Extracorporeal Treatment for Chloroquine, Hydroxychloroquine, and Quinine Poisoning: Systematic Review and Recommendations from the EXTRIP Workgroup

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Due to the number of contributing authors, the affiliations are listed at the end of this article.

ABSTRACT

Background Although chloroquine, hydroxychloroquine, and quinine are used for a range of medical conditions, recent research suggested a potential role in treating COVID-19. The resultant increase in prescribing was accompanied by an increase in adverse events, including severe toxicity and death. The Extracorporeal Treatments in Poisoning (EXTRIP) workgroup sought to determine the effect of and indications for extracorporeal treatments in cases of poisoning with these drugs.

Methods We conducted systematic reviews of the literature, screened studies, extracted data, and summarized findings following published EXTRIP methods.

Results A total of 44 studies (three in vitro studies, two animal studies, 28 patient reports or patient series, and 11 pharmacokinetic studies) met inclusion criteria regarding the effect of extracorporeal treatments. Toxicokinetic or pharmacokinetic analysis was available for 61 patients (13 chloroquine, three hydroxychloroquine, and 45 quinine). Clinical data were available for analysis from 38 patients, including 12 with chloroquine toxicity, one with hydroxychloroquine toxicity, and 25 with quinine toxicity. All three drugs were classified as non-dialyzable (not amenable to clinically significant removal by extracorporeal treatments). The available data do not support using extracorporeal treatments in addition to standard care for patients severely poisoned with either chloroquine or quinine (strong recommendation, very low quality of evidence). Although hydroxychloroquine was assessed as being non-dialyzable, the clinical evidence was not sufficient to support a formal recommendation regarding the use of extracorporeal treatments for this drug.

Conclusions On the basis of our systematic review and analysis, the EXTRIP workgroup recommends against using extracorporeal methods to enhance elimination of these drugs in patients with severe chloroquine or quinine poisoning.


Chloroquine, hydroxychloroquine, and quinine are used for a wide array of medical conditions, including malaria and connective tissue diseases, and more recently, preliminary studies have focused on their potential role for the treatment of the novel coronavirus disease 2019 (COVID-19).1–2 The expanded prescribing of chloroquine and hydroxychloroquine for COVID-19 and use of nonpharmaceutical chloroquine by the public resulted in severe toxicity and death.3–5 Despite appropriate supportive care and the advent of extracorporeal membrane oxygenation, mortality from chloroquine toxicity remains high.6 Some reviews and editorials have suggested that extracorporeal...
treatments (ECTRs) can enhance elimination of these drugs in poisoning.7,8

The Extracorporeal Treatments in Poisoning (EXTRIP) workgroup is composed of international experts representing diverse specialties and professional societies (Supplemental Table 1). Its mission is to provide recommendations on the use of ECTRs in poisoning (http://www.extrip-workgroup.org).9,10 The objective of this article is to present EXTRIP’s systematic review of the literature and recommendations for the use of ECTR in patients poisoned from chloroquine, hydroxychloroquine, or quinine.

BACKGROUND
Clinical Pharmacology and Pharmacokinetics

Bark from the Cinchona tree native to the Andean regions of South America was recognized as an effective treatment for malaria in the late 1600s.11,12 By the 1800s, extraction processes were developed, and quinine sulfate became widely available in tonic waters. Quinine remained the mainstay of malaria treatment until the 1920s when more effective synthetic antimalarials, such as chloroquine and its derivative hydroxychloroquine, were approved by the US Food and Drug Administration (FDA) in 1949 and 1955, respectively. These drugs exhibit a remarkable breadth of pharmacologic effects, including anti-inflammatory, anti-infective, immunomodulatory, and antineoplastic activity. Chloroquine and quinine are still popular therapeutics to prevent and treat uncomplicated malaria, whereas hydroxychloroquine is used primarily to treat connective tissue diseases, such as SLE, rheumatoid arthritis, and Sjogren syndrome.13 Despite a 2006 warning from the FDA regarding safety concerns, the use of quinine remains common for the treatment of leg cramps.14 Recently, because of their recognized antiviral activity, these drugs received enormous attention in both the lay press and medical journals as potential treatments of COVID-19,15 prompting the FDA and other governing agencies to issue an emergency use authorization for this purpose.16

Chloroquine, hydroxychloroquine, and quinine are primarily available as tablets, although injectable forms are available in some countries. Their physicochemical and pharmacokinetic properties are summarized in Table 1.

Chloroquine

Chloroquine has a molecular mass of 320 Da and is rapidly absorbed after enteral administration with almost complete oral bioavailability. It is only moderately bound to plasma proteins, so physiologic changes such as hypalbuminemia, binding interactions, and supratherapeutic concentrations that alter the extent of protein binding are not reported to have toxicologic implications.17,18 Chloroquine is extensively distributed throughout the body with a massive apparent volume of distribution of >100 L/kg. Approximately half of ingested chloroquine is excreted unchanged in urine, but the remainder is metabolized by cytochrome P450 (CYP) enzymes 2C8 and 3A4 to the primary metabolite desethylchloroquine.17,19 The total endogenous clearance of chloroquine is high, and its terminal elimination half-life (t1/2) is normally in excess of 10 days (Table 1). Given its considerable renal clearance, the t1/2 is prolonged in patients with impaired kidney function.17

Hydroxychloroquine

The molecular mass of hydroxychloroquine is 336 Da. It is rapidly absorbed after oral dosing, with time to peak plasma concentration of 2–6 hours.20,21 Hydroxychloroquine is moderately bound to plasma proteins and is extensively distributed throughout the body with an exceedingly large apparent volume of distribution.22 The drug is predominantly metabolized by CYP3A4 and to a lesser extent, by CYP2C8 to desethylhydroxychloroquine, with only about 20% of hydroxychloroquine excreted unchanged in urine.19,22 Similar to chloroquine, hydroxychloroquine has a high endogenous clearance and a long terminal t1/2 (Table 1).20,22

Quinine

Quinine has a molecular mass of 324 Da. After oral administration, quinine is rapidly absorbed with a time to peak plasma
concentration of 1.5–2.8 hours.\textsuperscript{17} It exhibits extensive protein binding and an apparent volume of distribution of 1–2.5 L/kg; inflammation, active malaria, and kidney impairment increase protein binding and decrease its volume of distribution.\textsuperscript{17,23,24} Quinine is predominantly (80%) metabolized by CYP3A4 in the liver to form the major metabolite 3-hydroxyquinine,\textsuperscript{25} whereas the remainder is excreted unchanged in urine.\textsuperscript{17,19} The total endogenous clearance of quinine ranges from 120 to 150 ml/min\textsuperscript{17} and is decreased by approximately 50% in patients with kidney failure (Table 1).\textsuperscript{26,27}

**Overview of Toxicity**

Quinine toxicity, classically referred to as cinchonism (from the Cinchona tree), consists of tinnitus, deafness, nausea, vomiting, and visual disturbances. Visual symptoms range from diplopia to blindness and reportedly occur in up to 20%–40% of poisoned patients.\textsuperscript{28–31} Chloroquine and hydroxychloroquine present similar toxic effects with notable differences; visual and auditory impairments are rarer with these poisons, whereas altered mental status is more prominent and includes agitation, delirium, altered consciousness, seizures, and coma.\textsuperscript{6,32–34} Rapid and profound hypokalemia occurs from intracellular potassium shifts.\textsuperscript{35–38} At high concentrations, all three drugs cause life-threatening cardiovascular toxicity as a result of their direct effects on the cardiac sodium and potassium channels. This cardiac channel blockade leads to prolongation of both the QRS complex and QT intervals on the electrocardiogram and hypotension.\textsuperscript{34,39,40} QT interval prolongation is reported in patients prescribed chloroquine and hydroxychloroquine for COVID-19. A recent randomized, controlled trial of chloroquine for COVID-19 was terminated early due to a new QTc >500 ms in 25% of patients prescribed 12 g over 10 days and in 11% of those prescribed 2.7 g over 5 days, accompanied by ventricular dysrhythmias and a trend to higher mortality.\textsuperscript{3} Similarly, a QTc>500 ms was reported in >10% of patients prescribed hydroxychloroquine and azithromycin for COVID-19.\textsuperscript{5}

The delay from ingestion of an acute overdose to cardiovascular collapse is typically short (<3 hours).\textsuperscript{34,39,41} In addition to the negative inotropy and chronotropy, ventricular dysrhythmias (monomorphic and polymorphic ventricular tachycardia, ventricular fibrillation) are common in severe poisoning.\textsuperscript{33,39,42}

The risk of toxicity correlates with the ingested dose, albeit with considerable interindividual variability. For all three drugs, acute ingestions of <2 g in the average adults are usually benign.\textsuperscript{32,34,39,43–46} Cardiovascular and neurologic impairments are expected following acute ingestions >2 g.\textsuperscript{32,34,39,43–47} Life-threatening toxicity and mortality are reported in untreated adult patients with acute ingestions >5 g.\textsuperscript{34,39,40,42–45,48,49} However, there are also reports of survival after massive acute ingestions, including 12 g of chloroquine,\textsuperscript{32} 36 g of hydroxychloroquine,\textsuperscript{50} and 31 g of quinine.\textsuperscript{51}

Although elevated concentrations of these drugs predict toxicity, results are rarely available in a turnaround time that is rapid enough to influence clinical decision making. A blood chloroquine concentration below 2.5 mg/L does not appear to cause toxicity,\textsuperscript{13} whereas concentrations between 2.5 and 5 mg/L are associated with mild neurologic impairment and dysrhythmias.\textsuperscript{43} Blood chloroquine concentrations above 5 mg/L are associated with severe cardiovascular poisoning, and life-threatening dysrhythmias.\textsuperscript{43} With prompt access to care, death is unlikely with blood chloroquine concentrations <10 mg/L.\textsuperscript{6,32} The likelihood of mortality increases steeply over 10 mg/L, although there are several cases of survival in excess of 30 mg/L.\textsuperscript{6,42} There are few toxicologic data on a concentration-response relationship for hydroxychloroquine, but blood hydroxychloroquine concentrations >2 mg/L are considered supratherapeutic,\textsuperscript{52} and life-threatening poisoning is described after overdose at blood and plasma concentrations over 20 mg/L.\textsuperscript{49,50,53} For quinine, a plasma concentration <10 mg/L is well tolerated and usually only causes minimal symptoms, such as tinnitus.\textsuperscript{30} With plasma concentrations between 10 and 15 mg/L, visual symptoms are usually present,\textsuperscript{28,30} and over 15 mg/L, cardiac dysrhythmias are reported.\textsuperscript{28,30} Quinine’s protein binding increases in active malaria, which lowers its free fraction, so patients with elevated parasitemia reportedly show no symptoms with plasma quinine concentrations up to 20 mg/L.\textsuperscript{17}

Antimalarial poisonings occur more commonly in sub-Saharan Africa and Europe (particularly in France, where chloroquine ingestion was popularized as a means of suicide in the 1980s).\textsuperscript{54–56} Although there are fewer reported cases of hydroxychloroquine overdose, several fatalities are described.\textsuperscript{36,48,57} In the United States, data from the American Association of Poison Control Centers in 2018 reported 826 human exposures to antimalarial drugs that resulted in

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**Table 1.** Physicochemical and pharmacokinetic properties of chloroquine, hydroxychloroquine, and quinine\textsuperscript{17,18,20–22,24,93–97}

<table>
<thead>
<tr>
<th>Properties</th>
<th>Chloroquine</th>
<th>Hydroxychloroquine</th>
<th>Quinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular mass, Da</td>
<td>320</td>
<td>336</td>
<td>324</td>
</tr>
<tr>
<td>pKa</td>
<td>10.1</td>
<td>9.67</td>
<td>9.05</td>
</tr>
<tr>
<td>Bioavailability, %</td>
<td>80–100</td>
<td>67–74</td>
<td>76–88</td>
</tr>
<tr>
<td>Volume of distribution, L/kg</td>
<td>120–150 (p, b), &gt;50 (p, b), 1.5–3.0 (p)</td>
<td>200–800 (p, b), 8–14 h (p)</td>
<td></td>
</tr>
<tr>
<td>Protein binding, %</td>
<td>50–75</td>
<td>40–70</td>
<td>80–95</td>
</tr>
<tr>
<td>Elimination t\textsubscript{1/2}, h</td>
<td>200–400 (p), 200–800 (p, b), 1000–1400 (b)</td>
<td>4–10 (b)</td>
<td></td>
</tr>
<tr>
<td>Total endogenous CL, ml/min</td>
<td>600–1000 (p, b), 140 (b)</td>
<td>200–600 (p, b), 100 (b)</td>
<td></td>
</tr>
<tr>
<td>Renal CL, %</td>
<td>40–50</td>
<td>15–20</td>
<td>20</td>
</tr>
<tr>
<td>Therapeutic concentration, mg/L</td>
<td>0.3–1.0 (b)</td>
<td>0.3–1.0 (b)</td>
<td>5–10 (p)</td>
</tr>
</tbody>
</table>

p, plasma; b, blood; t\textsubscript{1/2}, half-life; CL, clearance.
185 patients treated in health care facilities and three deaths.\textsuperscript{58} Mortality and morbidity remain high today with overdose of these drugs; for chloroquine, the overall mortality is approximately 5\%–8\%.\textsuperscript{3,4,10,56} but can exceed 10\% following large ingestions, even with modern standard care.\textsuperscript{5,6,2,4,44} Older cohorts reported higher mortality of >30\%, likely representing differences in critical care management.\textsuperscript{3,4,10,59} Mortality in hydroxychloroquine overdose appears considerably lower than for chloroquine.\textsuperscript{48,60–62} Reported cohorts for quinine poisoning are >20 years old, and they show a mortality rate near or under 5\%.\textsuperscript{28–31} and irreversible visual damage in 20\%–50\% of patients who had initial visual symptoms.\textsuperscript{28–31}

Aside from the ingested dose, clinical predictors of chloroquine mortality include a QRS complex duration >120 ms, systolic pressure <80 mm Hg,\textsuperscript{42} and the severity of hypokalemia.\textsuperscript{35,38,39} In another cohort of 69 patients poisoned with hydroxychloroquine who received an electrocardiogram, no patients with a QRS duration <120 ms died.\textsuperscript{61} In a series of six hydroxychloroquine ingestions, two presented with a QRS complex duration >150 ms, both had severe symptoms, and one patient died.\textsuperscript{48} The presence and severity of hypokalemia also predicts mortality for hydroxychloroquine.\textsuperscript{36,37,49,50}

Overdose from any of these drugs is a medical emergency. Standard care for quinine, chloroquine, and hydroxychloroquine poisoning includes early endotracheal intubation for exposures that are likely to be life threatening and those with hemodynamic instability, correction of hypokalemia, and institution of cardiac monitoring with close attention to the duration of the QRS complex and QT interval. Sodium bicarbonate boluses are often recommended for patients with QRS interval duration >120 ms for the treatment of sodium channel blockade; however, in the context of chloroquine and hydroxychloroquine, careful monitoring of the electrolyte status, particularly potassium, is necessary as alkalization can exacerbate hypokalemia and prolong the QT interval.\textsuperscript{49,63,64} Hypotension is treated with epinephrine (adrenaline) infusions, and seizures are treated with benzodiazepines. The role of high-dose diazepam for treatment of cardiotoxicity remains poorly defined.\textsuperscript{6,40,42} The use of diazepam and epinephrine was shown to statistically reduce mortality in patients ingesting >5 g of chloroquine,\textsuperscript{42} although a diazepam dose of 1.5 mg/kg over 24 hours did not reduce cardiotoxicity in patients ingesting 2–4 g of chloroquine.\textsuperscript{60} Activated charcoal is frequently administered to patients at high risk of toxicity, depending on the history of the ingestion and clinical status. In the last two decades, reports of extracorporeal membrane oxygenation use for severe chloroquine and hydroxychloroquine poisoning have increased, with mixed results.\textsuperscript{65}

Methods

The workgroup developed recommendations on the use of ECTR following the EXTRIP methodology previously published\textsuperscript{9} with modifications, updates, and clarifications. The methods and glossary are presented in full in Supplemental Material. For reference (Supplemental Material), the term “dialyzability” is used, as in a priori accepted methods and manuscripts, to reflect the ability of an ECTR to remove a clinically significant percentage of the total body burden of a poison. Clearance refers to the volume of blood (or solvent) cleared of poison per unit time. Importantly, CL\textsubscript{EC} represents solute clearance due exclusively to ECTR and is independent of endogenous systemic clearance (CL\textsubscript{SYS}; the sum of underlying renal and nonrenal clearances). CL\textsubscript{TOT} refers to total clearance and is the sum of CL\textsubscript{EC} and CL\textsubscript{SYS}. The panel had proposed that four distinct calculations were acceptable to estimate dialyzability with regards to poison elimination (Supplemental Table 3).

RESULTS

The results of the search and article selection are presented in Figure 1. A total of 44 articles were retained for final analysis, including three in vitro experiments,\textsuperscript{66–68} two animal experiments,\textsuperscript{69,70} 11 pharmacokinetic studies,\textsuperscript{24,71–80} and 28 patient reports and patient series.\textsuperscript{30,81–107} No comparative observational studies and no randomized trials were identified.

Toxicokinetic (Dialyzability)

Chloroquine, hydroxychloroquine, and quinine have molecular masses of <350 Da, so they will readily cross ECTR membranes. However, their pharmacokinetic characteristics (Table 1) are anticipated to limit the effect of ECTR according to previously described predictors of low dialyzability, notably volumes of distribution >1–2 L/kg and endogenous clearances >4 ml/min.\textsuperscript{66} The extensive protein binding of quinine is also expected to limit further the efficacy of diffusion- or convection-based techniques.\textsuperscript{66}

Toxicokinetic or pharmacokinetic data were available on 61 patients (13 chloroquine, three hydroxychloroquine, 45 quinine) and are summarized in Table 2. Although the concentrations of chloroquine and quinine decrease during ECTR (as expected from normal endogenous metabolism), neither appear to be removed to any significant amount by ECTRs: chloroquine clearance obtained during hemodialysis (50–75 ml/min) represented only 15\% of total body clearance.\textsuperscript{67} During chloroquine poisonings, hemoperfusion (HP) alone or in combination with hemodialysis (HD) removed negligible quantities: in the most favorable cases, 1.1 g were eliminated in 46 hours by HP-HD (11\% of the ingested dose),\textsuperscript{68} and 0.47 g were eliminated in 6.5 hours by HP (4.7\% of the ingested dose, likely an overestimate given the calculations provided).\textsuperscript{69} Rebound of chloroquine concentrations post-ECTR was noted in many publications.\textsuperscript{64–72} Neither HD nor HP removed >150 mg of quinine.\textsuperscript{30,73,74} Hemodialysis clearances of quinine did not surpass 15 ml/min,\textsuperscript{24,73,74} and sieving coefficients during convective techniques remained below 20\%.\textsuperscript{75–77} Interestingly, therapeutic plasma exchange (TPE), which seems best suited to remove
protein-bound drugs, removed only 8.5 mg of quinine in 3 hours (clearance was 12 ml/min). As expected, lower-efficiency techniques like peritoneal dialysis (PD) and exchange transfusion (ET) had an inconsequential effect on removal of either chloroquine or quinine. Dialyzability data for hydroxychloroquine were limited to three patients receiving routine hemodialysis, and extracorporeal drug removal was not observed.

**Table 2.** The pharmacokinetics of chloroquine, hydroxychloroquine, and quinine during ECTR (data shown combine both pharmacokinetic and toxicokinetic data)

<table>
<thead>
<tr>
<th>ECTR</th>
<th>t½ during ECTR</th>
<th>Endogenous t½, h</th>
<th>ECTR Clearance, ml/min</th>
<th>Endogenous Clearance, ml/min</th>
<th>Dialyzability</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chloroquine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HD</td>
<td>200</td>
<td>9–77</td>
<td>4</td>
<td>400–800</td>
<td>ND</td>
<td>C</td>
</tr>
<tr>
<td>HP-HD</td>
<td>11.9</td>
<td>0–54</td>
<td>2</td>
<td></td>
<td>ND</td>
<td>C</td>
</tr>
<tr>
<td>PD</td>
<td>1.1–1.5</td>
<td>61–135</td>
<td>3</td>
<td></td>
<td>ND</td>
<td>C</td>
</tr>
<tr>
<td>HP</td>
<td>2.0–6.7</td>
<td>3</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Hydroxychloroquine</strong></td>
<td></td>
<td></td>
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<tr>
<td>HD</td>
<td>&gt;200</td>
<td>a</td>
<td>3</td>
<td>100–300</td>
<td>ND</td>
<td>D</td>
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<tr>
<td><strong>Quinine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HD</td>
<td>21.2</td>
<td>0.2–13.8</td>
<td>17</td>
<td>100–150</td>
<td>ND</td>
<td>B</td>
</tr>
<tr>
<td>CRRT</td>
<td>5.7</td>
<td>0.3–3.7</td>
<td>3</td>
<td></td>
<td>ND</td>
<td>C</td>
</tr>
<tr>
<td>HD-HP</td>
<td>12.5–27.3</td>
<td>0.6–11.1b</td>
<td>8</td>
<td></td>
<td>ND</td>
<td>B</td>
</tr>
<tr>
<td>PD</td>
<td>1.4–5.1</td>
<td>11.8</td>
<td>1</td>
<td></td>
<td>ND</td>
<td>D</td>
</tr>
<tr>
<td>TPE</td>
<td>2.5–21.7</td>
<td>16.7–115</td>
<td>3</td>
<td></td>
<td>ND</td>
<td>D</td>
</tr>
</tbody>
</table>

Data shown combine both pharmacokinetic and toxicokinetic data. HD, hemodialysis; ND, not dialyzable; HP-HD, hemoperfusion and hemodialysis in series; PD, peritoneal dialysis; HP, hemoperfusion; CRRT, continuous renal replacement therapy; HD-HP, hemodialysis and hemoperfusion in series; ET, exchange transfusion; TPE, therapeutic plasma exchange.

**Footnotes:**

- Extracorporeal clearance could not be calculated due to hydroxychloroquine being undetectable in the dialysis effluent, but this indicates that ECTR clearance is below 44 ml/min, assuming dialysate flow of 500 ml/min.
- One value was excluded because it was assessed as likely an error.

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**Figure 1.** The literature search last performed on January 15th, 2020, after removal of duplicates and non-pertinent records, yielded 44 studies for analysis. No comparative observational studies or randomized trials were identified. EAPCCT, European Association of Poisons Centres and Clinical Toxicologists; NACCT, North American Congress of Clinical Toxicology; PK, pharmacokinetic.
On the basis of previously defined criteria (Supplemental Material), chloroquine, hydroxychloroquine, and quinine were categorized as non-dialyzable with a level of evidence presented in Table 2. Although much of the data are on the basis of ECTR technology prior to the year 2000, an increase in drug clearance with current ECTR technology is anticipated to be insufficient for the drugs to be reclassified as potentially dialyzable due to their intrinsic pharmacokinetic properties (Table 1). Although pharmacokinetic data for hydroxychloroquine were limited to three patients, empirically it is likely that hydroxychloroquine is non-dialyzable due to its enormous volume of distribution, which would also cause a substantial rebound in plasma concentration even if an ECTR transiently decreased its plasma concentration. The trivial effect of hemodialysis on hydroxychloroquine removal is illustrated in the following simulated patient. Assuming a patient weighing 50 kg ingests 10 g of hydroxychloroquine (volume of distribution = 50 L/kg) and oral absorption is 100%, then the predicted plasma concentration of hydroxychloroquine would be 4 mg/L. Assuming an ideal hemodialysis treatment (hemodialysis plasma flow = 240 ml/min [14.4 L/h] and 100% extraction through the dialyzer) and an absence of drug distribution or endogenous clearance during hemodialysis, a 4-hour hemodialysis treatment would remove only 230.4 mg, or approximately 2.3% of the ingested dose, calculated as follows:

<table>
<thead>
<tr>
<th>Table 3. Clinical description of included patients with poisoning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameters</td>
</tr>
<tr>
<td>Patient characteristics</td>
</tr>
<tr>
<td>Median age, yr</td>
</tr>
<tr>
<td>Men, %</td>
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<tr>
<td>Poisoning information</td>
</tr>
<tr>
<td>Median dose, g</td>
</tr>
<tr>
<td>Median time from ingestion to admission, h</td>
</tr>
<tr>
<td>Median plasma concentration, mg/L</td>
</tr>
<tr>
<td>Signs/symptoms/laboratory</td>
</tr>
<tr>
<td>Coma, %</td>
</tr>
<tr>
<td>Visual impairment, %</td>
</tr>
<tr>
<td>Hypotension, %</td>
</tr>
<tr>
<td>Respiratory depression, %</td>
</tr>
<tr>
<td>Severe dysrhythmia/cardiac arrest, %</td>
</tr>
<tr>
<td>Auditory impairment, %</td>
</tr>
<tr>
<td>AKI, %</td>
</tr>
<tr>
<td>Median potassium, mmol/L</td>
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<tr>
<td>Prolonged QRS complex duration, %</td>
</tr>
<tr>
<td>Median QRS complex duration, ms</td>
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<tr>
<td>Prolonged QT interval, %</td>
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<tr>
<td>Median QT interval, ms</td>
</tr>
<tr>
<td>Other treatments, %</td>
</tr>
<tr>
<td>Gastric lavage</td>
</tr>
<tr>
<td>Activated charcoal</td>
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<tr>
<td>Benzodiazepines</td>
</tr>
<tr>
<td>Bilateral stellate ganglion block</td>
</tr>
<tr>
<td>Cardiac pacing</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
</tr>
<tr>
<td>Vasopressors</td>
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<tr>
<td>ECTR, n</td>
</tr>
<tr>
<td>Hemodialysis</td>
</tr>
<tr>
<td>Hemoperfusion</td>
</tr>
<tr>
<td>Exchange transfusion</td>
</tr>
<tr>
<td>Hemoperfusion and hemodialysis in series</td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
</tr>
<tr>
<td>&gt;1 ECTR used</td>
</tr>
<tr>
<td>Outcome</td>
</tr>
<tr>
<td>Median LOS, d</td>
</tr>
<tr>
<td>Death, %</td>
</tr>
</tbody>
</table>

Percentages are on the basis of available data (if the data are not shown, they are removed). p, plasma; b, blood; LOS, length of stay ICU, intensive care unit.

*Blood concentration can estimated to be approximately four times as high as the plasma concentration.

Plasma concentration stated in the article was 6425 mol/L, likely an error.
<table>
<thead>
<tr>
<th>Study Design</th>
<th>Risk of Bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other Considerations</th>
<th>ECTR + Standard Care</th>
<th>Standard Care</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observational studies</td>
<td>Very serious&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Not serious</td>
<td>Serious&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Serious&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Publication bias strongly suspected&lt;sup&gt;a&lt;/sup&gt;</td>
<td>All reported patients receiving ECTR with standard care (large ingestions): 19/91 (&gt;4 g), 32 1/9 (&gt;5 g), 42 7/44 (median 4.6 g), 6 3/25 (median 3.9 g&lt;sup&gt;e&lt;/sup&gt;) = 8.4%–15.9%. Cohorts of hospitalized patients receiving standard care alone: (median blood chloroquine concentration &gt;8.1 mg/L): 13/61 = 21.3%</td>
<td>Cohorts of hospitalized patients receiving standard care alone: 0/48, 28 6/30, 31 19/165 = 6.3%–20.0%</td>
<td>Groups not comparable</td>
<td>Very low</td>
<td>Critical</td>
</tr>
<tr>
<td>Observational studies</td>
<td>Very serious&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Not serious</td>
<td>Serious&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Serious&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Publication bias strongly suspected&lt;sup&gt;a&lt;/sup&gt;</td>
<td>All reported patients receiving ECTR with standard care: 3/25 = 12.0%</td>
<td>Cohorts of hospitalized patients receiving standard care alone: 0/48, 28 6/30, 31 19/165 = 6.3%–20.0%</td>
<td>Groups not comparable</td>
<td>Very low</td>
<td>Critical</td>
</tr>
<tr>
<td>Observational studies</td>
<td>Very serious&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Not serious</td>
<td>Serious&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Serious&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Publication bias strongly suspected&lt;sup&gt;a&lt;/sup&gt;</td>
<td>All reported patients receiving ECTR with standard care: 6/23 = 26.1%</td>
<td>Cohorts of hospitalized patients receiving standard care alone: 19/91 (&gt;4 g), 32 1/9 (&gt;5 g), 42 7/44 (median 4.6 g), 6 3/25 (median 3.9 g&lt;sup&gt;e&lt;/sup&gt;) = 8.4%–15.9%. Cohorts of hospitalized patients receiving standard care alone: (median blood chloroquine concentration &gt;8.1 mg/L): 13/61 = 21.3%</td>
<td>Groups not comparable</td>
<td>Very low</td>
<td>Critical</td>
</tr>
</tbody>
</table>

<sup>a</sup> All reported patients receiving ECTR with standard care (large ingestions): 19/91 (>4 g), 32 1/9 (>5 g), 42 7/44 (median 4.6 g), 6 3/25 (median 3.9 g<sup>e</sup>) = 8.4%–15.9%. Cohorts of hospitalized patients receiving standard care alone: (median blood chloroquine concentration >8.1 mg/L): 13/61 = 21.3%.

<sup>b</sup> Groups not comparable.

<sup>c</sup> Very low.

<sup>d</sup> Critical.

<sup>e</sup> All reported patients receiving ECTR with standard care: 6/23 = 26.1%.

<sup>f</sup> Groups not comparable.

<sup>g</sup> Very low.

<sup>h</sup> Critical.

<sup>i</sup> All reported patients receiving ECTR with standard care: 3/25 = 12.0%.

<sup>j</sup> Groups not comparable.

<sup>k</sup> Very low.

<sup>l</sup> Critical.

<sup>m</sup> All reported patients receiving ECTR with standard care: 19/91 (>4 g), 32 1/9 (>5 g), 42 7/44 (median 4.6 g), 6 3/25 (median 3.9 g<sup>e</sup>) = 8.4%–15.9%. Cohorts of hospitalized patients receiving standard care alone: (median blood chloroquine concentration >8.1 mg/L): 13/61 = 21.3%.

<sup>n</sup> Groups not comparable.

<sup>o</sup> Very low.

<sup>p</sup> Critical.

<sup>q</sup> All reported patients receiving ECTR with standard care: 6/23 = 26.1%.

<sup>r</sup> Groups not comparable.

<sup>s</sup> Very low.

<sup>t</sup> Critical.
Table 4. Continued

<table>
<thead>
<tr>
<th>N studies</th>
<th>Study Design</th>
<th>Risk of Bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other Considerations</th>
<th>ECTR + Standard Care</th>
<th>Standard Care</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquine = 2 (no data for quinine)</td>
<td>Observational studies</td>
<td>Very serious</td>
<td>Not serious</td>
<td>Serious</td>
<td>Serious</td>
<td>Publication bias strongly suspected</td>
<td>All reported patients receiving ECTR with standard care: median 11.0 d (n=5)</td>
<td>Cohort of hospitalized patients receiving standard care alone: median ICU stay in survivors 4.5±7 d (range: 9 h to 60 d) in 153 patients</td>
<td>Groups not comparable</td>
<td>Very low</td>
<td>Important</td>
</tr>
<tr>
<td>Observational studies</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Strong association</td>
<td>Rate of serious complications of catheter insertion varies from 0.1% to 2.1%</td>
<td>Approximately 0</td>
<td>Absolute effect is estimated to be varying from 1 to 21 more serious complications per 1000 patients in the ECTR group</td>
<td>Moderate</td>
<td>Critical</td>
<td></td>
</tr>
<tr>
<td>ECTR</td>
<td>Observational studies</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Strong association</td>
<td>Rate of serious complications of ECTR varies according to the type of ECTR performed from 0.005% (HD and CRRT) to 0.6% (TPE) and up to 1.9% (HP)</td>
<td>Approximately 0</td>
<td>Absolute effect is estimated to be varying from &gt;0 to 19 more serious complications per 1000 patients in the ECTR group depending on the type of ECTR performed</td>
<td>Moderate</td>
<td>Critical</td>
<td></td>
</tr>
</tbody>
</table>

Bold text represents the likelihood of the measured outcome. “Requirement for extracorporeal membrane oxygenation/ECLS” and “permanent auditory deficit” were outcomes ranked critical, although no data were reported in the control group. ICU, intensive care unit; HD, hemodialysis; CRRT, continuous renal replacement therapy; TPE, therapeutic plasma exchange; HP, hemoperfusion.

Includes our systematic review of the literature on ECTR (12 patient reports) and four patient series on standard care alone.
Patient reports published on effect of ECTR. Uncontrolled and unadjusted for confounders, such as severity of poisoning, coingestions, supportive and standard care, and cointerventions. Confounding by indication is inevitable because ECTR is usually attempted in the sickest patients.

ECTR and standard care performed may not be generalizable to current practice (literature predating 2000).

Few events in small sample size: optimal information size criteria not met.

Publication bias is strongly suspected due to the study design (patient reports published in toxicology report very severe poisoning either with or without impressive recovery with treatments attempted).

Includes our systematic review of the literature on ECTR (25 patient reports) and two patient series on standard care alone.

Includes our systematic review of the literature on ECTR (23 patient reports) and three patient series on standard of care alone.

Permanent visual deficits varied from field constriction to complete blindness. This outcome was not systematically measured nor reported.

Includes our systematic review of the literature on ECTR (five patient reports) and one patient series on standard care alone.

For venous catheter insertion, serious complications include hemothorax, pneumothorax, hemomediatinum, hydromediatinum, hydrothorax, subcutaneous emphysema retroperitoneal hemorrhage, embolism, nerve injury, arteriovenous fistula, tamponade, and death. Hematoma and arterial puncture were judged not serious and thus, excluded from this composite outcome. Deep vein thrombosis and infection complications were not included considering the short duration of catheter use.

On the basis of five single-arm observational studies: two meta-analyses comparing serious mechanical complications associated with catheterization using or not using an ultrasound, which included six RCTs in subclavian veins\(^{104}\) and 11 in internal jugular veins\(^{105}\), two RCTs comparing major mechanical complications of different sites of catheterization\(^{106,107}\); and one large multicenter cohort study reporting all mechanical complications associated with catheterization.\(^{108}\) Rare events were reported from patient series and patient reports.

Not rated down for inconsistency because heterogeneity was mainly explained by variation in site of insertion, use of ultrasound, experience of the operator, populations (adults and pediatric), urgency of catheter insertion, practice patterns, and methodologic quality of studies.

Not rated down for indirectness because cannulation and catheter insertion were judged similar to the procedure for other indications.

Not rated down for imprecision because the wide range reported was explained by inconsistency.

The events in the control group are assumed to be zero (because no catheter is installed for ECTR); therefore, the magnitude of effect is at least expected to be large, which increases the confidence in the estimate of effect. Furthermore, none of the studies reported 95% confidence intervals that included the null value, and all observed complications occurred in a very short time frame (i.e., few hours).

For HD and CRRT, serious complications (air emboli, shock, and death) are exceedingly rare, especially if no net ultrafiltration. Minor bleeding from heparin, transient hypotension, and electrolytes imbalance were judged not serious. For HP, serious complications include severe thrombocytopenia, major bleeding, and hemolysis. Transient hypotension, hypoglycemia, hypocalcemia, and thrombocytopenia were judged not serious. For TPE, serious complications include citrate toxicity, severe allergic reaction, anaphylaxis, and vasovagal reaction. Hypotension, hypocalcemia, and urticaria were judged as not serious. All nonserious complications were excluded from this composite outcome.

HD/CRRT: on the basis of two single-arm studies describing severe adverse events per 1000 treatments in large cohorts of patients.\(^{109,110}\) TPE: on the basis of the two most recent one-arm studies reporting potential life-threatening adverse events.\(^{111,112}\) HP: on the basis of two small single-arm studies in poisoned patients.\(^{113,114}\) Rare events were reported in patient series and patient reports.

Assuming that patients in the control group would not receive any form of ECTR, the events in the control group would be zero; therefore, the magnitude of effect is at least expected to be large, which increases the confidence in the estimate of effect. Furthermore, none of the studies reported 95% confidence intervals that included the null value, and all observed complications occurred in a very short time frame (i.e., few hours).
Removal = Plasma flow × Time_{HD} × [Hydroxychloroquine]_{initial}
= (14.4 L/h) × (4 hour HD) × (4 mg/L) = 230.4 mg.
Then, 230.4 mg/10,000 mg ingested = 2.3% of ingested dose.

Moreover, the calculation illustrates the dialytic removal assuming a near “best-case scenario” associated with each of the important determinants of hydroxychloroquine dialyzability. Practically, the calculated concentration will be lower because the maximal oral bioavailability is about 74% and the Vd typically exceeds 50 L/kg, the extraction ratio is likely lower than 100% (i.e., the extracorporeal clearance would be <240 ml/min). Together, these would result in a lower removal of hydroxychloroquine than calculated.

Preclinical Data
In one animal experiment of chloroquine poisoning, nine dogs treated with HD were compared with nine controls. All dogs survived a dose of 5 mg/kg, whereas none did after 8 mg/kg.63 HD therefore failed to provide a survival advantage to chloroquine-poisoned dogs.

Clinical Data
Chloroquine
Among human reports, there were 12 patients (five fatalities) described from ten articles (Table 3). This cohort was somewhat dated, with the most recent one published in the year 2000. These patient reports were of low methodologic quality and lacked reporting of critical information.10 In only two patients was there an apparent temporal improvement with ECTR.70,84 Complications included hypothermia during PD80 and simultaneous declines of both hemoglobin and platelets during HP.70,84 As shown in the evidence table (Table 4), the cohort of 12 patients receiving ECTR was sicker (median dose 8.4 g, median plasma chloroquine concentration 4.7 mg/L, or blood chloroquine concentration 20.7 mg/L6) than other described cohorts. Despite the clinical severity, non-ECTR treatments were varied and heterogeneous (only 71% received benzodiazepines, none received ECLS). Mortality in the ECTR cohort was twice as high as the sickest cohort previously described.32 Considering the different degree of poisoning severity and wide range of provided treatments, the workgroup judged that no formal comparison between the ECTR cohort and historical controls was possible.

Hydroxychloroquine
There was a single patient report of ECTR used for hydroxychloroquine poisoning in which treatment was also confounded by the use of intravenous lipid emulsion.85

Quinidine
There were 25 patients described from 17 articles (Table 3). All were dated, with the most recent one published in 1993. The overall quality of patient reports was of low methodologic quality and generally lacked reporting of critical information. Low-efficiency techniques (PD, ET) were used in 40% of patients. Several reports claimed some degree of improvement (resolution of hemodynamic instability, visual recovery); in rare cases, dramatic improvements were noted with high-efficiency techniques,73,74,86 but in most, this occurred several hours following termination of the procedure, suggesting that this was coincidental and unrelated to the ECTR. There were three fatalities.30,87,88 Complications from ECTR included hypotension during hemodialysis89 and four cases of decreased platelet counts during hemoperfusion.57,90,91 Compared with historical cohorts (Table 4), mortality in patients receiving ECTR was higher (12% versus <5%), as was the incidence of permanent visual impairment (26% versus <5%), but as the ECTR group had more features of severity, a reliable assessment of clinical benefit from ECTR was not feasible.

Compared with standard care alone, there was no direct or indirect evidence of added benefit from ECTR, but there was evidence of added harms and costs related to the insertion of a double-lumen catheter and the procedure itself, the magnitude of which varied according to local practices, methods of catheterization, and type of ECTR used.92

DISCUSSION
Recommendation 1
In patients severely poisoned with chloroquine, we recommend against using ECTR in addition to standard care (strong recommendation, very low quality of evidence [1D]).

Rationale for Recommendation
The workgroup agreed almost unanimously that the risks and costs associated with ECTR surpass any potential benefit in chloroquine poisoning (results of votes: median =1, upper quartile =1, disagreement index =0). This is on the basis of both the very poor dialyzability of chloroquine as well as the absence of direct or indirect clinical benefit from published reports. Even if the patient reports are dated and do not reflect current management, the workgroup evaluated that the results would not show differences in outcomes had they been performed with present-day standard care. The workgroup could
not propose a hypothetical scenario in which ECTR would be beneficial for poison removal.

Research Gaps
There are no research gaps.

Recommendation 2
Similar to chloroquine, hydroxychloroquine was assessed as non-dialyzable. Because of limited clinical data and despite the lack of biologic plausibility, no recommendation was developed, as per a priori agreed methods (minimal requirement of three reported patients describing clinical outcomes).

Research Gaps
Because of the minimal data on dialyzability of hydroxychloroquine, the workgroup proposed that pharmacokinetic studies be performed to confirm or refute the current impression that hydroxychloroquine is non-dialyzable.

Recommendation 3
In patients severely poisoned with quinine, we recommend against using ECTR in addition to standard care (strong recommendation, very low quality of evidence [1D]).

Rationale for Recommendations
As opposed to chloroquine, quinine’s volume of distribution is smaller, although still large (1.5–3.0 L/kg). This, added to its extensive protein binding, limits its removal by diffusive and convective techniques, as confirmed from data presented above. Further, despite the dated and poor quality of the clinical evidence, when added to standard care ECTR did not provide any apparent benefit, but it did increase risks and costs. For these reasons, the workgroup strongly recommended against the use of ECTR (results of votes: median =1, upper quartile =1, disagreement index =0). Six of 37 participants would consider using ECTR in very limited settings, such as poisoning in a patient with a preexisting vascular access and an available charcoal cartridge or high-cutoff dialyzer. Therapeutic plasma exchange was not considered to be sufficiently efficient in increasing total clearance of quinine to justify its risks in any hypothetical scenario of quinine poisoning.

Research Gaps
Because of the questions and the remaining uncertainties related to quinine’s volume of distribution and in circumstances in which protein binding might be lower (potentially overdose), some members considered that there was some rationale in further testing the capacity of high-cutoff hemodialysis or hemoperfusion to remove quinine using current standards for assessing dialyzability. It is conceivable that with modern catheters, modern devices, and early use of these techniques after ingestion, a clinically relevant amount of quinine could be removed. The risk of the procedure would also be lowered assuming that a functional dialysis access is already available in study participants.

In conclusion, chloroquine, hydroxychloroquine, and quinine have low therapeutic indices and can cause major toxicity and death in poisoning even with modern standard care. The EXTRIP workgroup assessed the three drugs to be non-dialyzable. Data regarding the clinical efficacy of ECTRs were dated and of poor quality overall. The workgroup recommended against extracorporeal removal of chloroquine and quinine in addition to standard care.

DISCLOSURES

Thomas D. Nolin reports personal fees from MediBeacon, personal fees from CytoSorbents, and other from McGraw-Hill Education outside the submitted work. Marc Ghannoum is a scholar of the Fonds de Recherche du Québec - Santé. Darren Roberts acknowledges support of St. Vincent’s Centre for Applied Medical Research Clinician “Buy-Out” Program. All remaining authors have nothing to disclose.

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Marc Ghannoum, Sophie Gosselin, Robert S. Hoffman, Valery Lavergne, Thomas D. Nolin, and Darren M. Roberts designed the study; Ingrid Berling, Marc Ghannoum, Joshua D. King, Greene Shepherd carried out extractions; Ingrid Berling, Marc Ghannoum, Joshua D. King, Darren M. Roberts, and Greene Shepherd analyzed the data; Ingrid Berling, Marc Ghannoum, and Valery Lavergne made the tables and figures; all authors drafted and revised the paper; and all authors approved the final version of the manuscript.

SUPPLEMENTAL MATERIAL

This article contains the following supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2020050564/-/DCSupplemental.

Supplemental Figure 1. Approach to and implications of rating the quality of the evidence and strength of recommendations using the GRADE methodology.

Supplemental Figure 2. Voting process for recommendations.

Supplemental Material. Supplemental material includes methods; EXTRIP clinical practice guidelines; disclosure and management of potential COI; clinical question; search strategy, screening, and study selection; evidence review: dialyzability; assessment of toxicokinetic data; evidence review: clinical
outcomes; development of clinical recommendations; updating process; glossary; and references.
Supplemental Table 1. Represented societies.
Supplemental Table 2. EXTRIP criteria for assessing dialyzability.
Supplemental Table 3. Quality of individual studies for toxicokinetic outcomes.
Supplemental Table 4. Quality of evidence for toxicokinetic outcomes.

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META-ANALYSIS

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Chloroquine, Hydroxychloroquine, or Quinine Poisoning

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A) METHODS

**EXTRIP clinical practice guidelines**
As defined by the Institute of Medicine in 2011\(^1\), clinical practice guidelines are statements that include recommendations intended to optimize patient care by assisting practitioners and patients in making decisions about appropriate health care for specific clinical circumstances. They are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options. Attributes of good guidelines include validity, reliability, reproducibility, clinical applicability, clinical flexibility, clarity, multidisciplinary process, review of evidence and documentation.

The EXTRIP-2 workgroup pursued a second phase of the international multidisciplinary effort started in 2010. Using established methodology, the EXTRIP workgroup reviewed the literature and developed recommendations on the use of ECTR in the context of poisoning for a new set of 10 poisons. More specifically, the effect of ECTR was measured against standard care and alternative treatments. Potential benefits of ECTR were balanced with potential harms from the procedure. Outcomes measured included mortality, relevant clinical and physiological endpoints, complications associated with ECTR procedure, as well as the extent of extracorporeal removal of the drug (i.e. dialyzability).

When applicable, different populations (including end-stage kidney disease and pediatric patients), types of poisoning (acute, acute-on-chronic and chronic), and types of ECTR were evaluated. When developing recommendations, variation in clinical practice in different settings across the globe was considered especially regarding resource use, costs and availability of ECTR\(^2\). Implementation issues were addressed when appropriate.

**Workgroup composition**
The EXTRIP workgroup is an international collaborative comprising recognized experts from various clinical specialties (medical toxicology, emergency medicine, nephrology, critical care, pediatrics, and pharmacology). EXTRIP-2 workgroup renewed the participation of 15 members and invited 22 new experts to join the workgroup and increase representativeness across the world (See Table 1). Six co-chairs (M.G., V.L., B.H., D.R, S.G. and T.N), of which one is a non-voting guideline methodologist (V.L.), led and supervised the different aspects of the guideline development.
Table 1. Represented societies

<table>
<thead>
<tr>
<th>Represented societies</th>
<th>Represented societies</th>
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<tr>
<td>African Federation of Emergency Medicine</td>
<td>Chinese College of Emergency Physicians</td>
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<tr>
<td>Acute Dialysis Quality initiative</td>
<td>Chinese Medical Association</td>
</tr>
<tr>
<td>American College of Clinical Pharmacology</td>
<td>European Association of Poison Centres and Clinical Toxicologists</td>
</tr>
<tr>
<td>American Academy of Clinical Toxicology</td>
<td>European Renal Association-European Dialysis and Transplant Association</td>
</tr>
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<td>American College of Emergency Physicians</td>
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</tr>
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<td>American College of Medical Toxicology</td>
<td>European Society of Intensive Care Medicine</td>
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<tr>
<td>American Society of Nephrology</td>
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<tr>
<td>American Society of Pediatric Nephrology</td>
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<td>International Society of Nephrology</td>
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<tr>
<td>Asian Pacific Nephrology Association</td>
<td>Middle East and North Africa Clinical Toxicology Association</td>
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<tr>
<td>Australian and New Zealand Intensive Care Society*</td>
<td>National Kidney Foundation</td>
</tr>
<tr>
<td>Australian and New Zealand Society of Nephrology*</td>
<td>Pediatric Continuous Renal Replacement Therapy</td>
</tr>
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<td>Brazilian Association of Information Centres and Toxicologic Assistance*</td>
<td>Pediatric Critical Care Medicine</td>
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<td>Canadian Association of Emergency Physicians</td>
<td>Society of Critical Care Medicine</td>
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<td></td>
<td>The Renal Association</td>
</tr>
</tbody>
</table>

*This representation does not signify endorsement. Recommendations will be submitted to societies for review and potential endorsement.

Disclosure and management of potential COI
All prospective members were required to disclose any actual, potential, or perceived COI prior to inclusion in the workgroup. The disclosures were used to categorize the members as cleared for full participation, allowed to participate with recusal from certain aspects of guideline development, or disqualified from participation. The co-chairs remained free of any financial COI during the entire guideline development process, meaning avoidance of interests and relationships with pharmaceutical or device companies pertaining to the topic of poisoning. Members were required to disclose to the co-chairs any new activities that had the potential to be viewed as a COI prior to engaging in the activity, at the beginning of face-to-face meeting, and before submission of the manuscript. Co-chairs determined if specific activities were allowed under the COI rules. All COIs deemed as potential appearance of a conflict of interest were required to be included in the manuscript.

Clinical question
An initial list of relevant clinical questions was developed by the co-chairs and then approved by the entire workgroup prior to the first iteration of EXTRIP-2. Clinical questions were formulated following the standard PICO format. Comparator(s) of interest were more explicitly stated and defined (e.g. standard care with/without antidotes). For a clinical question to be formally developed into a recommendation, the workgroup agreed a priori that a minimum of 3 reported cases describing clinical outcomes for a specific poison was required.

Search strategy, screening, and study selection
One health sciences librarian in collaboration with one co-chair and the methodologist designed literature searches to address clinical questions. For the search strategy regarding the use of ECTR, the following electronic databases were searched: PubMed/Medline, EMBASE and Cochrane Database for systematic Reviews. Searches were not limited to English language or year of publication. To supplement the electronic searches, workgroup members had the option of contacting experts and manually searching journals, conference proceedings, reference lists, and regulatory agency websites for relevant articles.
The following search strategy was created: (dialysis or hemodialysis or haemodialysis or hemoperfusion or haemoperfusion or plasmapheresis or plasmaphaeresis or hemofiltration or hemodiafiltration or hemodiafiltration or plasma exchange or CRRT or CVV* or exchange transfusion) and ((quinine) OR (chloroquine) OR (hydroxychloroquine)).

If the initial search of the literature did not identify comparative studies where ECTR is measured against standard care alone (with or without an antidote, if applicable), complementary searches on the comparator of interest and on prognostic factors were developed. Potential complications of ECTR (associated with catheterization as well as related to the procedure itself) were comprehensively searched in PubMed/Medline for the best available evidence. A web-based international survey performed in 2014-2015 by the EXTRIP workgroup provided the main source of evidence to address other important considerations such as resource use, costs and availability of ECTR worldwide. This survey also informed potential implementation issues. Titles were screened for appropriateness by two workgroup members independently and full text papers were obtained and abstracted by the same two members into a standardized data extraction tool.

**Evidence review: dialyzability**

Dialyzability was defined a priori as the ability of any ECTR to remove a clinically significant percentage of the total body burden of the poison. Different criteria were used to semi-quantitively categorize the dialyzability of the poison for each ECTR (Table 2)

<table>
<thead>
<tr>
<th>Dialyzability</th>
<th>Primary criteria</th>
<th>Alternative criteria 1</th>
<th>Alternative criteria 2</th>
<th>Alternative criteria 3</th>
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<tr>
<td><strong>D, Dialyzable</strong></td>
<td>% Removed* &gt;30%</td>
<td>CLECTR / CLTOT (%)$ &gt;75%</td>
<td>T1/2ECTR / T1/2 (%)&amp; &lt;25%</td>
<td>REECTR / RETOT (%)# &gt;75%</td>
</tr>
<tr>
<td><strong>M, Moderately dialyzable</strong></td>
<td>&gt;10-30%</td>
<td>&gt;50-75%</td>
<td>&gt;25-50%</td>
<td>&gt;50-75%</td>
</tr>
<tr>
<td><strong>S, Slightly dialyzable</strong></td>
<td>≥3-10%</td>
<td>≥25-50%</td>
<td>≥50-75%</td>
<td>≥25-50%</td>
</tr>
<tr>
<td><strong>N, Not dialyzable</strong></td>
<td>&lt;3%</td>
<td>&lt;25%</td>
<td>&lt;75%</td>
<td>&lt;25%</td>
</tr>
</tbody>
</table>

$ Applicable to all modalities of ECTR, including hemodialysis, hemoperfusion, hemofiltration.
* Corresponds to % removal of ingested dose (adjusted for bioavailability) or total body burden, adjusted for a 6-hour ECTR period.
& Corresponds to the clearance by ECTR (CLECTR) compared to the total clearance (CLTOT i.e. endogenous + ECTR clearance)
# Corresponds to the apparent half-life during ECTR (T1/2ECTR) compared to the apparent half-life off ECTR (T1/2)

Assessment of toxicokinetic data

The quality of individual studies reporting on toxicokinetic outcomes was assessed according to a pre-defined set of criteria (see Table 3) and then summarized into a quality of the overall evidence (Table 4). If the latter was judged low or very low, literature from non-poisoning contexts was also considered, such as CKD pharmacokinetics, animal, and in-vitro studies.
Table 3: Quality of individual studies for toxicokinetic outcomes

<table>
<thead>
<tr>
<th>Quality of individual studies</th>
<th>Interpretation and application to individual studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Sufficient TK/PK data present; % removed is reported or can be calculated; reported calculations are appropriate.</td>
</tr>
<tr>
<td>Moderate</td>
<td>Sufficient TK/PK data present, but % removed is NOT reported or CANNOT be calculated; reported calculations (e.g., CLEC/CLTOT) are appropriate.</td>
</tr>
<tr>
<td>Low</td>
<td>Sufficient PK parameters may be reported, but supporting data absent or suspect, reported calculations inappropriate, or other serious limitations exist.</td>
</tr>
<tr>
<td>Very Low</td>
<td>Sufficient PK parameters and supporting data not adequately reported, questionable or no calculations reported. However, based on theoretical knowledge of Vd, protein binding, CLSYS, molecular weight, etc., some assumptions can be made about dialyzability.</td>
</tr>
<tr>
<td>Reject</td>
<td>Questionable parameters reported with no supporting data, fatal flaw in study design.</td>
</tr>
</tbody>
</table>

Table 4. Quality of evidence for toxicokinetic outcomes

<table>
<thead>
<tr>
<th>Quality of evidence</th>
<th>Reporting</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>A</td>
<td>We are confident that the true effect lies close to our estimate of the effect.</td>
</tr>
<tr>
<td>Moderate</td>
<td>B</td>
<td>The true effect is likely to be close to our estimate of the effect, but there is a possibility that it is substantially different.</td>
</tr>
<tr>
<td>Low*</td>
<td>C</td>
<td>The true effect may be substantially different from our estimate of the effect.</td>
</tr>
<tr>
<td>Very Low*</td>
<td>D</td>
<td>Our estimate of the effect is just a guess, and it is very likely that the true effect is substantially different from our estimate of the effect*.</td>
</tr>
</tbody>
</table>

*If the quality of the evidence is low or very low, literature from non-poisoning contexts may be used, such as pharmacokinetic studies in ESKD populations, animal, and in-vitro studies.

Evidence review: clinical outcomes
All outcomes of interest were identified a priori and the guideline workgroup explicitly rated their relative importance for decision making. Evidence summaries for each question were prepared by the members assigned to a specific drug or poison in collaboration with the methodologist. The risk of bias was assessed using the Cochrane risk of bias tool for randomized controlled trials, and modified domains to assess confounding bias, selection bias, and bias due to misclassification for non-randomized studies. The quality in the evidence (Figure 1) was initially assessed for each critical and important outcome, and then for each recommendation using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. GRADE evidence profile tables were developed in GRADEpro Guideline Development Tool (Evidence Prime CITE software) (GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University, 2015 (developed by Evidence Prime, Inc.). Available from gradepro.org.https://gradepro.org/cite/). The summaries of evidence were reviewed by all workgroup members for drafting of recommendations.
Development of clinical recommendations
The workgroup considered core elements of the GRADE evidence in the decision process, including the quality of evidence and balance between desirable and undesirable effects. Additional domains were acknowledged where applicable (feasibility, resource use, acceptability). For all recommendations, the workgroup members voted to reach agreement for final recommendations. The voting process followed the same set of rules as for EXTRIP-1 (i.e. anonymous online voting consisting of two-round modified Delphi with each statement voted on a 9-point Likert scale and final results interpreted according to EXTRIP voting rules based on median, lower or upper quartile (LQ or UQ) as appropriate, and disagreement index (DI) as calculated using RAND/UCLA Appropriateness Method (see Figure 2)), and was performed using SimpleSurvey software.
Figure 2: Voting process for recommendations

Statement regarding the use of ECTR in severe poisoning with toxin X

The workgroup votes on the statement (9-point Likert scale)
FOR (7-9) / NEUTRAL (4-6) / AGAINST (1-3)

- Median between 7-9 AND Disagreement index ≤ 1
  - Strong recommendation
    = “We recommend for...”

- Lower quartile between 7-9
  - Weak/Conditional recommendation
    = “We suggest for...”

- Median between 4-6 AND Disagreement index ≤ 1
  - No recommendation
    = “No recommendation” or “Research gap”

- Lower quartile between 4-6
  - No recommendation
    = “No agreement reached”

- Disagreement index > 1

* These recommendations can be formulated for or against a course of action (the figure only shows voting results FOR a course of action)

All recommendations were labeled as either “strong” or “weak/conditional” according to the GRADE approach. The words “we recommend” indicate strong recommendations and “we suggest” indicate weak recommendations. Figure A provides the suggested interpretation of strong and weak recommendations for patients, clinicians, and healthcare policy makers. High-quality evidence was expected to be lacking for the great majority of recommendations. According to GRADE guidance, strong recommendations in the setting of lower-quality evidence were only assigned when the workgroup members believed they conformed to one or several paradigmatic conditions. As per GRADE guidance on discordant recommendations, two paradigmatic situations presented in the development of EXTRIP-2 guideline: 1) low-quality evidence suggested benefit in a life-threatening situation (with evidence regarding harms being low or high), and 2) when low-quality evidence suggested benefit and high-quality evidence suggested harm.

If the workgroup could not make a recommendation for or against a particular management strategy due to either 1) a close balance between the benefits and harms (no recommendation), or 2) insufficient evidence making a recommendation too speculative (research gap), either a “no recommendation” or “research gap” recommendation was formulated (a “neutral recommendation” interpreted as a
“reasonable course of action” was no longer accepted). Although there is arguably ongoing need for research on virtually all of the topics considered in this guideline, “Research Needs” were noted for recommendations in which the need was believed by the workgroup to be particularly relevant.

The entire workgroup gathered in Montreal, Canada in November 2019 for the presentation of evidence summaries and the development of the recommendations for the ten new poisons. The subgroup assigned to a specific poison participated in the preparation of the draft guideline in collaboration with co-chairs.

**Updating process**
Ongoing screening of the literature will take place to determine the need for revisions based on the likelihood that any new data will have an impact on the recommendations. If necessary, the entire workgroup will reconvene to discuss potential changes.

**B) GLOSSARY**
- **Poison**: A xenobiotic (exogenous chemical, including medications and drugs) or an endogenously found chemical (e.g., iron, copper, vitamins) resulting from exogenous exposure with the potential to cause toxicity.
- **Poisoning**: Exposure to a poison causing or capable of causing toxicity, regardless of intent. It includes intoxication, toxicity, and overdose.
- **Severe Poisoning**: Exposure to a poison causing or capable of causing, if left untreated, end-organ damage.
- **Extracorporeal treatment (ECTR)**: A treatment, occurring outside the body, which promotes poison removal by mechanisms different from endogenous pathways. ECTR includes HD, continuous renal replacement therapy, extended dialysis, peritoneal dialysis (although technically occurring in the body), hemofiltration, hemodiafiltration, hemoperfusion, therapeutic plasma exchange and albumin/“liver” dialysis.
- **Dialyzability**: This term reflects the ability of ECTR to remove a clinically significant percentage of the total body burden of the poison.
- **Clearance**: The volume of blood (or solvent) cleared of poison per unit time, typically reported in units of mL/min. Importantly, $C_{ELCTR}$ represents solute clearance due exclusively to ECTR and is independent of endogenous clearance ($C_{ENDO}$; the sum of underlying renal and non-renal clearances). $C_{TOT}$ refers to total clearance and is the sum of $C_{ELCTR}$ and $C_{ENDO}$.
- **Shock or end-organ compromise**: Hypotension (systolic blood pressure $< 90$ mmHg or mean blood pressure $< 65$ mmHg) with the presence of cellular ischemia as evidenced by increased lactate concentration, acute kidney injury (AKI) as defined by the Kidney Disease Improving Global Outcomes (KDIGO) guideline, increased troponin, altered mental status, or decreased capillary refill.
- **Refractory hypotension**: per age-related defined standards, after adequate fluid challenge and vasopressor/inotropic support.
- **Refractory bradycardia**: per age-related defined standards, after vasopressor/inotropic support.
- **Altered mental status**: poison-induced impairment in at least one brain function (cognition, alertness, or orientation), in the absence of another cause.
- **Coma**: a deep state of unconsciousness as defined per the American Academy of Neurology.
- **Acute liver failure**: (a) the presence of hepatic encephalopathy of any degree; (b) evidence of moderately severe coagulopathy [i.e., international normalized ratio (INR) ≥1.5]; (c) presumed onset of acute illness of <26 weeks; and (d) the absence of cirrhosis.
- **Acute liver injury**: (a) evidence of moderately severe coagulopathy (INR ≥2.0); (b) presumed onset of acute illness <26 weeks; and (c) the absence of cirrhosis.
- **Kidney impairment**: CKD as stage 3B, 4, or 5 CKD (i.e., eGFR < 45 mL/min/1.73m²) or AKI as KDIGO stage 2 or 3 AKI. In the absence of a baseline creatinine, a GFR < 45 mL/min in adults; in children with no baseline creatinine, the use of KDIGO criteria of AKI stage 2 and 3 after imputing a baseline serum creatinine using the Schwartz 2009 formula assuming 120 mL/min of "normal" eGFR. The presence of oligo/anuria unresponsive to fluid resuscitation should be considered as impaired kidney function, regardless of serum creatinine concentration.

C) REFERENCES


