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Czech mass methanol outbreak 2012: Epidemiology, challenges and clinical features

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Objectives. Methanol poisonings occur frequently globally, but reports of larger outbreaks where complete clinical and laboratory data are reported remain scarce. The objective of the present study was to report the data from the mass methanol poisoning in the Czech Republic in 2012 addressing the general epidemiology, treatment, and outcomes, and to present a protocol for the use of fomepizole ensuring that the antidote was provided to the most severely poisoned patients in the critical phase. *Methods.* A combined prospective and retrospective case series study of 121 patients with confirmed methanol poisoning. *Results.* From a total of 121 intoxicated subjects, 20 died outside the hospital and 101 were hospitalized. Among them, 60 survived without, and 20 with visual/CNS sequelae, whereas 21 patients died. The total and hospital mortality rates were 34% and 21%, respectively. Multivariate regression analysis found pH < 7.0 (OR 0.04 (0.01–0.16), $p < 0.001$), negative serum ethanol (OR 0.08 (0.02–0.37), $p < 0.001$), and coma on admission (OR 29.4 (10.2–84.6), $p < 0.001$) to be the only independent parameters predicting death. Continuous hemodialysis was used more often than intermittent hemodialysis, but there was no significant difference in mortality rate between the two [29% ($n = 45$) vs 17% ($n = 30$), $p = 0.23$]. Due to limited stockpiles of fomepizole, ethanol was administered more often; no difference in mortality rate was found between the two [16% ($n = 70$) vs. 24% ($n = 21$), $p = 0.39$]. The effect of folate administration both on the mortality rate and on the probability of visual sequelae was not significant (both $p > 0.05$). *Conclusions.* Severity of metabolic acidosis, state of consciousness, and serum ethanol on admission were the only significant parameters associated with mortality. The type of dialysis or antidote did not appear to affect mortality. Recommendations that were issued for hospital triage of fomepizole administration allowed conservation of valuable antidote in this massive poisoning outbreak for those patients most in need.

Keywords Methanol poisoning; Epidemiology; Symptoms; Prognosis; Treatment; Outcomes

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Introduction

Mass methanol poisonings have represented a challenge for healthcare providers throughout the world since the 19th century.[1–4] Morbidity and mortality in methanol

poisonings remain high, timely diagnosis is difficult, and the onset of treatment is therefore often delayed.[5,6] The treatment consists of inhibition of alcohol dehydrogenase (ADH) with ethanol or fomepizole, correction of acidosis, folinic acid administration, and hemodialysis.[7]

In spite of the fact that mass or cluster methanol poisonings as a result of its use as a cheap substitute for ethanol occur rather frequently globally, mainly in the developing countries, reports of larger outbreaks where complete admission clinical and laboratory data, medical treatment protocols, and outcomes accurately documented and analyzed are scarce.[1,2]

In this study, we report data from the recent methanol mass poisoning in the Czech Republic in 2012 addressing the general epidemiology, laboratory- and clinical features, treatment, and outcomes from the outbreak.

Description of the outbreak

The following description of the outbreak is based on the data the authors obtained both directly, working on the daily basis in the *ad hoc* monitoring group established by the Ministry of Health (MoH) under the public health crisis preparedness section and collecting the information on-site, and indirectly, from mass media and medical reports. Methanol poisonings have been rare in the Czech Republic for more than 60 years, until September 2012. In August 2012, ten thousands liters of toxic spirits containing mixture of 33% of ethanol and 66% of methanol were produced in Zlin region by three Czech entrepreneurs with windshield liquids and further distributed to several illegal producers of strong alcoholic beverages; all of the specimens were mixed and bottled outside the facilities of legal producers.[8]

The liquor looked identical to original bottles of rum, vodka, and local spirits (plum brandy "Slivovitz", rum "Tuzemak", apricot brandy "Merunkovice", and others). All samples of toxic alcohol contained mixtures of methanol and ethanol, but the final proportion varied substantially, from 20% methanol/80% ethanol to 50% methanol/50% ethanol, in different kinds of strong alcoholic beverages with an alcohol content of around 40% ABV (alcohol by volume, or v/v). The toxic liquor was sold not only on the black market, but also in conventional stores.

The first three cases of methanol poisoning occurred on 2 September 2012 in the northeastern part of the Czech Republic (the Moravian-Silesian region); subsequently patients were soon found in 11 regions throughout the country (Fig. 1), as well as abroad. These three patients were admitted in severe condition on 3 September, but no methanol was found on admission, and the formate analysis was not available at this point of time; one of these patients died upon admission, and the other two died after a few hours. The diagnosis of methanol poisoning was later found to be the cause of death in the Forensic Institute. The next patients were admitted on 6 September, when the Czech Toxicological Information Center (TIC) and the MoH were informed and they started to monitor the situation in all hospitals throughout the country on a daily basis. A warning was issued nationwide, and mandatory reporting was initiated. A standardized registration form was sent to all hospitals from the TIC for a prospective registration of the patients.

The patients were treated in 30 different hospitals with available hemodialysis facilities in 11 regions of the Czech Republic. For laboratory confirmation of poisoning, quantitative serum methanol analysis was available in 15 toxicological and/or forensic laboratories of the regional university hospitals in 12 regions. Two departments of forensic medicine performed quantitative formate analysis in biological samples and autopsies using gas chromatography, whereas the enzymatic method of formate analysis supplemented this after the outbreak had started.

The antidote fomepizole was recently (2013) added to the WHO Essential Medicines List, but the availability, especially in the developing world, is still limited. Until September 2012,[9] fomepizole was not registered in the Czech Republic. On the 12th of September, the TIC asked the MoH for emergency permission for the distribution of fomepizole. The MoH issued permission the same day,

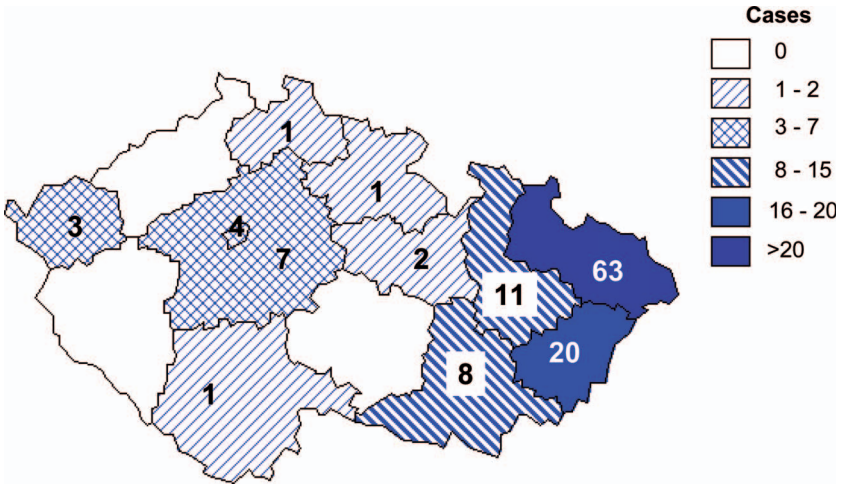


Fig. 1. "Situation map" of the methanol outbreak in the Czech Republic September-December 2012 (the administrative division of the country on 13 regions and the capital is shown by the contour lines) (colour version of this figure can be found in the online version at www.informahealthcare.com/ctx).

and from the following day, fomepizole was supplied to hospitals.

On 14 September, the MoH issued a prohibition of sales of strong alcoholic beverages containing more than 20% v/v (ABV) ethanol. This action, along with active mass media warning of the event, was followed by a significant decrease in the number of cases during the next weeks (Fig. 2). During the week 37 (10–16 September), there were 41 cases of poisoning; that week the prohibition was announced on Thursday, 14 September; during the next week (week 38) (17–23 September), there were only 15 cases of poisoning, i.e. number of cases reduced to one third.

There was a significant reduction in the number of cases of methanol poisonings in 2013 (12 cases) and during the first 6 months of 2014 (4 cases). The number of victims were likely reduced by a combination of the following factors: the ban of spirits, the police prompt action (the network of illegal production and distribution of toxic spirits had already been revealed in September 2012, and 80% of bottles with adulterated alcoholic beverages had been recovered by the police before they were sold to the consumers), and the effective spread of information through many channels. The experience from the Norwegian mass methanol poisoning in 2002–2004 indicated a possibility of sporadic cases of poisoning during a long period after the main bulk of the outbreak. According to the police reports, approximately 2000 liters of toxic spirits had not been recovered, but kept in private stocks.

Methods

Patients and procedures

Patients admitted to hospital during 2012 (September through December) were included in this study. The cases of acute methanol poisoning in the Czech Republic after 2012 ($n = 15$ from January 2013 to June 2014), and the cases of poisoning in Poland ($n = 8$ in 2012) and Slovakia ($n = 7$ in 2012) from the same source of methanol are not included here. A protocol for collection of data based on experience from a methanol outbreak in Norway in 2002–2004 was used.[1] The discharge reports of all hospitalized patients with a confirmed diagnosis and the results of neurological and ophthalmological examinations on admission, during hospitalization, and on discharge were collected and analyzed in the TIC. A detailed record of history of poisoning and the onset and dynamics of signs and symptoms of ocular and systemic toxicity were obtained either directly from the patients or from relatives of critically ill patients, upon admission. The patients who died outside hospital ($n = 20$) were diagnosed as methanol poisoning upon autopsy. No further data are presented on these victims.

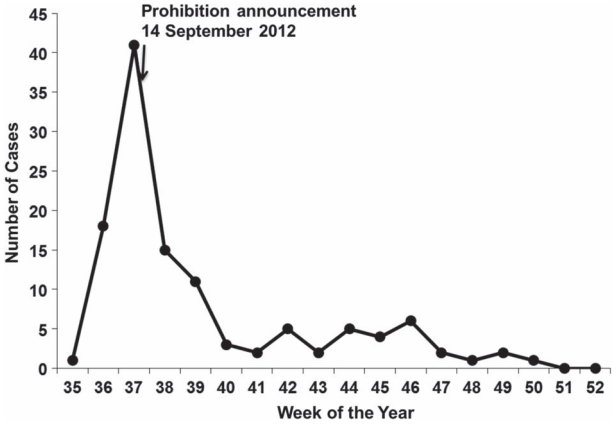


Fig. 2. Time frame of the methanol outbreak from September-December 2012.

Various laboratory analyzes were performed on admission (see Table 1). The urine was tested qualitatively for the presence of methanol and its metabolites.[10] Diagnosis was made when (i) a history of recent ingestion of illicit spirits was available and serum methanol was higher than 20 mg/dL (6.24 mmol/L) and/or an osmolal gap ≥ 20 mOsm/kgH_2O (that could not be explained by ethanol) was found, or (ii) there was a history/clinical suspicion of methanol poisoning; serum methanol was above the limit of detection with at least two of the following: pH < 7.3, serum bicarbonate < 20 mmol/L (20 mEq/L), and anion gap (calculated with potassium) ≥ 20 mmol/L (20 mEq/L).

The clinical examination protocol included complete ocular examination with standard ophthalmologic tests (visual acuity, visual fields, color vision, contrast sensibility, fundoscopy), cerebral computed tomography (CT) in symptomatic patients, and standard neurological examination. The patients were considered to have visual sequelae (VS) of acute methanol poisoning if the symptoms of toxic neuropathy of the optic nerve were documented on admission/during hospitalization, with pathologic findings on visual acuity, visual fields, color vision, and contrast sensitivity, or persisting lesions on fundoscopy with other symptoms of visual damage on discharge from the hospitals. The patients were considered as having CNS sequelae of poisoning if the symmetrical necrosis and hemorrhages of basal ganglia were present on computed tomogram of the brain. The hospitalized patients were divided into three groups according to the outcome: Group I: Survivors without sequelae; Group II: Survivors with visual and/or CNS sequelae; Group III: Patients who died.

Treatment

Bicarbonate was given as a buffer to patients with metabolic acidosis aiming at full correction; ethanol and/or fomepizole were given as antidotes. Uniform indications were applied for antidotal treatment and elimination techniques according to the AACT/EAPCCT practice guidelines on the treatment of methanol poisoning.[7]

Because there was a limited availability of fomepizole, the following antidote-saving approach was used: a) if fomepizole was not available, the standard scheme of ethanol administration to rapidly achieve the protective serum concentration of 100–150 mg/dL (21.7–32.6 mmol/L) was initiated as soon as possible. In cases of severe poisoning, fomepizole could be sent to the patient;

Table 1. Laboratory data on admission on 101 hospitalized patients according to the outcome groups (medians, ranges, IQR).

	Age [Years]	Serum-Methanol [mmo/L]	Serum-Ethanol [mmo/L]	Serum-Formate [mmo/L]	Serum-Lactate [mmol/L]	pH	pCO_2, [kPa]	HCO_3, [mmol/L]	BD [mmol/L]	AG, [mmol/L]	S-glucose [mmol/L]	Time to treatment [hours]
Group I	53	21.7	3.0	10.6	2.1	7.31	4.35	17.8	− 6.1	22	6.4	32
($n = 60$)	23–74	0–228.1	0–96.8	0–22.5	0.7–12.8	6.67–7.46	0.97–6.55	2.0–27.2	− 0.1– − 38.1	11–58	4.4–24.5	7–96
	24	36.9	18.3	14.7	1.6	0.25	1.42	14.0	− 18.0	12	1.9	28
Group II	53	43.9	0.0	14.4	5.9	7.02	3.2	5.1	− 21.0	32	9.6	42
($n = 20$)	33–73	6.2–218.5	0.0–49.5	8.9–21.2	0.5–16.3	6.65–7.39	1.3–5.2	2.5–18.7	− 6– − 36	17–50	5.5–19.8	12–72
	20	33.1	11.7	4.6	5.1	0.42	1.5	7.5	− 15.0	8	6.3	22
Group III	57	29.0	0.0	15.5	9.5	6.75	4.4	5.2	− 29.0	39	12.5	48
($n = 21$)	16–79	0–148.9	0.0–0.0	5.2–25.2	0.9–19.4	6.57–7.32	1.2–11.5	2.2–13.4	− 11–36	19–49	2.9–21.6	24–72
	17	37.3	0.0	3.2	6.4	0.28	1.8	4.0	− 7.0	10	6.3	39
Total ($n = 101$)	53	27.8	0.0	13.4	3.1	7.20	4.23	9.1	− 17.0	28	7.3	48
	16–79	0.0–228.1	0.0–96.8	0–25.2	0.5–19.4	6.57–7.46	1.0–11.5	2.0–27.2	− 0.1– − 38	11–58	2.9–24.5	7–96
	22	41.6	11.0	10.9	6.1	0.46	2.0	16.5	− 23.0	17	5.0	24
$P_{I=II}$	0.275	0.044*	0.188	0.001*	0.002*	< 0.001*	0.016*	< 0.001*	< 0.001*	0.009*	0.003*	0.414
$P_{I=III}$	0.235	0.711	< 0.001*	0.074	< 0.001*	< 0.001*	0.141	< 0.001*	< 0.001*	< 0.001*	< 0.001*	0.134
$P_{II=III}$	0.921	0.167	< 0.001*	0.968	0.020*	< 0.007*	0.616	0.194	0.009*	0.106	0.187	0.501

Group I – survivors without sequelae, Group II survivors with sequelae, Group III died.
BD, base deficit; AG, anion gap; OG, osmolal gap; IQR, interquartile range.
$P_{I=II}$, $P_{I=III}$, $P_{II=III}$ – results of Chi^2 test of difference in laboratory parameters between the Groups I, II, and III ((statistically significant differences).
To convert from mmol/L to mg/dL use the following conversion factors: methanol – 3.205; ethanol – 4.608; formate – 4.603; lactate – 9.009; glucose – 18.018. To convert bicarbonate and base deficit from mmol/L to mEq/L use the conversion factor 1.0. To convert kPa to mmHg (torr) use the conversion factor 7.501.

b) fomepizole treatment was prioritized in patients with serum methanol higher than 50 mg/dL (15.6 mmol/L) [or formate higher than 40 mg/dL (8.9 mmol/L)] and pH ≤ 7.0, or methanol higher than 30 mg/dL (9.4 mmol/L) and pH ≤ 7.0 in patients unable to hyperventilate ($pCO_2 > 3.07$ kPa or 23.0 mmHg); c) treatment with fomepizole was stopped and followed by ethanol administration when methanol concentration decreased below 30 mg/dL (9.4 mmol/L) given a normal pH, or 20 mg/dL (6.2 mmol/L) if metabolic acidosis was not yet corrected. The rationale for this approach was to decrease the risk of incomplete ADH blocking by possible fluctuations of ethanol levels in the most severely poisoned patients, especially during hemodialysis, and to avoid respiratory depression caused by ethanol in patients hyperventilating to compensate the acidosis.

Hemodialysis was performed if the patients filled any of the following criteria: serum methanol higher than 50 mg/dL (15.6 mmol/L), metabolic acidosis with a pH < 7.30, or had visual toxicity.[11] The mode of dialysis, intermittent hemodialysis (IHD) or continuous veno-venous hemodialysis/hemodiafiltration (CVVHD/HDF), was based on several factors, such as the hemodynamic stability of a patient on admission, or the severity of poisoning, but availability also played an important role; some smaller hospitals had only CVVHD/HDF available in the anesthesiology departments, whereas larger hospitals usually also had IHD available.

Laboratory investigations

Methanol was measured by a gas chromatographic method with flame ionization detection and a direct injection with internal standard (Gas Chromatograph Chrom 5, Laboratory Instruments Prague, Czech Republic), limit of detection 6 mg/dL (1.9 mmol/L) and day-to-day coefficient of variation 2.5–5.4%. Calibrators and controls were made by dilution of methanol p.a. (Penta, Czech Republic). Formate was measured enzymatically on a Hitachi analyzer (Hitachi 912, Hitachi Science Systems Ltd., Japan) using formate dehydrogenase (Roche, France) and nicotinamide adenine dinucleotide (NAD) (Roche, France), according to a previously published method.[12–14] Pure sodium formate (Sigma-Aldrich, USA) was used to prepare a standard of 4.6 mg/dL (1.0 mmol/L) in phosphate buffer and two control sera. Day-to-day coefficient of variation was 5.6%, and the upper reference limit was 2 mg/dL (0.44 mmol/L).

Serum ethanol was analyzed by gas chromatography with flame ionization detection and direct injection with an internal standard (Gas Chromatograph Chrom 5, Laboratory Instruments Prague, Czech Republic). The limit of detection was 4 mg/dL (0.87 mmol/L), and the day-to-day coefficient of variation was 3.8–7.1%. Ethanol standards were purchased (Erba Lachema, Czech Republic). Osmolality was measured by freezing point depression method on a Fiske one-ten osmometer. The reference range for the osmolal gap was − 9–19 mOsm/kg H_2O.[15] The osmolal contribution from ethanol was subtracted from the measured osmolality.

Statistical analyses

The admission laboratory data in the different groups were compared on a group by group basis using Two-Sample Assuming Unequal Variances (Equal Means), Two-sample F-Test for Variances, Bias test, and two-sample Kolmogorov–Smirnov test. Data are expressed as medians with range and arithmetic means with confidence interval, as appropriate. For comparison of the obtained results, common statistical tests have been used (t-Test: Two-Sample Assuming Equal Variances, t-Test: Two-Sample Assuming Unequal Variances (Equal Means), Two-sample F-Test for Variances, Bias test, and ANOVA).

Multivariate logistic regression was used to evaluate the different independent variables for mortality, whereas cumulative logit proportional odds model was used for various sequelae. The p-values were based on the likelihood-ratio tests. For the multivariate regression analysis, the whole population of 101 hospitalized patients was used without stratification.

All statistical calculations were carried out with a level of significance $\alpha = 0.05$. The calculations were performed using the R software, version 3.0.2. The cumulative logit models were fitted using the R package VGAM. The ROC analysis was performed using the R packages ROCR and pROC.

Ethics

The procedure of the study was approved by the General University Hospital Ethics Committee in Prague, Czech Republic.

Results

A total of 121 cases of methanol poisoning occurred during the period from 3 September 2012 until 1 January 2013 (Fig. 3). One hundred and one patients with a median age of 54 (range 16–79) years were treated in hospitals. Among the 101 hospitalized patients, there were 80 males, with a median age of 53 (range 23–79) years, and 21 females, with a median age of 57 (range 16–69) years.

Only 11% ($n = 11$) of the patients were admitted within 12 h after the methanol ingestion, 35% ($n = 35$) within 48 h, and 37% ($n = 37$) later than 48 h. In 18% ($n = 18$) of the cases, it was impossible to identify the time between the consumption of toxic spirits and admission to hospital. All of the patients who died were admitted more than 24 h after ingestion. According to the history from the discharge reports, 56% of the hospitalized patients were daily alcohol abusers. The type of toxic alcohol was known in 78 cases, and the approximate quantity in 67 cases. The median amounts of toxic spirits (volumes of the formulated spirits) consumed by males was 450 ml (range 100–1500 ml) and by females 200 ml (range 80–500 ml). Twenty-five (31%) of the males but only one female (5%) co-ingested other alcoholic beverages (wine, beer, whisky, home-made spirits) concomitantly ($p < 0.05$).

Admission laboratory data

Forty-one patients had detectable ethanol before hospital antidote treatment, with a median concentration of 65 mg/dL (8–446 mg/dL), that is, 14.1 mmol/L (1.7–96.8 mmol/L). Thirty of them were administered ethanol as a "first aid antidote" by ambulance medical staff during the transfer to a hospital. Six patients were not tested for serum ethanol before the antidote treatment was started. Laboratory data from the patients divided into the three outcome groups are given in Table 1. Three patients were found with negative methanol levels and positive formate

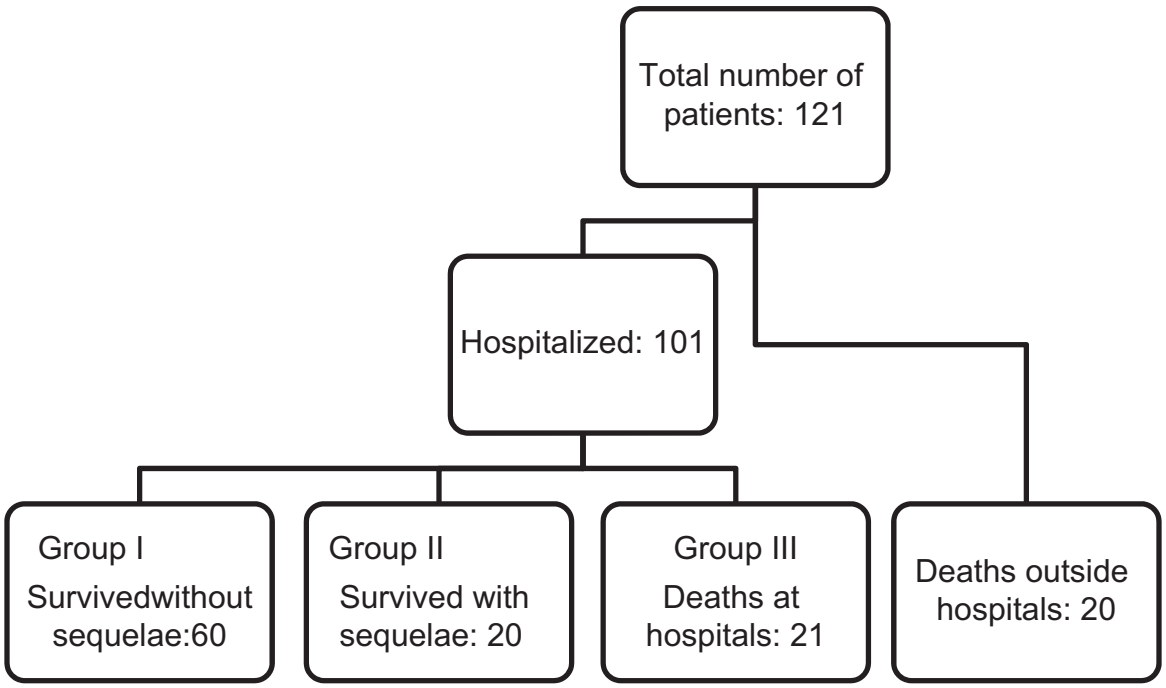


Fig. 3. Flow-chart of the patients in the methanol outbreak.

and twelve were found with a methanol concentration below the "toxic limit" (20 mg/dL or 6.24 mmol/L). The data were normally distributed with the following exceptions: a) serum methanol, ethanol, and osmolal gap in all groups; b) pH and lactate in Group I; and c) pCO_2, bicarbonate, and anion gap in Group III. Therefore, all data are presented as median (range).

Clinical symptoms

On admission, 25/101 (25%) of patients were asymptomatic, 18 of them with measurable ethanol in blood (all of them were given pre-hospital ethanol by the ambulance staff). The most common clinical symptoms on admission are shown in Table 2. Other less common symptoms involved fatigue (state of weariness characterized by a decreased capacity for work and reduced efficiency to respond to stimuli), headache (discomfort or pain of head), dizziness (impairment in spatial perception and stability), somnolence (drowsiness), anxiety (feelings of panic, fear, and uneasiness), alcoholic delirium (organic cerebral syndrome characterized by concurrent disturbances of consciousness and attention, perception, thinking, memory, psychomotor behavior, emotion, and the sleep-wake schedule), tremor (involuntary muscle contraction and relaxation involving oscillations or twitching of one or more body parts), seizures (medical condition where body muscles contract and relax rapidly and repeatedly, resulting in an uncontrolled shaking of the body), cardiac arrest(cessation of functional circulation of the blood due to failure of the heart to contract effectively), and respiratory arrest (cessation of normal breathing due to failure of the lungs to function effectively). Patients without symptoms were found to have formate concentrations on admission of 2–31 mg/dL (0.4–6.9 mmol/L).

Regarding the patients treated with enhanced elimination methods (75/101), the mean arterial pressure (MAP) in the patients treated with IHD was 112 (63–137) mmHg, and in the patients treated with CVVHD/HDF was 100 (43–152) mmHg. The difference in MAP was not significant between the groups of patients treated with different modes of hemodialysis ($p > 0.05$), but more patients on CVVHD/HDF were treated with pressors and inotropes to maintain MAP > 70 mmHg ($p < 0.01$). The difference in serum lactate between the groups of patients treated with different modes of hemodialysis was not significant ($p > 0.05$)

Treatment

Detailed information about the treatment given is presented in Table 3.

Bicarbonate was given aiming at full correction of the metabolic acidosis, and was therefore given in varying amounts.

In total 10/101 (10%) did not receive any antidote:

- 3/10 recovered without any sequelae: They all had low serum methanol on admission (6, 10, and 20 mg/dL (1.9, 3.1, and 6.2 mmol/L), respectively) and no metabolic acidosis; in two cases with serum methanol under 20 mg/dL (6.2 mmol/L), there was a history of methanol poisoning; serum methanol was above the limit of detection with serum bicarbonate 16.9 and 18.9 mmol/L (mEq/L), and anion gap 20 and 22 mmol/L (mEq/L), respectively;
- 2/10 recovered with sequelae: One patient with serum methanol of 17 mg/dL (5.3 mmol/L), pH 7.2, and serum ethanol of 228 mg/dL, or 49.5 mmol/L (self-administered shortly before admission), and one patient admitted in coma with severe metabolic acidosis and negative serum methanol: The family actively denied that the patient had been drinking alcohol, but serum formate concentration was > 2 mg/dL (0.4 mmol/L) and symmetrical hemorrhages of basal ganglia were present on computed tomogram;
- 5/10 patients died: Three were admitted to the hospitals on the 3rd of September: they were diagnosed post mortem, whereas the last two patients died on admission before any specific treatment was initiated.

A total of 26/101 (26%) patients did not receive hemodialysis: In 21 of them the criteria for hemodialysis were not fulfilled (see the Treatment section), all of them survived without sequelae; two patients died upon admission to the hospital before any treatment except unsuccessful resuscitation were carried out (see above); finally, in three cases the hemodialysis was not applied because of the negative serum methanol, coma on admission, and severe metabolic

Table 2. Clinical symptoms on admission on 101 hospitalized patients separated by the three outcome groups.

	No symptoms n (%)	Visual disturbances n (%)	Gastrointestinal symptoms n (%)	Dyspnea n (%)	Chest pain n (%)	Respiratory arrest n (%)	Coma n (%)
Group I ($n = 60$)	24 (40%)	16 (27%)	26 (43%)	12 (20%)	2 (3%)	0	5 (8%)
Group II (n = 20)	1 (5%)	14 (70%)	12 (60%)	9 (45%)	3 (15%)	2 (10%)	9 (45%)
Group III ($n = 21$)	0	12 (57%)	10 (48%)	11 (52%)	7 (33%)	4 (19%)	17 (81%)
Total (n = 101)	25 (25%)	42 (42%)	48 (48%)	32 (32%)	12 (12%)	6 (6%)	31 (31%)
$P_{I=II}$	0.003*	<0.001*	0.196	0.028*	0.062	0.013*	<0.001*
$P_{I=III}$	<0.001*	0.012*	0.734	0.005*	<0.001*	<0.001*	0.001*
$P_{II=III}$	0.300	0.393	0.427	0.636	0.172	0.413	0.017

Notes: Group I–survivors without sequelae, Group II survivors with sequelae, Group III died.
$P_{I=II}$, $P_{I=III}$, $P_{II=III}$ – results of Chi^2 test of difference in clinical symptoms on admission between the Groups I, II, and III (*Statistically significant differences).

Table 3. Treatment given in 101 hospitalized patients separated by the three outcome groups.

	Alkalization	Ethanol	Fomepizole	Folates	CVVHD/HDF	IHD
Group I ($n = 60$)	24 (40%)	49 (82%)	8 (13%)	47 (78%)	19 (32%)	20 (33%)
Group II ($n = 20$)	17 (85%)	10 (50%)	8 (40%)	17 (85%)	13 (65%)	5 (25%)
Group III ($n = 21$)	18 (86%)	11 (52%)	5 (24%)	11 (52%)	13 (62%)	5 (24%)
Total ($n = 101$)	59 (58%)	70 (69%)	21 (21%)	75 (74%)	45 (45%)	30 (30%)
$P_{I=II}$	<0.001*	0.005*	0.010*	0.519	0.008*	0.486
$P_{I=III}$	<0.001*	0.008*	0.260	0.023*	0.015*	0.416
$P_{II=III}$	0.948	0.879	0.265	0.025*	0.837	0.929

Notes: Group I – survivors without sequelae, Group II survivors with sequelae, Group III died.
CVVHD/HDF, continuous veno-venous hemodialysis/hemodiafiltration; IHD, intermittent hemodialysis.
$P_{I=II}$, $P_{I=III}$, $P_{II=III}$ – results of Chi2 test of difference in treatment given between the Groups I, II, and III (*Statistically significant differences).

acidosis corrected by the bicarbonate infusions with no definite diagnosis of methanol poisoning till death (the first cases in the outbreak).

26/101 (26%) patients did not receive folate:

- 10/26 died: 5 died from the reasons as illustrated above, 5/10 were not administered folates for unknown reasons;
- 3/26 survived with visual sequelae and 13/26 survived without sequelae. No definite reasons for lack of folate treatment were found.

Among the patients given folates, 64/80 (80%) survived, whereas 11/21 (52%) died ($p = 0.01$). However, this was not found as an independent prognostic marker in the multivariate regression analysis.

Outcome and prognosis

There were 21 fatalities in hospital (hospital mortality 21%), other 20 patients died at home or before reaching hospital, giving a total mortality of 34%. Twenty patients (20%) were discharged from hospital with sequelae, with visual impairment diagnosed in nine, CNS impairment in four, and both visual and CNS sequelae in seven cases.

Among the 25 asymptomatic patients on admission, there were 24 (96%) survivors without sequelae, one patient got visual sequelae, and none died. The patients with symptoms of visual toxicity on admission (42/101) got visual sequelae on discharge in 33% of cases, and died in 29% of cases. On admission these patients had gastrointestinal symptoms in 71% of cases, dyspnea in 55%, and chest pain in 21%. One third (15/42, 36%) of these patients became comatose during the transfer to the hospitals or shortly upon admission to the emergency departments of the hospitals, 5% of them had the episodes of respiratory arrest. Most of these patients (83%) were administered sodium bicarbonate to correct metabolic acidosis, 90% were treated with antidote (ethanol in 59% and fomepizole in 31% cases) and hemodialysis (CVVHD/HDF in 59% and IHD in 31%), and 71% of them were administered folate. The patients without visual sequelae on discharge were significantly less acidotic than those with visual damage ($p < 0.01$), and had lower serum methanol and formate (both $p < 0.01$). Coma upon admission was significantly more prevalent in the patients with visual sequelae ($p < 0.05$). The hospital treatment measures (hemodialysis, antidotes, folate substitution) in the patients without visual sequelae did not differ from the other groups.

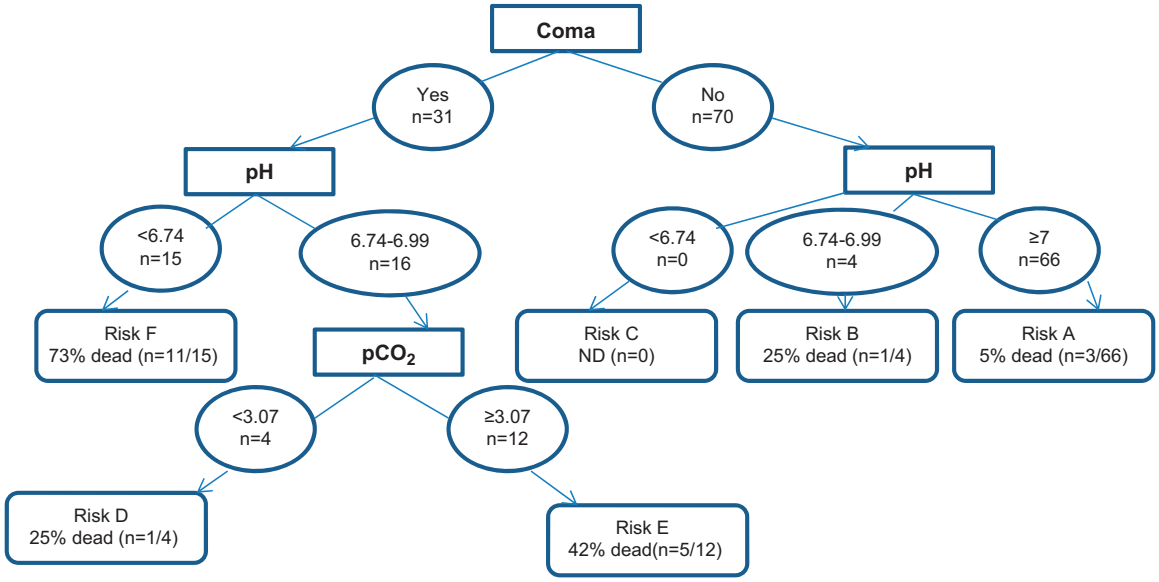
The 21 patients who died were more acidotic than the survivors with and without sequelae, and the difference in pH and base deficit was significant between all three groups, as can be seen from Table 1. A risk-assessment flow-chart and the corresponding outcome based on the state of consciousness, pH, and pCO_2 on admission is shown in Fig. 4. Among the patients who recovered without sequelae, there was a trend toward lower pCO_2 when pH was increasing, while the opposite trend was seen among the dying patients (pH decreased/pCO_2 increased) ($p = 0.001$) (Fig. 5).

Multivariate regression analysis evaluating the partial effect of laboratory and clinical features on mortality found coma, metabolic acidosis with $pH < 7.0$, and negative serum ethanol on admission to be the only independent parameters predicting death (Table 4). Arterial blood pH was the most important predicting parameter for the multivariate logistic regression model (logit) of risk of death. Receiver Operating Characteristics Curve (ROC) analysis of pH as the independent parameter predicting death showed the area under the curve (AUC) for pH: 0.93 (0.88–0.98 CI95%). The probability of death changed exponentially from approximately 77% for the cut-point 6.6–21% for the cut-point 7.0, as it can be seen on the Fig. 6. For the serum ethanol concentration on admission as the independent parameter predicting mortality the AUC was 0.77 (0.68–0.86 CI95%).

There were no significant differences in mortality rate between any of the treatment modalities (IHD vs. CVVHD/HDF, ethanol vs. fomepizole, or folate substitution "yes/no"). In the survivors, the difference in the prevalence of visual sequelae was not significant between those with and without folate therapy ($p = 0.08$). Most of the survivors with folate substitution (48/63, 76%), and half of those without folate therapy (8/16, 50%), were treated with hemodialysis.

Discussion

In our study, severity of metabolic acidosis, state of consciousness, and serum ethanol on admission were the only significant parameters predicting mortality in patients poisoned with methanol. There was no difference in mortality rate between the groups of patient with different modes of



Risk group	Name on figure	Number in total	Dead in group	Total mortality risk	Odds ratio (95%CI)*
1	A and B	70/101	4/70	6%	1
2	C	0	0	-	-
3	D	4/101	1/4	25%	6 (0-66)
4	E	12/101	5/12	42%	12 (3-54)
5	F	15/101	11/15	73%	45 (10-209)

*Odds ratio (OR) and 95% confidence intervals (CI) for death for all groups compared to risk group 1

Fig. 4. Risk assessment chart for the evaluation of outcome based on admission parameters with a risk score based on the scheme above; pCO_2 – values are given in kPa. Conversion factor mmHg to kPa is 7.5:1 (colour version of this figure can be found in the online version at www.informahealthcare.com/ctx).

enhanced elimination. The effect of folate substitution both on mortality rate and on the prevalence of visual sequelae in survivors was not significant, as earlier shown.[16] Most of the survivors were treated with hemodialysis, and probably the detoxifying effect of the pathway of tetrahydrofolate-mediated formate conversion was secondary to the formate elimination by hemodialysis. There was no difference in mortality rate between the groups treated with fomepizole or ethanol, but the study was not randomized, and the most severely poisoned patients were prioritized for fomepizole once this was available.

Poor outcome in methanol poisonings is primarily associated with the late diagnosis and delayed initiation of treatment. In our study, the time to treatment did not differ between the survivors without sequelae versus survivors with sequelae versus patients died (all $p > 0.05$), because the median time to presentation in all three groups was more than 24 h, and two thirds of the patients were admitted to hospital more than 48 h after the toxic spirit consumption with undetectable ethanol levels in 59%. A total of 63% of the patients were acidotic on admission, with high serum levels of formic and lactic acids. This all being said, the time from intake to diagnosis is highly relevant, yet clearly defined by the state of the patient on admission. The public

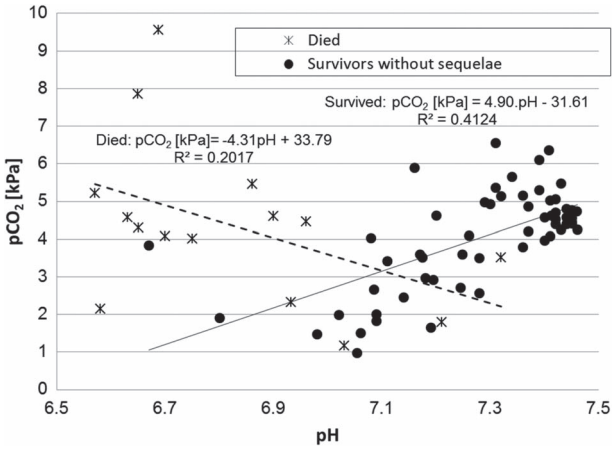


Fig. 5. The association between pH and serum pCO_2 as a prognostic factor ($p = 0.001$).

Table 4. The results of the multivariate analysis on the factors associated with mortality.

Independent variable	Threshold	Odds Ratio	95% confidence interval (CI)	*p* value
pH	≤7.0	0.04	0.01–0.16	$p < 0.001$
S-EthOH (mmol/L)	<0.9	0.08	0.02–0.37	$p < 0.001$
S-Formate (mmol/L)	>12	0.05	0.3–6.9	n.s.
Coma "no" *vs.* "yes"	–	29.4	10.2–84.6	$p < 0.001$

S-EthOH, serum ethanol on admission; S-Formate, serum formate on admission. To convert from mmol/L to mg/dL use the following conversion factors: ethanol – 4.608; formate – 4.603.

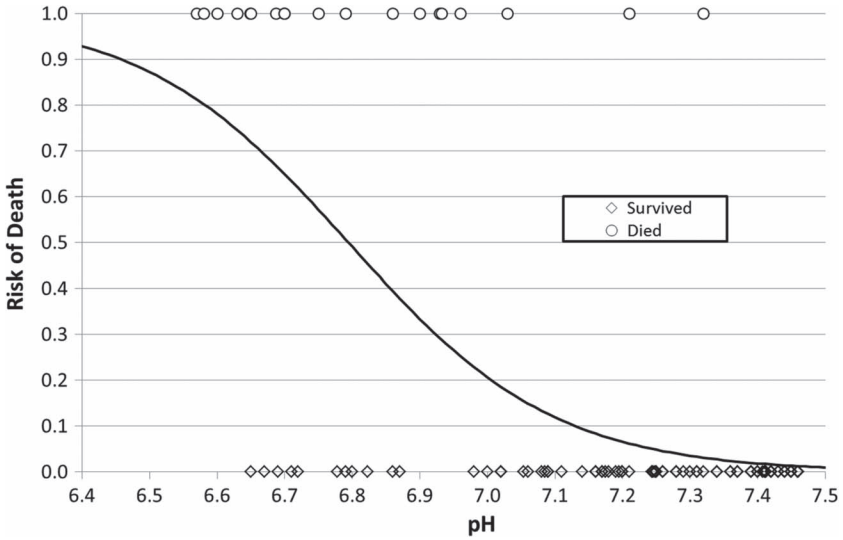


Fig. 6. Logistic regression (logit) diagram of Risk of death *versus* arterial blood pH on admission. OY – risk of death (0,0–0 risk; 1,0–100% risk); OX – arterial blood pH on admission.

health measures to reduce this crucial time, so called "active case finding" strategy, are important in the management of large outbreaks of methanol poisonings.[17]

Methanol concentration on admission has been suggested as a prognostic factor in some studies,[2,18] while others rejected this. The patients dying did, however, have a higher methanol concentration as a rule of thumb.[1,19–22] In the present study, we did not find any correlation as such between those who died and the survivors, but the survivors with sequelae had significantly higher serum methanol than the patients without sequelae. The fact that no consistent correlation with mortality was found suggested that most of the methanol had already been metabolized to the toxic formic acid in the later presentations. This adds to the important indication for introducing formate analysis,[23] as these patients will sometimes be admitted with a negative serum methanol level.

Our results confirm those from earlier studies, where poor outcome correlated well to the degree of metabolic acidosis.[1,17,18,24] The anion gap has earlier been shown to correlate well to the formate and lactate level,[5] and finding a significant difference between Group I versus II ($p = 0.009$) and I versus III ($p < 0.001$) is thus not surprising. Also, the lack of respiratory compensation when severely acidotic corresponded well to earlier reports.[1,12,23] Serum lactate accumulation plays a significant role in acidosis alongside the amount of formate[25] (as described by Jacobsen and Hovda in *Haddad and Winchester*: "the circulus hypoxicus"[26]). In our study, serum lactate concentration reflected the severity of disease; the patients who died (Group III) had the highest median serum lactate.

Further, there was a significant difference in lactate concentrations among all the groups, but the significant difference in formate concentrations was found only between those who survived with and without sequelae. The non-significant difference in formate concentrations between the survivors (Groups I and II) and those who died (Group III) can be explained by the fact that serum formate was not measured on admission in several patients who died (e.g., the first cases with negative methanol on admission); on the opposite, the lactate was measured routinely. On the other hand, a further explanation could be that the concentration of formate indicates the ability to inhibit the mitochondrial respiration through its toxic effect on the mitochondrial cytochrome oxidase, whereas the lactate level describes the "damage already being done", where the patient is no longer able to compensate the production of lactic acid and is starting to deteriorate. The normal range of formate is typically given as below 0.4 mmol/L (2 mg/dL), whereas patients are usually reported with symptoms when formate is above 8–10 mmol/L (approximately 40 mg/dL).[23] The actual toxic limit has not been defined in humans, as it is a product of concentration and time, as well as the degree of the metabolic acidosis: the more acidotic, the more toxic. The dissociation constant of formic acid (pKa) is 3.8, i.e. a pH-drop of 0.3 would mean doubling the undissociated formic acid levels, hence a significant increase in toxicity.

We found a significant difference in serum glucose on admission between the survivors without sequelae (Group I) and the two other groups ($p = 0.003$ and $p < 0.001$, respectively, Table 1). This corresponds well to the findings of Sanaei-Zadeh et al., suggesting that the stress-induced hyperglycemia seen in critically ill patients can be a prognostic factor.[27] However, correcting for the other prognostic parameters by multiple regression analysis, it was not found to be an independent prognostic parameter.

Most of our patients were symptomatic upon admission, and visual disturbances were more prominent in Groups II and III as compared to Group I. Almost one third of those with symptoms of visual toxicity on admission got visual sequelae, and one third died. Coma on admission was associated with poor outcome, as previously reported in other studies.[18,24]

In the Czech methanol outbreak, all the patients who fulfilled the AACT/EAPCCT criteria for hemodialysis (altogether 75 cases) received it without delay, so there was no problem with the availability of dialysis facilities. But the problem was with the availability of fomepizole, on the contrary. Only 21% of patients (e.g., one in five) received it. Complete lack of—or limitations in—fomepizole stocks is more of a rule than an exception. If the latter is the case (limited availability), an alternative strategy for using fomepizole is an option, as was the case during the present outbreak: When fomepizole was available, the patients with the most severe acidosis were prioritized for an initial treatment of fomepizole (loading dose plus 2–3 consecutive doses) in order to stabilize them and initiate hemodialysis, upon when ethanol was given in the continuation of this. This approach was not expected to give a significant difference in survival, but it was useful for the clinicians, so it could be considered a uniform tool to be further investigated in later outbreaks with limitations in fomepizole supply. Generally, the predefined recommendations on hospital triage for fomepizole administration and hemodialysis priority groups are likely to be useful in mass outbreaks with limitations in availability of fomepizole and dialyzing equipment.

We did not find any difference in survival in the patients receiving this strategy compared to the ones only receiving ethanol. This is not at all surprising as the groups were likely too small, and the fomepizole group was given a combination of both antidotes. Finally, we did not design this as a randomized control trial, but rather looking at aspects likely to simplify the treatment and possibly save more lives. The benefits of fomepizole application observed in the study were the indirect ones: mainly no need in thorough monitoring the serum ethanol level (each 1–2 h) during the hemodialysis in severely poisoned patients and less work overload on ICU doctors treating several poisoned patients simultaneously. This allowed for treating the most severely poisoned patients through the most critical phases, including the dialysis sessions where ethanol dosing is especially difficult.[28] In situations where the resources are even more overwhelmed than in the present situation, a priority list based on outcome prognostication as described by Paasma et al.[24] can be helpful.

The problem of fomepizole availability during mass methanol outbreaks is complex: the high price and relatively short shelf-life of the antidote, as well as the infrequency of mass or cluster poisonings (especially in the developed world), prevent regional hospitals from keeping adequate stocks for many—if any—patients. The role of Poison Control Centers in these situations can be expanded to operate the national stockpile of antidote and arranging a system of urgent distribution to those hospitals overloaded with new cases of poisonings. By monitoring the "situation map" of poisonings, we arranged a "four-spots" logistic system of *ad hoc* antidote distribution; three of them were situated in the eastern part of the country, where 80% of poisonings occurred during the first 4 months of the outbreak. Further, limitations regarding production can influence the availability of antidote in urgent situations. Only one producer of fomepizole operates in Europe, with limited production capability. From April 2013 to August 2014, this company has not been able to produce a new batch of fomepizole due to technical problems, and the delivery of antidote to the Czech Republic has this far been postponed beyond this date. A similar situation had to be the case for the rest of Europe as well, and so the distributors have been temporarily importing the US version of fomepizole (having a different concentration and preparation, thus with potential for wrong dosing). Therefore, all new cases of methanol poisoning during this period had to be treated with ethanol, irrespective of the patient's condition. Based on the Czech experience and the recent (2013) addition of fomepizole to the WHO Model List of Essential Medicines,[9] it seems reasonable to plan for a European central stockpile (and similarly a few global stockpiles) which can deliver on a larger scale in outbreaks of methanol poisoning. This would also ensure a more frequent use and circulation of the stock with fewer issues regarding the expiry date of the antidote.

Another major concern in a mass poisoning may be the availability of hemodialysis facilities. During the 4 months of the Czech methanol outbreak, all 75 patients who required enhanced elimination methods were dialyzed. The choice of the method of enhanced elimination (IHD or CVVHD/HDF) in each case was defined by several factors, such as the hemodynamic stability of a patient on admission and the severity of clinical symptoms of poisoning: i.e., CVVHD/HDF was used in patients with mean arterial pressure lower than 70 mm Hg. Nevertheless, an important factor was also the availability of dialyzing equipment in the various medical facilities: some smaller hospitals only had dialysis equipment in the anesthesiology departments, making CVVHD/HDF the only option. Larger hospitals usually had IHD equipment available, which made it possible to choose this modality in hemodynamically stable patients. The same limitations of access to conventional hemodialysis was reported in an Estonian methanol outbreak in 2001,[2] and will typically also be seen elsewhere.

Therefore, higher expenses could possibly be related to the longer duration of hospitalizations in the ICU and higher fomepizole consumption during 2 or 3 days of CVVHD/HDF where IHD could have been more appropriate. Moreover, CVVHD/HDF means longer elimination half-lives of methanol and its toxic metabolite formate, and longer time to correction of severe metabolic acidosis as compared to IHD.[29]

The hospital mortality rate in our study was 21%. Similar hospital mortality rates were reported in the recent methanol mass poisoning outbreaks in Estonia (23%) and Norway (18%).[1,2] In Norway, the same proportion of patients was asymptomatic, but fewer patients (24 vs. 31%) were comatose upon admission, which can be related to the lower proportion of methanol in toxic liquors (20/80 of methanol and ethanol vs. 50/50 in the majority of Czech samples). In Estonia, 35% of patients were comatose, and 14% were asymptomatic upon admission. Spirits containing 50/50 to 100/0 methanol/ethanol were consumed there, and the median serum methanol was higher in both Groups II and III

as compared to the Czech patients (71.4 mmol/L or 22.9 mg/dL vs. 43.9 mmol/L 14.1 mg/dL, and 110 mmol/L or 35.3 mg/dL vs. 29 mmol/L or 9.3 mg/dL, respectively). More patients in Norway were treated with fomepizole compared to the Czech Republic (71% vs. 21%), and ethanol only was used in all of the patients treated with antidotes in Estonia. The proportion of patients treated with hemodialysis was approximately the same in the Czech Republic (75%), Norway (73%), and Estonia (71%).

Strengths and limitations

The limitations of this study can be attributed to certain confounders: The data on some patients (such as history of poisoning and clinical symptoms on admission) were retrospective with their limitations. Possible variations in the time, amount and patterns of toxic spirits intake, individual differences in the methanol and formate metabolism, as well as the possible variations in the available modalities for treatment in different hospitals add to these limitations.

However, this is till date the most comprehensive data ever presented after a methanol outbreak: Most of the essential clinical and laboratory data on admission were collected during the hospitalizations using standardized forms distributed to the hospitals by the TIC during the first weeks of the outbreak. The groups of patients were comparable by age, circumstances of poisoning, latency period, and size; most of the collected data exhibited normal distribution. Further, the effect of each treatment modality and laboratory parameter on outcome was evaluated after adjustment for the effect of the remaining treatment modalities and laboratory parameters within the multivariate regression analysis.

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Declaration of interest

The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

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