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Delayed Antimicrobial Therapy Increases Mortality and Organ Dysfunction Duration in Pediatric Sepsis

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Abstract

Objectives—Delayed antimicrobials are associated with poor outcomes in adult sepsis, but data relating antimicrobial timing to mortality and organ dysfunction in pediatric sepsis are limited. We sought to determine the impact of antimicrobial timing on mortality and organ dysfunction in pediatric patients with severe sepsis or septic shock.

Design—Retrospective observational study.

Setting—PICU at an academic medical center.

Patients—One hundred thirty patients treated for severe sepsis or septic shock.

Interventions—None.

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This study was performed at The Children's Hospital of Philadelphia.

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Measurements and Main Results—We determined if hourly delays from sepsis recognition to initial and first appropriate antimicrobial administration were associated with PICU mortality (primary outcome); ventilator-free, vasoactive-free, and organ failure-free days; and length of stay. Median time from sepsis recognition to initial antimicrobial administration was 140 minutes (interquartile range, 74–277 min) and to first appropriate antimicrobial was 177 minutes (90–550 min). An escalating risk of mortality was observed with each hour delay from sepsis recognition to antimicrobial administration, although this did not achieve significance until 3 hours. For patients with more than 3-hour delay to initial and first appropriate antimicrobials, the odds ratio for PICU mortality was 3.92 (95% CI, 1.27–12.06) and 3.59 (95% CI, 1.09–11.76), respectively. These associations persisted after adjustment for individual confounders and a propensity score analysis. After controlling for severity of illness, the odds ratio for PICU mortality increased to 4.84 (95% CI, 1.45–16.2) and 4.92 (95% CI, 1.30–18.58) for more than 3-hour delay to initial and first appropriate antimicrobials, respectively. Initial antimicrobial administration more than 3 hours was also associated with fewer organ failure-free days (16 [interquartile range, 1–23] vs 20 [interquartile range, 6–26]; $p = 0.04$).

Conclusions—Delayed antimicrobial therapy was an independent risk factor for mortality and prolonged organ dysfunction in pediatric sepsis.

Keywords

antimicrobial; critically ill children; delay; mortality; sepsis; timing

The sepsis syndrome remains a major cause of morbidity and mortality in pediatrics. Over 75,000 children are hospitalized with severe sepsis in the United States each year at \$4.8 billion in healthcare costs (1). For critically ill children with sepsis admitted to a PICU, mortality is 10–20% (2–6). Antibiotic therapy is a central component of treatment for sepsis. The Surviving Sepsis Campaign recommends administration of empiric antimicrobial therapy within 1 hour of recognition of severe sepsis or septic shock in adult and pediatric patients (7). This recommendation is based on data that delayed antimicrobial administration is associated with mortality in critically ill adults with sepsis (8–12).

The impact of time to antimicrobial administration on mortality for pediatric patients with severe sepsis or septic shock is not clear. Several studies evaluating sepsis bundle implementation in the pediatric emergency department (ED) have shown decreased time to antimicrobial administration, but improved mortality has not yet been established (13, 14). Given the many goals of initial resuscitation for patients with severe sepsis and septic shock, including IV access, collection of blood cultures and other laboratory tests, and fluid resuscitation, it is important to understand where to prioritize antimicrobial administration. Furthermore, despite unproven benefit in pediatric patients, early antimicrobial administration is increasingly being used as a quality metric (15–18). Data are therefore needed to justify, and potentially motivate, compliance with this recommendation in pediatric centers.

We sought to test the hypothesis that delayed administration of antimicrobial therapy is associated with increased mortality and prolonged organ dysfunction in patients treated for severe sepsis or septic shock in a PICU.

METHODS

Population

We conducted a retrospective analysis of patients treated for severe sepsis or septic shock in an academic PICU from February 2012 through January 2013. Patients eligible for this study were identified as having severe sepsis or septic shock on a daily sepsis screening algorithm. Two investigators (S.L.W., J.C.F.) reviewed each positive screen to ensure that patients met criteria for severe sepsis or septic shock as defined by the International Pediatric Sepsis Consensus Conference (19). Consensus criteria define severe sepsis as 1) greater than or equal to 2 age-based systemic inflammatory response syndrome criteria, 2) confirmed or suspected invasive infection, and 3) cardiovascular dysfunction, acute respiratory distress syndrome, or greater than or equal to 2 organ system dysfunctions. Septic shock is defined as the subset of patients with cardiovascular dysfunction. Appropriate patients were then entered into a sepsis registry. The Institutional Review Board at The Children's Hospital of Philadelphia (CHOP) approved this research under a waiver of informed consent.

Inclusion criteria were 1) entry into the sepsis registry, 2) recognition and initial therapy for sepsis in the CHOP ED, PICU, inpatient ward, or operating theater, and 3) treatment in the PICU for severe sepsis or septic shock. Patients transferred from other facilities with sepsis were excluded because timing of initial interventions could not be consistently determined. For three patients with more than one episode of severe sepsis or shock, only the last episode was analyzed to limit misclassification bias.

Data Collection

Clinical data, such as laboratory values and medication administration start times, were directly populated into the sepsis registry from the electronic health record using locally developed computer algorithms. The accuracy of the automated data abstraction process has been previously described (20–22). Data elements available as text fields (e.g., radiograph results) were extracted by manual review. Variables included demographics, comorbid conditions, source of infection, microbiology, laboratory results, antimicrobial administration, treatment on the institution's clinical pathway for management of severe sepsis and septic shock, mechanical ventilation, use of vasoactive infusions, PICU length of stay (LOS), and vital status at PICU discharge. We used the Pediatric Complex Chronic Conditions score to classify comorbid conditions (23). We used published criteria to define organ system dysfunction (19), which was monitored for 28 days. Severity of illness was determined by the Pediatric Index of Mortality (PIM)-2 (24) and the Pediatric Logistic Organ Dysfunction scores (25). Definitions for source of infection were adapted from published criteria (26).

Antimicrobial administration was considered appropriate if the patient received an antimicrobial to which all identified microorganisms had in vitro sensitivity or, for cases where no pathogen was identified, the antimicrobials were consistent with local guidelines for empirical management of the likely source of infection causing sepsis (8, 10, 27). We calculated the time between sepsis recognition and administration for both the initial and

first appropriate antimicrobial agents. The time of sepsis recognition was defined as triage time for patients presenting to the ED or the first “sepsis-related” intervention for patients initially treated outside the ED (i.e., PICU, inpatient ward, or operating theater). “Sepsis-related” interventions included the clinician’s order for antimicrobial therapy, blood culture collection, IV fluid bolus, or transfer to the PICU (28). We selected time of sepsis recognition because the Surviving Sepsis Campaign recommends administration of empiric antibiotics within 1 hour of recognition of severe sepsis or septic shock (7). In pediatrics, sepsis recognition is also likely to precede onset of hypotension (14). Consequently, we determined that time from sepsis recognition would provide a clinically relevant baseline. For ED patients, sepsis recognition was defined as triage time because a previous study reported similar findings when considering delays in antibiotics from either ED triage or qualification for early goal-directed therapy (EGDT) (10), there is a precedent for this baseline in a prior study of a pediatric sepsis protocol (13), and this time was felt to be objective and practical to apply in a clinical setting.

Outcomes

The primary outcome was PICU mortality. Death occurring in the PICU is more likely to be related to the episode of severe sepsis or septic shock, whereas mortality measured at later time points is increasingly contaminated by deaths unrelated to sepsis (29, 30). Secondary outcomes were PICU LOS following sepsis recognition and the number of days from sepsis recognition through day 28 free from use of dopamine greater than or equal to 5 µg/kg/min or any dose of epinephrine, norepinephrine, dobutamine, phenylephrine, vasopressin, or milrinone (vasoactive-free days), non-elective invasive or non-invasive mechanical ventilation (ventilator-free days), or presence of any organ system dysfunction (organ failure-free days) (29).

Statistical Analysis

Statistical analysis was performed using STATA (Version 12.1, College Station, TX). Descriptive data are presented as medians with interquartile ranges (IQRs) for continuous variables and frequencies with percentages for categorical variables. The Wilcoxon rank sum and Fisher exact tests were used to compare continuous and categorical variables, respectively. We first used logistic regression to compare PICU mortality in patients administered antimicrobials at hourly time cutoffs for both initial and first appropriate antimicrobial administration (8, 10, 27). We then used multivariable logistic regression to assess potential confounding effects of select clinical variables on the association of delayed antimicrobial administration with mortality. Covariates were selected a priori based on biological plausibility, data availability, and prior studies (8, 10, 27). Potential confounders were included in the model one at a time, and those that changed the base model odds ratio (OR) by 10% or greater were considered to be true confounders (31). We also constructed a propensity score using logistic regression to account for clinical variables that demonstrated an association with delayed antimicrobial administration. We included variables with a significant difference between early and delayed antimicrobial administration at the p less than 0.05 level, as well as forced age, PIM-2, and source of infection into the propensity model (Supplemental Table 1, Supplemental Digital Content 1, <http://links.lww.com/CCM/B6>). The propensity score was then evaluated as a continuous variable in a separate

multivariable logistic regression model. Multiple imputation with 20 iterations was used to address missing lactate values for 38 patients under the “missing at random” assumption (32) because excluding these patients was felt to introduce bias (33). Both unadjusted and adjusted ORs with 95% CIs are presented. We used generalized linear regression to determine the association of delayed antimicrobial administration with vasoactive-free days, ventilator-free days, organ failure-free days, and PICU LOS. For secondary outcomes, we dichotomized time to antimicrobial administration by selecting the first timing cutoff identified as significant in the primary analysis. Statistical significance was defined as a *p* value less than 0.05.

RESULTS

One hundred thirty patients met inclusion criteria—27 (21%) with severe sepsis and 103 (79%) with septic shock. Patient characteristics are shown in Table 1. Sixty-four patients (49%) received initial treatment for severe sepsis or septic shock in the ED, and 66 (51%) received initial treatment in an inpatient setting. A source of infection was evident in 83% of cases (Table 2), and a microbial pathogen was identified in 72% (Table 3). Forty patients (31%) were treated on the institution’s clinical pathway for management of severe sepsis and septic shock (ED 50% vs inpatient setting 12%). The median PICU LOS after sepsis recognition was 9 days (IQR, 4–17 d), vasoactive-free days were 26 (24–28), ventilator-free days were 20 (5–28), and organ failure-free days were 19 (4–25). Overall PICU mortality was 16 of 130 patients (12%). Fourteen of the 16 deaths were directly attributable to sepsis; two deaths were hastened by sepsis but attributed to chronic lung disease of prematurity (Supplemental Table 2, Supplemental Digital Content 2, <http://links.lww.com/CCM/B7>).

All patients were treated with antibiotics; 6% and 5% were also treated with initial antiviral and antifungal therapy, respectively. No patients died prior to receiving antimicrobial therapy. In 78% of cases, the initial antimicrobial agent was appropriate. The overall median time from sepsis recognition to initial antimicrobial administration was 140 minutes (IQR, 74–277 min) and to first appropriate antimicrobial was 177 minutes (90–550 min). Mortality did not differ between patients who received appropriate (12 of 101, 12%) versus inappropriate (4 of 29, 14%) initial antimicrobial therapy (*p* = 0.76). The time from sepsis recognition to initial antimicrobial administration was shorter for patients initially treated in the ED (123; IQR, 67–180 min) compared with an inpatient (214; IQR, 78–678 min) setting (*p* < 0.01). Patients treated on the institution’s clinical pathway for management of severe sepsis and septic shock had a shorter time to initial antibiotic administration than patients who were not on this pathway (101 [IQR, 64–157 min] vs 181 [IQR, 75–443 min]; *p* < 0.01). As shown in Table 4, delay from antimicrobial order to administration accounted for much of these differences.

Tables 5 and 6 summarize the unadjusted ORs for death associated with progressive delays from sepsis recognition to initial (Table 5) and first appropriate (Table 6) antimicrobial administration. An escalating risk of mortality was observed with each hour delay from sepsis recognition to antimicrobial administration, although this did not achieve significance until 3 hours. Mortality was 21.2% for patients who received antimicrobials after the 3-hour time cutoff (Fig. 1). The OR for PICU mortality was 3.92 (95% CI, 1.27–12.06) for more

than 3-hour delay from sepsis recognition to initial antimicrobial administration and 3.59 (95% CI, 1.09–11.76) for more than 3-hour delay to first appropriate antimicrobial administration.

In multivariable analyses, PIM-2 score was the most important confounding variable (Tables 7 and 8). Location of sepsis recognition and use of the sepsis clinical pathway were considered as potential confounders but were ultimately excluded because it was evident that these variables were in the causal pathway for early antimicrobial administration. After controlling for PIM-2 score, the OR for PICU mortality was 4.84 (95% CI, 1.45–16.16) for more than 3-hour delay from sepsis recognition to initial antimicrobial administration and 4.92 (95% CI, 1.30–18.58) for more than 3-hour delay from sepsis recognition to first appropriate antimicrobial administration (Tables 7 and 8). A propensity score for receipt of antimicrobials within 3 hours was developed using variables associated with delayed therapy (Supplemental Table 1, Supplemental Digital Content 1, <http://links.lww.com/CCM/B6>) as well as age, PIM-2, and source of infection. By adjusting for this propensity score, we were able to simultaneously account for multiple potential confounders in a single model despite relatively few outcomes (34). Administration of initial antimicrobials more than 3 hours from sepsis recognition remained an independent risk factor for mortality (OR, 3.83; 95% CI, 1.06–13.82) in the propensity-adjusted model (Table 7).

Patients who received initial antimicrobial administration more than 3 hours from sepsis recognition had fewer organ failure-free days (median, 16 [IQR, 1–23] vs 20 [IQR, 6–26]; $p = 0.04$) after controlling for PIM-2, but there were no differences in vasoactive-free days, ventilator-free days, or PICU LOS (Table 9). However, the association of first appropriate antimicrobial administration more than 3 hours with organ failure-free days did not reach significance.

DISCUSSION

Delayed administration of initial and first appropriate antimicrobial therapy beyond 3 hours from recognition of severe sepsis and septic shock were independent risk factors for mortality in pediatric patients. Although we were not able to affirm the Surviving Sepsis Campaign recommendation to administer empiric antimicrobials within 1 hour of recognition of severe sepsis or septic shock in this pediatric cohort, it is evident that delays (> 3 hr) should be avoided.

Our findings, while novel in pediatric sepsis, are consistent with reports in other populations. The largest study to date in adult sepsis reported a logarithmic relationship between the duration of hypotension before appropriate antimicrobial administration and mortality with an average decrease in survival of 7.6% per hourly delay (8). A more recent study of adult ED patients with severe sepsis treated with an EGDT protocol also reported increased mortality when effective antibiotics were delayed beyond 1 hour (10). The FINNSEPSIS study group found delayed antibiotics beyond 3 hours to be the most significant early treatment variable associated with increased mortality (35). Similar negative effects of delayed antimicrobial therapy on patient outcomes have been reported in

critically ill cancer patients with sepsis (36), pneumonia (37), candidemia (11), and meningitis (38).

We chose to evaluate both initial and first appropriate antimicrobial therapy. Prior studies, however, suggest that time to first appropriate antimicrobial therapy is the critical determinant (8, 10). One prior study found that hourly delays in time to initial antibiotics were not associated with mortality (27). Although we acknowledge that time to first appropriate antimicrobial therapy is likely more important (39, 40), measuring compliance with this goal in a clinical setting is nearly impossible in real time. Whether antimicrobial selection was appropriate cannot be known until well after the initial resuscitation period, and retrospective ascertainment of the appropriateness of antimicrobial therapy is subject to interpretation for the nearly one third of patients with “culture-negative” sepsis. Consequently, we felt it important to analyze both timing intervals recognizing that the utility of time to initial antimicrobial administration requires a high rate of appropriate empiric antimicrobial selection.

Our rationale to use the time elapsed from recognition of sepsis rather than onset of hypotension was based on three considerations. First, the Surviving Sepsis Campaign currently recommends that empiric antimicrobials be administered within 1 hour of the recognition of severe sepsis and septic shock, not onset of hypotension (7). Second, since hypotension is a late finding in pediatric shock, time of sepsis recognition provides a more clinically relevant baseline from which to measure time to antimicrobial administration. For example, in a study examining an ED-based septic shock protocol in children, only 34% were hypotensive at triage (14). Lastly, considering only the time elapsed since onset of refractory hypotension may miss an important window of opportunity to provide early therapy.

We defined sepsis recognition as triage time for ED patients and first sepsis-related therapy for inpatients in order to identify the earliest point of contact between clinician and patient that was triggered by sepsis. Gaieski et al (10) found that delayed antibiotics were associated with increased mortality irrespective of time from ED triage or qualification for EGDT. To reduce subjectivity, we considered only time from triage for ED patients (13). For inpatients, prior studies have commonly used time of ICU admission as a starting point (36). Recognizing that initial therapy for sepsis often begins prior to ICU transfer, we used a composite measure for sepsis recognition time that included any sepsis-related intervention. Since our criteria for sepsis recognition differed between ED patients and inpatients, we looked explicitly at differences in time to antimicrobial administration between settings. Inpatients experienced a longer time to antimicrobial administration that was largely due to delays from clinician order to drug administration and lower utilization of the sepsis clinical pathway. Thus, differences in resource availability across hospital settings appeared to create a barrier to rapid antimicrobial administration for inpatients, consistent with prior studies (41, 42). Strategies that streamline processes of care, such as utilization of clinical pathways, electronic order sets, rapid access to commonly used antibiotics, and nursing education, decrease time to antibiotics and may ultimately reduce mortality in pediatric sepsis (16, 17, 43, 44).

This study has several limitations. First, as it was performed at a single center, caution should be taken in generalizing these results to institutions with different resources or that use other management strategies. In particular, measuring time to initial antimicrobial administration will only be relevant if a high proportion of patients receive appropriate empiric therapy (78% in this study), as it is unlikely that ineffective antibiotics benefit patients (40). Second, because we use standardized antimicrobial doses that reflect local pathogen susceptibility, we were not able to determine whether differences in antimicrobial dosing strategies may impact outcomes. Third, we lacked sufficient power to rule out a mortality risk with time cutoffs less than 3 hours. Larger studies are needed to determine whether the current guideline to administer empiric antibiotics to children within 1 hour of sepsis recognition confers incremental benefit over a 3-hour cutoff. Fourth, it is possible that rapid administration of antimicrobials is a marker of the overall intensity of care provided rather than a cause of mortality itself. However, our study strengthens a consistent observation across diverse study populations that delayed antimicrobials are associated with adverse outcomes. Finally, our ability to build large multivariable models was limited by a low number of deaths (45). To avoid model overfitting, we used a “change-in-estimate” strategy that has been used to evaluate for confounding in prior observational studies (46). We also performed a propensity score–adjusted analysis to simultaneously control for multiple covariates associated with delayed antimicrobial therapy. The consistent findings across these two analytical approaches strengthen the validity of our observed association between delayed antimicrobials and outcomes. However, we cannot rule out the possibility that an unmeasured factor confounded these findings.

CONCLUSIONS

Delayed antimicrobial therapy beyond 3 hours from sepsis recognition was an independent risk factor for mortality and prolonged organ failure in pediatric severe sepsis and septic shock. In keeping with current guidelines, empiric broad-spectrum antimicrobial therapy should be prioritized in the initial resuscitation of pediatric sepsis. Given the trend toward an escalating risk of mortality with delays of 1 and 2 hours from sepsis recognition to antimicrobial administration, further study is needed to define the optimal timing of antimicrobial administration in the pediatric population but delays more than 3 hours should be avoided.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Hartman ME, Linde-Zwirble WT, Angus DC, et al. Trends in the epidemiology of pediatric severe sepsis. *Pediatr Crit Care Med*. 2013; 14:686–693. [PubMed: 23897242]
2. Jaramillo-Bustamante JC, Marín-Agudelo A, Fernández-Laverde M, et al. Epidemiology of sepsis in pediatric intensive care units: First Colombian multicenter study. *Pediatr Crit Care Med*. 2012; 13:501–508. [PubMed: 22460772]
3. Kutko MC, Calarco MP, Flaherty MB, et al. Mortality rates in pediatric septic shock with and without multiple organ system failure. *Pediatr Crit Care Med*. 2003; 4:333–337. [PubMed: 12831416]
4. Proulx F, Joyal JS, Mariscalco MM, et al. The pediatric multiple organ dysfunction syndrome. *Pediatr Crit Care Med*. 2009; 10:12–22. [PubMed: 19057438]
5. Weiss SL, Parker B, Bullock ME, et al. Defining pediatric sepsis by different criteria: Discrepancies in populations and implications for clinical practice. *Pediatr Crit Care Med*. 2012; 13:e219–e226. [PubMed: 22460773]
6. Wong HR, Salisbury S, Xiao Q, et al. The pediatric sepsis biomarker risk model. *Crit Care*. 2012; 16:R174. [PubMed: 23025259]
7. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup: Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med*. 2013; 41:580–637. [PubMed: 23353941]
8. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med*. 2006; 34:1589–1596. [PubMed: 16625125]
9. Ferrer R, Artigas A, Suarez D, et al. Edusepsis Study Group: Effectiveness of treatments for severe sepsis: A prospective, multicenter, observational study. *Am J Respir Crit Care Med*. 2009; 180:861–866. [PubMed: 19696442]
10. Gaieski DF, Mikkelsen ME, Band RA, et al. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. *Crit Care Med*. 2010; 38:1045–1053. [PubMed: 20048677]
11. Morrell M, Fraser VJ, Kollef MH. Delaying the empiric treatment of *Candida* bloodstream infection until positive blood culture results are obtained: A potential risk factor for hospital mortality. *Antimicrob Agents Chemother*. 2005; 49:3640–3645. [PubMed: 16127033]
12. Garnacho-Montero J, Aldabo-Pallas T, Garnacho-Montero C, et al. Timing of adequate antibiotic therapy is a greater determinant of outcome than are TNF and IL-10 polymorphisms in patients with sepsis. *Crit Care*. 2006; 10:R111. [PubMed: 16859504]
13. Cruz AT, Perry AM, Williams EA, et al. Implementation of goal-directed therapy for children with suspected sepsis in the emergency department. *Pediatrics*. 2011; 127:e758–e766. [PubMed: 21339277]
14. Larsen GY, Mecham N, Greenberg R. An emergency department septic shock protocol and care guideline for children initiated at triage. *Pediatrics*. 2011; 127:e1585–e1592. [PubMed: 21576304]

15. Kissoon N, Carcillo JA, Espinosa V, et al. Global Sepsis Initiative Vanguard Center Contributors: World Federation of Pediatric Intensive Care and Critical Care Societies: Global Sepsis Initiative. *Pediatr Crit Care Med*. 2011; 12:494–503. [PubMed: 21897156]
16. Amado VM, Vilela GP, Queiroz A Jr, et al. Effect of a quality improvement intervention to decrease delays in antibiotic delivery in pediatric febrile neutropenia: A pilot study. *J Crit Care*. 2011; 26:103.e9–103. e12. [PubMed: 20619598]
17. Corey AL, Snyder S. Antibiotics in 30 minutes or less for febrile neutropenic patients: A quality control measure in a new hospital. *J Pediatr Oncol Nurs*. 2008; 25:208–212. [PubMed: 18539908]
18. Paul R, Neuman MI, Monuteaux MC, et al. Adherence to PALS sepsis guidelines and hospital length of stay. *Pediatrics*. 2012; 130:e273–e280. [PubMed: 22753559]
19. Goldstein B, Giroir B, Randolph A. International Consensus Conference on Pediatric Sepsis: International pediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med*. 2005; 6:2–8. [PubMed: 15636651]
20. Grundmeier, RW.; Chilutti, MR.; Ostapenko, S., et al. Defining the gold standard: Manual abstraction versus automated data extraction for a complex sepsis registry. Abstract Presented at the 6th Annual Mid-Atlantic Healthcare Informatics Symposium; Philadelphia, PA. April 26, 2013;
21. Prokosch HU, Ganslandt T. Perspectives for medical informatics. Reusing the electronic medical record for clinical research. *Methods Inf Med*. 2009; 48:38–44. [PubMed: 19151882]
22. Masino, AJ.; Italia, MJ.; Davidson, LM., et al. Research hospital data ETL with DataExpress: A Scala DSL for rapid ETL configuration and execution. Proceedings of Scala Days; London, UK. 2012;
23. Feudtner C, Hays RM, Haynes G, et al. Deaths attributed to pediatric complex chronic conditions: National trends and implications for supportive care services. *Pediatrics*. 2001; 107:E99. [PubMed: 11389297]
24. Slater A, Shann F, Pearson G. Paediatric Index of Mortality (PIM) Study Group: PIM2: A revised version of the Paediatric Index of Mortality. *Intensive Care Med*. 2003; 29:278–285. [PubMed: 12541154]
25. Leteurtre S, Martinot A, Duhamel A, et al. Validation of the paediatric logistic organ dysfunction (PELOD) score: Prospective, observational, multicentre study. *Lancet*. 2003; 362:192–197. [PubMed: 12885479]
26. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control*. 2008; 36:309–332. [PubMed: 18538699]
27. Puskarich MA, Trzeciak S, Shapiro NI, et al. Emergency Medicine Shock Research Network (EMSHOCKNET): Association between timing of antibiotic administration and mortality from septic shock in patients treated with a quantitative resuscitation protocol. *Crit Care Med*. 2011; 39:2066–2071. [PubMed: 21572327]
28. Thiel SW, Asghar MF, Micek ST, et al. Hospital-wide impact of a standardized order set for the management of bacteremic severe sepsis. *Crit Care Med*. 2009; 37:819–824. [PubMed: 19237883]
29. Curley MA, Zimmerman JJ. Alternative outcome measures for pediatric clinical sepsis trials. *Pediatr Crit Care Med*. 2005; 6:S150–S156. [PubMed: 15857550]
30. Marshall JC, Vincent JL, Guyatt G, et al. Outcome measures for clinical research in sepsis: A report of the 2nd Cambridge Colloquium of the International Sepsis Forum. *Crit Care Med*. 2005; 33:1708–1716. [PubMed: 16096445]
31. Maldonado G, Greenland S. Simulation study of confounder-selection strategies. *Am J Epidemiol*. 1993; 138:923–936. [PubMed: 8256780]
32. DeSouza CM, Legedza AT, Sankoh AJ. An overview of practical approaches for handling missing data in clinical trials. *J Biopharm Stat*. 2009; 19:1055–1073. [PubMed: 20183464]
33. van der Heijden GJ, Donders AR, Stijnen T, et al. Imputation of missing values is superior to complete case analysis and the missing-indicator method in multivariable diagnostic research: A clinical example. *J Clin Epidemiol*. 2006; 59:1102–1109. [PubMed: 16980151]
34. Braitman LE, Rosenbaum PR. Rare outcomes, common treatments: Analytic strategies using propensity scores. *Ann Intern Med*. 2002; 137:693–695. [PubMed: 12379071]

35. Varpula M, Karlsson S, Parviainen I, et al. Finnsepsis Study Group: Community-acquired septic shock: Early management and outcome in a nationwide study in Finland. *Acta Anaesthesiol Scand*. 2007; 51:1320–1326. [PubMed: 17944634]
36. Larché J, Azoulay E, Fieux F, et al. Improved survival of critically ill cancer patients with septic shock. *Intensive Care Med*. 2003; 29:1688–1695. [PubMed: 13680115]
37. Gacouin A, Le Tulzo Y, Lavoue S, et al. Severe pneumonia due to *Legionella pneumophila*: Prognostic factors, impact of delayed appropriate antimicrobial therapy. *Intensive Care Med*. 2002; 28:686–691. [PubMed: 12107671]
38. Proulx N, Fréchette D, Toye B, et al. Delays in the administration of antibiotics are associated with mortality from adult acute bacterial meningitis. *QJM*. 2005; 98:291–298. [PubMed: 15760921]
39. Leibovici L, Shraga I, Drucker M, et al. The benefit of appropriate empirical antibiotic treatment in patients with bloodstream infection. *J Intern Med*. 1998; 244:379–386. [PubMed: 9845853]
40. Ibrahim EH, Sherman G, Ward S, et al. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. *Chest*. 2000; 118:146–155. [PubMed: 10893372]
41. Bastani A, Galens S, Rocchini A, et al. ED identification of patients with severe sepsis/septic shock decreases mortality in a community hospital. *Am J Emerg Med*. 2012; 30:1561–1566. [PubMed: 22204997]
42. Lundberg JS, Perl TM, Wiblin T, et al. Septic shock: An analysis of outcomes for patients with onset on hospital wards versus intensive care units. *Crit Care Med*. 1998; 26:1020–1024. [PubMed: 9635649]
43. Tipler PS, Pamplin J, Mysliwiec V, et al. Use of a protocolized approach to the management of sepsis can improve time to first dose of antibiotics. *J Crit Care*. 2013; 28:148–151. [PubMed: 23102528]
44. Zambon M, Ceola M, Almeida-de-Castro R, et al. Implementation of the Surviving Sepsis Campaign guidelines for severe sepsis and septic shock: We could go faster. *J Crit Care*. 2008; 23:455–460. [PubMed: 19056006]
45. Peduzzi P, Concato J, Kemper E, et al. A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol*. 1996; 49:1373–1379. [PubMed: 8970487]
46. Christie JD, Shah CV, Kawut SM, et al. Lung Transplant Outcomes Group: Plasma levels of receptor for advanced glycation end products, blood transfusion, and risk of primary graft dysfunction. *Am J Respir Crit Care Med*. 2009; 180:1010–1015. [PubMed: 19661249]

Figure 1.

Time from sepsis recognition to initial antimicrobial administration with survival fraction. Total number of patients at hourly intervals from sepsis recognition to administration of initial antimicrobial therapy. The shaded portion of each bar indicates the number of nonsurvivors in each time interval.

TABLE 1

Characteristics of Study Cohort

Variable ^a	Value
Age, yr	7.7 (1.7–15.1)
Sex, <i>n</i> (%)	
Male	73 (56)
Female	57 (44)
Race, <i>n</i> (%)	
White	64 (49)
Black	42 (32)
Other	4 (3)
Unknown	20 (16)
Comorbid condition, <i>n</i> (%)	
None	53 (41)
One	51 (39)
Two	18 (14)
Three or more	8 (6)
Location of sepsis recognition, <i>n</i> (%)	
Emergency department	64 (49)
Inpatient ward	42 (32)
PICU	22 (17)
Operating theater	2 (2)
Pediatric Index of Mortality-2 score	3.3 (1.0–5.1)
Pediatric Logistic Organ Dysfunction score (day of sepsis recognition)	11 (10–20)
Baseline laboratory values ^b	
WBC count (1,000/ μ L)	10.7 (5.3–15.8)
Hemoglobin (g/dL)	10.2 (9.0–11.9)
Platelets (1,000/ μ L)	225 (96–355)
Creatinine (mg/dL)	0.4 (0.3–0.7)
International normalized ratio	1.29 (1.16–1.47)
Lactate (mmol/L)	2.0 (1.5–2.9)
Compliance with initial resuscitation goals, <i>n</i> (%)	
Blood culture before antimicrobials	102 (78)
Antimicrobial < 1 hr	24 (18)
Antimicrobial < 3 hr	66 (51)
Initial fluid bolus < 20 min	22 (17)
Initial fluid bolus < 60 min	46 (35)
Lactate measured	92 (71)

Variable ^a	Value
Central venous catheter, <i>n</i> (%)	90 (69)
Required vasoactive infusion, <i>n</i> (%)	96 (74)
Required mechanical ventilation, <i>n</i> (%)	81 (62)
Required extracorporeal membrane oxygenation, <i>n</i> (%)	1 (< 1%)

^aMedian values (interquartile range), unless indicated.

^bValues at or closest to time of sepsis recognition.

TABLE 2

Clinical Site Infections

Source	No. (%) of Patients
Respiratory	55 (43)
Primary bacteremia ^a	20 (15)
Abdominal	9 (7)
Genitourinary	8 (6)
Skin/soft tissue	8 (6)
CNS	7 (5)
Endocarditis	1 (< 1)
Unknown	22 (17)

^aBlood culture positive without other identifiable source.

TABLE 3

Suspected Microbiologic Pathogens Causing Sepsis

Microorganism	No. (%) of Patients ^a
Bacteria	62 (48)
Gram-positive organisms	37 (28)
<i>Staphylococcus</i> species	16 (12)
Methicillin-sensitive <i>Staphylococcus aureus</i>	6 (5)
Methicillin-resistant <i>S. aureus</i>	8 (6)
Coagulase-negative <i>Staphylococcus</i>	2 (2)
<i>Streptococcus</i> species	12 (9)
<i>Streptococcus pyogenes</i>	2 (2)
<i>Streptococcus pneumoniae</i>	5 (4)
<i>Streptococcus agalactiae</i>	1 (< 1)
<i>Streptococcus viridans</i>	3 (2)
Nonhemolytic <i>Streptococci</i>	1 (< 1)
<i>Enterococcus</i> species	5 (4)
<i>Corynebacterium</i> species	2 (2)
<i>Salmonella</i>	1 (< 1)
<i>Micrococcus</i>	1 (< 1)
Gram-negative organisms	28 (22)
<i>Escherichia coli</i>	4 (3)
<i>Klebsiella</i> species	3 (2)
<i>Pseudomonas</i> species	7 (5)
<i>Enterobacter</i> species	3 (2)
<i>Proteus</i> species	3 (2)
<i>Citrobacter</i> species	1 (< 1)
<i>Haemophilus influenza</i> species	2 (2)
<i>Moraxella catarrhalis</i>	2 (2)
<i>Bacillus</i> species	1 (< 1)
<i>Neisseria</i> species	1 (< 1)
<i>Stenotrophomonas maltophilia</i>	1 (< 1)
<i>Mycoplasma</i>	3 (2)
<i>Mycobacterium</i> species	1 (< 1)
<i>Rickettsia</i>	1 (< 1)
Virus	40 (31)
Influenza	3 (2)
Respiratory syncytial virus	7 (5)
Adenovirus	4 (3)
Rhinovirus	15 (12)
Parainfluenza	8 (6)
Yeast/fungus	5 (4)

Microorganism	No. (%) of Patients ^a
Polymicrobial infection	21 (16)
No microorganism isolated	36 (28)

^aPatients may have had more than one microorganism isolated.

TABLE 4

Timing (in min) of Initial Antimicrobial Administration by location and Sepsis Pathway

Time Interval	Emergency Department (<i>n</i> = 64)	Inpatient (<i>n</i> = 66)	<i>p</i>
Onset to order	89 (43–129)	58 (6–410)	0.62
Order to administration	22 (13–42)	71 (42–131)	< 0.001
Onset to administration	123 (67–180)	214 (78–678)	< 0.01

Time Interval	Pathway (<i>n</i> = 40)	No Pathway (<i>n</i> = 90)	<i>p</i>
Onset to order	74 (29–115)	85 (16–277)	0.26
Order to administration	27 (14–51)	49 (20–114)	< 0.01
Onset to administration	101 (64–157)	181 (75–443)	< 0.01

Data are presented as median (interquartile range).

TABLE 5

PICU Mortality: Sepsis Recognition to Initial Antimicrobial Administration

Time to Initial Antibiotics (hr)	No. of Patients	Mortality (%)	Difference (%)	Unadjusted OR	95% CI
1	24	8	5	1.67	0.35–7.91
> 1	106	13			
2	55	7	10	2.43	0.74–7.99
> 2	75	17			
3	78	6	17	3.92	1.27–12.06
> 3	52	23			
4	91	8	15	3.60	1.23–10.52
> 4	39	23			

OR = odds ratio.

TABLE 6

PICU Mortality: Sepsis Recognition to First Appropriate Antimicrobial Administration^a

Time to Initial Antibiotics (hr)	No. of Patients	Mortality (%)	Difference (%)	Unadjusted OR	95% CI
1	16	13	-1	0.98	0.20-4.78
> 1	114	12			
2	43	7	8	2.34	0.63-8.71
> 2	87	15			
3	66	6	13	3.58	1.09-11.76
> 3	64	19			
4	78	8	11	2.86	0.97-8.42
> 4	52	19			

OR = odds ratio.

^aFor 101 (78%) of patients, the initial antimicrobial agent was appropriate based on either culture sensitivities or recommended empiric therapy.

TABLE 7

Multivariable Analysis of the Association of a More Than 3-Hour Delay to Initial Antimicrobial Administration With Mortality

Variable	OR	95% CI	% Change in OR From base Model	<i>p</i>
Unadjusted base model	3.92	1.27–12.06	Reference	0.017
Adjusted for ^a				
Age	3.91	1.27–12.04	2.6	0.018
Sex	3.87	1.24–12.09	1.3	0.02
2 comorbid conditions	3.64	1.15–11.59	7.1	0.028
Malignancy	3.97	1.27–12.43	1.3	0.018
Pediatric Index of Mortality-2	4.84	1.45–16.16	23.5	0.01
Pediatric Logistic Organ Dysfunction, day 1	3.64	1.13–11.73	7.1	0.03
Lactate, day 1 maximum ^b	3.71	1.19–11.61	5.4	0.024
Fluid bolus < 20 min ^c	4.40	1.38–14.02	12.2	0.018
Fluid bolus < 60 min ^d	3.72	1.17–11.82	5.1	0.026
Propensity score-adjusted model	3.83	1.06–13.82	2.6	0.04

OR = odds ratio.

^aThe reported odds ratios are for the relationship between delayed initial antimicrobial administration > 3 hr from sepsis recognition and mortality, adjusted individually for each confounder variable listed.

^bMultiple imputation used to account for 38 missing values.

^cFirst fluid bolus administered within 20 min of sepsis recognition.

^dFirst fluid bolus administered within 60 min of sepsis recognition.

TABLE 8

Multivariable Analysis of the Association of a More Than 3-Hour Delay to First Appropriate Antimicrobial Administration With Mortality

Variable	OR	95% CI	% Change in OR From base Model	<i>p</i>
Unadjusted base model	3.58	1.09–11.76	Reference	0.036
Adjusted for ^a				
Age	3.54	1.08–11.67	1.1	0.037
Sex	3.53	1.06–11.79	1.4	0.04
2 comorbid conditions	3.32	0.99–11.12	7.3	0.052
Malignancy	3.52	1.06–11.72	1.7	0.04
Pediatric Index of Mortality-2	4.92	1.30–18.58	37.4	0.019
Pediatric Logistic Organ Dysfunction, day 1	3.49	1.01–12.02	2.5	0.048
Lactate, day 1 maximum ^b	3.37	1.01–11.28	5.9	0.049
Fluid bolus < 20 min ^c	3.52	1.07–11.61	1.7	0.039
Fluid bolus < 60 min ^d	3.43	1.04–11.35	4.2	0.043
Propensity score-adjusted model	3.23	0.90–11.62	9.8	0.072

OR = odds ratio.

^aThe reported odds ratios are for the relationship between delayed initial antimicrobial administration > 3 hr from sepsis recognition and mortality, adjusted individually for each confounder variable listed.

^bMultiple imputation used to account for 38 missing values.

^cFirst fluid bolus administered within 20 min of sepsis recognition.

^dFirst fluid bolus administered within 60 min of sepsis recognition.

TABLE 9**Morbidity With Delayed Initial Antimicrobials More Than 3 Hours**

Outcome	Time to Initial Antimicrobial Administration		Unadjusted <i>p</i>	Adjusted <i>p</i>^a
	3 Hr	> 3 Hr		
Vasoactive-free days	26 (24–28)	26 (23–28)	0.28	0.054
Ventilator-free days	21 (7–28)	18 (2–25)	0.08	0.11
Organ failure-free days	20 (6–26)	16 (1–23)	0.03	0.04
PICU length of stay, days	8 (3–19)	10 (5–17)	0.42	0.58

^a Adjusted for Pediatric Index of Mortality-2 score.