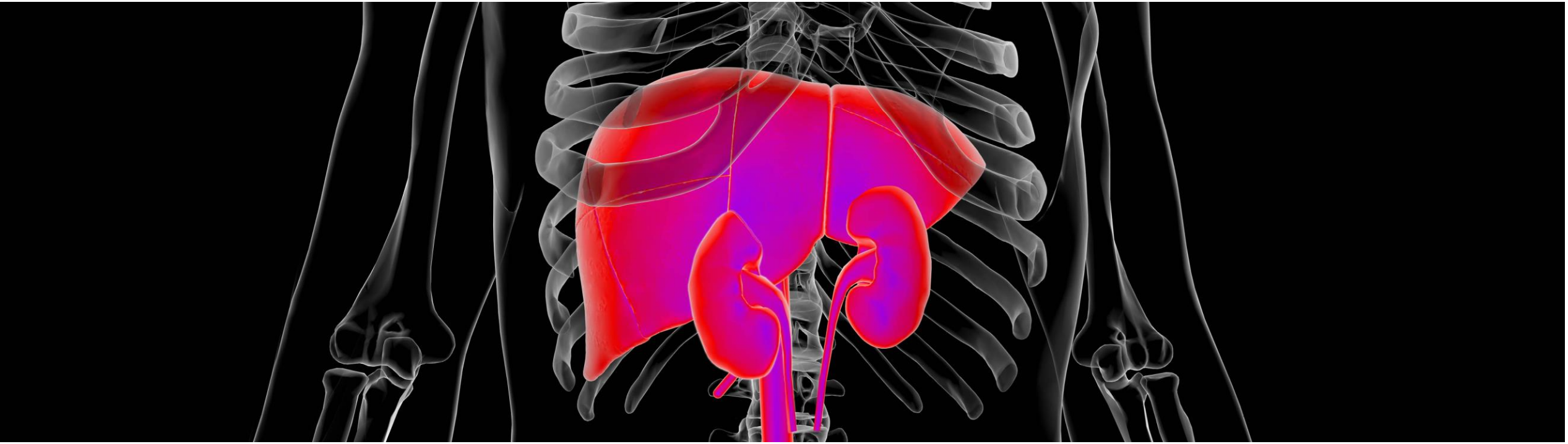
AKI in LIVER FAILURE



Dr. Shahrokh Ezzatzadegan

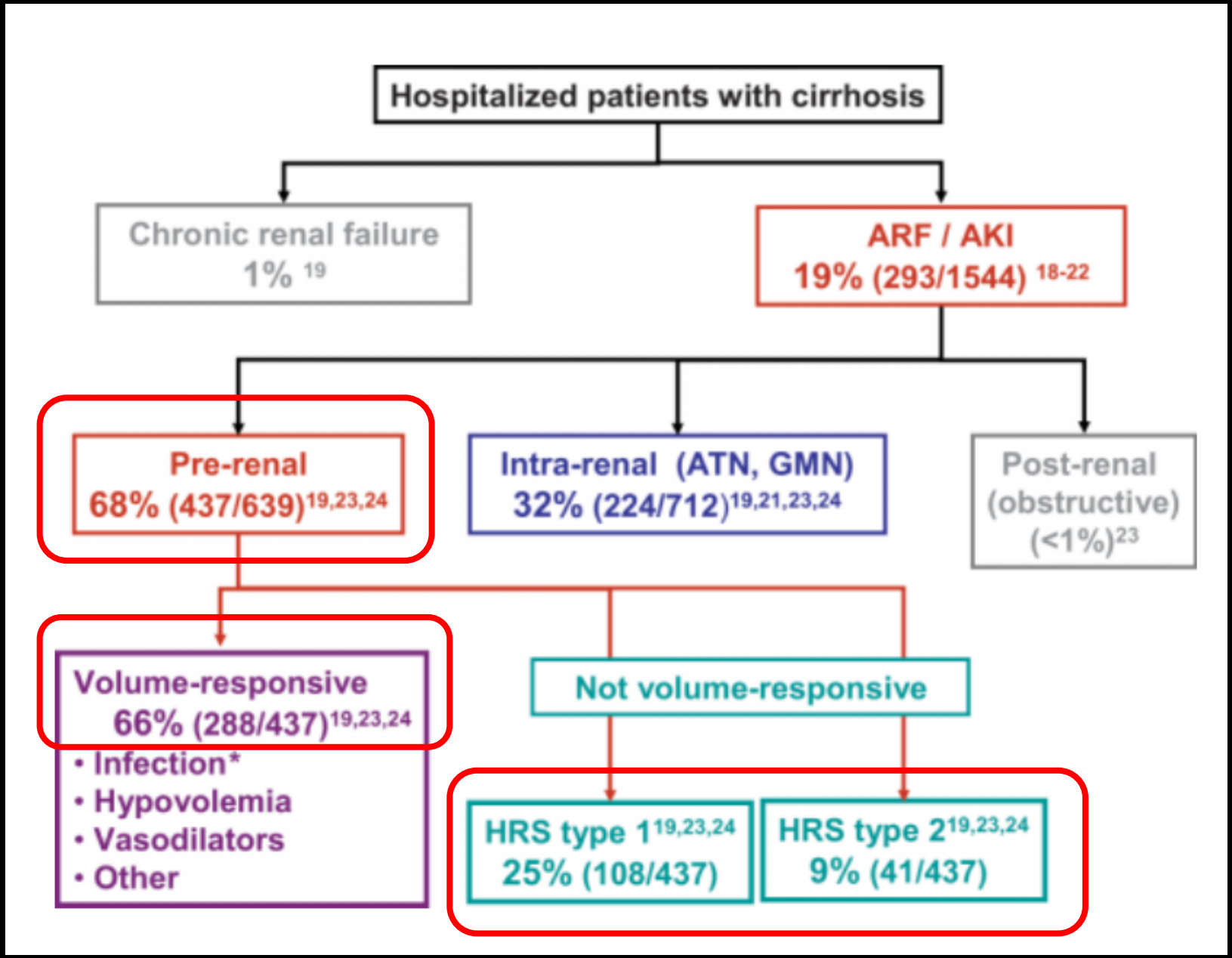
Associate Professor of Medicine

Shiraz University Of Medical Sciences

Outline

- Definition of kidney dysfunction in patients with cirrhosis
- Prevention and work-up
- Management

- Prevalence and types of AKI in hospitalized patients with cirrhosis

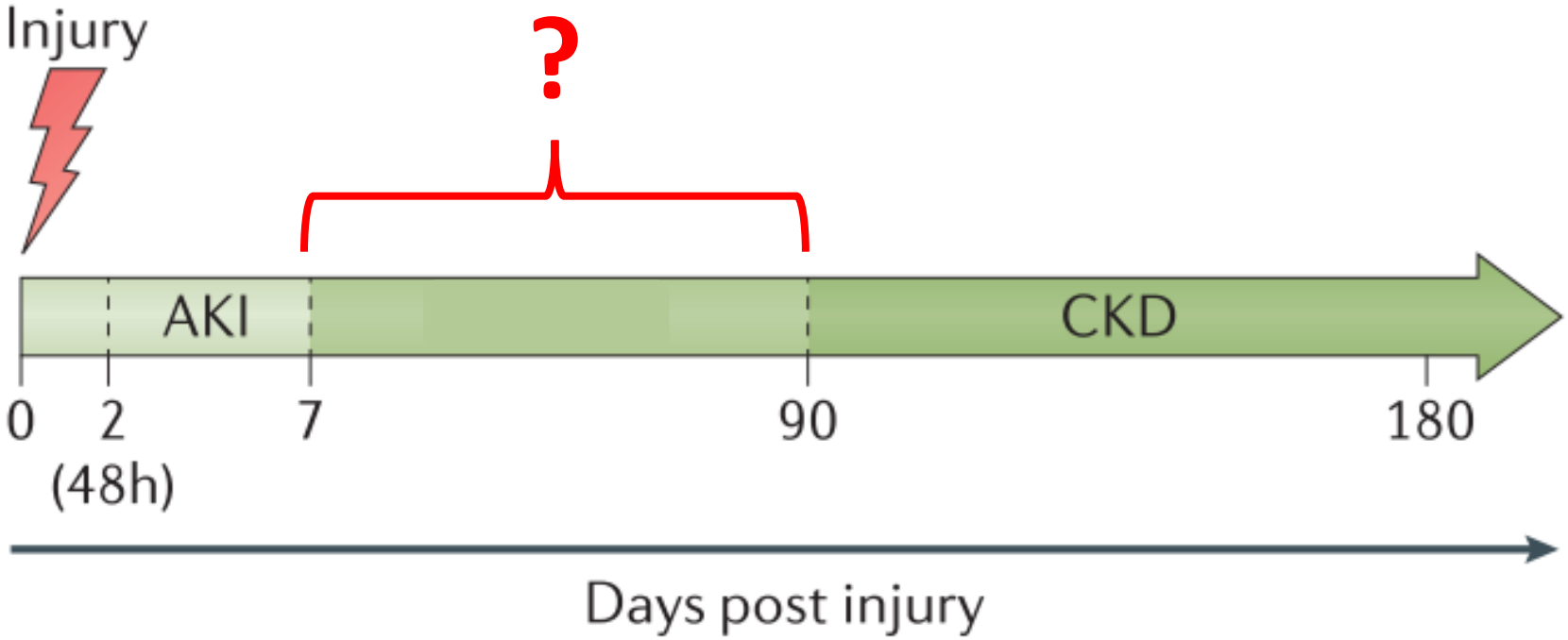


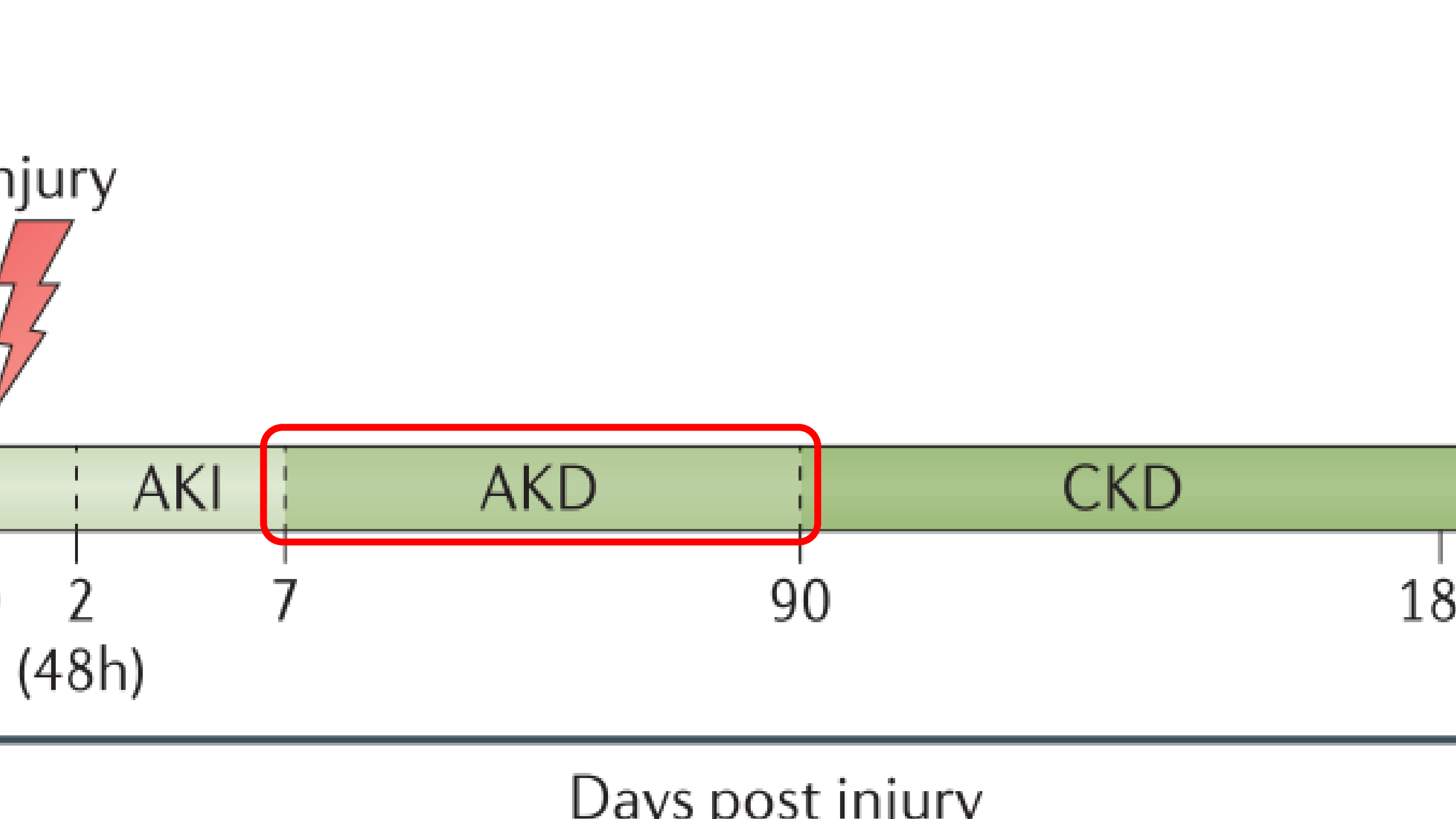
Acute kidney injury in cirrhosis. Hepatology. 2008;48(6):2064-77.

Section 2: AKI Definition

2.1.1: AKI is defined as any of the following (*Not Graded*):

- Increase in SCr by $\geqslant$0.3 mg/dl ($\geqslant$26.5 µmol/l) within 48 hours; or
- Increase in SCr to $\geqslant$1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or
- Urine volume $<$0.5 ml/kg/h for 6 hours.


Injury
?
AKI
CKD
0
2
(48h)
7
90
180
Days post injury


njury
AKI
AKD
CKD
2
7
90
18
(48h)
Days post injury

CONSENSUS STATEMENT

NATURE REVIEWS | NEPHROLOGY

OPEN

EXPERT CONSENSUS DOCUMENT

Acute kidney disease and renal recovery: consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup

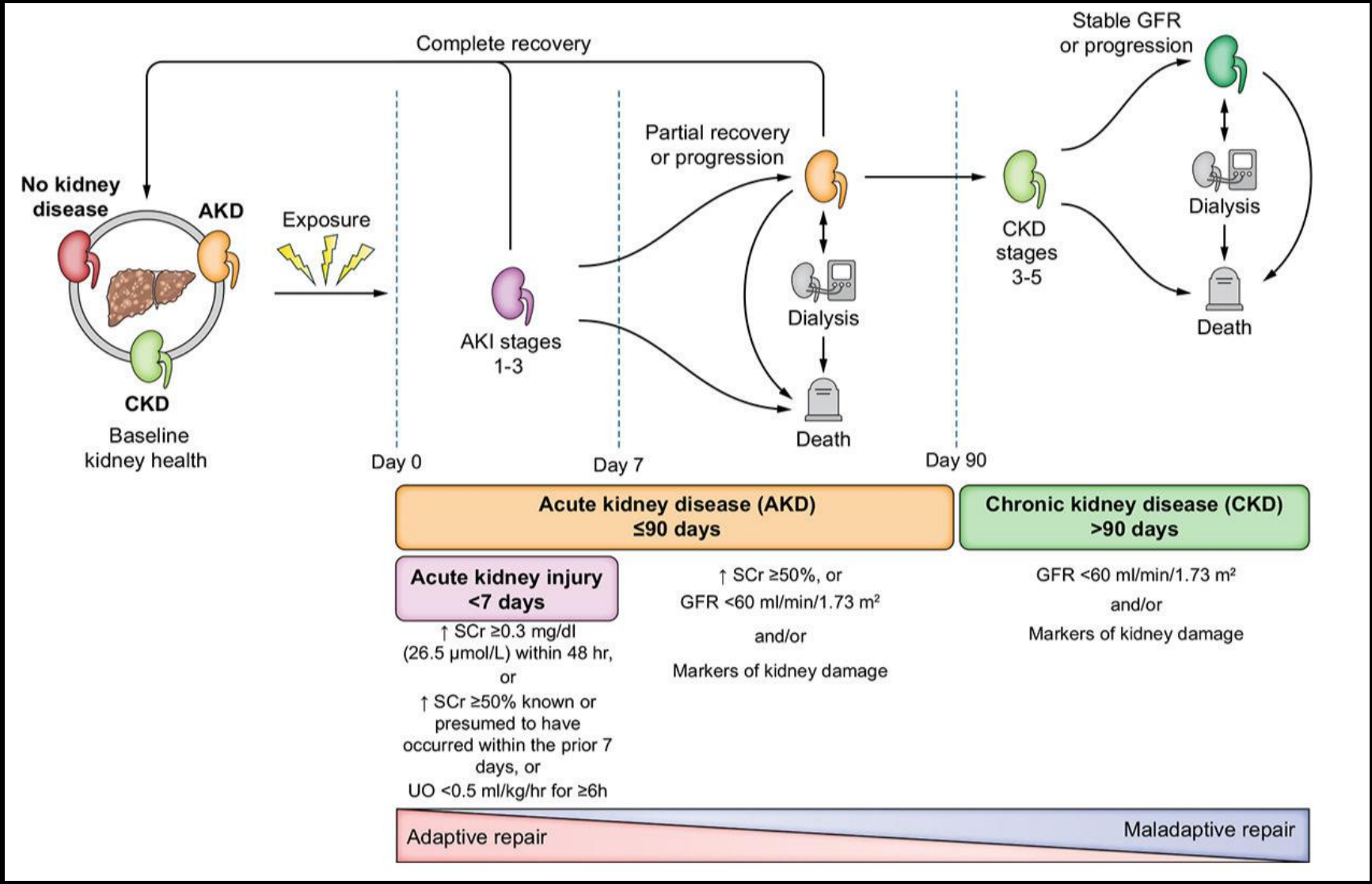
Box 3 | Definition of AKD and recovery from AKD

Consensus statement 2A:

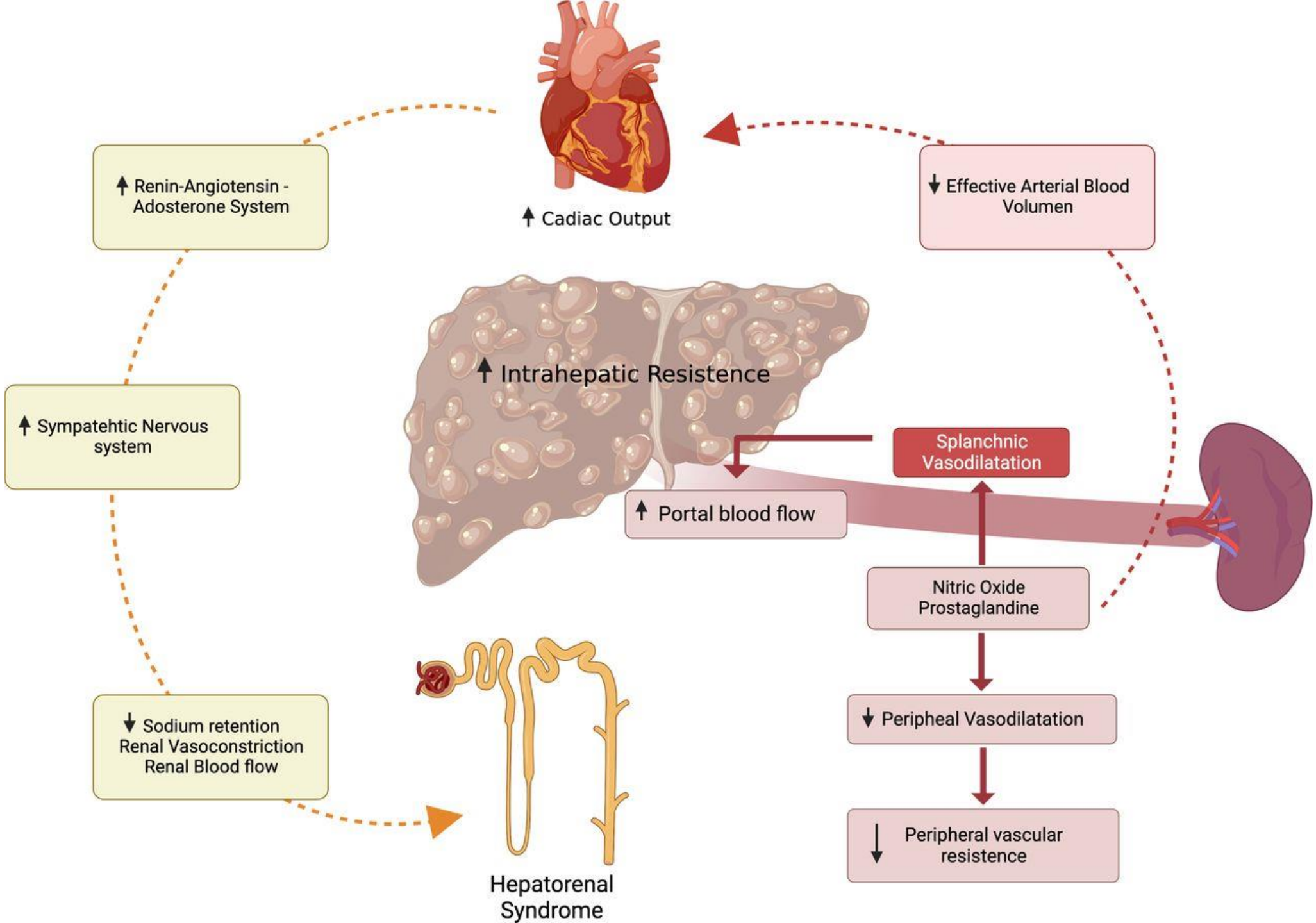
- Acute kidney disease (AKD) describes acute or subacute damage and/or loss of kidney function for a duration of between 7 and 90 days after exposure to an acute kidney injury (AKI) initiating event.

Nat Rev Nephrol. 2017;13(4):241-57

Clinical Course And Outcomes of AKI In Patients With Cirrhosis

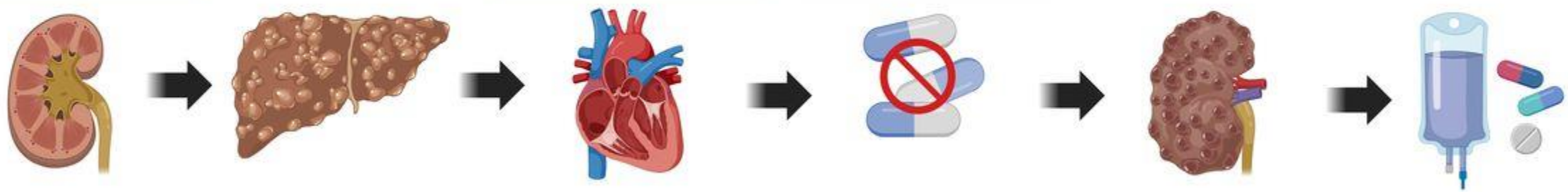


Journal of Hepatology. 2024;81(1):163-83.


↑ Renin-Angiotensin - Adosterone System
↑ Cadiac Output
↓ Effective Arterial Blood Volumen
↑ Sympatehtic Nervous system
↑ Intrahepatic Resistence
Splanchnic Vasodilatation
↑ Portal blood flow
Nitric Oxide Prostaglandine
↓ Sodium retention Renal Vasoconstriction Renal Blood flow
↓ Peripheal Vasodilatation
↓ Peripheral vascular resistence
Hepatorenal Syndrome

HRS-AKI Diagnosis

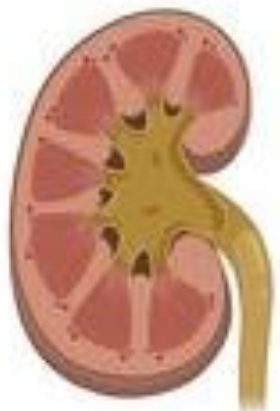
1	2	3	4	5	6
Diagnosis of AKI according to ICA-AKI criteria	**Cirrhosis with ascites**	**Absence of shock**	**No Current or recent use of nephrotoxic drugs**	**Absence of parenchymal disease**	**No complete response**
• Increase in sCr ≥0.3 mg/dl (≥26.5 µmol/L) within 48 hours. • Increase sCr ≥50% from baseline • Urine outpute < 0.5 mL/kg/ hr for 6 hours	• Diagnosis of Cirrhosis with presence of ascites.	• Absence of clinical signs of shock of any kind	• NSAIDS • Antibiotics • Diuretics • Other nephrotoxic drugs	• No proteinuria • No Hematuria • No urinary cast • Normal kidney ultrasound	No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin (1 g/kg of body weight)



1

Diagnosis of AKI according to ICA-AKI criteria

- Increase in sCr ≥0.3 mg/dl (≥26.5 µmol/L) within 48 hours.
- Increase sCr ≥50% from baseline
- Urine outpute < 0.5 mL/kg/hr for 6 hours



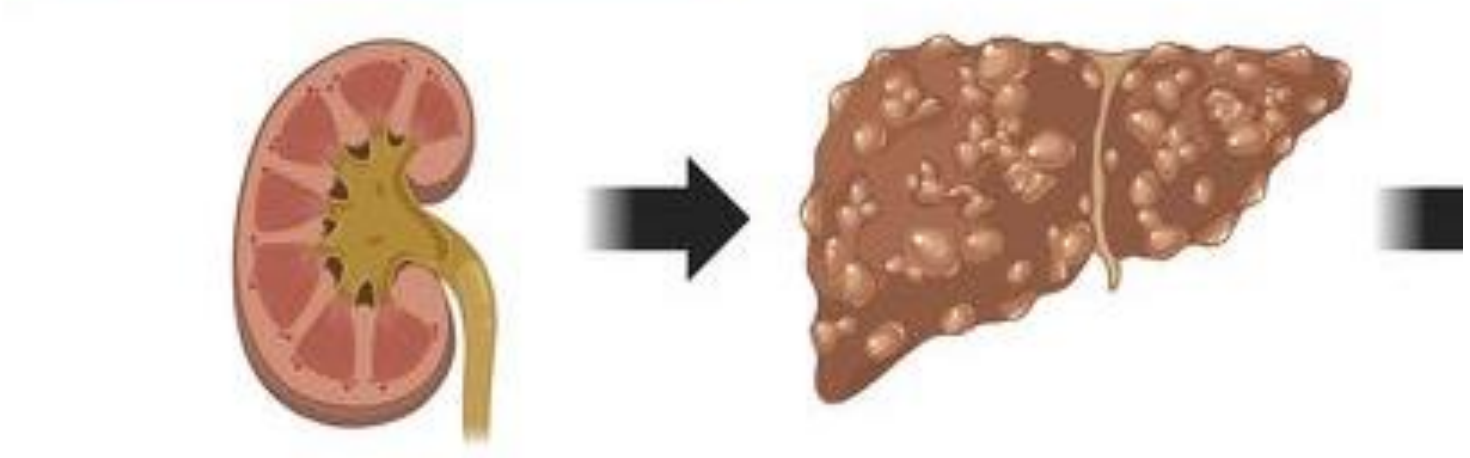
1

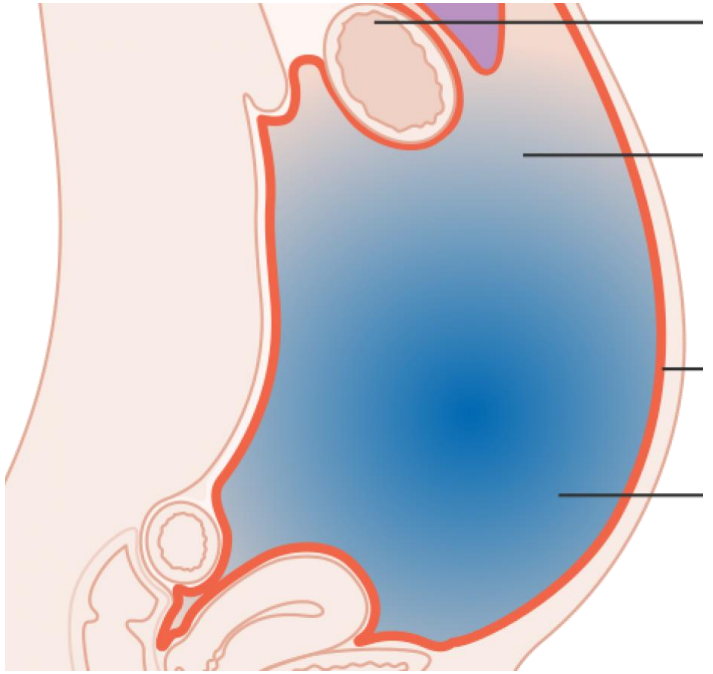
Diagnosis of AKI according to ICA-AKI criteria

2

Cirrhosis with ascites

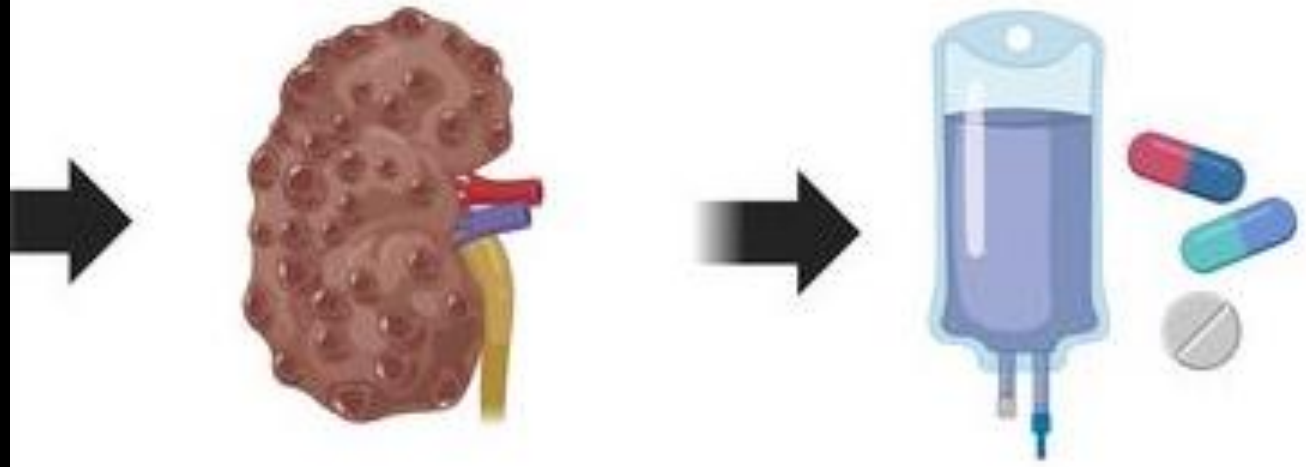
Cirrhosis with ascites is a sine qua non in the diagnosis of HRS





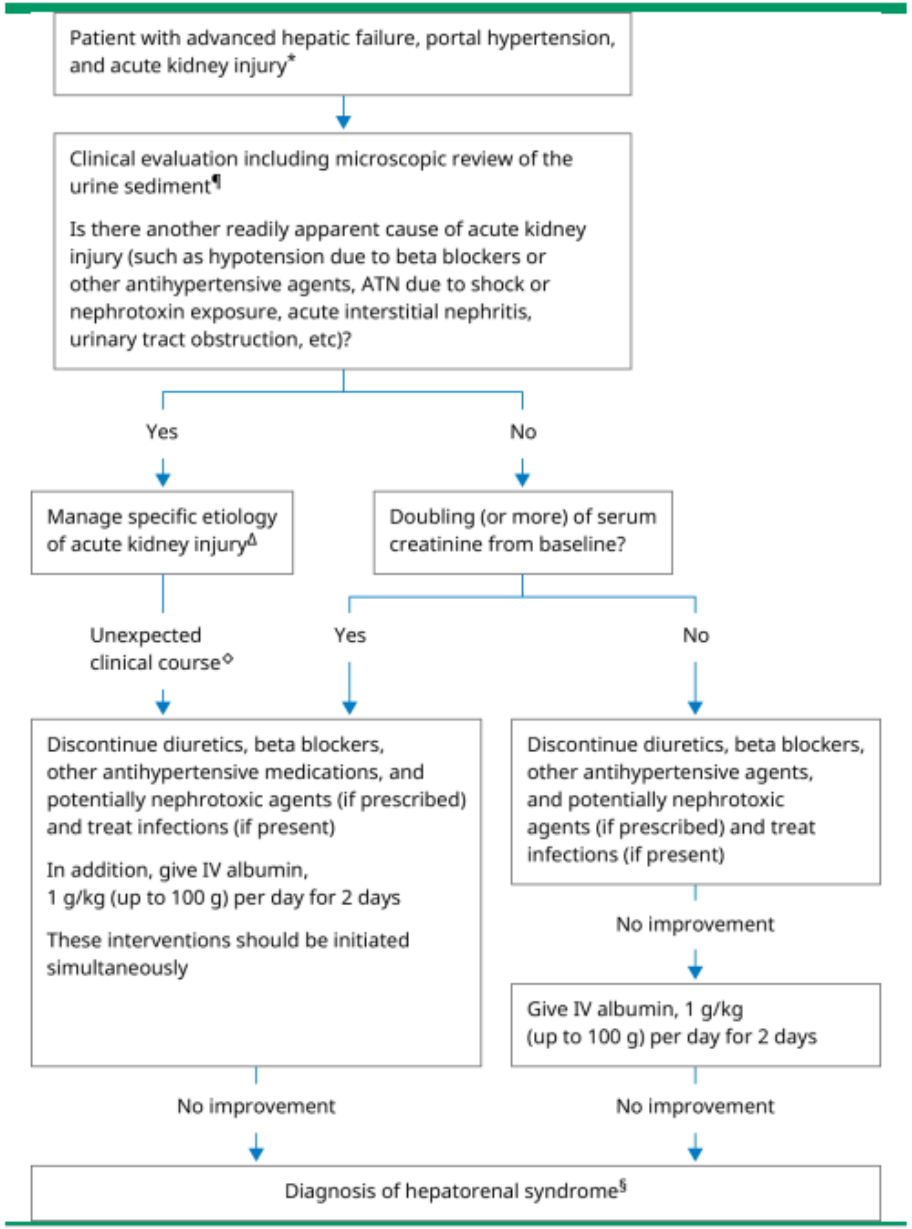
Journal of Hepatology. 2024;81(1):163-83.

Absence of parenchymal disease	No complete response
• No proteinuria • No Hematuria • No urinary cast • Normal kidney ultrasound	No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin (1 g/kg of body weight)



UpToDate®

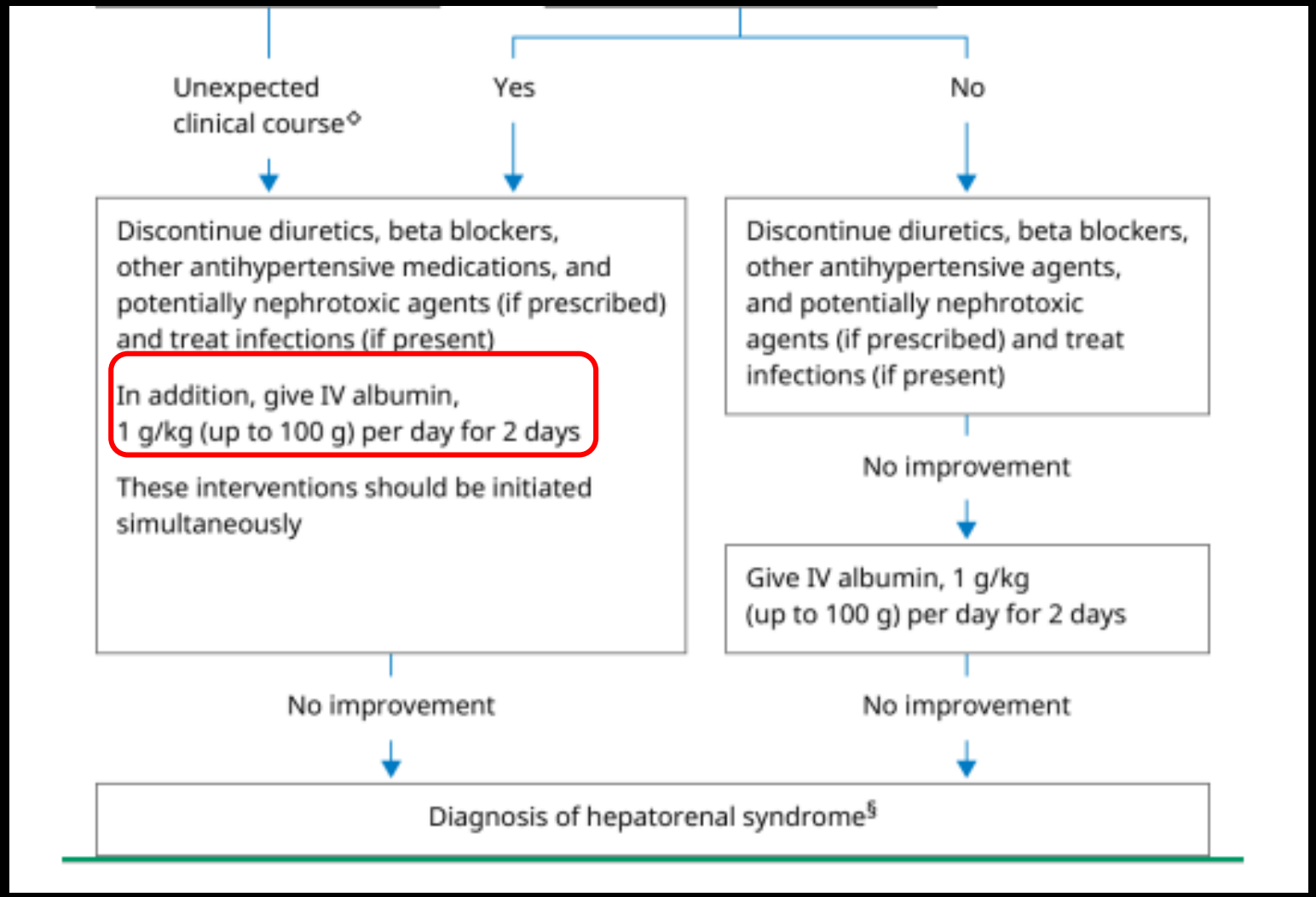
Diagnosis of hepatorenal syndrome



UpToDate®


MAN ALBUMIN 20%


48H


Unexpected clinical course◇
Yes
No
Discontinue diuretics, beta blockers, other antihypertensive medications, and potentially nephrotoxic agents (if prescribed) and treat infections (if present)
In addition, give IV albumin, 1 g/kg (up to 100 g) per day for 2 days
These interventions should be initiated simultaneously
Discontinue diuretics, beta blockers, other antihypertensive agents, and potentially nephrotoxic agents (if prescribed) and treat infections (if present)
No improvement
Give IV albumin, 1 g/kg (up to 100 g) per day for 2 days
No improvement
No improvement
Diagnosis of hepatorenal syndrome§

Published in final edited form as:
J Hepatol. 2024 July ; 81(1): 163–183. doi:10.1016/j.jhep.2024.03.031.

Acute kidney injury in patients with cirrhosis: Acute Disease Quality Initiative (ADQI) and International Club of Ascites (ICA) joint multidisciplinary consensus meeting

Mitra K. Nadim[1], **John A. Kellum**[2], **Lui Forni**[3], **Claire Francoz**[4], **Sumeet K. Asrani**[5], **Marlies Ostermann**[6], **Andrew S. Allegretti**[7], **Javier A. Neyra**[8], **Jody C. Olson**[9], **Salvatore Piano**[10], **Lisa B. VanWagner**[11], **Elizabeth C. Verna**[12], **Ayse Akcan-Arikan**[13], **Paolo Angeli**[14], **Justin M. Belcher**[15,16], **Scott W. Biggins**[17], **Akash Deep**[18], **Guadalupe Garcia-Tsao**[19,16], **Yuri S. Genyk**[20,21], **Pere Gines**[22], **Patrick S. Kamath**[23], **Sandra L. Kane-Gill**[24], **Manish Kaushik**[25], **Nuttha Lumlertgul**[26], **Etienne Macedo**[27], **Rakhi Maiwall**[28], **Sebastian Marciano**[29], **Raimund H. Pichler**[30], **Claudio Ronco**[31], **Puneeta Tandon**[32], **Juan-Carlos Q. Velez**[33,34], **Ravindra L. Mehta**[35], **François Durand**[4,36,*]

International Club of Ascites (ICA)

ADQI

Acute Disease Quality Initiative

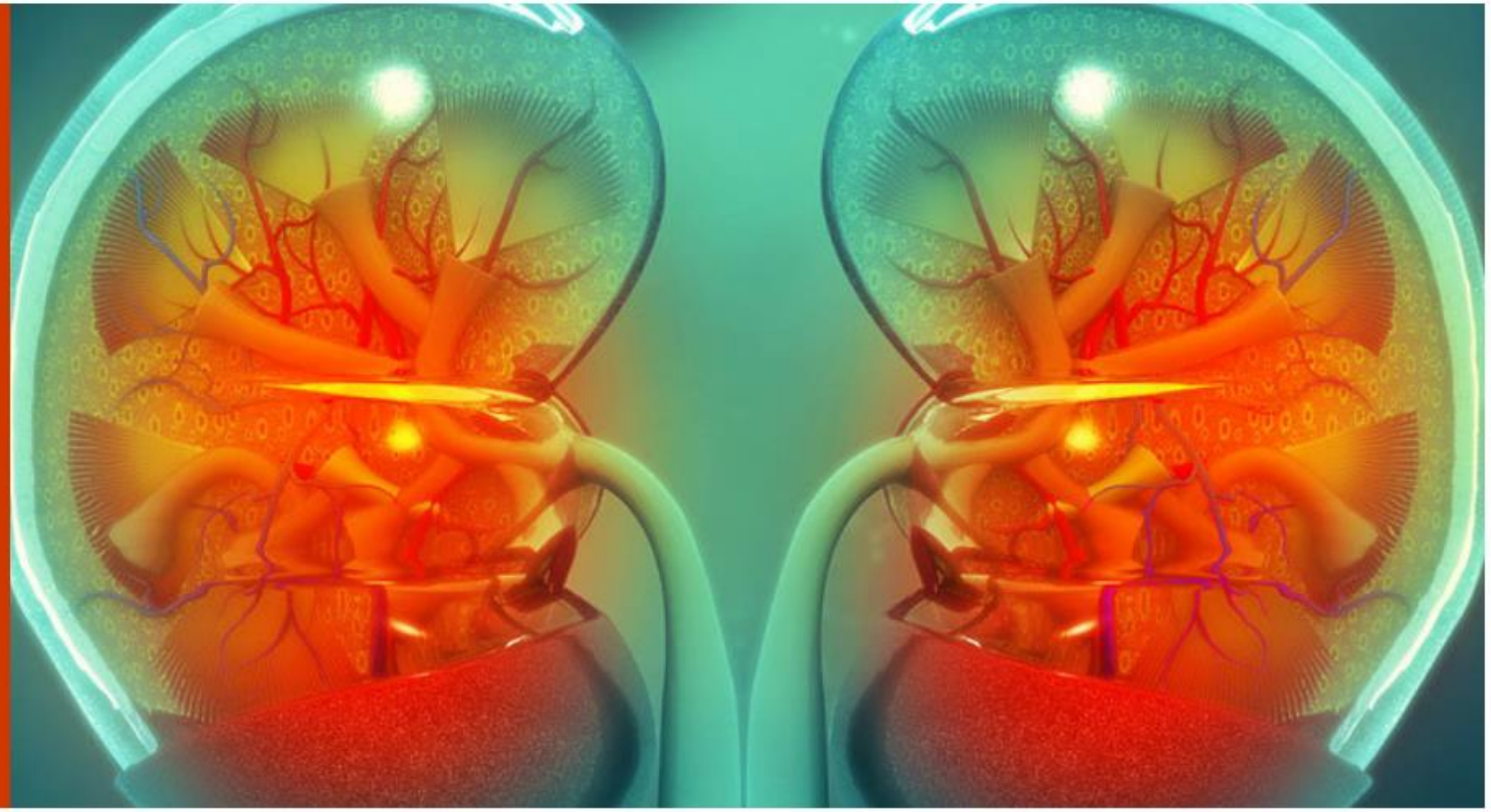
WWW.ADQI.ORG

About ADQI | Conferences | Publications | Images

Acute Disease Quality Initiative

A non-profit, member-run organization providing objective, dispassionate distillation of literature as it relates to the current state of practice of diagnosis and management of acute kidney injury and other conditions in critical care nephrology.

LEARN MORE



What are the diagnostic criteria for AKI due to HRS (HRS-AKI)?

Consensus statements

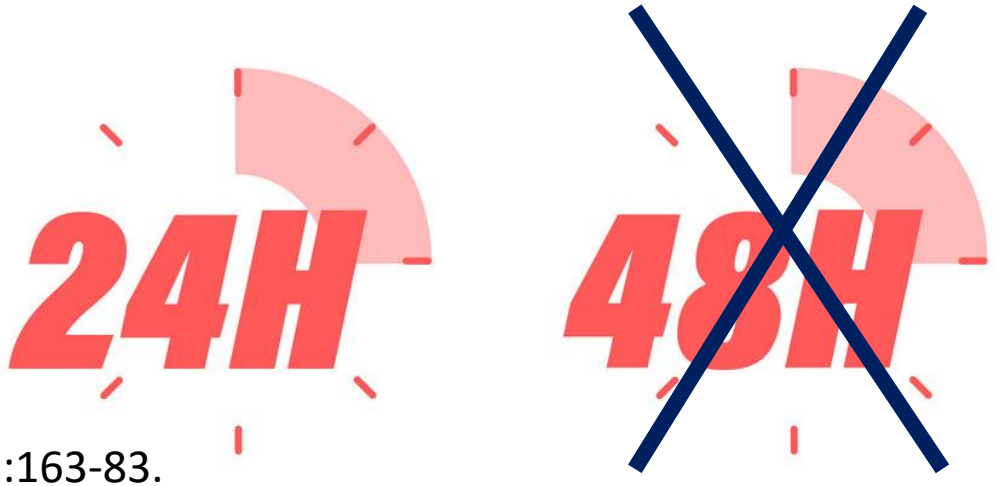
- HRS-AKI is a phenotype of AKI that is specific to patients with advanced cirrhosis and ascites; it may also occur in the presen[illegible]f tubular injury, proteinuria, and/or pre-existing CKD **(not graded).**
- We recommend the following diagnostic criteria for [illegible]S-AKI: a) cirrhosis with ascites; b) increase in SCr ≥0.3 mg/dl (26.5 μmol/L) [illegible]in 48 h or ≥50% from baseline value, known or presumed, to have occurred within the prior 7 days and/or UO ≤0.5 ml/kg for ≥6 h; c) absence of improvement in SCr and/or UO within 24 h following adequate volume resuscitation (when clinically indicated); and d) absence of strong evidence for an alternative explanation as the primary cause of AKI **(not graded).**
- We recommend against systematic administration of albumin for 48 h as a requisite for the diagnosis of HRS-AKI **(strong recommendation, grade D).**

Journal of Hepatology. 2024;81(1):163-83.

Evidence of intravascular volume depletion

Assessment of response to fluid resuscitation should be completed within 24 h

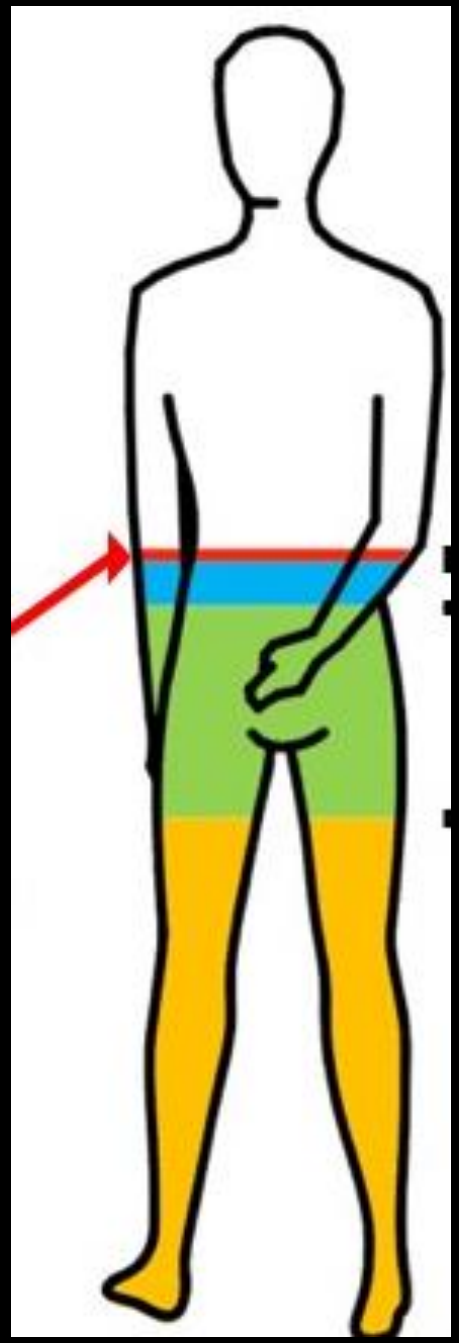
To ensure early diagnosis and initiation of treatment for HRS-AKI



Journal of Hepatology. 2024;81(1):163-83.

Where volume status is equivocal and/or difficult to assess

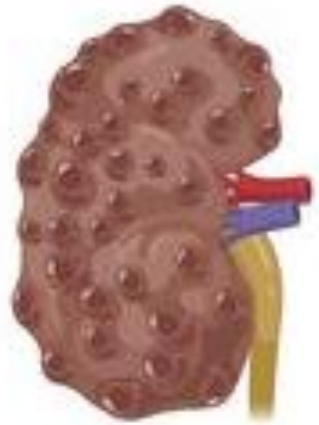
a fluid challenge (250–500 ml of crystalloid or 1–1.5 g/kg of 20–25% albumin



Journal of Hepatology. 2024;81(1):163-83.

Absence of parenchymal disease

- No proteinuria
- No Hematuria
- No urinary cast
- Normal kidney ultrasound



What are the diagnostic criteria for AKI due to HRS (HRS-AKI)?

Consensus statements

- HRS-AKI is a phenotype of AKI that is specific to patients with advanced cirrhosis and ascites; it may also occur in the presence of tubular injury, proteinuria, and/or pre-existing CKD **(not graded).**
- We recommend the following diagnosti iteria for HRS-AKI: a) cirrhosis with ascites; b) increase in SCr ≥0.3 mg/dl (μmol/L) within 48 h or ≥50% from baseline value, known or presumed, to e occurred within the prior 7 days and/or UO ≤0.5 ml/kg for ≥6 h; c) abse of improvement in SCr and/or UO within 24 h following adequate volume resuscitation (when clinically indicated); and d) absence of strong evidence for an alternative explanation as the primary cause of AKI **(not graded).**
- We recommend against systematic administration of albumin for 48 h as a requisite for the diagnosis of HRS-AKI **(strong recommendation, grade D).**

Journal of Hepatology. 2024;81(1):163-83.

Strong evidence for an alternative explanation should be sought

- Septic shock
- Acute glomerular injury
- Obstruction
- Nephrotoxin-induced AKI

Isolated proteinuria

might be related to comorbidities in the patient and pre-existing CKD and/or proteinuria

does not rule out HRS-AKI

Journal of Hepatology. 2024;81(1):163-83.

Box 1.

ICA-ADQI new diagnostic criteria for HRS-AKI.

- Cirrhosis with ascites
- Increase in serum creatinine ≥0.3 mg/dl (26.5 μmol/L) within 48 h or ≥50% from baseline value known or presumed to have occurred within the prior 7 days and/or urinary output ≤0.5 ml/kg for ≥6 h
- Absence of improvement in serum creatinine and/or urine output within 24 h following adequate volume resuscitation (when clinically indicated)
- Absence of strong evidence for an alternative explanation as the primary cause of AKI

Journal of Hepatology. 2024;81(1):163-83.

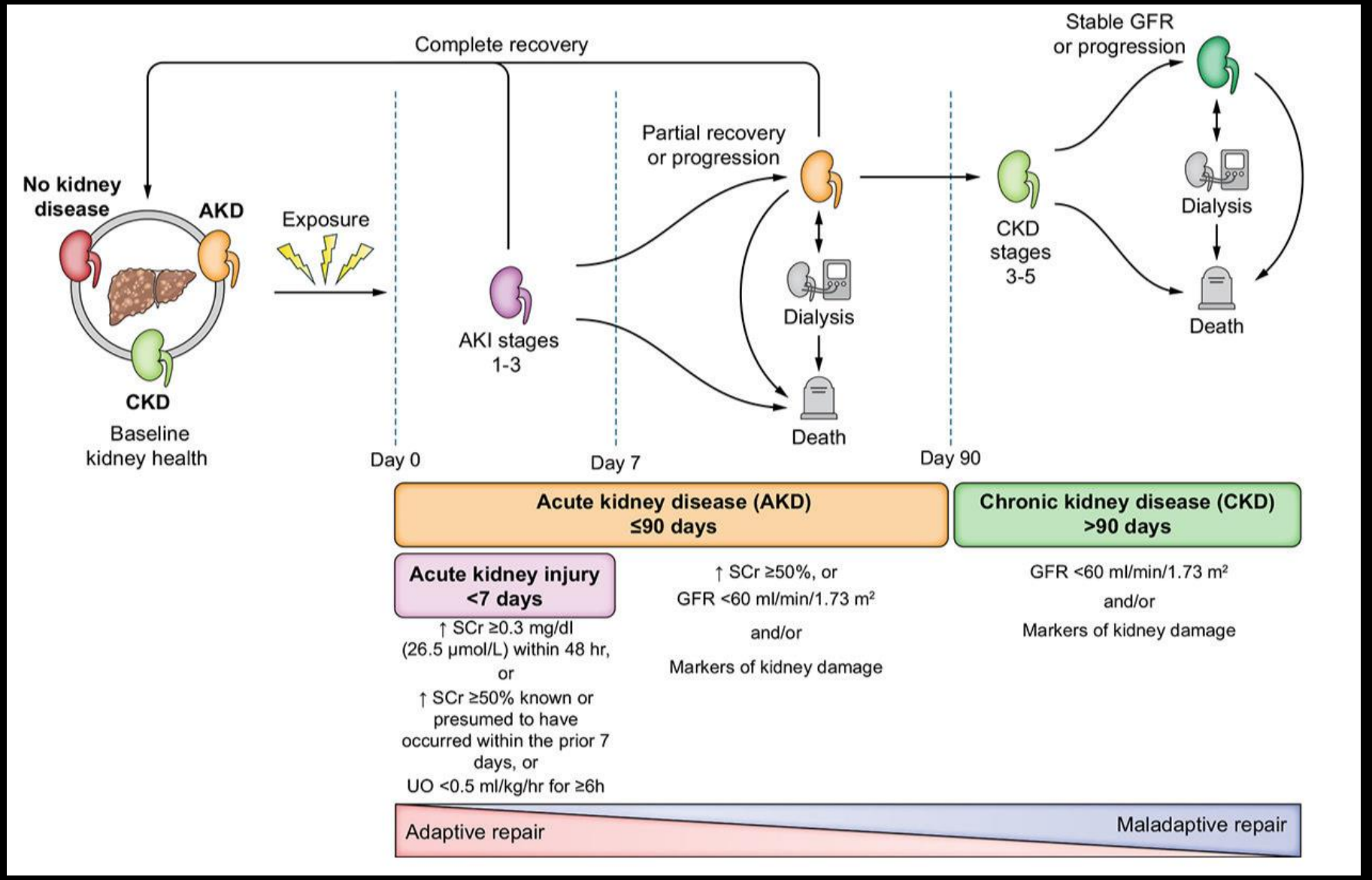
HEPATORENAL SYNDROME

HRS-1

OLD

HRS-2

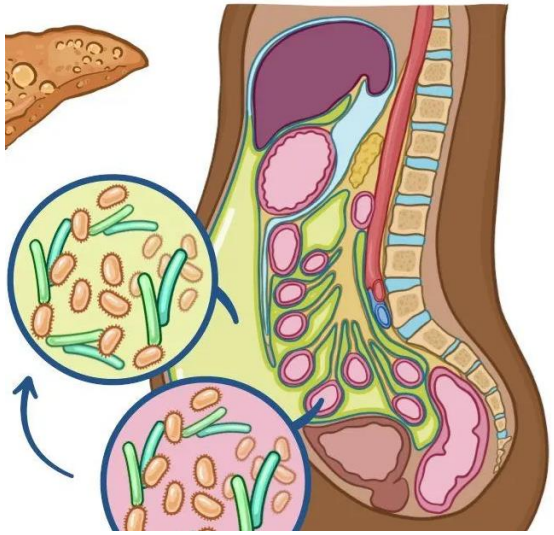
@msocoMD


Complete recovery
Stable GFR or progression
No kidney disease
AKD
Exposure
Partial recovery or progression
CKD stages 3-5
Dialysis
Dialysis
AKI stages 1-3
Death
Death
CKD
Baseline kidney health
Day 0
Day 7
Day 90
Acute kidney disease (AKD) ≤90 days
Chronic kidney disease (CKD) >90 days
Acute kidney injury <7 days
↑ SCr ≥0.3 mg/dl (26.5 µmol/L) within 48 hr, or
↑ SCr ≥50% known or presumed to have occurred within the prior 7 days, or
UO <0.5 ml/kg/hr for ≥6h
↑ SCr ≥50%, or
GFR <60 ml/min/1.73 m²
and/or
Markers of kidney damage
GFR <60 ml/min/1.73 m²
and/or
Markers of kidney damage
Adaptive repair
Maladaptive repair

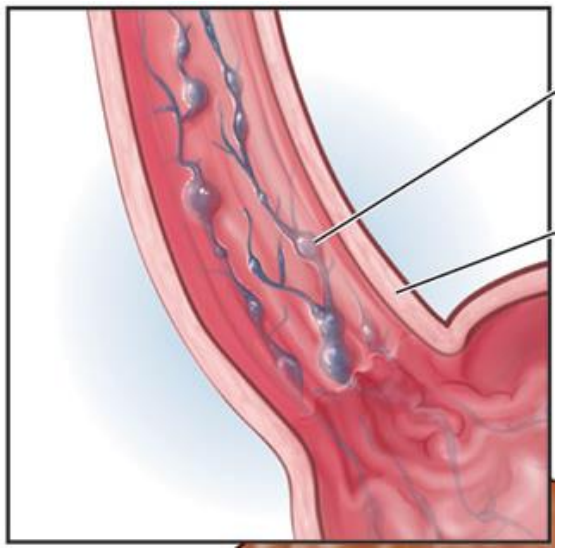
HEPATORENAL SYNDROME

OLD	NEW	CRITERIA	
HRS-1	HRS-AKI		
HRS-2		HRS-AKD: HRS for less than 90 days	HRS-CKD: HRS more than 90 days

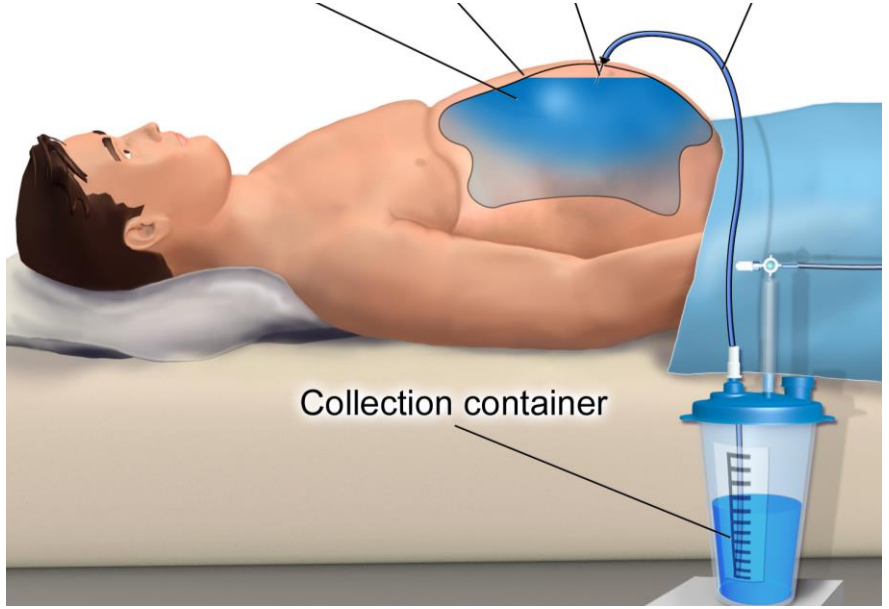
HRS AKI is most often precipitated by



Spontaneous bacterial peritonitis (SBP)



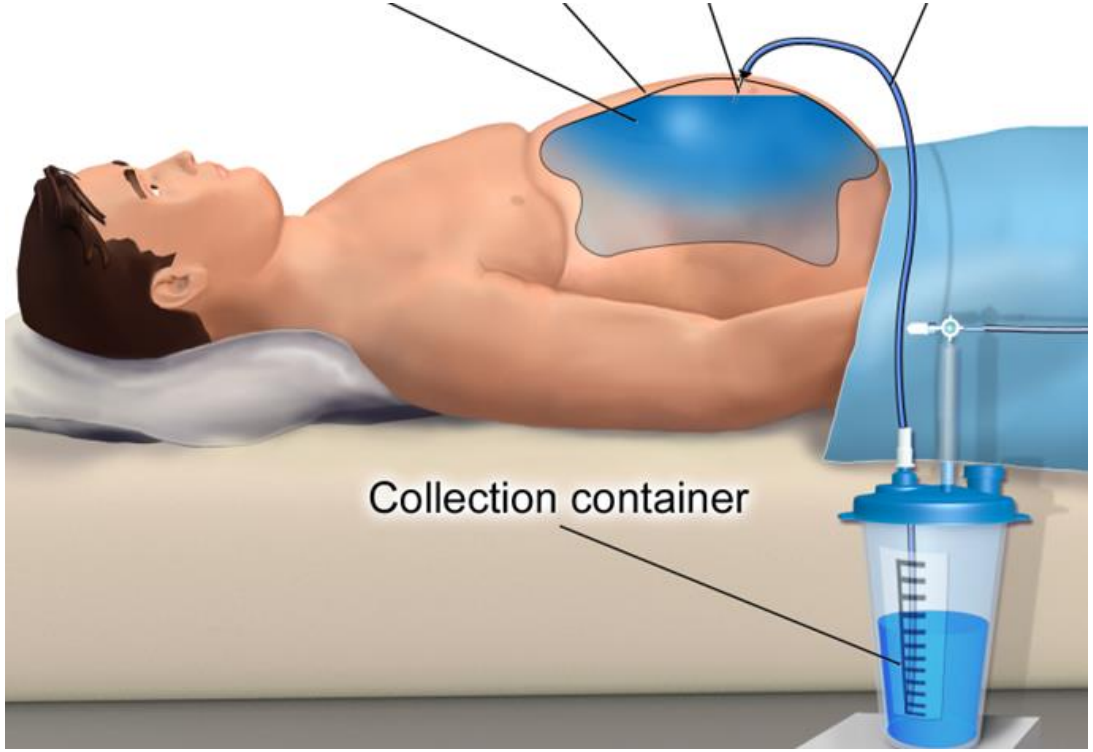
Variceal bleed



Large volume paracentesis (LVP) without sufficient albumin administration

Large volume paracentesis (LVP)

20–25% albumin

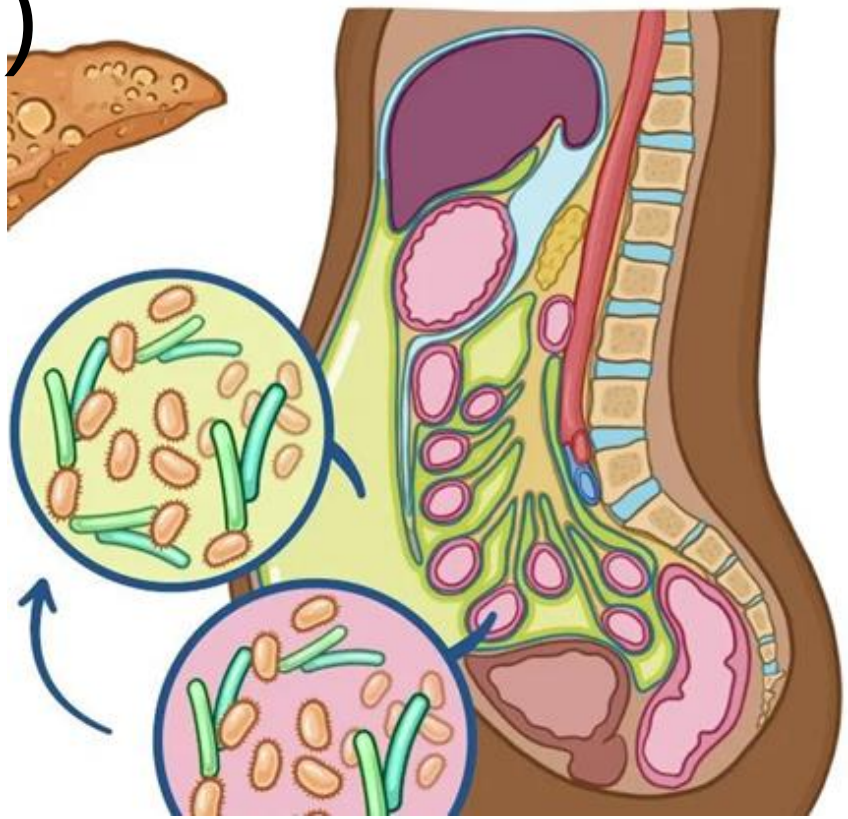


6–8 g for every liter over 5 L of ascites removed

Hepatology. 2012;55(4):1172-81.

Spontaneous bacterial peritonitis (SBP)

20 % albumin



1.5 g/kg on day 1 and
1.0 g/kg on day 3

N Engl J Med. 1999;341(6):403-9

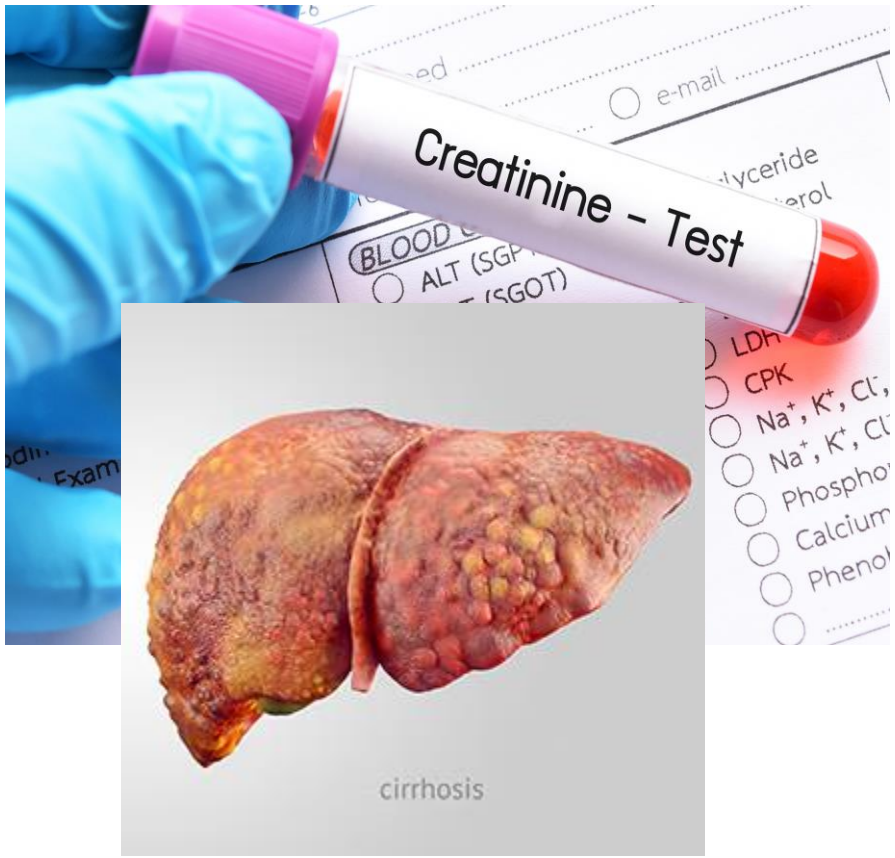
Not recommend albumin in patients with decompensated cirrhosis

- The prevention of AKI in patients with non-SBP infections
- Solely to maintain a serum albumin concentration >3.0 g/dl

Journal of Hepatology. 2024;81(1):163-83.

Serum Creatinine in Cirrhosis

- Diagnosis of AKI may be missed or delayed:
  - Reduced muscle mass
  - Interference with bilirubin
  - Increased volume of distribution in the setting of fluid overload



Liver Int. 2018;38(4):654-64


Creatinine vs
Cystatin C

Serum Cystatin C

- CysC allows for earlier diagnosis of AKI in patients with cirrhosis.
- Useful prognostic marker for renal outcomes and mortality.

Earlier

Liver Int. 2018;38(4):654-64.

Hydration solution in AKI and Cirrhosis

In cases of volume depletion

Crystalloids

preferentially balanced solutions

Lactated ringers or PlasmaLyte

J Hepatol. 2023;79(1):240-6.

Treatment of HRS AKI

The first-line option?

Vasoconstrictive + albumin

20–25% albumin (20–40 g/day)

- Terlipressin
- Norepinephrine
- Midodrine + octreotide

Table 1 | Study design and outcomes of randomized controlled trials of vasoactive drugs for treatment of hepatorenal syndrome-acute kidney injury (HRS-AKI)

Study	Trial design	Drug comparisons (No of patients)	No (%) HRS reversal	No (%) mortality
Terlipressin versus placebo/control				
Solanki et al, 2003[113]	Single center, single blind, placebo controlled	Terlipressin 1 mg every 12 h for 15 days (n=12) *v* placebo (n=12)	NA	Terlipressin 7/12 (58.3) *v* placebo 12/12 (100)
Neri et al, 2008[114]	Single center, open label	Terlipressin 1 mg every 8 h for 5 days followed by 0.5 mg every 8 h for 14 days (n=26) *v* albumin only for 15 days (n=26)	Terlipressin 21/26 (80) *v* control 5/26 (19)	Terlipressin 7/26 (26.9) *v* control: 15/26 (57.7)
Sanyal et al, 2008[115]	Multicenter, double blind, placebo controlled	Terlipressin 1 mg every 6 h up to 2 mg every 6 hours for 14 days (n=56) *v* placebo for 14 days (n=56)	Terlipressin 19/56 (33.9) *v* placebo 7/56 (12.5)	Terlipressin 32/56 (57.1) *v* placebo 35/56 (62.5)
Martin-Llahi et al, 2008[23]	Multicenter, open label	Terlipressin 1 mg every 4 h up to 2 mg every 4 h for 15	Terlipressin 6/17 (35.3) *v*	Terlipressin 17/23 (73.9) *v* control: 19/23 (82.6)
Boyer et al, 2				Terlipressin 32/97 (33) *v* placebo: 35/99 (35.3)
Wong et al, 2				Terlipressin 145/199 (72.9) *v* placebo 72/101 (71.3)
Terlipressin				
Alessandria et al, 2007[118]	Single center, open label	Terlipressin 1 mg every 4 h up to 2 mg every 4 h until HRS reversal or for maximum 14 days (n=4) *v* norepinephrine 0.1 µg/kg/min up to 0.7 µg/kg/min until HRS reversal or maximum 14 days (n=5)	Terlipressin 3/4 (75) *v* norepinephrine 4/5 (80)	Terlipressin 1/4 (25) *v* norepinephrine 1/5 (20)
Sharma et al, 2008[119]	Single center, open label	Terlipressin 0.5 mg every 6 h up to 2 mg every 6 h for 1 days (n=20) *v* norepinephrine 0.5 mg/h up to 3 mg/h fo 15 days (n=20)	Terlipressin 8/20 (40) *v* norepinephrine 10/20 (50)	Terlipressin 9/20 (45) *v* norepinephrine 9/20 (45)
Singh et al, 2012[120]	Single center, open label	Terlipressin 0.5 mg every 6 h up to 2 mg every 6 h until HRS reversal or for maximum 14 days (n=23) *v* norepinephrine 0.5 mg/h up to 3 mg/h until HRS reversal or for maximum 14 days (n=23)	Terlipressin 9/23 (39.1) *v* norepinephrine 10/23 (43.5)	Terlipressin 16/23 (69.5) *v* norepinephrine 15/23 (65.2)
Terlipressin versus midodrine plus octreotide				
Cavallin et al, 2015[121]	Multicenter, open label	Terlipressin 3-12 mg per 24 h until HRS reversal or for maximum 14 days (n=27) *v* midodrine 7.5-12.5 mg every 8 h orally plus octreotide 100-200 µg every 8 h subcutaneously until HRS reversal or for maximum of 14 days (n=22)	Terlipressin 15/27 (55.5) *v* midodrine plus octreotide 1/22 (4.5)	Terlipressin 8/27 (29.6) *v* midodrine plus octreotide 7/22 (31.8)

NA=not available.
*Data published in abstract format.

Terlipressin is the most effective drug treatment for HRS.

Terlipressin

- Acts as a V1 receptor agonist, which leads to vasoconstriction, particularly in the splanchnic circulation.

- The most serious side effects are related to vasoconstriction with a risk of myocardial infarction and intestinal ischemia.

Increasing the dose of terlipressin every 24 h if SCr has not decreased by 25% from baseline

- Dose: IV boluses at starting dose of 1 to 2 mg every four to six hours

Clin J Am Soc Nephrol 14: 774–781, 2019. doi: https://doi.org/10.2215/CJN.12451018

Norepinephrine

- Similar rates of hepatorenal syndrome reversal to terlipressin.
- Central line placement and admission to an ICU are needed for administration.
- IV at a dose of 0.5–3 mg/hr. Increasing the dose of norepinephrine every 4 h if MAP has not increased by 10 mmHg from baseline

Terlipressin plus albumin

significantly more effective than

midodrine and octreotide plus albumin

in improving renal function in patients with HRS

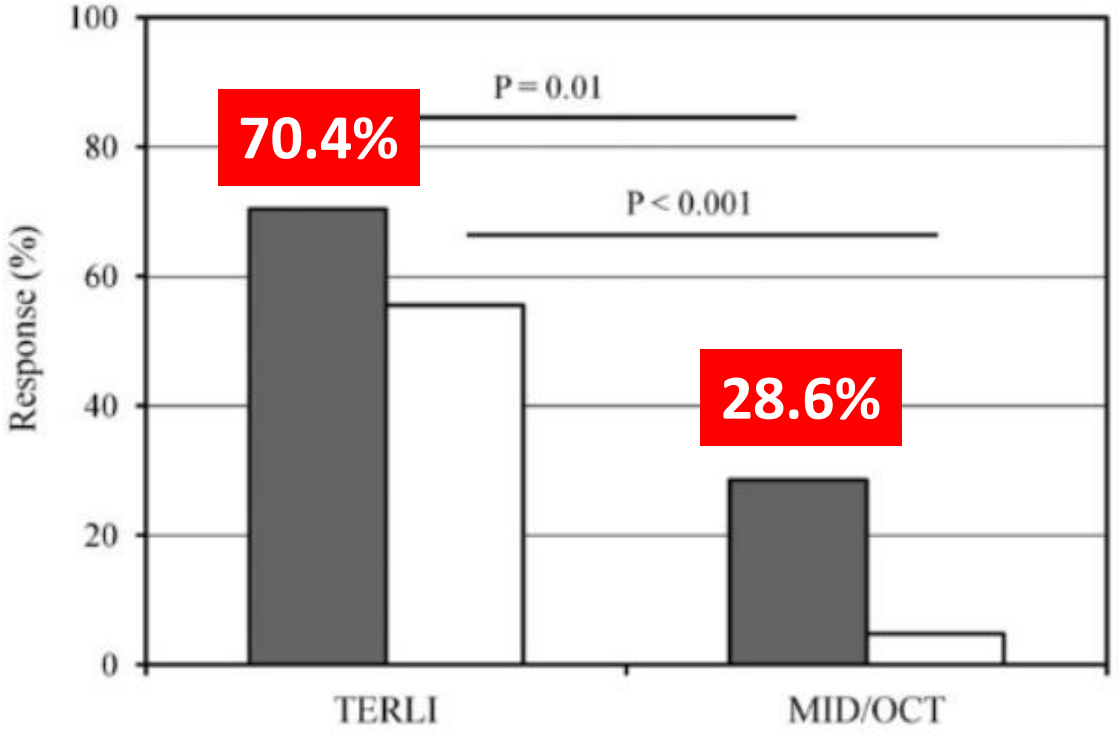


Fig. 2. Rates of response in patients who were randomized to terlipressin plus albumin (TERLI) or to midodrine and octreotide plus albumin (MID/OCT). Gray bars represent patients with complete or partial response; white bars represent patients with complete response.

Hepatology. 2015;62(2):567-74.

Treatment of HRS AKI

The first-line option?

Vasoconstrictive +

There is no improvement in transplant-free survival.

- Terlipressin
- Norepinephrine
- Midodrine + octreotide

Vasoconstrictors should seen as a bridge to transplantation or renal recovery, rather than a definitive cure.

Renal replacement therapy

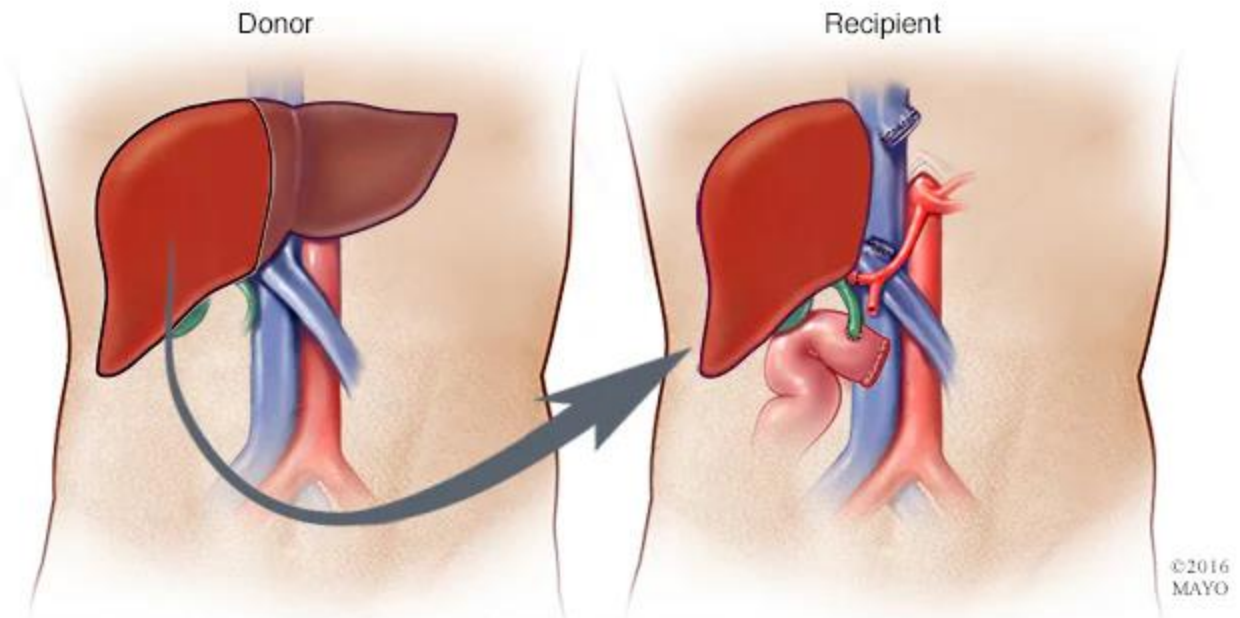
In patients unresponsive to drug treatment and with volume overload, uremia, or electrolyte derangements.

Does not improve survival in hepatorenal syndrome.

It should be reserved for use as a bridge to transplantation when transplantation is an option.

Short term mortality in patients with cirrhosis and AKI who are ineligible for transplantation approaches 90%.

Definitive Treatment




Thanks For Your
Attention