Extracorporeal Treatment in Poisoning

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POISON


BUG

Enhancing Elimination of poisons

- **Corporeal**
  - Urine Elimination Enhancement
    - Urine Alkalinization
    - Forced Diuresis; no significant benefit , is never recommended
  - Fecal Elimination Enhancement;
    - MDAC
    - Sodium polystyrene sulfonate
    - Prussian blue
    - Whole-bowel irrigation (WBI)
- **Extra Corporeal (ECTR)**

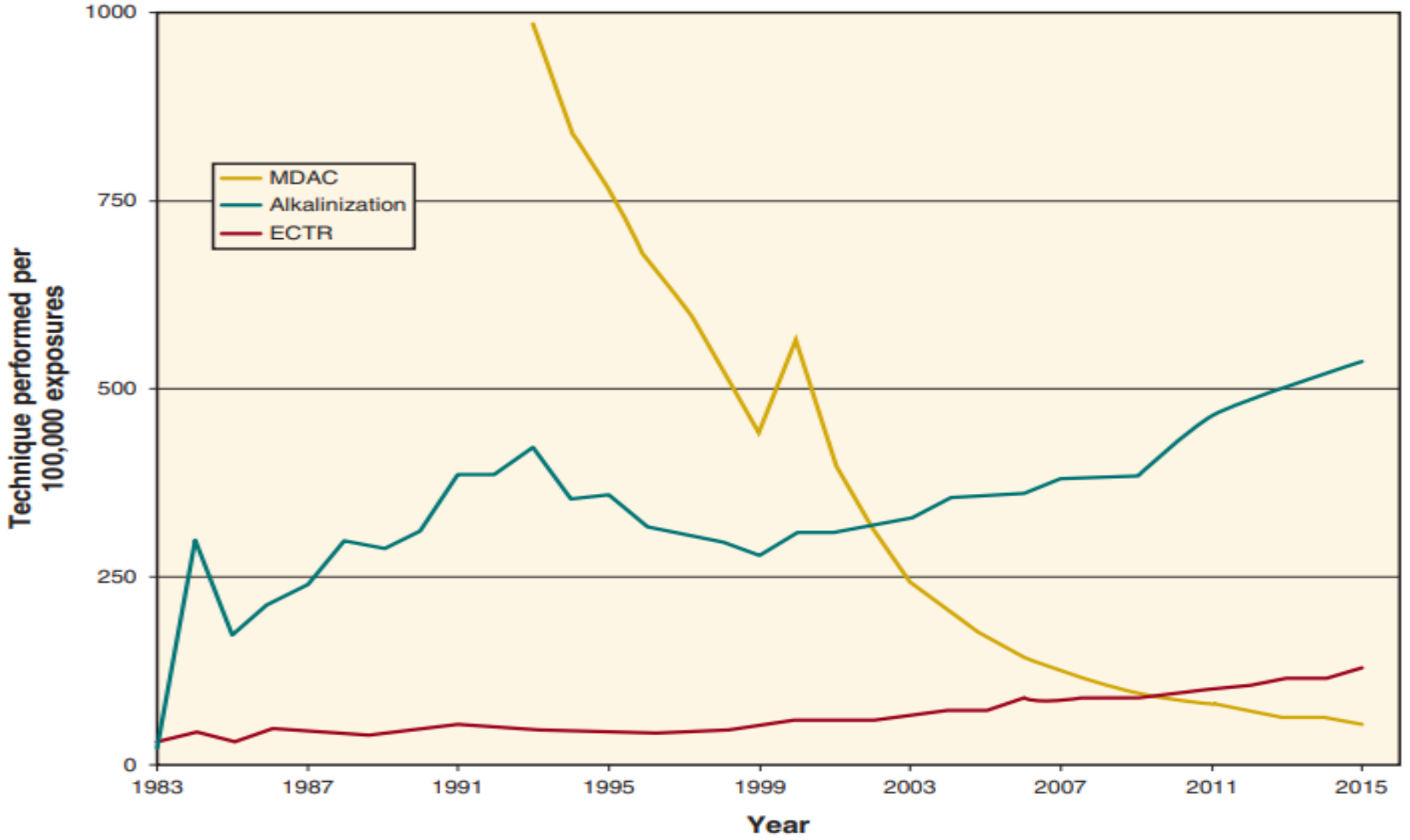


Fig. 67.1 This figure illustrates how often these various elimination enhancement techniques were used in the United States from 1983 to 2015. *ECTR,* Extracorporeal treatment; *MDAC,* multiple-dose activated charcoal.

ECTR

- Absolute indications: (all must be present)
  - Removability by ECTR
  - Physiologic processes fail to remove toxin(severe toxicity or organ failure or contraindication; eg; loss of consciousness in MDAC)
  - absence of preferable alternative treatments(i.e, Antidotes); NAC for acetaminophen
  - severe toxicity; life-threatening clinical signs (e.g., repeated seizures, respiratory depression, dysrhythmias) or prophylactic ECTR ; when delayed effect is expected

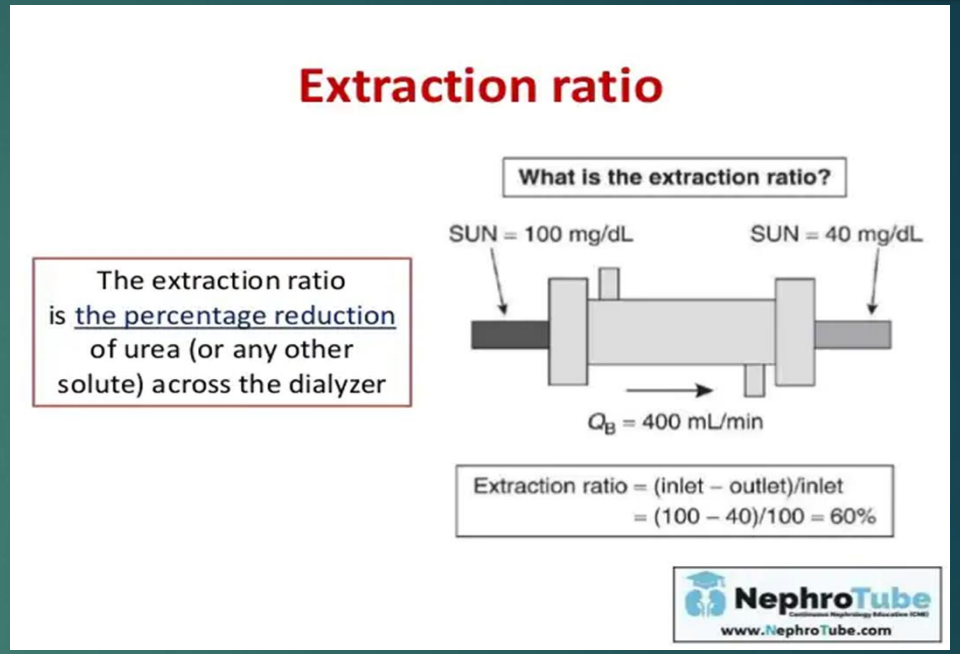
The clinicians should assess the risks of the specific exposure(ECTR VS. death, blindness,…) and the cost-effectiveness (ECTR VS. Hospital or ICU stay)

Endogenous Clearance;

If < 4 mL/ min per kg (or < 200ml/min), ECTR potentially is considered beneficial

ECTR

- Extractability (ER)
  - molecular size
  - water solubility
  - protein binding
- Volume of Distribution(VD)



Available Modalities

- Diffusion (hemodialysis, peritoneal dialysis)
- Convection (hemofiltration)
- Adsorption (hemoperfusion)
- Centrifugation (therapeutic plasma exchange)

Table 67.3 Summary of Extracorporeal Treatments[a]

Treatment	Process	Molecular Weight Cutoff (Da)	Protein Binding Cutoff	Relative Cost	Complications	Comments
Albumin dialysis	Diffusion, adsorption	<60,000–100,000	<95%	++++	++	Liver replacement support
CRRT	Convection and/or diffusion	<10,000–50,000	<80%	++	+	Correction of uremia and acid-base and E+ disorders
Exchange transfusion	Centrifugation, separation, filtration	None	None	++	++	Easier than other ECTRs in neonates; correction of hemolysis
Hemodialysis	Diffusion	<10,000	<80%	+	+	Correction of uremia and acid-base and E+ disorders
Hemofiltration	Convection	<50,000	<80%	++	+	Correction of uremia and acid-base and E+ disorders
Hemoperfusion	Adsorption	<50,000	<95%	++	+++	Saturation of cartridge requires changes
Peritoneal dialysis	Diffusion	<500–5000	<80%	++	++	Low efficacy
Plasma exchange	Centrifugation, separation, filtration	<1,000,000	None	+++	+++	

[a]All extracorporeal treatments above are less likely to be useful for poisons that have a high V_D or a high endogenous clearance.
CRRT, Continuous renal replacement therapy, *E+,* electrolyte; *ECTR,* extracorporeal treatment; +, low; ++, moderate; +++, high; ++++, very high.

IHD Advantages over other ETCR Modalities

- rapidly removes poisons
- corrects metabolic disequilibria such as AKI, volume overload, acid–base abnormalities, electrolyte disturbances, and even hypothermia
- the most available ECTR
- the least expensive
- quickest ECTR to implement

THE ONLY DISADVANTAGE OF IHD: HYPOTENSION

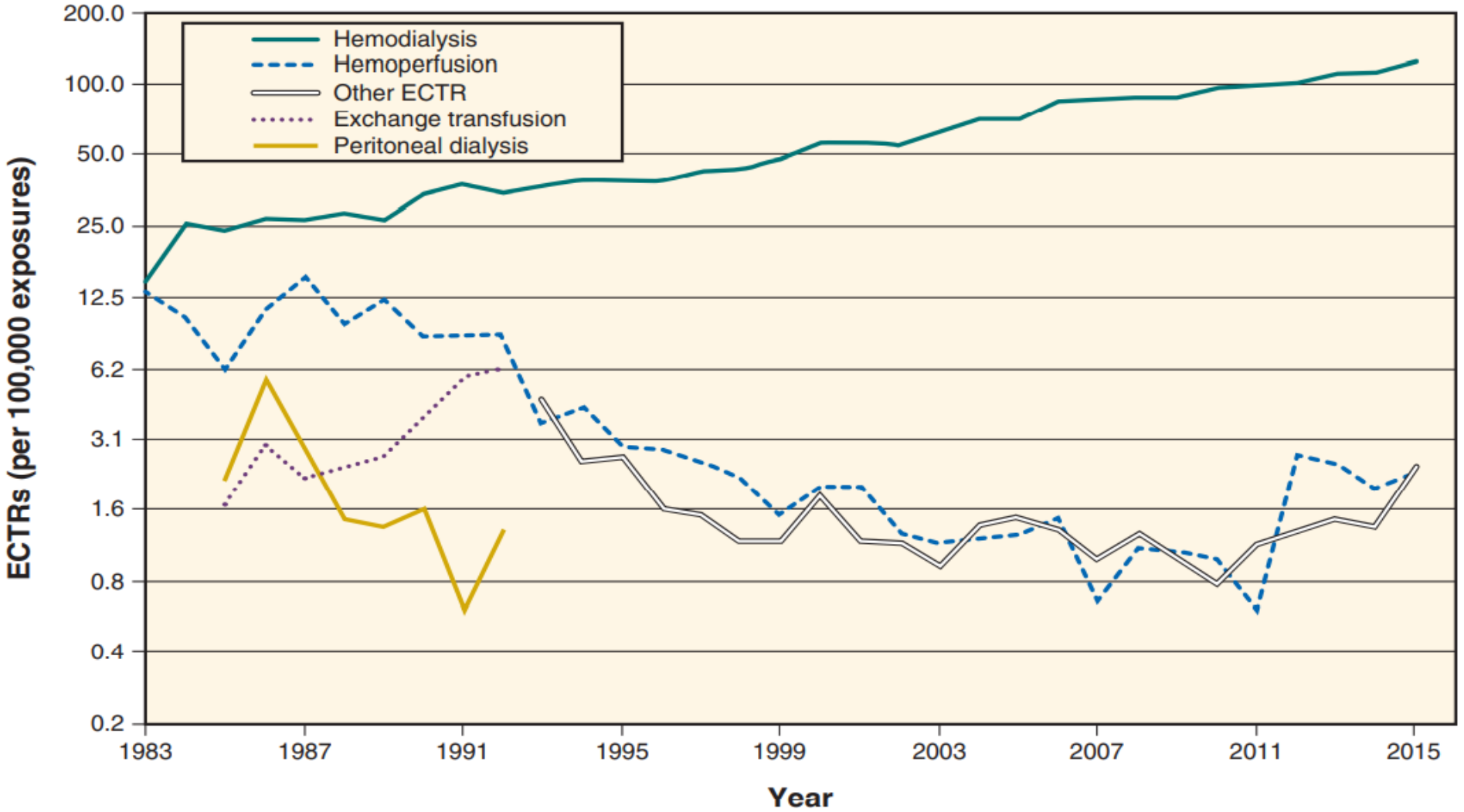


Fig. 67.2 This figure illustrates how often extracorporeal treatments were used in the United States from 1983 to 2015. *ECTR,* Extracorporeal treatment.

The characteristics in favor of efficient poison removal by IHD

- low molecular weight (<5000−10,000 Da)
- low VD (<1-2 L/Kg)
- low protein binding (<80%)
- low endogenous clearance (<4 mL/min per kg)

Box 67.1 Factors That May Enhance Poison Clearance During Hemodialysis

Larger surface area of dialysis membrane
High-flux dialyzer
High blood and dialysate flows
Increased ultrafiltration rate (with replacement solution)
Increased time on dialysis
Reduced recirculation
Two dialyzers in series
Two distinct extracorporeal circuits

EXTRIP (Extracorporeal Treatments in Poisoning)

- EXTRIP Workgroup : to provide evidence-based recommendations on the use of extracorporeal treatments in poisoning

Acetaminophen

- treatment of choice: NAC
- water-soluble and Dialysable
- ECTR is rarely necessary unless:
  - Severe AKI
  - following massive ingestions with a pattern of mitochondrial toxicity—coma, lactic metabolic acidosis, and/or cardiovascular instability

Intermittent hemodialysis (HD) : the preferred ECTR modality (1D)

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CRITICAL CARE

Extracorporeal treatment for acetaminophen poisoning: Recommendations from the EXTRIP workgroup

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2) Indications for ECTR:

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

1. If NAC is **NOT** administered and the [APAP] more than 1000 mg/L (6620 µmol/L) (1D) or more than 800 mg/L (5300 µmol/L) (2D)
2. If NAC is **NOT** administered and the patient presents with altered mental status, metabolic acidosis, elevated lactate, and the [APAP] is more than 700 mg/L (4630 µmol/L) (1D) or more than 500 mg/L (3300 µmol/L) (2D)
3. If NAC **is** administered and the patient presents with altered mental status, metabolic acidosis, elevated lactate, and the [APAP] is more than 900 mg/L (5960 µmol/L) (1D) or more than 800 mg/L (5300 µmol/L) (2D)

ECTR is not suggested.

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

ECTR is not recommended.

6. On the basis on the reported ingestion dose if NAC is administered (1D).

Toxic alcohols
methanol & ethylene glycol

- supportive care
- correction of the acidemia
- antidote therapy(fomepizole/ethanol)
- enhanced elimination with ECTRs

ECTR especially IHD is extremely efficient at removing alcohols and their toxic metabolites, as well as rapidly correcting metabolic acidosis

By ECTR the rate of clearance of alcohols and metabolites can reach 250 mL/min

Indications for ECTR

- Serum EG or methanol concentration > 50 mg/dL (8.0 mmol/L, or 15.6 mmol/L, respectively) if fomepizole is not used
- • Metabolic acidosis (pH < 7.2) or an AG > 28 mmol/L
- • Coma or seizures
- • Vision deficits secondary to methanol
- • AKI or chronic kidney disease (CKD)
- Prediction of prolonged hospital stay and high cost (in the case of methanol under fomepizole/ethanol tx)

If dialysis is initiated, doses of ethanol or fomepizole should be increased unless dialysate is enriched by ethanol

- IHD should be continued until the parent alcohol levels are < 20 mg/ dL and the metabolic acidosis is corrected
- When methanol concentrations are very high, dialysis for 18 to 21 hours may be required
- serum osmolality, electrolytes, and acid–base status should be monitored closely within 24 to 36 hours after dialysis because of redistribution and rebound and repeated dialysis may be necessary

Ophthalmologic abnormalities should not be considered an indication to continue dialysis

The expected duration of dialysis
4.7× Ln[initial EG concentration/ 2])
3.5 (× Ln[initial methanol concentration]/ 4)

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)

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Isopropanol

- only occasionally fatal
- Antidote treatment is not recommended
- Hemodialysis might be considered if the isopropanol levels are >400 mg/dL (67 mmol/L) and significant CNS suppression, renal failure, or hypotension exists

salicylate

- well removed by hemodialysis
- Hemodialysis should be considered when
  - Neurologic symptoms (e.g., confusion, seizures, coma)
  - Pulmonary edema
  - pH < 7.25
  - Serum salicylate concentration > 90 mg/dL (6.5 mmol/L)
  - Acute kidney injury
  - Clinical deterioration, despite appropriate treatment

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)**

Lithium carbonate

- supportive care, correction of Volume contraction, GI decontamination
- Well dialysable
- Low endogenic clearance
- ECTR:
  - Severe neurologic features (central hyperthermia, seizures, and/or depressed consciousness), Life-threatening cardiac dysrhythmias
  - Serum [Li] > 5 mmol/L (although good outcomes have been noted from much higher concentrations in acute poisoning without ECTR)
  - Kidney impairment with symptoms and serum [Li] > 4 mmol/L

Extracorporeal Treatment for Lithium Poisoning: Systematic Review and Recommendations from the EXTRIP Workgroup

Brian S. Decker, David S. Goldfarb, Paul I. Dargan, Marjorie Friesen, Sophie Gosselin, Robert S. Hoffman, Valéry Lavergne, Thomas D. Nolin, and Marc Ghannoum, on behalf of the EXTRIP Workgroup

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)

Anticonvulsants

Phenytoin	protein binding(90%–95%) (unchanged in overload) 70% in renal failure or hypoalbuminemia	**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*)
Barbiturates	protein binding : below 50%,	**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*)
Sodium valproate	90% protein binding 35% at overdose	**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)
Carbamazepine	protein binding : 75% (unchanged in overload)	**Indications for ECTR** ECTR is recommended if ANY of the following conditions are present: o If multiple seizures refractory to treatment occur (1D) o If life-threatening dysrhythmias occur (1D) ECTR is suggested if ANY of the following conditions are present: o If prolonged coma and/or respiratory depression requiring mechanical ventilation are present or expected (2D) o If significant toxicity persists, especially if carbamazepine concentrations rise or remain elevated, despite MDAC and support measures (2D)

Paraquat

- prompt assessment and aggressive management is essential
- small molecule, unbound to protein, small VD: removable by standard ECTRs (clearance >120 mL/min).
- distributes quickly to tissues
- IHD or HP: in early hours after exposure (especially within 4 hours)

HP: plasma paraquat level ≥ 0.1 mg/L (0.4 mcmol/L) (should be considered).

Repeated or continuous hemoperfusion may be needed for several days to maintain plasma levels below 0.1 mg/L

Theophylline

- an ideal candidate for extracorporeal elimination(150 mL/min)
- IHD is comparable with hp in the case of clearance but IHD is the preferred tx

- ECTR indications:
  - Serum theophylline concentration > 100 mg/L
  - Chronic poisoning with serum theophylline concentration > 60 mg/L
  - refractory seizures, shock, life-threatening dysrhythmias, inability to administer charcoal because of intractable vomiting, or extremes of age (60 years)
  - A rising serum theophylline concentration despite optimal therapy, or if MDAC cannot be administered

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)

Metformin

- relatively large VD (3 L/kg)
- dialyzer extraction ratios :60%
- ECTRs can remove a significant amount of metformin, especially when kidney function is impaired
- hemodialysis may rapidly correct the associated metabolic acidosis
- ECTR:
  - Lactate concentration > 180 mg/dL (20 mmol/L)
  - Arterial pH ≤ 7.1
  - Failure of supportive therapy in severe MALA
  - The presence of shock, impaired kidney function, or coma

- 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

Digoxin

- correction of hypokalemia, hypomagnesemia, and alkalosis
- oral-activated charcoal
- VD : large (8 L/kg in normal patients, 4.2 L/kg in dialysis patients)
- only 5% removable by a 4-hour hemodialysis treatment

Fab therapy remains preferred over hemoperfusion or plasmapheresis even in dialysis patients,

Digoxin

General statement

ECTR is not recommended in severe digoxin poisoning if Fab is administered (1D)

ECTR is not suggested in severe digoxin poisoning if Fab is not administered (2D)

Indications for ECTR

ECTR is not recommended in any of the following situations (1D):

- A suspected digoxin ingestion alone regardless if Fab is administered
- An elevated digoxin serum concentrations alone regardless if Fab is administered
- Cardiovascular disturbances if Fab is administered
- Serum potassium > 6.0 mmol/L

For removal of digoxin immune Fab complex in a patient with no clinical toxicity and impaired kidney function ECTR is not suggested in any of the following situations (2D):

- Cardiovascular disturbance if Fab is not administered
- Serum potassium between 6.0 and 7.0 mEq/L

For removal of digoxin immune Fab complex in a patient with clinical toxicity and impaired kidney function No agreement for ECTR was reached in the following situation:

- Serum potassium > 7.0 mmol/L

Choice of ECTR

- Neither intermittent hemodialysis nor hemoperfusion are suggested in severe digoxin poisoning (2D)
- Other ECTR modalities are not recommended for severe digoxin poisoning (1D)
- Therapeutic plasma exchange is not recommended to remove the digoxin immune Fab complex in patients with impaired kidney function (1D)

Others

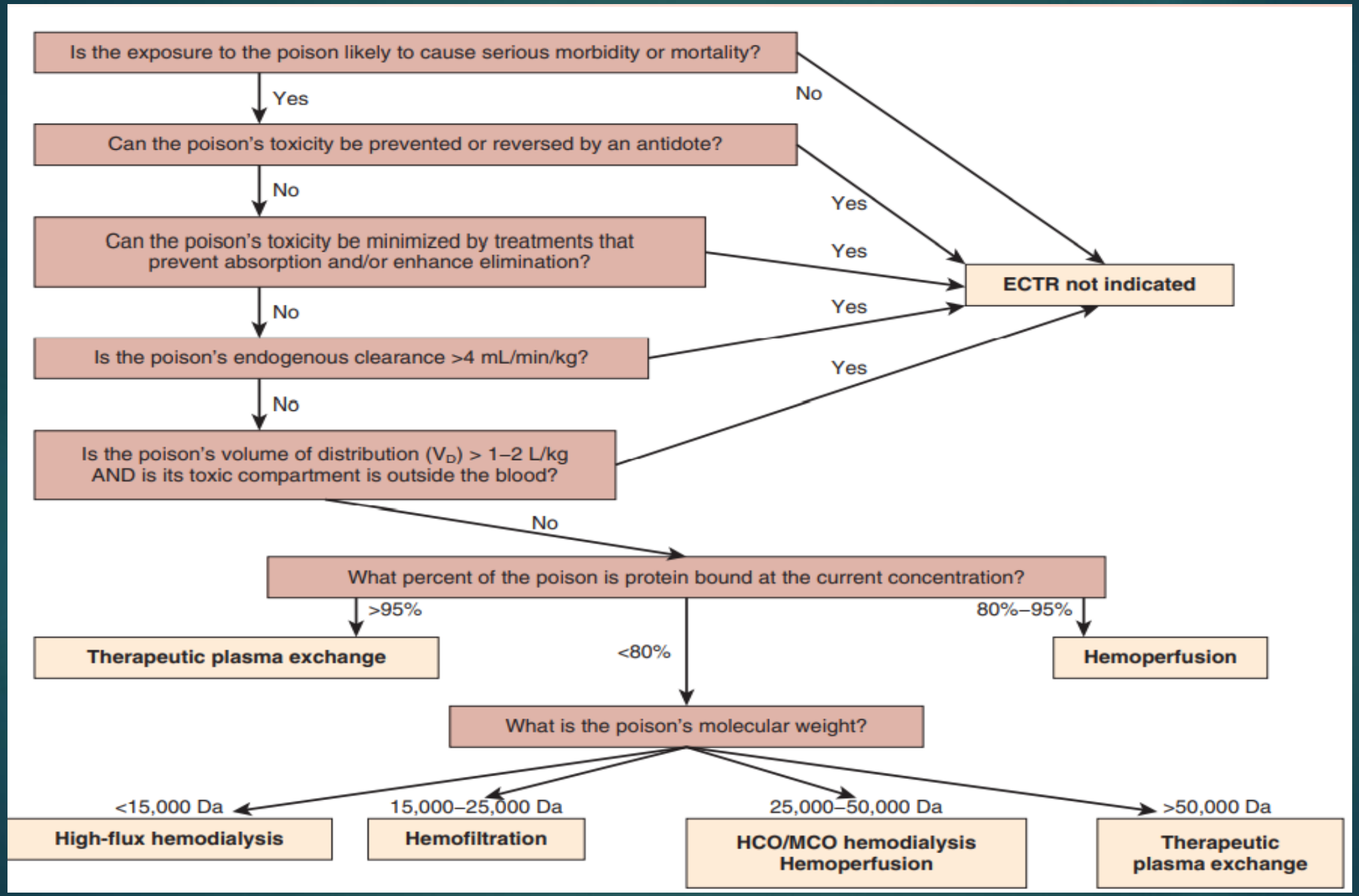
- Phenothiazines and TCAs; highly protein-bound , extremely large VD(14–21 L/kg); poorly removable by either HD or HP; tx is supportive; bicarbonate for widened QRS complex

- Sedatives and hypnotics; supportive therapy is often sufficient to treat overdose with Newer agents

Table 67.4 Physicochemical Characteristics and Toxicokinetics of Various Poisons

Poison	Molecular Weight (Da)	Protein Binding (%)	Volume of Distribution (L/Kg)	Endogenous Clearance in Healthy Adults (mL/min per kg)
Acetaminophen	151	20	1	5
Carbamazepine	236	75	1.2	1.3
Ethylene glycol	62	0	0.6	1.8
Isopropanol	60	0	0.6	1.2
Lithium	7	0	0.8	0.4
Metformin	166	5	5	10
Methanol	32	0	0.6	0.7
Methotrexate	454	50	0.8	1.5
Paraquat	186	5	1.0	8
Phenobarbital	232	40	0.7	0.2
Phenytoin	252	90	0.6	0.4
Salicylic acid	138	80[a]	0.2	1.5
Theophylline	180	60	0.5	0.7
Valproic acid	144	90[a]	0.2	0.1

[a]Protein binding saturation occurs at high concentration.


Is the exposure to the poison likely to cause serious morbidity or mortality?
Yes
No
Can the poison's toxicity be prevented or reversed by an antidote?
No
Yes
Can the poison's toxicity be minimized by treatments that prevent absorption and/or enhance elimination?
Yes
ECTR not indicated
No
Yes
Is the poison's endogenous clearance >4 mL/min/kg?
No
Yes
Is the poison's volume of distribution (V_D) > 1–2 L/kg AND is its toxic compartment is outside the blood?
No
What percent of the poison is protein bound at the current concentration?
>95%
80%–95%
<80%
Therapeutic plasma exchange
Hemoperfusion
What is the poison's molecular weight?
<15,000 Da
15,000–25,000 Da
25,000–50,000 Da
>50,000 Da
High-flux hemodialysis
Hemofiltration
HCO/MCO hemodialysis
Hemoperfusion
Therapeutic plasma exchange