Objectives: The Surviving Sepsis Campaign recommends rapid recognition and treatment of severe sepsis and septic shock. Few reports have evaluated the impact of these recommendations in pediatrics. We sought to determine if outcomes in patients who received initial care compliant with the Surviving Sepsis Campaign time goals differed from those treated more slowly.

Design: Single center retrospective cohort study.

Setting: Emergency department and PICU at an academic children’s hospital.

Patients: Three hundred twenty-one patients treated for septic shock in the emergency department and admitted directly to the PICU.

Interventions: None.

Measurements and Main Results: The exposure was receipt of emergency department care compliant with the Surviving Sepsis Campaign recommendations (delivery of IV fluids, IV antibiotics, and vasoactive infusions within 1 hr of shock recognition). The primary outcome was development of new or progressive multiple organ dysfunction syndrome. Secondary outcomes included mortality, need for mechanical ventilation or vasoactive medications, and hospital and PICU length of stay. Of the 321 children studied, 117 received Surviving Sepsis Campaign compliant care in the emergency department and 204 did not. New or progressive multiple organ dysfunction syndrome developed in nine of the patients (7.7%) who received Surviving Sepsis Campaign compliant care and 25 (12.3%) who did not ($p = 0.26$). There were 17 deaths; overall mortality rate was 5%. There were no significant differences between groups in any of the secondary outcomes. Although only 36% of patients met the Surviving Sepsis Campaign guideline recommendation of bundled care within 1 hour of shock recognition, 75% of patients received the recommended interventions in less than 3 hours.

Conclusions: Treatment for pediatric septic shock in compliance with the Surviving Sepsis Campaign recommendations was not associated with better outcomes compared with children whose initial therapies in the emergency department were administered more slowly. However, all patients were treated rapidly and we report low morbidity and mortality. This underscores the importance of rapid recognition and treatment of septic shock. (Pediatr Crit Care Med 2016; 17:e451–e458)

Key Words: multiple organ dysfunction syndrome; pediatric critical care; septic shock; severe sepsis; Surviving Sepsis Campaign
significantly improves survival in adults. This has also been shown in children with septic shock who have been treated with similar, pediatric specific guidelines (3–6). The growing body of evidence in support of this approach to treatment is now outlined in the Surviving Sepsis Campaign (SSC) guidelines, a joint effort of the Society of Critical Care Medicine and the European Society of Intensive Care Medicine focused on reducing mortality from sepsis worldwide. The most recent iteration of these guidelines was distributed internationally in 2012, and provides recommendations for the care of both adults and children with severe sepsis and septic shock (7).

The pediatric SSC guidelines recommend administration of IV fluid resuscitation, IV antibiotics, and infusion of vasoactive agents within the first hour of recognition and care of the patient with septic shock (7). In 2007, in consideration of the guidelines available at the time (8), our institution implemented an emergency department (ED) septic shock guideline to facilitate early recognition and rapid treatment of pediatric septic shock. Initially, the goals of this quality improvement initiative focused on improved recognition, and over time were modified to the provision of care consistent with SSC goals. Within the first 2 years of implementation, there was improved disease recognition at presentation to the ED, augmented rates of early treatment, and significantly decreased overall hospital length of stay (LOS), but mortality remained stable (from 7% to 6%) (9). Our hospital ED septic shock guideline has now been in place for over 8 years, and has aided identification of over 1,000 patients who met shock criteria during their ED admission.

While many investigations report lower mortality and resource utilization following implementation of septic shock protocols (9–12), few have specifically linked pediatric patient outcomes with receipt of bundled care within 1 hour of shock recognition that is recommended in the SSC guidelines. Additionally, two recently published large adult randomized controlled trials (RCTs) reported similar mortality from protocolized septic shock treatment compared with usual care (13, 14). Therefore, the objective of the current study was to evaluate the association between timely delivery of therapy for pediatric septic shock in the ED in accordance with the SSC guidelines, and outcomes in children admitted to the PICU. Our hypothesis is that children treated according to SSC recommendations will have decreased new or progressive multiple organ dysfunction syndrome (NP-MODS).

**MATERIALS AND METHODS**

**Study Design and Setting**

We evaluated the relationship between pediatric ED care for septic shock and outcomes of children requiring admission to the PICU. We retrospectively selected patients presenting to the ED with septic shock between 2008 and 2012, and reviewed the hospital course and clinical outcomes. The study was conducted at Primary Children’s Hospital (PCH), a tertiary care pediatric hospital with 40,000 ED visits per year and 2,000 PICU admissions per year. The University of Utah Institutional Review Board approved the study and waived requirement for informed consent.

**Participant Selection Criteria**

Initial patient selection was from the PCH Pediatric Septic Shock Project Database, which was established with initiation of the PCH ED septic shock guidelines in 2007. Patient records were flagged for initial review and possible inclusion in this database if they met any of the following broad criteria: 1) triage in the ED to “emergent” status; 2) lactate drawn during ED course; 3) PICU admission within 12 hours of presentation to ED; 4) repeat visits to the ED within 48 hours of initial visit; and 5) having a “rapid response” called on a patient within 12 hours of admission from the ED to an inpatient ward for management of sepsis. Following initial screening based on these criteria, patients were retained in this database if their condition met the American College of Critical Care Medicine/Pediatric Advanced Life Support (PALS) definition of septic shock: known or suspected infection accompanied by temperature abnormalities, vital sign abnormalities based on PALS vital sign parameters for age, and physical examination consistent with deficit in end-organ perfusion (5). The ACCM/PALS definition of septic shock was utilized instead of the 2005 Consensus Definition (15) because of its usefulness in bedside diagnosis and treatment in real time (16), as was necessary in the setting of our hospital’s septic shock initiative.

We included subjects for the present study if they were 18 years old or younger on ED admission, and were admitted directly from the ED to the PICU between January 2008 and December 2012. Any patient admitted initially to the inpatient floor and subsequently transferred to the PICU was excluded, as care provided during the inpatient stay may have altered the relationship between resuscitative ED care and patient outcomes. We included patients in the present study beginning in 2008 instead of 2007 when the ED Guideline was initiated so that the data reflected care of patients by adequately trained staff familiar with the recommended interventions.

**Exposures and Outcomes**

The exposure was receipt of care in the ED in compliance with the recommendations of the SSC, defined by administration of antibiotics within 1 hour of arrival, administration of at least 60 mL/kg IV resuscitation fluids within 1 hour of arrival (or less if the patient’s perfusion deficit was reversed prior to receiving 60 mL/kg as determined by improvement in vital signs and documentation of improved perfusion on clinical examination), and administration of an inotropic or vasoactive agent for fluid-refractory patients within 1 hour of arrival.

The primary outcome measure was the development of NP-MODS. Given the relatively low mortality rate in many pediatric illnesses, a surrogate measure of disease severity is often used. Sepsis is associated with MODS (17), and NP-MODS (the development of two or more organ dysfunctions during hospitalization) has been used as a surrogate measure in this way (18, 19). MODS assessment was based on cardiovascular, pulmonary, renal, neurologic, hematologic, and
hepatic function, and evaluated based on the patient’s worst function for a given time period based on the criteria outlined by Proulx et al (18, 19) (Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/PCC/A279).

In the present study, NP-MODS was assessed on days 1, 2, 5, 8, 12, 16, and 18 (or until hospital discharge, whichever was sooner). Data were abstracted both from the Intermountain Enterprise Data Warehouse (EDW) and by manual chart review. Additional outcome measures including mortality, PICU, and hospital LOS, and hospital resource utilization were investigated using the EDW. All data were stored within the University of Utah Division of Pediatric Critical Care Coordinating Center secure server.

Statistical Analysis
Standard descriptive statistics were used to summarize patient characteristics. Groups were compared by exposure, using Fisher exact test for categoric variables and Wilcoxon signed rank test for continuous variables. Relative risk ratios were calculated using Epi Info (Centers for Disease Control and Prevention, Atlanta, GA) to determine risk factors associated with development of NP-MODS and death. Multiple logistic regression was used to estimate the relationship between receipt of SSC compliant care and adjusted odds of NP-MODS (primary outcome). Variables were selected for inclusion in the multivariable models based on a priori clinical rationale, and included age, sex, presence of a complex chronic condition (CCC) (20), type of infection identified (bacterial vs viral), and Pediatric Index of Mortality (PIM) 2 scores. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS
There were 913 children who presented to the ED with septic shock during the study period. Of these, 321 children met inclusion criteria, and among these, there were 117 children (36%) who received timely care compliant with SSC guidelines and 204 who did not. There were no differences between groups with respect to sex, race, presence of a CCC, median PIM2 scores, or type or site of infection (Table 1). The most common site of infection in both groups was the lungs, and just over 60% of children had an infectious organism identified by either bacterial or viral testing. Younger children were more likely to receive SSC compliant care (median age, 3 vs 7 yr; p < 0.05). Children treated in the first 3 years of the study (2008–2010) were significantly less likely to have received SSC compliant care (rate ratio [RR], 0.6; 95% CI, 0.4–0.8).

An analysis of the interventions received during ED care between the two groups is shown in Table 2. Receipt of SSC compliant care was not associated with day (weekday vs weekend) or time (day shift vs night shift) of presentation (p = 0.49 and p = 0.85, respectively). Children who received SSC compliant care statistically differed from those who did not with respect to time to first fluid bolus (difference in median time, 16 min; p < 0.01). However, there was no difference in the total volume of IV fluids administered during the ED stay, and time to receipt of total IV fluids was similar (Fig. 1). Among the entire cohort, median time to first fluid bolus was 23.0 minutes (interquartile range, 10.0–39.5), and 62% of the cohort received adequate fluid resuscitation within the first hour of care (as determined by resolution of perfusion defect, improvement in vital signs). Those who received SSC compliant care had a significantly shorter median time to antibiotic administration (44 vs 94 min; p < 0.01) and time to administration of vasoactive infusion (47.5 vs 130 min; p < 0.01). There were 145 patients (45%) who did not receive antibiotics within 1 hour of ED arrival, and 18 patients (55%) who did not receive vasoactive medications within 1 hour of becoming hypotensive. Overall, 75% of patients received empiric antibiotics within 1.8 hours and vasoactive medications within 2.8 hours.

There were 119 children (37%) who had MODS on day 1 of their hospital stay, 133 (41%) with MODS at any point during hospitalization, and 34 (11%) who developed NP-MODS. There were 17 deaths (5%). Risk of death was significantly associated with presence of a CCC (RR, 5.0; 95% CI, 1.8–13.8), but risk of NP-MODS was not. Among those who died, only two were previously healthy. Fifteen of the deaths resulted from eventual withdrawal of support despite maximal and escalating therapies, including the two previously healthy children. Duration of hospitalization prior to death ranged from several hours to 1 month. There were no differences between groups with respect to development of NP-MODS, the maximum number of dysfunctional organ systems, individual organ dysfunctions (with the exception of hematologic), or mortality in either the adjusted or unadjusted analyses (Table 3).

Children with a documented bacterial infection were significantly more likely to develop NP-MODS compared to those with viral infections or no source of infection identified (p < 0.01, data not shown). Among patients with a CCC, receipt of SSC compliant care suggested a trend toward decreased risk of NP-MODS (RR, 0.17; 95% CI, 0.02–1.3) and mortality (RR, 0.14; 95% CI, 0.02–1.04); however, these differences did not achieve statistical significance. Among the entire cohort, 32% required mechanical ventilation during the hospitalization and 31% required blood pressure support with continuous infusion of vasoactive medications. Neither of these two measures, nor median hospital or PICU LOS, differed significantly between groups (Table 3).

DISCUSSION
This single center retrospective cohort study of ED septic shock care and PICU patient outcomes revealed no significant association between receipt of bundled care within 1 hour of ED arrival and development of NP-MODS, mortality, or hospital resource utilization. Interestingly, we also found that risk of death was associated with presence of a CCC but risk of NP-MODS was not. It is likely that those with NP-MODS who had a CCC were more likely to progress to death, while those who were previously healthy were more likely to recover. We had hypothesized that receiving care within 1 hour, in accordance with the current recommendations for pediatric septic shock (7), would be associated with improved outcomes.
Our findings are in contrast with several previously published investigations that showed a significant relationship between the timeliness of septic shock treatment and patient outcomes in both adults (2, 21–24) and children (3, 4, 9, 25), and which form the basis for the SSC Guidelines (7). Several recent studies that evaluated compliance with various components of the pediatric SSC Guidelines, in particular antibiotic administration within 1 hour and fluid bolus administration within 1 hour, have similarly reported decreased mortality, organ dysfunction, and hospital resource utilization (9, 26, 27).

When comparing these investigations to the present study, although the infectious profiles (site of infection, causative
organisms) were similar, our entire cohort had faster time to antibiotic and fluid bolus administration, as well as substantially lower hospital mortality rates. For example, 44% of our cohort received antibiotics within 1 hour of ED arrival, and 88% within 3 hours, compared to 18% and 51%, respectively, reported by Weiss et al (27). This group also reported a significant reduction in mortality, organ failure, vasoactive infusions, and ventilator days when antibiotics were given within 3 hours compared to later (27). It should be noted, however, that the Weiss et al (27) used a slightly different definition of septic shock, and therefore their cohort may have been more severely ill than that of the present study. A similar recent investigation of adult patients with septic shock also reported improvement in clinical outcomes with antibiotic receipt within 3 hours (28). If antibiotic administration within 3 hours is the time-point associated with significant improvement in clinical outcomes, the present study would likely not be able to detect this difference as the majority of our cohort received antibiotics within this timeframe.

Similar to use of antibiotics, fluid resuscitation and administration of vasoactive infusions were more consistent with the goals of the SSC in our cohort than what has been reported in previous pediatric studies (4, 9, 27). A
recent investigation in the adult septic shock population evaluated the effect of elapsed time of both interventions on mortality and found that patients who received larger volume fluid resuscitation within the first hour followed by vasoactive infusion over the next several hours had the lowest mortality rates (29). This would support the low mortality rate in our cohort as the majority of patients received adequate fluid resuscitation in the first hour, with initiation of a vasoactive infusion between hours 1 and 2.

Our study includes patients beginning in 2008, approximately 1 year after implementation of our ED septic shock guidelines and in the setting of continuous process improvement efforts focused on meeting the 1-hour time goals of the SSC. With this ongoing effort, children who presented to the ED in septic shock during the study period received resuscitative efforts that benefited from this focused quality effort. While only 36% of the study cohort received all bundle measures within 1 hour, many more received these interventions within 2 or 3 hours, and very few delayed beyond 3 hours. Thus, the two groups compared may not have had clinically important differences in their ED care despite statistically significant differences in the number of minutes to each intervention. While all children did not receive all interventions within the 1-hour goal of the SSC, the hospital initiative for improving ED septic shock care in accordance with the SSC apparently raised the level of care for all patients. By maintaining this as the goal, children received the care they needed on the time scale sufficient to improve outcomes. Compliance with the 1-hour goal has continued to improve at our institution and with that, we have decreased hospital mortality even further than is reported here (9).

Our findings are similar to those of the Randomized Trial of Protocol-Based Care for Early Septic Shock trial, a multicenter RCT that evaluated the effect of protocolized, goal-directed septic shock treatment similar to that proposed by Rivers et al (2), versus either protocol-based standard therapy, or usual care on 60-day mortality in adults with septic shock. In this investigation, while the three arms of the trial differed significantly in the volume and timing of resuscitative fluids, the use of vasopressors, endpoints used to manage resuscitative efforts (SvO2, central venous pressure, clinician judgment), mortality, organ failure, and hospital resource utilization did not differ among the three arms (13). Interestingly, the majority of patients received IV antibiotics as well as at least 2 L of IV fluids on average prior to randomization. Similar findings

<table>
<thead>
<tr>
<th>Outcome Variable</th>
<th>Surviving Sepsis Campaign Compliant</th>
<th>Unadjusted p Valuesa</th>
<th>Adjusted OR/Rate Ratiob</th>
<th>Adjusted Effect Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Organ dysfunction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum organ failures</td>
<td>1.0 (1.0–2.0)</td>
<td>1.0 (1.0–2.0)</td>
<td>0.14</td>
<td>1.07 (0.88–1.29)</td>
</tr>
<tr>
<td>New or progressive multiple organ dysfunction syndrome</td>
<td>25 (12.3%)</td>
<td>9 (7.7%)</td>
<td>0.26</td>
<td>0.61 (0.27–1.39)</td>
</tr>
<tr>
<td>Cardiovascular dysfunction</td>
<td>153 (75.0%)</td>
<td>97 (82.9%)</td>
<td>0.12</td>
<td>1.59 (0.85–2.96)</td>
</tr>
<tr>
<td>Respiratory dysfunction</td>
<td>65 (31.9%)</td>
<td>44 (37.6%)</td>
<td>0.33</td>
<td>0.97 (0.56–1.68)</td>
</tr>
<tr>
<td>Hematologic dysfunction</td>
<td>42 (20.6%)</td>
<td>37 (31.6%)</td>
<td>0.03</td>
<td>1.76 (1.02–3.05)</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>19 (9.3%)</td>
<td>9 (7.7%)</td>
<td>0.69</td>
<td></td>
</tr>
<tr>
<td>Hepatic dysfunction</td>
<td>12 (5.9%)</td>
<td>3 (2.6%)</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>Neurologic dysfunction</td>
<td>7 (3.4%)</td>
<td>2 (1.7%)</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital length of stay (d)</td>
<td>5.4 (3.0–10.2)</td>
<td>5.9 (2.9–12.0)</td>
<td>0.86</td>
<td>1.57 (–1.92 to 5.05)</td>
</tr>
<tr>
<td>PICU length of stay (d)</td>
<td>1.7 (0.9–4.2)</td>
<td>1.8 (0.8–5.7)</td>
<td>0.88</td>
<td>–0.05 (–2.73 to 2.63)</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>59 (28.9%)</td>
<td>43 (36.8%)</td>
<td>0.17</td>
<td>1.13 (0.64–1.98)</td>
</tr>
<tr>
<td>Continuous infusion of vasoactive agents</td>
<td>63 (30.9%)</td>
<td>38 (32.5%)</td>
<td>0.80</td>
<td>1.14 (0.67–1.95)</td>
</tr>
</tbody>
</table>

OR = odds ratio.
aUnadjusted p values are based on Fisher exact test for binary outcomes and the rank-sum test for others.
bNo aggressive care is the reference for odds ratios (ORs), rate ratios, and effect differences. Adjusted analyses control for age, sex, presence of complex chronic condition, type of infection, and Pediatric Index of Mortality 2 score. Logistic regression is used for binary outcomes with at least 30 cases. Poisson regression is used for maximum organ failures. Standard linear regression is used for length of stay. OR, rate ratio, and effect difference estimates are accompanied by 95% CIs.
cData are expressed as n (%) or median (interquartile range) for each group.
were recently reported in the Australasian Resuscitation In Sepsis Evaluation trial, another large RCT of adult septic shock patients (14). Despite the null findings of these two large RCTs as well as our study, the results of all three underscore the importance of early recognition and rapid treatment of the patient in septic shock (30, 31).

Our study has several limitations. Exposure assignment was performed by individuals who were unaware of patient outcomes, limiting systematic exposure misclassification; however, this assignment was based solely on information available from ED documentation, which was not always 100% complete, particularly with respect to care given prior to arrival at our facility. Furthermore, there is potential for confounding due to severity of illness, as those patients who presented with more severe disease may have been more likely to receive SSC compliant care, but may also have had worse outcomes secondary to their advanced disease process. To limit this, illness severity was controlled for in the adjusted analysis using PIM2 scores, though these did not differ significantly between the two groups. Further limiting our statistical analysis, the sample size may have been too small to detect a significant difference in NP-MODS, as our power analysis was based on a 45% MODS rate in children with septic shock and our cohort’s rate of MODS was only 41% and NP-MODS was only 11%. Additionally, patients in our cohort had lower PIM2 scores and fewer comorbid conditions than many other similar investigations, which makes it difficult to directly compare NP-MODS and mortality between studies. Alternatively, our patients may have also benefitted from the rapid treatment of their condition and reversal of the shock state, resulting in lower rates of morbidity and mortality. Finally, the retrospective design and relatively small single-center sample limits the generalizability of our results.

CONCLUSIONS
In this retrospective cohort study evaluating the effect of timely pediatric ED septic shock care on PICU patient outcomes, we found no difference between those who received all interventions within the first hour of care in compliance with SSC guidelines versus those who did not. Because patients who did not meet SSC guideline goals still received their resuscitative interventions quickly and overall had a very low mortality, our study reinforces the importance of early recognition and rapid treatment of pediatric septic shock. Although the SSC goal of 1 hour for receipt of initial therapy may not be the clinically significant cut point for improved outcomes, striving to achieve this goal through system improvement efforts has been essential to improving morbidity and mortality in our hospital.

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