OPEN

Outcomes of Single-Dose Empirical Antibiotic Treatment in Children With Suspected Sepsis Implemented in the Emergency Department

Suwimon Khanthathasiri, MD, Worapant Kriengsoontornkij, MD,* Apichaya Monsomboon, MD,† Wanatpreeya Phongsamart, MD,* Keswadee Lapphra, MD,* Orasri Wittawatmongkol, MD,* Supattra Rungmaitree, MD,* and Kulkanya Chokephaibulkit, MD*‡*

Objectives: Implementing a single-dose empirical antibiotic (SDEA) strategy at the emergency department (ED) in children with suspected sepsis may improve outcomes. We aim to evaluate the outcomes of the SDEA strategy for children with suspected sepsis at the ED in a tertiary care center in Bangkok.

Methods: Children who met the predefined checklist screening criteria for suspected sepsis were administered single-dose intravenous cefotaxime 100 mg/kg, or meropenem 40 mg/kg if they were immunocompromised or recently hospitalized. The medical records of children diagnosed with sepsis and septic shock caused by bacterial or organ-associated bacterial infections before and after implementation of the SDEA strategy were reviewed.

Results: A total of 126 children with sepsis before and 127 after implementation of the SDEA strategy were included in the analysis. The time from hospital arrival to antibiotic initiation was significantly reduced after implementation of the SDEA strategy: median, 241 (110–363) minutes before versus 89 (62–132) minutes after ($P < 0.001$), with an increased number of patients starting antibiotics within 3 hours of hospital arrival: 42.1% vs 85.0% ($P < 0.001$). Comparing before and after SDEA implementation, children receiving SDEA had a shorter median duration of antibiotic therapy: 7 (5–13.3) versus 5 (3–7) days ($P = 0.001$), shorter length of hospital stay: 10 (6–16.3) versus 7 (4–11) days ($P = 0.001$), and fewer intensive care unit admissions: 30 (23.8%) versus 17 (13.4%; $P = 0.036$); however, mortality was not different: 3 (2.4%) in both groups. In multivariate analysis, SDEA strategy was the independent factor associated with reduced intensive care unit admission or death. Adherence to SDEA was 91.4%. Single-dose empirical antibiotic was retrospectively considered not necessary for 22 children (11.9%), mostly diagnosed with viral infections afterward.

Conclusions: Single-dose empirical antibiotic at the ED is an effective strategy to reduce the time from hospital arrival to antibiotic initiation and can help improve outcomes of sepsis in children.

Key Words: empirical antibiotics, sepsis outcome, Thailand

(*Pediatr Emer Care* 2022;38: 426–430)

From the Departments of *Pediatrics and †Emergency Medicine and ‡Siriraj Institute of Clinical Research, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.

Disclosure: The authors declare no conflict of interest.

Reprints: Kulkanya Chokephaibulkit, MD, Department of Pediatrics, Faculty of Medicine Siriraj hospital, 2 Wanglang Rd, Bangkoknoi, Bangkok 10700, Thailand (e-mail: Kulkanya.cho@mahidol.ac.th).

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.pec-online.com).

ISSN: 0749-5161

Sepsis is a leading cause of death globally with more than 8 million people dying of sepsis annually.[1–3] In 2000–2015, it was reported that one-third of deaths in children were from infection, and the 3 most common causes of death were pneumonia, diarrhea, and malaria.[1]

There are many factors affecting the clinical outcome of sepsis. A major factor is the time to initiating effective antibiotics. Multiple studies in adults have shown that delayed antibiotic therapy for sepsis results in prolongation of hospitalization, increased duration and severity of end organ dysfunction, morbidity, and mortality.[4–6] Delayed antibiotic therapy in septic shock leads to a significant increase in the risk of mortality, whereas the impact on sepsis without shock was less so.[4] Delayed antibiotic therapy in adults increased the risk of mortality by 7.6% each hour after diagnosis of sepsis.[5] Likewise, in children with sepsis, delaying antibiotic treatment for more than 3 hours increased morbidity and mortality by 3.9-fold and extended the duration of end-organ damage.[7] Recently, a systematic review found no difference in mortality if antibiotic administration was started within 1 hour or less than 3 hours.[8]

The emergency department (ED) at most tertiary care centers are generally busy, and this can lead to a slow admission process and delayed initiation of antibiotic treatment, with the first administration often occurring after arriving at the pediatric ward. We implement a single-dose empirical antibiotic (SDEA) strategy at the ED for children with suspected sepsis to prevent delayed initiation of antibiotic treatment. This study reports the impact of our SDEA strategy on the outcomes of sepsis in children.

METHODS

Study Design and Data Collection

This study was conducted at Siriraj hospital, a large public tertiary care and referral center in Bangkok. The SDEA strategy was developed by a multidisciplinary group and was implemented at the ED in May 2018. If a child at the triage station met the criteria of suspected sepsis, they were assessed by an ED clinician within 15 minutes to approve the SDEA, targeting administration within 1 hour of hospital arrival (and after a blood drawn for bacterial culture). The criteria of suspected sepsis included children who had fever and abnormal vital signs for age that met the systemic inflammatory response syndrome criteria, infants who had high fever and looked toxic or with convulsion, and immunocompromised children who had fever or a history of fever.[9] Single-dose intravenous cefotaxime 100 mg/kg was administered, or meropenem 40 mg/kg if the child was immunocompromised or recently hospitalized.[10] A single normal saline solution (NSS) bolus dose was administered in children with unstable hemodynamics. Exclusion criteria for SDEA treatment included viral infection–associated symptoms

in children, such as maculopapular rash, or other viral diagnosis (Supplemental Fig. 1, http://links.lww.com/PEC/A996).

We retrospectively reviewed the medical records of inpatient children younger than 15 years who were diagnosed with sepsis, septic shock caused by bacterial or organ-associated bacterial infections by *International Classification of Diseases, Tenth Revision*, collectively defined as sepsis, and visited the ED before (January 2017 to December 2017) and after the SDEA strategy implementation (May 2018 to December 2019). The period between January 2018 and April 2018 was not included as this time was used to develop the SDEA work instruction and train the ED staff. The demographic data, the time from hospital arrival to antibiotic initiation, and outcomes of sepsis were collected. This study was approved by the institutional ethics committee at Siriraj Hospital.

Data Analysis

Descriptive analyses were presented using median (interquartile range [IQR]) and range. Variables for patients with predefined *International Classification of Diseases, Tenth Revision* for sepsis before and after the SDEA strategy implementation at the ED were compared using Mann-Whitney *U* test for continuous outcomes, and χ^2 or by Fisher exact test for categorical outcomes. We evaluated the factors associated with admission to intensive care unit (ICU) or death in univariate analysis including being in the before or after SDEA strategy period, age, host immune factors, receiving antibiotic at the ED or at the ward, and time from hospital arrival to antibiotic initiation. All of these factors were put into the multivariate analysis using logistic regression analysis. All statistical analyses were performed using SPSS Statistics for Windows, version 20.0 (IBM Corp, Armonk, NY).

RESULTS

Study Population

A total of 635 children visited the ED, and 244 received SDEA during the study period. Among the children who received SDEA, 185 (75.8%) were hospitalized, 38 (15.6%) were discharged home with follow-up after pediatric consultation, and 21 (8.6%) were referred to other hospitals because of health care coverage. Of those who were discharged home, 15 (39.5%) received oral antibiotics, none revisited ED or had worsening of clinical symptoms, and all recovered. All children referred were hospitalized, but none were admitted to the ICU or died. There were 51 patients (40.1%) also received a bolus dose of NSS at the ER. Thirteen children (2.0%) who met the predefined criteria but did not receive SDEA, all due to the clinician's judgment of probable viral infection, recovered well and did not receive antibiotic after admission. There were no adverse reactions reported following SDEA.

For children hospitalized at Siriraj Hospital, parenteral antibiotic treatment was not continued in 22 children (11.9%) because of other noninfectious diagnoses, whereas for the 163 children (88.1%) for whom antibiotic treatment was continued, 36 (22.1%) had a final diagnoses at discharge of viral infection (Fig. 1).

Impact of SDEA Strategy

There were 126 children before and 127 children after the SDEA strategy was implemented who visited the ED and were hospitalized with a final diagnosis of sepsis and septic shock caused by bacterial or organ-associated bacterial infections. The demographic characteristics of these 2 groups of children are shown in Table 1. The single-dose antibiotic prescribed at the ER

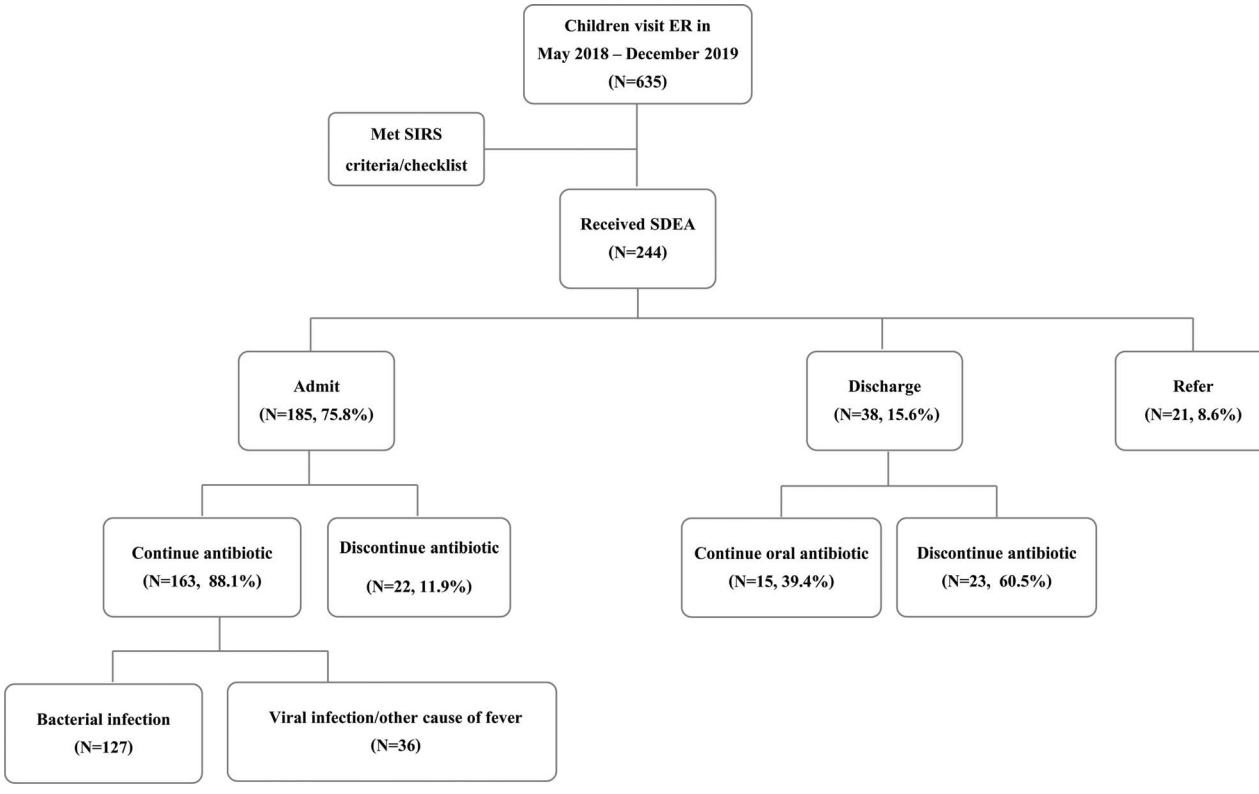

FIGURE 1. Consort diagram of the study population.

TABLE 1. Baseline Characteristics of Pediatric Patients Diagnosed With Sepsis and Septic Shock Caused by Bacterial or Organ-Associated Bacterial Infections: Comparing Before and After the SDEA Strategy (n = 253)

Characteristic	Before SDEA Strategy Group (n = 126)	After SDEA Strategy Group (n = 127)	*P*
Age, median age (IQR), mo	20.5 (4–35)	24.0 (11–60)	0.008
Range of age, n (%)			
<3 mo	30 (23.8)	12 (9.4)	0.002
<1 y	50 (39.7)	33 (26.0)	0.023
≥1 y	76 (60.3)	94 (74.0)	0.021
Sex, n (%)			
Male	67 (53.2)	72 (56.7)	0.614
Female	59 (46.8)	55 (43.3)	0.573
Comorbid conditions, n (%)	**92 (73.0)**	**77 (60.6)**	**0.045**
Congenital anomalies	17 (13.5)	5 (3.9)	0.007
Neuromuscular disease	18 (14.3)	9 (7.1)	0.070
Cardiovascular disease	13 (10.3)	4 (3.1)	0.025
Chronic lung disease	9 (7.1)	3 (2.4)	0.084
Chronic liver disease	8 (6.3)	6 (4.7)	0.596
CAKUT	10 (7.9)	5 (3.9)	0.195
Hematologic diseases	2 (1.6)	3 (2.4)	1.000
Malignancy with chemotherapy	30 (23.8)	46 (36.2)	0.039
Primary immune deficiency	13 (10.3)	7 (5.5)	0.170
Host immune status, n (%)			
Immunocompetent	78 (61.9)	67 (52.8)	0.163
Immunocompromised	48 (38.1)	60 (47.2)	0.144
Immunocompromised with neutropenia	29 (23.0)	48 (37.8)	0.011
Vital signs met the systemic inflammatory response syndrome criteria by age			
Body temperature, mean (SD), °C	38.4 (1.0)	38.9 (1.07)	0.003
Tachypnea or apnea, n (%)	47 (37.3)	60 (47.2)	0.127
Tachycardia or bradycardia, n (%)	109 (86.5)	119 (93.7)	0.061
Hypotension or poor perfusion, n (%)	14 (11.1)	11 (8.7)	0.535
Sites of infections identified*			
CNS infection	11	1	0.003
Bacteremia	22	13	0.104
Respiratory infection	38	31	0.306
Gastrointestinal infection	26	19	0.254
Urinary tract infection	16	15	0.702
Other organ-specific infection†	14	23	0.113
No organ-specific infection	30	44	0.059
Time from hospital arrival to administration of the first dose of antibiotics, n (%)			
1 h	9 (7.1)	29 (22.8)	<0.001
1–2 h	25 (19.8)	57 (44.9)	<0.001
>2–3 h	19 (15.1)	22 (17.3)	0.636
>3 h	73 (57.9)	19 (15.0)	<0.001
Outcomes of hospitalization			
Median time to first-dose antibiotic administration, minutes (IQR) [range]	241 (110, 363) [24, 1058]	89 (62, 132) [14, 1154]	<0.001
No. patients initiated ATB within 3 h of hospital arrival, n (%)	53 (42.1)	108 (85.0)	<0.001
Median duration of antibiotic therapy (IQR) [min, max], d	7 (5.0, 13.3) [1, 177]	5 (3, 7) [0, 21]	<0.001
Median length of hospitalization (IQR) [min, max], d	10 (6.0–16.3) [1, 177]	7 (4, 11) [0, 60]	<0.001
No. patients who required ICU admission, n (%)	30 (23.8)	17 (13.4)	0.036
Median ICU length of stay (IQR) [min, max], d	5.5 (3, 9) [1, 17]	3 (2, 8) [1, 40]	0.163
No. patients who required mechanical ventilation, n (%)	16 (12.6)	8 (6.3)	0.090
Median duration of mechanical ventilation (IQR) [min, max], d	7.5 (4–11) [1, 17]	9 (2, 21.75) [2, 35]	0.653
No. patients who required inotropic therapy, n (%)	17 (13.5)	7 (5.5)	0.033
Median duration of inotropic therapy (IQR) [min, max], d	2 (1–3) [1, 7]	1 (1, 4) [1, 6]	0.852
No. patients with organ dysfunction, n (%)	19 (15.1)	9 (7.1)	0.047
Mortality, n (%)	3 (2.4)	3 (2.4)	1.000

Total number of conditions was more than the number of patients because 1 patient may have multiple conditions.

*A patient may have multiple sites of infections.

†Other organ-specific infections were upper respiratory tract infection (21 patients), skin and soft tissue infection (11 patients), and hepatobiliary system infection (5 patients).

CAKUT indicates congenital anomalies of the kidney and urinary tract; CNS, central nervous system.

was cefotaxime in 64 children (50.3%), meropenem in 62 children (48.8%), and piperacillin-tazobactam in 1 child. Those in the after-SDEA strategy group were older (median age, 24.0 vs 20.5 months; $P = 0.008$) and had less comorbidities (60.6% vs 73.0%, $P = 0.045$) and a higher proportion of neutropenic patients (37.8% vs 23.0%, $P = 0.011$) compared with the before-SDEA group, but there was no difference in overall immunocompromised conditions between groups (47.2% vs 38.1%, $P = 0.144$). The before- SDEA strategy group also had more central nervous system infections. Overall, 37 bacterial pathogens (29.1%) were identified in patients from both periods, with *Salmonella* (n = 10 [27%]), *Escherichia coli* (n = 6 [16.2%]), and methicillin-sensitive *Staphylococcus aureus* (n = 5 [13.5%]) as the most common pathogens. In vitro susceptibility tests reported resistance to the SDEA in 8 cases, including 4 of 10 *Salmonella* isolates. All of these children had their treatment switched to appropriate antibiotics with no worsening of clinical symptoms before switching.

The median time from hospital arrival to first administration of antibiotics was 89 minutes for children in the after-SDEA strategy group, significantly shorter than the 241 minutes for children in the before-SDEA strategy group. The number of patients who received their first antibiotic treatment within 3 hours increased from 42.1% before implementation of the SDEA strategy to 85.0% after (Table 1). In all patients of both groups, we found that initiating antibiotic within 3 hours of hospital arrival reduced the total duration of antibiotic treatment (5 vs 7 days, $P = 0.001$), and length of stay (7 vs 10 days, $P < 0.001$), but did not affect the length of ICU admission or death (Supplementary Table 1, http://links.lww.com/PEC/A997).

Compared with before the implementation, the outcomes of hospitalization in the after-SDEA strategy group were better: shorter median duration of antibiotic therapy (7 vs 5 days, $P < 0.001$), shorter length of hospitalization (10 vs 7 days, $P < 0.001$), lower proportions of ICU admissions (23.8% vs 13.4%, $P = 0.036$), lower proportions requiring inotropic therapy (13.5% vs 5.5%, $P = 0.033$), and fewer with organ dysfunction (15.1% vs 7.1%, $P = 0.047$). Of note, the mortality rates were low, with no difference between before and after SDEA. In multivariate analysis, being in the after-SDEA strategy period was the only factor associated with lower ICU admission or death (adjusted odds ratio, 0.384 [95% confidential interval 0.180–0.822]; $P = 0.014$), after adjusting for the lapsed time from hospital arrival to antibiotic initiation (Table 2).

DISCUSSION

Early initiation of appropriate antibiotic therapy for sepsis unambiguously results in improved outcomes. The Surviving Sepsis Campaign 2020 recommends starting antibiotic therapy within 1 hour of recognition of septic shock and within 3 hours in sepsis-associated organ dysfunction.[11] Ensuing that all patients initiate appropriate antibiotic therapy within this period in the ER of a tertiary referral hospital is a challenge. In our setting in Thailand, inadvertent morbidity and mortality are rooted from delayed pediatric consultation, a slow admission process, and an inefficient pharmacy-dispensing process. To overcome these challenges, we developed a work instruction for physicians in the ED to expedite the clinical evaluation and initiation of single-dose antibiotic empirical treatment for children with suspected sepsis that does not require pediatric consultation.

Following several multidisciplinary meetings over 4 months, an SDEA strategy work instruction was finalized and implemented in the ED. The checklist criteria were not too broad but sufficient to cover all severe cases of pediatric sepsis. The streamline process was implemented with the target time from hospital arrival to SDEA administration of 1 hour. This report showed that this SDEA strategy is feasible and safe, and adherence to the work instruction was very high (91.4%). Only 23% of the children achieved the target of receiving SDEA within 1 hour; however, 85% received their first dose of antibiotic within 3 hours.

To ease the management, our SDEA strategy used 2 choices of antibiotics in standing order: cefotaxime for general cases and meropenem for patients who were immunocompromised or suspected of having hospital-associated infections. The choice of empirical antibiotic will depend on the local drug susceptibilities and may be different in children compared with adults where resistant pathogens are found more often. We found that our SDEA regimens were effective in most children with identifiable pathogens. Of note, *Salmonella*, *E. coli*, and methicillin-sensitive *S.*

TABLE 2. Multivariate Analysis of Factors Associated With ICU Admission or Death in Pediatric Patients Diagnosed With Sepsis and Septic Shock Cause by Bacterial or Organ-Associated Bacterial Infections (n = 253)

Factors	Mortality and ICU Admission		Crude Odds (95% CI)	*P*	Adjust Odds (95% CI)	*P*
	Yes (n = 50)	No (n = 203)				
Before SDEA strategy group	32 (64.0)	94 (46.3)	1	0.027	1	0.014
After SDEA strategy group	18 (36.0)	109 (53.7)	0.485 (0.256, 0.920)		0.384 (0.180, 0.822)	
Age	37 (74.0)	121 (59.6)	1	0.063	1	0.058
≥1 y						
<1 y	13 (26.0)	82 (40.4)	0.518 (0.260, 1.035)		0.494 (0.238, 1.026)	
Host						
Immunocompetent host	27 (54.0)	118 (58.1)	1	0.597	1	0.442
Immunocompromised host	23 (46.0)	85 (41.9)	1.183 (0.635, 2.203)		0.743 (0.349, 1.584)	
Without any comorbidity	11 (22.0)	79 (38.9)	1	0.028	1	0.061
Immunocompromised or with congenital/anatomical defect	39 (78.0)	124 (61.1)	2.259 (1.093, 4.669)		2.273 (0.963, 5.367)	
Received first-dose antibiotic at the ER	35 (70.0)	139 (68.5)	1	0.835	1	0.120
Received first-dose antibiotic at ward	15 (30.0)	64 (31.5)	0.931 (0.475, 1.825)		0.387 (0.117, 1.280)	
Time from hospital arrival to antibiotic initiation						
≤3 h	31 (62.0)	130 (64.0)	1	0.788	1	0.391
>3 h	19 (38.0)	73 (36.0)	0.931 (0.475, 1.825)		1.615 (0.540, 4.829)	

aureus were the most common pathogens in our setting and that 4 of the 10 *Salmonella* isolated were resistant to cefotaxime and meropenem. As antimicrobial resistance increased globally, the choice of antibiotic for SDEA strategy will need to be reviewed and modified accordingly.

Pediatric sepsis studies have demonstrated that protocol-based treatment focusing on timely delivery of appropriate treatments reduces mortality, length of hospital stay, and organ dysfunction.[3,12–14] Our SDEA strategy at the ED primarily focused on ensuring the first dose of antibiotics and a single NSS bolus dose in those with unstable hemodynamics results in an improvement of outcomes. We found the SDEA strategy implemented reduced the duration of antibiotic therapy, risk of ICU admission, inotropic drug requirements, number of patients with organ dysfunction, and total length of hospitalization. Moreover, after adjusting for duration of time to first antibiotic dose, we found our SDEA strategy reduced the risk of ICU admission and death in multivariate analysis. This result could also be influenced from the higher awareness of sepsis and timely fluid management.

Using SDEA without waiting for pediatric consultation or admission process could lead to unnecessary use of antibiotic in some children and may result in undesirable effects from overuse; however, this needs to be counterbalanced with the benefit of better outcomes from early sepsis treatment. The overuse of SDEA can be minimized by narrowing the criteria. During the pilot implementation of SDEA in our ED, we reviewed our criteria and adjusted it before settling with the criteria used in this study (Supplementary Fig. 1, http://links.lww.com/PEC/A996). We found that 11.9% of SDEA provided at the ED was deemed overused as the antibiotic was not given after admission; however, no adverse effects or drug hypersensitivity was observed.

Our study has several limitations; specifically, it is a single center at a tertiary hospital, and data were missing in 11 referred patients (4.5%). However, from medical records, these patients seemed well with stable vital signs before referral, none required NSS bolus at the ED, and the information later obtained from the parents indicated that none of them were admitted to the ICU or died. On the other hand, a single-center study has that advantage of reducing other confounding factors that may impact the evaluation of the SDEA strategy.

In conclusion, we demonstrated an effective SDEA strategy implemented in a busy ED in a large public tertiary hospital focusing on timely delivery of the first effective antibiotic dose and NSS bolus in pediatric patients with suspected sepsis. This strategy reduced the time from hospital arrival to antibiotic initiation and improved outcomes of sepsis in children. The SDEA strategy is simple, safe, and practicable for high-load EDs with relatively minimal overuse of single-dose antibiotic.

REFERENCES

1. Liu L, Oza S, Hogan D, et al. Global, regional, and national causes of under-5 mortality in 2000–15: an updated systematic analysis with implications for the sustainable development goals. *Lancet*. 2016;388:3027–3035.
2. Kissoon N, Carcillo JA, Espinosa V, et al. World Federation of Pediatric Intensive Care and Critical Care Societies: global sepsis initiative. *Pediatr Crit Care Med*. 2011;12:494–503.
3. Paul R, Neuman MI, Monuteaux MC, et al. Adherence to PALS sepsis guidelines and hospital length of stay. *Pediatrics*. 2012;130:e273–e280.
4. Weinberger J, Rhee C, Klompas M. A critical analysis of the literature on time-to-antibiotics in suspected sepsis. *J Infect Dis*. 2020;222(suppl 2): S110–S118.
5. 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.
6. Ferrer R, Martin-Loeches I, Phillips G, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. *Crit Care Med*. 2014;42:1749–1755.
7. Weiss SL, Fitzgerald JC, Balamuth F, et al. Delayed antimicrobial therapy increases mortality and organ dysfunction duration in pediatric sepsis. *Crit Care Med*. 2014;42:2409–2417.
8. Rothrock SG, Cassidy DD, Barneck M, et al. Outcome of immediate versus early antibiotics in severe sepsis and septic shock: a systematic review and meta-analysis. *Ann Emerg Med*. 2020;76:427–441.
9. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med*. 2017;43:304–377.
10. Strich JR, Heil EL, Masur H. Considerations for empiric antimicrobial therapy in sepsis and septic shock in an era of antimicrobial resistance. *J Infect Dis*. 2020;222(suppl 2):S119–S131.
11. Weiss SL, Peters MJ, Alhazzani W, et al. Surviving Sepsis Campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. *Pediatr Crit Care Med*. 2020;21:e52–e106.
12. Evans IVR, Phillips GS, Alpern ER, et al. Association between the New York sepsis care mandate and in-hospital mortality for pediatric sepsis. *JAMA*. 2018;320:358–367.
13. Lane RD, Funai T, Reeder R, et al. High reliability pediatric septic shock quality improvement initiative and decreasing mortality. *Pediatrics*. 2016; 138:e20154153.
14. Balamuth F, Weiss SL, Fitzgerald JC, et al. Protocolized treatment is associated with decreased organ dysfunction in pediatric severe sepsis. *Pediatr Crit Care Med*. 2016;17:817–822.