INSUFICIENCIA HEPATICA AGUDA
NUEVOS MECANISMOS Y NUEVOS TRATAMIENTOS

Andres T Blei
Northwestern University Feinberg School of Medicine

XXVII Jornadas de la Sociedad Canaria de Patología Digestiva
Targeting Acute Liver Failure in the 21st Century!
ACUTE LIVER FAILURE STUDY GROUP

Funded by NIH R03, FDA Orphan Grant, R01 (‘00-’05), now U-01 (‘05-10)

• 14 sites initially 1998, now 23
• Also 25 pediatric sites, since 2000
• 1,050 cases in adult, 500 in pediatric registry
• Prospective clinical data, serum, DNA, tissue
• Therapy trial: NAC for non-APAP ALF
• Numerous ancillary studies in progress
INSUFICIENCIA HEPATICA AGUDA

• Etiología

• Mecanismos de injuria hepatica

• Manejo de la Insuficiencia Hepatica Aguda

• Tratamiento
INSUFICIENCIA HEPATICA AGUDA

• Etiología

• Mecanismos de injuria hepatica

• Manejo de la Insuficiencia Hepatica Aguda

• Tratamiento
ETIOLOGY OF ALF IN THE USA:
Adult Registry (n = 973)

- ACM
- Drug
- HepB
- HepA
- AIH
- Ischemic
- Wilson’s
- Budd-Chiari
- Pregnancy
- Other
- Indeter
## COMPARISON OF DIFFERENT ALF ETIOLOGY GROUPS

<table>
<thead>
<tr>
<th></th>
<th>ACM n=407</th>
<th>Drug n=111</th>
<th>Indeterminate n=131</th>
<th>HepA/HepB n=29/69</th>
<th>All Others n=159</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median)</td>
<td>36.0</td>
<td>42.0</td>
<td>38.0</td>
<td>48.0/41.0</td>
<td>42.0</td>
</tr>
<tr>
<td>Sex (% F)</td>
<td>74</td>
<td>67</td>
<td>57</td>
<td>48/48</td>
<td>78</td>
</tr>
<tr>
<td>Jaundice (Days)</td>
<td>0.0</td>
<td>8.0</td>
<td>8.0</td>
<td>3.0/6.0</td>
<td>6.0</td>
</tr>
<tr>
<td>(median)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coma ¾ (%)</td>
<td>52</td>
<td>39</td>
<td>49</td>
<td>52/50</td>
<td>42</td>
</tr>
<tr>
<td>ALT (median)</td>
<td>4248</td>
<td>586</td>
<td>899</td>
<td>2622/1740</td>
<td>674</td>
</tr>
<tr>
<td>Bili (median)</td>
<td>4.5</td>
<td>20.9</td>
<td>22.7</td>
<td>11.8/19.7</td>
<td>15.8</td>
</tr>
<tr>
<td>Transplant (%)</td>
<td>9</td>
<td>42</td>
<td>41</td>
<td>31/49</td>
<td>35</td>
</tr>
<tr>
<td>Spontaneous Survival (%)</td>
<td>63</td>
<td>25</td>
<td>26</td>
<td>55/26</td>
<td>30</td>
</tr>
<tr>
<td>Overall Survival (%)</td>
<td>71</td>
<td>64</td>
<td>63</td>
<td>83/68</td>
<td>60</td>
</tr>
</tbody>
</table>
Cytochrome p450 leads to the formation of unstable compounds!

NAPQI (highly reactive intermediate) → Mercapturic Acid (nontoxic)

Hepatocyte Damage
- Covalent binding to cell proteins, including enzyme itself
- ADDUCTS

GSH glutathione-S-transferase

Glucuronidation (phase II)

Sulfation (phase II)

Nontoxic Metabolites

Cytochrome p450 2E1 (phase I)
Indeterminate Acute Liver Failure: A Riddle Wrapped in a Mystery Inside an Enigma
INDETERMINATE ALF

- Occult hepatitis B
- Parvovirus B19
- SEN virus
- CMV
- EBV
- Herpes virus 6
- Unsuspected acetaminophen
SPECTRUM OF DRUG-RELATED ALF: N=98

Gender  M:F  30:68 (69% F)
Mean Age  44 yrs
Race/Ethnicity:  
Cauc/AA/Hisp/Other  54/17/16/11

Causality:  
High prob/Prob/Poss  44/38/16

Outcomes:  
Survive w/o Transplant  23%
Transplanted  41%
Died  36%

Reuben A, (in preparation)
SPECTRUM OF DRUG-RELATED ALF: \(N=98\)

**Anti-TB drugs:** 16
- 8 INH without other anti-TB drugs
- 5 INH + rifampin + pyrazinamide
- 1 INH + ethambutol
- 2 rifampin + pyrazinamide

**Sulfa-related drugs:** 6
- TMP/SMX, sulfadiazine, sulfasalazine

**Other antibiotics:** 8
- 1 Amox-clavulanate
- 6 nitrofurantoin
- 1 ciprofloxacin
- 1 doxycycline
- 1 itraconazole
SPECTRUM OF DRUG-RELATED ACUTE LIVER FAILURE: II

Miscellaneous:
• Phenytoin 6; Valproate 1; PTU 4; Disulfiram 4
• Statins: 1 Atorvastatin; 2 Cerivastatin
• Herbals and/or dietary supplements: 9
  – including 2 Kava-Kava
• HAART: 2
• Halothane/Isoflurane: 2
• Bromfenac (Duract®): 4
  Troglitazone (Rezulin®): 4
DIAGNOSIS OF FULMINANT WILSON

• Markers of copper metabolism: Low specificity
  – Ceruloplasmin
  – Serum copper
  – 24 hr urine copper

• Standard liver chemistries
  – BR/Alk phos ratio
  – AST/ALT ratio

Schilsky et al, submitted
SERUM COPPER AND THE DIAGNOSIS OF FULMINANT WILSON’S DISEASE

Schilsky M, submitted
ROUTINE LIVER CHEMISTRIES
AND THE DIAGNOSIS OF FULMINANT WILSON’S DISEASE

Schilsky M, submitted
INSUFICIENCIA HEPATICA AGUDA

• Etiologia

• Mecanismos de injuria hepatica

• Manejo de la Insuficiencia Hepatica Aguda

• Tratamiento
DIFFERENT PATHWAYS TO CELL DEATH

Necrosis
(e.g. reperfusion injury, hypoxia, cholestasis)

Paraptosis

Anoikis
(caused by hepatocyte detachment)

Apoptosis
(e.g. FHF, (N)ASH, cholestasis)

Mitotic catastrophe

Autophagy
(e.g. reperfusion injury)

Death Stimulus

(e.g. death receptor ligands, TNF, bile acids, ischemia/reperfusion, ROS)

AASLD, Post Graduate Course 2006
TWO PATHWAYS TO APOPTOSIS
SPECIFIC ENTITIES

- Hepatic ischemia
  - Ischemia-reperfusion: Necrosis/autophagy
- Hepatitis B
  - Effector-cells
    - CTL, NK, NKT cells
- Acetaminophen
  - Metabolic activation
  - Innate immune system
MECHANISM OF HEPATOCYTE DEATH IN VIRAL HEPATITIS
CK-18 (+) staining of oval cells after APAP injury

Hepatology 2005; 41:1252-60
INSUFICIENCIA HEPATICA AGUDA

- Etiología
- Mecanismos de injuria hepatica
- Manejo de la Insuficiencia Hepatica Aguda
- Tratamiento
MANEJO DE LA INSUFICIENCIA HEPATICA AGUDA

• Terapeuticas especificas

• Multiples complicaciones

• Trials clinicos de sistemas artificiales/bioartificiales
**N-ACETYLCYSTEINE**

**Acetaminophen-induced ALF**
- Controlled trial
- ↑ survival vs. controls
- 48% (12/25) vs. 20% (5/25)  
  \[p = 0.037,\]  
  [95% CI 3% to 53%]

**BMJ. 1991; 303:1026-9**

**Mechanism of benefit**

**Mice:**
Improves mitochondrial tricarboxylic acid (TCA) cycle metabolism by stimulation of carbon flux through PDH

Hepatology 2006; 43:454-63

**Humans:**
Better hemodynamics/ O₂ transport
But, ↓ Systemic Vasc Resist.

Improved cerebral oxygenation
But, contradictory results
TREATMENT FOR OTHER ETIOLOGIES

- **Herpetic hepatitis**
  - 141 cases identified
  - 37% treated with iv acyclovir, 4.2±1.8 days after symptom onset
  - Death
    - Treated: 47%
    - Non-treated: 70%
  - OLT
    - 4 died
    - 1 recurrent HSV

- **Acute fatty liver of pregnancy**
  - Delivery

- **Amanita phalloides**
  - Charcoal
  - Iv Penicillin

- **Autoimmune hepatitis**
  - ? Role of steroids

- **Hepatitis B**
  - ? Lamivudine

*Levitsky J, Blei AT (submitted)*
MANEJO DE LA INSUFICIENCIA HEPATICA AGUDA

• Terapeuticas especificas

• Multiples complicaciones

• Trials clinicos de sistemas artificiales/bioartificiales
Management of ALF
Recommendations of the ALF Group

• NOT RECOMMENDED
  – For Bleeding Prophylactic FFP
  – For Circulatory dysfunction Vasopressin
TERLIPRESSIN IN ALF

- Intracranial Pressure
- Cerebral Blood Flow
Management of ALF
Recommendations of the ALF Group

• **NOT RECOMMENDED**

  - Bleeding
  - Circulatory dysfunction
  - Cerebral edema
  - Renal failure

  Prophylactic FFP
  Vasopressin
  Corticosteroids
  Intermitent Hemodialysis
Management of ALF
Recommendations of the ALF Group

• RECOMMENDED
  – Surveillance cultures/empiric antibiotics
And● = pts with infection prior to worsening of HE,
suggesting a pathogenic role for infection.
△and ○ = pts in whom infection was a later event.

Gastroenterology 2003;125:755-64
MANAGEMENT OF ALF
RECOMMENDATIONS OF THE ALF GROUP

• RECOMMENDED
  – Surveillance cultures/empiric antibiotics
  – Enteral nutrition
  – Gastric anti-secretory agents
  – Correction of hypo/hyperglycemia
  – Norepinephrine for circulatory dysfunction
  – Continuous renal replacement
  – Adrenal insufficiency
CIRCULATORY SUPPORT
Adrenal Insufficiency

SST response abnormal in non-survivors.

Hepatology 2002:36:395-402
BRAIN EDEMA IN ALF
CONTROVERSIES IN BRAIN EDEMA
ICP MONITORING

Bernuau J, Durand F

Intracranial Pressure Monitoring in Patients with Acute Liver Failure: a Questionable Invasive Surveillance

Hepatology August 2006

Wendon J, Larsen F

Intracranial Pressure Monitoring in Acute Liver Failure. A Procedure With Clear Indications

Hepatology August 2006
CORRECTING THE COAGULOPATHY

Recombinant factor VII

• However,
  – 2/6 bleeds in the ALF report occurred on rFVII
  – Thrombotic complications reported (n=4)
    
    Can J Anesth 2005

  – Insufficient data to recommend routine use of rFVII
INDUCING HYPERNATREMIA TO PREVENT ↑ICP

Increase in serum sodium

Reduction of ICP

Murphy et al, Hepatology 2004; 39:464-70
WHO GETS BRAIN EDEMA?

- Hyperacute Liver Failure
- Concomitant role of other osmotic challenges
  - Hyponatremia
  - Hyperglycemia
- Increased cerebral blood flow
  - Terlipressin experience
  - Measures that reduce CBF reduce ICP
    - Indomethacin administration
    - Mild hypothermia
TEMPERATURE AND ICP
NOT-CANDIDATES FOR OLT

Jalan et al. 1999 and 2004
PROS AND CONS OF MILD HYPOTHERMIA

• Pros
  – Animal studies show prevention of brain edema
  – Animal studies show ↑ survival in models of ALF
  – Wider use in ICU: Standard of care as neuroprotectant after cardiac arrest

• Cons
  – Cannot be used at early stage of ALF
  – Concern with possible side effects
    • Infection
    • Pancreatitis
  – Concern with possible impairment of hepatic regeneration
MANEJO DE LA INSUFICIENCIA HEPATICA AGUDA

• Terapeuticas especificas

• Multiples complicaciones

• Trials clinicos de sistemas artificiales/bioartificiales
“Well, I do have this recurring dream that one day I might see results.”
LARGE CLINICAL TRIALS

**COMPLETED**
- BioArtificial Liver
  - 171 pts  
  - 11 sites  
    - *US, Europe*
    - *Commercial sponsor*

**IN PROGRESS**
- NAC for non-Acetaminophen induced ALF
  - Aims at ~ 200 pts  
    - 19 sites  
      - *US*
      - *Sponsored by NIH*
- Large volume plasmapheresis in ALF
  - Aims at ~ 180 pts  
    - 3 sites  
      - *Europe*
      - *No commercial sponsor*
- MARS for severe ALF
  - Aims at 110 pts  
    - 16 sites  
      - *France*
      - *Sponsored by French Ministry*
DIFFICULTIES WITH TRIALS IN ALF

- Large number of centers but relatively few patients each
- Control group: Standard Medical Therapy
  - Management protocols not well defined
  - Control of multiple variables
  - No Sham therapy
- Liver Transplantation, a major modifier
- Lumping or splitting the disease?

NEED FOR LIVER SUPPORT SYSTEMS HAS NEVER BEEN GREATER
NON-ACETAMINOPHEN - INDUCED ALF NAC TRIAL

- Double-blind Randomized Controlled Trial
- 3 days of iv NAC (150 mg/day) vs placebo
- Wide range of etiologies
- 175 patients entered
- DSMB overview
  - Discontinued November 23, 2006
  - Futile to continue the study
PRINCIPLES OF BAL

- Plasma Separator
- Pump
- Charcoal Column
- Reservoir
- Bioreactor with Hepatocytes
- Oxygenator/Heater
## Survival with Bioartificial Liver

<table>
<thead>
<tr>
<th>Etiology</th>
<th>n</th>
<th>Control* [n (%)]</th>
<th>BAL* [n (%)]</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>171</td>
<td>53/86 (62)</td>
<td>60/85 (71)</td>
<td>0.259</td>
</tr>
<tr>
<td>FHF/SHF</td>
<td>147</td>
<td>44/74 (59)</td>
<td>53/73 (73)</td>
<td>0.117</td>
</tr>
<tr>
<td>PNF</td>
<td>24</td>
<td>9/12 (75)</td>
<td>7/12 (58)</td>
<td>0.667</td>
</tr>
</tbody>
</table>

*Survivors/total patients.

FHF, fulminant hepatic failure; SHF, subfulminant hepatic failure; PNF, primary nonfunction post-transplantation; BAL, bioartificial liver.

*Ann Surg 2004;239:664*
RANDOMIZED CONTROLLED TRIAL
HIGH VOLUME PLASMAPHERESIS

begun 1998; 2nd interim analysis; n=120; P=0.06 by COX analysis)

[145 of 182 patients enrolled 10/1/2006]

FS Larsen et al. Unpublished data
THREE TYPES OF ALBUMIN DIALYSIS

Single Pass Albumin Dialysis (SPAD)

Molecular Adsorbents Recirculating System (MARS)

Am J Gastroenterol. 2005 Feb;100(2):468-75
SURVIVAL WITH MARS
ACUTE-ON-CHRONIC LIVER FAILURE

Cumulative survival

Hospital days

SMT (n=11)
SMT + MARS (n=12)
p<0.05

Hepatology 2002; 36:949-958
**MARS FOR HEPATIC ENCEPHALOPATHY IN ACUTE-ON-CHRONIC LIVER FAILURE**

<table>
<thead>
<tr>
<th></th>
<th>MARS n=39</th>
<th>SMT n=31</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HE Grade 3</td>
<td>20</td>
<td>19</td>
<td>NS</td>
</tr>
<tr>
<td>HE Grade 4</td>
<td>19</td>
<td>12</td>
<td>NS</td>
</tr>
<tr>
<td>Child-Pugh</td>
<td>13 ± 1</td>
<td>13 ± 1</td>
<td>NS</td>
</tr>
<tr>
<td>MELD</td>
<td>31 ± 2</td>
<td>31 ± 2</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Hassanein et al, Submitted for publication*
PRIMARY ENDPOINT (ITT)
Improvement in HE

n = 70

p = 0.044
WHAT DO WE DO IN 2006?

OPTIMIZE INTENSIVE CARE
IT TAKES A VILLAGE TO BUILD A LIVER

Signaling Factors

Scaffold Proteins

Nutrients

Stem cells

BLOOD In Flow

Nature Biotech 2005;23:1237-9
PROMETHEUS AND THE EAGLE
ACETAMINOPHEN (APAP) ADDUC TS ASSAY

- HPLC-EC detects APAP-cysteine residues
- Highly sensitive and specific
- Remains positive up to 9 days after ingestion
- Present in 20% of indeterminate cases, peds and adults

**Patient Group**

- Known APAP
- Other ALF
- APAP No tox
- Indeterminate with adducts
  - n=7
- Indeterminate
  - n=29

**Acetaminophen-CYS (umol/L)/mg protein**

A | B | C | D | E

0.0 | 0.5 | 1.0 | 1.5 | 2.0 | 2.5 | 3.0
ACETAMINOPHEN ADDUCTS IN VIRAL HEPATITIS ALF

- 72 patients with ALF due to HAV or HBV; 10 + APAP controls
- All patients were anti-HBc or HAV IgM positive
- 9/72 (12%) overall (17% HAV and 10% HBV)
- 8/9 had a history of APAP ingestion (all < 4 gm/d)
- Adduct levels: APAP 5.58 nmol/mL vs AVH-APAP 0.45 nmol/mL (AVH-APAP levels are 1/10 APAP OD)
  (Pos adducts = > 0.02 nmol/mL)

Herpes hepatitis

- 141 cases identified
- 37% treated with iv acyclovir, 4.2±1.8 days after symptom onset
- Death
  - Treated: 47%
  - Non-treated: 70%
- OLT
  - 4 died
  - 1 recurrent HSV

Levitsky J, Blei A (submitted)
ACETAMINOPHEN ADDUCTS IN VIRAL HEPATITIS ALF

The admission serum ALT and total bilirubin levels differed among the 3 groups (p<0.002).

<table>
<thead>
<tr>
<th></th>
<th>ALT (IU/L)</th>
<th>T Bili (mg/dl)</th>
<th>Died*</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVH only</td>
<td>1,580</td>
<td>19.8</td>
<td>27%</td>
</tr>
<tr>
<td>APAP-AVH</td>
<td>2,658</td>
<td>9.7</td>
<td>67%</td>
</tr>
<tr>
<td>APAP</td>
<td>5,570</td>
<td>5.0</td>
<td></td>
</tr>
</tbody>
</table>

* P = 0.017
BINDING TO DEATH RECEPTORS
THE BRAIN IN ALF
FOUR CLINICAL SCENARIOS

• Development of HE
  – Search for precipitants!
  – Insufficient data lactulose/ non-absorbable ATB

• Agitation
  – Will culminate in intubation
  – Propofol
    • Short half-life
    • < cerebral vasodilatation
THE BRAIN IN ALF
# 3 – SUBCLINICAL SEIZURE ACTIVITY

• Controlled trial of phenytoin

<table>
<thead>
<tr>
<th></th>
<th>Phen (n=20)</th>
<th>Control (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SC Seizure</td>
<td>15%</td>
<td>40%</td>
</tr>
<tr>
<td>Pupil abnormal</td>
<td>25%</td>
<td>50%</td>
</tr>
<tr>
<td>BE at autopsy</td>
<td>2/11 (22%)</td>
<td>7/10 (70%)</td>
</tr>
</tbody>
</table>

Hepatology. 2000; 32:536-41

• Randomized controlled trial of phenytoin

<table>
<thead>
<tr>
<th></th>
<th>Phen (n=22)</th>
<th>Control (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SC Seizure</td>
<td>22%</td>
<td>25%</td>
</tr>
<tr>
<td>Brain edema</td>
<td>16/22</td>
<td>15/22</td>
</tr>
<tr>
<td>Mech. Ventil.</td>
<td>10/22</td>
<td>12/22</td>
</tr>
<tr>
<td>Death</td>
<td>70%</td>
<td>68%</td>
</tr>
</tbody>
</table>

J Hepatol 2004; 41:89-96
BRAIN EDEMA IN ALF
ALF Study Group
MONITORING OF ICP
SURVIVAL POST-OLT

30-day survival post-OLT(%)

Non-ICP group
ICP group

n= 11 9 29 31
ACETAMINOPHEN NON-ACETAMINOPHEN

Liver Transplantation 2005; 11:1581-9
UNRECOGNIZED BRAIN EDEMA IN PATIENTS LISTED FOR OLT

Liver Transplantation 2005; 11:1581-9
WHO GETS BRAIN EDEMA?

• Hyperacute Liver Failure

• Concomitant role of other osmotic challenges
  – Hyponatremia
  – Hyperglycemia
MILD HYPOTHERMIA FOR BRAIN EDEMA
Rats after PCA receiving an NH₃ infusion

GLYCOLYSIS
OXIDATIVE STRESS

Cooling

OSMOTIC DISTURBANCE

CYTOKINE BINDING TO E.CELLS

↑ CBF
MILD HYPOTHERMIA IMPROVES SURVIVAL IN ACETAMINOPHEN (APAP) - MICE

Gastroenterology (in press)