

Liver and the Kidney

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- Medical School: Brown University
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 - Associate Professor of Medicine, HMS
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 - Co-chair, HRS-HARMONY research collaborative
- Areas of Interest
 - AKI in cirrhosis, hepatorenal syndrome
 - Critical Care Nephrology

Disclosures

Consulting: Mallinckrodt Pharmaceuticals, Bioportio, Acta Pharmaceuticals, PharmaIN

DMSB: Astrazeneca

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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.

What is the cause of his AKI?

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

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

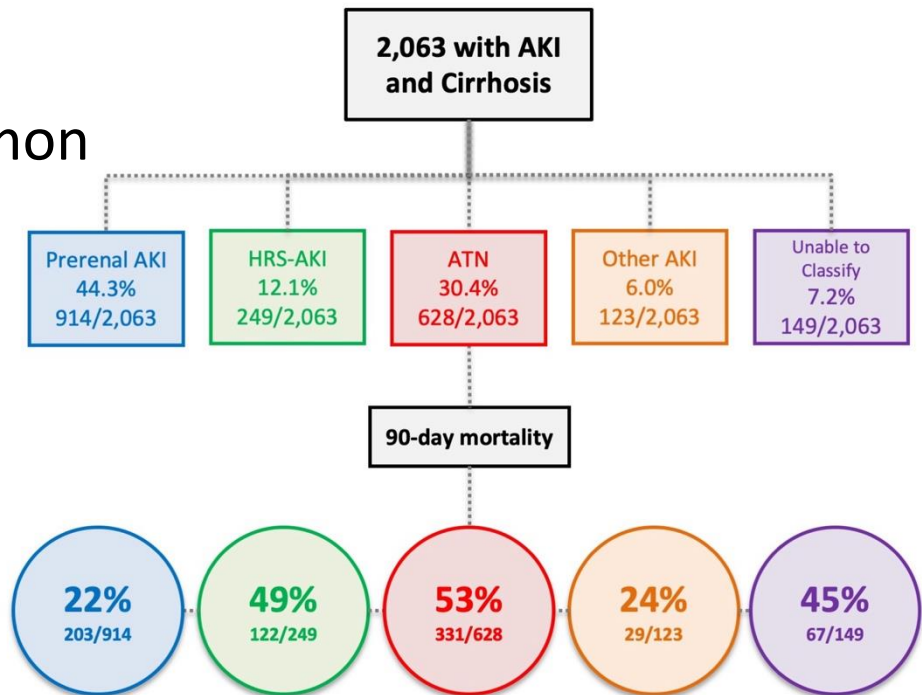
1. Background and physiology of HRS
2. Diagnostic criteria and approach to AKI in cirrhosis
3. Pre-transplant treatment updates
 - Vasoconstrictors
 - Renal replacement therapy

Outline

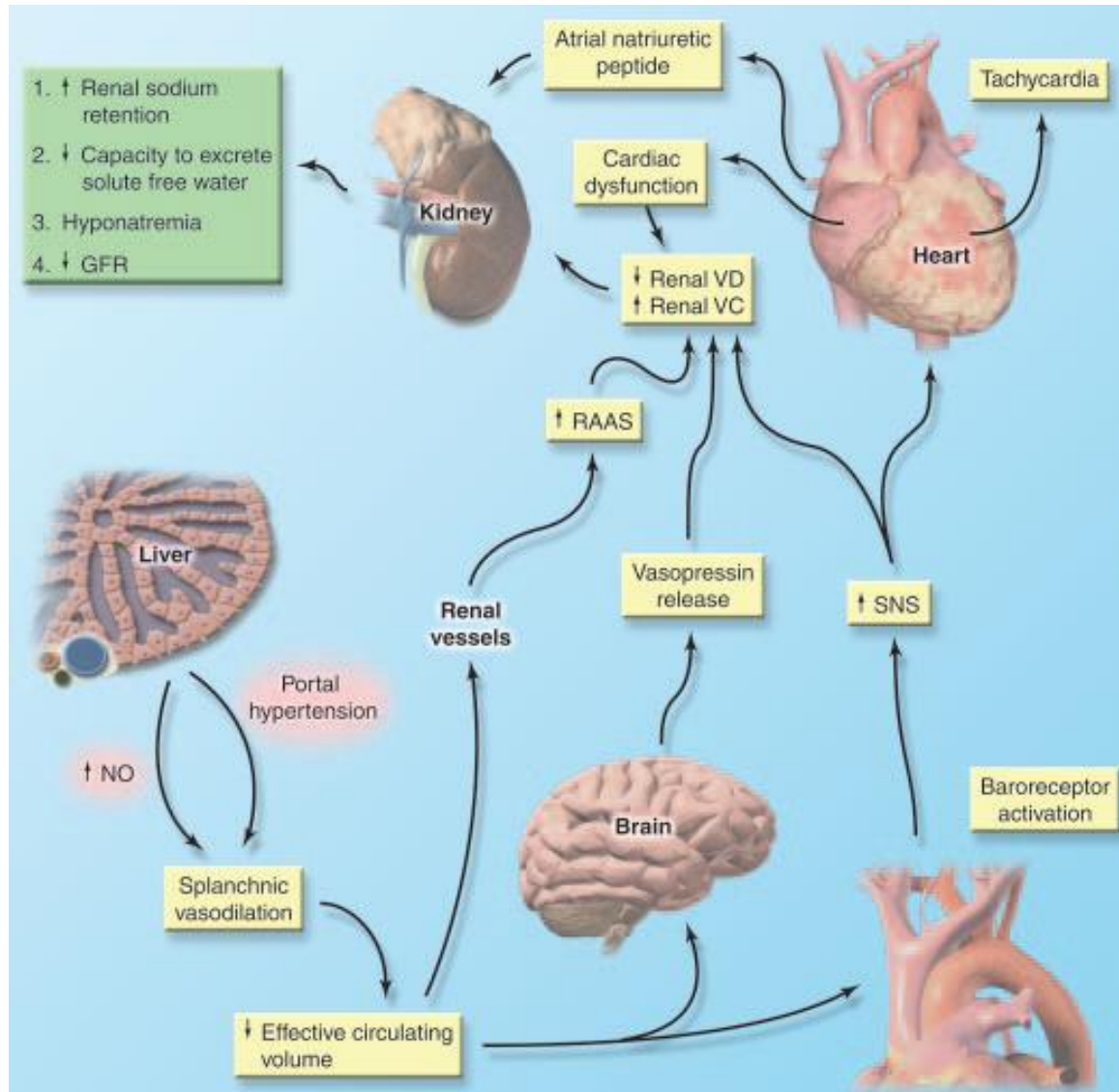
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Background: AKI in Cirrhosis

- AKI in cirrhosis is **common**
 - 50% of decompensated cirrhosis
- HRS is “rare” but may feel common
- **High mortality**
 - Untreated HRS: 90% mortality
 - More recent: 50% mortality
- **Difficult to diagnosis HRS**
 - Prerenal injury vs. HRS vs. ATN
 - HRS is a syndrome without a definitive test
 - Overlapping triggers (e.g., infection)
 - Management is different based on type of AKI



Pathophysiology of HRS (and ascites)



Normal Circulation

Hepatorenal Physiology

Hepatorenal Physiology

Hepatorenal Physiology

Hepatorenal Syndrome

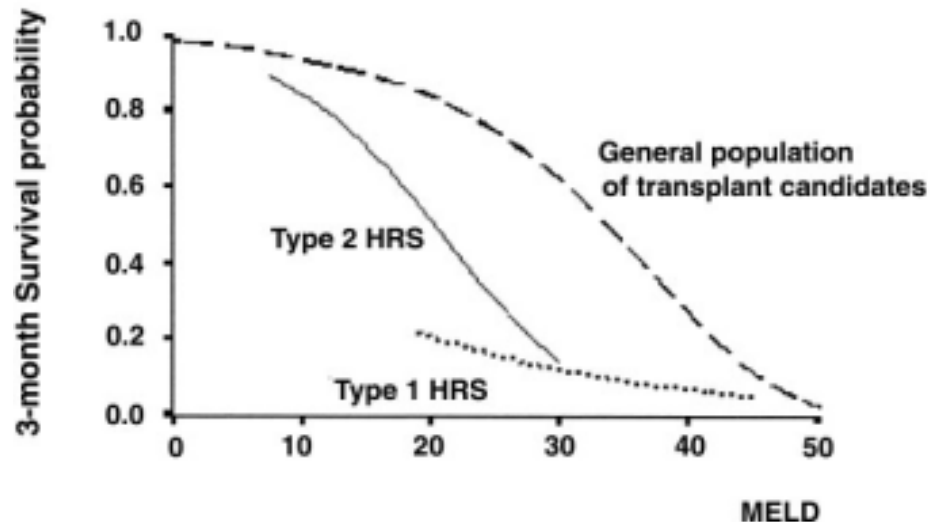
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MELD does not capture acute decompensation, ACLF score emerges



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 ≥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

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.

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 $\geq 50\%$ from baseline within 7 days, and/or UO ≤ 0.5 mL/kg for ≥ 6 h
- 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

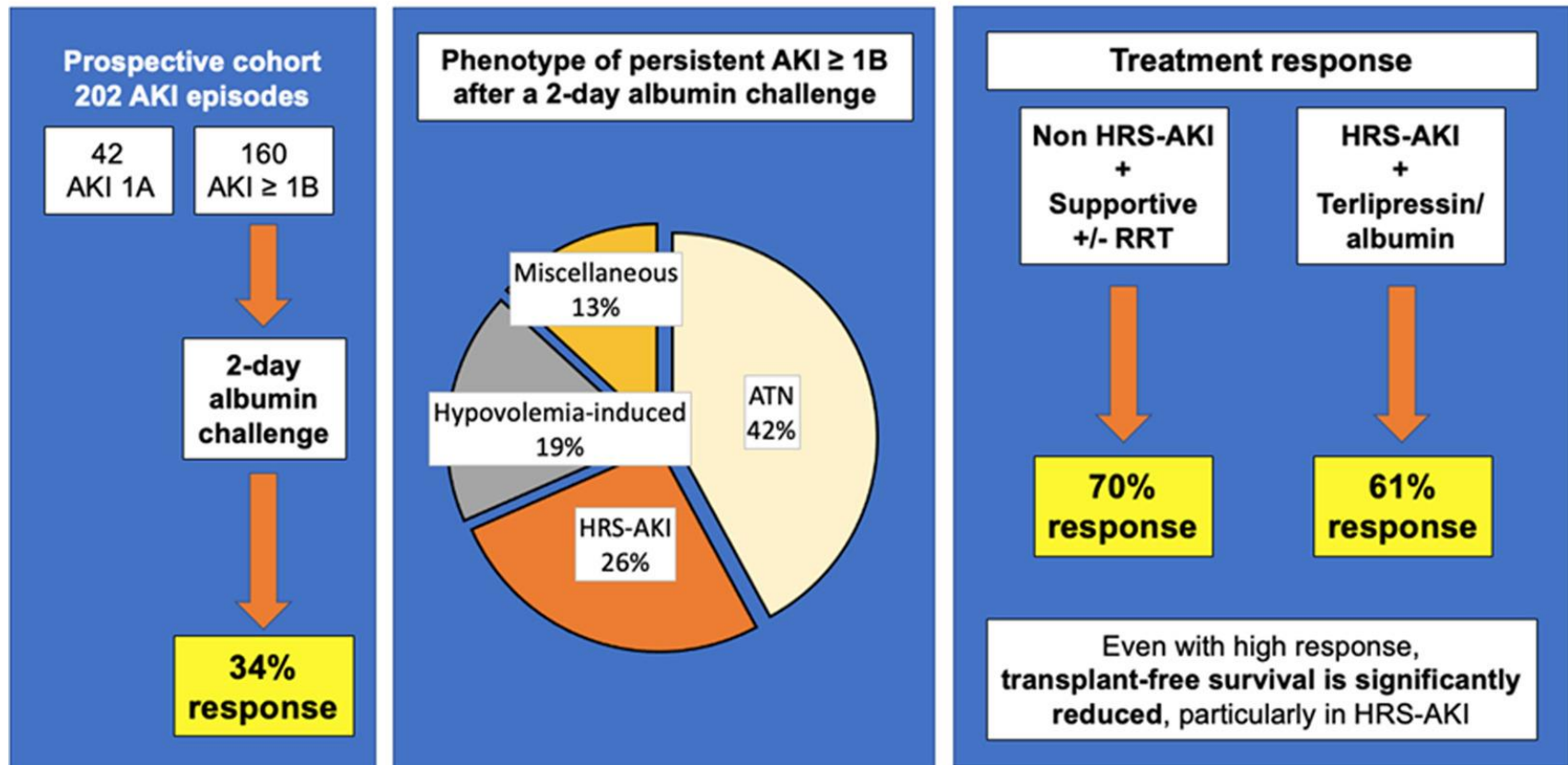
(Strong recommendation, grade D)

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

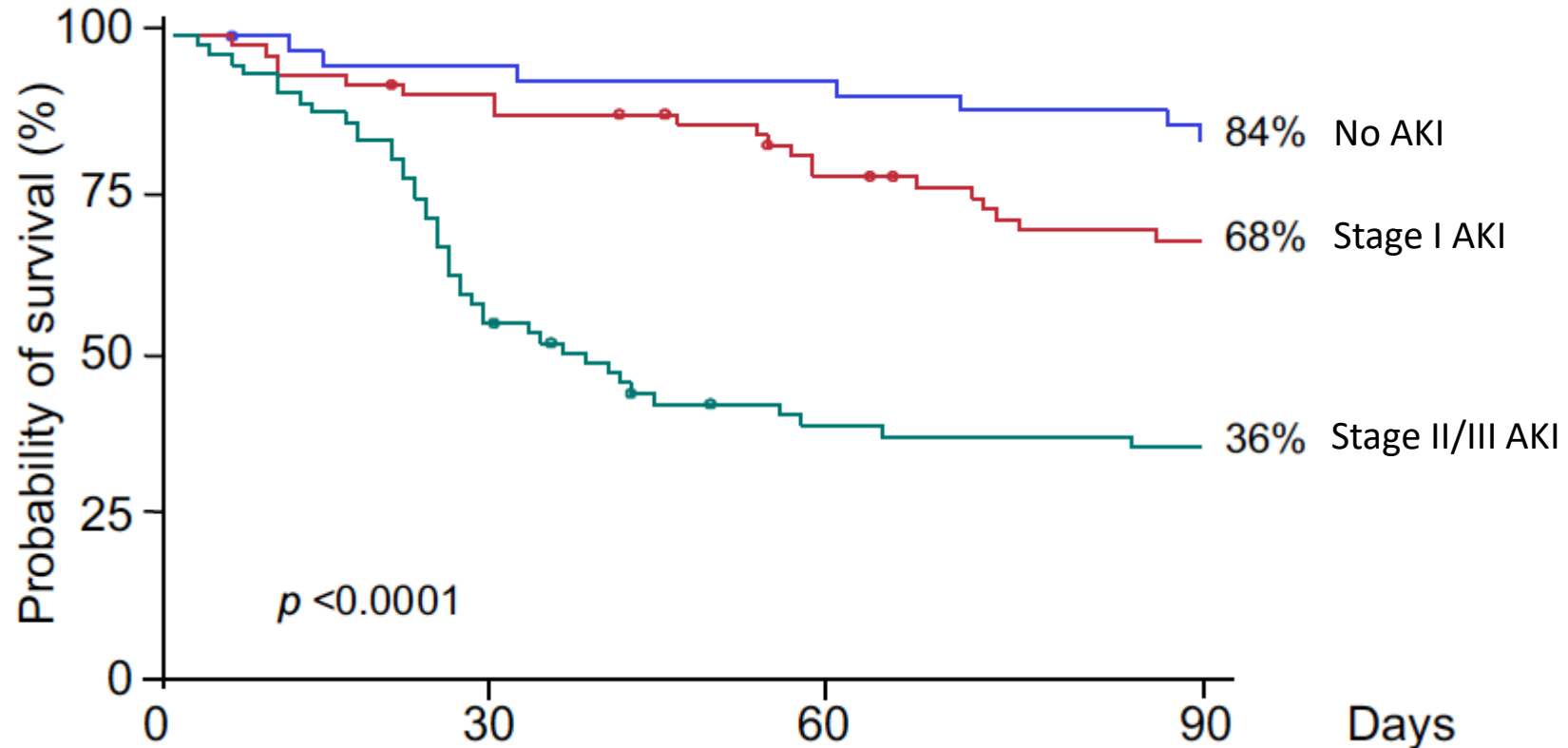
(Strong recommendation, grade D)

2015 ICA (2018 EASL) Approach Works Fairly Well

Outcomes of AKI in cirrhosis using the new EASL management algorithm

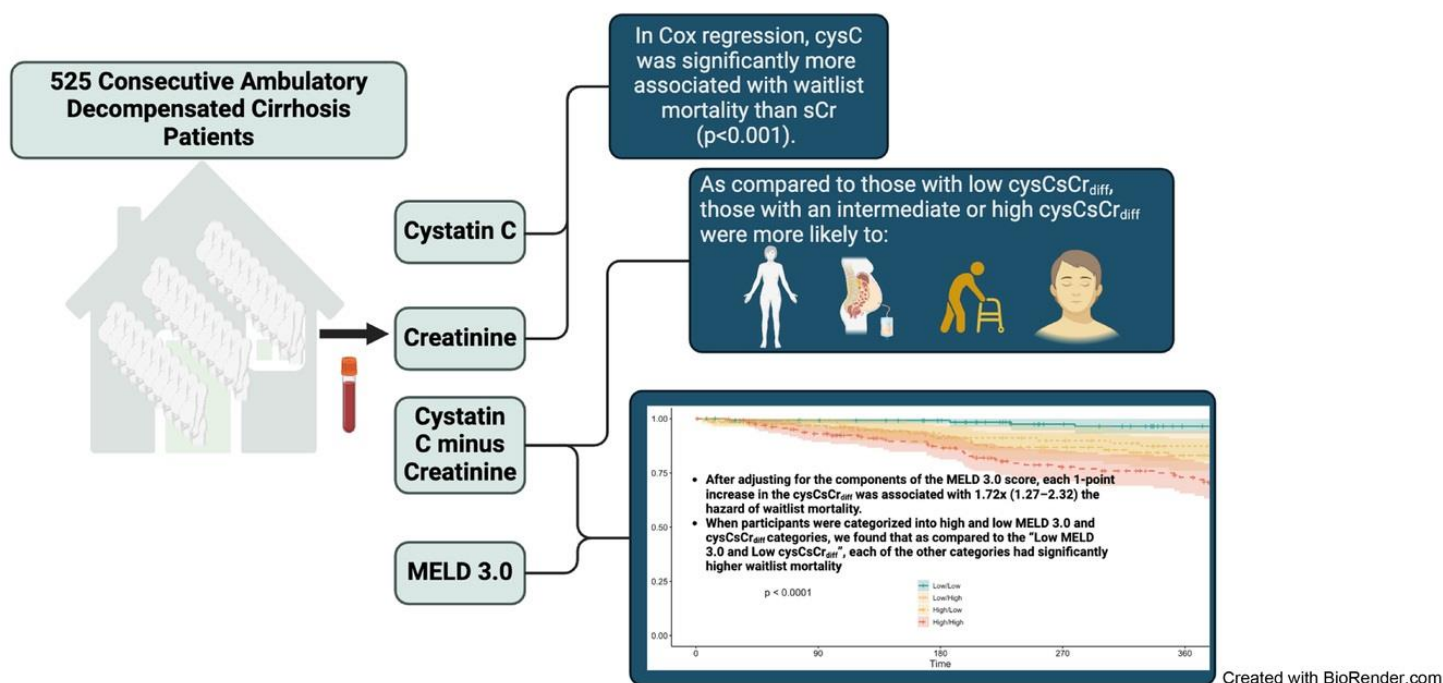


AKIN Stage and Mortality

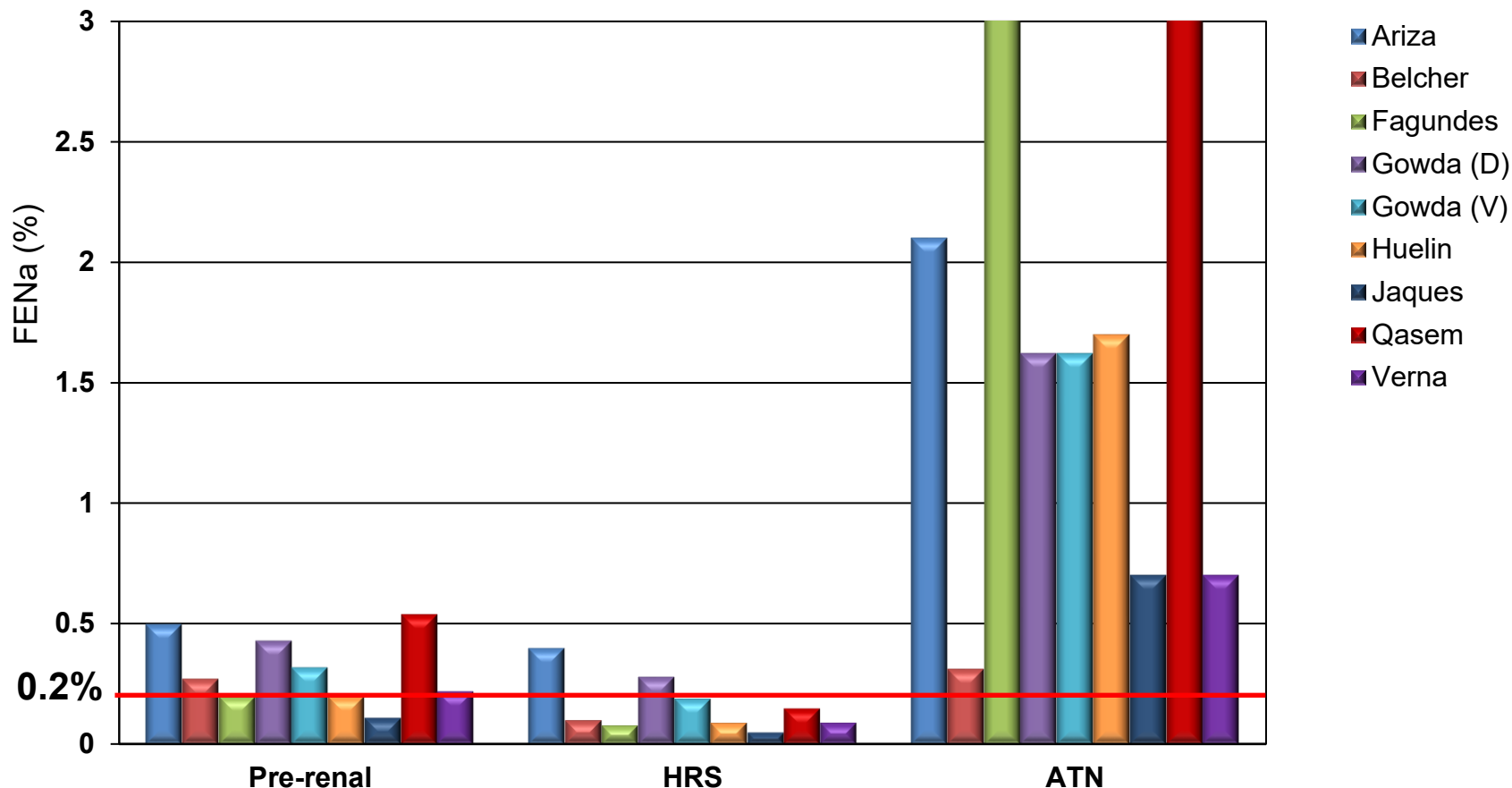


Cystatin C Predicts Waitlist Mortality

Cystatin C and the Difference between Cystatin C and Serum Creatinine: Improved Metrics to Predict Waitlist Mortality Among Decompensated Cirrhosis Patients



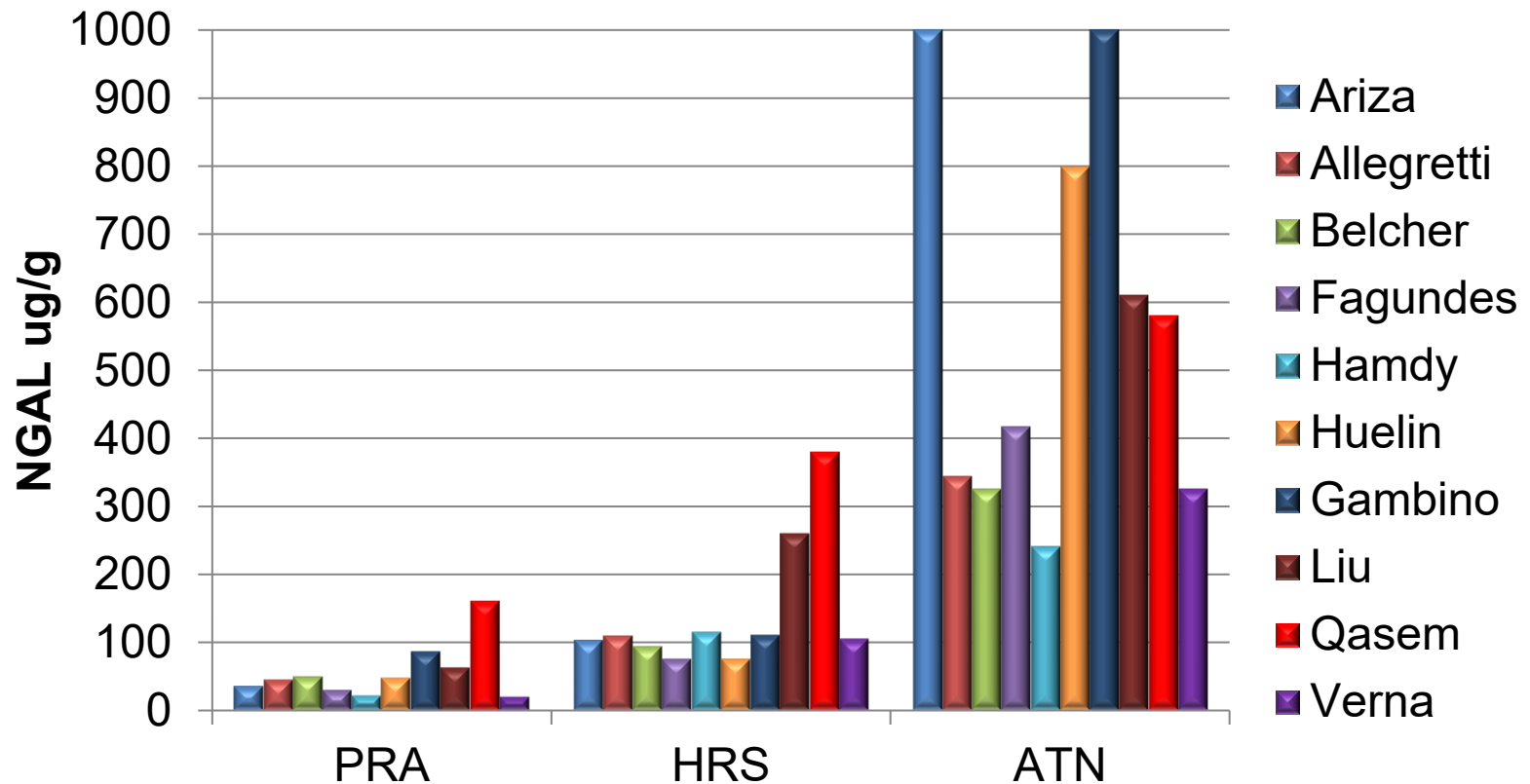
FENa in AKI and Cirrhosis Distinguishes PRA, HRS, ATN



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Slide courtesy of Justin Belcher, MD PhD

NGAL has had Consistent Performance in AKI in Cirrhosis



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Slide courtesy of Justin Belcher, MD PhD

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.

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

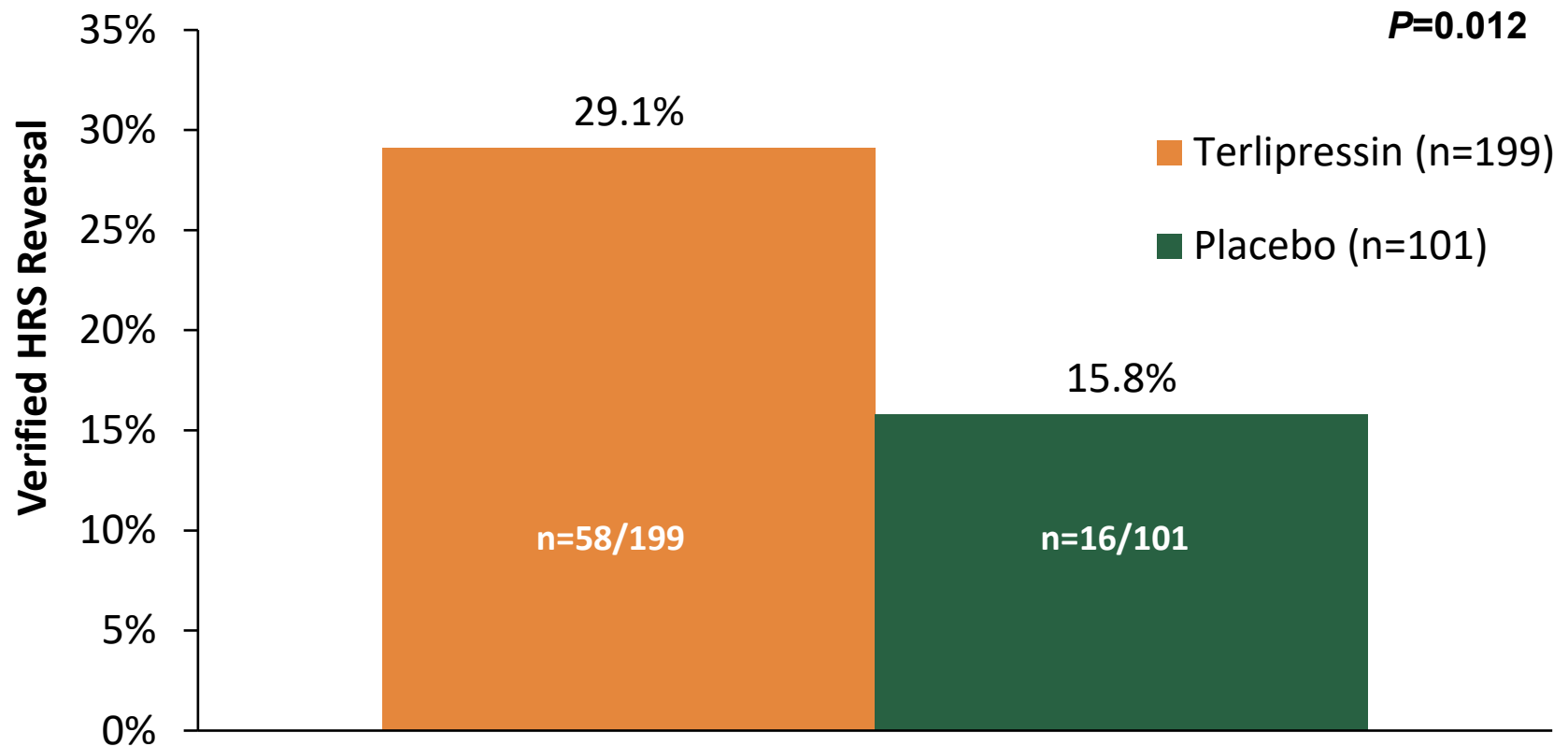
- **VIBES**

- **Volume: IV albumin** 1 g/kg x 48 hr initially*
- **Infection:** antibiotics, SBP ppx
- **Bleeding:** endoscopy, TIPS
- **Encephalopathy:** lactulose/rifaxmin
- **Screening/Surgery:** Transplant evaluation

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

CONFIRM Study: Verified HRS Reversal



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%)

Serious Adverse Events

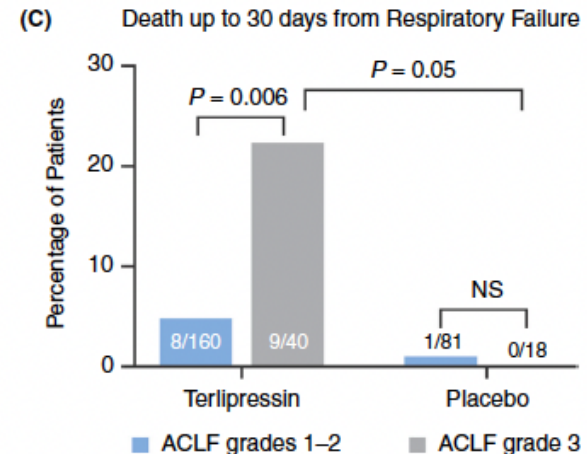
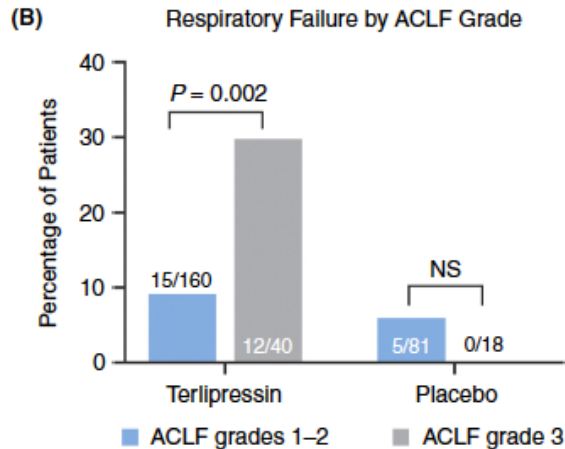
Parameter, n (%)	Terlipressin (n=200)	Placebo (n=99)
Serious adverse events – overall	130 (65.0)	60 (60.6)
Respiratory failure	20 (10.0)	3 (3.0)
Abdominal pain	10 (5.0)	1 (1.0)
Hepatic failure	9 (4.5)	10 (10.1)
Multiple organ dysfunction syndrome	9 (4.5)	3 (3.0)
Sepsis	9 (4.5)	0 (0.0)
Intestinal ischemia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

Warnings Around Terlipressin

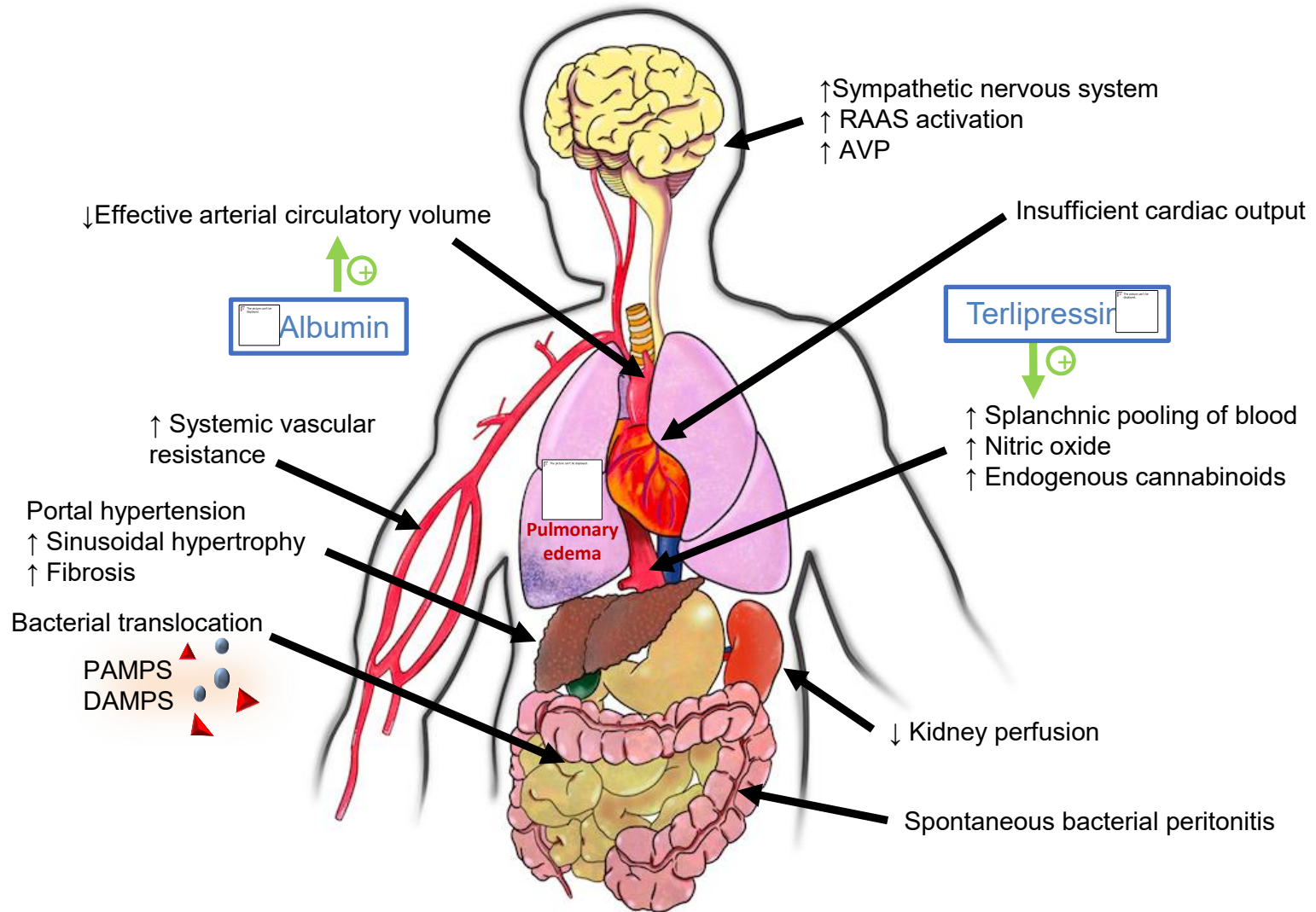
WARNING: SERIOUS OR FATAL RESPIRATORY FAILURE

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., SpO₂) before initiating TERLIVAZ.

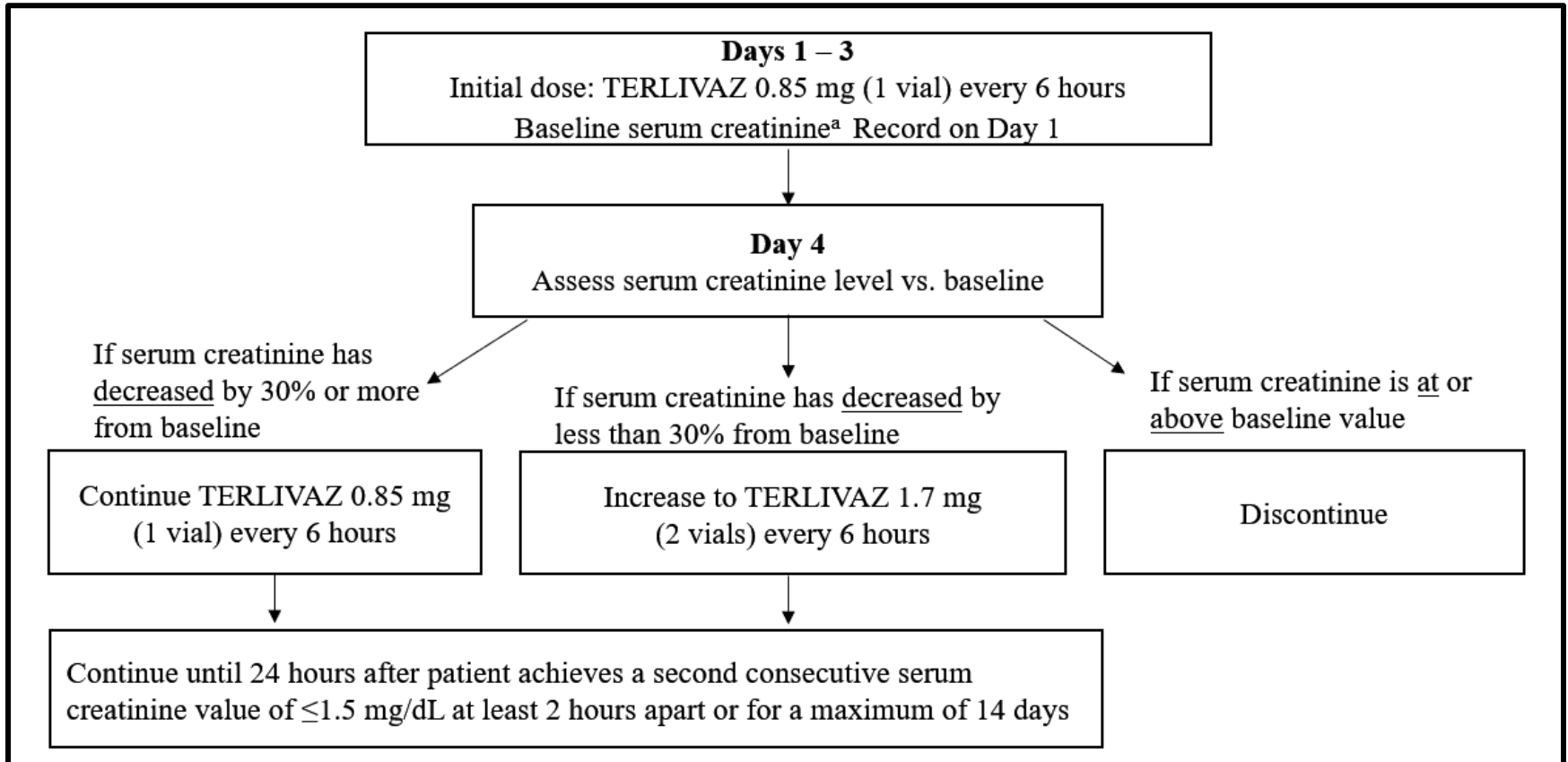
Do not initiate TERLIVAZ in patients experiencing hypoxia (e.g., SpO₂ <90%) until oxygenation levels improve. Monitor patients for hypoxia using continuous pulse oximetry during treatment and discontinue TERLIVAZ if SpO₂ decreases below 90% (2.1, 4, 5.1).



Terlipressin's Adverse Events and Albumin Dosing



Terlipressin Dosing



Continuous Terlipressin Algorithm

Terlipressin continuous infusion dosing in adults for hepatorenal syndrome-acute kidney injury (HRS-AKI)

Days 1 and 2:

- Record day 1 serum creatinine (FN1)
- Administer continuous IV infusion of terlipressin acetate 2 mg/day (terlipressin 1.7 mg/day) (FN2)
- At any time during treatment course, stop terlipressin if any discontinuation criteria are met (refer to Inset)

Inset: Terlipressin discontinuation criteria:

- No improvement in serum creatinine after three days of therapy
- Serum creatinine improved to within 0.3 mg/dL of baseline
- Serious adverse reaction
- Initiation of kidney replacement therapy
- Liver transplantation
- Total duration of therapy 14 days

Day 3: Assess serum creatinine and compare with day 1 value.
Has creatinine decreased by $\geq 25\%$?

No

Increase continuous infusion dose to terlipressin acetate 4 mg/day
(terlipressin 3.4 mg/day)

Yes

Continue current terlipressin dose

Day 4: Assess serum creatinine and compare with day 1 value.
Is creatinine $\geq$ day 1 value?

No

Yes

Stop terlipressin

On day 5, and then every two days following, assess serum creatinine
and compare with the value from two days prior.

Over the two day interval, has creatinine decreased by $\geq 25\%$?

Yes

Continue current terlipressin dose

No

Increase terlipressin acetate dose by 2 mg/day (terlipressin dose by 1.7 mg/day) in
a stepwise fashion to a maximum dose of terlipressin acetate 12 mg/day
(terlipressin 10.2 mg/day).

Stop terlipressin after 14 days or when any
discontinuation criteria are met (refer to inset)

HARMONY (US real world terlipressin) vs CONFIRM (clinical trial)

	HARMONY N = 243	CONFIRM N = 199
AE Definition	Adverse event leading to terli discontinuation	Serious Adverse Event (SAE)
HRS Reversal	30.9%	31.7%
Abdominal Pain	3.3%	5%
Respiratory Failure	9.5%	10%
Ischemia	1.2%	<2%
Bradycardia	2.5%	<2%
Death by 90 days	40.5%	51%
MELD (1.0) at terli initiation	32	32.7
Transplant Rate (90 days)	28.4%	23%

Cirrhosis + Indication for Renal Replacement

Already Listed

Not Listed but
Potential Candidate

Contraindication
to Transplant

RRT as bridge to transplant

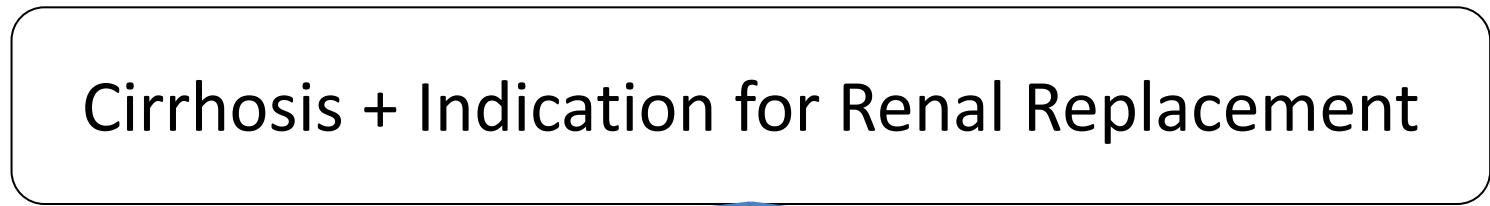
Initiate RRT

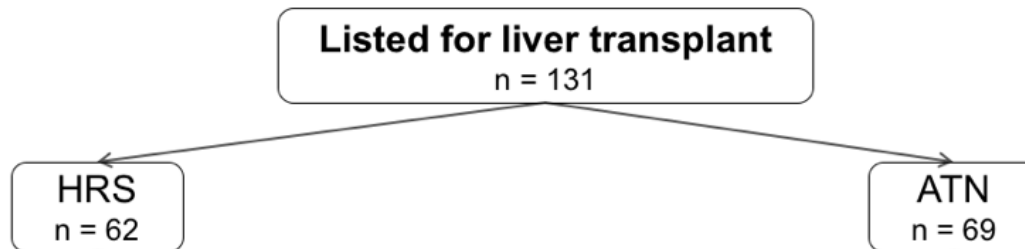
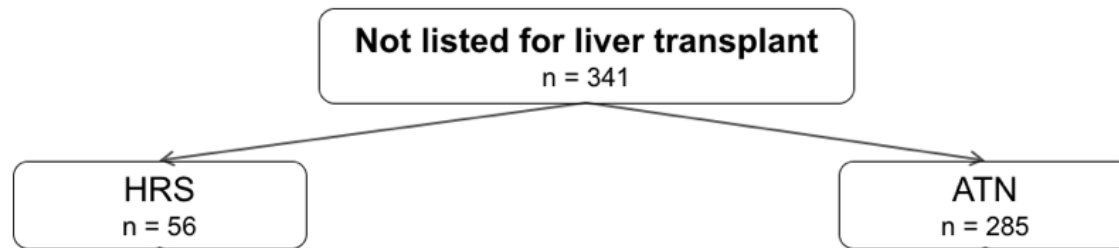
Expedited transplant workup

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?





Cirrhosis + Indication for Renal Replacement

Already Listed

RRT as bridge to transplant

Initiate RRT

Not Listed but
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Expedited transplant workup

Initiate RRT

Contraindication
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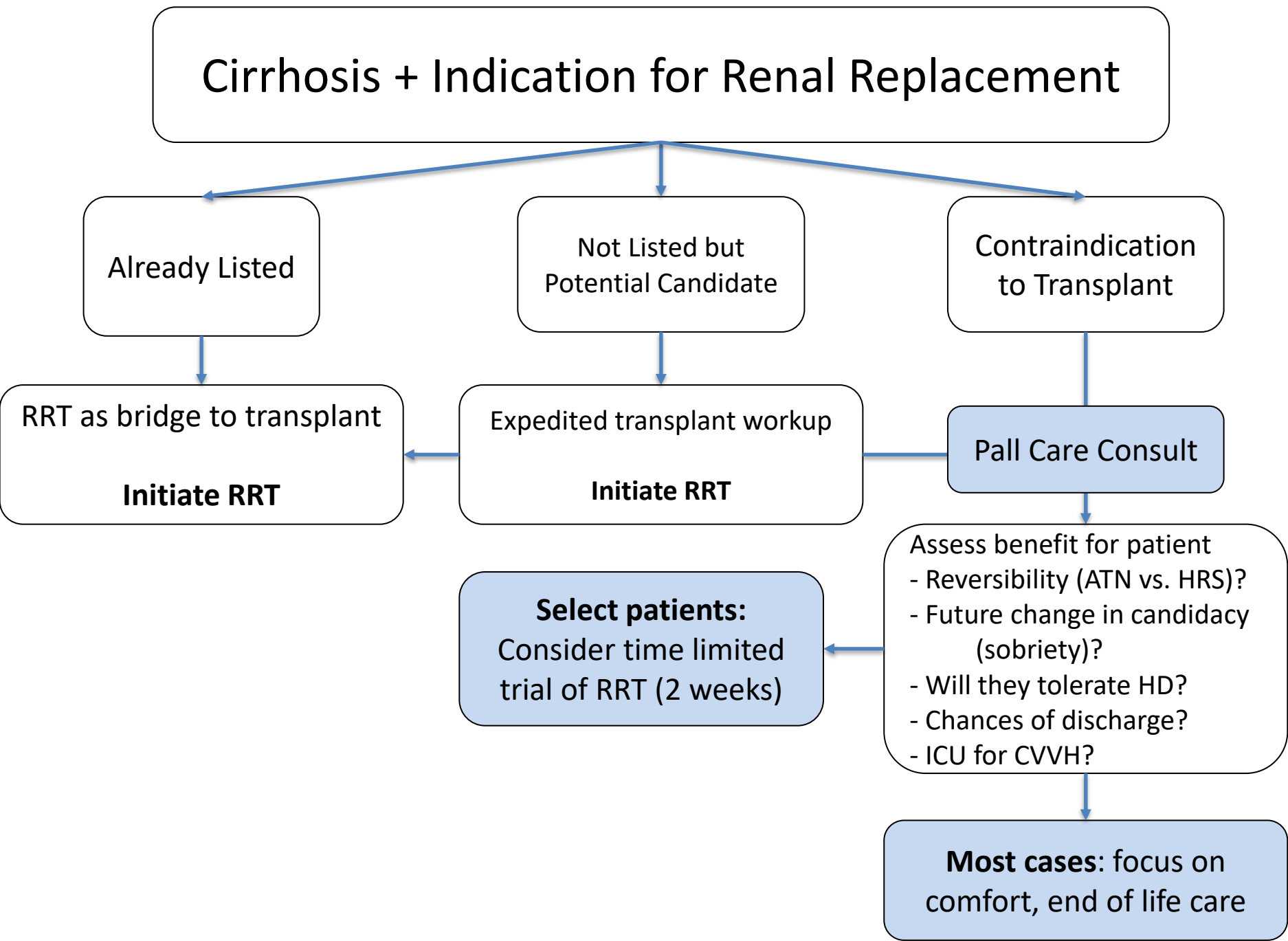
Pall Care Consult

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

2017 SLK 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

99%

Take Home Messages

- AKI in cirrhosis has high mortality regardless of cause.
- Diagnostic criteria for HRS are meant to guide your clinical suspicion, though overlap exists between HRS and ATN.
- HRS-AKI is largely a hemodynamic insult and first line treatment is terlipressin, where available, but should be used after a risk/benefit assessment.

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 considered 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

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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