Management of ascites in patients with cirrhosis and CKD in cirrhosis

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Disclosures

• 2014-2018: Sequana Medical AG Advisory Board
• 2016-2018: Biovie Advisory Board and patent application
• 2016: Gilead (Italy): Advisory Board and grant
• 2014-2018: Bhering: speaker invitation and travel grant
• 2016: Kedrion speaker invitation
• 2018: Ferring: Advisory Board
Agenda

- Prevalence, definition and type of CKD in cirrhosis
- Management in patients with structural CKD
- Management in patients with HRS-CKD
Types of renal Impairment in hospitalized patients with cirrhosis

- **CKD** (1%)  
- **AKI** (19%)

**AKI** is defined by either an Increase in sCr by 50% within 7 days or increase in sCr by 0.3 mg/dl within 2 days

*Adapted from G. Garcia-Tsao et al. Hepatology 2008; 48 : 2064—2077*
# US Burden prediction for NAFLD/NASH for 2030

<table>
<thead>
<tr>
<th></th>
<th>2015</th>
<th>2030</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAFLD</td>
<td>83 milions</td>
<td>101 milions</td>
</tr>
<tr>
<td>NASH</td>
<td>16.5 milions</td>
<td>27 milions</td>
</tr>
<tr>
<td>NASH/NAFLD %</td>
<td>20</td>
<td>27</td>
</tr>
<tr>
<td>Decompensated cirrhosis</td>
<td>40.000</td>
<td>104.430</td>
</tr>
<tr>
<td>HCC</td>
<td>5,000</td>
<td>12,240</td>
</tr>
</tbody>
</table>

## Definition of Kidney Disease

<table>
<thead>
<tr>
<th>Definition</th>
<th>Functional criteria</th>
<th>Structural criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AKI</strong></td>
<td>Increase in sCr by 50% within 7 days or increase in sCr by 0.3 mg/dl within 2 days</td>
<td>No criteria</td>
</tr>
</tbody>
</table>
| **AKD**    | AKI or GFR < 60 ml/min per 1.73 m² for < 3 months  
Decrease in GFR ≥ 35% or increase in sCr ≥ 50% for < 3 months | Kidney damage for < 3 months |
| **CKD**    | GFR < 60 ml/min per 1.73 m² for > 3 months | Kidney damage for ≥ 3 months |

### National Kidney Foundation Kidney Disease Outcome Quality Initiative: Classification of CKD

<table>
<thead>
<tr>
<th>GFR (ml/min/1.73m²)</th>
<th>With kidney damage</th>
<th>Without kidney damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; = 90</td>
<td>Stage 1</td>
<td>Normal</td>
</tr>
<tr>
<td>60-89</td>
<td>Stage 2</td>
<td>Decreased GFR*</td>
</tr>
<tr>
<td>30-59</td>
<td>Stage 3</td>
<td>3</td>
</tr>
<tr>
<td>15-29</td>
<td>Stage 4</td>
<td>4</td>
</tr>
<tr>
<td>&lt; 15</td>
<td>Stage 5</td>
<td>5</td>
</tr>
</tbody>
</table>

* may be normal for age

**Kidney failure** is defined as either a) GFR < 15 (ml/min/1.73m²), or b) a need to start renal replacement therapy (RRT)

Estimated Glomerular Filtration Rate (GFR) by serum creatinine-based equations versus measured GFR

S. Rosi et al. Liver Int. 2015; 35: 2108-2014
## Proposal of a new classification of hepatorenal syndrome

<table>
<thead>
<tr>
<th>Old classification</th>
<th>New classification</th>
<th>Criteria</th>
</tr>
</thead>
</table>
| Type 1 HRS         | HRS-AKI            | a) Absolute increase in sCr ≥ 0.3 mg/dl within 48 hours and/or  
b) Urinary output ≤ 0.5ml/Kg B.W. ≥ 6 hours*  
or  
b) Percent increase in sCr ≥ 50 % using the last available value of outpatient sCr within 3 months as the baseline value |
| Type 2 HRS         | HRS-NAKI           | HRS without the criteria for AKI |
|                    | HRS-AKD            | eGFR < 60 mL/min per 1.73 m² for < 3 months in the absence of other (structural) causes |
|                    | HRS-CKD            | eGFR < 60 mL/min per 1.73 m² for ≥ 3 months in the absence of other (structural) causes |

*P. Angeli et al 2018 (manuscript submitted)*
Treatment of patients with ascites and CKD

- Patients with CKD with structural renal damage
  - To prevent the progression of CKD
- Patients with HRS-CKD
  - To optimize the control of ascites
- Patients with HRS-AKI on HRS-CKD or structural CKD
  - To prevent the onset of HRS and other complications
  - To reduce mortality
Contraindications to TIPS

- Child-Pugh score > 11
- serum bilirubin > 6 mg/dl
- serum creatinine > 3 mg/dl
- history of recurrent grade ≥ 2 hepatic encephalopathy
- age greater than 72
- serious cardiac or pulmonary dysfunction
- complete portal vein thrombosis
- multifocal HCC
- ongoing bacterial infection

*F. Salerno et al. Hepatology 2004; 40: 629-635*
Potential indications and timing for RRT in patients with cirrhosis

**Indications**

- CKD (stage 4-5)
- Kidney failure
- Persistent AKI

**Timing**

- Refractory fluid overload
- Severe electrolyte imbalance
- Severe acid-base imbalance
- Symptomatic azotemia
- Refractory hepatic encephalopathy
Treatment of patients with ascites and CKD

- Patients with CKD with structural renal damage
- Patients with HRS-CKD
- Patients with HRS-AKI on HRS-CKD or structural CKD
Aims of treatment of patients with ascites and HRS-CKD

• To optimize the treatment of refractory ascites
• To prevent other complications
• To reduce mortality
70 Patients with cirrhosis and refractory ascites
ongoing therapeutic paracentesis plus diuretics

25 Patients were assigned to SOC: Therapeutic paracentesis plus diuretics

The assignment was based on the possibility of patients to receive human albumin at their home

45 Patients were assigned to SOC (Therapeutic paracentesis plus diuretics) + Albumin 40 grams/week,

END OF THE STUDY
Death
TIPS
OLT
Lost at the follow-up (24 months)

M. Di Pascoli et al. Liver Int. ; 2018 : (in press)
Complications according to assigned group in patients with refractory ascites

M. Di Pascoli et al. Liver Int. ; 2018 : (in press)
Two-year mortality according to assigned group in patients with refractory ascites

Cumulative incidence of mortality

Time (months)

Standard of care
Albumin

$p = 0.032$

M. Di Pascoli et al. Liver Int. ; 2018 : (in press)
Three month rate of control of ascites according to assigned group in patients with refractory ascites

V. Singh et al. J. Hepatol. 2012 ; 56 : 348-354
Effects of albumin (A) at a dose of 40g/15 days plus midodrine (M) at a dose of 15-30 mg/day versus placebo in patients with cirrhosis and ascites

E. Sola et al. J Hepatol. 2018; [Epub ahead of print]
Effects of albumin (A) at a dose of 40g/15 days plus midodrine (M) at a dose of 15-30 mg/day versus placebo in patients with cirrhosis and ascites

Probability of developing complications

One year survival

E. Sola et al. J Hepatol. 2018; [Epub ahead of print]
Transjugular porto-systemic shunt (TIPS)
Published controlled clinical trials: paracentesis versus TIPS

- Narahara Y. et al. J. Gastroenterol 2011 ; 46 : 78.83
Published meta-analysis: paracentesis versus TIPS


Salerno F. et al. Gastroenterology 2007 ; 133 : 825-834.

A meta-analysis of TIPS versus paracentesis in patients with refractory ascites

Recurrence of ascites

Lebrec 1996
Rossle 2000
Gines 2002
Sanyal 2003
Salerno 2004
TOTAL

Lower with TIPS

A. Albillos et al. J. Hepatol. 2005; 43: 990-996
Changes of urine sodium excretion at 3 months after paracentesis or TIPS

* $= P \leq 0.005$ versus baseline

Proportion of complete responders after TIPS over time

A meta-analysis of TIPS versus paracentesis in patients with refractory ascites

A. Albillos et al. J. Hepatol. 2005; 43: 990-996
## Clinical outcome in patients with refractory ascites according to the assigned treatment

<table>
<thead>
<tr>
<th>Events</th>
<th>TIPS (n° = 35)</th>
<th>Paracentesis (n° = 35)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic encephalopathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients n° (%)</td>
<td>27 (77%)</td>
<td>23 (66%)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Episodes/patient</td>
<td>2.2±0.4</td>
<td>1.1±0.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Moderate (I-II grade) Patients n° (%)</td>
<td>18 (51%)</td>
<td>14 (40%)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Moderate (I-II grade) Episodes/patient</td>
<td>1.1±0.3</td>
<td>0.6±0.1</td>
<td>N.S.</td>
</tr>
<tr>
<td>Severe (III-IV grade) Patients n° (%)</td>
<td>21(60%)</td>
<td>12(34%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Severe (III-IV grade): episodes/patient</td>
<td>1.1±0.2</td>
<td>0.5±0.02</td>
<td>&lt;0.025</td>
</tr>
</tbody>
</table>

*P. Gines et al. Gastroenterology 2002; 123: 1839-1847*
Cumulative 30-days probability of remaining free of hepatic encephalopathy after TIPS

A meta-analysis of TIPS versus paracentesis in patients with refractory ascites

A. Albillos et al. J. Hepatol. 2005; 43: 990-996
Cumulative probability of transplant-free survival according to treatment with TIPS or paracentesis: a meta-analysis of individual data

F. Salerno et al. Gastroenterology 2007; 133: 825-834
Estimated probability of death for cirrhotic patients with refractory ascites treated with TIPS

F. Salerno et al. Gastroenterology 2007 ; 133 : 825-834
### Recommendations for TIPS in the management of ascites

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Grade of evidence</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIPS is not recommended in patients with serum bilirubin &gt;3 mg/dl and a platelet count lower than 75 x 10^9/L, current hepatic encephalopathy grade ≥2 or chronic hepatic encephalopathy, concomitant active infection, progressive renal failure, severe systolic or diastolic dysfunction, or pulmonary hypertension.</td>
<td>III</td>
<td>1</td>
</tr>
</tbody>
</table>

Their application excludes more than 50% of patients with refractory ascites from treatment.

*EASL CPGs for the management of decompensated cirrhosis. J. Hepatol. 2018 (Epub ahead of print)*
TIPS in the management of ascites

Recurrent ascites
- Definitely better

Refractory ascites
- Probably too late

EASL CPGs for the management of decompensated cirrhosis. J. Hepatol. 2018 (Epub ahead of print)
Procedure failures according to the assigned group

TIPS

LVP plus Alb

p < 0.001

C. Bureau et al. Gastroenterology 2017; 152 : 157-163
### Clinical outcomes in patients according to the treatment group

<table>
<thead>
<tr>
<th>Outcome</th>
<th>TIPS (n°29)</th>
<th>LVP + Alb (n°33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N° of paracentesis per patient (mean±SD)</td>
<td>1±1</td>
<td>10±7***</td>
</tr>
<tr>
<td>Volume extracted (l/patient, mean±SD)</td>
<td>6±10</td>
<td>64±47***</td>
</tr>
<tr>
<td>Albumin infusion (g/patient, mean±SD)</td>
<td>39±70</td>
<td>550±458***</td>
</tr>
<tr>
<td>Days in hospital (mean±SD)</td>
<td>17±28</td>
<td>35±40*</td>
</tr>
<tr>
<td>Patients with overt HE</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Episodes of overt HE per patient (mean±SD)</td>
<td>1.6±0.7</td>
<td>1.7±0.8</td>
</tr>
<tr>
<td>Episodes of overt HE grade &gt; 2 (n°)</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Patients with PHT-related bleeding (n°)</td>
<td>0</td>
<td>6*</td>
</tr>
<tr>
<td>Patients with hernia-related complications (n°)</td>
<td>0</td>
<td>6*</td>
</tr>
<tr>
<td>Patients with HRS (n°)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Patients with sepsis</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>HCC (n°)</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

* = p < 0.05, ** = p < 0.01, *** = P < 0.001

*C. Bureau et al. Gastroenterology 2017; 152: 157-163*
Probability of free transplant survival according to the assigned treatment

**Table 2.** Prognostic Parameters Associated With Survival Without Liver Transplantation in Univariate and Multivariate Analyses

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients alive without LT (n = 11)</th>
<th>Patients dead or received transplant (n = 51)</th>
<th>Univariate P value</th>
<th>Multivariate HR (95% CI); P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR, mean ± SD</td>
<td>1.4 ± 0.3</td>
<td>1.5 ± 0.2</td>
<td>.09</td>
<td>0.8 (0.3–2.3); NS</td>
</tr>
<tr>
<td>Serum sodium, mmol/L, mean ± SD</td>
<td>129 ± 3</td>
<td>134 ± 4</td>
<td>.001</td>
<td>0.9 (0.9–1.0); NS</td>
</tr>
<tr>
<td>Bilirubin, mmol/L, mean ± SD</td>
<td>27 ± 21</td>
<td>15 ± 12</td>
<td>.05</td>
<td>1.0 (1.0–1.0); NS</td>
</tr>
<tr>
<td>TIPS/paracentesis, %</td>
<td>93/73</td>
<td>7/27</td>
<td>.048</td>
<td>2.0 (1.1–4.0); .03</td>
</tr>
</tbody>
</table>

HR, hazard ratio; INR, international normalized ratio; LT, liver transplantation.

*C. Bureau et al. Gastroenterology 2017; 152: 157-163*
# Recommendations for TIPS in the management of ascites

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Grade of evidence</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with refractory or recurrent ascites should be evaluated for TIPS insertion</td>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td>Patients for whom paracentesis is ineffective (e.g. due to the presence of loculated ascites)</td>
<td>III</td>
<td>1</td>
</tr>
<tr>
<td>TIPS insertion is recommended in patients with recurrent ascites as it improves survival and in patients with refractory ascites as it improves the control of ascites.</td>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td>The use of small-diameter PTFE-covered stents is recommended to reduce the risk of TIPS dysfunction and hepatic encephalopathy.</td>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td>TIPS is not recommended in patients with serum bilirubin &gt;3 mg/dl and a platelet count lower than 75 x 10⁹/L, current hepatic encephalopathy grade ≥2 or chronic hepatic encephalopathy, concomitant active infection, progressive renal failure, severe systolic or diastolic dysfunction, or pulmonary hypertension.</td>
<td>III</td>
<td>1</td>
</tr>
</tbody>
</table>

*EASL CPGs for the management of decompensated cirrhosis. J. Hepatol. 2018 (Epub ahead of print)*
Automated Low-Flow Ascites (ALFA) Pump

- Battery-powered pump
- Wireless charger
- Bladder and peritoneal catheters
- Pump programmer
Study Overview: consort

C. Boreau et al. J. Hepatol. 2017; 67: 940-949
Large volume paracentesis

C. Boreau et al. J. Hepatol. 2017; 67: 940-949
Six month survival

C. Boreau et al. J. Hepatol. 2017; 67: 940-949
Quality of life

M. Stepanova et al. Qual. Life Res. 2018; Doi:10.1007/s11136-018-1813-8 (Epub ahead of print)
## Treatment Emergent Serious Adverse Effects (TE SAEs)

<table>
<thead>
<tr>
<th>System/Organ</th>
<th>AP (n°=27)</th>
<th>SOC (n°=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n° of patients with at least one TE SAE</td>
<td>23 (85.2%)</td>
<td>14 (45.2%)</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>14 (51.9%)</td>
<td>3 (9.7%)</td>
</tr>
<tr>
<td>Infections</td>
<td>9 (33.3%)</td>
<td>8 (25.8%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>7 (25.9%)</td>
<td>2 (6.5%)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>6 (22.2%)</td>
<td>1 (3.2%)</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>4 (14.8%)</td>
<td>1 (3.2%)</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>4 (14.8%)</td>
<td>3 (9.7%)</td>
</tr>
<tr>
<td>Others</td>
<td>7 (25.9%)</td>
<td>1 (3.2%)</td>
</tr>
</tbody>
</table>

*C. Boreau et al. J. Hepatol. 2017; 67: 940-949*
# Re-interventions

<table>
<thead>
<tr>
<th>Issue leading to re-intervention</th>
<th>Re-interventions (n°=9)</th>
<th>Time to reintervention (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>System component replaced or repositioned</strong></td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>- Lack of communication</td>
<td>1</td>
<td>94</td>
</tr>
<tr>
<td>- Bladder catheter</td>
<td>3</td>
<td>5, 20, 113</td>
</tr>
<tr>
<td>- Peritoneal catheter</td>
<td>2</td>
<td>6, 177</td>
</tr>
<tr>
<td><strong>System explanted</strong></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>- Wound infection</td>
<td>2</td>
<td>8, 50</td>
</tr>
<tr>
<td>- Wound dehiscence</td>
<td>1</td>
<td>79</td>
</tr>
</tbody>
</table>

*C. Boreau et al. J. Hepatol. 2017; 67: 940-949*
EASL CPGs: Other recommendations for the management of ascites

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Level I</th>
<th>Level 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>At present the addition of clonidine or midodrine to diuretic treatment cannot be recommended</td>
<td>III</td>
<td>1</td>
</tr>
<tr>
<td>Alfapump implantation in patients with refractory ascites not amenable to TIPS insertion is suggested in experienced centres. However, close patient monitoring is warranted because of the high risk of adverse events including renal dysfunction and technical difficulties.</td>
<td>I</td>
<td>2</td>
</tr>
</tbody>
</table>

EASL CPGs for the management of decompensated cirrhosis. J. Hepatol. 2018 (Epub ahead of print)
Aims of treatment of patients with ascites and HRS-CKD

- To prevent or optimize the treatment of refractory ascites
- To prevent other complications
- To reduce the mortality
- To improve renal function?
Individual values of serum creatinine in patients with type 2 HRS

Probability of type 2 HRS recurrence in patients with cirrhosis

C. Alessandria et al. Dig. Liver Dis. 2009; 41: 298-302
Transplant free survival post terlipressin therapy in patients with type 1 or type 2 HRS

AG. Testro et al. J. Gastroenterol. 2008; 23: 1535-1540
Three year survival after LT according to the presence or absence (reversal) of type 2 HRS at the time of LT

Summary

• The main clinical feature of patients with CKD, particularly of those with HRS-CKD is refractory ascites.
• Long-term treatment with albumin seems to prevent the development of other complications and to improve survival in patients with refractory ascites.
• TIPS should be considered in:
  ✓ Patients with recurrent ascites
  ✓ Patients with refractory ascites
  ✓ Patients in whom paracentesis is uneffective
• TIPS may improve survival in patients with recurrent ascites.
• The role of other procedures (i.e. Alfa pump) in the management of refractory ascites should be further investigated.
• Actually there is no valid reason to treat HRS-CKD.