Toxicology & ECTR

PYNICU Friday lecture

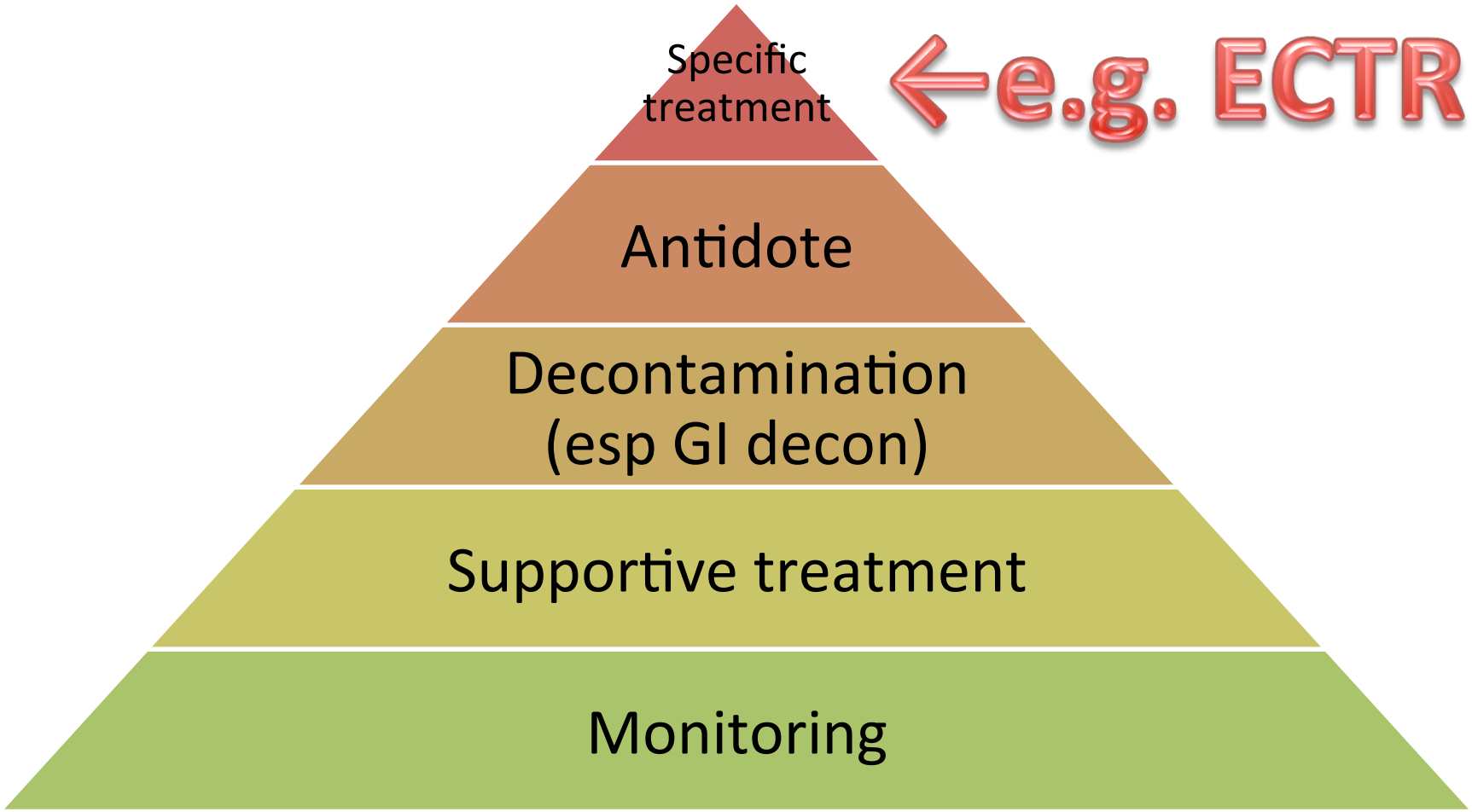
Dec 2, 2016

Dr TY Li / Dr HP Shum

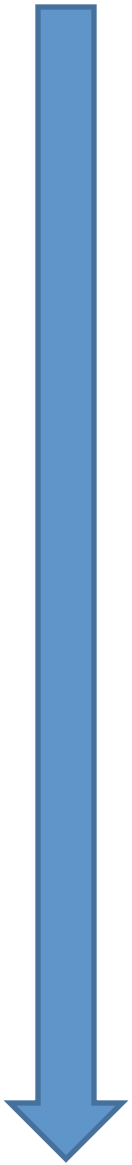
Outline

- History of ECTR in poisoning
- Outline of method of ECTR
- Development of EXTRIP
- Recommendations of EXTRIP

Treatment pyramid of poisoned patient

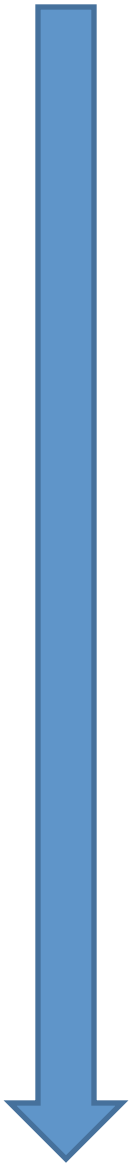


History



1800s	Thomas Graham, father of modern nephrology develop the principles of dialysis
1913	Abel and colleagues, construct the 1st artificial kidney aim to remove salicylates from a living animal, rather than treating kidney failure
1924	Haas and colleagues performed the 1st successful dialysis in human beings
1943	Kolff built a rotation drum kidney that could be used practically for acute kidney failure
1948	Bywaters and Joekes first reported the use of dialysis in a human case of salicylate poisoning, similar to that carried out by Abel in animals 34 years earlier
1950s	Schreiner even published his first series in 1958, thereby solidifying the promise of hemodialysis as a therapeutic option for poisoning and popularizing its use

Paul Doolan
Laurence Kyle
George Schreiner
were the most prominent pioneers



1970s	most poisonings were considered amenable to treatment by dialysis
1980s	New skepticism toward extracorporeal therapies, helped by better understanding of toxicokinetic principles as well as improved supportive care for poisoned patients
2000s	another pendulum swing, as the introduction of better dialysis membranes has permitted new possibilities, especially for poisons not traditionally considered ‘‘dialyzable’’

Theoretically, higher the body burden of a poison, higher the toxicity

So, shall we?

Determining ques:

1. Can ECTR remove the poison?
2. Can removal of poison after ECTR improve survival?

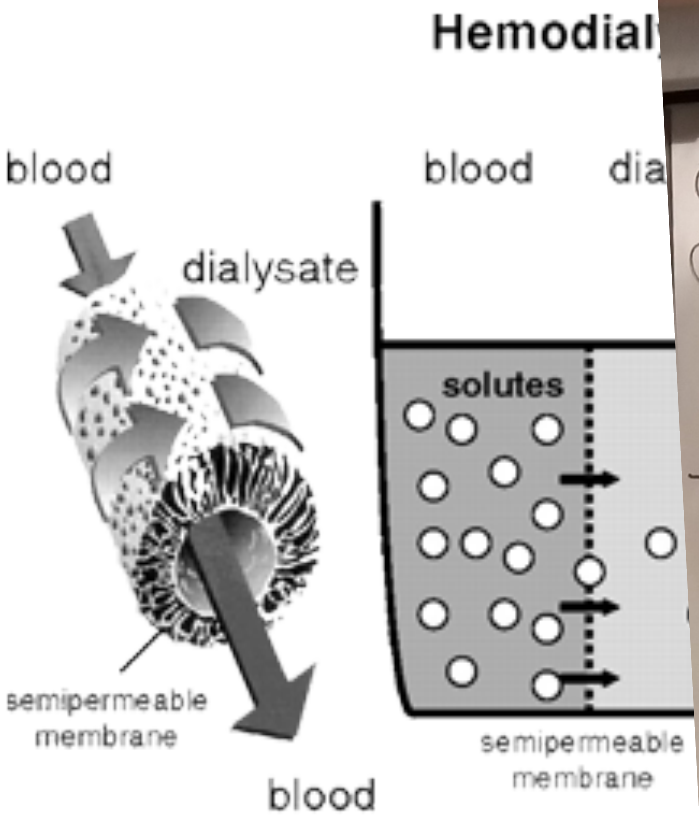
Can ECTR remove the poison?

1. Technology
2. Endogenous clearence
3. Protein binding
4. Vd

Blood purification in toxicology: nephrology's ugly duckling.
Ghannoum M, Nolin TD, Lavergne V, Hoffman RS; EXTRIP workgroup.
Advances in chronic kidney disease. 2011 18(3):160-6

Methods of ECTR

- Haemodialysis (HD)
- Haemofiltration (HF)
- Haemoperfusion (HP)
- Molecular adsorbent recirculating system (MARS)



Small molecules
(low molecular weight)
Low protein-binding
Low Vd
Water soluble

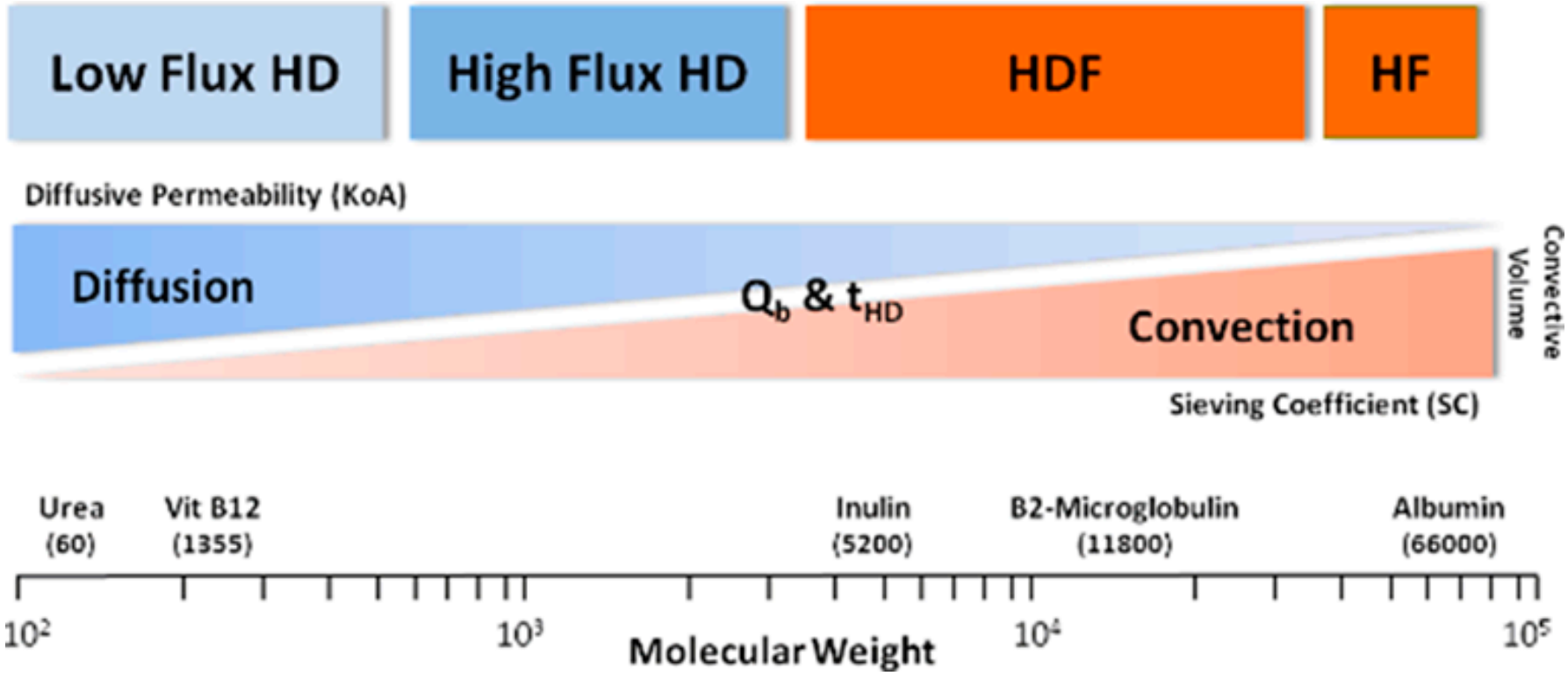

Low Flux HD
High Flux HD
HDF
HF
Diffusive Permeability (KoA)
Diffusion
Q_b & t_{HD}
Convection
Convective Volume
Sieving Coefficient (SC)
Urea (60)
Vit B12 (1355)
Inulin (5200)
B2-Microglobulin (11800)
Albumin (66000)
10^2
10^3
10^4
10^5
Molecular Weight

Table Necessary properties for extracorporeal removal by three different techniques

	Hemodialysis	Hemofiltration	Hemoperfusion
Solubility	water	water	water or lipid
Molecular weight	<500 Da	<40 000 Da	<40 000 Da
Protein binding	low (<80%)	low	low or high
Volume of distribution	<1 l/kg	<1 l/kg	<1 l/kg
Endogenous clearance	<4 ml/min/kg	<4 ml/min/kg	<4 ml/min/kg
Distribution time	short	longer	short

Orlowski JM, Hou S, Leikin JB. Extracorporeal removal of drugs and toxins. In: Ford M, Delaney KA, Ling L, et al., editors. Clinical toxicology, 1st ed. St Louis, MO: WB Saunders Company; 2001. pp. 43–50.

Intermitten HD

- For toxic substance which is water-soluble, with low molecular weight, low protein-binding, low Vd

- Clearance of toxic substance depends on:
- Membrane surface area & type
- Blood flow rate
- Dialysate flow rate

Risk of rebound toxicity after cessation of HD, due to redistribution of toxin

CVVH / CVVHD

- Advantage:
- Large pore hollow fibres, allowing the convective removal of molecules upto 40 kDa
- Haemodynamically unstable patient
- Prolonged duration of therapy minimize risk of rebound effect

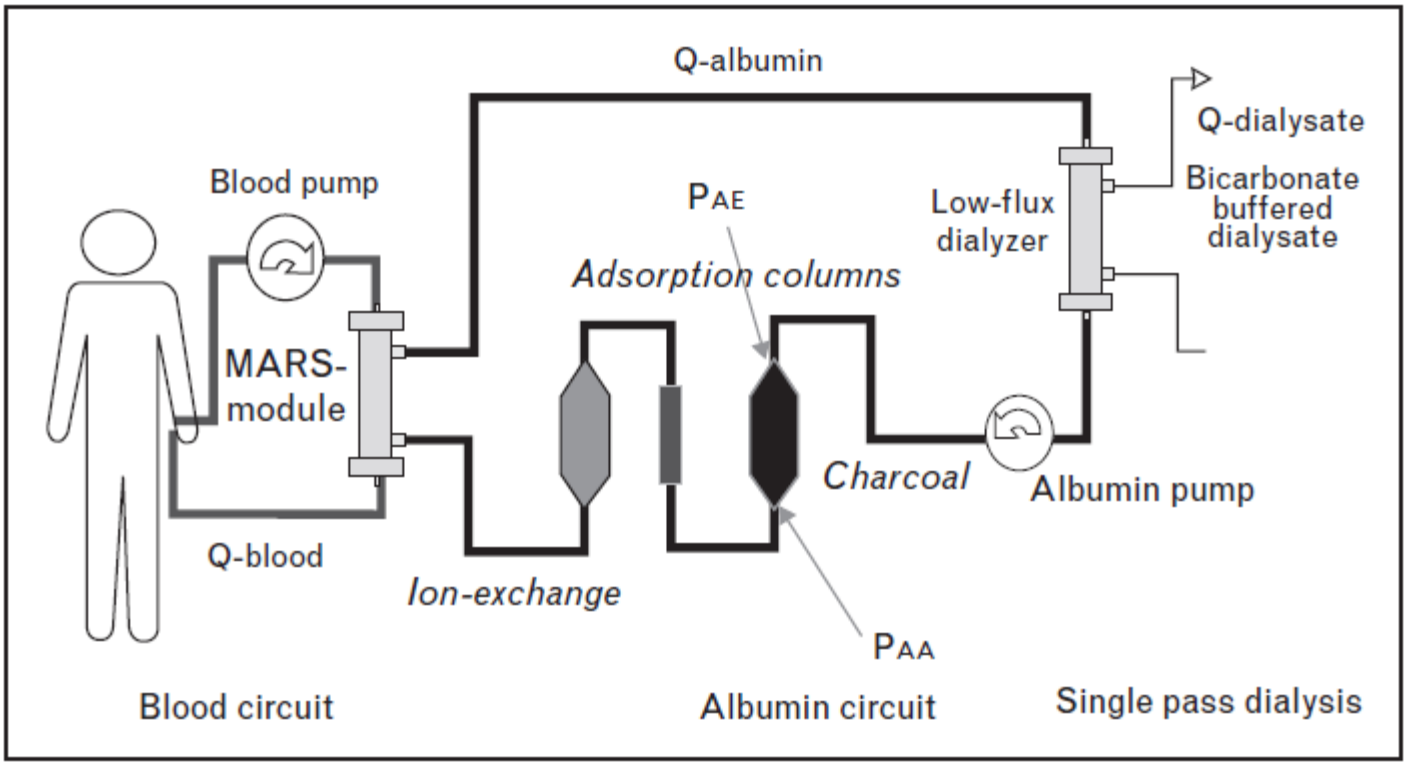
- Disadvantage:
- Lower clearance compared to HD

Hemoperfusion (HP)

- The blood pass through a cartridge containing a sorbent material able to adsorb the toxin
- three- types of sorbents
  - *charcoal-based sorbents* (1000-1500 kDa, but cannot remove protein-bound molecules)
  - *synthetic resins* (more effective for protein-bound & lipid-soluble molecules)
  - *anion exchange resins*

- Disadvantage:
  - technically more difficult than HD
  - cannot correct acid-base, electrolyte and fluid abnormalities

MARS



- Remove albumin-bound toxic molecules

These are bread and butter for a nephrologist, but not us !

So what should we do?

Mnemonics

METAL

- Methanol, Metformin
- Ethylene Glycol
- Theophylline
- Aspirin
- Lithium

SLIME

- Salicylates
- Lithium
- Isopropanolol
- Methanol
- Ethylene Glycol

I-STUMBLE

- Isopropyl alcohol
- Salicylates
- Theophylline
- Uremia
- Methanol
- Barbiturate, Beta-blockers (water soluble e.g. atenolol)
- Lithium
- Ethylene Glycol

http://www.extrip-workgroup.org/

Represented Societies

The following societies have delegated an active participant to the workgroup

American Academy of Clinical Toxicology

American College of Emergency Physicians

American College of Medical Toxicology

American Society of Nephrology

American Society of Pediatric Nephrology

Asia Pacific Association of Medical Toxicology

Associacao Brasileira de Centros de Informacao e Assistencia Toxicologica e Toxicologistas Clinicos

Association of Physicians of India

French Society of Intensive Care

German Society of Nephrology

Indian Society of Critical Care Medicine

INDO-US Emergency and Trauma Collaborative

Associations des Spécialistes en Médecine d'Urgence du Québec

Australian and New Zealand Intensive Care Society

Australian and New Zealand Society of Nephrology

Canadian Association of Poison Control Centres

International Pediatric Nephrology Association

International Society of Nephrology

Latin American Society of Nephrology and Hypertension

National Kidney Foundation

Canadian Association of Emergency Physicians

Chinese College of Emergency Physicians

Association des Médecins d'Urgence du Québec

Chinese Medical Doctor Association

Pediatric Continuous Renal Replacement Therapy

Pediatric Critical Care Medicine

Quebec Society of Nephrology

Sociedade Brasileira de Nefrologia

European Association of Poison Centres and Clinical Toxicologists

European Renal Best Practice

European Society for Emergency Medicine

European Society of Intensive Care Medicine

Sociedade Brasileira de Toxicologia

Society of Critical Care Medicine

The Renal Association

Box 1. Strength of Recommendation and Level of Evidence Scaling on Clinical Outcomes

Strength of recommendation (consensus based)

Level 1 = Strong recommendation. (The course of action is considered appropriate by the large majority of experts with no major dissension. The panel is confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects.)

Level 2 = Weak recommendation. (The course of action is considered appropriate by the majority of experts but some degree of dissension exists among the panel. The desirable effects of adherence to the recommendation probably outweigh the undesirable effects.)

Level 3 = Neutral position. (The course of action could be considered appropriate in the right context.)

No recommendation = No agreement was reached by the group of experts.

Level of evidence (based on the GRADE system)

Grade A = High level of evidence (the true effect lies close to our estimate of the effect)

Grade B = Moderate level of evidence (the true effect is likely to be close to our estimate of the effect, but there is a possibility that it is substantially different)

Grade C = Low level of evidence (the true effect may be substantially different from our estimate of the effect)

Grade D = Very low level of evidence (our estimate of the effect is just a guess, and it is very likely that the true effect is substantially different from our estimate of the effect)

Abbreviation: GRADE, Grading of Recommendations Assessment, Development, and Evaluation.

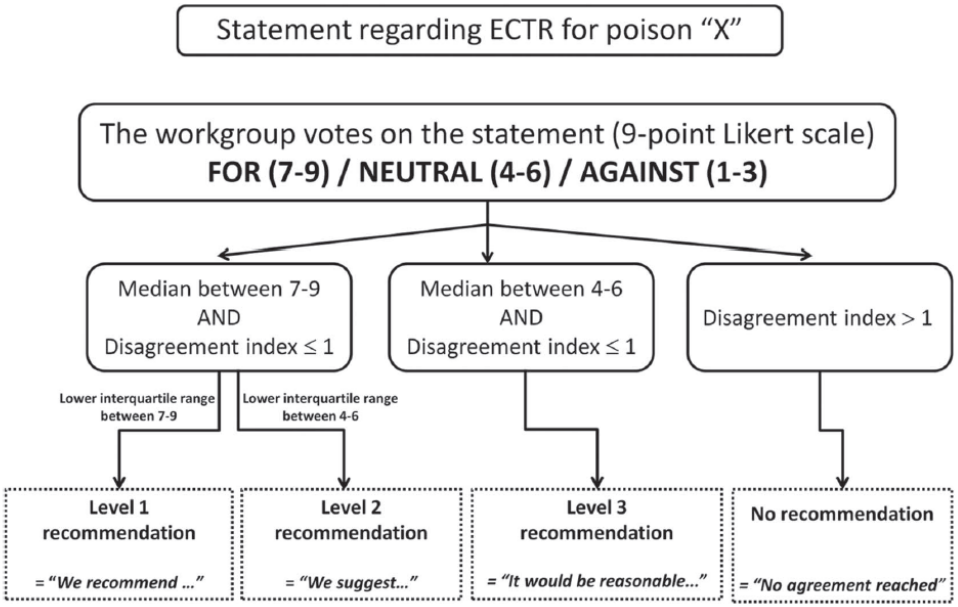


Fig. 1. Strength of recommendation algorithm.

Table 4. Criteria of dialyzability.

Dialyzability[A]	Primary criteria % Removed[B]	Alternative criteria 1 CL_{ECTR}/CL_{TOT} (%)[C]	Alternative criteria 2 $T_{1/2\ ECTR}/T_{1/2}$ (%)	Alternative criteria 3 Re_{ECTR}/Re_{TOT} (%)[C]
D, Dialyzable	> 30	> 75	< 25	> 75
M, Moderately dialyzable	> 10–30	> 50–75	> 25–50	> 50–75
S, Slightly dialyzable	≥ 3–10	≥ 25–50	≥ 50–75	≥ 25–50
N, Not dialyzable	< 3	< 25	> 75	< 25

[A]Applicable to all modalities of ECTR, including hemodialysis, hemoperfusion, and hemofiltration.
[B]Corresponds to % removal of ingested dose or total body burden in a 6-hour ECTR period.
[C]Measured during the same period of time.
ECTR = Extracorporeal treatment, CL_{ECTR} = Extracorporeal clearance, CL_{TOT} = Total clearance, RE_{ECTR} = Extracorporeal removal, RE_{TOT} = Total removal, $T_{1/2\ ECTR}$ = Half-life with ECTR, $T_{1/2}$ = Half-life without ECTR.
*These criteria should only be applied if measured or calculated (*not reported*) endogenous half-life is > 4h (otherwise, ECTR is not considered clinically relevant). Furthermore, the primary criteria are preferred for poisons having a large Vd (> 5 L/Kg).

EXTRIP recommendation
13 available so far

- Acetaminophen
- Salicylates

- Barbiturates
- Carbamazepine
- Phenytoin
- Valproate

- ~~Digoxin~~
- Theophylline

- Metformin
- Methanol
- ~~TCA~~
- Lithium
- Thallium

Table 2. Physical chemical and toxicokinetic parameters of acetaminophen.

Molecular weight	151.2 Daltons
Volume of distribution	0.8–1.0 L/kg
Protein binding	25%
Oral bioavailability	60%–95%
Therapeutic range	8–20 mg/L (55–133 µmol/L)
Conversion factor	1 mg/L = 6.62 µmol/L
Toxic exposure	Single acute ingestion > 150 mg/kg (adults) > 200 mg/kg (children)
Half-life (therapeutic)	1–2 h
Lethal dose	> 500 mg/kg

EXTRIP recommendation for Panadol overdose

Table 8. Executive summary of recommendations.

General Recommendation
- **ECTR is suggested in *severe* APAP poisoning (2D)**

ECTR is recommended:
- If the [APAP] more than 1000 mg/L (6620 µmol/L) and NAC is ***NOT*** administered (1D).
- If the patient presents with altered mental status, metabolic acidosis, with an elevated lactate, and an [APAP] is more than 700 mg/L (4630 µmol/L) and NAC is ***NOT*** administered (1D).
- If the patient presents with an altered mental status, metabolic acidosis, an elevated lactate, and an [APAP] is more than 900 mg/L (5960 µmol/L) even if NAC ***is*** administered (1D).

ECTR is not recommended
- On the basis of the reported ingested dose if NAC is administered (1D).

ECTR is not suggested
- On the basis of reported ingested dose alone even if NAC is ***NOT*** administered (2D).
- Solely on the basis of the [APAP] if NAC is administered (2D).

Cessation of ECTR
- ECTR is recommended until sustained clinical improvement is apparent (1D).

Choice of ECTR
- Intermittent hemodialysis is the preferred ECTR in patients with APAP poisoning (1D).
- The following are acceptable alternatives if HD is not available:
  - Intermittent HP (1D)
  - CRRT (3D)
  - Exchange transfusion in neonates (2D)

Miscellaneous
1. NAC therapy should be continued during ECTR at an increased rate (1D).

Clinical toxicology. 52(8):856-67.

4) Choice of ECTR

Intermittent hemodialysis is the preferred ECTR in patients with APAP poisoning (1D). Intermittent hemoperfusion (1D) or continuous renal replacement modalities (3D) are valid alternatives if intermittent hemodialysis is not available. Exchange transfusion is an adequate alternative to HD in neonates (2D).

Rationale: There are insufficient human data to confidently advocate HP over HD. In general, in acute liver failure charcoal hemoperfusion is not associated with any benefit, irrespective of the underlying etiology including APAP overdose. It is unlikely that future direct comparison over a 2–6 h ECTR session would help to resolve this question, as high clearance limited to a short time might not necessarily be superior to a lower clearance over a longer time. Pragmatic considerations, such as the availability of charcoal cartridges, trained personal, the known side effects of HP on platelets and calcium in a patient prone to coagulopathy and/or co-existing fluid, and electrolyte abnormalities from AKI, will likely dictate the choice of modality. Continuous techniques offer lower clearances and thus should only be considered whether hemodialysis or hemoperfusion is not available. Clearances obtained with exchange transfusion are lower, and the evidence inconclusive. However exchange transfusion might be reserved for the rare neonate in whom this modality is technically easier. No cases with peritoneal dialysis were reviewed. Various reasons underline the preference of HD over HP; faster correction of acidosis, lack of availability of the HP cartridges, longer duration of sessions, lack of thrombocytopenia and potential effect on coagulation during coagulopathy are concerns with APAP-induced hepatic failure.

Some other examples

Salicylate

Table 1. Salicylate physicochemical and toxicokinetic properties.

Physciochemical characteristic	Result
Molecular mass, Da	180 (acetylsalicylic acid)
Volume of distribution, L/kg	0.2 (up to 0.5 in overdose)
Protein binding, %	90 (30 in overdose)
Oral bioavailability, %	68 (acetylsalicylic acid)
Therapeutic range, mmol/L (mg/dL)	0.4–1.8 (5–25)
Toxic exposure, mg/kg	>150
Lethal exposure, mg/kg	>500
Half-life (therapeutic), h	2–4
Conversion factor	mg/dL×0.072=mmol/L

EXTRIP recommendation for salicylate poisoning

GENERAL RECOMMENDATION

ECTR is recommended in severe salicylate poisoning (1D).

INDICATIONS FOR ECTR

ECTR is recommended if any of the following are met:

- If [salicylate] >7.2 mmol/L (100 mg/dL) (1D)
- If [salicylate] >6.5 mmol/L (90 mg/dL) in the presence of impaired kidney function (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), ECTR is suggested if any of the following are met:

- If [salicylate] >6.5 mmol/L (90 mg/dL) (2D)
- If [salicylate] >5.8 mmol/L (80 mg/dL) in the presence of impaired kidney function (2D)
- If the systemic pH is ≤7.20 (2D)

ECTR CESSATION

ECTR cessation is indicated if

- Clinical improvement is apparent (1D) *and*
- [salicylate] <1.4 mmol/L (19 mg/dL) (1D) *or* ECTR has been performed for a period of at least 4–6 h when salicylate concentrations are not readily available (2D)

CHOICE OF ECTR MODALITY

- Intermittent HD is the preferred modality in patients with salicylate poisoning (1D)
- The following are acceptable alternatives if HD is not available:
  - Intermittent HP (1D)
  - CRRT (3D)
  - Exchange transfusion in neonates (1D)
- **Miscellaneous: It is recommended to continue intravenous bicarbonate therapy between ECTR sessions (1D)**

Ann Emerg Med. 266(2):165-81.

Barbiturates

Table 1. Physicochemical and Pharmacokinetic Properties of Barbiturates

	Long Acting	Short Acting
Representative barbiturate	Phenobarbital	Pentobarbital
Molecular weight (Da)	232	226
pKa	7.2	7.9
Volume of distribution (L/kg)	0.25-1.2	0.5-1.0
Protein binding (%)	20-60	35-70
Elimination half-life (h)	80-120	15-48
Duration of action (h)	6-12	3-4
Total endogenous clearance (mL/min)	5-12	18-39
Hepatic clearance (mL/min)	4-9	18-37
Renal clearance (mL/min)	1-3	0.2-2
MDAC clearance (mL/min)	84	NA
HD clearance (mL/min)	23-174	8-85
HP clearance (mL/min)	26-290	49-115
PD clearance (mL/min)	4-8	4-8
ET clearance (mL/min)	7	NA
Potentially fatal ingested dose (g)	>5	>3
Potentially fatal serum concentration (mg/L)	80	50

Note: Data from.[16,25,26,105,135]

Abbreviations: ET, exchange transfusion; HD, intermittent hemodialysis; HP, hemoperfusion; MDAC, multiple dose activated charcoal; NA, not available; PD, peritoneal dialysis; pKa, logarithmic acid dissociation constant.

Am J Kidney Dis 64(3): 347-358.

EXTRIP recommendation for Barbiturate overdose

Box 2. Executive Summary of Recommendations

General Statement Regarding Suitability of ECTR

- ECTR is recommended in severe long-acting barbiturate poisoning. (*1D*)

Indications for ECTR

- If prolonged coma is present or expected (*1D*)
- If shock is present after fluid resuscitation (*1D*)
- If, despite MDAC treatment, toxicity persists (*1D*)
- If, despite MDAC treatment, serum barbiturate concentration rises or remains elevated (*2D*)
- If respiratory depression necessitating mechanical ventilation is present (*2D*)

Choice of ECTR

- Intermittent HD is the preferred mode of ECTR of severe barbiturate poisoning (*1D*)
- HP (*1D*) or CRRT (*3D*) are acceptable alternative modalities in adults if HD is not available

Cessation of ECTR

- Cessation of ECTR is indicated when clinical improvement is apparent (*1D*)

Am J Kidney Dis 64(3): 347-358.

Carbamazepine

Table 2. Carbamazepine physicochemical and toxicokinetic data.

Molecular weight	236 Daltons
Volume of distribuition	0.8–1.4 L/kg
Protein binding	75%
Oral bioavailability	80–100%
Therapeutic range	4–12 mg/L (17–51 µmol/L)
Toxic exposure	>20 mg/kg
Toxic blood concentrations	Adults: >20 mg/L (85 µmol/L) Children: >12 mg/L (51 µmol/L)

Clin Toxicol (Phila) 52(10): 993-1004.

EXTRIP recommendation for carbamazepine overdose

Table 8. Executive summary of recommendations.

General statement

ECTR is suggested in severe carbamazepine poisoning (2D)

Indications for ECTR

ECTR is recommended if ANY of the following conditions are present:

- If multiple seizures refractory to treatment occur (1D)
- If life-threatening dysrhythmias occur (1D)

ECTR is suggested if ANY of the following conditions are present:

- If prolonged coma or respiratory depression requiring mechanical ventilation are present or expected (2D)
- If significant toxicity persists, especially if carbamazepine concentrations rise or remain elevated, despite MDAC and support measures (2D)

Cessation of ECTR

Cessation of ECTR is indicated when:

- Clinical improvement is apparent (1D)
- Carbamazepine concentration is below 10 mg/L (42 µmol/L) (2D)

Choice of ECTR

- Intermittent hemodialysis is the preferred ECTR in carbamazepine poisoning (1D)
- The following are alternatives if hemodialysis is not available:
  - Intermittent hemoperfusion (1D)
  - Continuous renal replacement therapy (3D)

Miscellaneous

MDAC should be continued during ECTR (1D)

ECTR, Extracorporeal treatment; MDAC, Multiple-dose activated charcoal.

Clin Toxicol (Phila) 52(10): 993-1004.

EXTRIP recommendation for phenytoin overdose

Box 2. Executive Summary of Recommendations

General statement regarding use of ECTR

1: ECTR would be reasonable in selected cases of severe phenytoin poisoning. (*3D*)

Indications for ECTR

2.1: ECTR is suggested if prolonged coma is present or expected. (*2D*)

2.2: ECTR would be reasonable if prolonged incapacitating ataxia is present or expected. (*3D*)

2.3: We recommend *not* to perform ECTR solely based on suspected dose of phenytoin ingested. (*1D*)

2.4: We recommend *not* to perform ECTR solely based on serum phenytoin concentration. (*1D*)

Cessation of ECTR

3: ECTR should be discontinued when clinical improvement is apparent. (*1D*)

Choice of ECTR

4.1: Intermittent hemodialysis is the preferred ECTR in phenytoin poisoning. (*1D*)

4.2: Intermittent hemoperfusion is an acceptable alternative if intermittent hemodialysis is not available. (*1D*)

Abbreviation: ECTR, extracorporeal treatment.

Am J Kidney Dis. 67(2):187-97

valproate

Table 2. VPA: Physical and TK properties.

Molecular mass	144 D
Volume of distribution	0.1–0.5 L/kg
Protein binding	Variable 94% at therapeutic concentration 15% when [VPA] > 1000 mg/L
Oral bioavailability	68–100%
Elimination half-life (therapeutic)	12 h
Endogenous clearance	5–10 mL/min
Conversion factor	1 mg/L = 6.94 µmol/L
Therapeutic range	50–100 mg/L (347–694 µmol/L)
Toxic exposure	> 200 mg/kg
Lethal exposure	> 1000 mg/kg

Clin Toxicol (Phila) 53(5): 454-465.

EXTRIP recommendation for Valproate overdose

Table 8. Executive summary of recommendations.

General Recommendation
ECTR is recommended in severe VPA poisoning (1D)
Indications
ECTR is recommended if any of the following is present:
If the [VPA] is > 1300 mg/L (9000 µmol/L) (1D)
If shock is present (1D)
If cerebral edema is present (1D)
ECTR is suggested if any of the following is present:
If the [VPA] is > 900 mg/L (6250 µmol/L) (2D)
If coma or respiratory depression requiring mechanical ventilation is present (2D)
If acute hyperammonemia is present (2D)
If pH is ≤ 7.10 (2D)
Cessation of ECTR is indicated if any of the following is present:
Clinical improvement is apparent (1D)
[VPA] is between 50 and 100 mg/L (350–700 µmol/L) (2D)
Choice of ECTR
Intermittent hemodialysis is the preferred ECTR in VPA poisoning (1D)
If hemodialysis is not available, both intermittent hemoperfusion (1D) and CRRT (2D) are acceptable alternatives

VPA, valproic acid; ECTRs, extracorporeal treatments; CRRTs, continuous renal replacements therapies.

Clin Toxicol (Phila) 53(5): 454-465.

Theophylline

Table 2. Theophylline: physicochemical and toxicokinetic data.

	Theophylline	Caffeine
Molecular mass	180.2 Da	194 Da
Conversion	1 mg/L = 5.55 µmol/L	1 mg/L = 5.15 µmol/L
Protein binding	50%	35%
Oral bioavailability	> 90% (therapeutic)	> 90%
Volume of distribution	0.5 L/kg	0.7 L/kg
Elimination half-life	Neonates: 30 h Adults: 8–10 h	Neonates: 80 h Adults: 2.5–4.5 h
Therapeutic concentration	5–15 mg/L (28–83 µmol/L)	N/A
Toxic concentration	> 25 mg/L (139 µmol/L)	> 30 mg/L (155 µmol/L)
Toxic dose	> 15 mg/kg	> 15 mg/kg
Lethal dose	> 100 mg/kg	> 150 mg/kg

Clin Toxicol (Phila) 53(4): 215-229

EXTRIP recommendation for Theophylline overdose

Table 8. Executive summary of recommendations.

1) General Statement: ECTR is recommended in severe theophylline poisoning (1C)
2) Indications of ECTR

ECTR is recommended if

- [Theophylline] > 100 mg/L (555 µmol/L) in acute exposure (1C)
- Seizures are present (1D)
- Life-threatening dysrhythmias are present (1D)
- Shock is present (1D)
- There is a rising serum [theophylline] despite optimal therapy (1D)
- There is clinical deterioration despite optimal therapy (1D)

ECTR is suggested if

- [Theophylline] > 60 mg/L (333 µmol/L) in chronic exposure (2D)
- The patient is < 6 months or > 60 years old and the [theophylline] > 50 mg/L (278 µmol/L) in chronic exposure (2D)
- Gastrointestinal decontamination cannot be administered (2D)

3) Cessation of ECTR:
   - Cessation of ECTR is recommended when clinical improvement is apparent OR the [theophylline] < 15 mg/L (83 µmol/L) (1D)
4) Choice of ECTR:
   - Intermittent hemodialysis is the preferred recommended ECTR (1C)
   - The following are acceptable alternatives if hemodialysis is not available
     - Hemoperfusion (1C)
     - CRRT (3D)
   - Exchange transfusion is an alternative to hemodialysis in neonates (2D)
5) Miscellaneous: MDAC should be continued during ECTR (1D)

Clin Toxicol (Phila) 53(4): 215-229

metformin

TABLE 1. Metformin: Physicochemical and Toxicokinetic Data

Molecular weight	165 Da
Volume of distribution	1–5 L/kg
Protein binding	Negligible
Oral bioavailability	55%
Time to peak concentration	Immediate release: 1–3 hr Extended release: 6–8 hr
Endogenous half-life (therapeutic use, normal GFR)	2–6 hr
Endogenous clearance (therapeutic use, normal GFR)	400–650 mL/min
Therapeutic concentration	0.5–3 mg/L
Lethal plasma concentration	> 50 mg/L
Toxic dose	> 100 mg/kg (pediatrics) > 5 g (adults)

GFR = glomerular filtration rate.

Crit Care Med. 43(8):1716-30

EXTRIP recommendation for Metformin overdose

TABLE 8. Executive Summary of Recommendations

General
ECTR is recommended in severe metformin poisoning (1D)
Indications
ECTR is recommended if
Lactate concentration > 20 mmol/L (180 mg/dL) (1D)
Blood pH ≤ 7.0 (1D)
Standard therapy (supportive measures, bicarbonate, etc.) fails (1D)
ECTR is suggested if
Lactate concentration is 15–20 mmol/L (135–180 mg/dL) (2D)
Blood pH 7.0–7.1 (2D)
Comorbid conditions that lower the threshold for initiating ECTR
Impaired kidney function (1D)
Shock (1D)
Decreased level of consciousness (2D)
Liver failure (2D)
Cessation of ECTR is indicated when
Lactate concentration is < 3 mmol/L (27 mg/dL) and pH > 7.35 (1D)
Choice of ECTR
As an initial ECTR, intermittent HD with bicarbonate buffer is preferred (1D), but CRRT is an acceptable alternative if HD is not available (2D)
After the initial ECTR session, either HD (1D) or CRRT (1D) is appropriate if necessary

ECTR = extracorporeal treatment, HD = hemodialysis, CRRT = continuous renal replacement therapy.

Crit Care Med. 43(8):1716-30

methanol

BOX 1. Physicochemical and Pharmacokinetic Properties of Methanol

Molecular weight	Methanol, 32.04 g/mol; formic acid, 46.03 g/mol
Solubility (log P)	Methanol, −0.69; formic acid, −0.54 (both water soluble)
Toxic dose (adult)	30 mL or grams (35), but marked interindividual susceptibility
	60 mL can be lethal (25, 28, 66)
Toxic blood concentrations	≥ 200 mg/L (9.4 mmol/L) is often listed as an indication for medical treatment although data supporting this are limited and a higher concentration may be acceptable (34)
Absorption	In volunteers, methanol is rapidly absorbed with a maximum concentration within 1 hr of ingestion (15)
	In acute poisoning, the maximum concentration is usually noted at the time of admission but it has been observed up to 8–10 hr postadmission (59, 68–72)
	Rarely, poisoning has occurred following inhalational (73–76) or percutaneous (77) exposures
Distribution	Limited protein binding and single compartment kinetics
	Volume of distribution of 0.6–0.8 L/kg (15–19)
Metabolism	Methanol is metabolized by ADH to formaldehyde, which is rapidly oxidized to formic acid, which spontaneously dissociates to formate and a hydrogen ion
	Formate is the principle mediator of morbidity and mortality from methanol poisoning
Elimination	Other routes of methanol elimination include renal (clearance, 5–6 mL/min) and nonrenal (presumed respiratory; 7–13 mL/min) (19, 46)
	Methanol undergoes either first- or zero-order elimination depending on the dose (15–19)
	The apparent elimination half-life of methanol is 2.3–13.7 hr in the absence of antidote therapy (9, 71)
	The inhibition of ADH-mediated metabolism of methanol prolongs its apparent elimination half-life to a mean of 54 hr (9–11) although it may vary between 9 and 87 hr (9–11, 17, 30, 37–39, 78–82)

ADH = alcohol dehydrogenase.

Critical Care Medicine 43(2): 461-472.

EXTRIP recommendation for Methanol overdose

BOX 3. Role of Extracorporeal Treatment in the Treatment of a Patient With Methanol Poisoning

We recommend ECTR is initiated in the following circumstances:

1) Severe methanol poisoning (grade 1D), including any of:
   a) Coma (grade 1D)
   b) Seizures (grade 1D)
   c) New vision deficits (grade 1D)
   d) Metabolic acidosis from methanol poisoning
      i) Blood pH ≤ 7.15 (grade 1D)
      ii) Persistent metabolic acidosis despite adequate supportive measures and antidotes (grade 1D)
   e) Serum anion gap > 24 mmol/L (grade 1D); calculated by serum $[Na^+] - [Cl^-] - [Hco_3^-]$.

2) Serum methanol concentration
   a) > 700 mg/L or 21.8 mmol/L in the context of fomepizole therapy (grade 1D)
   b) > 600 mg/L or 18.7 mmol/L in the context of ethanol treatment (grade 1D)
   c) > 500 mg/L or 15.6 mmol/L in the absence of an ADH blocker (grade 1D)
   d) In the absence of a methanol concentration, the osmolal/osmolar gap may be informative (grade 1D)

3) In context of impaired kidney function (grade 1D)

To optimize the outcomes from ECTR, we recommend:

4) Intermittent hemodialysis is the modality of choice in methanol poisoning (grade 1D). Continuous modalities are acceptable alternatives if intermittent hemodialysis is not available (grade 1D).

5) ADH inhibitors are to be continued during ECTR for methanol poisoning (grade 1D) as well as folic acid

6) ECTR can be terminated when the methanol concentration is < 200 mg/L or 6.2 mmol/L and a clinical improvement is observed (grade 1D)

ECTR = extracorporeal treatment, ADH = alcohol dehydrogenase.

Critical Care Medicine 43(2): 461-472.

Lithium

Table 2. Lithium physicochemical and toxicokinetic properties

Molecular mass	7 Da
Volume of distribution	0.7–0.9 L/kg
Protein binding	0%
Oral bioavailability	Immediate release: 95%–100%; modified release: 60%–90%
Therapeutic serum concentration	0.6–1.2 mEq/L
Half-life (therapeutic)	12–27 h
Conversion factor	1 mmol/L=1 mEq/L
Toxic dose (acute poisoning)	>1 g elemental Li

Table 3. Indications for extracorporeal treatment in the treatment of lithium poisoning

Indication for ECTR	Goldfrank's *Toxicologic Emergencies*, 9th Ed. (216)	EMedicine (emedicine.medscape.com) (215)	Toxbase (toxbase.org) (214)	Toxinz (toxinz.com) (213)	Olson's *Poisoning and Drug Overdose*, 6th Ed. (212)	UpToDate (uptodate.com) (211)	Murray's *Toxicology Handbook*, 2nd Ed. (210)
Absolute [Li^+] regardless of symptoms (mEq/L)	≥4	≥4	≥7.5			>4	
[Li^+] in chronic exposure (mEq/L)	≥2.5	≥2.5	>4	>4		>2.5	>2.5
Symptoms/signs	Neurotoxicity, kidney impairment	Neurotoxicity	Neurotoxicity	Neurotoxicity	Seizures or impaired mental status, kidney impairment	Significant toxicity, kidney impairment	Neurotoxicity

ECTR, extracorporeal treatment. Modified from reference 28, with permission.

Clin J Am Soc Nephro 10(5):875-87

EXTRIP recommendation for Lithium overdose

Table 7. Executive summary of recommendations

General
ECTR is recommended in patients with severe Li poisoning (1D)
Indications
ECTR is recommended (1D)
If kidney function is impaired and the $[Li^+]$>4.0 mEq/L
In the presence of a decreased level of consciousness, seizures, or life-threatening dysrhythmias irrespective of $[Li^+]$
ECTR is suggested (2D)
If the $[Li^+]$>5.0 mEq/L
If confusion is present
If the expected time to obtain a $[Li^+]$<1.0 mEq/L with optimal management is >36 h
Cessation of ECTR is recommended (1D)
When the $[Li^+]$<1.0 mEq/L or clinical improvement is apparent
After a minimum of 6 h of ECTR if the $[Li^+]$ is not readily available
After interruption of ECTR, serial $[Li^+]$ measurements should be obtained over 12 h to determine use of subsequent ECTR sessions (1D)
Choice of ECTR
Intermittent hemodialysis is the preferred ECTR (1D)
Continuous RRT is an acceptable alternative if intermittent hemodialysis is not available (1D)
After initial treatment, both continuous RRT and intermittent hemodialysis are equally acceptable (1D)

Clin J Am Soc Nephro 10(5):875-87

Thallium

Table 2. Thallium physicochemical and toxicokinetic data

Variable	Level
Molecular weight (g/mol)	204.4
Volume of distribution (L/kg)	3–10
Protein binding (%)	0
Oral bioavailability (%)	90–100
Therapeutic range	NA
Toxic blood concentrations (mg/L)	>0.1
Intervention blood concentration (mg/L)	≥1.0
Lethal dose (mg/kg)	>6–8

Clin J Am Soc Nephrol 2012 7(10): 1682-1690

EXTRIP recommendation for thallium overdose

Table 4. Executive summary of recommendations

General statement
- ECTR is recommended in severe Tl poisoning (1D)

Indications for ECTR
- *ECTR is indicated if ANY of the following conditions are present:*
  - If Tl exposure is highly suspected on the basis of history or clinical features (2D)
  - Assuming Tl concentrations are readily available, if Tl concentration is >1.0 mg/L (2D)
  - Assuming Tl concentrations are readily available, if Tl concentration is between 0.4 and 1.0 mg/L (3D)

Timing of ECTR
- ECTR should be initiated as soon as possible, ideally within 24–48 hr of Tl exposure (1D)

Cessation of ECTR
- ECTR is suggested until Tl serum concentration is <0.1 mg/L for a minimal duration of 72 hr (2D)

Choice of ECTR
- Intermittent hemodialysis is the preferred initial ECTR, especially after an acute Tl ingestion (1D)
- Intermittent hemoperfusion or continuous renal replacement modalities are valid alternatives if intermittent hemodialysis is not available (1D)

ECTR, extracorporeal treatment; Tl, thallium.

Clin J Am Soc Nephrol 2012 7(10): 1682-1690

EXTRIP did NOT recommend ECTR

- Digoxin
  - Digoxin-specific Fab is an effective treatment that can reverse toxic effects of cardiac glycosides rapidly

- TCA

Thank you