Drug-Induced Liver Injury (DILI)
Acute Liver Failure 2017

DILI Conference June 6-7

William M. Lee, MD, FACP, FACG, FAASLD
Professor of Internal Medicine
Meredith Mosle Chair in Liver Disease
UT Southwestern Medical Center
Dallas, TX
Acute Liver Failure

CAUSE
- Hep B
- DILI
- Budd-Chiari
- Hep A
- Autoimmune
- Indeterminate
- HSV
- Wilson Disease
- Acetaminophen

EFFECT
- Coma
- Coagulopathy
- Shock
- Bleeding
- Infection
- Renal failure
Acute Liver Failure Study Group: based at UTSW

Rationale: Network to study a rare disease

- Began in 1998, currently 12 adult sites
- 2,400 cases in adult, ~1,100 in PALF registry
- Three directions:
  - Prospective clinical data, sera, urine, plasma, DNA
  - Numerous ancillary studies
  - Therapy trials as well
Etiology of Acute Liver Failure in the USA Adult Registry (n = 2,436)

ALF Study Group, Jan 2017

APAP: 1115
Drug: 261
Hep B: 173
Hep A: 38
Autoimm: 163
Ischemic: 155
Wilson's: 29
Budd-Chiari: 18
Pregnancy: 24
Other: 163
Indeter: 289
Aim: Discuss Clinical Trends in DILI that leads to ALF

Topics:

• Regulatory side
• Current snapshot of DILI-ALF
• Which drugs cause DILI-ALF?
• Diagnosis/vignettes
• Prognosis/Outcomes
• Treatments
• Predicting Outcome
### DILI: Most common reason for FDA action(s)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Use</th>
<th>Regulatory action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bromfenac</td>
<td>Analgesic</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>Troglitazone</td>
<td>Diabetes</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>Felbamate</td>
<td>Anticonvulsant</td>
<td>Restricted Use</td>
</tr>
<tr>
<td>Pemoline</td>
<td>CNS stimulant</td>
<td>Restricted Use</td>
</tr>
<tr>
<td>Tolcapone</td>
<td>Parkinson’s disease</td>
<td>Restricted Use</td>
</tr>
<tr>
<td>Trovafloxacin</td>
<td>Antibiotic</td>
<td>Restricted Use</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>Analgesic</td>
<td>Warnings</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>Immunosuppressant</td>
<td>Warnings</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>Antipsychotic</td>
<td>Warnings</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Antiviral (HIV)</td>
<td>Warnings</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Antituberculosis</td>
<td>Warnings</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Antituberculosis</td>
<td>Warnings</td>
</tr>
<tr>
<td>Terbinafine</td>
<td>Antifungal</td>
<td>Warnings</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Anticonvulsant</td>
<td>Warnings</td>
</tr>
<tr>
<td>Zafirlukast</td>
<td>Asthma</td>
<td>Warnings</td>
</tr>
</tbody>
</table>

**Lumericoxib**  
**NSAID**  
Not approved (2003)

**Ximelagatran**  
**Anticoagulant**  
Not approved (2006)

**Telithromycin**  
**Antibiotic**  
Restricted Use (2007)

**Solithromycin**  
**Antibiotic**  
Not approved (2016)
### Most frequent DILI agents in adults

<table>
<thead>
<tr>
<th>Category</th>
<th>ALFSG N=137</th>
<th>DILIN N=899</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amox/Clavulanate</td>
<td>0</td>
<td>91</td>
</tr>
<tr>
<td>INH (w/wo rif/pyraz)</td>
<td>25</td>
<td>28</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>11</td>
<td>42</td>
</tr>
<tr>
<td>Sulfa (TMP/SMX, sulfasalazine)</td>
<td>12</td>
<td>31</td>
</tr>
<tr>
<td>Minocycline</td>
<td>6</td>
<td>28</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Others</td>
<td>13</td>
<td>115</td>
</tr>
<tr>
<td>Herbal and Dietary Supplements</td>
<td>14</td>
<td>145</td>
</tr>
<tr>
<td>CNS</td>
<td>18</td>
<td>82</td>
</tr>
</tbody>
</table>
## Comparison of Different ALF Etiology Groups

\[ N = 2,436 \]

<table>
<thead>
<tr>
<th></th>
<th>APAP N=1115</th>
<th>Drug n=261</th>
<th>Indeterminate n=282</th>
<th>HepA/HepB n=38/173</th>
<th>All Others N=560</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median)</td>
<td>37</td>
<td>46</td>
<td>40</td>
<td>50/43</td>
<td>45</td>
</tr>
<tr>
<td>Sex (% F)</td>
<td>76</td>
<td>69</td>
<td>61</td>
<td>45/46</td>
<td>70</td>
</tr>
<tr>
<td>Jaundice to coma (Days)</td>
<td>1</td>
<td>12</td>
<td>10</td>
<td>4/8</td>
<td>7</td>
</tr>
<tr>
<td>Coma ≥3 (%)</td>
<td>53</td>
<td>36</td>
<td>47</td>
<td>53/50</td>
<td>40</td>
</tr>
<tr>
<td>ALT (median IU)</td>
<td>3798.5</td>
<td>648</td>
<td>870</td>
<td>2316.5/1415</td>
<td>774</td>
</tr>
<tr>
<td>Bili (median)</td>
<td>4.3</td>
<td>19.2</td>
<td>20.1</td>
<td>12.3/18.8</td>
<td>12.7</td>
</tr>
<tr>
<td>Tx (%)</td>
<td>8.6</td>
<td>38</td>
<td>42</td>
<td>34/39</td>
<td>29</td>
</tr>
<tr>
<td>Spontaneous Survival (%)</td>
<td>64.4</td>
<td>25</td>
<td>23</td>
<td>50/19</td>
<td>31</td>
</tr>
<tr>
<td>Overall Survival (%)</td>
<td>71.5</td>
<td>59</td>
<td>61</td>
<td>74/53</td>
<td>55</td>
</tr>
</tbody>
</table>
Entities that masquerade as hepatotoxicity

- **Hepatitis C**
- **Herbs not admitted to**
- **Gall stone passage (choledocholithiasis)**
- **Ischemic injury: shock, hypoxia, CHF, illicit drugs**
- **Rhabdomyolysis**

- **Any one can be associated with AST/ALT > 1,000**
All Natural
And Dangerous

RESTORES
VIM & VIGOR
Herbal and Dietary Supplements (HDS): mostly a black box

- Use of HDS often under-reported, comprise 21% DILI-ALF
- Multiple preparations, multiple ingredients in each
- Likely culprits: weight loss products, body building
- Several recent ‘epidemics’, clusters of cases:
  - Hydroxycut, Oxyelite Pro, Herbalife®
- Outcomes overall are worse than for Rx drugs: Spont survival: 17% vs 34%; OLT: 56% vs 32%

Treatment for DILI-ALF

- Make the diagnosis: excluding other likely causes
- Stop the agent and hope
- Good Intensive care: guidelines offer expert opinion
- Steroids not considered effective
- NAC effective in the only randomized controlled trial
- Transplantation is often required
Primary/secondary outcomes in the NAC trial

The most impressive difference was in transplant free survival in coma grades I-II. * = statistically significant
## NAC Results by Etiology

<table>
<thead>
<tr>
<th></th>
<th>Overall survival</th>
<th>Transplant free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PLB</td>
<td>NAC</td>
</tr>
<tr>
<td>DILI N=45</td>
<td>17/26</td>
<td>15/19</td>
</tr>
<tr>
<td></td>
<td>65%</td>
<td>79%</td>
</tr>
<tr>
<td>AIH N=26</td>
<td>10/15</td>
<td>7/11</td>
</tr>
<tr>
<td></td>
<td>67%</td>
<td>64%</td>
</tr>
<tr>
<td>HBV N=37</td>
<td>6/12</td>
<td>19/25</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>76%</td>
</tr>
<tr>
<td>Indeterm N=41</td>
<td>18/26</td>
<td>9/15</td>
</tr>
<tr>
<td></td>
<td>69%</td>
<td>60%</td>
</tr>
</tbody>
</table>
Outcomes in Adults with Acute Liver Failure from 1998-2013: An Observational Cohort Study

Have changes in management/outcomes occurred?

- 2070 patients in 16 yrs, with 21 day outcomes known
- No differences in etiologies or disease severity, referral patterns or time to referral
- Results: decline in:
  - Listing, deaths, transplantation
  - Use of vasopressors, ventilation, blood products
- Overall and transplant-free survival improved.

Overall and transplant-free survival over time: 1998-2013

*Legacy sites have enrolled at least one subject in each of the 16 years of the registry. They include: Northwestern University, University of California at San Francisco, University of Michigan, University of Washington, and the University of Texas Southwestern Medical Center. Note that p-values represent trends over time tested with the Cochran-Armitage test.

Treatment modalities over time

Note that p-values represent trends over time tested with the Cochran-Armitage test.

Use of N-acetylcysteine over 16 years: 1998-2013

Note that p-values represent trends over time tested with the Cochran-Armitage test.

Determinants of Outcome Among Patients with Acute Liver Failure Listed for Liver Transplantation in the US
Focusing only on those who were listed.

- 617 patients of 1696 (36%) listed between 2000 and 2013.
- Listing and receiving a LT depended on etiology
  - APAP: only 22% listed, 36% of those rec’d LT, 24% died
  - Non-APAP (DILI, Hep B, Autoimmune): 57% listed, 74% rec’d LT, 15% died.
- Transplanted patients more closely resembled survivors than those that had died.

Outcomes in ALF: 1998-2013
Overall: 1696, of whom 614 (36%) listed

<table>
<thead>
<tr>
<th>APAP: n=173 (22%)</th>
<th>non-APAP: n=441 (56%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sicker at listing</td>
<td>Less sick</td>
</tr>
<tr>
<td>36% received LT</td>
<td>74% received LT</td>
</tr>
<tr>
<td>Time to death: 2 days</td>
<td>Time to death 4.5 days</td>
</tr>
<tr>
<td>54% of deaths w/in 24 hours of listing</td>
<td></td>
</tr>
</tbody>
</table>

Median time to LT: 4 days

Non-APAP patients more likely to survive to 4 days to receive a graft.
ALFSG Prognostic Score
Significance of Etiology and Coma Grade
ALFSG Prognostic Score

Predicted SS:

(Touch score above for formula)

Hepatic Encephalopathy?

Etiology?

Vasopressor Used?

Bilirubin?

INR?

Favorable

(acetaminophen overdose, pregnancy, ischemia, or hepatitis A)

Unfavorable

(all other causes)
ALFSG Prognostic Score

Logit SS =
  2.67
  - 0.95 * (Hepatic Encephalopathy)
  + 1.56 * (Etiology)
  - 1.25 * (Vasopressor Use)
  - 0.7 * (ln bilirubin)
  - 1.35 * (ln INR)

Predicted SS =
  1 / (1 + e^(-1*Logit SS))

Hepatic Encephalopathy = 0 or 1
Etiology = 0 or 1
Vasopressor Use = 0 or 1

ALFSG website
acuteliverfailure.org
Case: Is this hepatotoxicity?

- 51 yr old enters with acute liver failure, INR 3.2
- History: Uterine leiomyosarcoma with 2 debulking operations in 2010; since she has rec’d gemcitabine, adriamycin and more gemcitabine, tolerated well. Three months pta began pazopanib (Votrient®) for evident recurrence, now enters feeling ‘terrible’ for 1 week.
- Liver labs all WNL 2 weeks ago
- Exam shows very tired, icteric woman with cool extremities.
- Bili 5.8: Alk P 208, AST/ALT 2032/1965, INR 3.2.
- Differential: Pazopanib hepatotoxicity or something else?
Case cont’d

Something else!

Echocardiogram
1. The left ventricular chamber size is normal with global hypokinesis and severe global dysfunction. Biplane EF is 11%.
2. Normal right ventricular size and moderately reduced systolic function.
3. There is a mural apical thrombus visualized in the LV.

Diagnosis: Ischemic hepatopathamy secondary to pazopanib cardiac toxicity. ? role of prior adriamycin, Pazopanib hepatotoxicity less likely

Epocrates: Pazopanib: Warning re: Hepatotoxicity and CHF
Overall Summary: DILI and ALF 2017

- Identifying drug-induced hepatotoxicity early is vital
- Bad outcomes occur: poor survival without transplant
- Be aware of agents that cause toxicity and alert to new ones (TKIs will have significant toxicity)
- NAC may well improve survival—off label use
- Use Livertox.nih.gov to look things up.
- Acuteliverfailure.org for further information
## Adult Study Sites in the ALFSG 2017

<table>
<thead>
<tr>
<th></th>
<th>UT Southwestern</th>
<th>U Washington</th>
<th>UCSF</th>
<th>Northwestern University</th>
<th>Michigan</th>
<th>Univ Alabama Birmingham</th>
<th>VCU</th>
<th>MUSC Charleston</th>
<th>Yale University</th>
<th>University of Kansas</th>
<th>The Ohio State University</th>
<th>University of Alberta</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lee/Tujios/Bowling</td>
<td>Liou/Strom</td>
<td>Hameed/Dobai</td>
<td>Ganger/Gottstein</td>
<td>Fontana/Mao</td>
<td>McGuire/Ridgel</td>
<td>Stravitz/Taylor</td>
<td>Koch/Crolley</td>
<td>Schilsky/Stavris</td>
<td>Olson/Taylor/Watson/Peterman</td>
<td>Hanje/Gray</td>
<td>Karvellas/Baig</td>
</tr>
</tbody>
</table>

**UTSW: Admin Center**

- Angela Bowling
- Nahid Attar
- Rehana Mohammed
- Sycil Mathew
- Debra Rowan
- Jody Rule, PhD

**MUSC: Data Coordinating Center**

- Valerie Durkalski, PhD
- Caitlyn Ellerbe, PhD
- Holly Tillman
- Kristen Clasen
- Michelle Gottfried
- Sarah Williams
Targeting Acute Liver Failure in the 21st Century!

acuteliverfailure.org