FINAL PROJECT REPORT

OHIO DEPARTMENT OF PUBLIC SAFETY: OHIO EMFTS RESEARCH GRANT

Title: Ohio Pediatric Prehospital Sepsis Screen (OH! PS)

Year of Grant Submission: 2017, with one year extension granted in 2018

Date of Final Report: June 30, 2019

Principal Investigator:
Lynn Babcock, MD, MS
Professor Clinical Pediatrics
Division of Emergency Medicine
Cincinnati Children's Hospital Medical Center
3333 Burnet Avenue Cincinnati, OH 45229
Email lynn.babcock@cchmc.org

Co-investigators:
Holly Depinet, MD, MPH, Cincinnati Children's Hospital Medical Center
Julia Lloyd, MD, Nationwide Children's Hospital
Jareen Meinzen-Derr, PhD, Cincinnati Children's Hospital Medical Center

Embargo Request: We are requesting a 1 year embargo from making the full-text report publically available. Dissemination of this report into the public domain during this time frame may impair our goal to publish these findings in a peer-reviewed journal. We permit a record of our report to be visible, but we are requesting it only include metadata, such as the title, author, year, and executive summary.

EXECUTIVE SUMMARY

Recognition of sepsis in children is very challenging for emergency medicine services (EMS) providers given the relatively low frequency of encounters, along with age-dependent variations in vital signs and exam findings. A tool to help EMS providers in Ohio screen children for sepsis could facilitate earlier recognition, interventions, transport disposition decisions, and earlier ED goal-directed therapy, ultimately improving patient outcomes. Using data from July 2013 to June 2017 abstracted from comprehensive in-hospital sepsis registries at Cincinnati Children's Hospital Medical Center (CCHMC) and Nationwide Children's Hospital (NCH) and related patient's electronic health records (EHR) and prehospital care records (PCR) we generated data to inform the preliminary design of a pediatric prehospital sepsis screening tool. Patients of interest were children, ages 0-21, with presumed severe sepsis/septic shock directly transported to the site hospitals via EMS. First, we used a retrospective cohort design to describe characteristics, interventions, and outcomes for children with presumed severe sepsis/septic shock who are evaluated in the prehospital setting by EMS providers compared to children with presumed severe sepsis/septic shock who arrive via other modes. Second, we applied a case-control methodology to identify the factors associated with an increased risk of presumed severe sepsis/septic shock among a group of medically ill children evaluated in the prehospital setting by EMS providers. We found that one quarter of all children with presumed severe sepsis/septic shock interact with EMS prior to arrival at these two large Ohioan Children's Hospitals. These children as compared to those who arrived by their own mode of transport may be underserved, as indicated by larger percentages of children of black race and publically insured, and be a potentially sicker subset of children with sepsis substantiated by the higher proportion of hypotension on arrival, more frequently elevated lactic acid levels in the ED, intubation in the ED, and admission to the ICU, as well as longer hospital and ICU length of stays. Earlier fluid resuscitation occurred earlier in those transported by EMS yet beyond the goal of 15 minutes from arrival; however, receipt of antibiotics in both groups (EMS and

self-transport) did not differ and was beyond the 60 minute best-practice target. Factors reliably captured more than 80% of the time in the prehospital setting and were predictive of children with presumed severe sepsis/septic shock on arrival to the ED included abnormal heart rate, oxygen saturation, mental status, and respiratory rate. Collectively, these results indicate that a prehospital sepsis screen tool could be derived from variables routinely collected in the prehospital setting. Validation of the prehospital sepsis screening tool and an associated prehospital care algorithm has the potential to impact care for a vulnerable critically ill subset of children with sepsis.

TABLE OF CONTENTS

TITLE PAGE	1
EXECUTIVE SUMMARY	2
TABLE OF CONTENTS	4
1. KEY INVESTIGATORS	5
2. PURPOSE OF THE STUDY	6
3. BACKGROUND	8
4. METHODS	11
5. RESULTS	15
6. CONCLUSIONS	24
7. STATUS OF CURRENT WORK	30
8. RECOMMENDATIONS	31
9. REFERENCES	32

1. KEY INVESTIGATORS

Lynn Babcock, MD, MS – Principal Investigator: Dr. Babcock is a Professor of Pediatrics at the University of Cincinnati. She is employed as board-certified pediatric emergency medicine physician in the Division of Pediatric Emergency Medicine at Cincinnati Children's Hospital Medical Center. She has an extensive academic portfolio that includes numerous clinical, teaching, administrative and research pursuits. She designed the study, lead all study activities, supervised the conduct of the study and data collection activities at Cincinnati Children's, interpreted the analysis, presented data at national meetings, and prepared all reports, presentations, and manuscripts.

Holly Depinet, MD, MPH – Co-Investigator: Dr. Depinet (Brodzinski), MD, MPH, is an Assistant Professor at the University of Cincinnati. She is employed as a pediatric emergency medicine physician within the Division of Pediatric Emergency Medicine at Cincinnati Children's Hospital Medical Center. She is involved in the EM Quality Research Focus Group, Hospital-wide Safety Research Committee and national collaboratives aimed at improving care for pediatric sepsis. Dr. Depinet assisted with the design of the study, supervised the collection of data at Cincinnati, and prepared key reports and manuscripts.

Jareen Meinzen-Derr, PhD – Statistician: Dr. Meinzen-Derr is a Professor of Pediatrics at the University of Cincinnati. She is employed in the Division of Biostatistics at Cincinnati Children's Hospital Medical Center. She assisted with the design of the study, conducted the analysis, and assisted with the preparation of key reports, presentations, and manuscripts.

Julia Lloyd, MD – Co-Investigator: Dr. Lloyd is an Assistant Professor in the Department of Pediatrics at The Ohio State University and an attending physician in the Emergency Department at Nationwide Children's Hospital. She assisted with the design of the study, lead the conduct of the study and collection of the data at Nationwide Children's Hospital, presented research findings at national meetings, and prepared key reports and manuscripts.

2. PURPOSE OF STUDY

Each year in Ohio, there are over 34,000 cases of sepsis, which are associated with up to 10% mortality.[1] Sepsis is a syndrome identified by a constellation of clinical signs and symptoms in a patient with suspected infection, whereas septic shock is the presence of sepsis plus cardiovascular organ dysfunction.[2,3] While early goal-directed treatment improves patient outcomes, early recognition of sepsis, and particularly those in shock, is the necessary first step in this process.[2,4,5] In absence of a gold standard diagnostic test, sepsis screening tools rely on a combination of vital signs and clinical findings to facilitate recognition and prompt earlier treatment.[5-7] Despite growing use of these tools in pediatric and adult emergency departments (EDs) and in the prehospital setting by emergency medicine services (EMS) personnel for adults, **prehospital sepsis screening tools for children are absent**.[5-14] Recognition of sepsis in children is very challenging for EMS providers given the relatively low frequency of encounters, along with age-dependent variations in vital signs and exam findings.[15-17] Thus, we set forth to generate data to inform the preliminary design of a pediatric prehospital sepsis screening tool that could facilitate earlier recognition, interventions, transport disposition decisions, and earlier ED goal-directed therapy, ultimately improve patient outcomes.

The objectives of this project were to describe the prehospital presentations of children with presumed severe sepsis/septic shock and ascertain prehospital variables that can discern them. We extracted data from comprehensive in-hospital sepsis registries, patient's electronic health records (EHR) and prehospital care records (PCR) who were transported by EMS for presumed severe sepsis/septic shock to one of two large Ohioan hospitals, Nationwide Children's Hospital (NCH) and Cincinnati Children's Hospital Medical Center (CCHMC), over the time period July 2013 to June 2017. Using mixed methodology, we addressed the following aims and answered the following hypotheses:

Aim 1: To describe characteristics, interventions, and outcomes for children with presumed severe sepsis/septic shock who are evaluated in the prehospital setting by EMS providers.

Design: Retrospective cohort of children with presumed severe sepsis/septic shock who arrive via EMS as compared to other modes of arrival.

Hypothesis 1.1: Children with presumed severe sepsis/septic shock evaluated in the prehospital setting by EMS providers will have a shorter time to initiation of first fluid bolus and to first dose of antibiotics as compared to children who arrive via other modes.

Hypothesis 1.2: Children with identified presumed severe sepsis/septic shock who arrive by EMS will have improved outcomes, including mortality and length of intensive care and hospital stays as compared to other children who arrive via other modes.

Outcomes: Primary outcomes were time to initiation of the first bolus and the first dose of antibiotics. Secondary outcomes were 3 and 30 day in-hospital mortality, total hospital length of stay (days), intensive care length of stay (days), and duration of pressor use (hours).

Aim 2: To identify factors associated with an increased risk of presumed severe sepsis/septic shock in children among a group of medically ill children evaluated in the prehospital setting by EMS providers.

Design: Case-control of children who arrive via EMS comparing those with presumed severe sepsis/septic shock to those with other medical illnesses.

Hypothesis 2: A set of high-risk screening variables that are readily captured by EMS (>70% of the time) will have high sensitivity (> 90%) for identifying children with presumed severe sepsis/septic shock in the prehospital setting.

Outcome: The primary outcome was presumed severe sepsis/septic shock upon arrival to the receiving ED.

3. BACKGROUND

Pediatric sepsis is a significant problem with high morbidity. Pediatric septic shock is a problem that is both common (>175,000 hospital admissions for children annually) and serious (mortality up to 21%).[18] Time sensitive, goal-directed treatment improves patient outcomes, including mortality and duration of intensive care and hospital stays.[5] Sepsis and septic shock are diagnoses that are along a spectrum of disease severity, from ill, but compensating to critical.[2] Though definitions vary, pediatric sepsis is frequently defined as patients with known/suspected infection who meet systemic inflammatory response syndrome criteria. Severe sepsis and septic shock are a smaller, sicker subset of this group, with the wording "severe sepsis" referring to patients with sepsis plus cardiovascular dysfunction or acute respiratory distress syndrome, or signs of two types of end-organ failure (renal, hepatic, etc.,); and "septic shock" referring to patients with sepsis plus cardiovascular dysfunction.[2] All categories can include patients with normal or abnormal blood pressures.

National efforts to decrease morbidity associated with sepsis for children have initially focused on designing and implementing screening tools help detect sepsis in ED settings. Identification of children with sepsis is the necessary first step to initiate care; however, identifying these children is challenging in busy ED settings since clinical signs and symptoms are the primary means of sepsis identification.[13] Even with structured screening tools, identification is still an obstacle.[19-21] Several sites have shown that the use of ED shock protocols, including a screening tool, rapid clinician assessments, and standardized pathway, implemented via quality improvement methods, can improve time to critical interventions such as fluids and vasopressors, and outcomes such as mortality, intensive care unit length of stay and acute kidney injury.[5-7,13,14,22,23] Building on these successes, several national collaboratives, including the CHA 2012 IPSO collaborative and the 2013-2016 ED-based AAP Pediatric Septic Shock Quality Improvement Collaborative, have worked to implement these protocols in pediatric EDs.[11] The next

step, a national, hospital-wide collaborative, is underway in IPSO. This includes the use of screening tools throughout the hospital, coupled with standardized care pathways to improve early recognition and therapy for pediatric septic shock. The aims of IPSO are to reduce sepsis mortality by 75 percent and reduce hospital-onset severe sepsis by 75%. IPSO plans to address all stages of sepsis across the care continuum, starting with the ED and intensive care and then expanding to prehospital and ambulatory settings in subsequent phases.

Ohio hospitals, including CCHMC and NCH, are leading the way to improve outcomes for patients with sepsis by focusing on early recognition. In 2015, The Ohio Hospital Association (OHA) launched its first phase of its initiative, OHA Signs of Sepsis (SOS), to decrease sepsis-related morbidity by 30% by 2018.[1] Participating hospitals are identifying gaps in care, implementing a 3-hour bundle designed to promote timely recognition and treatment in the ED, and uploading process measure and outcome data for analysis. Prior to the OHA initiative, in 2013, the two largest Children's Hospitals, CCHMC and NCH, implemented ED triage sepsis screening tools based upon guidance from the AAP Septic Shock Collaborative to improve recognition and emergent care processes. Since the introduction of these tools, the timeliness of delivery of fluid boluses and antibiotics has improved at both sites and the processed are continually being optimized.

Application of sepsis screening tools using select clinical variables in the prehospital setting for adults has been shown to decrease time to the initiation of antibiotics and other goal-directed treatments. In the prehospital setting for adults, temperature, heart rate, respiratory rate, systolic blood pressure, mean arterial pressure, and lactate have independently been identified as indicative of sepsis and are in various manners being utilized by some EMS as screening tools.[8,10,12,24,25] While evidence is currently being collected, it is hypothesized that screening tools applied in the prehospital setting at the first

encounter may facilitate earlier recognition by prehospital providers, assist with transport decisions, encourage earlier interventions in the field and in the hospital, mobilize hospital resources earlier, and ultimately improve patient outcomes in a similar manner to the improvements in care from implementation of trigger tools in ED triage.[26-28] In a recent systematic review examining the impact of prehospital care on outcomes associated with sepsis in adults, EMS identification of sepsis lead to a decrease of 30-50 minutes for initiation of antibiotic therapy.[29] Factors that led to this included ED pre-alert and EMS IV placement. Guidance about early recognition and prehospital management of the adult septic patient was recently outlined in a 2013 White Paper generated from the Central Ohio Trauma System.[12] It proposes generating a prehospital sepsis alert to the receiving hospital if the following criterion are met: systolic hypotension (<90 mmHg) or 2 or more of the following variables – heart rate >90 beats per minute, temperature <96.8 or >100.4°F, respiratory rate ≥ 20 breaths per minute, acute alerted mental status, and lactate ≥ 4mmol/L. Although the paper notes that young children are at increased risk of sepsis, no pediatric-specific guidance was outlined. While EMS crews do not utilize a pediatric screening tool in our communities, we hypothesize that they can recognize a critically ill child prompting either a pre-alert to our EDs or placement of an IV in the field, which could lead to shorter time to initiation of first fluid bolus and to first dose of antibiotics *(Hypothesis 1.1)*. Given this hypothesis that these patients were likely to receive earlier resuscitation, we hypothesized that EMS care could potentially lead to improved sepsis related outcomes *(Hypothesis 1.2).*

Prehospital care of children is challenging for paramedics primarily because there is less exposure, with children accounting for approximately 10% of all EMS runs.[16,17,30-33] Fewer exposures results in less experience and less comfort dealing with children, particularly more critically ill.[30] In addition, pediatric patients present increased levels of difficulty for procedures such as intravenous access, are more problematic to transport safely, and there are often fewer destinations with pediatric expertise.[34-37]

Prehospital pediatric sepsis screening tools have not been developed or tested. In addition to the challenges inherent in prehospital pediatric care itself, pediatric screening for severe sepsis/septic shock is especially challenging since normal vital signs (an important component of sepsis screening tools) differ by age, mental status can be difficult to ascertain in upset children, and the difficulty in obtaining intravenous access makes point of care lab screening less feasible. Several of the published sepsis screening tools incorporate laboratory data that cannot be obtained in prehospital settings, such as white blood cell counts, while others, such as lactate, are not routinely captured by all EMS agencies. These limitations may impair translation of adult sepsis screening tools to the pediatric population in the prehospital setting. Thus, there is a critical need for development and implementation of pediatric-specific screening tools for sepsis applicable to the unique challenges of the prehospital environment. We hypothesize that a pediatric prehospital sepsis screening tool can be developed and ultimately be implemented and lead to improved sepsis related outcomes, as has been done for adults (*Hypothesis 2).*

4. METHODS

Design: To address Aim 1, we used a retrospective cohort study design of children with presumed severe sepsis/septic shock who arrive via EMS as compared to other modes. To address Aim 2, we used a case-control study design of children who arrive via EMS comparing those with presumed sepsis to those with other medical illnesses.

Study Population: Children, ages 0 to 21 years, were selected if they were treated in either the participating EDs from November 2013 to June 2017. Mode of transport was determined from documentation in a form field in the EHR. If mode of transport was not documented, patients were classified as EMS-transported if there was an affiliated PCR or there was annotation in the chart reflecting EMS transport, otherwise they were classified as self-transported. Interfacility transports (i.e.,

any transfer, after initial assessment and stabilization from a health care facility) were excluded. Selection of patients with presumed severe sepsis/septic shock utilized an intention-to-treat approach and included any patient who received a blood culture, antibiotics and 2 or more boluses in the ED setting and one of the following additional criteria: (i) diagnostic code (ICD-9/10) consistent with severe sepsis/septic shock. (ii) intensive care unit admission or rapid floor to intensive care unit transfer within 12 hours of admission; (iii) lactate/procalcitonin; or (iv) positive sepsis screening by either paper or electronic measures resulting in treatment for severe sepsis/septic shock.

Retrospective Cohort Study Population: The exposed group consisted of all children, ages 0 through 21 years, who had presumed severe sepsis/septic shock as previously defined. The unexposed group were children with presumed severe sepsis/septic shock that presented directly via their own mode of transportation, i.e. self-transported, to one of the two aforementioned EDs.

Case-Control Study Population: Cases were children with presumed severe sepsis/septic shock. Up to two controls for each case were selected at each site from a query of the electronic health records for children, 0-21 years of age, transported by EMS during the study period for a medically-related illness but who did not have presumed severe sepsis/septic shock. Children were identified as having a medically-related illness by the exclusion of patients with diagnostic codes assigned the relevant ED visit related to injuries, trauma, external causes of morbidity, cardiac arrest, behavioral health, psychiatric conditions, pregnancy and childbirth related conditions. Manual review of all prehospital care record was performed to ensure eligibility. To adjust for temporal changes in care and processes, the selection of controls was further refined to include those who presented closest in time and no more than one year of the index case. Controls were matched to the index case on age (+/- one year) in an effort to

account for age-dependent variations in sepsis risk and ED Emergency Severity Index triage category code (Levels 1-5) in an attempt to match on severity of illness and index of suspicion for sepsis.

Methods of Data Extraction and Measurement : For the unique encounters during the study period, data was extracted from each site's prospectively collected sepsis registry, the patient's electronic health record (EHR), and the patient's prehospital care record (PCR) which are scanned and uploaded into the EHR. Hospital data extracted included demographic characteristics, payer source, history of high-risk chronic medical conditions (including malignancy, asplenia, including sickle cell disease, bone marrow transplant, central or indwelling line or catheter, solid organ transplant, immunodeficiency, immunocompromised, or immunosuppression, significant hypoxic-ischemic encephalopathy, or recent or ongoing chemotherapy), triage category, triage vital signs and triage exam findings – temperature, heart rate, respiratory rate, systolic blood pressure, mental status, oxygen saturation, capillary refill, skin findings, ED primary diagnosis, ED disposition, and care time stamps. Time stamp associated with the triage heart rate time was used as the triage time. ICD-10 codes listed in the medical history were used to categorize high-risk chronic medical conditions using the Complex Chronic Condition Classification System, version 2, developed by Feudtner et al.[38] Time to antibiotics or fluids were determined by the difference in time stamp associated with the start of the first bolus, or first antibiotic, respectively, to the time stamp associated with the triage heart rate.

Prehospital data abstracted included: patient chief complaint, paramedic impression, temperature, Glasgow Coma Scale score, level of alertness (alert, verbal, pain, unresponsive - AVPU), capillary refill time and quality, respiratory rate, heart rate, oxygen saturation, and blood pressure. Other variables collected included end-tidal carbon dioxide, field interventions/procedures, number of procedure attempts, cardiac arrest, and resuscitation efforts. Interventions including vascular access attempt (unsuccessful, successful, or none) and type (intravenous or intraosseous), and fluid administration and

volume were obtained. EMS demographic data extracted included agency name, unit type, type of response and response mode. Time data was extracted to calculate times of interventions – dispatch, arrival on scene, arrival at patient, scene departure, and arrival time at hospital. EMS patient contact time was calculated as the difference from time at patient (or if missing time at scene) to hospital arrival time. If hospital arrival time was missing on the EMS run sheet, arrival time from hospital triage was used. Both specific data fields and narrative were reviewed to ensure capture of relevant data, and where multiple data points are documented, the first value was used. Discrepancies were reviewed and rectified in consultation between two study team members. EMS provider impressions were categorized in accordance to the National EMS Information System broader provider impression category framework.

For clinical signs, normative ranges were established based upon best-evidence. Heart rate, respiratory rate and systolic blood pressure were based on age-categorized Pediatric Advanced Life Support (PALS) criteria. Mental status was categorized as abnormal if the was Glasgow Coma Scale was < 15 or it was documented as anything other than “alert” on the Alert-Verbal-Pain-Unresponsive (AVPU) level of alertness scale in the narrative. Delayed perfusion was defined as either capillary refill > 3 seconds or was documented as “prolonged” or “delayed” in the narrative. Hypoxia was defined as peripheral capillary oxygen saturation (SpO2) of < 93%. Abnormal temperature was determined by age-based cut offs and included either hypothermia or hyperthermia – < 3 months of age: <36 or > 38°C, and >3 months of age: <36 or >38.5°C. Abnormal glucose was determined using age-based cut-offs and included either hypo- or hyperglycemia --0-1 month: <50 or >140 mg/dL, and >1 month: <70 or >140 mg/dL.

Analysis to Date: Basic descriptive statistics to summarize the patient characteristics, EMS care parameters and processes, ED care parameters and processes, and in-hospital outcomes. If values were

missing in either the sepsis registry or the prehospital records, they were recorded as not documented. Categorical data are summarized by frequencies and percentages and continuous data are presented as median and interquartile ranges (IQR). For Aim 1, cohort study, the significant differences in characteristics, process and outcomes were tested between the EMS-transported and self-transported groups using t-tests for continuous measures and chi-square test for categorical measures and nonparametric methods when appropriate. Similar analyses were performed to detect differences in potential confounders and covariates. Kaplan-Meier survival curves, using the cumulative incidence proportion (1 – survival), were created to demonstrate the proportions of study patients receiving the outcome measures at various points of elapsed time. Future analysis will include survival analysis controlling for covariates such as disease severity. For Aim 2, case-control study, significant differences between cases and controls were summarized using t-tests for continuous measures and chi-square test for categorical measures and nonparametric methods when appropriate. Frequency of capture and abnormality of common screening factors were calculated. To determine the risk factors associated with presence of presumed severe sepsis/ septic shock in children transported by EMS, bivariable odds ratios with 95% confidence intervals were calculated. Future analysis will include multivariable analysis controlling for covariates.

5. RESULTS

Aim 1:

Of all the patients evaluated in the two participating EDs for presumed severe sepsis/septic shock, 24.3% (355/1458) arrived via EMS versus by their own mode of transportation. The group transported by EMS (n=355) were compared to the group that was self-transported (n=1458) and the demographics and patient level factors are presented in Table (1). There are some statistical differences between the races and payor status in the two groups with a greater percentage of black children and those with

public insurance being transported by EMS. The percentage of patients with chronic medical conditions placing them at higher risk for sepsis was higher for those who were self-transported. ED care practices differed between groups with children with severe sepsis/septic shock transported by EMS more frequently being assigned higher triage category, receiving care in the ED resuscitation suite, and hypotension on arrival, as compared to those who were self-transported.

Table 1. Patient Characteristics and Arrival Metrics of Children with Presumed Severe Sepsis/Septic Shock who Arrived via EMS versus Self-Transport

		EMS	Self-Transport	p-value
		N=355	N=1458	
Patient Characteristics				
	Median Age, years [IQR]	7.1 [2.1-14.0]	6.1 [2.5-12.9]	0.53
	Sex, % Male	58.60%	52.90%	0.05
	Race*			0.08
	White	67.60%	70.90%	
	Black	22.30%	17.00%	
	Other	9.60%	11.90%	
	Ethnicity, % Non-Hispanic	96.30%	94.50%	0.29
	Payer Status*			<0.0001
	Private	29.00%	45.60%	
	Public	68.70%	46.10%	
	Other	2.00%	7.70%	
	High Risk Condition*	33.50%	58.70%	<0.0001
ED Arrival Metrics				
	ED Triage Category (Acuity)*			<.0001
	Critical	17 (4.8%)	20 (1.4%)	
	Emergent	295 (83.1%)	1247 (85.5%)	
	Urgent	32 (9%)	161 (11%)	
	Non-Urgent	2 (0.6%)	18 (1.2%)	
	Care in the Resuscitation Suite*	186 (52.5%)	321 (22%)	<0.0001
	Age-dependent Tachycardia	222 (62.7%)	893 (61.3%)	0.62
	Hypotension*	45 (12.8%)	79 (5.4%)	<.0001

For those who arrived by EMS, 125 prehospital care records were missing from the hospital medical record. A total of 74 unique EMS agencies from 3 different states transported the 230 children who had presumed severe sepsis/septic shock and a prehospital record. Of these, 206 were transported by

Advanced Life Support (ALS) units, 156 patients were placed on oxygen; 63 patients via non-rebreather mask, and 21 patients were intubated. Vascular access was attempted on 35 patients and successful in 14 patients, with all being peripheral IVs and no intraosseous needles were attempted. IV fluids were administered to 6 patients, and patients received on average 5 mL/kg. Medications were administered to 47 patients, of which the most common medication was albuterol or a duonebulizer (albuterol + ipratropium bromide). A benzodiazepine was given to 11 patients. The median EMS patient contact time was 37 minutes (IQR 29-46).

Table 2 displays a selection of ED tests and interventions and hospital-based outcomes for patients with presumed severe sepsis/septic shock. The median time to first bolus was significantly shorter (37 minutes) in those patients transported by EMS, when compared to those self-transported (56 minutes). Time to antibiotics showed some trend towards significance, but was not found to be significantly different between groups (80.5 vs 87 minutes). EMS patients were also more likely to be admitted to the ICU.

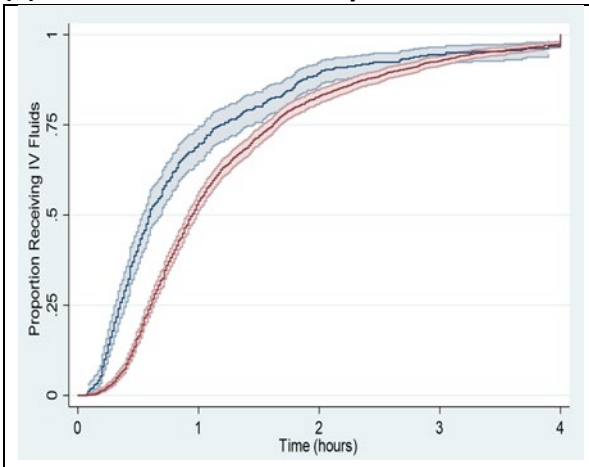
THE REST OF THIS PAGE WAS INTENTIONALLY LEFT BLANK

Table 2. ED Care Processes and Hospital Based Outcomes of Children with Presumed Severe Sepsis/Septic Shock who Arrived via EMS versus Self-Transport

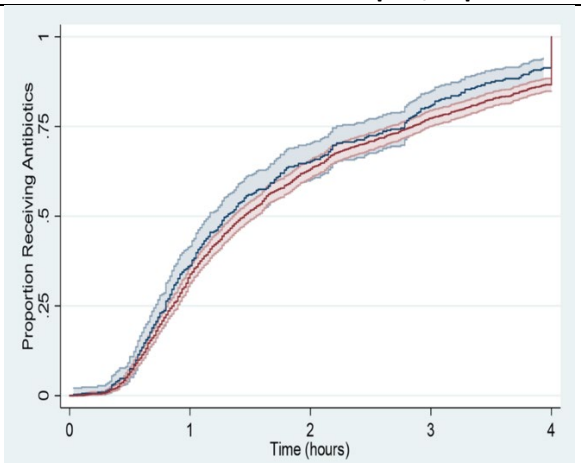
		EMS	Self-Transport	p-value
		N=355	N=1458	
ED Process Outcomes				
	Lactic Acid Obtained	245 (69%)	859 (58.9%)	
	Median value [IQR]	2.4 [1.5-3.8]	1.9 [1.3-2.7]	<0.0001
	% > 2 mmol/L	148 (60.4%)	352 (41%)	<0.0001
	Pressors Initiated in ED	21 (9%)	71 (4.9%)	0.003
	Intubated in ED	52 (14.7%)	41 (2.8%)	<.0001
	Median Time to First Bolus, minutes [IQR]	36 [21-71]	57 [36-97]	<0.0001
	Median Time to Antibiotics, minutes [IQR]	78.5 [48-167]	86 [51-170]	0.14
	ICU Admission	77.1%	49.1%	<0.0001
Hospital Based Outcomes				
	Median Hospital Length of Stay, days [IQR]	6 [3-12]	4 [2-8]	<0.0001
	Median Intensive Care Unit Length of Stay, hours [IQR]	69 [31.5-151]	47 [24-112.5]	0.0007
	3 day mortality	7 (2%)	11 (0.8%)	0.065
	30 day mortality	11 (3.1%)	20 (1.4%)	0.024

THE REST OF THIS PAGE WAS INTENTIONALLY LEFT BLANK

Figure 2. Survival Curves for Cumulative Incidence Proportion for Time to (a) Initiation of IV Fluids and (b) Initiation of Antibiotics by Mode of Arrival in Children with Presumed Severe Sepsis/Septic Shock



(a) Initiation of IV fluids, p<0.0001
____ EMS Transported
____ Self-Transported



(b) Initiation of Antibiotics, p<0.0001
____ EMS Transported
____ Self-Transported

The Kaplan-Meier survival curves (using failure function to demonstrate cumulative incidence) representing the proportion of patients with presumed severe sepsis/septic shock receiving first IV fluid bolus and antibiotics by mode of arrival at varying elapsed time intervals are demonstrated in Figures 1 and 2. For both endpoints, patients transported by EMS had a significantly elevated Cox Proportional Hazard Ratio than those self-transported.

Aim 2:

For both sites, 220 cases (children with presumed severe sepsis/septic shock transported by EMS) were identified and had medically ill controls transported by EMS matched on site of presentation, age, date of presentation. Two controls were identified for 210 cases, whereas only one control was identified for 10 cases, as displayed in Table 3.

Table 3. Case: Control Study Population		
	Site 1	**Site 2**
Cases (Presumed Severe Sepsis/Septic Shock + EMS)	157	63
Matched Controls (Medical Illness + EMS)	12	118
Matching Case: Control Ratios		
2:1	155	55
1:1	2	8

Demographic characteristics of cases were similar to controls with respect to age, sex, ethnicity, payor, yet differed in terms of race, with more controls being of black race, Table 4. Most patients were deemed critically ill upon arrival to the ED as represented by the high percentage who were categorized at ESI Triage Category 2. EMS patient contact time for cases was statistically longer than controls by a median of 3 minutes. EMS field interventions (vascular access or IV fluids) were minimal. Table 4 also describes the frequency of the most common EMS provider impressions (categorized using the NEMSIS broader categories), as well as the most common hospital primary diagnoses. EMS frequently classified children with septic shock as having either respiratory or general illnesses; rarely with infection or shock, both categories that could include severe sepsis/septic shock.

The frequency of capture of common sepsis screening factors for both cases (septic shock) and for controls (other medical illness) are displayed in Figure 1. The total bar represents the frequency of capture of the variable, whereas the red bar represents the proportion that was abnormal as previously defined in the methods and the gray bar represents the proportion that was normal. The green line at 70% represents the threshold we proposed of acceptable routine capture to be a plausible predictor to be included in a prehospital sepsis screen. EMS capture rates of sepsis screening factors were highest (>70%) for mental status, heart rate, respiratory rate and oxygen saturation. Prehospital systolic blood pressure (BP) was only captured 55% of the time by EMS. Prehospital perfusion, temperature, and glucose were less frequently captured by EMS.

The odds of association of prehospital captured factors with patients who had presumed severe sepsis/septic shock is displayed in Figure 2. Age-based abnormal heart rate (tachycardia or bradycardia), hypoxia, alteration in mental status, and tachypnea all had odd ratios greater than 1 with 95% confidence intervals that did not cross 1 suggesting that there are associated with prediction of severe sepsis/septic shock on arrival in the ED. When captured, hypotension also may be associated with prediction of severe sepsis/septic shock, but the confidence interval was very wide. Lastly, when captured, delayed perfusion, abnormal temperature (hypo or hyperthermia), or abnormal glucose were not associated with presumed severe sepsis/septic shock.

THIS REST OF THIS PAGE WAS INTENTIONALLY LEFT BLANK

Table 4. Description of the Case: Control Study Population

	Cases N=220 n (%)	Matched Controls N=430 n (%)
Age - median in years [IQR]	7.2 [1.9-14.7]	7.2 [2.0-15]
Sex		
Male	131 (59.5%)	251 (58.4%)
Female	89 (40.5%)	179 (41.6%)
Race*		
White	142 (64.5%)	215 (50%)
Black	57 (25.9%)	178 (41.4%)
Other	21 (9.6%)	37 (8.6)
Ethnicity		
Non-Hispanic	213 (96.8%)	409 (95.1%)
Hispanic	6 (2.7%)	18 (4.2%)
Unknown	1 (0.5%)	3 (0.7%)
Payor		
Private	62 (28.3%)	140 (32.6%)
Public	153 (69.9%)	285 (66.3%)
Self-pay/other	4 (1.8%)	5 (1.1%)
EMS Patient Contact Time - median in min [IQR]* †	29 [21-38]	26 [18-35]
EMS Vascular Access		
Yes	13 (5.9%)	60 (14%)
Failed	20 (9.1%)	17 (4%)
No/not documented	187 (85%)	353 (82.1%)
Intravenous (IV) Fluids Initiated	6 (2.7%)	7 (1.6%)
Most Common Paramedic Impression		
Respiratory	84 (38.2%)	122 (28.4%)
General Ill	60 (27.3%)	96 (22.3%)
Central Nervous System	24 (10.9%)	82 (19.1%)
Psychiatric/Behavioral	11 (5%)	25 (5.8%)
Gastrointestinal	8 (3.6%)	20 (4.7%)
Diabetes	5 (2.3%)	12 (2.8%)
Pain, non-abdominal	3 (1.4%)	27 (6.3%)
Shock	1 (0.5%)	1 (0.2%)
Infection	2 (0.9%)	2 (0.5%)
Cardiac/Circulatory	1 (0.5)	8 (1.9%)
ED Triage Category		
1 (highest)	4 (1.8%)	5 (1.2%)
2	198 (90%)	390 (90.7%)
3	17 (7.7%)	31 (7.2%)
4	1 (0.5%)	4 (0.9%)
Most Common Hospital Primary Diagnosis		
Sepsis	24 (15.1%)	1 (0.3%)
Pneumonia	18 (11.3%)	7 (2.2%)
Convulsions (unspecified)	1 (0.6%)	21 (6.6%)
Acute Bronchiolitis	5 (3.1%)	12 (3.8%)
Acute Upper Respiratory Infection	5 (3.1%)	10 (3.1%)
Simple Febrile Convulsions	1 (0.6%)	14 (4.4%)
Acute Obstructive Laryngitis	0	14 (4.4%)
Syncope/Collapse	1 (0.6%)	11 (3.5%)
Sickle Cell Disease with Crisis	1 (0.6%)	9 (2.8%)
Epilepsy	1 (0.6%)	9 (2.8%)
Pneumonitis (food/vomit)	8 (5%)	0

* statistically significant difference ($p<0.05$) between cases and controls

† times missing from 17 encounters

Figure 1. Common Sepsis Screening Factors: EMS Capture Rates and Normality of Values

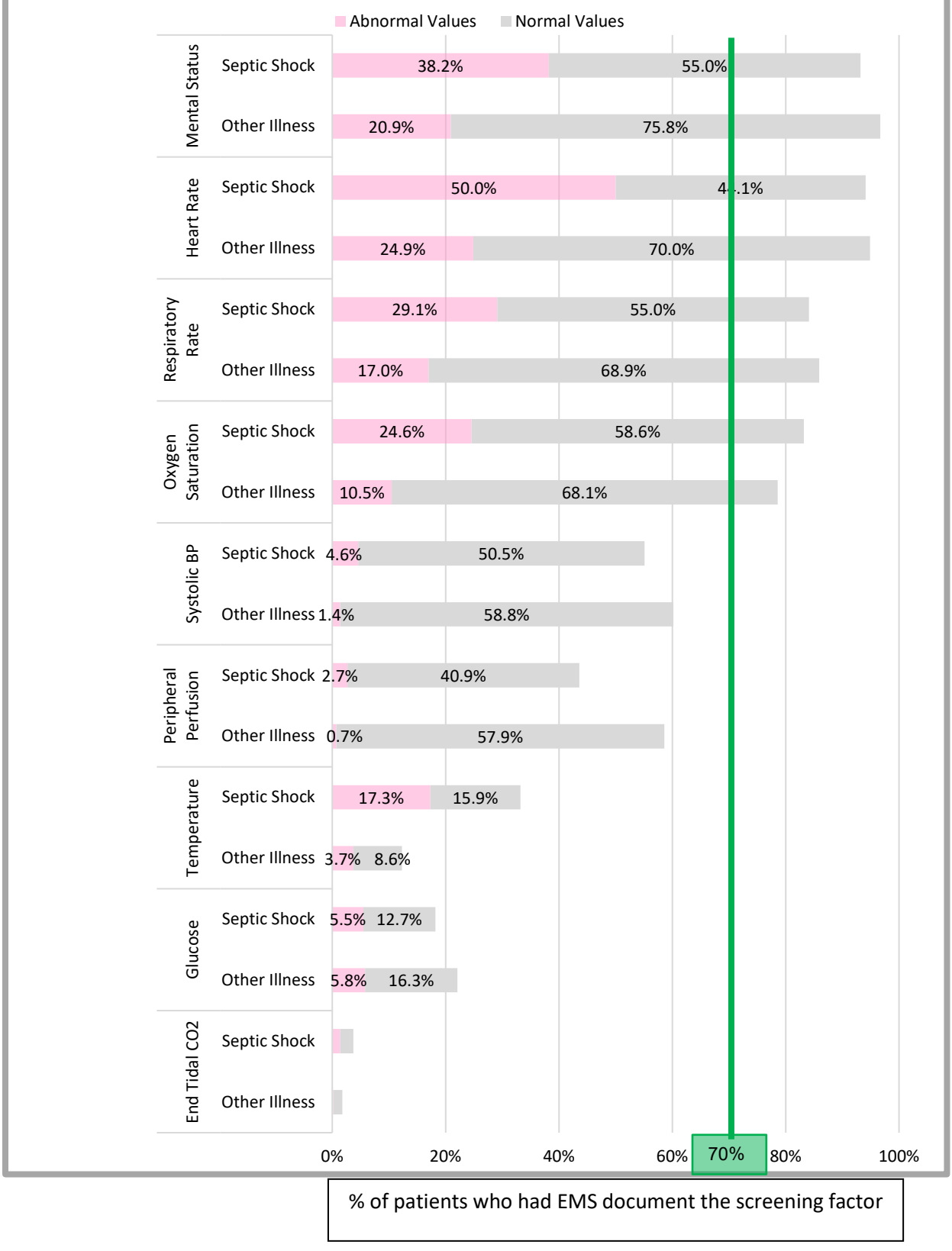
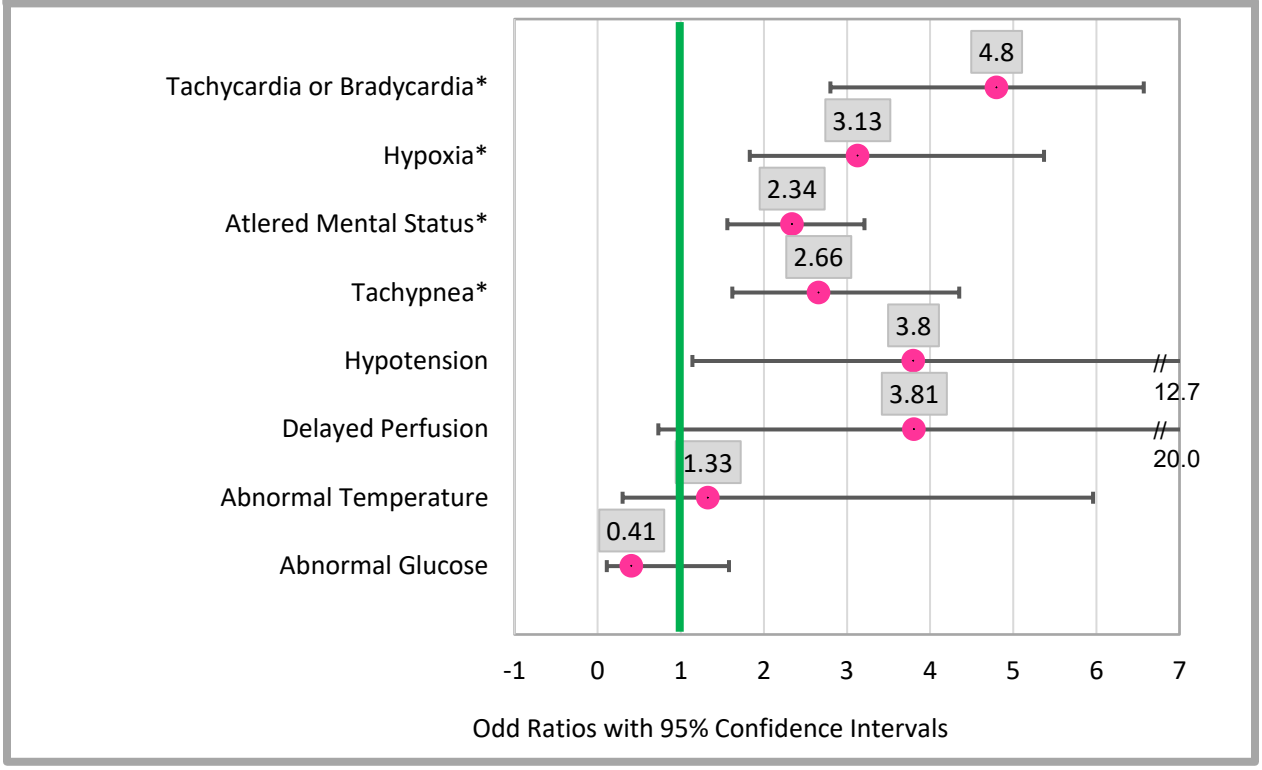


Figure 2. Association of Prehospital Factors Captured by EMS with Presumed Septic Shock



* captured >70% of the time by EMS during routine care
● odd ratio

6. CONCLUSIONS

Aim 1:

Of all the children with presumed severe sepsis/septic shock who are cared for in two large Ohioan children's hospitals, nearly one quarter had contact with EMS prior to arrival. As hypothesized, children with presumed severe sepsis/septic shock evaluated in the prehospital setting by EMS providers compared to children who arrive via other modes did have a shorter time to initiation of first fluid bolus, yet time to first dose of antibiotics was no different between groups. Despite earlier fluid resuscitation and contrary to our hypothesis that this earlier intervention would lead to improved outcomes, these children transported by EMS had longer length of intensive care and hospital stays as compared to other children who arrive via other modes. Although sepsis remains a high cause of mortality in patients

worldwide, mortality was infrequent in either study group. Outcomes were likely not affected since the children arriving by EMS were sicker as determined by the higher proportion of hypotension on arrival, elevated lactic acid levels in the ED and intubation in the ED. These children arriving by EMS also were more likely to have a higher (more critical) triage level, receive initial care in the ED resuscitation suite which also may be indicators of severity but arrival by EMS may influence initial ED assessment and be considered more critical by the receiving hospital staff.

While the children with presumed severe sepsis/septic shock transported by EMS were similar in age and sex as those who arrived by their own mode of transport, a larger percentage were of black race and publically insured indicating they may be of lower socioeconomic status and may have a lack of self-transportation options. These demographics are similar to those historically served by EMS, underscoring the importance of improved recognition and care of these critically ill but traditionally medically underserved children. On the other hand, children with pre-existing chronic medical conditions were more likely to arrive via own mode of transport. Parents of these children with likely have interacted frequently with the medical community and may have secured a private means of transportation in the event that their child becomes ill, e.g. a child with leukemia and a central line has a high likelihood of needing urgent medical attention.

According to the Shock Guideline in the National Model EMS Model Guidelines, Version 2.2 (2019), EMS providers are to initiate early fluid resuscitation if sepsis is suspected.[39] In our population, this rarely happened as only 15.3% had vascular access attempted and 1.7% received any intravenous fluids. Although the guidelines also suggest placement of an intraosseous needle if IV access could not be secured, none were placed. Given that the median EMS patient contact time was 37 minutes (IQR 29-46), EMS likely had sufficient time to achieve the recommendation of administering 30 ml/kg over less

than 15 minutes prior to arrival. While progression of illness from the prehospital setting to hospital setting may have occurred, many patients had documented abnormal vital signs prior to arrival in the ED (see Figure 1 from Aim 2). Barriers to adherence to guidance are unknown and likely multi-factorial; however, a standardized approach with tools to facilitate recognition and guide care may improve adherence to care goals including fluid and antibiotic administration similar to effect these tools have had in the ED and hospital setting. [5-7,14] In one study of adults, the effect of prehospital initiation of fluids was associated with reduced likelihood of organ failure and mortality, yet the effect of prehospital fluid resuscitation for children with severe sepsis/septic shock is not known.[27]

Upon arrival to the ED, patients arriving via EMS did receive fluid resuscitation sooner than children who arrived by their own transportation. Time decreases in fluid resuscitation have also been seen in adult patients with severe sepsis/septic shock arriving via EMS.[26-28] However, the median times of in-hospital initial fluid resuscitation of 36 [21-71] and 57 [36-97] minutes, EMS and self-transport respectively, were still outside of the national ED benchmark of in-hospital delivery of 20 mL/kg of isotonic fluids within the first 15 minutes. Similarly, time to antibiotics of 78.5 [48-167] and 86 [51-170] minutes, EMS and self-transport respectively, was outside the recommended ED benchmark of 60 minutes from arrival to the ED. In contrast to our results that showed no difference in times to antibiotics based on mode of arrival, adults with severe sepsis/septic shock arriving by EMS typically receive antibiotics faster.[26,28,40] Our findings indicate a need to assess hospital-based delays in administration to improve this metric. Ongoing analysis is evaluating the impact of severity of illness on these in-hospital process measures. In a recent systematic review, adults arriving via EMS receive antibiotics 30-50 minutes sooner than those arriving by private transportation if EMS identifies sepsis and informs the receiving clinician; thus, similar results could be seen in pediatric patients if EMS utilized similar processes improve recognition in children.[29]

Aim 2:

In a group of medically ill children who are transported by EMS to one of two large Ohioan children's hospitals, a combination of abnormal mental status, heart rate, respiratory rate and oxygen saturation may be helpful in identifying children who may have severe sepsis/septic shock. These factors are routinely documented by EMS providers, as evident by capture rates of over 80% for each one. In medically ill children, prospective assessment of the test characteristics of a screening tool that incorporates these factors is needed prior to wide-spread implementation. Subsequently, effect on EMS recognition, and on EMS and ED process measures, including initiation of intravenous fluids and antibiotics, as well as patient outcomes, including length of stays and outcomes, can be assessed.

While it is unknown if severe sepsis/septic shock was considered by EMS providers in our population during the encounters with children diagnosed with presumed severe sepsis/septic shock in the ED, EMS rarely documented their final categorical impression as either infection, which could represent earlier in the sepsis severity spectrum, or shock for those in septic shock. Not unlike the ED, quality improvement initiatives may need to be instituted to improve recognition. In seven children's hospitals, implementation of ED-based screening tools bundled with care pathways improved clinical assessment and adherence to the initial fluid resuscitation benchmark of 15 minutes, yet did not impact time to antibiotics nor mortality.[41] Along with robust educational interventions, methods of screening included the incorporation of observed clinical signs and symptoms into either automated electronic or paper-based screening tools were bundled with risk-based clinical decision support to guide further management and/or a method to trigger initial clinical assessment. Translation of this work into the prehospital setting may similarly improve recognition, which is critical to guiding interventions and improving outcomes.

For adults in the prehospital setting, there are over 10 different screening tools that incorporate different combinations and numbers of common variables associated with severe sepsis/septic shock.[42] The variables we identified were included in varying frequency within these 10 tools; respiratory rate was included in 9 of tools, heart rate was in 8, oxygen saturation in 5, and mental status in 4 of the 10 tools. Temperature and systolic blood pressure are both frequently included factors (8/10 and 6/10, respectively) in these adult prehospital screens, yet in our population, these were infrequently documented during routine care. Hypotension is also a key factor in most ED-based tools, and when documented it may be associated with sepsis in our population, yet it was infrequently captured and larger patient numbers are needed to confirm. If additional evidence indicates blood pressure or temperature are essential screening factors for a robust prehospital screening tool, aggressive quality improvement processes would need to be implemented to ensure capture of those variables in the field.

For clinical prehospital practice, a severe sepsis/septic shock screen should primarily be designed to rule out the concern, thus if the screen is negative, the patient does not have severe sepsis/septic shock, i.e., a high negative predictive value. Of those adult prehospital sepsis screens that were tested, negative predictive values were all greater than 80%.[42] Positive predictive values for these tools ranged widely from 19% to 63%. If the screen is positive, initiation of a sepsis-related care pathway has the potential to impact ED and EMS process measures and patient outcomes. In a few separate studies in adults, use of prehospital sepsis screen, did prompt earlier ED fluid resuscitation, and in one study, earlier first antibiotic administration, yet this was not a universal effect. [10,26,28,29,40,43,44] Although there is some evidence that prehospital administration of fluids and antibiotics may improve outcomes in adults, it may be best to first focus on prehospital recognition of sepsis in children with ED notification since prehospital vascular access in these children was infrequently accomplished.

Limitations:

The retrospective nature of this study imparts limitations due to the reliance and interpretation of documentation during routine clinical practice in the medical record, particularly the prehospital care record. Although most factors associated with sepsis are quantitative variables such as heart rate, others are more qualitative, such as mental status and assessment of peripheral perfusion, impairing reliability. Recall bias may also affect prehospital factors if and when documentation does not incur in real-time. Since there is no gold standard method to diagnose sepsis, the use of our definition of presumed severe sepsis/ septic shock based on ED sepsis treatment may limit translation of our results to other settings. Our results are limited in generalizability due to restricted geographic setting, inclusion of only patients evaluated in two large urban children's hospitals, and relatively short EMS patient contact times; however, patients were transported by 73 different EMS agencies improving the generalizability.

7. STATUS OF CURRENT WORK

To date we have completed all outlined work detailed in the grant proposal. We have collected all necessary data, conducted the analyses detailed herein, and are completing additional analyses in preparation for scientific publication. We have submitted 3 abstracts to 2 national meetings which resulted in 3 national presentations. We have been asked to share our results and contribute to two national webinars with different target audiences – one for Emergency Medicine Services for Children and the other for the Children's Hospital Association. These presentations are listed below:

1. **Babcock L**, Lloyd J, Depinet H, Semenova O, Meinzen-Derr J. Prehospital Capture of Variables Commonly Used in Emergency Department Sepsis Screening Tools. Platform Presentation. American Academy of Pediatrics National Conference & Exhibition. Orlando, FL. November 2018.
2. Lloyd J, Semenova O, Depinet H, Meinzen-Derr J, Babcock L. Does Prehospital Care Prime Emergency

Department Sepsis Care? Poster Presentation. American Academy of Pediatrics National Conference & Exhibition. Orlando, FL. November 2018.

3. Babcock L, Brown K. Pediatric Sepsis in the Prehospital Setting. Emergency Medical Services for Children Webinar. November 14, 2018
4. **Babcock L,** Lloyd J, Depinet H, Semenova O, Keener M, Meinzen-Derr J. Prehospital pediatric sepsis screen: what factors should be included? Poster Presentation. Pediatric Academic Societies, Baltimore, MD. April 2019.
5. Babcock L, Brown K. Pediatric Sepsis Screening in Emergency Medicine Services. Children's Hospital Association Webinar, April 8, 2019.

We have two manuscripts in final stages of preparation and anticipate submission to high-impact peer-reviewed scientific journals within the next 4 months. Funding from this grant has allowed us to collect sufficient data to prepare a subsequent prospective multi-center national grant to prospectively derive and validate a prehospital sepsis screening tool for children.

8. RECOMMENDATIONS

Children transported by EMS with presumed septic shock represent a unique vulnerable population, potentially of lower socioeconomic status, who are critically ill and in need of timely resuscitation. Based on our interpretation of the results, we propose that EMS providers in our setting should focus on recognition of severe sepsis/septic shock in pediatric patients as opposed to intervention, given the brief transport times and lack of in-field interventions performed. In absence of a dedicated prehospital intervention bundle, prehospital transport alone did help decrease time to ED fluid resuscitation, but it did not impact time The low capture rate of certain variables, especially blood pressure, suggests that the current hospital-based sepsis screening tools used for children cannot be reliably applied to the prehospital setting. During routine clinical practice, abnormal prehospital heart rate, respiratory rate,

oxygen saturation, and mental status are associated with presumed severe sepsis/septic shock on arrival to the ED and may be useful factors in a prehospital sepsis screen designed for medically ill children. Prospective collection of these and other potential screen factors in a larger geographically diverse setting is needed next to generate a reliable, sensitive, and practical pediatric prehospital sepsis screening tool.

9. REFERENCES

1. Ohio Hospital Association. Reducing Sepsis Mortality in Ohio. https://ohiohospitals.org/sepsis. Accessed March 24, 2017.
2. Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatric critical care medicine.* 2005;6(1):2-8.
3. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive care medicine.* 2013;39(2):165-228.
4. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *New England Journal of Medicine.* 2001;345(19):1368-1377.
5. Cruz AT, Perry AM, Williams EA, Graf JM, Wuestner ER, Patel B. Implementation of goal-directed therapy for children with suspected sepsis in the emergency department. *Pediatrics.* 2011;127(3):e758-766.
6. Lane RD, Funai T, Reeder R, Larsen GY. High Reliability Pediatric Septic Shock Quality Improvement Initiative and Decreasing Mortality. *Pediatrics.* 2016;138(4).
7. Paul R, Melendez E, Stack A, Capraro A, Monuteaux M, Neuman MI. Improving adherence to PALS septic shock guidelines. *Pediatrics.* 2014;133(5):e1358-1366.
8. Wallgren UM, Castrén M, Svensson AE, Kurland L. Identification of adult septic patients in the prehospital setting: a comparison of two screening tools and clinical judgment. *European Journal of Emergency Medicine.* 2014;21(4):260-265.
9. Baez AA, Cochon L. Acute Care Diagnostics Collaboration: Assessment of a Bayesian clinical decision model integrating the Prehospital Sepsis Score and point-of-care lactate. *The American journal of emergency medicine.* 2016;34(2):193-196.
10. Guerra WF, Mayfield TR, Meyers MS, Clouatre AE, Riccio JC. Early detection and treatment of patients with severe sepsis by prehospital personnel. *J Emerg Med.* 2013;44(6):1116-1125.
11. Children's Hospital Association. Sepsis Collaborative: Improving Pediatric Sepsis Outcomes (IPSO). https://www.childrenshospitals.org/sepsiscollaborative. Accessed March 24, 2017.
12. Adkins E, Koser S, Allion A, et al. White paper for early recognition and prehospital management of the adult septic patient. In: Central Ohio Trauma Systems, ed2013.
13. Thompson GC, Macias CG. Recognition and Management of Sepsis in Children: Practice Patterns in the Emergency Department. *J Emerg Med.* 2015;49(4):391-399.
14. Larsen GY, Mecham N, Greenberg R. An emergency department septic shock protocol and care guideline for children initiated at triage. *Pediatrics.* 2011;127(6):e1585-1592.
15. Cottrell EK, O'Brien K, Curry M, et al. Understanding safety in prehospital emergency medical services for children. *Prehospital Emergency Care.* 2014;18(3):350-358.
16. Drayna PC, Browne LR, Guse CE, Brousseau DC, Lerner EB. Prehospital Pediatric Care: Opportunities for Training, Treatment, and Research. *Prehosp Emerg Care.* 2015;19(3):441-447.
17. Foltin GL, Dayan P, Tunik M, et al. Priorities for pediatric prehospital research. *Pediatr Emerg Care.* 2010;26(10):773-777.
18. Balamuth F, Weiss SL, Neuman MI, et al. Pediatric severe sepsis in U.S. children's hospitals. *Pediatr Crit Care Med.* 2014;15(9):798-805.
19. Launay E, Gras-Le Guen C, Martinot A, et al. Suboptimal care in the initial management of children who died from severe bacterial infection: a population-based confidential inquiry. *Pediatric Critical Care Medicine.* 2010;11(4):469-474.

20. Inwald DP, Tasker RC, Peters MJ, Nadel S, Paediatric Intensive Care Society Study G. Emergency management of children with severe sepsis in the United Kingdom: the results of the Paediatric Intensive Care Society sepsis audit. *Arch Dis Child.* 2009;94(5):348-353.
21. Scott HF, Donoghue AJ, Gaieski DF, Marchese RF, Mistry RD. Effectiveness of physical exam signs for early detection of critical illness in pediatric systemic inflammatory response syndrome. *BMC Emerg Med.* 2014;14:24.
22. Balamuth F, Alpern ER, Grundmeier RW, et al. Comparison of Two Sepsis Recognition Methods in a Pediatric Emergency Department. *Acad Emerg Med.* 2015;22(11):1298-1306.
23. Arikan AA, Williams EA, Graf JM, Kennedy CE, Patel B, Cruz AT. Resuscitation bundle in pediatric shock decreases acute kidney injury and improves outcomes. *The Journal of pediatrics.* 2015;167(6):1301-1305.
24. Seymour CW, Rea TD, Kahn JM, Walkey AJ, Yealy DM, Angus DC. Severe sepsis in pre-hospital emergency care: analysis of incidence, care, and outcome. *American journal of respiratory and critical care medicine.* 2012;186(12):1264-1271.
25. Robson W, Nutbeam T, Daniels R. Sepsis: a need for prehospital intervention? *Emergency Medicine Journal.* 2009;26(7):535-538.
26. Studnek JR, Artho MR, Garner CL, Jones AE. The impact of emergency medical services on the ED care of severe sepsis. *Am J Emerg Med.* 2012;30(1):51-56.
27. Seymour CW, Cooke CR, Heckbert SR, et al. Prehospital intravenous access and fluid resuscitation in severe sepsis: an observational cohort study. *Crit Care.* 2014;18(5):533.
28. Band RA, Gaieski DF, Hylton JH, Shofer FS, Goyal M, Meisel ZF. Arriving by emergency medical services improves time to treatment endpoints for patients with severe sepsis or septic shock. *Academic Emergency Medicine.* 2011;18(9):934-940.
29. Smyth MA, Brace-McDonnell SJ, Perkins GD. Impact of Prehospital Care on Outcomes in Sepsis: A Systematic Review. In: *West J Emerg Med.* Vol 17.2016:427-437.
30. Lerner EB, Dayan PS, Brown K, et al. Characteristics of the pediatric patients treated by the Pediatric Emergency Care Applied Research Network's affiliated EMS agencies. *Prehospital Emergency Care.* 2014;18(1):52-59.
31. Browne LR, Shah MI, Studnek JR, et al. 2015 Pediatric Research Priorities in Prehospital Care. *Prehospital Emergency Care.* 2016;20(3):311-316.
32. Remick K, Caffrey S, Adelgais K. Prehospital provider scope of practice and implications for pediatric prehospital care. *Clinical Pediatric Emergency Medicine.* 2014;15(1):9-17.
33. Shah MN, Cushman JT, Davis CO, Bazarian JJ, Auinger P, Friedman B. The epidemiology of emergency medical services use by children: an analysis of the National Hospital Ambulatory Medical Care Survey. *Prehosp Emerg Care.* 2008;12(3):269-276.
34. Remick K, Gross T, Adelgais K, Shah MI, Leonard JC, Gausche-Hill M. Resource Document: Coordination of Pediatric Emergency Care in EMS Systems. *Prehospital Emergency Care.* 2017:1-9.
35. Lillis KA, Jaffe DM. Prehospital intravenous access in children. *Annals of emergency medicine.* 1992;21(12):1430-1434.
36. Losek JD, Szewczuga D, Glaeser PW. Improved prehospital pediatric ALS care after an EMT-paramedic clinical training course. *The American journal of emergency medicine.* 1994;12(4):429-432.
37. Myers LA, Arteaga GM, Kolb LJ, Lohse CM, Russi CS. Prehospital peripheral intravenous vascular access success rates in children. *Prehospital Emergency Care.* 2013;17(4):425-428.
38. Feudtner C, Feinstein JA, Zhong W, Hall M, Dai D. Pediatric complex chronic conditions classification system version 2: updated for ICD-10 and complex medical technology dependence and transplantation. *BMC Pediatr.* 2014;14:199.

39. NASEMSO Medical Directors Council. NASEMSO National Model EMS Clinical Guidelines, Version 2.2. https://nasemso.org/wp-content/uploads/National-Model-EMS-Clinical-Guidelines-2017-PDF-Version-2.2.pdf. Published 2019. Accessed.
40. Femling J, Weiss S, Hauswald E, Tarby D. EMS patients and walk-in patients presenting with severe sepsis: differences in management and outcome. *South Med J.* 2014;107(12):751-756.
41. Paul R, Melendez E, Wathen B, et al. A Quality Improvement Collaborative for Pediatric Sepsis: Lessons Learned. *Pediatric Quality & Safety.* 2018;3(1).
42. Smyth MA, Brace-McDonnell SJ, Perkins GD. Identification of adults with sepsis in the prehospital environment: a systematic review. *BMJ Open.* 2016;6(8):e011218.
43. Bayer O, Schwarzkopf D, Stumme C, et al. An Early Warning Scoring System to Identify Septic Patients in the Prehospital Setting: The PRESEP Score. *Academic Emergency Medicine.* 2015;22(7):868-871.
44. Bayer O, Stumme C, Schneider K, et al. Evaluation of 1 year prehospital emergency sepsis care: An observational study. *Infection.* 2013;41(1):S66-S66.