Seminars in Dialysis

BLOOD PURIFICATION IN POISONING

A Stepwise Approach for the Management of Poisoning with Extracorporeal Treatments

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ABSTRACT

The use of an extracorporeal treatment (ECTR) in a poisoned patient may be life-saving in a limited number of scenarios. The decision-processes surrounding the use of ECTR in poisoning is complex: most nephrologists are not trained to assess a poisoned patient while clinical toxicologists rarely prescribe ECTRs. Deciding on which ECTR is most appropriate for a poison requires a good understanding of the poison's physicochemical and pharmacokinetic properties. Further, a detailed understanding of the capabilities and limitations of the different ECTRs can be useful to select the most appropriate ECTR for a given clinical situation. This manuscript provides a stepwise approach to assess the usefulness of ECTRs in poisoning.

Background

Hemodialysis was invented 100 years ago when John J. Abel, Leonard G. Rowntree, and Benjamin B. Turner demonstrated the removal of salicylates from the plasma of animals (1). Although this discovery paved the way to the widespread use of hemodialysis in the treatment of uremia, its use in poisoned patients remained more limited and controversial. In 2012, 2414 extracorporeal treatments (ECTRs) were reported to the United States Poison Control Centers in the context of poisoning, hemodialysis being by far the most common modality used. Overall, ECTRs are currently employed in approximately 0.1% of all poisonings (2,3).

The use of ECTRs in poisoning is potentially complex: most nephrologists are not trained in clinical toxicology and do not necessarily have the experience to accurately assess a poisoned patient. Clinical toxicologists rarely prescribe ECTRs and may not be knowledgeable in the various intricacies of available ECTRs (e.g., hemodialysis, hemofiltration, hemoperfusion). Furthermore, for many nonnephrologists, ECTRs are often viewed as very invasive, costly, and associated with an unacceptable incidence of complications.

The EXtracorporeal TReatments In Poisoning (EXTRIP) workgroup is developing recommendations on the use of ECTR for at least 16 poisons (4,5). However, poisoning can occur following exposure to many other medicines and chemicals, and new ones are continuously being marketed and discovered. A working understanding of toxicokinetics and risk assessment may allow the clinician to estimate the usefulness of ECTR in various poisoning settings that are not necessarily covered by the immediate EXTRIP scope, even when the data are limited.

Risk Assessment

The immediate stabilization of a poisoned patient includes supporting the airway, breathing and circulation, consideration of gastrointestinal decontamination, and techniques to enhance poison elimination such as multiple doses of oral activated charcoal or urinary alkalinization. Other medical interventions that may be necessary include volume repletion, rewarming, and the treatment of seizures

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and arrhythmias. After the initial stabilization of a poisoned patient, a comprehensive risk assessment must be performed to determine whether or not to use ECTR and if so, which type.

Obviously, ECTR is not needed if the xenobiotic to which a patient was exposed has benign clinical consequences. Some xenobiotics have a large safety profile, such as water soluble vitamins, minerals, and dextrose. Various drugs, like benzodiazepines, antibiotics, and proton-pomp inhibitors are also considered relatively safe when taken in isolation, even after large ingestions, and rarely require active interventions aside from supportive care. For other drugs, inexpensive, safe, and effective antidotes (e.g., naloxone for opiate poisoning) obviate the need for ECTR.

Paracelsus introduced the concept of dose–response to toxicology (*"Solely the dose determines that a thing is not a poison")* more than 500 years ago. Knowledge of the dose–response relationship helps to predict what constitutes a toxic dose when determining which patients are at highest risk. For example, valproic acid ingestions over 400 mg/kg usually induce severe toxicity, while exposures below 100 mg/kg are rarely a cause for concern (6). In contrast, colchicine is more toxic such that in children, it is suggested that exposures below 0.5 mg/kg are associated with survival, whereas exposures above 0.8 mg/kg can be lethal (7), although several exceptions have been published (8). An acute acetaminophen ingestion below 150 mg/kg is not expected to cause toxicity, but the risk of hepatotoxicity increases in a dose-dependent manner with ingestions beyond this. Measurement of the serum concentration of the poison can predict delayed development of toxicity in an initially asymptomatic patient through the use of a nomogram, such as paraquat (9,10) and acetaminophen (11), to help triage those patients who may benefit the most from more advanced therapies.

A potentially toxic ingestion in an asymptomatic patient is rarely, by itself, an indication to perform extracorporeal elimination (although there are exceptions, such as a very recent exposure to paraquat). However, it may prompt early referral to a center that provides hemodialysis or hemoperfusion, if the poison is likely to be removed by these techniques (see below). Close communication with a poison center or a clinical toxicologist is recommended to help assess the risk for a given patient.

Evidence-Based Toxicology

The benefit of an intervention is best demonstrated by well-designed studies where the treatment group is compared to a control group. Unfortunately, randomized controlled trials in poisoned patients comparing ECTR to a control are absent in the Western literature, according to an extensive literature review performed by the EXTRIP workgroup (5). The difficulties of performing good quality studies in the field of ECTR for poisoning are numerous and already described elsewhere (4,12).

Human observational studies, which constitute a lower form of evidence (13), are also rare and often confounded by indication, i.e., the intervention group is often more clinically ill than the nontreated group. Here, the absence of an effect by ECTR could simply relate to differences in baseline characteristics in the two groups. Although this may cause studies to rarely demonstrate a benefit from ECTR, this is not always the case. For example, patients who underwent hemodialysis or hemoperfusion in acute theophylline poisoning had a more favorable outcome than those who did not receive any, despite showing more profound toxicity at baseline (14).

Nevertheless, in the absence of quality controlled studies, strong mechanistic hypotheses support the potential effect from ECTR at removing a clinically significant amount from the body and several animal studies have validated this hypothesis (15,16).

Expected Clinical Benefits from Extracorporeal Treatments

In order to decide whether blood purification is indicated for a specific poisoning, the clinician must anticipate what benefits are expected from the procedure. Some exposures can be lethal (e.g., massive salicylate ingestions, paraquat), while others may cause irreversible tissue damage (e.g., methanol-induced blindness). In the circumstance that ECTR is expected to prevent these severe outcomes, the advantages of ECTR would outweigh disadvantages such as cost and the potential for complications of the procedure. However, to be effective, the initiation of ECTR in these cases is time-critical.

An alternative circumstance is where treatment of the poisoning with supportive care and antidotes may prevent immediate death, but the patient is likely to experience prolonged admission in a critical care unit requiring mechanical ventilation. Such is the case for poisons causing central nervous system depression such as barbiturates and other anticonvulsants. Another example is administration of hemodialysis to patients with methanol poisoning without acidosis (17), where ECTR is not likely to affect morbidity or mortality. In both cases, ECTR has the potential to reduce hospitalization and associated costs, including duration of admission to the ICU (which is a limited and expensive resource), and limit complications associated with prolonged immobilization.

It is apparent that the indications for ECTR are less absolute in the latter examples than the former ones, and in each occasion, the clinician must anticipate what potential benefit will be derived from the procedure on a case-by-case basis.

Alternative Therapies

The pertinence of ECTR must be weighed against the availability and effect of alternative treatments. Antidotes are useful therapies that can rapidly counteract the toxic effect of a poison. Specific antidotes, like antibodies, are available to reverse the effects of certain snake/spider envenomation or drugs, like digoxin. However, an antidote's effect may be limited in some cases, so that addition of ECTR may have additional benefits. For example, although acetaminophen is readily cleared by hemodialysis, the antidote N-acetylcysteine has largely obviated the necessity of ECTR except in patients presenting early after a massive ingestion with signs of mitochondrial toxicity (coma, lactic acidosis) (18,19). Alternatively, some antidotes do not completely counteract all the toxic effects of a poison, so that ECTR may be an important adjunct to antidotal therapy, for example in isoniazid poisoning (20,21). Unfortunately, antidotes are limited in number and they can be costly, sometimes much more than ECTR.

Corporeal elimination techniques, including multiple-dose activated charcoal or urine alkalinization, enhance clearance of poisons and improve clinical outcome in selected cases (22–26). Poison clearance with these techniques can be substantial, although head-to-head comparisons with ECTR for poisons treated with MDAC, such as phenobarbital, salicylates, theophylline, and carbamazepine usually show a clearance advantage for ECTR (27–29). Corporeal techniques are usually less invasive, less expensive, and more widely available to clinicians in a timely manner. However, there are also complications associated with their use and they may be contraindicated in various settings (e.g., poison-induced ileus). In the appropriate clinical scenario, alternate treatments and ECTR can be combined and the benefit is potentially additive.

Extracorporeal Removal of Poisons: Toxicokinetic Considerations

In the absence of data confirming clinical benefit from ECTR, a proper evaluation of the physicochemical and toxicokinetic properties of a specific poison can guide decision-making. A basic understanding of the following 4 critical determinants will permit the clinician to determine whether ECTR may successfully enhance poison removal: (1) molecular weight, (2) protein binding, (3) endogenous clearance, and (4) volume of distribution (Table 1).

Molecular Weight

The molecular weight (MW) of a substance strongly influences its likelihood to be cleared by ECTR. Hemodialysis (HD), which is based on diffusion, is the modality with the greatest limitations based on MW. Historically, the first dialyzers cleared substances with MW up to 500 Da. However, newer more porous, high-flux synthetic dialyzers allow significant removal of larger molecules (30–33); for example, the clearance of vitamin B_{12} (MW = 1356) is increased more than 2–4 fold (31). The clearance of vancomycin (MW = 1448 Da) by HD was almost zero in the 1960s (34), but has increased to 55 ml/minute (35) in the 1980s, and then to 100–150 ml/minute today (36–38). Teicoplanin (MW = 1875 Da) can also now be readily removed by hemodialysis (39). Clearance of molecules over 5000 Da (like osteocalcin) was negligible with low-flux dialyzers but is considerable with newer filters (30). Even middle molecules with a size up to 10,000 Da, such as β2-microglobulin can be removed during HD treatment (30,31,40,41). Recently introduced high cut-off (HCO) dialyzers are even more porous (cut-off = 45,000 Da) and are currently being studied to remove light chains in multiple myeloma (42).

In comparison, hemofiltration (HF), which relies on convection, can clear molecules sized 40,000 Da or more (33,43–48). This is supported by the excellent removal of β2-microglobulin and myoglobin (MW = 17,000 Da), with reduction ratios above 60%(30,33,43,49,50). Even albumin loss (MW = 66,000 Da) occurs with some filters (51,52). The addition of diffusion to convection, named hemodiafiltration, does not alter the molecular cut-off of convection, when used alone. These principles of

TABLE 1. Pharmacokinetic properties of a poison to assess its potential for extracorporeal therapy removal

	HD	HF	HP	Albumin dialysis	PD	ET	TPE
Mechanism of removal	Diffusion	Convection	Adsorption	Diffusion/Convection	Diffusion	Separation	Centrifugation/ Separation/ Convection
MW cut-off	Low-flux: 1000 Da High-flux: 11,000 Da	40 000 Da with exceptions	5000–10,000 Da	MARS/SPAD: 60,000 Da, Prometheus: ≈100,000 Da	<500 Da	No restriction	1,300,000 Da
Protein binding	<80% with exceptions	<80% with exceptions	<90%	Likely high	Likely low	No restriction	No restriction
V_D	Low V_D, (<1–2 l/kg), with exceptions					Requires very low V_D	

HD: hemodialysis, HF: hemofiltration, HP: hemoperfusion, PD: peritoneal dialysis, ET: exchange transfusion, TPE: therapeutic plasma exchange, MW: molecular weight, MARS: molecular adsorbent recirculating system, SPAD: single pass albumin dialysis, V_D: volume of distribution.

diffusion and convection are equally valid whether hemodialysis/filtration is administered by continuous renal replacement therapies or intermittently (44–47,53–55).

For adsorptive based techniques, like hemoperfusion, the efficacy of the technique decreases when the MW is higher than 5000–10,000 Da (32,56,57). However, with albumin dialysis, greater thresholds are possible. For example, the molecular adsorbent recirculating system (MARS™) and single pass albumin dialysis (SPAD) can clear molecules up to 60,000 Da (58,59) while the Prometheus system has a cut-off of approximately 200,000 Da (40,60,61). The Albuflow filter used with Prometheus has a sieving coefficient of 1.0 for β-microglobulin, 0.6 for albumin, and 0.3 for molecules as large as 150,000 Da (40).

Therapeutic plasma exchange (TPE) and exchange transfusion have the least restrictions regarding size, as poisons in excess of 1,000,000 Da, including those entirely protein-bound, can readily be cleared with these techniques (62–68). Examples include rituximab (MW = 145,000) and immunoglobulins like IgM (MW = 925,000) (66,67,69,70).

Figure 1 depicts the range of MWs and degrees of protein binding for existing medicines. The preferred ECTR for the various medicines based on these properties is indicated. As illustrated, the great majority of poisons have a MW in the 100–1000 Da range, and are therefore amenable to removal by intermittent HD, assuming that protein binding, endogenous clearance and volume of distribution are not limiting (Fig. 1). For larger molecules, hemofiltration or TPE can be considered. Table 2 presents expected clearance for the most commonly used techniques in poisoning. As presented earlier, the maximal clearance in optimal situations are obtained by either HD, HF, or hemoperfusion (HP).

Protein Binding

Albumin is the most abundant protein in the blood and is responsible for the majority of nonspecific binding of drugs and poisons (71). Because the albumin-poison complex is large (>67,000 Da), it cannot diffuse across most dialysis filters and hemofilters (see above) (31). Only the free, unbound form of the poison in the plasma can be removed by either diffusive or convective techniques. For these reasons, poisons that have a protein binding (PB) of 80% or more are usually not considered amenable to removal by either HD or HF (72). There are several exceptions to this principle:

1. Some xenobiotics, such as salicylates, 4-chloro-2-methylphenoxyacetic acid, and valproic acid exhibit saturable binding in overdose (73–79). Here, the free fraction (that which is unbound to serum proteins) increases as their serum concentration rises, which potentially increases poisoning severity because the free fraction exerts toxicity; however, it also facilitates removal by ECTR (80). For example, salicylate's PB falls from 90% at therapeutic concentrations to 50% when it reaches 800 mg/l which is a level where significant symptoms might occur, and extracorporeal purification may be beneficial (81).
2. Some poisons show little to no saturable binding in overdose conditions, such as carbamazepine (PB = 75%) and phenytoin (PB = 90%). Despite this, reports show that they are relatively well eliminated by diffusive and convective techniques, especially with newer high-flux/high-efficiency filters (27,82–85). These observations suggest that the free (unbound) poison is continuously removed by ECTR, and it is also in rapid equilibrium with bound poison that quickly dissociates from albumin into the free form.

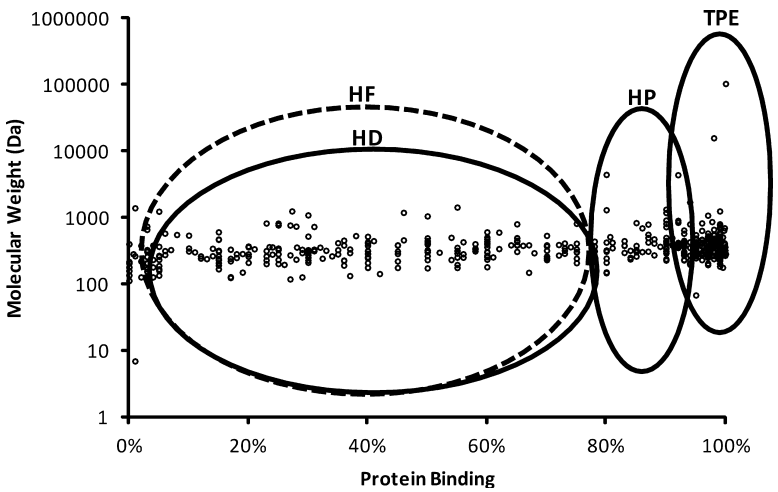

FIG. 1. Relationship between a drug's or poison's molecular weight and protein binding characteristics and the method of extracorporeal clearance that is anticipated to maximize clearance. Circles indicate for which poisons a specific ECTR is most useful. HD: Hemodialysis, HP: Hemoperfusion, HF: Hemofiltration, TPE: Therapeutic plasma exchange.

TABLE 2. Maximal clearance with any extracorporeal treatment.

ECTR	Conditions	Maximal clearance
Peritoneal dialysis	2L exchange every hour, 50% equilibration of dialysate compared to plasma	16 ml/minute
TPE	A Q_B = 140 ml/minute and a plasma removal rate 50 ml/minute	50 ml/minute
Intermittent HD/HF/HP	A Q_B = 400 ml/minute, hematocrit = 40%, extraction ratio = 100%	240 ml/minute
CRRT	A Q_B = 180 ml/minute, high volume CRRT (effluent flow = 45 ml/hour/kg), weight = 70 kg	52 ml/minute
Exchange transfusion	1L whole blood exchanged/hour, hematocrit = 40%	10 ml/minute

HD: hemodialysis, HF: hemofiltration, HP: hemoperfusion, CRRT: continuous renal replacement therapy, ECTR: extracorporeal treatment.

3. New dialyzers and hemofilters with higher MW cut-offs developed for specific clinical conditions, such as multiple myeloma, can remove poison-protein complexes. However, no data are presently available to review their role or efficacy in poisoning.

Adsorbent-based techniques (hemoperfusion) are considered more efficient for removing protein-poison complexes than HF or HD, because the adsorbent (either resin or charcoal) itself competes with albumin for binding. As long as PB remains under 90%, there will be no major limitation to HP removal (86). For highly bound poisons, clearance by HP is undoubtedly superior to conventional HD with low-flux dialyzers, although it remains disputed if this remains true for newer dialyzers. Poisons traditionally cleared by HP, like theophylline and carbamazepine, are now removed to a similar extent by modern dialyzers (87–89). Hemoperfusion is reviewed in more detail in the current issue of this Journal (90).

Albumin dialysis techniques, such as MARS and SPAD, also remove protein-bound poison indirectly via competitive binding to exogenous albumin in the enriched dialysate (60). In comparison, Prometheus can theoretically clear protein-bound poison directly, by eliminating the albumin-poison complex through a higher cut-off membrane (91). Evidence supporting the efficacy of albumin dialysis in removing highly protein-bound poisons is currently limited (92,93).

TPE and exchange transfusion are also capable of clearing albumin-poison complexes. Although the clearance attainable by plasma exchange is relatively low, in many cases, it is likely to be the only practical option for poisons that are over 90% bound to proteins (94), like cisplatin (62,95) and levothyroxine (68). Replacement fluid during TPE (e.g., albumin 5% and/or fresh frozen plasma) must also be tailored to the requirements of the poison needing to be removed. For example, in the case of a poison which is bound to albumin, removal by TPE without replacement of albumin could theoretically increase its free fraction and cause a resurgence of clinical toxicity, at least transiently. Similarly, one could also consider using a combination of 5% albumin and FFP in drugs that are highly bound to alpha-1-acid glycoprotein, such as quinidine, although alpha-1-acid glycoprotein has a low binding capacity (80) and there are no studies to confirm the clinical efficacy of this approach.

Endogenous Clearance

To justify the inherent costs, effort, and potential complications associated with ECTR, as a minimum, it should significantly increase total-body elimination. The mechanism by which ECTR achieves this is by enhanced elimination, so that the significance of the clearance achieved by ECTR should be considered relative to endogenous clearance for the same poison under similar circumstances. Extracorporeal clearance is usually limited to 400 ml/minute, which represents the maximal blood flow achievable by intermittent hemodialysis. In contrast, for medicines that undergo extensive and rapid enzymatic (e.g., hepatic) clearance, endogenous clearance may exceed 2000 ml/minute (e.g., labetalol, cocaine, verapamil, toluene) so the contribution of ECTR for such poisons will be minor. Therefore, the lower the poison's endogenous clearance, the higher the potential for ECTR to have a toxicokinetic impact.

A criterion that may indicate that ECTR can significantly increase clearance is that a poison's endogenous clearance should be below 4 ml/minute/kg to qualify for extracorporeal removal (72,96). An important consideration here is determining when endogenous clearance is compromised; for example, when a xenobiotic is extensively eliminated by the kidneys and the patient has concomitant acute kidney injury (AKI), the benefit from ECTR is increased compared to that in a patient with intact kidney function.

Several publications recommend that clearances attained by ECTR should be at least 30% of the endogenous clearance (33,46,47), although this criterion by itself is questionable when considered in isolation, as discussed later in regards to half-life. For example, in the case of lithium, a 7 ml/minute increase in total-body clearance by ECTR, compared to 25 ml/minute in a patient with normal kidney function, the clinical benefit is likely to be minimal.

If a poison has a very short half-life (e.g., <2 hours), its toxic effects will likely be short-lived so that ECTR will probably not alter the natural course of the poisoning. This is even more important considering that there is always a delay between the time hemodialysis is prescribed and is actually commenced. Clinical examples where this is relevant include cocaine, many β-adrenergic agonists, and monoamine oxidase inhibitors.

Volume of Distribution

ECTR only removes xenobiotics located in the blood compartment. Poisons that distribute in total body water are small and hydrophilic and have a volume of distribution (V_D) equal to 0.6 l/kg. On the other hand, a poison with a large V_D has characteristics of high lipophilicity and/or binding to proteins or tissues. Poisons that have a larger V_D are located preferentially outside of the vascular space.

As the V_D increases, the usefulness of any ECTR decreases substantially (55). This can be illustrated by the following reported example (97): if a 60 kg patient ingests 2400 mg of amitriptyline, assuming complete absorption and distribution (V_D = 20 l/Kg), the maximum plasma amitriptyline concentration will be 2.0 μg/ml. If charcoal HP is performed for 4 hours, with blood flow 350 ml/minute (or plasma flow 200 ml/minute for hemocrit 40%), assuming in the best case scenario an extraction ratio of 100%, the HP clearance will be 200 ml/minute. Therefore, a maximum of 400 μg will be removed per minute, for a total removal of less than 100 mg over 4 hours. Therefore, despite a high plasma clearance, HP will only decrease total-body drug burden by less than 5%.

Although no precise cut-offs exist, a V_D >1–2 l/kg is usually a deterrent to extracorporeal removal (55,96). However, there are several reports showing that ECTR removes substantial body stores of medicines with a V_D larger than 1 l/kg, such as carbamazepine (V_D = 1.2 l/kg) (98), thallium (V_D = 3 l/kg) (99), and metformin (V_D = 3 l/kg) (100–102). Unfortunately, it is not possible to generalize about the effect of ECTR for other poisons with a V_D greater than 1 l/kg. Also, no particular ECTR is preferred over another in the case of poisons with a large V_D, including TPE and albumin dialysis (65,103–105). However, given that half-life depends on the ratio of V_D to CL, it is necessary to use an ECTR that maximizes CL when treating a poison with a large V_D.

Another, and perhaps more important consideration, is whether the poison displays multicompartmental kinetics, in particular when there is slow intercompartmental transfer, from tissues to the vascular space for example. These factors slow redistribution from peripheral compartments back to the central compartment and this is often characterized by an increase in serum concentration after cessation of ECTR (also called *rebound*). Although rebound may not always lead to a clinical deterioration, the serum concentration should be monitored closely because it may indicate the need for a second treatment. Alternatively, longer durations of ECTR may be required to maximize the removal of poison that has distributed into deeper, less accessible, compartments.

In overdose, although the V_D of a poison may be large, there may be slow or delayed distribution into tissue compartments or ongoing absorption from the gut (1,103). ECTRs may, in that scenario, remove substantially greater body stores than would be predicted by standard toxicokinetic modeling, especially when initiated shortly after exposure.

The Choice of ECTR Modality

Once a decision is made to prescribe ECTR for a poisoned patient, the clinician must carefully review the available options and tailor the purification technique to the patient's condition and the physicochemical and toxicokinetic properties of the poison to be removed. The different extracorporeal treatments available are reviewed separately in this current issue.

Clinical and Practical Considerations

The presence of concomitant severe AKI will likely require an ECTR that can sustain kidney function as well as remove the poison. Here, HD or HF are preferred over plasma exchange or hemoperfusion, which do not eliminate uremic toxins or correct electrolyte disturbances to a significant extent, and do not permit fluid removal in volume-overloaded patients. Similarly, liver support therapies (SPAD, Prometheus, MARS) can transiently compensate for the deficient hepatic function and are sometimes considered a bridge for liver transplantation.

The presence of poison-mediated hypotension often prompts clinicians to use less efficient ECTR techniques like continuous renal replacement therapy (CRRT) instead of intermittent techniques (46,78). However, because net fluid loss is rarely required in poisoned patients, it is uncertain if CRRT causes less hypotension compared to intermittent techniques which are more efficient.

Patients who are especially prone to bleeding should be prescribed a technique that minimizes systemic anticoagulation. Hemodialysis, for example, can be performed with saline flushes alone, whereas this is more difficult for hemoperfusion. Furthermore, thrombocytopenia is a known complication of hemoperfusion so it may best be avoided in favor of another technique in patients at high bleeding risk.

Commonly, the types of ECTRs available in a particular center are limited. This has practical implications because the clinician may choose whether to use the available ECTR, or transfer the patient to another center for an alternative ECTR that may be preferred. For example, if CRRT is the only ECTR available in a center, then prompt availability at the expense of lower poison clearance needs to be weighed against delayed initiation of a more efficient treatment (e.g., HD) in another center. This choice must be made on a case-by-case basis, depending on the time required for patient transfer, the relative difference in efficiency between the ECTRs, and the overall clinical condition of the patient.

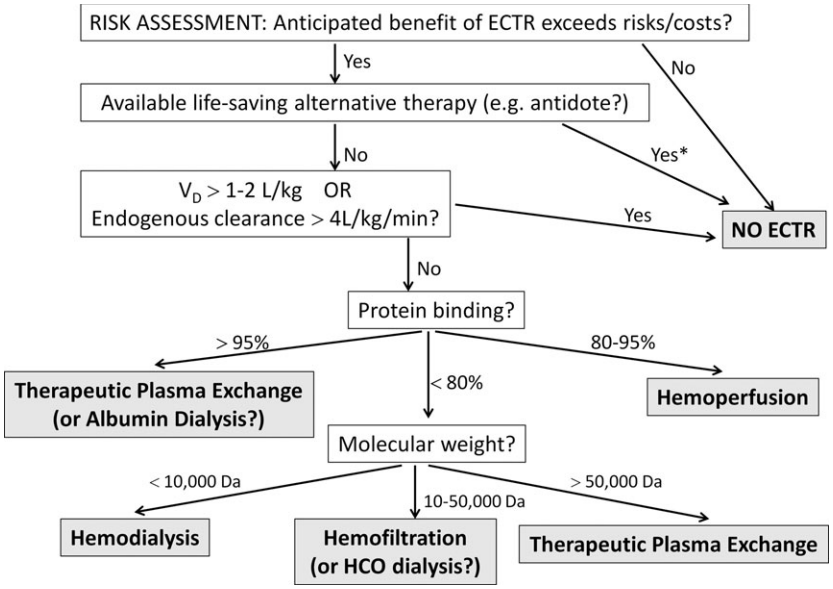

FIG. 2. Stepwise approach for the initiation of extracorporeal techniques for enhanced elimination in a poisoned patients. HCO HD: High cut-off hemodialysis, V_D: Volume of distribution, ECTR: extracorporeal treatment. *In some cases where an antidote is available it may also be appropriate to administer ECTR.

Some techniques are simpler to administer than others. Exchange transfusion does not require a (relatively) complicated extracorporeal circuit and it is relatively simple to use in newborns and small children poisoned with low V_D xenobiotics (salicylates, theophylline) (106,107). Whatever the technique chosen, dosing adjustment of all concomitant medications (including antidotes) may be needed, depending on their actual removal by ECTR.

The overall approach that is discussed above is summarized with the following simplified algorithm (Fig. 2). It should be noted, however, that exceptions are expected to this approach; each case must be individualized according to the patient's condition and the available resources. Consultation with colleagues experienced in clinical toxicology and the prescription of ECTR is encouraged.

Conclusion

For the vast majority of poisonings, sound medical judgment and appropriate supportive care are more important than active elimination enhancement techniques. However, a clinician attending to a poisoned patient needs to assess the risk of the specific exposure and consider the cost-benefit ratio of ECTR. Complications associated with ECTR are usually minimal and costs of a single hemodialysis treatment, including equipment and nursing/physician fees, are anticipated to be minor compared to the cost of a single day in an ICU. In the absence of adequate clinical outcome data, further studies are required. These should, as a minimum, demonstrate significant drug removal with ECTR, based on the portion of body stores removed or the change in total clearance. Empirical decisions regarding the decision to initiate a particular ECTR requires knowledge of the poison's physicochemical and toxicokinetic characteristics. Although hemodialysis is the most efficient method of clearing poisons with a low V_D, PB and MW, and limited endogenous clearances, there are various other circumstances where it can also be useful. Additional benefits such as rapid correction of life-threatening acid-base abnormalities and restoration of volume status are other considerations, but these decisions are based on usual clinical criteria rather than above-mentioned factors.

References

1. Abel JJ, Rowntree LG, Turner BB: On the removal of diffusible substances from the circulating blood by dialysis. *Trans Assoc Am Physicians* 58:51–54, 1913
2. Holubek WJ, Hoffman RS, Goldfarb DS, Nelson LS: Use of hemodialysis and hemoperfusion in poisoned patients. *Kidney Int* 74:1327–1334, 2008
3. Mowry JB, Spyker DA, Cantilena LR, Jr, Bailey JE, Ford M: 2012 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 30th Annual Report. *Clin Toxicol (Phila)* 51:949–1229, 2013
4. Ghannoum M, Nolin TD, Lavergne V, Hoffman RS: Blood purification in toxicology: nephrology's ugly duckling. *Adv Chronic Kidney Dis* 18:160–166, 2011
5. Lavergne V, Nolin TD, Hoffman RS, Robert D, Gosselin S, Goldfarb DS, Kielstein JT, Mactier R, MacLaren R, Mowry JB, Bunchman TE, Juurlink D, Megarbane B, Anseeuw K, Winchester JF, Dargan PI, Liu KD, Hoegberg LC, Li Y, Calello D, Burdmann EA, Yates C, Laliberte M, Decker BS, Mello-Da-Silva CA, Lavonas E, Ghannoum M: The EXTRIP (Extracorporeal Treatments In Poisoning) workgroup: guideline methodology. *Clin Toxicol* 50:403–413, 2012
6. Isbister GK, Balit CR, Whyte IM, Dawson A: Valproate overdose: a comparative cohort study of self poisonings. *Br J Clin Pharmacol* 55:398–404, 2003
7. Bismuth C, Gaultier M, Conso F: [Medullary aplasia after acute colchicine poisoning. 20 cases]. *Nouv Presse Med* 6:1625–1629, 1977
8. Ozdemir R, Bayrakci B, Teksam O: Fatal poisoning in children: acute colchicine intoxication and new treatment approaches. *Clin Toxicol (Phila)* 49:739–743, 2011

9. Proudfoot AT, Stewart MS, Levitt T, Widdop B: Paraquat poisoning: significance of plasma-paraquat concentrations. *Lancet* 2:330–332, 1979
10. Hart TB, Nevitt A, Whitehead A: A new statistical approach to the prognostic significance of plasma paraquat concentrations. *Lancet* 2:1222–1223, 1984
11. Rumack BH, Peterson RC, Koch GG, Amara IA: Acetaminophen overdose. 662 cases with evaluation of oral acetylcysteine treatment. *Arch Intern Med* 141:380–385, 1981
12. Tenenbein M: Good reasons to publish in Clinical Toxicology. *J Toxicol Clin Toxicol* 36:137–138, 1998
13. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, Guyatt GH, Harbour RT, Haugh MC, Henry D, Hill S, Jaeschke R, Leng G, Liberati A, Magrini N, Mason J, Middleton P, Mrukowicz J, O'Connell D, Oxman AD, Phillips B, Schunemann HJ, Edejer TT, Varonen H, Vist GE, Williams JW, Jr, Zaza S: Grading quality of evidence and strength of recommendations. *BMJ* 328:1490, 2004
14. Woo OF, Pond SM, Benowitz NL, Olson KR: Benefit of hemoperfusion in acute theophylline intoxication. *J Toxicol Clin Toxicol* 22:411–424, 1984
15. Prichard S, Chirito E, Chang T, Sniderman AD: Microencapsulated charcoal hemoperfusion: a possible therapeutic adjunct in digoxin toxicity. *J Dial* 1:367–377, 1977
16. Hill JB, Palaia FL, McAdams JL, Palmer PJ, Maret SM: Efficacy of activated charcoal hemoperfusion in removing lethal doses of barbiturates and salicylate from the blood of rats and dogs. *Clin Chem* 22:754–760, 1976
17. Ellsworth H, Engebretsen KM, Hlavenka LM, Kim AK, Cole J, Harris CR, Stellpflug SJ: A cost comparision of fomepizole and hemodialysis in the treatment of methanol and ethylene glycol toxicity. *Clin Toxicol* 49:515–627, 2011
18. Wiegand TJ, Margaretten M, Olson KR: Massive acetaminophen ingestion with early metabolic acidosis and coma: treatment with IV NAC and continuous venovenous hemodiafiltration. *Clin Toxicol (Phila)* 48:156–159, 2010
19. Sivilotti ML, Juurlink DN, Garland JS, Lenga I, Poley R, Hanly LN, Thompson M: Antidote removal during haemodialysis for massive acetaminophen overdose. *Clin Toxicol (Phila)* 51:855–863, 2013
20. Megarbane B, Borron SW, Baud FJ: Current recommendations for treatment of severe toxic alcohol poisonings. *Intensive Care Med* 31:189–195, 2005
21. Tai WP, Yue H, Hu PJ: Coma caused by isoniazid poisoning in a patient treated with pyridoxine and hemodialysis. *Adv Ther* 25:1085–1088, 2008
22. Myschetzky A, Lassen NA: Urea-induced, osmotic diuresis and alkalization of urine in acute barbiturate intoxication. *JAMA* 185:936–942, 1963
23. de Silva HA, Fonseka MM, Pathmeswaran A, Alahakone DG, Ratnatilake GA, Gunatilake SB, Ranasinha CD, Lalloo DG, Aronson JK, de Silva HJ: Multiple-dose activated charcoal for treatment of yellow oleander poisoning: a single-blind, randomised, *placebo*-controlled trial. *Lancet* 361:1935–1938, 2003
24. Brahmi N, Kouraichi N, Thabet H, Amamou M: Influence of activated charcoal on the pharmacokinetics and the clinical features of carbamazepine poisoning. *Am J Emerg Med* 24:440–443, 2006
25. Vale J, Krenzelok EP, Barceloux VD: Position statement and practice guidelines on the use of multi-dose activated charcoal in the treatment of acute poisoning. American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. *J Toxicol Clin Toxicol* 37:731–751, 1999
26. Proudfoot AT, Krenzelok EP, Vale JA: Position Paper on urine alkalinization. *J Toxicol Clin Toxicol* 42:1–26, 2004
27. Sikma MA, van den Broek MP, Meulenbelt J: Increased unbound drug fraction in acute carbamazepine intoxication: suitability and effectiveness of high-flux haemodialysis. *Intensive Care Med* 38:916–917, 2012
28. Muller CH, Lankisch PG: Resin hemoperfusion for carbamazepine intoxication. [German]. *Intensivmedizin und Notfallmedizin* 26 (3):145–148, 1989
29. Roberts DM, Buckley NA: Enhanced elimination in acute barbiturate poisoning—a systematic review. *Clin Toxicol (Phila)* 49:2–12, 2011
30. Maduell F, Navarro V, Cruz MC, Torregrosa E, Garcia D, Simon V, Ferrero JA: Osteocalcin and myoglobin removal in on-line hemodiafiltration versus low- and high-flux hemodialysis. *Am J Kidney Dis* 40:582–589, 2002
31. Matzke GR: Status of hemodialysis of drugs in 2002. *J Pharm Pract* 15:405–418, 2002
32. Kawasaki C, Nishi R, Uekihara S, Hayano S, Otagiri M: Charcoal hemoperfusion in the treatment of phenytoin overdose. *Am J Kidney Dis* 35:323–326, 2000
33. Ward RA, Schmidt B, Hullin J, Hillebrand GF, Samtleben W: A comparison of on-line hemodiafiltration and high-flux hemodialysis: a prospective clinical study. *J Am Soc Nephrol* 11:2344–2350, 2000
34. Lindholm DD, Murray JS: Persistence of vancomycin in the blood during renal failure and its treatment by hemodialysis. *N Engl J Med* 274:1047–1051, 1966
35. De Bock V, Verbeelen D, Maes V, Sennesael J: Pharmacokinetics of vancomycin in patients undergoing haemodialysis and haemofiltration. *Nephrol Dial Transplant* 4:635–639, 1989
36. Decker BS, Kays MB, Chambers M, Kraus MA, Moe SM, Sowinski KM: Vancomycin pharmacokinetics and pharmacodynamics during short daily hemodialysis. *Clin J Am Soc Nephrol* 5:1981–1987, 2010
37. Klansuwan N, Ratanajamit C, Kasiwong S, Wangsiripaisan A: Clearance of vancomycin during high-efficiency hemodialysis. *J Med Assoc Thai* 89:986–991, 2006
38. Foote EF, Dreitlein WB, Steward CA, Kapoian T, Walker JA, Sherman RA: Pharmacokinetics of vancomycin when administered during high flux hemodialysis. *Clin Nephrol* 50:51–55, 1998
39. Wolter K, Claus M, Wagner K, Fritschka E: Teicoplanin pharmacokinetics and dosage recommendations in chronic hemodialysis patients and in patients undergoing continuous veno-venous hemodialysis. *Clin Nephrol* 42:389–397, 1994
40. Vienken J, Christmann H: How can liver toxins be removed? Filtration and adsorption with the Prometheus system. *Ther Apher Dial* 10:125–131, 2006
41. Winchester JF, Harbord NB, Rosen H: Management of poisonings: core curriculum 2010. *Am J Kidney Dis* 56(4):788–800, 2010
42. Martin-Reyes G, Toledo-Rojas R, Torres-de Rueda A, Sola-Moyano E, Blanca-Martos L, Fuentes-Sanchez L, Martinez-Esteban MD, Diez-de los Rios MJ, Bailen-Garcia A, Gonzalez-Molina M, Garcia-Gonzalez I: Haemodialysis using high cut-off dialysers for treating acute renal failure in multiple myeloma. *Nefrologia* 32:35–43, 2012
43. Ahrenholz PG, Winkler RE, Michelsen A, Lang DA, Bowry SK: Dialysis membrane-dependent removal of middle molecules during hemodiafiltration: the beta2-microglobulin/albumin relationship. *Clin Nephrol* 62:21–28, 2004
44. Bohler J, Donauer J, Keller F: Pharmacokinetic principles during continuous renal replacement therapy: drugs and dosage. *Kidney Int Suppl* 2:4–28, 1999
45. Bugge JF: Pharmacokinetics and drug dosing adjustments during continuous venovenous hemofiltration or hemodiafiltration in critically ill patients. *Acta Anaesthesiol Scand* 45:929–934, 2001
46. Kim Z, Goldfarb DS: Continuous renal replacement therapy does not have a clear role in the treatment of poisoning. *Nephron Clin Pract* 115:c1–c6, 2010
47. Forni LG, Hilton PJ: Continuous hemofiltration in the treatment of acute renal failure. *N Engl J Med* 336:1303–1309, 1997
48. Kaiser JP, Oppermann M, Gotze O, Deppisch R, Gohl H, Asmus G, Rohrich B, von Herrath D, Schaefer K: Significant reduction of factor D and immunosuppressive complement fragment Ba by hemofiltration. *Blood Purif* 13:314–321, 1995
49. Amyot SL, Leblanc M, Thibeault Y, Geadah D, Cardinal J: Myoglobin clearance and removal during continuous venovenous hemofiltration. *Intensive Care Med* 25:1169–1172, 1999
50. Bammens B, Evenepoel P, Verbeke K, Vanrenterghem Y: Removal of the protein-bound solute p-cresol by convective transport: a randomized crossover study. *Am J Kidney Dis* 44:278–285, 2004
51. Ronco C, Breuer B, Bowry SK: Hemodialysis membranes for high-volume hemodialytic therapies: the application of nanotechnology. *Hemodial Int* 10(Suppl 1):S48–S50, 2006
52. Ward RA: Protein-leaking membranes for hemodialysis: a new class of membranes in search of an application? *J Am Soc Nephrol* 16:2421–2430, 2005
53. Jeffrey RF, Khan AA, Prabhu P, Todd N, Goutcher E, Will EJ, Davison AM: A comparison of molecular clearance rates during continuous hemofiltration and hemodialysis with a novel volumetric continuous renal replacement system. *Artif Organs* 18:425–428, 1994
54. Joy MS, Matzke GR, Frye RF, Palevsky PM: Determinants of vancomycin clearance by continuous venovenous hemofiltration and continuous venovenous hemodialysis. *Am J Kidney Dis* 31:1019–1027, 1998
55. Pond SM: Extracorporeal techniques in the treatment of poisoned patients. *Med J Aust* 154:617–622, 1991
56. Chang TM: Microencapsulated adsorbent hemoperfusion for uremia, intoxication and hepatic failure. *Kidney Int Suppl* 7:387–392, 1975
57. Tessore V, Luboz MP, Denti E: Use of uncoated activated carbon hemoperfusion in acute poisoning: *in vitro* studies. *Contrib Nephrol* 29:65–75, 1982
58. Rubik J, Pietraszek-Jezierska E, Kaminski A, Skarzynska A, Jozwiak S, Pawlowska J, Drewniak T, Prokurat S, Grenda R, Kalicinski P: Successful treatment of a child with fulminant liver failure and coma caused by *Amanita phalloides* intoxication with albumin dialysis without liver transplantation. *Pediatr Transplant* 8:295–300, 2004

59. Stadlbauer V, Krisper P, Aigner R, Haditsch B, Jung A, Lackner C, Stauber RE: Effect of extracorporeal liver support by MARS and Prometheus on serum cytokines in acute-on-chronic liver failure. *Crit Care* 10:R169, 2006
60. Krisper P, Stauber RE: Technology insight: artificial extracorporeal liver support—how does Prometheus compare with MARS? *Nat Clin Pract Nephrol* 3:267–276, 2007
61. Mitzner S, Klammt S, Stange J, Schmidt R: Albumin regeneration in liver support-comparison of different methods. *Ther Apher Dial* 10:108–117, 2006
62. Chu G, Mantin R, Shen YM, Baskett G, Sussman H: Massive cisplatin overdose by accidental substitution for carboplatin. Toxicity and management. *Cancer* 72:3707–3714, 1993
63. Pierga JY, Beuzeboc P, Dorval T, Palangie T, Pouillart P: Favourable outcome after plasmapheresis for vincristine overdose. *Lancet* 340:185, 1992
64. Kuhlmann U, Schoenemann H, Muller T, Keuchel M, Lange H: Plasmapheresis in life-threatening verapamil intoxication. *Artif Cells Blood Substit Immobil Biotechnol* 28:429–440, 2000
65. Gambi D, Oggioni R, Mangani V, Librenti M, Manescalchi F, Tulli G: [Acute carbamazepine poisoning treated with plasmapheresis. Description of a clinical case]. *Minerva Anestesiol* 59:547–552, 1993
66. Solomon A, Fahey JL: Plasmapheresis therapy in macroglobulinemia. *Ann Intern Med* 58:789–800, 1963
67. Fahey JL, Barth WF, Solomon A: Serum hyperviscosity syndrome. *JAMA* 192:464–467, 1965
68. Jha S, Waghdhare S, Reddi R, Bhattacharya P: Thyroid storm due to inappropriate administration of a compounded thyroid hormone preparation successfully treated with plasmapheresis. *Thyroid* 22:1283–1286, 2012
69. Ibrahim RB, Liu C, Cronin SM, Murphy BC, Cha R, Swerdlow P, Edwards DJ: Drug removal by plasmapheresis: an evidence-based review. *Pharmacotherapy* 27:1529–1549, 2007
70. Puisset F, White-Koning M, Kamar N, Huart A, Haberer F, Blasco H, Le Guellec C, Lafont T, Grand A, Rostaing L, Chatelut E, Pourrat J: Population pharmacokinetics of rituximab with or without plasmapheresis in kidney patients with antibody-mediated disease. *Br J Clin Pharmacol* 76:734–740, 2013
71. Faed EM: Protein binding of drugs in plasma, interstitial fluid and tissues: effect on pharmacokinetics. *Eur J Clin Pharmacol* 21:77–81, 1981
72. De Pont ACJM: Extracorporeal treatment of intoxications. *Curr Opin Crit Care* 13:668–673, 2007
73. Higgins RM, Connolly JO, Hendry BM: Alkalinization and hemodialysis in severe salicylate poisoning: comparison of elimination techniques in the same patient. *Clin Nephrol* 50:178–183, 1998
74. Licari E, Calzavacca P, Warrillow SJ, Bellomo R: Life-threatening sodium valproate overdose: a comparison of two approaches to treatment. *Crit Care Med* 37:3161–3164, 2009
75. Franssen EJ, van Essen GG, Portman AT, de Jong J, Go G, Stegeman CA, Uges DR: Valproic acid toxicokinetics: serial hemodialysis and hemoperfusion. *Ther Drug Monit* 21:289–292, 1999
76. Khan E, Huggan P, Celi L, MacGinley R, Schollum J, Walker R: Sustained low-efficiency dialysis with filtration (SLEDD-f) in the management of acute sodium valproate intoxication. *Hemodial Int* 12:211–214, 2008
77. van Kuelen JG, van Wijk JA, Touw DJ, van der Deure J, Markhorst DG, Gemke RJ: Effectiveness of haemofiltration in valproic acid intoxication. *Acta Paediatr* 90:958–959, 2001
78. Goodman JW, Goldfarb DS: The role of continuous renal replacement therapy in the treatment of poisoning. *Semin Dial* 19:402–407, 2006
79. Roberts DM, Dawson AH, Senarathna L, Mohamed F, Cheng R, Eaglesham G, Buckley NA: Toxicokinetics, including saturable protein binding, of 4-chloro-2-methyl phenoxyacetic acid (MCPA) in patients with acute poisoning. *Toxicol Lett* 201:270–276, 2011
80. Roberts DM, Buckley NA: Pharmacokinetic considerations in clinical toxicology: clinical applications. *Clin Pharmacokinet* 46:897–939, 2007
81. Borkan SC: Extracorporeal therapies for acute intoxications. *Crit Care Clin* 18(2):393–420, 2002
82. Schuerer DJ, Brophy PD, Maxvold NJ, Kudelka T, Bunchman TE: High-efficiency dialysis for carbamazepine overdose. *J Toxicol Clin Toxicol* 38:321–323, 2000
83. Tapolyai M, Campbell M, Dailey K, Udvari-Nagy S: Hemodialysis is as effective as hemoperfusion for drug removal in carbamazepine poisoning. *Nephron* 90:213–215, 2002
84. Ghannoum M, Troyanov S, Ayoub P, Lavergne V, Hewlett T: Successful hemodialysis in a phenytoin overdose: case report and review of the literature. *Clin Nephrol* 74:59–64, 2010
85. Harder JL, Heung M, Vilay AM, Mueller BA, Segal JH: Carbamazepine and the active epoxide metabolite are effectively cleared by hemodialysis followed by continuous venovenous hemodialysis in an acute overdose. *Hemodial Int* 15:412–415, 2011
86. Kawasaki CI, Nishi R, Uekihara S, Hayano S, Kragh-Hansen U, Otagiri M: How tightly can a drug be bound to a protein and still be removable by charcoal hemoperfusion in overdose cases? *Clin Toxicol (Phila)* 43:95–99, 2005
87. Shalkham AS, Kirrane BM, Hoffman RS, Goldfarb DS, Nelson LS: The availability and use of charcoal hemoperfusion in the treatment of poisoned patients. *Am J Kidney Dis* 48:239–241, 2006
88. Sentsov VG, Brusin KM, Meledin VY, Novikova OV, Urazaev TH: Comparison of charcoal hemoperfusion and hemodialysis in treatment of severe carbamazepine intoxications [abstract]. *Clin Toxicol (Phila)* 45:346, 2007
89. Shannon MW: Comparative efficacy of hemodialysis and hemoperfusion in severe theophylline intoxication. *Acad Emerg Med* 4:674–678, 1997
90. Ghannoum M, Bouchard J, Nolin T, Ouellet G, Roberts DM: Hemoperfusion for the treatment of poisoning: technology, determinants of poison clearance and application in clinical practice. *Semin Dial* ???:???–???, 2014
91. Laleman W, Wilmer A, Evenepoel P, Elst IV, Zeegers M, Zaman Z, Verslype C, Fevery J, Nevens F: Effect of the molecular adsorbent recirculating system and Prometheus devices on systemic haemodynamics and vasoactive agents in patients with acute-on-chronic alcoholic liver failure. *Crit Care* 10:R108, 2006
92. Churchwell MD, Pasko DA, Smoyer WE, Mueller BA: Enhanced clearance of highly protein-bound drugs by albumin-supplemented dialysate during modeled continuous hemodialysis. *Nephrol Dial Transplant* 24:231–238, 2009
93. Sen S, Ratnaraj N, Davies NA, Mookerjee RP, Cooper CE, Patsalos PN, Williams R, Jalan R: Treatment of phenytoin toxicity by the molecular adsorbents recirculating system (MARS). *Epilepsia* 44:265–267, 2003
94. Kan G, Jenkins I, Rangan G, Woodroffe A, Rhodes H, Joyce D: Continuous haemodiafiltration compared with intermittent haemodialysis in the treatment of methanol poisoning. *Nephrol Dial Transplant* 18:2665–2667, 2003
95. Choi JH, Oh JC, Kim KH, Chong SY, Kang MS, Oh DY: Successful treatment of cisplatin overdose with plasma exchange. *Yonsei Med J* 43:128–132, 2002
96. Fertel BS, Nelson LS, Goldfarb DS: Extracorporeal removal techniques for the poisoned patient: a review for the intensivist. *J Intensive Care Med* 25:139–148, 2010
97. Garella S: Extracorporeal techniques in the treatment of exogenous intoxications. *Kidney Int* 33:735–754, 1988
98. O'Malley G, Zebley T, Wilcox B, Raja R, Firpo J: A massive carbamazepine overdose treated with high-efficiency hemodialysis [abstract]. *Clin Toxicol (Phila)* 44:684–685, 2006
99. Brodersen HP, Theilmeier A, Korsten S, Arendt U, Larbig D, Reis HE: Acute poisoning by a potentially lethal dose of thallium: quantitative comparison of different methods of elimination. [German]. *Intensiv- und Notfallbehandlung* 17(4):204–207, 1992
100. Lalau JD, Andrejak M, Moriniere P, Coevoet B, Debussche X, Westeel PF, Fournier A, Quichaud J: Hemodialysis in the treatment of lactic acidosis in diabetics treated by metformin: a study of metformin elimination. *Int J Clin Pharmacol Ther Toxicol* 27:285–288, 1989
101. Perrot D, Claris O, Guillaume C, Bouffard Y, Delafosse B, Motin J: Metformin and lactic acidosis: value of initial plasma assay of metformin and hemodialysis. *Ann Med Interne (Paris)* 137:169–170, 1986
102. Barrueto F, Meggs WJ, Barchman MJ: Clearance of metformin by hemofiltration in overdose. *J Toxicol Clin Toxicol* 40:177–180, 2002
103. Ouellette SM, Visconti JA, Kennedy MS: A pharmacokinetic evaluation of the effect of plasma exchange on tobramycin disposition. *Clin Exp Dial Apheresis* 7:225–233, 1983
104. Alet P, Lortholary O, Fauvelle F, Tod M, Genereau T, Louchahi M, Leon A, Guillevin L, Petitjean O: Pharmacokinetics of teicoplanin during plasma exchange. *Clin Microbiol Infect* 5:213–218, 1999
105. Ibrahim RB, Balogun RA: Medications in patients treated with therapeutic plasma exchange: prescription dosage, timing, and drug overdose. *Semin Dial* 25:176–189, 2012
106. Manikian A, Stone S, Hamilton R, Foltin G, Howland MA, Hoffman RS: Exchange transfusion in severe infant salicylism. *Vet Hum Toxicol* 44:224–227, 2002
107. Osborn HH, Henry G, Wax P, Hoffman R, Howland MA: Theophylline toxicity in a premature neonate—elimination kinetics of exchange transfusion. *J Toxicol Clin Toxicol* 31:639–644, 1993