Extracorporeal Membrane Oxygenation for Poisonings Reported to U.S. Poison Centers from 2000 to 2018: An Analysis of the National Poison Data System*

Jon B. Cole, MD[1–3]; Travis D. Olives, MD, MPH, MEd[1–3]; Alexandru Ulici, PharmD[1]; John M. Litell, DO[2,3,4]; Stacey A. Bangh, PharmD[1]; Ann M. Arens, MD[1–3]; Michael A. Puskarich, MD, MS[2,3]; Matthew E. Prekker, MD, MPH[2,3,5]

Objectives: To assess trends in the use of extracorporeal membrane oxygenation for poisoning in the United States.

Design: Retrospective cohort study.

Setting: The National Poison Data System, the databased owned and managed by the American Association of Poison Control Centers, the organization that supports and accredits all 55 U.S. Poison Centers, 2000–2018.

Patients: All patients reported to National Poison Data System treated with extracorporeal membrane oxygenation.

Interventions: None.

Measurements and Main Results: In total, 407 patients met final inclusion criteria (332 adults, 75 children). Median age was 27 years (interquartile range, 15–39 yr); 52.5% were male. Median number of ingested substances was three (interquartile range, 2–4); 51.5% were single-substance exposures. Extracorporeal membrane oxygenation use in poisoned patients in the United States has significantly increased over time ($z = 3.18$; $p = 0.001$) in both adults (age > 12 yr) and children (age ≤ 12 yr), increasing by 9–100% per year since 2008. Increase in use occurred more commonly in adults. We found substantial geographical variation in extracorporeal membrane oxygenation use by geospatially mapping the ZIP code associated with the initial call, with large, primarily rural areas of the United States reporting no cases. Overall survival was 70% and did not vary significantly over the study period for children or adults. Patients with metabolic and hematologic poisonings were less likely to survive following extracorporeal membrane oxygenation than those with other poisonings (49% vs 72%; $p = 0.004$).

Conclusions: The use of extracorporeal membrane oxygenation to support critically ill, poisoned patients in the United States is increasing, driven primarily by increased use in patients greater than 12 years old. We observed no trends in survival over time. Mortality was higher when extracorporeal membrane oxygenation was used for metabolic or hematologic poisonings. Large, predominantly rural regions of the United States reported no cases of extracorporeal membrane oxygenation for poisoning. Further research should focus on refining criteria for the use of extracorporeal membrane oxygenation in poisoning. (*Crit Care Med* 2020; 48:1111–1119)

Key Words: critical care; extracorporeal membrane oxygenation; poisoning; poisons; rural health; shock

Poisoning is now a leading cause of mortality in the United States (1, 2). After opioids and sedative-hypnotics, the leading causes of fatal poisonings in the United States are drugs that cause acute cardiogenic shock or respiratory failure (3). Standard therapies to treat shock from poisoning include high-dose inotropes and vasopressors (4), glucagon (5), high-dose insulin (6), methylene blue (7), and IV lipid emulsion (8), all of which have varying degrees of success. In the past decade, many centers have turned to extracorporeal membrane oxygenation (ECMO) to support patients with severe poisoning refractory to these therapies (9).

Both venoarterial ECMO and venovenous ECMO represent conceptually appealing therapies in severe poisoning (10). For patients with cardiogenic shock refractory to multiple therapies (e.g., severe calcium channel-blocker poisoning), venoarterial ECMO preserves organ perfusion and allows time

*See also p. 1235.

[1]Minnesota Poison Control System, Minneapolis, MN.

[2]Department of Emergency Medicine, Hennepin Healthcare, Minneapolis, MN.

[3]Department of Emergency Medicine, University of Minnesota Medical School, Minneapolis, MN.

[4]Department of Critical Care Medicine, Abbott Northwestern Hospital, Minneapolis, MN.

[5]Department of Medicine, Division of Pulmonary and Critical Care Medicine, Hennepin Healthcare, Minneapolis, MN.

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for metabolism of the offending drug, effectively providing a bridge to recovery in otherwise moribund patients. Similarly, venovenous ECMO augments gas exchange in patients with severe lung injury (e.g., hydrocarbon aspiration) facilitating gentle or no mechanical ventilation and mitigating ventilator-induced lung injury.

Recent data suggest that the use of ECMO for poisoning may be increasing (11, 12). However, these reports are drawn from a database maintained by the Extracorporeal Life Support Organization (ELSO). Not all centers capable of ECMO report data to ELSO; thus, it is unclear if these data accurately reflect trends in the use of ECMO for poisoned patients. Furthermore, ELSO collects data from centers around the world, and it is unclear how trends reflected in these data apply specifically to the United States. Finally, the two published analyses of the ELSO database evaluated only adults; trends in the use of ECMO for severely poisoned children are poorly described. Recently a single state's poison control system reported an overall increase in discussing the use of ECMO for poisoning but identified only 16 cases of ECMO utilization for poisoning in 20 years (with no increasing trend over time) (13).

The primary aim of this study was to determine if ECMO use for the treatment of poisoning is increasing in the United States. We used the National Poison Data System (NPDS), a database that collates data from poison centers covering all 50 U.S. states. Secondary aims included assessing the geographic distribution of ECMO use for poisoning and describing clinical characteristics, including responsible poisons, concomitant therapies, and clinical outcomes.

MATERIALS AND METHODS

Study Design and Setting

This was a retrospective cohort study of patients reported to the NPDS from January 1, 2000, to December 31, 2018, for which ECMO was coded as a recommended or performed therapy. This study was approved by our institutional review board.

The NPDS is owned and managed by the American Association of Poison Control Centers, the organization that supports and accredits all 55 U.S. poison centers. It contains over 66 million exposure cases involving over 437,000 different products since 1983 (3). Pharmacists and nurses with specialty training in toxicology collect all NPDS data in real time. These trained experts use a systematic tool to prospectively track therapies and assign to each case clinical effects, clinical outcomes, and reasons for exposure (14). Individual cases are assigned a global clinical outcome on a 5-point Likert scale ("no effect," "minor effect," "moderate effect," "major effect," "death") per NPDS criteria by the consulting poison center during the course of usual care. All therapies, clinical effects, and clinical outcomes have standardized definitions; a complete list of NPDS codes is available free online (14). Definitions of selected NPDS codes used in the present study are included in **Supplementary Table 1** (Supplemental Digital Content 1, http://links.lww.com/CCM/F511). Poison centers that contribute to the NPDS maintain follow-up by communicating directly with bedside caregivers for each case. All therapies discussed with the treating team are recorded in an electronic database and are coded as "Recommended," "Recommended and Performed," or "Performed."

Selection of Participants

We identified all cases reported to NPDS from 2000 to 2018 with ECMO coded as a therapy. A limitation of NPDS is that it does not capture the ECMO circuit configuration (venovenous or venoarterial). We excluded all cases where the purported poison(s) was coded as "no effect," "confirmed nonexposure," "unrelated effect," "judged as nontoxic exposure," or "judged as minimal clinical effects possible" or where ECMO was recommended but not performed. All cases were reviewed by two board-certified medical toxicologists and excluded if consensus review determined the case details suggested miscoding (e.g., ECMO performed for dermal exposure to benign substance with "no effect" as the outcome); all remaining cases were then reviewed to determine if the purported exposure might plausibly have caused a critical illness necessitating use of ECMO.

After toxicologist review, ingested substances were grouped based on similar mechanisms/classes. Substances that caused inhibition of oxidative phosphorylation (e.g., cyanide), generated organic acids (e.g., methanol) or that interfered with basic cellular replication (e.g., colchicine) were grouped collectively as hematologic/metabolic poisons. For this study, NPDS provided three-digit ZIP codes, omitting the final two digits, as the unusual nature of these cases could make the patient identifiable with knowledge only of the five-digit ZIP code. Patients were dichotomized by age: "adults" were defined as age greater than 12 years; "children" as age less than or equal to 12 years. These age cutoffs were chosen for anatomical reasons—most children age greater than 12 are able to be cannulated for peripheral ECMO with adult-sized catheters.

Data Analysis

We calculated medians, interquartile ranges (IQRs), and ranges where appropriate. Descriptive statistics were calculated using Stata, Version 15.1 (StataCorp, College Station, TX) and Microsoft Excel 2013 (Microsoft, Redmond, WA). NPDS three-digit ZIP codes were geospatially mapped using ArcGIS Online (Esri, Redlands, CA) after re-coding to the lowest corresponding five-digit ZIP code (e.g., 554XX mapped to 55401) to identify geographic trends. Trends over time were assessed using a chi-square test for trend. Differences between categorical variables were compared using a chi-square test.

RESULTS

We identified 575 unique cases with ECMO coded for poisoning, from which 71 were excluded as likely coding errors after medical toxicologist review. Of the remaining 504, 97 were excluded for not being treated with ECMO (73 were coded as "Recommended only," and 24 were coded as "Recommended but not Performed"). This left 407 cases for final analysis (332 adults, 75 children). Of these 407, 74 were coded as "Recommended and Performed," and 333 were coded as "Performed only."

The median age was 27 years (IQR, 15–39 yr); 52.6% of patients were male. The median number of exposed substances was three (IQR, 2–4), while 51.5% were single-substance exposures. Aspiration was significantly more common in children than in adults (23% vs 3%; $p < 0.0001$), as were unintentional exposures (79% vs 23%; $p < 0.0001$). Additional demographic data are displayed in **Table 1**.

Since 2000, the use of ECMO for poisoned patients reported to NPDS has increased from six episodes in 2000 to 88 episodes in 2018 (test for trend, $z = 3.82$; $p < 0.0001$) (**Fig. 1**). This increase in trend occurred for both adults ($p < 0.0001$) and children ($p = 0.038$).

Survival among all study patients was 70%. Across the study period we observed no significant change in survival in either children ($z = –0.08$; $p = 0.934$) or adults ($z = 0.57$; $p = 0.568$) (Fig. 1). In sensitivity analysis, results of tests for trend did not vary when the 10 cases coded as "unable to follow" were excluded. Cases classified as metabolic or hematologic poisonings had a significantly lower survival rate than nonmetabolic/hematologic poisons (49% vs 72%; $p = 0.004$). Clinical characteristics of patients, including clinical effects and concomitant therapies, are shown in **Table 2**.

A complete list of every individual substance is included in **Supplementary Table 2** (Supplemental Digital Content 1, http://links.lww.com/CCM/F511). Poisoning from a single substance was significantly more common in children than adults (87% vs 44%; $p \leq 0.0001$). The most frequently identified classes of drugs or poisons in adult cases were sedative/hypnotics (26%), antidepressants (25%), calcium channel blockers (19%), and opioids (17%). In children, the most common classes were hydrocarbons (37%), antiarrhythmics (15%),

TABLE 1. Demographic Information, Including Reason for Poisoning, Medical Outcomes, and Routes of Exposure For the Entire Cohort and Dichotomized by Age

Demographic	Entire Cohort ($n = 407$)	Patients Age > 12 ($n = 332$)	Patients Age ≤ 12 ($n = 75$)
Age, yr, median (interquartile range)	24 (15–39)	32.6 (19–43)	1.4 (1–3)
Gender, male, *n* (%)	214/407 (52.6)	168/332 (50.6)	46/75 (61.3)
Single-substance mortality, *n* (%)	59/210 (28.1)	39/145 (26.9)	22/65 (33.8)
Multiple-substance mortality, *n* (%)	61/197 (31)	58/186 (31.2)	3/11 (27.3)
Reason, *n* (%)			
Adverse reaction	26 (6.4)	20 (6)	6 (8)
Intentional	248 (60.9)	241 (72.6)	7 (9.3)
Other	3 (0.7)	2 (0.6)	1 (1.3)
Unintentional	93 (22.9)	34 (10.2)	59 (78.7)
Unknown	37 (9.1)	35 (10.5)	2 (2.7)
Medical outcome, *n* (%)			
Death	122 (30)	98 (29.5)	24 (32)
Major effects	256 (62.9)	210 (63.3)	46 (61.3)
Moderate effects	19 (4.7)	16 (4.8)	3 (4)
Unable to follow	10 (2.5)	8 (2.4)	2 (2.7)
Route of exposure, *n* (%)			
Aspiration with ingestion	26 (6.4)	9 (2.7)	17 (22.7)
Bite/sting	2 (0.5)	1 (0.3)	1 (1.3)
Dermal	8 (2)	5 (1.5)	3 (4)
Ingestion	305 (74.9)	243 (73.2)	62 (82.7)
Inhalation/nasal	48 (11.8)	47 (14.2)	1 (1.3)
Ocular	8 (2)	7 (2.1)	1 (1.3)
Other	4 (1)	3 (0.9)	1 (1.3)
Parenteral	29 (7.1)	21 (6.3)	8 (10.7)
Unknown	33 (8.1)	32 (9.6)	1 (1.3)

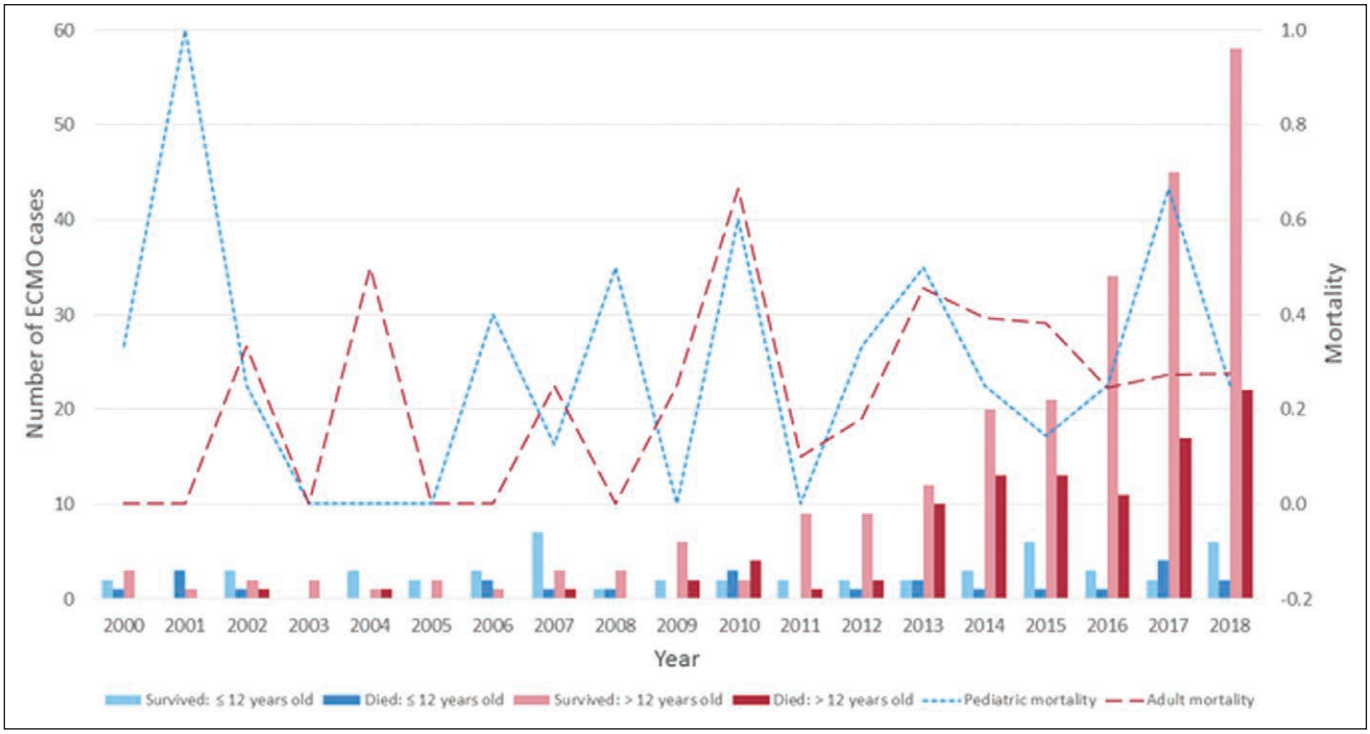

Figure 1. Trends in extracorporeal membrane oxygenation (ECMO) utilization, including use and mortality: 2000–2018.

antihistamines (8%), and unknown poisons (8%). Poisons responsible for single-substance cases are summarized in **Table 3**.

The geospatial distribution of cases, mapped by site of first call to a regional Poison Center (**Fig. 2*A***), identified large areas of the United States without ECMO cases. Five-digit ZIP codes were available for cases from our own Poison Center and were geospatially mapped to their corresponding three-digit ZIP codes; geospatial maps for our three-state region were identical with both the three-digit and five-digit ZIP code methodology (**Fig. 2*B***). The most common states that used ECMO for poisoning were Pennsylvania ($n = 45$), Texas ($n = 27$), Minnesota ($n = 24$), Maryland ($n = 22$), Michigan ($n = 20$), and New York ($n = 20$). A complete list of clinical effects and therapies performed in addition to ECMO are reported in **Supplementary Tables 3** and **4** (Supplemental Digital Content 1, http://links.lww.com/CCM/F511).

DISCUSSION

Based upon cases reported to U.S. Poison Centers, the use of ECMO for poisoning increased over the study period in both adults and children; this increase was driven primarily by adults. We found substantial variation in the geographic distribution of the use of ECMO for poisoning with large, predominantly rural areas of the United States reporting no cases. Survival did not vary significantly over the study period. Patients with metabolic and hematologic poisonings supported with ECMO were less likely to survive than those with other poisonings.

To our knowledge, this is the largest reported cohort of poisoned patients supported with ECMO. The overall survival in our U.S. cohort (70%) is comparable to existing literature for this indication, much of which comes from France and primarily involves adult venoarterial ECMO. Daubin et al (15) reported 17 cases of refractory cardiogenic shock in adults from 1997 to 2007 and found an overall survival rate of 76%, including a remarkable 71% survival rate in those experiencing cardiac arrest. Masson et al (16) attempted to quantify the marginal benefit of ECMO for poisoning in adults by comparing two similar facilities that treated severe poisonings, yet only one had ECMO capability. They found a significant survival difference favoring ECMO (86% vs 48%; $p = 0.02$). In addition to concerns related to selection bias, the authors noted that if a single additional patient in the ECMO group had died, this difference would no longer be statistically significant, underscoring the small sample size. Wang et al (17) published 10 cases reported to an American toxicology database from 2010 to 2013, of which eight survived (80%). This series included both venoarterial ECMO and venovenous ECMO. Baud et al (18) reported on the use of venoarterial ECMO in 112 cases and noted a 26% overall survival rate; however, 71 of these patients experienced cardiac arrest. Among patients who did not suffer cardiac arrest, survival ranged from 45% to 100% depending on the toxic exposure. Ramanathan et al (11) published data on poisoning cases in the ELSO database from 1999 to 2014 and found an overall survival rate of 59%, significantly higher for venovenous ECMO (34/49, 69%) than venoarterial ECMO (13/49, 39%). Patients in this series who received venovenous ECMO for aspiration pneumonia or inhalational injury did particularly well (89.3% survival). Weiner et al (12) published an updated analysis of adults receiving venoarterial ECMO in the ELSO database from 2003 to 2018 and found 104 cases, of which 53% survived. More recently, Lewis et al (13) published more than 20 years of data from the California Poison Control

TABLE 2. Clinical Characteristics by Mortality

Clinical Characteristic	Survived (*n* = 285)	Died (*n* = 122)
Number of cases receiving ECMO, *n* (%)	285 (70)	122 (30)
Age, yr, median (IQR)	24 (15–37)	25 (14–47)
Male gender, *n* (%)	143 (50.2)	71 (58.2)
Single-substance cases, *n* (%)	149 (52.3)	61 (50)
Multiple ingestion cases, *n* (%)	136 (47.7)	61 (50)
Substances ingested, median (IQR, range)	3 (2–4, 2–16)	3 (2–4, 2–12)
Selected clinical effects (related), *n* (%)		
Acidosis	106 (37.2)	58 (47.5)
Asystole	24 (8.4)	38 (31.1)
Aspartate transaminase, alanine transaminase > 1,000	11 (3.9)	11 (9)
Bleeding (other)	11 (3.9)	7 (5.7)
Bradycardia	52 (18.2)	28 (23)
Cardiac arrest	48 (16.8)	63 (51.6)
Coma	96 (33.7)	44 (36.1)
Conduction disturbance	62 (21.8)	28 (23)
Creatine phosphokinase elevated	35 (12.3)	18 (14.8)
Creatinine increased	50 (17.5)	34 (27.9)
Dysrhythmias (other)	23 (8.1)	13 (10.7)
Fever/hyperthermia	54 (18.9)	10 (8.2)
Hematemesis/upper gastrointestinal bleed	7 (2.5)	3 (2.5)
Hypotension	162 (56.8)	74 (60.7)
Hypothermia	8 (2.8)	9 (7.4)
Intracranial bleed	0 (0)	2 (1.6)
Oliguria/anuria	25 (8.8)	13 (10.7)
Renal failure	23 (8.1)	24 (19.7)
Respiratory arrest	26 (9.1)	43 (35.2)
Tachycardia	114 (40)	45 (36.9)
Selected therapies (performed), *n* (%)		
Alkalinization	101 (35.4)	58 (47.5)
Antiarrhythmic	24 (8.4)	20 (16.4)
Calcium	78 (27.4)	51 (41.8)
Cardioversion	15 (5.3)	9 (7.4)
Charcoal, single doses	28 (9.8)	14 (11.5)
Cardiopulmonary resuscitation	65 (22.8)	52 (42.6)
ECMO	285 (100)	122 (100)
Fomepizole	6 (2.1)	4 (3.3)
Glucagon	43 (15.1)	14 (11.5)
Hemodialysis	57 (20)	47 (38.5)
Hyperbaric oxygen	0 (0)	1 (0.8)
Insulin	64 (22.5)	36 (29.5)
Lavage, gastric	8 (2.8)	3 (2.5)
Methylene blue	10 (3.5)	11 (9)
N-acetylcysteine (IV)	27 (9.5)	13 (10.7)
Pacemaker	22 (7.7)	12 (9.8)
Steroids	27 (9.5)	17 (13.9)
Vasopressors	198 (69.5)	100 (82)
Whole bowel irrigation	7 (2.5)	3 (2.5)

ECMO = extracorporeal membrane oxygenation, IQR = interquartile range.

System's experience and found 16 cases in which ECMO was used, primarily in children, with an overall survival rate of 81%.

Our study found no change in survival over time despite increased use of ECMO. This may represent increasing availability and consideration of ECMO for poisonings. However, given the high mortality rates observed in this study, further research is needed to determine the optimal patient selection for this resource intensive therapy. Similar to previous studies, we found that cardiopulmonary failure requiring ECMO was commonly associated with poisons that cause either cardiogenic shock (e.g., calcium channel blockers, beta-blockers, antidysrhythmics, antidepressants) or acute respiratory failure from aspiration or chemical injury (e.g., opioids, sedative/hypnotics, hydrocarbons, irritant gases). Among poisons known to cause acute cardiac failure, we found overall mortality rates to be similar (Table 3), suggesting that the etiology of cardiogenic shock—sodium channel blockade, beta-adrenergic blockade, or calcium channel blockade—may not be as important as timely recognition and treatment of refractory cardiogenic shock (a similar paradigm as in acute respiratory failure).

We also identified a substantial number of cases in which ECMO was used for metabolic and hematologic poisoning and found that these patients died more frequently. The primary function of ECMO is to restore tissue perfusion, either

TABLE 3. Summary of Responsible Poisons for Single-Substance Cases

Poison	Total Survivors, *n* (%)	Total Fatalities, *n* (%)	Adults Survivors, *n* (%)	Adults Fatalities, *n* (%)	Pediatric Survivors, *n* (%)	Pediatric Fatalities, *n* (%)
Entire cohort (*n* = 210)	151 (72)	59 (28)	106 (73)	39 (27)	43 (66)	22 (34)
Hydrocarbons (*n* = 32)	22 (69)	10 (31)	3 (43)	4 (57)	19 (76)	6 (24)
Calcium channel blocker (*n* = 22)	17 (77)	5 (23)	17 (77)	5 (23)	–	–
Verapamil	8 (88)	1 (12)	8 (88)	1 (12)	–	–
Diltiazem	4 (57)	3 (43)	4 (57)	3 (43)	–	–
Amlodipine	4 (80)	1 (20)	4 (80)	1 (20)	–	–
Unknown (*n* = 20)	15 (75)	5 (25)	14 (78)	4 (22)	1 (50)	1 (50)
Antiarrhythmic and antimalarial (*n* = 19)	13 (68)	6 (32)	7 (70)	3 (30)	6 (67)	3 (33)
Flecainide	9 (82)	2 (12)	3 (60)	2 (40)	6 (100)	–
Hydroxychloroquine	2 (67)	1 (33)	2 (67)	1 (33)	–	–
Cardiac glycoside	1 (33)	2 (66)	1 (100)	–	–	2 (100)
Lidocaine	1 (50)	1 (50)	1 (100)	–	–	1 (100)
Opioids (*n* = 18)	18 (100)	–	17 (100)	–	1 (100)	–
Antidepressant (*n* = 15)	9 (60)	6 (40)	9 (64)	5 (36)	–	1 (100)
Bupropion	7 (58)	5 (42)	7 (64)	4 (36)	–	1 (100)
Tricyclic antidepressants	2 (67)	1 (33)	2 (67)	1 (33)	–	–
Metabolic and hematologic poisons (*n* = 15)	9 (60)	6 (40)	6 (54)	5 (46)	2 (50)	2 (50)
Carbon monoxide	4 (100)	–	3 (100)	–	1 (100)	–
Aluminum phosphide	1 (50)	1 (50)	1 (100)	–	–	1 (100)
Hydrogen sulfide	2 (100)	–	2 (100)	–	–	–
Sodium azide	–	2 (100)	–	2 (100)	–	–
Colchicine	–	1 (100)	–	1 (100)	–	–
Methanol	–	1 (100)	–	1 (100)	–	–
Methylene chloride	1 (100)	–	–	–	1 (100)	–
Metformin	1 (100)	–	–	1 (100)	–	–
Mushroom (*Amanita bisporigera*)	–	1 (100)	–	–	–	1 (100)
Irritant gases and caustics (*n* = 11)	8 (73)	3 (27)	6 (75)	2 (25)	2 (67)	1 (33)
Sedative/hypnotics (*n* = 8)	6 (75)	2 (25)	6 (100)	–	–	2 (100)
Antihistamines (*n* = 7)	6 (86)	1 (14)	4 (100)	–	2 (67)	1 (33)
Diphenhydramine	4 (80)	1 (20)	3 (100)	–	1 (50)	1 (50)
Antihistamine not otherwise specified	2 (100)	–	1 (100)	–	1 (100)	–
Sympathomimetics (*n* = 6)	5 (83)	1 (17)	5 (83)	1 (17)	–	–
Acetaminophen (*n* = 5)	3 (60)	2 (40)	2 (50)	2 (50)	1 (100)	–
Nonsteroidal anti-inflammatory (*n* = 5)	4 (80)	1 (20)	–	–	1 (50)	1 (50)
Ibuprofen	3 (100)	–	3 (100)	–	–	–
Salicylates	1 (50)	1 (50)	–	–	1 (50)	1 (50)
Anticonvulsants (*n* = 3)	3 (100)	–	1 (100)	–	2 (100)	–
Beta-blockers (*n* = 3)	3 (100)	–	3 (100)	–	–	–
Metals (*n* = 3)	–	3 (100)	–	1 (100)	–	2 (100)

Dashes indicate there were no cases in this category, or 0 (0).

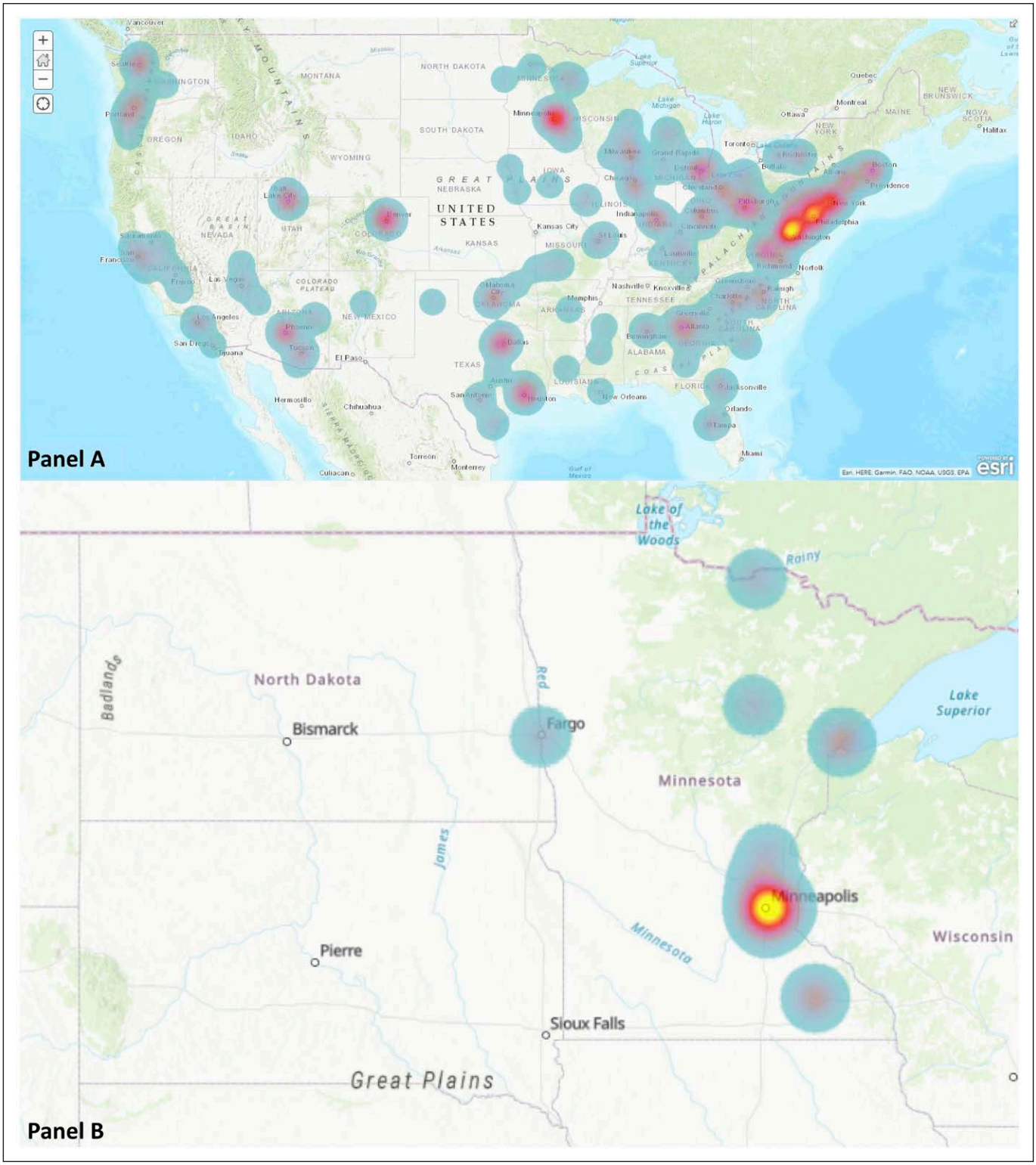

Figure 2. Density of extracorporeal membrane oxygenation utilization for poisoning from 2000 to 2018. **A**, The entire United States (no cases were reported from Alaska or Hawaii). **B**, The three states covered by the authors' Poison Center (Minnesota, North Dakota, and South Dakota).

by augmenting oxygenation of venous blood via venovenous ECMO or increasing perfusion to critical organs like the heart and brain and augmenting oxygenation via venoarterial ECMO. If the primary mechanism of poisoning occurs at the level of basic cellular function—such as inhibition of oxidative phosphorylation by cyanide—the use of ECMO to increase systemic oxygen delivery should not be expected to improve outcomes. The problem in these instances is one of oxygen processing, not supply. Nevertheless, poisons that are primarily metabolic may heterogeneously affect different organ

systems. Mohan et al (19–21) have reported the successful use of ECMO to treat aluminum phosphide poisoning, a condition characterized by inhibition of oxidative phosphorylation. In retrospective single-center studies, they reported increased survival when ECMO was used, specifically in patients with a left ventricular ejection fraction of less than 40% (21). It is plausible that some mitochondrial poisonings may result in cardiac myocyte dysfunction before more widespread cellular dysfunction. In these patients whose primary manifestation of metabolic poisoning is cardiogenic shock, ECMO may still be a viable therapeutic option by providing sufficient hemodynamic support to allow clearance of the offending poison before it can cause more widespread inhibition of adenosine triphosphate production. Patients with metabolic and hematologic poisonings have complex pathophysiology resulting in recalcitrant shock states that may not always be appropriate for ECMO. Extracorporeal support in poisoned patients is a novel use of an expensive (22) and invasive (23) intervention. ECMO support can be associated with difficult clinical and ethical decisions for physicians, patients, and their advocates (24–26); all of these parties stand to benefit from further efforts to refine which poisoned patients are most likely to benefit from ECMO. Optimal patient selection for this subset of poisoned patients remains an area for future investigation (27).

The geographic distribution of cases in our study is notable for two reasons. Large areas of the United States, almost all rural, reported no cases. Although it is possible that poisonings severe enough to benefit from ECMO rarely occur in rural areas, it is more likely that rural patients do not have access to ECMO in a reasonable time frame, or perhaps were rapidly transferred to urban areas before a poison center was contacted. Analysis of our own poison center's ZIP codes suggests that at least some rural poisonings are captured in NPDS coding and that use of three-digit ZIP codes does not limit this capture (Fig. 2). Nevertheless, our data serve as a reminder that health disparities, such as access to the full spectrum of critical care support, still exist in rural areas. We also noted substantial geographic variation in the use of ECMO, even among urban areas. For instance, we identified 24 cases of ECMO use associated with our own poison center that serves a population of 7.3 million living in three states, while in California, a state of over 39 million people, only 16 ECMO cases were reported during an even longer period of time according to a separate report (13). Further investigation will illuminate whether this reflects reporting bias (e.g., California hospitals under-reporting ECMO use to poison centers) or if there are true geographic variations in practice. If these data are accurate, there may be an opportunity to compare outcomes regionally to explore the potential benefit of ECMO (or lack thereof) in poisoned patients, which for several reasons will likely never be testable in a randomized clinical trial.

This study has several limitations. In addition to the limitations inherent in retrospective studies, poison center data have several characteristics that deserve consideration (28–30).

First, poison center data may have meaningful clinical inaccuracies, such as the coding errors excluded after manual review in the first step of our study. Furthermore, reporting cases to poison centers is voluntary and complete follow-up data are sometimes lacking. As an additional example, 10 cases included for analysis (Table 1) were coded as "unable to follow, judged as potentially toxic exposure" despite receiving ECMO; all were coded as "survived." Results of tests for trend, however, did not vary when these cases were excluded. In addition, care should be taken when examining the cases we excluded from our analysis coded as "Recommended" but not performed. An inherent limitation of NPDS coding is that we are unable to determine if this recommendation came from the poison specialist (nurse/pharmacist) or the consulting medical toxicologist, or under what circumstances this recommendation was made. For example, these may have been cases where ECMO was discussed as a possible therapy only if the patient deteriorated rapidly, and as such, could represent cases where ECMO was likely never truly indicated.

Second, confirmatory blood or urine testing is frequently lacking in poison center data. It is likely poisoning cases severe enough to require ECMO are diagnosed clinically rather than by toxicology assays, as confirmatory testing is frequently unavailable in a timely manner and typically adds little to the clinical picture in severe shock.

Third, it is likely that not every case of poisoning treated with ECMO was identified by our methods. However, as this is the largest study to date and given the observed changes in the frequency of ECMO used for poisoning, we believe the overall conclusions regarding increasing usage are valid.

Fourth, due to NPDS coding practices, we cannot distinguish between the use of ECMO in venovenous, venoarterial, or hybrid configurations. Nor can we capture cases involving more than one configuration as the effects of the poisoning evolve. This makes commenting upon overall survival rates difficult, as patients treated with venovenous ECMO have generally higher survival rates than those treated with venoarterial ECMO (11). This highlights an important area for improvement in U.S. Poison Center data collection and an area for future research.

Last, as noted above, the geographic data in our study may not accurately capture the origin of the case or the site of the poisoning.

CONCLUSIONS

The use of ECMO to support poisoned patients in the United States is increasing, primarily among patients older than 12 years old. We observed no change in survival over time. Mortality was higher in metabolic and hematologic poisonings, likely due to the interplay between the pathophysiology of the poison and the mechanisms of ECMO support. Large regions of the United States, primarily rural areas, reported no cases of poisoning treated with ECMO this century. Further research should focus on clarifying the timing and indications for the use of ECMO in poisoning, and on the frequency of poisonings originating in rural areas that would potentially benefit from timely access to a center with ECMO capability.

Drs. Cole, Olives, Ulici, and Prekker conceived and designed the study. Drs. Cole and Olives supervised the conduct of the study, data collec-

tion, and screened all cases for coding errors. Drs. Cole, Olives, and Ulici analyzed the data. Dr. Cole drafted the article and full access to all of the data takes responsibility for the article as a whole. Dr. Puskarich provided guidance on data analysis. All authors critically appraised the article and contributed substantially to its revision.

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For information regarding this article, E-mail: jonbcole@gmail.com

REFERENCES

1. Lippold KM, Jones CM, Olsen EO, et al: Racial/ethnic and age group differences in opioid and synthetic opioid-involved overdose deaths among adults aged ≥18 years in metropolitan areas - United States, 2015-2017. *MMWR Morb Mortal Wkly Rep* 2019; 68:967–973
2. Hempstead K, Phillips J: Divergence in recent trends in deaths from intentional and unintentional poisoning. *Health Aff (Millwood)* 2019; 38:29–35
3. Gummin DD, Mowry JB, Spyker DA, et al: 2017 annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 35th annual report. *Clin Toxicol (Phila)* 2018; 56:1213–1415
4. Levine M, Curry SC, Padilla-Jones A, et al: Critical care management of verapamil and diltiazem overdose with a focus on vasopressors: A 25-year experience at a single center. *Ann Emerg Med* 2013; 62:252–258
5. Bailey B: Glucagon in beta-blocker and calcium channel blocker overdoses: A systematic review. *J Toxicol Clin Toxicol* 2003; 41:595–602
6. Cole JB, Arens AM, Laes JR, et al: High dose insulin for beta-blocker and calcium channel-blocker poisoning. *Am J Emerg Med* 2018; 36:1817–1824
7. Laes JR, Williams DM, Cole JB: Improvement in hemodynamics after methylene blue administration in drug-induced vasodilatory shock: A case report. *J Med Toxicol* 2015; 11:460–463
8. Levine M, Hoffman RS, Lavergne V, et al; Lipid Emulsion Workgroup: Systematic review of the effect of intravenous lipid emulsion therapy for non-local anesthetics toxicity. *Clin Toxicol (Phila)* 2016; 54:194–221
9. de Lange DW, Sikma MA, Meulenbelt J: Extracorporeal membrane oxygenation in the treatment of poisoned patients. *Clin Toxicol (Phila)* 2013; 51:385–393
10. Keller SP: Management of peripheral venoarterial extracorporeal membrane oxygenation in cardiogenic shock. *Crit Care Med* 2019; 47:1235–1242
11. Ramanathan K, Tan CS, Rycus P, et al: Extracorporeal membrane oxygenation for poisoning in adult patients: Outcomes and predictors of mortality. *Intensive Care Med* 2017; 43:1538–1539
12. Weiner L, Mazzeffi MA, Hines EQ, et al: Clinical utility of venoarterial-extracorporeal membrane oxygenation (VA-ECMO) in patients with drug-induced cardiogenic shock: A retrospective study of the Extracorporeal Life Support Organizations' ECMO case registry. *Clin Toxicol (Phila)* 2019 Oct 16. [online ahead of print]
13. Lewis J, Zarate M, Tran S, et al: The recommendation and use of extracorporeal membrane oxygenation (ECMO) in cases reported to the California Poison Control System. *J Med Toxicol* 2019; 15:169–177
14. American Association of Poison Control Centers: National Poison Data System (NPDS): NPDS Coding Users' Manual© Version 4.1. 2019. Available at: http://bezoar.georgiapoisoncenter.org/wpcontent/uploads/2014/07/NPDS-2019.pdf Accessed January 9, 2020
15. Daubin C, Lehoux P, Ivascau C, et al: Extracorporeal life support in severe drug intoxication: A retrospective cohort study of seventeen cases. *Crit Care* 2009; 13:R138
16. Masson R, Colas V, Parienti JJ, et al: A comparison of survival with and without extracorporeal life support treatment for severe poisoning due to drug intoxication. *Resuscitation* 2012; 83:1413–1417
17. Wang GS, Levitan R, Wiegand TJ, et al; Toxicology Investigators Consortium: Extracorporeal membrane oxygenation (ECMO) for severe toxicological exposures: Review of the Toxicology Investigators Consortium (ToxIC). *J Med Toxicol* 2016; 12:95–99
18. Baud F, Lamhaut L, Jouffoy R, et al: [Peripheral circulatory support in acute poisoning: 10 years' experience]. *Emergencias* 2016; 28:252–262
19. Mohan B, Gupta V, Ralhan S, et al: Role of extracorporeal membrane oxygenation in aluminum phosphide poisoning-induced reversible myocardial dysfunction: A novel therapeutic modality. *J Emerg Med* 2015; 49:651–656
20. Mohan B, Singh B, Gupta V, et al: Outcome of patients supported by extracorporeal membrane oxygenation for aluminum phosphide poisoning: An observational study. *Indian Heart J* 2016; 68:295–301
21. Mohan B, Gupta V, Ralhan S, et al: Impact of extra-corporeal membrane oxygenation on outcome of aluminium phosphide poisoning complicated with myocardial dysfunction. *Clin Toxicol* 2019; 57:1095–1102
22. Blum JM, Lynch WR, Coopersmith CM: Clinical and billing review of extracorporeal membrane oxygenation. *Chest* 2015; 147:1697–1703
23. Cheng R, Hachamovitch R, Kittleson M, et al: Complications of extracorporeal membrane oxygenation for treatment of cardiogenic shock and cardiac arrest: A meta-analysis of 1,866 adult patients. *Ann Thorac Surg* 2014; 97:610–616
24. DeMartino ES, Braus NA, Sulmasy DP, et al: Decisions to withdraw extracorporeal membrane oxygenation support: Patient characteristics and ethical considerations. *Mayo Clin Proc* 2019; 94: 620–627
25. Sonntag EA: When clinical advances outpace ethics. *AMA J Ethics* 2019; 21:375–379
26. Abrams DC, Prager K, Blinderman CD, et al: Ethical dilemmas encountered with the use of extracorporeal membrane oxygenation in adults. *Chest* 2014; 145:876–882
27. Brodie D, Vincent JL, Brochard LJ, et al; International ECMO Network (ECMONet): Research in extracorporeal life support: A call to action. *Chest* 2018; 153:788–791
28. Lévy A, Bailey B, Letarte A, et al: Unproven ingestion: An unrecognized bias in toxicological case series. *Clin Toxicol (Phila)* 2007; 45:946–949
29. Prosser JM, Smith SW, Rhim ES, et al: Inaccuracy of ECG interpretations reported to the poison center. *Ann Emerg Med* 2011; 57:122–127
30. Hoffman RS: Understanding the limitations of retrospective analyses of poison center data. *Clin Toxicol (Phila)* 2007; 45:943–945