A Case of Fulminant Hepatic Failure due to Exertional Heat Stroke

Lynn J. Hernan, MD
Rohit Pinto, MBBS
Pediatric Critical Care
Agenda

• Case
• Discuss exertional heat stroke (EHS)
  • Presentation
  • Physiology
  • Treatment / Outcome
• Define Fulminant Hepatic Failure (FHF)
• Treatment of FHF
• Liver Transplantation
• Statistics regarding Liver Transplantation
  • US
  • NY State
• Resolution of Case
Educational Objectives

- Recognize exertional heat stroke (EHS)
- Know emergency management of EHS
- Define Fulminant Hepatic Failure (FHF)
- Understand treatment of FHF
- Recognize indications for referral for transplant
- Recognize outcome of FHF +/- transplant
- Understand transplantation statistic
Bradford ER
16 yr (70 kg) previously healthy male

• History
  • 1 hr ago - collapsed while running 3.6 miles
  • LOC at scene
  • EMS arrived
    • lethargic and pale
    • Glu = 62 - Given Dextrose
    • L leg jerking, stiffening, eye deviation, incontinence
    • Given 2 mgs ativan
    • Emesis in ambulance
Bradford ER PE

- **Vitals**
  - Temp = 39.2°C
  - HR = 107
  - BP = 98/45
  - RR = 18
  - Pulse ox = 100% on 2 Lpm O₂
Bradford ER PE

- CNS
  - Lethargic, arousable
  - Single word answers
  - Pupils equal & reactive
- CVS - normal
- Resp - normal
- Abd - normal
- MS - normal
Bradford ED Labs

- CBC
  - WBC = 8.6
  - Hgb = 17.6
  - Plts = 313
- BUN = 15
- Creatinine = 2.1
- LFTs
  - AST = 35
  - ALT = 13
- CK = 747 (30-200)
- Troponin = 0.14 (0 - 0.3)

- UA
  - SG = 1.025
  - Protein >300
  - Blood Large
  - RBCs = 2-5/hpf
- Urine tox - Neg
- VBG
  - 7.26/33/78/14/-11
Bradford ER Course

- Given 4 L NS
- Became combative
  - Ativan and versed
  - Loaded with Dilantin
  - Head CT - normal
- EKG – Normal
- Called CHOB for transfer of care
  - Seizure
  - Dehydration
  - Heat Exhaustion
- STAT team transfer unremarkable
Hospital Day 1 - CHOB ER

- **Vital Signs**
  - Temp = 37.4°C
  - HR = 90
  - RR = 15
  - BP = 143 / 43
  - cap refill < 2 seconds
  - Pulse ox = 99% on room air

- **PE normal**
Ca – 8.1
Alk Phos - 181  Bili – 0.8
AST - 91      CK – 3098
ALT - 31      Ammonia - 77
GGT- 30

Blood Gas -7.32/37/76/19/-6.4

CSF – Neg

UA = Heme 3+, 3-5 RBCs
Hospital Day 1 - CHOB Floor

• History
  • Second 4 mile run of day
  • Felt dizzy while running
  • LOC - cannot remember falling
  • Skipped breakfast, not drinking fluids day of race
  • Denies energy supplement / protein supplements

• PE normal except
  • BP = 165 / 43
Admission Diagnosis

- Heat exhaustion
- Dehydration
- Syncope
- Seizure disorder
- Rhabdomyolysis
- Renal insufficiency due to
  - Myoglobinuria
  - ATN
Hospital Day 1 - CHOB Floor

- **Therapies**
  - Hydration

- **Testing**
  - ECHO - Normal
  - Renal Consult
    - Hydration goal - UO = 3 ml/kg/h
    - Add NaHCO$_3$ if acidic
  - Neuro Consult
    - EEG – Normal awake study
    - Hold Dilantin
Hospital Day 1 - CHOB Course

- Hematemasis
  - Started on Zantac
  - Coagulation profile sent
    - Thrombocytopenic (plt = 47)
    - PT = 27.8  PTT =36.9  INR = 2.6

- Suboptimal urine output
  - ↑IVF
Hospital Day 1 - CHOB Floor

• PE remained unchanged
• Biochemical parameters continued to deteriorate
  • AST = 91 → 1688
  • ALT = 31 → 1476
  • PT = 27.8 → 32.0
  • Platelets = 47
    • Ordered repeat plt count = 37

• Patient transferred to PICU
Hospital Day 2 - PICU Course

• **Hx**
  • Mild right upper quadrant pain

• **PE - normal except**
  • Twitchy
  • Widened pulse pressure

• **Therapeutics**
  • IVF with Bicarb
  • FFP - bolus, then continuous infusion
  • Vitamin K
  • Platelet transfusion

• **Diagnostics**
  • GI consult
  • Hematology consult
    • Factor levels sent
  • Close monitoring of LFTs, coagulation panel, plts
Liver Transaminases

Bradford

Units/L

Floor

PICU

Time (hours)

AST

ALT
Prothrombin Time (PT)
Summary of PICU Course

- Patient's clinical status never changed
  - Hemodynamically stable
  - CNS status stable

- Progression elevation of liver enzymes
- Progression of profound coagulaopathy
What are your options?

• Continued conservative management
  • What are you going to do if he deteriorates?

• Transfer for liver transplant evaluation
  • Now
  • When he deteriorates
PICU Decision

- Patient transferred to Strong Memorial Hospital PICU
  - Patient transported on FFP drip
  - Uneventful transport
Exertional Heat Illnesses
Exertional Heat Illness

Exertional hyperthermia

Heat cramps

Heat exhaustion

Exertional heat stroke

Irreversible cell injury and death*

* Most deaths within 12 hours to 1 week
Definitions

• **Heat Illness** - inability to maintain normal body temperature
  - Excessive heat production
  - Decreased heat transfer to environment

• **Heat stroke**
  - Cellular injury $\rightarrow$ denatured proteins
  - Recover
  - Die
    - Necrosis
    - Apoptosis
  - Adult mortality = 12%
  - Adolescent athletes - 3rd leading cause of death
Types of Heat Illnesses

- **Heat Stress**
  - Physiologic discomfort
  - Decreased exercise tolerance
  - Normal core temperature
- **Heat syncope**
  - Peripheral vasodilation
- **Heat cramps**
  - Salt deficiency
- **Heat Exhaustion**
  - Intense discomfort, thirst
  - Mild CNS dysfunction
    - Confusion
    - Nausea
    - Vomiting
  - Core temperature = 38 - 40°C
- **Heat Stroke**
  - Exposure to heat
  - Neurologic dysfunction
  - Core temperature > 40°C
  - Infantile heat stroke = Hemorrhagic shock and encephalopathy syndrome
Differentiation of EHS from Classic Heat Stroke

- **EHS**
  - H/o prolonged intense physical exertion
  - Sweaty skin
  - Not acclimatized
  - Young, athletic
  - Usually male
    - Military
    - Sports - football
  - Hepatic failure - 5%

- **Classic Heat Stroke**
  - H/o warm environment - passive exposure
    - Infant
    - Elderly
  - Anhydrosis
  - Hot, flushed skin
  - Impaired sweating
    - Drugs
    - Illnesses
  - Usually during heat waves
  - Hepatic failure uncommon
Exertional Heat Stroke

- Athlete produces more metabolic heat than can be dissipated into environment → ↑core temperature
  - Risk highest with intense or fast-paced activity in hot, humid environment
  - Not acclimatized
  - CNS dysregulation of temperature control
Incidence of EHS

Recognition of Exertional Heat Stroke

• **Symptoms - nonspecific**
  - Fatigue
  - Impaired judgment
  - Weakness
  - Flushing
  - Chills
  - Hyperventilation
  - Dizziness
  - Collapse

• **Diagnosis**
  - Appropriate history and
  - Core T>40°C and
  - CNS dysfunction

• **Differential Diagnosis**
  - Cardiac arrest
  - Hypoglycemia
  - Hyponatremia
  - Heat exhaustion

Any evidence of renal or hepatic dysfunction in first 24 hours should lead to presumptive diagnosis of heat stroke. US Army statement
American College of Sports Medicine Position Stand on Exertional Heat Illnesses during Training and Competition
*Medicine & Science in Sports & Exercise* 2007

- **Levels of Evidence**

  - **A** - consistent, good quality patient- or subject-oriented evidence
  
  - **B** - inconsistent or limited-quality or subject-oriented evidence
  
  - **C** - consensus, usual practice, opinion, disease-oriented evidence, or case series for diagnosis, treatment, prevention, or screening
Exertional Heat Stroke

• Recognition
  • Need rectal temperature (B)
  • Early symptoms (B)
    • Clumsiness, stumbling
    • HA
    • Nausea
    • Dizziness
    • Apathy, confusion
    • LOC

• At collapse
  • Hypotension
  • Tachycardia
  • Hyperventilation
  • Sweaty, cool skin

Exertional Heat Illness

- Exertional Heat Stroke (EHS) (B)
  - Rectal T>40°C at collapse and
  - CNS changes

- Dehydration (A)
  - ↓ exercise performance
  - ↓ time to exhaustion
  - ↑ heat storage

Exertional Heat Stroke

- ↑ risk (B) with
  - Obesity
  - Low fitness level
  - Lack of heat acclimatization
  - Dehydration
  - H/o EHS
  - Sleep deprivation
  - Sweat gland dysfunction
  - Sunburn
  - Viral illness or diarrhea

- ↓ risk (C) with
  - Physical training
    - Appropriate level
    - Appropriate time
  - Cardiac fitness
  - Heat acclimatization

Physiology of Heat Regulation

- CNS
  - hypothalamus
  - spinal cord
- Skin
- Core T > shell T
  - gradient for heat dissipation
Physiology of Exertional Heat Stroke-1

- **Exercise and hot humid environment → ↑ core T**
  - Brain T > core T
  - ↑ brain T →
    - ↓ heat removal (compared to normal)
    - ↓ CBF
    - Changes in brain wave activity and perceived exertion
  - Dehydration through sweat - if >3 - 5% BW fluid loss
    - ↓ sweat production
    - ↓ skin perfusion
    - ↓ heat removal

- **Near maximal exercise levels**
  - ↑ skeletal muscle blood flow
    - Provide glucose
    - Remove waste
    - Remove heat
  - ↓ splanchnic and skin blood flow → ↓ heat removal
Physiology of Exertional Heat Stroke -2

- Increasing core T ➞
  - ↑ Brain T > core T
    - ↓ central control of blood flow distribution ➞
    - Loss of splanchnic and skin vasoconstriction ➞
    - ↓ SVR and ↑ cardiac dysfunction ➞
    - ↓ CO ➞
    - ↓ heat removal

- Cycle continues until collapse
Goals of Treatment for EHS

• **Rapid ↓ core temperature**
  - Stop heat production - STOP exercising
  - IMMEDIATE external cooling
  - Goal: rectal T < 40°C within 30 - 60 min
    - No reported morbidity or mortality when goal met

• **Maintenance of vascular volume**
  - IVF

• **Seizure treatment**
  - Benzodiazepines

• **Symptomatic treatment of other abnormalities**
Exertional Heat Stroke

• **Treatment**
  - Cold water immersion (A)
    - Fastest cooling rate (0.15 - 0.24°C/min)
    - Lowest morbidity and mortality
  - Ice water sheets/towels + ice packs to head, trunk, extremities, groin (C)
    - Acceptable cooling rate (0.12 - 0.16°C/min)
  - Unacceptable - ice packs to neck, axilla, groin
    - Cooling rate of 0.04 - 0.08°C/min

• **Golden hour as in trauma resuscitation**

• **Stop cooling at rectal T ~39°C**

Rapid Cooling for EHS

Mortality and morbidity related to area under the curve

Temperature (°C)

Time (min)

Early Intervention
Late Intervention

Won’t they vasoconstrict and shiver in cold or ice-water, and increase core temperature?

• No

• Cold water can reliably induce hypothermia in normal people after ~ 20 minutes.
Core Cooling - Cold Water Immersion

![Graph showing core temperature changes over time, comparing EHS and Normothermic conditions.](image-url)
Fulminant Hepatic Failure
Fulminant Hepatic Failure

Rapid development of severe liver dysfunction in previously normal child.
### Etiology of FHF in Children

<table>
<thead>
<tr>
<th>Etiology</th>
<th>&lt; 1 year old</th>
<th>≥ 1 year old</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic</td>
<td>42</td>
<td>47</td>
</tr>
<tr>
<td>Neonatal hemochromatosis</td>
<td>16</td>
<td>27</td>
</tr>
<tr>
<td>Undetermined</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>Viral hepatitis</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
<td>2</td>
</tr>
</tbody>
</table>

Cochran and Losek, Pediatric Emergency Care 23: 2007
Clinical Problems of FHF - 1

- **Coagulation abnormalities**
  - ↓ production of factors
  - DIC → ↑ consumption of factors, plts
  - Thrombocytopenia

- Resistant to FFP and vitamin K
- **Therapy - Factor VII**
  - Initiates clotting cascade
  - Short t½ - first depleted
  - Dose: 5 - 110 mcg/kg (80 mcg/kg)
Clinical Problems of FHF - 2

- Hepatic Encephalopathy
  - Pathogenesis
    - Failure of liver metabolism of toxins
      - Ammonia - produced in gut
      - Lactulose and neomycin not effective as chronic liver failure
      - Protein restricted diet
      - Urea cycle activation agents - provide substrate for processes that remove ammonia from portal blood

- Endogenous benzodiazepine-like substances
  - Transient improvement with flumazenil

- Cerebral edema
  - Glutamine hypothesis - cytotoxic
  - Cerebral vasodilation - vasogenic
    - Arteriolar dilation
    - Impaired autoregulation

- ↑ ICP - major cause of death
  - 80% have cerebral edema
  - Monitor and treat
Clinical Problems of FHF - 2

• Hepatic Encephalopathy
  • Classification
    • Grade 1: mood changes, confusion
    • Grade 2: drowsy, inappropriate behavior
    • Grade 3: sleepy but arousable, obeys simple commands
    • Grade 4:
      • 4A - comatose, arousable to painful stimuli
      • 4B - deep coma, unarousable
Clinical Problems of FHF - 3

- **Immune deficiencies**
  - Infection
    - Primary cause of death - 11 - 20%
    - Extrahepatic sepsis contraindication for transplant
  - Pathology
    - Complement deficiency and dysfunction
    - ↓ PMN adherence and killing
    - Dysfunctional Kupffer cells
      - Help clear endotoxin
      - Prevent release of cytokines into portal system
  - Consider prophylactic antibiotics
Clinical Problems of FHF - 4

• **Energy Production Deficiencies**
  • Hypoglycemia
    • Impaired glycogen storage
    • ↓ gluconeogenesis
  • Use of fat and protein stores
    • Muscle and fat breakdown
  • ↑ insulin, glucagon, growth hormone → catabolism
Treatment of FHF

- **Medical**
  - Goal - stabilize until recovery of function
  - Otherwise, symptomatic treatment as outlined
  - N-acetylcysteine (mucomyst)
    - Acetominophen OD
    - Timely presentation

- **Surgical**
  - Failure of medical management
  - Transplantation
    - Cadavaric donor
    - Living-related donor

- **Other**
  - extracorporeal systems (liver dialysis)
    - Porcine hepatocytes
    - Human hepatoblastoma cell line
<table>
<thead>
<tr>
<th>Dysfunction</th>
<th>Treatment</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypermetabolic State</strong></td>
<td>IV glucose</td>
<td>Monitor glucose</td>
</tr>
<tr>
<td></td>
<td>Hyperalimentation</td>
<td>Low protein diet</td>
</tr>
<tr>
<td><strong>Coagulopathy</strong></td>
<td>FFP infusion</td>
<td>Shock + bleeding</td>
</tr>
<tr>
<td></td>
<td>Platelet transfusion</td>
<td>Plt &lt; 20K + bleeding</td>
</tr>
<tr>
<td></td>
<td>Cryoprecipitate infusion</td>
<td>Bleeding risk - PT, INR</td>
</tr>
<tr>
<td></td>
<td>rFVIIa</td>
<td>Bleeding risk - PT, INR</td>
</tr>
<tr>
<td></td>
<td>Plasmapheresis</td>
<td>Invasive</td>
</tr>
<tr>
<td><strong>Immune deficiency</strong></td>
<td>Cefuroxime, consider Ampho B</td>
<td>prophylaxis</td>
</tr>
<tr>
<td><strong>Encephalopathy</strong></td>
<td>Bowel cleansing - lactulose, neomycin</td>
<td>Short-lived benefits</td>
</tr>
<tr>
<td></td>
<td>Flumazenil</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urea cycle activation agent</td>
<td></td>
</tr>
<tr>
<td><strong>Cerebral Edema</strong></td>
<td>Intraventricular monitor</td>
<td>Keep CPP &gt; 40</td>
</tr>
<tr>
<td><strong>Hepatic Failure</strong></td>
<td>Medical</td>
<td>Coagulopathy, encephalopathy</td>
</tr>
<tr>
<td></td>
<td>Plasmapheresis</td>
<td>Acetaminophen OD, ? other</td>
</tr>
<tr>
<td></td>
<td>N-acetylcysteine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Surgical</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Transplantation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Extracorporeal systems</td>
<td></td>
</tr>
</tbody>
</table>

Cochran and Losek, Pediatric Emergency Care 23: 2007
Indications for Transplantation

- Referral for evaluation
  - Recovery is not evident

- Transplantation
  - Failure of medical management
Indication for Pediatric Liver Transplant (n - 10,497)


- Extrahepatic Biliary Atresia - 27.8%
- Acute hepatic necrosis - 12.1%
  - Drug-induced - 8.3% (1% of total)
  - Etiology unknown - 65.3% (7.9% of total)
  - Acute viral infection - 26.4% (3.2% of total)
- Metabolic diseases - 11.5%
- Biliary atresia or hypoplasia, other - 9.9%
- Other - 6.2%
- TPN - induced - 5.7%
- CF - 1.6%

Source: UNOS.org
Liver Transplantation Statistics
Liver Transplants
January 1, 1988 - June 30, 2007

Source: UNOS.org
US Liver Transplant Candidates
as of September 7, 2007

Adult
(n=16,055 or 96%)

Pediatric
(n = 692, or 4%)

11-17 yrs old
(n=243, or 35%)

6-10 yrs old
(n=159, or 23%)

1-5 yrs old
(n=235, or 34%)

<1 yr old
(n=55, or 8%)

Source: UNOS.org
NYS Liver Transplant Candidates as of September 7, 2007

- Adult (n=1,853 or 97%)
- Pediatric (n = 51, or 3%)
- 11-17 yrs old (n=22, or 43%)
- 6-10 yrs old (n=9, or 18%)
- 1-5 yrs old (n=17, or 33%)
- <1 yr old (n=3, or 6%)

Source: UNOS.org
NY State Pediatric Liver Transplantation
January 1, 1988 - December 31, 2006

Source: UNOS.org
Time to Pediatric Liver Transplant - US
as of September 7, 2007

Source: UNOS.org
Percent (Liver Transplant) - US

Patients listed 1999 - 2004

Source: UNOS.org
US Survival (%)
(Pediatric Liver Transplants 1997 - 2004)

Percent Survival

Age at Transplantation

< 1 yr old
1 - 5 yrs old
6 - 10 yrs old
11 - 17 yrs old

1 yr post transplant
3 yrs post transplant
5 yrs post transplant

Source: UNOS.org
NYS Liver Transplant Patient Survival
as of August 31, 2007

Source: UNOS.org
Back to Our Case
Patient continued to be clinically stable
- Normal CNS
- Normal cardiopulmonary status
Follow up labs

- Hepatitis Panels – Neg
- EBV Titre - Neg for infection
- Lyme Disease - Neg

- Factor Levels
  - Factor 2 = 33% L
  - Factor 5 = 15% L
  - Factor 7 = <13% L
  - Factor 8 = 232% H
  - Factor 10 = 17% L
Course of Liver Transaminases

Bradford

Rochester

PICU

Floor

Units/L

Time (hours)

AST

ALT
Course of INR

Time (hours)
Course of Platelets
The Happy Ending

- Patient discharged home in 4 days
  - Without a liver transplant
  - AST 273, ALT 1679

- Normal coagulation
  - PT 15.3, PTT 32.3, INR 1.2
  - Platelet count = 207

- Normal renal function
  - BUN = 9
  - Cr = 0.8
Thank You