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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

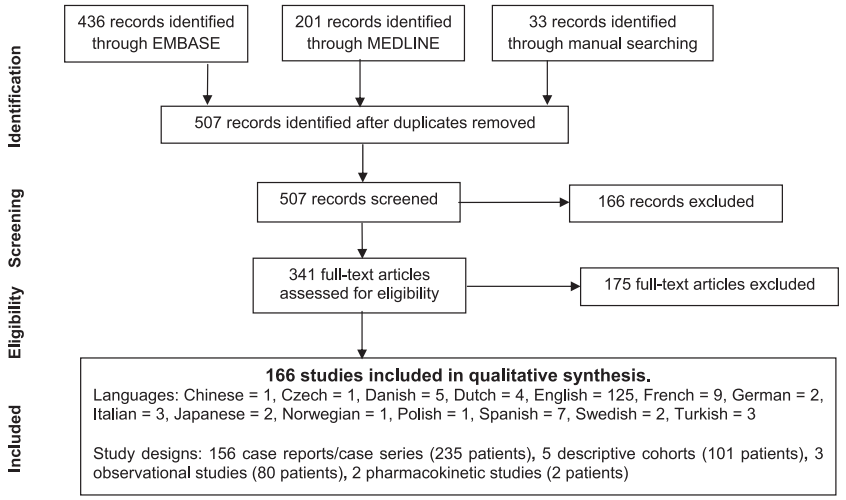

Figure 1. | Flow diagram for lithium records search (October 1, 2014).

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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References

1. Ghannoum M, Nolin TD, Lavergne V, Hoffman RS; EXTRIP workgroup: Blood purification in toxicology: Nephrology's ugly duckling. *Adv Chronic Kidney Dis* 18: 160–166, 2011
2. Lavergne V, Nolin TD, Hoffman RS, Roberts D, Gosselin S, Goldfarb DS, Kielstein JT, Mactier R, Maclaren R, Mowry JB, Bunchman TE, Juurlink D, Megarbane B, Anseeuw K, Winchester JF, Dargan PI, Liu KD, Hoegberg LC, Li Y, Calello DP, Burdmann EA, Yates C, Laliberté M, Decker BS, Mello-Da-Silva CA, Lavonas E, Ghannoum M: The EXTRIP (EXtracorporeal TReatments In Poisoning) workgroup: Guideline methodology. *Clin Toxicol (Phila)* 50: 403–413, 2012
3. Ghannoum M, Nolin TD, Goldfarb DS, Roberts DM, Mactier R, Mowry JB, Dargan PI, Maclaren R, Hoegberg LC, Laliberté M, Calello D, Kielstein JT, Anseeuw K, Winchester JF, Burdmann EA, Bunchman TE, Li Y, Juurlink DN, Lavergne V, Megarbane B, Gosselin S, Liu KD, Hoffman RS; Extracorporeal Treatments in Poisoning Workgroup: Extracorporeal treatment for thallium poisoning: Recommendations from the EXTRIP Workgroup. *Clin J Am Soc Nephrol* 7: 1682–1690, 2012
4. Yates C, Galvao T, Sowinski KM, Mardini K, Botnaru T, Gosselin S, Hoffman RS, Nolin TD, Lavergne V, Ghannoum M; EXTRIP workgroup: Extracorporeal treatment for tricyclic antidepressant poisoning: Recommendations from the EXTRIP Workgroup. *Semin Dial* 27: 381–389, 2014
5. Mactier R, Laliberté M, Mardini J, Ghannoum M, Lavergne V, Gosselin S, Hoffman RS, Nolin TD; EXTRIP Workgroup: Extracorporeal treatment for barbiturate poisoning: Recommendations from the EXTRIP Workgroup. *Am J Kidney Dis* 64: 347–358, 2014
6. Gosselin S, Juurlink DN, Kielstein JT, Ghannoum M, Lavergne V, Nolin TD, Hoffman RS; Extrip Workgroup: Extracorporeal treatment for acetaminophen poisoning: Recommendations from the EXTRIP workgroup. *Clin Toxicol (Phila)* 52: 856–867, 2014
7. Ghannoum M, Yates C, Galvao TF, Sowinski KM, Vo TH, Coogan A, Gosselin S, Lavergne V, Nolin TD, Hoffman RS; EXTRIP workgroup: Extracorporeal treatment for carbamazepine poisoning: Systematic review and recommendations from the EXTRIP workgroup. *Clin Toxicol (Phila)* 30: 1–12, 2014
8. Meltzer H: Antipsychotic agents and lithium. In: *Basic and Clinical Pharmacology*. 12th Ed. edited by Katsung BG, Masters SB, Trevor AJ, New York, USA, McGraw-Hill Medical, 2012, pp 501–520
9. McKnight RF, Adida M, Budge K, Stockton S, Goodwin GM, Geddes JR: Lithium toxicity profile: A systematic review and meta-analysis. *Lancet* 379: 721–728, 2012
10. Geddes JR, Burgess S, Hawton K, Jamison K, Goodwin GM: Long-term lithium therapy for bipolar disorder: Systematic review and meta-analysis of randomized controlled trials. *Am J Psychiatry* 161: 217–222, 2004
11. Cipriani A, Pretty H, Hawton K, Geddes JR: Lithium in the prevention of suicidal behavior and all-cause mortality in patients with mood disorders: A systematic review of randomized trials. *Am J Psychiatry* 162: 1805–1819, 2005
12. Meyer JM: Pharmacotherapy of psychosis and mania. In: *Goodman and Gilman's the pharmacological basis of therapeutics*. 12th Ed. edited by Brunton LL, New York, USA, McGraw-Hill Professional, 2011, pp 417–456
13. Timmer RT, Sands JM: Lithium intoxication. *J Am Soc Nephrol* 10: 666–674, 1999
14. Okusa MD, Crystal LJ: Clinical manifestations and management of acute lithium intoxication. *Am J Med* 97: 383–389, 1994
15. Finley PR, Warner MD, Peabody CA: Clinical relevance of drug interactions with lithium. *Clin Pharmacokinet* 29: 172–191, 1995
16. Friedberg RC, Spyker DA, Herold DA: Massive overdoses with sustained-release lithium carbonate preparations: Pharmacokinetic model based on two case studies. *Clin Chem* 37: 1205–1209, 1991
17. Bosse GM, Arnold TC: Overdose with sustained-release lithium preparations. *J Emerg Med* 10: 719–721, 1992
18. Jaeger A, Sauder P, Kopferschmitt J, Tritsch L, Flesch F: When should dialysis be performed in lithium poisoning? A kinetic study in 14 cases of lithium poisoning. *J Toxicol Clin Toxicol* 31: 429–447, 1993
19. Meltzer E, Steinlauf S: The clinical manifestations of lithium intoxication. *Isr Med Assoc J* 4: 265–267, 2002
20. Mowry JB, Spyker DA, Cantilena LR Jr., Bailey JE, Ford M: 2012 annual report of the American association of poison control centers' national poison data system (NPDS): 30th annual report. *Clin Toxicol (Phila)* 51: 949–1229, 2013
21. Khasraw M, Ashley D, Wheeler G, Berk M: Using lithium as a neuroprotective agent in patients with cancer. *BMC Med* 10: 131–132, 2012

22. Waring WS: Management of lithium toxicity. *Toxicol Rev* 25: 221–230, 2006
23. Colak Oray N, Arici A, Yanturali S, Kalkan S, Tuncok Y: Lithium poisoning: Is the lithium level a guide? *Anadolu Psikiyatri Derg* 12: 198–203, 2011
24. Gadallah MF, Feinstein EI, Massry SG: Lithium intoxication: Clinical course and therapeutic considerations. *Miner Electrolyte Metab* 14: 146–149, 1988
25. Hansen HE, Amdisen A: Lithium intoxication. (Report of 23 cases and review of 100 cases from the literature). *Q J Med* 47: 123–144, 1978
26. Menghini VV, Albright RC Jr.: Treatment of lithium intoxication with continuous venovenous hemodiafiltration. *Am J Kidney Dis* 36: E21, 2000
27. Bazilinski N, Mathew J: Lithium intoxication. *Int J Artif Organs* 9: 5–6, 1986
28. Roberts DM, Gosselin S: Variability in the management of lithium poisoning. *Semin Dial* 27: 390–394, 2014
29. Oakley PW, Whyte IM, Carter GL: Lithium toxicity: An iatrogenic problem in susceptible individuals. *Aust N Z J Psychiatry* 35: 833–840, 2001
30. Kayrak M, Ari H, Duman C, Gul EE, Ak A, Atalay H: Lithium intoxication causing ST segment elevation and wandering atrial rhythms in an elderly patient. *Cardiol J* 17: 404–407, 2010
31. Canan F, Kaya A, Bulur S, Albayrak ES, Ordu S, Ataoglu A: Lithium intoxication related multiple temporary ECG changes: A case report. *Cases J* 1: 156, 2008
32. Kayrak M, Duman C, Gul EE, Sonmez O, Kaya Z, Ari H: A bizarre electrocardiographic pattern due to chronic lithium therapy. *Ann Noninvasive Electrocardiol* 15: 289–292, 2010
33. Mateer JR, Clark MR: Lithium toxicity with rarely reported ECG manifestations. *Ann Emerg Med* 11: 208–211, 1982
34. Puhr J, Hack J, Early J, Price W, Meggs W: Lithium overdose with electrocardiogram changes suggesting ischemia. *J Med Toxicol* 4: 170–172, 2008
35. Porto FH, Leite MA, Fontenelle LF, Marrocos RP, Szczerback NF, de Freitas MR: The Syndrome of Irreversible Lithium-Effectuated Neurotoxicity (SILENT): One-year follow-up of a single case. *J Neurol Sci* 277: 172–173, 2009
36. Adityanjee, Munshi KR, Thampy A: The syndrome of irreversible lithium-effectuated neurotoxicity. *Clin Neuropharmacol* 28: 38–49, 2005
37. Zallo Atxutegi E, Pacheco MT, Izaguirre NB, Ansorena MAP: Syndrome of irreversible lithium-effectuated neurotoxicity. A propos of a case. *Psiquiatria Biologica* 15: 56–58, 2008
38. Favin FD, Klein-Schwartz W, Oderda GM, Rose SR: In vitro study of lithium carbonate adsorption by activated charcoal. *J Toxicol Clin Toxicol* 26: 443–450, 1988
39. Linakis JG, Lacouture PG, Eisenberg MS, Maher TJ, Lewander WJ, Driscoll JL, Woolf AD: Administration of activated charcoal or sodium polystyrene sulfonate (Kayexalate) as gastric decontamination for lithium intoxication: An animal model. *Pharmacol Toxicol* 65: 387–389, 1989
40. Benson BE, Hoppu K, Troutman WG, Bedry R, Erdman A, Höjer J, Mégarbane B, Thanacoody R, Caravati EM; American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists: Position paper update: Gastric lavage for gastrointestinal decontamination. *Clin Toxicol (Phila)* 51: 140–146, 2013
41. Smith SW, Ling LJ, Halstenson CE: Whole-bowel irrigation as a treatment for acute lithium overdose. *Ann Emerg Med* 20: 536–539, 1991
42. Anonymous: Position paper: Whole bowel irrigation. *J Toxicol Clin Toxicol* 42: 843–854, 2004
43. Bretaudeau Deguigne M, Hamel JF, Boels D, Harry P: Lithium poisoning: The value of early digestive tract decontamination. *Clin Toxicol (Phila)* 51: 243–248, 2013
44. 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)* 48: 34–41, 2010
45. Mardini J, Lavergne V, Roberts D, Ghannoum M: Case reports of extracorporeal treatments in poisoning: Historical trends. *Semin Dial* 27: 402–406, 2014
46. Holubek WJ, Hoffman RS, Goldfarb DS, Nelson LS: Use of hemodialysis and hemoperfusion in poisoned patients. *Kidney Int* 74: 1327–1334, 2008
47. Offerman SR, Alsop JA, Lee J, Holmes JF: Hospitalized lithium overdose cases reported to the California Poison Control System. *Clin Toxicol (Phila)* 48: 443–448, 2010
48. Bailey B, McGuigan M: Lithium poisoning from a poison control center perspective. *Ther Drug Monit* 22: 650–655, 2000
49. The AGREE Collaboration: Appraisal of guidelines for research & evaluation. AGREE instrument. In: *SCHOOL*, edited bySGSHM, London, The AGREE Collaboration, 2001
50. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, Guyatt GH, Harbour RT, Haugh MC, Henry D, Hill S, Jaeschke R, Leng G, Liberati A, Magrini N, Mason J, Middleton P, Mrukowicz J, O'Connell D, Oxman AD, Phillips B, Schünemann HJ, Edejer T, Varonen H, Vist GE, Williams JW Jr., Zaza S; GRADE Working Group: Grading quality of evidence and strength of recommendations. *BMJ* 328: 1490, 2004
51. Fitch K, Bernstein SJ, Aguilar MD, Burnand B, LaCalle JR, Lazaro P, Loo MVH, McDonnell J, Vader JP, Kahan JP: The RAND/UCLA Appropriateness Method User's Manual. In: RAND (Ed.) Santa Monica, USA, RAND, 2011
52. Achong MR, Fernandez PG, McLeod PJ: Fatal self-poisoning with lithium carbonate. *Can Med Assoc J* 112: 868–870, 1975
53. Agarwal SK, Tiwari SC, Dash SC: Spectrum of poisoning requiring haemodialysis in a tertiary care hospital in India. *Int J Artif Organs* 16: 20–22, 1993
54. Allain P, Alquier P, Fresneau D, Hachet P: Study of lithium elimination during poisoning with anuria. *Therapie* 28: 1135–1142, 1973
55. Amdisen A: Clinical features and management of lithium poisoning. *Med Toxicol* 3: 18–32, 1988
56. Amdisen A, Skjoldborg H: Haemodialysis for lithium poisoning. *Lancet* 2: 213, 1969
57. Ananth J, Djenderedjian A, Mendoza R, Cheung D: Acute and chronic lithium toxicity: Case reports and a review. *Lithium* 3: 139–145, 1992
58. Apte SN, Langston JW: Permanent neurological deficits due to lithium toxicity. *Ann Neurol* 13: 453–455, 1983
59. Ayuso Gatell A, León Regidor MA, Mestre Saura J, Díaz Boladeras RM, Sirvent Calvera JM, Nolla Panadés M: Acute lithium poisoning. Treatment with continuous arteriovenous hemofiltration. Apropos of a case. *Rev Clin Esp* 185: 195–197, 1989
60. Bailey AR, Sathianathan VJ, Chiew AL, Paterson AD, Chan BS, Arora S: Comparison of intermittent haemodialysis, prolonged intermittent renal replacement therapy and continuous renal replacement haemofiltration for lithium toxicity: A case report. *Crit Care Resusc* 13: 120–122, 2011
61. Baños Gallardo M, Rojo Ortega JM, Argüelles Toraño M: Hemodialysis treatment in lithium poisoning. *Rev Clin Esp* 183: 156–157, 1988
62. Beckmann U, Oakley PW, Dawson AH, Byth PL: Efficacy of continuous venovenous hemodialysis in the treatment of severe lithium toxicity. *J Toxicol Clin Toxicol* 39: 393–397, 2001
63. Bejar JM: Cerebellar degeneration due to acute lithium toxicity. *Clin Neuropharmacol* 8: 379–381, 1985
64. Bellomo R, Boyce N: Current approaches to the treatment of severe lithium intoxication. *Lithium* 3: 245–248, 1992
65. Bellomo R, Kearly Y, Parkin G, Love J, Boyce N: Treatment of life-threatening lithium toxicity with continuous arterio-venous hemodiafiltration. *Crit Care Med* 19: 836–837, 1991
66. Bertaso L, Buttazzoni C: Lithium intoxication: Treatment with continuous arterio-venous hemofiltration (C.A.V.H.). A case report. *Acta Anaesthesiol Ital* 44: 261–263, 1993
67. Bilanakis N, Gibiriti M: Lithium intoxication, hypercalcemia and "accidentally" induced food and water aversion: A case report. *Prog Neuropsychopharmacol Biol Psychiatry* 28: 201–203, 2004
68. Borrás-Blasco J, Sirvent AE, Navarro-Ruiz A, Murcia-López A, Romero-Crespo I, Enriquez R: Unrecognized delayed toxic lithium peak concentration in an acute poisoning with sustained release lithium product. *South Med J* 100: 321–323, 2007

69. Bosak AR, Graeme KA, Evans MD: Hemodialysis treatment of monomorphic ventricular tachycardia associated with chronic lithium toxicity. *J Med Toxicol* 10: 303–306, 2014
70. Bosinski T, Bailie GR, Eisele G: Massive and extended rebound of serum lithium concentrations following hemodialysis in two chronic overdose cases. *Am J Emerg Med* 16: 98–100, 1998
71. Bouffard Y, Claris O, Greffe J, Perrot D, Delafosse B, Motin J: Acute lithium poisoning. Value of hemodialysis and determination of intraerythrocytic lithium. *Presse Med* 13: 1456–1457, 1984
72. Branger B, Peyrière H, Zabadani B, Vécina F, Abbar M: Voluntary lithium salt poisoning; risks of slow release forms. *Nephrologie* 21: 291–293, 2000
73. Brown EA, Pawlikowski TR: Lithium intoxication treated by peritoneal dialysis. *Br J Clin Pract* 35: 90–91, 1981
74. Camacho Pulido JA, Rucabado Aguilar I, Estecha Foncea MA, Quesada Blanca JL, Jurado Lara B, Jimenez Sanchez JM: Shock and severe hypoxemia in lithium intoxication. *Farm Clin* 12: 509–510, 1995
75. Cavaliere F, Guerrini P, Ciuni C, Magalini SI: A case of mixed lithium and phenothiazine poisoning with a fatal outcome. *Recenti Prog Med* 75: 877–882, 1984
76. Chebrolu SB, Yang HK, Hariman A, Tzamaloukas AH, Kjellstrand CM, Ing TS: Treatment of severe lithium poisoning and dialysis-induced hypophosphatemia with phosphorus-enriched hemodialysis: A case report. *Chin Med J (Engl)* 118: 1405–1408, 2005
77. Chen L, Pym H: Rapid onset of neurological symptoms and lithium toxicity on starting meloxicam. *Aust N Z J Psychiatry* 44: 95, 2010
78. Christian MR, Thompson TM: Continuous veno-venous hemodialysis (CVVHD) after acute-on-chronic lithium overdose. *Clin Toxicol*, 49: 540, 2011
79. Clendeninn NJ, Pond SM, Kaysen G, Barraza JJ, Farrell T, Becker CE: Potential pitfalls in the evaluation of the usefulness of hemodialysis for the removal of lithium. *J Toxicol Clin Toxicol* 19: 341–352, 1982
80. Danel V, Rhodes AS, Saviuc P, Hanna J: Severe lithium intoxication: Two cases. *Jeur* 14: 134–136, 2001
81. De Ridder K, De Meester J, Demeyer I, Verbeke J, Nollet G: Management of a lithium intoxication. *Tijdschr Geneeskd* 58: 769–772, 2002
82. Desatnik P, Prütz KG: A very serious case of lithium poisoning. Good results with continuous arteriovenous dialysis. *Lakartidningen* 92: 643–645, 1995
83. Dhondt A, Verstraete A, Vandewoude K, Segers H, Eloot S, Decruyenaere J, Vanholder R: Efficiency of the Genius batch hemodialysis system with low serum solute concentrations: The case of lithium intoxication therapy. *Am J Kidney Dis* 46: e95–e99, 2005
84. Dias N, Hocken AG: Oliguric renal failure complicating lithium carbonate therapy. *Nephron* 10: 246–249, 1973
85. Diaz de Leon Ponce M, Juarez Diaz Gonzalez N, Ceron Hernandez A: Extracorporeal dialysis in lithium intoxication. *Rev Med Inst Mex Seguro Soc* 21: 521–523, 1983
86. Dieryck J: Lithium poisoning: Rare but dangerous. *Tijdschr Geneeskd* 39: 269–275, 1983
87. Dupuis RE, Cooper AA, Rosamond LJ, Campbell-Bright S: Multiple delayed peak lithium concentrations following acute intoxication with an extended-release product. *Ann Pharmacother* 30: 356–360, 1996
88. el-Mallakh RS, Lee RH: Seizures and transient cognitive deterioration as sequelae of acute lithium intoxication. *Vet Hum Toxicol* 29: 143–145, 1987
89. Eyer F, Pfab R, Felgenhauer N, Lutz J, Heemann U, Steimer W, Zondler S, Fichtl B, Zilker T: Lithium poisoning: Pharmacokinetics and clearance during different therapeutic measures. *J Clin Psychopharmacol* 26: 325–330, 2006
90. Favarel-Garrigues B, Favarel-Garrigues JC, Bourgeois M: 2 cases of severe poisoning by lithium carbonate. *Ann Med Psychol (Paris)* 1: 253–257, 1972
91. Fenves AZ, Emmett M, White MG: Lithium intoxication associated with acute renal failure. *South Med J* 77: 1472–1474, 1984
92. Fiaccadori E, Maggiore U, Parenti E, Greco P, Cabassi A: Sustained low-efficiency dialysis (SLED) for acute lithium intoxication. *Nephrol Dial Transplant* 24: 329–332, 2008
93. Gill J, Singh H, Nugent K: Acute lithium intoxication and neuroleptic malignant syndrome. *Pharmacotherapy* 23: 811–815, 2003
94. Giuliani E, Iseppi D, Orlandi MC, Alfonso A, Barbieri A: Prolonged neurological burden in severe lithium intoxication. *Minerva Anestesiol* 76: 463–465, 2010
95. Goddard J, Bloom SR, Frackowiak RS, Pusey CD, MacDermot J, Liddle PF: Lithium intoxication. *BMJ* 302: 1267–1269, 1991
96. Green ST, Dunn FG: Severe leucopenia in fatal lithium poisoning. *Br Med J (Clin Res Ed)* 290: 517, 1985
97. Groleau G, Barish R, Tso E, Whye D, Browne B: Lithium intoxication: Manifestations and management. *Am J Emerg Med* 5: 527–532, 1987
98. Guerin JM, Barbotin-Larrieu P, Lustman C: Acute voluntary life-threatening carbonate lithium poisoning. *Arch Intern Med* 150: 920, 1990
99. Haghfelt T, Lund JO, Jorgensen HE, Baastrup PC: Lithium poisoning and kidney function. *Nord Med* 86: 1465–1471, 1971
100. Handler J: Lithium and antihypertensive medication: A potentially dangerous interaction. *J Clin Hypertens (Greenwich)* 11: 738–742, 2009
101. Hanna ME, Lobao CB, Stewart JT: Severe lithium toxicity associated with indapamide therapy. *J Clin Psychopharmacol* 10: 379–380, 1990
102. Hansen HE, Pedersen EB, Amdisen A: Renal function and plasma aldosterone during acute lithium intoxication. *Acta Med Scand* 205: 593–597, 1979
103. Havle N, Ilnem MC, Yener F, Dayan C: Patients with very high serum lithium levels may not have a poor clinical outcome. *Klinik Psikofarmakoloji Bulteni* 19: 206–207, 2009
104. Hawkins JB, Dorken PR: Lithium. *Lancet* 1: 839–840, 1969
105. Hazouard E, Ferrandière M, Rateau H, Doucet O, Perrotin D, Legras A: Continuous veno-venous haemofiltration versus continuous veno-venous haemodialysis in severe lithium self-poisoning: A toxicokinetics study in an intensive care unit. *Nephrol Dial Transplant* 14: 1605–1606, 1999
106. Heinrich TW, Biblo LA, Schneider J: Torsades de pointes associated with ziprasidone. *Psychosomatics* 47: 264–268, 2006
107. Hughes PM, Pemberton DM, Dobbinson TL: Lithium toxicity and haemodialysis. *N Z Med J* 97: 23–24, 1984
108. Humbert G, Fillastre JP, Leroy J, Maitrot B, Tobelem G, Leroux G, Lavoine A: Lithium poisoning. *Sem Hop* 50: 509–514, 1974
109. Ilagan MC, Carlson D, Madden JF: Lithium toxicity: Two case reports. *Del Med J* 74: 263–270, 2002
110. Jacobsen D, Aasen G, Frederichsen P, Eisenga B: Lithium intoxication: Pharmacokinetics during and after terminated hemodialysis in acute intoxications. *J Toxicol Clin Toxicol* 25: 81–94, 1987
111. Jaeger A, Sauder P, Kopferschmitt J, Jaegle ML: Toxicokinetics of lithium intoxication treated by hemodialysis. *J Toxicol Clin Toxicol* 23: 501–517, 1985-1986
112. Jenniskens-Bruins JJ, Gerards LJ: Lithium poisoning in a newborn infant. *Tijdschr Kindergeneeskd* 60: 76–78, 1992
113. Jensen H, Ladefoged J: Delayed absorption of lithium in intoxication: A case history. *Eur J Clin Pharmacol* 8: 285, 1975
114. Jensen JP, Kortsen H, Søorensen E: Lithium poisoning. Report of a case treated with hemodialysis. *Ugeskr Laeger* 136: 1505–1507, 1974
115. Josephs W, Schilken P, Wiechmann HW, Grotz J: Successful detoxication of a potentially letal lithium intoxication by hemofiltration. *Intensivmed Notfallmed* 25: 241–243, 1988
116. Kansagra A, Nambiar S, Beth N, Yang E, Patel P,Karetzky M: Acute respiratory distress syndrome secondary to acute lithium intoxication. *Crit Care Med* 38: A274, 2010
117. Kansagra AJ, Yang E, Nambiar S, Patel PS, Karetzky MS: A rare case of acute respiratory distress syndrome secondary to acute lithium intoxication. *Am J Ther* 21: e31–e34, 2014
118. Kasahara H, Shinozaki T, Nukariya K, Nishimura H, Nakano H, Nakagawa T, Ushijima S: Hemodialysis for lithium intoxication: Preliminary guidelines for emergency. *Jpn J Psychiatry Neurol* 48: 1–12, 1994

119. Kelleher SP, Raciti A, Arbeit LA: Reduced or absent serum anion gap as a marker of severe lithium carbonate intoxication. *Arch Intern Med* 146: 1839–1840, 1986
120. Kerbusch T, Mathôt RA, Otten HM, Meesters EW, van Kan HJ, Schellens JH, Beijnen JH: Bayesian pharmacokinetics of lithium after an acute self-intoxication and subsequent haemodialysis: A case report. *Pharmacol Toxicol* 90: 243–245, 2002
121. Kirschner RI, Barthold CL: Cluster of chronic lithium toxicity in a correctional facility. *Clin Toxicol* 49: 515–627, 2011
122. Kleinert A, Kołaciński Z: Acute suicidal poisoning with lithium carbonate. *Pol Tyg Lek* 46: 464–465, 1991
123. Kondziela JR: Extreme lithium intoxication without severe symptoms. *Hosp Community Psychiatry* 35: 727–728, 1984
124. Lai CL, Chen WJ, Huang CH, Lin FY, Lee YT: Sinus node dysfunction in a patient with lithium intoxication. *J Formos Med Assoc* 99: 66–68, 2000
125. Lang E, König L: Lithium—poisonings. *Act Nerv Super (Praha)* 16: 197–198, 1974
126. Lavender S, Brown JN, Berrill WT: Acute renal failure and lithium intoxication. *Postgrad Med J* 49: 277–279, 1973
127. Lawler PG, Cove-Smith JR: Acute respiratory failure following lithium intoxication. A report of two cases. *Anaesthesia* 41: 623–627, 1986
128. Leblanc M, Raymond M, Bonnardeaux A, Isenring P, Pichette V, Geadah D, Quimet D, Ethier J, Cardinal J: Lithium poisoning treated by high-performance continuous arteriovenous and venovenous hemodiafiltration. *Am J Kidney Dis* 27: 365–372, 1996
129. Lee YC, Lin JL, Lee SY, Hsu CW, Weng CH, Chen YH, Yang CW, Yen TH: Outcome of patients with lithium poisoning at a far-east poison center. *Hum Exp Toxicol* 30: 528–534, 2011
130. Lins R, de Broe ME: Serious poisoning in maintenance therapy with lithium carbonate. *Ned Tijdschr Geneeskd* 124: 545–548, 1980
131. Vasileiou I, Giaginis C, Klonaris C, Theocharis S: Insight into pain-inducing and -related gene expression: a challenge for development of novel targeted therapeutic approaches. *Fundam Clin Pharmacol* 25: 48–62, 2011
132. Long AN, Oktaei H, Childress RD, Solomon SS: Rapid reversal of lithium-induced hyperparathyroidism: a case report. *Journal of Investigative Medicine*, 59: 372, 2011
133. Lum G: Lithium self-intoxication treated with hemodialysis. *Lab Med* 38: 667–668, 2007
134. Lundholm B, Landgren A: Chronic lithium poisoning can be difficult to discover. *Lakartidningen* 107: 496–497, 2010
135. Manor E: A case of reversible tachy-bradycardia syndrome and permanent neurological sequelae in lithium intoxication. *Arch Toxicol* 53: 384–385, 1983
136. Manto M, Godaux E, Jacquy J, Hildebrand JG: Analysis of cerebellar dysmetria associated with lithium intoxication. *Neurol Res* 18: 416–424, 1996
137. Marshall SM, Kesson CM: Severe lithium poisoning. *Drug Intell Clin Pharm* 15: 598–599, 1981
138. Meertens JH, Jagernath DR, Eleveld DJ, Zijlstra JG, Franssen CF: Haemodialysis followed by continuous veno-venous haemodiafiltration in lithium intoxication; a model and a case. *Eur J Intern Med* 20: e70–e73, 2009
139. Menegueti MG, Basile-Filho A, Martins-Filho OA, Auxiliadora-Martins M: Severe arrhythmia after lithium intoxication in a patient with bipolar disorder admitted to the intensive care unit. *Indian J Crit Care Med* 16: 109–111, 2012
140. Meyer RJ, Flynn JT, Brophy PD, Smoyer WE, Kershaw DB, Custer JR, Bunchman TE: Hemodialysis followed by continuous hemofiltration for treatment of lithium intoxication in children. *Am J Kidney Dis* 37: 1044–1047, 2001
141. Newland KD, Mycyk MB: Hemodialysis reversal of lithium overdose cardiotoxicity. *Am J Emerg Med* 20: 67–68, 2002
142. Nishiwaki T, Tanaka K, Sekiya S: Acute lithium intoxication in pregnancy. *Int J Gynaecol Obstet* 52: 191–192, 1996
143. Nurnberger JI Jr.: Diuretic-induced lithium toxicity presenting as mania. *J Nerv Ment Dis* 173: 316–318, 1985
144. Oakley PW, Dawson AH, Whyte IM: Lithium: Thyroid effects and altered renal handling. *J Toxicol Clin Toxicol* 38: 333–337, 2000
145. O'Connor J, Gleeson J: Acute lithium intoxication: Peritoneal dialysis or forced diuresis? *N Z Med J* 95: 790–791, 1982
146. Paholpak S: Severe lithium toxicity treated by hemodialysis: A case report. *J Med Assoc Thai* 72: 112–116, 1989
147. Pandey S, Jain S, Chatterjee R: Acute lithium toxicity: Two cases with different outcomes. *Neurol India* 56: 484–485, 2008
148. Peces R, Fernández EJ, Regidor D, Peces C, Sánchez R, Montero A, Selgas R: Treatment of acute lithium intoxication with high-flux haemodialysis membranes. *Nefrologia* 26: 372–378, 2006
149. Peces R, Pobes A: Effectiveness of haemodialysis with high-flux membranes in the extracorporeal therapy of life-threatening acute lithium intoxication. *Nephrol Dial Transplant* 16: 1301–1303, 2001
150. Pedersen RS, Svendsen O: Lithium poisoning treated with hemodialysis. Review and a case report. *Ugeskr Laeger* 138: 3325–3327, 1976
151. Perale L, Strizzolo L, Apollonio L, Calci M: Adynamic ileus in chronic lithium intoxication. *J Emerg Med* 38: 502, 2010
152. Perrier A, Martin PY, Favre H, Muller AF, Urban P, Chevrolet JC: Very severe self-poisoning lithium carbonate intoxication causing a myocardial infarction. *Chest* 100: 863–865, 1991
153. Perrot D, Bouffard Y, Roux H: Suicidal acute poisoning with lithium. *Journal de Toxicologie Medicale* 2: 49–53, 1982
154. Phillips BD, Gopalakrishnan G, Gohh R, Hennessey JV: Lithium toxicity precipitated by profound hypothyroidism. *Thyroid* 18: 651–654, 2008
155. Plenge U, Møller AM: Development of sustained vasodilatory shock and permanent loss of hearing after severe lithium carbonate poisoning. *Ugeskr Laeger* 170: 354, 2008
156. Pond SM: Extracorporeal techniques in the treatment of poisoned patients. *Med J Aust* 154: 617–622, 1991
157. Prencipe M, Cicchella A, Del Giudice A, Di Giorgio A, Scarlatella A, Vergura M, Aucella F: The acute renal and cerebral toxicity of lithium: A cerebro-renal syndrome? A case report. *G Ital Nefrol* 30: 30.3.18, 2013
158. Pringuey D, Yzombard G, Charbit JJ, Portugal H, Saingra S, Frayssinet R, Milech T, Dufour H: Lithium kinetics during hemodialysis in a patient with lithium poisoning. *Am J Psychiatry* 138: 249–251, 1981
159. Rose SR, Klein-Schwartz W, Oderda GM, Gorman RL, Young WW: Lithium intoxication with acute renal failure and death. *Drug Intell Clin Pharm* 22: 691–694, 1988
160. Rosen PB, Stevens R: Action myoclonus in lithium toxicity. *Ann Neurol* 13: 221–222, 1983
161. Sahin Yildiz T, Hosten T, Toker K, Solak M: Life-threatening acute lithium intoxication and treatment methods (case report). *Anestezi Dergisi* 14: 210–212, 2006
162. Satar S, Alpay NR, Sebe A, Gokel Y: Emergency hemodialysis in the management of intoxication. *Am J Ther* 13: 404–410, 2006
163. Sato Y, Taki K, Honda Y, Takahashi S, Yoshimura A: Lithium toxicity precipitated by thyrotoxicosis due to silent thyroiditis: Cardiac arrest, quadriplegia, and coma. *Thyroid* 23: 766–770, 2013
164. Saxena S, Mallikarjuna P: Severe memory impairment with acute overdose lithium toxicity. A case report. *Br J Psychiatry* 152: 853–854, 1988
165. Schindler BA, Ramchandani D: Partial complex status epilepticus in a lithium-toxic patient. *Psychosomatics* 34: 521–524, 1993
166. Schmitt C, Furet Y, Perrotin D, Paintaud G: Acute lithium intoxications, review of the literature and cases study. *Therapie* 64: 55–63, 2009
167. Scoble JE, McLean A, Munn S, Varghese Z, Sweny P, Moorhead JF: Lithium nephrotoxicity and red cell lithium. *Nephrol Dial Transplant* 5: 904, 1990
168. Slørdal L, Samstad S, Bathen J, Spigset O: A life-threatening interaction between lithium and celecoxib. *Br J Clin Pharmacol* 55: 413–414, 2003
169. Smith D, Keane P, Donovan J, Malone K, McKenna TJ: Lithium encephalopathy. *J R Soc Med* 96: 590–591, 2003
170. Sood MM, Richardson R: Negative anion gap and elevated osmolar gap due to lithium overdose. *CMAJ* 176: 921–923, 2007
171. Swartz CM, Jones P: Hyperlithemia correction and persistent delirium. *J Clin Pharmacol* 34: 865–870, 1994
172. Szerlip HM, Heeger P, Feldman GM: Comparison between acetate and bicarbonate dialysis for the treatment of lithium intoxication. *Am J Nephrol* 12: 116–120, 1992

173. Takahashi T, Ito S, Gonai S: Difficulty in determining when to end continuous hemodialysis for lithium intoxication: Case report. *Chudoku Kenkyu* 24: 42–45, 2011
174. Talwalkar NC, Balakrishna N: "Haemodialysis in lithium poisoning". *J Assoc Physicians India* 34: 597–598, 1986
175. Tapolyai M, Campbell M, Dailey K, Udvari-Nagy S: Hemodialysis is as effective as hemoperfusion for drug removal in carbamazepine poisoning. *Nephron* 90: 213–215, 2002
176. Temte JL, MacGorman L, Benson-Lein C: Intentional overdose by intravaginal insertion of lithium carbonate. *JAMA* 272: 1723–1724, 1994
177. Thiel A, Nau R, Lehmann K, Willers T: Intoxication in manic patients following chaotic self-administration of lithium. *Acta Psychiatr Scand* 88: 289–291, 1993
178. Thornley-Brown D, Galla JH, Williams PD, Kant KS, Rashkin M: Lithium toxicity associated with a trichobezoar. *Ann Intern Med* 116: 739–740, 1992
179. Treysman L, Meehan TJ, Schlieben DJ, Ducre B, Erickson TB: Pharmacokinetic modeling of lithium elimination during 67 continuous hours of high flux hemodialysis. *Clin Toxicol* 48: 647, 2010
180. Tunkel AR, D'Antonio J, Engel-Kominsky S, Browne B: Predicting the clinical course in intentional drug overdose. *Arch Intern Med* 148: 253, 1988
181. Unei H, Ikeda H, Murakami T, Tanigawa K, Kihira K: Detoxication treatment for carbamazepine and lithium overdose. *Yakugaku Zasshi* 128: 165–170, 2008
182. Uzu T, Ichida K, Ko M, Tsukurimichi S, Yamato M, Takahara K, Ohashi M, Yamauchi A, Nomura M: Two cases of lithium intoxication complicated by type 2 diabetes mellitus. *J Japan Diabetes Soc* 44: 767–770, 2001
183. van Bommel EF, Kalmeijer MD, Ponssen HH: Treatment of life-threatening lithium toxicity with high-volume continuous veno-venous hemofiltration. *Am J Nephrol* 20: 408–411, 2000
184. Vermeire S, Vanbrabant P, Van Boxstael P, Sabbe M: Severity (and treatment) of chronic lithium poisoning: Clinical signs or lab results as a criterion? *Acta Clin Belg* 65: 127–128, 2010
185. Von Hartitzsch B, Hoenich NA, Leigh RJ, Wilkinson R, Frost TH, Weddel A, Posen GA: Permanent neurological sequelae despite haemodialysis for lithium intoxication. *BMJ* 4: 757–759, 1972
186. Wang SY, Lin HH, Chen WY, Yang YY: Lithium intoxication—report of 10 cases. *Taiwan Yi Xue Hui Za Zhi* 84: 960–968, 1985
187. Wanscher MC, Frifelt JJ, Molsted K: Double-lumen hemodialysis catheters in the treatment of acetylsalicylic acid and lithium poisoning. *Ugeskr Laeger* 148: 2160–2161, 1986
188. White B, Larry J, Kantharia BK: Protracted presyncope and profound bradycardia due to lithium toxicity. *Int J Cardiol* 125: e48–e50, 2008
189. Wilkinson A, Gavine A, Black K: Lithium toxicity presenting as delirium in an older patient. *Practitioner* 253: 28–30, 2009
190. Wilson JH, Donker AJ, van der Hem GK, Wientjes J: Peritoneal dialysis for lithium poisoning. *BMJ* 2: 749–750, 1971
191. Zabaneh RI, Ejaz AA, Khan AA, Nawab ZM, Leehey DJ, Ing TS: Use of a phosphorus-enriched dialysis solution to hemodialyze a patient with lithium intoxication. *Artif Organs* 19: 94–95, 1995
192. Zingraff J, Jungers P, Drüeke T, Man NK, Crosnier J: Accidental lithium poisoning in a patient with chronic hemodialysis. *Nouv Presse Med* 4: 3181, 1975
193. Voiculescu A, Hefter H, Falck M, Kutkuhn B, Grabensee B: Hemodialysis in severe lithium intoxication. *Intensivmed Notfallmed* 32: 433–437, 1995
194. Herrera de Pablo E, Climent B, García Escrivá D, Pérez Silvestre J, Herrera Pablo P, Herrera A: Analysis of the poisonings by lithium in a department of internal medicine. *Med Interna* 25: 209–212, 2008
195. Liu WC, Tsai TJ: Management of lithium intoxication. *J Int Med Taiwan* 12: 241–249, 2001
196. Bailey B, McGuigan M: Comparison of patients hemodialyzed for lithium poisoning and those for whom dialysis was recommended by PCC but not done: What lesson can we learn? *Clin Nephrol* 54: 388–392, 2000
197. Lopez JC, Perez X, Labad J, Esteve F, Manez R, Javierre C: Higher requirements of dialysis in severe lithium intoxication. *Hemodial Int* 16: 407–413, 2012
198. Megarbane B, Baud F: Do we have to clear plasma or cells from toxicant? A lesson from lithium poisoning. *Clin Toxicol (Phila)* 40: 313–314, 2002
199. Bjarnason NH, Munkner R, Kampmann JP, Tornoe CW, Ladefoged S, Dalhoff K: Optimizing lithium dosing in hemodialysis. *Ther Drug Monit* 28: 262–266, 2006
200. Zetin M, Plon L, Vaziri N, Cramer M, Greco D: Lithium carbonate dose and serum level relationships in chronic hemodialysis patients. *Am J Psychiatry* 138: 1387–1388, 1981
201. Swartz CM, Dolinar LJ: Encephalopathy associated with rapid decrease of high levels of lithium. *Ann Clin Psychiatry* 7: 207–209, 1995
202. Schmidt JJ, Lorenzen J, Chatzikyrkou C, Lichtinghagen R, Kielstein JT: Total collected dialysate lithium concentration after successful dialysis treatment in case of intoxication. *BMC Pharmacol Toxicol* 15: 49, 2014
203. Bouchard J, Roberts DM, Roy L, Ouellet G, Decker BS, Mueller BA, Desmeules S, Ghannoum M: Principles and operational parameters to optimize poison removal with extracorporeal treatments. *Semin Dial* 27: 371–380, 2014
204. Mason RW, McQueen EG, Keary PJ, James NM: Pharmacokinetics of lithium: Elimination half-time, renal clearance and apparent volume of distribution in schizophrenia. *Clin Pharmacokinet* 3: 241–246, 1978
205. Goodman JW, Goldfarb DS: The role of continuous renal replacement therapy in the treatment of poisoning. *Semin Dial* 19: 402–407, 2006
206. Lavergne V, Ouellet G, Bouchard J, Galvao T, Kielstein JT, Roberts DM, Kanji S, Mowry JB, Calello DP, Hoffman RS, Gosselin S, Nolin TD, Goldfarb DS, Burdmann EA, Dargan PI, Decker BS, Hoegberg LC, Maclaren R, Megarbane B, Sowinski KM, Yates C, Mactier R, Wiegand T, Ghannoum M: Guidelines for reporting case studies on extracorporeal treatments in poisonings: Methodology. *Semin Dial* 27: 407–414, 2014
207. Groleau G: Lithium toxicity. *Emerg Med Clin North Am* 12: 511–531, 1994
208. Ghannoum M, Roberts DM, Hoffman RS, Ouellet G, Roy L, Decker BS, Bouchard J: A stepwise approach for the management of poisoning with extracorporeal treatments. *Semin Dial* 27: 362–370, 2014
209. Ouellet G, Bouchard J, Ghannoum M, Decker BS: Available extracorporeal treatments for poisoning: Overview and limitations. *Semin Dial* 27: 342–349, 2014
210. Daly F, Little M, Cadogan M: Lithium. In: *Toxicology handbook*. 2nd Ed. Chastwood, Australia, Churchill Livingstone, 2011, pp 260–263
211. Perrone J, Chatterjee P: Lithium poisoning. In: TRAUB, S. (Ed.) *UpToDate*. Waltham, USA, 2014
212. Benowitz N: Lithium. In: *Poisoning & Drug Overdose*. 6th Ed. edited by Olson KR, New York, USA, Mcgraw-Hill, 2011
213. National Poison Centre: Lithium. In: Fountain J. (Ed.) *Toxinz*. Dunedin, New Zealand, NPC, 2014
214. National Poisons Information Services: lithium. In: NPIS (Ed.) *Toxbase*. Edinburgh, UK, UK Health Departments, 2014
215. Lee DC, Gupta A: Lithium toxicity. In: WebMD (Ed.) *Medscape*. New York, USA, 2013
216. Greller HA: Lithium. In: *Goldfrank's Toxicologic Emergencies, 9th ed* edited by Nelson LS, Howland MA, et al, New York, USA, McGraw Hill, 2011, pp 142

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