The Kidney In Crisis: Acute Care Pediatric Nephrology

Extracorporeal Therapies in Poisoning

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EXTRIP Co-Chair
Objectives

• Understand the history of extracorporeal treatments (ECTR) in poisoning
• Describe the epidemiology of ECTR in poisoning
• Understand the EXTRIP process
• Explain the indications for ECTR in common pediatric poisonings
Background

• Hemodialysis was pioneered as an acute intervention for toxin removal
  – Abel JJ, et al. Trans Assoc Am Physicians. 1913;58:51-54

• Intermittent HD has become the accepted standard for CKD and severe AKI

• Very limited data on any ECTR modality in poisoning
Year of publication: No restriction

No comprehensive guidelines on ECTR in poisoning have ever been published!
Background

• American Association of Poison Control Centers collects data on ~2.5 million exposures each year
• Vast majority are in children
• In 2011, ECTR was used 2337 times
  – HD 2323; HP 14
• These numbers include HD in poisoned patients with AKI/CKD.
  – Not necessarily for toxin removal
Use of hemodialysis and hemoperfusion in poisoned patients

William J. Holubek¹, Robert S. Hoffman²,³,⁴, David S. Goldfarb⁴,⁵ and Lewis S. Nelson²,³,⁴
Background

• Not a single randomized controlled trial on the use of ECTR for
  – Aminophylline / theophylline
  – Lithium
  – Methanol
  – Ethylene glycol
  – Salicylates
  – Valproic acid

• All data from low-quality evidence
General Rules

• Toxin requirements
  – MW
    • Small enough to pass through membrane
  – Volume of distribution
    • $\leq 1\text{L/kg}$
  – Low protein binding

– Can overcome some protein binding issues with HP if toxin is adsorbed to activated charcoal
The Availability and Use of Charcoal Hemoperfusion in the Treatment of Poisoned Patients

Anna S. Shalkham, MD, Barbara M. Kirrane, MD, Robert S. Hoffman, MD, David S. Goldfarb, MD, and Lewis S. Nelson, MD

Am J Kidney Dis 2006;48:239-241

• 10/34 NYC 911 receiving hospitals had HD cartridges
  – Stock: 1-4 adult; only 1 had a pediatric cartridge
  – Only 3 cases of HP in the last 5 years
    • 2 theophylline; 1 aluminum
General Rules: No Specific Data

• Consider ECTR in a toxin that is amenable when:
  – Patients fail to respond adequately to supportive care
  – The normal route of elimination is impaired
  – A high [serum] indicates that serious morbidity or mortality is likely
General Rules: No Specific Data

• Consider ECTR in a toxin that is amenable when (cont):
  – Patients with concurrent disease or in an age group (very young or old) associated with increased risk of morbidity or mortality from the overdose
  – Concomitant fluid, electrolyte, or acid base disorders are present
This is Why We Need EXTRIP

28 members from 12 countries
Medical Specialties Represented by EXTRIP

- **Nephrology**
  - ASN, ASPN, ANZSN, SBN, CSN, ERBP, GSN, ISN, IPNA, NKF, SQN, LASNH, RA

- **Pharmacology**

- **Critical Care**
  - ANZICS, SCCM, PCCM, ESICM, SRLF, PCRRRT

- **Clinical Toxicology**
  - AACT, ACMT, EAPCCT, APAMT, SBTox, CAPCC, ABRACIT, SCTF

- **Emergency Medicine**
  - ACEP, CAEP, CCEP, EuSEM, AMUQ, ASMUQ
Evaluation of ECTR

- Advantages of ECTR
- Complications of ECTR
- Costs of ECTR
- Alternative therapies
  - Supportive care
  - Decontamination
  - Antidotes
Methodology

• Established guideline methodology for scope and rigor
  – AGREE instrument¹

• 16 toxins
  – By pertinence and epidemiology

Quality of the evidence: GRADE\textsuperscript{1}

Score of recommendations

- E.g. Parachute for survival after plane jumping

  (1 D)

  Strength of recommendation: How strongly does the workgroup support the recommendation?

  Quality of the evidence: How good is the evidence supporting the recommendation?
Strength Of The Recommendations

Two voting rounds with a modified Delphi method, between which deliberation and discussion are encouraged.

Statement regarding ECTR for Poison "X"

The workgroup votes on the statement (9-point Likert scale):

FOR (7-9) / NEUTRAL (4-6) /AGAINST (1-3)

Median between 7-9
AND
Disagreement index ≤ 1

Median between 4-6
AND
Disagreement index ≤ 1

Disagreement index > 1
(for any median values)

Lower quartile between 7-9
Level 1 recommendation = "We recommend..."

Lower quartile between 4-6
Level 2 recommendation = "We suggest..."

Level 3 recommendation = "It would be reasonable..."

No recommendation = "No agreement reached"

Search strategy Example

• **Keywords**
  
  `[((poisoning OR overdose OR toxicity OR intoxication) OR (clearance OR pharmacokinetic OR drug dosing)) AND (dialysis OR hemodialysis OR haemodialysis OR hemoperfusion OR haemoperfusion OR plasmapheresis OR plasma exchange OR exchange transfusion OR hemofiltration OR haemofiltration OR hemodiafiltration OR haemodiafiltration OR extracorporeal therapy OR CRRT OR renal replacement therapy)]`

• **Accessed May 1st 2012**
Exhaustive literature review

MEDLINE = 14,874 records
EMBASE = 10,278 records
Other databases + Manual searching = 2557 records

Total = 20,443 articles

Non-RCTs = 7,449 articles
Non-RCTs + editorials discarded = 3,434 articles
Reviews + editorials discarded = 2,091 articles

- Animal studies = 78
- In vitro studies = 54
- PK/drug-dosing studies = 92
- Case reports/series = 1687
- Observational studies = 134
- RCTs = 46

Articles covering other toxins discarded
Language of publication: No restriction

77% = ENGLISH

27 languages
62 translators!
First recommendation: Thallium
Salicylates: Pharmacokinetics

- Half-life = 2 to 4 hours
- Weak acid (pKa = 3.0)
- Vd = 0.15 to 0.35 L/Kg
  - Variable and increases in overdose
- Hepatic metabolism
- Renal excretion of free drug
  - First order kinetics at low doses
  - Complex kinetics at higher doses

Figure 1. Post-Mortem Blood and Tissue Salicylate Levels Obtained from Rats as Soon as Possible after Death from Salicylate Overdoses.

The dashed lines include all the brain levels.
Fig 2. Autoradiograms of C14-salicylic acid in cat brain at 1 hour.
Clinical Features of Toxicity - early

- **GI**: Nausea and vomiting
- **CNS**: Tinnitus, altered mental status
- **Resp**: tachypnea; ARDS
- **Metabolic**: respiratory alkalosis and metabolic acidosis
- **Hyperthermia**
Clinical Features of Toxicity - middle

- GI: Nausea and vomiting
- CNS: **Tinnitus**, altered mental status
- Resp: tachypnea; ARDS
- Metabolic: respiratory alkalosis **and metabolic acidosis**
- Hyperthermia
Clinical Features of Toxicity - late

- GI: Nausea and vomiting
- CNS: Tinnitus, **altered mental status**
- Resp: tachypnea; **ARDS**
- Metabolic: respiratory alkalosis and metabolic acidosis
- **Hyperthermia**
Prognostication: Done: Pediatrics 1960
Limitations of Done

- 38 patients; 29 are children; single acute OD
- Average half-life 20hrs in OD
- Poor definitions of mild; moderate; severe
  - Moderate: “Severe hyperpnea, prominent neurologic disturbances (marked lethargy and/or excitability) but not coma or convulsions”
- Limited acid-base information
  - All severe or fatal cases had pH < 7.22
- Questionable kinetic estimation of $t_o$
Efficacy of Standard Treatments Largely Unquantified

- Airway and blood pressure support
- Gastric emptying
- Single and multiple dose activated charcoal
- Fluid and electrolyte replacement
- Enhanced elimination
  - Urinary alkalinization
Urinary [ASA] as a Function of pH

\[
\text{Log}[\text{ASA}] = (0.52 \times \text{pH}) - 2.1
\]

Kallen 1966
Criteria for Dialyzability

Table 7. Summary of the effect for dialyzability.

<table>
<thead>
<tr>
<th>Dialyzability &amp;</th>
<th>Primary criteria % Removed*</th>
<th>Alternative criteria 1 $\frac{CL_{EC}}{CL_{TOT}}$ (%)#</th>
<th>Alternative criteria 2 $\frac{T_{1/2_{EC}}}{T_{1/2}}$ (%)</th>
<th>Alternative criteria 3 $\frac{Re_{EC}}{Re_{TOT}}$ (%)#</th>
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<td>D, Dialyzable</td>
<td>$\geq 30$</td>
<td>$&gt; 75$</td>
<td>$&lt; 25$</td>
<td>$&gt; 75$</td>
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<tr>
<td>M, Moderately dialyzable</td>
<td>$&gt; 10 – 30$</td>
<td>$&gt; 50 – 75$</td>
<td>$&gt; 25 – 50$</td>
<td>$&gt; 50 – 75$</td>
</tr>
<tr>
<td>S, Slightly dialyzable</td>
<td>$\geq 3 – 10$</td>
<td>$\geq 25 – 50$</td>
<td>$\geq 50 – 75$</td>
<td>$\geq 25 – 50$</td>
</tr>
<tr>
<td>N, Not dialyzable</td>
<td>$&lt; 3$</td>
<td>$&lt; 25$</td>
<td>$&gt; 75$</td>
<td>$&lt; 25$</td>
</tr>
</tbody>
</table>

These criteria should only be applied if measured or calculated (not reported) endogenous half-life is $> 4$ hours (otherwise, ECTR is considered not clinically relevant). Furthermore, the primary criteria is preferred for poisons having a large Vd ($> 5$L/Kg).

&Applicable to all modalities of ECTR, including hemodialysis, hemoperfusion, hemofiltration.

*Corresponds to % removal of ingested dose or total body burden in a 6-hour ECTR period.

#Measured during the same period of time.

- ASA is dialyzable – Level of Evidence = B
  - Primary criterion and Alternative criteria 1 and 2
ECTR should be performed in severe Salicylate poisoning (1 D)

- Strong recommendation: ≥ 85% of members strongly recommended ECTR
- Very low evidence: No observational studies or RCTs
Choice of ECTR

- Intermittent HD is the preferred method of ECTR (1D).
- The following are acceptable alternatives if HD is not available
  - HP (1D)
  - CRRT (3D)
  - Exchange transfusion is an adequate alternative to HD in neonates (1D)
Criteria

- [ASA]
  - If [ASA] > 6.5 mmol/L in acute exposure (2D)
  - If [ASA] > 7.2 mmol/L in acute exposure (1D)
Criteria

- [ASA] in the presence of *impaired kidney function*:
  - If [ASA] > 5.8 mmol/L in acute exposure (2D)
  - If [ASA] > 6.5 mmol/L in acute exposure (1D)
Additional Criteria

- pH
  - If the pH is below 7.20 (2D)
  - If the pH is below 7.10 (1D)
- In the presence of altered mental status (1D)
- In the presence of new hypoxemia requiring supplemental oxygen (1D)
- If standard therapy (supportive measures, bicarbonate etc.) fails (1D)
Cessation of ECTR

- Clinical improvement is apparent (1D)
- [ASA]
  - < 1.4 mmol/L (1D)
  - < 1.8 mmol/L (2D)
- For a period of 4-6h if ASA concentrations are not readily available (2D)
Lithium: Pharmacokinetics

- Molecular weight: 7Da
- $V_D$: 0.7–0.9 L/kg
  - Slow alpha distribution with intracellular compartmentalization
- Protein binding: 0%
- Renal clearance (with normal renal function): 10–40 mL/min
Endogenous Lithium Elimination

- Kidneys (95%)
  - Handled in proximal tubule like Na⁺
- Sweat and Saliva (5%)
- Half-life: 20 – 24 hours
  - May be prolonged
    - Chronic use
    - Renal insufficiency
    - Overdose
<table>
<thead>
<tr>
<th>Not dialyzable</th>
<th>Slightly dialyzable</th>
<th>Moderately dialyzable</th>
<th>Dialyzable</th>
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<tr>
<td>0</td>
<td>1</td>
<td>1</td>
<td>25</td>
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ECTR should be performed in severe Li poisoning (1 D)

**Strong recommendation:**
100% of members strongly recommended ECTR (7,8 or 9)

**Very low evidence:**
No observational studies or RCTs
HD is the Preferred Modality

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<table>
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<th>75th percentile</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>≤1</td>
<td>9</td>
<td>8</td>
<td>We recommend</td>
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The following ECTRs are indicated for treatment of severe lithium poisoning (Level of evidence: D)

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<td>1</td>
<td>2</td>
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**EXTRIP**
THE EXTRACORPOREAL TREATMENTS IN POISONING WORKGROUP
If Li levels are not readily available, ECTR should be performed for a minimum of.... (Level of evidence: D)

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<th>75 th percentile (if needed)</th>
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<td>3</td>
<td>5</td>
<td>We suggest not to</td>
</tr>
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</table>

- Recommendation: 6h
When to do HD

- Acute, Acute-on-therapeutic, or Chronic overdose with normal kidney function regardless of symptoms
  - Suggested: >5.0 mEq/L
When to do HD

- Acute, Acute-on-therapeutic, or Chronic overdose with impaired kidney function (CKD or AKI GFR) regardless of symptoms
  - Suggested: >3.0 mEq/L
  - Recommended: >4.0 mEq/L
Expect Rebound

- Bad Rebound
  - Ongoing absorption - Failure of GI decontamination
    - Only 3 cases of clinical deterioration, parallel to Li rebound, have been described following ECTR termination (Borras-Blasco, 2007; Branger, 2000; Friedberg, 1991) — All extended release preparations

- Redistribution from intracellular stores
  - Tissue concentrations falling
    - In all other rebound cases, increase in [Li] DID NOT cause clinical deterioration following ECT
  - Golden opportunity to further elimination
From: Amdisen Medical Toxicology 3: 18-32 (1988)

The graph shows the lithium concentration (mmol/L) over time after the start of haemodialysis (h). Two curves are depicted:

- **Serum**: The concentration decreases rapidly, reaching a plateau around 10 mmol/L after 20 hours.
- **CSF**: The concentration decreases more gradually, remaining below 1 mmol/L throughout the observation period.

The x-axis represents time after the start of haemodialysis, ranging from 0 to 40 hours.

The graph is part of the EXTRIP guidelines, which stand for the Extracorporeal Treatments in Poisoning Workgroup.
Valproic acid

- Molecular weight: 144 Da
- Volume of distribution: 0.1-0.5 L/kg
- Protein binding vs plasma:
  - > 90% at 40 mg/L
  - 81.5% at 130 mg/L
  - 54-70% at > 150 mg/L
  - 35% at > 300 mg/L
  - 15% > 1000 mg/L
1) **Dialyzability:**
Valproic acid is not, slightly, moderately dialyzable, or dialyzable (Level of evidence: D)

<table>
<thead>
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<th>Not dialyzable</th>
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<td>MD</td>
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The EXTRIP: THE EXTRACORPOREAL TREATMENTS IN POISONING WORKGROUP
Recommendations

- ECTR for [VPA]:
  - Reasonable > 450 mg/L
  - Suggested > 850 mg/L
  - Recommended > 1250
- Recommended for coma or cerebral edema
- Suggested for hyperammononemia
- Suggested for metabolic acidosis (pH < 7.05)
Recommendations for other poisons

**Uncompleted poisons:**
- Ethylene glycol, Paraquat,
- Organophosphates, Methotrexate

- Tricyclics
- Digoxin
- Phenytoin
- Acetaminophen
- Carbamazepine
- Lithium
- Salicylates
- Valproic Acid
- Theophylline
- Metformin
- Barbiturates *(Long-acting)*
- Methanol