

Extracorporeal Treatment for Metformin Poisoning: Systematic Review and Recommendations From the Extracorporeal Treatments in Poisoning Workgroup

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Background: Metformin toxicity, a challenging clinical entity, is associated with a mortality of 30%. The role of extracorporeal treatments such as hemodialysis is poorly defined at present. Here, the Extracorporeal Treatments In Poisoning workgroup, comprising international experts representing diverse professions, presents its systematic review and clinical recommendations for extracorporeal treatment in metformin poisoning.

Methods: A systematic literature search was performed, data extracted, findings summarized, and structured voting statements developed. A two-round modified Delphi method was used to achieve consensus on voting statements and RAND/UCLA Appropriateness Method to quantify disagreement. Anonymized votes and opinions were compiled and discussed. A second vote determined the final recommendations.

Results: One hundred seventy-five articles were identified, including 63 deaths: one observational study, 160 case reports or

series, 11 studies of descriptive cohorts, and three pharmacokinetic studies in end-stage renal disease, yielding a very low quality of evidence for all recommendations. The workgroup concluded that metformin is moderately dialyzable (level of evidence C) and made the following recommendations: extracorporeal treatment is recommended in severe metformin poisoning (1D). Indications for extracorporeal treatment include lactate concentration greater than 20 mmol/L (1D), pH less than or equal to 7.0 (1D), shock (1D), failure of standard supportive measures (1D), and decreased level of consciousness (2D). Extracorporeal treatment should be continued until the lactate concentration is less than 3 mmol/L (1D) and pH greater than 7.35 (1D), at which time close monitoring is warranted to determine the need for additional courses of extracorporeal treatment. Intermittent hemodialysis is preferred initially (1D), but continuous renal replacement therapies may be considered if hemodialysis is unavailable (2D). Repeat extracorporeal treatment sessions may use hemodialysis (1D) or continuous renal replacement therapy (1D).

Conclusion: Metformin poisoning with lactic acidosis appears to be amenable to extracorporeal treatments. Despite clinical evidence comprised mostly of case reports and suboptimal toxicokinetic data, the workgroup recommended extracorporeal removal in the case of severe metformin poisoning. (*Crit Care Med* 2015; 43:1716–1730)

Key Words: biguanide; hemodialysis; hemofiltration; lactate; overdose; toxicity

Metformin, a biguanide, is the most commonly prescribed oral antidiabetic drug in the United States (1), Europe (2), and Australia (3). Metformin inhibits gluconeogenesis, facilitates cellular glucose uptake, and decreases insulin resistance in patients with non–insulin-dependent diabetes.

Metformin poisoning can cause severe toxicity including death. Various treatments are used, in particular extracorporeal treatments (ECTRs) such as hemodialysis and hemofiltration. Indeed, a recent literature review noted that metformin poisoning was the most common toxicological indication for ECTR (4). However, the actual indications for ECTR are poorly defined. The objective of this article is to present a systematic review of the literature and recommendations for the use of ECTR in patients with metformin toxicity.

Pharmacology and Pharmacokinetics

Metformin is a small molecule (165 Da) with an oral bioavailability of 55% (5), available in immediate- and extended-release preparations (Table 1). Metformin is not protein bound, and its apparent volume of distribution is 1–5 L/kg (accounting for bioavailability), with distribution into intracellular compartments, including erythrocytes (5, 6). Metformin undergoes limited metabolism and is eliminated largely unchanged by the kidneys (7, 8). Total body clearance can surpass 500 mL/min (7–9) but decreases proportionally with reductions in glomerular filtration rate (7, 10). Peak concentrations in therapeutic dosing

TABLE 1. Metformin: Physicochemical and Toxicokinetic Data

Molecular weight	165 Da
Volume of distribution	1–5 L/kg
Protein binding	Negligible
Oral bioavailability	55%
Time to peak concentration	Immediate release: 1–3 hr Extended release: 6–8 hr
Endogenous half-life (therapeutic use, normal GFR)	2–6 hr
Endogenous clearance (therapeutic use, normal GFR)	400–650 mL/min
Therapeutic concentration	0.5–3 mg/L
Lethal plasma concentration	> 50 mg/L
Toxic dose	> 100 mg/kg (pediatrics) > 5 g (adults)

GFR = glomerular filtration rate.

are 1.5–3.0 mg/L. The elimination half-life of metformin is multiphasic, initially 4–8 hours (7, 8), followed by terminal elimination half-life of approximately 20 hours in patients with normal kidney function (5).

Other biguanides, such as phenformin and buformin, are minimally used worldwide. Because their toxicologic profiles differ from metformin, the following systematic review and recommendations only apply to metformin.

Definitions

Metformin-associated lactic acidosis (MALA) refers to a blood lactate concentration greater than 5 mmol/L and arterial pH less than 7.35 in association with metformin exposure (11). In practice, acidemia may occur due to multiple metabolic processes, of which hyperlactatemia is only one contributor. However, for simplicity, we will refer here to all cases of acidemia with an elevated lactate concentration as lactic acidosis.

MALA may be subcategorized into two specific entities: “incidental (or chronic) MALA” results from metformin accumulation and is associated with alterations in lactate production and/or clearance. Conversely, “intentional or acute MALA,” sometimes termed “MILA” (metformin-induced lactic acidosis), applies when metformin appears to be directly responsible for lactic acidosis, particularly following acute overdose (12–15). The distinction between MALA and MILA is often blurred, and this review refers to both scenarios as MALA.

Mechanism of Toxicity and Risk Factors

Metformin has direct effects on metabolism, including inhibition of pyruvate carboxylase, which impairs the conversion of lactate to pyruvate, and impaired cellular respiration (16). This

results in both increased production and decreased metabolism of lactate, often referred to as “type B lactic acidosis.”

The relationship between metformin and lactic acidosis has been questioned (17, 18), primarily from randomized controlled trials in patients with normal kidney function (19). In particular, early studies noted this poor correlation, which may have reflected suboptimal timing of sample collection, or underappreciation of metformin’s distribution kinetics (15, 20). More recent studies noted a relationship between metformin and lactate concentrations (15, 21), and other evidence supports this association (22). Indeed, in some cases, metformin appeared to directly cause lactic acidosis (23), and animal studies suggest that the toxicity is dose-dependent (5).

Because the elimination of metformin is predominantly by the kidneys, the most common factor contributing to metformin toxicity is impaired kidney function (24). The risk of lactic acidosis is further compounded by factors that increase the production of lactate, or impair its clearance, including hypotension, dehydration, ischemia, sepsis, and liver impairment.

Epidemiology

The estimated prevalence of MALA is less than 0.01–0.09 cases/1,000 patient years (24). A total of 8,229 metformin exposures were reported to the U.S. Poison Control Centers in 2013 (25). Overall, MALA may be more commonly noted from chronic exposures (26) and may carry greater mortality especially in susceptible patients (27). Nevertheless, a massive acute intentional overdose can also produce fatal lactic acidosis (13, 14).

Relevance of the Serum Metformin Concentration

The clinical utility of metformin assays is controversial: a high metformin concentration (> 20–50 mg/L) was prognostic of poor outcome in certain studies (15, 28), although others failed to show a correlation (17, 21, 27, 29–31). A very high metformin concentration may predict a precipitous clinical decline in an otherwise asymptomatic patient following an intentional poisoning (14, 32–35). It is likely that publications that did perform metformin sampling incorrectly classified some cases as MALA (15, 21).

Treatment

The mainstay of initial therapy for MALA, regardless of chronicity or cause, is resuscitation and supportive care. There is no specific antidote available to reverse the toxic effects of metformin. Gastrointestinal decontamination may be indicated soon after an acute overdose. Bicarbonate has been used to correct acidemia, although there are concerns that it may exacerbate intracellular acidosis, induce a leftward shift of the oxyhemoglobin dissociation curve, provide an excessive sodium load (36), and cause various electrolyte abnormalities (37).

Although ECTRs are often initiated in patients with metformin toxicity, existing recommendations for ECTR initiation are unclear and include impaired kidney function, significant electrolyte disturbances, severe metabolic acidosis, and a failure of supportive care (38–43). Therefore, more specific recommendations are required to support clinicians who may encounter cases of MALA.

METHODS

The Extracorporeal Treatments In Poisoning (EXTRIP) workgroup is composed of international experts representing diverse specialties and professional societies (Table 2) to provide recommendations on the use of ECTRs in poisoning (<http://www.extrip-workgroup.org>). Rationale, background, objectives,

TABLE 2. Represented Societies in The Extracorporeal Treatments In Poisoning Workgroup

Acute Dialysis Quality Initiative	European Renal Best Practice
American Academy of Clinical Toxicology	European Society For Emergency Medicine
American College of Emergency Physicians	European Society of Intensive Care Medicine
American College of Medical Toxicology	French Society of Intensive Care
American Society of Nephrology	German Society of Nephrology
American Society of Pediatric Nephrology	Indian Society of Critical Care Medicine
Asia Pacific Association of Medical Toxicology	INDO-US Emergency & Trauma Collaborative
Association of Physicians of India	International Pediatric Nephrology Association
Australian and New Zealand Intensive Care Society	International Society of Nephrology
Australian and New Zealand Society of Nephrology	Latin American Society of Nephrology and Hypertension
Brazilian Association of Information Centres and Toxicologic Assistance	National Kidney Foundation
Brazilian Society of Nephrology	Pediatric Continuous Renal Replacement Therapy
Brazilian Society of Toxicology	Pediatric Critical Care Medicine
Canadian Association of Poison Control Centres	Quebec Association of Emergency Physicians
Canadian Association of Emergency Physicians	Quebec Association of Specialists in Emergency Medicine
Canadian Society of Nephrology	Quebec Society of Nephrology
Chinese College of Emergency Physicians	Renal Association
Chinese Medical Doctor Association	Society of Critical Care Medicine
European Association of Poison Centres and Clinical Toxicologists	Spanish Clinical Toxicology Foundation

This list includes societies that are officially represented for the guideline process. The present document solely reflect the work of authors alone.

complete methodology, and first recommendations have been previously published (44–53).

Predetermined methodologies, incorporating guidelines from Appraisal of Guidelines Research and Evaluation (54) and Grading of Recommendations Assessment, Development and Evaluation (55), were used and are described elsewhere (45). The primary literature search was conducted on July 12, 2012, in Medline, Embase, and Cochrane library (Review and Central).

The search strategy was ([metformin OR glucophage] AND [dialysis OR hemodialysis OR haemodialysis OR hemoperfusion OR haemoperfusion OR plasmapheresis OR plasma exchange OR exchange transfusion OR hemofiltration OR haemofiltration OR hemodiafiltration OR haemodiafiltration OR extracorporeal therapy OR CRRT]).

A manual search of conference proceedings of the European Association of Poisons Centres and Clinical Toxicologists and North American Congress of Clinical Toxicology annual scientific meetings (2002–2012) and Google Scholar was performed, as well as the bibliography of each article obtained during the literature search.

A subgroup of EXTRIP completed the literature search, reviewed each article, extracted data, and summarized findings. The level of evidence assigned to each clinical recommendation was determined by the subgroup and epidemiologist (Table 3). Grading for dialyzability was on criteria listed in Table 4 and the level of evidence supporting this grading presented in Table S1 (Supplemental Digital Content 1, <http://links.lww.com/CCM/B287>). The clinical and toxicokinetic data were submitted to participants who weighed the potential benefits of the procedure against its cost, availability, alternative treatments, and related complications and who then voted on predetermined statements.

The strength of recommendations was evaluated by a two-round modified Delphi method for each proposed voting statement (Fig. 1), and RAND/UCLA Appropriateness Method was used to quantify disagreement between voters (56). Anonymous votes with comments were sent to the epidemiologist who then compiled and returned a summary to each participant. The workgroup met in person to exchange ideas and debate statements. A second vote was later conducted, and these results were used in determining the final EXTRIP recommendations. The literature search was updated on November 1, 2014, using the methodology described above; new articles and the updated data summary were submitted to every participant who then finalized their votes.

RESULTS AND DISCUSSION

Results of the literature search are summarized in Figure 2. A total of 175 studies were included in the final analysis: one retrospective observational study (30 patients) (57), 11 uncontrolled retrospective cohort studies with aggregate analysis (463 patients) (17, 21, 27, 30, 58–64), 160 case reports or case series allowing extraction of patient-level data (292 patients) (10, 13–15, 29, 32–37, 65–211), and three pharmacokinetic studies in end-stage renal disease (ESRD) (38 patients) (212–214). No randomized controlled trials were identified.

TABLE 3. Strength of Recommendation and Level of Evidence Scaling on Clinical Outcomes

Strength of Recommendation (Consensus-Based)	Level of Evidence (Based on Grading of Recommendations Assessment, Development and Evaluation System)
<p>Level 1 = Strong recommendation = “We recommend...”</p> <p>The course of action is considered appropriate by the large majority of experts with no major dissension. The panel is confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects</p>	<p>Grade A = High level of evidence</p> <p>The true effect lies close to our estimate of the effect</p>
<p>Level 2 = Weak recommendation = “We suggest...”</p> <p>The course of action is considered appropriate by the majority of experts but some degree of dissension exists amongst the panel. The desirable effects of adherence to the recommendation probably outweigh the undesirable effects</p>	<p>Grade B = Moderate level of evidence</p> <p>The true effect is likely to be close to our estimate of the effect, but there is a possibility that it is substantially different</p>
<p>Level 3 = Neutral recommendation = “It would be reasonable...”</p> <p>The course of action could be considered appropriate in the right context</p>	<p>Grade C = Low level of evidence</p> <p>The true effect may be substantially different from our estimate of the effect</p>
<p>No recommendation</p> <p>No agreement was reached by the group of experts</p>	<p>Grade D = Very low level of evidence</p> <p>Our estimate of the effect is just a guess, and it is very likely that the true effect is substantially different from our estimate of the effect</p>

Clinical Outcomes

A small retrospective observational study evaluated patients admitted to ICU with a diagnosis of MALA, irrespective of the type of exposure, and compared clinical outcomes in patients receiving hemodialysis ($n = 16$) with those who did not ($n = 14$) (57). Mortality rates were similar in both groups despite the dialysis group being sicker (higher Simplified Acute Physiology Score II, lower arterial bicarbonate, and higher creatinine concentration) and trended to have greater baseline comorbidities (higher

TABLE 4. Criteria for Dialyzability^a

Dialyzability ^b	Primary Criteria	Alternative Criteria 1	Alternative Criteria 2	Alternative Criteria 3
	Percent Removed ^c	Extracorporeal Clearance/Total Clearance (%)	Half-Life of Extracorporeal Treatment/ <i>T</i> _{1/2} (%)	Extracorporeal Removal/Total Removal (%) ^d
D, Dialyzable	> 30	> 75	< 25	> 75
M, Moderately dialyzable	> 10–30	> 50–75	> 25–50	> 50–75
S, Slightly dialyzable	≥ 3–10	≥ 25–50	≥ 50–75	≥ 25–50
N, Not dialyzable	< 3	< 25	> 75	< 25

^aThese criteria should only be applied if measured or calculated (not reported) endogenous half-life is > 4 hr (otherwise, extracorporeal treatment [ECTR] is considered not clinically relevant). Furthermore, the primary criteria are preferred for poisons having a large *V*_d (> 5 L/kg).

^bApplicable to all modalities of ECTR, including hemodialysis, hemoperfusion, and hemofiltration.

^cCorresponds to % removal of ingested dose or total body burden in a 6-hr ECTR period.

^dMeasured during the same period of time.

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Charlson Index). The study was also potentially underpowered. Nevertheless, the similarity in clinical outcome despite the presence of confounding-by-indication may suggest a potential benefit from hemodialysis (215).

Pooled analysis of other uncontrolled descriptive cohorts did not permit individual data extraction but included 463 patients with MALA, 219 of whom received ECTR, and 72 deaths (mortality, 15.6%) (17, 21, 27, 30, 58, 59, 62, 63). The remainder of the evidence was derived from case reports and case series. Although these may be useful for describing the spectrum of severity, it is not possible to infer the clinical effect of ECTR from such publications. The level of evidence is therefore very low for all clinical recommendations.

Demographic data, clinical presentation, treatments given, and outcome among the 292 patients described in case reports and case series are reported in **Table 5**. Approximately 80% of the patients had chronic metformin toxicity.

Average ingestion in the acute cases was 54.6 g. The acute group had a higher peak metformin concentration (average, 126.2 mg/L vs 43.2 mg/L), a higher peak lactate (average, 24.6 mmol/L vs 18.6 mmol/L), and a higher pH (average, 6.97 vs 6.90). Acute kidney injury (AKI) was a predominant comorbid condition at admission in both types of exposures. Decreased consciousness was a common symptom in acute cases, as was hypotension. Other less common symptoms included vision loss (87, 136, 179) and encephalopathy (125, 128). Of the acute cases who developed life-threatening signs, several were either asymptomatic (14, 32–35) or very mildly symptomatic at admission (13, 37, 65, 94, 133, 138, 171, 185, 194) and became toxic rapidly following ingestion.

Bicarbonate and mechanical ventilation were more commonly administered to patients with acute poisoning. IV bicarbonate failed to completely correct acidemia in several reports (77, 165, 185), although dose-ranging data were not apparent. Intermittent hemodialysis was the predominant ECTR in both types of exposure, followed by continuous renal replacement therapy (CRRT). Other ECTRs, such as peritoneal dialysis, therapeutic plasma exchange (203), and hemoperfusion (117), were used infrequently.

Our systematic review identified 63 fatalities with patient-level data (an additional 72 deaths were noted but data were aggregated). Deaths were more common in patients following an acute exposure (30.3% vs 19.5% following chronic poisoning), a finding contrary to another report (27). The mean peak metformin concentration

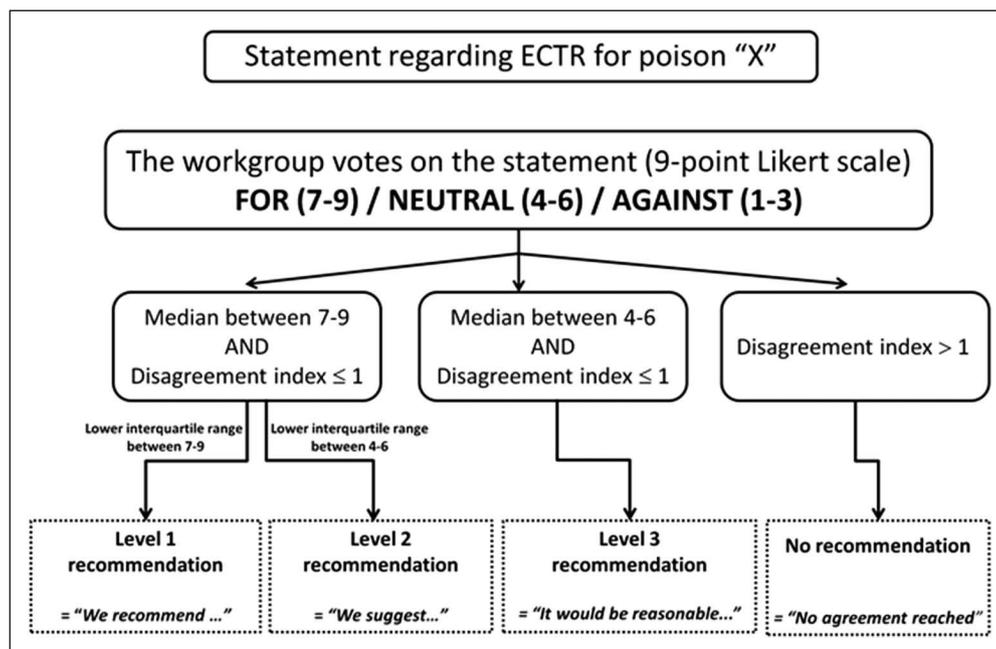


Figure 1. Delphi method (two rounds) for each recommendation.

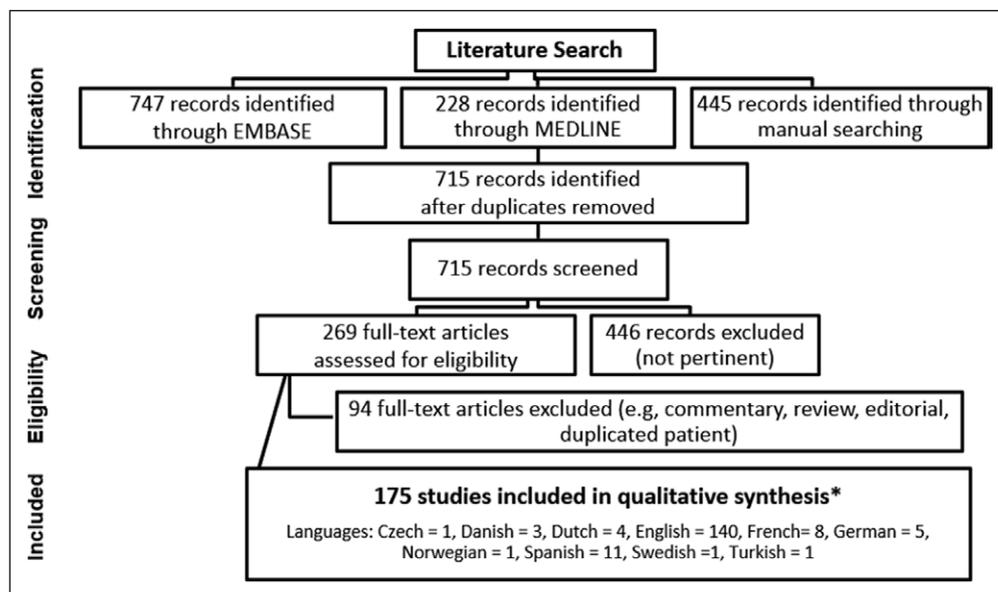


Figure 2. Flow diagram (November 1, 2014). ECTR = extracorporeal treatment.

in fatalities was 67.3 mg/L compared with 56.6 mg/L in survivors. The overall mortality rate was comparable to most publications (21, 57, 58, 62), but lower than others that reported a mortality of up to 50% (216). Of note, approximately half of the reported fatalities occurred several days after admission and after the commencement of ECTR and appeared to be unrelated to features of severe metformin toxicity or the ECTR.

However, these observations may be limited by the controversy and complexity with diagnosing MALA, so interpretation should be cautioned by the presence of confounders and publication bias.

Dialyzability

Metformin has a small size and limited protein binding, so it is freely diffusible through hemodialyzers (high extraction ratios) (34) and hemofilters (high sieving coefficient) (123). The limiting factor for its extracorporeal elimination is the relatively large volume of distribution (V_D), although it may be reduced in the context of AKI (7) and possibly poisoning (159). Although speculative, this may be due to insufficient time for equilibration with peripheral or intracellular compartments (6). The determination of dialyzability by comparing extracorporeal clearance to endogenous clearance is somewhat unreliable because endogenous metformin clearance can vary from almost nil in anuric patients to more than 500 mL/min in those with intact kidney function (7, 8). For comparison, extracorporeal clearance of metformin can exceed 200 mL/min with intermittent dialysis (10, 34, 172, 213, 214) and up to 50 mL/min with CRRT (13, 76, 123) (Table 6). A possible method for evaluating the effect of ECTR on total metformin clearance, relative to creatinine clearance, is shown in Figure S1 (Supplemental Digital Content 1, <http://links.lww.com/CCM/B287>).

Table 6 summarizes the kinetic data for intermittent and continuous ECTRs in regard to $T_{1/2}$ and clearance, and Table 7 shows the dialyzability grading of individual patients based

on predetermined criteria (45) (Table 4). Metformin appears more dialyzable by intermittent hemodialysis compared to continuous modalities, which is further supported by data in patients undergoing both techniques (144, 185). One study suggested a comparable effect between continuous venovenous hemodialysis using a dialysate flow of 5 L/hr and intermittent hemodialysis (62); however, as only the proportional decrease in metformin concentration was analyzed (not actual removal) and data are not fully presented, definite conclusions cannot be derived.

Research in patients with ESRD suggests removal of

approximately 15% of the daily dose of metformin by maintenance hemodialysis (213, 214). Although metformin removal is less marked with CRRT (79, 148), it may still be appreciable in the clinical context of severe AKI (76) (Fig. S1, Supplemental Digital Content 1, <http://links.lww.com/CCM/B287>). With these complexities in mind, metformin dialyzability is best estimated by quantifying metformin removal in effluent and comparing this to the ingested dose (if known, and adjusted for bioavailability) or total body content (10, 172).

Considering the factors above and following the results presented in Table 7 and the relatively limited data on dialyzability, the workgroup agreed with the following statement: Metformin is moderately dialyzable (level of evidence = C). However, it is acknowledged that the actual grading of dialyzability varies with kidney function and ECTR modality (Fig. S1, Supplemental Digital Content 1, <http://links.lww.com/CCM/B287>).

RECOMMENDATIONS

General Statement

ECTR is recommended in severe metformin poisoning (1D) (Table 8).

Rationale: The mortality from MALA is uniformly high in reported studies, approximately 30–50% (21, 31, 57, 58, 62, 216), and treatment options are limited to supportive care. The potential benefits of ECTR in metformin toxicity go beyond metformin removal, which as shown above can be substantial, and include the following: 1) more rapid, predictable, and safe correction of acidemia than can be achieved with bicarbonate therapy, 2) improvement in hyperlactatemia, although this may reflect restored hemodynamics rather than removal of lactate by ECTR per se (83, 217), 3) correction of electrolyte abnormalities (64) as well as reversal of hypothermia (77, 146), and 4) support of impaired kidney function.

TABLE 5. Clinical Data of Included Cases Who Received Extracorporeal Treatment for Metformin Toxicity^a

Clinical Data	Acute/Acute-on-Chronic (n = 56)	Chronic (n = 236)
Patient demographics		
Mean age (yr)	40.4 (range, 14–74)	67.5 (range, 20–90)
Sex (% male)	55	39
Poisoning exposure		
Mean quantity metformin ingested (g)	54.6 (range, 5–144.5)	NA
Mean metformin daily dose (g)	NA	2.1 (range, 0.5–6)
Delay between ingestion and admission (hr)	8.5 (range, 1–48)	NA
Mean peak metformin concentration (mg/L)	126.2 (range, 10.2–380)	43.2 (range, 0–412)
Clinical symptoms and signs		
Mean peak lactate (mmol/L)	24.6 (range, 4.2–77.3)	18.6 (range, 2.9–113.6)
Mean lowest pH	6.97 (range, 6.7–7.33)	6.90 (range, 6.08–7.47)
Decreased consciousness (%)	66	34
Abdominal pain (%)	14	17
Visual symptoms (%)	0	3
Hypothermia (%)	34	23
Acute kidney injury (%)	66	85
Hypotension (%)	61	47
Hypoglycemia (%)	32	10
Other treatments used		
Bicarbonate (%)	64	41
Mechanical ventilation (%)	50	35
ECTR modality used, n (%)		
Hemodialysis	23 (41)	108 (46)
Continuous renal replacement therapy	20 (36)	99 (42)
Sustained low-efficiency dialysis/sustained low-efficiency daily dialysis	0 (0)	4 (2)
Peritoneal dialysis	1 (2)	4 (2)
Intermittent hemodiafiltration	0 (0)	1 (0)
More than 1 ECTR	12 (21)	19 (8)
Unclear	0 (0)	2 (1)
Outcome, n (%)		
Fatalities	17 (30)	46 (19)

NA = not applicable, ECTR = extracorporeal treatment.

^aThese only include cases in which data from individual patients were described (descriptive cohort that did not include patient-level data were excluded). Given the nature of the data, a statistical comparison of the groups was considered inappropriate.

Although data are anecdotal and reporting bias cannot be excluded, most of the patients treated with ECTR (especially intermittent hemodialysis) improved after initiation and had a favorable outcome, including patients who ingested more than 2 g/kg, had a pH less than 6.7, had a lactate concentration over 30 mmol/L, or a metformin concentration over 100 mg/L (28,

29, 34–37, 66, 73, 88, 91, 98, 104, 111, 116–119, 130, 138, 139, 145, 160, 161, 163, 172, 174, 181, 183, 185, 188, 198, 204, 208, 209, 218–220). Occasionally, this reported improvement was dramatic, soon after the initiation of ECTR (34, 86, 96, 98, 144, 166–168, 191). Conversely, there were also cases where little to no improvement was noted during ECTR (13, 14, 76, 84, 107,

TABLE 6. Median Pharmacokinetic-Toxicokinetic Variables for All Techniques

Type of ECTR	ECTR Clearance (mL/min)			$T_{1/2}$ (Hr)		
	Median	Range	<i>n</i>	Median	Range	<i>n</i>
Endogenous (normal glomerular filtration rate, therapeutic dose)	500			2–6 (20–35 in overdose)		
Hemodialysis	148	68–228	10	4.2	1.5–24	24
Continuous renal replacement therapy	34	9–71.3	7	16.6	9.7–45.9	21
Peritoneal dialysis				113.5		1
Sustained low-efficiency dialysis				5.9		1

ECTR = extracorporeal treatment.

155, 162, 184, 198), which may reflect a delay in ECTR initiation (e.g., tardiness in ensuring central vascular access or unnecessarily prolonged bicarbonate therapy) (13, 14, 162, 198), a treatment shortened prematurely (e.g., metabolic derangements not fully corrected) (107), and/or the use of a less efficient ECTR on the basis of hemodynamic instability (13, 76, 198).

Despite the absence of randomized clinical trials and given the unlikelihood that these will be conducted, all 27 panel members strongly voted for ECTR in severe metformin poisoning. The benefit of ECTR, when toxicity is severe as defined by any of the conditions below, was deemed to outweigh potential risks, complications, and costs of the procedure.

Indications

ECTR is recommended if

Lactate concentration > 20 mmol/L (1D)

Blood pH is less than or equal to 7.0 (1D)

Standard therapy (including supportive care and bicarbonate) fails (1D)

ECTR is suggested if

Lactate concentration > 15–20 mmol/L (2D)

Blood pH < 7.0–7.1 (2D)

Comorbid conditions that lower the threshold for initiating ECTR:

Shock (1D)

Impaired kidney function (1D)

Liver failure (2D)

Decreased level of consciousness (2D)

Rationale: Although not uniformly accepted (12, 221), factors associated with poor prognosis in MALA, which in turn influence recommendations for ECTR (27, 28), include hyperlactemia (29, 63) (> 18.5 mmol/L [222], > 15 mmol/L [27], or > 25 mmol/L [28]) and acidemia (63) (< 7.2 [27], < 6.9 [222], < 6.7 [58]). Not surprisingly, failure of standard therapies achieved strong consensus as an independent criterion for ECTR (1D). These recommendations are consistent with several sources (41, 42, 62) but less interventional than other authors who

suggest that any elevation of lactate over the reference range, or a low arterial pH, requires ECTR (201).

The decision to commence ECTR should not be based solely on the suspicion of a large metformin ingestion (1D), despite reports of asymptomatic patients developing MALA following an intentional overdose, in the absence of other risk factors (14, 94). This recommendation was felt to be warranted because of uncertainties relating to ingestion history (223) and because the metformin dose-response relationship is poorly defined.

As mentioned above, the prognostic value of metformin concentrations in acute metformin overdose remains debatable, and life-threatening toxicity can be observed in chronic toxicity from metformin concentrations close to the reported therapeutic range (17, 29, 142). For these reasons, even in situations where metformin assays are quickly available and a high concentration is confirmed, the workgroup declined to specify a specific threshold as a criterion for ECTR, until more information on the interpretation of such results is available.

Nevertheless, because of the high mortality associated with MALA, if either a large ingestion and/or an elevated metformin concentration is suspected or confirmed, many participants proposed that early referral should be made to a center

TABLE 7. Pharmacokinetic-Toxicokinetic Grading for Individual Patients^a

Pharmacokinetic/ Toxicokinetic Grading	Intermittent Hemodialysis	Continuous Renal Replacement Therapy
D, Dialyzable	3	0
M, Moderately dialyzable	5	4
S, Slightly dialyzable	1	3
N, Not dialyzable	0	2

^aThis table included any patient who had sufficient kinetic variables for grading according to Table 4. For example, if an article reports removal of 5 g of metformin during 6 hr of hemodialysis, in a patient who ingested 40 g (accounting for bioavailability), this would qualify as “moderately dialyzable.”

TABLE 8. Executive Summary of Recommendations

General
ECTR is recommended in severe metformin poisoning (1D)
Indications
ECTR is recommended if
Lactate concentration > 20 mmol/L (180 mg/dL) (1D)
Blood pH ≤ 7.0 (1D)
Standard therapy (supportive measures, bicarbonate, etc.) fails (1D)
ECTR is suggested if
Lactate concentration is 15–20 mmol/L (135–180 mg/dL) (2D)
Blood pH 7.0–7.1 (2D)
Comorbid conditions that lower the threshold for initiating ECTR
Impaired kidney function (1D)
Shock (1D)
Decreased level of consciousness (2D)
Liver failure (2D)
Cessation of ECTR is indicated when
Lactate concentration is < 3 mmol/L (27 mg/dL) and pH > 7.35 (1D)
Choice of ECTR
As an initial ECTR, intermittent HD with bicarbonate buffer is preferred (1D), but CRRT is an acceptable alternative if HD is not available (2D)
After the initial ECTR session, either HD (1D) or CRRT (1D) is appropriate if necessary

ECTR = extracorporeal treatment, HD = hemodialysis, CRRT = continuous renal replacement therapy.

that provides ECTR, even in the absence of other indications for ECTR. This can be justified given the higher likelihood that such a patient will eventually meet ECTR indications, so timely access to ECTR would be useful (76).

Consensus was achieved with four comorbid conditions that potentially modify treatment recommendations, although discussion conceded that these may be contributed to by concomitant metabolic derangements reflected in serum pH and lactate values. Because metformin is almost exclusively eliminated by the kidneys, the presence of impaired kidney function (definition in the **online supplement**, Supplemental Digital Content 1, <http://links.lww.com/CCM/B287>) will extend the length (and potentially severity) of toxicity, thereby lowering the threshold for ECTR (1D). Liver failure (definition in online supplement, Supplemental Digital Content 1, <http://links.lww.com/CCM/B287>) should also prompt a lower treatment threshold (2D) as its presence appears to impair lactate

handling and removal. It was also proposed that a lower threshold for commencing ECTR be applied if shock (definition in online supplement, Supplemental Digital Content 1, <http://links.lww.com/CCM/B287>) (1D) or a decreased level of consciousness (2D) were present.

Cessation of ECTR

Cessation of ECTR is indicated when lactate concentration is less than 3 mmol/L and pH is more than 7.35 (1D).

Rationale: These are practical and preferred endpoints for ECTR cessation in the context of MALA because assays are usually rapidly available in centers that provide ECTR, and adverse effects are minimized when these targets are attained.

The workgroup suggested that there should not be a specific metformin concentration target for ECTR cessation because of its poor correlation on outcomes. Furthermore, there are reports of resistant acidemia despite negligible metformin concentrations (15, 29, 142) and even cases of reduction of metformin concentrations with concomitant worsening of lactate during ECTR (138). However, some workgroup participants considered that ECTR should be continued until the metformin concentration, if readily obtainable, is below 3 mg/L (within the therapeutic range).

Factors influencing the duration of ECTR until the above targets are achieved are poorly defined. It is anticipated that longer treatments will be required with extremely abnormal lactate and pH measurements. The duration of ECTR likely depends on the initial metformin concentration, its elimination half-life during ECTR (Table 6), operator characteristics during ECTR (224), and endogenous clearance. In one study, a 15-hour treatment with a high-efficiency ECTR was usually sufficient to reduce metformin concentration to reference values (27), but this finding has not been validated; there are several examples of patients requiring more than 24 hours of hemodialysis or CRRT to reduce metformin concentrations to the therapeutic range (32, 35, 111, 143, 182).

Because metformin concentrations may increase or “rebound” after ECTR (i.e., redistribute from deeper compartments into the intravascular space), treatment of insufficient duration may result in a marked resurgence of lactic acidosis (66, 78, 80, 83, 84, 99, 116, 117, 137, 140, 144, 158, 169, 171, 182, 189, 203, 205). Deaths have been reported when ECTR was stopped too early, despite an initial improvement (78, 137, 142, 169).

Due to the unpredictable nature of rebound, close monitoring of the acid-base status is essential to determine if ECTR should be recommenced. In some cases, an extended duration or repeat session may be needed (117). The added cost and complication rate of extending ECTR are relatively marginal once it is already commenced. The dialysis catheter should remain in place until the clinician is reassured that relapse is unlikely.

Choice of ECTR

As an initial ECTR session, intermittent hemodialysis with bicarbonate buffer is preferred (1D), but CRRT is an acceptable alternative if hemodialysis is not available (2D).

After the initial ECTR session, either hemodialysis (1D) or CRRT (1D) is appropriate, if necessary.

Rationale: Intermittent hemodialysis was recommended as the first-line initial ECTR by the workgroup because it is superior in terms of its correction of acidemia and removal of metformin and lactic acid (144). Compared with other ECTRs, hemodialysis is the most available ECTR worldwide, is relatively inexpensive, and is associated with fewer complications (225). Bicarbonate-based dialysate buffers are standard today and are preferable to acetate-based buffers that fail to correct serum bicarbonate as quickly (226, 227); replacement or dialysate solutions containing lactate may delay correction of hyperlactatemia (211, 228–230).

Although intermittent hemodialysis is preferable to CRRT, the latter is an acceptable alternative if hemodialysis cannot be performed. A proposed advantage of CRRT is its improved tolerability in hemodynamically unstable patients, but this is questioned in situations where net ultrafiltration (e.g., fluid removal) is not required (98). Because hemodynamic instability is likely induced by the extreme metabolic derangements related to metformin, the more efficient intermittent techniques may still be preferred in the presence of hypotension. Several lethalties were observed when lesser efficient techniques were used (13, 76, 198).

To strengthen the workgroup's preference for high-efficiency techniques, it appears that ECTR modality and dose directly influence outcome: in two studies, use of an additional catheter and extracorporeal circuit augmented the clinical improvement and lactate removal compared to a single circuit (35, 104). Some patients only improved after blood flow and effluent flow were maximized (106). Lactate clearance is also greater with intermittent techniques (6 hr of hemodialysis was superior to 24 hr of CRRT in one study [231]), increases with higher effluent rates (232), and is enhanced by the use of high-flux/high-efficiency dialyzers (compared to conventional filters) (66), although it is acknowledged that lactate removal by ECTR may be inferior to endogenous routes, when intact (217). For these reasons, once an ECTR modality is chosen, operator characteristics should be optimized to maximize clearance (higher blood flow, dialysate and/or ultrafiltrate flow, and higher efficiency membranes) (224); if CRRT is chosen, the prescribed dose should be superior to that usually favored for patients with AKI.

After the first ECTR session, either hemodialysis or CRRT is considered acceptable if a subsequent treatment becomes necessary. Because metformin is not bound to plasma proteins, hemoperfusion (117, 233), liver assist devices, or plasma exchange (203) do not offer any advantages over hemodialysis or CRRT, and they also do not effectively correct acid-base abnormalities (234). Metformin clearance and normalization of acidemia are unlikely to be achieved by peritoneal dialysis in severe cases (78, 120, 132).

CONCLUSIONS

ECTR, in particular intermittent hemodialysis, is a vital tool in the management of metformin toxicity. Although the pathophysiology and prognosis differ significantly based on the

mechanism of acidosis, the use of pH and serum lactate as variables to initiate dialysis is most aligned with the current state of the literature. The EXTRIP workgroup recommends ECTR in patients with severe lactic acidosis, with consideration of mitigating factors that may lower the threshold for treatment, and recommends cautious cessation of therapy with ongoing clinical monitoring. Further study is needed to determine the utility of metformin concentrations and the optimal length of ECTR.

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