Extracorporeal Removal in Poisoning
An Update from EXTRIP

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Disclosures

- Expenses (no honorarium) covered by the EXTRIP Group for attendance at an EXTRIP Guidelines Meeting in 2012

- No other relevant disclosures
Objectives

- History and current use of extracorporeal treatments in poisoning
- Available techniques and advances
- EXTRIP (EXtracorporeal Treatments In Poisoning)
  - Methodology
  - Overview of work of the group
  - Current status of guidelines
First description of haemodialysis
- John Abel, 1913: removal of salicylate in dogs

First clinical reports in poisoning 1947/8

Greater focus since then on AKI / ESRD
- Numerous renal consensus guidelines

Development of numerous techniques
- IHD, HPF, IHF, IHDF, CA/CVVHF, CA/CVVHDF, SLED, SLED-f, PIRRT, MARS, SPAD, SCUF etc...
How commonly is ECTR used in poisoning?

- Best available data: US poisons center data

2012:
- 2.2M human exposure cases reported to a US poisons center
- Use of ECTR mentioned in 2414 cases (≈ 0.1%)

Mowry JB et al. NPDS. *Clin Toxicol (Phila)* 2013

- Limited/no data from elsewhere in the world
How commonly is ECTR used in poisoning?

- Best available data: US poisons center data
Use of hemodialysis and hemoperfusion in poisoned patients

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Use of hemodialysis and hemoperfusion in poisoned patients

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Other sources of data: ToxIC

- 2011 ToxIC
  - 6456 cases
  - 109 (1.7%) HD
  - 28 (0.4%) CRRT

- 2012 ToxIC
  - 7269 cases
  - 126 (1.7%) HD
  - 35 (0.5%) CRRT
What techniques are available?

- Classical technique = Intermittent Haemodialysis (IHD)
- Dialysate infused countercurrent to dialysis membrane
  - Solutes removed by diffusion
- Advantages
  - Good removal of small (500-1000 Da) molecules
  - Rapid correction acid-base / electrolyte disturbance
- Disadvantages
  - Haemodynamic compromise
  - Generally only available in renal centres and requires a nephrologist / renal nurse
  - Potential for rebound

Ouellet G et al. *Semin Dialysis* 2014
Rebound may not always be bad ...
Haemoperfusion

- Drug removal by adsorption to charcoal or resin; no renal replacement
- Widely used in 1950s-1970/80s
- Limited availability in N America/Europe now
- Still widely used in Asia
  - >20 commercial HPF cartidges available
  - Recent studies with HPF in paraquat and OP poisoning (including RCTs in China)
- Additional complications
- Greater haemodynamic stress & anticoagulation required

Ghannoum M et al. *Semin Dialysis* 2014
Haemofiltration

- Removal of solutes by convection
- Pressure gradient across membrane removes water and solutes up to 10-30 kDa
  - Less efficient at removing small solutes

- Haemodiafiltration (HDF)
  - Addition of dialysate allows both convective and diffusive removal

- HF and HDF: Intermittent or continuous (CRRT)
- CVVHF/HDF have replaced CAVHF/HDF
  - Widely available on most ICUs

Ouellet G et al. Semin Dialysis 2014
Other techniques

- SLED (sustained low efficiency dialysis)
- PIRRT (prolonged intermittent renal replacement therapy)
  - Intermediate duration and blood/dialysate flow between IHD and CRRT
- SLED-f (sustained low efficiency diafiltration)
  - Intermediate between IHD and CVVHDF
  - Limited availability and limited data in poisoning
  - Kinetically promising for poisoning: modelling studies
- Others e.g. plasma exchange, exchange transfusion, albumin dialysis (MARS/ELAD)

Ouellet G et al. *Semin Dialysis* 2014
Other factors and advances

- Continuous/semi-continuous techniques generally decrease the potential for rebound
  - Balanced against less efficient LMW drug removal

- Significant advances in all techniques in recent years
  - Membranes e.g. surface area, material morphology, fibre length and thickness, hydroliphiicity
  - Blood and dialysate flow rates

- Can make interpretation of publications from previous years difficult with regards current techniques
Numerous factors influence drug / other solute removal

- Blood and dialysate flow rate
  - Most important for small drugs
  - Blood flow often limited in haemodynamically compromised poisoned patients

- Efficiency
  - Surface area, mass transfer coefficient of membrane
  - ↑ efficiency = ↑ capacity to clear LMW solutes

- Flux
  - Largely relates to pore size
  - ↑ pore-size/flux = ↑ permeability of water
    = ↑ large solute removal
So what about EXTRIP?

- **Aim** = To produce evidence based guidelines on the use of extracorporeal techniques for drug removal in the poisoned patient
So what about EXTRIP?

- Multidisciplinary: nephrology, critical care, toxicology, paediatrics, kinetics, emergency medicine
- 28 members from 12 countries
Specialties and Societies Represented in EXTRIP

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

**Pharmacology / Kinetics**

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

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

**Emergency Medicine**
- ACEP, CAEP, CCEP, EuSEM, AMUQ, ASMUQ
EXTRIP Methodology

- Benefits of ECTR
- Risks of ECTR
- Costs of ECTR
- Alternative therapies
  - Supportive care
  - Decontamination
  - Antidotes
EXTRIP Methodology

- Thallium was the ‘test’ toxin for EXTRIP
- Followed by review of 16 toxins
- By pertinence and epidemiology
The EXTRIP Initial 16 Toxins

- Acetaminophen
- Barbiturates (long acting)
- Carbamazepine
- Digoxin
- Ethylene glycol
- Lithium
- Metformin
- Methanol
- Methotrexate
- Organophosphates
- Paraquat
- Phenytoin
- Salicylates
- Theophylline
- Tricyclic antidepressants
- Valproic acid
Multilanguage literature search

- > 7500 articles reviewed
- 27 languages
- 62 translators
- 77% English

Languages:
- English
- Spanish
- Italian
- Norwegian
- Portuguese
- German
- Russian
- Danish
- Serbocroat
- Turkish
- French
- Japanese
- Czech
- Hungarian
- Slovak
- Chinese
- Polish
- Dutch
- Swedish
- Korean
- HP or HD for the treatment of poisoned patients
- Number of publications per year 1953 - 2012

Ghannoum M et al. *Semin Dialysis* 2014
Time and geographical trends

- First year of publication
EXTRIP Methodology

- Subgroups of 3 reviewed / assessed papers on 3 toxins
- Rigorous, standardised methodology used to assess the papers
  - AGREE instrument
  - Transparent and reproducible
- Assessment of “dialysability” of each toxin
- Summary produced for review by whole EXTRIP group

### EXTRIP Methodology

**Clinical Toxicology** (2012), **50**, 403–413

The **EXTRIP (EXtracorporeal TReatments In Poisoning)** workgroup: Guideline methodology


<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 $T_{1/2_EC}/T_{1/2_TOT}$ (%)</th>
<th>Alternative criteria 3 $\frac{Re_{EC}}{Re_{TOT}}$ (%)#</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>D, Dialyzable</strong></td>
<td>&gt;30</td>
<td>&gt;75</td>
<td>&lt;25</td>
<td>&gt;75</td>
</tr>
<tr>
<td><strong>M, Moderately dialyzable</strong></td>
<td>&gt;10 – 30</td>
<td>&gt;50 – 75</td>
<td>&gt;25 – 50</td>
<td>&gt;50 – 75</td>
</tr>
<tr>
<td><strong>S, Slightly dialyzable</strong></td>
<td>≥3 – 10</td>
<td>≥25 – 50</td>
<td>≥50 – 75</td>
<td>≥25 – 50</td>
</tr>
<tr>
<td><strong>N, Not dialyzable</strong></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 >4hours (otherwise, ECTR is considered not clinically relevant). Furthermore, the primary criteria is preferred for poisons having a large Vd (>5L/Kg).

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

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

*Measured during the same period of time.
Scoring of recommendations

**Quality of the evidence:**
How good is the evidence to support the recommendation?

**Strength of recommendation:**
How strongly does the workgroup support the recommendation?
Quality of the evidence (A-D):

- How good is the evidence to support the recommendation?
Strength of Recommendations

- Specific statements produced by the subgroups e.g.
  
  "Haemodialysis is indicated for methanol poisoning if the pH is less than 7.2"

  "Haemoperfusion is indicated for acute lithium poisoning if coma is present"

- Two anonymous voting rounds by the whole EXTRIP workgroup using a modified Delphi method

- Voting based on a 9-point Likert Scale
EXTRIP Methodology

Strength of Recommendations

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

- **Median between 4-6**
  - AND Disagreement index ≤ 1
  - **Lower quartile between 4-6**
    - Level 2 recommendation = "We suggest..."

- **Disagreement index > 1**
  - (for any median values)
  - **Level 3 recommendation = "It would be reasonable..."**

- **No recommendation = "No agreement reached"**
Scoring of recommendations

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

- Strong recommendation: ‘We recommend (should)...’ Level 1
- Weak recommendation: ‘We suggest (might)...’ Level 2
- Neutral position: ‘It would be reasonable to...’ Level 3
- No recommendation: ‘No agreement reached...’

Quality of the evidence: How good is the evidence to support the recommendation?

<table>
<thead>
<tr>
<th>Quality of evidence score</th>
<th>Reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>A</td>
</tr>
<tr>
<td>Moderate</td>
<td>B</td>
</tr>
<tr>
<td>Low*</td>
<td>C</td>
</tr>
<tr>
<td>Very Low*</td>
<td>D</td>
</tr>
</tbody>
</table>

- Primary angioplasty for STEMI = 1A
- Ventilation for respiratory failure = 1A or 1B
Other work from EXTRIP Group

- Special issue in *Seminars in Dialysis* 2014 In Press
  - ‘100 years of ECTR in poisoning’
  - Available ECTR techniques for poisoning
  - Historical trends in ECTR use in poisoning
  - Hemoperfusion for poisoning
  - ‘Stepwise approach’: kinetics and ECTR in poisoning
  - EXTRIP guideline for tricyclic antidepressants

- Cost-analysis of ECTR in poisoning

- Recommendations for case reports describing ECTR in poisoning
Current status of EXTRIP reviews

- Thallium
  - Published

- Carbamazepine, TCA, barbiturates
  - Submitted for publication

- Carbamazepine, methanol, acetaminopen, digoxin, lithium, metformin
  - Workgroup agreement, papers being drafted

- Ethylene glycol, methotrexate, organophosphates, paraquat
  - Not completed
Uncompleted poisons:
Ethylene glycol, Paraquat, Organophosphates, Methotrexate
Conclusions

- Extracorporeal techniques have been used for many decades in poisoning
- Increasing diversity of techniques available
- EXTRIP
  - Multidisciplinary group
  - Evidence based recommendations for ECTR in poisoning
    - In the absence of good evidence, rigorous methods used to ensure consensus amongst experts
- See www.extrip-workgroup.org for information, news and latest recommendations