

# Extracorporeal Treatment in the Management of Acute Poisoning: What an Intensivist Should Know?

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## Abstract

Extracorporeal treatment (ECTR) represents a treatment modality promoting removal of endogenous or exogenous poisons and supporting or temporarily replacing a vital organ. This article aims to provide a brief overview of the technical aspects and the potential indications and limitations of the different ECTRs, highlighting the important characteristics of poison amenable to ECTR and the most appropriate prescriptions used in the setting of acute poisoning. The various principles that govern poison elimination by ECTR (diffusion, convection, adsorption, and centrifugation) and how components of the ECTR can be adjusted to maximize clearance have also been discussed.

**Keywords:** End-stage kidney disease, extracorporeal treatment, hemoperfusion, intermittent hemodialysis

## INTRODUCTION

Majority of exposures due to poisonous substances need supportive care only. Extracorporeal treatments (ECTRs) are required in 0.1% of intoxications.<sup>[1]</sup> ECTR represents a heterogeneous group of treatments promoting removal of endogenous or exogenous poisons, supporting or temporarily replacing a vital organ, or a combination of these two. Use of hemodialysis for the elimination of toxic substances predates its use for end-stage kidney disease (ESKD) by many years. The first successful *in vivo* experiment with hemodialysis was carried out in 1913, and removal of salicylates from poisoned animals was demonstrated.<sup>[2]</sup> Yet after so many years, the application of ECTR in the management of poisoned patients remains debatable. A multidisciplinary and multinational collaborative known as Extracorporeal treatment in poisoning (EXTRIP) workgroup has been established with the aim to clarify the role of ECTRs in clinical practice through the development of evidence- and expert opinion-based recommendations.<sup>[3]</sup>

## PRINCIPLES AND METHODS OF TOXIC SUBSTANCE REMOVAL

The various methods available for toxic substance removal by ECTR are diffusion, convection, adsorption, and centrifugation [Table 1].

## Diffusion-hemodialysis

In intermittent hemodialysis (IHD), the movement of particles (solutes) is driven by diffusion, i.e., a concentration gradient from one compartment to another through a semi-permeable membrane. Characteristics influencing solute clearance through diffusion include the magnitude of the concentration gradient (blood and dialysate flow rates), duration of therapy, and the filter composition. The maximum possible clearance of the solute corresponds to the slower of the two flows ( $Q_b$  – blood flow rate and  $Q_d$  – dialysate flow rate), which will be the rate-limiting step. The clearance of small water-soluble solutes will exceed that of larger particles because the mobility of the solute between the compartments influences clearance. Targeting a  $Q_d/Q_b$  ratio  $>2.5:1$  may be ensured so that clearance of small molecules is not restricted by dialysate flow.<sup>[4]</sup> Countercurrent direction of dialysate flow provides 20%–30% better clearances for small molecules than a concurrent direction of flow. Increasing  $Q_b$  also increases the clearance of middle molecules such as vancomycin when a high-flux filter is used. Similar results were shown

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**Table 1: Important parameters for optimizing clearance with the different extracorporeal therapies**

	For small molecules (MW <500-1000 Da)	For middle-sized molecules	For protein-bound molecules (>80%)
Intermittent hemodialysis	High Qb (up to 400 ml/minute) Ratio Qd: Qb $\geq$ 2.5 High-efficiency filter	High-flux filter with a large surface area High Qb Adding a second filter	High Qd Filter with a large surface area
Intermittent hemofiltration	High Qb, High Q <sub>UF</sub> Maximize postdilution then add predilution	High Qb, High Q <sub>UF</sub> . Maximize postdilution then add predilution High-flux filter	High-flux filter Predilution
CRRT	High Qeffluent (Qd > Q <sub>UF</sub> ) High Qb Maximize postdilution then add predilution High-efficiency filter Filter changed <48 h	High Qeffluent (Q <sub>UF</sub> > Qd) Maximize convection: CVVH > CVVHDF (because replacement fluid is greater) High Qb High-flux filter, Filter changed <48 h	
Hemoperfusion	Charcoal vs. resin column (depending on poison) High Qb (max 350 mL/min) Filter change <4 h		
Therapeutic plasma exchange	Centrifugation or filtration $\geq$ 2 plasma volumes exchanged, Central catheter High Qb (100-200 ml/min for filtration and 100 ml/min for centrifugation) Replacement fluid tailored to the poison Heparin vs. citrate anticoagulation		
For all processes	Right jugular catheter $\geq$ femoral. For a femoral site, use catheter >20 cm long. Subclavian site probably equivalent to jugular but avoid in patients at risk for end-stage renal disease. Both subclavian and jugular sites may require X-ray confirmation of placement		

in poisonings due to phenobarbital, lithium, and phenytoin, where clearance plateaued when Qb exceeded approximately 300 ml/min in the context of Qd 500 ml/min. Increases in Qb and Qd are associated with a lesser increase in the clearance of middle-sized molecules by diffusion, such as Vitamin B12 and  $\beta$ 2-microglobulin with no significant change for larger molecules such as dextran.<sup>[5]</sup> Qb is usually limited to <400 ml/min when using an intravascular catheter due to blood turbulence and resistance in the tubing. Augmenting Qd increases clearance by approximately 10%–20% for small-molecular-weight (MW) molecules but does not affect the clearance of larger molecules.<sup>[6,7]</sup> There is an improved clearance of larger MW solutes relative to small MW solutes with high-flux membranes. The simultaneous use of more than one filter, or even two distinct circuits, can increase clearance.<sup>[8]</sup> The benefit of either configuration (series or parallel) provides an incremental clearance gain of approximately 5%–7% due to the effect of increasing the surface area for filtration and improving clearance of small molecules, particularly in very large sized patients.<sup>[8]</sup>

Albumin dialysis may facilitate the clearance of highly protein-bound toxins because the unbound fraction diffuses into the dialysate side where it binds to albumin and is trapped. There will be a protein-binding disequilibrium on the blood side and more drug would become unbound and cross the membrane to be cleared.<sup>[9]</sup> A favorable impact of larger albumin concentration on the clearance of protein-bound toxins has been observed for diazepam, valproic acid, and carbamazepine.

IHD is frequently available, least expensive with fewer complications, and quickest to implement when compared to hemoperfusion, therapeutic plasma exchange (TPE), or albumin dialysis. The ability of IHD to treat concomitant metabolic disorders and its significant clearance capacity for a wide spectrum of toxic substances<sup>[10]</sup> are the main reasons why IHD remains the treatment of choice for most poisonings. The duration of IHD in poisoning can be prolonged depending on the clinical setting and nursing availability. The dialysate is usually tailored to the patient requiring dialysis as these poisoned patients may have a very different metabolic profile than one with renal failure.

### Convection-hemofiltration

In hemofiltration (HF), poison and solvent are simultaneously removed by convection and replaced by a physiological solution, whereas intermittent hemodiafiltration (HDF) combines convection and diffusion. In convection, there is a movement of solvent and solutes according to a pressure gradient (solvent drag) and, to maintain volume homeostasis, an ultrapure replacement fluid is reinfused to the patient. Convection efficacy is mainly dependent on the size of the dialyzer membrane pores. Convection allows removal of poisons as large as 25,000 Da. As the large majority of known poisons have a low MW (<2000 Da), HF would not seem to be more advantageous than HD in the majority of poisonings. Factors influencing solute clearance during convection include Qb, ultrafiltration rate (Q<sub>UF</sub>), the site of fluid replacement, and the type of hemofilter. Solute clearance increases when either Qb or Q<sub>UF</sub> is increased. The difference in clearances

between convection and diffusion increases as the solute's MW increases. Increases in Qb have a more limited effect on the removal of larger molecules such as  $\beta_2$ -microglobulin compared with smaller molecules.<sup>[11]</sup> Postdilution HF is associated with an increased risk of clotting of the filter and requires anticoagulation, which is not essential in predilution.<sup>[12]</sup> Clearances of middle-sized solutes up to 10,000 Da are higher with a high-flux membrane and become negligible with an MW >20,000 Da. Another advantage of a larger filter surface area is that it can withstand greater transmembrane pressures for a longer period of time,<sup>[6]</sup> allowing higher Qb and convective fluxes across the membrane. Protein-leaking membranes, named as high cutoff (HCO) or "superflux" membranes, are highly permeable membranes with improved removal of protein-bound solutes and large-sized unbound solutes at the expense of a heavier albumin loss.<sup>[13]</sup> Protein-leaking membranes can be used for poisons that are highly protein bound, considering the fact that albumin loss likely has negligible clinical significance when these filters are used for a limited number of sessions.<sup>[14]</sup> Diffusion and convection have a comparable effect on the clearance of smaller MW molecules (<500–1000 Da), while convection provides much higher clearances for middle MW molecules (1000–10,000 Da) compared with diffusion. Therefore, the clearance of small MW molecules can be enhanced by adding convection to diffusion, thereby increasing the total effluent rate.<sup>[15]</sup> However, the opposite is not true for middle MW molecules. In HDF, ultrafiltration and predilution may have a negative impact on transmembrane concentration gradients; however, the addition of convection may improve the clearance of some solutes such as phosphorus.<sup>[16]</sup>

## CONTINUOUS RENAL REPLACEMENT THERAPY/ SUSTAINED LOW-EFFICIENCY DIALYSIS

Continuous renal replacement therapies (CRRTs) are often used in the critical care setting to manage acute kidney injury, especially in fluid overloaded, hemodynamically unstable patients. Poison clearance with CRRT is 50%–80% less than that obtained with intermittent modalities because of lower blood and/or effluent flow rates.<sup>[17]</sup> For example, clearances for methanol are usually limited to under 50 ml/min with CRRT, while they can surpass 200 ml/min with IHD. CRRT following an HD session is used by some clinicians to minimize a re-increase in poison concentration, or rebound. Sustained low-efficiency dialysis (SLED) is a hybrid technique usually provided as a prolonged treatment using both reduced Qd and Qb and differs from CRRT in three areas namely shorter duration, higher Qd than CRRT, and can be administered using the same equipment as standard IHD. Although SLED uses a higher Qd than CRRT, the small solute clearance between these two modalities is reportedly similar.<sup>[10]</sup> The modeled clearance of middle and large solutes during CRRT is greater than that during SLED, likely due to the extended duration and additional convective clearance in CRRT.<sup>[18]</sup> In lithium poisoning, following dialysis, poison may transfer from the site of central nervous system (CNS) toxicity to a relatively

more benign vascular compartment<sup>[19]</sup> and may further present an added opportunity for extracorporeal removal. When poison removal is urgent, SLED and CRRT are not the treatments of choice unless no other method is available or ultrafiltration is needed in an unstable patient.<sup>[20]</sup>

## Adsorption/hemoperfusion

Adsorption is a process by which particles located in the blood compartment bind reversibly or irreversibly to the surface of a column (or sorbent). Its contribution to total clearance is variable, and cannot be easily predicted by considering the type of filter and/or the MW of the poison.<sup>[21]</sup> It has a minor effect on clearance compared with convection and diffusion, is more pronounced for middle and large MW molecules, and largely occurs within the 1<sup>st</sup> h after a filter change. During HP, whole blood passes through a charcoal-coated cartridge onto which the poison can be adsorbed.<sup>[22]</sup> However, HP requires greater systemic anticoagulation than do other ECTRs, and the prescribed blood flow must not exceed 350 ml/min to avoid the risk of hemolysis.<sup>[23]</sup> HP also nonselectively adsorbs platelets, white blood cells, calcium, and glucose.<sup>[24]</sup> Further, a charcoal cartridge costs ten times more than a high-efficiency dialyzer, does not bind all poisons (e.g., alcohols and certain metals), and needs to be replaced every 2 h because of cartridge saturation, which decreases poison clearance.<sup>[25]</sup>

## Centrifugation-therapeutic plasma exchange

Centrifugation separates the whole blood into various components according to their specific gravity. The most important factor influencing clearance with centrifugation is the total volume of plasma exchanged per session. In the treatment of a poisoned patient, the American Society for Apheresis guidelines recommend an exchange volume of one to two total plasma volumes per day until clinical symptoms have decreased and the release of toxin from tissues is no longer significant.<sup>[26]</sup> Poison clearance during these techniques cannot exceed 50 ml/min. Their role in the treatment of acute poisoning is only considered for tightly and/or highly protein-bound poisons (>95%) or poisons with MW over 50,000 Da such as monoclonal antibodies,<sup>[27]</sup> but even then, the benefit is debatable considering the complications of these techniques including bleeding, hypocalcemia, and hypersensitivity reactions. The clearance capacity of TPE is much lower than that of IHD, IHF, or HP.<sup>[28]</sup> There is some support for it in exposures to the mushroom *Amanita Phalloides*, thyroxine, vincristine, and cisplatin. It should only be considered when alternative ECTRs are useless or unavailable while taking into account its higher cost and complication rates.

## Peritoneal dialysis

The use of peritoneal dialysis (PD) is infrequent in poisoning, due to its limited clearance capacity. For example, clearances for theophylline are 10 ml/min with PD compared to 85 ml/min with IHD.<sup>[29]</sup>

## Exchange transfusion

In toxicology, exchange transfusion is seldom used but has been described in poisoning with xenobiotics highly bound

to erythrocytes such as cyclosporine or tacrolimus and to treat methemoglobinemia induced by a toxic exposure (e.g., propranolol, aniline, dapsone, and sodium nitrite). Exchange transfusion has the advantage of being simpler to use in infants and has been tried in that population for poisonings to salicylates, theophylline, and barbiturates.<sup>[30]</sup>

### Cerebrospinal fluid exchange

Cerebrospinal fluid (CSF) exchange is occasionally performed in patients with life-threatening neurological symptoms to certain poisons. The CSF is drained passively via a ventricular catheter and replaced by a sterile solution containing albumin and sodium chloride into the lumbar subarachnoid space.

### Extracorporeal life support

Extracorporeal life support includes extracorporeal membrane oxygenation (ECMO), emergency cardiopulmonary bypass, intraaortic balloon pumps, and left ventricular assist devices. ECMO is increasingly used as a bridge to recovery in clinically refractory patients with cardiovascular and/or pulmonary failure not responding to conventional medical therapies.<sup>[30]</sup> Extracorporeal liver-assist devices remain occasionally used to support liver function in poison-induced hepatotoxicity.<sup>[31]</sup>

## RISK ASSESSMENT OF PATIENTS AND CONSIDERATION OF EXTRACORPOREAL TREATMENT [TABLE 2]

The majority of poisoned patients who present to the emergency department are successfully treated only with supportive care and recover without any complication. ECTR is typically reserved for the small subset of patients who are likely to suffer life-threatening toxicity, prolonged admission in the intensive care unit with coma and mechanical ventilation (e.g., barbiturate overdose), a high likelihood of permanent disability (e.g., methanol overdose), or develop toxicity despite standard supportive measures. ECTR is usually not indicated if the poison has limited intrinsic toxicity and if the

**Table 2: Indications of extracorporeal treatment**

Exposure to the poison likely to cause serious morbidity and mortality
Poison toxicity unlikely to be prevented or reversed by an antidote
Poison toxicity unlikely to be minimized by treatments that prevent absorption and/or enhance elimination
Poison's endogenous clearance <4 ml/min/kg
Volume of distribution <1-2 L/kg

**Table 3: Extracorporeal treatment options**

>95% of poison is protein bound at current concentration - therapeutic plasma exchange
80%-95% of poison is protein bound - hemoperfusion
<80% of poison is protein bound
Poison's MW - 1500 Da - high-flux HD
Poison's MW - 15-20,000 Da - hemofiltration
Poison's MW - 20-50,000 Da - high cutoff/middle cutoff HD, hemofiltration
Poison's MW - >50,000 Da - therapeutic plasma exchange
MW: Molecular weight; HD: Hemodialysis

estimated threshold dose (in mg/kg) or plasma concentration is not associated with toxicity.<sup>[32]</sup> Apart from antidotes which can prevent, limit, or reverse toxicity, several therapies may either prevent absorption (gastric emptying, activated charcoal, or whole-bowel irrigation) or enhance elimination (multiple dose-activated charcoal or urinary alkalization). When these alternative treatments are either not available or unlikely to be sufficient, timely consideration for ECTR is indicated if the poison is considered dialyzable.

## CHARACTERISTICS OF POISONS TREATED WITH EXTRACORPOREAL TREATMENT [TABLE 3]

Dialysability of a poison depends on its physicochemical and toxicokinetic properties. The primary determinants of poison removal by ECTR are the MW, the volume of distribution (VD), hydrophilicity and lipophilicity, protein and tissue binding, and endogenous clearance. The low MW poisons are easily dialyzable. High-efficiency high-flux dialyzers with diffusive modalities are capable of clearing poisons in the middle MW range (< 15,000 Da). Convective modalities such as HF and HDF allow clearance of solutes approaching 25,000 Da. New HCO and middle-cutoff membranes may remove poisons up to 50,000 Da.<sup>[33,34]</sup> ECTR only clears poisons from the intravascular compartment, so poisons exhibiting a smaller VD (<1 L/kg) are easily removed by ECTR. Early preemptive initiation of ECTR during the absorption and distribution phases may promote the removal of a significant amount of poisons with a large VD. Hydrophilic poisons distribute primarily in total body water, exhibit a smaller VD, and are more readily removed by ECTR, whereas lipophilic poisons distribute throughout extravascular tissues, especially adipose tissue, leading to a large VD. The degree of plasma protein and tissue binding of a poison is inversely related to its extracorporeal clearance because only unbound poison (free fraction) is removed by most ECTRs. Poisons that are >80% protein bound are poorly removed by hemodialysis. Some drugs (salicylates and valproic acid) have high protein-binding ability at therapeutic concentrations but saturate at high plasma concentrations, increasing the free concentration and rendering them more easily removed by ECTR.<sup>[35]</sup> If endogenous clearance is high, then an ECTR is unlikely to benefit unless there is impaired kidney function.<sup>[36]</sup> Indications other than poison removal (e.g., acute kidney injury or acidemia) may be the reason for ECTR.<sup>[37,38]</sup>

## DIALYSIS PRESCRIPTIONS TO MAXIMIZE CLEARANCE [TABLE 1]

As earlier explained, the dialysis prescriptions to maximize extracorporeal elimination are higher blood flow, higher dialysate flow, higher ultrafiltration rate, postfilter replacement with HF, larger filter or kidney (surface area and flux), and longer duration.<sup>[39]</sup> The solute clearance cannot exceed the lowest flow rate i.e. plasma flow rate in case of hemodialysis and effluent flow rate in case of CRRT. An increase in effective

flow rates and/or filter size will produce an approximately proportional increase in solute clearance at lower flows, but there is a smaller incremental increase in clearance at higher flows with diffusion than with convection techniques.<sup>[39]</sup>

**What to be monitored during extracorporeal treatment for the poisoned patient?**

Initiation of an ECTR during the absorption phase is beneficial because a larger proportion of the poison in the intravascular compartment is available for removal by ECTR during this time. The duration of ECTR should be tailored to the clinical situation, so the “routine” 4-h treatment reserved for patients with ESKD should be challenged in the treatment of a poisoned patient. Treatment duration can be increased for >10 h, as needed, for example, with dabigatran, ethylene glycol, and methanol poisoning. A precise estimate of the duration of ECTR to achieve a target concentration is possible when the elimination half-life is calculated using serial plasma concentrations obtained during treatment, allowing for individualized decision-making like in ethylene glycol and other poisons.<sup>[40]</sup> A rebound in the plasma concentration may be anticipated after completion of the ECTR, particularly in the case of hydrophilic drugs taken for chronic therapy, such as dabigatran and lithium toxicity.<sup>[41,42]</sup> However, rebound that occurs from ongoing absorption can produce much higher concentrations, resulting in clinical toxicity. The typical dialysis solutions containing high bicarbonate, low potassium, and absent phosphate concentrations, which may be harmful, particularly with prolonged treatments and poisoned patients, may even require supplemental electrolytes, such as phosphate. Anticoagulation should be decided with caution because some poisons are associated with an increased risk of bleeding—for example, methanol-associated intracerebral hemorrhage or poisons inducing systemic anticoagulation. In both cases, regional citrate or anticoagulant-free strategies are preferred. Predilution IHDF can be performed without anticoagulation, whereas postdilution IHDF usually requires anticoagulation because of increased viscosity of blood in the hemofilter.

**Extracorporeal treatment in poisoning workgroup**

A group of experts in 2010 met to discuss the terms of reference to develop guidelines on the use of ECTR in severe poisoning based on systematic reviews of the literature combined with multidisciplinary expert consensus.<sup>[3]</sup> This workgroup reviewed several poisons and provided recommendations that include specific indications for ECTR [Table 4]. The intent of the ECTR may be considered either as “therapeutic” as in lithium-induced neurotoxicity or “prophylactic” as in high salicylate concentration in a minimally symptomatic patient.

Recommendations for salicylates, lithium, theophylline, valproate, or thallium provide indications for ECTR based on specific cutoff plasma concentrations irrespective of the signs or symptoms.<sup>[43]</sup> ECTR mainly reduces the overall cost of antidote therapy and length of hospital stay in the case of early methanol poisoning prior to the development of acidosis. The workgroup also provided criteria for ECTR cessation, which usually depends on a noticeable clinical improvement of toxic symptoms, targets of surrogate parameters of toxicity (e.g., pH or lactate), or a specific poison concentration below which toxicity is no longer expected. Other recommendations include the preferred type of ECTR for every reviewed poison (favoring intermittent HD in all circumstances) and specific miscellaneous recommendations regarding anticoagulation, special populations, and antidotal dose. The executive summaries of all EXTRIP recommendations are published at <http://www.extrip-workgroup.org/recommendations>. For tricyclic antidepressants and digoxin, the adverse effects of ECTR outweigh any potential benefit of ECTR, and thus the recommendations are not to perform ECTR.<sup>[44,45]</sup>

**MANAGEMENT OF ACUTE POISONING WITH SOME SELECTED AGENTS AND PREFERRED EXTRACORPOREAL TREATMENT TECHNIQUES [TABLE 5]**

Acute poisoning with any agents require initial stabilization of patients, administration of agent-specific antidotes if available, and ECRTs if indicated as mentioned in detail earlier. In poisoning with acetaminophen, activated charcoal should be given to patients presenting within 4 h of ingestion. N-acetylcysteine (NAC) orally or intravenously (IV) should be given if the likelihood of toxicity is high or serum acetaminophen levels are above 150 mg/L. Although acetaminophen is easily removed by dialysis or hemoperfusion, NAC remains the treatment of choice. Aspirin is well removed by hemodialysis due to its low VD. In barbiturates, poison removal with hemodialysis using a synthetic membrane dialysis equals that of hemoperfusion and should be contemplated in case of prolonged coma in spite of activated charcoal and urinary alkalinization.<sup>[46]</sup> In the case of paraquat poisoning, survival depends on the amount ingested and plasma level with respect to the time of ingestion. Plasma level above 3 mg/L is usually fatal regardless of when it is measured.<sup>[47]</sup> Repeated or continuous hemoperfusion may be needed. Hemodialysis should be used in the first 24 h after poisoning. Use of antioxidants is investigational.<sup>[48]</sup>

Lithium (Li) is very well removed by hemodialysis. Hemodialysis should be considered when serum lithium level is >3.5 mmol/L, serum Li is >2.5 mmol/L in patients

**Table 4: Level of recommendations as reviewed by Extracorporeal treatment in poisoning (EXTRIP) workgroup**

Recommendation against	Neutral	Suggestion for	Recommendation for
Digoxin, tricyclic antidepressant	Phenytoin	Acetaminophen Carbamazepine	Barbiturates, lithium, methanol, metformin, salicylates, thallium, theophylline, valproate

**Table 5: Management of acute poisoning with some selected agents**

Agents	Initial management	Preferred technique/ recommendations	Remarks
Acetaminophen (MW 151 Da)	N-Acetylcysteine therapy. Can be recommended even after 24 h	HD or hemoperfusion	Moderately water soluble and minimally protein bound
Aspirin (MW 180 Da)	MDAC. Urine alkalinization	HD when serum level >90 mg/dl or there is evidence of acidemia, neurological involvement, or noncardiogenic pulmonary edema	VD of only 0.15 L/kg. The drug is about 50% protein bound
Digoxin (MW 781 Da)	Correction of dyselectrolytemia, alkalosis, and oral activated charcoal administration	Hemoperfusion or plasmapheresis. In dialysis patients - Fab therapy	VD of digoxin is large (8 L/kg) and the drug is 25% protein bound. Only 5% of body load is removed by HD
Lithium carbonate (MW 7 Da)	Prompt rehydration. Stop diuretics. Sodium polystyrene sulphonate	HD with high-clearance dialyzer for 8-12 h as lithium may rebound. Prolonged continuous hemodiafiltration reduces rebound of lithium posttreatment	0% protein bound with VD of 0.8 L/kg. Repeated dialysis may be needed until serum Li levels remain below 1.0 mmol/L for 6-8 h after dialysis
Paraquat (MW 257 Da)	Gastric lavage-activated charcoal or Fuller's earth with cathartic	Hemoperfusion	Repeated or continuous hemoperfusion to maintain plasma levels <0.1 mg/L. Large VD and slow intercompartmental transfer rate
Beta-blocker	Beta-agonist, high-dose glucagon	Consider HD or hemoperfusion only when treatment with glucagon and other pharmacotherapy fails	Nadolol, sotalol, and atenolol are removed by HD. Acebutolol is dialyzable. Propranolol, metoprolol, and timolol are not removed by HD
Barbiturates (MW 232 Da)	MDAC, urine alkalinization	HD or hemoperfusion	Phenobarbital is 50% protein bound, but VD is only 0.5 L/kg
Ethylene glycol (MW 62 Da)	Management of acidosis with soda bicarbonate. Antidote - ethanol or fomepizole. Judicious intravenous fluids, pyridoxine, thiamine	HD	HD until acidosis has resolved and level <20 mg/dl. Repeat dialysis may be needed due to rebound elevation due to redistribution
Methanol (MW 32 Da)	Sodabarbonate. Antidote - ethanol or fomepizole	HD	HD will be continued until the acid is corrected and serum methanol <20 mg/dl
Isopropanol (MW 60 Da)	Correction of hypotension and hypoglycemia	HD if isopropanol level >40 mg/dl, neurological depression, renal failure, or hypotension	High serum osmolal gap without acidosis in association with increased urinary or serum acetone level is highly suggestive of isopropanol poisoning
Mushroom poisoning	Activated charcoal, silibinin, referral to a poison center/liver transplant center	HD or hemoperfusion - some survival benefits	Plasmapheresis - experimental treatment option
Tricyclic antidepressants/ phenothiazines	Supportive treatment including bicarbonate treatment	HD or hemoperfusion	Large VD and highly protein bound. So, the total amount removed by HD/hemoperfusion is very small
Phenytoin	Stop the drug	HD or hemoperfusion	90% protein bound and VD of 0.64 L/kg. Despite high protein binding, it is removed moderately well by HD/hemoperfusion
Sodium valproate (MW 166 Da)	Stop the drug	High-flux HD with or without hemoperfusion	Small VD, metabolized by the liver and has significant protein binding
Carbamazepine (MW 180 Da)	Stop the drug	Hemoperfusion for severe intoxication	High-flux HD reported having good results
Dabigatran	Stop the drug	HD Continuous venovenous hemodiafiltration may be useful in severe cases	HD kinetics seem to follow first-order elimination during dialysis

MDAC: Multiple dose-activated charcoal; MW: Molecular weight; HD: Hemodialysis; VD: Volume of distribution

with symptoms or with renal insufficiency, or when levels are expected to rise following recent massive ingestion. Due to rebound following hemodialysis, repeated dialysis sessions

may be required until serum Li levels remain below 1.0 mmol/L for 6–8 h after dialysis.<sup>[49]</sup> Hemodialysis has a minimal role in the treatment of beta-blocker overdose and is effective only

with hydrophilic, minimally protein-bound beta-blockers such as atenolol.<sup>[50]</sup> Nadolol, sotalol, acebutolol, and atenolol are reportedly removed by hemodialysis, but drugs such as propranolol, metoprolol, and timolol are not. CRRT can be used if the patient is unable to tolerate traditional hemodialysis due to pronounced hypotension.

In severe ethylene glycol or methanol poisoning, hemodialysis should be initiated as early as possible if any one of the following is present: severe acidosis (pH < 7.25–7.30), renal failure, visual signs or symptoms, deteriorating vital signs despite intensive support care, or ethylene glycol or methanol levels >50 mg/dl unless fomepizole is being administered and the patient is asymptomatic with a normal pH.<sup>[51,52]</sup> Theophylline is well adsorbed by charcoal and so activated charcoal should be used in significant poisoning even with IV theophylline overdose. Hemoperfusion or high-efficiency hemodialysis is indicated if vomiting prevents the use of activated charcoal, or it can be used in addition in patients with seizures, hypotension, or arrhythmia. In acute intoxication with levels above 100 mg/L and chronic toxicity with levels above 60 mg/L, hemodialysis/hemoperfusion should be considered.<sup>[53]</sup> Simultaneous hemodialysis and charcoal hemoperfusion should be considered in cases of extreme theophylline intoxication.<sup>[54]</sup> Preferred ECTRs and initial management in case of poisoning due to some important selected agents are as summarized in Table 5.

## CONCLUSION

Poisoning is a medical emergency and, in severe cases, extracorporeal treatments may be urgently required to prevent or reverse major toxicity. The different options include IHD, intermittent HF, HDF, CRRT, hemoperfusion, TPE, exchange transfusion, and PD. Characteristics of poison and different modalities of ECTRs may differ. EXTRIP recommendations are based on low-quality evidence but are the best guidance till now. With high-quality data, evolving epidemiology, and newer treatments, the existing recommendations may evolve.

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