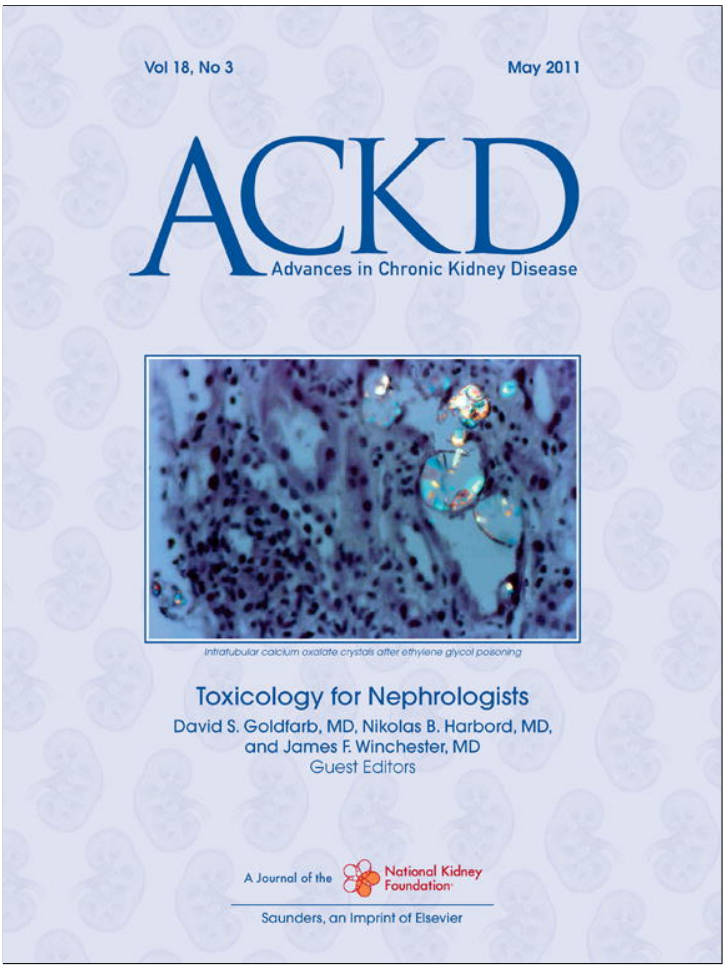

Blood Purification in Toxicology: Nephrology's Ugly Duckling

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for the EXTRIP workgroup

Contrary to popular opinion, application of extracorporeal therapies for poisonings predates their use for ESRD. Despite this observation, the science of blood purification in toxicology remains desperately stagnant today. In fact, much of our current knowledge is derived from George Schreiner's 1958 review. Original publications are almost exclusively composed of case reports and case series, from which good inference is impossible. Until randomized controlled trials become available, the medical community would be well served by a group mandated to systematically review available literature, extract relevant information, provide recommendations based on current evidence, and propose research initiatives. The EXtracorporeal TReatments In Poisoning workgroup, formed by several international experts in different medical fields and represented by over 20 societies, now has this mission.

Key Words: Hemodialysis, Extracorporeal therapy, Hemoperfusion, Overdose, Intoxication, Poisoning

Any internal medicine resident can state the accepted indications for acute hemodialysis. Emergency physicians regularly deal with hyperkalemia and fluid overload in their units and are well-acquainted with situations necessitating urgent dialysis. Although most physicians are aware of the potential benefits of extracorporeal treatments (ECTRs) in the treatment of selected poisonings (eg, lithium, methanol), its precise application, indications, contraindications, and judicious timing largely remain a mystery to the medical community.

Most clinicians forget that the use of ECTR for acute poisonings was already thriving in the 1960s, while it was still contraindicated for ESRD. It is therefore remarkable that these indications have suffered such different fates: its use in ESRD has flourished and benefited from a remarkable input of research, investment, and dynamism; several national and international guidelines have been published on a wide variety of topics ranging from bone metabolism to vascular access.[1,2] Conversely, although medical toxicology benefited indirectly from the technical advancements in equipment (ie, dialysis machines, filters) and improved procedures (ie, water purification, anticoagulation), there has been a paucity of good science in that area, apart from scattered individual efforts and sporadic panels.[3] This cannot be explained by sheer numbers; in 2008, there were more than 350,000 prevalent patients with ESRD receiving chronic hemodialysis in the United States,[4] whereas the American Association of Poison Control Centers documented 150,000 poisonings considered to be at least "moderate" in severity.[5]

For the sake of uniformity and simplicity, we have preferentially used the terms "poisons" and "poisoning" in the text: a poison includes xenobiotics (exogenous chemicals, including therapeutic drugs) and endogenously found chemicals (eg, iron, copper, vitamins) resulting from exogenous exposure. Poisoning, although usually implying intent, will be defined as exposure to a chemical causing or capable of causing toxicity. It includes intoxication, toxicity, and overdose.

Historical Perspective

Although Thomas Graham developed the principles of dialysis in the 1800s and is generally considered the father of modern nephrology, the construction of the first artificial kidney is attributed to Abel and colleagues in 1913.[6] Interestingly, the aim of the technique was primarily to remove salicylate from the blood of a living animal, instead of treatment of kidney failure. This experiment was successful, and opened the door for renal replacement therapies.

Haas and colleagues performed the first successful dialysis in human beings in 1924, but it was not until 1943 that Kolff built a rotation drum kidney that could be used practically for acute kidney failure.[7] In 1948, Bywaters and Joekes first reported the use of dialysis in a human case of salicylate poisoning, similar to that carried out by Abel in animals 34 years earlier.[8] Several other physicians followed suit, among whom Paul Doolan, Laurence Kyle, and George Schreiner were the most prominent pioneers. By the end of the 1950s, several poisons had been shown to be dialyzable, including barbiturates, salicylates, and hypnotics. Schreiner even published his first

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1548-5595/$36.00

doi:10.1053/j.ackd.2011.01.008

series in 1958, thereby solidifying the promise of hemodialysis as a therapeutic option for poisoning and popularizing its use.[9] By 1970, most poisonings were considered amenable to treatment by dialysis.[10] The 1980s saw a new skepticism toward extracorporeal therapies, helped by better understanding of toxicokinetic principles as well as improved supportive care for poisoned patients. The last 10 years have yet again seen another pendulum swing, as the introduction of better dialysis membranes has permitted new possibilities, especially for poisons not traditionally considered "dialyzable."

Although hemodialysis undoubtedly remains the most popular ECTR for kidney failure and poisoning, it is worthwhile to observe how other techniques have come to light. In 1958, Schreiner essentially invented hemoperfusion, by using an anion exchange column to help remove pentobarbitone from blood,[9] a technique later refined by Rosenbaum and Chang,[9a] among others. Later, in 1964, Yatzidis used charcoal-based hemoperfusion for treatment of uremia and poisoning,[11] although its use for the former indication was later abandoned.

Exchange transfusion became popular for hemolytic disease of the newborn in 1925 but only appeared in toxicology circles in 1950, when Axtrup used it for 2 poisoned children.[12] Abel described *plasmapheresis* as a technique to separate plasma from blood elements,[13] although its indication for uremia was soon abandoned. Rubinstein and colleagues performed plasmapheresis in 1959 for a patient with thrombotic thrombocytopenic purpura,[14] whereas Kuzmin and Vedenskii used this technique for an atropine overdose case in 1967.[15]

Hemofiltration was unintentionally discovered in 1977 by Kramer and colleagues, with the realization that arterial flow could provide a pressure gradient for filtration, after which fluids lost with solutes could be substituted by an appropriate replacement solution.[16] Its potential in poisoning management was soon recognized.[17]

Although peritoneal dialysis is not, per se, an ECTR (because poison removal does not occur outside the body), it too became a popular treatment for poisoning. Ganter pioneered its use in 1923,[18] but survival by a patient with acute kidney failure was only reported by Frank and colleagues in 1946.[19] Not more than a year later, Baggenstoss described the first case of poisoning treated by peritoneal dialysis.[20]

Why the Confusion?

The confusion reigning over the role of ECTR in poisonings can be better illustrated by a survey conducted by us among 30 Canadian nephrologists (and discussed later in text). The following 3 clinical situations were presented and all participants were asked in which case they would consider ECTR:

1. A 24-year-old man presenting 7 hours after ingesting 80 gm of aspirin with severe symptomatic salicylate toxicity, including metabolic acidosis and seizures. All nephrologists (100%) surveyed indicated that they would perform dialysis.
2. A 45-year-old man presenting 12 hours after an acute lithium ingestion, completely asymptomatic, with a serum lithium concentration of 4.4 mEq/L. In this situation, 80% of nephrologists surveyed indicated that they would perform dialysis without delay. When asked why, the majority explained this choice as based on "current evidence."
3. An 18-year-old woman presenting with severe tricyclic antidepressant poisoning. Only 30% of nephrologists surveyed indicated that they would perform dialysis or hemoperfusion without delay. Another 33% considered dialysis or hemoperfusion to be useless in this setting.

CLINICAL SUMMARY

- Hemodialysis remains a valuable therapeutic option for severe poisonings today.
- Yet, indications of extracorporeal therapy are often based on erroneous toxicokinetic and/or clinical assumptions.
- Recommendations by a mandated group would help gather current evidence and standardize current practice.

Problems Interpreting Data

The use of extracorporeal therapy for poisonings was historically guided by intuitive, although debatable, assumptions: the higher the body burden of a poison, the higher its toxicity. Conversely, the more this poison can be removed, the lesser the toxicity. From these premises, ECTR can show clinical efficacy only if: (1) ECTR can remove poison, and (2) removal of poison by ECTR enhances survival.

Can ECTR Remove the Poison?

How does one assess removal of poisons by ECTR? This concept is understood and applied in pharmacokinetic studies evaluating extracorporeal clearance of therapeutic drugs in chronic dialysis patients; drug dosage, in this case, is simply modified to account for the quantity cleared by dialysis. In medical toxicology, ideally, removal of poison from the target organ, instead of plasma, would be assessed (ie, central nervous system for lithium, heart muscle for digoxin, lung parenchyma for paraquat). Despite the existence of numerous pharmacokinetic parameters that can be easily measured or calculated, such as total systemic clearance, percent body burden eliminated, percent ingested dose removed, half-life, extraction ratio, and others, none of them correlates with poison concentration at the target organ.

Extracorporeal removal depends on various physical and pharmacokinetic characteristics of the incriminated poison. An understanding of how these apply to the particular context of poisoning, as well as common shortcomings of their interpretation, are now described.

Obsolete Technology

Presently, a significant portion of our toxicological knowledge is based on reports that do not necessarily represent the reality of current extracorporeal technology. As compared with 30 years ago, use of high-flux and high-efficiency dialysis membranes is now standard practice in dialysis centers. They have superior molecular cutoff values (10,000 Da vs 500 Da), larger surface areas (2.5 m^2 vs 0.5 m^2), and enhanced ultrafiltration coefficients (50-90 vs 5 mL/h/mm Hg), as compared with older cuprophane membranes. At equivalent blood and dialysate flow rates, the newer synthetic polymer filters permit a 2-fold increase in small molecule (eg, urea) clearances and a 5-fold increase in clearance of larger molecules (eg, vitamin B_{12}). Furthermore, newer catheters permit higher blood flows, which will also enhance poison removal. These factors explain why dialysis could now be considered, for example, in a severe vancomycin overdose, whereas older reports would dismiss it as being useless.[21] Furthermore, this also has an effect on the choice of therapy; although hemoperfusion was considered the preferable ECTR in the 1980s,[22] dialysis has largely supplanted hemoperfusion as a method of detoxification in the United States because of improved clearance and a preferable safety profile.[23]

Protein Binding

Because the protein–poison complex is characteristically bigger than pore size, poisons that are highly protein-bound are not considered dialyzable. In poisoning, however, protein binding sites become saturated, increasing the proportion of free, and therefore dialyzable, poison. This explains the high removal rate of protein-bound drugs (such as valproate and salicylate) that is achieved in actual poisoning. Furthermore, even if the proportion of bound poison remains significant, it can still dissociate rapidly from its binding sites, assuming it has a small binding constant, such as for phenytoin.[24]

Endogenous Clearance

The favorite kinetic parameter published in reports is extracorporeal clearance. These data, although useful, are incomplete by themselves: extracorporeal clearance must always be compared with endogenous systemic clearance to assess pertinence. Even if a poison is small and largely unbound to plasma protein, an extracorporeal clearance of 120 mL/min (which seems to be high) will be clinically insignificant if endogenous systemic clearance of the poison is 1000 mL/min. Schreiner had already asserted this in 1958, when he described that dialysis could only be considered if the "amount of poison dialyzed constitutes a significant addition to the normal body mechanisms."[9] This explains why certain street drugs, like cocaine, are not listed among poisons that can be dialyzed. It is generally considered that extracorporeal clearance must represent at least 30% of total clearance to be a significant contributor to drug removal *in vivo*, but this statement has yet to be challenged after 40 years.[25]

Volume of Distribution

ECTR only removes poisons located in the intravascular compartment. Because poisons having a high volume of distribution (Vd) distribute to extravascular compartments, they are not susceptible to extracorporeal elimination unless there is rapid poison transfer from tissue to plasma during the procedure. Therefore, reports of high extracorporeal clearance of digoxin and tricyclic antidepressants should be interpreted with much caution because poison removal in these cases is only limited to plasma. In fact, a 4-hour dialysis or hemoperfusion is not expected to remove more than 1% of total body stores of these poisons.[26] However, if ECTR is initiated while absorption is ongoing, or quickly after absorption, the poison might not fully distribute into deep compartments (the initial Vd is lower) and therefore may be more amenable to ECTR removal.

Does the Removal of the Poison Enhance Survival or Outcome?

Supposing there exists enough evidence to support efficient poison removal by ECTR, this alone does not signify improved outcome. Too many case reports assume this intuitive causal relationship to be correct, but such conclusions should never be inferred unless supported by properly designed studies. For example, the herbicide paraquat has all the physical characteristics associated with high extracorporeal clearance (ie, low molecular weight, low protein binding, low Vd). However, dialysis will generally not alter the dreadful clinical course associated with paraquat poisoning unless it is initiated early after ingestion.[27]

Conversely, dialysis seems to improve outcome of metformin poisoning, although it does not seem to be very dialyzable (high Vd).[28] Perhaps factors other than poison removal, such as acidosis correction, can account for the observed clinical improvement. Similarly, although tricyclic antidepressants are poorly removed by ECTR (high protein binding, high Vd), some clinicians remain uncertain of the role of ECTRs in tricyclic poisoning (see question 3 in the aforementioned survey), despite it not being supported by recent reviews.[29] However, authors have occasionally reported spectacular improvement after the procedure.[30,31] Although these

results have been dismissed as anecdotal, alternative explanations should be sought and the data analyzed as diligently as reports that support more comforting clinical intuition. Complex toxicodynamics are most likely implicated, although not yet elucidated.

The sophistication of supportive care and the advent of new antidotes have also significantly modified current dialysis recommendations. Although dialysis has historically been considered life-saving for severe ethylene glycol poisoning, the advent of fomepizole, a potent inhibitor of the enzyme alcohol dehydrogenase, has potentially obviated the need for dialysis in patients presenting without acidosis and kidney failure.[32]

Trials, or Lack Thereof

Efficacy and safety of therapeutic interventions in medicine are usually validated by a robust series of dependable studies. In an ideal world, an experiment would recreate a set of circumstances where only the studied intervention would differ. The closest study design reproducing this model is a randomized controlled trial (RCT). By allocating patients in different groups based solely on chance, randomization limits variability between groups before the intervention and permits less biased estimation of the effect of the intervention (in this case, ECTR). For these reasons, RCTs are considered the gold standard of epidemiologic studies.

The first randomized placebo-controlled trial was carried out in 1948, when streptomycin was studied for pulmonary tuberculosis.[33] Supported by the Food and Drug Administration, who responded to the thalidomide scandal by requiring evidence-based data for drug approval, RCTs became the preferred clinical investigation tool in the 1970s and were universally endorsed in the 1990s.

Whereas most medical specialties are dependent on this type of evidence, medical toxicology is still plagued by its paucity. We undertook a preliminary EMBASE and PubMed Medline search of nearly 4000 publications, but failed to identify even one RCT evaluating ECTR in poisoning versus supportive care. The lone RCT identified compared 2 different ECTRs in paraquat poisoning.[34]

Lower down the epidemiologic hierarchy are observational studies, 40 of which were identified in our literature search. Extracorporeal intervention, in this case, can still be controlled even though allocation is not randomized. This process can result in a bias commonly found in toxicology, confounding-by-indication, which occurs when the severity of disease becomes a confounder of the treatment–outcome relationship. For example, in patients poisoned with lithium, no mortality difference was observed between patients for whom hemodialysis was done and those for whom it was not done.[35] In fact, had the groups been comparable at baseline (the treated group was likely to be sicker), dialysis might have improved outcome.

Apart from editorials and reviews, the large majority of published literature in toxicology is composed of case reports and case series. They have some value but are plagued by publication bias (a conclusive result has a better chance of being published). Although the quality of clinical evidence must be assumed to be low, they can provide valuable toxicokinetic information, especially when the patient is compared with himself/herself (before/after ECTR as compared with during ECTR). Some authors have compared their series with historical controls, but time-related differences, notably the delivery of supportive therapy, are usually to be expected in these undertakings.

The Parachute Example

Clinicians remain up-to-date by reviewing pertinent documentation available to them. The first example in the aforementioned survey shows that the nephrology community is knowledgeable on the reported indications of dialysis in acute salicylate poisoning: severe central nervous system features or plasma concentrations of more than 5.6 to 7.2 mmol/L.[36-38] However, this unanimous vote may seem surprising considering the lack of a prospective trial.

The parachute example[39] is often used in the epidemiologic milieu: everyone but the most cynical would recommend the use of a parachute when jumping out of a plane, although there are no data supporting its use. To subject this intervention to a prospective trial would not only ridicule the human mind but would also be soundly unethical. We should therefore accept that "under exceptional circumstances, common sense might be applied when considering the potential risks and benefits of interventions."[39]

No therapeutic drug created today may benefit from this free ticket; although the drug may seem extremely promising, health agencies usually require a succession of studies investigating safety, efficacy, cost-effectiveness, pharmacokinetics, and so on, before approval can be granted. However, interventions (especially nonpharmacologic) that predated the universal adoption of RCTs are more difficult to evaluate; they often enjoy a passionate following by the medical community. No one would reconsider today the utility of ventilatory support for respiratory failure or dialysis for ESRD, although none of them underwent the scrutiny of a RCT. It is still unclear today whether ECTR for salicylate poisoning fits within this description.

Furthermore, even procedures that are more objectively circumspect can be backed by dogmatic statements (eg, "Patients with acute lithium toxicity and concentrations over 4 mEq/L *must* be dialyzed"). RCTs involving dialysis of lithium-poisoned patients would therefore be difficult to justify because randomization to the untreated group would likely be viewed by many as being

unethical. This is illustrated by the second question of the survey: a large majority of physicians would recommend dialysis, backed by a variety of sources,[40,41] although it is very possible that this specific patient would do well without dialysis.

The following list includes methodological reasons why RCTs based on the role of ECTR in poisoning would be difficult to design:

1. Consent is difficult to obtain in urgent situations.
2. Although poisonings as a whole occur commonly, poisons themselves cannot be regrouped together. Severe poisonings can therefore be considered a rare disease. Consequently, RCTs in this context are doomed to remain small in size with slow accrual rates. Several epidemiological tools would then be needed to overcome the small number of subjects included, such as matching, restriction, risk-stratification (if possible), or modeling.
3. Poisoned patients have extremely heterogeneous characteristics at baseline: demographics, type and timing of the exposure, variable elimination capacity, and clinical presentation may vary enormously. This heterogeneity will require larger samples sizes (ie, recruitment of more subjects) to attain sufficient statistical power.
4. Mortality from poisoning is low. To properly assess efficacy of dialysis in lithium poisoning, for example, one would require either the study of a subpopulation having a higher mortality or the study of a different outcome (such as coma or tremors). Both low-risk patients (who would survive regardless of treatment) and severely poisoned patients (who are likely to die anyway) should be excluded from mortality analyses. If the studied outcome remains yet too rare, perhaps another epidemiological tool should be used instead of a RCT.

These methodological challenges, although real, can usually be overcome. However, ethical obstacles to RCT designs could be considered more difficult to address; because ECTRs have existed for cases of poisoning for >50 years, clinicians and patient groups may show reluctance to measure ECTR versus placebo in a specified poisoning. Instead, researchers might decide to investigate one ECTR versus another. Toxicology science would certainly welcome, for example, a trial comparing continuous therapies with intermittent dialysis in lithium poisoning. Similarly, there might be more support for a trial that includes "gray areas," such as patients with acute serum lithium concentrations between 3 and 5 mEq/L, instead of a trial solely including sicker candidates. Finally, few clinicians would contest the design of a trial evaluating ECTR in poisoning of a new drug, whereas this would probably be more difficult for methanol or salicylates. The current dichotomy of opinions regarding ECTR in poisoning is summarized in Table 1.

Such are the challenges facing investigators interested in designing RCTs for extracorporeal therapies in poisoning.

The EXtracorporeal TReatments In Poisoning Workgroup

Until the nephrology and toxicology communities are blessed by the publication of well-powered, prospective clinical trials of ECTR in poisoning, we are left with imprecise data and diverging opinions. However, it is possible, even desirable, to arrive at a consensus. Some recommendations, such as the parachute example, would be overwhelmingly supported by a designated panel and undoubtedly provide clinicians with standards of good practice. Such consensus can be sought through an international collaboration with experts from

Table 1. Summary of Arguments and Counterarguments Regarding ECTR in Poisoning

Popular Arguments Regarding ECTR in Poisoning	Counterarguments
High incidence of complications	The incidence and severity of complications in ECTR are largely exaggerated by non-nephrologists.
Expensive	Treatment is usually limited to one session, which is relatively inexpensive for a potentially life-saving intervention (eg, compared with 3 times weekly for chronic dialysis).
Benefits of ECTR are completely unproven	Although benefits of ECTR can only be verified by robust trials, these would be considered unethical in poisonings where existing opinion is overwhelming (eg, the parachute example).
Contrary to most interventions in medicine, the effect of ECTR is quantifiable, for example, removal of poison can be measured	Although removal of poison from plasma can be measured, this does not imply removal of poison from its toxic action site. Furthermore, removal of poison does not necessarily translate into improved outcome.
Evidence in this field is doomed to be limited to case reports, case series, and biased observational data	Trials could and should be performed for certain poisons where current opinion is not so overwhelming (eg, valproic acid poisoning) and in particular, situations where management is uncertain, for example, ECTR for salicylates concentration between 4 and 6 mmol/L.

Abbreviation: ECTR, extracorporeal treatment.

Table 2. EXTRIP Participating Members

Name	Field	Location
Timothy E. Bunchman	Pediatric Nephrology/Critical Care	USA
Emmanuel A. Burdmann	Nephrology	Brazil
Diane P. Calello	Pediatric Toxicology	USA
Kim P. Dalhoff	Toxicology	Denmark
Paul I. Dargan	Toxicology	UK
Marc Ghannoum, chair	Nephrology	Canada
David S. Goldfarb	Nephrology	USA
Robert S. Hoffman, co-chair	Toxicology/Emergency Medicine	USA
David N. Juurlink	Toxicology/Clinical Pharmacology	Canada
Jan T. Kielstein	Nephrology	Germany
Martin Laliberté	Toxicology/Emergency Medicine	Canada
Valery Lavergne	Epidemiology/Biostatistics	Canada
Eric J. Lavonas	Toxicology/Emergency Medicine	USA
Yi Li	Toxicology/Emergency Medicine	China
Kathleen D. Liu	Nephrology	USA
Robert Maclaren	Pharmacology/Kinetics	USA
Bruno Mégarbane	Toxicology/Critical Care	France
James B. Mowry	Toxicology/Kinetics	USA
Bruce A. Mueller	Pharmacology/Kinetics	USA
Thomas D. Nolin, co-chair	Pharmacology/Kinetics	USA
Darren M. Roberts	Nephrology/Toxicology/Kinetics	Australia
James F. Winchester	Nephrology	USA

Abbreviation: EXTRIP, EXtracorporeal TReatments In Poisoning.

multidisciplinary fields, including physicians who deal with poisonings and/or extracorporeal therapies (nephrology, medical toxicology, pediatrics, emergency medicine, critical care). Furthermore, a workgroup could recruit experts, such as kineticists and clinical pharmacologists, capable of quantifying poison elimination from ECTR.

This workgroup now exists as the EXTRIP (*Extracorporeal TReatments in Poisoning*) workgroup (Table 2) and is currently represented by 20 recognized societies (Table 3), all of which have delegated an active participant. Supported by the Acute Dialysis Quality Initiative, its objective is to draft recommendations on the use of ECTR in the setting of severe poisoning, based on current literature, scientific evidence, and expert opinion. More specifically, the workgroup will review the effects of ECTR for a set of preselected poisons and how they apply to different contexts (acute, acute-on-chronic, and chronic poisoning) and special populations (children, CKD, hepatic dysfunction, pregnant women). The potential benefit of ECTR will be weighed against available alternative therapies and against complications associated with the procedure.

Table 3. Associations Represented in the EXTRIP Workgroup

American Academy of Clinical Toxicology
American College of Medical Toxicology
American Society of Nephrology
American Society of Pediatric Nephrology
Asia Pacific Association of Medical Toxicology
Australian and New Zealand Intensive Care Society
Australian and New Zealand Society of Nephrology
Canadian Association of Poison Control Centres
Canadian Association of Emergency Physicians
Chinese Medical Doctor Association
European Association of Poison Centres and Clinical Toxicologists
European Renal Best Practice
European Society of Emergency Medicine
European Society of Intensive Care Medicine
German Society of Nephrology
International Society of Nephrology
National Kidney Foundation
Quebec Society of Nephrology
Society of Critical Care Medicine
Pediatric Critical Care Medicine

Abbreviation: EXTRIP, EXtracorporeal TReatments in Poisoning.

After evaluating the quality of the evidence with recognized tools (Grading the Quality of Evidence and the Strength of Recommendation [GRADE] approach[43]), the workgroup will analyze and interpret the data. From this analysis, a vote from the workgroup will be conducted. When sufficient evidence is not available to support the recommendation, comprehensive expert opinion will be given, with place for dissension. Because most of the literature is suspected to be of poor quality, rigor and transparency of the process will be an important aspect of the recommendations (Appraisal of Guidelines Research and Evaluation [AGREE] instrument[42]).

This process will permit evaluation of the validity of refurbished statements, put into perspective newer technology, grade the importance of the various outcomes, assess the quality of the literature, voice the deficiencies in the field, and orient future research. Publication of the proposed methodology should be available in the near future and final recommendations in 2012.

Over the last decades, the use and popularity of ECTR for poisoning have gone through cycles of enthusiasm and disillusionments, namely because of misinterpretation of the pharmacokinetic and clinical data. Until

good trials or, failing that, comprehensive registries are available, physicians treating poisoned patients will continue to rely on poor quality evidence and theoretical arguments. Hopefully, the publication of recommendations will standardize current practice and offer future direction of research. At the very least, we hope to garner enthusiasm for a topic long disinvested by nephrologists.

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