Review Article

Recommendations for the Role of Extracorporeal Treatments in the Management of Acute Methanol Poisoning: A Systematic Review and Consensus Statement

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Objective: Methanol poisoning can induce death and disability. Treatment includes the administration of antidotes (ethanol or fomepizole and folic/folinic acid) and consideration of extracorporeal treatment for correction of acidemia and/or enhanced elimination. The Extracorporeal Treatments in Poisoning workgroup aimed to develop evidence-based consensus recommendations for extracorporeal treatment in methanol poisoning.

Design and Methods: Utilizing predetermined methods, we conducted a systematic review of the literature. Two hundred seventy-two relevant publications were identified but publication and selection biases were noted. Data on clinical outcomes and dialyzability were collated and a two-round modified Delphi process was used to reach a consensus.

Results: Recommended indications for extracorporeal treatment: Severe methanol poisoning including any of the following being attributed to methanol: coma, seizures, new vision deficits, metabolic acidosis with blood pH ≤7.15, persistent metabolic acidosis despite adequate supportive measures and antidotes, serum anion gap higher than 24 mmol/L; or, serum methanol concentration 1) greater than 700 mg/L (21.8 mmol/L) in the context of fomepizole therapy, 2) greater than 600 mg/L or 18.7 mmol/L in the context of ethanol treatment, 3) greater than 500 mg/L or 15.6 mmol/L in the absence of an alcohol dehydrogenase blocker; in the absence of a methanol concentration, the osmolal/osmolar gap may be informative; or, in the context of impaired kidney function. Intermittent hemodialysis is the modality of choice and continuous modalities are acceptable alternatives. Extracorporeal treatment can be terminated when the methanol concentration is <200 mg/L or 6.2 mmol/L and a clinical improvement is observed. Extracorporeal Treatments in Poisoning inhibitors and folic/folinic acid should be continued during extracorporeal treatment. General considerations: Antidotes and extracorporeal treatment should be initiated urgently in the context of severe poisoning. The duration of extracorporeal treatment extracorporeal treatment depends on the type of extracorporeal treatment used and the methanol exposure. Indications for extracorporeal treatment are based on risk factors for poor outcomes. The relative importance of individual indications for the triaging of patients for extracorporeal treatment, in the context of an epidemic when need exceeds resources, is unknown. In the absence of severe poisoning but if the methanol concentration is elevated and there is adequate alcohol dehydrogenase blockade, extracorporeal treatment is not immediately required. Systemic anticoagulation should be avoided during extracorporeal treatment because it may increase the development or severity of intracerebral hemorrhage.

Conclusion: Extracorporeal treatment has a valuable role in the treatment of patients with methanol poisoning. A range of clinical indications for extracorporeal treatment is provided and duration of therapy can be guided through the careful monitoring of biomarkers of exposure and toxicity. In the absence of severe poisoning, the decision to use extracorporeal treatment is determined by balancing the cost and complications of extracorporeal treatment to that of fomepizole or ethanol. Given regional differences in cost and availability of fomepizole and extracorporeal treatment, these decisions must be made at a local level. (*Crit Care Med* 2015; 43:461–472)

Key Words: acidosis; antidotes; consensus guidelines; Delphi process; dialysis; dialyzability; enhanced elimination; extracorporeal treatment; indications; intoxication; methanol; morbidity; mortality; poisoning; systematic review; triage

Methanol poisoning is responsible for significant death and disability, particularly in epidemics associated with contamination of illicit or homemade alcoholic beverages (1–3). If specific interventions are inadequate or delayed, mortality exceeding 40% as well as visual impairment and motor and cognitive disorders may occur (4–8).

Methanol is metabolized first by hepatic alcohol dehydrogenase (ADH) to formaldehyde then to formic acid, which is considered the major toxic compound (**Fig. 1**). Antidotes, including ethanol and fomepizole, which are competitive inhibitors of ADH, prevent this toxic biotransformation and progression of clinical toxicity (**Table 1**). Based on their physicochemical and pharmacokinetic properties, methanol and formate are anticipated to be readily removed by extracorporeal treatments (ECTRs). These procedures may contribute to improvement in clinical outcome by direct toxin removal, correction of acidemia, or both. However, despite an established role in the treatment of methanol poisoning, lack of consensus still persists regarding specific indications for ECTR use (**Table S1**, Supplemental Digital Content 1, http://links.lww.com/CCM/B129). As ECTR is a limited resource, especially in the context of an outbreak, determination of which patients should receive priority treatment is crucial. Furthermore, because ADH inhibition significantly prolongs the elimination half-life of methanol to a mean of 54 hours (9–11), removal of methanol by ECTR is likely to shorten the duration of ICU admission, thereby having economic and practical benefits on healthcare resource use (12).

The EXTRIP (Extracorporeal Treatments in Poisoning) workgroup developed evidence-based consensus recommendations for ECTR indications in the management of methanol poisoning. We applied a predetermined rigorous methodology including a systematic review of the literature and engaged experts in the field to develop consensus statements. We also sought to identify limitations in the existing data, which may prompt further research in the field.

METHODS

EXTRIP is composed of international experts representing diverse specialties and professional societies to provide recommendations on the use of ECTR in poisoning (http://www.extrip-workgroup.org) (13). The predetermined methodology incorporated guidelines from Appraisal of Guidelines for Research and Evaluation and Grading of Recommendations Assessment, Development and Evaluation (GRADE) and it is described in detail elsewhere (14).

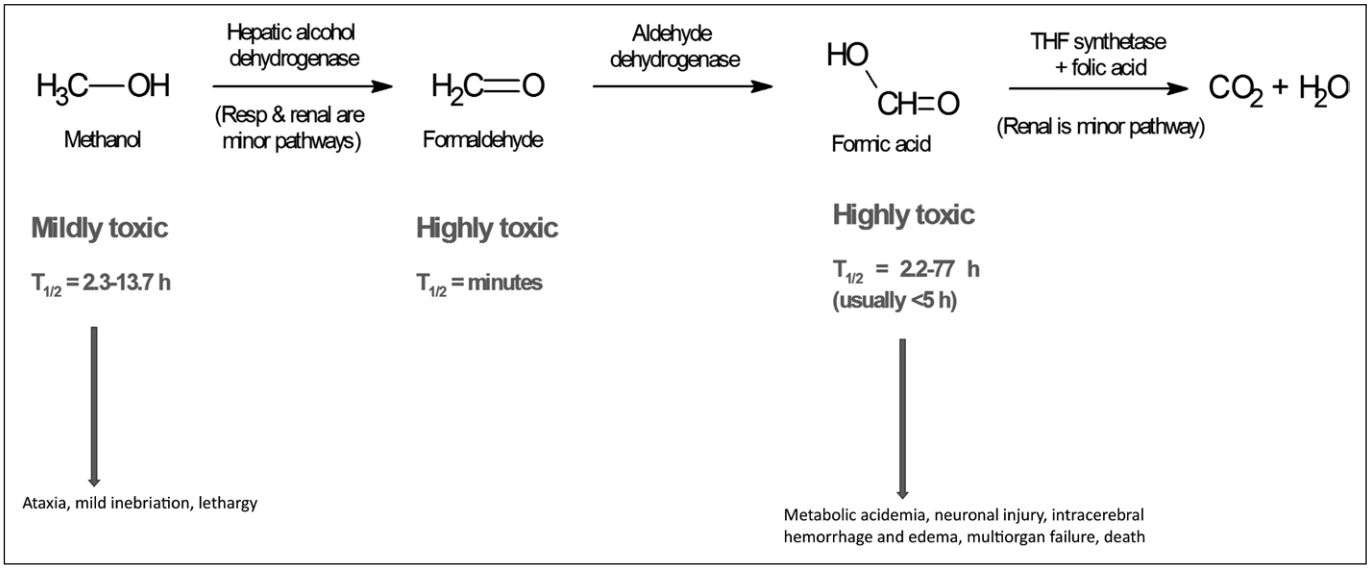

Figure 1. Metabolic biotransformation and clinical manifestations of methanol.

A systematic review of the literature was conducted. Both Medline and Embase were queried using the strategy below without limitation by language or year of publication (accessed May 15, 2012, but subsequently updated, see below):

[(methanol OR methyl alcohol) AND (overdos* OR toxicity OR intoxication OR poisoning) 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 OR renal replacement therapy)]

The bibliography for each identified study was manually searched, as well as the Cochrane Library, http://www.google.com, leading medical textbooks and online references,

TABLE 1. Physicochemical and Pharmacokinetic Properties of Methanol

Molecular weight	Methanol, 32.04 g/mol; formic acid, 46.03 g/mol
Solubility (log P)	Methanol, −0.69; formic acid, −0.54 (both water soluble)
Toxic dose (adult)	30 mL or grams (35), but marked interindividual susceptibility
	60 mL can be lethal (25, 28, 66)
Toxic blood concentrations	≥ 200 mg/L (9.4 mmol/L) is often listed as an indication for medical treatment although data supporting this are limited and a higher concentration may be acceptable (34)
Absorption	In volunteers, methanol is rapidly absorbed with a maximum concentration within 1 hr of ingestion (15)
	In acute poisoning, the maximum concentration is usually noted at the time of admission but it has been observed up to 8–10 hr postadmission (59, 68–72)
	Rarely, poisoning has occurred following inhalational (73–76) or percutaneous (77) exposures
Distribution	Limited protein binding and single compartment kinetics
	Volume of distribution of 0.6–0.8 L/kg (15–19)
Metabolism	Methanol is metabolized by ADH to formaldehyde, which is rapidly oxidized to formic acid, which spontaneously dissociates to formate and a hydrogen ion
	Formate is the principle mediator of morbidity and mortality from methanol poisoning
Elimination	Other routes of methanol elimination include renal (clearance, 5–6 mL/min) and nonrenal (presumed respiratory; 7–13 mL/min) (19, 46)
	Methanol undergoes either first- or zero-order elimination depending on the dose (15–19)
	The apparent elimination half-life of methanol is 2.3–13.7 hr in the absence of antidote therapy (9, 71)
	The inhibition of ADH-mediated metabolism of methanol prolongs its apparent elimination half-life to a mean of 54 hr (9–11) although it may vary between 9 and 87 hr (9–11, 17, 30, 37–39, 78–82)

ADH = alcohol dehydrogenase.

personal libraries, and abstracts from leading clinical toxicology conferences since 2002, to identify other potentially relevant publications.

Each potentially relevant article was reviewed and trained physicians and/or pharmacists extracted relevant data into a preformatted spreadsheet. Publications without original data were excluded (14). These data were audited and interpreted by a smaller multidisciplinary expert group who prepared a summary of the data and proposed recommendations and voting documents for consideration by the entire group. The reviewers followed the principles of the GRADE system to guide assessment of quality of evidence from high (A) to very low (D) and to determine the strength of recommendations as strong (1), weak (2), or neutral (3).

Dialyzability was graded according to predetermined criteria (14). Here, if sufficient pre- or post-ECTR samples were not available, we considered the baseline half-life of methanol during ADH inhibition to be 54 hours based on the mean result in two studies (a similar effect is noted whether ethanol or fomepizole is used) (9–11). A volume of distribution (V_d) of 0.77 L/kg was used for toxicokinetic calculations based on a volunteer study (15). The V_d calculated in other studies ranged between 0.5 and 0.8 L/kg (16–19), depending on assumptions made by these studies, but since the V_d used was at higher end of this range, our calculations represent a conservative estimate.

A two-round modified Delphi method (**Fig. S1**, Supplemental Digital Content 1, http://links.lww.com/CCM/B129) was used to reach a formal consensus on proposed voting statements, and RAND/UCLA Appropriateness Method was used to quantify disagreement between voters (20). Initial anonymous votes with comments were returned to the methodologist who then compiled and returned the synthesis to each participant to allow reflection and debate prior to the second round of voting. A face-to-face meeting was conducted in June 2012 during which evidence summary, statements, vote results, and comments were discussed. Voting was completed in January 2013, and the statistician compiled these results into a summary statistic and provided anonymous comments to the working group for consideration. Statistics included the median score, lower interquartile (LIQ) or upper interquartile score, and disagreement index (DI) (20).

Throughout this process, the group considered the balance between benefits of ECTR and complications, costs, and accessibility. Voting was performed on the understanding that the condition being treated was attributed solely to methanol.

Each of the proposed recommendations for ECTR was contextualized by the strength of the recommendation and level of evidence (**Table 2**).

Proposed recommendations were presented at two clinical toxicology conferences (Asia-Pacific Association of Medical Toxicology, Hong Kong, December 2012 and European Association of Poison Control Centres and Clinical Toxicologists, Copenhagen, May 2013) to seek feedback from experts in the field.

The search strategy was rerun on January 3, 2014, to identify publications since the initial search that were sufficiently high quality to alter the level of evidence and/or recommendations.

CONSENSUS STATEMENTS

Following the two-round Delphi process, recommendations regarding ECTR for the treatment of acute methanol poisoning were determined and these are summarized in **Table 3** along with the strength of the recommendation. In this article, we discuss the rationale and data supporting the indications chosen by the EXTRIP group. The primary results of the voting are listed in **Table S2** (Supplemental Digital Content 1, http://links.lww.com/CCM/B129).

ROLE OF ECTR IN SPECIFIC CLINICAL CIRCUMSTANCES

We recommend ECTR in the following circumstances in a patient with methanol poisoning.

Severe Methanol Poisoning (Grade 1D)

Rationale: Severe methanol poisoning is a life-threatening condition that requires that all available treatments be provided in a timely manner. There is mechanistic evidence supporting a positive effect of ECTR on clinical outcomes.

TABLE 2. 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) (83)
Level 1 = strong recommendation (almost all experts would propose this course of action)	Grade A = high level of evidence (the true effect lies close to our estimate of the effect)
Level 2 = weak recommendation (most experts would propose this course of action)	Grade B = moderate level of evidence (the true effect is likely to be close to our estimate of the effect, but there is a possibility that it is substantially different)
Level 3 = neutral position (some experts would propose this course of action but noncompliance with the recommendation would be fully acceptable in the right context)	Grade C = low level of evidence (the true effect may be substantially different from our estimate of the effect)
No recommendation (no agreement was reached by the group of experts)	Grade D = very low level of evidence (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)

TABLE 3. Role of Extracorporeal Treatment in the Treatment of a Patient With Methanol Poisoning

We recommend ECTR is initiated in the following circumstances:

1) Severe methanol poisoning (grade 1D), including any of:
   a) Coma (grade 1D)
   b) Seizures (grade 1D)
   c) New vision deficits (grade 1D)
   d) Metabolic acidosis from methanol poisoning
      i) Blood pH ≤ 7.15 (grade 1D)
      ii) Persistent metabolic acidosis despite adequate supportive measures and antidotes (grade 1D)
   e) Serum anion gap > 24 mmol/L (grade 1D); calculated by serum $[Na^+] - [Cl^-] - [HCO_3^-]$.

2) Serum methanol concentration
   a) > 700 mg/L or 21.8 mmol/L in the context of fomepizole therapy (grade 1D)
   b) > 600 mg/L or 18.7 mmol/L in the context of ethanol treatment (grade 1D)
   c) > 500 mg/L or 15.6 mmol/L in the absence of an ADH blocker (grade 1D)
   d) In the absence of a methanol concentration, the osmolal/osmolar gap may be informative (grade 1D)

3) In context of impaired kidney function (grade 1D)

To optimize the outcomes from ECTR, we recommend:

4) Intermittent hemodialysis is the modality of choice in methanol poisoning (grade 1D). Continuous modalities are acceptable alternatives if intermittent hemodialysis is not available (grade 1D).

5) ADH inhibitors are to be continued during ECTR for methanol poisoning (grade 1D) as well as folic acid

6) ECTR can be terminated when the methanol concentration is < 200 mg/L or 6.2 mmol/L and a clinical improvement is observed (grade 1D)

ECTR = extracorporeal treatment, ADH = alcohol dehydrogenase.

Possible clinical benefits of ECTR include prevention of toxicity and facilitation of recovery, in particular reversal of neurotoxicity. Formic acid generation (Fig. 1) impacts on outcomes from methanol poisoning, but data supporting a clinically significant increase in elimination of formate by ECTR are lacking (**Table 4**; **online supplement**, Supplemental Digital Content 1, http://links.lww.com/CCM/B129). Clinical features that are consistent with severe methanol poisoning are listed below.

Coma (Grade 1D). *Rationale*: Coma is a marker of severity in methanol poisoning (2, 4–8, 21, 22).

Seizures (Grade 1D). *Rationale*: Seizures are a marker of severity in methanol poisoning (6, 21, 22).

New Vision Deficits (Grade 1D). *Rationale*: New vision deficits are a marker of severity in methanol poisoning, and prompt treatment may allow reversal or halt progression of ocular toxicity (4–8, 21, 22).

TABLE 4. Toxicokinetic Summary of the Effect of Extracorporeal Treatments on the Elimination of Methanol and Formate[a,b]

Type of Extracorporeal Treatment	Methanol Clearance (mL/min)			Methanol $T_{1/2}$ (hr)			Formate $T_{1/2}$ (hr)		
	Average	Range	*n*	Average	Range	*n*	Average	Range	*n*
Intermittent hemodialysis	208	77–400	38	3.4	0.6–13.1	114	3.0	0.6–10.3	39
Sorbent hemoperfusion				6.87	6.87	1	1.0	1	1
Peritoneal dialysis	37	5–70	2	13	2–49	13			
Continuous renal replacement therapy	36.7	17–48	3	8.6	3.5–12	4			

$T_{1/2}$ = half-life.

[a]Patients who had more than one ECTR may appear at more than one place.

[b]Data obtained in the initial search. A subsequent publication reported median half-lives: methanol 3.7 hr by intermittent hemodialysis ($n = 11$) and 8.1 hr by continuous venovenous hemodialysis (filtration) ($n = 13$), and formate 1.6 and 3.6 hr, respectively; both $p < 0.001$ (47).

Metabolic Acidosis From Methanol Poisoning.

Blood pH ≤ 7.15 (grade 1D). *Rationale*: Clinical outcomes relate to the degree of acidemia at admission in patients with methanol poisoning. There is a correlation between admission blood pH, severe outcomes, and serum formate concentration (5–7, 21, 23). Arterial pH values less than 7.0 predicted death in one series (22) while a pH greater than 7.22 predicted survival in another (24); of note, the majority of these patients were treated with ECTR. However, the clinical utility of a single pH criterion for initiating ECTR is limited by the variability within groups classified on the basis of outcome; for example: median pH, 6.78 (range, 6.64–7.29) in deaths; 7.14 (range, 6.75–7.53) in those with permanent disability; and 7.19 (range, 6.65–7.58) in survivors (4). Of note, poor outcomes may relate, in part, to a failure of respiratory compensation for the metabolic acidosis (2, 5–7).

Voting indicated that a higher (more conservative) threshold pH may be accepted in certain circumstances such that we also suggest initiation of ECTR at blood pH 7.15–7.20 (although this was a lower level suggestion at grade 2D compared to the recommendation at blood pH ≤ 7.15).

Persistent metabolic acidosis despite adequate supportive measures and antidotes (grade 1D). *Rationale*: In some cases, administration of sodium bicarbonate with other standard therapies and in the absence of ECTR is associated with acceptable outcomes including an improvement in visual acuity (25–28). However, acidemia may persist despite bicarbonate therapy, requiring administration of large doses, which increases the risk of complications such as tetany, hypernatremia, or volume overload (29). Persistent or refractory metabolic acidosis may suggest delayed presentation following massive methanol ingestion, incomplete inhibition of ADH due to inadequate dosing of ethanol or fomepizole, and/or other metabolic processes.

Benefits of ECTR in the context of persistent metabolic acidosis include rapid bicarbonate replacement without inducing the above-mentioned adverse effects and enhancement of methanol and possibly formate elimination (online supplement, Supplemental Digital Content 1, http://links.lww.com/CCM/B129).

The base deficit may be a better reflection of the severity of metabolic acidosis, and a base deficit greater than 15 mmol/L is a proposed indication for ECTR in methanol poisoning (30, 31). In another study, aggregation of the results of 220 patients predicted death with an odds ratio of 13.1 when the base deficit exceeded 25 (95% CI, 5.1–33.8) although this risk factor was not independent of pH (2). The group did not vote on the role of base deficit, and so this is not an EXTRIP recommendation.

Serum anion gap higher than 24 mmol/L (grade 1D) calculated by serum [Na+] – [Cl^-] – [Hco_3^-]. *Rationale*: The anion gap (AG) correlates with the serum formate concentration (32). Here, an AG of 20 mmol/L is approximately equal to a serum formate concentration of 5 mmol/L (200 mg/L), which has been suggested to be the minimum toxic concentration (33); it should be noted that the normal endogenous concentration of formate is less than 0.3 mmol/L (< 12 mg/L) (33). A systematic review of the literature (119 eligible patients, 21 of whom died) noted a significantly higher mean admission (pretreatment) AG in patients who died compared to survivors (41 and 31 mmol/L, respectively). Here, the AG exceeded 30 mmol/L in each death, and the area under the receiver operating characteristic curve for AG was 0.79 (24).

Voting indicated that a lower (more conservative) threshold serum AG may be acceptable in certain circumstances such that we suggest initiation of ECTR at serum AG of 20–24 mmol/L (although this was a lower level suggestion at grade 2D [median = 7, LIQ = 5.25, DI = 0.37] compared to the recommendation at a serum AG > 24 mmol/L).

Serum Methanol Concentration

a. Greater than 700 mg/L or 21.8 mmol/L in the context of fomepizole therapy (grade 1D);
b. Greater than 600 mg/L or 18.7 mmol/L in the context of ethanol treatment (grade 1D);
c. Greater than 500 mg/L or 15.6 mmol/L in the absence of an ADH blocker (grade 1D);
d. In the absence of a methanol concentration, the osmolal/osmolar gap may be informative (grade 1D).

Rationale: A serum methanol concentration greater than or equal to 300 mg/L (9.4 mmol/L) is often listed as an indication for medical treatment although data supporting this cutoff value are limited (34).

A serum methanol concentration greater than 500 mg/L (15.6 mmol/L) is widely considered an indication for ECTR in acute methanol poisoning (Table S1, Supplemental Digital Content 1, http://links.lww.com/CCM/B129). However, data supporting the clinical relevance of this value are extremely limited.

To our knowledge, 500 mg/L (15.6 mmol/L) was first proposed as a treatment threshold in an observational study by Gonda et al (35) in 1978, but this threshold value was unreferenced and unjustified. By contrast, other investigators have indicated that ECTR is required when the methanol concentration exceeds 1,000 mg/L (31.2 mmol/L) (36, 37).

Most of the publications documented the treatment of patients who had a methanol concentration greater than 500 mg/L (15.6 mmol/L). The evidence supporting the withholding of ECTR for higher methanol concentrations is thus limited, and we were unable to ascertain an upper threshold. However, some authors have suggested that ECTR is not required when the serum methanol concentration is less than or equal to 600 mg/L (18.7 mmol/L) and there is only moderate acidemia (pH, 7.12–7.33) (38). Furthermore, fomepizole may obviate the need of ECTR in poisoned patients referred early with preserved kidney function and in the absence of any neurological or visual impairment (30, 39).

Because inhibition of ADH prevents the toxic complications of methanol poisoning, the serum methanol concentration alone may not be an absolute or precise indication for ECTR. However, an elevated methanol concentration may represent an increased potential for adverse outcomes, for example, in the context of subtherapeutic ethanol concentrations.

The apparent elimination half-life of methanol is variable when its metabolism by ADH is inhibited, but it is generally prolonged with a mean of 54 hours (9–11). A therapeutic ethanol concentration must be maintained until the methanol concentration declines to a nontoxic threshold, usually after a number of days. This can be problematic because ethanol has adverse effects that are poorly tolerated by patients and it requires careful dose titration and frequent monitoring, usually in a high dependency unit. Compared with ethanol, fomepizole reliably inhibits ADH, and in patients with minimal clinical features of methanol poisoning, its use can avoid the requirement for admission to a high dependency unit. This reduces expenses associated with admission to such units, but fomepizole is more expensive than ethanol (12, 30, 40).

The use of ECTR for the treatment of asymptomatic methanol poisoning may be economically favorable and practical (12), which is discussed further in the online supplement (Supplemental Digital Content 1, http://links.lww.com/CCM/B129).

Voting indicated that a lower (more conservative) threshold serum methanol concentration may be appropriate in certain circumstances such that we suggest initiation of ECTR at serum methanol concentration of 600–700 mg/L or 18.7–21.8 mmol/L in the context of fomepizole therapy, 500–600 mg/L or 15.6–18.7 mmol/L in the context of ethanol treatment, or 400–500 mg/L or 12.5–15.6 mmol/L in the absence of an ADH blocker. However, these cutoff values were all a lower level suggestion at grade 2D compared to the recommended cutoffs listed above which were grade 1D.

Unfortunately, methanol assays are not a standard laboratory test in many healthcare institutions across the world. A surrogate measure for the concentration of methanol is the osmolal/osmolar gap (OG; determined by freezing point depression), after accounting for the concentration of ethanol. The OG is more readily available and correlates in an approximately linear relationship with the serum concentration of methanol, where a 20 mOsm/kg H_2O gap is approximately equal to 20 mmol/L (641 mg/L) of methanol (32, 41, 42). Although the reference range for OG is less than 10 mOsm/kg H_2O (43), false-positive results are noted in patients with suspected toxic alcohol poisoning when the OG is less than 30 mOsm/kg H_2O (44, 45). Further, the calculated serum OG can vary depending on the formula and laboratory test platforms used.

A particular OG that would prompt ECTR cannot be recommended or suggested because this was not voted on. However, a number of participants indicated that a suitable indication for ECTR is an OG of 25–30 mOsm/kg H_2O based on recent research (44, 45), and others suggested 20, 40, 50, or 60 mOsm/kg H_2O.

However, it should be recalled that 30 mOsm/kg H_2O correlates with a methanol concentration that exceeds 900 mg/L (28.1 mmol/L). Therefore, treatment should not be withheld in patients with an OG less than 30 mOsm/kg H_2O in whom there is a high index of suspicion of significant methanol poisoning or exposure based on other factors.

In the Context of Impaired Kidney Function (Grade 1D)

Rationale: Renal clearance of methanol is approximately 5–6 mL/min, which is approximately 25–50% of systemic clearance, following inhibition of ADH (19, 46). Elimination of methanol (and probably formate) is prolonged in the context of impaired kidney function. ECTR is recommended in this circumstance to accelerate methanol and formate elimination. A study reporting prognostic factors for methanol poisoning noted that a creatinine of 106 μmol/L was associated with an odds ratio of 15 for death (95% CI, 3.9–58.2) on univariate analysis, but this was not confirmed with multiple regression (2). The EXTRIP definition of impaired kidney function, from the perspective of poison clearance, is defined in the online supplement (Supplemental Digital Content 1, http://links.lww.com/CCM/B129).

Intermittent Hemodialysis Is the Modality of Choice in Methanol Poisoning (Grade 1D): Continuous Modalities Are Acceptable Alternatives If Intermittent Hemodialysis Is Not Available (Grade 1D)

Rationale: Toxicokinetic data were available in 173 patients (**Table 5**) so animal or in vitro studies were not considered; however, data in only 38 patients were of moderate or high methodological quality. In the context of ADH blockade, methanol was considered dialyzable in the vast majority of cases (**Table 6**). Additional toxicokinetic data ($n = 24$) supporting these recommendations were recently published (47). Adequately conducted studies that measured clinical endpoints were not identified. Other data regarding factors that influence extracorporeal clearance and the effect of other modalities are included in the online supplement (Supplemental Digital Content 1, http://links.lww.com/CCM/B129).

TABLE 5. Number of Patients Included in the Review of Clinical and Toxicokinetic Data

Type of Study	Full-Text Articles Obtained	No. of Articles Included in Toxicokinetic Analysis	No. of Patients Included in Toxicokinetic Analysis	No. of Patients Included in Clinical Analysis
Randomized controlled trials	0	0	0	0
Controlled nonrandomized observational studies	15	4	37	458
Case reports/series	190	72	173	546

TABLE 6. Summary of Dialyzability of Methanol by Individual Extracorporeal Therapies

	Methanol			
Degree of Dialyzability	Intermittent hemodialysis	Continuous Renal Replacement Therapy	Peritoneal Dialysis	Sorbent Hemoperfusion
No. of patients with available data				
Dialyzable	131	2	15	1
Moderately dialyzable	3	5	1	
Slightly dialyzable			14	
Not dialyzable			1	

ADH Inhibitors Are To Be Continued During ECTR for Methanol Poisoning (Grade 1D) as well as Folic Acid

Rationale: A variety of methods for administration of ethanol are observed, including IV, enteral, or addition to the dialysate solution. Dosage requires consideration of the patients' history of alcohol intake, and regular blood tests are required for dose titration (48). Ethanol and fomepizole are removed by ECTR, placing the patient at risk of subtherapeutic antidote concentrations and methanol toxicity if the antidote dosage is not increased. In the case of ethanol, the maintenance dosage should be at least doubled and then titrated as required (49). In the case of fomepizole, which is usually administered every 12 hours, a suggested approach in the context of ECTR is to administer the loading dose of 15 mg/kg, followed by an infusion of 1–1.5 mg/kg/hr, or to repeat the loading dose every 4 hours (30).

Early initiation of ECTR following a single dose of fomepizole may have avoided the need for ongoing antidote therapy in three cases (50–52), particularly when there is an early presentation without markers of systemic poisoning such as acidosis. However, the workgroup adopted a conservative approach and voted to continue antidotes during ECTR.

ECTR Can Be Terminated When the Methanol Concentration Is Less Than 200 mg/L or 6.2 mmol/L and a Clinical Improvement Is Observed (Grade 1D)

Voting indicated that in the circumstance that a methanol concentration was not available in a clinically meaningful time, then the OG can be used as a surrogate marker for methanol concentration. However, this was considered a lower level suggestion (grade 2D) compared to the recommendation for methanol concentration (grade 1D). For example, it has been proposed that treatment can be discontinued when OG less than 20 mOsm/kg H_2O on two samples taken at least 1 hour apart and in the absence of acidemia (53).

Rationale: It is not possible to provide an accurate estimation of the duration of ECTR in the absence of details about the starting concentration and rate of removal. It had previously been suggested that an empiric duration of 8 hours of ECTR be prescribed when the amount of toxicant was not known and methanol concentrations or an OG are not available (28, 54), but this can be associated with over- or underdialysis (53). More recently, based on the elimination half-life of formate, an empiric duration of 8 hours for intermittent hemodialysis and 18 hours for continuous modalities has been recommended (47).

Others have stated that ECTR should be continued until resolution of acidemia, correction of the AG, and methanol concentration less than 250–300 mg/L (7.8–9.4 mmol/L) (37, 55) or undetectable (39). ECTR can rapidly correct acidemia in some cases, but an excess of 24 hours may be required in others and acidosis may recur (53, 56). In the case of a patient who was treated with continuous venovenous hemodialysis, acidemia persisted for 5 days (57).

If an empiric duration of hemodialysis between 4 and 8 hours is chosen, acid-base status should be monitored after cessation of hemodialysis to detect recurrence of poisoning which may prompt the reinitiation of hemodialysis. Potentially, the duration of ECTR can be predicted mathematically, see the online supplement (Supplemental Digital Content 1, http://links.lww.com/CCM/B129).

GENERAL CONSIDERATIONS REGARDING THE USE OF ECTR IN THE TREATMENT OF METHANOL POISONING

Publication and Selection Bias

Publication and selection bias were noted in the existing publications so the level of evidence is low and the risk-benefit cannot be defined because of the lack of robust comparative clinical studies. In total, 490 potentially eligible publications were identified of which 205 were included (**Fig. 2** and Table 5).

We did not identify any human randomized controlled trials, and the 15 nonrandomized controlled studies were small or biased due to the selection of controls by indication (**Table S3**, Supplemental Digital Content 1, http://links.lww.com/CCM/B129). The large number of case reports and case series provided information of varying quality. When the search strategy was rerun, there were no new high-quality intervention studies, but a pharmacokinetic study was noted.

Reports describing patients with significant methanol poisoning in whom ECTR was withheld were rare in the last 50 years. When ECTR was withheld, this was because of a relative contraindication to ECTR, for example, shock refractory to vasopressor amines where prognosis was already very poor (6). This prevented us from calculating the relative risk of adverse outcomes from historical cohorts not receiving ECTR. Some

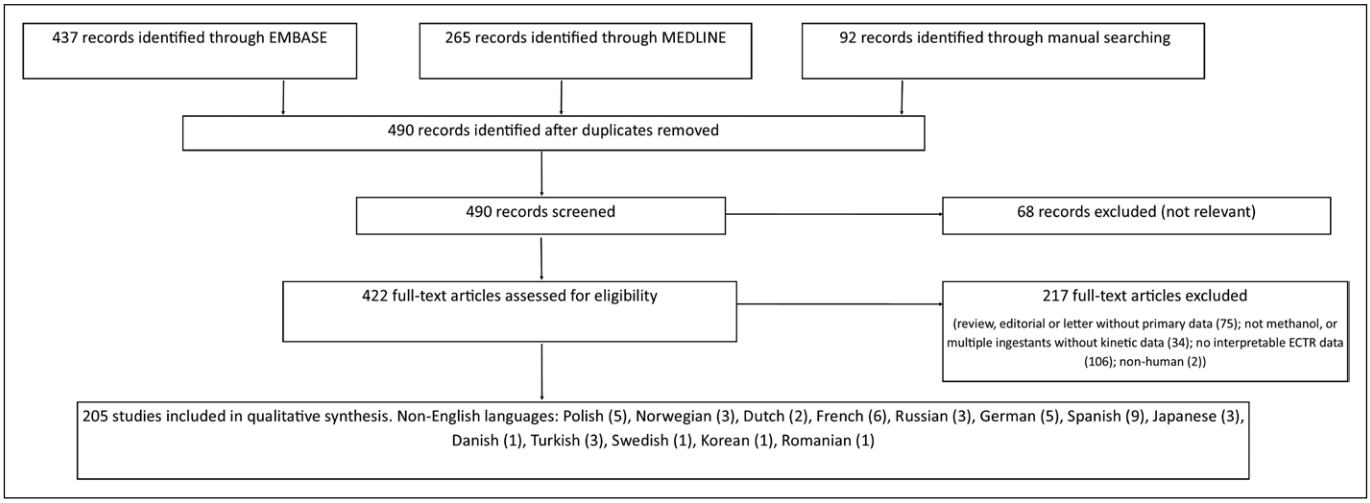

Figure 2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart showing the results of the systematic review. ECTR = extracorporeal treatment.

retrospective studies reported risk factors for death, such as low pH (5–7, 23, 58) or high base deficit (30), but ECTR was administered regardless in most cases.

Influence of ECTR on Clinical Outcomes

Despite the biases and limitations of the available clinical data, the findings of some studies were considered potentially useful for guiding decisions regarding ECTR in methanol poisoning. For example, they provided some evidence supporting the effect of ECTR in reversing acidemia and potentially visual disturbances. However, this observation is not necessarily independent of the effect of coadministered antidotal therapy. Vision deficits also improved in some patients who did not receive ECTR but were administered various antidotes, including ADH blockade (5, 59, 60). Experimental studies in dogs also noted that control animals developed neurological symptoms that subsequently recovered without ECTR (61). Clinical benefits may not be readily realized because baseline neuronal injury (including vision deficits) was incompletely documented in a number of cases due, in part, to an altered level of consciousness at the time of presentation.

Timing of ECTR

Delayed treatment initiation in patients with severe poisoning is associated with significant permanent morbidity and mortality, regardless of the treatment (4–7). However, there are insufficient data to determine which patients are unlikely to benefit from ECTR on the basis of clinical and laboratory features. Although prognostic tools exist, they were not designed with the intent of developing a triage tool, so their performance in this capacity is unclear.

ECTR can be implemented nonemergently when there is adequate ADH blockade and in the absence of acute clinical indications for ECTR. Ethanol (1000 mg/L, 20–30 mmol/L) is a competitive substrate for ADH and fomepizole is a direct inhibitor of ADH, both of which inhibit the formation of formate. This is because the toxicity of methanol is primarily mediated via the production of formate. The serum concentration of formate correlates with severity of metabolic acidosis (10, 32, 62–64) which, in turn, is associated with clinical outcomes in particular mortality (4–6, 22, 23, 37).

Early presentation postingestion, in particular when there is coingestion of ethanol, may be associated with limited features of metabolic acidosis. In the circumstance that ethanol or fomepizole therapy has been promptly initiated to prevent the formation of formate, subsequent ECTR does not need to be initiated urgently. Instead, this can be commenced at a later time, that is, following transfer to a center with ECTR facilities or to allow time for the arrival of dialysis staff. This is supported by a case series in which hemodialysis was withheld in patients with serum methanol concentrations exceeding 4,800 mg/L (150 mmol/L) in the context of therapeutic ethanol concentrations and in the absence of other indications, without apparent adverse effects (65).

Other Potential Indications for ECTR

ECTR is not suggested solely on the basis of a suspected dose of ingestion (grade 2D) because there is a poor correlation between the amount of methanol reported to be ingested and clinical outcomes (25, 28, 66). Further, the simultaneous presence of both a normal AG and OG largely excludes a diagnosis of methanol poisoning so it is reasonable to obtain these investigations prior to planning ECTR. It is anticipated that when such investigations are unavailable that ECTR would also not be available. Therefore, if there is a high index of suspicion of a significant exposure based on the history or symptoms, then ADH blockade should be initiated and the patient would be transferred to another institution for definitive investigation and management.

Consensus was not obtained on all voting items (see the online supplement, Supplemental Digital Content 1, http://links.lww.com/CCM/B129).

Practical Considerations With ECTR and the Triage of Patients

Significant shortcomings in the existing literature imply that the above-mentioned recommendations are not absolute.

The above-discussed factors predict poor outcomes, but this does not necessarily mean that they are useful for the triage and prioritizing of patients to receive fomepizole. This is also reflected in the lack of agreement in terms of absolute and relative indications in the literature (Table S1, Supplemental Digital Content 1, http://links.lww.com/CCM/B129). Therefore, in the absence of the above-mentioned indications for ECTR, the role of ECTR in the treatment of an individual with methanol poisoning should be considered on a case-by-case basis. Further, there may be relative contraindications to ECTR despite fulfilling these indications. For example, clinical features suggesting a moribund state suggest that treatment is unlikely to be useful. Therefore, an individual approach is required in each case and this can be a complex decision process.

If fomepizole is available and the patient is minimally symptomatic, the decision to perform ECTR, and the duration, is an economical one. If fomepizole is not available, then adverse effects and complexity of ethanol therapy preclude a prolonged treatment course, so if ethanol therapy is required for longer than 2–3 days, then ECTR should be considered.

Since alternative methods to enhance the elimination of methanol do not exist, we recommend early communication with a nephrologist in cases of significant methanol poisoning. Of note, in the absence of severe poisoning and if antidote therapy is administered sufficiently early, it is safe and acceptable to delay ECTR to allow for the arrival of dialysis staff or, in some cases, organize safe transfer to another institution. Recognizing the interpatient variability in the elimination half-life of methanol, this may also allow time for serial blood tests to estimate the half-life in that patient, permitting a more accurate assessment of the likely duration of medical care in the absence of ECTR.

Systemic anticoagulation should be avoided because it is possible that administration of anticoagulants may increase the development or severity of intracranial hemorrhage (67). However, ECTR can be performed without systemic anticoagulation by frequent flushing of the ECTR circuit by saline or regional anticoagulation.

Strengths and Limitations

A limitation of these consensus statements is the scarcity of high-quality studies, in particular the lack of randomized controlled trials. However, strengths in the process used to develop these guidelines lead us to conclude that these recommendations are useful. These are the first consensus-based recommendations determined using a rigorous evidence-based literature review that was not limited by language or publication year. Further, expert opinion was obtained through the input of participants of various backgrounds and training, including various specialties from multiple regions across the world and practice settings. Leading relevant clinical societies were engaged in the process.

Future Research Questions

Given the high morbidity and mortality that follow methanol poisoning, mechanistic data supporting the effect of ECTR, and the epidemic nature of methanol outbreaks (often characterized by delayed presentation to hospitals), we anticipate that it will be difficult to conduct randomized controlled trials confirming the efficacy of ECTR. However, further observational studies can provide useful data to assist with decisions about the initiation of ECTR in a given individual, including the triaging of patients in the early stage. Clinical questions that could be addressed in such studies are discussed in the online supplement (Supplemental Digital Content 1, http://links.lww.com/CCM/B129).

CONCLUSIONS

ECTR has been used in the treatment of methanol poisoning since the 1960s. Despite a lack of randomized controlled trials confirming a clinical benefit, ECTR appears to improve biochemical derangements and enhance the elimination of methanol. On this basis, we support the use of ECTR in the treatment of symptomatic methanol poisoning. It remains to be clarified whether or not ECTR enhances the elimination of formate (the principle toxic mediator) and also whether it improves clinical outcomes compared with inhibition of ADH, folate supplementation, and correction of acidemia without ECTR. Regional differences in the cost and availability of fomepizole and ECTR mean that decisions to use ECTR on the basis of economics must be determined at a local level.

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