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Protocolized treatment is associated with decreased organ dysfunction in pediatric severe sepsis

Fran Balamuth, MD, PhD, MSCE[1,2], **Scott L. Weiss, MD, MSCE**[3,4], **Julie C. Fitzgerald, MD, PhD**[3,4], **Katie Hayes, BS**[2], **Sierra Centkowski, BA**[1], **Marianne Chilutti, MS**[5], **Robert W. Grundmeier, MD**[1,5], **Jane Lavelle, MD**[1,2], and **Elizabeth R. Alpern, MD, MSCE**[6,7]

[1]University of Pennsylvania Perelman School of Medicine Department of Pediatrics

[2]Children's Hospital of Philadelphia, Division of Emergency Medicine

[3]University of Pennsylvania School of Medicine, Department of Anesthesia and Critical Care

[4]Children's Hospital of Philadelphia Department of Anesthesia and Critical Care

[5]Children's Hospital of Philadelphia Department of Biomedical and Health Informatics

[6]Northwestern University Feinberg School of Medicine Department of Pediatrics

[7]Ann and Robert H. Lurie Children's Hospital of Chicago Division of Emergency Medicine

Abstract

Objective—To determine whether treatment with a protocolized sepsis guideline in the emergency department (ED) was associated with a lower burden of organ dysfunction (OD) by hospital day 2 compared to non-protocolized usual care in pediatric patients with severe sepsis.

Design—Retrospective cohort study

Setting—Tertiary care children's hospital from January 1, 2012–March 31, 2014.

Measurements and Main Results—Subjects with international consensus defined severe sepsis and pediatric intensive care unit (PICU) admission within 24 hours of ED arrival were included. The exposure was the use of a protocolized ED sepsis guideline. The primary outcome was complete resolution of OD by hospital day 2. One hundred eighty nine subjects were identified during the study period. Of these, 121 (64%) were treated with the protocolized ED guideline and 68 were not. There were no significant differences between the groups in age, sex, race, number of comorbid conditions, ED triage level, or OD on arrival to the ED. Patients treated with protocolized ED care were more likely to be free of OD on hospital day 2 after controlling for sex, comorbid condition, indwelling central venous catheter, PIM-2 score, and timing of antibiotics and intravenous fluids (adjusted OR 4.2, 95% CI 1.7, 10.4).

Corresponding Author: Fran Balamuth MD, PhD, MSCE, Division of Emergency Medicine CTRB 9206, Children's Hospital of Philadelphia, 3501 Civic Center Blvd., Philadelphia, PA 19104, balamuthf@email.chop.edu, Phone: 215 590 7295, Fax: 215 590 4454.

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Conclusions—Use of a protocolized ED sepsis guideline was independently associated with resolution of OD by hospital day 2 compared to non-protocolized usual care. These data indicate that morbidity outcomes in children can be improved with the use of protocolized care.

MeSH Keywords

Pediatrics; Sepsis; Critical Care; Emergency Medicine

Introduction

There are over 75,000 cases of pediatric sepsis annually in the United States, resulting in significant morbidity and mortality, and health care costs.[1–3] Multiple studies have demonstrated that adherence to protocolized sepsis treatment guidelines can improve both process metrics and resource utilization in pediatric sepsis, including decreased time to antibiotics and fluid resuscitation[4,5] and a shorter hospital length of stay.[6]

While several studies have reported an association of early antibiotics with improved mortality rates and decreased duration of organ dysfunction,[7] data showing a direct impact of protocolized treatment guidelines on patient clinical outcomes are lacking in pediatric studies. The relatively low mortality rate due to pediatric sepsis, particularly in children with initial sepsis care in the ED setting (compared to hospital-acquired sepsis), has limited the power of quality improvement studies to demonstrate that protocolized care improves this important clinical outcome[8,9]. However, morbidity related to organ dysfunction remains substantial in pediatric sepsis, even in centers with protocol based early and aggressive sepsis care in place.[10]

Importantly, OD has been associated with increased risk of mortality and higher resource utilization and costs in pediatric sepsis.[1,11–13] In particular, the number of affected organ systems and the persistence of organ dysfunction despite resuscitation reflects the severity of illness and has been associated with adverse outcomes, including mortality in sepsis.[12,13] Reflecting this point, recent randomized trials in pediatric sepsis and other critical illnesses have used duration of organ failure as the primary efficacy outcome rather than mortality.[14,15] Importantly, studies have indicated that over 90% of sepsis related organ dysfunction occurs in the first two days of hospitalization.[8, 16, 17] We therefore sought to determine whether treatment with a protocolized sepsis guideline in the ED was associated with a lower burden of OD by hospital day 2 compared to non-protocolized usual care in pediatric patients with severe sepsis.

Methods

Study Design and Setting

This was a retrospective cohort study at a tertiary care children's hospital with approximately 90,000 emergency department (ED) visits and 4000 pediatric intensive care unit (PICU) admissions annually. The Institutional Review Board at The Children's Hospital of Philadelphia (CHOP) approved this research under a waiver of informed consent.

Study Population

We included subjects ages >56 days and <18 years of age treated in our ED from January 1, 2012 through March 31, 2014 and who had severe sepsis or septic shock within 24 hours of ED triage and required PICU admission. Severe sepsis and septic shock (referred to collectively as *severe sepsis*) was defined using international consensus guidelines.[18] All patients treated in the PICU during the study period were screened for severe sepsis using a standardized form completed by a multidisciplinary PICU team as part of routine clinical care. All patients with a positive initial screen were reviewed by two critical care physicians to confirm the diagnosis of severe sepsis. Discrepancies in determination of eligibility were resolved by consensus at monthly meetings (SW, JF, FB). We excluded infants <56 days because at our institution, these infants are treated according to a separate febrile young infant protocol due to the unique physiology and pathogens seen in this young age group.

Data Collection

The data source for this study was the CHOP Sepsis Registry. The registry contains over 150 data elements extracted either directly from the electronic health record (EHR) using locally developed computer algorithms or by manual medical record review. Automated extracted data elements include demographic data, past medical history, ED vital signs, ED and hospital laboratory results, ED and hospital therapies, ED and hospital length of stay, and vital status at discharge.[7,19] The structure and process of the automated data extraction has been previously described.[20–22] Data elements available as text fields (e.g., x-ray results, physical exam findings) were extracted by medical record review. PICU severity of illness scores were obtained from the virtual PICU[23] and included the Pediatric Index of Mortality (PIM-2)[24] and the Pediatric Risk of Mortality III (PRISM-III[25],) scores. PIM2 is determined based on data from the first hour of PICU care, and PRISM III is determined based on data from the first 24 hours of PICU care.[24,25]

Exposure—The exposure was utilization of a protocolized sepsis guideline, including a computerized physician order set in the ED. Details of the protocol are included in Appendix 1. The protocol was available for all patients during the study period but utilization was at the discretion of the treatment team. Treatment teams were educated to identify early signs of severe sepsis/septic shock and utilize the treatment protocol, and were sent monthly reminders to reinforce the use of the guideline. We defined protocol use as patients for whom the sepsis order set was utilized, identified by a default computer entry automatically applied to all patients for whom the order set was activated. We defined usual care as patients who were cared for without utilization of the sepsis order set. The protocol referred to within the text and Appendix is the one that was in place during the study period. The institutional protocol has since had several updates.

Outcomes

The primary outcome was complete resolution of OD by hospital day 2. OD was determined at ED presentation, PICU admission, and on two subsequent hospital days using international consensus criteria for sepsis-associated organ dysfunction.[18] Utilizing these criteria, the presence or absence of cardiovascular, respiratory, neurologic, renal, hepatic,

and hematologic dysfunction were determined on ED arrival, hospital admission, hospital day 1 and 2. Utilizing these criteria, the presence or absence of cardiovascular, respiratory, neurologic, renal, hepatic, and hematologic dysfunction were determined on ED arrival, hospital admission, hospital day 1 and 2. Consistent with consensus guidelines for organ dysfunction in pediatric sepsis, we excluded pre-existing chronic organ dysfunction (for example, a patient with known pre-existing chronic thrombocytopenia due to a non-sepsis condition with thrombocytopenia at the usual range) and only included new or worsening organ dysfunction.[18] Secondary outcomes included PICU and hospital length of stay (LOS), time from ED triage to initial antibiotic and fluid therapy, need for transfer to a higher level of care within 24 hours of admission, and mortality. Covariates examined included age, sex, PRISM-III and PIM2 scores, ED triage emergency severity index level, and the presence of complex chronic conditions (CCC). The CCC classification scheme uses a validated grouping of ICD9-CM codes to categorize comorbid disease processes into the following nine categories: malignancy, hematology/immune, respiratory, gastrointestinal, metabolic, neuromuscular, cardiovascular, renal, and other congenital abnormalities.[26, 27]

Statistical Analysis

Descriptive data are presented as medians with interquartile ranges (IQR) for continuous variables and frequencies with percentages for categorical variables. The Wilcoxon rank sum and Fisher's exact tests were used to compare continuous and categorical variables, respectively. We used multivariable logistic regression to determine the independent association of protocol use with OD resolution by day 2. Covariates were selected *a priori* based on biological plausibility, data availability, and prior studies,[28–30] and were included in the final model if found to be significant at the $p<0.2$ level on univariate analysis. All statistical analyses were carried out using Stata 12.1 (College Station, Tx).

Results

One hundred eight-nine PICU patients with severe sepsis were identified during the study period. Of these, 121 (64%) were treated with the sepsis protocol/order set in the ED and 68 (36%) were treated with usual care in the ED. There were no significant differences between protocol and usual care patients in terms of age, sex, race, or number of CCC (Table 1). The monthly proportion of patients treated with the protocol during the study period is shown in Supplemental Figure 1. There were no significant differences in ED triage level or OD present on ED arrival in protocol vs. usual care patients. Protocol patients had higher initial median lactate levels in the ED (Table 1). On arrival to the PICU, there was no statistically significant differences in either median PIM-2 and PRISM-III scores, or OD between usual care patients and protocol patients (Table 2).

Table 2 provides comparison of outcomes in protocol compared to usual care patients. Protocol patients were more likely to be OD free on hospital day 1 (RR 4.4, 95% CI 2.0, 9.7) and hospital day 2 (RR 5.2, 95% CI 2.5, 10.8). Protocol patients without ED OD were less likely to develop new OD in the first 2 hospital days (RR 0.3, 95% CI 0.1, 0.7). Protocol patients compared to usual care patients had shorter PICU and hospital LOS, and were less likely to have subsequent transfer to a higher level of care if initially admitted to the

inpatient floor within 24 hours of ED arrival (RR 0.3, 95% CI 0.2, 0.6). There was no difference in hospital mortality between groups.

Detailed process metrics related to protocol compared to usual care are shown in Table 3. Protocol patients had shorter time to initial IV antibiotics, initial IV fluid bolus, and third IV fluid bolus compared to usual care patients. Protocol patients also received a higher total volume of fluid per kg in the ED compared to usual care patients.

We performed univariate analysis to determine candidate confounding variables, and included the following variables in a multivariable model: presence of any comorbid condition, presence of a central line, PIM-2 score, receipt of antibiotics in less than 120 minutes from ED triage, and receipt of initial IV fluids in less than 120 minutes from ED triage. The following variables were considered in univariate analysis but were not included in the final model: age, race, number of comorbid conditions, and ED triage level. In our multivariable logistic regression model, utilization of the ED protocol remained independently associated with complete resolution of OD by hospital day 2 (adjusted OR 4.2, 95% CI 1.7, 10.4). (Table 4)

Discussion

We demonstrated in this single center retrospective study that children with severe sepsis treated using a protocolized care guideline and order set in the ED compared to those treated with non-protocolized usual care were more likely to be free of organ dysfunction on hospital day 2. The benefit of treatment using a protocolized guideline could not be explained by baseline differences in severity of illness or pre-existing comorbid conditions. Our findings extend the work of others that protocolized care improves timeliness and is associated with decreased morbidity in pediatric severe sepsis. [4–6, 31] Specifically, we demonstrate that use of a protocolized ED guideline is independently associated with reduced morbidity related to organ dysfunction in pediatric severe sepsis

In 2012, we implemented a protocolized plan to organize and streamline resuscitative and antimicrobial therapy for pediatric patients with suspected severe sepsis in our ED. Between 2012 and 2014, although there was not full penetrance of use of the protocolized approach, our data show that there was not a differential in application of the approach based on measured severity of illness.

This study provides evidence that implementation of protocolized acute care therapies decreased the presence of organ dysfunction at hospital day 2. We chose day 2 because evidence suggests that over 90% of sepsis associated organ dysfunction occurs by the second hospital day[16,17], and because we were interested in identifying a proximal outcome measure that was likely to be influenced by initial ED resuscitation. Such proximal outcome measures are important components of evaluating the success of novel ED based diagnostics and therapeutics, particularly because mortality in this setting is quite low, and single center studies are unlikely to be powered to detect differences in mortality. This data is supported by a recent single center study by Arikan et al. demonstrating decreased acute kidney injury in children treated with an ED based sepsis protocol.[31]

We did not identify any statistical difference in the mortality rate by protocolized care compared to usual care. However, attention to mortality differences should be included in future assessments of protocolized care in pediatric sepsis as our study was limited by the small number of patients who died.

The precise reasons behind the success of our protocolized care strategy are likely multi factorial. We note with interest that neither the inclusion of timeliness of antibiotics nor initial IV fluid bolus in our multivariable regression models could fully account for the improved outcomes observed in patients treated with the sepsis protocol, indicating that factors other than timely therapy are likely to be important. One possibility is that improvements in care come not only from improved timeliness, but also from group level processing by the care team that comes from the overt statement that a patient is being cared for within the sepsis protocol.

It is also important to interpret this study in the context of several recent large randomized clinical trials in adults which compared patient outcomes following early goal-directed therapy versus standardized or usual care in the US, Britain, and Australia/New Zealand.[29–31] These studies did not demonstrate outcome differences based on method used. However, the objective of these trials was to compare protocol-based early goal-direct therapy to an alternative protocol-based therapy. Even the inclusion of a “usual care” arm in one of these studies did not exclude use of a local protocolized approach. These studies indicate that all components of early goal directed therapy (EGDT) including routine measurement of central venous pressure (CVP) and central venous oxygen saturation (ScvO2) may not be necessary in all adults with septic shock. Notably, neither our protocolized approach nor non-protocolized usual care approach to resuscitation of pediatric septic shock in our ED included routine CVP and ScvO2 monitoring. Unlike these trials, our objective was to compare protocolized care (which is early and goal-directed but not as prescriptive as formal EGDT) to a non-protocolized approach.

There are several limitations to this study. It is important to note the possibility that there are unmeasured confounders that explain worse outcomes in patients who did not receive the protocol that are independent of the protocol itself. This would likely be some unmeasured “complexity” factor that makes sepsis recognition challenging and also is associated with poor outcomes. We did not note significant differences between the groups in terms of ICU based severity scores (PRISM-III and PIM-2), although it is important to note that these scores are determined after ED therapies are received. There are currently no widely utilized pediatric ED based severity scores, though it would be interesting in the future to apply one such candidate scoring system, the pediatric risk of admission (PRISA) score[35] in this population. Conversely, it is possible that there was misclassification bias in that some patients did in fact receive care that was the same as protocolized care but did not use the associated order set, and thus would be included in the usual care group. However, this would have biased the study towards the null hypothesis. In addition, because this was a single center study, the external validity of our findings to other centers is not clear. As an important corollary to this, results of sepsis studies involving fluid resuscitation in the United States should be interpreted with great caution in resource-limited settings where aggressive fluid therapy has been shown to be associated with increased mortality.[36]

However, while the contents and directives of a protocol may need to be region- and site-specific, a protocolized approach to a complex resuscitative strategy may still find overall utility in various settings.

In conclusion, we found that pediatric patients with severe sepsis treated according to a protocolized care guideline and order set in the ED had lower rates of organ dysfunction at two days following ED presentation than patients treated per usual care. Patients cared for within the sepsis guideline also had, improved processes of care and decreased hospital length of stay. This study suggests that protocololized based approach to emergency department therapy for children with sepsis may improve both process of care and patient outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic characteristics of the study population. Subjects had international consensus defined severe sepsis or septic shock and required PICU admission within 24 hours of ED stay. An ED sepsis protocol was introduced before the study period, and utilization was at the discretion of the treatment team. Complex chronic conditions are defined by Feudtner et al 2001.[27]

	Sepsis Protocol in ED		
Demographic	**Yes**	**No**	**p**
Total n	121	68	
	N (%)		
Age			
57 days- <1 year	15 (12.4)	7 (10.3)	0.95
1 year- <4 years	27 (22.3)	16 (23.5)	
4 years-<13 years	53 (43.8)	32 (47.1)	
>=13 years	26 (21.5)	13 (19.1)	
Sex			
Female	49 (40.5)	38 (55.9)	0.05
Race			
Caucasian	56 (45.9)	39 (57.4)	0.21
African American	48 (39.3)	20 (29.4)	
Asian/Indian	3 (2.5)	4 (5.9)	
Other/Unknown	15 (12.3)	5 (7.4)	
ED Illness Severity			
ED Triage = ESI 1 or 2	101 (83.4)	58 (86.6)	0.57
At least 1 ED organ dysfunction	103 (85.1)	56 (83.6)	0.78
Median initial lactate (mmol/L)	2.2 (1.5, 3.1)	1.4 (0.9, 2.2)	0.001
Presence of Indwelling Central Line	14 (11.6)	17 (25.4)	0.02
Complex chronic conditions (CCC)			
No CCC	58 (47.9)	28 (41.2)	0.447
At least 1 CCC	63 (52.1)	40 (58.8)	0.447
>=2 CCC	20 (16.5)	11 (16.2)	1

Table 2

PICU and hospital length of stay, illness severity, organ dysfunction, and mortality outcomes in sepsis protocol patients vs non-protocol (usual care) patients.

	Sepsis Protocol		Odds Ratio (95% CI)	p
	Yes (n=121)	**No (n=68)**		
Length of Stay (Median hours, IQR)				
PICU LOS	69.0 (35.8–120.9)	196.5 (100.5–339.7)		<0.001
Hospital LOS	140.0 (93.5–237.6)	347.7 (211.8–557.9)		<0.001
Illness severity score on PICU arrival (Median, IQR)				
PIM2	1.1 (1.0, 2.1))	3.6 (1.0, 4.9)		0.14
PRISM	3 (0,10)	6 (3, 10)		0.10
PICU Care Requirements				
Ever needed vasoactive support n(%)	48 (39.6)	18 (26.9)	1.4 (0.9, 2.3)	0.10
Ever needed invasive mechanical ventilation	8 (6.6)	11 (16.4)	0.4 (0.2, 0.9)	0.03
Ever needed PRBC transfusion	8 (6.6)	2 (3.0)	2.2 (0.5, 10.1)	0.3
Bacterial organism isolated	42 (34.7)	24 (35.8)	0.9 (0.6, 1.4)	0.7
Transfer to higher level of care n (%)				
Floor to PICU transfer <24h	10 (8.2)	18 (26.9)	0.3 (0.2, 0.6)	0.006
Organ Dysfunction				
Organ dysfunction free on hospital admission	18 (14.9)	11 (16.4)	0.9 (0.4, 2.0)	0.80
Organ dysfunction free D1	49 (40.5)	9 (13.4)	4.4 (2.0, 9.7)	<0.001
Organ dysfunction free D2	61 (50.4)	11 (16.4)	5.2 (2.5, 10.8)	<0.001
Developed new organ dysfunction on D1 or D2	5 (4.1)	11 (16.4)	0.3 (0.1, 0.7)	0.004
Mortality				
In hospital mortality	4 (3.3)	2 (2.9)	1.1 (0.2, 5.9)	0.9

Table 3

Process metrics in sepsis protocol patients vs non-protocol (usual care) patients. Times were measured from ED triage.

	Sepsis Protocol		Odds Ratio (95% CI)	p
Median minutes (IQR)	**Yes (n=121)**	**No (n=68)**		
Time from ED triage to initial Abx	102.5 (55–165)	175 (104–281)		<0.001
Time from ED triage to initial NS bolus	64 (28–106)	88 (39–196)		0.01
Time from ED triage to third NS bolus	192 (109–254)	407 (226–802)		<0.001
Total ED fluid received (median, IQR in ml/kg)	55 (37, 60)	39 (20, 53)		0.004
% with initial IVF <60 min n(%)	52 (46.0)	23 (36.5)	1.4 (0.8, 2.7)	0.25
% with IVF <120 min	92 (81.4)	41 (65.1)	2.2 (1.1, 4.6)	0.02
% getting initial abx within 60 minutes	30 (26.3)	8 (12.3)	2.5 (1.1, 5.8)	0.03
% getting initial abx within 120 minutes	64 (56.1)	18 (28.1)	3.2 (1.7, 6.3)	0.001
ED LOS	228 (150, 342)	243 (168, 366)		0.63

Table 4

Multivariable logistic regression evaluating the outcome of lack of organ dysfunction on hospital day 2. Variables were included in the model if p<0.2 on univariate analysis

Organ Failure Free Day 2	OR (adjusted)	p	95% CI
ED sepsis protocol	4.23	0.002	1.7, 10.4
Sex	1.23	0.59	0.6,2.6
Central line	0.95	0.98	0.3, 2.8
PIM-2 score	0.61	<0.005	0.5, 0.8
Any comorbidity	0.92	0.79	0.4, 1.9
Antibiotics < 120 min	0.93	0.9	0.4, 2.2
Bolus < 120 min	3.1	0.04	1.1, 8.8