Common Toxidromes and the Role of Extracorporeal Detoxification

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Extracorporeal modalities have been used for detoxification for decades, with hemodialysis the preferred and most commonly used modality. Salicylates, lithium, methanol, and ethylene glycol are the most common poisonings treated with dialysis. For each of these common poisonings, a description of the toxidrome including pharmacokinetics, clinical presentation, an overview of treatment, and the role and application of dialysis is outlined. Inhibition of alcohol dehydrogenase to prevent the formation of toxic metabolites in methanol and ethylene glycol is discussed in detail, including the use of fomepizole and ethanol to complement and in some cases prevent the need for hemodialysis. Hemodialysis has been attempted to treat many poisonings, often without success. A description of EXTRIP (Extracorporeal Treatments in Poisoning), a multidisciplinary project examining the evidence for extracorporeal treatments in poisoning, is also described. Recommendations for poisoning with acetaminophen, baclofen, barbiturates, carbamazepine, digoxin, metformin, phenytoin, thallium, theophylline, tricyclic antidepressants, and valproic acid are provided in a comprehensive table.

Key Words: Hemodialysis, Salicylates, Lithium, Methanol, Ethylene glycol

Extracorporeal modalities have been used for detoxification for decades, with hemodialysis the preferred and most commonly used modality.[1] The toxidromes reviewed below—salicylates, lithium, methanol, and ethylene glycol—are the most common poisonings treated with dialysis.[2]

SALICYLATES

Salicylates are compounds chemically related to salicylic acid, a medicinal derivative of the bark of the willow tree. A subclass of nonsteroidal anti-inflammatory drugs that include acetylsalicylic acid (aspirin) and methyl salicylate (oil of wintergreen), they are widely available without prescription and ingested or used topically for their analgesic, antipyretic, and anti-inflammatory properties. Salicylates have a well-characterized acute and chronic toxicity, and will be well known to nephrologists. Although ingested aspirin is the most common toxic exposure, methyl salicylate has lethal potential if ingested in small quantities, particularly in children.

When ingested, salicylates are absorbed in the jejunum, although enteric coating of tablets may significantly prolong absorption time. It should be noted that bismuth salicylate (eg, Pepto-Bismol; Procter & Gamble) ingestion also results in significant enteric salicylate absorption.[3] Over application of concentrated topical formulations of methyl salicylate, such as over-the-counter pain relieving cream (eg, Bengay; Johnson & Johnson), can cause fatal toxicity, demonstrating dermal absorption of this lipid soluble salicylate.[4] Dermal absorption of trolamine salicylate (eg, Aspercreme; Chattem Inc) may be significantly less than methyl salicylate.[5] Upon absorption and following metabolism, both acetylsalicylic acid and salicylic acid are bound by serum albumin. Metabolism of acetylsalicylic acid (and other salicylates) to salicylic acid occurs by hydrolysis during first pass metabolism. Salicylic acid is partly eliminated unchanged, via the kidneys, which can be increased with urinary alkalinization (see article in this issue with a section on Enhanced Elimination). Salicylic acid is also eliminated following conjugation with glycine and glucuronic acid.

Clinical features of acute intoxication include tinnitus, deafness, tachycardia, diaphoresis, flushing, nausea and vomiting, hypovolemia, and findings of petechiae.[6] Organ dysfunction occurs due to uncoupled oxidative phosphorylation, mitochondrial dysfunction, and cytotoxicity. The most severe presentation is acute respiratory distress syndrome and cerebral edema due to increased vascular permeability. A mixed acid-base disorder is classic, with hyperventilation and respiratory alkalosis, and high anion gap metabolic acidosis. Eventual respiratory fatigue produces a respiratory acidosis. Of note, mitochondrial toxicity of salicylates can also result in a type B lactic acidosis. In young children, hyperventilation and respiratory alkalosis may not be evident, and central nervous system (CNS) signs (agitation, lethargy, coma) that correlate with acidemia may be more pronounced. Additionally, chronic toxicity may involve symptoms of CNS dysfunction in the setting of normal salicylate concentrations.

Treatment involves initial fluid volume resuscitation and gastrointestinal decontamination with multiple-dose activated charcoal. Continuous intravenous bicarbonate infusion should be administered to correct acidemia and reduce entry of salicylate to the CNS, as well as enhance elimination by ion trapping in the urine. Alkalemia in the setting of a respiratory alkalosis is not a contraindication to sodium bicarbonate infusion. Urinary pH of >7.5 should be targeted, with careful observation to prevent alkalemia and electrolyte derangements such as hypokalemia and ionized hypocalcemia.[7] Urinary alkalinization may be sufficient therapy in mild poisonings, but should

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also be started as an initial therapy in patients determined to need dialysis, and following dialysis during assessment for rebound. Fluid resuscitation and bicarbonate should not, however, be given to patients with acute respiratory distress syndrome or cerebral edema.

Despite protein binding, salicylates are dialyzable due to low molecular weight and small volume of distribution. Intermittent hemodialysis is the preferred modality and is recommended for any patient with levels greater than 100 mg/dL, severe acidemia (pH $<$ 7.2), CNS dysfunction, and risk of pulmonary edema; and for levels greater than 90 mg/dL in patients with impaired kidney function.[8] When attempted, hemodialysis should be performed with high-efficiency and high-flux hemofilters for at least 4 hours. Repeat levels should be drawn at approximately 2-hour intervals following treatment due to the possibility of drug rebound. Repeat hemodialysis treatments may be required, until levels remain below 20 mg/dL.

LITHIUM

Lithium (Li^{3+}) salts are used to treat bipolar affective disorder. Treatment efficacy explains the continued pharmacologic use of this metal despite a narrow therapeutic window and acute and chronic toxic potential. Lithium carbonate in extended release formulation is more widely prescribed, although immediate release formulations and lithium citrate may be encountered. The route of exposure is ingestion. Immediate-release lithium is rapidly absorbed, reaching peak blood concentration within 3 hours, while sustained release formulations peak within 6 hours. Once absorbed, lithium is not metabolized and does not bind with proteins, but distributes widely in total body water. A slower phase of distribution into the CNS follows, with passage across the blood-brain barrier. Lithium is filtered, transported like sodium, and eliminated from the body by the kidneys. Clearance will be reduced by any decrease in glomerular filtration rate (GFR) or increase in proximal tubular reabsorption, as with hypovolemia, nonsteroidal anti-inflammatory drug use, and thiazide diuretics. Clearance will increase with improved GFR or natriuresis as with volume expansion, loop diuretics, and distal tubule diuretics such as amiloride and triamterene. In fact, most cases of lithium toxicity involve acute overdosage or accumulation during chronic therapy.

CLINICAL SUMMARY

- Salicylates, lithium, methanol, and ethylene glycol are the most common poisonings treated with dialysis.
- Fomepizole and ethanol are competitive inhibitors of the oxidation of methanol and ethylene glycol, and prevent the formation of toxic metabolites.
- The EXTRIP group has been reviewing and publishing evidence-based recommendations on the use of dialysis and related therapies in poisoning.

Acute neurologic toxicity involves CNS symptoms progressing from lethargy and confusion to obtundation, coma, or seizures. Motor symptoms include fine tremor, spasticity and hyperreflexia, dystonia or choreiform movements, cogwheel rigidity, and cerebellar signs. Acute toxicity may also present with vomiting and diarrhea, or cardiac effects such as myocarditis with electrocardiogram changes, or heart block. Nephrotoxicity, most frequently, is noted to be nephrogenic diabetes insipidus. This impairment of urinary concentrating ability results from cellular Li^{3+} accumulation and interruption of glycogen synthase kinase-3β decreasing insertion of aquaporin 2 into the luminal surface of collecting duct cells.[9] Chronic renal toxicity of lithium includes persistent nephrogenic diabetes insipidus, distal renal tubular acidosis, chronic cystic interstitial nephritis, and nephrotic glomerulopathies.[10] Long-term lithium therapy and high cumulative dose or history of toxicity have been associated with progressive kidney disease; although in the absence of toxicity, other studies have shown no long-term decline in GFR with chronic lithium therapy.[11] A more unusual chronic finding is the syndrome of irreversible lithium-effectuated neurotoxicity that includes cerebellar and cognitive deficits, and may be the result of demyelination.[12]

For acute intoxication, with levels less than 2.5 mEq/L, volume expansion with isotonic saline is usually sufficient, as drug-induced urinary concentrating defects and volume depletion are typical. Although volume resuscitation may improve kidney function and endogenous renal lithium clearance, forced diuresis does not increase lithium clearance.[13] Activated charcoal is not beneficial as it does not bind the ionized lithium, but enteric decontamination with polyethylene glycol whole bowel irrigation can reduce the risk of severe poisoning even following significant ingestion.[14] Sodium polystyrene sulfonate resin also binds ingested lithium and modestly reduces the oral bioavailability,[15] decreases half-life, and increases elimination.[16] Due to low molecular weight, lack of protein binding, high water solubility, and a low V_d, lithium is readily dialyzable. The role of extracorporeal therapy has been systematically reviewed, and evidence-based indications provided.[17] Conventional intermittent hemodialysis is the preferred modality. Mean clearance of lithium with intermittent hemodialysis can exceed 100 mL/min, as compared with mean endogenous renal clearance of only 10 mL/min in intoxicated subjects. Intervention is recommended for all patients with decreased consciousness, seizures, or severe dysrhythmia, and any patient with a level $>$4.0 mEq/L and impaired kidney function. Extracorporeal intervention is suggested for any patient who is confused, with a level $>$5.0 mEq/L, or expected to have a level above 1.0 mEq/L after 36 hours of supportive care. Treatment with dialysis should continue until clinical improvement or level $<$1.0 mEq/L. Initial treatment should involve intermittent hemodialysis with a high-efficiency dialyzer for at least 4 hours. Physicians should anticipate rebound in level about 6-12 hours following treatment due to redistribution or continued absorption, and continuous renal replacement therapy can be considered for subsequent treatment.

METHANOL

Methanol is a widely available, but potentially fatal intoxicant. Intentional ingestion of methanol intended for use as a commercial or industrial solvent or automotive fuel is a common presentation in suicide attempts. Due to similar appearance and odor to ethanol, accidental ingestion of methanol is frequent among derelict alcoholics, or in outbreaks of mass poisoning from adulterated bootleg liquor. Ingestion is the major route of poisoning, although toxicity may occur with dermal absorption or inhalation. As little as 10 mL of pure methanol can cause blindness, while ingestion of 30 mL can be fatal.[18] Ingested methanol is rapidly and completely absorbed with peak blood levels by 30-60 minutes.[19] Elimination (and toxification) occurs via biotransformation, while only 5% of methanol is excreted unchanged in the urine. Intoxication may present with inebriation, somnolence, and stupor, and an evident osmolar gap. A latent period follows, 12-24 hours, during which biotransformation within the liver and kidneys results in the toxic metabolites formaldehyde (by alcohol dehydrogenase or AD) and formic acid (by aldehyde dehydrogenase), and a high anion gap metabolic acidosis (Fig 1). Retinal toxicity causing blurred vision and blindness, and evident optic disc hyperemia, is frequent. Vomiting, gastrointestinal distress, and pancreatitis may be pronounced. Severe complications include necrosis of the putamen,[20] coma, opisthotonus, convulsions, and death. Severe acidosis is usually evident from the Kussmaul (deep and labored) respirations. Formic acid is the principal cytotoxin, inhibiting cytochrome oxidase while also increasing anion gap and decreasing bicarbonate.

Due to rapid absorption and distribution, there is no role for enteric decontamination, unless early presentation allows gastric lavage shortly after ingestion.[21] Treatment focuses on prevention of the formation of toxic metabolites through inhibition of AD, promotion of end metabolism through administration of folinic acid, and dialysis to remove methanol and metabolites and correction of metabolic acidosis. Although ethanol and fomepizole (4-methylpyrazole or 4-MP) both inhibit AD,[22] fomepizole has more predictable kinetics, longer duration of action, and fewer adverse effects. Cost may be prohibitive, but fomepizole is preferred if available. Dosing is 15 mg/kg intravenous (IV) loading and then 10 mg/kg IV every 12 hours, increased to 15 mg/kg IV every 12 hours for prolonged intoxications, or schedule shortened to every 4 hours and a dose given at the start if dialysis is necessary. If fomepizole is unavailable, ethanol can be used to competitively inhibit AD. An intravenous infusion of 10% ethanol should be used (loading dose of 800 mg/kg [or 8 mL/kg] followed by 80-130 mg/kg/h [or 0.8-1.3 mL/kg/h]), with regular monitoring to maintain a serum ethanol concentration of 100-200 mg/dL. Higher maintenance dose may be necessary (150 mg/kg/h or 1.5 mL/kg/h) in chronic drinkers. In cases where fomepizole and IV ethanol are unavailable, a 20% ethanol solution may be administered orally or via nasogastric tube. Folinic acid is a cofactor for the enzymatic end metabolism of formate to H_2O and CO_2, and 50 mg IV should be administered at intervals. The use of

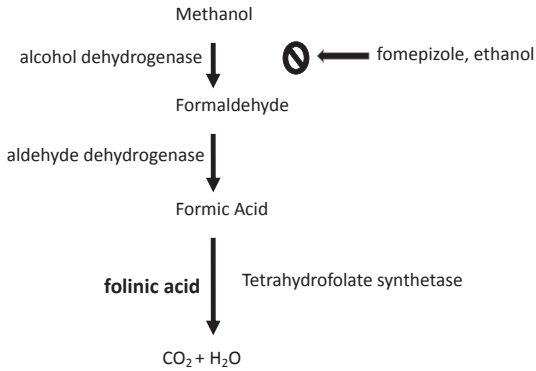

Figure 1. Metabolism of methanol.

extracorporeal modalities for methanol poisoning has been systematically reviewed, resulting in evidence-based recommendations.[23] Intermittent hemodialysis is the preferred modality and is recommended for likely or confirmed poisoning in the setting of a new neurologic or vision deficit; or metabolic acidosis or acidemia with pH $\leq$ 7.15; or elevated anion gap >24 mmol/L; or methanol concentration > 70 mg/dL with fomepizole, or > 50 mg/dL without an AD blocker; or impaired kidney function. Treatment should involve intermittent hemodialysis with a high-efficiency dialyzer for at least 4 hours, during which mean clearance of methanol exceeds 200 mL/min. Dialysis should continue until levels are below 20 mg/dL, with monitoring for rebound of plasma concentrations. Recent studies have confirmed the superiority of intermittent dialysis over continuous therapies for efficient acidosis correction, as expected.[24]

With less severe poisoning, and methanol levels below 20 mg/dL, fomepizole treatment alone is sufficiently safe and effective.[25] Kinetic studies during fomepizole treatment have shown greatly prolonged methanol half-life—mean 52 hours, maximum 87 hours. Dialysis is considerably more expedient, cost-effective, and prevents prolonged intensive care unit admission than fomepizole alone.[26,27]

ETHYLENE GLYCOL

Another toxic alcohol commonly ingested by suicidal persons or accidently by alcoholics is ethylene glycol. Widely

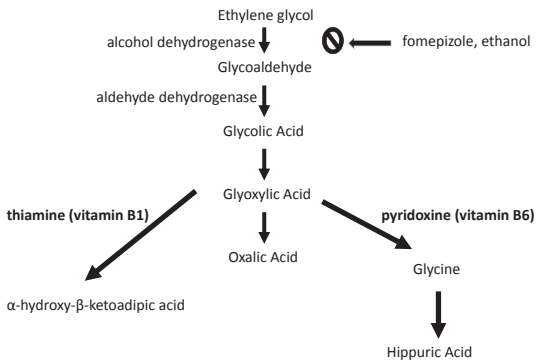

Figure 2. Metabolism of ethylene glycol.

Table 1. Recommendations for Extracorporeal Detoxification in Select Poisonings

Drug/Intoxicant	Treatment Recommendations
Acetaminophen[34]	Severe poisoning with acetaminophen in the setting of any of the following: • level >1000 mg/L, and NAC is not administered • level >700 mg/L and altered mental status, metabolic acidosis, and elevated lactate, and NAC is not administered • level >900 mg/L and altered mental status, metabolic acidosis, and elevated lactate, even if NAC is administered Intermittent hemodialysis is the preferred modality
Baclofen[35,36] (not EXTRIP)	Severe poisoning with baclofen in the setting of any of the following and in the presence of acutely decreased GFR or ESRD: • encephalopathy, seizures, coma, or areflexia • hypothermia, respiratory depression, or hypotension Intermittent hemodialysis is the preferred modality
Barbiturate[37]	Severe poisoning with long-acting barbiturates in the setting of any of the following: • prolonged coma is present or expected • shock after resuscitation • toxicity despite multiple-dose activated charcoal Suggested intervention: • levels rise or remain elevated despite multiple-dose activated charcoal • mechanical ventilation is necessary Intermittent hemodialysis is the preferred modality
Carbamazepine[38]	Severe poisoning with carbamazepine in the setting of any of the following: • severe seizures, refractory to treatment • severe dysrhythmias Suggested intervention: • levels rise or remain elevated despite multiple-dose activated charcoal • prolonged coma or mechanical ventilation is necessary or expected Intermittent hemodialysis is the preferred modality
Digoxin[39]	Dialysis or extracorporeal treatment is not indicated for digoxin poisoning in any setting, including removal of digoxin-fab complexes
Ethylene glycol (not EXTRIP)	Likely or confirmed poisoning in the setting of any of the following: • acute kidney injury • anion gap metabolic acidosis • EG level >50 mg/dL (possible management with fomepizole rather than dialysis if no AKI or acidosis) Intermittent hemodialysis is the preferred modality
Lithium[17]	Likely or confirmed poisoning in the setting of any of the following: • decreased level of consciousness, seizures, or life-threatening dysrhythmia • level >4.0 mEq/L while kidney function is impaired Suggested intervention: • level >5.0 mEq/L • confusion • expected level >1.0 mEq/L with optimal management for 36 h Intermittent hemodialysis is the preferred initial modality
Metformin[40]	Severe poisoning with metformin in the setting of any of the following: • lactate level >20 mmol/L • acidemia with pH < 7.0 • shock, failure of supportive care, or decreased level of consciousness Intermittent hemodialysis is the preferred initial modality

(*Continued*)

Table 1. Recommendations for Extracorporeal Detoxification in Select Poisonings (*Continued*)

Drug/Intoxicant	Treatment Recommendations
Methanol[23]	Likely or confirmed poisoning in the setting of any of the following: • new neurologic or vision deficit • metabolic acidosis or acidemia with pH ≤ 7.15 • elevated anion gap >24 mmol/L • methanol concentration >70 mg/dL or 21.8 mmol/L in the context of fomepizole, or >50 mg/dL or 15.6 mmol/L in the absence of an AD blocker • impaired kidney function Intermittent hemodialysis is the preferred modality
Phenytoin[41]	Reasonable in severe poisoning with phenytoin in the setting of the following: • prolonged coma, present or expected • severe ataxia Intermittent hemodialysis is the preferred modality
Salicylates[8]	Likely or confirmed severe salicylate poisoning in the setting of any of the following: • level >100 mg/dL • level >90 mg/dL and impaired kidney function • altered mental status/CNS dysfunction, independent of salicylate concentration, without alternative explanation • hypoxemia or acute respiratory distress syndrome Suggested intervention when failure of supportive therapy or any of the following: • level >90 mg/dL • level >80 mg/dL and kidney impairment • pH ≤ 7.20 Intermittent hemodialysis is the preferred modality
Thallium[42]	Severe poisoning with thallium in the setting of any of the following: • high likelihood of thallium exposure by history or findings • thallium concentration >0.4 mg/L Intermittent hemodialysis is the preferred initial modality
Theophylline[43]	Severe poisoning with theophylline in the setting of any of the following: • level >100 mg/L in acute exposure • seizures • severe dysrhythmias • shock • rising level or deterioration despite supportive care Suggested intervention: • level >60 mg/L in chronic exposure • level >50 mg/L in patients <6 months or >60 years old • when multiple-dose activated charcoal cannot be administered Intermittent hemodialysis is the preferred modality
Tricyclic antidepressants[44]	Dialysis and extracorporeal treatments are not recommended for tricyclic antidepressant poisoning in any setting
Valproic acid[45]	Severe poisoning with valproic acid in the setting of any of the following: • level >1300 mg/L • shock • cerebral edema Suggested intervention: • level >900 mg/L • coma or mechanical ventilation is necessary • hyperammonemia • pH < 7.1 Intermittent hemodialysis is the preferred modality

Abbreviations: AD, alcohol dehydrogenase; AKI, acute kidney injury; CNS, central nervous system; EG, ethylene glycol; ESRD, end-stage renal disease; GFR, glomerular filtration rate; NAC, N-acetylcysteine.

available in antifreeze and de-icing solutions, it is odorless and sweet tasting, and also a significant cause of toxicity in pets. Ingestion is the principal route of poisoning, with dermal or inhalational exposure unlikely. Ingested ethylene glycol is readily absorbed, reaching peak blood levels in 1-4 hours, and is water-soluble and not protein bound.[28] As with methanol, elimination (and toxification) occurs through biotransformation, with about 20% excreted unchanged in the urine. Intoxication presents with inebriation (without odor), nausea and vomiting, as well as nystagmus, ataxia, and CNS depression. This period of intoxication lasts up to 12 hours, during which an osmolar gap is evident. From 12 to 36 hours, sequential biotransformation within the liver and kidneys results in the toxic metabolites glycolaldehyde (by AD) and glycolic acid (by aldehyde dehydrogenase), and finally oxalic acid (by glycolic acid oxidase via glyoxylic acid; and by glycolic acid dehydrogenase) (Fig 2). The osmolar gap disappears with metabolism of the parent alcohol and may not be present with late presentation. As organic acids accumulate, they cause a high anion gap metabolic acidosis and there is evident tachycardia, Kussmaul respirations, hypocalcemia with tetany, QT prolongation, and congestive heart failure. Oxalic acid is the principal cytotoxin, and deposits as calcium oxalate crystals in the myocardium and pericardium, cerebral vessels and meninges, and kidneys. Acute kidney injury with oliguria, interstitial nephritis, and hemorrhagic tubular necrosis with hematuria, and calcium oxalate crystalluria and stones are indicative of ethylene glycol nephrotoxicity.

Although gastric lavage may recover unabsorbed alcohol if performed within a few hours of ingestion, the role of enteric decontamination in the treatment of ethylene glycol poisoning is not established. As with methanol, treatment focuses on prevention of the formation of toxic metabolites through inhibition of AD, promotion of end metabolism, as well as elimination of ethylene glycol and metabolites with dialysis. Competitive inhibition of AD with fomepizole[29] or ethanol will prevent biotransformation of ethylene glycol and toxicity. Fomepizole is preferred if available, and dosing is as with methanol (see above). Fomepizole is indicated for patients with high clinical suspicion of ethylene glycol poisoning, and evident osmolar gap (>10 mOsm/L), anion gap metabolic acidosis (pH $\leq$ 7.15), or oxalate crystalluria, or with ethylene glycol level greater than 20 mg/dL. If fomepizole is unavailable, ethanol can be used to competitively inhibit AD (see above). Pyridoxine (50 mg IV every 6 hours for 24 hours, with magnesium) and thiamine (100 mg IV every 6 hours) should be administered to aid the conversion of glyoxylic acid to glycine or α-hydroxy-β-ketoadipic acid, respectively, rather than oxalate.[25] Dialysis effectively clears ethylene glycol and metabolites and corrects acidosis and metabolic derangements. Intermittent hemodialysis is the preferred modality and is indicated for likely or confirmed poisoning in the setting of acute kidney injury, anion gap metabolic acidosis, and levels greater than 50 mg/dL. Treatment should involve intermittent hemodialysis with a high-efficiency dialyzer for at least 4 hours. As with other toxins, levels may rebound and repeated treatments may be necessary until levels remain below 20 mg/dL. The mean elimination half-life of ethylene glycol during AD inhibition is 17 hours, markedly shorter than the 52 hours seen with methanol. As the mean elimination half-life is reduced to less than 3 hours with dialysis, the routine use of dialysis is effective but not essential. In fact, kinetic studies have shown that patients with ethylene glycol poisoning, and levels greater than 50 mg/dL without kidney injury or acidosis, can be managed with early administration of fomepizole alone, and without hemodialysis.[30,31] A systematic review of extracorporeal therapy in ethylene glycol is currently underway. Of note, several additional toxic alcohols cause similar poisonings, including diethylene glycol and propylene glycol.

RECOMMENDATIONS FOR EXTRACORPOREAL TREATMENT IN THE MANAGEMENT OF POISONING

Extracorporeal treatments for poisonings have been attempted for a great many toxins, far in excess of successful treatments. Due to drug properties and kinetics as well as modality-specific factors, extracorporeal treatments enhance the elimination of only a small number of clinically significant toxins. Nevertheless, the use of dialysis to treat patients poisoned with nondialyzable toxins is actually increasing, although this may be the result of concomitant medical indications rather than attempts at detoxification.[32] Since 2011, a multidisciplinary group, Extracorporeal Treatments in Poisoning (EXTRIP), has been reviewing and publishing evidence-based recommendations. The methodology involved and the grading of available evidence should establish guidelines to standardize the use of extracorporeal detoxification for the poisoned patient.[33] EXTRIP has announced additional forthcoming reviews, including ethylene glycol and baclofen. The current standard indications for dialysis are summarized in the table below, including EXTRIP recommendations when available (Table 1).

REFERENCES

1. Gummin DD, Mowry JB, Spyker DA, Brooks DE, Osterthaler KM, Banner W. 2017 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 35th annual report. *Clin Toxicol (Phila).* 2018;56(12):1213-1415.
2. Mardini J, Lavergne V, Roberts D, Ghannoum M. Case reports of extracorporeal treatments in poisoning: historical trends. *Semin Dial.* 2014;27(4):402-406.
3. Nwokolo CU, Mistry P, Pounder RE. The absorption of bismuth and salicylate from oral doses of pepto-bismol (bismuth salicylate). *Aliment Pharmacol Ther.* 1990;4(2):163-169.
4. *Muscle-pain reliever is blamed for Staten Island Runner's Death.* Associated Press; June 10, 2007.
5. Morra P, Bartle WR, Walker SE, Lee SN, Bowles SK, Reeves RA. Serum concentrations of salicylic acid following topically applied salicylate derivatives. *Ann Pharmacother.* 1996;30(9):935-940.
6. Pearlman BL, Gambhir R. Salicylate intoxication: a clinical review. *Postgrad Med.* 2009;121(4):162-168.
7. Proudfoot AT, Krenzelok EP, Vale JA. Position paper on urine alkalinization. *J Toxicol Clin Toxicol.* 2004;42(1):1-26.
8. Juurlink DN, Gosselin S, Kielstein JT, et al, EXTRIP Workgroup. Extracorporeal treatment for salicylate poisoning: systematic review

and recommendations from the EXTRIP workgroup. *Ann Emerg Med.* 2015;266(2):165-181.
9. Trepiccione F, Christensen BM. Lithium-induced nephrogenic diabetes insipidus: new clinical and experimental findings. *J Nephrol.* 2010;23(Suppl 16):S43-S48.
10. Hansen HE, Hestbech J, Sorensen JC, Norgard K, Heilskov J, Amidsen A. Chronic interstitial nephropathy in patients on long-term lithium therapy. *Q J Med.* 1979;48(192):577-591.
11. Clos S, Rauchhaus P, Severn A, Cochrane L, Donnan PT. Long-term effect of lithium maintenance therapy on estimated glomerular filtration rate in patients with affective disorders: a population-based cohort study. *Lancet Psychiatry.* 2015;2(12):1075-1083.
12. Adityanjee, Munshi KR, Thampy A. The syndrome of irreversible lithium-effectuated neurotoxicity. *Clin Neuropharmacol.* 2005;28(1):38-49.
13. Okusa MD, Crystal LJ. Clinical manifestations and management of acute lithium intoxication. *Am J Med.* 1994;97(4):383-389.
14. Bretaudeau Deguigne M, Hamel JF, Boels D, Harry P. Lithium poisoning: the value of early digestive tract decontamination. *Clin Toxicol (Phila).* 2013;51(4):243-248.
15. Bélanger DR, Tierney MG, Dickinson G. Effect of sodium polystyrene sulfonate on lithium bioavailability. *Ann Emerg Med.* 1992;21:1312-1315.
16. Ghannoum M, Lavergne V, Yue CS, Ayoub P, Perreault MM, Roy L. Successful treatment of lithium toxicity with sodium polystyrene sulfonate: a retrospective cohort study. *Clin Toxicol (Phila).* 2010;48(1):34-41.
17. Decker B, Goldfarb DS, Dargan PI, et al, EXTRIP Workgroup. Extracorporeal treatment for lithium poisoning: systematic review and recommendations from the EXTRIP workgroup. *Clin J Am Soc Nephro.* 2015;10(5):875-887.
18. Vale A. Methanol. *Medicine.* 2007;35(12):633-634.
19. Barceloux DG, Bond GR, Krenzelok EP, Cooper H, Vale JA, American Academy of Clinical Toxicology Ad Hoc Committee on the Treatment Guidelines for Methanol Poisoning. American Academy of Clinical Toxicology practice guidelines on the treatment of methanol poisoning. *J Toxicol Clin Toxicol.* 2002;40(4):415-446.
20. LeWitt PA, Martin SD. Dystonia and hypokinesis with putaminal necrosis after methanol intoxication. *Clin Neuropharmacol.* 1988;11(2):161-167.
21. Graw M, Haffner HT, Althaus L, Besserer K, Voges S. Invasion and distribution of methanol. *Arch Toxicol.* 2000;74:313-321.
22. Brent J, McMartin K, Phillips S, Aaron C, Kulig K. Fomepizole for the treatment of methanol poisoning. *N Engl J Med.* 2001;344:424-429.
23. Roberts DM, Yates C, Megarbane B, et al, EXTRIP workgroup. Recommendations for the role of extracorporeal treatments in the management of acute methanol poisoning: a systematic review and consensus statement. *Crit Care Med.* 2015;43(2):461-472.
24. Zakharov S, Pelclova D, Navratil T, et al. Efficiency of acidemia correction on intermittent versus continuous hemodialysis in acute methanol poisoning. *Clin Toxicol (phila).* 2017;55(2):123-132.
25. Hovda KE, Andersson KS, Urdal P, Jacobsen D. Methanol and formate kinetics during treatment with fomepizole. *Clin Toxicol (Phila).* 2005;43:221-227.
26. Zakharov S, Pelclova D, Navratil T, et al. Fomepizole versus ethanol in the treatment of acute methanol poisoning: comparison of clinical effectiveness in a mass poisoning outbreak. *Clin Toxicol (Phila).* 2015;53:797-806.
27. Maskell KF, Beckett S, Cumpston KL. Methanol kinetics in chronic kidney disease after fomepizole: a case report. *Am J Ther.* 2016;23(6):e1949-e1951.
28. Brent J. Current management of ethylene glycol poisoning. *Drugs.* 2001;61(7):979-988.
29. Brent J, McMartin K, Phillips S, et al. Fomepizole for the treatment of ethylene glycol poisoning. Methylpyrazole for toxic alcohols study group. *N Engl J Med.* 1999;340:832-838.
30. Levine M, Curry SC, Ruha AM, et al. Ethylene glycol elimination kinetics and outcomes in patients managed without hemodialysis. *Ann Emerg Med.* 2012 Jun;59(6):527-531.
31. McMartin K, Jacobsen D, Hovda KE. Antidotes for poisoning by alcohols that form toxic metabolites. *Br J Clin Pharmacol.* 2016;81(3):505-515.
32. Campion GH, Wang JJ, Hoffman RS, et al. Extracorporeal treatments in poisonings from four non-traditionally dialysed toxins (acetaminophen, digoxin, opioids and tricyclic antidepressants): a combined single-centre and national study. *Basic Clin Pharmacol Toxicol.* 2019;124(3):341-347.
33. Lavergne V, Nolin TD, Hoffman RS, et al. The EXTRIP (EXtracorporeal TReatments in Poisoning) workgroup: guideline methodology. *Clin Toxicol.* 2012;50(5):403-413.
34. Gosselin S, Juurlink DN, Kielstein JT, Ghannoum M, Lavergne V, Nolin TD, EXTRIP workgroup. Extracorporeal treatment for acetaminophen poisoning: recommendations from the EXTRIP workgroup. *Clin Toxicol.* 2014;52(8):856-867.
35. Wu VC, Lin SL, Lin SM, Fang CC. Treatment of baclofen overdose by haemodialysis, 2005 haemodialysis: a pharmacokinetic study. *Nephrol Dial Transpl.* 2005;20(2):441-443.
36. Hsieh MJ, Chen SC, Weng TI, Fang CC, Tsai TJ. Treating baclofen overdose by hemodialysis. *Am J Emerg Med.* 2012;30(8):1654.e5-1654.e7.
37. Mactier R, Laliberte M, Mardini J, et al, EXTRIP Workgroup. Extracorporeal treatment for barbiturate poisoning: recommendations from the EXTRIP Workgroup. *Am J Kidney Dis.* 2014;64(3):347-358.
38. Ghannoum M, Yates C, Galvao TF, et al, EXTRIP workgroup. Extracorporeal treatment for carbamazepine poisoning: systematic review and recommendations from the EXTRIP workgroup. *Clin Toxicol (Phila).* 2014;52(10):993-1004.
39. Mowry JB, Burmann EA, Anseeuw K, et al, EXTRIP Workgroup. Extracorporeal treatment for digoxin poisoning: systematic review and recommendations from the EXTRIP Workgroup. *Clin Toxicol (Phila).* 2016;54(2):103-114.
40. Calello D, Liu KD, Wiegand TJ, et al, EXTRIP Workgroup. Extracorporeal treatment for metformin poisoning: systematic review and recommendations from the extracorporeal treatments in poisoning workgroup. *Crit Care Med.* 2015;43(8):1716-1730.
41. Anseeuw K, Mowry JB, Burdmann EA, et al, EXTRIP Workgroup. Extracorporeal treatment in phenytoin poisoning: systematic review and recommendations from the EXTRIP (Extracorporeal Treatments in poisoning) workgroup. *Am J Kidney Dis.* 2016;67(2):187-197.
42. Ghannoum M, Nolin TD, Goldfarb DS, et al, EXTRIP Workgroup. Extracorporeal treatment for thallium poisoning: recommendations from the EXTRIP Workgroup. *Clin J Am Soc Nephrol.* 2012;7(10):1682-1690.
43. Ghannoum M, Wiegand TJ, Liu KD, et al, EXTRIP workgroup. Extracorporeal treatment for theophylline poisoning: systematic review and recommendations from the EXTRIP workgroup. *Clin Toxicol (phila).* 2015;53(4):215-229.
44. Yates C, Galvao T, Sowinski KM, et al, EXTRIP workgroup. Extracorporeal treatment for tricyclic antidepressant poisoning: recommendations from the EXTRIP Workgroup. *Semin Dial.* 2014;27(4):381-389.
45. Ghannoum M, Laliberté M, Nolin TD, et al, EXTRIP Workgroup. Extracorporeal treatment for valproic acid poisoning: systematic review and recommendations from the EXTRIP workgroup. *Clin Toxicol (Phila).* 2015;53(5):454-465.