RENAL DISEASE
IN END STAGE LIVER DISEASE

Mitchell L Shiffman, MD
Director
Liver Institute of Virginia
Bon Secours Health System
Richmond and Newport News, VA
## POTENTIAL CONFLICTS OF INTEREST

<table>
<thead>
<tr>
<th>Company</th>
<th>Roles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbvie</td>
<td>Advisor meetings, Grant support, Speaker</td>
</tr>
<tr>
<td>Bayer</td>
<td>Speaker</td>
</tr>
<tr>
<td>Bristol Myers-Squibb</td>
<td>Advisor meetings, grant support, Speaker</td>
</tr>
<tr>
<td>Conatus</td>
<td>Grant support</td>
</tr>
<tr>
<td>CymaBay</td>
<td>Grant support</td>
</tr>
<tr>
<td>Daiichi Sankyo</td>
<td>Speaker</td>
</tr>
<tr>
<td>Exalenz</td>
<td>Grant support</td>
</tr>
<tr>
<td>Galectin</td>
<td>Grant support</td>
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<tr>
<td>Genfit</td>
<td>Grant support</td>
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<tr>
<td>Gilead</td>
<td>Advisor meetings, Grant support, Speaker</td>
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<tr>
<td>Intercept</td>
<td>Advisor meetings, Grant support, Speaker,</td>
</tr>
<tr>
<td>Immuron</td>
<td>Grant support</td>
</tr>
<tr>
<td>Merck</td>
<td>Grant support, Advisor meetings, Speaker,</td>
</tr>
<tr>
<td>NGM Bio</td>
<td>Grant support</td>
</tr>
<tr>
<td>Novartis</td>
<td>Grant support</td>
</tr>
<tr>
<td>Optum Rx</td>
<td>Consulting</td>
</tr>
<tr>
<td>Salix</td>
<td>Advisor meeting</td>
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<tr>
<td>Shire</td>
<td>Grant support</td>
</tr>
</tbody>
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## CanMEDS Roles Covered

<table>
<thead>
<tr>
<th>Role</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Expert</td>
<td>(as Medical Experts, physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional values in their provision of high-quality and safe patient-centered care. Medical Expert is the central physician Role in the CanMEDS Framework and defines the physician’s clinical scope of practice.)</td>
</tr>
<tr>
<td>Communicator</td>
<td>(as Communicators, physicians form relationships with patients and their families that facilitate the gathering and sharing of essential information for effective health care.)</td>
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<tr>
<td>Collaborator</td>
<td>(as Collaborators, physicians work effectively with other health care professionals to provide safe, high-quality, patient-centred care.)</td>
</tr>
<tr>
<td>Leader</td>
<td>(as Leaders, physicians engage with others to contribute to a vision of a high-quality health care system and take responsibility for the delivery of excellent patient care through their activities as clinicians, administrators, scholars, or teachers.)</td>
</tr>
<tr>
<td>Health Advocate</td>
<td>(as Health Advocates, physicians contribute their expertise and influence as they work with communities or patient populations to improve health. They work with those they serve to determine and understand needs, speak on behalf of others when required, and support the mobilization of resources to effect change.)</td>
</tr>
<tr>
<td>Scholar</td>
<td>(as Scholars, physicians demonstrate a lifelong commitment to excellence in practice through continuous learning and by teaching others, evaluating evidence, and contributing to scholarship.)</td>
</tr>
<tr>
<td>Professional</td>
<td>(as Professionals, physicians are committed to the health and well-being of individual patients and society through ethical practice, high personal standards of behaviour, accountability to the profession and society, physician-led regulation, and maintenance of personal health.)</td>
</tr>
</tbody>
</table>
RENAL DISEASE IN ESLD CATEGORIES

• Renal disease develops in 20-25% of patients with cirrhosis
  ▪ Systemic disorder causing renal and liver disease
  ▪ A renal disease which is separate from the liver disease
  ▪ Renal disease that is caused by ESLD

• Overall survival is poor:
  ▪ 50% at 1 month
  ▪ 20% at 6 months

66 year old male with chronic HCV and bridging fibrosis by LBX. He had a virologic response then relapse with PEGINF and RBV in 2010 and PEGINF-BOC-RBV in 2012. He now has increasing lethargy, swelling of the abdomen and lower extremities.

**EXAM:** Sclera anicteric, obvious ascites, 3+ lower extremity edema.

**LABS:** Sodium 141, creatinine 3.1 mg/dL, TBILI 1.0 mg/dL, albumin 1.5 g/dL, INR 1.0
UA: 4+ protein, 1+ blood
CTP 8, MELD 20,

**US:** Echogenic liver consistent with chronic liver disease.
# RENAL DISEASE IN ESLD SYSTEMIC DISORDERS

<table>
<thead>
<tr>
<th></th>
<th>Liver Disease</th>
<th>Renal Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viruses</td>
<td>Chronic HCV or HBV</td>
<td>Glomerulonephritis</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>NASH</td>
<td>Diabetic nephropathy</td>
</tr>
</tbody>
</table>
| Infiltrative disorders | Amyloidosis  
Myeloma                      | Amyloidosis  
Myeloma                    |
| Hypotension         | Shock liver                    | ATN                         |
| Drug toxicity       | Acute necrosis                 | ATN                         |
A 42 year old female with cirrhosis secondary to ETOH. She has never developed a complication of cirrhosis. She has not consumed ETOH since she first found out she had cirrhosis. PMH is significant for poorly controlled HTN and CKD with baseline Screat 3.5 mg/dL.

EXAM: No ascites. No edema. No asterixis.
LABS: Sodium 141, creatinine 3.8 mg/dL, TBILI 1.0 mg/dL, albumin 4.0 g/dL, INR 1.0 CTP score 7, MELD 19, Fibroscan 42 kPa
RENAL DISEASE IN ESLD
BASIC PRINCIPLES

• The kidney is more susceptible to acute injury in patients with cirrhosis
  ▪ Dehydration
  ▪ Hypotension
  ▪ Medications
• Serum creatinine under estimates GFR in patients with cirrhosis
  ▪ Especially in patients with muscle wasting
  ▪ Screat of > 1.5 mg/dL is indicative of severe renal impairment
• Ascites precedes the development of CKD or HRS in patients with cirrhosis
• Kidney function declines with worsening liver disease and leads to excess mortality

NK Bozanich, PY Kwo
Clin Liver Dis 2015: 19; 45-56.
For patients with moderate liver impairment:
- TBILI of 2.5 mg/dL
- INR 1.5

Screatinine has the greatest impact on MELD score

In general there is a 1 point increase in MELD for each 0.25 point increase in Screat

Hyponatremia increases the MELD especially when this is low
A 67 year old male with cirrhosis secondary to Primary HFE. A variceal bleeding 1 year ago was treated with banding. Mild ascites resolved with step 1 diuretics. Mild HE is well controlled with lactulose QD. Phlebotomy has reduced ferritin to under 50 ng/ml. He developed severe hip pain has been taking NSAIDS for the past 3 months.

EXAM: No obvious ascites. 2+ lower extremity edema.
LABS: Sodium 141, creatinine 2.4 mg/dL, TBILI 1.5 mg/dL, albumin 3.5 g/dL, INR 1.3 CTP 8, MELD 19 Urine NA 45 mEq
AKI AND CIRRHOSIS
AVOID NEPHROTOXIC AGENTS

• Cirrhosis increases the susceptibility of the kidney to develop acute nephrotoxicity
• NSAIDs
  ▪ Inhibit renal prostaglandin production
  ▪ Decrease GFR
• Neomycin
  ▪ Portal hypertension increases intestinal mucosal permeability
• ACE inhibitors
  ▪ Lead to sodium retention
• IV contrast during imaging studies
NSAID INDUCED AKI WITH CIRRHOSIS PROGNOSIS

CIRRHOSIS AND PORTAL HYPERTENSION IMPACT ON RENAL FUNCTION

- Portal Hypertension
  - Decrease SVR
  - Increase Renin-Angiotensin
  - Increase Vasopressin
  - Sodium retention
  - Decreased GFR
  - Water retention

- Increased epinephrine
  - Sympathetic tone
  - Increased Cardiac Output

- Bacterial translocation
- Inflammatory cytokines
- Dilatation of splanchnic arteries
RENAL DISEASE IN ESLD
ROLE OF ASCITES

- The MOST common complication of ESLD
- Leads to other complications:
  - SBP
  - Hyponatremia
  - AKI
  - CKD
  - Hepatorenal syndrome

G D'Amico et al.
COMPLICATIONS OF ASCITES INCREASE MORTALITY

RENAL DISEASE IN ESLD
CASE 4-ACUTE AKI

- Most patients with cirrhosis and AKI do not have HRS
- Dehydration from
  - Diuretics
  - Bleeding
- Readily reversible:
  - Volume expansion
  - IV albumin to limit ascites
  - Some normal saline
  - Stop diuretics

![Graph showing the decrease in creatinine levels over 20 days.]

**IV albumin 25 gm Q6H**
45 year female with cirrhosis secondary to NASH. She developed ascites for the first time 1 year ago. This initially resolved with step 1 diuretics. This is her 6\textsuperscript{th} hospitalization in the past 3 months for ascites and AKI. During each hospitalization she is given 0.9\% NS to correct hyponatremia and started back on diuretics. She has had 6 paracentesis removing 5-8 liters each. HE is treated with lactulose and rifaxamine.

**EXAM:** 5’2”; 250 pounds, distended abdomen with obvious ascites, 4+ edema to the hips. Mild HE. No muscle wasting.

**LABS:** Sodium 115, K 4.5, creatinine 2.1 mg/dL, TBILI 1.1 mg/dL, Albumin 1.8 g/dL, INR 1.3, CTP 10, MELD 26
HYPONATREMIA AND AKI
INTRAVENOUS ALBUMIN

PA McCormick et al.
Gut 1990; 31:204-207.
RENAL DISEASE IN ESLD
ROLE OF IV ALBUMIN

- Improves vascular oncotic pressure
  - Enhances movement of tissue fluid into vasculature
  - Decreases edema
  - Decreases ascites
- Expands vascular space
  - Improves renal perfusion
  - Enhances urine output
  - Increases serum sodium
  - Lowers Serum Creatinine

- Dose is 25 gm Q 6 H until
  - Anasarca resolved
  - Sodium back to normal
  - Creatinine back to normal or plateaued
  - Start diuretics once Sna > 130
SEVERE ASCITES AND ANASARCA
IV ALBUMIN

- Start IV albumin 25 gms
- Q6 hours
- Large volume paracentesis on admission
- Use for several days until serum sodium improved and creatinine is normal then add diuretics
- Continue IV albumin until serum sodium is normal
- Discharge on oral diuretics
- Anasarca
IV ALBUMIN IN SBP

- Occurs in 30% with ascites
- In hospital mortality 20%
- Mortality and AKI reduced significantly with IV albumin
  - RCT, N=126
  - Cefotaxime + IV albumin
  - Mean age 60 years
  - ETOH cirrhosis 30%
  - Mean CTP score 10
  - Culture positive 54%
  - E Coli 21%

P Sort et al
IV ALBUMIN AS MAINTENANCE THERAPY

- Randomized controlled trial
- SOC vs IV albumin
- 40 mg BIW x 2 weeks then QW
- N=431
- 33 Italian centers
- Inclusion criteria:
  - Ascites
  - Spironolactone >200 mg/d
  - Furosemide > 25 mg QD

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<thead>
<tr>
<th></th>
<th>ALB</th>
<th>SOC</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>77%</td>
<td>66%</td>
<td>0.028</td>
</tr>
<tr>
<td>Survival (OR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paracentesis</td>
<td>0.46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refractory ascites</td>
<td>0.54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>0.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-SBP infections</td>
<td>0.70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AKI</td>
<td>0.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HRS</td>
<td>0.38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HE Stage III-IV</td>
<td>0.48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variceal bleeding</td>
<td>1.07</td>
<td></td>
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P Caraceni et al.
EASL 2017
RENAL DISEASE IN ESLD
HEPATORENAL SYNDROME

- Cirrhosis and ascites
  - Serum creatinine > 1.5 mg/dL
  - Urine sodium <10 mEq/L
  - Urine output less than 500 cc/day
  - Serum sodium < 130 mEq/L
  - Absence of hematuria, proteinuria or intrinsic renal disease
  - Absence of urinary tract obstruction
  - No response to volume expansion with IV albumin
- Type 1: Cirrhosis with rapidly progressive renal failure
- Type 2: Cirrhosis with subacute renal failure
- HRS in the setting of ALF

F Salerno
HEPATORENAL SYNDROME
TYPE 1 AND TYPE 2

<table>
<thead>
<tr>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid rise in Screat which doubles to &gt;2.5 mg/dL within days - 2 weeks</td>
<td>Slow rise in Screat over weeks to months</td>
</tr>
<tr>
<td>Precipitating factor</td>
<td>No precipitating factor</td>
</tr>
<tr>
<td>Infection</td>
<td>Bacterial infections</td>
</tr>
<tr>
<td></td>
<td>Fungal infections</td>
</tr>
<tr>
<td></td>
<td>SIRS related to infections</td>
</tr>
<tr>
<td>Acute on chronic liver injury</td>
<td>DILI including ETOH</td>
</tr>
<tr>
<td></td>
<td>Acute hepatitis</td>
</tr>
<tr>
<td></td>
<td>Shock liver</td>
</tr>
<tr>
<td>Renal hypoperfusion</td>
<td>Sepsis with hypotension</td>
</tr>
<tr>
<td></td>
<td>Variceal bleeding</td>
</tr>
</tbody>
</table>
HEPATORENAL SYNDROME RISK

RISK OF HRS (%)

1 Year
5 Years

10 MELD Score
Patients with Cx and Acites

18 ETOH Hepatitis DF>32

ALF

SJ Munoz
HEPATORENAL SYNDROME SURVIVAL

TREATMENT OF HRS
MIDODRINE + OCTREOTIDE

HRS Type 1
N=102

HRS Type 2
N=60

SURVIVAL (%)

0 20 40 60 80 100

0 4 8 12

WEEKS

Change in CrCl

0 5 10 15 20 25 30

HRS1 HRS2

M+OCT+ALB Control

C Skagen et al.
TREATMENT OF HRS
TERLIPRESSIN

M Cavallin et al.
PORTAL HYPERTENSION
BETA-BLOCKERS

- A primary treatment for patients with portal hypertension
- Reduces risk of first variceal bleeding
- Reduces risk of rebleeding from esophageal varices
- Reduces bleeding in severe portal gastropathy
- This does not mean that all patients with cirrhosis should be taking beta-blockers
  - Effective in patients with larger varices
  - Does not prevent varices from appearing or growing
  - Beta-blockers have adverse events
  - May lead to AKI and increase mortality in patients with ascites
BETA-BLOCKERS IMPACT OF ASCITES

BETA-BLOCKERS
IMPACT OF SBP

Use of beta-blockers significantly increased the risk of AKI and HRS in patients who developed SBP

- RCT, N=602
- Mean age 57 years
- ETOH cirrhosis 55%
- Mean MELD 17
- Child class C 50%
- 90 day mortality with AKI in patients on beta-blockers and h/o SBP is 80%

M Mandorfer et al
Gastroenterol 2014; 146:1680-1690.
RENAL DISEASE IN ESRD
SUMMARY

• Not all renal dysfunction in cirrhosis is HRS
• Avoid nephrotoxic agents in patients with cirrhosis
• IV albumin is essential for treating the complications of renal disease in ESLD
  ▪ Hyponatremia
  ▪ AKI
  ▪ Anasarca
  ▪ SBP to reduce risk of HRS
  ▪ Adjunct to treatment of HRS
• Propranolol should not be used in patients with ascites