Acute Liver Failure: An Orphan Disease

Fulminant Hepatic Failure

- Most severe form of liver injury but rare, 2000/yr
- Devastating: survival <10% in earlier era
- Definition: INR ≥ 1.5, any grade enceph, acute illness
- UNOS Status 1a
- Fascinating
- Frustrating
- Hard to treat
- Difficult to study
Fulminant hepatic failure due to halothane
Acute Liver Failure Study Group
Rationale: Network to study a rare disease

- Began in 1998, 13 adult, 15 pediatric sites
- 1,850 cases in adult, ~1,100 in pediatric registry
- New added definition: ALI—INR > 2.0/no enceph
- Three directions:
  - Prospective clinical data, sera, plasma, DNA, tissue
  - Numerous ancillary studies in progress
  - Therapy trials: NAC trial done, others on the way

Funding: NIDDK U-01 through 2015

ACG 2011 Postgraduate Course • October 29-30, 2011
Etiology of Acute Liver Failure in the USA Adult Registry (n = 1,696)

Comparison of Different ALF Etiology Groups
N = 1,696

<table>
<thead>
<tr>
<th></th>
<th>APAP n=787</th>
<th>Drug n=202</th>
<th>Indeterminate n=219</th>
<th>HepA/HepB n=37/123</th>
<th>All Others N=328</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median)</td>
<td>37</td>
<td>47</td>
<td>38</td>
<td>48/43</td>
<td>45</td>
</tr>
<tr>
<td>Sex (% F)</td>
<td>76</td>
<td>66</td>
<td>60</td>
<td>46/45</td>
<td>73</td>
</tr>
<tr>
<td>Jaundice (Days)</td>
<td>0</td>
<td>8</td>
<td>8</td>
<td>3/5</td>
<td>4</td>
</tr>
<tr>
<td>(median)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coma ≥3 (%)</td>
<td>53</td>
<td>37</td>
<td>50</td>
<td>51/55</td>
<td>43</td>
</tr>
<tr>
<td>ALT (median)</td>
<td>3846</td>
<td>685</td>
<td>849</td>
<td>2124/1702</td>
<td>677</td>
</tr>
<tr>
<td>Bili (median)</td>
<td>4.4</td>
<td>19.8</td>
<td>22.0</td>
<td>12.5/19.1</td>
<td>14.6</td>
</tr>
<tr>
<td>Tx (%)</td>
<td>9</td>
<td>40</td>
<td>45</td>
<td>32/41</td>
<td>30</td>
</tr>
<tr>
<td>Spontaneous</td>
<td>67</td>
<td>31</td>
<td>27</td>
<td>54/24</td>
<td>38</td>
</tr>
<tr>
<td>Survival (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Survival (%)</td>
<td>75</td>
<td>68</td>
<td>69</td>
<td>84/61</td>
<td>65</td>
</tr>
</tbody>
</table>
**Acetaminophen: our biggest problem**

<table>
<thead>
<tr>
<th></th>
<th>Intentional (n=251)</th>
<th>Unintentional (n=296)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (%)</td>
<td>77</td>
<td>71</td>
<td>NS</td>
</tr>
<tr>
<td>Age</td>
<td>35</td>
<td>39</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ACM dose(g)</td>
<td>38/38</td>
<td>47/7.5</td>
<td>NS</td>
</tr>
<tr>
<td>Coma (% ≥3)</td>
<td>39</td>
<td>55</td>
<td>&lt; 0.026</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>6053</td>
<td>4207</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Alcohol use/abuse (%)</td>
<td>50/18</td>
<td>50/17</td>
<td>NS</td>
</tr>
<tr>
<td>Antidepressant t</td>
<td>39</td>
<td>34</td>
<td>NS</td>
</tr>
<tr>
<td>History of depression</td>
<td>45</td>
<td>24</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Narcotic cpd (%)</td>
<td>18</td>
<td>63</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Multiple preps</td>
<td>5</td>
<td>38</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Spont surv (%)</td>
<td>70</td>
<td>65</td>
<td>NS</td>
</tr>
</tbody>
</table>
**Acetaminophen (APAP) adducts assay**

- HPLC-EC detects APAP-cysteine residues (smoking gun)
- Highly sensitive and specific
- Excellent correlation with AST
- Remains positive up to 9 days after ingestion
- Present in 20% of indeterminate cases, peds and adults

Multi-organ Failure in ALF

- Cerebral edema: 10-30%
- Circulatory abnormality with shock
- Renal dysfunction: 55%
- Coagulopathy: 100% but is it real?
- Infection: 20%
- ARDS: <10%
- Cardiac abnormalities (rare)

Establish Diagnosis: Acute Liver Failure
(Increased prothrombin time, altered mentation, recent onset hepatic illness)

Admit to ICU

Evaluate Etiology: History, lab

- Acetaminophen? History, levels, high AST
  - Yes
  - NAC
  - Silibinin
- Mushroom Toxicity: History, muscarinic symptoms
  - Yes
  - CVVH, OLT
- Wilson Disease? High bilirubin, low AP
  - Yes
  - Coma I-II
  - In ICU, no sedation
  - List for OLT
  - Intubate
- Drug-induced, viral hepatitis, unknown.
  - (History, viral serologies)
  - Consider NAC for non-acetaminophen, nucleoside analogue for Hep B, good coma care

Estimate Severity: Labs, Etiology, Coma grade

- Coma I-II
- Coma III-IV
- NAC
- Silibinin
- CVVH, OLT

General measures:
PPI, mannitol ready, observe for infection, daily PT/INR
Evaluate for OLT
Management of cerebral edema

US ALFSG: Management Strategies in Use

**Most use:**
- ↑ Head of bed
- quiet room
- brain imaging with CT
- intubation for gr III/IV HE
- mannitol for ICH
- CVVHD if dialysis needed
- careful hemodynamic monitoring (art line, CVP, PA cath)

**Many use:**
- hyperventilation (ICH)
- antibiotic prophylaxis

*Widely variable use of lactulose*

Approx 1/2 centers using ICP monitoring

? Hypothermia?
? Seizure prophylaxis?
? Continuous EEG?
? Hypertonic saline
1,696 Patients enrolled
660 (39%) listed

Spontaneous survivors
N=826 (49%)

Transplanted
N=409 (24%)

Died (Not Transplanted)
N=461 (27%)

Alive
N=371 (91%)

Died
N=38 (9%)

Overall survival: N=1,197 (71%)

Prognosis in ALF: Etiology is a Main Determinant

Transplant free survival rates differ greatly

Good prognosis:
- APAP 66%
- Ischemia 66%
- Pregnancy 55%
- Hepatitis A 56%

Bad prognosis:
- Drugs 27%
- Indeterminate 25%
- Autoimmune 26%
- Hepatitis B 26%
- Wilson Disease 0%

(Age is NOT an important determinant)*

*Schiødt FV, et al. Liver Transplant 2009
Transplant-free survival by etiology and coma grade

Coma grade I-II patients had ~50% better survival than III-IV

Therapies for the overall condition ALF

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Rationale</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total body washout</td>
<td>Detoxify</td>
<td>No help; harmful</td>
</tr>
<tr>
<td>Heparin</td>
<td>DIC</td>
<td>No help; harmful</td>
</tr>
<tr>
<td>Steroids</td>
<td>Inflammation</td>
<td>No help</td>
</tr>
<tr>
<td>Prostaglandins</td>
<td>Cytoprotection</td>
<td>No help</td>
</tr>
<tr>
<td>Activated charcoal</td>
<td>Clear toxins</td>
<td>No help</td>
</tr>
<tr>
<td>Plasmapheresis</td>
<td>Clear toxins</td>
<td>Possible</td>
</tr>
<tr>
<td>Cell systems</td>
<td>Replace liver</td>
<td>May improve coma</td>
</tr>
<tr>
<td>Cell transplants</td>
<td>Replace liver</td>
<td>Not enough data</td>
</tr>
<tr>
<td>NAC</td>
<td>GSH donor</td>
<td>Positive trial</td>
</tr>
</tbody>
</table>
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>Etiology</th>
<th>PLB</th>
<th>NAC</th>
<th>PLB</th>
<th>NAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>DILI N=45</td>
<td>17/26 (65%)</td>
<td>15/19 (79%)</td>
<td>7/26 (27%)</td>
<td>11/19 (58%)</td>
</tr>
<tr>
<td>AIH N=26</td>
<td>10/15 (67%)</td>
<td>7/11 (64%)</td>
<td>4/15 (27%)</td>
<td>1/11 (9%)</td>
</tr>
<tr>
<td>HBV N=37</td>
<td>6/12 (50%)</td>
<td>19/25 (76%)</td>
<td>2/12 (17%)</td>
<td>10/25 (40%)</td>
</tr>
<tr>
<td>Indeterm N=41</td>
<td>18/26 (69%)</td>
<td>9/15 (60%)</td>
<td>6/26 (23%)</td>
<td>6/15 (40%)</td>
</tr>
</tbody>
</table>
Ornithine Phenyl Acetate: STOP-ALF Trial

Lower ammonia to manage cerebral edema

- Ammonia is the putative cause for cerebral edema
- OPA traps ammonia and allows renal excretion
- Could be used prophylactically or as treatment
- IV, few side effects, might work in cirrhosis also
- ALFSG will study in APAP patient group beginning in 12/11

Acute Liver Failure 2011

Determine quickly the diagnosis/etiology/severity

- Acetaminophen most common etiology, good prognosis, hyperacute features: 2/3 will survive
- DILI, Hep B, Autoimmune, Indeterminate poor prognosis, slower evolution: 1 in 4 will survive
- NAC appears effective for non-acetaminophen with early coma grade
- Prognosis depends on coma grade and etiology
- When in doubt, assume the worst
**Acute Liver Failure 2011**

"Dos and Don’ts—if you don’t have to"

- **Do:** Quiet room, head up 30°, monitor closely for CNS change, replete volume, consider intubation at coma grade 2-3
- **Don’t:**
  - Sedate unless agitated
  - Give FFP unless bleeding
  - Give antibiotics without cause
  - Give lactulose if planning OLT

**Summary/Conclusions**

- Evaluate quickly, take these cases seriously
- Refer to a transplant center if likelihood of OLT
  - Subacute etiologies, advanced coma grades
- Good coma care
  - Attention to volume, replace glucose, phosphate, vigilance for infection, bleeding, consider CVVH
  - Give specific antidotes: err on side of giving NAC
Study Sites (Adult) in the ALFSG 2009

- UT Southwestern
- U Washington
- UCSF
- Mt. Sinai NYC
- Univ Nebraska Omaha
- Baylor Dallas
- Univ Pittsburgh
- Northwestern Univ
- OHSU, Portland
- UCLA
- Michigan
- Univ Alabama Birmingham
- Mass General
- Columbia/Cornell NYC
- VCU
- Mayo Clinic: Rochester, Jax
- UC Davis
- Einstein Philadelphia
- MUSC Charleston
- Pennsylvania
- Yale University

Lee/Larson/Sanders
Liou
Fix
Liu/Zuniga
McCashland/Teten
Murray/Coultrup
Shakil/Gooch
Ganger/Gottstein
Zaman/Ingram/Wilson
McClune/Peacock/Melgoza
Fontana/Welch
McGuire/Hogue
Chung/Rutherford/Lundmark/Gustafson
Brown/Odeh-Ramadan
Stravitz/White/Topaz
Hay, Raj,Kramer: Groettum/Kontras
Rossaro/Dhillwal
Munoz/Riera/Carmody
Reuben/Minshall
Reddy/Wirjosemito
Schilsy/Emre/Engle/Snyder

www3.utsouthwestern.edu/liver
Targeting Acute Liver Failure in the 21st Century!