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Selected Topics: Toxicology

EVALUATING THE UTILITY OF TOXICOLOGIC ANALYSIS IN PEDIATRIC OUT-OF-HOSPITAL CARDIAC ARREST

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☐ **Abstract—Background: The cause of a pediatric out-of-hospital cardiac arrest (OHCA) may go unexplained in the emergency department setting but can be secondary to a toxicologic etiology. It is unclear how toxicologic screens are used in the postarrest period after a pediatric OHCA. Objectives: The primary objectives are to describe 1) when the toxicology screen (urine and serum) is used, 2) patient characteristics, and 3) toxicology screen results. We hypothesized that toxicology screens are frequently used but that positive results are uncommon. Methods: This was a retrospective study of pediatric OHCA patients admitted to the Penn State Health Children's Hospital pediatric intensive care unit as transfers from the emergency department between January 1, 2011 and May 31, 2018. We reviewed the electronic health record and evaluated for toxicology screen completion, patient characteristics, and toxicology screen results. Results: One hundred forty-one patients had a pediatric OHCA. Sixty-three (44.7%) patients did not have a toxicology screen completed. A toxicology screen had a higher completion rate for children >11 years of age (n = 26 [78.8%]; p = 0.0024), and in unwitnessed arrests (n = 48 [66.7%]; p = 0.0052). Four cases (5.1%) revealed the presence of substances that were not administered by a medical provider or were illicit. Conclusion: Our study found that in pediatric OHCA, toxicologic screens were completed but were not routinely sent in our institution. There may be factors such as clinician bias or the severity of a patient's illness that impact the approach to toxicologic screening in pediatric OHCA. In addition to the history and physical examination, emergency physician and pediatric intensivists should consider routinely sending toxicologic screens to assist in uncovering any accidental or malicious explanation for the event.**

☐ **Keywords—cardiac arrest; critical care; patient care; pediatrics; toxicology**

INTRODUCTION

Pediatric out-of-hospital cardiac arrest (OHCA) is a rare but critical event that can result in severe multiorgan system dysfunction and low survival (1,2). Thus, the emergency physician and the pediatric intensivist must be prepared to manage many different organ systems to avoid another arrest or clinical situations that can cause further neurologic injury. While performing all these functions, the underlying cause should be determined and, if identified, treated to prevent further events.

The etiology of OHCA is varied. This can include hypoxia, an underlying cardiac condition, trauma, intracerebral hemorrhage, brain tumors, sepsis, acute poisoning, and various metabolic conditions (3–6). When an early diagnostic workup is undertaken after a cardiac arrest, it can help clinicians (emergency physicians and pediatric intensivists) provide high-quality care during resuscitation, guide efforts in secondary prevention (i.e.,

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implantable defibrillator placement), and may inform clinicians regarding the possible outcomes (7).

One tool that can be used in the evaluation of a pediatric cardiac arrest is the toxicology screen (8). While uncommon, toxicologic causes for pediatric OHCA are known to occur (9). With the presence of various antidotes and specific targeted management strategies for acute poisoning victim, the sequelae (i.e., dysrhythmias) of the pediatric OHCA may be reversed when identified (7). Routine use of toxicologic screens, however, may be of questionable benefit. These tests often do not change clinical management already initiated in the emergency department setting and the results can be negative despite the patient presentation indicating otherwise (10,11). Thus, if a toxicology screen is obtained in a pediatric OHCA patient with a suspected toxicologic etiology where the focus is on resuscitative efforts, it may be for other reasons, such as to confirm the underlying condition later on in the patient's hospitalization. The frequency and the utility for such an indication during the postarrest period, however, is unclear.

The primary objectives of this present study are to describe 1) when the toxicology screen is used in pediatric OHCA during the postarrest period, 2) the patient characteristics of those who had a toxicology screen sent, and 3) the results of the toxicology screen.

METHODS

Study Design

This was a retrospective study of pediatric patients with OHCA admitted to the pediatric intensive care unit (PICU) from an emergency department setting at the Penn State Health Children's Hospital for postarrest management. A retrospective review was completed between January 1, 2011 and May 31, 2018. The study was reviewed by our institutional review board and determined to not meet the definition of human subject research because the data were deidentified.

Study Setting

The PICU at the Penn State Health Children's Hospital is an 18-bed, tertiary care facility in which medical, general surgical, and cardiothoracic patients are treated. All pediatric patients with OHCA who were admitted from the emergency department setting to the Penn State Health Children's Hospital PICU and who were ≤18 years of age were included. OHCA was defined as an arrest that occurred outside of any hospital. Thus, we excluded patients who, after chart review, were determined to have had a witnessed cardiac arrest within a hospital or a similar medical setting either spontaneously or caused by a medical intervention, including anesthesia, intubation, or inadvertent medication administration. In cases where the patient was being treated by emergency medical services (EMS) providers, we included those cases when the patient arrested en route but not if it was immediately after a medical intervention (i.e., intubation, medication administration, etc). If a patient was brought to the hospital and was found in arrest or if a patient was apneic, received chest compressions, and ultimately required an intensive care unit admission, we included these patients as an out-of-hospital arrest (full arrest unclear).

Data Collection

Using the Virtual PICU Systems (VPS, LLC, Los Angeles, CA) database, we identified patients who were <18 years of age and who were reported to have suffered a cardiac arrest. After we obtained this list of patients, we used our electronic health record to perform a chart review of each case. Data collected included demographic (age, sex, and race), if the arrest was witnessed or unwitnessed, if a comprehensive quantitative serum toxicology screen was completed (sent to determine substance presence and amount), if a qualitative urine toxicology screen was completed (sent to determine only substance presence), the results of the toxicology screen, and if other toxicology relevant laboratory values were sent (including acetaminophen level, salicylate level, and ethanol level). Toxicology screens reviewed were focused on those obtained by our institution's emergency department and PICU. Pre-existing medical conditions were determined using the patient's medical history. For toxicology screens that were positive, we also further reviewed these charts to determine whether the medications reported were administered before the screen was sent. Pediatric Risk of Mortality III (PRISM 3) and Pediatric Index of Mortality 2 (PIM 2) scores from the Virtual PICU Systems database were also collected for each patient.

Toxicology Screening Tests

Our institution refers urine and serum toxicology screens to an outside STAT toxicology laboratory (Atlantic Diagnostic Laboratories, LLC, Bensalem, PA). This laboratory uses multiple heterogenous and homogenous immunoassays to screen for 13 (serum) and 15 (urine) target substances or drug categories. Liquid chromatography–tandem mass spectrometry screens verify the presence or absence of fentanyl/metabolites/analogues in serum. Dual-column gas chromatography–flame ionization detector identifies the presence or absence of volatiles. Liquid chromatography–tandem

mass spectrometry screens for the qualitative identification in serum and urine (Supplemental Table 1).

Statistical Analysis

Clinical and demographic characteristics were reported as proportions. The Fisher exact test and Cochran-Armitage test was applied to compare the proportions or trends by presence of screening. Marginal homogeneity for paired data was examined using the McNemar test with continuity correction.

RESULTS

Patient Demographics

Two-hundred and ten patients were identified as having a cardiac arrest requiring admission to the PICU between January 2011 and May 2018. Sixty-nine patients were not included because they had a witnessed cardiac arrest at a rehabilitation facility (n = 2), a special needs facility (n = 2), within our institution (n = 48), at a medical clinic (n = 1), after an EMS intervention (n = 1), at an outside institution (n = 14), and an arrest that initially occurred at an outside institution and recurred within our institution (n = 1). In sum, after thorough chart review, 141 subjects suffered a clear OHCA that were included in this study (Table 1). The median age of the patients was 2.6 years. Eighty-seven patients (61.7%) were male, and 54 (38.3%) patients were female. The Median PIM2 and PRISM3 (in which 2 cases were unavailable) mortality scores were 1.3 and 26. Sixty-three patients (44.7%) survived hospitalization and 78 (55.3%) patients died. Seventy-two pediatric patients (51.1%) who had an OHCA were unwitnessed, 68 (48.2%) were witnessed, and 1 (0.7%) was undetermined from the chart review. Forty-three patients (30.5%) were identified as having a pre-existing medical condition. The reported etiologies of cardiac arrest were as follows: cardiac (n = 13 [9.2%]), neurologic (n = 10 [7.1%]), respiratory (n = 90 [63.8%]), self-inflicted (n = 9 [6.4%]), sepsis (n = 2 [1.4%]), trauma (n = 15 [10.6%]), and unknown (n = 2 [1.4%]).

Toxicology Screen Utilization

Of 141 patients who had an OHCA, 63 (44.7%) patients did not have a toxicology screen completed, 15 (10.6%) only had a urine toxicology screen completed, 3 (2.1%) only had a serum toxicology screen completed, and 60 (42.6%) patients had both serum and urine toxicology screens completed. Sixteen (11.3%) patients separately had a serum ethanol level checked, 11 (7.8%) had a salicylate level checked, and 13 (9.2%) had an acetaminophen

Table 1. Demographics of Toxicology Screen Utilization

	Toxicology Screen Completed, n (%)	Toxicology Screen Not Completed, n (%)	*p* Value
No. of patients with OHCA	78 (55.3)	63 (44.7)	
Age, years			0.0024
≤11	52 (48.1)	56 (51.9)	
>11	26 (78.8)	7 (21.2)	
Sex			0.8619
Male	49 (56.3)	38 (43.7)	
Female	29 (53.7)	25 (46.3)	
Race			0.3426
Asian/Indian/Pacific Islander	1 (100.0)	0 (0.0)	
Black or African American	15 (62.5)	9 (37.5)	
Hispanic or Latino	2 (66.7)	1 (33.3)	
Other/mixed	9 (60.0)	6 (40.0)	
Unspecified	8 (80.0)	2 (20.0)	
White	43 (48.9)	45 (51.1)	
Patient outcome			0.6099
Survived	33 (52.4)	30 (47.6)	
Did not survive	45 (57.7)	33 (42.3)	
Pre-existing condition			0.5823
Yes	22 (51.2)	21 (48.8)	
No	56 (57.1)	42 (42.9)	
Type of arrest			0.0052
Witnessed	29 (42.6)	39 (57.4)	
Unwitnessed	48 (66.7)	24 (33.3)	
Undetermined	1 (100.0)	0 (0.0)	
PIM 2 score			0.7827
Median (25th-75th percentiles)	1.4 (−1.5 to 2.0)	1.2 (−1.6 to 2.6)	
PRISM 3 score			0.1249
Median (25th-75th percentiles)	28 (13–34)	22 (7–35)	

OHCA = out-of-hospital cardiac arrest; PIM 2 = Pediatric Index of Mortality 2; PRISM 3 = Pediatric Risk of Mortality III.

level checked. In all, 78 (55.3%) pediatric OHCAs had a toxicology screen completed (Figure 1, Table 1).

A statistically higher toxicology screening rate occurred in those >11 years of age (n = 26 [78.8%]) when compared with those ≤11 years of age (n = 52 [48.1%]; $p = 0.0024$; Table 1).

There were no statistically significant differences in toxicology screen utilization based on sex, race, patient outcome, presence of a pre-existing medical condition, and admission mortality scores. Unwitnessed (n = 48 [66.7%]) when compared with witnessed (n = 29 [42.6%]) OHCAs were statistically more likely to have a toxicology screen ($p = 0.0052$; Table 1).

Toxicology Screen Results

Of 141 patients, 63 had serum and 75 had urine toxicology screens. Among them, 60 patients had both (ie, serum and urine) screens. More patients had urine tests only (n = 15) than serum tests only (n = 3; $p = 0.0095$). Among the 60 patients who had both serum and urine tests, 26 had both positive results and 15 had both negative results. Among the 19 patients with discordant test results, there was a trend toward a higher likelihood of finding a urine positive screen (n = 14) than a serum positive screen (n = 5; $p = 0.0665$).

For the serum toxicology screen, 33 of 63 tests sent reported detection of the following substances: acetone (n = 1), acetaminophen (n = 3), atropine (n = 2), benzodiazepine (n = 22), caffeine (n = 3), cotinine (a nicotine metabolite) (n = 1), fentanyl (n = 6), ibuprofen (n = 3), lidocaine (n = 2), marijuana (n = 2), midazolam (n = 1), naproxen (n = 2), oxycodone (n = 2), phenytoin (n = 9), salicylates (n = 1), trazodone (n = 1), and venlafaxine (n = 1; Table 2). The cases where venlafaxine, trazodone, and oxycodone detected were acknowledged but unexplainable by the provider managing the patient at the time. These cases were referred to child protective services. In the patient in whom venlafaxine was detected a quantitative level was sent, and this substance nor its metabolite were detected. This case was subsequently referred to the coroner's office. No quantitative levels were sent for trazodone nor oxycodone. In general, no significant clinical and demographic characteristics differences were observed between the groups with positive and negative test results.

Of the serum ethanol, salicylate, and acetaminophen levels checked separately, none of these substances were detected.

For the urine toxicology screen, 46 of 75 tests sent reported detection of the following substances: 7-aminoclonazepam (n = 1), acetaminophen (n = 7), atropine (n = 1), barbiturate (n = 1), benzodiazepine (n = 28), chlorphenarime (n = 1), cocaine metabolite benzoylecgonine (n = 1), cotinine (n = 2), fentanyl (n = 26), ibuprofen (n = 1), lidocaine (n = 5), marijuana inactive metabolite 11-nor-9-carboxy-Δ9-tetrahydrocanabinol (n = 1), opiate (n = 2), oxycodone metabolites (oxymorphone, noroxycodone, and noroxymorphone) (n = 2), propofol (n = 1), ranitidine (n = 1), salicylate (n = 2), sertaline (n = 1), and trazodone (n = 1; Table 2).

Medically Induced (Iatrogenic) Toxicology Screen Results

Of the 6 serum toxicology screens that reported detection of fentanyl, all were administered by our hospital or by the outside hospital or EMS before the patient's arrival.

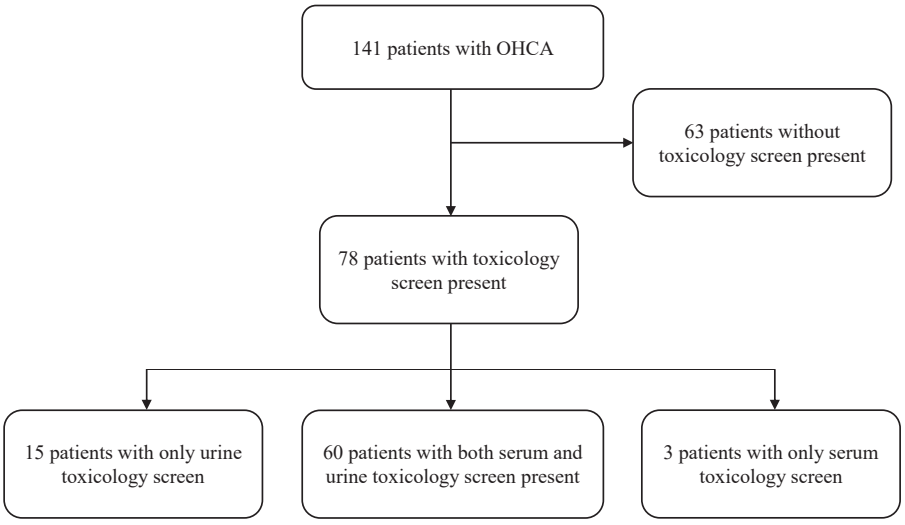

Figure 1. Overview of toxicology screens present in pediatric out-of-hospital cardiac arrest (OHCA) patient's electronic health records.

Table 2. Quantity of Positive Toxicology Results Divided by Age Group and Type of Toxicologic Screen

	Positive Toxicology Results, n					
	Blood Toxicologic Screen			Urine Toxicologic Screen		
	Patient Age, Years			Patient Age, Years		
	<1	1–11	>11	<1	1–11	>11
Nonclinically significant positive toxicologic screen						
Multiple substances	14	21	21	23	24	32
Unusual and illicit substances detected						
Cocaine	—	—	—	1	0	0
Marijuana	—	—	2	0	0	1
Oxycodone	1	—	1	1	0	1
Trazodone	—	1	—	0	1	0
Venlafaxine	—	—	1	—	—	—

Of the 23 tests that detected a benzodiazepine (n = 22) or midazolam (n = 1), all were confirmed to have received a benzodiazepine by our hospital or by an outside hospital or EMS before the patient's arrival with the exception of 1 that was unable to be determined by chart review. We were only able to confirm in 2 (22.2%) cases that PHENYTOIN was administered by either our hospital or outside our institution, 7 were unable to be determined. In general, no significant clinical and demographic characteristics differences were observed between the groups with positive and negative test results.

Of the 26 urine toxicology screens that reported detection of fentanyl, all were administered by our hospital or by an outside hospital or EMS before the patient's arrival with the exception of 2 (7.7%) that were unable to be determined from chart review. Of the 28 tests that detected benzodiazepine, all were confirmed to have received a benzodiazepine by our hospital, by an outside hospital or EMS before the patient's arrival with the exception of 2 (7.1%) that were unable to be determined by chart review. In addition, we also confirmed the case where propofol was detected was administered by EMS and the case where a barbiturate was detected was administered by an outside hospital. The 2 patients in whom cocaine and oxycodone were detected—both <1 year of age—were reported to child protective services. In general, no significant clinical and demographic characteristics differences were observed between the groups with positive and negative test results.

DISCUSSION

This study found that for pediatric OHCA a toxicology screen was completed most of the time, particularly for children >11 years of age and in unwitnessed arrests. In most of these cases, the substances detected were likely of no clinical consequence, but 4 cases did reveal unusual as well as illicit substances. These results may have implications on the utility of obtaining toxicology screens for forensic evaluation during the postarrest period after a pediatric OHCA in the emergency department setting.

The utility of obtaining a toxicology screen in a pediatric patient in any situation is of questionable benefit. Toxicology results leading to change in a clinical benefit are uncommon, and if a patient did have a positive screen for a substance that warrants a change in patient management, the symptoms are often detected and treated before the screen returns (10–12). In addition, there are limitations to the toxicology screens available and therefore a negative result does not necessarily indicate that a toxin is not or was never present (13). Therefore, prioritization of clinical judgement is often suggested.

Reasons for obtaining a toxicologic analysis, however, are not solely limited to guiding patient management. Though rare, it is known that patients with brief resolved unexplained events, where the patient often undergoes resuscitative efforts, can be caused by toxic substances. A study by Pitetti and associates found that 23 (8.4%) of 274 children whose history were more likely to have included a viral prodome or an event that occurred during sleep had clinically significant positive toxicology screens in the emergency department including over-the-counter drugs as well as illicit substances (14). Case reports have been reported for ethanol ingestion and may be an under recognized cause of brief resolved unexplained events (15). Therefore, in addition to clinical signs and symptoms (i.e., an altered sensorium), a toxicology screen can confirm the presence of an unusual or illicit substance, increase the suspicion for malicious intentional poisoning, and may lead the provider to discover that the child may be in an unsafe environment (16). Evaluations and referrals to child protective services are uncommon in children who have been poisoned (whether exploratory or maliciously intentional) as well

as finding a positive clinically significant post mortem toxicology screen (4,17,18). However, it does occur and may be an underrecognized entity (18). Some toxins can result in a severe condition, such as pediatric cardiac arrest, and therefore careful consideration on sending a toxicology screen as soon as possible may be necessary to help protect the patient and other children within the same household (3).

In this present study, our clinicians sent a toxicologic analysis of 55.3% of OHCA patients, where 4 cases revealed remarkable results. Clinical judgement likely guided this aspect of the diagnostic workup, thus ensuring proficient clinical care as well as recognizing the possibility of child maltreatment. It is unlikely, however, that consistent clinical reasoning and a level of suspicion was applied to all patients with OHCA because there were disparities in the patient population that had a toxicology analysis sent. Most toxicologic analyses were sent for patients >11 years of age. Witnessed arrests, where the etiology can also be undetermined, also had fewer toxicologic analyses sent when compared with unwitnessed arrests. This study highlights the challenges emergency physicians and pediatric intensivists have in their approach to patient care. Namely, the presence of an unconscious bias and a drive to use personal experience, knowledge, and pathophysiologic rationale to inform clinical care rather than the evidence, especially in urgent situations (19,20). While there were only 4 cases where the toxicology screen revealed the presence of an unusual or illicit substance, there is a possibility that there would have been more cases had our clinicians screened more. Even though unlikely and perhaps unthinkable a diagnosis may be (as in the case of poisoning with malicious intent), emergency physicians and pediatric intensivists must remember to engage in a systematic approach to the diagnostic workup of patients with OHCA.

In addition to demonstrating that toxicology screens are not sent on all patients with OHCA, the patients with positive screens rarely received follow-up quantitative levels. This may have profound implications from diagnostic and forensic standpoints. It may indicate an underappreciation of toxicology as a cause of pediatric cardiac arrest or an overreliance on an autopsy to determine the cause of an arrest. Even though a postmortem autopsy with a comprehensive toxicology is a possibility, there is no guarantee an autopsy will be performed unless the clinical circumstances are suspicious. Therefore, emergency medicine providers should consider, whenever possible or when clinically appropriate, to obtain a urine or preferably a serum toxicology screen that is as comprehensive as possible for OHCAs. While we acknowledge that a toxicology screen rarely impacts the clinical management of a patient, it is important from a forensic standpoint, and toxicologic causes of pediatric cardiac arrest should not be taken lightly. The pediatric intensivist should confirm the presence of a toxicology screen obtained at an outside hospital, follow-up the results in collaboration with the referring emergency medicine provider, and consider sending their own toxicology screen if the outside hospital's toxicology screen is less comprehensive. In addition, if a positive screen is detected whether at an outside hospital or within the provider's own institution, follow-up serum quantitative levels should be considered to confirm the presence of the substance and to facilitate the next steps with regard to the diagnostic evaluation and protection of the child.

Often, even after return of spontaneous circulation and stabilization of various organ systems, the patient's condition after an arrest can result in the clinical diagnosis of brain death. To begin the process of pediatric brain death determination, the clinician is required to review and ensure the absence of confounding factors including metabolic and toxic states. In cases where the etiology of the arrest is unclear, further testing, including use of a toxicologic analysis, may be needed to ensure that toxins that can mimic brain death are not present (21). Consideration of a toxicologic analysis may also be necessary in certain clinical states where the metabolism of a drug can be impaired, including organ system dysfunction as well as when therapeutic hypothermia is used (21). Therefore, it may be necessary to obtain a routine toxicologic analysis as part of the pediatric brain death determination process, especially when the etiology of the arrest or history is unclear.

Limitations

There were various limitations in this study. This was a single-center retrospective study. Obtaining a toxicologic analysis may have been delayed as stabilization of a critically ill patient was appropriately prioritized over eliciting the etiology of the arrest. In our institution, we recently added the toxicology analysis as part of an electronic health record pediatric cardiac arrest order set. It is unknown how this impacted the clinical decision-making process during the postarrest evaluation, but even though it was present, it still required a clinician to actively select the test during the admission if it was desired. Postmortem autopsy is considered the criterion standard for determining the etiology of OHCA (4). Unless the clinical circumstances warrant it, however, not all patients may undergo an autopsy and may potentially underestimate the etiologies of cardiac arrest in survivors (4). Our comprehensive serum toxicology screen detected salicylates while separate salicylate serum levels were not

detected. The results, therefore, are dependent on the sensitivity or lower level of detection for each drug with the potential for false negatives (22).

CONCLUSIONS

Pediatric OHCA is a rare entity. Toxicologic screens are a clinical tool that can be used to identify the etiology, but it was not routinely sent in our institution. In the toxicology screens that were sent, our institution identified a small number of cases where an OHCA may have been associated with a clinically significant substance found on toxicology analysis. While toxicology screens should be used in cases where the history and physical examination warrant it to increase its yield, the critically ill child may never be in a clinical situation where the value of a toxicology screen can be adequately deliberated by the clinician. There are, however, forensic reasons to obtain a toxicology screen. Accidental and malicious etiologies are a possibility in patients with pediatric OHCA, and therefore we urge emergency physicians and pediatric intensivists who routinely manage these patients to consider sending a toxicology screen because it may provide insight on the cause of the arrest, allow for forensic evaluation, and may protect from child maltreatment.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jemermed.2020.07.020.

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ARTICLE SUMMARY

1. Why is this topic important?

Toxicologic screens may be used as part of a diagnostic evaluation for pediatric out-of-hospital cardiac arrest (OHCA). It is unclear, however, how often the toxicologic screen is applied in the postarrest period and if its results are of clinical utility.

2. What does this study attempt to show?

The study attempts to show how often the toxicologic screen is sent in the post-arrest period and its results.

3. What are the key findings?

Our institution found that the toxicology screen was not part of the routine diagnostic workup for pediatric OHCA, and in those that were sent, a small number of cases may have been associated with a clinically significant substance found on toxicology analysis.

4. How is patient care impacted?

While toxicology screens should be used in cases where the history and physical examination warrant it to increase its yield, the critically ill child may never be in a clinical situation where the value of a toxicology screen can be adequately deliberated by the clinician. This can allow unconscious biases, overreliance on a clinician's experiential knowledge, and pathophysiologic reasoning to dominate the diagnostic approach to an OHCA patient. Because accidental and malicious etiologies are a possibility in pediatric OHCA, we urge clinicians who routinely manage these patients to highly consider sending a toxicology screen because it may provide more insight on the cause of the arrest and may protect from child maltreatment.