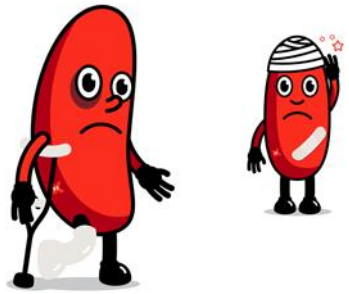

بسم الله الرحمن الرحيم

Acute Kidney Injury in Patients with Cirrhosis

Presented By: Dr.M.Hassanian



- Common condition in patients with cirrhosis
- Up to 50% of hospitalized patients with cirrhosis
- 58% of such patients in ICU
- Associated with high morbidity and mortality and an increased incidence of CKD after liver transplantation

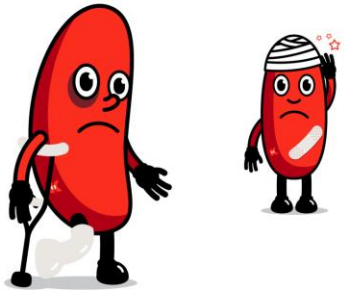
Causes of AKI

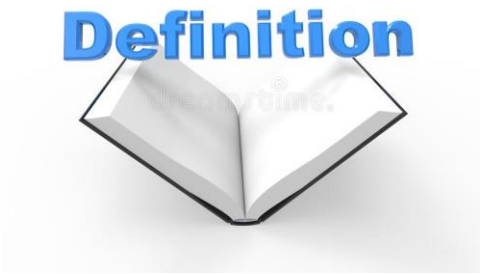
- Renal hypoperfusion (most cases:hypovolemia → 50%)

  A unique cause of AKI due to renal hypoperfusion in patients with cirrhosis is the HRS, which is the result of renal vasoconstriction (15- 20%)

- Intrinsic structural kidney injury (ATN → 30%)

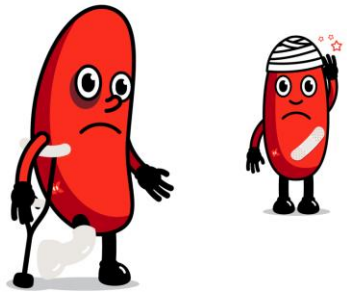
- Postrenal injury due to urinary obstruction (1%)





AKI

- Increase in serum creatinine ≥0.3 mg/dl within 48 hr
- Increase ≥1.5 times baseline level, which is known or presumed to have occurred within previous 7 days
- Urinary output <0.5 ml/kg/hr in 6 h



Hepatorenal syndrome (HRS)

Presence of cirrhosis and ascites

Diagnosis of AKI by KDIGO Criteria

Hepatorenal syndrome (HRS)

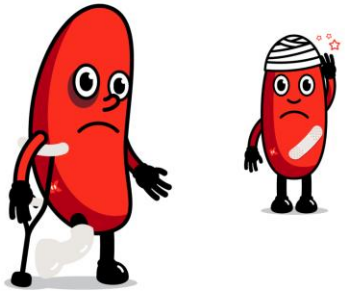
No improvement of serum creatinine after at least 48 h of diuretic withdrawal and volume expansion with albumin

Absence of shock

No macroscopic signs of structural kidney disease:

- microhematuria (>50 RBCs/HPF)
- proteinuria >500 mg/day,
- abnormal renal US

No current or recent use of nephrotoxic drugs



Hepatorenal syndrome (HRS)

✓ Type 1 (HRS-1): HRS-AKI:

Absolute increase in serum creatinine ≥0.3 mg/dl within 48 hr

Increase in serum creatinine >1.5 times baseline level

Urinary output <0.5 ml/kg/hr for 6 hr

✓ Type 2 (HRS-2): HRS-CKD: eGFR <60 ml/min/1.73 m2 for ≥3 mo in the absence of other(structural) causes

- HRS-AKD: eGFR<60 ml/min/1.73 m2 for <3 mo in the absence of other(structural) causes or <50% increase in serum creatinine with last outpatient value within previous 3 mo as baseline level

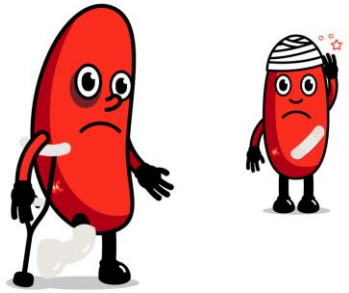
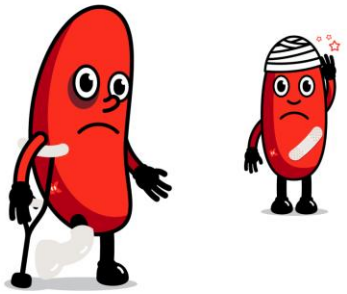


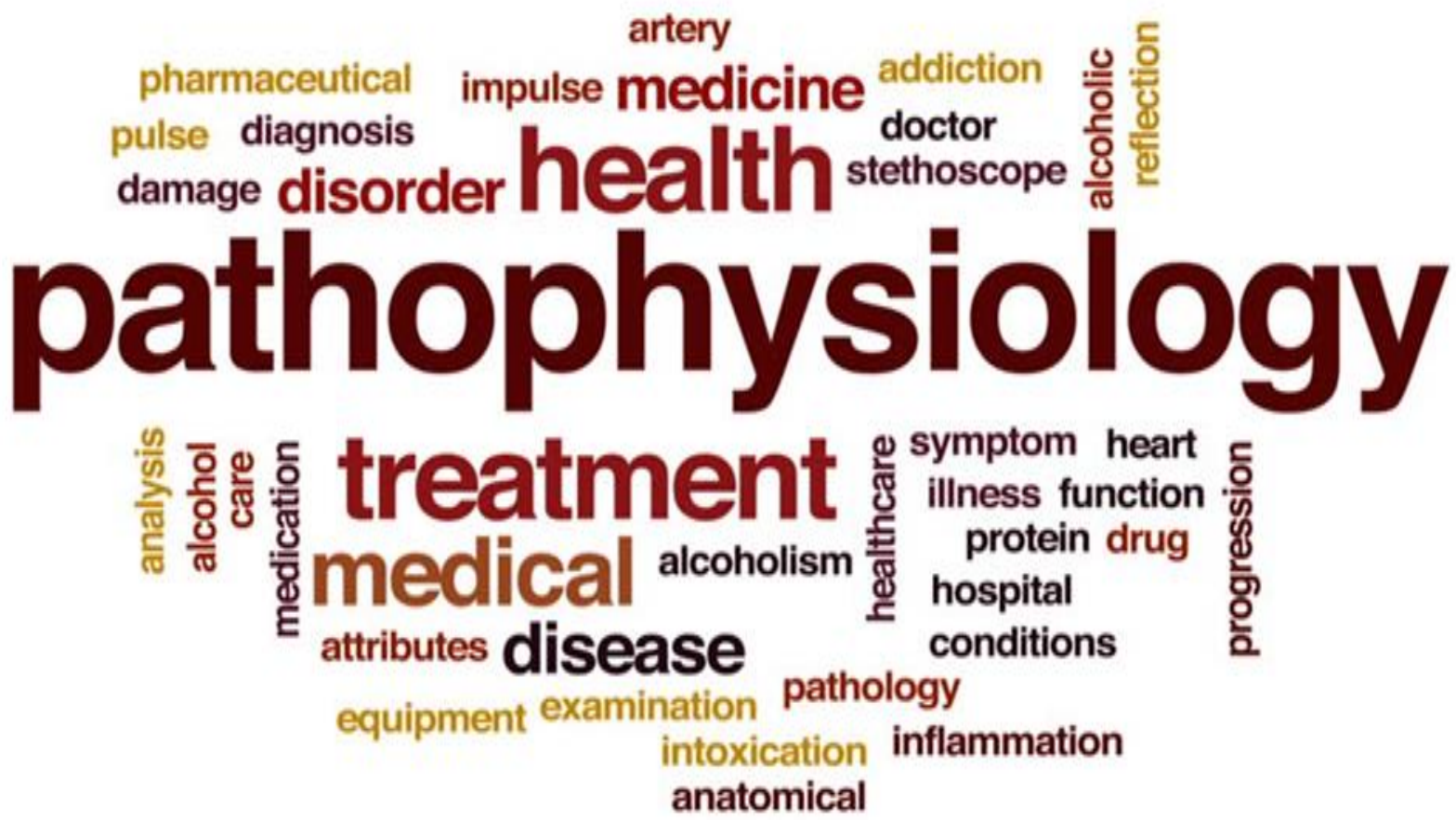
Table 1. Definitions of Acute Kidney Injury (AKI) and the Hepatorenal Syndrome (HRS) in Patients with Cirrhosis.*

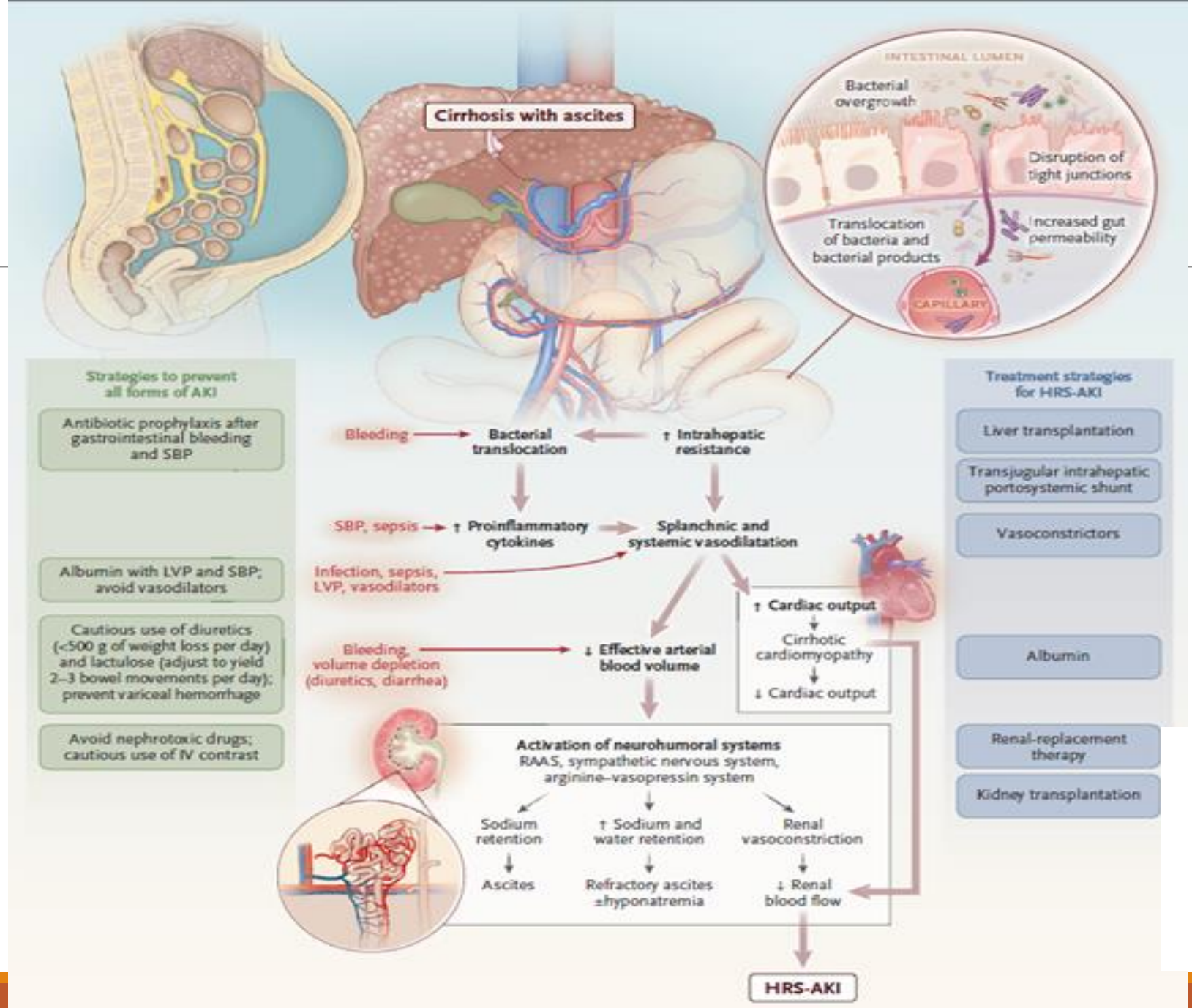
Variable or Definition	International Ascites Club, Salerno et al.[7] (2007)	Acute Disease Quality Initiative, Nadim et al.[8] (2012)	International Club of Ascites, Angeli et al.[9] (2015)	Angeli et al.[10] (2019)
Baseline serum creatinine level	—	—	Serum creatinine measured in previous 3 mo; in patients with >1 value within previous 3 mo, the value closest to time of hospital admission should be used; in patients without a previous serum creatinine value, the value on admission should be used as baseline	Similar to 2015 definition[9]
AKI	—	Increase in serum creatinine ≥0.3 mg/dl within 48 hr or increase ≥1.5 times baseline level	Increase in serum creatinine ≥0.3 mg/dl within 48 hr or increase ≥1.5 times baseline level, which is known or presumed to have occurred within previous 7 days	Absolute increase in serum creatinine ≥0.3 mg/dl within 48 hr or ≥1.5 times baseline level or urinary output <0.5 ml/kg/hr in 6 hr

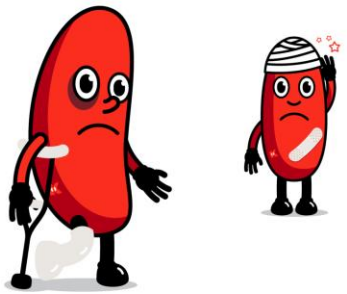


AKI stage	—	Stage 1: increase in serum creatinine ≥0.3 mg/dl or ≥1.5–2 times baseline level Stage 2: increase in serum creatinine >2–3 times baseline level Stage 3: increase in serum creatinine >3 times baseline level or ≥4.0 mg/dl with an acute increase ≥0.5 mg/dl or initiation of renal-replacement therapy	Similar to 2012 definition[8]	Similar to 2012 definition[8]
HRS	Cirrhosis with ascites Serum creatinine >1.5 mg/dl with no improvement (decrease ≤1.5 mg/dl) after at least 2 days of diuretic withdrawal and volume expansion with albumin (1 g/kg/day, maximum of 100 g/day) Absence of shock No current or recent treatment with nephrotoxic drugs Absence of parenchymal kidney disease as indicated by proteinuria >500 mg/day, microhematuria >50 red cells/high-power field, or abnormal renal findings on ultrasonography	Similar to 2007 definition[7]	Similar to 2007 definition,[7] except for removal of serum creatinine >1.5 mg/dl and inclusion of AKI diagnosis according to KDIGO serum creatinine criteria (i.e., increase in serum creatinine ≥0.3 mg/dl within 48 hr or ≥1.5 times baseline level)	Similar to 2015 definition,[9] except for addition of urinary output <0.5 ml/kg/hr for ≥6 hr as a criterion for AKI; suggestion of HRS-AKI with FeNa of <0.2% (FeNA <0.1% highly predictive)

HRS type 1	Rapid, progressive renal failure, defined by doubling of initial serum creatinine (to a level >2.5 mg/dl) in <2 wk	A specific form of AKI	—	HRS-AKI: absolute increase in serum creatinine ≥0.3 mg/dl within 48 hr or increase in serum creatinine >1.5 times baseline level; or urinary output <0.5 ml/kg/hr for 6 hr
HRS type 2	Serum creatinine increased from 1.5 to 2.5 mg/dl, with steady or slowly progressive course; typically associated with refractory ascites	A specific form of CKD	—	HRS-CKD: eGFR <60 ml/min/1.73 m^2 for ≥3 mo in the absence of other (structural) causes HRS-AKD: eGFR <60 ml/min/1.73 m^2 for <3 mo in the absence of other (structural) causes or <50% increase in serum creatinine with last outpatient value within previous 3 mo as baseline level

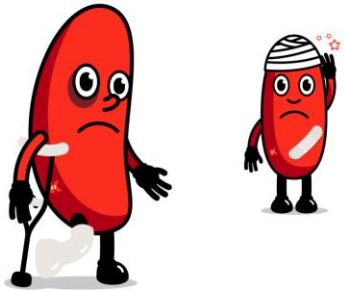

artery
pharmaceutical
impulse
medicine
addiction
alcoholic
reflection
pulse
diagnosis
doctor
health
damage
disorder
stethoscope
pathophysiology
analysis
alcohol
care
medication
treatment
healthcare
symptom
heart
illness
function
protein
drug
medical
alcoholism
hospital
progression
attributes
disease
conditions
pathology
equipment
examination
intoxication
inflammation
anatomical

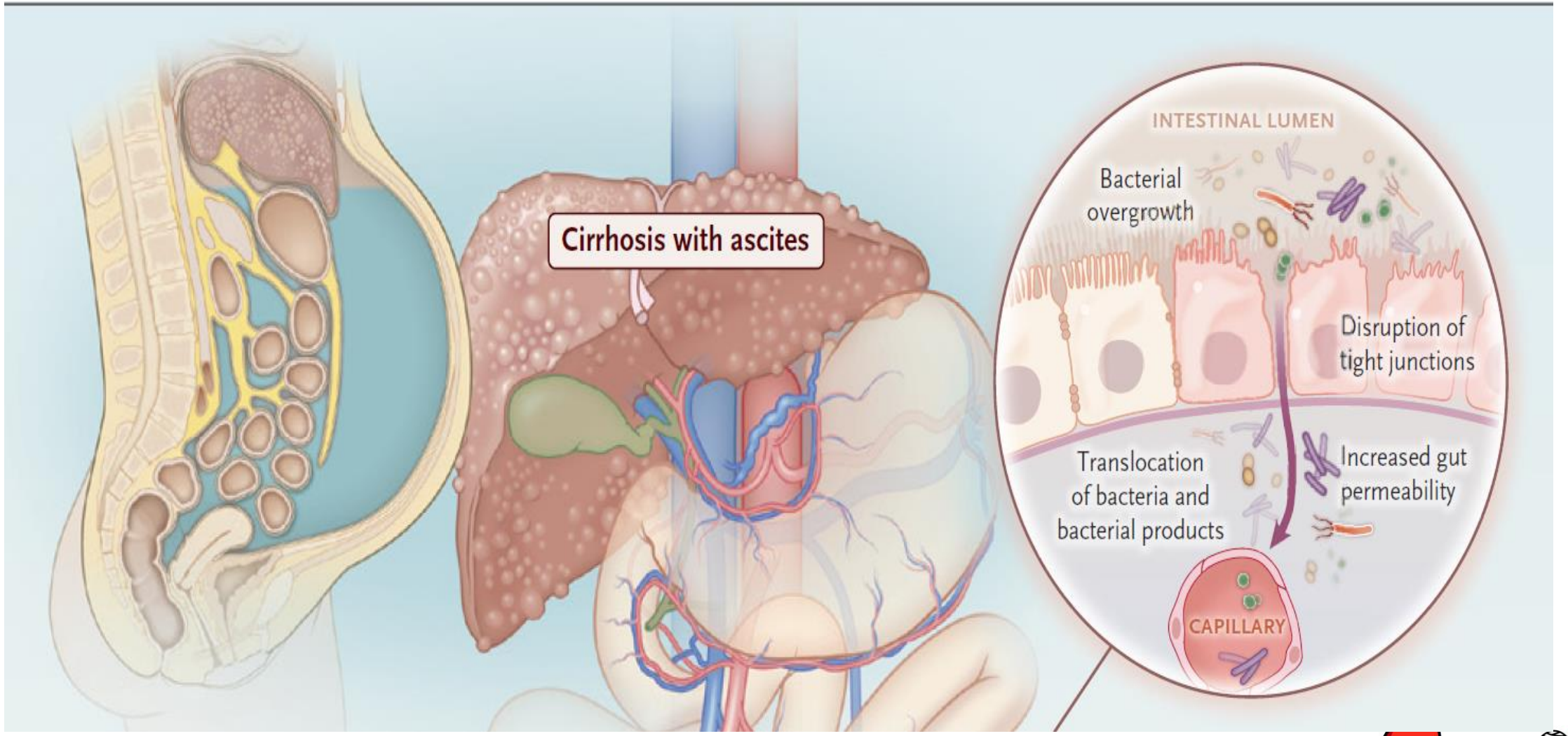

Cirrhosis with ascites
INTESTINAL LUMEN
Bacterial overgrowth
Disruption of tight junctions
Translocation of bacteria and bacterial products
Increased gut permeability
CAPILLARY
Strategies to prevent all forms of AKI
Antibiotic prophylaxis after gastrointestinal bleeding and SBP
Albumin with LVP and SBP; avoid vasodilators
Cautious use of diuretics (<500 g of weight loss per day) and lactulose (adjust to yield 2–3 bowel movements per day); prevent variceal hemorrhage
Avoid nephrotoxic drugs; cautious use of IV contrast
Bleeding
Bacterial translocation
↑ Intrahepatic resistance
SBP, sepsis
↑ Proinflammatory cytokines
Splanchnic and systemic vasodilatation
Infection, sepsis, LVP, vasodilators
↑ Cardiac output
Cirrhotic cardiomyopathy
↓ Cardiac output
Bleeding, volume depletion (diuretics, diarrhea)
↓ Effective arterial blood volume
Activation of neurohumoral systems
RAAS, sympathetic nervous system, arginine–vasopressin system
Sodium retention
↑ Sodium and water retention
Renal vasoconstriction
Ascites
Refractory ascites ±hyponatremia
↓ Renal blood flow
HRS-AKI
Treatment strategies for HRS-AKI
Liver transplantation
Transjugular intrahepatic portosystemic shunt
Vasoconstrictors
Albumin
Renal-replacement therapy
Kidney transplantation



Pathophysiology

- **Portal hypertension**; increased intrahepatic resistance due to distortion of the liver architecture (fibrosis and nodules), increase in intrahepatic vascular tone
- Activation of vasodilators in the splanchnic circulation (Nitric Oxide) leads to progressive splanchnic and systemic vasodilatation

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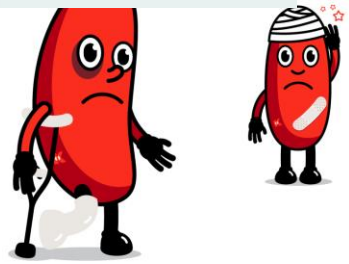

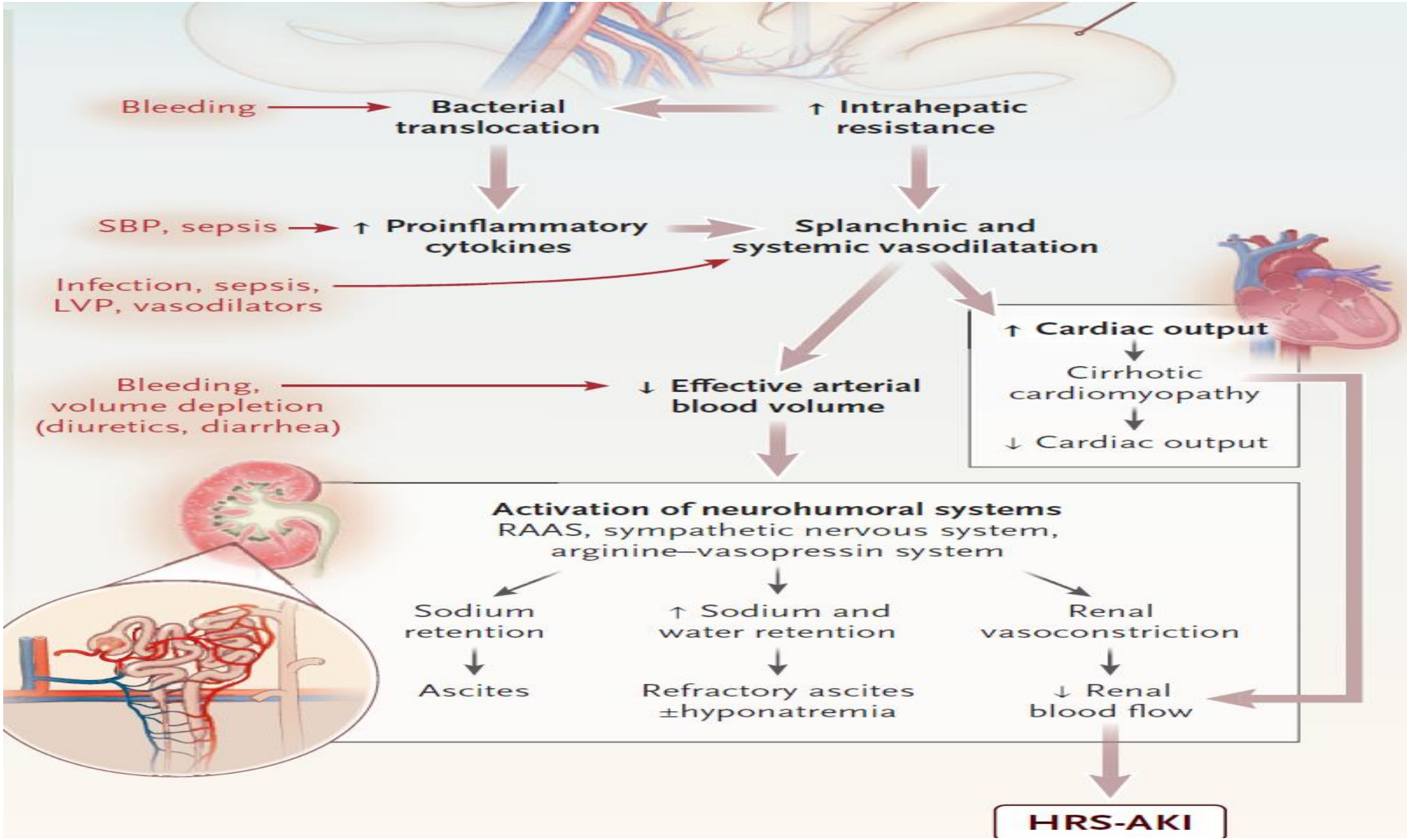
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Infection, sepsis, LVP, vasodilators
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Activation of neurohumoral systems
RAAS, sympathetic nervous system, arginine–vasopressin system
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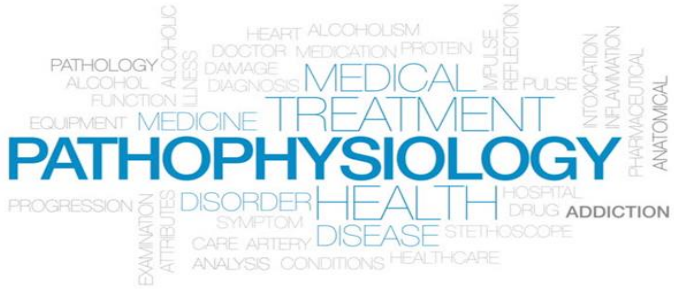
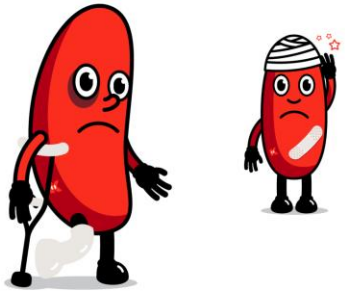
Renal vasoconstriction
Ascites
Refractory ascites ±hyponatremia
↓ Renal blood flow
HRS-AKI



- ⬇ Renal blood flow ⟶ decrease in the (GFR) and a prerenal type of kidney injury that does not respond to volume expansion that is, HRS-AKI

- Renal vasoconstriction in patients with cirrhosis is not countered by the release of vasodilatory substances (PGs) because of a decrease in their production and local release of vasoconstrictors such as endothelin

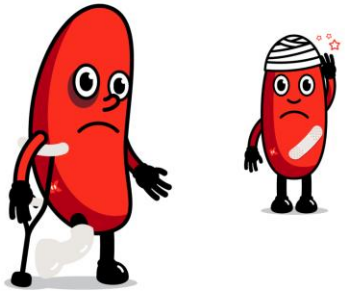


Assessment of Kidney Function

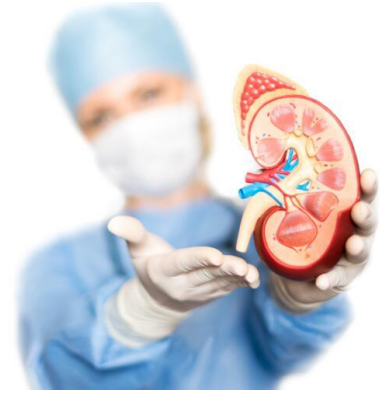
eGFR equations based on:

- Serum creatinine
- Cystatin C

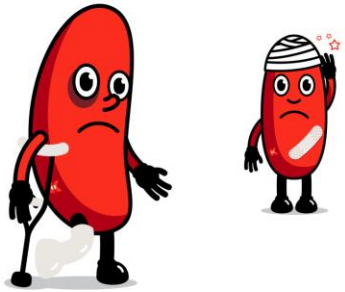
Determining kidney function in the general population of persons with stable serum Cr levels



Assessment of Kidney Function



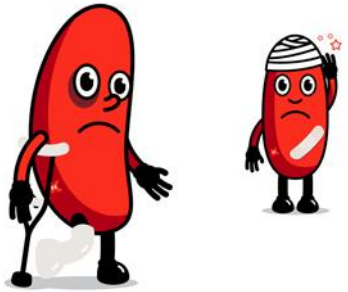
- Overestimates the GFR in patients with cirrhosis:
  - ✓Decreased creatinine production due to liver disease
  - ✓ Protein calorie malnutrition
  - ✓ Muscle wasting
- In patients with AKI and fluid overload, an increase in the serum creatinine level can lag by several hours to days, despite a decrease in the GFR



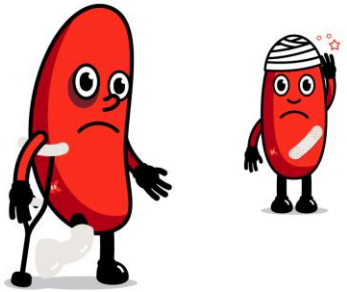
Assessment of Kidney Function…

- eGFR equations tend to overestimate the true GFR by 10 to 20 ml/min/1.73 m2 of BSA, especially in patients with a GFR of less than 40, Ascites, or both

- The accuracy of eGFR measurements is particularly important in patients with cirrhosis because eGFR is one of the factors used to determine candidacy for simultaneous liver and kidney transplantation



Diagnostic Workup and Management of AKI



Presentation with cirrhosis and AKI

Conduct history and physical examination: consider risk factors that may suggest cause of AKI (e.g., recent shock, fever, recent initiation of diuretics, diarrhea)
Review medications list for active or recent nephrotoxin or exposure to IV contrast
Discontinue diuretics, NSAIDs, ACEI or ARB, NSBB
Perform diagnostic paracentesis to rule out SBP
Perform urinary tests: microscopical assessment of urinary sediment, FeNa, FeUrea, NGAL (if available)

Renal Hypoperfusion (most common)
Hypovolemia (e.g., from diuretics, diarrhea, gastrointestinal bleeding)
Hepatorenal syndrome (HRS-AKI)

Intrinsic or Parenchymal Kidney Injury
ATN (most common; e.g., from sepsis, IV contrast, medications, bile cast nephropathy)
AIN: from antibiotics, NSAIDs, PPI
Glomerular diseases: e.g., IgA, MPGN, cryoglobulinemia

Urinary Obstruction (least common)
Urethral obstruction, ureteral obstruction

Assess volume status (physical examination, POCUS, chest radiography, echocardiography)

ATN: discontinue nephrotoxic agents
AIN: discontinue offending agent
Consider kidney biopsy
Glomerular disease: specific treatment

Determine postvoid residual volume
Renal ultrasonography

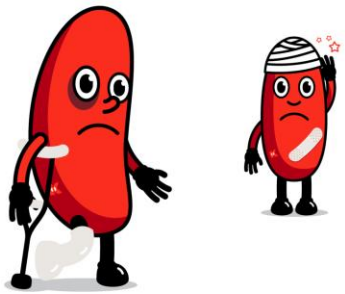
Intravascular volume depletion

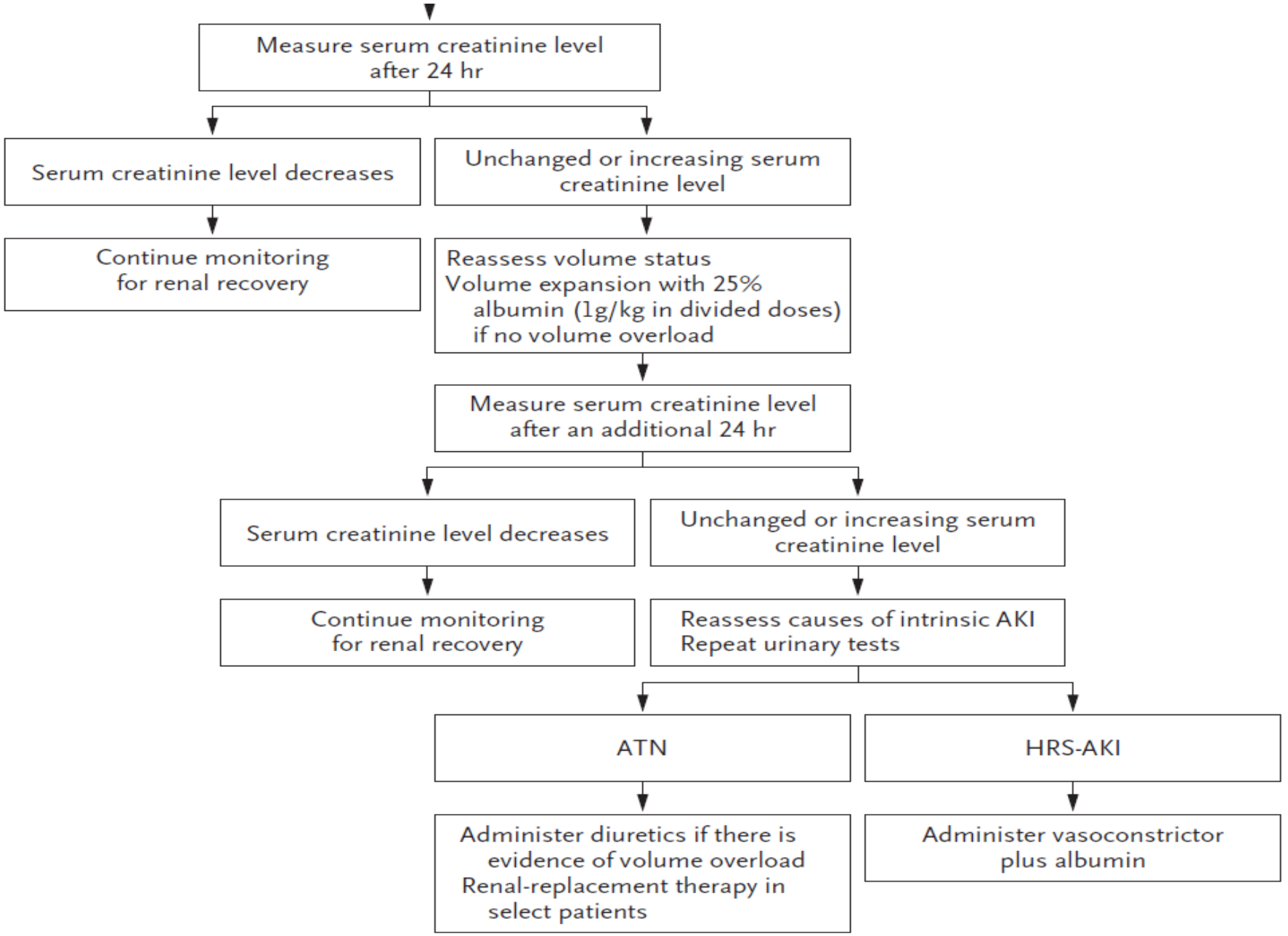
Equivocal volume status

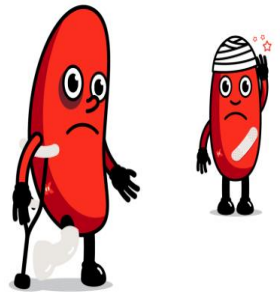
Crystalloid solutions

25% albumin 1g/kg (≤100 g/day in divided doses)

Measure serum creatinine level after 24 hr

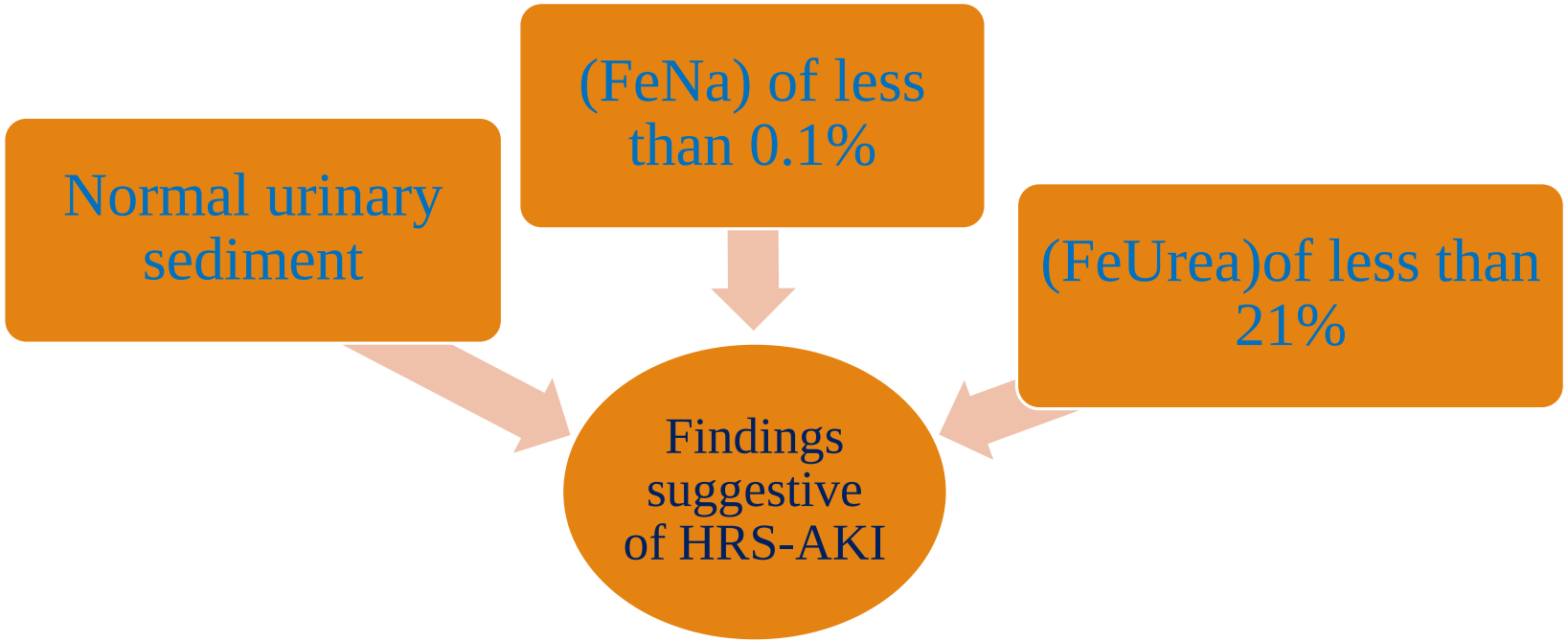


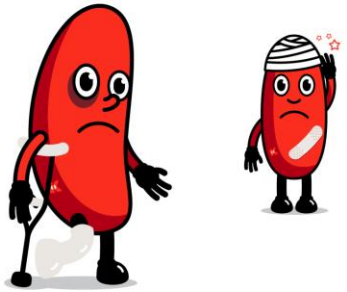

Measure serum creatinine level after 24 hr
Serum creatinine level decreases
Unchanged or increasing serum creatinine level
Continue monitoring for renal recovery
Reassess volume status
Volume expansion with 25% albumin (1g/kg in divided doses) if no volume overload
Measure serum creatinine level after an additional 24 hr
Serum creatinine level decreases
Unchanged or increasing serum creatinine level
Continue monitoring for renal recovery
Reassess causes of intrinsic AKI
Repeat urinary tests
ATN
HRS-AKI
Administer diuretics if there is evidence of volume overload
Renal-replacement therapy in select patients
Administer vasoconstrictor plus albumin



Diagnostic Workup and Management of AKI

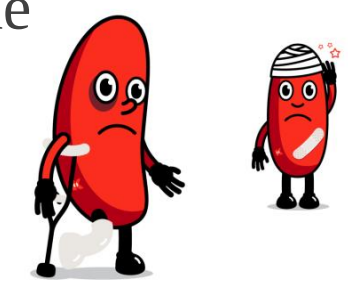
- Urinary tests are important in differentiating between HRS-AKI and various causes of AKI that are due to intrinsic or parenchymal kidney injury





Diagnostic Workup and Management of AKI

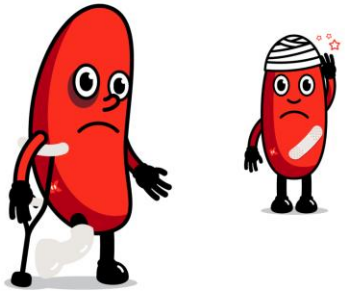
- A urinary neutrophil gelatinase–associated lipocalin (NGAL) level greater than 220 to 244 μg/gr of creatinine is suggestive of (ATN)
- Volume overload is suggested by the presence of anasarca, jugular venous distention, a chest film showing pulmonary congestion, or an elevated right ventricular systolic pressure in echo
- Diuretics may need to be initiated or continued if there is evidence of volume overload



TREATMENT

Treatment of HRS-AKI

- Pharmacologic Therapy
- Transjugular Intrahepatic Portosystemic Shunt
- Renal-Replacement Therapy
- Liver Transplantation



Pharmacologic Therapy

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

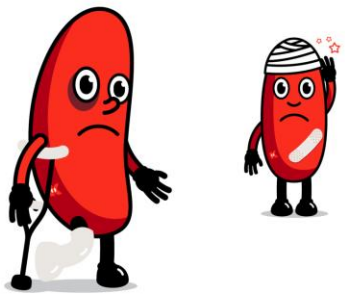
FDA label
Administer 1 mg intravenously every 6 hr as IV bolus
EASL guidelines
Administer 1 mg intravenously every 4–6 hr as IV bolus or by continuous IV infusion at initial dose of 2 mg/day

Terlipressin contraindicated or unavailable

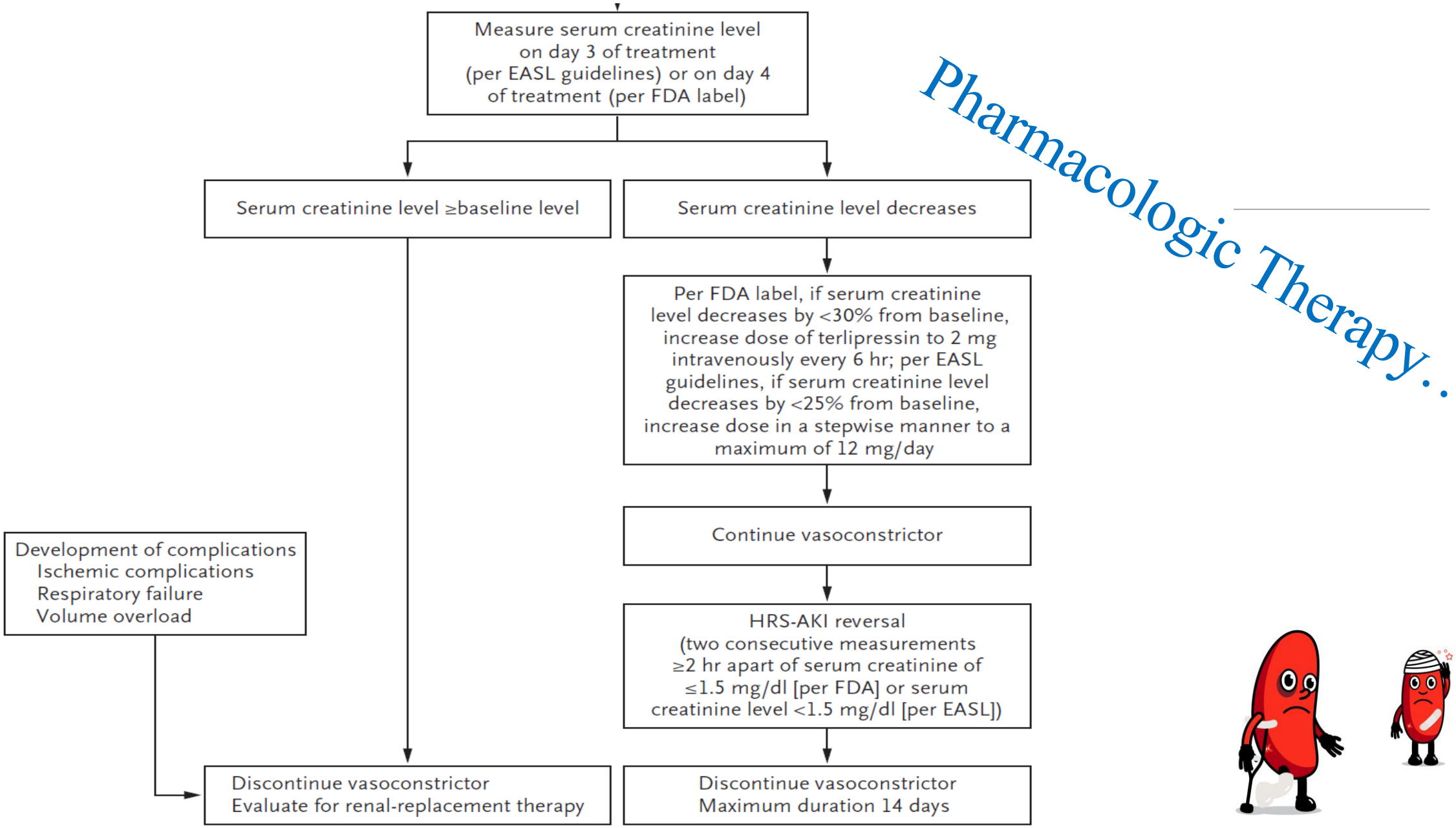
Norepinephrine

Administer 0.5–3.0 mg/hr (continuous IV infusion)
Titrate to achieve an increase in MAP >10 mm

Measure serum creatinine level on day 3 of treatment (per EASL guidelines) or on day 4 of treatment (per FDA label)

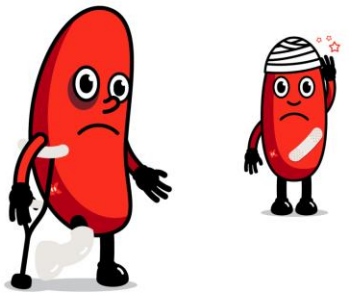


Pharmacologic Therapy…



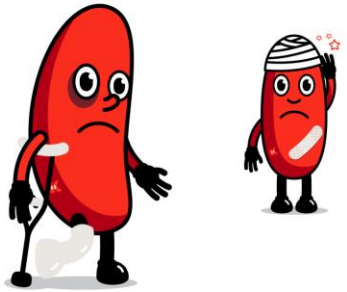
Pharmacologic Therapy

- Albumin infusion should be decreased, and cautious use of Terlipressin in patients with volume overload
- Terlipressin should be withheld if (SpO2) is less than 90%
- Terlipressin side effects include myocardial infarction,peripheral or mesenteric ischemia, and pulmonary edema



Pharmacologic Therapy

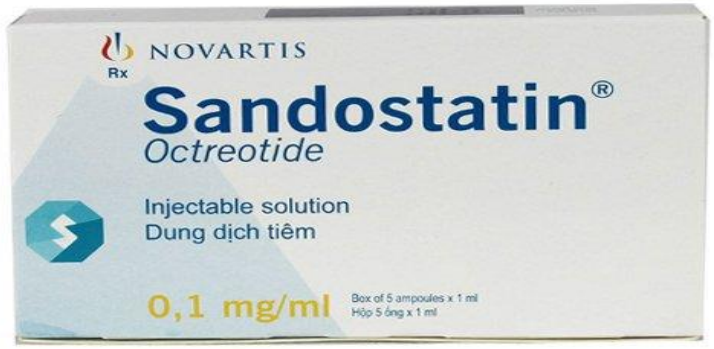
- Norepinephrine use is limited to the ICU and requires placement of a central catheter
- It may be considered as an alternative if Terlipressin is contraindicated or unavailable
- Side effects of Norepinephrine include ischemic events and cardiac dysrhythmias



Pharmacologic Therapy

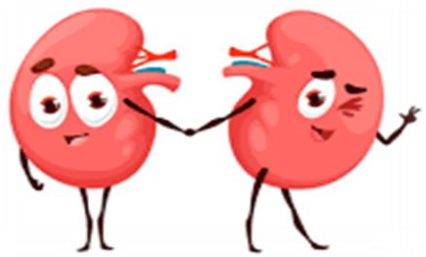
- The combination of Midodrine (7.5 to 15 mg orally three times a day) and Octreotide (100 to 200 μg subcutaneously three times a day), given over a period of 24 to 48 hours, may be considered if Terlipressin is unavailable or contraindicated and a transfer to the ICU for Norepinephrine infusion is not an option

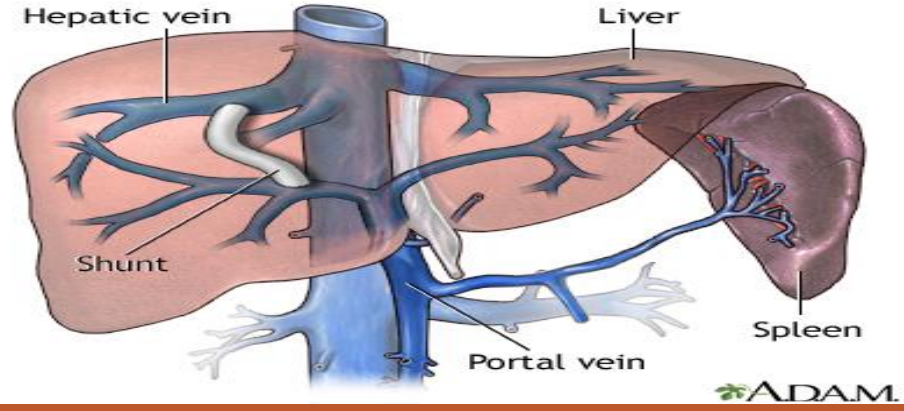
- Midodrine may cause bradyarrhythmias



Transjugular Intrahepatic Portosystemic Shunt

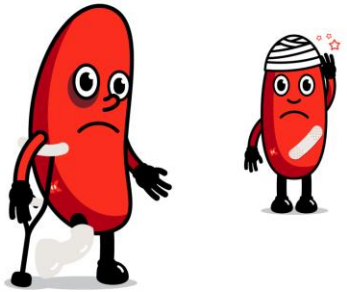
- An important therapeutic option in patients with portal hypertension is the placement of a (TIPS) that may improve kidney function by redistributing blood volume and reducing portal pressure
- There is currently insufficient evidence to recommend TIPS for HRS-AKI





Renal-Replacement Therapy

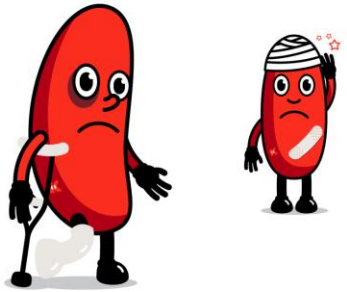
- RRT should be individualized on the basis of life-threatening indications that are refractory to medical treatment (Hyperkalemia, Acidosis, or fluid overload), Uremic complications, the trajectory of kidney function, or the overall prognosis



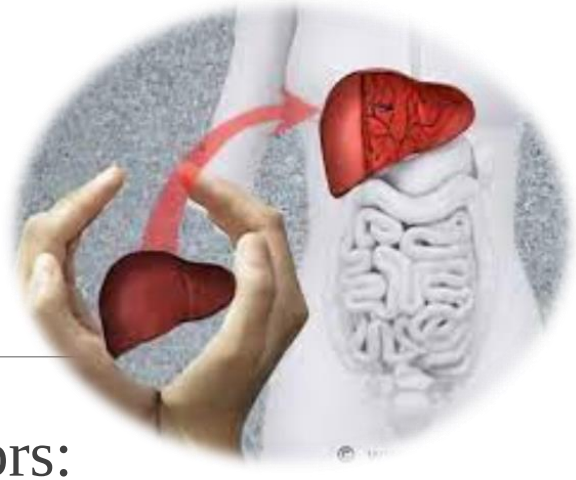
Liver Transplantation

Liver transplantation is the treatment of choice in patients with HRS-AKI

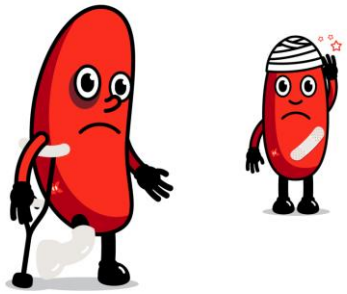
Simultaneous liver and kidney transplantation is a potential therapeutic option for patients with prolonged kidney dysfunction before liver transplantation



Liver Transplantation



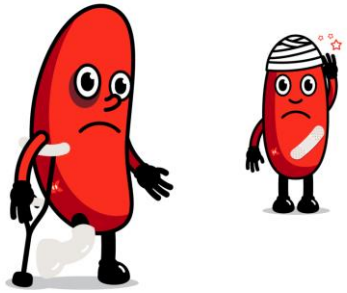
- Criteria for simultaneous liver and kidney transplantation included factors:
  - ✓Prolonged duration of AKI
  - ✓Dialysis
  - ✓Presence of CKD
- **Kidney biopsy** may assist in diagnosis and determining the reversibility of kidney dysfunction and the need for simultaneous liver and kidney transplantation.



Liver Transplantation

- Indications for simultaneous liver kidney transplant (SLK) in patients with cirrhosis and renal dysfunction:

- ✓ End Stage Liver Disease and one or more of the following:
  - End Stage Renal Disease requiring hemodialysis
  - Chronic Kidney Disease with GFR <30 mL/min* for >3 months
  - Kidney biopsy showing >30% glomerulosclerosis & interstitial fibrosis
  - Acute Kidney Injury with creatinine >2.0 mg/dL and/or requiring dialysis for >8 week



Prevention of AKI

- Cautious use of diuretics(<500 g of weight loss per day)
- Cautious use of lactulose (2–3 bowel movements/day)
- Prevention of variceal hemorrhage
- Antibiotic prophylaxis afterGIB and SBP
- Albumin with LVP and SBP

Prevention of AKI…

- Intravenous albumin infusions at a dose of 4 to 6 g per liter of ascites removed have been shown to ameliorate circulatory dysfunction and prevent AKI after large volume paracentesis (removal of >5 liters).

- Albumin infusions have also been shown to reduce the incidence of AKI and to decrease mortality among patients with SBP

Prevention of AKI…

- Betalactam antibiotics
- PPI

Allergic interstitial injury

- Radiocontrast dye
- Amphotericin B
- Aminoglycosides
- Vancomycin

Direct renal tubule toxicity

- NSAID
- RAAS blocker

Direct nephrotoxic effects by impairing intra renal blood flow

Medications

Prevention of AKI…

- Kidney function should be closely monitored in patients with cirrhosis and ascites while they are receiving these medications
- Cautious use of IV contrast, especially in patients with an eGFR < 45

Editorial

JOURNAL OF HEPATOLOGY

Acute kidney injury in cirrhosis: An immediate threat but also a ticking time bomb

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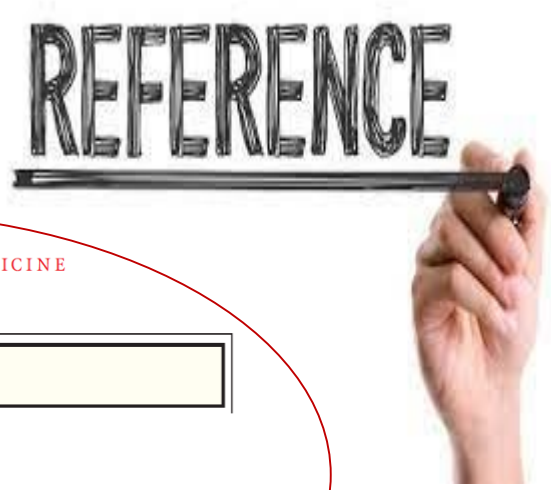
See Article, pages 1132–1139



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REVIEW ARTICLE

C. Corey Hardin, M.D., Ph.D., *Editor*

Acute Kidney Injury in Patients with Cirrhosis

Mitra K. Nadim, M.D., and Guadalupe Garcia-Tsao, M.D.

Review Article

Acute Kidney Injury in Patients with Cirrhosis

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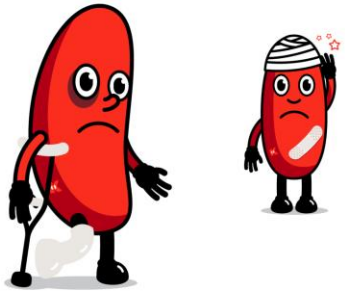
REVIEW

Acute kidney injury and hepatorenal syndrome in cirrhosis

Kapil Gupta, Abhishek Bhurwal, Cindy Law, Scott Ventre, Carlos D Minacapelli, Savan Kabaria, You Li, Christopher Tait, Carolyn Catalano, Vinod K Rustgi




THANK
YOU!