Updates on Ascites and Hepatorenal Syndrome

Florence Wong
University of Toronto

May 26, 2019
Natural History of Liver Disease

Onset of chronic liver disease → Diagnosis of cirrhosis → Decompensation (Ascites, PHT bleeds, Encephalopathy, Jaundice) → Liver Tx or Death

- Years to decades
- 5-7% per annum
- Weeks-months
Complications of Cirrhosis

- Portal Hypertension
- Variceal Hemorrhage
  - Ascites
  - Encephalopathy
  - Jaundice
- Spontaneous bacterial peritonitis
- Hepatorenal syndrome
Stages of Cirrhosis

Compensated

State 0: no varices, MPH
LSM >15 and <20
or HVPG >5 and <10 mmHg

State 1: no varices, CSPH
LSM ≥20 or HVPG ≥10 mmHg

State 2:
Varices (= CSPH)

Decompensated

State 3:
bleeding

State 4:
first non-bleeding
decompensation

State 5:
second decompensating event

End state

State 6: late decompensation:
refractory ascites, persistent PSE
or Jaundice, infections, renal, other
organs dysfunction

ACLF

DEATH

(D’Amico G et al, J Hepatol 2018)
Poor Survival After Decompensation

(Bruno et al, Am J Gastro 2013)
18th Century Patient with Ascites
Increased Portal Flow & Splanchnic Vasodilatation

(Wong F, Nat Review Gastro Hepatol 2012)
Vasodilatation & Reduction in EABV

Normal

Cirrhosis with ascites
Head-Out-Water Immersion

- Exerts hydrostatic pressure on vascular columns of the body

- Forces the blood from the lower extremities into the intrathoracic vascular compartment

- Lowers the levels of Na retaining neurohormonal systems

- Pressure exerted increases by 22.4mmHg for every foot depth of water

- Net results is a natriuresis & diuresis
Head-Out-Water Immersion

(Epstein M, Clin Sci 1972)
The Comforts of Bath, England
The Use of Albumin

**Functional properties**
- **Oncotic properties**
  - Regulation of fluid distribution
- **Non-oncotic properties**
  - Antioxidant
  - Solubilization and transport
  - Immunological modulation
  - Endothelial stabilization
  - Haemostatic effect
  - Regulation of extracellular pH

**Target mechanisms**
- Effective hypovolaemia
- Endothelial dysfunction
- Systemic inflammation
- Oxidative stress
- Harmful molecules (PAMPs, DAMPs, PGE₂, etc.)
- Drug metabolism

*(Bernardi M. et al, Nat Rev Gastroenterol Hepatol 2018)*
Albumin Can Improve The Intravascular Volume

Cirrhosis with ascites

Cirrhosis with ascites & excess diuretic use

↑↑Activation of vasoconstrictor Systems esp. vasopressin

Renal failure & hyponatremia

Albumin Can Improve The Intravascular Volume
The Italian ANSWER Study

Serum Albumin Levels

Overall Survival

Albumin dose: 40gm 2X weekly for 2 weeks, then 40gm weekly

The Italian ANSWER Study

Time to First Paracentesis

Incidence of Refractory Ascites

Albumin dose: 40gm 2X weekly for 2 weeks, then 40gm weekly

The Spanish MACHT Study

Median dose of Midodrine 23mg/day, albumin dose: 40gm every 2 weeks

(Sola E, et al. J Hepatol 2018)
Why the Discrepancies

- Patients in the ANSWER study had a median MELD of 12-13, while those in MACHT study had a median MELD of 16-17

- Different doses of albumin used

- Shorter follow-up with the MACHT study

- Will await the American PRECIOUSA study
Anti-inflammatory Effects of Albumin

- Patients with decompensated cirrhosis & renal dysfunction
- 12 week infusion of albumin in non-infected patients
- Low dose (1gm/kg of body weight/2 weeks) versus high dose (1.5gm/kg of body weight/week)
- Assess effects on
  - serum albumin
  - plasma renin
  - cardiocirculatory function
  - portal pressure
  - plasma cytokine levels

(Fernandez J. et al, Gastroenterology 2018)
Effects of Infused Albumin on Serum Albumin

(Fernandez J. et al, Gastroenterology 2018)
Effects of Infused Albumin on Inflammatory Markers

(Fernandez J. et al, Gastroenterology 2018)
Effects of Infused Albumin on Inflammatory Markers

(Fernandez J. et al, Gastroenterology 2018)
Non-Oncotic Properties of Albumin

- Obstruction to portal flow
- Portal hypertension
- ↑ Shear stress to splanchnic vessels
- ↑ Vasodilators
  - Splanchnic vasodilation
  - ↓ EABV
  - Altered renal response to activation of vasoconstrictor systems
  - Renal failure

- ↑ Translocation of gut bacteria & bacterial products
  - Hepatocyte necrosis
  - DAMPs
  - Bacterial infection
  - PAMPs
  - Immune activation
  - Inflammatory response
    - ↑ Chemokines, cytokines, NO

- Alcohol
- Viral hepatitis
- DILI
Use of Albumin in Management of Ascites

- Dose of albumin seems important
- Dampening down inflammation may improve ascites control
- Need to monitor serum albumin
- Excessively high serum albumin may be counter-productive
What about Patients With Difficult to Control Ascites

- The elderly >65 years of age
- Patients with prior spontaneous hepatic encephalopathy
- MELD >18
- Portal vein thrombosis
- Pulmonary hypertension
- Heart failure
The Solution

The alfapump® System

Automatically and continually moves ascites from the abdominal cavity to the bladder, where it is excreted naturally from the body.

- Significantly reduces the need for paracentesis
- Improves patient quality of life
- Avoids the risks of current therapeutic options
Pump in situ
ALFA pump provides continuous small volume ascites drainage
ALFA Pump Report

Pump serial no.: 6285
Days since implant: 47
Total volume of fluid removed: 36.2 liters
Average daily volume of the last 7 complete days: 861.8 ml

The alfapump is functioning very well and has been adequately charged.

Please find below the daily statistics from the last 8 days for this alfapump.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>25.02.2019</td>
<td>900</td>
<td>861</td>
<td>96</td>
<td>26:52</td>
</tr>
<tr>
<td>26.02.2019</td>
<td>900</td>
<td>867</td>
<td>96</td>
<td>12:46</td>
</tr>
<tr>
<td>27.02.2019</td>
<td>900</td>
<td>859</td>
<td>95</td>
<td>19:59</td>
</tr>
<tr>
<td>28.02.2019</td>
<td>900</td>
<td>858</td>
<td>95</td>
<td>16:22</td>
</tr>
<tr>
<td>01.03.2019</td>
<td>900</td>
<td>865</td>
<td>96</td>
<td>30:05</td>
</tr>
<tr>
<td>02.03.2019</td>
<td>900</td>
<td>856</td>
<td>95</td>
<td>27:10</td>
</tr>
<tr>
<td>03.03.2019</td>
<td>900</td>
<td>866</td>
<td>96</td>
<td>03:32</td>
</tr>
<tr>
<td>04.03.2019 (incomplete) data from 00:00 to 06:40</td>
<td>900</td>
<td>0</td>
<td>0</td>
<td>00:00</td>
</tr>
</tbody>
</table>
Control of Ascites

• Pump is set to work from 0800-2200 hours

• Average volume per pump cycle: ~6ml

• Average time between pump cycles: 5-6 minutes

• Median follow-up time of 30 patients in North America: 361 days (27-764)

• Total ascites removed in 12 months: 317.9±121.9 litres/patient (=53 large volume paracenteses of 5 litres each)

• Average daily ascites volume removed: 883±338ml
Control of Ascites with alfpump

**Number of LVPs**

- Pre-3M
- Post-3M
- Post-12M

**Paracentesis Count**

- None <5L
- None ≥5L
- <5L
- ≥5L

*p<0.05*
Quality of Life Changes

CLDQ Score

- Baseline: n=28
- 1M: n=28
- 3M: n=25
- 6M: n=20
- 9M: n=18
- 12M: n=17

Ascites Q

- Baseline: n=27
- 1M: n=27
- 3M: n=25
- 6M: n=19
- 9M: n=17
- 12M: n=17

Statistical significance:
- CLDQ Score: p<0.001
- Ascites Q: p=0.006
Vasoconstrictor activities post-pump insertion

Plasma renin activity
Norepinephrine

Continued monitoring of renal function and intermittent albumin infusions may be required

(Sola E, et al, Liver Transplantation 2017)
Survival post-pump insertion
The Evolving Concept of Renal Dysfunction in Cirrhosis

IAC defined HRS 1

ADQI defined RIFLE criteria

IAC modified diagnosis of HRS 1

IAC modified RIFLE criteria

IAC further defined AKI diagnostic criteria

KDIGO modified AKIN & RIFLE criteria

IAC & ADQI defined AKI for cirrhosis

KDIGO criteria For AKI

Biomarkers: Susceptibility Diagnosis Prognosis

# Acute Kidney Injury (AKI) in Cirrhosis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline SCr</td>
<td>Stable SCr ≤3 months&lt;br&gt;If not available, a stable SCr closest to the current one&lt;br&gt;If no previous SCr at all, use admission SCr</td>
</tr>
<tr>
<td>Definition of AKI</td>
<td>( \uparrow ) in SCr ≥ 26.5 ( \mu )mol/l (0.3 mg/dL) ≤ 48 hours, or&lt;br&gt;( \uparrow ) 50% from baseline</td>
</tr>
<tr>
<td>Staging</td>
<td>Stage 1: ( \uparrow ) SCr ≥26.4( \mu )mol/L (0.3mg/dL) or&lt;br&gt;( \uparrow ) SCr ≥1.5 – 2.0 X from baseline&lt;br&gt;Stage 2: ( \uparrow ) SCr &gt;2.0 - 3.0 X from baseline&lt;br&gt;Stage 3: ( \uparrow ) SCr &gt;3.0 X from baseline, or&lt;br&gt; SCr ≥352( \mu )mol/L (4.0mg/dL) with an acute ( \uparrow ) of&lt;br&gt; ≥ 26.4( \mu )mol/L (0.3mg/dL), or&lt;br&gt;Initiation of renal replacement therapy</td>
</tr>
</tbody>
</table>
AKI – Hepatorenal Syndrome

**Diagnostic Criteria**

1. Cirrhosis and ascites;

2. Stage 2 or 3 AKI;

3. No improvement of serum creatinine (decrease of creatinine ≤ 0.3mg/dl of baseline) after at least 48 hours of diuretic withdrawal and volume expansion with albumin (1 g/kg b.w./day for 2 days);

4. Absence of hypovolemic shock or severe infection requiring vasoactive drugs to maintain arterial pressure;

5. No current or recent treatment with nephrotoxic drugs;

6. Proteinuria <500 mg/day and no microhematuria (<50 RBCs/ml).

*(Angeli P. et al, International Ascites Club, Gut 2015)*
Diagnosis of AKI in Cirrhosis
Role of Biomarkers

(Piano S. et al, Seminars in Liver Dis 2018)
Diagnosis of AKI in Cirrhosis
Role of Biomarkers

(Belcher J. et al. J Hepatology, 2014)
Diagnosis of AKI in Cirrhosis
Role of Biomarkers

(Belcher J. et al. J Hepatology, 2014)
Management of AKI in Cirrhosis

Volume expansion with albumin (1gm/kg, max 100gm/day)

- Regression of AKI
  - Close Monitoring

- Stable
  - Further Rx at physician’s discretion
  - Treat according to AKI etiology if not HRS
    - ? Response
      - Yes
      - No
        - Progression
          - Treat with vasoconstrictors & albumin if meeting AKI-HRS diagnostic criteria#
            - ? Response
              - Yes
              - No
                - Start renal replacement therapy if patient is liver transplant candidate

(Wong F. & Angeli P., J Hepatol 2017)
Baseline Serum Creatinine Matters

(Wong F. et al, Am J Gastro 2017)
Severity of Liver Dysfunction Matters

(Piano S. et al, Clin Gastro Hepatol 2018)
Dose Response to Albumin in AKI

(Salerno F. et al, BMC Gastroenterology)
Terlipressin is the most commonly studied drug for HRS1

(Facciorusso A. et al, Lancet Gastroenterol Hepatol 2017)
Terlipressin vs. Midodrine/Octreotide for HRS1

(Cavallin M. et al, Hepatology, 2015)
Terlipressin versus Norepinephrine for HRS1 Meta-analysis

(Mattos AZ. et al, Euro J Gastroenterology & Hepatology 2016)
Terlipressin versus Norepinephrine in the Context of ACLF

ACLF = bilirubin >5mg/dl + INR >1.5 plus ascites ± HE in <4 weeks

(Arora V. et al. Hepatology 2018)
Small reduction in serum creatinine with treatment can improve survival

(Belcher J. et al. PLOS one, 2015)
Summary

• Renal failure is the most common organ failure in decompensated cirrhosis

• Need to recognize it early in order to initiate timely treatment

• Terlipressin is the most commonly used vasoconstrictor worldwide for AKI in cirrhosis

• Small improvement in serum creatinine with treatment is beneficial

• Refer for consideration for liver transplant early

• Early transplantation is associated with improved outcomes
The Future - Biomarkers

- Normal
- Increased risk
- ↓GFR
- Damage
- Kidney failure
- Death

Window for early targeted intervention

Biomarkers identify susceptibility
Biomarkers for diagnostic criteria including creatinine, decreased urine output
Biomarkers identify injury mechanisms
Biomarkers to track progression

(Murray P. et al, Kidney Int 2013)