New directions in the treatment of liver cirrhosis in 2017

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Outline

• Cirrhosis: why this term is not enough to define the disease

• Stage-specific, pathophysiology-oriented treatment: what’s new
Compensated and decompensated cirrhosis are as two different diseases

D'Amico G and Garcia-Tsao G. J Hepatol. 2006
<table>
<thead>
<tr>
<th>Stage</th>
<th>1</th>
<th>2</th>
<th>3</th>
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<td>Clinical features</td>
<td>No varices No ascites</td>
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<td>Death at 1 year</td>
<td>1.5%</td>
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Compensated cirrhosis
Progression from compensated to decompensated cirrhosis

\[ \approx 36\% \text{ at 5 years} \]

\[ 7\% \text{ per year} \]

Major determinant: PORTAL HYPERTENSION

D’Amico G Baveno VI 2015
Portal hypertension drives the transition from Stage 1 (no varices) to Stage 2 (varices) and further

**Patients free of varices**

![Graph showing patients free of varices with risk P=0.0001 for CSPH (HVPG ≥ 10 mmHg).](image)

**Risk of decompensation**

- HR 5.7
- 95% CI 2.7-12
- CSPH (HVPG ≥ 10 mmHg)
- No clinically sign PH

![Graph showing risk of decompensation with MELD; Albumin.](image)

**References**

Groszmann, NEJM 2005

Ripoll, Gastroenterology 2007

MELD; Albumin
Aim of therapy in compensated cirrhosis: prevent decompensation

• Avoid the development of CSPH in those with subclinical PH
• Reduce portal pressure in patients with CSPH*
  • Mild decreases (≥ 10%) are sufficient to prevent clinical events, but ideally a decrease ≥20% or HVPG <10 mmHg should be achieved
• Ideally: improve liver function

*In 2017 we have non-invasive tools to identify CSPH!
• HVPG measurement gold-standard, but:

• P-S collateral circulation on imaging is sufficient to rule in CSPH (all etiologies) (2b;B).

• In patients with untreated virus-related disease, non-invasive methods are sufficient to rule in CSPH: liver stiffness (TE) \( \geq 20–25 \text{ kPa} \), alone or combined to platelet count and spleen size (2b; B)
Use of non-invasive tests: towards personalisation of screening of CSPH

The ANTICIPATE study

How can we prevent/improve PH?
Determinants of portal pressure increase in cirrhosis

Pressure = Resistance * Flow

Ongoing liver injury due to the etiologic factor

Increase in hepatic resistance
- Mechanical (70%): architectural changes (>>fibrosis)
- Dynamic: increased vascular tone

Increased Portal Flow
Collateralisation
Hyperdynamic circulation

Second step
Treating the etiologic factor to improve portal hypertension

- Alcohol abstinence
- Iron depletion
- Suppression of HBV viremia
- Clearance of HCV infection
- Correction of obesity
SVR after DAAs leads to a decrease in HVPG in HCV-related cirrhosis: retrospective study

Among patients with HVPG≥12 mmHg (n=19), a decrease ≥ 20% or to <12 mmHg was observed in 53% (10/19)

Among patients with HVPG≥10 mmHg (n=24) a decrease ≥10% was observed in 67% (16/24)

In patients with subclinical PH (n=7) HVPG normalized in 86% (6/7)

Mandorfer M et al. J Hepatol 2016
Changes in HVPG at SVR-24 in 226 patients with cirrhosis and CSPH treated with DAA: prospective study

All pts had baseline HVPG > 10 mmHg

Lens et al. AASLD 2016
Decrease of HVPG below specific thresholds at SVR-24

Most patients with CSPH remain at risk of events after therapy

Lens et al. AASLD 2016
Long-term: Sofosbuvir Plus Ribavirin over 48 weeks on HVPG

• 46 pts with cirrhosis and portal hypertension
• SVR12 after SOF + RBV for 48 weeks: 72%
• In these patients, clinically meaningful HVPG reductions (≥20%) were observed in:
  • 24% of patients at end of treatment (33 patients were re-assessed)
  • 89% of patients at post-treatment Week 48 (9 patients were re-assessed)

Continued improvement in liver physiology, as measured by HVPG, is possible after achieving SVR:

long term clinical benefits likely greater than those observed at EOT

Afdhal N et al. J Viral Hep 2017
Obesity: risk factor for first decompensation in cirrhosis of any etiology

Log-Rank 7.60, p=0.022

Risk of decompensation in obese: 3 times higher as normal weight

N=161

p = 0.002

7/47 (14.9%)  
20/65 (30.8%)  
21/49 (42.9%)

N  OW  OB

p = 0.03  p = 0.07

Patients at risk

Lifestyle intervention improves HVPG in patients with cirrhosis and obesity

Body weight
Average $\Delta$ = -5 Kg; -5.2%
P<0.0001 vs. baseline

HVPG
Average $\Delta$ = -1.7 mmHg; -10.7%
P<0.0001

No decompensation during LS intervention
Child and MELD score unchanged

Berzigotti et al. Hepatology 2017
Reducing the increased hepatic vascular tone

**Endothelial dysfunction**: primary factor increasing the hepatic vascular tone

**Increased Vasoconstrictors**: Antagonize
- Carvedilol
- prazosin
- ARA

**Decreased Vasodilators**: Enhance
- Statins
- antioxydants
- NO-donors
- OCA (maybe)
Regulation of sinusoidal endothelial cells phenotype: Role of the transcription factor KLF2 and its pharmacological activation

Increasing KLF2 expression by KLF2 gene transfer leads to a significant reduction of liver fibrosis and of α-SMA expression in cirrhotic rats.

Dekker RJ et al., Blood. 2002
Parmar KM et al., J Biol Chem 2005
Sen-Banerjee S et al., Circulation 2005
Gracia-Sancho J... Bosch J., Gut. 2011
Marrone G ....Bosch., J Hepat. 2012
Abraldes J ...Bosch J. Gastroenterology 2009
Abraldes J...Bosch J. J Hepatol 2007
Zafra C... Bosch J. Gastroenterology 2004
Simvastatin decrease HVPG in patients with cirrhosis

Liver Blood Flow did not change (decreased hepatic resistance)

Additive effect on top of beta-blockers

Abraldes J...Bosch J. Gastroenterology 2009
Abraldes J...Bosch J. J Hepatol 2007
Zafra C... Bosch J. Gastroenterology 2004
Statins are associated with a decreased risk of decompensation and death in compensated HCV cirrhosis*

*Propensity score matched study
Stage 2: compensated with varices

Mechanism driving progression:
Flow-mediated further increase in PP
How can we prevent/improve PH?
Determinants of portal pressure increase in cirrhosis

Pressure = Resistance * Flow

Hepatic resistance
Mechanical (70%): fibrosis
Dynamic: increased vascular tone

Increased Porto-collateral Flow
Collateralisation
Hyperdynamic circulation

Non-selective beta-blockers mainstay in large varices

Ongoing liver injury due to the etiologic factor

Early event

Second step
**PREDESCI Study**
Preventing the Decompensation of Cirrhosis: RCT

- Patients with compensated cirrhosis (n=210)
- Absence of any previous decompensation
- HVPG $\geq$ 10 mmHg
- No varices or small varices not requiring therapy (no RWM)
- No contraindications for NSBBs

<table>
<thead>
<tr>
<th>Propranolol</th>
<th>Matching Placebo</th>
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<tr>
<td>Carvedilol if HVPG did not ↓ $\geq$ 10% in iv propranolol test</td>
<td>(double-blind) (by stratum)</td>
</tr>
</tbody>
</table>

Villanueva et al. AASLD 2016
Primary end-point in patients with varices (all small): decompensation-free survival

**HR (95% CI): 0.39 (0.17-0.88)**

**P value: 0.019**

*Gray test*

**DEVELOPMENT OF PRIMARY END-POINT**

- **PLACEBO GROUP**
  - 20/58 (34%)

- **β-BLOCKER GROUP**
  - 8/56 (14%)

**Secondary endpoint:**

Ascites incidence

58% reduction on beta-blockers

Villanueva A et al. AASLD 2016
# Stages of cirrhosis and aim of therapy

<table>
<thead>
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<th>Stage</th>
<th>Clinical features</th>
<th>Compensated Cirrhosis</th>
<th>Decompensated Cirrhosis</th>
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<tbody>
<tr>
<td>1</td>
<td>No varices</td>
<td>No ascites</td>
<td>3</td>
</tr>
<tr>
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<td>No ascites</td>
<td>4</td>
</tr>
<tr>
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<th>Aim of therapy</th>
<th>Prevent decompensation</th>
<th>Prevent further decomp.</th>
<th>Reduce mortality</th>
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</tr>
</thead>
</table>

Decompensated cirrhosis
Stage 3: variceal bleeding

Mechanism driving progression:
Further increase in PP
Simvastatin associated to NSBB+EVL improves survival after variceal bleeding (BLEPS Study)

**Survival**

![Survival graph](#)

- **Simvastatin**
  - Survival function for Death
  - Time to any-cause death (months)
  - HR: 0.387 (0.152 to 0.986)
  - p = 0.030

- **Placebo**

**Rebleeding**

![Rebleeding graph](#)

- **Simvastatin**
  - Survival function for HR
  - Time to any-cause HR (months)
  - p = 0.583

- **Placebo**

* less deaths due to bleeding and infections

Abraldes et al. Gastroenterology 2016
Stage 4: Ascites

Mechanism driving progression
Hyperdynamic circulation leading to:
- Low peripheral resistance and decrease in effective volemia
- Activation of vasoactive systems: RAA, NA, ADH
- Sodium and water retention
LONG-TERM ALBUMIN ADMINISTRATION IN PATIENTS WITH DECOMPENSATED CIRRHOSIS

FINAL RESULTS OF THE “ANSWER” STUDY

Caraceni P, Bernardi M, and the ANSWER Study Investigators
Patients with cirrhosis and **uncomplicated ascites** (no refractory, creatinine ≤1.5 mg/dl)

Treated at least with: anti-mineralocorticoid drug 200 mg/day + furosemide 25 mg/day

**STUDY PROTOCOL**

<table>
<thead>
<tr>
<th>STANDARD MEDICAL TREATMENT (SMT)</th>
<th>SMT + HUMAN ALBUMIN 40 g twice a week x 2 weeks then 40 g/week</th>
</tr>
</thead>
<tbody>
<tr>
<td>OLT 18 months</td>
<td>INDICATION TO TIPS 18 months</td>
</tr>
<tr>
<td>TIPS 18 months</td>
<td></td>
</tr>
</tbody>
</table>
**INCIDENCE OF REFRACTORY ASCITES**

<table>
<thead>
<tr>
<th>Months</th>
<th>N at risk SMT</th>
<th>N at risk SMT + HA</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>213</td>
<td>218</td>
</tr>
<tr>
<td>3</td>
<td>147</td>
<td>175</td>
</tr>
<tr>
<td>6</td>
<td>98</td>
<td>142</td>
</tr>
<tr>
<td>9</td>
<td>78</td>
<td>125</td>
</tr>
<tr>
<td>12</td>
<td>65</td>
<td>109</td>
</tr>
<tr>
<td>15</td>
<td>57</td>
<td>95</td>
</tr>
<tr>
<td>18</td>
<td>26</td>
<td>39</td>
</tr>
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**Hazard Ratio (HA+SMT vs SMT)**

<table>
<thead>
<tr>
<th>Hazard Ratio (95% CI)</th>
<th>Log-rank P value</th>
</tr>
</thead>
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<tr>
<td>0.54 (0.29-0.62) (−46%)</td>
<td>&lt; 0.0001</td>
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</table>
OVERALL SURVIVAL

Hazard Ratio (HA+SMT vs SMT)

<table>
<thead>
<tr>
<th>Months</th>
<th>SMT</th>
<th>SMT + HA</th>
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<tbody>
<tr>
<td>0</td>
<td>213</td>
<td>218</td>
</tr>
<tr>
<td>3</td>
<td>158</td>
<td>182</td>
</tr>
<tr>
<td>6</td>
<td>110</td>
<td>153</td>
</tr>
<tr>
<td>9</td>
<td>90</td>
<td>135</td>
</tr>
<tr>
<td>12</td>
<td>76</td>
<td>121</td>
</tr>
<tr>
<td>15</td>
<td>65</td>
<td>109</td>
</tr>
<tr>
<td>18</td>
<td>28</td>
<td>43</td>
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Survival probability

- SMT: 66%
- SMT + HA: 78%

Hazard Ratio (HA+SMT vs SMT):
0.62 (95% CI 0.40-0.95) (−38%)

Log-rank P value: 0.0285
Stage 5: further episodes of decompensation

Mechanism driving progression: further increase in portal pressure and liver failure driven by inflammation
Bacterial translocation is a driver
Recurrent ascites: TIPS vs. LVP + Albumin (RCT)


TIPS improved survival vs. LVP + A
A Randomized Trial of 6-Month Norfloxacin Therapy in Patients with Child-Pugh class C Cirrhosis

Moreau R, Elkrief L, NORFLOCIR Study Group
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Norfloxacin (N=144)</th>
<th>Placebo (N=147)</th>
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<tr>
<td>Child-Pugh score</td>
<td>11 ± 1</td>
<td>11 ± 1</td>
</tr>
<tr>
<td>MELD score</td>
<td>21 ± 5</td>
<td>21 ± 5</td>
</tr>
<tr>
<td>Ascites (%)</td>
<td>88</td>
<td>89</td>
</tr>
<tr>
<td>Ascitic fluid protein (g/L)</td>
<td>14 ± 6</td>
<td>13 ± 7</td>
</tr>
<tr>
<td>HCC (%)</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Nonselective β-blockers (%)</td>
<td>44</td>
<td>47</td>
</tr>
<tr>
<td>Corticosteroids (%)</td>
<td>22</td>
<td>22</td>
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Ca. 80% alcoholic cirrhosis in both groups

Ca. 40% with HA in both groups
Primary Endpoint: mortality at 6 months

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<tr>
<th>Months</th>
<th>SHR*</th>
<th>95% CI</th>
<th>P</th>
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<tr>
<td></td>
<td>Unadjusted</td>
<td>0.586</td>
<td>0.346 to 0.992</td>
</tr>
<tr>
<td></td>
<td>Adjusted**</td>
<td>0.575</td>
<td>0.338 to 0.979</td>
</tr>
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*Fine & Gray model. **For nonselective β-blockers and corticosteroids

Placebo (n=144)

Norfloxacin (n=147)

Secondary outcome: infection rate markedly reduced in the Norfloxacin group

P=0.045 by Gray test
Take Home Messages

• Cirrhosis prognosis depends on the clinical stage: tailored treatment is needed

• In compensated:
  • **Etiology: clearance of HCV** improves PH, but CSPH remains in 60% of cases 6 months after therapy (still at risk of decompensation); **lifestyle intervention** is safe and decreases HVPG in obese patients
  • **Statins and non-selective beta-blockers/carvedilol** decrease HVPG, prevent decompensation and increase survival

• In decompensated:
  • **Simvastatin** added to standard therapy improves survival in patients who bled from varices
  • **Albumin** added to standard therapy improves survival in patients with uncomplicated ascites; **TIPS** improves survival in recurrent ascites
  • **Norfloxacin** improves survival in patients with (alcoholic) Child C cirrhosis
Swiss Liver Center, UVCM
Inselspital Bern

Prof. Jean-François Dufour
Prof. Andrea De Gottardi
Prof. Nasser Semmo
Dr. Stefania Casu
Dr. Guido Stirnimann
Dr. Maria Gabriela Delgado
Dr. Cristina Margini
Dr. Giuseppe Murgia
Dr. Stephanie Klein
Dr. Susana Rodrigues

Guest Professor
Prof. Jaime Bosch

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