Therapeutic Strategy in Severe Alcoholic Hepatitis:
Present to future development of New molecules

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Assessment of Disease severity
At admission
During treatment
DF and MELD predict AH mortality

**DF**
- Extensively validated
- DF >32 predicts high mortality
- 4.6 (PT – Control) + Bilirubin
- Especially useful to determine need for steroid treatment: in patients with severe AH

**MELD**
- INR is more reproducible than PT
- Easily available calculators
- Cut point can be based on toxicity of proposed treatment.
- May be used to categorize mild, moderate and severe AH.

Lower but still important risk of death in patients with DF<32…

![Graph showing probability of 90-day mortality vs MELD score](www.mayoclinic.org/gi-rst/mayomodel7.html)

*20%*
Lille model: a tool for new strategies

Evaluation of Lille model on overall patients (n=438)

http://www.lillemode.com

Lille score < 0.45: 85±2.5%
p<0.00001

Lille score ≥ 0.45: 25±3.8%

Louve A et al, Hepatology 2007
Fig. 3. Receiver operating characteristic curves for survival at 6 months in the validation cohort as determined by the Lille model versus the evaluation of the Maddrey function ($P = 0.02$), the MELD score ($P = 0.0003$) and the Glasgow score ($P = 0.002$).
Lille model: a tool for new strategies

Evaluation of Lille model on overall patients (n=438)

Survival (\%)

- Complete responders (Lille \leq 0.16)
- Partial responders (0.16 < Lille < 0.56)
- Null responders (Lille \geq 0.56)

Days

- 91.1\pm 2.7\%  
- 79.4\pm 3.8\%  
- 53.3\pm 5.1\%

p < 0.0000001

Philippe Mathurin, John O’Grady, Robert L Carithers, Martin Phillips, Alexandre Louvet, Charles L Mendenhall, Marie-José Ramond, Sylvie Naveau, Willis C Maddrey, Timothy R Morgan

Combining Data from Liver Disease Scoring Systems
outcome as a continuum in probabilities of death

For example, predicted 6-month mortality
- complete responders with MELD scores of 15–45 (Lille score 0.16) was 8.5% to 49.7%, compared with 16.4%–75.2% for non-responders (Lille score 0.45).
- According to the joint-effect model, for 2 patients with the same baseline MELD score of 21, the patient with a Lille score of 0.45 had a 1.9-fold higher risk of death than the patient with a Lille score of 0.16 (23.7% vs 12.5%)
Present Therapeutic strategy
Prednisolone or Pentoxifylline for Alcoholic Hepatitis

**Pentoxifylline vs Corticosteroids**

**28-Day Mortality**

- **Prednisolone**
  - Yes: OR = 0.72 (0.52-1.01), p = 0.056
  - No: OR = 1.07 (0.77-1.49), p = 0.686

**Pentoxifylline**

Thursz NEJM 2015
# Independent Prognostic Factors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio (95% CI)</td>
</tr>
<tr>
<td>Prednisolone vs no prednisolone</td>
<td>0.609 (0.409 – 0.090)</td>
</tr>
<tr>
<td>Prothrombin ratio</td>
<td>1.381 (1.129 – 1.691)</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>1.002 (1.001 – 1.003)</td>
</tr>
<tr>
<td>Age</td>
<td>1.050 (1.029 – 1.071)</td>
</tr>
<tr>
<td>White Blood Cells</td>
<td>1.030 (1.002 – 1.060)</td>
</tr>
<tr>
<td>Urea</td>
<td>1.065 (1.015 – 1.118)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.564 (1.048 – 2.332)</td>
</tr>
<tr>
<td>Hepatic Encephalopathy</td>
<td>3.073 (2.050 – 4.605)</td>
</tr>
</tbody>
</table>

Pentoxifylline vs Corticosteroids

Thursz NEJM 2015
Corticosteroids as a first therapeutic option in the treatment of alcoholic hepatitis

End of the controversy on the short-term benefit?

Comparative Effectiveness of Pharmacological Interventions for Severe Alcoholic Hepatitis: A Systematic Review and Network Meta-analysis

Meta-Analysis of therapeutic options

**Electronic database search:**
- PubMed - 396
- OVID Medline - 295
- Scopus - 780
- Embase, EMB Reviews - 513

10 additional records identified through other sources (manual abstract search)

614 records after duplicates removed

Excluded based on title and abstract review - 571
- Basic science articles, review articles, editorials
- Observational studies
- Unrelated to severe alcoholic hepatitis
- Reported non-effective interventions or interventions not used in clinical practice (colchicine, anti-tumor necrosis factor agents, anabolic steroids, etc.)

614 abstracts reviewed

43 full texts reviewed

Excluded - 21
- Reviews/commentaries/non-RCT study design (9)
- Unable to stratify by severe vs. non-severe alcoholic hepatitis - CS (4), PTX (1)
- Follow-up of initial study (5)
- Duration of intervention short, and inadequate follow-up (2)

22 studies included in quantitative synthesis (meta-analysis)

**Figure 1.** Flow sheet summarizing study identification and selection. CS, corticosteroids; PTX, pentoxifylline; RCT, randomized controlled trial.
**Meta-Analysis of therapeutic options**

**NAC alone vs Placebo: No effect**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1.1 N-acetylcysteine vs. Placebo</td>
<td>Events Total</td>
<td>Events Total</td>
<td>Weight</td>
</tr>
<tr>
<td>Moreno 2010</td>
<td>8</td>
<td>27</td>
<td>3</td>
</tr>
<tr>
<td>Stewart 2007</td>
<td>20</td>
<td>39</td>
<td>19</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>28</td>
<td>66</td>
<td>58</td>
</tr>
</tbody>
</table>

Total events: 28 vs 22

Heterogeneity: Tau² = 0.02; Chi² = 1.08, df = 1 (P = 0.30); I² = 7%
Test for overall effect: Z = 0.51 (P = 0.61)
Meta-Analysis of therapeutic options

**Pentoxifylline vs Placebo:**
No effect in direct meta-analysis

---

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akrivadis 2000</td>
<td>13</td>
<td>24</td>
<td>29.4%</td>
<td>0.56 [0.32, 0.98]</td>
</tr>
<tr>
<td>Paladugu 2006</td>
<td>4</td>
<td>7</td>
<td>15.3%</td>
<td>0.65 [0.24, 1.77]</td>
</tr>
<tr>
<td>Sidhu - PTX vs. placebo - 2012</td>
<td>5</td>
<td>10</td>
<td>17.0%</td>
<td>0.50 [0.20, 1.25]</td>
</tr>
<tr>
<td>Thursz - STOPAH 2014</td>
<td>50</td>
<td>45</td>
<td>38.3%</td>
<td>1.15 [0.80, 1.66]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>350</strong></td>
<td><strong>363</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.74 [0.46, 1.18]</strong></td>
</tr>
</tbody>
</table>

Total events: 72 / 86

Heterogeneity: $\tau^2 = 0.11; \chi^2 = 6.33, df = 3 (P = 0.10); \hat{I}^2 = 53$

Test for overall effect: $Z = 1.25 (P = 0.21)$
Meta-Analysis of therapeutic options

Corticosteroids vs Placebo: Improvement in short-term mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>1.1.3 Corticosteroid vs. Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cabre 2000</td>
<td>9</td>
<td>36</td>
<td>11</td>
<td>35</td>
</tr>
<tr>
<td>Carithers 1989</td>
<td>2</td>
<td>35</td>
<td>11</td>
<td>31</td>
</tr>
<tr>
<td>Depew 1980</td>
<td>8</td>
<td>15</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>Helman 1971</td>
<td>1</td>
<td>9</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Lesesne 1978</td>
<td>2</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Maddrey 1978</td>
<td>1</td>
<td>5</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Ramond 1992</td>
<td>4</td>
<td>32</td>
<td>11</td>
<td>29</td>
</tr>
<tr>
<td>Thursz - STOPAH 2014</td>
<td>38</td>
<td>269</td>
<td>45</td>
<td>270</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>65</td>
<td>408</td>
<td>102</td>
<td>401</td>
</tr>
</tbody>
</table>

Total events

Heterogeneity: \( \tau^2 = 0.19; \) \( \chi^2 = 13.96, \) df = 7 (\( P = 0.05 \)); \( I^2 = 50\%

Test for overall effect: \( Z = 2.72 (P = 0.006) \)
Supplementary Figure 3. Ranking probabilities of treatment for severe alcoholic hepatitis, for short-term mortality.
Meta-Analysis of therapeutic options
No significant effect on Medium-Term mortality

<table>
<thead>
<tr>
<th>Pharmacological intervention</th>
<th>Medium-term mortality (3-12 m)</th>
<th>Risk of acute kidney injury</th>
<th>Risk of developing infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compared with placebo/no intervention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-acetylcysteine (NAC)</td>
<td>1.21 (0.70-2.11)</td>
<td>0.88 (0.35-2.25)</td>
<td>3.07 (1.47-6.54)</td>
</tr>
<tr>
<td>Pentoxifylline (PTX)</td>
<td>1.11 (0.78-1.58)</td>
<td>0.45 (0.27-0.76)</td>
<td>0.67 (0.42-1.08)</td>
</tr>
<tr>
<td>Corticosteroids (CS)</td>
<td>1.12 (0.83-1.52)</td>
<td>0.59 (0.34-1.01)</td>
<td>1.21 (0.84-1.77)</td>
</tr>
<tr>
<td>CS + NAC</td>
<td>0.67 (0.33-1.36)</td>
<td>0.23 (0.08-0.62)</td>
<td>0.39 (0.17-0.85)</td>
</tr>
<tr>
<td>CS + PTX</td>
<td>0.97 (0.69-1.38)</td>
<td>0.34 (0.17-0.68)</td>
<td>1.19 (0.77-1.83)</td>
</tr>
</tbody>
</table>
Corticosteroids are the only remaining pharmacological option for severe alcoholic hepatitis: a meta-analysis of individual data on 1974 patients.

Mark Thursz, Alexandre Louvet, Dong Joon Kim, Julien Labreuche, Stephen Atkinson, Sandeep Sidhu, John O’Grady, RL Carithers Marie-José Ramond, Charles Mendenhall, Willis C Maddrey, Tim Morgan, Alain Duhamel, Philippe Mathurin
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% of response (Lille score< 0.45)

Survival

<table>
<thead>
<tr>
<th></th>
<th>Corticosteroids + PTX</th>
<th>Corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>60.4%</td>
<td>64.8%</td>
</tr>
<tr>
<td>20%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pentoxifylline
p=0.6
No pentoxifylline
Combinative therapies
Where are we?
Corticosteroids + pentoxifylline

n=133

Corticosteroids + Placebo

n=137

End point = 6 month survival

270 patients included

AH biopsy proven

Madddrey ≥ 32

Jaundice < 3 months

n=270

Mathurin P et al, JAMA 2013

Fig. 3: Cumulative incidence of hepatorenal syndrome in the two groups.

PTX-C: pentoxifylline + prednisolone

Plac-C: placebo + prednisolone

p=0.07

8.4% (n=11)

15.3% (n=21)

p=0.007

3.05%

11.7%

6.3%
N-acetylcysteine and corticosteroids: The near future?

How to improve management?
Complete responders
Lille score ≤0.16 [≤35th percentile]

Partial responders
Lille score 0.16 - 0.56 [35-70th percentile]

Null responders
Lille score ≥0.56 [≥ 70th percentile]

P Mathurin, Gut 2011
Infection in severe alcoholic hepatitis treated with steroids: Early response to therapy is the key factor

25 % already infected at admission

25 % being infected upon steroids

Prednisolone

Infection before steroids

Infection after steroids (2 months)

A Louvet, Gastroenterology 2009
**Infection and severe alcoholic hepatitis**

**Corticosteroids started**
7 days after diagnosis of infection
After control of infection

**Median time infection**
14 days after steroids

---

**Figure 1:** Survival impact of infection diagnosed before initiation of corticosteroids

- Patients not infected before initiation of steroids
- Patients infected and treated with antibiotics before initiation of steroids

- Survival at 60 days:
  - Not infected: 71.6±3.4%
  - Infected and treated with antibiotics: 70.9±6.1%

- p-value: 0.99

---

**Figure 2:** 2-month survival according to the development of infection after corticosteroids

- Patients without development of infection
- Patients with development of infection after initiation of corticosteroids

- Survival at 60 days:
  - Without infection: 77.5±3.2%
  - With infection: 46.4±6.9%

- p-value: <0.00001

---

A Louvet, Gastroenterology 2009
### Multivariate analysis

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascitis</td>
<td>1.75</td>
<td>(0.78-3.9)</td>
<td>0.2</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>1.2</td>
<td>(0.6-2.2)</td>
<td>0.6</td>
</tr>
<tr>
<td>Maddrey</td>
<td>1.9</td>
<td>(0.99-1.01)</td>
<td>0.6</td>
</tr>
<tr>
<td>Infection</td>
<td>1.2</td>
<td>(0.6-2.3)</td>
<td>0.5</td>
</tr>
<tr>
<td>MELD</td>
<td>1.1</td>
<td>(1.02-1.22)</td>
<td>0.006</td>
</tr>
<tr>
<td>Lille model</td>
<td>17.3</td>
<td>(5.4-54.9)</td>
<td>&lt;0.00001</td>
</tr>
</tbody>
</table>
Prednisolone is significantly associated with infections reported as SAEs (p=0.005, OR 2.24, [95% CI 1.27 – 3.94])

Prednisolone is significantly associated with infections reported after 7 days of treatment (p=0.014, OR 1.47, [95%CI 1.08 – 1.98])
# Association between Incident Infection and Prognostic Scores

<table>
<thead>
<tr>
<th>Scoring system</th>
<th>28-day infection</th>
<th>120-day infection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>mDF</td>
<td>1.009 (1.004 – 1.014)</td>
<td>0.00038</td>
</tr>
<tr>
<td>MELD</td>
<td>1.06 (1.04 – 1.09)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>GAHS</td>
<td>1.24 (1.10 – 1.41)</td>
<td>0.001</td>
</tr>
<tr>
<td>Lille</td>
<td>2.20 (1.35 – 3.57)</td>
<td>0.002</td>
</tr>
<tr>
<td>Lille (w/o day 7)</td>
<td>1.85 (1.00 – 3.41)</td>
<td>0.049</td>
</tr>
</tbody>
</table>

Atkinson EASL 2016
Elevated bDNA is associated with the development of infection by day 7

Vergis N, Gastroenterology 2017
Bacterial DNA – Stratified Approach

Vergis N, Gastroenterology 2017
Acute Kidney Injury

AKI network [AKIN] criteria

↑ creatinine at least 0.3 mg/dL (or a 50% increase) from baseline within 48 H

Altamirano J, Clin Gastroenterol Hepatol 2012
Insights in future plan of development
Drivers of mortality at short and long-term a prospective study

464 patients with severe AH admitted to Lille liver unit

Short-term Outcome = 6 months

Alive Patients at 6 months

Long-term Outcome = 62 [25-102] months

Total of 10413 patients-months were compiled
Total of 1581 alcohol consumption (corresponding to 2554 patients-months)

Louvet A, Hepatology 2017
### Drivers of mortality at short-term

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Patients</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At risk</td>
<td>Death</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Alcohol relapse</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1445*</td>
<td>139</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Yes (≥30 g/day)</td>
<td>161*</td>
<td>9</td>
<td>1.56 (0.74-3.30)</td>
</tr>
<tr>
<td>Lille model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.45</td>
<td>238</td>
<td>46</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>≥0.45</td>
<td>160</td>
<td>102</td>
<td>6.08 (4.26-8.65)</td>
</tr>
<tr>
<td>Per 0.1 increase</td>
<td>398</td>
<td>148</td>
<td>1.38 (1.31-1.46)</td>
</tr>
<tr>
<td>MELD score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per 5-point increase</td>
<td>373</td>
<td>137</td>
<td>1.64 (1.45-1.85)</td>
</tr>
</tbody>
</table>

Louvet A, Hepatology 2017
Drivers of mortality at long-term

Table 4. Association between long-term outcome mortality and alcohol relapse, response to corticosteroids (Lille Model) and disease severity at baseline (MELD score)

Figure 2. Dose-relationship between alcohol consumption and long-term mortality after initiation of corticosteroids treatment
Drivers of mortality at short and long-term: a prospective study

- Using responders and alcohol consumption <30 g/d as a reference
- HR of death = 2.15 for non-responders and alcohol <30 g/d
- HR of death = 4.12 for responders and alcohol ≥30 g/d
- HR of death = 8.34 for non-responders and ≥30 g/day
Drivers of mortality at short and long-term a prospective study

3-MONTH PERIOD OR 6-MONTH PERIOD
OPTIMAL PERIOD FOR STUDIES TESTING DRUG PREVENTING LIVER INJURY

AFTER 3 MONTHS OR 6 MONTHS
AVOID STUDIES TESTING DRUG PREVENTING LIVER INJURY
Time-Frame for testing molecules:
We need to look outside the liver field
SHORT-TERM OUTCOME
Tissue Repair Is The Issue and endpoint

Stent-Retriever Thrombectomy after Intravenous t-PA vs. t-PA Alone in Stroke

The primary study-outcome measure was disability at 90 days, as assessed by means of the modified Rankin scale, a global measure of disability

Table 2. Primary and Secondary Outcomes.*

<table>
<thead>
<tr>
<th>Clinical efficacy outcome</th>
<th>Intravenous</th>
<th>Stent Retriever plus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional independence at 90 days — no./total no. (%)‡</td>
<td>33/93 (35)</td>
<td>59/98 (60)</td>
</tr>
<tr>
<td>Change in NIHSS score at 27 hr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients with data</td>
<td>92</td>
<td>97</td>
</tr>
<tr>
<td>Mean change</td>
<td>−3.9±6.2</td>
<td>−8.5±7.1</td>
</tr>
<tr>
<td>Death at 90 days — no./total no. (%)§</td>
<td>12/97 (12)</td>
<td>9/98 (9)</td>
</tr>
</tbody>
</table>

Saver JL, NEJM 2015
No data in terms of long-term mortality as stent-retriever thrombectomy is not designed to influence drivers of long-term recurrence or mortality.
LONG-TERM OUTCOME
Patient Behavior Is The Issue

21st-Century Hazards of Smoking and Benefits of Cessation in the United States
Prabhat Jha, M.D., Chinthanie Ramasundarahettige, M.Sc., Victoria Landsman, Ph.D., Brian Rostron, Ph.D., Michael Thun, M.D., Robert N. Anderson, Ph.D., Tim McAfee, M.D., and Richard Peto, F.R.S.

Figure 3. Effect of Smoking Cessation on Survival to 80 Years of Age, According to Age at the Time of Quitting.
Conclusion: Tight blood pressure control in patients with hypertension and type 2 diabetes achieves a clinically important reduction in the risk of deaths related to diabetes, complications related to diabetes, progression of diabetic retinopathy, and deterioration in visual acuity.
LONG-TERM OUTCOME
Exposure of therapy preventing the expected events: a prerequisite

CONCLUSIONS

The benefits of previously improved blood-pressure control were not sustained when between-group differences in blood pressure were lost. Early improvement in blood-pressure control in patients with both type 2 diabetes and hypertension was associated with a reduced risk of complications, but it appears that good blood-pressure control must be continued if the benefits are to be maintained. (UKPDS 81; Current Controlled Trials number, ISRCTN75451837.)

<table>
<thead>
<tr>
<th>No. of Events</th>
<th>Less-tight control</th>
<th>Tight control</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>170</td>
<td>259</td>
</tr>
<tr>
<td>1999</td>
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RR Holman, NEJM 2008
Phase I study:

Key points:

1. Time of exposure and low competitive risk of mortality
2. Identification of therapeutic pathways involved in liver injury
3. Better classification of disease profile
Combining Data from Liver Disease Scoring Systems: an interesting approach to select patients

Louvet A, Gastroenterology 2015

Optimal candidates Phase I studies
Suboptimal candidates Phase I studies

Lille model
MELD score
NEAR FUTURE
French Randomized controlled trial
Antibiocor HAA study

AH biopsy proven; Jaundice < 3 months
Maddrey ≥ 32 and MELD ≥ 21
ClinicalTrials.gov Identifier:
NCT02281929

Prednisolone + placebo

Prednisolone + Augmentin®
[Amoxycilline 1g x 3/j + 125 mg x 3/j Clavunalic Acid]

End point = 2 month-survival
Statistical Hypothesis 83% vs 67% [α Risk = 5%; β Risk : 20% (n= 280 patients)]
Last update 210 patients have been included
Phase II Controlled trial from Gilead
Inhibition of apoptosis using GS-4997 (ASK1 inhibitor)

AH biopsy proven or possible AH (NIAA consortium definition)
≥ 32 Maddrey <60

Primary Objective = evaluate the safety and tolerability of GS-4997
Secondary Objectives = improvement of liver function, 28-day survival
Conclusion

Cortisteroids improve short-term survival of patients with severe AH (Maddrey criteria $\geq 32$)

Pentoxyfilline is not efficient

Combination of these 2 molecules is not effective

Progress have been made in the management of patients with severe AH treated with steroids
Conclusion

Corticosteroids should be interrupted in null-responders after 7 days of therapy.

Development of an infection during steroids treatment is linked to the response of treatment evaluated by the Lille model.

In terms of survival, only response to treatment is useful for prediction of the evolution whereas infection rather seems to be a consequence of it.
Conclusion

Combinative therapy NAC + corticosteroids is an interesting approach.

Progress have been made to reach consensus of experts for study design.

Study design will be an important issue.

Network of collaboration between basic researchers and clinicians are warranted.