DISCLOSURE
The author declared no competing interests.

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Extracorporeal removal of toxins

Pallavi K. Tyagi[1], James F. Winchester[1] and Donald A. Feinfeld[1]

Holubek *et al.* reviewed data on extracorporeal removal (ECR) of toxins from the Toxic Exposure Surveillance System (TESS) from 1985 to 2005. Hemodialysis use increased, but hemoperfusion nearly disappeared. Lithium, ethylene glycol, salicylate, and, increasingly, acetaminophen still often necessitate hemodialysis; ECR for theophylline has disappeared. TESS data do not separate continuous renal replacement therapy from hemodialysis, and not all poisonings were reported in this system. Nonetheless, these trends are useful to the nephrology community.

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Extracorporeal removal (ECR) techniques used for clearance of toxins can be a critical step in the management of chemical or drug poisoning. The use of these techniques for removal of toxins can be justified if there is evidence of severe toxicity and if the total-body elimination of the toxin can be increased by 30% or more by the extracorporeal technique.[1] Large randomized controlled trials of ECR in toxicology are hard to come by and, for obvious reasons, difficult to perform. Specific extracorporeal techniques and their indications remain a matter of debate. Application of extracorporeal modalities requires a thorough knowledge of drug pharmacokinetics and of the techniques available. The technology of choice for the removal of a particular toxin, however, may not be immediately available to physicians in clinical practice.

Holubek *et al.*[2] (this issue) describe trends in the use of ECR for removal of toxins in the United States over a 21-year period of poison-center data recorded in the Toxic Exposure Surveillance System (TESS) database from 1985 to 2005. TESS is a uniform data set of cases reported from poison centers in the United States. Categories of information include the patient, caller, route of exposure, substance or substances, clinical picture, treatment, and medical outcomes. The trend was an increase in hemodialysis (HD) use with a decrease in hemoperfusion (HP) over the final 10 years. This may be attributed to a change in the technology itself as well as a change in the profiles of drugs causing overdose. Improvement in HD technologies over the years, with use of newer synthetic membranes at greater blood flow rates, has resulted in drug elimination rates similar to that achieved through HP.[3] HP cartridges are expensive and have limited shelf life, and some require sterilization. It is technically more difficult to perform, cannot correct the acid–base fluid and electrolyte abnormalities associated with intoxications, and can cause thrombocytopenia, leukopenia, and hypocalcemia. According to TESS data from 2004, only 27 of the almost 2.5 million exposures reported to United States poison control centers were managed with charcoal HP.[4] Shalkham *et al.* reported the availability of charcoal HP cartridges in only approximately one-third of hospitals receiving emergency patients in New York City, and only three in-hospital HD units had performed HP in the past five years, on three cases.[5] The use of theophylline and barbiturate drugs, which were traditionally removed by HP, has declined, leading to a decline in the use of HP for their elimination.[6]

The role of continuous renal replacement therapy (CRRT), available since the late 1970s, in the treatment of poisoning is still under debate and is not currently reported in the TESS database. The use of continuous veno-venous hemofiltration (CVVH) and continuous veno-venous hemodiafiltration (CVVHD) have been reported in poisonings with salicylates, barium, lithium, carbamazepine, phenobarbital, methanol, iodine, pilsicainide, mercury, metformin, valproic acid, and tetramine. CVVH and CVVHD are considered continuous therapies because they are applied for a longer time (24–48 hours) than HD (usually 4–6 hours). An advantage of CVVH and CVVHD is that they are better tolerated than HD in hemodynamically unstable patients. CVVH achieves solute clearance by convection (solvent drag effect) through the membrane, with pore dimensions larger

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than those of conventional HD membranes. In CVVHD, diffusive transport of molecules is combined with filtration in order to increase the solute clearance. Drugs and chemicals must meet given criteria in order to reach a high extraction ratio, that is, low molecular weight, low volume of distribution, and weak protein binding. Compared with HD, the properties of the membranes used for CVVH and CVVHD allow the removal of poisons with higher molecular weights (up to 40,000 da for CVVH and CVVHD compared with less than 500 da for HD). However, the toxicokinetic requirements for an efficient toxin removal do not differ between the two techniques: small volume of distribution (<1 liter per kg), low endogenous clearance (<4 ml/min/kg), and an extraction ratio exceeding endogenous elimination.[7]

The phenomenon of rebound must be considered in the evaluation of removal of drugs. Depending on the volume of distribution of a particular drug, a large quantity may be protein bound or stored intracellularly, as in muscle or adipose tissue. After cessation of ECR, any drug removed from the extracellular space can have a concentration gradient that causes drugs to move from their intracellular stores to the extracellular space, leading to a rebound increase in the plasma levels. CRRT can prevent rebound because of its constant clearance of substances with the clinical advantage of preventing rebound, for example, of lithium.[8] Disadvantages of CRRT include that it requires patients to be sedentary for a long period of time; the need for anticoagulation; and that it may not be available at many smaller hospitals. The debate over CRRT versus HD continues, and the decision should be made on a case-by-case basis, keeping in mind that one modality can be followed by the other should the clinical status of the patient warrant such change. In cases in which the blood level of the toxin is very high, HD would be the preferred treatment if the patient can tolerate it.[9]

Figure 1 shows the percentage of all ECR treatments that were performed for 10 toxins during each of the four quinquennia reviewed by Holubek *et al.*[2] Lithium, ethylene glycol, and salicylate remained the major toxins for which HD

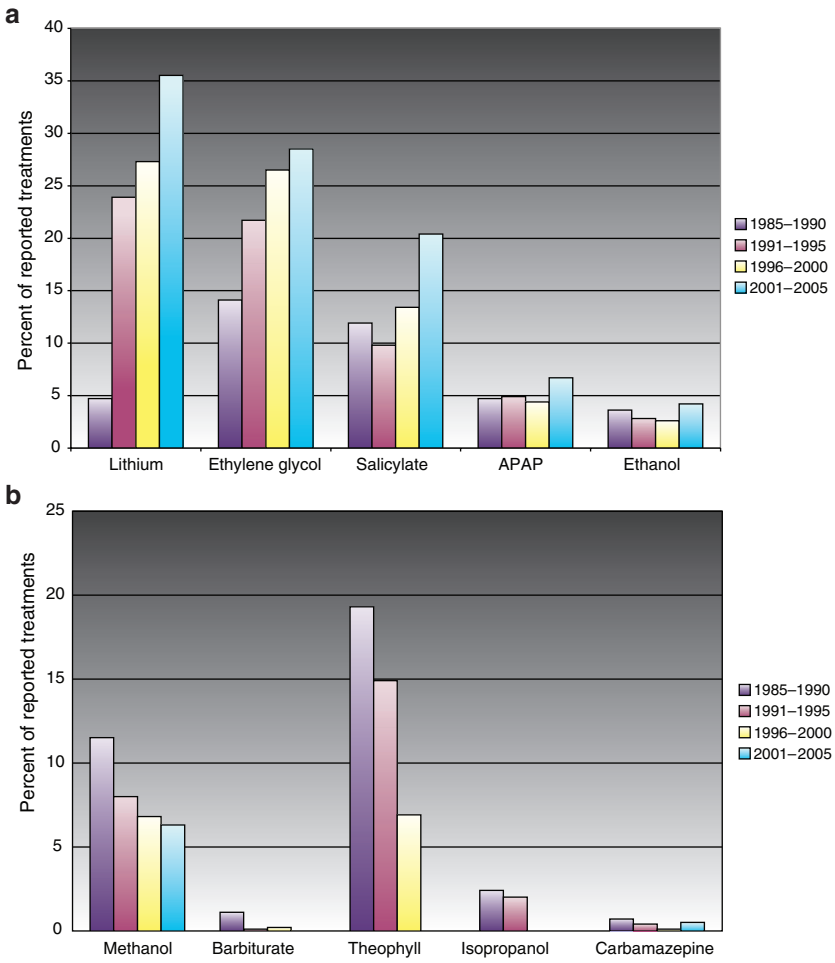

Figure 1 | Trends in toxin-removal treatments. (**a**) Percentage of treatments reported for toxins with increasing use of ECR.[2] (**b**) Percentage of treatments reported for toxins with decreasing or steady use of ECR.[2] APAP, acetaminophen.

was performed, while ECR for acetaminophen and valproic acid poisoning has increased dramatically in recent years (Figure 1a), reflecting their increased use and hence likelihood of overdose. While theophylline and isopropanol have largely disappeared as indications for ECR (Figure 1b), HD and even HP continue to be used to treat ethanol poisoning.

Since 1989, acetaminophen has been the sixth most common reason for HD, and in 2001 it became the fifth most common exposure, replacing theophylline. Toxic exposures to acetaminophen (paracetamol) have increased in other countries as well. In November 2003, paracetamol was made available in non-pharmacy outlets in Norway. In 2004, there was a considerable increase in inquiries to poison centers regarding acute and chronic paracetamol exposures. The number of severe paracetamol exposures presented to poison centers nearly doubled from 2003 to 2006.[10] The Swedish Poisons Information Centre has observed a continuously increasing number of inquiries related to paracetamol overdose in adolescents and young women.[11] Although the possible benefit in terms of toxin removal from HD or HP late in acetaminophen poisoning has been questioned, a series of patients dialyzed more than 14 hours after ingestion of the drug had a smaller rise in hepatic enzymes than those with a similar overdose who were not dialyzed.[12]

The data of Holubek *et al.*[2] were collected from the TESS database, which has a number of limitations. Reporting to TESS is not regulated or required; instead, callers are seeking diagnostic or treatment assistance or information. As a result, the incidence of certain subsets of poisoning

is underreported in TESS, most notably substance abuse and poisoning fatalities. During the quinquennium 1985–1990, about one-fifth of the calls to poison centers were not included in TESS,[4] so the trends in the report might not be as robust as they might have been if data collection had been more universal. TESS data are collected during telephone consultations; thus, bedside confirmation and data collection are not necessarily conducted by specialists in poison information. However, because calls are initiated by the general public, health-care professionals, and emergency first responders, the data collected provide a broader narrative of poisoning exposures than those from traditional health-care databases. Data quality may improve as data are collected and documented by specialists in poison information during the evaluation of the exposure and determination of the potential toxicity and therapeutic needs. It is also worth bearing in mind that the trend of the use of ECR in the United States may not necessarily reflect trends in Europe and the rest of the world.

Newer techniques for removal of toxins, such as Molecular Adsorbent Recirculating System (MARS), although still not widely available, may eventually become more common and replace HD as the modality of choice for removal of certain toxins. Efficacy of MARS in the removal of protein-bound drugs such as phenytoin, diltiazem, and theophylline has been described in case reports, but its availability remains limited.

The epidemiological trend of extracorporeal toxin removal in the United States has been changing, as has the profile of drugs removed by these techniques. With the use of newer techniques and change in drugs used in medical therapy, the trends will continue to evolve, with nephrologists playing a central role in the use of these therapeutic modalities.

DISCLOSURE
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Interstitial fibrosis: tubular hypothesis versus glomerular hypothesis

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The pathogenesis of renal interstitial fibrosis leading eventually to renal failure is highly debatable. Whereas the so-called tubular hypothesis, involving an increased tubular uptake of potentially toxic substances that induce a variety of cytokines, growth factors, and profibrogenic factors, is based to a large extent on cell-culture studies, the glomerular hypothesis is based mainly on careful morphological observations. Unraveling the pathways appears to be extremely complex, but *in vivo* studies appear to offer the most reliable results.

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Most if not all glomerular diseases involving extracapillary injury progressively develop extensive fibrotic processes, leading to nephron destruction and terminal renal failure. Two hypotheses have been put forward to account for this evolution. The first proposes that the primary event is tubular: the increased amount of protein that gains access to the proximal tubule, which results in increased protein trafficking in the proximal tubule cells, is toxic for the cells, thus triggering a number of inflammatory and fibrotic pathways. The second proposes that the primary event is glomerular: the formation of glomerular crescents leads to encroachment on the glomerular–tubular junction and subsequent tubular degeneration. Two recent studies provide additional data in this context.

Motoyoshi *et al.*[1] (this issue) induced massive glomerular proteinuria in a mouse model, mating mosaic megalin kidney knockout mice with a transgenic mouse, NEP25, in which podocytes

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Use of hemodialysis and hemoperfusion in poisoned patients

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Extracorporeal removal techniques such as hemodialysis, charcoal hemoperfusion, and peritoneal dialysis have been used to remove toxins from the body. To define trends in the use of these techniques for toxin removal, we analyzed the 19,351 cases requiring extracorporeal removal reported to U.S. poison centers from 1985–2005. The number of such patients who received hemodialysis, excluding those with other medical indications, (normalized per million calls) increased from 231 to 707 whereas hemoperfusion decreased from 53 to 12 in the years 1985–2005. Peritoneal dialysis decreased from 2.2 in 1985 to 1.6 in 1991. The most common toxins removed by hemodialysis were lithium and ethylene glycol. There were more dialysis treatments for poisonings with valproate and acetaminophen in 2001–2005 than for methanol and theophylline, although hemodialysis for acetaminophen removal is generally not recommended. Theophylline was the most common toxin removed by hemoperfusion from 1985–2000, but carbamazepine became the most frequent toxin for removal during 2001–2005. Our study shows that the profile of toxins and the type of extracorporeal technique used to remove the toxins have changed over the years.

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KEYWORDS: antidotes; charcoal; epidemiology; overdose; poisoning; toxicology

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Extracorporeal removal techniques such as hemodialysis (HD) and charcoal hemoperfusion (HP), and less so peritoneal dialysis (PD), effectively increase the clearance of certain toxins. Historically, these techniques have been recommended as treatment for a serious overdose from a select number of toxins, including salicylates, lithium, ethylene glycol, methanol, and theophylline.[1] Extracorporeal removal has also been used for cases of serious poisoning from a variety of other toxins, such as methotrexate, valproic acid, and phenobarbital.[2–4] In recent years the indications for extracorporeal removal have changed as new drugs have been introduced and others have become obsolete. Improvements in supportive care, changes in gastrointestinal decontamination philosophies,[5,6] and the introduction of relevant antidotes, such as fomepizole, also influence the indications for extracorporeal removal of toxins. Unfortunately, the current epidemiology of the use of extracorporeal removal techniques for poisoning is largely unknown.

The American Association of Poison Control Centers developed the National Data Collection System in 1983 as a database to gather and catalogue exposures reported to participating poison centers. Ten years later, in 1993, this system was revamped with fields that allowed collection of more detailed information on each reported exposure, and it was renamed the Toxic Exposure Surveillance System (TESS). In 2007 it became the National Poison Data System.

The TESS database possesses information on each reported exposure under the following major fields: Demographics of Exposure, Route of Exposure, Clinical Effects, Therapeutics, and Outcomes. Each major field has many minor fields allowing detailed information to be recorded, usually in a check-box fashion. Specifically, the Therapeutics field allows specialists in poison information to record both the recommendation for and the actual occurrence of a variety of therapeutic options including gastrointestinal decontamination, antidote administration, cardiac and respiratory support modalities, and extracorporeal removal techniques.

Since its inception, the TESS database has been periodically modified to expand certain data fields, as well as to delete others. In 1985, TESS could only record the names of

up to two toxins for each case. Beginning in 1993, TESS could record the total number of toxins involved for each case but could only document the names of two toxins. Also, the field for PD was removed and thus no longer recorded. Beginning in 2000, TESS was able to record a limitless number of toxin exposures with the names of each specific toxin for each case. The American Association of Poison Control Centers summarizes select portions of the data in a published annual report. Through 1986, specific information about the indications for extracorporeal removal was included in these annual reports but not since.

The purpose of this study was to define trends in the use of HD, HP, and PD as therapeutic modalities for toxic exposures in the United States over a 21-year period of poison center data recorded in the TESS database.

RESULTS

From 1985 to 2005 there were a total of 21,341 cases that had HD, HP, and/or PD recommended and/or performed with 19,351 cases receiving extracorporeal removal. There were 13,995 one-toxin exposures, of which 12,706 received HD, 1261 received HP, and 28 received PD. There were 3577 two-toxin exposures, of which 3531 received HD, 351 received HP, and 6 received PD; 311 cases were exposed to two toxins listed in Table 1. There were 1779 multi-toxin exposures, of which 2027 received HD and 89 received HP (PD was no longer recorded in TESS); 292 cases were exposed to two toxins listed in Table 1, 18 cases exposed to three toxins, and 3 cases exposed to four toxins (Figure 1).

When normalized for the number of cases reported annually (per million calls), the number of cases receiving HD has steadily increased from 231 in 1985 to 707 in 2005. The normalized number of cases receiving HP was 53 in 1985, sharply rose to a high of 132 in 1987, and then rapidly decreased to below 29 by 1995 (Figure 2). The normalized number of cases receiving PD was 2.2 in 1985, rising to a high of 5.5 in 1986, and then decreasing to 1.6 by 1991 (Figure 3).

The most common toxins responsible for HD are shown in Table 2. During this 21-year period, lithium and ethylene glycol were the most common. Although salicylates, methanol, and theophylline rounded out the top five from 1985 to 2000, from 2001 to 2005, valproic acid and acetaminophen increased dramatically, surpassing methanol and theophylline.

The most common toxins responsible for cases receiving HP are shown in Table 3. Theophylline was the most common toxin from 1985 to 2000, but then fell off from 2001 to 2005. Carbamazepine consistently remained high on the list, becoming the most common toxin for HP from 2001 to 2005.

After excluding cases with non-toxin-related, medical indications for extracorporeal treatment, the normalized numbers of cases receiving HD and/or HP for aminophylline and theophylline, antiepileptics (for example, carbamazepine, phenytoin, valproic acid), ethylene glycol, lithium, methanol, mushrooms, paraquat, salicylates, and sedative hypnotics (for example, carisoprodol, chloral hydrate, ethchlorvynol, meprobamate) were calculated. The trends for the most commonly accepted indications (for example, theophylline, ethylene glycol, lithium, methanol, and salicylates) are shown graphically in Figure 4, whereas the results for the remaining toxins are listed in Table 4.

The normalized number of theophylline cases per million calls receiving HD was at a high of 28 in 1994 and decreased to 4.5 in 2005. A similar trend was observed in normalized number of cases receiving HP, with a high of 21.3 in 1994, decreasing to 1.3 in 2003. There were no theophylline cases reportedly receiving HP in 2004 or 2005. Interestingly, the normalized number of ethylene glycol cases receiving HD and/or HP has increased from 74.2 in 1993 to 171.2 in 2005, whereas cases of methanol exposures experienced a less dramatic increase from 25.1 in 1993 to 40.4 in 2005. The normalized number of lithium cases receiving HD and/or HP also increased from 81.1 in 1993 to 141.5 in 2005. The normalized number of salicylate cases receiving HD and/or HP experienced a large increase from 30.3 in 1993 to 89.1 in 2005.

For our *post hoc* analysis, there were a total of 248 cases that had extracorporeal removal performed during the years 2000–2005: 243 received HD, 4 cases received HP, and 1 additional case as receiving both HD and HP. We excluded 108 cases with an exposure to a toxin not listed in Table 1. Of the remaining 140 cases with an exposure to a toxin listed in Table 1, 5 cases were thought to have received extracorporeal removal for another non-toxin-related issue, meaning that 5 out of the 140 cases (3.6%) would be falsely included using our inclusion criteria and assumptions. Further *post hoc* analysis revealed 13 cases that would have been excluded for having unrelated medical indications for HD. Of these 13 cases, 12 most likely received HD for toxin-related issues, meaning that 12 out of the 140 cases (8.6%) were falsely excluded.

DISCUSSION

We report the first comprehensive epidemiologic analysis of TESS data regarding the use of extracorporeal removal techniques. During the 21-year period of poison center data collection there was an increase in reported use of HD and a decrease in the reported use of HP. Several reasons may account for these trends. First and foremost, because of the improved efficacy of HD it may have replaced HP in many cases. Currently, synthetic dialysis membranes (for example, polysulfone) with greater dialysance are used more frequently than older cellulose acetate or cuprophane membranes.[7] Using theophylline as an example, these newer high-flux membranes and advanced HD technologies have allowed HD to obtain similar clearance rates when compared to the classical HP technique. This is supported by a growing number of new indications to use HD to remove molecules with larger molecular weights including vancomycin, methotrexate, and phenobarbital.[7] Computerized ultrafiltration control and bicarbonate-based (rather than acetate-based)

Table 1 | Toxins with generally accepted indications for extracorporeal removal in an overdose setting

Toxins	TESS: major category	TESS: minor category
Aminoglycosides[a]	Systemic	Antibiotic: systemic (p.o., i.v., i.m.) preparation
	Topical	Antibiotic: topical (dermal, otic, ophthalmic, nasal) preparation
	Unknown	Antibiotic: unknown preparation
Aminophylline	Aminophylline/theophylline	Aminophylline/theophylline
Atenolol[a]	β-Blocker	β-Blocker (include propanolol)
Carbamazepine	Carbamazepine	Carbamazepine
Carisoprodol	Carisoprodol	Aspirin with carisoprodol
	Carisoprodol (formulated alone)	Carisoprodol (formulated alone)
Chloral hydrate	Chloral hydrate	Chloral hydrate
Disopyramide[a]	Antiarrhythmic: other	Antiarrhythmic (quinidine, bretyllium, procainamide, etc.)
Ethchlorvynol	Ethchlorvynol	Ethchlorvynol
Ethylene glycol	Ethylene glycol	Automotive product
	Ethylene glycol	Excluding automotive/aircraft/boat product
Isopropanol	Isopropanol	Glass cleaner
	Isopropanol	Excluding rubbing alcohols and cleaning substance
	Isopropanol	Misc. cleaning agent
	Isopropanol	Wall/floor/tile/all-purpose cleaner
	Isopropanol with methyl salicylate	Rubbing alcohol
	Isopropanol without methyl salicylate	Rubbing alcohol
Lithium	Lithium	Lithium
	Lithium	Disc battery: lithium
Meprobamate	Meprobamate	Meprobamate
Methanol	Methanol	Automotive product
	Methanol	Excluding automotive product
	Methanol	Misc. cleaning agent
Methotrexate[a]	Antineoplastic	Antineoplastic drugs—miscellaneous
Mushroom	Cyclopeptide	Mushroom: cyclopeptide
	Orellanine	Mushroom: orellanine
	Other potentially toxic	Other potentially toxic mushroom
	Unknown	Unknown mushroom
Paraquat	Paraquat	Paraquat
Phenobarbital[a]	Long acting	Barbiturate: long acting
	Short/intermediate acting	Barbiturate: short and intermediate acting
	Unknown type	Barbiturate: unknown
Phenothiazine	Phenothiazine	Phenothiazine
Phenytoin	Phenytoin	Phenytoin
Salicylates	Adult formulation	Aspirin
	Aspirin with other ingredient	Aspirin with other ingredient
	Aspirin without other ingredient	Aspirin without other ingredient
	Camphor/methyl salicylate	Camphor and methyl salicylate
	Codeine	Aspirin with codeine
	DXM	APAP/ASA decon/antihist/without PPA/DXM
	Methyl salicylate	Methyl salicylate
	Other drug: adult formulation	Aspirin with other drug
	Other opioid	Aspirin with other opioid
	Oxycodone	Aspirin with oxycodone
	Pediatric formulation	Aspirin
	Salicylate containing	Antacid: salicylate containing
	Unknown formulation	Aspirin: unknown if adult or pediatric
	With opioid	ASA/decon/antihist/PPA/without opioid
	With opioid	ASA/decon/antihist/without PPA and opioid
Theophylline	Aminophylline/theophylline	Aminophylline/theophylline
Trichloroethanol[a]	Chlorinated hydrocarbon only	Chlorinated hydrocarbon only (alone)
	Halogenated hydrocarbon: other	Other halogenated hydrocarbon
	Other	Other type of alcohol
	Unknown	Unknown type of alcohol
	Unknown rubbing alcohol	Rubbing alcohol: unknown
Valproic acid	Valproic acid	Valproic acid

APAP, acetaminophen; ASA, acetylsalicylic acid or aspirin; DXM, dextromethorphan; PPA, phenylpropanolamine; TESS, toxic exposure surveillance system.
[a]These toxins were not analyzed because they did not have their own specific Major or Minor Category in the TESS database.

dialysate are other innovations during the study period that have improved patient tolerance of HD. Along with improved HD technique there has been a substantial decrease in the availability of HP cartridges[8] and some evidence suggesting rapid saturation of HP cartridges resulting in a reduced extraction ratio.[9] As a result of these factors, it is reasonable

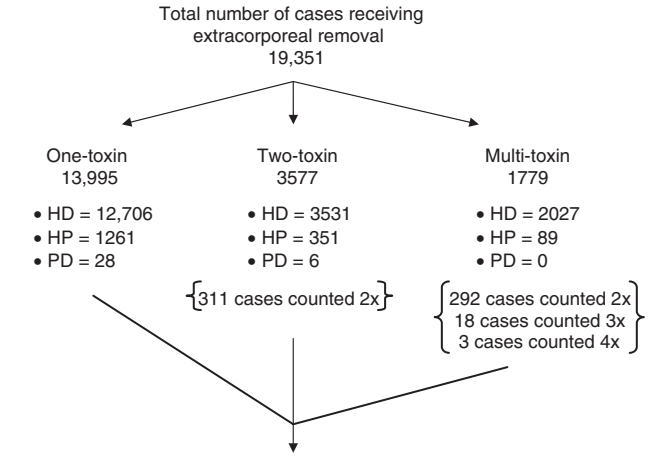

Figure 1 | Summary of analysis of TESS data. HD, hemodialysis; HP, charcoal hemoperfusion; PD, peritoneal dialysis.

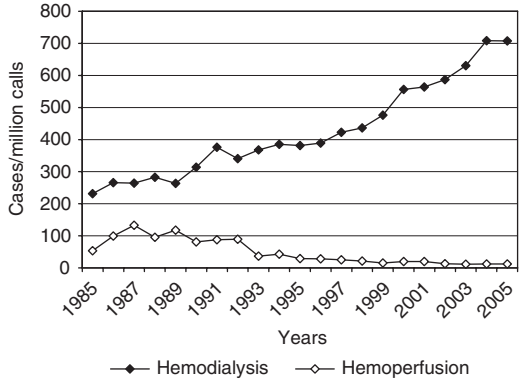

Figure 2 | Normalized number of cases receiving hemodialysis and hemoperfusion.

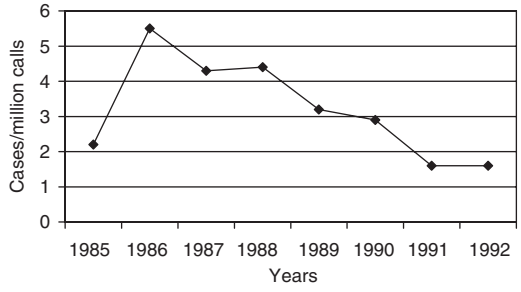

Figure 3 | Normalized number of cases receiving peritoneal dialysis. Peritoneal dialysis was no longer recorded in TESS after 1992.

to assume that many practicing nephrologists are less comfortable and experienced with HP and opt for HD instead.

The increased rates of HD use may also be reflective of a number of real and confounding events. It is possible that the severity of poisoning has increased, necessitating more aggressive interventions. In fact, data actually suggest increased national mortality rates from unintentional poisoning.[10] In addition, there may be trends in pharmacotherapeutics that result in more overdoses with drugs that are amenable to treatment with HD. The increased utilization of valproic acid in psychiatric patients might serve as an example of this shift. Likewise, the improved safety and availability of HD may have resulted in an increased use in cases that would have previously been treated conservatively. Alternatively, it is possible that there is a trend toward more aggressive treatment strategies by practitioners, or an increased awareness of HD as a treatment modality. The cost of HP cartridges is quite high in comparison to HD membranes in the United States and this contributes to their diminished availability;[8] this may not be an issue elsewhere in the world. Finally, it must be acknowledged that these trends might represent reporting biases on the behalf of treating physicians and improved follow-up and documentation on the part of poison centers. However, increased reporting frequency by treating physicians could not account for the changes as the rates of extracorporeal removal for HP and for some toxins have gone down, suggesting that the data reflect true and accurate trends. Whether such trends are occurring outside the United States is not known.

Regardless of any of the above reasons for the increased use of HD compared to HP, replacing HP with HD may not be appropriate in all clinical settings. For example, Table 4 shows that HD was the only extracorporeal removal technique performed for several patients exposed to paraquat. Although we do not know the circumstances or the specific reasons HD was initiated, we must stress that HP is the modality of choice for extracorporeal removal of paraquat and should be started as soon as possible (within 2–4 h) for maximum effectiveness.[11,12] Attempts to remove the drug later after exposure may be futile.

It is unclear what effect fomepizole has had on the use of HD in the treatment of methanol and ethylene glycol intoxications. Figure 4 clearly shows an increase in the use of extracorporeal removal techniques for both of these toxins. The decision of when and whether to use fomepizole alone, fomepizole with HD, or HD alone can be complicated and includes variables such as the clinical setting, acid-base status, manifestations of toxicity, serum level of toxic alcohol, and the availability of HD.[13,14]

The declining use of HP also parallels the decline in theophylline as an indication for extracorporeal removal. Prescriptions of this drug for asthma and chronic obstructive pulmonary disease have declined during the study period due to its toxicity and narrow therapeutic window.[15,16] Its

Table 2 | The most common toxins responsible for cases receiving hemodialysis (total number)

1985–1990	1991–1995	1996–2000	2001–2005
Lithium (397)	Lithium (714)	Lithium (1178)	Lithium (2583)
Ethylene glycol (290)	Ethylene glycol (649)	Ethylene glycol (1138)	Ethylene glycol (2077)
Methanol (236)	Salicylates (358)	Salicylates (580)	Salicylates (1490)
Salicylates (233)	Aminophylline (284)	Methanol (289)	Valproic acid (516)
Aminophylline (229)	Methanol (240)	Aminophylline (240)	Acetaminophen (474)
Phenothiazine (73)	Acetaminophen (135)	Acetaminophen (192)	Methanol (463)
Ethanol (73)	Ethanol (84)	Valproic acid (170)	Ethanol (297)
Acetaminophen (71)	Phenothiazine (65)	Ethanol (111)	Benzodiazepine (281)
Isopropanol (49)	Isopropanol (59)	Other (90)	Other (274)

Table 3 | The most common toxins responsible for cases receiving hemoperfusion (total number)

1985–1990	1991–1995	1996–2000	2001–2005
Aminophylline (167)	Aminophylline (162)	Aminophylline (58)	Carbamazepine (38)
Acetaminophen (25)	Barbiturate (24)	Carbamazepine (16)	Lithium (30)
Barbiturate[a] (23)	Acetaminophen (12)	Benzodiazepine (14)	Ethylene glycol (22)
Carbamazepine (15)	Carbamazepine (11)	Valproic acid (13)	Acetaminophen (19)
Without opioid[b] (11)	Salicylates (8)	Other (12)	Valproic acid (17)
Mushroom (11)	Mushroom (6)	Ethylene glycol (9)	SSRI (17)
Salicylates (10)	Unknown[c] (5)	SSRI (9)	Phenothiazine (15)
Unknown[c] (9)	Amitriptyline (5)	Barbiturate[a] (8)	Ethanol (12)
Food poisoning[d] (8)	Valproic acid (4)	Lithium (7)	Biguanide (11)
Desipramine (8)	Doxepin (4)	Methanol (7)	Other (10)
Amitriptyline (8)	Barbiturate[e] (4)		Salicylates (10)
Antiarrhythmic[f] (8)	Antiarrhythmic[f] (4)		Carisoprodol (10)
	Bee/wasp/hornet (4)		
	Gastrointestinal irritant (4)		

SSRI, selective serotonin reuptake inhibitor.
[a]Long acting.
[b]Combination medication including a decongestant and antihistamine with or without acetaminophen, aspirin and phenylpropanaolamine.
[c]Unknown substance, unlikely to be a drug.
[d]Bacterial food poisoning: unknown type.
[e]Short and intermediate acting.
[f]Other antiarrhythmic: quinidine, bretylium, procainamide, etc.

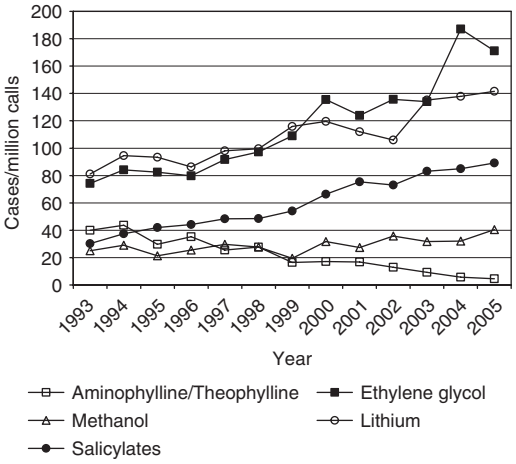

Figure 4 | Trends for the most commonly accepted indications for hemodialysis and/or hemoperfusion.

availability to adolescents who may be prone to using the drugs inappropriately or in suicide gestures has declined as well. This drug constituted one of the more frequent indications for HP but is now reasonably well removed by HD, which also addresses associated electrolyte abnormalities.

PD is an extracorporeal removal modality whose effectiveness not only relies on dialysate flow rate, the surface area of the peritoneum and the molecular weight of the compound, but is also dramatically decreased in hypotensive patients. Comparing PD and HD with regards to the half-life, clearance rate, and drug removal of theophylline, PD performance was much worse,[17] suggesting a limited role of PD in the overdose setting where rapid removal of toxin is desired. The very low number of cases reported to TESS and its eventual removal from the database in 1993 support the hypothesis that PD is too slow to be useful and should never be the method of choice for extracorporeal removal in the toxic exposure setting.

The *post hoc* analysis of our poison center data shows that our methods do incur a false inclusion rate of approximately 3.6% of cases and a false exclusion rate of approximately 8.6%. The net effect, if the New York data are representative of the national TESS data, is that cases are underreported and trends showing increases in overall numbers of procedures and for individual toxins are real. All of these cases were identified from their documentation, usually performed by specialists in poison information. Checking an incorrect box or not marking a specific box could result in the inclusion or

Table 4 | Number of cases receiving hemodialysis and/or hemoperfusion normalized per million calls reported to TESS

Exposure	Therapy	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
Carbamazepine	Total	5.1	3.1	1.5	7.4	4.1	4.5	5.9	6.5	4.0	6.3	4.2	6.2	5.0
	HD	3.4	0.5	0.5	5.1	0.9	2.7	4.1	4.2	2.6	5.9	2.9	4.5	4.5
	HP	1.7	2.6	1.0	2.8	3.2	1.8	1.8	2.8	1.3	1.3	1.7	1.6	0.8
Carisoprodol	Total	0.6	0.0	1.0	0.9	0.5	3.6	1.4	3.2	2.6	4.6	4.6	4.5	3.3
	HD	0.6	0.0	1.0	0.9	0.5	3.6	1.4	3.2	2.2	4.2	4.6	4.5	3.3
	HP	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.4	0.4	0.0	0.0	0.0
Chloral hydrate	Total	1.7	2.1	2.5	0.9	0.5	0.0	1.4	0.0	0.9	0.8	0.0	0.0	1.2
	HD	1.1	2.1	2.5	0.9	0.5	0.0	1.4	0.0	0.9	0.8	0.0	0.0	1.2
	HP	0.6	0.0	0.5	0.0	0.0	0.0	0.0	0.0	0.0	0.4	0.0	0.0	0.0
Ethchlorvynol	Total	1.1	0.5	0.5	0.0	0.9	0.0	0.0	0.0	0.4	0.0	0.0	0.0	0.0
	HD	0.6	0.5	0.5	0.0	0.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	HP	1.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.4	0.0	0.0	0.0	0.0
Meprobamate	Total	1.7	1.6	0.5	1.4	0.0	0.0	0.0	0.0	0.4	0.0	0.4	0.4	0.0
	HD	1.1	1.6	0.5	1.4	0.0	0.0	0.0	0.0	0.4	0.0	0.4	0.4	0.0
	HP	0.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Mushroom	Total	1.7	0.0	0.5	0.5	1.8	1.3	0.9	0.9	1.3	1.7	0.8	0.4	0.4
	HD	1.1	0.0	0.5	0.5	1.8	1.3	0.9	0.9	0.0	1.3	0.8	0.4	0.4
	HP	0.6	0.0	0.0	0.0	0.5	0.0	0.0	0.0	1.3	0.8	0.0	0.0	0.0
Paraquat	Total	2.3	0.5	0.0	1.4	0.0	0.0	0.9	0.5	0.9	0.8	0.8	0.0	0.8
	HD	1.7	0.0	0.0	1.4	0.0	0.0	0.5	0.5	0.9	0.8	0.8	0.0	0.8
	HP	0.6	0.5	0.0	0.5	0.0	0.0	0.5	0.0	0.4	0.0	0.0	0.0	0.0
Phenytoin	Total	2.9	2.1	3.0	1.9	2.7	2.2	2.3	5.1	0.9	1.7	1.7	2.1	1.7
	HD	2.9	1.0	2.5	1.9	2.7	1.8	1.4	5.1	0.9	1.7	1.7	1.6	1.2
	HP	0.6	1.0	0.5	0.0	0.0	0.4	0.9	0.0	0.0	0.0	0.0	0.4	0.4
Valproic acid	Total	2.9	5.2	5.4	9.7	14.1	16.1	22.7	23.5	25.1	24.4	21.7	21.3	20.6
	HD	1.1	5.2	4.4	8.8	12.8	14.7	20.9	22.6	24.7	24.4	20.9	21.3	20.6
	HP	1.7	0.5	1.0	0.9	1.8	2.2	2.3	0.9	0.4	0.0	1.3	0.4	0.4

HD, hemodialysis; HP, charcoal hemoperfusion.

exclusion of cases; however, it would be unlikely for this to influence the trend in the data.

In addition to potential reporting biases discussed above, it is essential to note that the TESS database does not contain a specific field that allows for qualitative or quantitative confirmation of the reported toxin, such as a serum level. This information is typically located in the free text fields, which are not stored on the national level and therefore not available for routine analysis. However, we assume that these exposures are indeed intoxications for several reasons. First, these patients are receiving an extracorporeal removal therapy which is a complex process involving a nephrology consult, the placement of a large-bore intravenous catheter, and usually an extracorporeal removal team or center. Second, although the overall database is comprised largely of self-reported calls from home, these cases are unique in that the information is usually provided by medical personnel calling from a health care facility to request assistance in managing an ill patient.

We assumed if a case was exposed to a toxin with common indications for extracorporeal removal (listed in Table 1) and received HD, HP, or PD, then they received this therapy for that toxin. One can create scenarios that can explain why this may not be the case. For example, a patient who experiences hypotension caused by a calcium channel blocker overdose may develop renal failure requiring HD; however, if this patient was also on carbamazepine, we would have classified this case as HD for carbamazepine. Although our *post hoc* analysis did show a false inclusion rate of 3.6%, our false exclusion rate was higher at 8.6%.

Finally, continuous renal replacement therapy has been used increasingly for toxin removal, as this may be the only extracorporeal removal technique practical for hemodynamically unstable patients.[11,18,19] However, there are currently no data fields in TESS to allow trends to be tracked. As the efficacy and effectiveness of these continuous modalities in the treatment of the poisoned patient remains unproven,[19] the accumulation of data regarding the current utilization patterns of these techniques would be worth accomplishing in future TESS efforts.

Our data suggest that acetaminophen is increasingly reported as a toxin leading to use of extracorporeal removal. Although acetaminophen is amenable to extracorporeal removal, HD is rarely if ever indicated. Virtually all patients present after peak plasma concentration is achieved, *N*-acetylcysteine is an antidote with documented efficacy, and

extracorporeal removal has never been demonstrated to alter outcome in this setting. The explanation for increasing use of HD in our data requires further investigation.

In conclusion, among cases with toxic exposures reported to United States poison centers between the years 1985 and 2005, the use of HD has increased and the use of HP has decreased. PD was never commonly reported, generally has no accepted indications in poisoning, and is no longer recorded in TESS. Ethylene glycol and lithium were the most common toxins responsible for HD during this time period, and HD as a treatment modality for these exposures continues to increase in frequency. Theophylline, once a common potential toxin leading to HD and/or HP, has decreased dramatically as an indication. The profile of toxins responsible for HD and HP appears to be changing with, for example, increased reports of acetaminophen and valproic acid exposures, which requires further evaluation.

MATERIALS AND METHODS

Data were accessed for all cases recorded electronically in the TESS database from 1985 to 2005 where therapeutic options for HD, HP, or PD were not null. This approach yielded four different types of cases where extracorporeal removal was (1) performed, (2) recommended and performed, (3) recommended but not performed, and (4) recommended, but unknown if performed. Data were entered into a Microsoft Access database, from which queries were built and tallied.

Cases were initially divided into one-toxin exposures, two-toxin exposures, and multi-toxin (three or more) exposures. Only cases in which extracorporeal removal was known to have been performed were used for further analysis. Each toxin exposure recorded in TESS contains two headings: Major Category and Minor Category. The Major Category is either a common toxin (for example, methanol), a class of toxin (for example, benzodiazepine), or a toxin description (for example, adult formulation), whereas the Minor Category either mirrors the Major Category, further classifies the Major Category (for example, automotive product), or specifies the Major Category (for example, aspirin: adult formulation).

A list of toxins that have generally accepted indications for extracorporeal removal in overdose was adopted from a standard reference[1] and is presented along with the corresponding descriptors from TESS in Table 1. As illustrated in the table, some toxins did not have specific entries in the TESS database and thus could not be analyzed. These included aminoglycosides, atenolol, disopyramide, methotrexate, phenobarbital, and trichlorethanol. In addition, even though ethanol is amenable to extracorporeal removal, it was not included in Table 1 because the clinical circumstances in which ethanol removal is appropriate are extremely rare, it is a very common co-ingestion in an intentional overdose, and it is also used as a therapy for toxic alcohol ingestion.

For the purposes of this study, cases with exposures to any of the toxins listed in Table 1 that had extracorporeal removal performed were assumed to have received that therapy for that particular toxin. Cases with exposures to combination products that contained a toxin listed in Table 1 were assumed to have extracorporeal removal for the listed toxin; for example, if the exposure was a combination of an opioid and aspirin, then it was assumed extracorporeal removal was performed for salicylate removal. However, if a combination product contained two toxins listed in Table 1 (for example, 'aspirin with carisoprodol'), then this product remained as its own individual category and was not counted separately for each toxin. Thus, cases exposed to two or more different toxins in Table 1 were counted twice or more, one for each toxin; the total number of these cases was reported. Cases with exposure to the same toxin in two different preparations were only counted once; for example, exposure to 'aspirin' and 'aspirin with oxycodone' would be counted once for salicylates.

Using this methodology, the most common toxins responsible for cases receiving HD and HP were totaled annually and reported as total number of procedures performed. To correct for potential biases introduced by annual variations in the size of the database (resulting from reporting trends and changes in the number of participating poison centers) these cases were normalized using the total number of exposures reported in each published annual TESS report. To help identify possible trends, the annual results were then grouped according to the following time periods: 1985–1990, 1991–1995, 1996–2000, and 2001–2005. Further analysis of PD therapy was not performed, as this therapy was not recorded in TESS after 1992.

Selected toxins listed in Table 1 were examined for trends in the use of HD and HP. These included aminophylline and theophylline, antiepileptics (for example, carbamazepine, phenytoin, valproic acid), ethylene glycol, lithium, methanol, mushrooms, paraquat, salicylates, and sedative hypnotics (for example, carisoprodol, chloral hydrate, ethchlorvynol, meprobamate). Initially, as described above, only those cases that had HD or HP either 'performed' or 'recommended and performed' were included. Next, the Clinical Effects major field for these cases was analyzed. Cases with renal effects (for example, creatinine, hemo/myoglobinuria, oliguria/anuria, renal failure) or miscellaneous effects (for example, creatine phosphokinase elevated, electrolyte abnormality, rhabdomyolysis) marked 'unrelated' or 'unknown if related' to the toxin were excluded from further analysis to prevent inclusion of cases where the toxin was present, but an extracorporeal removal technique was performed for commonly accepted medical reasons. As the ability to document if clinical effects were 'related', 'unrelated', or 'unknown if related' was introduced in the database in 1993, this analysis includes data only from 1993 to 2005. Again, as previously described, these cases were then normalized to the annual number of calls received by poison centers.

In an attempt to understand the limitations of this database we undertook a *post hoc* analysis of our own poison center's data. Our poison center is one of the oldest continually operated centers in the USA and receives between 40,000 and 50,000 exposures each year, representing approximately 2% of the national database. Because we have the complete records (including the free text areas) we were specifically able to address many of the potential limitations (for example, inability of TESS to record serum levels of particular toxins). Searchable computerized data exist at our center from 1 January 2000 forward. The complete electronic record of all cases receiving HD and/or HP from 2000 to 2005 were retrieved and printed from the database. All cases were sorted by two of the authors (WH and RH) as described in the methodology above. Those cases with an exposure to toxins listed in Table 1 were given to two medical toxicology fellows employed at the poison center who were unaware of the present paper. For each case they were asked one question: do the free text notes contradict that extracorporeal removal was performed for the toxin-related issue? When they disagreed, a third fellow was used to adjudicate the results. The number of these cases would give an indication of a false inclusion

rate. In addition, in an attempt to ascertain a false exclusion rate, the two authors (WH and RH) reviewed these cases again selecting those that would have been excluded for having unrelated medical indications for HD, as described in the methodology above. Cases with evidence in the free text to suggest that extracorporeal removal was indeed performed for a toxin-related issue were totaled and a false exclusion rate was calculated.

DISCLOSURE

All the authors declared no competing interests.

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Author contributions: William J Holubek had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Holubek, Hoffman, Goldfarb, Nelson.

Acquisition of data: Holubek.

Analysis and interpretation of data: Holubek, Hoffman, Goldfarb, Nelson.

Drafting of the paper: Holubek, Hoffman.

Critical revision of the paper for important intellectual content: Holubek, Hoffman, Goldfarb, Nelson.

Statistical analysis: Holubek.

Supervision: Hoffman, Goldfarb, Nelson.

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