New Developments in the Management of Acute Liver Failure

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Learning Objectives

• Describe 3 new approaches to the management of acute liver failure at UCSF

• Describe how the diagnosis of acetaminophen toxicity can be facilitated by a point-of-care test

• Describe how the novel drug ornithine phenylacetate can improve the outcome of patients with acute liver failure

• Describe how a checklist can assist in the management of acute liver failure
Acute Liver Failure

- Coagulopathy
- Encephalopathy
- No pre-existing liver disease
Etiology of ALF in the US

- Acetaminophen: 46%
- Indeterminate: 15%
- Autoimmune
- Viral
- Drug
Acetaminophen-Related ALF

- Patients unaware of the risks may not recall taking the medication
- Plasma acetaminophen concentrations are often undetectable by the time liver injury has occurred
- Unintentional cases present late when encephalopathy may already be present
Acetaminophen Metabolism

![Diagram showing the metabolism of acetaminophen (APAP) into NAPQI, which can form protein adducts leading to necrosis.](adapted_from_larson_clin_liver_dis_2007)

- **Glucuronic Acid**
- **Sulfate**
- **Mercaptopyruvic Acid**
- **GSH Transferase**
- **Cytochrome P450**
- **Covalent Binding**

Adapted from Larson Clin Liver Dis 2007
Acetaminophen-Protein Adducts

- Known APAP overdose
- Non-APAP
- Indeterminate, protein adducts+
- Indeterminate, protein adducts−

Davern et al Gastroenterology 2006;130:687-694
Measuring Acetaminophen-Protein Adducts Using a Dipstick

• Proof-of-concept study
• Sample of blood from patient with ALF
  – HPLC-EC
  – Dipstick
    • Visual interpretation (positive, negative, indeterminate)
    • Dipstick reader
• Medical team blinded to assay results
Infection

Bleeding

Intracranial hypertension

Renal failure

Hypoglycemia

Multi-Organ System Failure

Shock

COMPLICATIONS
ALFSG Outcomes

- Spontaneous survivors: 28%
- Transplanted: 48%
- Died without transplant: 24%

Overall survival 70%
Coma grade I-II patients had ~50% better survival than III-IV.
NH₃
(ammonia)
NH$_3$ (primarily from gut)

- glutamate
- glutamine synthetase
- astrocyte
- glutamine

Chronic Liver Failure
export of organic osmolytes compensates

Acute Liver Failure
export of organic osmolytes overwhelmed

Abnormal Neurotransmission

Hepatic encephalopathy

Hepatic encephalopathy + cerebral edema

Adapted from T. Stravitz

Ammonia and Cerebral Herniation


230 μmol/L

118 μmol/L

p<0.001

Arterial ammonia (μmol/L)
Ammonia, ICH & Survival

Intracranial hypertension

Cumulative survival

Ammonia Capture

• OPA acts on 2 key enzymatic pathways favoring reduction in circulating ammonia

• Supplies substrate (glutamate) to maintain glutamine formation

• Shifts the glutamate pool to glutamine
Effect of OCR-002 on Ammonia & Intracranial Pressure (ALF Model)

OP - but neither O, nor P alone - significantly reduces arterial ammonia
Effect of OCR-002 on Ammonia & Intracranial Pressure (ALF Model)

The reduction in ammonia levels prevents a rise in ICP
Safety & Tolerability of Ornithine Phenylacetate for the treatment of Acute Liver Failure
Primary Objective

• Evaluate the safety and tolerability of OCR-002 in patients with acute liver failure/severe acute liver injury due to acetaminophen overdose

Secondary Objectives

• Evaluate the steady state pharmacokinetic and pharmacodynamic profile of OCR-002 in patients with intact and impaired renal function using urinary PAGN as a surrogate marker

• Evaluate the effect of OCR-002 on venous ammonia levels

• Evaluate the effect of OCR-002 on neurological function
Management of ALF

complex

multiple critical steps

not standardized

few controlled studies

heterogeneous
Checklists

• Decrease human error
• Standardize a process
• Reduce variability
• Improve performance and teamwork
• Reminders of only the most critical steps, rather than steps that practitioners never fail to do

# ENGINE FAILURE DURING FLIGHT

<table>
<thead>
<tr>
<th>• Airspeed</th>
<th>68 KIAS</th>
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**FLY THE AIRPLANE!**

| • Fuel Shutoff Valve | ON (IN) |
| • Fuel Selector | BOTH |
| • Auxiliary Fuel Pump | ON |
| • Mixture | RICH |
| • Ignition Switch | BOTH |
Catheter-related Blood Stream Infection
Care Team Checklist

Purpose: To work as a team to decrease patient harm from catheter-related blood stream infections
When: During all central venous or central arterial line insertions or re-wires
By whom: Bedside nurse

1. Today's date
   month / day / year

2. Procedure:
   □ New line  □ Re-wire

   Drape entire patient in a sterile fashion
   □    □    □

   During the procedure, did the housestaff:
   Use sterile gloves
   □    □    □
   Use hat, mask and sterile gown
   □    □    □
   Maintain a sterile field
   □    □    □

   Did all personnel assisting with procedure follow
   the above precautions
   □    □    □

   After the procedure:
   Was a sterile dressing applied to the site
   □    □    □

   Please return completed form to the designated location in your ICU.

CRBSI 11.3/1000 → 0/1000 catheter days
Mortality: 1.5% → 0.8%

Complications: 11% → 7%

Has the patient confirmed his/her identity, site, procedure, and consent?
- Yes

Is the site marked?
- Yes

Is the anaesthesia machine and monitor check complete?
- Yes

Is the pulse oximeter on the patient functioning?
- Yes

Does the patient have a:
- Known allergy?
  - No
  - Yes

Difficult airway or aspiration risk?
- No
  - Yes, and equipment/assistance available

Risk of >500ml blood loss (7ml/kg in children)?
- No
  - Yes, and two IVs/central access and fluids planned

Before skin incision
(with nurse, anaesthetist and surgeon)

- Confirm all team members have introduced themselves by name and role.
- Confirm the patient’s name, procedure, and where the incision will be made.
- Has antibiotic prophylaxis been given within the last 60 minutes?
  - Yes

Before patient leaves operating room
(with nurse, anaesthetist and surgeon)

Nurse Verbally Confirms:
- The name of the procedure
- Completion of instrument, sponge and needle counts
- Specimen labelling (read specimen labels aloud, including patient name)
- Whether there are any equipment problems to be addressed

Patient, Anaesthetist and Nurse:
- Are the key concerns for recovery and management of this patient?

Is essential imaging displayed?
- Yes
  - Not applicable

This checklist is not intended to be comprehensive. Additions and modifications to fit local practice are encouraged.

Revised 1 / 2009

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Haynes et al NEJM 2009; 360;491-499
Checklist for ALF

• Management of ALF is an ideal process for a checklist
• Improve and standardize management of ALF
• Content sources:
  – Published guidelines
  – Expert opinion
  – Consensus
Checklist for ALF

• Pilot testing to begin at 10 ALFSG sites

• Survey users for usability and content

• Long-term outcomes:
  – Process measures
  – Proportion of indeterminate etiologies
  – Spontaneous/overall survival
Summary

Point of care dipstick assay for acetaminophen-protein adducts can facilitate diagnosis of acetaminophen-related acute liver failure
Summary

Ornithine phenylacetate can lower circulating ammonia levels and may improve encephalopathy and intracranial pressure in ALF.
A checklist can improve and standardize the management of ALF.