Use of extracorporeal treatments in the management of poisonings

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Historically, the clinical application of extracorporeal treatments (ECTRs), such as hemodialysis or hemoperfusion, was first intended for poisoned patients. With time, ECTRs were used almost indiscriminately to facilitate the elimination of many poisons, albeit with uncertain clinical benefit. To determine the precise role of ECTRs in poisoning situations, multiple variables need to be considered including a careful risk assessment, the poison's characteristics including toxicokinetics, alternative treatments, the patient's clinical status, and intricacies of available ECTRs, all of which are reviewed in this article. Recently, evidence-based and expert opinion-based recommendations from the EXTRIP workgroup were also published to help minimize the knowledge gap in this area.

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The use of hemodialysis for enhancing the elimination of exogenous poisons predates its use for end-stage kidney disease (ESKD) by many decades (Here, the general term *poison* refers to any medicine, drug, natural toxin, or other potentially toxic substance that may induce illness following poisoning regardless of the intention.).

In fact, the first successful *in vivo* experiment with hemodialysis was carried out in 1913 and demonstrated removal of salicylates from poisoned animals.[1] Yet, more than 100 years later, the application of extracorporeal treatment (ECTR) in the management of poisoned patients remains a topic of controversy, uncertainty, and debate. Recently, a multidisciplinary and multinational collaborative known as EXTRIP (EXtracorporeal TReatment In Poisoning) aimed to clarify the role of ECTRs in clinical practice through the development of evidence- and expert opinion–based recommendations.[2] This article will review both the theoretical rationale of ECTRs and their practical application in the management of the poisoned patient.

Approach for the consideration of ECTR

Clinical toxicity results from a complex interplay of factors that include a poison's intrinsic properties, dose, formulation, route of administration, and the presence of co-ingestants, as well as the underlying health of the patient. Despite the ubiquity of poisons, the vast majority of poisoned patients who present to a modern health care facility are successfully treated and recover without sequelae, having only received supportive care.[3]

ECTR is typically reserved for the small subset of patients who either are likely to suffer life-threatening toxicity (e.g., salicylate overdose), 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. The following discussion provides an approach to assess the potential usefulness of ECTR in a poisoned patient. This approach (Figure 1) should be used when evidence-based decision support (such as those developed by EXTRIP[4]) are lacking.

Risk assessment and alternate therapies

The risk assessment attempts to estimate the likelihood of significant sequelae after a specific exposure. If the identified

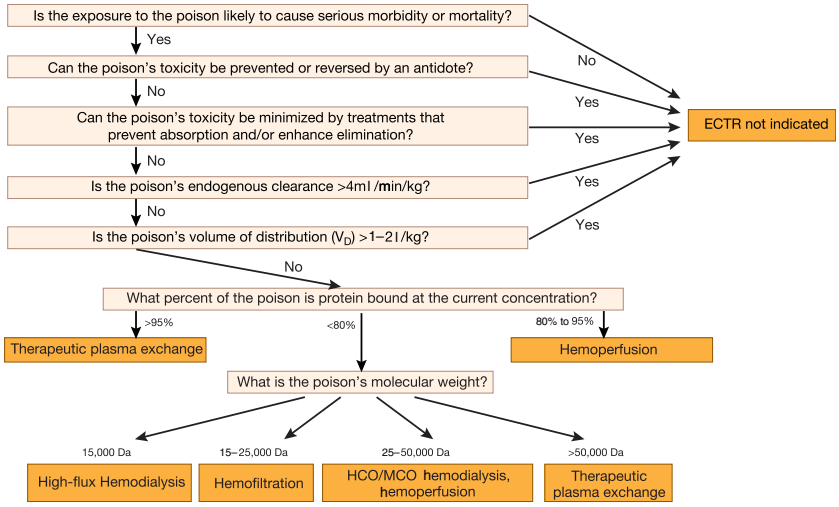

Figure 1 | An overall clinical approach for the consideration of an extracorporeal treatment for the management of a generic poison. HCO, high-cutoff membrane; MCO, middle-cutoff membrane.

poison has limited intrinsic toxicity and if the estimated threshold dose (in mg/kg) or plasma concentration is not associated with toxicity, ECTR is usually not indicated. When the actual poison concentration cannot be readily measured, the maximum possible concentration can be approximated from the following equation:

$$\text{Concentration} = \text{bioavailable dose}/(\text{volume of distribution} \times \text{body weight in kg})$$

The applicability of this estimation is limited by many toxicokinetic factors such as unpredictable bioavailability in overdose and a changing volume of distribution at high concentration (e.g., salicylates).

The next step is to evaluate whether alternative modalities to prevent, limit, or reverse toxicity are available, such as antidotes. For example, sulfonylureas can cause lethal hypoglycemia, but the use of ECTR is unnecessary given the relative efficacy, ease, safety, and cost-effectiveness of dextrose and octreotide administration. A similar argument can be constructed regarding the use of naloxone in opioid overdoses. Likewise, for most patients with acetaminophen (paracetamol) poisonings, acetylcysteine is highly cost-effective at preventing or mitigating toxicity, making ECTR unnecessary, except in rare cases of massive ingestions with acidemia due to mitochondrial toxicity when the efficacy of acetylcysteine is reduced.[5]

In addition to antidotes, several therapies may either prevent absorption (gastric emptying, activated charcoal, or whole bowel irrigation) or enhance elimination (multiple dose activated charcoal or urinary alkalinization). When used appropriately, these techniques slow the progression of toxicity thereby negating requirements for ECTR. Further discussion regarding techniques for decontamination and enhanced elimination are beyond the scope of this work, so the reader is referred to standard reviews.[6,7]

When the patient has either developed life-threatening manifestations of poisoning or appears likely to do so, and alternative treatments are either not available or unlikely to be sufficient, timely consideration for ECTR is indicated if the poison is considered dialyzable (Figure 1).

Characteristics of poisons amenable to ECTR

The physicochemical and toxicokinetic properties of a poison predict whether it is "dialyzable", or able to be cleared from the plasma by an extracorporeal device. Perhaps more importantly, these properties predict the extent to which ECTR enhances total body clearance, thereby lowering the total body load faster than without the treatment. The primary determinants of poison removal by ECTR are the molecular weight (MW), volume of distribution (V_D), hydro- and lipophilicity, protein and tissue binding, and endogenous clearance.

The lower the MW the more likely that a poison is dialyzable. Contemporary high-efficiency high-flux dialyzers with diffusive modalities are capable of clearing poisons in the middle MW range ($< \cong$ 15,000 Da). Convective modalities such as hemofiltration and hemodiafiltration can permit clearance of solutes approaching 25,000 Da. New high-cutoff and middle-cutoff membranes may remove poisons up to 50,000 Da, although data are limited and the membranes' availability restricted.[8,9]

Perhaps the most important determinant of effective removal by ECTR is the poison's V_D. The V_D relates the amount of poison in the body to the concentration in plasma or blood. Because ECTR only clears poisons from the intravascular compartment, poisons exhibiting a smaller V_D (<1 L/kg) are more amenable to removal by ECTR.[10] The larger the V_D, the greater the fraction of poison located in extravascular tissues and thus not exposed to the extracorporeal filter.[11] Importantly, even if the poison could be cleared from the plasma by an extracorporeal device, if the poison exhibits

a large V_D (>2 L/kg), then overall removal by ECTR will be low. These considerations particularly apply to cases in which the poison has already been absorbed and distributed. However, it is conceivable that early pre-emptive initiation of ECTR during the absorption and distribution phase may promote the removal of a significant amount of poisons with a large V_D, although the extent to which this occurs is poorly defined.

Hydrophilic poisons distribute primarily in total body water, exhibit a smaller V_D, and are more readily removed by ECTR, whereas lipophilic poisons distribute throughout extravascular tissues, especially adipose tissue, leading to a large V_D.

The degree of plasma protein and tissue binding of a poison inversely relates to its extracorporeal clearance because only unbound poison (free fraction) is removed by most ECTRs. A poison-protein complex may exceed 65,000 Da and is too large to be filtered. In general, poisons that are >80% protein bound are poorly removed by hemodialysis. It is important to note that for some drugs (notably salicylates and valproic acid) protein binding is "high" at therapeutic concentrations, but saturates at high plasma concentrations, increasing the free concentration and rendering them more amenable to removal by ECTR.[12,13]

A final important consideration is the patient's underlying endogenous (systemic) poison clearance, which is the sum of renal and non-renal clearance. If endogenous clearance is high, then an ECTR is unlikely to significantly increase total clearance enough to justify its use.[2,11] For example, endogenous metformin clearance, in the setting of normal kidney function, is 600 ml/min, which far exceeds the clearance achieved by HD (240 ml/min). As such, ECTR is usually not recommended for enhanced elimination in metformin overdose unless there is impaired kidney function;[14] however, in cases of acute kidney injury, then even modest metformin removal by ECTR is potentially beneficial.

With these considerations, only a small number of poisons are considered amenable to ECTR removal. Table 1 presents some of these, as reported by US poison control centers (2010–2014), although the reason for ECTR may have been for indications other than poison removal (e.g., acute kidney injury or acidemia).[15,16]

Table 1 | Number of ECTRs performed in the US, 2010–2014

Poison	Number of ECTRs performed
Ethylene glycol	2072
Lithium	1924
Salicylate	1520
Acetaminophen	959
Ethanol	423
Methanol	345
Metformin	319
Benzodiazepines	308
Cardiac glycosides	260
Calcium channel blockers	205
Valproic acid	183
Beta adrenergic antagonists	134
Atypical antipsychotics	130
Methadone	97
Oxycodone	86
NSAIDs	81
Tricyclic antidepressants	69
Cocaine	68
Heroin	67
Isopropanol	62

ECTR, extracorporeal treatment.

ECTR selection in the treatment of poisoning

ECTRs are classified according to their mechanism: diffusion (hemodialysis and peritoneal dialysis), convection (hemofiltration), adsorption (hemoperfusion), and centrifugation (therapeutic plasma exchange).[17,18] Each modality has potentially differing impacts on enhancing the elimination of a poison from the body.

Intermittent hemodialysis. During intermittent hemodialysis (HD), the poison diffuses down the concentration gradient from the plasma through a semipermeable membrane to a countercurrent dialysate. HD has several distinct advantages over other ECTRs: it removes poisons rapidly due to the high blood and dialysate flows, and it simultaneously corrects other derangements such as uremia and acid-base and electrolyte abnormalities.[19] HD is the most available ECTR, the least expensive, and the quickest to implement.[20] For these reasons, HD remains the preferred modality for the majority of poisonings. This is reflected by current practice trends[15,21,22] (Figure 2) and EXTRIP recommendations.[5,14,23–33]

Hemoperfusion. During hemoperfusion (HP), whole blood passes through a charcoal-coated cartridge (resin cartridges are no longer used in many countries) onto which the poison can be adsorbed.[34] Compared with diffusion, adsorption is less limited by MW or protein binding. However, HP requires greater systemic anticoagulation than do other ECTRs, and prescribed blood flow must not exceed 350 ml/min to avoid the risk of hemolysis.[35] HP also nonselectively adsorbs platelets, white blood cells, calcium, and

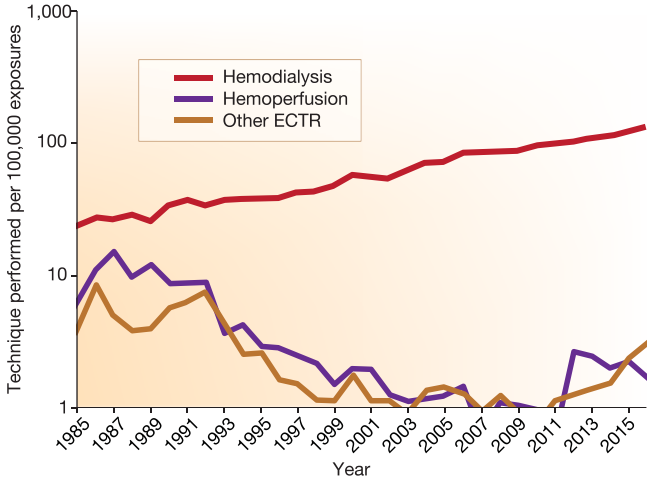

Figure 2 | US poison center trends in the use of hemodialysis, hemoperfusion, and other extracorporeal treatments.

glucose.[36,37] Further, a charcoal cartridge costs 10 times more than a high-efficiency dialyzer,[20] does not bind all poisons (e.g., alcohols and certain metals),[38] and needs to be replaced every 2 hours because of cartridge saturation, which decreases poison clearance.[39,40]

Hemofiltration. During hemofiltration (HF), poison and solvent are simultaneously removed by convection and replaced by a physiological solution. Factors that govern poison elimination by HF are similar to those described for diffusion, although convection allows removal of poisons as large as 25,000 Da.[18] Because the large majority of known poisons have a low MW (<2,000 Da), HF would not seem to offer an advantage over HD in the majority of poisonings.

Continuous renal replacement therapy. 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. However, poison clearance with CRRT is 50% to 80% less than that obtained with intermittent modalities because of lower blood and/or effluent flow rates.[14,24,32] Additionally, net fluid removal is rarely required in poisonings. For these reasons, intermittent modalities are favored, although some clinicians use CRRT following an HD session to minimize a re-increase in poison concentration, or rebound, although the advantages of this practice are debatable (see below).

Therapeutic plasma exchange and plasmapheresis. These techniques involve separation of plasma from blood cells that is either (i) filtrated or (ii) discarded and replaced by a physiological solution. Poison clearance during these techniques cannot exceed 50 ml/min.[17,41] 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,[42] but even then the benefit is debatable considering complications of these techniques including bleeding, hypocalcemia, and hypersensitivity reactions.[43,44]

Others. Several other ECTRs may enhance the elimination of poisons, such as peritoneal dialysis and exchange transfusion. Because they do not require an extracorporeal circuit, they have been used in resource-limited settings and may also be easier to perform in neonates. However, poison clearance is barely one-tenth that achieved with HD.[17] There are several reports of extracorporeal liver-assist devices for removal of protein-bound poisons,[45–47] although achievable clearance is usually inferior to the less costly and more available ECTRs mentioned above. Extracorporeal liver-assist devices remain occasionally used to support liver function in poison-induced hepatotoxicity.[48–51]

Practical factors may alter the preference for a specific ECTR; for example, if nursing or organizational constraints only permit the initiation of CRRT, it may be preferable to initiate this lower-efficiency technique in-center rather than initiate a lingering transfer to a center that provides intermittent HD.

Figure 3 shows a graphical illustration of the effect of various ECTRs on time to achieve a safe concentration in a methanol-poisoned patient; the superiority of intermittent HD over other ECTRs is apparent.

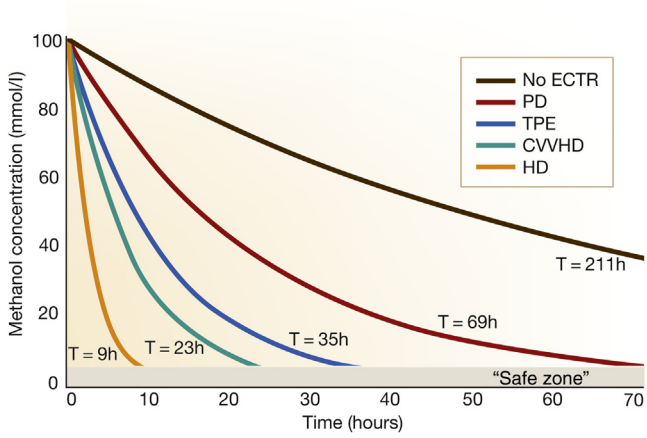

Figure 3 | Simulation of the effect of different extracorporeal treatments for methanol poisoning. Theoretical model of a methanol-poisoned patient with an initial concentration of 100 mmol/l (320 mg/dl) treated with fomepizole and either nothing, hemodialysis (HD), continuous venovenous hemodialysis (CVVHD), therapeutic plasma exchange (TPE), or peritoneal dialysis (PD). The time (T) to achieve a safe plasma concentration is shown. Assumptions are V_D = 0.6 l/kg, weight = 70 kg, endogenous body clearance of methanol with fomepizole = 10 ml/min, HD methanol clearance = 240 ml/min, CVVHD methanol clearance = 80 ml/min, TPE methanol clearance = 50 ml/min, and PD methanol clearance = 20 ml/min.[32]

Operational parameters to maximize poison clearance

The following operational parameters maximize extracorporeal elimination: higher blood flow, higher dialysate flow, higher ultrafiltration rate, post-filter replacement with hemofiltration, larger filter or kidney (surface area and flux), and longer duration.[18] The clearance cannot exceed the lowest flow rate, which for hemodialysis is plasma flow and for CRRT is effluent flow. These relationships are well-described in the nephrology literature, and there are increasing data confirming this in toxicology, including methanol[52] and dabigatran.[53]

An increase in effective flow rates (in the absence of recirculation, for example due to catheter type or placement) 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.[18] So, although newer technology permits higher flow rates, clinical and pharmacokinetic benefits may not be marked in poisoning.

Prescribing ECTR for the poisoned patient

Prompt initiation of an ECTR during the absorption phase, which in the case of acute poisonings can persist for 4 or more hours,[11] is probably beneficial. This is because a higher proportion of the poison is in the intravascular compartment and thus available for removal by ECTR during this time.

In the acutely poisoned patient, the femoral site is often preferred because a confirmatory radiograph is not required, and therefore allows earlier initiation of ECTR. The higher rate of infectious complications attributed to femoral catheters may not apply to poisoning situations in which ECTR is rarely performed for more than 1 to 3 days.[54]

The duration of ECTR should be tailored to the clinical situation, rather than the usual generic 3 to 4 hours used for maintenance dialysis. Poisoned patients are at low risk of dialysis disequilibrium, and treatments can be easily prolonged for >10 hours, as needed, for example, with dabigatran,[53] ethylene glycol,[55] and methanol.[52]

In the case of enhanced elimination, duration depends on the apparent half-life achieved by ECTR. This may be based on previous data, such as for ethylene glycol poisoning, in which a single concentration predicts the duration of hemodialysis if performed according to certain operational parameters.[55] A more 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. This was reported for ethylene glycol[56] and other poisons.[11] However, a rebound in the plasma concentration may be anticipated to occur after completion of the ECTR, particularly in the case of hydrophilic drugs taken for chronic therapy, such as dabigatran[53] and lithium,[57] due to extensive extravascular distribution when the rate of drug redistribution is slower than the rate of removal by ECTR. This form of rebound usually increases the plasma concentration by less than 25% following the first ECTR, and for poisons with an extravascular mechanism of toxicity (e.g., lithium), rebound rarely contributes to a decline in clinical status.[58] In contrast, rebound that occurs from ongoing absorption can produce much higher concentrations, result in clinical toxicity, and may require additional ECTR sessions.

Further, poisoned patients do not commonly experience the same metabolic derangements as those with ESKD or acute kidney injury. In these cases, the typical dialysis solutions containing high-bicarbonate, low-potassium, and absent phosphate concentrations may cause harm, particularly with prolonged treatments. Poisoned patients may even require supplemental electrolytes, such as phosphate.[59]

The method of anticoagulation should be decided in view of the exposure, because some poisons are associated with an increased risk of bleeding—for example, methanol-associated intracerebral hemorrhage[32] or poisons inducing systemic anticoagulation.[53] In both cases, regional citrate or anticoagulant-free maneuvers are preferred.

EXTRIP

In 2010, a group of experts met to discuss the terms of reference for what evolved to become the EXTRIP workgroup. A novel methodology was established to develop rigorous and transparent guidelines on the use of ECTR in severe poisoning based on systematic reviews of the literature combined with multidisciplinary expert consensus.[2]

The current body of evidence. Similar to other treatments that were grandfathered prior to the requirement for quality data confirming the effect for an intervention, the scientific evidence showing a clinical benefit from ECTRs in poisoned patients is incomplete: among the 8000 articles identified in the MEDLINE database during the first round of the EXTRIP process, 2 poorly designed controlled trials were identified.[60,61] Observational studies were also exceedingly rare[62–64] and have inherent limitations, especially confounding-by-indication, in which the severity of disease confounds the treatment-outcome relationship. Less than 2% were *in vitro* or animal experiments, which have uncertain generalizability to humans. The remainder of the literature consisted of case reports or case series, which represent a very low quality of evidence.

Given the widely accepted role of ECTR for several types of poisonings, the absence of clinical equipoise in most cases would render the sanction of a placebo-controlled trial from ethics committees highly unlikely. Fortunately, several reports provided detailed, generalizable, and reliable information on toxicokinetics. Because the body burden of poison or its concentration can often be related to clinical outcomes, it is expected (but not assured) that surrogate toxicokinetic endpoints such as changes in poison concentration, half-lives, clearances, and amount removed can predict improvement in clinical outcomes. Caution is needed to assess the quality of a toxicokinetic report because of various pitfalls in the interpretation of data: for example, a decreasing poison concentration may be an unreliable observation if this can be attributed to distribution rather than clearance (extracorporeal and/or endogenous).[11,65] Criteria to guide the writing of a case report[66] and tools to quantify and assess toxicokinetic data[2] now exist.

Recommendations. The EXTRIP workgroup reviewed several poisons and provided recommendations that include specific indications for ECTR. In summary, the intent of the ECTR may be considered either as "therapeutic" (i.e., performed to reverse or mitigate established clinical toxicity as in, for instance, lithium-induced neurotoxicity) or "prophylactic" (i.e., performed prior to the development of expected toxicity if left untreated, as in, for instance, high salicylate concentration in a minimally symptomatic patient). In one such example, a prospective study showed that in patients exposed to toxic concentrations of theophylline, the group who received ECTR prophylactically had a significantly better outcome than did those who only received ECTR after the appearance of symptoms.[67] As such, recommendations for salicylates, lithium, theophylline, valproate, or thallium provide indications for ECTR based on specific cut-off plasma concentrations irrespective of signs or symptoms.[25,26,29,32] In the case of early methanol poisoning (prior to the development of acidosis), ECTR mainly reduces the overall cost of antidote therapy and length of hospital stay.

EXTRIP also provided criteria for ECTR cessation, which usually depends on a noticeable clinical improvement of toxic symptoms, targets of surrogate parameters of toxicity

Table 2 | Level of recommendation for ECTR according to the poison, as reviewed by EXTRIP

Recommendation against	Suggestion against	Neutral	Suggestion for	Recommendation for
Tricyclic antidepressants		Phenytoin	Acetaminophen	Barbiturates
Digoxin			Carbamazepine	Lithium
				Methanol
				Metformin
				Salicylates
				Thallium
				Theophylline
				Valproate

ECTR, extracorporeal treatment.
Planned review has not yet been completed for *Amanita*, baclofen, bromates, chloroquine, dabigatran, dapsone, diethylene glycol, ethylene glycol, isoniazid, fluoride, isopropanol, methotrexate, organophosphate, paraquat, and quinine.

(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 dosage, as needed.

The executive summaries of all EXTRIP recommendations are published at http://www.extrip-workgroup.org/recommendations and summarized according the level of recommendation in Table 2. For tricyclic antidepressants and digoxin, the adverse effects of ECTR were considered to outweigh any potential benefit of ECTR, and thus the recommendations are indeed ***not to perform*** ECTR for the sole purpose of poison removal.[31,33]

Conclusion

The EXTRIP recommendations are not definitive due to the low quality of available data but are the best guidance to date. It is expected that with higher-quality data, evolving epidemiology, and new targeted treatments, existing recommendations may evolve. Therefore, all clinicians involved in the treatment of poisoned patients have a responsibility to accurately measure and report the effect of renal replacement therapies in acute poisoning.[66] Recent recommendations offer a reasonable framework to uniformize and elevate the standard of care of this critical aspect of poisoning management.

DISCLOSURE

All the authors declared no competing interests.

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