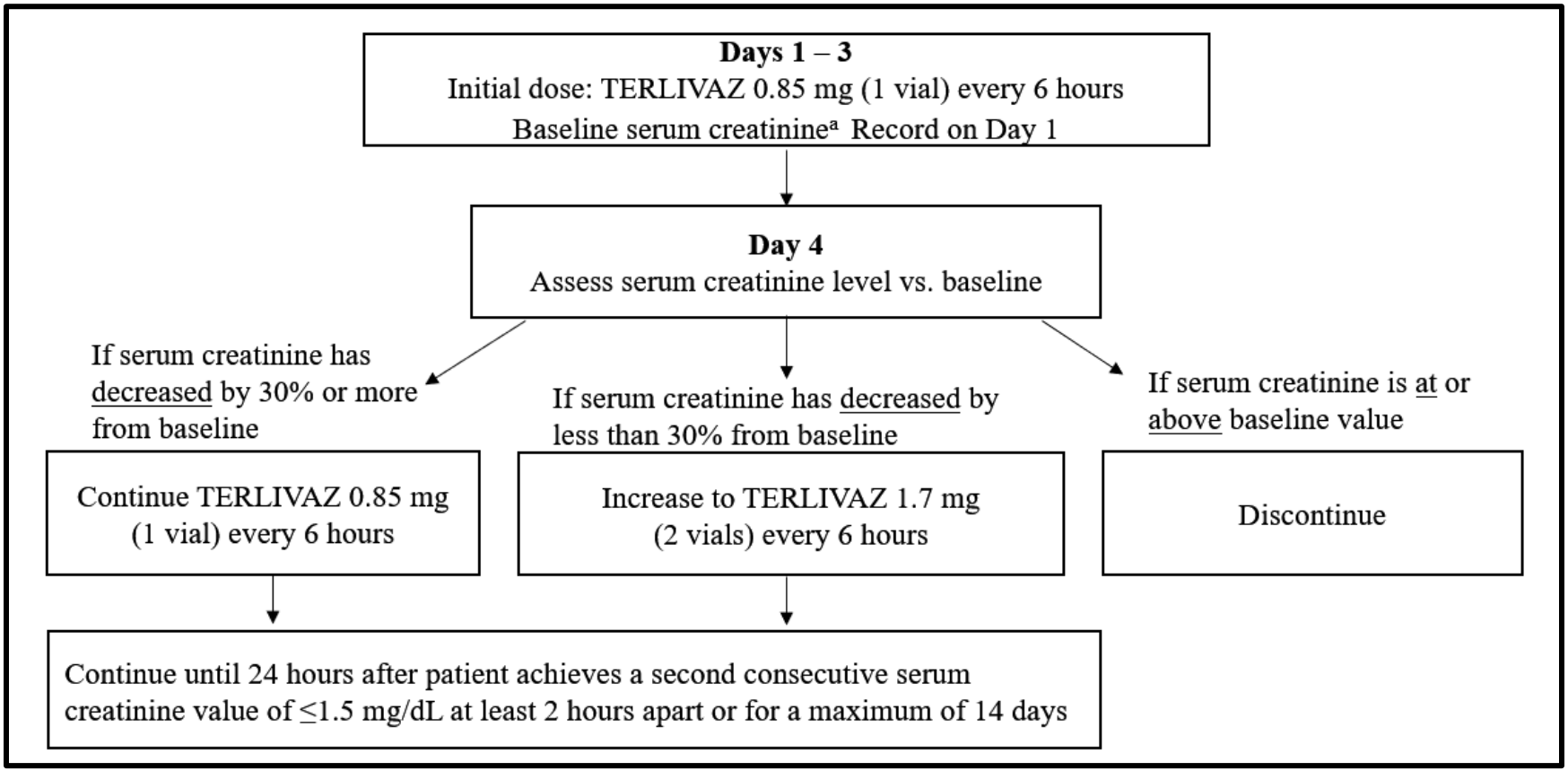
FDA Label, Terlipressin. Wong et al. APT 2022.

Terlipressin's Adverse Events and Albumin Dosing



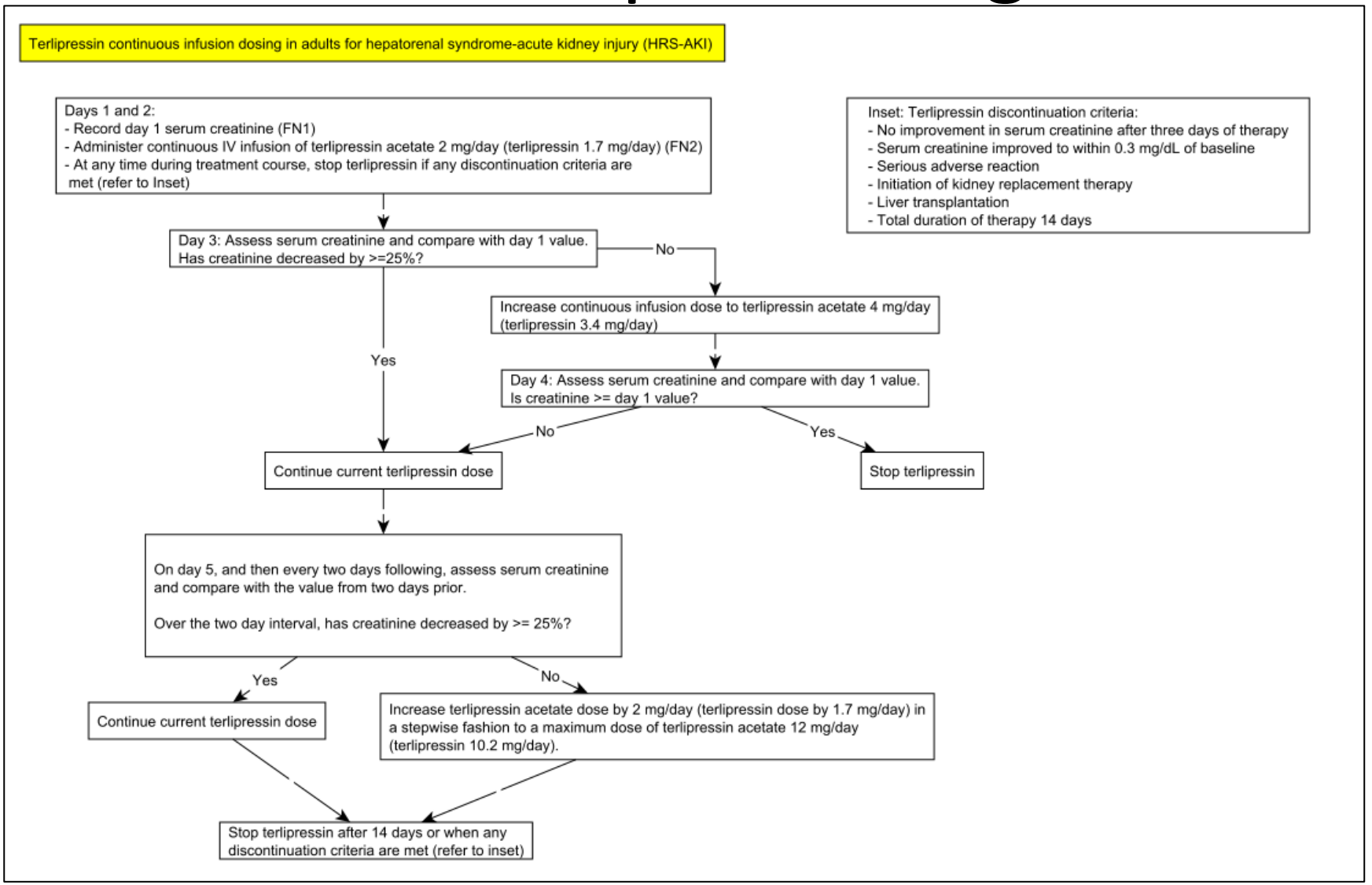
Belcher, Allegretti, et al. AJKD 2021.

Terlipressin Dosing

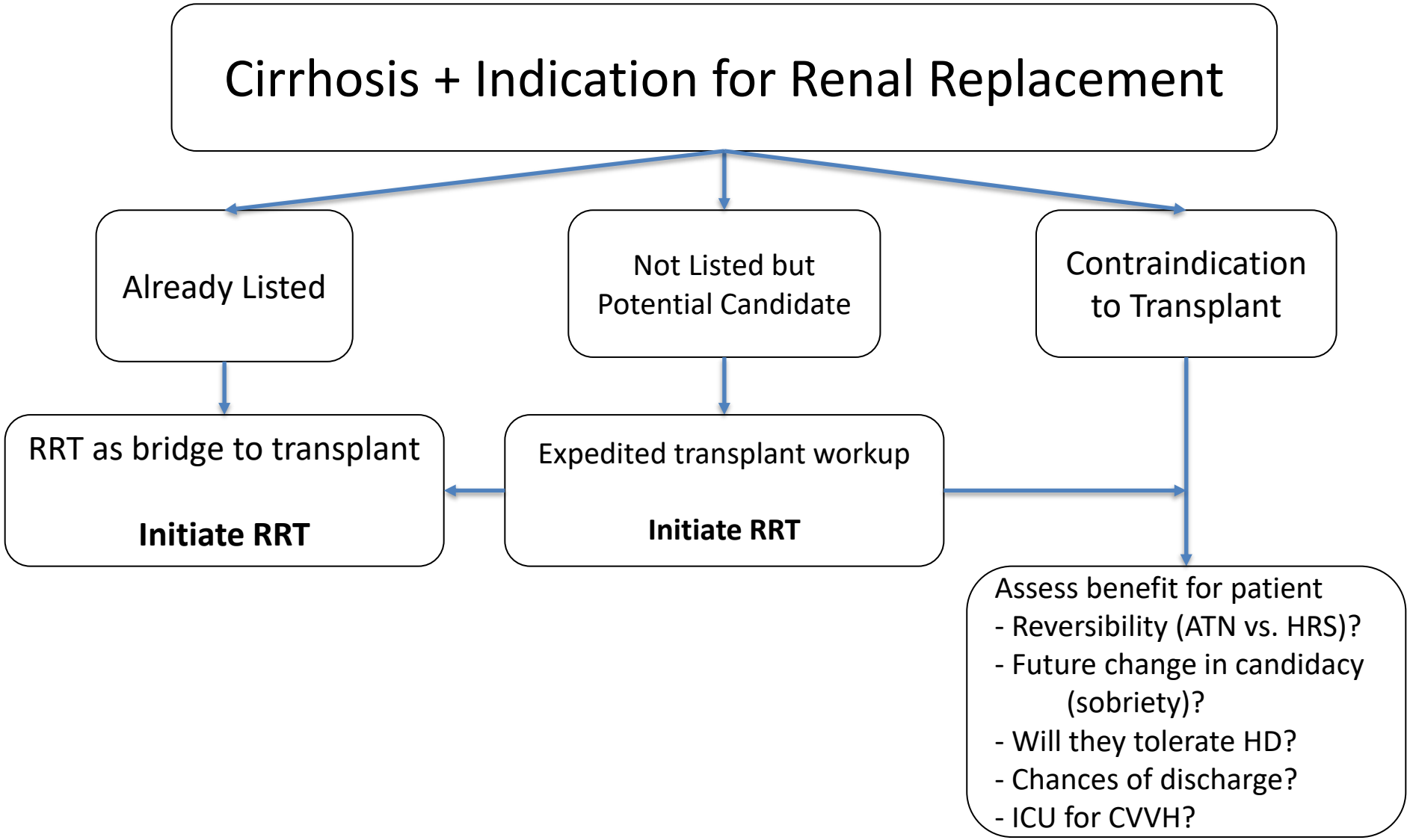


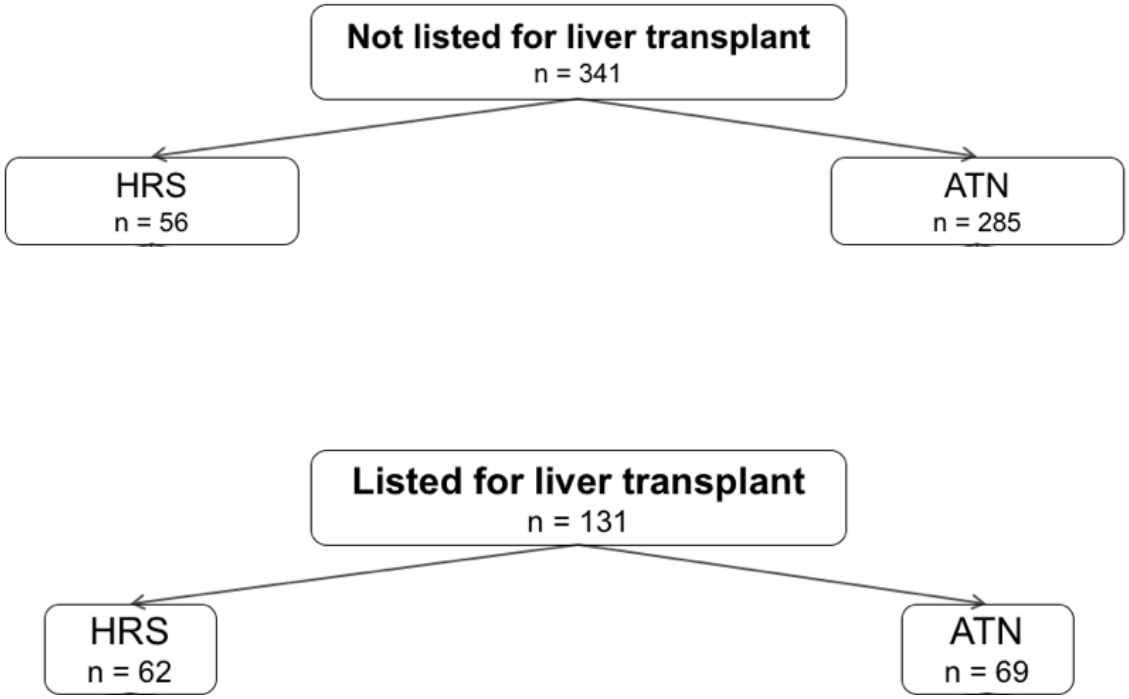
FDA Label (Terlipressin), September 2022

Continuous Terlipressin Algorithm

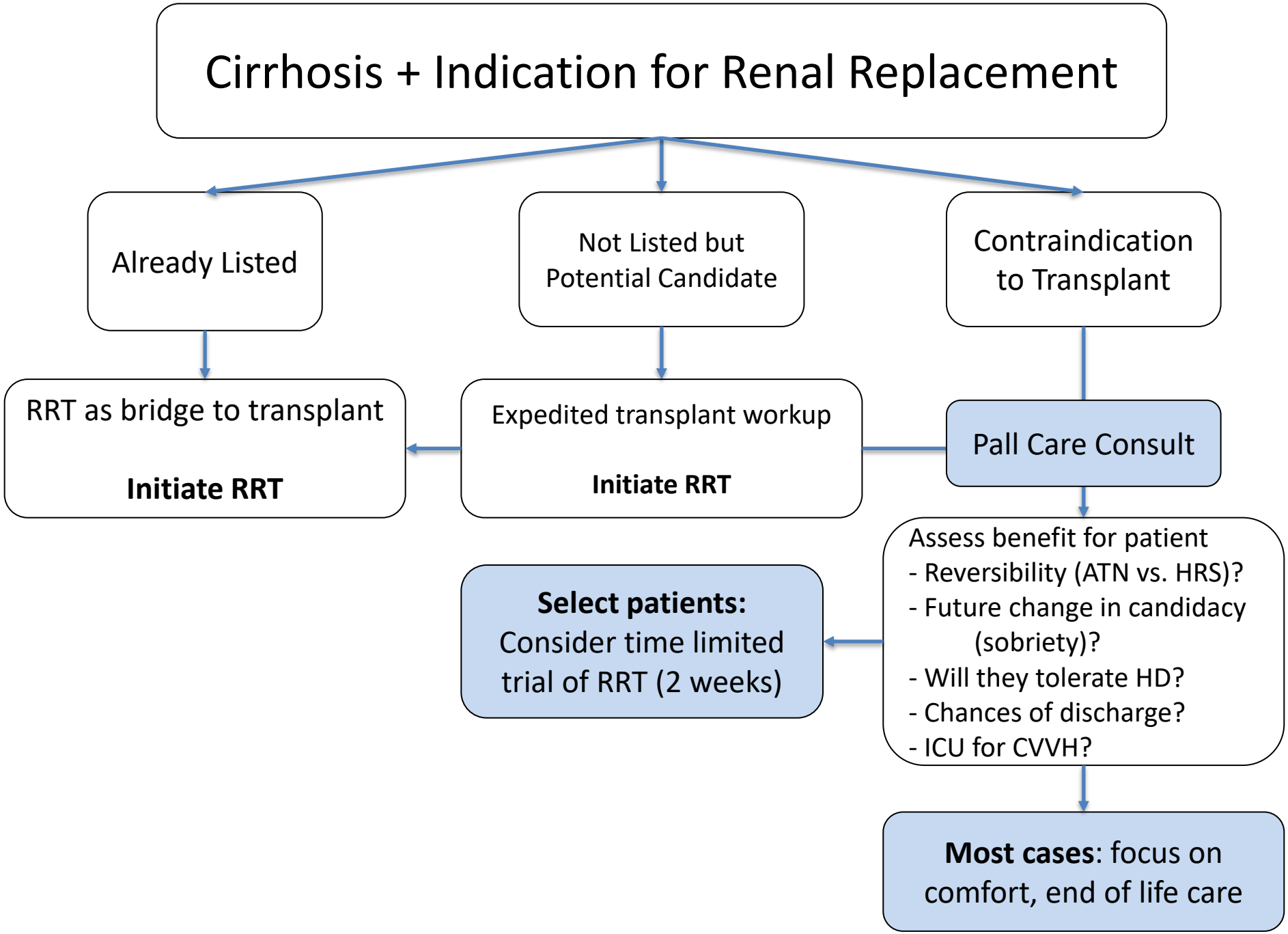


Allegretti AS and Wong F. Uptodate.com


Cirrhosis + Indication for Renal Replacement
Already Listed
Not Listed but Potential Candidate
Contraindication to Transplant
RRT as bridge to transplant
Initiate RRT
Expedited transplant workup
Initiate RRT
Assess benefit for patient
- Reversibility (ATN vs. HRS)?
- Future change in candidacy (sobriety)?
- Will they tolerate HD?
- Chances of discharge?
- ICU for CVVH?



Allegretti et al. CJASN 2018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RRT as bridge to transplant
Initiate RRT
Expedited transplant workup
Initiate RRT
Pall Care Consult
Assess benefit for patient
- Reversibility (ATN vs. HRS)?
- Future change in candidacy (sobriety)?
- Will they tolerate HD?
- Chances of discharge?
- ICU for CVVH?
Select patients:
Consider time limited trial of RRT (2 weeks)
Most cases: focus on comfort, end of life care

Simultaneous Liver Kidney Transplant

- Public health issue:
  - Transplants are limited resource
  - OLT outcomes better with normal post op Cr but…
  - Kidney allografts last longer in ESRD alone compared to SLK
- 2017 OPTN guidelines do not consider etiology of kidney disease

Simpson et al. Transplantation 2006
Locke et al. Transplantation 2008
Davis et al. AJT 2007

Simultaneous Liver-Kidney Criteria

SLK Medical Eligibility Criteria

Transplant nephrologist must confirm candidate has <u>one</u> of the following:	And transplant hospital must report to UNOS and document <u>one</u> of the following in the medical record:
1. Chronic kidney disease with measured or calculated GFR less than or equal to 60 mL/min for greater than 90 consecutive days	• Dialysis for ESRD • Most recent eGFR/CrCl is at or below **30** mL/min at or after registration on kidney waiting list
2. Sustained acute kidney injury	One or a combination of both of the following **in the past six weeks**: • Dialysis for six consecutive weeks • eGFR/CrCl at or below 25 mL/min for six consecutive weeks. The program must confirm criteria continues to be met **at least once every seven days**.
3. Metabolic disease	Diagnosis of: • Hyperoxaluria • Atypical HUS from mutations in factor H or factor I • Familial non-neuropathic systemic amyloid • Methylmalonic aciduria

Courtesy Eliot Heher

Take Home Messages

- AKI in cirrhosis has high mortality regardless of cause.
- HRS-AKI is largely a hemodynamic insult and first line treatment is terlipressin, where available.

Review Question 2

A 59 year old man with alcoholic cirrhosis and ascites presents with a fever and abdominal pain. He is well appearing. Blood pressure is 97/50, he is jaundiced, and his abdomen is distended. His serum creatinine on admission was 3.1 mg/dL (from 0.8 mg/dL three weeks prior). His MELD-Na score on admission is 27. A diagnostic paracentesis confirms a spontaneous bacterial peritonitis. He is placed on intravenous ceftriaxone, given intravenous albumin, and on hospital day 3, his creatinine was 4.1 mg/dL, with worsening ascites and new lower extremity edema. What is the next step in management?

a. Supportive care
b. Placement of TIPS
c. Initiation of renal replacement therapy
d. Continue intravenous albumin and initiate vasoconstrictor therapy
e. Immediately transfer the patient via helicopter to a liver transplant center in a region with low median MELD score at the time of transplant.

Review Question 2 Answer

Answer: Continue intravenous albumin and initiate vasoconstrictor therapy. This patient has hepatorenal syndrome and warrants a trial of medical therapy. This consists of continued intravenous albumin (20-40 g/day) and vasoconstrictor therapy (terlipressin, if available) with a goal to increase mean arterial pressure by 10 mmHg or more.

a. Supportive care. Incorrect, patients with hepatorenal syndrome who are candidates should be tried on vasoconstrictors.

b. Placement of TIPS. Incorrect, this patient's high MELD score is a relative contraindication to TIPS. TIPS is not indicated for hepatorenal syndrome, though there is evidence that TIPS can improve renal function in less sick patients.

c. Initiation of renal replacement therapy. Incorrect. Renal replacement therapy can be consider if this patient fails to respond to medical management.

d. Continue intravenous albumin and initiate vasoconstrictor therapy

e. Immediately transfer the patient via helicopter to a liver transplant center in a region with low median MELD score at the time of transplant. Incorrect. This patient should be referred to a liver transplant center, but first should be medically stabilized, then evaluated at a local center.

Review Question 3

The patient from Question 1 did not respond to maximal vasoconstrictor therapy, and was listed for liver transplant. His course was complicated by septic shock, and anuric AKI, consistent with a superimposed acute tubular necrosis. He was transferred to the intensive care unit and then started on continuous renal replacement therapy. His infection was treated and he was transitioned to the general medical floor and continued hemodialysis. Three weeks after admission, the patient received an offer for a liver transplant. Which of the following is the recommended option for transplant?

a. Liver transplant alone
b. Simultaneous liver and kidney transplant
c. Renal biopsy at the time of liver transplant, with determination of kidney transplant based on pathology findings.
d. Discussion between the transplant nephrologist and transplant surgeon about the patient's likelihood to recover renal function post transplant.

Review Question 3 Answer

- **Answer: Liver transplant alone**
- UNOS guidelines require 6 weeks of renal replacement therapy (or sustained AKI with a GFR <25 mL/min) as an indication for simultaneous liver and kidney transplant. Etiology of AKI, clinical course, pathology, or other comorbidities do not factor into this decision.

Thank You and Questions

References

Allegretti, et al. *Int J Nephrology*. 2015
Gines, et al. *Gastroenterology*. 1993
Wadei et al. *CJASN.* 2006
Ruiz-del-Arbol, et al. *Hepatology.* 2005
Alessandria et al. Hepatology 2005.
Angeli et al. *Gut.* 2015
Israelsen, et al. *J Gastro and Hep*. 2015.
Fagundes, et al. *Journal of Hepatology* 2013.
Pouria et al. *NDT*. 1999;14:2279
McGuire et al. *Ann Int Med* 2006;144:735
Sort, et al. *NEJM*. 1999
Allegretti, et al. *Cochrane Reviews* 2017.
Maddurkuri, et al. *Dig Dis Sci*. 2014.
Simpson et al. *Transplantation* 2006
Locke et al. *Transplantation* 2008
Davis et al. *AJT* 2007
Kim, et al. *NEJM* 2008
Belcher, et al. *Hepatology*, 2014.
Ariza, et al. *J Hep*. 2016.
Huelin et al. *Hepatology* 2019
Allegretti, Sola, Gines. *AJKD* 2020.
Wong, et al. NEJM 2021.

Clinical Trials

Clinical Trials	Change in Management	
CONFIRM (terlipressin vs. placebo) for HRS (Wong et al, NEM 2021)	29.1% vs 15.8% Verified HRS reversal favoring terli. No mortality difference between arms	Terlipressin now FDA approved and guideline recommended as first line HRS-AKI therapy