The Evolving Challenge of Infections and Renal Dysfunction in the Cirrhotic Patient

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I have nothing to disclose

Objectives

- Epidemiology of infections and renal dysfunction in cirrhosis
- Brief explanation of mechanisms of infections, AKI and CKD in cirrhosis
- How to approach infections in cirrhotics and treatment considerations
- Identification and management of renal dysfunction in cirrhotics
- Prevention strategies

Epidemiology of infections in cirrhosis

- 2/3 of cirrhotics with extrahepatic organ failure have sepsis
- Longer hospital admissions with increasing cost
- Inpatient mortality > 50% (Decompensation < ACLF)
- High mortality have been observed with SARS-CoV-2 infection
- Community acquired (48%/strategies?), Health care associated (26%) and Nosocomial (26%)
- Positive bacterial cultures ontained in only 59% of patients
- Most commont infection is SBP follow by UTI and Pneumonia
- Increasing prevalence of infections with MDR organisms

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Pathogenesis of Infections in Cirrhosis

- Immune dysfunction
  - Both innate and adaptive imunity
  - Impaired in gut immunity
- Reduction in bile flow
- Gut barrier dysfunction -> progresses with advancing stages
  - Bacterial translocation
    - Decrease beneficial bacteria with increase in pathobionts like gram (-) rods and gram (+) cocci
- External factors
  - Overuse of PPI and antibiotics
  - Alcohol use
  - Frailty
  - Multiple admissions and invasive procedures

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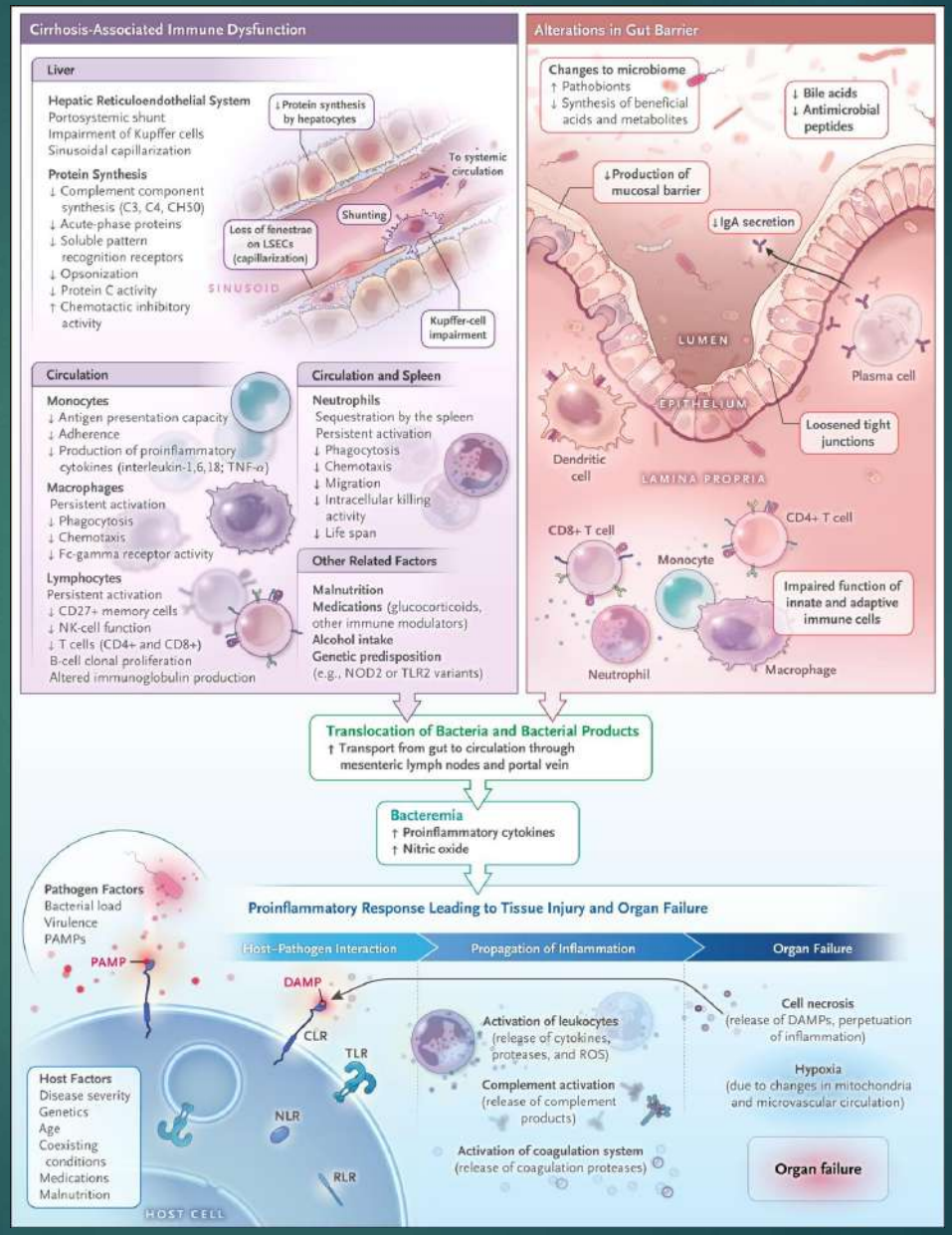
Role of Changes in the Gut–Liver Axis and Cirrhosis-Associated Immune Dysfunction in the Development of Infections



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Types of Infections

- Spontaneous bacterial peritonitis
- Urinary tract infections
- Pneumonia
- Spontaneous bacteremia
- Skin and soft tissue infections
- Clostridioides difficile infection
- Fungal infections

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Spontaneous Bacterial Peritonitis

- IV antibiotics should be started empirically in all patients with an ascites/pleural fluid PMN count >250/mm^3
- First ine antibiotic for community-acquired SBP/SBE is IV third generation cephalosporin
- In patients with a health care associated or nosocomial infection or recent exposure to broad- spectrum antibiotics or who are admitted with sepsis or septic shock, empirical therapy with broad-spectrum antibiotics should be initiated as the first line

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Spontaneous Bacterial Peritonitis

- Response to empirical antibiotic therapy may be assessed by repeating diagnostic paracentesis/thoracentesis 2 days after initiation
  - A decrease in fluid PMN <25% from baseline indicates lack of response
  - Broadening of antibiotic coverage and rule out secondary bacterial peritonitis
- Patients with SBP should be treated with IV albumin in addition to antibiotics (1.5 mg/kg at day 1 and 1mg/kg at day 3)
- NSBBs should be temporarily held in patients with SBP who develop hypotension (MAP <65 mm Hg) or AKI

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Abdominal Paracentesis

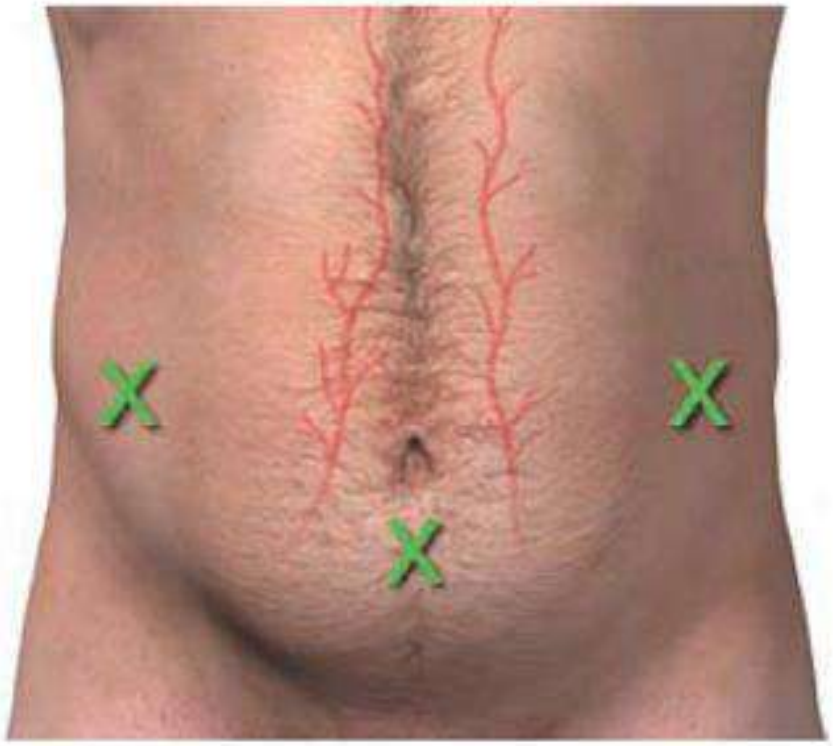

Fig. 1. Diagram of the abdomen showing the three usual sites for abdominal paracentesis. The author prefers the left lower quadrant site. Reproduced from Thomsen TW, Shaffer RW, White B, Setnik GS. Paracentesis. N Engl J Med 2006;355:e21, with permission from the Massachusetts Medical Society. Copyright (2006) Massachusetts Medical Society. All rights reserved.

Thomsen et al. N Engl J Med 2006; 355:e21

SBP Prophylaxis

- Acute gastrointestinal bleeding
- Advanced cirrhosis (Child–Pugh score ≥9)
- Bilirubin level ≥3 mg/dL
- Low ascites fluid protein level (<1.5 g per deciliter)
- Impaired renal function (serum creatinine level ≥1.2 mg/dL or BUN level ≥25 mg/dL
- Hyponatremia (serum sodium level ≤130 mmol/L)
- Patient with prior episode of SBP (Secondary prophyaxis)
  - High rate of recurrence
  - Until liver transplantation or death
- Norfloxacin, alternatives such as ciprofloxacin, rifaximin, and sulfamethoxazole/trimethoprim

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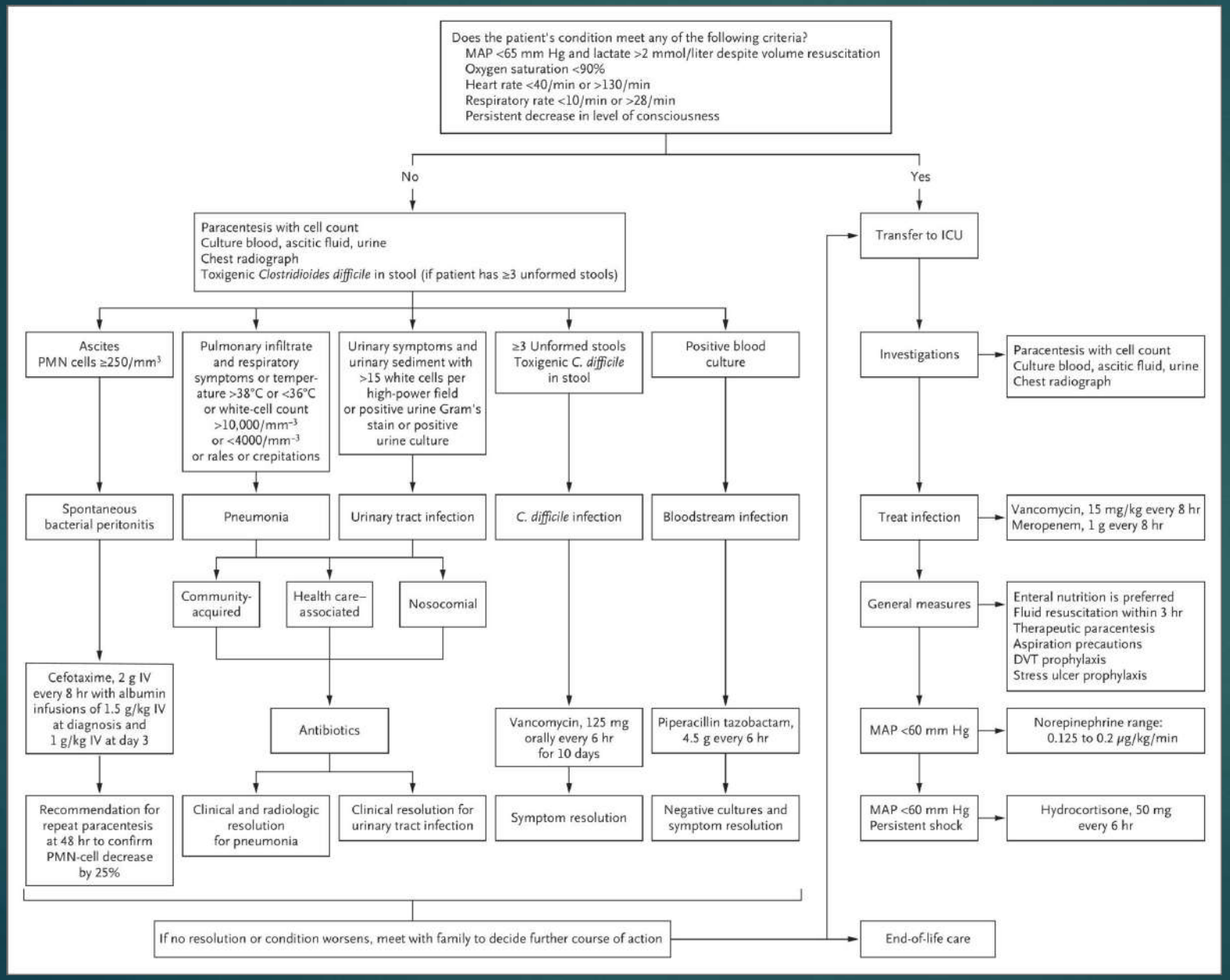
Algorithm for the Care of Patients with Cirrhosis and Suspected Infection



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Vaccines

- Influenza
- Pneumococcal (Prevnar/Pneumovax)
- Herpes zoster
- Hepatitis A and B
- Tetanus–diphtheria–acellular pertussis
- Measles–mumps–rubella
- Varicella vaccines
- *Covid-19 vaccines clinical trials have not included patients with cirrhosis but due to high risk of death in these patients it is recommended

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Estimated Glomerular Filtration Rate

	Equation/Formula
Cockcroft-Gault (mL/min)	Male: $[(140 - \text{age}) \times (\text{weight})]/72 \times \text{sCr}$ Female: GFR $\times$ 0.85 BSA corrected: $\text{GFR}_{cg} \times (1.73/\text{BSA})$ (= mL/min/1.73 m^2)
MDRD (mL/min/1.73 m^2)	Male: $170 \times (\text{sCr})^{-0.999} \times (\text{age})^{-0.176} \times (\text{sU})^{-0.170} \times (\text{sAlb})^{+0.318}$ Black male: MDRD $\times$ 1.180 Female: MDRD $\times$ 0.76 Black female: MDRD $\times$ 0.762 $\times$ 1.180
CKD-EPI (mL/min/1.73 m^2)	Male: $141 \times \text{minimum}(\text{sCr}/0.9, 1)^{-0.411} \times \text{max}(\text{sCr}/0.9, 1)^{-1.209} \times 0.993^{\text{Age}}$ Black male: CKD-EPI $\times$ 1.159 Female: $141 \times \text{minimum}(\text{sCr}/0.7, 1)^{-0.329} \times \text{max}(\text{sCr}/0.7, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018$ Black female: CKD-EPI (female) $\times$ 1.159

Abbreviations: BSA, body surface area; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Diseases; Alb, serum albumin; sCr, serum creatinine; sU, serum uric acid.

Cole et al. The Medical clinics of North America 2012; 96:955-74

Renal Dysfunction in Cirrhotic Patients

- Renal dysfunction is frequent in patient with cirrhosis and is implicated with poor outcomes
  - Increased mortality prior to LT
  - Higher rates of primary graft nonfunction
  - Inferior graft and patient survival rates post-LT
- sCr is used in MELD score and has more than twice the weight bilirubin
  - More patients with renal dysfunction being transplanted
- Acute and chronic renal dysfunction occur more commonly in patients with cirrhosis
  - Prevalence of renal disease increases with severity of liver disease
  - AKI complicates the course of up to 70% of admitted patients with cirrhosis
  - AKI incidence is 23% in all hospitalized adults and 60% in all patients admitted to ICU

Pena Polanco et al. *Gastroenterology and Hepatology 2021;*17(5):211-20

Stages of Acute Kidney Injury

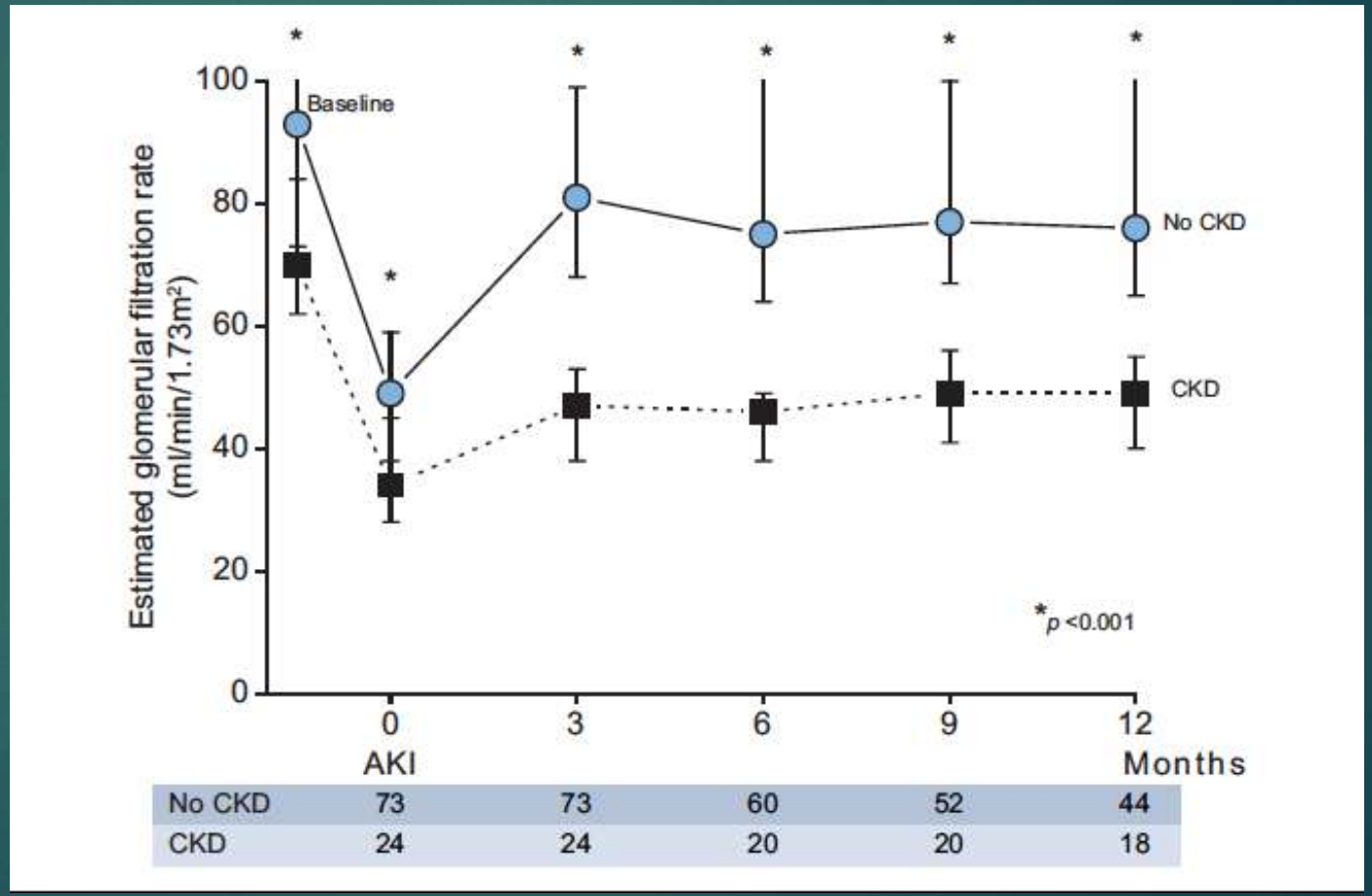
Stage	Change in Serum Creatinine
1	Increase ≥0.3 mg/dL or ≥1.5- to 2-fold from baseline
1 - A	Peak serum creatinine <1.5 mg/dL
1 - B	Peak serum creatinine ≥1.5 mg/dL
2	Increase >2- to 3-fold from baseline
3	Increase >3-fold from baseline or ≥4.0 mg/dL with an acute increase of ≥0.3 mg/dL or initiation of renal replacement therapy

- An absolute change in sCr concentration of 0.3 mg/dL is considered diagnostic for AKI
  - Peak sCr occurs at 48 – 72 hrs
- Kidney injury can occur in the absence of increasing sCr concentration, representing an emerging condition called subclinical AKI

Pena Polanco et al. *Gastroenterology and Hepatology 2021;*17(5):211-20

Development of CKD after AKI in Cirrhosis

- 25% of patients with cirrhosis who survive an episode of acute kidney injury develop CKD
- Transition to CKD is associated with increased risk of AKI, cirrhotic complications and hospital re-admissions



Bassegoda et al. Journal of Hepatology 2020; 72:1132-39

Criteria for the Diagnosis of Hepatorenal Syndrome–Acute Kidney Injury

- Cirrhosis with ascites
- Diagnosis of acute kidney injury according to International Club of Ascites–Acute Kidney Injury criteria
- Absence of shock
- No sustained improvement of renal function (serum creatinine <1.5 mg/dL) following at least 2 days of diuretic withdrawal, and volume expansion with albumin at 1 g/kg/day up to a maximum of 100 g/day
- No current or recent exposure to nephrotoxic agents
- Absence of parenchymal renal disease as defined by proteinuria <0.5 g/day, no microhematuria (<50 red blood cells/high-power field), and normal renal ultrasonography

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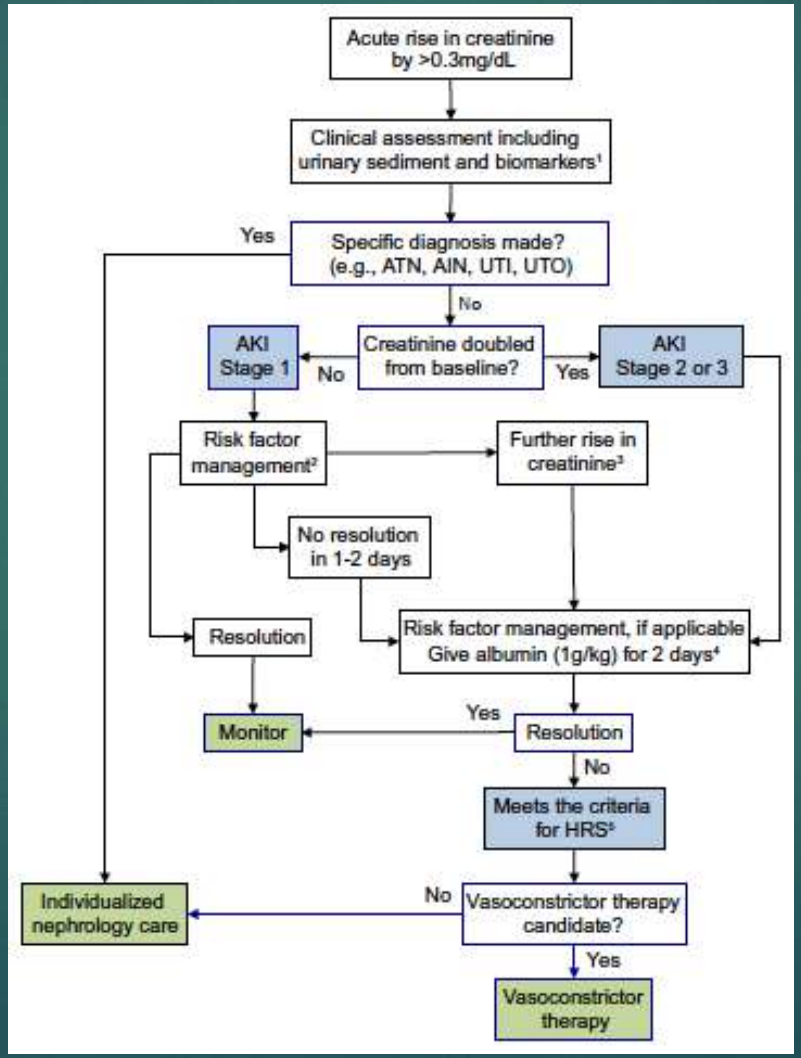
Proposed algorithm for the diagnosis and management of AKI in cirrhosis



Biggins et al. HEPATOLOGY 2021; 74(2):1014-48

Common Causes of Renal Dysfunction in Patients With Cirrhosis and Recommended Interventions

Causes of Renal Dysfunction	Common Clinical Scenarios	Interventions
Volume depletion	Excessive diuresis	• Discontinue diuretics. • Replete volume with crystalloids.
	Diarrhea	• Replete volume with crystalloids. • Perform workup to determine etiology of dysfunction and establish specific treatments. • Stop or reduce the dose of laxatives (eg, lactulose).
	Gastrointestinal hemorrhage	• Replete volume with crystalloids and blood products. • Use hemostatic interventions (eg, endoscopic variceal ligation).
Medications	NSAIDs, aminoglycosides, calcineurin inhibitors	• Stop medications. • Adjust dose of calcineurin inhibitors.
Viruses	HBV and HCV causing glomerular diseases	• Consider antiviral therapy with oral agents, with dose adjusted for severity of renal dysfunction.

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Common Causes of Renal Dysfunction in Patients With Cirrhosis and Recommended Interventions

Causes of Renal Dysfunction	Common Clinical Scenarios	Interventions
Hepatorenal syndrome–acute kidney injury (HRS-AKI)	Spontaneous bacterial peritonitis, severe acute alcoholic hepatitis	• Use vasoconstrictors and albumin. • Administer renal replacement therapy as a bridge to liver transplantation. • Use antibiotics for spontaneous bacterial peritonitis.
Hepatorenal syndrome–chronic kidney disease (HRS-CKD)	Refractory ascites	• Use vasoconstrictors and albumin. • Perform repeated paracentesis with colloid replacement. • Consider TIPS as bridge to liver transplantation.
Acute tubular necrosis	Sepsis	• Replete volume. • Improve hemodynamics and renal perfusion. • Avoid nephrotoxic drugs.

Pena Polanco et al. *Gastroenterology and Hepatology 2021;*17(5):211-20

Prevention of AKI

- Treat and prevent possible precipitating factors
  - Gastrointestinal bleeding
  - Bacterial infections
  - Avoid LVP without albumin administration
- IV albumin together with antibiotics
  - Reduces the incidence of HRS-AKI and improves survival in patients with SBP

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Eligibility Criteria for SLK Transplantation

- AKI ≥6 consecutive weeks with one or a combination of both
  - Dialysis
  - eGFR/CrCl ≤25 mL/min
- CKD with GFR ≤60 mL/min for >90 days with one of the following:
  - End-stage renal disease
  - eGFR/CrCl ≤30 mL/min at the time or after registration on kidney waiting list
- Metabolic diseases (Hyperoxaluria, familial non-neuropathic systemic amyloidosis, methylmalonic aciduria)
- Safety net:
  - Any patient who is registered on the kidney waitlist between 60 and 365 days after LT and is either on chronic hemodialysis or has an eGFR <20 mL/min will qualify for increased priority

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