Pediatric Severe Sepsis: Current Trends and Outcomes From the Pediatric Health Information Systems Database*

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The article falls under nonhuman subject category and was approved by Children's Healthcare of Atlanta and Children's Hospital Association Institutional Review Board.

Dr. Ruth performed background research, design and concepts of study, guided data extraction, directed analysis, prepared article, and approved final version as submitted. She had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr. McCracken assisted in the study methodology, carried out the initial statistical analyses, developed the figures and tables, reviewed and revised the article, and has approved the article as submitted. Dr. Fortenberry carried out the initial analyses, prepared the article, reviewed and revised the manuscript and figures, and approved the article as submitted. Dr. Hall is principal biostatistician at Children's Hospital Association and extracted and built database. Dr. Simon was involved with design, data analysis and critical review of the article, and approved the article as submitted. Dr. Hebbar conceptualized and designed the study, prepared the article, and approved the article as submitted.

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Objective: To 1) describe the characteristics and outcomes over time of PICU patients with severe sepsis within the dedicated U.S. children's hospitals, 2) identify patient subgroups at risk for mortality from pediatric severe sepsis, and 3) describe overall pediatric severe sepsis resource utilization.

Design: Retrospective review of a prospectively collected multi-institutional children's hospital database.

Setting: PICUs in 43 U.S. children's hospitals.

Patients: PICU patients from birth to younger than 19 years were identified with severe sepsis by modified Angus criteria and *International Classification of Diseases,* 9th Revision*,* codes for severe sepsis and septic shock.

Interventions: None.

Measurements and Main Results: Data from the Pediatric Health Information System database collected by the Children's Hospital Association from 2004 to 2012. Pediatric severe sepsis was defined by 1) *International Classification of Diseases,* 9th Revision*,* codes reflecting severe sepsis and septic shock and 2) *International Classification of Diseases, 9th Revision,* codes of infection and organ dysfunction as defined by modified Angus criteria. From 2004 to 2012, 636,842 patients were identified from 43 hospitals. Pediatric severe sepsis prevalence was 7.7% (49,153) with an associated mortality rate of 14.4%. Age less than 1 year (vs age 10 to < 19) (odds ratio, 1.4), underlying cardiovascular condition (odds ratio, 1.4) and multiple organ dysfunction, conferred higher odds of mortality. Resource burden was significant with median hospital length of stay of 17 days (interquartile range, 8–36 d) and PICU length of stay of 7 days (interquartile range, 2–17 d), with median cost/day of $4,516 and median total hospitalization cost of $77,446. There was a significant increase in the severe sepsis prevalence rate from 6.2% to 7.7% from 2004 to 2012 ($p < 0.001$) and a significant decrease in mortality from 18.9% to 12.0% ($p < 0.001$). Center mortality was negatively correlated with prevalence ($r_s = -0.48$) and volume ($r_s = -0.39$) and positively correlated with cost ($r_s = 0.36$).

Conclusions: In this largest reported pediatric severe sepsis cohort to date, prevalence increased from 2004 to 2012 while associ-

ated mortality decreased. Age, cardiovascular comorbidity, and organ dysfunction were significant prognostic factors. Pediatric severe sepsis remains an important cause for PICU admission and mortality and leads to a substantial burden in healthcare costs. Individual center's prevalence and volume are associated with improved outcomes. (*Pediatr Crit Care Med* 2014; 15:828–838)
Key Words: epidemiology; outcome; pediatric critical care; sepsis; severe sepsis; trends

Pediatric severe sepsis (PSS) has been a leading cause of morbidity and mortality for infants and children in the United States. Bacterial sepsis of the newborn and septicemia have remained among the top 10 leading causes of death in children 0–14 years old (1). Previous epidemiologic studies have evaluated severe sepsis in neonates and children in broad state-level databases (2–4). Utilizing population-based Washington state discharge data not limited to PICU patients, Czaja et al (2) found a 6.8% early mortality rate in 7,183 patients with PSS between 1990 and 2004. In 2003, Watson et al (3) reported analysis of a larger database derived from hospital discharge registries from seven states in 1995, noting a neonatal/pediatric sepsis incidence of 0.56 cases/1,000 children. An updated review of the same databases in 2012 with data reported for 2000 and 2005 found increased PSS prevalence and decreased mortality (4). Although valuable, data from these studies were not exclusive to children's hospitals or PICUs, and the data collection at 5-year intervals from Weiss et al (5) excluded the ability to perform annual trend analysis.

The last decade has seen major refinements in therapy of severe sepsis. Strategies such as early administration of antibiotics (6) and goal-directed therapy (7–10) have been accepted as standards of practice, although use in children has generally been extrapolated from adult studies. In 2002, the Surviving Sepsis Campaign was launched with the goal to reduce mortality from sepsis by 25% in 5 years (11). An expert panel of the American College of Critical Care Medicine (ACCM) formulated standard guidelines in 2003 for the management of pediatric and neonatal severe sepsis and septic shock (12), with subsequent revision in 2013 (13). The impact of these interventions and guidelines on patient outcomes in recent years remains uncertain.

One major difficulty in evaluating sepsis prevalence and outcomes across institutions is the problem of establishing a reliable case definition of severe sepsis. The use of *International Classification of Diseases,* 9th Revisio*n* (ICD-9) codes for severe sepsis have been shown to lack sensitivity in comparison with other methods of capturing cases of severe sepsis in adults (14). A number of studies of adult and pediatric sepsis have employed the American College of Chest Physicians/Society of Critical Care Medicine definition of an ICD-9 infection code plus organ dysfunction, as validated by Angus et al (15), and subsequently modified for pediatric patients (5). Inconsistencies between various methods for identifying sepsis in administrative data remain (14, 16). Therefore, evaluation of pediatric sepsis data could benefit from using several definitions of PSS.

The primary objective of this study is to describe the characteristics of a large cohort of PICU patients with PSS from 2004 to 2012, utilizing several administrative definitions of severe sepsis. We used the Pediatric Healthcare Information Systems (PHIS) database, the nation's largest pediatric hospital-specific administrative data registry maintained by the Children's Hospital Association (CHA). The PHIS registry provides clinical and administrative data from dedicated children's hospitals, which generally provide state-of-the-art pediatric care for the most complex pediatric patients. Although the data are not population based, as state discharge data are, PHIS offers other advantages of providing detailed information about a select but informative sample of the nature of severe illness and care for children. PHIS data have been used in several studies evaluating epidemiologic characteristics and resource utilization in other pediatric conditions (17, 18). Further study objectives were to describe trends in outcomes of patients with PSS, to identify patient subgroups at risk for mortality from PSS, and to report overall PSS resource utilization. We hypothesized that PSS in children's hospital PICUs occurred with increasing prevalence and with increasing associated comorbidities, resource burden, and mortality over the time period studied.

MATERIALS AND METHODS

Data Collection

This study was an observational cohort review of a prospectively collected administrative database. The study was approved by institutional review boards from CHA and Children's Healthcare of Atlanta. Requirement for informed consent was waived. All patient-related data were de-identified prior to review and enrollment.

Data for this multicenter cohort were obtained from the PHIS database, maintained by CHA, a national collaborative representing more than 220 children's hospitals across the United States. CHA maintains a registry of demographic, outcome, and resource utilization data from 43 freestanding tertiary care children's hospitals (**Supplemental Table 1**, Supplemental Digital Content 1, http://links.lww.com/PCC/A116). Hospitals participating in the database are located in noncompeting markets of 27 states plus the District of Columbia and account for 15% of all pediatric hospitalizations in the United States. These hospitals provide discharge data, including patient demographics, diagnoses, and procedures. Billing data include medications, radiologic imaging studies, laboratory tests, and supplies charged to each patient. Data are de-identified prior to inclusion in the database. CHA (Overland Park, KS) and participating hospitals jointly assure data integrity and quality as previously described (19, 20).

Data from all 43 participating CHA hospitals were used in our analysis. All children from birth to 19 years admitted to a PICU from January 2004 to December 2012 were identified. PICU admission was determined by a specific database flag. Patients formerly admitted to a neonatal ICU (NICU) and discharged were included in review. Patients admitted to both a NICU and PICU during the same hospitalization were

excluded from the cohort since PHIS flags did not distinguish in which unit a severe sepsis episode occurred. Thus 2,269 NICU/PICU patients with PSS were excluded.

For the purpose of reviewing trends in prevalence rates and mortality, we identified a subgroup of 33 children's hospitals that were CHA members and contributed continuous data from the entire 2004–2012 time span for trend analysis.

PICU patients were defined as having PSS if they demonstrated any of the below criteria:

1. ICD-9 code for severe sepsis (995.92)
2. ICD-9 code for septic shock (785.52)
3. An ICD-9 code of infection plus at least one ICD-9 code of organ dysfunction (modified Angus criteria) (15).

To account for the evolution of sepsis billing codes over the past 15 years, we utilized a modified approach to the Angus criteria based on an updated set of ICD-9 codes for severe sepsis and septic shock, as defined in 2012 by Weiss et al (5) (modified Angus criteria) (**Supplemental Table 2**, Supplemental Digital Content 1, http://links.lww.com/PCC/A116). In the Weiss modification, patients with *International Classification of Diseases, 9th Revision, Clinical Modification* codes specific for septicemia, sepsis with acute organ dysfunction, and septic shock were additionally included.

Underlying patient disease comorbidities were determined using the definition of a Pediatric Complex Chronic Condition (21) (**Supplemental Table 3**, Supplemental Digital Content 1, http://links.lww.com/PCC/A116). Length of ICU and hospital stays were calculated and reported as median with interquartile range (IQR) being 25th and 75th percentiles. Site of infection was classified based on grouped ICD-9 codes reflective of a specific source of sepsis (e.g., pneumonia, meningitis, and bacteremia); selected organisms were classified based on ICD-9 codes, but culture results were not specifically available for this determination. Hospitalization charges were supplied by CHA as the total amount charged to the patient by individual hospitals. Cost was estimated by multiplying the total hospital charge by the hospital-specific ratio of cost-to-charge. All reported cost figures were adjusted for inflation and standardized to the year 2012 using U.S. Bureau of Labor Statistics published data for medical cost inflation (22).

Statistical Analysis

Statistical analyses were performed using SAS 9.3 (Cary, NC). Statistical significance was assessed at the 0.05 level unless otherwise noted. Descriptive statistics were calculated for all variables of interest. Chi-square tests were used to compare categorical variables, and two-sample *t* tests or Wilcoxon rank-sum tests were used to compare continuous variables between two groups or years. The Cochran-Armitage test for trend was used to identify trends in prevalence rates and mortality rates over time. Although it was possible for a patient to have multiple PICU admissions for severe sepsis over the 9-year cohort, such patients could not be uniquely identified in the PHIS database. Thus, multiple PICU admissions were treated as independent for the purposes of statistical analyses. A hierarchal logistic model was used to identify characteristics of patients with severe sepsis that were associated with an increased risk of mortality while adjusting for PSS cases clustered within hospitals. Initially univariate analysis was used to identify a subset of variables associated with mortality. Variables found to be significant at the 0.15 level in univariate analysis were eligible for inclusion in the final model. To obtain the final model, we performed a stepwise backward elimination procedure in which all candidate predictors were initially included in the model. Variables not significant at the 0.05 level were then systematically removed, provided that they did significantly change the overall model fit when removed. A repeated-measures analysis of variance model was used to assess for changes in the estimated cost of PSS over time while adjusting for the correlation among costs from the same hospital. To evaluate potential impact of length of stay (LOS) and mortality on individual hospital costs, we stratified our cost analysis based on LOS and mortality. Eight separate groups were created using mortality status (survived and died) and four quartiles for LOS: 0–8, 9–17, 18–36, and more than 36 days. The relationship between hospital and cost was then modeled separately for each of the eight groups. Correlations among continuous variables were assessed using Spearman rank-order correlation coefficient. Hospitalization cost was adjusted to the year 2012 as described above.

RESULTS

Prevalence of Severe Sepsis

During the study period, 43 participating hospitals reported a total of 636,842 patient admissions to the PICU. Of these, 49,153 patients met PSS definition based on presence of either modified Angus criteria or an ICD-9 sepsis code, for an overall prevalence of PICU PSS of 7.7%. Defining PSS by modified Angus criteria alone identified 39,372 patients (prevalence 6.2%). PSS as defined solely by either ICD-9 code 995.92 or ICD-9 code 785.52 identified 19,776 patients (3.1% prevalence) (**Fig. 1**). Of the total, 9,995 patients were identified as PSS by both modified Angus criteria and use of at least one ICD-9 sepsis code.

We performed a limited analysis comparing subgroups of patients with PSS identified by 1) ICD-9 sepsis codes alone (n = 9,781), 2) modified Angus criteria alone (n = 29,377), and 3) both modified Angus criteria/at least one ICD-9 sepsis code (n = 9,995). Children identified by Angus criteria alone or both Angus/ICD-9 criteria were more likely to have comorbidities compared with children identified using only ICD-9 codes (76.5% vs 73.0% vs 66.4%, respectively; $p < 0.001$). Median LOS was significantly longer in patients identified by modified Angus criteria (median, 18 d) and combined criteria (20 d) compared with those identified by ICD-9 code criteria alone (13 d) ($p < 0.001$ for both comparisons). Rates of extracorporeal membrane oxygenation (ECMO) and continuous renal replacement therapy (CRRT) utilization were higher in patients identified by both Angus/ICD-9 criteria compared with Angus criteria and ICD-9 criteria alone (ECMO, 6.0%, 3.6%, and 2.5%, respectively; $p < 0.001$; CRRT, 10.2%, 3.6%,

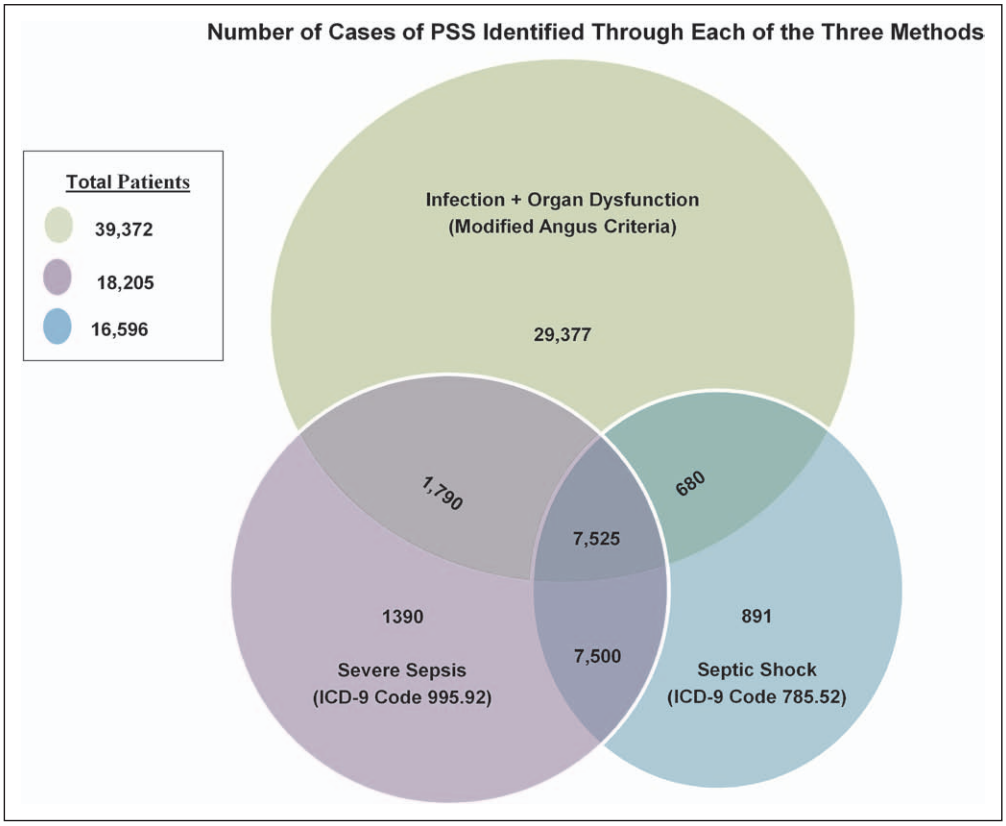

Figure 1. Patient cohorts with pediatric severe sepsis (PSS) from Pediatric Healthcare Information Systems as identified by various criteria. Total patients identified by three different criteria are noted in legend. Patient numbers identified by overlapping diagnostic criteria are noted within each area.

and 1.9%, respectively; $p < 0.001$). Patients with PSS identified by both modified Angus and ICD-9 criteria had significantly higher mortality (26.4%) compared with patients identified only by modified Angus criteria (11.2%) or only by ICD-9 sepsis codes (11.7%) ($p < 0.001$). No other clinically significant differences in patient characteristics were seen between PSS definition subgroups.

Further analysis was performed on the total PSS cohort ($n = 49,153$).

Clinical Characteristics

PSS clinical characteristics are noted in **Table 1**. Children aged 1–4 years made up the largest group (24.8%) in the cohort, followed by children younger than 1 year (23.6%). Median ICU LOS was 7 days (IQR, 2–17 d). Median hospital LOS was 17 days (IQR, 8–36 d).

Seventy-four percent of patients had one or more underlying comorbidities, of which cardiovascular disease was the most common (26.6%). Patients with PSS and with at least one comorbidity increased steadily from 64.9% in 2002 to 76.6% in 2012 ($p < 0.001$). Most patients had at least one organ dysfunction (91.1%), and over 53% of patients with PSS had at least two organ dysfunctions.

Sites and selected organisms associated with infection are described in **Table 2**. A presumed site of infection based on ICD-9 code description was noted in 91.5% of patients with PSS, with two or more sites of infection noted in 60%. Most common sites noted were bloodstream (67.8%), respiratory tract (57.2%), and genitourinary system (21.6%). The most common causative organisms noted were *Staphylococcus* species (9.9%) and *Streptococcus* species (5.4%). The prevalence in the percentage of PSS patients with influenza increased from 2008 (2.9%) to 2009 (7.8%), with prevalence returning to 2.1% in 2010. This was concurrent with a rise in the PSS prevalence rate in 2009 (**Fig. 2*A***). No statistically significant trends of infection rate were seen in other organisms. Bacterial or fungal coinfection was noted in 16% of patients with a documented organism.

Patient Survival

During the time period, 20,655 PICU deaths were reported (PICU mortality rate 3.2%). Of patients meeting PSS criteria during PICU admission, 7,074 patients died, for a mortality rate in PSS patients of 14.4% (95% CI, 14.1–14.7%). Of total PICU deaths during the time period, 34.2% of patients had an associated PSS diagnosis. Mortality was highest in children less than 1 year (19.2%), followed by children 1–4 years old (13.8%). Children with a at least one comorbidity had a higher mortality rate (15.8%) than children without any reported comorbidities (10.4%) ($p < 0.001$). Among patients with PSS with specific comorbidities, mortality was highest in patients with malignancies (22.4%), hematological or immunological disorders (20.3%), and cardiovascular disease (20.0%). Mortality rate in patients with a specific reported bacterial organism identified was 13.2%. Although fungal infection alone was rare (< 1%), PSS mortality was high in this group (20.1%) relative to the overall mortality rate.

Hierarchical logistic modeling identified several patient characteristics associated with increased odds of mortality (**Table 3**). Patient age was associated with mortality; odds of death in children younger than or 1 year old was 1.4 times higher than for children 10–19 years old ($p < 0.001$). Odds of mortality increased with increasing number of organs with dysfunction and was highest in children with five or more systems affected (odds ratio [OR] = 20.1; 95% CI, 16.2–25.1; $p < 0.001$). After adjusting for age and organ dysfunction, children with malignancies had greater odds of mortality compared with children without malignancies (OR = 1.9; 95% CI, 1.8–2.1; $p < 0.001$). Similarly, children with hematological

TABLE 1. Demographic Characteristics of PICU Patients Diagnosed With Pediatric Severe Sepsis Identified Using Either Angus Criteria or *International Classification of Diseases*, 9th Revision, Codes

Variable	PSS Count (% of PSS Admissions)	Mortality Count (% of PSS Deaths)
Patients with PSS	49,153	7,074
Gender (%)		
Male	25,940 (52.8)	3,779 (53.4)
Female	23,211 (47.2)	3,294 (46.6)
Age at admission		
Mean years ± SD	7.2 ± 6.3	6.4 ± 6.3
Median years (25th–75th percentile)	5.5 (1–13)	3.0 (0–12)
Age group at admission (%)		
Less than 1 yr	11,617 (23.6)	2,225 (31.5)
1–4 yr	12,174 (24.8)	1,675 (23.7)
5–9 yr	7,466 (15.2)	902 (12.8)
10–14 yr	9,371 (19.1)	1,174 (16.6)
15–18 yr	8,525 (17.3)	1,098 (15.5)
Median total hospitalization days (25th–75th percentile)	17 (8–36)	17 (4–47)
Median ICU days (25th–75th percentile)	7 (2–17)	11 (3–29)
Comorbidities[a] (%)		
Any condition	36,248 (73.8)	5,731 (81.0)
Neurologic	12,913 (26.3)	1,609 (22.7)
Cardiovascular	13,085 (26.6)	2,612 (36.9)
Respiratory	3,397 (6.9)	554 (16.3)
Renal	2,920 (5.9)	444 (7.8)
Gastroenterology	2,584 (5.3)	455 (6.4)
Hematology/immunology	3,427 (7.0)	694 (9.8)
Metabolic disorder	6,377 (13.0)	1,069 (15.1)
Malignancy	8,543 (17.4)	1,581 (22.3)
Other	6,747 (13.7)	913 (12.9)
Acute organ dysfunction: number of systems affected (%)		
0	4,380 (8.9)	201 (2.8)
1	18,534 (37.7)	1,288 (18.2)
2	17,926 (36.5)	2,740 (38.7)
3	5,831 (11.9)	1,765 (25.0)
4	1,876 (3.8)	788 (11.1)
5+	603 (1.2)	292 (4.1)

PSS = pediatric severe sepsis.

[a]Because patients could have multiple comorbidities, percentages add to more than 100%.

Number describes absolute volumes and as a percent of PSS admissions. Mortality reflects absolute volume and as percentage of total PSS deaths.

disorders (OR = 1.5; 95% CI, 1.4–1.6; $p < 0.001$) and cardiovascular conditions (OR = 1.4; 95% CI, 1.3–1.5; $p < 0.001$) had increased odds of mortality.

Median individual PSS patient total hospital cost, adjusted for inflation, was $77,446 (IQR, $32,545–$183,458) with a median daily cost of $4,516 (IQR, $3,251–$6,442).

TABLE 2. Prevalence and Mortality Noted With Site of Infection and Specific Organisms Identified in Patients With Pediatric Severe Sepsis

Characteristic Group	No. Cases (% of Patients With Pediatric Severe Sepsis) (*n* = 49,153) (%)	Mortality in Group (%)
Site of infection[a]		
Respiratory	28,105 (57.2)	5,221 (18.6)
Cardiovascular	4,299 (8.7)	722 (16.8)
Abdominal	4,119 (8.4)	655 (15.9)
Bloodstream	33,342 (67.8)	5,333 (16.0)
Genitourinary	10,625 (21.6)	1,426 (13.4)
CNS	1,886 (3.8)	299 (15.9)
Device	4,565 (9.3)	718 (15.7)
Postsurgical shock	79 (0.2)	5 (6.3)
Wound/soft tissue	1,426 (2.9)	173 (12.1)
Other[b]	4,685 (9.5)	353 (7.5)
Selected pathogens		
Bacterial		
Streptococcus	2,640 (5.4)	311 (11.8)
Group B	206 (0.4)	19 (9.2)
Streptococcus pneumoniae	382 (0.8)	43 (11.3)
Staphylococcus	4,885 (9.9)	565 (11.6)
Methicillin-susceptible *Staphylococcus aureus*	2,466 (5.0)	274 (11.1)
Methicillin-resistant *Staphylococcus aureus*	771 (1.6)	66 (8.6)
Klebsiella pneumonia	1,673 (3.4)	232 (13.9)
Escherichia coli	2,155 (4.4)	230 (10.7)
Haemophilus influenza	580 (1.2)	45 (7.8)
Proteus mirabilis	299 (0.6)	27 (9.0)
Fungal		
Candidiasis	1,740 (3.5)	450 (25.9)
Aspergillus	497 (0.9)	237 (47.8)
Viral coinfection		
Adenovirus	459 (2.2)	129 (28.1)
Rhinovirus	1,101 (2.2)	142 (12.9)
Influenza (unspecified)	1,230 (2.5)	197 (16.0)
Flu A with pneumonia	604 (1.2)	108 (17.9)
H1N1	185 (0.4)	27 (14.6)
Respiratory syncytial virus	306 (0.6)	51 (16.7)
Coxsackie	5 (0.01)	0 (0.0)
Parvovirus	38 (0.08)	7 (18.4)
Varicella	74 (0.15)	15 (20.3)
Herpes zoster	140 (0.28)	34 (24.3)
Herpes Simplex	682 (1.4)	133 (19.5)

[a]Patients can have multiple sites of infection; therefore, percentages will sum to over 100%.
[b]Other is defined as patients not meeting one of the above sites of infection. This could include those with an undetermined site of infection.

Trends and Correlations

Thirty-three hospitals reported data over the complete 9-year period. Trend analysis on yearly prevalence rates, mortality, and hospitalization costs was performed on this cohort, with 535,184 PICU admissions and 40,747 cases of PSS (7.6% prevalence) identified.

During the cohort period, PICU admissions increased from 2004 ($n = 54,681$) to 2012 ($n = 63,569$). Similarly, the number of PSS admissions also increased, from 3,408 to 4,889 as did the proportion of PICU admissions with a diagnosis of PSS (6.2–7.7%). The highest annual PSS prevalence rate occurred in 2009 (8.4%), and the largest year-over-year increase (0.7%) occurred from 2006 to 2007. In contrast to the rising PSS prevalence rate, overall PSS mortality in this group significantly decreased from 2004 (18.9%) to 2012 (12.0%) (**Fig. 2***A*) ($p < 0.001$). The proportion of patients with PSS and multiple organ dysfunction (≥ 2 organs) slightly decreased over the time period (56.5–51.3%; $p < 0.001$), whereas the proportion of PSS patients with associated comorbidities increased over the time period, from 69.4% in 2004 to 76.6% in 2012 ($p < 0.001$).

Median total hospitalization cost, adjusted for inflation, decreased over the time period (from $86,156 in 2004 to $72,308 in 2012; $p = 0.002$). There were significant differences in the cost of PSS among hospitals ($p < 0.001$) (**Fig. 3**). Even after stratifying by LOS quartiles and by mortality, PSS cost still differed significantly between hospitals ($p < 0.001$). Estimated total cost of hospitalization was significantly correlated with LOS ($r_s = 0.90$; $p < 0.001$). Median inflation-adjusted PSS cost/day also significantly decreased over the time period ($4,563–$4,413; $p = 0.002$). Median cost of hospitalization was significantly higher in patients who died (died vs survived, $142,501 vs $72,936; $p < 0.001$) despite no significant difference in median LOS between nonsurvivors (median 17 d) and survivors (17 d). However, there was a significant difference in LOS at the 75th percentile between survivors and nonsurvivors (35 vs 47 d, respectively; $p < 0.001$). In these 33 hospitals, the total burden of hospital cost for patients with severe sepsis from 2004 to 2012 was $6,575,327,932.

Individual institutional PSS prevalence and associated mortality rate varied significantly between the 33 hospitals (Fig. 2*B*). Individual center PSS prevalence ranged from 4.5% to 13.1%. Mortality ranged from 3.9% to 23.0%. Aggregated data from 2004 to 2012 for each of the 33 hospitals demonstrated a significant inverse correlation between individual hospital PSS prevalence and PSS mortality rate ($r_s = –0.48$; 95% CI, –0.70 to –0.15; $p = 0.005$) (**Fig. 2*B***). Analysis of individual hospital PSS patient volume revealed a

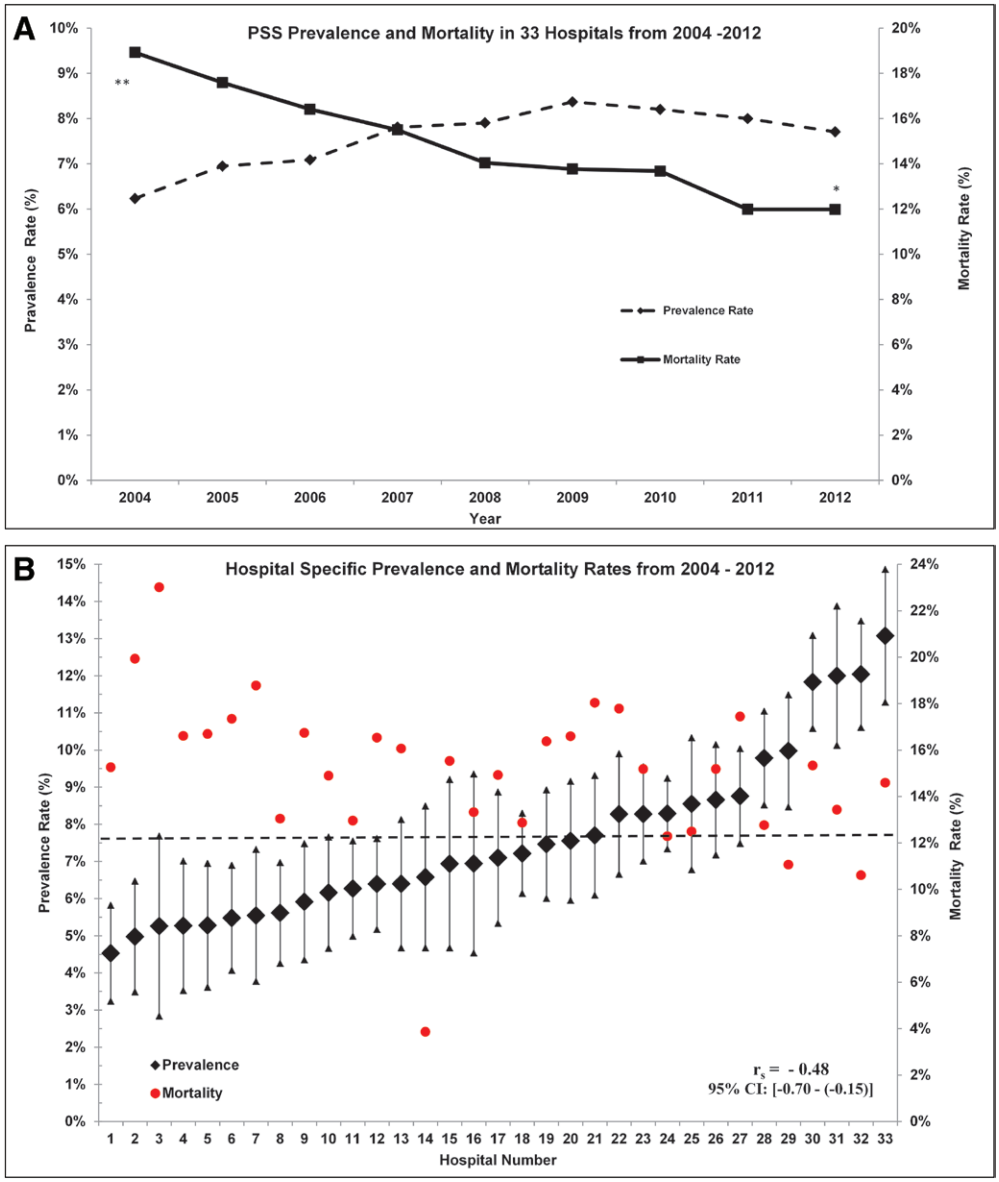

Figure 2. A, Change in overall prevalence and mortality rates of children with pediatric severe sepsis (PSS). Data are from 33 hospitals for which continuous data were available for the time period. Prevalence rates significantly increased ($p < 0.001$) and mortality rates significantly decreased ($p < 0.001$) over time. **B**, Hospital-specific prevalence and mortality for pediatric patients with severe sepsis. *Diamonds* represent prevalence, *triangles* represent 95% CIs, and *circles* represent mortality rates. There is significant negative correlation between prevalence and mortality ($r_s = –0.48$; 95% CI, –0.70 to –0.15; $p = 0.005$).

TABLE 3. Risk Factors Associated With Mortality in Children With Pediatric Severe Sepsis

Risk Factor	Level	Adjusted OR (95% CI)	*p*
Age	< 1 yr	1.43 (1.33–1.54)	< 0.001
	1–4 yr	1.02 (0.95–1.10)	0.588
	5–9 yr	0.96 (0.88–1.04)	0.325
	10 to < 19 yr (reference)	–	Calculated (reference)
Organ dysfunction (no. of systems affected)	0 (reference)	–	Calculated (reference)
	1	1.61 (1.38–1.88)	< 0.001
	2	3.80 (3.27–4.43)	< 0.001
	3	9.18 (7.85–10.73)	< 0.001
	4	15.52 (13.05–18.46)	< 0.001
	5+	20.15 (16.18–25.09)	< 0.001
Cardiovascular	Yes	1.41 (1.33–1.50)	< 0.001
	No (reference)	–	
Hematology/immunology	Yes	1.49 (1.35–1.64)	< 0.001
	No (reference)	–	
Malignancy	Yes	1.93 (1.79–2.08)	< 0.001
	No (reference)	–	

OR = odds ratio.

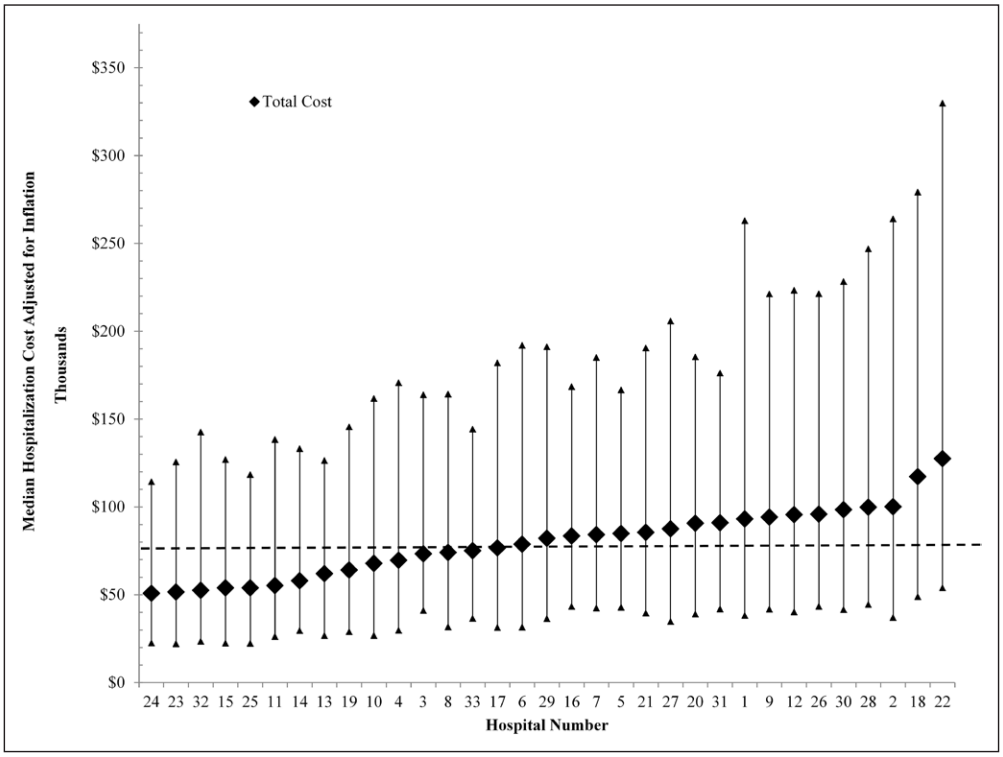

Figure 3. Median total hospitalization cost of patients with pediatric severe sepsis by hospital. *Diamonds* represent aggregate median costs from 2004 to 2012 after inflation, and *triangles* are 25th and 75th percentiles. *Dashed line* represents overall median cost ($77,598). Hospital number correlates with Figure 2.

similar negative correlation to mortality (r_s = –0.38; 95% CI, –0.64 to –0.05; p = 0.02). Aggregated relationships among prevalence, mortality rates, and cost are demonstrated in **Figure 4*A***. Higher individual hospital PSS cost was also positively correlated with higher mortality rates (r_s = 0.36; 95% CI, 0.02–0.63; p = 0.04) (Fig. 4*B*). No correlation was seen between hospital PSS prevalence and PSS cost (–0.004; 95% CI, –0.346 to 0.339; p = 0.93).

DISCUSSION

This review represents the largest reported cohort analysis of PICU patients with severe sepsis to date. The overall prevalence of PSS in PICU patients was 7%, and the yearly prevalence rates increased over the study period. This rise is consistent with the noted increase in prevalence of patient comorbidities. In spite of rising comorbidities, a concomitant 37% reduction in annual PSS mortality rate occurred over time. Unlike previous pediatric sepsis reviews, the 1- to 4-year-old age group represented the largest proportion of our cohort (24.8%). This

Figure 4. A, Association of individual center pediatric severe sepsis (PSS) prevalence, mortality, and cost. Horizontal axis represents median hospital prevalence, vertical axis represents median hospital mortality, and *bubble size* represents relative center median cost. Individual center prevalence was negatively correlated with mortality ($r_s = -0.48$; 95% CI, −0.70 to −0.15; $p = 0.005$). **B**, Association of individual center PSS cost and mortality. Horizontal axis represents median hospital mortality, vertical axis represents median cost, and *bubble size* represents relative center prevalence. Higher cost was positively correlated with higher mortality rates ($r_s = 0.36$; 95% CI, 0.02–0.63; $p = 0.04$). PHIS = Pediatric Healthcare Information Systems.

analysis focused on PICU patients with PSS, excluding patients who were in the NICU or who had been in the NICU during the same hospitalization. However, this study included former NICU patients who had been discharged and required readmission to a PICU. This subgroup of former preterm infants remains at a higher risk of infection during the first year of life (23, 24). Consistent with previous data analyses, younger age, presence of comorbidities, and multiple organ dysfunction conferred increased mortality risk in PSS. Mortality was highest in infants less than 1 year. Neonatal comorbid conditions such as chronic lung disease and delayed recognition and treatment of septic shock could account for increased relative risk of death in infants.

Subgroup analysis did demonstrate that patients meeting PSS definition based on both modified Angus criteria definition and at least one ICD-9 sepsis code identified a smaller subgroup with significantly worse severity of illness and higher mortality. We chose to perform analysis of the broader category of patients with PSS to better capture the breadth of severe sepsis in PICU patients. Further analysis of these case definition subgroups is outside the scope of this study, but focus on the combined subgroup could be useful for more specific studies on high-risk patients.

Staphylococcus species were the most commonly coded causative organisms for PSS. The prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) was low; however, specific ICD-9 coding for MRSA did not exist until 2009, making determination of true prevalence difficult. Prevalence of *Haemophilus influenzae* and *Streptococcus pneumoniae* infection was low over the time period.

This analysis differs from previous epidemiologic studies of pediatric sepsis in several aspects. Previous studies evaluated sepsis prevalence through state discharge data encompassing all hospital systems and NICUs. The focus of the

PHIS database review was to provide specific assessment of prevalence and characteristics of PSS in a large cohort of nonneonatal pediatric patients from dedicated children's hospitals. These hospitals likely have a higher proportion of patients with comorbidities and more severe illness than other series utilizing broad state discharge data (3, 4). Thus, the higher prevalence of PSS (7%) in the current study is difficult to compare to that of other pediatric database reviews. Previous studies based on nonfederal state data have also included NICU patients. We elected to specifically evaluate sepsis only in patients admitted to a PICU. Further review of neonatal sepsis data from PHIS is in progress. Finally, this review evaluates the most recent data possible from up to 2012, compared with previous data only available to 2005.

The nature of this review does not allow determination of specific causes for decreased mortality over time. Possible factors could include better overall recognition of sepsis, improved institution of goal-directed therapy (7), and utilization of Surviving Sepsis Campaign Guidelines and the ACCM pediatric sepsis guidelines (13, 25). Given the increase in comorbidities that might have been expected to increase mortality, the actual decrease in death rates is both encouraging and suggestive of the benefits of the above changes. Of note, implementation of ACCM sepsis guidelines in adults was associated with significant reduction in mortality (26). Additional explanations for apparent increases in PSS prevalence rates over time could include increasing use of sepsis codes for less critically ill children than in previous years. Increased PICU bed availability and/or lowered admission thresholds with resultant increases in less severely ill ICU pediatric patients with sepsis could also potentially impact PSS prevalence rates. Of note, the proportion of patients with PSS and multiple organ dysfunction did demonstrate a slight decrease. This could be related to either increased recognition of PSS or improvements in recognition and care to lower organ failure progress. However, comorbidities (generally associated with higher risk of mortality) significantly increased through the period as well. These findings provide potentially conflicting supporting evidence and emphasize the potential value of more specific severity of illness scoring in administrative databases to allow for more consistent comparisons.

We found significant variability in PSS prevalence, outcomes, and costs between hospitals. Notably a significant negative correlation between hospital PSS prevalence and mortality was also seen between center volume and mortality. Reasons for this volume/outcome relationship are uncertain but could be related to experience in sepsis management, available resources, or other undetermined factors. Higher PSS cost was associated with higher mortality, suggesting that greater resource utilization was not associated with improved outcomes. Of note, the 75th percentile for LOS in nonsurvivors was much higher than survivors (47 vs 35 d), suggesting higher intensity of care and possibly explaining the higher overall costs of care associated with nonsurvival.

Finally, this review underscores the financial burden of PSS, as demonstrated by a cumulative annual cost of over 730 million dollars for the 33 selected children's hospitals alone.

Limitations

This analysis is limited by the inherent features of an administrative database. Data to allow calculation of severity of illness measures such as Pediatric Risk of Mortality III scores are not available, nor are some therapeutic interventions such as specific antibiotic or fluid use. Site of infection and causative organisms were determined based on coding and not on evaluation of actual culture reports, potentially leading to incomplete coding or underestimation of contributing organisms. Differences in coding approaches could account for the higher prevalence of identified sites and organisms compared with studies using state health database reporting (4). Other variables such as vaccination status, race, and birth weight were not consistently captured and thus were excluded in analysis. Efforts to provide shared data use between administrative databases and clinically driven pediatric critical care databases, such as the Virtual PICU database registry (27), could provide desirable synergy for future work in sepsis and other disease processes.

The PHIS database also captures patients in tertiary and quaternary care children's hospitals. It is possible that hospitals contributing to this database have greater resources that led to better pediatric outcomes than centers without full pediatric services, limiting the ability to generalize to all facilities caring for pediatric patients. Although robust in nature, patients from institutions in the PHIS database only account for 15% of all U.S. pediatric hospitalizations, making generalization similarly limited. However, it is likely that this database represents a higher overall complexity and severity of illness than that of non-CHA institutions.

CONCLUSIONS

PSS prevalence in PICUs has increased over the past decade, with an increased prevalence of comorbidities but a decrease in mortality. Individual center PSS prevalence, volume, and costs demonstrate variability and are significantly correlated with mortality. Further evaluation to identify clinical contributors to center-specific variability could identify opportunities for earlier sepsis identification and optimization of therapies.

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