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

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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

META-ANALYSIS

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

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Significance Statement

Although poisoning by chloroquine, hydroxychloroquine, or quinine is relatively uncommon, recent use of chloroquine and hydroxychloroquine for COVID-19 has elevated concerns regarding management of such poisonings. To investigate the effect of and indications for extracorporeal treatments in cases of poisoning with these drugs, the Extracorporeal Treatments in Poisoning workgroup conducted systematic reviews of the relevant literature, screened studies, extracted data, and summarized findings. The group concluded that chloroquine, hydroxychloroquine, and quinine are not dialyzable (not amenable to clinically significant removal by extracorporeal treatments) and the current clinical evidence does not support the use of such treatments for chloroquine and quinine poisonings. Considering that data on extracorporeal treatments for hydroxychloroquine toxicity are sparse, the group proposed pharmacokinetic studies to confirm or refute the current impression that the drug is non-dialyzable.

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 hypoalbuminemia, 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 ($t_{1/2}$) is normally in excess of 10 days (Table 1). Given its considerable renal clearance, the $t_{1/2}$ 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 $t_{1/2}$ (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

Table 1. Physicochemical and pharmacokinetic properties of chloroquine, hydroxychloroquine, and quinine[17,18,20–22,24,93–97]

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

p, plasma; b, blood; $t_{1/2}$, half-life; CL, clearance.

concentration of 1.5–2.8 hours.[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.[17,23,24] Quinine is predominantly (80%) metabolized by CYP3A4 in the liver to form the major metabolite 3-hydroxyquinine,[25] whereas the remainder is excreted unchanged in urine.[17,19] The total endogenous clearance of quinine ranges from 120 to 150 ml/min[17] and is decreased by approximately 50% in patients with kidney failure (Table 1).[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.[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 agitated delirium, altered consciousness, seizures, and coma.[6,32–34] Rapid and profound hypokalemia occurs from intracellular potassium shifts.[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.[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.[3] Similarly, a QTc>500 ms was reported in >10% of patients prescribed hydroxychloroquine and azithromycin for COVID-19.[5]

The delay from ingestion of an acute overdose to cardiovascular collapse is typically short (<3 hours).[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.[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.[32,34,39,43–46] Cardiovascular and neurologic impairments are expected following acute ingestions >2 g.[32,34,39,43–47] Life-threatening toxicity and mortality are reported in untreated adult patients with acute ingestions >5 g.[34,39,40,42–45,48,49] However, there are also reports of survival after massive acute ingestions, including 12 g of chloroquine,[32] 36 g of hydroxychloroquine,[50] and 31 g of quinine.[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,[43] whereas concentrations between 2.5 and 5 mg/L are associated with mild neurologic impairment and dysrhythmias.[43] Blood chloroquine concentrations above 5 mg/L are associated with severe cardiovascular poisoning, and life-threatening dysrhythmias.[43] With prompt access to care, death is unlikely with blood chloroquine concentrations <10 mg/L.[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.[6,42] There are few toxicologic data on a concentration-response relationship for hydroxychloroquine, but blood hydroxychloroquine concentrations >2 mg/L are considered supratherapeutic,[52] and life-threatening poisoning is described after overdose at blood and plasma concentrations over 20 mg/L.[49,50,53] For quinine, a plasma concentration <10 mg/L is well tolerated and usually only causes minimal symptoms, such as tinnitus.[30] With plasma concentrations between 10 and 15 mg/L, visual symptoms are usually present,[28,30] and over 15 mg/L, cardiac dysrhythmias are reported.[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.[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).[54–56] Although there are fewer reported cases of hydroxychloroquine overdose, several fatalities are described.[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

185 patients treated in health care facilities and three deaths.[58] Mortality and morbidity remain high today with overdose of these drugs; for chloroquine, the overall mortality is approximately 5%–8%[32,40,56] but can exceed 10% following large ingestions, even with modern standard care.[6,32,42,44] Older cohorts reported higher mortality of >30%, likely representing differences in critical care management.[34,39,59] Mortality in hydroxychloroquine overdose appears considerably lower than for chloroquine.[48,60–62] Reported cohorts for quinine poisoning are >20 years old, and they show a mortality rate near or under 5%[28–31] and irreversible visual damage in 20%–50% of patients who had initial visual symptoms.[28–31]

Aside from the ingested dose, clinical predictors of chloroquine mortality include a QRS complex duration >120 ms, systolic pressure <80 mm Hg,[42] and the severity of hypokalemia.[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.[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.[48] The presence and severity of hypokalemia also predicts mortality for hydroxychloroquine.[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.[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.[6,40,42] The use of diazepam and epinephrine was shown to statistically reduce mortality in patients ingesting over 5 g of chloroquine,[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.[40] 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.[65]

Methods

The workgroup developed recommendations on the use of ECTR following the EXTRIP methodology previously published[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_{EC} represents solute clearance due exclusively to ECTR and is independent of endogenous systemic clearance (CL_{SYS}; the sum of underlying renal and nonrenal clearances). CL_{TOT} refers to total clearance and is the sum of CL_{EC} and CL_{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,[66–68] two animal experiments,[69,70] 11 pharmacokinetic studies,[24,71–80] and 28 patient reports and patient series.[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.[66] The extensive protein binding of quinine is also expected to limit further the efficacy of diffusion- or convection-based techniques.[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.[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),[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).[69] Rebound of chloroquine concentrations post-ECTR was noted in many publications.[68–72] Neither HD nor HP removed >150 mg of quinine.[30,73,74] Hemodialysis clearances of quinine did not surpass 15 ml/min,[24,73,74] and sieving coefficients during convective techniques remained below 20%.[75–77] Interestingly, therapeutic plasma exchange (TPE), which seems best suited to remove
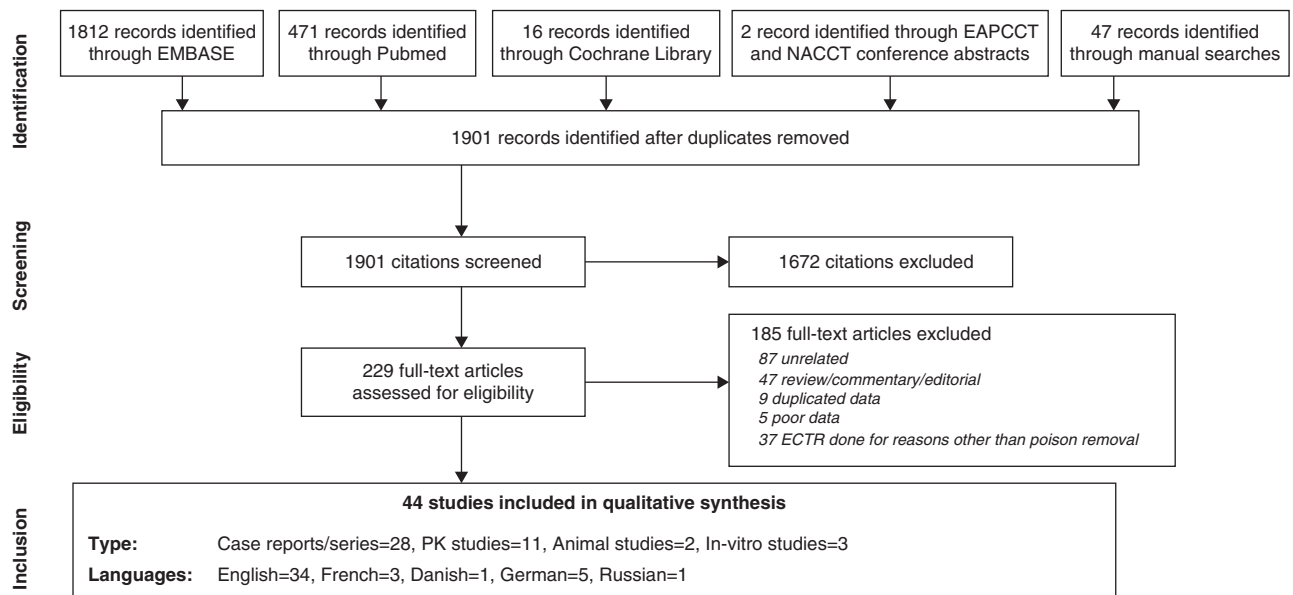
Figure 1. The litterature search last performed on January 15th, 2020, after removal of duplicates and non-pertinent records, yielded 44 studies for analysis. No comparative observational studies or randomized trials were identified. EAPCCT, European Association of Poisons Centres and Clinical Toxicologists; NACCT, North American Congress of Clinical Toxicology; PK, pharmacokinetic.

protein-bound drugs, removed only 8.5 mg of quinine in 3 hours (clearance was 12 ml/min).[74] As expected, lower-efficiency techniques like peritoneal dialysis (PD) and exchange transfusion (ET) had an inconsequential effect on removal of either chloroquine or quinine.[74,78–81] Dialyzability data for hydroxychloroquine were limited to three patients receiving routine hemodialysis, and extracorporeal drug removal was not observed.[82]

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

ECTR	$t_{1/2}$ during ECTR		Endogenous $t_{1/2}$, h	ECTR Clearance		Endogenous Clearance, ml/min	Dialyzability	Level of Evidence
	h	n		ml/min	n			
Chloroquine								
HD			>200	9–77	4	400–800	ND	C
HP-HD	11.9	1		0–54	2		ND	C
PD				1.1–1.5	2		ND	C
HP	2.0–6.7	3		61–135	3		ND	C
Hydroxychloroquine								
HD	>20	3	>200	a	3	100–300	ND	D
Quinine								
HD	21.2	1	8–14	0.2–13.8	17	100–150	ND	B
CRRT				0.3–3.7	3		ND	C
HD-HP	5.7	1					ND	D
ET	1.4–5.1	3		<4.6	2		ND	C
PD	12.5–27.3	3		0.6–11.1[b]	8		ND	B
TPE				11.8	1		ND	D
HP	2.5–21.7	2		16.7–115	3		ND	D

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.
[a]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.
[b]One value was excluded[103] because it was assessed as likely an error.

Table 3. Clinical description of included patients with poisoning

Parameters	Chloroquine, 12 patients	Hydroxychloroquine, 1 patient	Quinine, 25 patients
Patient characteristics			
Median age, yr	25.5	33	23
Men, %	33.3	0	44
Poisoning information			
Median dose, g	8.4	30	6.0
Median time from ingestion to admission, h	1.5	3.0	3.5
Median plasma concentration, mg/L	4.7 (p), 19 (b)[a]	uncertain[b]	15.1
Signs/symptoms/laboratory			
Coma, %	60	100	42
Visual impairment, %	28	0	87
Hypotension, %	83	100	28
Respiratory depression, %	82	100	21
Severe dysrhythmia/cardiac arrest, %	64	100	21
Auditory impairment, %	0	0	88
AKI, %	20	100	29
Median potassium, mmol/L	2.6	3.0	4.0
Prolonged QRS complex duration, %	80	100	7
Median QRS complex duration, ms	140	140	110
Prolonged QT interval, %	83	100	23
Median QT interval, ms	490	576	420
Other treatments, %			
Gastric lavage	70	100	69
Activated charcoal	78	100	6
Benzodiazepines	71	100	0.6
Bilateral stellate ganglion block	0	0	33
Cardiac pacing	10	100	6
Mechanical ventilation	75	100	25
Vasopressors	86	100	31
ECTR, n			
Hemodialysis	0	100	7
Hemoperfusion	8		5
Exchange transfusion	0		5
Hemoperfusion and hemodialysis in series	2		1
Peritoneal dialysis	2		5
>1 ECTR used	0		2
Outcome			
Visual sequelae, %	0	0	26
Median LOS, d	11	6 (ICU)	13
Death, %	42	0	12

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.
[a]Blood concentration can estimated to be approximately four times as high as the plasma concentration.[6,69]
[b]Plasma concentration stated in the article was 6425 mol/L, likely an error.

On the basis of previously defined criteria (Supplemental Material),[9] 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,[82] 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 4. Evidence profile table: ECTR plus standard care compared with standard care in patients severely poisoned with chloroquine or quinine

	Quality Assessment						Summary of Findings				
N studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	ECTR + Standard Care	Standard Care	Effect	Quality	Importance
Mortality											
Chloroquine=5[a]	Observational studies	Very serious[b]	Not serious	Serious[c]	Serious[d]	Publication bias strongly suspected[e]	All reported patients receiving ECTR with standard care (median ingestion of 8.4 g, median concentration 9.7 mg/L): 5/12 =**41.7%**	Cohorts of hospitalized patients receiving standard care alone (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)[44] = **8.4%–15.9%.** Cohorts of hospitalized patients receiving standard care alone: (median blood chloroquine concentration >8.1 mg/L):13/61[32]=**21.3%**	Groups not comparable	Very low	Critical
Quinine=3[f]	Observational studies	Very serious[b]	Not serious	Serious[c]	Serious[d]	Publication bias strongly suspected[e]	All reported patients receiving ECTR with standard care: 3/25 =**12.0%**	Cohorts of hospitalized patients receiving standard care alone: 0/48,[28] 5/165[29] =**0%-3%**	Groups not comparable	Very low	Critical
Permanent visual deficit											
Quinine=4[g]	Observational studies	Very serious[b,h]	Not serious	Serious[c]	Serious[d]	Publication bias strongly suspected[e]	All reported patients receiving ECTR with standard care: 6/23 =**26.1%**	Cohorts of hospitalized patients receiving standard care alone: 3/48,[28] 6/30,[31] 19/165[29] =**6.3%-20.0%**	Groups not comparable	Very low	Critical

Table 4. Continued

N studies	Quality Assessment						Summary of Findings				
	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	ECTR + Standard Care	Standard Care	Effect	Quality	Importance
Length of hospitalization Chloroquine=2 (no data for quinine)[i]	Observational studies	Very serious[b]	Not serious	Serious[c]	Serious[d]	Publication bias strongly suspected[e]	All reported patients receiving ECTR with standard care: median **11.0 d** (n=5)	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[32]	Groups not comparable	Very low	Important
Serious complications of catheter insertion[j] 5[k]	Observational studies	Not serious	Not serious[l]	Not serious[m]	Not serious[n]	Strong association[o]	Rate of serious complications of catheter insertion varies from **0.1% to 2.1%**	**Approximately 0**	Absolute effect is estimated to be varying from **1 to 21 more serious complications per 1000 patients** in the ECTR group	Moderate	Critical
Serious complications of ECTR[p] 6[q]	Observational studies	Not serious	Not serious	Not serious	Not serious	Strong association[r]	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)	**Approximately 0**	Absolute effect is estimated to be varying from >**0 to 19 more serious complications per 1000 patients** in the ECTR group depending of the type of ECTR performed	Moderate	Critical

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.
[a]Includes our systematic review of the literature on ECTR (12 patient reports) and four patient series on standard care alone.

[b]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.

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

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

[e]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).

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

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

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

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

[j]For venous catheter insertion, serious complications include hemothorax, pneumothorax, hemomediastinum, hydromediastinum, 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.

[k]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.

[l]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.

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

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

[o]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).

[p]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, arrhythmia, and vasovagal reaction. Hypotension, hypocalcemia, and urticaria were judged as not serious. All nonserious complications were excluded from this composite outcome.

[q]IHD/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.

[r]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).

$$\text{Removal} = \text{Plasma flow} \times \text{Time}_{HD} \times [\text{Hydroxychloroquine}]_{initial}$$
$$= (14.4 \text{ L/h}) \times (4 \text{ hour HD}) \times (4 \text{ mg/L}) = 230.4 \text{ mg}.$$
$$\text{Then, } 230.4 \text{ mg}/10,000 \text{ mg ingested} = 2.3\% \text{ of ingested dose}.$$

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.[83] 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 case 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 PD[80] 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/L[6]) 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]

Quinine

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 hemodialysis[89] and four cases of decreased platelet counts during hemoperfusion.[87,90,91] 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.[10] 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.

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.

REFERENCES

1. Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Mailhe M, et al: Hydroxychloroquine and azithromycin as a treatment of COVID-19: Results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents* 56: 105949, 2020

2. Colson P, Rolain JM, Lagier JC, Brouqui P, Raoult D: Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. *Int J Antimicrob Agents* 55: 105932, 2020

3. Borba MGS, Val FFA, Sampaio VS, Alexandre MAA, Melo GC, Brito M, et al: Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: A randomized clinical trial. *JAMA Netw Open* 3: e208857, 2020

4. Magagnoli J, Narendran S, Pereira F, Cummings T, Hardin JW, Sutton SS, et al.: Outcomes of hydroxychloroquine usage in United States veterans hospitalized with COVID-19 [published online ahead of print June 5, 2020]. *Med* doi:10.1016/j.medj.2020.06.001

5. Chorin E, Dai M, Shulman E, Wadhwani L, Bar-Cohen R, Barbhaiya C, et al: The QT interval in patients with COVID-19 treated with hydroxychloroquine and azithromycin. *Nat Med* 26: 808–809, 2020

6. Mégarbane B, Bloch V, Hirt D, Debray M, Résiére D, Deye N, et al: Blood concentrations are better predictors of chioroquine poisoning severity than plasma concentrations: A prospective study with modeling of the concentration/effect relationships. *Clin Toxicol (Phila)* 48: 904–915, 2010

7. Duggin GG: Extracorporeal techniques in the treatment of poisoned patients. *Med J Aust* 155: 62–63, 1991

8. Winchester JF, Harbord NB: Intoxications amenable to extracorporeal removal. *Adv Chronic Kidney Dis* 18: 167–171, 2011

9. Lavergne V, Nolin TD, Hoffman RS, Roberts D, Gosselin S, Goldfarb DS, et al: The EXTRIP (EXtracorporeal TReatments In Poisoning) workgroup: Guideline methodology. *Clin Toxicol (Phila)* 50: 403–413, 2012

10. Lavergne V, Ouellet G, Bouchard J, Galvao T, Kielstein JT, Roberts DM, et al: Guidelines for reporting case studies on extracorporeal treatments in poisonings: Methodology. *Semin Dial* 27: 407–414, 2014

11. Lee MR: Plants against malaria. Part 1. Cinchona or the Peruvian bark. *J R Coll Physicians Edinb* 32: 189–196, 2002

12. Achan J, Talisuna AO, Erhart A, Yeka A, Tibenderana JK, Baliraine FN, et al: Quinine, an old anti-malarial drug in a modern world: Role in the treatment of malaria. *Malar J* 10: 144, 2011

13. Cabral RTS, Klumb EM, Carneiro S: Patients opinion and adherence to antimalarials in lupus erythematosus and rheumatoid arthritis treatment. *J Dermatolog Treat* 31: 264–269, 2020

14. Diener HC, Baurecht W: [Tolerability, compliance, quality of life, and clinical outcome during treatment with quinine sulfate in patients with nocturnal calf cramps. A multicenter non-interventional study (NIS) in adults]. *MMW Fortschr Med* 161: 24–31, 2019

15. Kupferschmidt K, Cohen J: Race to find COVID-19 treatments accelerates. *Science* 367: 1412–1413, 2020

16. Food and Drug Administration (FDA): Request for emergency use: Authorization for use of chloroquine phosphate or hydroxychloroquine sulfate supplied from the strategic national stockpile for treatment of 2019 coronavirus disease, 2020. Available at: https://www.fda.gov/media/136534/download. Accessed April 20, 2020

17. Krishna S, White NJ: Pharmacokinetics of quinine, chloroquine and amodiaquine. Clinical implications. *Clin Pharmacokinet* 30: 263–299, 1996

18. Ofori-Adjei D, Ericsson O, Lindström B, Sjöqvist F: Protein binding of chloroquine enantiomers and desethylchloroquine. *Br J Clin Pharmacol* 22: 356–358, 1986

19. Plantone D, Koudriavtseva T: Current and future use of chloroquine and hydroxychloroquine in infectious, immune, neoplastic, and neurological diseases: A mini-review. *Clin Drug Investig* 38: 653–671, 2018

20. Lim HS, Im JS, Cho JY, Bae KS, Klein TA, Yeom JS, et al: Pharmacokinetics of hydroxychloroquine and its clinical implications in chemoprophylaxis against malaria caused by *Plasmodium vivax*. *Antimicrob Agents Chemother* 53: 1468–1475, 2009

21. Tett SE, Cutler DJ, Day RO, Brown KF: Bioavailability of hydroxychloroquine tablets in healthy volunteers. *Br J Clin Pharmacol* 27: 771–779, 1989

22. Furst DE: Pharmacokinetics of hydroxychloroquine and chloroquine during treatment of rheumatic diseases. *Lupus* 5: S11–S15, 1996

23. Silamut K, Molunto P, Ho M, Davis TM, White NJ: Alpha 1-acid glycoprotein (orosomucoid) and plasma protein binding of quinine in falciparum malaria. *Br J Clin Pharmacol* 32: 311–315, 1991

24. Roy L, Bannon P, Villeneuve J-P, Leblanc M: Quinine pharmacokinetics in chronic haemodialysis patients. *Br J Clin Pharmacol* 54: 604–609, 2002

25. Mirghani RA, Hellgren U, Bertilsson L, Gustafsson LL, Ericsson O: Metabolism and elimination of quinine in healthy volunteers. *Eur J Clin Pharmacol* 59: 423–427, 2003

26. Rimchala P, Karbwang J, Sukontason K, Banmairuroi V, Molunto P, Na-Bangchang K: Pharmacokinetics of quinine in patients with chronic renal failure. *Eur J Clin Pharmacol* 49: 497–501, 1996

27. Newton P, Keeratithakul D, Teja-Isavadharm P, Pukrittayakamee S, Kyle D, White N: Pharmacokinetics of quinine and 3-hydroxyquinine in severe falciparum malaria with acute renal failure. *Trans R Soc Trop Med Hyg* 93: 69–72, 1999

28. Dyson EH, Proudfoot AT, Prescott LF, Heyworth R: Death and blindness due to overdose of quinine. *Br Med J (Clin Res Ed)* 291: 31–33, 1985

29. Boland ME, Roper SM, Henry JA: Complications of quinine poisoning. *Lancet* 1: 384–385, 1985

30. Bateman DN, Blain PG, Woodhouse KW, Rawlins MD, Dyson H, Heyworth R, et al: Pharmacokinetics and clinical toxicity of quinine overdosage: Lack of efficacy of techniques intended to enhance elimination. *Q J Med* 54: 125–131, 1985

31. Mackie MA, Davidson J, Clarke J: Quinine—acute self-poisoning and ocular toxicity. *Scott Med J* 42: 8–9, 1997

32. Clemessy JL, Taboulet P, Hoffman JR, Hantson P, Barriot P, Bismuth C, et al: Treatment of acute chloroquine poisoning: A 5-year experience. *Crit Care Med* 24: 1189–1195, 1996

33. Jaeger A, Sauder P, Kopferschmitt J, Flesch F: Clinical features and management of poisoning due to antimalarial drugs. *Med Toxicol* 2: 242–273, 1987

34. Britton WJ, Kevau IH: Intentional chloroquine overdosage. *Med J Aust* 2: 407–410, 1978

35. Jaeger A, Sauder P, Kopferschmitt J, Flesch F: [Hypokalemia in chloroquine poisoning]. *Presse Med* 16: 1658–1659, 1987

36. Fung HT, Lam KK, Wong OF, Lau B, Kam CW: A case of fatal hydroxychloroquine overdose. *Hong Kong J Emerg Med* 14: 53–57, 2007

37. Ling Ngan Wong A, Tsz Fung Cheung I, Graham CA: Hydroxychloroquine overdose: Case report and recommendations for management. *Eur J Emerg Med* 15: 16–18, 2008

38. Angel G, Guerre Berthelot P, Rogier C: Hypokalaemia related to acute chloroquine poisoning. *Lancet* 346: 1625, 1995

39. Vitris M, Aubert M: [Chloroquine poisoning: Our experience apropos of 80 cases]. *Dakar Méd* 28: 593–602, 1983

40. Clemessy JL, Angel G, Borron SW, Ndiaye M, Le Brun F, Julien H, et al: Therapeutic trial of diazepam versus placebo in acute chloroquine intoxications of moderate gravity. *Intensive Care Med* 22: 1400–1405, 1996

41. Di Maio VJ, Henry LD: Chloroquine poisoning. *South Med J* 67: 1031–1035, 1974

42. Riou B, Barriot P, Rimailho A, Baud FJ: Treatment of severe chloroquine poisoning. *N Engl J Med* 318: 1–6, 1988

43. Vitris M, Larregle B, Aubert M: [Importance of chloroquine levels in chloroquine poisoning]. *Dakar Méd* 28: 103–112, 1983

44. Demaziere J, Saissy JM, Vitris M, Seck M, Ndiaye M, Gaye M, et al: [Effects of diazepam on mortality from acute chloroquine poisoning]. *Ann Fr Anesth Reanim* 11: 164–167, 1992

45. Constantin B, Charmot G: [Voluntary poisoning by chloroquine. Apropos of 20 cases]. *Therapie* 21: 387–395, 1966

46. Langford NJ, Good AM, Laing WJ, Bateman DN: Quinine intoxications reported to the Scottish Poisons Information Bureau 1997-2002: A continuing problem. *Br J Clin Pharmacol* 56: 576–578, 2003

47. Czajka PA, Flynn PJ: Nonfatal chloroquine poisoning. *Clin Toxicol* 13: 361–369, 1978

48. Isbister GK, Dawson A, Whyte IM: Hydroxychloroquine overdose: A prospective case series. *Am J Emerg Med* 20: 377–378, 2002

49. Gunja N, Roberts D, McCoubrie D, Lamberth P, Jan A, Simes DC, et al: Survival after massive hydroxychloroquine overdose. *Anaesth Intensive Care* 37: 130–133, 2009

50. de Olano J, Howland MA, Su MK, Hoffman RS, Biary R: Toxicokinetics of hydroxychloroquine following a massive overdose. *Am J Emerg Med* 37: 2264.e5-2264.e8, 2019

51. Glick L, Mumford J: Quinine amblyopia; treatment by stellate ganglion block. *BMJ* 2: 94–96, 1955

52. Durcan L, Clarke WA, Magder LS, Petri M: Hydroxychloroquine blood levels in systemic lupus erythematosus: Clarifying dosing controversies and improving adherence. *J Rheumatol* 42: 2092–2097, 2015

53. Miller D, Fiechtner J: Hydroxychloroquine overdosage. *J Rheumatol* 16: 142–143, 1989

54. Nwobodo EO, Obi J: Chloroquine overdose and leucopenia in Nigerians. *Isr J Med Sci* 29: 817–818, 1993

55. Elmalem J, Garnier R, Thomas G, Efthymiou ML: Increased incidence of suicide with chloroquine. *Concours Med* 108: 2450, 1986

56. Ball DE, Tagwireyi D, Nhachi CF: Chloroquine poisoning in Zimbabwe: A toxicoepidemiological study. *J Appl Toxicol* 22: 311–315, 2002

57. Merino Argumánez C, Sáez de La Fuente I, Molina Collado Z, Suárez Pita D, Mestre Gómez B, Sanchez Izquierdo JA: Hydroxychloroquine, a potentially lethal drug. *Med Intensiva* 41: 257–259, 2017

58. Gummin DD, Mowry JB, Spyker DA, Brooks DE, Beuhler MC, Rivers LJ, et al: 2018 annual report of the American association of poison control Centers' national poison data system (NPDS): 36th annual report [published correction appears in *Clin Toxicol (Phila)* 57: e1, 2019]. *Clin Toxicol (Phila)* 57: 1220–1413, 2019

59. Bondurand A, N'Dri D, Coffi S, Saracino E: Chloroquine intoxication at the University Hospital of Abidjan. *Afr J Med Sci* 179: 239–242, 1983

60. Soichot M, Megarbane B, Chevillard L, Khoudour N, Laprevote O, Bourgogne E: Blood concentrations of hydroxychloroquine and its metabolites in hydroxychloroquine-poisoned patients: Usefulness on admission to the intensive care unit and pharmacokinetics. *Clin Toxicol* 52: 701, 2014

61. Kim T, Cheema N, DesLauriers C, Bryant S: Hydroxychloroquine poisoning and the potential for cardiotoxicity. *J Med Toxicol* 14: 32–33, 2018

62. Cheema N, Bryant SM: Hydroxychloroquine and cardiotoxicity: A retrospective review of regional poison center data. *Clin Toxicol* 51: 712, 2013

63. Curry SC, Connor DA, Clark RF, Holland D, Carrol L, Raschke R: The effect of hypertonic sodium bicarbonate on QRS duration in rats poisoned with chloroquine. *J Toxicol Clin Toxicol* 34: 73–76, 1996

64. Marquardt K, Albertson TE: Treatment of hydroxychloroquine overdose. *Am J Emerg Med* 19: 420–424, 2001

65. Mégarbane B, Mohebbil-Amoli S, Theodore J, Deye N, Brun P, Malissin I, et al: Prognosis factors of poisonings treated with extracorporeal life support in the ICU. *Crit Care* 12[Suppl 2]: 359, 2008

66. Ghannoum M, Hoffman RS, Gosselin S, Nolin TD, Lavergne V, Roberts DM: Use of extracorporeal treatments in the management of poisonings. *Kidney Int* 94: 682–688, 2018

67. Akintonwa A, Odutola TA, Edeki T, Mabadeje AF: Hemodialysis clearance of chloroquine in uremic patients. *Ther Drug Monit* 8: 285–287, 1986

68. Maier RD, Benkert B: [Toxicological aspects of fatal chloroquine poisoning over a period of several days]. *Z Rechtsmed* 92: 27–33, 1984

69. Boereboom FT, Ververs FF, Meulenbelt J, van Dijk A: Hemoperfusion is ineffectual in severe chloroquine poisoning. *Crit Care Med* 28: 3346–3350, 2000

70. Heath A, Ahlmén J, Mellstrand T, Wickström I: Resin hemoperfusion in chloroquine poisoning. *J Toxicol Clin Toxicol* 19: 1067–1071, 1982

71. Garnier R, Elmalem J: Haemoperfusion in chloroquine poisoning. *Br Med J (Clin Res Ed)* 291: 141, 1985

72. Reichel C, Paar WD: Inefficacy of hemoperfusion in the treatment of chloroquine poisoning. *Intensivmed* 28: 492–494, 1991

73. Floyd M, Hill AV, Ormston BJ, Menzies R, Porter R: Quinine amblyopia treated by hemodialysis. *Clin Nephrol* 2: 44–46, 1974

74. Sabto JK, Pierce RM, West RH, Gurr FW: Hemodialysis, peritoneal dialysis, plasmapheresis and forced diuresis for the treatment of quinine overdose. *Clin Nephrol* 16: 264–268, 1981

75. Liotier J, Richard D, Deteix P, Coudoré F, Souweine B: Quinine clearance during continuous veno-venous high-volume hemofiltration. *Intensive Care Med* 34: 1925–1926, 2008

76. Jacobs F, Nicolaos G, Prieur S, Brivet F: Quinine dosage may not need to be reduced during continuous venovenous hemodiafiltration in severe anuric malaria. *Clin Infect Dis* 39: 288–289, 2004

77. Davies JG, Greenwood EF, Kingswood JC, Sharpstone P, Street MK: Quinine clearance in continuous venovenous hemofiltration. *Ann Pharmacother* 30: 487–490, 1996

78. Held H: Effectiveness of peritoneal dialysis in the therapy of quinine poisoning. *Deut med Wochenschr* 97: 1793–1795, 1972

79. Dupont B, Clausen E, Rasmussen S, Rehfeldt J: [Quinine poisoning. A case treated with intravenous sodium nitrite, forced diuresis, and peritoneal dialysis]. *Ugeskr Laeger* 132: 50–53, 1970

80. McCann WP, Permisohn R, Palmisano PA: Fatal chloroquine poisoning in a child: Experience with peritoneal dialysis. *Pediatrics* 55: 536–538, 1975

81. Lareng L, Fabre M, Jean D, Bourzai V: Nivaquine intoxication. *Cah Anesthesiol* 28: 223–231, 1980

82. Jallouli M, Galicier L, Zahr N, Aumaître O, Francès C, Le Guern V, et al; Plaquenil Lupus Systemic Study Group: Determinants of hydroxychloroquine blood concentration variations in systemic lupus erythematosus. *Arthritis Rheumatol* 67: 2176–2184, 2015

83. Van Stone JC: Hemodialysis and chloroquine poisoning. *J Lab Clin Med* 88: 87–90, 1976

84. Trafford JA, Jones RH, Evans R, Sharp P, Sharpstone P, Cook J: Haemoperfusion with R-004 Amberlite resin for treating acute poisoning. *BMJ* 2: 1453–1456, 1977

85. McBeth PB, Missirlis PI, Brar H, Dhingra V: Novel therapies for myocardial irritability following extreme hydroxychloroquine toxicity. *Case Rep Emerg Med* 2015: 692948, 2015

86. Gibbs JL, Trafford A, Sharpstone P: Quinine amblyopia treated by combined haemodialysis and activated resin haemoperfusion. *Lancet* 1: 752–753, 1985

87. Goldenberg AM, Wexler LF: Quinine overdose: Review of toxicity and treatment. *Clin Cardiol* 11: 716–718, 1988

88. Hillman E, Harpur ER: Hazards to health. Quinine poisoning. *N Engl J Med* 264: 138–139, 1961

89. Shimanko II, Yaroslavsky AA: Early hemodialysis in severe poisoning with ethylene glycol, quinine and pachycarpine[Russian]. *Sov Med* 37: 92–96, 1974

90. Bodenhamer JE, Smilkstein MJ: Delayed cardiotoxicity following quinine overdose: A case report. *J Emerg Med* 11: 279–285, 1993

91. Morgan MD, Rainford DJ, Pusey CD, Robins-Cherry AM, Henry JG: The treatment of quinine poisoning with charcoal haemoperfusion. *Postgrad Med J* 59: 365–367, 1983

92. Bouchard J, Lavergne V, Roberts DM, Cormier M, Morissette G, Ghannoum M: Availability and cost of extracorporeal treatments for poisonings and other emergency indications: A worldwide survey. *Nephrol Dial Transplant* 32: 699–706, 2017

93. Paintaud G, Alván G, Ericsson O: The reproducibility of quinine bioavailability. *Br J Clin Pharmacol* 35: 305–307, 1993

94. Tett SE: Clinical pharmacokinetics of slow-acting antirheumatic drugs. *Clin Pharmacokinet* 25: 392–407, 1993

95. Gustafsson LL, Walker O, Alván G, Beermann B, Estevez F, Gleisner L, et al: Disposition of chloroquine in man after single intravenous and oral doses. *Br J Clin Pharmacol* 15: 471–479, 1983

96. Laurin LP, Lévesque R, Roy L: Hemodiafiltration does not improve drug protein binding compared to conventional hemodialysis: An *in vitro* study. *Blood Purif* 33: 307–308, 2012

97. Walker O, Birkett DJ, Alván G, Gustafsson LL, Sjöqvist F: Characterization of chloroquine plasma protein binding in man. *Br J Clin Pharmacol* 15: 375–377, 1983

98. Donadio JV Jr., Whelton A, Kazyak L: Quinine therapy and peritoneal dialysis in acute renal failure complicating malarial haemoglobinuria. *Lancet* 1: 375–379, 1968

99. Franke U, Proksch B, Müller M, Risler T, Ehninger G: Drug monitoring of quinine by HPLC in cerebral malaria with acute renal failure treated by haemofiltration. *Eur J Clin Pharmacol* 33: 293–296, 1987

100. Hall A, Yardumian A, Marsh A: Exchange transfusion and quinine concentrations in falciparum malaria. *Br Med J (Clin Res Ed)* 291: 1169–1170, 1985

101. Sharma AM, Keller F, Boeckh M, Heitz J, Borner K: Quinine dosage in severe malaria with renal failure necessitating haemodialysis. *Eur J Clin Pharmacol* 36: 535–536, 1989

102. Sukontason K, Karbwang J, Rimchala W, Tin T, Na-Bangchang K, Banmairuroi V, et al: Plasma quinine concentrations in falciparum malaria with acute renal failure. *Trop Med Int Health* 1: 236–242, 1996

103. Markham TN, Dodson VN, Eckberg DL: Peritoneal dialysis in quinine sulfate intoxication. *JAMA* 202: 1102–1103, 1967

104. Brass P, Hellmich M, Kolodziej L, Schick G, Smith AF: Ultrasound guidance versus anatomical landmarks for subclavian or femoral vein catheterization. *Cochrane Database Syst Rev* 1: CD011447, 2015

105. Brass P, Hellmich M, Kolodziej L, Schick G, Smith AF: Ultrasound guidance versus anatomical landmarks for internal jugular vein catheterization. *Cochrane Database Syst Rev* 1: CD006962, 2015

106. Parienti JJ, Mongardon N, Mégarbane B, Mira JP, Kalfon P, Gros A, et al; 3SITES Study Group: Intravascular complications of central venous catheterization by insertion site. *N Engl J Med* 373: 1220–1229, 2015

107. Shin HJ, Na HS, Koh WU, Ro YJ, Lee JM, Choi YJ, et al: Complications in internal jugular vs subclavian ultrasound-guided central venous catheterization: A comparative randomized trial. *Intensive Care Med* 45: 968–976, 2019

108. Björkander M, Bentzer P, Schött U, Broman ME, Kander T: Mechanical complications of central venous catheter insertions: A retrospective multicenter study of incidence and risks. *Acta Anaesthesiol Scand* 63: 61–68, 2019

109. Wong B, Zimmerman D, Reintjes F, Courtney M, Klarenbach S, Dowling G, et al: Procedure-related serious adverse events among home hemodialysis patients: A quality assurance perspective. *Am J Kidney Dis* 63: 251–258, 2014

110. Tennankore KK, d'Gama C, Faratro R, Fung S, Wong E, Chan CT: Adverse technical events in home hemodialysis. *Am J Kidney Dis* 65: 116–121, 2015

111. Mokrzycki MH, Kaplan AA: Therapeutic plasma exchange: Complications and management. *Am J Kidney Dis* 23: 817–827, 1994

112. Sutton DM, Nair RC, Rock G: Complications of plasma exchange. *Transfusion* 29: 124–127, 1989

113. Yang X, Xin S, Zhang Y, Li T: Early hemoperfusion for emergency treatment of carbamazepine poisoning. *Am J Emerg Med* 36: 926–930, 2018

114. Shannon MW: Comparative efficacy of hemodialysis and hemoperfusion in severe theophylline intoxication. *Acad Emerg Med* 4: 674–678, 1997

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