Liver-Kidney Crosstalk in Liver and Kidney Diseases

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Hepatonephrologist busily at work. Original artwork by Thomas Mattix, Mattix
GFR measurements in Liver Disease

• Accurate estimation of glomerular filtration rate (GFR) in liver disease is important for detection of kidney disease, safe drug dosing, and allocation of organs.

• All methods that use creatinine to estimate GFR overestimate GFR, and the degree of overestimation is highest when GFR is lower and liver disease is more severe.

• The use of cystatin C to estimate GFR in liver disease is potentially promising but has yielded mixed results.
GFR measurements in Liver Disease

Low creatinine production
  • Low muscle mass
  • Low liver production of creatine
  • Malnutrition

Interference with creatinine assays
  • High bilirubin
Hepatitis B in CKD/ESRD

• Goal of treatment of chronic HBV is to achieve sustained suppression of HBV replication to prevent cirrhosis, hepatic failure, and HCC

• Currently, there are 5 oral agents that have been approved for the treatment of chronic HBV infection: 3 nucleoside (lamivudine, telbivudine, and entecavir) and 2 nucleotide (adefovir dipivoxil and tenofovir disoproxil fumarate) analogues
Hepatitis B in CKD/ESRD

• The main advantages of nucleos(t)ide analogues (NA), compared with interferon, is that they have high antiviral potency and on-therapy efficacy, improved safety and tolerability profiles, and the convenience of oral administration

• Entecavir and Tenofovir- 1st line

• One year virological remission rates of 67% to 76% in HBeAg-positive and 90% to 93% of HBeAg-negative patients

• 3-, 5-, and 6-year accumulating/maintaining remission rates of greater than 90% with minimal risk of resistance (1.2% for entecavir and 0% for tenofovir at 5-6 years)
Anti-HBV therapy and Nephrotoxicity

- Cumulative mean loss of eGFR after 1, 3, and 5 years was −3.8, −5.5, and 10.3 mL/min/1.73 m², respectively with Tenofovir.
- In addition to impaired creatinine clearance, adefovir or Tenofovir can cause proximal tubule dysfunction (by disrupting mitochondrial DNA replication, causing subsequent mitochondrial dysfunction, and impaired cell function and/or death)- leads to the development of hypophosphatemia.
- Dose in ESRD: once weekly after HD (50% cleared by hemodialysis)
Hepatitis C in CKD/ESRD

• All patients except those with limited life expectancy should be treated
• Urgent initiation of treatment should be offered to patients with advanced fibrosis (Metavir F3), compensated cirrhosis (Metavir F4), liver transplant candidates, and patients with severe extrahepatic manifestations of HCV (eg, Type 2 or 3 essential mixed cryoglobulinemia with end-organ manifestations, nephrotic syndrome, membranoproliferative glomerulonephritis).
HCV in ESRD Treatment

- Six distinct HCV genotypes that have been identified. The vast majority of patients with chronic HCV are infected with genotypes 1 to 3 (in the United States, 70% with Genotype 1 [a and b], 16% with Genotype 2, 12% with Genotype 3, 1% with Genotype 4, and <1% with Genotype 5, and 1% with Genotype 6.)
HCV in ESRD Treatment

• 3 highly effective and well-tolerated options for the initial treatment of Genotype 1
  • Fixed dose of Paritapavir (protease inhibitor), Ritonavir and Ombitasvir (nucleoside polymerase inhibitor) plus Dasabuvir (non-nucleoside polymerase inhibitor) and Ribavirin for 12-24 weeks- Sustained Virologic Response of 95-97% (SAPPHIRE-1 and PEARL-VI trials)
  • Second: fixed dose combination of Ledipasvir and Sofosbuvir for 12 weeks- SVR of 95-99% (ION-1 and ION-3 trials)
  • Third option: Simepravir (protease inhibitor), plus Sofosbuvir (non-nucleoside polymerase inhibitor) for 12-24 weeks
Anti-HCV Therapies and Renal Function

• In mild-to-moderate kidney impairment (CrCl >30 mL/min), no dosage requirement is required when using sofosbuvir, simeprevir, fixed-dose combination of ledipasvir, sofosbuvir, or fixed-dose combination of paritaprevir/ritonavir/ombitasvir plus dasabuvir to treat or retreat HCV infection (Class I, Level A). For patients with CrCl <30 mL/min, treatment can be considered by an expert because data on safety and efficacy are not available for these patients (Class IIb, Level C)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mild Kidney Impairment (eGFR 60-89 mL/min)</th>
<th>Moderate Kidney Impairment (eGFR 30-59 mL/min)</th>
<th>Severe Kidney Impairment (eGFR &lt;30 mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paritaprevir</td>
<td>19% ↑</td>
<td>33% ↑</td>
<td>45% ↑</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>42% ↑</td>
<td>80% ↑</td>
<td>114% ↑</td>
</tr>
<tr>
<td>Dasabuvir</td>
<td>21% ↑</td>
<td>37% ↑</td>
<td>50% ↑</td>
</tr>
<tr>
<td>Ombitasvir</td>
<td>Unchanged</td>
<td>Unchanged</td>
<td>Unchanged</td>
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</tbody>
</table>

Abbreviations: AUC, area under the curve; eGFR, estimated glomerular filtration rate.
Anti-HCV Therapies and Renal Function

• In subjects with ESRD, Sofosbuvir and GS-331007 AUC were 28% and 1280% higher, respectively, when Sofosbuvir was administered 1 hour before HD in contrast to 60% higher and 2070% higher, respectively, when Sofosbuvir was dosed 1 hour after HD (there were no studies performed in peritoneal dialysis).
• Doses that should be used for patients with severe kidney impairment or ESRD is unclear.
• Ongoing studies to address the question.
Dialysis Modalities in ESRD patients with Cirrhosis- Issues with HD

- Increased risk of bleeding. This causes problems in patients with arteriovenous access. Catheters have increased risk of infection and catheter malfunction.
- No evidence-based recommendation regarding the use of anticoagulants in cirrhotic patients, but minimum use of anticoagulation should be the goal

Dialysis Modalities in ESRD patients with Cirrhosis- Issues with HD

Intradialytic hypotension: Limits the amount of ultrafiltration and results in sustained or worsening ascites. Patients with cirrhosis and ascites have decreased peripheral vascular resistance due to a variety of reasons, including cardiac dysfunction, high circulating levels of nitric oxide (peripheral and splanchnic vasodilatation) and systemic inflammation.

- Sudden reduction in intravascular volume by ultrafiltration during HD exacerbates the hypotension. Higher levels of nitric oxide during HD could further complicate this.
- HD can exacerbate encephalopathy (increased brain water).
- Dialysis adequacy measures are inaccurate due to slower urea equilibration after HD.

Dialysis Modalities in ESRD patients with Cirrhosis

Advantages of peritoneal dialysis
• No need for anticoagulation
• Less hypotension
• Drainage of ascitic fluid
• Continuous solute clearance
• Caloric loading with glucose

Disadvantages of Peritoneal Dialysis
• Protein losses into dialysate (Selgas et al., protein losses were initially high, at >30 g/day, and decreased significantly over time, to <10 g/day)
• Increased peritonitis rates (?) and inability to perform due to limited manual dexterity
Hepatic portal venous gradient (HPVG) is normally 5 mm Hg or less. Ascites will not develop unless HPVG is 10-12 mm Hg or more.

Development of HRS requires Portal Hypertension.
Spectrum of renal diseases in cirrhosis

Acute kidney injury
- Structural renal disease e.g. ATN, GN
- Post-renal obstruction

Functional renal failure
- Pre-renal azotemia
- HRS–AKI
- Non-HRS–AKI
- HRS–CKD

Nature Reviews | Gastroenterology & Hepatology

Causes of AKI in Cirrhosis

Pre-renal (68%)-
66% are volume responsive
Not volume responsive-34%
• HRS type 1 (25%)
• HRS type 2 (9%)

Intrarenal (32%)
Obstruction/nephrotoxic (less than 1%)
New AKI definition in Cirrhosis

<table>
<thead>
<tr>
<th>Subject</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>Baseline sCr</td>
<td>A value of sCr obtained in the previous 3 months, when available, can be used as baseline sCr. In patients with more than one value within the previous 3 months, the value closest to the admission time to the hospital should be used. In patients without a previous sCr value, the sCr on admission should be used as baseline.</td>
</tr>
<tr>
<td>Definition of AKI</td>
<td>Increase in sCr ≥0.3 mg/dL (≥26.5 μmol/L) within 48 h; or a percentage increase sCr ≥50% from baseline which is known, or presumed, to have occurred within the prior 7 days.</td>
</tr>
<tr>
<td>Staging of AKI</td>
<td>Stage 1: increase in sCr ≥0.3 mg/dL (26.5 μmol/L) or an increase in sCr ≥1.5-fold to twofold from baseline.</td>
</tr>
<tr>
<td></td>
<td>Stage 2: increase in sCr &gt;two to threefold from baseline.</td>
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<td></td>
<td>Stage 3: increase of sCr &gt;threefold from baseline or sCr ≥4.0 mg/dL (353.6 μmol/L) with an acute increase ≥0.3 mg/dL (26.5 μmol/L) or initiation of renal replacement therapy.</td>
</tr>
<tr>
<td>Progression of AKI</td>
<td>Progression of AKI to a higher stage and/or need for RRT</td>
</tr>
<tr>
<td>Response to treatment</td>
<td>No response</td>
</tr>
<tr>
<td></td>
<td>Partial response</td>
</tr>
<tr>
<td></td>
<td>No regression of AKI</td>
</tr>
<tr>
<td></td>
<td>Regression of AKI stage with a reduction of sCr to ≥0.3 mg/dL (26.5 μmol/L) above the baseline value.</td>
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<tr>
<td></td>
<td>Regression of AKI to a lower stage</td>
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<td></td>
<td>Full response</td>
</tr>
<tr>
<td></td>
<td>Return of sCr to a value within 0.3 mg/dL (26.5 μmol/L) of the baseline value.</td>
</tr>
</tbody>
</table>

AKI, acute kidney injury; RRT, renal replacement therapy; sCr, serum creatinine.
HRS-AKI

Box 1  Diagnostic criteria of hepatorenal syndrome (HRS) type of acute kidney injury (AKI) in patients with cirrhosis

**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.

ICA, International Club of Ascites; NSAIDs, non-steroidal anti-inflammatory drugs; RBCs, red blood cells.
HRS- Functional Nature

Johnson Feehalyy
Pathogenetic mechanism of acute kidney injury in cirrhosis

The pathogenesis of hepatorenal syndrome

- GI bleeding
- Spontaneous bacterial peritonitis/infections/bacterial translocation
- Large Volume Paracentesis
- Overdiuresis
- Inflammation: Cytokines, Nitric oxide
- Sinusoidal portal hypertension and Systemic arterial vasodilatation
- Hypoperfusion
- Cholestasis
- Liver and kidney dysfunction
The Pathogenesis of Hepatorenal Syndrome

Severe baseline circulatory dysfunction
Splanchnic vasodilation and cardiac dysfunction

Excessive inflammatory response to infection or to other precipitating event

Rapid deterioration of cardiovascular function and organ blood perfusion

Kidneys

Intrarenal vasodilator imbalance
Type 1 HRS

Other organs

Liver
Jaundice, coagulopathy

Brain
Encephalopathy

Adrenal glands
Adrenal insufficiency

Gut
Increased translocation of bacteria and endotoxins
Pathogenesis of Hepatorenal Syndrome

• Hemodynamic changes
• Mesangial contraction (endothelin-1 mediated)
• Hepatic dysfunction (Acute on Chronic Liver Failure)
• Precipitating factors (GI bleed, infections, diuretics, large volume paracentesis, nephrotoxins)
Hemodynamic factors in HRS

Cirrhosis and portal hypertension

Arterial vasodilatation

RAAS

SNS

Central hypovolaemia
hypodynamic circulation

Hepatorenal syndrome

Cirrhotic cardiomyopathy

Hepatopulmonary syndrome
Renal Blood Flow in Cirrhotic Cardiomyopathy

**Fig. 2.** Renal blood flow (RBF) decreases with the advancement of renal vasoconstriction and the clinical stage (47). Data originally published by Ring-Larsen H. in Scand J Clin Lab Invest 1977.
Potential impact of ‘cirrhotic cardiomyopathy’.

<table>
<thead>
<tr>
<th>Cardiac morphology</th>
<th>Normal</th>
<th>Hypertrophy (Fibrosis, oedema)</th>
<th>Hypertrophy/ Dilatation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac function</td>
<td>Normal</td>
<td>Diastolic dysfunction</td>
<td>Systolic dysfunction/ Cardiac failure</td>
</tr>
<tr>
<td>Hepatic function</td>
<td>Compensated cirrhosis</td>
<td>Compensated/Mild uncompensated cirrhosis Asciots</td>
<td>Decompensated cirrhosis Ascites Renal dysfunction</td>
</tr>
<tr>
<td>Systemic circulation</td>
<td>Signs of vasodilatation</td>
<td>Hyperdynamic state</td>
<td>Hyperdynamic state/ Decreasing cardiac output</td>
</tr>
<tr>
<td>Cardiac findings</td>
<td>QT↑</td>
<td>QT↑↑, E/A ↓, DT↑, LVEF↑</td>
<td>QT↑↑, Dysynchronised electrical and mechanical systole, LAV and LVEDVT↑, LVEF</td>
</tr>
</tbody>
</table>

Søren Møller, and Mauro Bernardi Eur Heart J 2013;34:2804-2811
Mesangial cell contraction in Hepatorenal Syndrome

Liver disease
AVP, Thromboxane A2 and Endothelin-1
Mesangial cell contraction
Decreased $K_{UF}$

Figure 3: The glomeruli within the kidney are dynamic structures, invaginated with mesangial cells which express actin. These contractile cells control the surface area of glomeruli available for filtration. The cells contract in response to certain agonists such as endothelin 1 (ET-1), thromboxane A$_2$ (TXA$_2$), arginine vasopressin (AVP), or leukotriene D$_4$ (LTD$_4$). Vasodilatory prostaglandins such as prostaglandin E$_2$ (PGE$_2$) can cause relaxation of mesangial cells.

Dagher, M. Gut 2001;49:729–737
NSAID Sensitivity in Liver Disease

Indomethacin was administered to patients with Cirrhosis and Ascites

Role of Portal Hypertension (hepatorenal reflex)

• Linked to systemic vasodilatory state
• Sinusoidal hypertension and portal vein distension leads to increased renal sympathetic activity and vasoconstriction
Role of Hepatic Dysfunction in HRS

- Role of nitric oxide
- Increased renal sensitivity to norepinephrine
- Increased bile acids- systemic vasodilatation
- Increased systemic inflammation
Renal dysfunction in cirrhosis is not just a vasomotor nephropathy

Renal dysfunction on the background of cirrhosis

- Chronic kidney disease
  - independent of underlying cirrhosis or associated with it
- Associated with circulatory dysfunction in cirrhosis

Hypovolemia
- Good response to fluids
- Tubular markers of renal injury are usually absent
- The kidneys are histologically normal

Hepatorenal syndrome
- Moderate response to terlipressin/albumin
- Tubular markers of renal injury may be present
- The kidneys are likely to be histologically normal

Associated with infection/inflammation and possible kidney injury
- Poor response to terlipressin/albumin
- Tubular markers of renal injury are highly likely to be present
- The kidneys are likely to be histologically abnormal
Acute-on-Chronic Liver Failure (ACLF)

• Distinct from traditional decompensated cirrhosis
• Based not only on the presence of organ failure(s) and high mortality rate
• Younger age, alcoholism, precipitating events (bacterial infections, active alcoholism), and higher levels of systemic inflammation.
• ACLF is cannot be explained entirely by severe sepsis or severe alcoholic hepatitis
• ACLF is occurs in 31% of hospitalized patients with cirrhosis who have an acute complication of their liver disease. In these patients, ACLF is the most common cause of death
Acute-on-Chronic Liver Failure (ACLF)

Jalan, R et al. Journal of Hepatology 2012 vol. 57, 1336–1348
Systemic Inflammatory Response Syndrome in Cirrhosis

- Cytokine-induced hepatocyte apoptosis and necrosis
- ER stress blocks protein synthesis
- Altered liver reserve

Sepsis
- Endotoxemia
- NO
- Inflammatory cytokines
- Vasodilatation
- Organ perfusion

Acute renal failure
- 24–27% in SBP-unrelated sepsis
- 30–40% in SBP-related sepsis

Death

Acute-on-chronic liver failure

Circulatory failure
- HRS
- Ischemic ATN
- Toxic ATN

Respiratory failure
- ARDS

Coagulation failure
- Tissue factor activation
- DIC

Relative adrenal insufficiency
- Vascular hyporesponsiveness
- Septic encephalopathy

Short-term mortality: 10–20% without organ failure, 30–50% with 1 organ failure, and 55–100% with >1 organ failure

ATN: acute tubular necrosis; ARDS, acute respiratory distress syndrome; DIC, disseminated intravascular coagulation; ER, endoplasmic reticulum; HRS, hepatorenal syndrome; LV, left ventricle; NO, nitric oxide
Bacterial translocation and SIRS

Sarin, SK et al. NATURE REVIEWS GASTROENTEROLOGY &
Cholestasis and Renal Dysfunction

• Possible due to increased F2-Isoprostanes
• Systemic circulatory dysfunction
• Bile casts
Bile cast nephropathy

• ~85% of patients who were diagnosed with HRS had evidence of renal tubular bile casts

• Terlipressin was effective in only 13% of patients with serum bilirubin levels >10 mg/dl compared with 67% of patients with lower serum bilirubin levels

• In bile duct–ligated mouse model, a significantly higher serum bile acid level associated with AKI and tubular injury

Intra-abdominal Hypertension and Post-Paracentesis Circulatory Dysfunction

- Intra-abdominal pressure (IAP) of >12 mm Hg
- Up to 11% of patients with refractory ascites develop HRS: Renal biopsy of animals with IAP showed evidence of constrictive renal tubular lumen, interstitial inflammatory infiltrates, casts and hyperemia in the renal interstitium
- An abrupt drop in IAP following large volume paracentesis, without the use of plasma expanders, may actually precipitate HRS

Proposed algorithm for the management of AKI in Cirrhosis

Stage 1 AKI
- Close monitoring:
  - Remove risk factors (withdrawal of nephrotoxic drugs, vasodilators and NSAIDs, decrease or withdrawal of diuretics, treatment of infections* when diagnosed), plasma volume expansion in case of hypovolaemia

  Resolution
  Stable
  Progression

  Close follow up

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

  Further treatment of AKI decided on a case-by-case basis
  Specific treatment for other AKI phenotypes
  Vasoconstrictors and albumin

Modified with permission from BMJ © Angeli, P. et al. Gut 64, 531–537 (2015)
Role of TIPS in HRS

- Mortality rates are 1% to 2%, and the morbidity rate is 10%
- Arrhythmias, hemolysis, worsening of liver function and encephalopathy
- Shunt stenosis can occur
- A long-term study of 31 cirrhotic patients with HRS (14 type 1 and 17 type 2) who were not transplant candidates and did not have severe liver failure confirmed that TIPS improved renal function and survival compared with controls

Johnson and Feehally. Comprehensive Clinical
Extracorporeal Liver Support Therapy

- Numerous studies have suggested that albumin dialysis (molecular adsorbent recirculating system [MARS] or fractionated plasma separation and adsorption [FPSA]) may have beneficial effects in patients with type 1 HRS.
- Particular benefit in sicker patients with MELD score more than 30.
Liver Transplantation for HRS

- Liver transplantation is the treatment of choice in patients with advanced cirrhosis, with type 1 and type 2 HRS.
- The hemodynamic and neurohumoral changes improve within 1 month after transplant.
- With HRS, lower 3-year survival after transplant (60%) compared to those without HRS (80%).
- Up to 7% patients remain dialysis dependent and have chronic damage features (proteinuria).
Indications for Simultaneous Liver-Kidney Transplant in Cirrhosis

Thank You