Pediatric Exposures Reported to the Toxicology Investigators Consortium, 2010–2015

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Background and Objective: Poisoning is the leading cause of injury death in pediatric patients. Hospital and provider readiness, including pharmacy stocking, depends on reliable surveillance data describing local patterns of age-specific clinically significant exposures and the therapeutic modalities employed in their treatment. We aimed to characterize trends in clinically significant toxic exposures and their management.

Methods: We performed a retrospective review of patients 18 years or younger in the American College of Medical Toxicology's Toxicology Investigators Consortium (ToxIC) Registry, a self-reporting database completed by bedside consulting medical toxicologists. We reviewed cases from January 1, 2010, through December 31, 2015. In 2015, ToxIC included 101 health care facilities. Data collected included demographics, geographic region, encounter and exposure details, survival, and therapeutic modalities employed, including antidotes, antivenoms, gastric decontamination, enhanced elimination, hyperbaric oxygen therapy, and extracorporeal membrane oxygenation.

Results: From 2010 to 2015, 11,616 consults were recorded in ToxIC. Pediatric consultations increased from 934 (23.7%) in 2010 to 2425 (29.9%) in 2015 ($P < 0.001$). Exposures were most commonly reported in females (57.8%) and adolescents (59.4%). Intentional ingestions (55.5%) comprised the majority of cases. The most frequent agents of exposure were analgesics (21.0%). There were 38 deaths reported (0.9%). The antidote used most commonly was N-acetylcysteine (11.0%). Geographic variation was demonstrated in prevalence of envenomations and heavy metal exposures, their respective treatments, and overall use of decontamination.

Conclusions: Toxicology consultations for pediatric exposures increased from 2010 to 2015. Understanding which pediatric exposures require toxicologist management, the therapies most frequently employed, and geographical patterns is paramount to facility-level planning, pharmacy stocking, and provider education.

Key Words: antidote, poisoning, toxicology

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Toxicological exposures rank among the leading causes of injury-related mortality and morbidity in children. In 2016, the American Association of Poison Control Centers' National Poison Data System (NPDS) received more than 2 million human exposure calls, with more than half (60.4%) involving the pediatric population.[1] Pediatric toxicological exposures have a large impact on the health care system and account for approximately 90,000 emergency department (ED) visits annually, with adolescent overdoses increasing in recent years.[2–4]

The majority of pediatric exposure calls received by the NPDS are managed at home.[1,5–8] As the numbers of toxic pediatric exposures and overdoses continue to rise, it is important to understand the epidemiology of clinically significant pediatric exposures requiring health care evaluation and the proper utilization of treatment modalities. For example, despite rising prevalence of pediatric exposures, shortages of antidotes and antivenins are quite common.[9,10] Lack of comprehensive and accurate surveillance data may contribute to shortages, as the quantity and need for these therapies are not well documented.[5,9,10]

In 2010, the American College of Medical Toxicology (ACMT) established the Toxicology Investigators Consortium (ToxIC) registry, a national surveillance registry completed by medical toxicologists or subspecialty trainees following a bedside consultation. The ToxIC registry is unique in that it contains detailed information about exposures and ingestions severe enough to require health care evaluation and a consultation from a medical toxicologist: 93.4% of ToxIC consultations take place in the ED or inpatient settings.[11] In comparison, only 22.2% of calls to poison centers originate from health care facilities (HCFs).[5] Toxicology Investigators Consortium consultation data may, when used as an adjunct to larger surveillance data systems such as NPDS, strengthen the reporting landscape in pediatric toxicology by providing valuable epidemiological information to health care providers, trainees, and public health officials to guide proper education and facility readiness.

The objectives of this study were to describe the evaluation and management of pediatric ingestions and exposures as reported by medical toxicologists in the ACMT ToxIC registry. We reviewed the ToxIC database to describe (1) the epidemiology of pediatric presentations receiving medical toxicologist consultation, (2) the treatment modalities used in their management (decontamination, antidote, supportive care), (3) mortality data and factors associated with fatal toxicological exposures, and (4) regional practice

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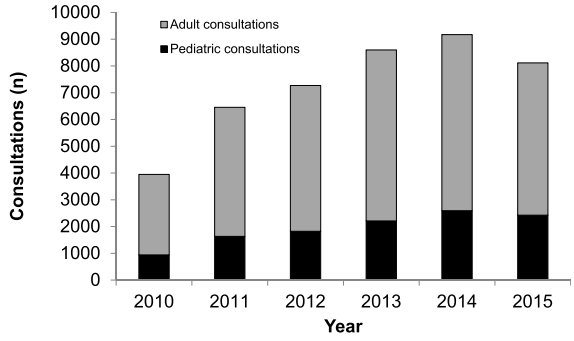

*The number of participating pediatric institutions varied annually; there were 10 US pediatric institutions reporting to ToxIC in 2010, 9 in 2011 and 2012, 14 in 2013, 13 in 2014, and 16 in 2015

FIGURE 1. Proportion of pediatric consultations reported to ToxIC, by year.*

variations by describing geographical trends in use of decontamination, as well as heavy metal exposures and envenomations, along with their respective treatments.

METHODS

This was a retrospective review of the ACMT ToxIC registry, a self-reporting national registry completed by medical toxicologists in the United States.[12] Following bedside consultation in the ED, inpatient, or outpatient setting, patient-level encounter data are entered into the registry by the consulting medical toxicologist. A standardized, deidentified, password-protected, encrypted, Health Insurance Portability and Accountability Act of 1996–compliant online data collection form is used to enter patient demographics, presenting signs and symptoms, clinical course, treatment, outcomes, agent of exposure, and reasons for consultation. Participating institutions may be of any care level and may be academic or nonacademic. In 2015, the registry included 101 participating institutions, 16 of which were dedicated pediatric HCFs.[11–15] Between 2010 and 2015, the number of participating pediatric institutions has varied (Fig. 1).

Subjects 18 years or younger were included if they received a bedside consultation by a medical toxicologist as reported in a US institution between January 1, 2010, and December 31, 2015. In some cases, a toxicology consult took place, but a toxicological etiology could not be confirmed; these were included in our analysis. Data elements collected included demographics (age and sex), HCF location (US state), intent (intentional, exploratory, occupational), route of exposure, administration of antidotes or other supportive modalities and treatments (decontamination, extracorporeal measures, intubation, etc), and survival. Intentional was defined as attempt at self-harm, misuse or abuse, or therapeutic use. Unintentional was defined as unintended use, such as an accidental or exploratory ingestion. Nonpharmacologic support was defined as cardiopulmonary resuscitation, extracorporeal membrane oxygenation (ECMO), pacemaker, balloon pump, hyperbaric oxygen, therapeutic hypothermia, bypass, intubation, transfusion, cardioversion, intravenous fluid resuscitation, and transplantation. Using the Centers for Disease Control and Prevention census track criteria, participating HCFs were classified by geographical region.[16]

Descriptive statistics were used to report demographics, exposures, and treatments, with categorical variables summarized as frequency and proportion. χ^2 Tests were used to compare geographic variations in prevalence of envenomations and heavy metal exposures, as well as the use of decontamination, chelators, and antivenins. We also compared differences in the annual proportion of recorded pediatric consultations over time. All statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC). This study was approved on behalf of ACMT ToxIC and was granted exemption from our local institutional review board, whereas the registry itself is approved by the Western Institutional Review Board.

RESULTS

From January 1, 2010, to December 31, 2015, there were 11,616 consultations in patients 18 years or younger recorded in the ACMT ToxIC registry (21.5% of all consultations). Pediatric consultations reported to the registry increased significantly, from 23.7% (95% confidence interval [CI], 22.4%–25.0%) of all recorded events in 2010 to 29.9% (95% CI, 28.9%–30.9%) in 2015 (Fig. 1). The most common pediatric age group receiving consultation was 13 to 18 years of age (59.4%; 95% CI, 58.5%–60.3%). Intentional ingestion represented the most common source of exposure (55.2%; 95% CI, 54.3%–56.1%) (Table 1).

Overall, pharmaceuticals accounted for the majority of exposures (69.5%; 95% CI, 68.6%–70.3%) (Table 2), with 26.0% (95% CI, 25.2%–26.8%) being polypharmacy ingestions. The most common pharmaceutical exposures were nonopioid analgesics (2181 [18.8%]), antidepressants (1106 [9.5%]), and cardiovascular medications (765 [6.6%]) (Table 2).

Activated charcoal (single or multidose) was used in 689 patients (5.9% of all consults; 95% CI, 5.5%–6.4%) (Table 4). Administration was most common in the South, with an annual regional incidence of 22.2 per 1000 total exposures, followed by the Midwest (6.7 per 1000 exposures), West (5.8 per 1000 exposures), and Northeast (3.5 per 1000 exposures). Overall, antidotes were used in 25.2% (95% CI, 24.5%–26.1%) of patients receiving toxicologist consultation. N-acetylcysteine (11.0%) was the most commonly used antidote, followed by naloxone (4.1%) and sodium bicarbonate (4.1%) (Table 3). Nonpharmacologic supportive measures were reported in 780 patients (6.7%; 95% CI, 6.3%–7.2%) (Table 4). Extracorporeal supportive modalities (hemodialysis, continuous renal replacement therapy, and exchange transfusion) were used in 57 patients (0.5%; 95% CI, 0.4%–0.6%) (Table 4). Twenty patients received ECMO (Table 4); 18 (85%; 95% CI, 69.9%–97.2%) survived. The agents of exposure associated with ECMO included antidepressant/antipsychotic,[6] sedative-hypnotics,[5] cardiovascular,[4] gas/vapors,[4] and anticonvulsants.[3] Note that some of these patients ingested multiple agents.

There were 549 recorded envenomations through the United States. Envenomations and associated use of antivenin

TABLE 1. Demographics and Intent for Pediatric Consultations Reported to ToxIC From 2010 Through 2015

	N = 11,616	% of All Consultations (95% CI)
Age, y		
<2	1558	13.4 (12.8–14.0)
2–6	2148	18.5 (17.8–19.2)
7–12	1013	8.7 (8.2–9.3)
13–18	6897	59.4 (58.5–60.3)
Female	6679	57.5 (56.6–58.4)
Intent		
Intentional ingestion	6408	55.2 (54.3–56.1)
Unintentional Ingestion	3359	28.9 (28.1–29.8)
Unknown	1849	15.9 (15.3–16.6)

TABLE 2. Agents of Exposure for Pediatric Consultations Reported to ToxIC From 2010 Through 2015

Exposures	n = 11,616	% of All Consultations (95% CI)
Pharmaceuticals	8067	69.4 (68.6–70.3)
Analgesic	2181	18.8 (18.1–19.5)
Antidepressant	1106	9.5 (9.0–10.1)
Cardiovascular	765	6.6 (6.2–7.1)
Anticholinergic/antihistamine	687	5.9 (5.5–6.4)
Antipsychotic	588	5.1 (4.7–5.5)
Sedative-hypnotic/muscle relaxant	583	5.1 (4.6–5.4)
Sympathomimetic	513	4.4 (4.1–4.8)
Opioid	484	4.2 (3.8–4.6)
Anticonvulsant	340	2.9 (2.6–3.3)
Psychoactive	311	2.7 (2.4–3.0)
Cough and cold	208	1.8 (1.6–2.1)
Diabetic medication	197	1.7 (1.5–2.0)
Lithium	104	0.9 (0.7–1.1)
Envenomations	549	4.7 (4.4–5.1)
Household products	229	2.0 (1.7–2.2)
Heavy metals	219	1.9 (1.7–2.2)
Gases/vapors/irritants/dusts	144	1.2 (1.1–1.5)
Hydrocarbons	134	1.1 (1.0–1.4)
Herbals/dietary supplements/ vitamins	127	1.1 (0.9–1.3)

varied by region. The South had the highest annual incidence for envenomations (21.3 per 1000 exposures) and antivenom use (17.4 per 1000 exposures), followed by the West (13.0 per 1000 exposures and 10.0 per 1000 antivenom uses) and the Midwest (8.6 per 1000 exposures and 2.5 per 1000 antivenom uses). Envenomations (0.4 per 1000 exposures) and antivenom use (0.07 per 1000 exposures) were much less common in the Northeast.

There were 200 total heavy metal exposures reported to the ACMT ToxIC Registry, most commonly lead and iron (Table 2). Overall, chelation was rare; 90 patients received chelation therapy, with most of these receiving dimercaptosuccinic acid (60%). The

TABLE 3. Antidotes Employed in the Management of Pediatric Patients Reported to ToxIC From 2010 Through 2015

Toxicological Treatment	N = 11,616	% of All Reported Exposures (95% CI)
Antidotes	2937	25.2 (24.5–26.1)
N-acetylcysteine	1284	11.0 (10.5–11.6)
Naloxone/nalmefene	481	4.1 (3.8–4.5)
Sodium bicarbonate	477	4.1 (3.8–4.5)
Physostigmine	215	1.8 (1.6–2.1)
Flumazenil	76	0.6 (0.5–0.8)
Octreotide	60	0.5 (0.4–0.7)
Atropine	52	0.4 (0.3–0.6)
Cyproheptadine	50	0.4 (0.3–0.6)
Fomepizole	42	0.4 (0.3–0.5)
Glucagon	28	0.2 (0.2–0.4)
Other	172	1.4 (1.3–1.7)

TABLE 4. Decontamination and Supportive Modalities Employed for Pediatric Patients in ToxIC From 2010 Through 2015

Treatment Modality	n	% of All Reported Exposures (95% CI)
Decontamination and enhanced elimination	866	7.5 (7.0–8.0)
Activated charcoal (single and multidose)	689	5.9 (5.5–6.4)
Urinary alkalinization	120	1.0 (0.9–1.2)
Hemodialysis	33	0.3 (0.2–0.3)
CRRT	22	0.2 (0.1–0.3)
Exchange transfusion	2	0.02 (0.01–0.07)
Chelators	93	0.8 (0.7–1.0)
DMSA	57	0.5 (0.4–0.6)
EDTA	14	0.1 (0.07–0.2)
Deferoxamine	12	0.1 (0.06–0.2)
BAL	8	0.1 (0.04–0.14)
DMPS	1	0.001
Penicillamine	1	0.001
Nonpharmacologic interventions	780	6.7 (6.3–7.2)
Intubation/ventilator	667	5.7 (5.3–6.2)
Cardiopulmonary resuscitation	32	0.3 (0.2–0.4)
Transfusion	26	0.2 (0.2–0.3)
Hyperbaric oxygen	21	0.2 (0.1–0.3)
ECMO	20	0.2 (0.1–0.3)

CRRT indicates Continuous Renal Replacement Therapy; DMSA, dimercaptosuccinic acid; BAL, 2,3-dimercaprol; DMPS, 2,3-dimercaptopropane-1-sulfonic acid.

Midwest reported the highest annual incidence of heavy metal exposures, 4.3 per 1000 exposures, whereas chelator use was 0.8 per 1000 exposures, followed by the South (3.2 per 1000 exposures, 1.3 chelator use per 1000 exposures), the Northeast (2.3 per 1000 exposures, 1.4 chelator use per 1000 exposures), and the West (1.4 per 1000 exposures, 0.6 chelator use per 1000 exposures).

There were 38 deaths reported in the registry (Table 5). The majority (68.4%; 95% CI, 52.5%–81.1%) were from intentional ingestions in the adolescent population. Opioids (9 [23.7%]), sedative-hypnotics (6 [15.8%]), cardiovascular drugs (6 [15.8%]), and sympathomimetics (6, 15.8%) were the most commonly reported exposures leading to death. There were no deaths due to household products. There were 9 deaths in patients younger than 2 years. These included 5 unintentional ingestions: 2 cases of oxycodone and 1 case each of morphine, dextroamphetamine, and amphotericin. There was 1 intentional ingestion of atorvastatin. One death was due to phenobarbital, but intent was unknown, and an additional death from carbon monoxide. One death received toxicology consultation but was due to unknown etiology (Table 5).

DISCUSSION

From 2010 through 2015, there were more than 11,000 pediatric patients and almost 40 deaths reported in the ACMT ToxIC registry, representing almost a third of all medical toxicology consultations. These findings emphasize the burden of clinically significant pediatric exposures on the health care system.[1,5–8,17] The most common pediatric demographic data reported to the registry were adolescent intentional pharmaceutical ingestions. This reflects not only the medical needs of these patients, but also

TABLE 5. Pediatric Deaths From Toxicologic Exposures Reported to ToxIC From 2010 Through 2015*

	n = 38	% of All Deaths (95% CI)
Age, y		
<2	9	23.7 (13.0–39.2)
6–12	5	13.2 (5.8–27.3)
13–18	24	63.2 (47.3–76.6)
Female	19	50.0 (35.0–65.2)
Substance		
Opioid	9	23.7 (13.0–39.2)
Sedative-hypnotic	6	15.8 (7.4–30.4)
Cardiovascular	6	15.8 (7.4–30.4)
Sympathomimetic	6	15.8 (7.4–30.4)
Gas/vapor	4	10.5 (4.2–24.1)
Other	30	

*Multiple etiological agents may be responsible for each case.

the current health crisis of mental health disorders and associated self-harm behaviors.[18] The surveillance data within ToxIC are an important adjunct on following the epidemiology of pediatric toxicological exposures. It can provide additional information on what HCFs and providers should be prepared for when treating clinically significant pediatric exposures requiring health care evaluation, including medications commonly involved in overdose and unintentional exposures, as well as trends in novel and known drugs of abuse.

Utilizing ToxIC as a surveillance mechanism, HCFs can identify national and local practice patterns and inform best practices as recommended by medical toxicologists, including evaluating and educating on proper use of decontamination (such as activated charcoal), antidote utilization, enhanced elimination, other supportive modalities, and even associated adverse events. Supplementing toxicology surveillance data with regional, provider-level data may guide local institutional antidote inventory, in addition to other supportive measures. In 2015, US poison centers reported antidotes were used 184,742 times.[5] In 2018, an expert consensus regarding guidelines for stocking of antidotes in hospitals was published and recommended 44 antidotes, of which 23 should be immediately be available and 14 within an hour of the decision to administer.[10] Despite these recommendations, survey data collected across North America and Europe have demonstrated that a majority of HCFs are inadequately stocked with many common or critical antidotes.[9] Several antidotes and treatments commonly recommended by medical toxicologists in the registry have been shown to be often absent or insufficiently stocked, including atropine, benzodiazepines, digoxin Fab, intravenous fat emulsion, naloxone, and various antivenins.[9] Interestingly, cost does not appear to be the primary factor affecting antidote/treatment stocking,[19] and the availability of a given antidote may occur at the expense of others, without clear justification.[20] These shortages place patients at risk of severe outcomes. In contrast, there are also regional differences that can prevent unnecessary costs in stocking antidotes that are rarely used. For example, we identified regional differences in heavy metal exposures, envenomations, and associated treatments. There were minimal heavy metal exposures in the West and South and minimal envenomations reported in the Northeast and Midwest. This importance of regional differences was emphasized in recommendations from a collaboration of expert medical toxicologists pertaining to antidote guideline for HCFs providing emergency care.[10] They emphasized using regional differences and the catchment areas served by an HCF when evaluating antidotes and other treatments. Furthermore, these differences also demonstrate regional strengths and gaps in clinical experience and education and can be especially helpful for general pediatric, emergency medicine, and medical toxicology training programs.

Limitations include the ACMT ToxIC registry is a self-reported database by medical toxicologists. Although there are incentives to participate in the registry, cases are entered at the consulting provider's discretion, and all cases may not have been captured. Most institutions where medical toxicologists are available for consultation are large-volume, regional, academic HCFs. Some of the interventions reported in the ACMT ToxIC registry, including ECMO, may also not be available in all participating institutions. Thus, patients and treatment modalities reported in the registry may be an underrepresentation of overall pediatric toxicological exposures requiring health care evaluation. The overall increase in pediatric consultations from 2010 through 2015 is likely related to the increase in participating HCFs. From 2010 through 2015, total participating institutions increased from 56 to 101, with pediatric institutions increasing from 10 to 16. However, the proportion of pediatric exposures increased despite a variation in participating pediatric institutions over the study period. Some cases may not be laboratory-proven toxicological ingestions, and the listed agent of exposure may not have been laboratory confirmed; however, the inclusion of these cases in the database by the consulting medical toxicologist suggests a strong clinical suspicion for a toxicological etiology. Finally, some data elements may be incomplete, as not all data fields are required.

CONCLUSIONS

In summary, there were more than 11,000 pediatric toxicological consultations reported from 2010 through 2015 to the ACMT ToxIC registry. The proportion of pediatric patients evaluated by a medical toxicologist increased significantly over the study period. Intentional pharmaceutical ingestions in adolescents were the most common clinical scenario, demonstrating the ongoing significant health impact of adolescent mental health disorders. There were regional differences in envenomations, heavy metal exposures, and use of their respective antivenin and chelators. This registry provides additional regional toxicosurveillance data directly from consulting medical toxicologists, which, when used in complement with larger databases, may help to guide provider education and inform best practices, antidote inventory stocking, and institutional preparedness for clinically significant pediatric toxicological exposures.

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