Can we test liver function to predict the natural course and assess treatment effects in Hepatitis C?

Gregory T. Everson, MD
Professor of Medicine
Director of Hepatology
University of Colorado Denver
In Patients with Chronic Hepatitis C:

Can we measure Hepatic Reserve?  
Can we identify the At-Risk Patient?  
Can we track progression or recovery from DILI?

Gregory T. Everson, MD  
Professor of Medicine  
Director of Hepatology  
University of Colorado Denver
Disclosures

• Intellectual property filings with University of Colorado Denver – 6 patents have been issued from 12/2013 to 7/2015; others pending.

• Founder, Manager and Equity Member of HepQuant LLC

The HepQuant (dual cholate) tests discussed in this presentation are NOT FDA APPROVED. They are currently for investigational use only.
Can we measure Hepatic Reserve?
Methods

Fibrosis Stage on liver biopsy as the Invasive “Gold Standard”

Measuring Function and Physiology
Hepatic Reserve

Dual Cholate SHUNT

Estimating Fibrosis

Liver Stiffness

Metabolism
Breath Tests

SPECT scan
Biomarkers

IV and Oral Clearance Curves

Serum Concentration vs. Time (minutes)
Dual Cholate*

* HepQuant® SHUNT test
Cholic Acid (CA) Transporters

Hepatic Artery

Intravenous 13C-CHOLATE

Portal-Systemic Shunting

Hepatocytes

OATP1B1

OATP1A2

OATP1B3

NTCP

BAAT

Portal Vein

13C-CHOLATE

Enterocytes

OST-α/β

MRP3

IBABP

ASBT

OATP1A2

ENTERO CYTES

OST-α/β

MRP3

IBABP

ASBT

OATP1A2

Oral 4D-CHOLATE

Stomach

Small Intestine

Colon
Elements of Functional Impairment
Measured by the Dual Cholate SHUNT Test

Healthy Liver

- Hepatic Vein
- Hepatic Artery
- Portal Vein
- Portal Blood Compounds
- Systemic Blood Compounds

Diseased Liver

- Hepatic Vein
- Hepatic Artery
- Portal Vein
- Portal Blood Compounds
- Systemic Blood Compounds

Factors:
- Viruses
- EtOH
- Auto-Immune
- Biliary
- Fat, other
Dual Cholate SHUNT test

Test Administration

Oral (D4-cholate, 40 mg) and IV (13C-cholate, 20 mg)
Timed blood draws at t = 5, 20, 45, 60 and 90 minutes
Serum shipped to analytical lab
A Disease Severity Index (DSI) is measured from HFRs and SHUNT

Laboratory Analysis

Isotope Ratiometry-Mass Spectrometry

IV and Oral Clearance Curves

- IV Clearance Curve
- Oral Clearance Curve

Serum Concentration (uM) vs. Time (minutes)
Single Point STAT test

- Oral dose only – D4 cholate 40 mg
- One blood draw at 60 minutes
- Serum separated and shipped to HQ lab
- Result is STAT (estimate of Portal HFR and DSI)
Decline of Hepatic Functional Reserve

% Hepatic Reserve vs Stage of Disease

y = -5.9065x + 99.431
R² = 0.9842

Healthy Persons
F0-F1
F2
F3
F3-F4
F4
F5
F6
F5-F6
Post-LT mix of CTP A B C
Decompensated CTP B C
Decompensated Waiting List Pts
Theoretical Limit
SHUNT and STAT Measure Hepatic Reserve.
Can we identify the At-Risk Patient?
SHUNT (DSI) Predicts Risk for Clinical Outcome

With Number of Subjects at Risk and 95% Confidence Limits

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>n=52</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTP +2</td>
<td>18</td>
</tr>
<tr>
<td>Var Bleed</td>
<td>4</td>
</tr>
<tr>
<td>Ascites</td>
<td>8</td>
</tr>
<tr>
<td>Enceph</td>
<td>3</td>
</tr>
<tr>
<td>Asc+Enc</td>
<td>3</td>
</tr>
<tr>
<td>Death</td>
<td>16</td>
</tr>
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<td>Death</td>
<td>16</td>
</tr>
</tbody>
</table>
### STAT and SHUNT (DSI) Independently Predict Clinical Outcome

Ishak Fibrosis Stage

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrosis ISHAK 5,6 vs 2,3,4</td>
<td>4.00</td>
<td>2.15</td>
<td>7.44</td>
<td>&lt;0.001</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
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<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrosis ISHAK 5,6 vs 2,3,4</td>
<td>2.21</td>
<td>1.08</td>
<td>4.52</td>
<td>0.030</td>
</tr>
<tr>
<td>Platelets per unit</td>
<td>0.99</td>
<td>0.98</td>
<td>1.00</td>
<td>0.002</td>
</tr>
<tr>
<td>Age per year</td>
<td>0.98</td>
<td>0.94</td>
<td>1.01</td>
<td>0.192</td>
</tr>
<tr>
<td>Gender Male vs Female</td>
<td>0.87</td>
<td>0.46</td>
<td>1.64</td>
<td>0.669</td>
</tr>
<tr>
<td>Race Black vs Non-Hispanic, White</td>
<td>0.76</td>
<td>0.29</td>
<td>1.99</td>
<td>0.578</td>
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<tr>
<td>Race Hispanic/other vs Non-Hispanic, White</td>
<td>1.37</td>
<td>0.68</td>
<td>2.77</td>
<td>0.373</td>
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### STAT

<table>
<thead>
<tr>
<th>Variable</th>
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<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>STAT tertile 0.73-1.19</td>
<td>2.59</td>
<td>0.70</td>
<td>9.56</td>
<td>0.154</td>
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<tr>
<td>STAT tertile &gt;1.19</td>
<td>9.82</td>
<td>2.82</td>
<td>34.22</td>
<td>&lt;0.001</td>
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<tr>
<td>Fibrosis ISHAK 5,6 vs 2,3,4</td>
<td>1.58</td>
<td>0.79</td>
<td>3.17</td>
<td>0.199</td>
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<tr>
<td>Platelets per unit</td>
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<td>0.99</td>
<td>1.00</td>
<td>0.059</td>
</tr>
<tr>
<td>Age per year</td>
<td>0.98</td>
<td>0.94</td>
<td>1.02</td>
<td>0.263</td>
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<tr>
<td>Gender Male vs Female</td>
<td>1.10</td>
<td>0.58</td>
<td>2.08</td>
<td>0.771</td>
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<tr>
<td>Race Black vs Non-Hispanic, White</td>
<td>0.69</td>
<td>0.26</td>
<td>1.81</td>
<td>0.451</td>
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<tr>
<td>Race Hispanic/other vs Non-Hispanic, White</td>
<td>1.01</td>
<td>0.49</td>
<td>2.05</td>
<td>0.987</td>
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</tbody>
</table>

### SHUNT (DSI)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSI tertile 15.395-19.898</td>
<td>2.40</td>
<td>0.64</td>
<td>9.04</td>
<td>0.196</td>
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<tr>
<td>DSI tertile &gt;19.898</td>
<td>14.01</td>
<td>3.84</td>
<td>51.08</td>
<td>&lt;0.001</td>
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<tr>
<td>Fibrosis ISHAK 5,6 vs 2,3,4</td>
<td>1.15</td>
<td>0.52</td>
<td>2.54</td>
<td>0.730</td>
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<tr>
<td>Platelets per unit</td>
<td>0.99</td>
<td>0.99</td>
<td>1.00</td>
<td>0.117</td>
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<tr>
<td>Age per year</td>
<td>0.98</td>
<td>0.94</td>
<td>1.02</td>
<td>0.300</td>
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<tr>
<td>Gender Male vs Female</td>
<td>1.23</td>
<td>0.64</td>
<td>2.38</td>
<td>0.538</td>
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<tr>
<td>Race Black vs Non-Hispanic, White</td>
<td>0.48</td>
<td>0.18</td>
<td>1.26</td>
<td>0.136</td>
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<tr>
<td>Race Hispanic/other vs Non-Hispanic, White</td>
<td>0.97</td>
<td>0.47</td>
<td>2.00</td>
<td>0.940</td>
</tr>
</tbody>
</table>
SHUNT and STAT identify the At-Risk Patient.
Can we track progression or recovery from DILI?
Measuring Change in DSI

Δ DSI v3.3

F0 - F3  LTx Cirrh  Decomp  HALT C SVR  HALT C Cntrl  HALT C NR  PSC

p <0.002  p <0.02  p = NS  p <0.001  p = NS

-----SOLAR 1 On-Rx Wk 4  -----  --------------  HALT C ---------------
Functional deterioration related to SBP occurring on Day 7 of treatment

DSI or MELD Score

24 Wk Rx

Ongoing Ascites, Variceal Rx, Encephalopathy

SBP

SVR
GI Bleed

Missed Last Test at Wk 48 due to GIB. Has varices, edema, encephalopathy

DSI or MELD Score

Weeks from Initiation of Treatment

12 Wks Rx
Function Map for Chronic Liver Disease

- **Portal HFR (mL/min/kg)**
- **Systemic HFR (mL/min/kg)**

**SHUNT (%)**:
- 100
- 80
- 60
- 40
- 20

**Healthy**
- **Mild Disease**
- **Moderate Disease**
- **Severe Disease**
PSC Patient during and after AIH Flare

SHUNT (%): 100  80  60  40  20

Healthy
Mild Disease
Moderate Disease
Severe Disease

Baseline 1  2/25/2011
Baseline 2  3/7/2011
AIH Flare  4/6/2012
Recovery  9/10/2012
SHUNT and STAT can track progression or recovery from DILI.
• Quantify underlying hepatic reserve
• Identify the At-Risk Group
• Track progression or recovery from DILI
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- **HALT-C Trial (NIDDK, Roche)**
  - James Everhart
  - Jay Hoofnagle
  - Leonard Seeff
  - Elizabeth Wright
  - Teresa Curto
  - Mitch Shiffman
  - Timothy Morgan
  - John Hoefs

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  - Clark Kulig
  - Steve Helmke

- **Advanced Disease Study (BUMC)**
  - James Trotter
  - Jacque O’Leary

- **Reproducibility Study (HepQuant LLC)**
  - James Burton

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  - Ariana Wallack
  - Michael Cookson

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