# Outcomes of Severe Methanol Intoxication Treated with Hemodialysis: Report of Seven Cases and Review of Literature

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*To identify factors associated with the outcome of severe methanol intoxication treated with hemodialysis, we analyzed the clinical course of 7 patients admitted with serum methanol level higher than 50 mg/dL, and therefore requiring hemodialysis. Four patients (group A) had adverse outcomes (1 death, 3 severe neurological deficits and/or blindness) and 3 patients (group B) had no adverse outcomes. Compared to group B, group A appeared to have a longer delay between ingestion of methanol and arrival at the emergency department (ED), a longer wait in the ED until ethanol infusion was started (3.6 ± 2.7 vs 1.3 ± 0.9 hr, p < 0.05), and, on admission, higher serum methanol (504 ± 219 vs 321 ± 228 mg/dL, p < 0.05), higher serum osmolality (460.5 ± 98.2 vs 397.6 ± 52.3 mOsm/kg, p < 0.05), higher serum osmolal gap (162.6 ± 76.7 vs 105.6 ± 52.9 mOsm/kg, p < 0.05), lower arterial pH (6.86 ± 0.08 vs 7.38 ± 0.16, p < 0.01), lower serum bicarbonate (4.6 ± 1.6 vs 19.9 ± 5.7 mmol/L, p < 0.01), and higher serum anion gap (36.5 ± 1.3 vs 14.3 ± 6.7 mEq/L, p < 0.01). Delay in the ED until hemodialysis was started did not differ (group A 6.4 ± 2.6 hr, group B 5.3 ± 3.5 hr), while duration of hemodialysis until serum methanol levels became permanently undetectable was longer in group A (15.0 ± 0.5 vs 8.4 ± 4.4 hr, p < 0.01). The ingested dose of methanol and the delay between ingestion and initiation of therapy to block methanol metabolism (ethanol infusion) and remove methanol from the body (hemodialysis) appear to be the critical factors influencing the outcome of methanol intoxication. Early diagnosis and initiation of treatment before substantial parts of the ingested methanol have been metabolized are of paramount importance in ensuring a favorable outcome.*

## Introduction

Methanol has commercial and industrial uses as a solvent. It is found in paint remover, windshield washing solutions, antifreeze, and fuel for small engines used in various hobbies. It is cheap and has been consumed as a substitute for ethanol because the initial symptoms of methanol intoxication, including drowsiness and inebriation, resemble those of ethanol intoxication. However, methanol intoxication has severe delayed manifestations, including vomiting, vertigo, upper abdominal pain, dyspnea, Kussmaul respiration, blurred vision, dilated pupils with absent light reflex and hyperemia of the optic discs, blindness, and profound coma. Shock, permanent blindness, permanent neurological sequelae, and death may follow severe methanol intoxication [1–3].

The aims of treatment of methanol intoxication are to slow methanol metabolism, to neutralize the toxic effects of methanol metabolites, and to remove methanol from the body. Hemodialysis (HD), which is very effective in removing methanol from the body [4], represents the mainstay of treatment of severe methanol poisoning [1]. The combination of HD and medical treatment has decreased both mortality and permanent neurological sequelae [1]. However, adverse outcomes of severe methanol intoxication are still encountered. The purpose of this report was to identify factors associated with these adverse outcomes.

## Patients and methods

We performed a retrospective analysis of the medical records of patients with severe methanol intoxication requiring HD admitted to the University of New Mexico Hospital and the New Mexico Veterans Affairs Health Care System between 1996 and 2000. This study was approved by the Human Research Review Committee of the University of New Mexico School of Medicine.

Information abstracted from the patient records included ethnic background, gender, age, history of ethanol or substance abuse, reason for the ingestion of methanol, distance from the hospital, time between ingestion and arrival at the emergency department (ED), clinical manifestations on arrival at the ED, delays between arrival at the ED and initiation of medical treatment and HD, pertinent initial physical examination findings and laboratory values, duration and complications of the hospital course, and status at discharge.

Hemodialysis was performed with the use of Bard temporary central vein dialysis catheters (Bard Access Systems, Salt Lake City, UT, U.S.A.), the Gambro Cobe Centrysystem 3 (Gambro Renal Products, Lakewood, CO, U.S.A.) or Fresenius H (Fresenius USA, Concord, CA, U.S.A.) dialysis

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machines, and Fresenius F-80 dialyzers (Fresenius USA, Lexington, MA, U.S.A.).

Serum methanol concentration was determined using gas chromatography Model 3920 (PerkinElmer Inc., Boston, MA, U.S.A.). Serum ethanol concentration was measured using an enzymatic method (alcohol dehydrogenase). Serum electrolytes, urea nitrogen, glucose, and ethanol concentrations were measured on a Vitros 950 instrument (Ortho Clinical Diagnostics, Rochester, NY, U.S.A.). Serum osmolality was determined by freezing point depression (Advanced Instruments Inc., Norwood, MA, U.S.A.). Arterial blood gases were measured using a Radiometer America Inc. instrument (Westlake, OH, U.S.A.).

The identified patients with severe methanol intoxication were divided into two groups: group A consisted of patients with adverse outcomes (death, permanent neurological deficits, permanent blindness); group B consisted of patients without apparent adverse outcomes. Group A was compared to group B. Variables compared were those mentioned in the previous paragraph.

Continuous variables are expressed as mean ± standard deviation. The two-tailed paired t-test was used to compare continuous variables in the same group (before, after treatment), and the two-tailed unpaired Student's t-test was used to compare continuous variables between groups A and B. Categorical variables were compared using Fisher's exact test.

## Results

We identified 7 patients, 2 women and 5 men, that were admitted with severe methanol intoxication and received HD. Four of these patients were Native American, 2 were Hispanic, and 1 was Caucasian. Four patients were residing in Albuquerque and 3 were transferred in from Western Arizona. All 7 patients had a history of ethanol abuse. In addition, 4 patients had a history of other substance abuse, including cocaine, isopropyl alcohol, marijuana, and "household products." Methanol represented a suicide attempt in 3 patients. The remaining 4 patients ingested methanol to get inebriated.

The patients were divided into two groups. Group A consisted of 4 patients with adverse outcomes. One patient in this group died as a consequence of methanol intoxication within 48 hours after admission. Two patients developed both permanent blindness and severe neurological sequelae, including coma with decorticate posture and severe cognitive defect. The fourth group A patient developed permanent blindness. Group B consisted of 3 patients who were discharged from the hospital without apparent adverse outcomes.

Gender (each group contained 1 woman) and distance from the hospital were not different between the groups. Two of the group A patients were Albuquerque residents and the other two were transferred in from a distance exceeding 200 miles. Two group B patients were living in Albuquerque and 1 was transferred in from a distance exceeding 200 miles.

Age of the patients also did not differ between the groups (group A 42.3 ± 9.0 years, group B 41.7 ± 12.3 years).

All patients were intoxicated on admission. All group A patients had Kussmaul breathing. Two group A patients were in deep coma, with dilated pupils not reacting to light, and hyperemic optic discs. One of these 2 patients had severe respiratory distress and hypotension. A third group A patient was seen in the ED twice. In the first visit, the patient was intoxicated, with slurred speech and wide gate, but no other findings. He appeared to improve during his first ED visit and was discharged. He returned 8 hours later with blurred vision, severe abdominal pain, and intractable vomiting, and lapsed into coma soon after arriving in the ED. The last group A patient had dilated pupils and hyperemic optic discs. Inebriation was the only clinical manifestation in the 3 patients in group B.

The time from ingestion of methanol until arrival in the ED could not be determined in 1 group A patient and 1 group B patient. Two group A patients were brought to the ED at least 24 hours after ingestion. One of these 2 patients had been in jail for drunken behavior for several hours before he developed deep coma. The second patient, as noted, was discharged from the ED without a proper diagnosis 8 hours prior to his final admission. The last group A patient was brought to the ED 14.5 hours after ingestion. Two group B patients were brought to the ED 7.5 and 14.5 hours after ingestion.

Table I shows the delays from arrival at the ED until the initiation of ethanol infusion and HD, and the duration of medical treatment and HD. Delay in the ED until ethanol infusion was started was more than twice longer in group A than in group B. This delay was due to delay in confirming the diagnosis of methanol intoxication. Delay until initiation of HD and duration of medical treatment did not differ between the groups. Duration of HD was almost twice as long in group A than in group B. The delays between initiation of ethanol infusion and initiation of HD were due to delays in calling a nephrology consult, arrival of dialysis personnel at the hospital, placement of a HD catheter, and preparation of the HD apparatus.

Table II shows relevant admission biochemistry test results. Group A had higher serum methanol concentration,

TABLE I    Delays in treatment and duration of treatment of 4 patients (Group A) that had adverse outcomes (1 death, 3 severe neurological deficits and/or blindness) and in 3 patients (Group B) that had no adverse outcomes due to severe methanol intoxication.

|  | Group A | Group B | p *Value* |
|---|---|---|---|
| Ethanol infusion initiation[a] (hours) | 3.6±2.7 | 1.3±0.9 | <0.05 |
| Hemodialysis initiation[a] (hours) | 6.4±2.6 | 5.3±3.5 | NS |
| Duration, ethanol infusion (hours) | 32.8±10.9 | 26.6±7.3 | NS |
| Duration, hemodialysis (hours) | 15.0±0.5 | 8.4±4.4 | <0.01 |

[a] Time interval between arrival in the Emergency Department and treatment initiation.

serum osmolality measured by cryoscopy, serum osmolal gap, and serum anion gap, and lower arterial pH and serum bicarbonate concentration than group B. Linear regression of serum osmolal gap on serum methanol level, when group A and group B were analyzed together, was as follows:

Serum methanol level (mmol/L)
 = –3.562 + 0.896(serum osmolal gap), $r = 0.862$, $p < 0.01$.

Arterial $pCO_2$ did not differ between the groups (Table II). All patients in group A had severe metabolic acidosis (highest arterial pH 6.93, highest serum bicarbonate 7 mmol/L). Two of the 3 patients in group B had normal acid–base parameters and 1 had a moderate metabolic acidosis (arterial pH 7.26, serum bicarbonate 13 mmol/L). Serum ethanol levels were undetectable on admission in all 7 patients. Screening for toxic substances, other than methanol, in the blood and urine was also negative in all 7 patients.

Table III shows the comparison of hematological parameters between the admission values and the values obtained in the first blood test after cessation of medical treatment during the second hospital day (final values). Initial hematocrit, hemoglobin, and white blood cell count were higher than the

TABLE II     Admission biochemistry values for 4 patients (Group A) that had adverse outcomes (1 death, 3 severe neurological deficits and/or blindness) and for 3 patients (Group B) that had no adverse outcomes due to severe methanol intoxication.

|  | *Group A* | *Group B* | p *Value* |
|---|---|---|---|
| Serum methanol (mg/dL) | 504±219 | 321±228 | <0.05 |
| Serum methanol (mmol/L) | 148.2±64.4 | 94.4±67.1 | <0.05 |
| Serum osmolality (mOsm/kg) | 460.5±98.2 | 397.6±52.3 | <0.05 |
| Serum osmolal gap[a] (mOsm/kg) | 162.6±76.7 | 105.6±52.9 | <0.05 |
| Arterial pH | 6.86±0.08 | 7.38±0.16 | <0.01 |
| Arterial $pCO_2$ (mmHg) | 31.8±14.9 | 32.3±4.9 | NS |
| Serum bicarbonate (mmol/L) | 4.6±1.6 | 19.9±5.7 | <0.01 |
| Serum anion gap (mEq/L) | 36.5±1.3 | 14.3±6.7 | <0.01 |

[a] Osmolal gap = measured (from depression of freezing point) osmolality (mOsm/kg) – {2 × serum sodium (mmol/L) + [serum urea nitrogen (mg/dL)] / 2.8 + [serum glucose (mg/dL)] / 18}.

TABLE III     Hematology values for 4 patients (Group A) that had adverse outcomes (1 death, 3 severe neurological deficits and/or blindness) and in 3 patients (Group B) that had no adverse outcomes due to severe methanol intoxication.

|  | *Group A* | | *Group B* | |
|---|---|---|---|---|
|  | Admission | Final[a] | Admission | Final[a] |
| Hematocrit (%) | 44.5±7.54 | 33.2±3.7[b] | 38.9±2.3 | 38.5±2.6 |
| Hemoglobin (g/dL) | 14.6±2.2 | 11.3±1.3[b] | 13.2±0.8 | 13.1±0.9 |
| WBC count ($10^3$/mm$^3$) | 15.7±9.8 | 9.5±3.2[c] | 9.1±2.3 | 11.1±5.1 |
| Platelets ($10^3$/mm$^3$) | 266±89 | 274±174 | 204±22 | 235±53 |

[a] First value after the end of hemodialysis and medical treatment for methanol intoxication.
[b] $p < 0.01$.
[c] $p < 0.05$.

corresponding final values in group A, but not in group B. Platelet counts did not differ between the initial and final measurement in either group.

All patients received HD until serum methanol levels became undetectable. In addition, all patients received ethanol infusion for several hours (Table I) and infusion of folinic acid. Blood ethanol levels were monitored frequently and were kept above 100 mg/dL throughout the ethanol infusion. All group A patients and the group B patient who developed metabolic acidosis received sodium bicarbonate infusions. Gastric lavage was performed in 1 group A and 1 group B patient. The group A patient who developed respiratory distress syndrome was maintained on artificial respiration for several hours prior to his death.

One group A patient expired during the second day of hospitalization, with adult respiratory distress syndrome and hypotensive shock. He had completed a prolonged HD procedure on the first day and ethanol infusion had been stopped several hours prior to death. Methanol had been undetectable in serum on repeated measurements several hours prior to death. The remaining 3 patients in group A had prolonged hospital stays ranging between 14 and 62 days, with the first 5 or 6 days spent in intensive care units, and were discharged to highly skilled rehabilitation facilities. Duration of hospitalization in group B ranged between 2 and 3 days, with the first day spent in intensive care units. Group B patients were discharged home.

## Discussion

Methanol is a hydrophilic small molecular weight substance readily absorbed from the gastrointestinal tract. Peak blood levels are obtained between 30 and 90 minutes after ingestion, and methanol volume of distribution is approximately equal to body water [1]. These characteristics make methanol easily dialyzable. Marc-Aurele and Schreiner reported high clearances of methanol by HD [4]. Peritoneal dialysis provides lower clearances of methanol than HD [5], but could be used if HD is not feasible.

In humans, methanol elimination through respiration or urinary excretion is small. More than 90% of ingested methanol is metabolized in the liver [6]. Hepatic alcohol dehydrogenase slowly oxidizes methanol to formaldehyde. Formaldehyde is further oxidized to formic acid by aldehyde dehydrogenase and other enzymes [7]. The half-life of methanol in severe intoxication exceeds 24 hours. A blood ethanol level in excess of 100 mg/dL competitively inhibits methanol metabolism and greatly prolongs the half-life of methanol [1].

Like other alcohols, ingestion of methanol causes inebriation. Unlike ethanol, however, the products of methanol metabolism (formaldehyde, formic acid) can cause permanent toxicity, including severe retinal and neural tissue damage [8,9]. Using imaging techniques, lesions in the white matter, putamen, and basal ganglia are seen in patients with neurological deficits after methanol intoxication [10,11].

Early manifestations of methanol intoxication are similar to ethanol inebriation and may improve temporarily. Later manifestations, discussed in the Introduction, follow a lucid interval of several hours and are severe [1]. Metabolic acidosis with an increased serum anion gap develops simultaneously with the delayed clinical manifestations [12]. The major anions accounting for the anion gap are formate and lactate [13]. Pancreatitis may also develop [14,15]. In an analysis of 323 cases of methanol intoxication, Bennett *et al.* reported a case fatality rate of 12.5% prior to the use of HD [16].

Winchester has standardized the principles of treatment of methanol intoxication [1]. We followed these principles in this study. Gastric lavage is indicated if the patient is seen early. Ethanol administration is the principal medical treatment, aiming at slowing the metabolism of methanol. Intravenous infusion of 10% ethanol in 5% glucose solution, with a loading dose of 0.6 g/kg, which will provide an equilibrated blood ethanol level around 100 mg/dL [17], followed by an infusion sufficient to maintain this blood ethanol level, should be started as soon as possible. The maintenance dose of intravenous ethanol may vary substantially between individuals, is higher in drinkers than in non-drinkers, and is best established by monitoring blood ethanol levels. Ethanol infusion may be the only intervention required in patients with initial plasma methanol level less than 20 mg/dL [18].

Acidosis with serum bicarbonate less than 15 mmol/L and arterial pH less than 7.35 requires administration of sodium bicarbonate [19]. Folinic acid is used because it was found, in experimental animals, to enhance the metabolism of formic acid to carbon dioxide and water [20].

Pyrazole compounds inhibit alcohol dehydrogenase. Fomepizole (4-methylpyrazole), which is used to treat ethylene glycol poisoning, is a potent and relatively safe inhibitor of alcohol dehydrogenase, has a long half-life, and has recently been used to treat methanol poisoning [21–23]. This compound was reported to reverse central blindness in a patient with methanol intoxication and moderately severe acidosis (arterial pH 7.19) [24]. In another report, 4 patients with initial serum methanol level greater than 50 mg/dL and no visual abnormalities were treated with fomepizole and no HD and recovered fully, while 4 other patients with visual abnormalities at presentation were treated with both fomepizole and HD, and with only partial remission of the visual abnormalities [25]. Fomepizole inhibits formation of acetaldehyde and formic acid from methanol, but also has no effect on the metabolism of already formed acetaldehyde or formic acid, and consequently does not have any influence on the toxic effects of these compounds. Thus, fomepizole may replace ethanol but not, usually, HD, which will be needed to rapidly remove acetaldehyde and formic acid if these compounds are present in the blood.

Fomepizole can be taken orally, but its preferred method of administration to intoxicated patients is by slow intravenous infusion (over 30 minutes) of the medication diluted in normal saline or 5% dextrose in water. The loading dose is 15 mg/kg, followed by maintenance doses of 10 – 15 mg/kg every 12 hours until the serum methanol concentration decreases to levels below 10 mg/dL. Fomepizole is dialyzable; consequently, concomitant use of dialysis and fomepizole requires dosing of the drug every 4 hours. The use of fomepizole is contraindicated in patients with known serious hypersensitivity to pyrazole compounds. The side effects of the drug may include neurological symptoms (seizures, vertigo, confusion, slurred speech, headache), digestive symptoms (abdominal pain, vomiting, diarrhea, altered taste), cardiovascular symptoms (dysrhythmia, hypotension), eosinophilia, and rash and phlebitis at the site of the injection.

Fomepizole is approved for the treatment of methanol poisoning in Canada and the United States, and is available in most European countries and in Japan (information from the manufacturer). In the United States, fomepizole is dispensed as Antisol (Orphan Medica, Minnetonka, MN, U.S.A.). The cost of a four-vial pack, which is sufficient for the treatment of a 70 kg man (not placed on HD), is $4,600. If HD is used along with fomepizole, the cost of the latter increases because of the need to repeat the injections frequently.

Hemodialysis has been the principal treatment for removing methanol from the body [26], rapidly clearing methanol, as well as its principal metabolites formaldehyde and formic acid [4]. Rebound increases in serum methanol levels may develop after premature discontinuation of HD. Winchester recommends initiation of HD if methanol levels exceed 50 mg/dL [1]. Initial serum methanol levels in the patients of the present study were more than 50 mg/dL. Dialysate containing bicarbonate is preferable. Ethanol clearance through the dialyzer is similar to that of methanol. To prevent decreases in serum ethanol levels during HD, either an increase in the dose of infused ethanol or addition of ethanol to the dialysate [27–29] is indicated. Pharmacokinetic principles can be applied to determine the duration of HD [17,30,31].

Despite potent means of removing methanol from the body and favorably modifying its metabolism, adverse outcomes of methanol intoxication are still encountered [3]. Our purpose was to identify potentially reversible factors contributing to these adverse outcomes. We want to stress the following points: prevention of methanol intake by education of populations at risk and other public health measures should be the primary focus of health care services; and, although the number of subjects in this study was small, its findings agreed, in general, with those of other studies. Therefore, we feel confident that our findings do not represent aberrant observations.

One factor that may contribute to the toxicity of methanol is the dose ingested. In the present study, the group with adverse outcomes had substantially higher blood methanol levels on admission (Table II) and longer time intervals between ingestion and admission. Therefore, this group unequivocally ingested a larger dose of methanol than the group

without adverse outcomes. The dose of ingested methanol is not a factor that could be modified by the health-care providers managing the intoxicated patient.

Prompt initiation of treatment can lead to survival of patients with extreme overdoses of methanol [32]. Delay in the initiation of specific treatment until after the severe sequelae have become established is the second important factor affecting the outcome of methanol intoxication. Patients with adverse outcomes were admitted with ophthalmologic and neurological complications, profound acidemia (Table II), and evidence of hemoconcentration (Table III), all of which, in addition to being predictors of poor outcomes, are signs of delays in seeking medical care [1,33]. The major delay in initiation of treatment was the time interval between ingestion and arrival at the ED. In 2 of the 4 patients with adverse outcomes, this time interval was prolonged because of misdiagnosis. The wait in the ED until the start of ethanol infusion was also longer in the group with adverse outcomes (Table I). Initiation of HD is inevitably delayed by the process of preparation for this procedure.

Presumptive diagnosis of methanol intoxication and initiation of treatment prior to the development of retinal and neurological complications and acidosis are of paramount importance. We suggest that treatment with ethanol, fomepizole, and folinic acid infusion should be started prior to the confirmation of methanol intoxication in patients in whom there is a reasonable level of suspicion. Police or paramedics, who are usually the first to see intoxicated patients, should be trained about the need for early intervention and the epidemiology and clinical signs of methanol intoxication. A methanol breath test [34] will greatly facilitate early diagnosis of methanol intoxication. Until this test is widely applied, performance at the initial encounter of a breath ethanol test, which provides a reasonable approximation of both blood ethanol level and the total dose of ethanol ingested [35,36], and calculation of the serum osmolal gap may provide enough evidence to justify initiation of treatment. The osmolal gap requires measurement of serum osmolality, sodium, urea nitrogen, and glucose. The methodology and equipment for measuring the biochemistries needed to determine osmolal gap are available in every hospital laboratory.

Osmolal gap is the difference between osmolality measured by cryoscopy and osmolality estimated as the sum of the osmotic contribution of normal serum solutes. As indicated in Table II, osmolal gap is calculated as follows:

$$\text{Osmolal gap} = \text{measured osmolality (mOsm/kg)} - \{2 \times \text{serum sodium (mmol/L)} + [\text{serum urea nitrogen (mg/dL)}] / 2.8 + [\text{serum glucose (mg/dL)}] / 18\}.$$

High values of osmolal gap ($> 10$ mOsm/kg) indicate the presence of high concentrations of usually exogenous small molecular weight substances in the plasma. Concomitant ingestion of ethanol and methanol is rather frequent. In a patient with ethanol intoxication, the osmolal gap formula can be modified to show the presence of a second small molecular weight solute (*i.e.*, methanol) as follows:

$$\text{Osmolal gap} = \text{measured osmolality (mOsm/kg)} - \{2 \times \text{serum sodium (mmol/L)} + [\text{serum urea nitrogen (mg/dL)}] / 2.8 + [\text{serum glucose (mg/dL)}] / 18 + [\text{serum ethanol (mg/dL)}] / 4.6\}.$$

Ethanol concentration in exhaled air can be substituted for serum ethanol concentration in the second formula.

In experimental studies, the osmolal gap provides a very accurate estimate of the molar concentration of ingested alcohols [37]. In clinical practice, the osmolal gap may be insensitive in detecting methanol intoxication [38], if the measurement of serum osmolality is inaccurate and if patients are evaluated late, after methanol metabolism has been completed [39]. The clinical use of osmolal gap is as a means of early screening of intoxication. Calculation of osmolal gap as soon as the patient is seen negates the second criticism. To address the first criticism, we tested the agreement between osmolal gap and simultaneously measured serum methanol levels. Mean osmolal gap and serum methanol, expressed in millimoles per liter, were close (Table II). In addition, regression of osmolal gap on serum methanol levels revealed reasonable agreement. Therefore, we suggest that the osmolal gap, properly used, is of assistance in determining ingestion of large amounts of small molecular weight substances other than ethanol. In such patients, the finding of an increased osmolal gap should be a signal for immediate initiation of medical treatment and a call to the nephrologist while awaiting verification of the nature of the substance ingested.

In conclusion, methanol intoxication may have adverse outcomes even in patients treated appropriately with ethanol infusion and hemodialysis. Delay in the diagnosis leads to adverse outcomes. Early suspicion of methanol intake and screening by the concomitant determination of blood ethanol concentration in a breath test and of the serum osmolal gap will lead to timely initiation of treatment, including hemodialysis, and could improve the outcome of methanol intoxication.

### Acknowledgment

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