RESEARCH ARTICLE

Antibiotic Timing in Pediatric Septic Shock

Roni D. Lane, MD,[a] Jared Olson, PharmD,[b,c] Ron Reeder, PhD,[d] Benjamin Miller, MS,[d] Jennifer K. Workman, MD, MS,[d] Emily A. Thorell, MD, MS,[c] Gitte Y. Larsen, MD, MPH[d]

ABSTRACT

BACKGROUND AND OBJECTIVES: National guidelines advocate for the administration of antibiotics within 1 hour to children with septic shock, although there is variance in the pediatric evidence-based literature supporting this benchmark. Our objective for this study was to describe the association of target time to antibiotic administration (TTAA) with outcomes of children treated for suspected septic shock in a pediatric emergency department. Septic shock is suspected when signs of perfusion and/or hypotension are present. The primary outcome was mortality. Secondary outcomes included PICU admission, hospital and PICU length of stay, and organ dysfunction resolution by hospital day 2.

METHODS: We conducted a retrospective study of children <18 years of age admitted from the pediatric emergency department and treated for suspected septic shock between February 1, 2007, and December 31, 2015. Associations between TTAA and outcomes were evaluated by using multivariable linear and logistic regression models obtained from stepwise selection.

RESULTS: Of 1377 patients, 47% were boys with a median age of 4.0 (interquartile range 1.4–11.6) years, 1.5% (20) died, 90% were compliant with TTAA goals, 40% required PICU admission, 38% had ≥2 unique complex chronic conditions, 71% received antibiotics in ≤2 hours, and 30% had a culture-positive bacterial etiology. There were no significant associations between TTAA and outcomes.

CONCLUSIONS: We found no association with TTAA and any clinical outcomes, adding to the growing body of literature questioning the timing benchmark of antibiotic administration. Although the importance of antibiotics is not in question, elucidating the target TTAA may improve resource use and decrease inappropriate or unnecessary antibiotic exposure.

www.hospitalpediatrics.org
DOI:https://doi.org/10.1542/hpeds.2019-0250

Address correspondence to Roni D. Lane, MD, Division of Pediatric Emergency Medicine, The University of Utah and Primary Children's Hospital, PO Box 581289, Salt Lake City, UT 84158. E-mail: roni.lane@hsc.utah.edu

HOSPITAL PEDIATRICS (ISSN Numbers: Print, 2154-1663; Online, 2154-1671).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

Dr Lane conceptualized and designed the study, contributed to the design of the data collection instruments, drafted the initial manuscript, and revised the manuscript; Drs Olson, Thorell, Workman, and Larsen contributed to the design of the study and critically reviewed, contributed to, and revised the manuscript; Dr Reeder verified and supervised the analyses and contributed to and revised the manuscript; Mr Miller designed the data collection instruments, conducted the analyses, and contributed to and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

[a]Divisions of Pediatric Emergency Medicine, [c]Pediatric Infectious Diseases, and [d]Critical Care, Department of Pediatrics, The University of Utah, Salt Lake City, Utah; and [b]Primary Children's Hospital Pharmacy, Salt Lake City, Utah

Pediatric mortality due to septic shock has declined despite increasing prevalence in the United States.[1–3] However, pediatric septic shock continues to impact morbidity, mortality, and health care costs.[4–8] In addition to early recognition and rapid escalation of care, national guidelines support antibiotic administration within 1 hour of suspected septic shock determination.[6,9–11] Recommendations are largely based on adult studies revealing improved outcomes associated with timely antibiotic administration in patients treated for severe sepsis or septic shock,[12–18] although target time to antibiotic administration (TTAA) varied. In contradiction, a 2015 meta-analysis of 11 studies revealed no association between mortality and timeliness of antibiotic administration.[19] Few relevant studies have been published in pediatrics, yielding inconsistent results with respect to revealing an association between outcomes and timeliness of antibiotic administration.[20–23] Likely in response to the Surviving Sepsis Campaign (SSC) recommendations[6,10,24,25] and/or state or federal mandates, there has been an uptick in articles and editorials challenging the 1-hour recommendation for antibiotic administration,[19,26–29] some challenging the appropriateness,[30] and others, the feasibility.[31]

Motivated by the disparities between guideline recommendations and available evidence, we sought to investigate the association between TTAA among children treated for suspected septic shock in the pediatric emergency department (PED) and mortality, PICU admission, organ dysfunction (OD) resolution by hospital day (HD) 2, and PICU and hospital length of stay (LOS).

METHODS

Setting

The hospital is a 289-bed, freestanding, university-affiliated, tertiary pediatric hospital with ~42 000 PED visits annually, 13 000 general admissions, and 2600 PICU admissions. It serves as a pediatric referral center for the state and surrounding regions, including portions of 5 neighboring states. The study was approved, and a waiver of informed consent was granted, by the university-affiliated institutional review board and hospital privacy board.

Design and Subjects

In 2007, a quality improvement initiative aimed at improving early recognition and management of children with suspected septic shock was launched in the PED. We used the pragmatic clinical definition of suspected septic shock adapted from the American College of Critical Care Medicine (ACCM).[11,32,33] Specifically, in the context of temperature abnormality and suspected infection, suspected septic shock is identified if there are signs of altered perfusion (delayed or flash capillary refill time), diminished pulses, altered mental status, or cool, mottled extremities. The determination of suspected septic shock typically occurs during a bedside huddle after an electronic alert identifies a possible patient (or after assessment by a registered nurse if no alert is triggered at triage). The initiative is supported by a multidisciplinary team that identifies patients via medical record review for inclusion in the PED septic shock database. Only patients with documented findings supporting the diagnosis of suspected septic shock are included; those whose clinical findings are attributable to an alternative diagnosis are excluded (eg, toxic ingestion). The database includes all patients who are treated in the PED for suspected septic shock and admitted to the PICU or an inpatient unit. The detailed methods for patient identification and inclusion in the database have been previously published.[34]

For this retrospective cohort study, we included children from the database who were <18 years of age and admitted between February 1, 2007, and December 31, 2015. Patients were excluded from the study if (1) they received antibiotics before arrival to the PED, (2) the antibiotic administration time was not documented, or (3) they never received antibiotics in the PED. Patient demographics and details of presentation and of the care provided in the PED were abstracted from the database. Other data elements abstracted from the data warehouse or from a manual chart review included infection type, presence of a complex chronic condition (CCC),[35] PICU admission, Pediatric Index of Mortality 2 (PIM2) score,[36] resource use, OD, and mortality. Infection type was classified as bacterial, viral, or fungal on the basis of positive culture results or a viral polymerase chain reaction test. For children not admitted to the PICU, the PIM2 score was set to 0.

Exposures and Outcomes

The exposure was TTAA, defined as the time between the recognition of suspected septic shock (time 0) and the start time of the first intravenous (IV) antibiotic administered in the PED. For patients presenting to the PED with suspected septic shock, triage time was considered time 0. Antibiotic selection was provider dependent; however, providers were strongly encouraged to use the condition-specific antibiotic selection tool included in the PED suspected septic shock guideline. The antibiotic selection tool was developed in conjunction with the hospital antibiotic stewardship team. If a multi-antimicrobial regimen was required to adequately treat a patient's condition, the start time of the first antibiotic in the regimen was used for TTAA.

The primary outcome measure was 30-day in-hospital mortality. Secondary outcomes included PICU admission rate and hospital LOS. For the subset of patients who required PICU admission, additional outcome measures included PICU LOS and resolution of OD by HD 2. Fortunately, mortality from pediatric suspected septic shock is decreasing in the United States.[1,3] This has made it challenging to link mortality with specific interventions. OD has been used as a morbidity outcome measure in children who are critically ill[37,38] and has been associated with mortality and resource use in children with sepsis.[5,20,39–43] Previous studies have indicated that the majority of sepsis-related OD occurs in the first 72 hours of admission,[4,40] and failure of OD resolution by HD 2 has been used in investigations of pediatric suspected septic shock.[44] In our study, OD for specific organ systems was defined as follows: Cardiovascular dysfunction was defined as requiring support with a vasopressor or inotrope at any dose. Respiratory

dysfunction was defined as requiring support with either invasive or noninvasive positive pressure ventilation (excluding high-flow nasal cannula). Other organ systems dysfunction included hematologic, renal, and hepatic systems and was defined on the basis of the criteria suggested by Goldstein et al.[45]

Statistical Analyses

Descriptive statistics were used to summarize the cohort demographics. Frequencies with percentages were used to describe categorical variables, whereas medians with interquartile ranges (IQRs) were used to describe continuous variables. TTAA was the primary predictor of all multivariable models and was included as a continuous variable by using 30-minute increments. Logistic regression was used to investigate the relationship between predictors and binary outcomes. Output from logistic models is presented as odds ratios (ORs) with associated 95% confidence intervals (CIs). Linear regression was used to investigate the relationship between predictors and continuous outcomes. Output from linear models is presented as parameter estimates with associated 95% CIs. All variables significantly associated with an outcome in univariable analyses with a P value $<.10$ were considered for corresponding multivariable analyses. Final multivariable models for each outcome were constructed by using stepwise selection requiring a P value $<.10$ to enter and remain in the model. TTAA was the primary predictor of interest and was therefore forced into each multivariable model. All statistical analyses were performed by using SAS (version 9.4; SAS Institute, Inc, Cary, NC).

RESULTS

Demographics and clinical characteristics of the cohort are shown in Table 1. There were 1377 patients who were treated for suspected septic shock in the PED during the study period. The median age was 4.0 years (IQR 1.4–11.6); 47% of patients were boys, 38% had ≥2 unique CCCs, and 30% had a culture-positive bacterial etiology. The median TTAA was 65 (IQR 42–112) minutes, and 78% of patients received antibiotics in ≤2 hours. There were 20 deaths (1.5%), and 556 (40%) patients required PICU admission.

TABLE 1 Select Patient Characteristics and Clinical Variables (N = 1377)

	Results
Age, median (Q1, Q3), y	4 (1.4, 11.6)
Age category, *n* (%)	
≤3 mo	143 (10)
4–23 mo	298 (22)
2–5 y	378 (28)
6–11 y	226 (16)
≥12 y	332 (24)
Male sex, *n* (%)	646 (47)
Hispanic or Latino and/or white, *n* (%)	1160 (84)
≥2 CCCs, *n* (%)	237 (38)
Infection type, *n* (%)	
Bacterial[a]	412 (30)
Viral	472 (34)
Fungal	20 (1.5)
No microorganism identified	473 (34)
Met sepsis criteria at triage, *n* (%)	1288 (94)
Time to antibiotic, h, *n* (%)	
≤1	644 (47)
>1–≤2	430 (31)
>2–≤3	201 (15)
>3	102 (7)
30-d mortality, *n* (%)	20 (1.5)
Hospital LOS, median (Q1, Q3), d	6 (3, 11)
Patients admitted to PICU, *n* (%)	556 (40)
PIM2 score, median (Q1, Q3)	1.2 (0.9, 3.9)
PICU LOS, median (Q1, Q3), d	2 (1, 4)
OD-free on admission, *n* (%)	209 (38)
OD-free on HD 2, *n* (%)	255 (46)

CFU, colony-forming unit; Q1, first quartile; Q3, third quartile.

[a] Includes cultures from blood, urine, cerebrospinal fluid, tracheal aspirate, bronchioalveolar lavage, soft tissue, bone, and joint. Coagulase-negative *Staphylococcus* was considered a pathogen if it was present in ≥2 blood cultures. Urine culture results were considered positive if they contained ≥50 000 CFUs per mL. More than 1 culture type could be positive for each admission.

Primary Outcome

There was no significant association between TTAA and mortality (Table 2). Odds of mortality were significantly decreased among patients who met sepsis criteria at triage and received timely IV fluids. We forced TTAA into our final multivariable model and found that it had no meaningful impact on other estimates and was not a

TABLE 2 Multivariable Associations With 30-Day Mortality Among Patients Admitted to the PICU (N = 556)

Variable	OR (95% CI)	*P*
IV-fluid compliant	0.18 (0.06 to 0.51)	.001
Met sepsis criteria at triage	0.25 (0.08 to 0.83)	.024
TTAA (OR is for a 30-min increase)	0.95 (0.74 to 1.21)	.660

The model includes the variables listed as well as the PIM2 score.

TABLE 3 Multivariable Associations With PICU Admission ($N = 1377$)

Variable	OR (95% CI)	*P*
Presence of ≥2 CCCs	1.82 (1.28 to 2.58)	<.001
Age category	—	<.001
≤3 mo	3.68 (1.44 to 9.43)	.007
4–23 mo	0.83 (0.51 to 1.37)	.466
2–5 y	0.48 (0.31 to 0.76)	.002
6–11 y	0.89 (0.56 to 1.44)	.646
≥12 y	Reference	—
Met sepsis criteria at triage	0.26 (0.10 to 0.65)	.004
Bacterial infection	2.36 (1.62 to 3.43)	<.001
TTAA (OR is for a 30-min increase)	0.95 (0.87 to 1.04)	.255

—, not applicable.

significant predictor (OR 0.95 [95% CI: 0.74–1.21]; $P = .66$). We also investigated whether this result was unduly influenced by outliers (long time to antibiotics) and found the result to be unaffected. For the subset of patients with a culture-positive bacterial infection, there was no significant association between TTAA and mortality (univariable OR 1.00 [95% CI: 0.75–1.34]; $P = .9951$).

Secondary Outcomes

There were no significant associations between TTAA and PICU admission rate (Table 3) or hospital LOS (Supplemental Tables 5 through 11). Among patients admitted to the PICU, there were no significant associations between TTAA and any OD resolution by HD 2 (Table 4) or PICU LOS (Supplemental Tables 5 through 11).

DISCUSSION

In this cohort of pediatric patients treated for suspected septic shock in the PED, there were no significant associations between timeliness of antibiotic administration and mortality, OD resolution by HD 2, LOS, or PICU admission.

Nationally published guidelines,[9,10] including the SSC,[6,24,25] recommend administration of antibiotics within 1 hour of septic shock recognition. However, there is inconsistent evidence in the literature regarding this benchmark. Guidelines, including those in the SSC, were largely informed by adult studies favoring improved mortality with earlier antibiotic administration.[15,18,46] Since then, the adult literature has had conflicting results with respect to mortality and increasing TTAA, some revealing benefit,[13,16,47] and others, none.[14,48,49] A 2015 meta-analysis of 11 studies revealed no mortality benefit of antibiotic administration within 3 hours of emergency department (ED) triage or 1 hour of shock recognition. Likewise, pediatric evidence supporting the 1-hour benchmark is also conflicting and more sparse.[20–23,50,51] In a cohort of patients in the PICU with septic shock, Oliveira et al[50] found no statistical difference in TTAA between survivors and nonsurvivors. Weiss et al[20] described an escalating risk of PICU mortality and fewer organ-failure free days with hourly delays in antibiotic administration, which only became significant after 3 hours from sepsis recognition. van Paridon et al[22] found that among children admitted to a PICU with sepsis, early timing of appropriate antibiotics was not independently associated with PICU LOS, ventilator days, or change in the pediatric logistic OD score from day 1 to 3. Furthermore, authors of 2 studies reported an increased risk of 30-day[23] and 1-year[51] mortality when antibiotics were administered in the first hour. In 2018, Evans et al[52] reported a decreased risk of in-hospital mortality among pediatric patients with sepsis or septic shock for whom a sepsis bundle was completed within 1 hour of protocol initiation; however, individual elements of the bundle, including broad-spectrum antibiotic administration, did not significantly impact mortality.

Nuances in individual studies may have affected detection of an association between TTAA and outcomes. In our cohort, the majority of patients (78%) received antibiotic therapy in ≤2 hours, and it is likely that this, along with a low mortality rate, limited the power to detect significant relationships between exposure and outcomes. A pediatric substudy of the Antibiotic Intervention in Severe Sepsis Edusepsis Project revealed similar findings and limitations.[53] In the quality improvement initiative, the median TTAA decreased from 60 to 30 minutes, but there was no significant difference in mortality between the pre- and postintervention groups (16% vs 13%, respectively).

There are discrepancies between guideline recommendations, quality metrics, and available evidence that should give practitioners pause. It is incumbent on providers to negotiate these discrepancies while providing optimal care for patients and being mindful of resource use. The Infectious Diseases Society of America chose not to support the 2016 SSC guidelines. However, they note in their position statement, "If there is a possibility that a patient with shock might have an infection, it is understandable and appropriate to administer broad spectrum antibiotics and fluids immediately."[54] This reflects a paradigm clinicians can likely agree with until clarity regarding the timing benchmark for antibiotic administration is established via evidence-based literature.

TABLE 4 Multivariable Associations With OD Resolution on HD 2 Among Patients Admitted to the PICU ($N = 556$)

Variable	OR (95% CI)	*P*
Presence of ≥2 CCCs	0.61 (0.38 to 0.98)	.039
PIM2 score	0.01 (0.00 to 1.16)	.056
Bacterial infection	0.40 (0.25 to 0.66)	<.001
TTAA (OR is for a 30-min increase)	1.01 (0.89 to 1.13)	.933

Despite our results, we continue to enthusiastically support efforts to improve early recognition and escalated management of children with suspected septic shock and strongly advocate for timely administration of antibiotics. We support efforts to parse the benchmark for timeliness. The 1-hour goal is difficult to achieve, even in centers with established pathways.[23,44,52] This time goal also impacts resource use,[26] potentially affecting the care of other patients, and can result in hasty administration of inappropriate or unnecessary antibiotics. Determining the benchmark of TTAA could have significant ramifications at the patient, provider, institution, and population level.

The optimal timing of antibiotic administration cannot be determined with a prospective, randomized, blinded design because of the potential ethical issues associated with delaying antibiotic administration in the target population. Rigorous and well-designed large collaborative initiatives may be most helpful in elucidating this important question, such as the Children's Hospital Association Improving Pediatric Sepsis Outcomes collaborative (started in 2017; anticipated completion of current phase is 2021).[55] Collaborative work also may be best suited to identify who among pediatric patients with sepsis would benefit from the earliest antibiotic administration and who could safely undergo further evaluation to determine appropriate antibiotic selection or necessity.

Our study has several limitations. First, this is a retrospective study in which we primarily used data abstracted by a manual chart review and is therefore reliant on accurate record keeping. We attempted to mitigate this by clarifying ambiguous findings in the chart by querying providers when possible. Second, we excluded patients who had antibiotics administered before arrival because the TTAA for these patients was not consistently available. The impact of excluding this subset of patients is unclear. Third, we only abstracted culture data from facilities within the health care network and thus may have missed positive culture results obtained from hospitals outside the system. Fourth, this is a single-center study, and results may not be generalizable to other institutions. Fifth, the use of codes established by Feudtner et al[35] for CCCs may overestimate the burden of chronic disease in our patient population. Sixth, typical to ED-based, sepsis-related research, it is not possible to identify the exact time of suspected septic shock onset. The majority of patients in the cohort (94%) were recognized at triage, and it is impossible to determine when the shock state began before arrival. Lastly, a gold standard definition for suspected pediatric septic shock, before the onset of hypotension, is lacking. To improve early recognition, we used a definition of suspected septic shock based on bedside clinical findings adapted from the ACCM guidelines,[11,32] which likely resulted in an overall less ill population than one generated by surveillance definitions such as those published by Goldstein et al.[45] Nevertheless, to the best of our knowledge, the definitions provided in the ACCM guidelines have not been validated and may have had imperfect sensitivity and specificity for identifying pediatric patients with suspected septic shock. In a previously published subset of patients from this cohort who were critically ill and admitted to the PICU, findings similar to those of the current study were observed. Compared with patients who received antibiotics in >1 hour, those who received antibiotics in ≤ 1 hour did not have an increased risk of new or progressive multiple OD syndrome or death.[21]

CONCLUSIONS

In this cohort of pediatric patients treated for suspected septic shock in a PED, we found no association between timeliness of antibiotic administration and mortality, OD resolution, hospital or PICU LOS, or PICU admission. These results contribute to the growing body of literature calling for evidence-based investigation of the antibiotic timing metric and identifying the patient population for whom the earliest antibiotic administration may benefit.

Acknowledgments

We thank Katy Welkie, RN, MBA (Chief Executive Officer, Primary Children's Hospital), and Dr Ed Clark, MD, MBA, for their tremendous support of this project throughout the years. We are grateful for the countless hours provided by Susan Masotti and Ernest Chan for data collection, compilation, management, and analysis. In addition, we thank all of the ED staff for making this project successful.

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