Extracorporeal Treatment for Lithium Poisoning: Systematic Review and Recommendations from the EXTRIP Workgroup

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Abstract

The Extracorporeal Treatments in Poisoning Workgroup was created to provide evidence-based recommendations on the use of extracorporeal treatments in poisoning. Here, the EXTRIP workgroup presents its recommendations for lithium poisoning. After a systematic literature search, clinical and toxicokinetic data were extracted and summarized following a predetermined format. The entire workgroup voted through a two-round modified Delphi method to reach a consensus on voting statements. A RAND/UCLA Appropriateness Method was used to quantify disagreement, and anonymous votes were compiled and discussed in person. A second vote was conducted to determine the final workgroup recommendations. In total, 166 articles met inclusion criteria, which were mostly case reports, yielding a very low quality of evidence for all recommendations. A total of 418 patients were reviewed, 228 of which allowed extraction of patient-level data. The workgroup concluded that lithium is dialyzable (Level of evidence=A) and made the following recommendations: Extracorporeal treatment is recommended in severe lithium poisoning (1D). Extracorporeal treatment is recommended if kidney function is impaired and the [Li^+] is >4.0 mEq/L, or in the presence of a decreased level of consciousness, seizures, or life-threatening dysrhythmias irrespective of the [Li^+] (1D). Extracorporeal treatment is suggested if the [Li^+] is >5.0 mEq/L, significant confusion is present, or the expected time to reduce the [Li^+] to <1.0 mEq/L is >36 hours (2D). Extracorporeal treatment should be continued until clinical improvement is apparent or [Li^+] is <1.0 mEq/L (1D). Extracorporeal treatments should be continued for a minimum of 6 hours if the [Li^+] is not readily measurable (1D). Hemodialysis is the preferred extracorporeal treatment (1D), but continuous RRT is an acceptable alternative (1D). The workgroup supported the use of extracorporeal treatment in severe lithium poisoning. Clinical decisions on when to use extracorporeal treatment should take into account the [Li^+], kidney function, pattern of lithium toxicity, patient's clinical status, and availability of extracorporeal treatments.

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Due to the number of contributing authors, the affiliations are provided in the Supplemental Material.

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Introduction

The Extracorporeal Treatments in Poisoning (EXTRIP) Workgroup consists of an international panel of experts whose primary mission is to develop evidence-based recommendations for the use of extracorporeal treatments (ECTRs) for poisonings (1–7). Members of the EXTRIP Workgroup provide expertise from a broad range of medical specialties and represent diverse professional societies (Table 1). This document presents recommendations for ECTR in the setting of lithium poisoning based on the evidence from a systematic review.

Lithium was the first agent with demonstrable therapeutic use in the manic phase of bipolar disorder (8) and remains effective at both protecting against depression and mania and reducing the risk of suicide (8–11). The positive clinical attributes of lithium, however, need to be considered in light of its significant adverse effect profile and exceedingly narrow therapeutic index.

Pharmacology

Despite considerable research, the mechanism of action of lithium in the treatment of bipolar disorder remains poorly elucidated. Lithium is known to modulate effects of two signal transduction pathways and three neurotransmitters. Specifically, lithium suppresses inositol signaling through depletion of intracellular inositol and inhibits glycogen synthase kinase-3 (8,12). Glycogen synthase kinase-3 is a constitutively active enzyme that is thought to decrease neurotrophic and neuroprotective processes (8). Lithium has also been shown to decrease the release of norepinephrine and dopamine from nerve terminals and may transiently increase the release of serotonin (12).

Lithium is a small (molecular mass=7 Da) monovalent cation with properties similar to those of sodium. Lithium is administered as either lithium citrate (liquid formulation) or lithium carbonate (solid formulation) (8,13). After therapeutic oral administration, immediate-release lithium preparations are almost completely absorbed, with peak serum lithium concentrations (Li^+) occurring in 30 minutes to 2 hours (8,14,15), whereas modified-release preparations yield peak [Li^+] generally at 4–5 hours (13). In overdose, prolonged gastric absorption and clumping from insoluble aggregates may occur,

Table 1. Represented societies and official representative

Acute Dialysis Quality Initiative (Marc Ghannoum)
American Academy of Clinical Toxicology (Robert S. Hoffman)
American College of Emergency Physicians (Timothy J. Wiegand)
American College of Medical Toxicology (Timothy J. Wiegand)
American Society of Nephrology (Kathleen D. Liu)
American Society of Pediatric Nephrology (Timothy Bunchman/Véronique Phan)
Asia Pacific Association of Medical Toxicology (Darren M. Roberts, Ashish Bhalla)
Association of Physicians of India (Ashish Bhalla)
Australian and New Zealand Intensive Care Society (Darren M. Roberts)
Australian and New Zealand Society of Nephrology (Darren M. Roberts)
Brazilian Association of Poison Control Centers and Clinical Toxicologists (Tais F. Galvao)
Brazilian Society of Nephrology (Emmanuel A. Burdmann)
Brazilian Society of Toxicology (Tais F. Galvao)
Canadian Association of Poison Control Centres (David N. Juurlink)
Canadian Association of Emergency Physicians (Martin Laliberté)
Canadian Society of Nephrology (Marc Ghannoum)
Chinese College of Emergency Physicians (Yi Li)
Chinese Medical Doctor Association (Yi Li)
European Association of Poison Centres and Clinical Toxicologists (Bruno Mégarbane, Paul I. Dargan)
European Renal Best Practice (Jan T. Kielstein, Robert Mactier)
European Society for Emergency Medicine (Kurt Anseeuw)
European Society of Intensive Care Medicine (Bruno Mégarbane)
French Society of Intensive Care (Bruno Mégarbane)
German Society of Nephrology (Jan T. Kielstein)
International Pediatric Nephrology Association (Timothy Bunchman/Véronique Phan)
Indian Society of Critical Care Medicine (Ashish Bhalla)
INDO-US Emergency & Trauma Collaborative (Ashish Bhalla)
International Society of Nephrology (Emmanuel A. Burdmann)
Latin American Society of Nephrology and Hypertension (Emmanuel A. Burdmann)
National Kidney Foundation (David S. Goldfarb)
Pediatric Continuous Renal Replacement Therapy (Timothy Bunchman/Véronique Phan)
Pediatric Critical Care Medicine (Timothy Bunchman/Véronique Phan)
Quebec Association of Emergency Physicians (Sophie Gosselin)
Quebec Association of Specialists in Emergency Medicine (Sophie Gosselin)
Quebec Society of Nephrology (Marc Ghannoum)
Renal Association (Robert Mactier)
Society of Critical Care Medicine (James B. Mowry and Rob Maclaren)
Spanish Clinical Toxicology Foundation (Cristopher Yates)

especially with lithium carbonate, which is the least soluble of the lithium salts, providing a reservoir of lithium for continued absorption (16,17).

Lithium distributes widely in total body water and does not bind to serum proteins (14). The initial volume of distribution of lithium is 0.5 L/kg; however, it subsequently increases to 0.7–0.9 L/kg with time (8,13). Tissue distribution of lithium follows a multiple compartment model with a delayed diffusion from the extracellular to the intracellular compartment (18). Lithium is rapidly taken up by the kidney, thyroid, and bone (15,18). However, diffusion into the cerebrospinal fluid and the brain is delayed by approximately 24 hours compared with its appearance in plasma (15,19). Lithium undergoes no metabolism, is freely filtered in the glomerulus, and is excreted entirely in the urine (8,14). Approximately 80% of the lithium that is filtered by the glomerulus is reabsorbed: 60% by the proximal tubule and 20% by the thick ascending limb of the loop of Henle and collecting duct (13). Clinical conditions that decrease GFR or given its biochemical similarity to sodium, increase proximal tubule reabsorption, such as volume depletion and thiazide diuretics, will increase [Li^+] (13,15). The terminal elimination half-life of lithium is widely variable and depends on a patient's age, kidney function, and duration of lithium therapy (13). Typically, the half-life of lithium is 12–27 hours, but it can be as high as 58 hours in the elderly or patients who take lithium chronically (14).

Overview of Lithium Poisoning

Data from the US Poison Control Centers documented 6815 toxic lithium exposures in 2012, 17% of which had at least a moderately severe effect, including 11 deaths (20). There are three clinically recognized patterns of lithium poisoning: acute, acute on chronic, and chronic (13,21,22). Acute lithium poisoning occurs in patients who are lithium naïve and overdose on lithium. Acute-on-chronic lithium poisoning occurs in patients who have an existing body burden of lithium from maintenance therapy and are acutely exposed to a large burden of lithium. Chronic lithium poisoning occurs in patients on maintenance lithium therapy in the clinical context of a recently increased lithium dose, a decline in kidney function, or a drug-drug interaction that impairs elimination (13,21).

The clinical relationship between [Li^+] and toxicity is complex (23–25). The therapeutic steady-state [Li^+] is 0.6–1.2 mEq/L (8,13,21,26,27) (Table 2). In general, mild lithium toxicity is observed at steady-state [Li^+] of

1.5–2.5 mEq/L. Moderate toxicity can be observed when [Li^+] reach 2.5–3.5 mEq/L, and severe toxicity can be observed when [Li^+] are >3.5 mEq/L (18,21). However, clinical features are both highly variable and greatly dependent on the specific pattern of poisoning (21); symptoms may be absent or minor, with markedly elevated [Li^+] in acute lithium poisoning (18,21,28), whereas they may be prominent in chronic toxicity, with serum lithium concentrations as low as 1.5 mEq/L, reflecting higher brain lithium concentrations (18,21). The delayed diffusion of lithium to the brain explains the absence or delay of symptoms in patients with acute lithium poisoning, despite highly elevated [Li^+] (18,21,29). For these reasons, these serum lithium concentrations are only a guide to potential risk of toxicity and should always be interpreted in the context of the patient's history, clinical findings, and kidney function.

The central nervous system (CNS) is the organ system predominantly affected, particularly in those patients with chronic lithium poisoning: mild lithium poisoning typically encompasses drowsiness, nausea, vomiting, tremor, hyperreflexia, agitation, muscle weakness, and ataxia (18,21). More prominent symptoms include stupor, rigidity, hypertonia, and hypotension. The most severe cases manifest as coma, convulsions, myoclonus, and cardiopulmonary collapse (18,21). Because the distinction between these gradations can often be subtle, they are best thought of as a natural progression of a potentially severe overdose. Only the gastrointestinal symptoms tend to distinguish acute poisoning, where they are expected and prominent, from chronic toxicity, where they are almost invariably absent. Other clinical findings can include electrocardiographic changes, such as transient ST segment depression, bradycardia, sinus node dysfunction, and inverted T waves in the lateral precordial leads (13,14,30–34).

The syndrome of irreversible lithium-effectuated neurotoxicity (SILENT) is a neurologic complication of lithium toxicity (35–37). Currently, the prevalence of SILENT is unknown and limited to a small number of case reports. Patients with SILENT have chronic, largely cerebellar sequelae, even after lithium has been discontinued and concentrations have fallen to therapeutic or nondetectable values. The clinical features of SILENT may include tremor, extrapyramidal symptoms, gait difficulties, nystagmus, dysarthria, and cognitive deficits (35–37). Currently, there are no definitive treatments for SILENT, although clinicians have recommended more stringent patient selection for lithium therapy, lower therapeutic [Li^+] as a prophylactic measure, and aggressive extracorporeal lithium removal, even after nontoxic concentrations have been achieved in those with lithium poisoning (36).

Table 2. Lithium physicochemical and toxicokinetic properties

Molecular mass	7 Da
Volume of distribution	0.7–0.9 L/kg
Protein binding	0%
Oral bioavailability	Immediate release: 95%–100%; modified release: 60%–90%
Therapeutic serum concentration	0.6–1.2 mEq/L
Half-life (therapeutic)	12–27 h
Conversion factor	1 mmol/L=1 mEq/L
Toxic dose (acute poisoning)	>1 g elemental Li

Management of patients with severe lithium poisoning begins with supportive care, including discontinuation of lithium and volume resuscitation with intravenous isotonic saline (14,21). Activated charcoal is not favored for gastrointestinal decontamination after an acute overdose because it does not bind lithium (38,39). If required, gastric lavage (40) and/or whole bowel irrigation with a polyethylene glycol electrolyte lavage solution may be performed (41,42), although there are no data to show improved outcome with any decontamination procedure (43). Sodium polystyrene sulfonate has been suggested to enhance elimination of lithium but is yet to have a clearly demonstrable role (44).

Owing to its favorable pharmacokinetic parameters, the most efficient reported intervention to remove lithium from a poisoned patient is intermittent hemodialysis (HD), and it is currently advocated for patients with severe toxicity (21,22). In fact, lithium remains one of the poisons where ECTR is most often reported and recommended (45,46), although it is still infrequently used in this context (47,48). Currently, there is discordance in published recommendations and variability in decision making by clinicians regarding indications for ECTR in the setting of lithium poisoning (28). This lack of a clinical consensus stems in part from the complex pharmacology of lithium that prevents a direct relationship between [Li^+] and toxicity, which may lead to some patients currently being either undertreated or unnecessarily exposed to ECTR. Moreover, no large-scale study on lithium poisoning has been published to date. Thus, the current [Li^+] thresholds that serve as indicators for ECTR are largely derived from the opinion of a few authors without a systematic review of the evidence. Some examples of these current recommendations are shown in Table 3 (28).

Methodology

Predetermined methodology incorporating guidelines from the Appraisal of Guidelines for Research and Evaluation (49) and Grades of Recommendation Assessment, Development and Evaluation (50) is described in detail elsewhere (2,3). The latest literature search was conducted on October 1, 2014, and included searches in Medline, Embase, the Cochrane library (Review and Central), conference proceedings of the European Association of Poisons Centres and Clinical Toxicologists and North American Congress of Clinical Toxicology annual meetings, and Google Scholar.

The search strategy was as follows: ([lithium] and [dialysis or hemodialysis or haemodialysis or hemoperfusion or haemoperfusion or plasmapheresis or plasma exchange or exchange transfusion or hemofiltration or haemofiltration or hemodiafiltration or haemodiafiltration or extracorporeal therapy or continuous RRT (CRRT)]).

Dialyzability (on the basis of criteria listed in Supplemental Table 1) and clinical data from every included article were summarized. The potential benefit of the procedure was weighed against its cost, availability, alternative treatments, and related complications. The level of evidence assigned to each clinical recommendation was determined by the

Table 3. Indications for extracorporeal treatment in the treatment of lithium poisoning

Indication for ECTR	Goldfrank's *Toxicologic Emergencies*, 9th Ed. (216)	EMedicine (emedicine.medscape.com) (215)	Toxbase (toxbase.org) (214)	Toxinz (toxinz.com) (213)	Olson's *Poisoning and Drug Overdose*, 6th Ed. (212)	UpToDate (uptodate.com) (211)	Murray's *Toxicology Handbook*, 2nd Ed. (210)
Absolute [Li^+] regardless of symptoms (mEq/L)	≥4	≥4	≥7.5			>4	
[Li^+] in chronic exposure (mEq/L)	≥2.5	≥2.5	>4	>4		>2.5	>2.5
Symptoms/signs	Neurotoxicity, kidney impairment	Neurotoxicity	Neurotoxicity	Neurotoxicity	Seizures or impaired mental status, kidney impairment	Significant toxicity, kidney impairment	Neurotoxicity

ECTR, extracorporeal treatment. Modified from reference 28, with permission.

subgroup and epidemiologist (Supplemental Table 2). All of this information was submitted to the entire workgroup for consideration along with structured voting statements on the basis of a predetermined format. The workgroup met in person to exchange ideas and debate statements. The strength of recommendations was evaluated by a two-round anonymous modified Delphi method for each proposed voting statement (Supplemental Figure 1), and the RAND/UCLA Appropriateness Method was used to quantify disagreement between voters (51).

Results

The results of the literature search are shown in Figure 1. In total, 507 articles were identified after duplicates were removed, of which 341 full-text articles were retrieved and 166 studies were finally included for analysis. In total, 156 case reports/case series (235 patients) (16,18,23,25,26,30–34,37,44,52–193), five descriptive cohorts (101 patients) (24,47,48,194,195), three observational studies (80 patients) (196–198), and two pharmacokinetic studies (two patients) (199,200) were included. Reliable information on patient-level data was possible in 228 patients (Table 4).

Clinical Outcomes

One prospective cohort study included patients in whom HD was recommended by a poison control center and compared those who actually received HD (n=8) with those who did not (n=9) (196). Groups were deemed comparable for all baseline characteristics, although the small number of patients included does not allow reliable comparison (for example, initial [Li^+] was 4.30 in the HD group and 2.71 in the control group with a P value=0.18). Additionally, patient selection was potentially subject to confounding by indication. Clinical outcome (death and sequalae) in both groups were not found to be statistically different, but this interpretation is limited by the study being underpowered and by potential confounders (age, type of poisoning, [Li^+], coingestants, etc).

Another observational retrospective study of 14 patients identified clinical and biochemical makers on admission that were associated with a greater number of HD sessions (197); no significant association between the number of HD sessions and outcomes, including length of intensive care unit stay, can be derived from the study, because the analysis was also underpowered. A third comparative study showed significant worsening neurologic status in a group of patients who were dialyzed, but the study was only presented in abstract form (198). Because these studies had serious limitations and because the rest of the clinical literature review was solely comprised of case reports and uncontrolled descriptive cohorts, the quality of the evidence was considered to be very low for all recommendations.

The clinical features of reported patients with lithium toxicity are presented in Table 4. There were slightly more patients with chronic than acute toxicity (123 versus 93 patients, respectively); it was often impossible to ascertain whether patients had been taking lithium previously, and therefore, it was not feasible to differentiate between acute and acute-on-chronic poisoning. Average [Li^+] were higher in those patients after an acute ingestion (5.7 versus 3.4 mEq/L for patients with chronic toxicity). Prominent neurologic

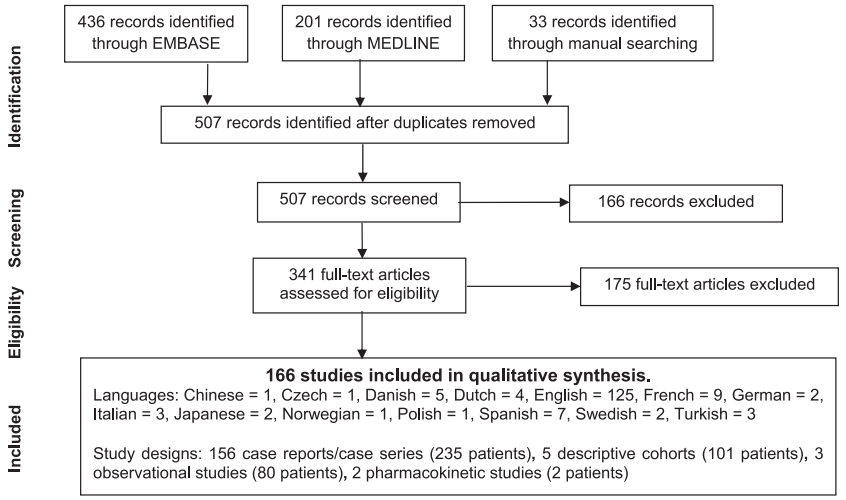

Figure 1. | Flow diagram for lithium records search (October 1, 2014).

symptoms were present in both types of poisoning, although they appeared less frequently and less severely in patients with acute cases, especially if ECTR was performed within 24 hours of ingestion. Seizures were reported almost as frequently in chronic and acute poisonings (63,66,88,115,128,137,161,165,187). Many types of abnormal cardiac rhythms were identified from our literature search in both types of toxicity patterns. AKI was a common feature on presentation (more so in patients with chronic toxicity).

For all groups, HD was, by far, the predominant ECTR modality used. Most (83%) of the reported patients experienced some degree of clinical improvement either during or on cessation of ECTR. There were 14 deaths reported from 228 patients included (23,25,52,70,74,75,93,96,104,119,139,159,162) (slightly more in those who were acutely poisoned). In these patients, the cause of death was cardiopulmonary failure, sepsis, brain death, or unrelated to lithium. Although its interpretation should be cautioned by the presence of confounders and publication bias, the mean peak [Li^+] after acute exposures was higher in fatalities compared with that of survivors (8.7 versus 5.5 mEq/L, respectively). The majority of reported adverse events observed during ECTR included hypotension (112,159,161,185), an acute drop in hemoglobin (179), upper extremity vein thrombosis (125), peritonitis attributed to a peritoneal dialysis (PD) catheter (137,186), and HD catheter-related sepsis (144). Although clinical improvement was usually observed during ECTR, deterioration during the procedure was reported in some patients (198,201). One review suggested that several patients with cognitive deterioration were reported during ECTR, but the search strategy for the review of patient worsening is unclear, and individual patients were not referenced (201).

Dialyzability

The favorable chemical and pharmacologic properties of lithium (low molecular weight, low protein binding, relatively low V_D, and low endogenous clearance) (Table 2) suggest that lithium should be readily dialyzable, and this is confirmed by the literature review. High-efficiency HD can achieve a lithium clearance of 180 mL/min (21,89,148,202) when operator characteristics are maximized (Table 5) (185,203). Comparatively, kidney (and total body) clearance of lithium can reach, at best, approximately 25% of GFR or 30–40 mL/min. Because impairment of kidney function often accompanies lithium toxicity and because lithium itself has long-term effects on kidney function, lower lithium clearances are usually reported, reaching an average of 10.6 mL/min for our cohort (14,204). The reported lithium half-life during HD was always shorter than that before and/or after dialysis, when it was calculated (18,70,71,97,110,111,149,193,202). Exact lithium removal by ECTR was quantified in several reports (usually using older dialysis technology) (56,62,71,107,126,172,183,192,202) and shown to be significant, sometimes even in excess of 25 mEq/h (71).

There are limited data with intermittent hemodiafiltration and sustained low-efficiency HD, but both seem to provide excellent clearance (60). As expected by their lower effluent and blood flow rates, CRRTs are approximately three times less efficient than HD (205). This difference is best confirmed in patients undergoing both CRRT and HD (60,82,138,140). Likewise, PD only provides clearance of 9–14 mL/min (14,89,128,190).

The effect of ECTR on lithium elimination from other body compartments is less often reported, but the decrease of lithium concentration in red blood cells (71,167,172) and cerebrospinal fluid (111,149,193) seems to parallel that from the serum. In one report, ECTR did not seem to reduce endogenous renal elimination (18). Like other small solutes (*e.g.*, urea), there is evidence that maximizing blood flow (128,185,193), increasing effluent flow (105,128), and using a high-efficiency dialyzer (149) improve lithium clearance during ECTR.

Averaged clearance parameters (Table 5) and kinetic grading of individual patients (Table 6) confirm the high dialyzability for lithium. This is substantiated by a large number of reports where systematic measurements and correct calculations were performed, including several where lithium removal was quantified in effluent/dialysate, the preferred method for assessing dialyzability (2,206).

Table 4. Clinical data related to the accepted cases of patients who received extracorporeal treatment for lithium toxicity

Clinical data	Acute/Acute on Chronic (*n*=93)	Chronic (*n*=123)	Unknown (*n*=12)
Patient demographics			
Mean age (yr)	40.3 (range=16–69)	52.5 (range=0–80)	41.2 (range=23–69)
Sex (% men)	44	34	20
Mean length of lithium therapy (yr)	N/A	7.8 (range=0–42)	5.5 (range=1–10)
Poisoning exposure			
Mean elemental lithium ingestion (mEq)[a]	798 (range=67–2630)	N/A	N/A
Mean peak lithium concentration (mEq/L)	5.7 (range=1.1–14.6)	3.4 (range=0.6–6.3)	3.7 (range=2.1–6.7)
Mean delay between ingestion and admission (h)	17.6 (range=0.5–288)	N/A	N/A
Clinical symptoms and signs			
Decreased consciousness (%)	52	87	83
Seizure (%)	10	12	0
Ataxia (%)	6	22	17
Hyperthermia (%)	8	4	8
Gastrointestinal (%)	29	19[b]	25
Dysrhythmias (%)	25	33	8
AKI (%)	30	72	17
Mean creatinine on admission (mg/dL)	2.1 (range=0.6–6.4)	2.9 (range=0.8–16)	2.0 (range=1.1–2.9)
ECTR			
Mean delay between admission and ECTR initiation (h)	17.6 (range=1–120)	32.3 (range=1–168)	13.5 (range=3–24)
Hemodialysis (%)	69.9	82.9	58.3
Continuous RRT (%)	12.9	6.5	0
Sustained low-efficiency dialysis (%)	1.1	0	0
Hemoperfusion (%)	1.1	0	0
Exchange transfusion (%)	0	0.8	0
Peritoneal dialysis (%)	4.3	4.9	41.7
Intermittent hemodiafiltration (%)	0	0.8	0
>1 ECTR (%)	10.8	4.1	0
Outcome			
Sequelae *n* (%)	14 (15.1)	25 (20.3)	1 (8.3)
Fatalities *n* (%)	7 (7.5)	6 (4.9)	1 (8.3)

These only include cases in which patient-level data could be extracted. Given the nature of the data, it was felt that a statistical comparison of the groups was inappropriate. N/A, not applicable.
[a]Lithium carbonate (300 mg) contains 8 mEq or 56.4 mg elemental lithium.
[b]Gastrointestinal symptoms were usually coexisting conditions in chronic lithium poisoning.

Table 5. Aggregate clearances obtained in the reported patients

Method of Removal	Clearance (mL/min)	
	Mean	Range
Endogenous	10.6	1.5–39.6 (*n*=53)
Peritoneal dialysis	10.9	9–14 (*n*=5)
Hemodialysis	106.9	40–180 (*n*=39)
Continuous RRT	43.1	19–64 (*n*=19)

According to the dialyzability criteria in Supplemental Table 2, the workgroup agreed that lithium was dialyzable (level of evidence=A).

Lithium Rebound

Lithium rebound is defined as an increase in [Li^+] observed after ECTR cessation. This phenomenon may be caused by either a redistribution of lithium from deeper compartments/red blood cells to the plasma or by ongoing absorption from the gastrointestinal tract. Postredistribution lithium rebound characteristically occurs after high-efficiency techniques; the rise in [Li^+] is maximal after 6–12 hours (reaching 0.5–1.0 mEq/L) (18,47,64,70,79,89,110,111,207) and not associated with recurrent symptoms as lithium moves away from the toxic compartment (56). By contrast, rebound from ongoing absorption can occur in poisonings from extended-release formulations or patients with decreased gastrointestinal motility; they can be noticeably much greater in extent (16,68,71,72,87,91,152,178) and may be associated with recurrence of symptoms or clinical deterioration, because the absorbed drug will ultimately distribute into the CNS and other tissues. In every reported patient with lithium rebound associated with clinical deterioration, the rise was attributed to ongoing absorption of extended-release formulations (16, 68,72).

Table 6. Kinetic grading for individual patients

TK/PK Grading	Number of Patients with PK/TK Grading		
	Peritoneal Dialysis	Hemodialysis	Continuous RRT
Dialyzable	2	30	9
Moderately dialyzable	2	4	3
Slightly dialyzable	3	1	0
Not dialyzable	1	0	0

Patients who had more than one extracorporeal treatment may appear at more than one place. PK, pharmacokinetics; TK, toxicokinetics.

Recommendations

(1) General Statement

We recommend ECTR in patients with severe lithium poisoning (1D).

Rationale. Poisoning to lithium can be life threatening, and treatment options to prevent or reverse toxic symptoms are limited (Table 7). Lithium is highly dialyzable, and data from the majority of reports showed clinical improvement when ECTR was used. ECTR, such as HD, can reduce the lithium concentration from the blood at a rate exceeding normal kidney clearance by severalfold (even with the addition of aggressive volume expansion), and although unproven, it is also likely to remove it more rapidly from the CNS where toxicity occurs. Despite the absence of randomized clinical trials and the low likelihood that these will ever be conducted, all 27 panel members strongly voted for ECTR in patients with severe lithium poisoning (median vote=9). The benefit of ECTR when lithium poisoning is severe, as defined by any of the conditions below, was deemed to significantly outweigh potential risks, complications, and costs of the procedure.

(2) Indications for ECTR

ECTR is recommended if any of the following conditions are present (1D):

(1) If kidney function is impaired and the [Li^+] is >4.0 mEq/L.
(2) In the presence of a decreased level of consciousness, seizures, or life-threatening dysrhythmias, irrespective of the [Li^+].

ECTR is suggested if any of the following conditions are present (2D):

(3) If [Li^+] is >5.0 mEq/L.
(4) If significant confusion is present.
(5) If the expected time to reduce [Li^+] to <1.0 mEq/L with optimal management is >36 hours.

Rationale. Even if the correlation between the [Li^+] and clinical features of toxicity is controversial (23–25), the workgroup suggested that ECTR is indicated above a [Li^+] of 5.0 mEq/L; this is because of the possibility that toxicity will occur above this threshold, even if clinical features of toxicity are initially absent. Also, better removal by ECTR is possible when the [Li^+] in the intravascular space is high. The workgroup suggests that this clinical approach be considered, regardless of the pattern of lithium poisoning: the literature review revealed that the outcomes of patients with acute ingestions were less benign than originally thought and that a threshold of 5.0 mEq/L, which is higher than most other quoted sources, would justify ECTR. A patient who presents with acute lithium poisoning warrants close monitoring and consideration for ECTR, even if asymptomatic.

Because the kidneys are the exclusive organs for lithium elimination, impaired kidney function should lower the threshold for ECTR initiation (4.0 mEq/L, regardless of clinical features; 1D). For the purpose of this assessment, the EXTRIP Workgroup defined impaired kidney function from the perspective of poison elimination as (1) stage 3B, 4, or 5 CKD (*i.e.*, eGFR<45 mL/min per 1.73 m^2); (2)

Table 7. Executive summary of recommendations

General
ECTR is recommended in patients with severe Li poisoning (1D)
Indications
ECTR is recommended (1D)
If kidney function is impaired and the [Li^+]>4.0 mEq/L
In the presence of a decreased level of consciousness, seizures, or life-threatening dysrhythmias irrespective of [Li^+]
ECTR is suggested (2D)
If the [Li^+]>5.0 mEq/L
If confusion is present
If the expected time to obtain a [Li^+]<1.0 mEq/L with optimal management is >36 h
Cessation of ECTR is recommended (1D)
When the [Li^+]<1.0 mEq/L or clinical improvement is apparent
After a minimum of 6 h of ECTR if the [Li^+] is not readily available
After interruption of ECTR, serial [Li^+] measurements should be obtained over 12 h to determine use of subsequent ECTR sessions (1D)
Choice of ECTR
Intermittent hemodialysis is the preferred ECTR (1D)
Continuous RRT is an acceptable alternative if intermittent hemodialysis is not available (1D)
After initial treatment, both continuous RRT and intermittent hemodialysis are equally acceptable (1D)

Kidney Disease Improving Global Outcomes stage 2 or 3 AKI; (*3*) in the absence of a baseline, a serum creatinine of 2 mg/dl (176 μmol/L) in adults and 1.5 mg/dL (132 μmol/L) in elderly/low-muscle mass patients; and (*4*) in children with no baseline creatinine, a serum creatinine greater than two times the upper limit of normal for age and sex. The presence of oligo/anuria should raise awareness of impaired kidney function, regardless of serum creatinine concentration.

Regardless of the [Li^+], ECTR is recommended (1D) in any patient manifesting clinical features of decreased consciousness, seizures, or dysrhythmias to rapidly reduce the lithium burden. Seizures are usually a manifestation of severe lithium neurotoxicity (25). Various abnormal cardiac rhythms can occur in lithium poisoning (47), although life-threatening dysrhythmias are rare; when present, they seemed to improve with active treatment, including ECTR (33,69,75,135,139,141,157).

Any delays in reducing the [Li^+] in these symptomatic patients may increase the risk for chronic neurotoxicity. A similar rationale is used to justify ECTR if the expected time to achieve a safe [Li^+] (<1 mEq/L) is >36 hours. Given the risks inherent in protracted periods of lithium toxicity, it is prudent to proceed with ECTR if this clinical scenario is anticipated. Finally, the reported amount of ingestion is very unreliable and should not be used as the sole clinical justification for ECTR. However, there are reports of patients with massive lithium overdoses who were asymptomatic on admission but eventually developed life-threatening clinical features (52,60,122). Such patients should be closely monitored for [Li^+], kidney function, and clinical status. Early communication with a dialysis team should be initiated, and preemptive transfer to a unit dispensing ECTR should be considered for those patients presenting with a massive lithium ingestion if the risk assessment justifies it (208). Efforts should be targeted to limit the time in initiating ECTR after the patient develops one of the aforementioned criteria.

(*3*) Cessation of ECTR

Cessation of ECTR is recommended (1D):

(*1*) If either the [Li^+] is <1.0 mEq/L or clinical improvement is apparent.
(*2*) After a minimum of 6 hours of ECTR if the [Li^+] is not readily measurable.

After interruption of ECTR, serial [Li^+] measurements should be performed over 12 hours to determine the need for subsequent ECTR sessions (1D).

Rationale. An initial session of ECTR should provide sufficient time for removal of a toxic lithium burden. At a [Li^+] <1 mEq/L, it is unlikely that the patient will manifest any life-threatening toxicity, and this is, therefore, an endpoint for ECTR cessation. If [Li^+] are not available in a clinically meaningful timeframe, a minimum length of 6 hours of ECTR will provide for acceptable lithium removal as well as a margin of safety on the assumption of a lithium half-life of 2 hours on modern high-efficiency HD (72,83,89,149,193). It is also reasonable to stop ECTR if significant clinical improvement is apparent. After ECTR cessation, serial [Li^+] should be obtained over 12 hours to determine the extent of lithium rebound; although this rebound may not be clinically significant (see above), additional ECTR sessions may provide for additional opportunity to remove more lithium. If ongoing absorption is suspected, a longer observation period may be warranted (72). The dialysis catheter should remain in place until no additional ECTRs sessions are anticipated.

(*4*) Choice of ECTR

(*1*) Intermittent HD is the preferred ECTR modality in lithium poisoning (1D).
(*2*) CRRT is an acceptable alternative if intermittent HD is not available (1D).
(*3*) After an initial treatment with intermittent HD, both CRRT and intermittent HD are equally acceptable modalities for additional lithium removal (1D)

Rationale. Intermittent HD is the most efficient ECTR at reducing the body burden of lithium. The rapid and sustained clearance of lithium from poisoned patients provided by HD may help ameliorate ongoing signs of toxicity and prevent chronic sequelae. Among the various ECTRs, HD is the most widely available, the least expensive, and the best adapted to quickly eliminate small molecules, like lithium. Although CRRT is less efficient at lithium removal, it is an acceptable alternative if intermittent HD is not available. The better hemodynamic tolerance attributed to CRRT over intermittent HD is questionable in lithium poisoning, when net fluid removal is not required. Preliminary data with both sustained low-efficiency HD and intermittent hemodiafiltration seem to justify their role as potential alternatives to HD. Charcoal hemoperfusion is useless (181), because charcoal does not adsorb lithium (38,39). The data for other ECTRs, such as exchange transfusion, liver support therapies, and therapeutic plasma exchange, are almost nonexistent and would not be expected to provide similar clearance to the more common and efficient diffusive techniques (209). The clearances obtained with PD are even inferior to CRRT, and it is, therefore, not recommended. After an initial treatment, if ECTR is required to remove more lithium, either a repeat intermittent dialysis session or a switch to CRRT was considered an equivalent alternative; prolonged treatment with either HD (179) or CRRT (128) may help remove lithium from the CNS, a compartment that diffuses more slowly into the blood. There is limited evidence from simulation models that HD followed by CRRT will result in lower intracellular lithium concentration compared with either individually, although repeated HD was not studied in the model (138). To optimize clearance, it is proposed to maximize operational parameters (203), including blood flow (128,185,193), effluent flow (105,128), and performant filters (149). If CRRT is chosen, the delivered dose should be also maximized (*i.e.*, above the standard 20–25 ml/kg per hour usually prescribed for AKI).

Conclusions

Lithium's narrow therapeutic index continues to make it a challenging drug to manage, with toxicity always a concern. The workgroup recommended that ECTR be used in patients with severe toxicity to minimize the length of time that the brain is exposed to toxic lithium concentrations. ECTR

should be particularly considered when there is concomitant kidney impairment, there is evidence of neurotoxicity, or [Li^+] is >5.0 mmol/L. The current literature has shown that HD is the most effective tool to rapidly reduce [Li^+] in poisoned patients.

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