

Extracorporeal Treatment for Methotrexate Poisoning

Systematic Review and Recommendations from the EXTRIP Workgroup

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Abstract

Methotrexate is used in the treatment of many malignancies, rheumatological diseases, and inflammatory bowel disease. Toxicity from use is associated with severe morbidity and mortality. Rescue treatments include intravenous hydration, folinic acid, and, in some centers, glucarpidase. We conducted systematic reviews of the literature following published Extracorporeal Treatments In Poisoning (EXTRIP) methods to determine the utility of extracorporeal treatments in the management of methotrexate toxicity. The quality of the evidence and the strength of recommendations (either “strong” or “weak/conditional”) were graded according to the GRADE approach. A formal voting process using a modified Delphi method assessed the level of agreement between panelists on the final recommendations. A total of 92 articles met inclusion criteria. Toxicokinetic data were available on 90 patients (89 with impaired kidney function). Methotrexate was considered to be moderately dialyzable by intermittent hemodialysis. Data were available for clinical analysis on 109 patients (high-dose methotrexate [>0.5 g/m²]: 91 patients; low-dose [≤ 0.5 g/m²]: 18). Overall mortality in these publications was 19.5% and 26.7% in those with high-dose and low-dose methotrexate-related toxicity, respectively. Although one observational study reported lower mortality in patients treated with glucarpidase compared with those treated with hemodialysis, there were important limitations in the study. For patients with severe methotrexate toxicity receiving standard care, the EXTRIP workgroup: (1) suggested against extracorporeal treatments when glucarpidase is not administered; (2) recommended against extracorporeal treatments when glucarpidase is administered; and (3) recommended against extracorporeal treatments instead of administering glucarpidase. The quality of evidence for these recommendations was very low. Rationales for these recommendations included: (1) extracorporeal treatments mainly remove drugs in the intravascular compartment, whereas methotrexate rapidly distributes into cells; (2) extracorporeal treatments remove folinic acid; (3) in rare cases where fast removal of methotrexate is required, glucarpidase will outperform any extracorporeal treatment; and (4) extracorporeal treatments do not appear to reduce the incidence and magnitude of methotrexate toxicity.

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Introduction

Toxicity from methotrexate is commonly described and affects many organs. Treatment is supportive, including folinic acid (leucovorin) and glucarpidase in specific circumstances. The use of extracorporeal treatments is controversial.

The Extracorporeal Treatments In Poisoning (EXTRIP) workgroup is composed of international experts representing diverse specialties (Supplemental Table 1, <http://www.extrip-workgroup.org>), and the workgroup methodology is summarized in the Supplemental Material and Supplemental Tables 2–6 (1–6). We present EXTRIP's systematic review and recommendations for the use of extracorporeal treatments in patients with methotrexate toxicity.

Pharmacology

Methotrexate inhibits the intracellular folate cycle by competitively inhibiting dihydrofolate reductase, thereby reducing substrates for cell division. Methotrexate is used for various indications including

malignancies, rheumatoid arthritis, and inflammatory bowel disease.

Methotrexate is a small molecule with moderate protein binding (30%–60%), which is not appreciably saturable (Table 1) (7–12). Oral bioavailability is limited by saturable active drug transporters (13,14) which limit absorption at high doses and can be protective in acute overdose (15). Methotrexate distributes slowly but extensively into erythrocytes (16–18). About 10%–20% of methotrexate is excreted in bile (19,20) or metabolized in the liver (influenced by genetic polymorphisms) (21,22). The remainder is eliminated by the kidneys (13,23), correlating with GFR (11,24,25), and additionally, methotrexate is both filtered and actively secreted in the tubules (25,26); although at high concentrations, tubular secretion becomes saturated. For this reason, the reported kidney clearance of methotrexate varies from 40 to 200 ml/min depending on serum concentration (27). In summary, the pharmacokinetics of methotrexate are complex and depend on several variables,

Table 1. Pharmacokinetics of methotrexate

Pharmacokinetic Parameter	Value	Reference
Molecular mass (Da)	454	
Oral bioavailability	100% <20 mg/m ² <20% at >200 mg/m ²	(13,15,34,129,263–266)
Time to maximum concentration (h)	1–2	(12,13,34,265,267)
Protein binding	30%–60%	(7–10,13,34,181,195,227,242,268–273)
Volume of distribution (L/kg)^a		
No AKI/CKD	0.3–1.2	(18,23,30–32,34,36,190,195,205,216,268,274–276)
AKI/CKD	0.5–1.2	
Terminal elimination $t_{1/2}$ (h)		
No AKI/CKD	5–15	(13,23,31–37,170,180,183,188,194,195,197,200,203,205–207,209,210,212–216,221–224,227,230,232,235,237,245,250,268,277–281)
AKI/CKD	25–35	
Total body clearance (ml/min)^a		
No AKI/CKD	80–220	(12,18,28,31–36,53,56,190,195,216,222,265,268,275,276,281–291)
AKI/CKD	20–40	
Kidney clearance (ml/min)		
No AKI/CKD	50–200	(8,12,23,27,182,204,292–294)

^aTotal body clearance and volume of distribution were obtained from intravenous data. If these data were unavailable but reported for oral data, then values were adjusted for bioavailability.

resulting in wide inter- and intra-patient differences (28,29) regarding volume of distribution (30–32), clearance (31,33,34), and half-life ($t_{1/2}$) (34–37).

Overview of Methotrexate Toxicity

Intravenous high-dose methotrexate and oral low-dose methotrexate can result in toxicity even at therapeutic doses. We describe these situations in detail in order to delineate potential indications for extracorporeal treatments. A third situation occurs from intrathecal methotrexate (38–46), but this is outside EXTRIP's scope.

Toxicity from Therapeutic High-Dose Methotrexate. In early studies of high-dose methotrexate (defined as doses >0.5 g/m²), toxicity occurred regularly with death in up to 6% of patients (24,47–52). Therapeutic drug monitoring of methotrexate predicts toxicity (46,53–55), and the risk of AKI and mucositis increases exponentially as the methotrexate concentration rises (56,57). With better monitoring and protocolized therapy (urine alkalinization, leucovorin), the incidence of toxicity has decreased considerably (58). Delayed methotrexate clearance refers to methotrexate concentrations predictive of complications (Supplemental Table 7) (46,59,60) including AKI (21,37,57,58,61–65), mucositis (56,66–68), myelosuppression (63,66,69,70), hepatotoxicity (63), infections (61), and mortality (71–73).

AKI reduces methotrexate clearance, prolonging the exposure to high methotrexate concentrations. AKI also prevents administration of further methotrexate doses, compromising treatment of the underlying malignancy. The mechanism of AKI is tubular precipitation of methotrexate and metabolites (especially at acidic pH) and direct tubular toxicity. AKI can be compounded by infection and coadministration of NSAIDs and proton-pump inhibitors (74). In contemporary cohorts, AKI occurs in 0.5%–1.0% of courses of 5 g/m² in children with acute lymphocytic leukemia and approximately 2% of courses of 12 g/m² in patients with osteosarcoma (58,59,75). The incidence of AKI is higher in adults, occurring in up to 40% of cohorts (21,33,63,64,67,76–85). AKI is usually nonoliguric, and serum creatinine concentration

peaks 2–7 days after infusion (59,71,85–88). About 1%–10% of patients with AKI require temporary kidney replacement therapy (59,64,70,71,75,86,88–92). AKI usually resolves in survivors (70,88,93,94), but up to 10% of patients have a reduced GFR at 3 months (71,78,79). In 28 children who developed AKI, there was an average GFR reduction of 20 ml/min per 1.73 m² on long-term follow-up (95), although this was not confirmed in another study of 253 children with a maximal follow-up of 35 years (96). Long-term dialysis after methotrexate-induced AKI is extremely uncommon (59,97).

Other toxicities after high-dose methotrexate include high-grade myelosuppression in 5%–10% of patients (33,49,51,69,80,84,98,99) with a nadir at 2 weeks (52), hepatotoxicity in 8%–30% of patients (33,77,80,84,90,100–102), and mucositis in 10%–30% of patients (33,37,49,51,53,56,59,68,77,82,84,86,99,101–105). In modern cohorts, inpatient mortality related to high-dose methotrexate is uncommon, but increases to approximately 4%–12% in those that develop AKI (58,71,73,85).

Aside from AKI, risk factors for the development of toxicity include dose (62,81,82), duration of intravenous infusion (especially infusions >36 hours) (106), shorter interval between doses (107), higher number of cycles of methotrexate treatment (56), and type of underlying malignancy being treated; the latter potentially relates to patient selection and different treatment protocols (21,49,64,78,108). Variables that are associated with a poorer prognosis include urine pH <7.5 (109), anemia (109), and low serum albumin concentration (81,110).

Toxicity from Therapeutic Low-Dose Methotrexate. Toxicity from oral, subcutaneous, or intravenous low-dose methotrexate can occur after therapeutic error in the setting of kidney impairment and unintentional mis-dosing; for example, a weekly dose of methotrexate erroneously taken daily. About 25% of patients on long-term low-dose oral methotrexate develop some degree of toxicity that limits treatment (111–113), including myelosuppression (1%–10%) (112–120), elevated liver enzymes (10%–25%) (112,113,117,120–123), and mucositis (5%–20%) (112,113,118).

Preexisting CKD (113,115,124,125), kidney failure (even after a single dose of 2.5 mg) (32,126–135), or AKI during maintenance methotrexate therapy (113,136–138) are major risk factors for developing toxicity. Other risk factors include length of exposure, weekly dosing, cumulative dose (111,115,137,139,140), and lack of folate supplementation (141). Factors associated with a poorer prognosis include lower white blood cell counts (118,125) and low serum albumin concentration (138).

Mortality in patients developing toxicity from oral methotrexate is 5%–30% (115–117,119,125–128,137,138,142–145). In contrast to high-dose methotrexate, therapeutic drug monitoring has little value in low-dose methotrexate toxicity (129), as no correlation exists between toxicity and methotrexate concentrations, and morbidity is reported at undetectable concentrations (68,130,137,138).

Single Oral Overdose. Acute single oral ingestions, either unintentional or with intended self-harm, usually carry little risk because of saturable absorption kinetics limiting bioavailability (129,131–135,139,146–150), except when impaired kidney function is present.

Treatment

Standard care of methotrexate toxicity includes methotrexate cessation and intravenous hydration (Supplemental Table 1). Methotrexate is a weak acid (pKa of approximately 5.0) so urine alkalinization will increase its solubility in the kidney tubules and enhance its elimination (8), thereby reducing the incidence of AKI and myelosuppression (151,152). Leucovorin mitigates the risk of toxicity of high-dose methotrexate by bypassing dihydrofolate reductase to restart the intracellular folate cycle. Leucovorin rescue is usually given per protocol in at least two doses starting at 36–42 hours after the initiation of high-dose methotrexate and continued until the methotrexate concentration is <0.1 – 0.2 $\mu\text{mol/L}$ (153). Leucovorin's effect is limited at high methotrexate concentrations (154). In patients with toxicity from low-dose methotrexate, leucovorin is also used (155). If intravenous leucovorin is unavailable, the oral form is an acceptable alternative (81). Folic acid is ineffective as an antidote.

Glucarpidase (carboxypeptidase-G2) is a recently approved methotrexate antidote. It is a recombinant enzyme that hydrolyzes methotrexate to inactive metabolites 4-deoxy-4-amino-methylpteroic acid (DAMPA) and glutamate. Glucarpidase lowers the serum methotrexate concentration by 90%–95% within minutes of administration (58,59,75, 87,90,91,156,157). The catalytic effect of glucarpidase persists for 48–72 hours (46,86). Some workgroups have proposed that glucarpidase be used when the methotrexate concentration is above specific thresholds in the setting of AKI (Supplemental Table 7) (46) with the rationale that prolonged leucovorin rescue could decrease the cure rate of malignancy (leucovorin overrescue) (158,159). Glucarpidase is not indicated for low-dose methotrexate toxicity.

Three studies comparing the clinical benefit of glucarpidase with standard care have not clearly demonstrated a benefit with regard to mortality, length of stay, extrarenal complications, or incidence and severity of AKI (71,85,160). In observational cohorts, mortality rates in methotrexate-toxic patients who received glucarpidase were between 0%

and 6% but as high as 23% (71,75,85,86,90,91,161,162) and may have been attributable to inadequate leucovorin rescue (70,97,163). Median time to kidney function recovery in cohorts receiving glucarpidase is between 10 and 23 days (59,71,75,86,87,91,157,164,165), but this took months in a subset of patients (71,79,166); although groups are not directly comparable, time to kidney recovery is similar in historical cohorts (70,97,163).

There are additional concerns regarding glucarpidase: (1) it cleaves intravascular methotrexate but has no effect on intracellular methotrexate (the compartment relevant to toxicity); (2) it hydrolyzes leucovorin, thereby antagonizing its protective effects (167); (3) after glucarpidase, methotrexate concentrations cannot be monitored by immunoassays because of crossreactivity with DAMPA (46,168); (4) rebound in plasma methotrexate concentration from cells occurs in approximately 60% of patients (58,86); (5) its availability is limited (169,170); and (6) its current cost exceeds US\$20,000 (71,85,171–173). In summary, although the kinetic effect of glucarpidase at lowering plasma methotrexate concentrations is indisputable, data confirming clinical benefits are lacking.

Methods

The workgroup performed systematic reviews of the literature and developed clinical recommendations following published EXTRIP methodology (2) with modifications, updates, and clarifications. The quality of the evidence and the strength of recommendations (either “strong” or “weak/conditional”) were graded according to the GRADE approach (Supplemental Figure 1). A formal voting process using a modified Delphi method assessed the level of agreement between panelists on the final recommendations (Supplemental Figure 2). The full methods are presented in the online supplement (Supplemental Tables 3–6).

Results

Results of the literature search (first performed on March 1, 2019 and last updated November 18, 2020) are presented in Supplemental Figure 3.

A total of 1376 articles were identified after removal of duplicates. In the final analysis, 92 articles were included, including two *in vitro* experiments (174,175), four animal experiments (176–179), 84 case reports and case series (24,35,88,90,126,163,170,171,180–255), one pharmacokinetic modeling study (256), and one observational study (160). Although several articles were designed as pharmacokinetic studies in kidney failure patients (170,190,204,225,242), many participants in these studies developed methotrexate-associated toxicity and were included in case reports.

Systematic Review

A) Dialyzability. Methotrexate has a low molecular weight and moderate protein binding, so it passes easily through modern dialyzers and hemofilters, which is confirmed by *in vitro* and animal experiments (174). Activated charcoal adsorbs methotrexate better than resins (177,183), although both are limited by cartridge saturation (176). In one porcine study, resin hemoperfusion provided a 2–3-

fold greater initial clearance than hemodialysis, which was negated at 3 hours because of saturated adsorption (178).

Toxicokinetic data related to extracorporeal treatments were available on 90 patients. Because of the inherent complexity of methotrexate toxicokinetics detailed above, determination of the ability of extracorporeal treatments to remove methotrexate is challenging. In general, high-efficiency techniques such as intermittent hemodialysis, online hemodiafiltration, and hemoperfusion showed the highest extraction ratios and sieving coefficients, both up to 40%–80%, with clearance occasionally exceeding 100 ml/min (197,204,211,213,218,227). Intermittent hemodialysis was the most efficient extracorporeal treatment, with the shortest apparent $t_{1/2}$ and highest clearance (Table 2). Most of the publications were dated and did not use modern dialytic technologies that are expected to provide even better clearances. Hemoperfusion was efficient but had decreased efficacy after 2 hours (191). Other techniques, including continuous KRTs (CKRTs), therapeutic plasma exchange, and peritoneal dialysis, had inferior effects on methotrexate removal.

To compare the relative efficacy of extracorporeal treatments, many publications used the percentage decrease in methotrexate concentrations (44,189,201,212,232,237,240, 241). However, this metric has little value unless it is adjusted for kidney function and duration of the extracorporeal treatment because serum concentrations are expected to decrease spontaneously due to endogenous processes. More informative is the comparison of methotrexate $t_{1/2}$ or clearance on and off extracorporeal treatment (Table 2), or ideally, the quantified amount of methotrexate removed during extracorporeal treatment (Supplemental Table 8); this was estimated in 13 patients, although extracorporeal treatment was performed a median of 50 hours after methotrexate infusion. Again, hemodialysis with or without hemoperfusion provided the greatest percentage of methotrexate body content removed per period of time. In rare cases when the extracorporeal treatment was initiated rapidly after a single dose of methotrexate (before distribution into cells and tissues), the effect was considerable (179,194,204,210).

Kidney function affects the grading of dialyzability because the contribution of extracorporeal clearance to total clearance increases as kidney function declines. Given the limitations of dialyzability assessment because of the aforementioned uncertainties, the workgroup conservatively considered methotrexate moderately dialyzable by hemodialysis in patients with impaired kidney function (level of evidence=C, Table 3). Methotrexate was slightly dialyzable by CKRT (level of evidence=B). Only one of the included patients had normal kidney function (200); although no dialyzability assessment was possible, hemodialysis would theoretically be expected to increase total clearance by 20%–60%.

Other Findings Related to Methotrexate Dialyzability. Few articles compare the kinetics of extracorporeal treatments with that of glucarpidase. Assuming that glucarpidase reduces methotrexate concentrations by 95% in 15 minutes, this represents a $t_{1/2}$ of 3 minutes, or several orders of magnitude shorter than observed during a hemodialysis session. This was confirmed in all studies in which both glucarpidase and extracorporeal treatments were given (58,171,210,213, 217,224,227,238,245,247). Some reports noted that dialysis clearance is concentration dependent (190,195,238,244), although this is surprising in the absence of saturation of

protein binding or membrane adsorption; this may have been caused by detection sensitivity of the assay at low concentration, or redistribution of methotrexate from red blood cells in the outlet, inflating that methotrexate concentration. Addition of albumin to the dialysate increased CKRT clearance by 20% at most, with massive increase in cost (218,227). One study in the 1990s reported catheter recirculation up to 30% during hemodialysis (204), although this effect may not apply with catheters used today. Extracorporeal treatments appear to accelerate elimination of methotrexate metabolites 7-hydroxymethotrexate and 5-methyltetrahydrofolate in blood (191). In 62 patients in whom it could be evaluated, methotrexate concentration rose after extracorporeal treatments in 42 patients. The increase in methotrexate concentration (“rebound”) after extracorporeal treatment averaged 76% (median=33%). The magnitude of rebound was greater after more efficient techniques such as intermittent hemodialysis or hemoperfusion compared with CKRT or peritoneal dialysis. Of note, rebound is also reported post glucarpidase, and extracorporeal treatments have been used to minimize this effect in some cases.

Dialyzability of Leucovorin. Leucovorin is readily removed by hemodialysis and hemoperfusion, with an apparent plasma $t_{1/2}$ of less than 3 hours during these procedures (191,257).

Dialyzability of Glucarpidase. No data exist. However, glucarpidase has a molecular mass of 83 kDa and is only expected to be removed by therapeutic plasma exchange or exchange transfusion.

B) Clinical Summary of Methotrexate-Toxic Patients Receiving Extracorporeal Treatment.

High-Dose Methotrexate. One retrospective single-center study of patients with cancer with methotrexate toxicity (2010–2017) was identified (160). Patients receiving glucarpidase ($n=30$, four also received dialysis) were compared with those who did not ($n=701$, 58 received dialysis). Compared with the nonglucarpidase group, the glucarpidase group had statistically shorter hospital stay and lower 90-day mortality. By mathematically transforming the presented data, patients receiving hemodialysis ($n=58$) had a 50.6% inpatient mortality, compared with 18.1% in controls ($n=643$). Conclusions from these results are severely limited by selection bias, confounding-by-indication, residual confounding, and insufficient data to adjust for clinical and demographic differences between groups.

The remainder of the evidence is on the basis of case reports spanning 40 years, during which treatment has changed greatly, especially leucovorin rescue. In most cases, extracorporeal treatments were performed because of high methotrexate concentrations and/or AKI, although it is unclear if they were performed predominantly to support kidney function or to remove methotrexate. The clinical summary of included cases is presented in Table 4. All survivors were weaned off KRT, and in all but six patients (171,191,210,216,234,247), kidney function returned to baseline in a median time of 14.5 days. The overall mortality was 19.5%, half of which was directly attributed to methotrexate.

Historical cohorts treated solely with standard care are difficult to compare with the cohort receiving extracorporeal treatment because of their lower index of severity. Also, in

Table 3. Final dialyzability grading on the basis of the number of patients with impaired kidney function according to Extracorporeal Treatments in Poisoning criteria

Dialyzability Grading	HD (n)	HP (n)	HP-HD (n)	High-Cutoff HD (n)	Online HDF (n)	CKRT (n)	CKRT-PRP (n)	Therapeutic Plasma Exchange (n)	PRP (n)	Exchange Transfusion (n)	PD (n)	SPAD (n)
Dialyzable	9	4	2	1	1	3 ^a	1	2				1
Moderately dialyzable	5		1	1	1	1						
Slightly dialyzable	2					3		1	1			1
Not dialyzable	1					1		1		1	4	
Final grading and level of evidence	Moderately dialyzable, B	Dialyzable, C	Dialyzable, D	Moderately dialyzable, D	Moderately dialyzable, D	Slightly dialyzable, B	Moderately dialyzable, D	Slightly dialyzable, C	Slightly dialyzable, D	Not dialyzable, D	Not dialyzable, C	Slightly dialyzable, D

Grading of dialyzability is defined in Supplemental Table 4, and level of evidence for dialyzability is defined in Supplemental Table 5. HD, hemodialysis; n, number of patients; HP, hemoperfusion; HDF, hemodiafiltration; CKRT, continuous KRT; PRP, plasma resin perfusion; PD, peritoneal dialysis; SPAD, single-pass albumin dialysis.

^aOne additional patient had normal kidney function and methotrexate was assessed as dialyzable with CKRT (200).

all glucarpidase studies, concurrent dialysis was allowed. Mortality in historical controls with delayed methotrexate clearance and/or AKI is approximately 5% whether they received glucarpidase (59,71,75,85,86,90,91,161,162) or were solely treated with standard care (Table 5) (58,59,70,85,163).

Despite heterogeneity in groups at baseline, no benefit was observed from extracorporeal treatment when compared with standard care regarding other important outcomes. For example, dialysis dependence at 3 months was 0% in both the extracorporeal treatment cohort and controls receiving glucarpidase (71,75) or standard care alone (59,70,71,78,86,91,165). Six of 60 patients receiving extracorporeal treatment had abnormal kidney function after the episode of toxicity; although the follow-up for these cases was limited (<1 month), this rate was comparable to controls (59,70,71,75,78,79,86,87,95,96,157,163,165). Finally, the time required for recovery from AKI was comparable in all groups, although this analysis is limited by different definitions used for AKI and different criteria for kidney recovery. We identified 21 cases where extracorporeal treatment was added to glucarpidase; although these numbers are low and descriptions limited, no incremental clinical benefit can be deduced from extracorporeal treatment in that scenario. The times for recovery of pancytopenia and mucositis were also comparable in all groups.

Low-Dose Methotrexate. Compared with the cohort of high-dose methotrexate, most of these patients had preexisting kidney failure (Table 4). Plasma concentrations were also considerably lower than in the cohort receiving high-dose methotrexate. Overall mortality was 26.7%, half of which was from a direct consequence of methotrexate. Again, no benefit was observed from extracorporeal treatment compared with standard care alone in historical controls with regard to mortality, length of stay, time of recovery of pancytopenia, or time of recovery of mucositis, although the first group was assumed to be sicker (Table 5) (125,127,128,138). This analysis contains confounding as a large proportion of these patients were already receiving long-term hemodialysis for kidney failure. There were no cases of intentional overdose treated by extracorporeal treatment.

Complications Related to Extracorporeal Treatments. Many complications were reported, although it is unclear if some were related to the procedure, methotrexate, underlying disease, or comorbidities. Complications include hypotension during hemodialysis requiring switch to CKRT (252,254), myocardial infarction and ventricular tachycardia (243), hypokalemia and hypophosphatemia (213), cardiac arrest (186), abdominal pain and loss of consciousness that required termination of hemoperfusion (163), thrombocytopenia and/or leucopenia (mostly related to hemoperfusion) (163,190,191,195,199,208,212), and bleeding from catheter site (191). Because of baseline immunosuppression and cytopenia and because multiple extracorporeal sessions are often performed, the risk of catheter infection is higher (225). Costs are variable but are considerably greater with glucarpidase compared with hemodialysis, although the incidence of serious adverse events is lower.

Recommendations

Methotrexate toxicity is a medical emergency and carries serious risks of multisystem disease and mortality. General

Table 4. Clinical summary of methotrexate toxicity from individual cases

Variable	High-Dose Methotrexate (>0.5 g/m ²) n=91	Low-Dose Methotrexate (≤0.5 g/m ²) n=18
Patient characteristics		
Age, yr	19 [13, 52]	52 [46, 62]
Male sex, %	57	65
Preexisting kidney failure, %	6	67
Symptoms, signs, and laboratory		
Dose methotrexate, g/m ²	7.1 [3.1, 10.6]	0.01 [0.01, 0.07]
Highest [methotrexate], μmol/L	N/A	0.5 [0.1, 3.0]
24 h [methotrexate], μmol/L	306 [90.1, 582]	N/A
48 h [methotrexate], μmol/L	48 [11.9, 157]	N/A
72 h [methotrexate], μmol/L	14 [11.9, 157]	N/A
Altered consciousness, %	30	0
Mucositis, %	65	75
Leukopenia, %	71	81
Anemia, %	67	79
Thrombocytopenia, %	71	81
AKI caused by methotrexate, %	92	22
AKI by other cause, %	1	11
Elevated liver function tests, %	66	33
Non-ECTR treatments		
Mechanical ventilation, %	12	14
Urine alkalinization, %	100	75
Folic acid, %	0	19
Folinic acid, %	100	88
Glucarpidase, %	23	6
ECTR		
Hemodialysis, %	35	39
Hemoperfusion, %	9	6
Exchange transfusion, %	1	0
Continuous KRT, %	10	6
Therapeutic plasma exchange, %	2	0
Hemodialysis-hemoperfusion in series, %	1	6
Online hemodiafiltration, %	4	0
High-cutoff hemodialysis, %	1	0
Peritoneal dialysis, %	1	17
2 ECTRs, %	25	28
3 ECTRs, %	8	0
4 ECTRs, %	2	0
Time from methotrexate to first ECTR, h	48 [24, 77]	49 [30, 104]
Outcome		
Intensive care stay, d	10 [8.5, 12]	3
Hospital stay, d	17 [11, 24]	16.5 [14.5, 30]
Time to normalization of kidney function, d	14.5 [10, 21]	9.5 [7, 12]
Time necessitating KRT, d	1 [0, 5]	1 [0.5, 1.5]
Time to resolution of mucositis, d	4.5 [4, 5]	14.5 [11, 18]
Time to resolution of cytopenia, d	8 [0, 5]	10 [6, 14.5]
Survival, %	80.5	73.3
Death related to methotrexate, %	9.1	13.3
Death unrelated to methotrexate, %	10.4	13.3

Data are median with interquartile range when applicable. N/A, not applicable; ECTR, extracorporeal treatment.

recommendations for extracorporeal treatments in methotrexate toxicity are presented in Box 1. Although extracorporeal treatments accelerate elimination of plasma methotrexate substantially, the panel did not support their use for severe methotrexate toxicity as an addition to standard care, as an alternative to glucarpidase, or as an addition to glucarpidase in most clinical contexts. The reasons are the following: (1) extracorporeal treatments, like glucarpidase, mainly remove methotrexate from the intravascular compartment and have little effect on intracellular stores (where toxicity occurs) because methotrexate does not exit cells easily (258,259); (2) delayed methotrexate clearance is

defined by methotrexate testing performed ≥24 hours after infusion; therefore, considerable methotrexate distribution into tissues has already occurred before extracorporeal treatment can be initiated; (3) once methotrexate toxicity is present, removing methotrexate from the intravascular compartment does not result in shorter duration of toxicity (Table 5); (4) extracorporeal treatments remove leucovorin, which is crucial to restart the folate cycle; and (5) in the rare occurrence in which methotrexate needs to be removed from blood rapidly, glucarpidase will perform a few orders of magnitude quicker than any extracorporeal technique.

Table 5. Effect of ECTRs in patients severely poisoned with methotrexate receiving standard care

Table 5. Effect of ECTRs in patients severely poisoned with methotrexate receiving standard care													
Outcomes	Quality Assessment					Summary of Findings						Importance	
	Study Design and No. of Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	ECTR (Intervention Groups)		No ECTR (Control Groups)		Effect of ECTR		Quality
							ECTR	ECTR+Glucarpidase	Glucarpidase ^{a,b}	Standard Care Alone			
Inpatient mortality HDMTX	Observational studies (n=1) ^c	Serious ^d	Not serious	Not serious	Serious ^e	Not serious	50.6% (29 of 58)(160)	3.3% (1 of 30) (160)	Overall=5.0% with AKI (44 of 872), <1% in kids (59,71,75,85,86,90, 91,161,162)	18.1% (116 of 643) (160)	Groups not comparable at baseline	⊖○○○ VERY LOW	CRITICAL
	Observational studies (n=14) ^f	Very serious ^g	Not serious	Serious ^h	Serious ⁱ	Publication bias strongly suspected ^j	Overall=19.6% (11 of 56) Due to MTX=5.4% (3 of 56)	Overall=15% (3 of 20) Due to MTX=15% (3 of 20)		Overall=5.9% with AKI (13 of 204) <1% in kids (58,70,73,85,97,163)	Groups were judged comparable at baseline except for the ECTR+glucarpidase group. Mortality due to MTX in the ECTR without glucarpidase group was comparable to both control groups presenting with AKI	⊖○○○ VERY LOW	CRITICAL
	LDMTX	Observational studies (n=3) ^k	Very serious ^g	Not serious	Serious ^h	Serious ⁱ	Publication bias strongly suspected ^j	Overall=26.7% (4 of 15)Due to MTX=13.3% (2 of 15)	N/A ^a	N/A ^a	Overall=18.6% (11 of 59) (128,138)	Groups not comparable at baseline	⊖○○○ VERY LOW
Time to recovery of kidney function HDMTX	Observational studies (n=15) ^l	Very serious ^g	Not serious	Serious ^h	Serious ⁱ	Publication bias strongly suspected ^j	Median=14 d (n=32)	Median=17 d (n=14)	Median range=10–28 d (9 studies, n=602) Adults + kids (59,75,87,91,92,156, 157,164,165)	Median range=9–16 d (4 studies, n=127) ECTR+glucarpidase Adults + kids (70,88,97,163,296)	Groups were judged comparable at baseline except for the ECTR+glucarpidase group. No formal statistical comparison possible due to reporting of aggregate data, but reported median time to recovery of kidney function seems comparable between the ECTR group and both control groups	⊖○○○ VERY LOW	IMPORTANT
Length of stay HDMTX	Observational studies (n=1) ^c	Serious ^d	Not serious	Not serious	Serious ^e	Not serious	Mean=40.2 d (n=58) (160)	Mean=14.7 d (n=30) (160)		Mean=20.2 d (n=643) (160)	Groups not comparable at baseline	⊖○○○ VERY LOW	IMPORTANT
	Observational studies (n=3) ^m	Very serious ^g	Not serious	Serious ^h	Serious ⁱ	Publication bias strongly suspected ^j	Mean=19.4 d (n=20)	Mean=16.2 d (n=6)	Mean=11.6 d (n=33) (64,71)	Mean=22 d (n=21) (71)	Groups were judged comparable at baseline except for the ECTR+glucarpidase group. No formal statistical comparison possible due to reporting of aggregate data, but reported mean length of stay seems comparable between groups	⊖○○○ VERY LOW	IMPORTANT

Table 5. (Continued)

Box 1. General Recommendations of Extracorporeal Treatments in Methotrexate Poisoning In patients with severe methotrexate poisoning receiving standard care treatments including folinic acid rescue therapy:

- 1) We suggest AGAINST performing extracorporeal treatments when glucarpidase is not administered (weak recommendation; very low-quality evidence) (median: 2; upper quartile: 5.25; disagreement index: 0.61)
- 2) We recommend AGAINST performing extracorporeal treatments when glucarpidase is administered (strong recommendation; very low-quality evidence) (median: 1; upper quartile: 3; disagreement index: 0.13)
- 3) We recommend AGAINST performing extracorporeal treatments instead of administering glucarpidase (strong recommendation; very low-quality evidence) (median: 1; upper quartile: 3; disagreement index: 0.29)

Neither the presence of life-threatening toxicity (cytopenia, mucositis, AKI) nor high 24-hour or 48-hour methotrexate cut-off concentration would constitute an indication for extracorporeal treatment, although they would be indications for more intensive leucovorin rescue. By the time there is bone marrow aplasia or mucositis, the plasma methotrexate concentration will be too low for there to be a meaningful effect of extracorporeal treatments. Acute oral self-poisoning is not an indication for preemptive treatment because toxicity seldom occurs in this scenario. The workgroup notes that all usual indications for KRT, aside from methotrexate removal, remain valid. There are no kinetic or other clinical arguments to add extracorporeal treatments to glucarpidase.

The workgroup acknowledged that a benefit from extracorporeal treatments may be expected in very limited and rare circumstances, when a large methotrexate burden is present in plasma. Situations that favor the benefit-risk ratio toward extracorporeal treatments include a short time after methotrexate infusion (less than 6 to 12 hours); an exposure likely to cause toxicity (e.g., >0.5 mg/kg in a patient with kidney failure); pregnancy; an iatrogenic error such as high-dose methotrexate administration to the wrong patient; or acute shortages of leucovorin (226,260–262). In all of these circumstances, glucarpidase would be preferred if available. These exceptions explain why recommendation 1 was worded as a “suggestion against extracorporeal treatments” as opposed to a “recommendation against extracorporeal treatments.”

If an extracorporeal treatment is required, intermittent high-efficiency hemodialysis is preferred. Online hemofiltration would presumably offer comparable clearance, although data are absent. Hemoperfusion will not outperform hemodialysis because of the moderate protein binding of methotrexate and extensive cartridge saturation. Other techniques such as therapeutic plasma exchange, liver support devices, and peritoneal dialysis do not offer adequate clearances and are associated with more complications, especially in a methotrexate-toxic patient. A target methotrexate concentration <0.1 $\mu\text{mol/L}$ is reasonable for cessation of extracorporeal treatment. There is little justification in awaiting clinical improvement for cessation, as this may take several weeks, long after which there is no serum methotrexate to remove. Methotrexate rebound is expected after extracorporeal treatment because of redistribution, and a session can be repeated if present. Leucovorin is crucial in restoring the intracellular

folate cycle and is removed by extracorporeal treatments; it should be readministered immediately after the procedure.

Research Gap. Properly designed studies of clinical outcomes and/or cost-effectiveness evaluating controls versus extracorporeal treatments versus glucarpidase (each combined with leucovorin rescue) are needed, especially before the individuals develop toxicity. Data are needed on the clinical effects of methotrexate rebound after extracorporeal removal, and how this influences the frequency and duration of intermittent hemodialysis. If subsequent data fail to show a benefit of glucarpidase on clinical outcomes, then extracorporeal removal of methotrexate is unlikely to be beneficial. Data suggest that leucovorin is readily dialyzable by hemodialysis. Data on dosage adjustments of leucovorin during and after extracorporeal treatments are needed.

Conclusion

The EXTRIP workgroup assessed that methotrexate was moderately dialyzable but did not support the use of extracorporeal treatments for severe methotrexate toxicity in most clinical contexts when standard care (including leucovorin) is administered. In rare cases where fast removal of methotrexate is required, glucarpidase will outperform extracorporeal treatments.

Disclosures

All prospective members were required to disclose any actual, potential, or perceived conflict of interest before 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 coauthors remained free of any financial conflict of interest 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 coauthors any new activities that had the potential to be viewed as a conflict of interest before engaging in the activity, at the beginning of face-to-face meeting, and before submission of the manuscript. Coauthors determined if specific activities were allowed under the conflict of interest rules. All conflicts of interest deemed as potential appearance of a conflict of interest were required to be included in the manuscript. M. Ghannoum is a scholar of the Fonds de Recherche du Québec-Santé, reports employment with the Government of Quebec, and serves as EXTRIP chair. D.S. Goldfarb reports employment with New York Harbor VAMC; consultancy agreements with Allena, Alnylam, AstraZeneca, Synlogic, and Travere; ownership interest in Dr. Arnies; research funding from Dicerna and Travere; honoraria from Synlogic and Travere; patents and inventions with The Ravine Group/Dr. Arnies, Inc., Manufacturer of Moonstone; serving as a scientific advisor or member of International Cystinuria Foundation and National Kidney Foundation of Greater New York; and serving on the Editorial Boards of *CJASN*, *Current Opinion in Nephrology and Hypertension*, *JASN*, *Kidney International*, and *Urolithiasis*. R.S. Hoffman reports honoraria from UpToDate. V. Lavergne reports employment with the Infectious Diseases Society of America. P. Meyers reports consultancy agreements with Boehringer Ingelheim, Genentech, and Saliarius; research funding from Boehringer Ingelheim; honoraria from Genentech; speakers

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Supplemental Material

This article contains the following supplemental material online at <http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.08030621/-/DCSupplemental>.

Supplemental Table 1. Represented societies.

Supplemental Table 2. Standard care.

Supplemental Table 3. PRISMA-P 2015 checklist.

Supplemental Table 4. EXTRIP criteria for assessing dialyzability.

Supplemental Table 5. Quality of individual studies for toxicokinetic outcomes.

Supplemental Table 6. Quality of evidence for toxicokinetic outcomes.

Supplemental Table 7. Methotrexate concentrations associated with increased risk of complications.

Supplemental Table 8. Quantification of methotrexate mass removal during ECTR.

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 Figure 3. Result of literature search.

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