Evaluation of Acute Kidney Injury in Cirrhotic Patient: HRS and Beyond

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• NO CONFLICT OF INTEREST
PLAN

• FREQUENCY AND PROGNOSIS of Cirrhosis with AKI
• DEFINITION and DIAGNOSIS AKI: Particularity of Cirrhosis
• SPECTRUM AKI-Cirrhosis
• HISTORY + PHYSIOPATHOLOGY AKI-HRS
• AKI CLASSIFICATION
• HRS
• MANAGEMENT
• FUTURE PERSPECTIVES
• TAKE HOME MESSAGE

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FREQUENCY AND PROGNOSIS

- cirrhosis are more prone to developing (AKI)
  - 20–50% among hospitalized with the majority stage 1.
  - yearly incidence of 8–12%, HRS-AKI
  - precipitating event
    - overdose of diuretics
    - large-volume paracentesis without albumin replacement
    - gastrointestinal bleeding
    - bacterial infections

- (sCr) in (MELD) Score: pivotal prognostic role of renal function
  - poor prognosis even small increases in sCr levels
    - AKI stage 1 and a sCr of<1.5 mg/dL already a 3.5-fold increase in 30-day mortality
  - an important predictor for short-term mortality
  - mortality is still about 60% and higher: HRS-AKI
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DEFINITION AKI: Particularity of Cirrhosis

• Acute kidney injury (AKI): significant reduction in (GFR) over a short time period.

• sCr: marker of excretory renal function
  • traditional diagnostic criteria: Increase (sCr) by 50% from baseline/ final value 1.5 mg/dL
  • Cirrhosis: baseline creatinine production is lower
    • muscle wasting
    • Increased dilution from volume expansion
    • decreased creatinine synthesis
    • increased tubular secretion of creatinine
    • interference with assays for sCr by elevated bilirubin
    • limitations in assessing (GFR)

• Oliguria?
  • many patients with cirrhosis and ascites maintain a preserved renal function despite being oliguric due to sodium and water retention

• cystatin superfamiliy of cysteine protease inhibitors
  • Not influenced by age, muscle mass, the presence of high bilirubin or malignancy
  • influenced by: low serum albumin levels, elevated WBC and elevated CRP

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CONSENSUS

• to improve applicability into clinical practice of patients with cirrhosis
  • Acute Kidney Injury Network (AKIN)

  • Kidney Disease Improving Global Outcome (KDIGO) diagnostic criteria for AKI

  • INTERNATIONAL CLUB FOR ASCITIS (ICA criteria)
Current diagnostic criteria of AKI in patients with cirrhosis

• AKI in cirrhosis: an acute increase in serum creatinine
  • 0.3 mg/dL within 48 hours
  • by 50% from a stable baseline serum creatinine (sCr) within 3 months (presumed to have developed within the past 7 days when no prior readings are available)

• Overestimation of GFR in cirrhosis
  • sCr-based equations: MDRD
  • even when combining sCr and CysC (CKD-EPI) formula

• wide applicability, the MDRD-6 formula has been recommended to estimate GFR in patients with cirrhosis until better alternatives become available in clinical routines
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Spectrum of causes for AKI in cirrhosis

• prerenal AKI (i.e. hypovolemia due to gastrointestinal bleeding, aggressive diuretic treatment, lactulose-induced diarrhea or infections)

• HRS-type AKI (HRS-AKI), which is defined as a potentially reversible deterioration of renal function unresponsive to volume resuscitation, caused by renal vasoconstriction in the absence of alternative identifiable causes

• intrinsic causes such as acute tubular necrosis

• postrenal causes
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Association between the liver and the kidney from a historical point of view

- in 1863 by Austin Flint

- 1920s -1950s James Gordon Heyd: Flint’s syndrome or Heyd’s syndrome

- In 1927, Furtwangler: a case series on fulminant cortical necrosis in both kidneys following hepatic trauma. He suspected endotoxin-induced vasospasm and ischemia

- During the following decades, the ‘hepatorenal syndrome’ own entity of renal failure in patients with cirrhosis characterized by fulminant progression and high mortality

- The first consensus conference on a uniform definition for the hepatorenal syndrome (HRS) took place in 1978 in Sassary, Italy.

- Understanding of the pathophysiology of HRS has led to several reclassifications and redefinitions.

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Pathophysiology of the HRS:
CLASSIC VASODILATION + NEW HYPOTHESIS: SIRS THEORY

HRS is closely linked to the development of ascites.

1988, Schrier and colleagues
HRS-AKI as part of a multiorgan failure syndrome/systemic inflammatory response syndrome (SIRS) – a new hypothesis

• Until 2007, sepsis was an exclusion criteria for HRS

• systemic inflammation also plays an important role in the development of complications of portal hypertension in cirrhosis

• SIRS and sepsis
  • SBP and sepsis represent the most common precipitating event AKI-HRS
  • supposedly lead to renal blood flow redistribution, resulting in ischemia and subsequent tubular injury
  • Toll-like receptor 4 (TLR4): overexpressed in kidney tissue and urine in patients with cirrhosis and AKI (including HRS-AKI patients) following an inflammatory insult
  • In cirrhosis, high levels of LPS increase portal pressure promoting hepatic decompensation
    • particles of the cell wall of Gram-negative bacteria and represent natural ligands to TLR4. LPS are strong pro-inflammatory factors by inducing TNF-α.
    • lead to deterioration of the systemic circulation, shock and multiorgan failure
<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Title</th>
<th>Major criteria</th>
<th>Minor criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1979</td>
<td>Earley [34]</td>
<td>Sassari’s Diagnostic Criteria</td>
<td>Progression of blood creatinine &gt; 1.5 mg/dL over several days in absence of nephrotoxins; Urine/plasma osmolality &gt; 1.0; Urine/plasma creatinine &gt; 50; Urine sodium &lt; 10 mEq/L, often &lt; 5 mEq/L; No sustained improvement after plasma expansion to a central venous pressure of 10 cm H₂O; Chronic or acute liver disease with hepatic failure and portal hypertension; Low GFR (&lt;1.5 mg/dL or 24-hour creatinine clearance &lt; 40 mL/min); Absence of shock, bacterial infection, recent treatment with nephrotoxic drugs, absence of gastrointestinal or renal fluid loss; No sustained improvement in renal function following withdrawal of diuretics and plasma expansion with 1.5 L of isotonic saline; Proteinuria &lt; 500 mg/L and absence of obstructive uropathy or renal parenchymal disease in ultrasound</td>
<td>Volume &lt; 800 mL/day; 2 urinary protein excretion; Onset of disease spontaneously over course of liver disease or in association with infections, bleeding, paracentesis, diuretic therapy or other forms of volume loss; Characteristics may be followed by tubular dysfunction; Post-mortem renal histology may be normal; Urine volume &lt; 500 mL/d; Urine sodium &lt; 10 mEq/L; Urine osmolality greater than plasma osmolality; Serum sodium concentration &lt; 130 mEq/L</td>
</tr>
<tr>
<td>1996</td>
<td>Arroyo et al. [35]</td>
<td>Definition and Diagnostic Criteria of Refractory Ascites and Hepatorenal Syndrome in Cirrhosis</td>
<td>Type I HRS: Rapid progressive reduction of renal function in &lt; 2 weeks as marked by: (i) doubling of serum creatinine to &gt; 2.5 mg/dL or (ii) 24-hour creatinine clearance &lt; 20 mL/min</td>
<td>Ongoing bacterial infections are not an exclusion criterion for the diagnosis of HRS; Type I HRS typically occurs in acute deterioration of circulatory function, characterized by arterial hypotension and activation of endogenous vasoconstrictor systems; Type II HRS is typically associated with refractory ascites</td>
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<td>2007</td>
<td>Salerno et al. [21]</td>
<td>Diagnosis, Prevention and Treatment of Hepatorenal Syndrome in Cirrhosis</td>
<td>Cirrhosis with ascites; Serum creatinine &gt; 1.5 mg/dL; No improvement of serum creatinine (increase to &lt; 1.5 mg/dL) after at least 2 days of diuretic withdrawal and volume expansion with albumin; Absence of shock; No current or recent treatment with nephrotoxic drugs; Absence of parenchymal kidney damage (proteinuria &gt; 500 mg/dL; &gt; 30 RBCs/high-power field) or abnormal renal ultrasonography</td>
<td>Type I HRS: Rapid progressive renal failure with: (i) doubling of serum creatinine to &gt; 2.5 mg/dL in less than 2 weeks or (ii) 50% reduction of 24-hour creatinine clearance to &lt; 20 mL/min in less than 2 weeks</td>
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<td>2009</td>
<td>Runyon [132]</td>
<td>AASLD Practice Guidelines Management of Adult Patients with Ascites Due to Cirrhosis: An Update</td>
<td>Cirrhosis with ascites; Serum creatinine &gt; 1.5 mg/dL; No improvement of serum creatinine (increase to &lt; 1.5 mg/dL) after at least 2 days of diuretic withdrawal and volume expansion with albumin; Absence of shock; No current or recent treatment with nephrotoxic drugs; Absence of parenchymal kidney damage (proteinuria &gt; 500 mg/dL; &gt; 30 RBCs/high-power field) or abnormal renal ultrasonography</td>
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<td>2012</td>
<td>Runyon [134]</td>
<td>Introduction to the revised AASLD Practice Guideline management of adult patients with ascites due to cirrhosis</td>
<td></td>
<td>Ongoing bacterial infections are not an exclusion criterion for the diagnosis of HRS; Type I HRS typically occurs in acute deterioration of circulatory function, characterized by arterial hypotension and activation of endogenous vasoconstrictor systems; Type II HRS is typically associated with refractory ascites</td>
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<td>2010</td>
<td>The European Association for the Study of the Liver [129]</td>
<td>EASL Practice Guidelines on the management of ascites, spontaneous bacterial peritonitis and hepatorenal syndrome in cirrhosis</td>
<td>Cirrhosis with ascites, Serum creatinine &gt; 1.5 mg/dL, Absence of shock, Absence of hypovolemia as defined by no sustained improvement of renal function 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 treatment with nephrotoxic drugs, Abnormal proteinuria (&lt; 0.5 g/day), Microhematuria of &lt; 50 RBCs/high-power field, Normal ultrasonography</td>
<td>It is important to exclude other causes of renal failure as early as possible, such as hypovolemia, shock, parenchymal renal diseases, concomitant use of nephrotoxic drugs, Parenchymal renal diseases should be suspected in presence of significant proteinuria or microhematuria, or if renal ultrasound demonstrates abnormalities, a renal biopsy may aid in exclusion of other renal diseases, HRS should be considered in case of significant increase in serum creatinine to &gt; 1.5 mg/dL, Repeated measurement of serum creatinine over time is helpful in early diagnosis of HRS, particularly in hospitalized patients, Patients with type 2 HRS may eventually develop type 1 HRS</td>
</tr>
<tr>
<td>2012</td>
<td>Nadim et al. [14]</td>
<td>Hepatorenal syndrome: the 8th international consensus conference of the Acute Dialysis Quality Initiative Group [133]</td>
<td>Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites</td>
<td>The term 'hepatorenal disorders' should be used for any renal dysfunction in advanced cirrhosis, AKI: rise in sCr &gt; 50% from baseline or by ≥ 0.3 mg/dL</td>
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<td>2015</td>
<td>Angell et al. [37]</td>
<td>HRS-AKI (former type 1 HRS): Diagnosis of cirrhosis and ascites, Diagnosis of AKI according to International Club of Ascites-AKI criteria (AKI stage 2 or 3)</td>
<td>No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with 1 g albumin per kg body weight, Abnormality of shock, No current or recent use of nephrotoxic drugs (NSAIDs, contrast media, etc.), No evidence of structural kidney injury (proteinuria &gt; 500 mg/day, &gt; 50 RBCs/high-power field, parenchymal damage in renal ultrasonography)</td>
<td>HRS-AKI does not exclude structural or tubular damage, Urinal markers may become important in the differential diagnosis of HRS and ATN</td>
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In the past two decades, 2 types of HRS:

- type 1HRS describes a fulminant decline in renal function in patients with advanced liver disease that is associated with a detrimental prognosis.

- type 2HRS is defined as slowly progressive functional renal failure that typically occurs in patients with refractory ascites.
• most recent definition criteria in 2015 EASL: type 1HRS as a special entity the ‘HRS type of AKI’ (HRS-AKI) by both
  • a community of hepatologists (ICA)
  • Acute Dialysis Quality Initiative (ADQI), a community of nephrologists
  • AKIN/KDIGO criteria that constitute the basis for the International Club of Ascites (ICA)-AKI criteria in patients with cirrhosis.
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AKI CLASSIFICATION

• three stages according to severity.
  • Stage 1 AKI small changes in sCr
  • stages 2 and 3 AKI: a two-fold and three-fold increase in sCr

<table>
<thead>
<tr>
<th>ICA-AKI Stage 1</th>
<th>Increase in serum creatinine $\geq$0.3 mg/dl or Increase in serum creatinine by $\geq$50–100% from baseline</th>
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<tr>
<td>ICA-AKI Stage 2</td>
<td>Increase in serum creatinine by $\geq$100–200% from baseline</td>
</tr>
<tr>
<td>ICA-AKI Stage 3</td>
<td>Increase in serum creatinine by $\geq$200% from baseline or Increase in serum creatinine to $\geq$4 mg/dL with an acute increase by $\geq$0.3 mg/dL or Need for renal replacement therapy</td>
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HRS type of AKI (HRS-AKI, formerly known as type 1 HRS)

- The hepatorenal syndrome type of AKI (HRS-AKI) is defined as stage 2 ICA-AKI that is diagnosed after other causes of renal failure have been ruled out.

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**Diagnostic criteria of hepatorenal syndrome**

- Presence of cirrhosis and ascites
- No improvement in serum creatinine after 2 consecutive days of withdrawal of diuretics and plasma volume expansion with albumin (1 g per kg of body weight, maximum 100 g/day)
- Absence of shock
- Exclusion of recurrent or recent use of nephrotoxic agents (e.g. NSAIDs, aminoglycosides, contrast media)
- Exclusion of parenchymal kidney disease:
  - absence of proteinuria (>500 mg/day)
  - absence of microhematuria (>50 RBCs per high-power field)
  - normal renal ultrasonography

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HRS type of AKI (HRS-AKI, formerly known as type 1 HRS)

• the newer ICA criteria focus on the relative increase in creatinine rather than absolute values
  • In order to prevent misclassification
  • treatment delay,
  • since also smaller rises in SCr (e.g. in case of stage 1 AKI) have been shown to have a negative prognostic impact in patients with cirrhosis.
• threshold of 2.5mg/dL NOT A CRITERIA
• Neither Oliguria
Hepatorenal syndrome type 2 (HRS-CKD)

- Type 2HRS: prevalence ranges from 16% - 61%
  - stable or slowly progressive impairment in renal function
  - patients with decompensated liver disease
  - refractory ascites
  - usually oliguria over a course of several weeks or months, marked by excessive salt and water retention and a slow but steady incline in renal retention parameters
  - a diagnosis by exclusion
    - one or several other potential causes for kidney disease
  - same specific diagnostic criteria for HRS-AKI
  - prognosis in HRS type 2 is poor
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Management of AKI and specific treatment for HRS-AKI

• early recognition
• correction of potential trigger events
• Preventing further hemodynamic deterioration: non-selective betablockers
• review of all medications drugs
  • Nephrotoxics
  • may induce or aggravate arterial hypotension (e.g. vasodilators or non-selective beta-blockers [NSBBs])
• In volume-depleted patients,
  • diuretic therapy and/or lactulose should be withdrawn
  • plasma volume should be expanded with albumin, or blood transfusions in anemic patients
• Early empiric antibiotic treatment
Management of AKI and specific treatment for HRS-AKI

- therapeutic response
  - Decrease of sCr to a value within 0.3 mg/dL of baseline

- Patients should be followed closely for early detection of recurrent episodes of AKI.

- Follow-up assessment of sCr
  - every 2–4 days during hospitalization
  - every 2–4 weeks during the first 6 months
Management of AKI and specific treatment for HRS-AKI

• AKI stage 2 or 3 or presence of HRS-AKI
  • diuretics should be withdrawn immediately

• plasma volume expansion with albumin for 2 consecutive days (1 g per kg of body weight, maximum 100 g/day) then ongoing with 20–40 g/day
  • Albumin is particularly beneficial in patients with SIRS or sepsis, since it has scavenging, anti-oxidant and endothelial-stabilizing functions.
Management of AKI and specific treatment for HRS-AKI

• vasoconstrictors (i.e. terlipressin, norepinephrine or midodrine plus octreotide) in combination with i.v. albumin
  • A bolus of terlipressin significant reduction in portal pressure over a 3- to 4-hour period and also increases mean arterial pressure
  • continuous infusion might be preferred over bolus administration
  • caution in patients with cardiovascular disease
  • impact on survival is less clear
  • beneficial in patients with SIRS or sepsis and might also prevent variceal bleeding during the period of discontinuation of NSBBs
  • Norepinephrine (initial dose: 0.5mg/hour; max. dose studied in randomized controlled trials: 3mg/hour) is an equally effective
Management of AKI and specific treatment for HRS-AKI

• Complete response decrease in sCr to a value within 0.3mg/dL of baseline

• A regression of at least one AKI stage is considered as partial response

• If there is no response after 3 days of treatment, the vasoconstrictor dose should be increased.

• In non-responders, treatment should be discontinued after 14 days.

• In responders, longer treatment durations can be used as a bridging therapy to liver transplantation.
Management of AKI and specific treatment for HRS-AKI

- (TIPS) may represent a good bridging strategy to liver transplantation—especially in patients with HRS type 2
- CI:
  - cardiac insufficiency,
  - pulmonary hypertension
  - uncontrolled systemic infections
  - or sepsis and biliary obstruction
  - anatomical abnormalities
- NO survival benefit of renal replacement therapy (RRT) or extracorporeal liver support (ELS) for HRS-AKI and HRS type 2
  - Bridge to LT.?
Stage 1 AKI

Close monitoring
Remove risk factors (withdrawal of nephrotoxic drugs, vasodilators and NSAIDs, decrease/withdrawal of diuretics, treatment of infections* when diagnosed), plasma volume expansion in case of hypovolemia

Resolution Stable Progression

Close follow up

Futher treatment of AKI decided on a case-by-case basis

Stage 2 and 3 AKI

Withdrawal of diuretics (if not withdrawn already) and volume expansion with albumin (1 g/kg) for 2 days

Response

YES NO

Meets criteria of HRS

NO YES

Specific treatment for other AKI phenotypes Vasoconstrictors and albumin
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future perspectives

• Novel urinary biomarkers
  • urinary neutrophilgelatinase-associated lipocalin (uNGAL):
    • urinary biomarker for tubular damage
  • Interleukin 18 (IL-18)
    • kidney injury molecule-1 (Kim-1) and liver-type fattyacid binding protein

• High with ATN and low in patients with prerenal azotemia, with levels in HRS-AKI in the intermediate range
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TAKE HOME MESSAGE

• AKI is a frequent event for cirrhotic hospitalized patients
• Even small increase of creatinine may lead to worse prognosis of cirrhosis
• HRS-AKI and HRS-CKD have poor prognosis
• Early detection and management may improve outcome.
• Mortality is still 60% in HRS.
• THANK YOU