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Comparison of Pediatric Severe Sepsis Managed in U.S. and European ICUs

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Abstract

Objectives—Pediatric severe sepsis remains a significant global health problem without new therapies despite many multicenter clinical trials. We compared children managed with severe sepsis in European and U.S. PICUs to identify geographic variation, which may improve the design of future international studies.

Design—We conducted a secondary analysis of the Sepsis PRevalence, OUtcomes, and Therapies study. Data about PICU characteristics, patient demographics, therapies, and outcomes were compared. Multivariable regression models were used to determine adjusted differences in morbidity and mortality.

Setting—European and U.S. PICUs.

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Patients—Children with severe sepsis managed in European and U.S. PICUs enrolled in the Sepsis PRevalence, OUtcomes, and Therapies study.

Interventions—None.

Measurements and Main Results—European PICUs had fewer beds (median, 11 vs 24; $p < 0.001$). European patients were younger (median, 1 vs 6 yr; $p < 0.001$), had higher severity of illness (median Pediatric Index of Mortality −3, 5.0 vs 3.8; $p = 0.02$), and were more often admitted from the ward (37% vs 24%). Invasive mechanical ventilation, central venous access, and vasoactive infusions were used more frequently in European patients (85% vs 68%, $p = 0.002$; 91% vs 82%, $p = 0.05$; and 71% vs 50%; $p < 0.001$, respectively). Raw morbidity and mortality outcomes were worse for European compared with U.S. patients, but after adjusting for patient characteristics, there were no significant differences in mortality, multiple organ dysfunction, disability at discharge, length of stay, or ventilator/vasoactive-free days.

Conclusions—Children with severe sepsis admitted to European PICUs have higher severity of illness, are more likely to be admitted from hospital wards, and receive more intensive care therapies than in the United States. The lack of significant differences in morbidity and mortality after adjusting for patient characteristics suggests that the approach to care between regions, perhaps related to PICU bed availability, needs to be considered in the design of future international clinical trials in pediatric severe sepsis.

Keywords

children; Europe; management; outcome; pediatric intensive care unit; shock

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Pediatric severe sepsis remains a significant global health problem (1–6). In 2013, an estimated 6.3 million children died worldwide with 52% resulting from infections (7). Identification of novel therapies will require a new phase of multicenter international clinical trials (8). However, substantial variability exists in pediatric infection mortality reported across geographic regions (7, 9). These differences may stem from several factors, including differences in the approach to healthcare delivery and availability of intensive care resources. Understanding systematic differences in patient characteristics, approach to therapy, and rate of adverse outcomes is necessary to ensure that existing regional variation is appropriately accounted for in the design of future multicenter international clinical trials for pediatric severe sepsis.

Data from the Surviving Sepsis Campaign have previously demonstrated a higher unadjusted mortality in adults with severe sepsis treated in European ICUs compared with the U.S. ICUs but noted that this difference disappeared after adjusting for admission source and illness severity. These results raise concerns that variability in the approach to critical care between regions, particularly with regard to ICU bed availability, may affect outcomes (10). Although such differences can modify the impact of a novel therapy if implemented based on the need for ICU admission, similar regional comparisons have not been made for children with severe sepsis treated in PICUs.

The Sepsis PRevalence, OUtcomes, and Therapies (SPROUT) study recently reported the prevalence, therapies, and outcomes of pediatric severe sepsis across PICUs worldwide.

SPROUT investigators (Appendix 1) screened nearly 7,000 PICU patients in 128 sites across 26 countries for severe sepsis using pediatric sepsis consensus criteria (11). The largest number of sites and enrolled patients originated from Europe and the United States. For the current analysis, we used data from the SPROUT study to compare PICU characteristics, patient demographics, therapies, and outcomes for children with severe sepsis treated in Europe versus the United States. We hypothesized that disparities in outcomes for children with severe sepsis managed in Europe versus the United States would be largely explained by differences in patient characteristics.

MATERIALS AND METHODS

SPROUT was a prospective, cross-sectional point prevalence study with data collection performed on five study days spaced over 1 year from June 2013 to June 2014 (11). Follow-up data about outcomes were also collected. Sites were recruited by open invitation through established research networks, and participation was voluntary. Ethics approval was obtained at all sites with waiver of informed consent granted at all but three sites (two in Europe and one in the United States) at which written consent was required for data collection. Although the details of the SPROUT study methodology and primary results have been previously published (11, 12), the data in this study are limited to novel comparative analyses between Europe and the United States not previously reported.

All patients 18 years old being treated in a participating PICU at 9:00 AM local time on each study day were screened for severe sepsis using a standardized form with the “2005 International Pediatric Sepsis Consensus Conference” criteria: 1) at least two systemic inflammatory response syndrome criteria, 2) confirmed or suspected invasive infection, and 3) cardiovascular dysfunction, acute respiratory distress syndrome, or at least two organ dysfunctions (13). The subset of patients with septic shock defined by cardiovascular dysfunction was included within the spectrum of severe sepsis. Only clinical data available within the 24 hours preceding the 9:00 AM study day time were considered for screening, yielding a study cohort with active severe sepsis. Patients who were 18 years old or older, corrected gestational age less than 42 weeks, or who had surgery involving cardiopulmonary bypass in the preceding 5 days were excluded. Only patients enrolled with severe sepsis from a PICU in either Europe or the United States were included in the current analysis.

Data were collected about PICU characteristics and patient demographics, treatment, and outcomes within a 48-hour window around the study day (9:00 AM before to 9:00 AM after the study day). For severity of illness, the Pediatric Index of Mortality-3 (PIM3) score (14) was calculated at PICU admission and the Pediatric Logistic Organ Dysfunction score (15) was calculated on the study day. For all enrolled patients, the first-day meeting criteria for severe sepsis was determined. Multiple organ dysfunction syndrome (MODS) was defined as two or more concurrent organ system dysfunctions, and new or progressive MODS (NPMODS) was determined by following patients for seven consecutive days after severe sepsis recognition (16). Each patient was followed up for 90 days or until discharge from the hospital to determine mortality and functional disability outcomes. The Pediatric Overall Performance Category (POPC) ordinal scale (1 [normal] to 6 [death]) was used to assess new functional disability or change from baseline for all hospital survivors (17). Hospital-

acquired infections (HAI) were those infections that occurred more than 48 hours following hospital admission.

The primary outcome of comparison was all-cause hospital mortality censored at 90 days from the study day or hospital discharge. Secondary outcomes included PICU mortality, PICU and hospital length of stay (LOS), vasoactive- and ventilator-free days from the day of severe sepsis recognition through day 28, NPMODS, and change in functional disability status (POPC). A composite outcome of death or moderate-severe disability worsened from baseline was also determined.

Statistical Analysis

Data were analyzed using STATA (version 12.1; StataCorp LP, College Station, TX). Categorical results are presented as proportions and analyzed using the Fisher exact or chi-square tests. Continuous data are presented as medians with interquartile range (IQR) and analyzed using the Wilcoxon signed rank test. Variables that differed between European and U.S. patients were tested as possible confounders in the association of geographic region with outcomes using multivariable regression models. We defined a confounder as a covariate that changed the odds ratio (OR) between region and the outcome by at least 10%. The following covariates were tested for confounding: age, source of PICU admission, comorbid conditions, PIM3, MODS at sepsis recognition, site of infection, any bacteremia, and hospital- versus community-acquired infection. Although none of these variables met our a priori criteria for confounding, based on the strength of association with region in bivariate analyses, we used age, source of PICU admission, HAI, PIM3, and bacteremia in final multivariable models and present adjusted OR (aOR) with the 95% CIs. We used logistic regression to test the association of region with outcomes for categorical outcomes and negative binomial regression for count outcomes (e.g., LOS and vasoactive-free days). Collinearity across covariates included in the final regression models was ruled out by ensuring the variance inflation factor was less than two for each variable.

Because U.S. sites included a larger number of older patients (leading to a substantial age discrepancy between groups as we note above), we included a control for age in the multivariate models. To further control for age, we also performed a supplemental analysis that assessed outcome differences independent of age by matching all European patients by age to a subsample of U.S. patients to better remove any residual confounding effect of age on outcome. We then reestimated the multivariate models using this matched dataset. In addition, because PIM3 uses systolic blood pressure uncorrected for age as part of the risk prediction, we tested whether observed regional differences in severity of illness reflected by PIM3 were attributable to the younger age of European patients by assessing both the correlation between age and PIM3 using Spearman correlation and comparing PIM3 in patients 1 year old or older versus less than 1 year old. We also attempted to account for site-to-site variation but given the low number of patients enrolled at each site, including a fixed effect for each site overfit the data and resulted in an incidental parameters problem. As an alternative, we estimated a mixed-effects logistic regression model, allowing for a random intercept by site. However, the inclusion of the random effect was not statistically significant, suggesting that baseline mortality did not vary significantly by site such that

estimates from the mixed-effects logistic regression model were nearly identical to those from standard logistic regression. Therefore, for simplicity, we present only the results from standard regression models.

RESULTS

Centers in Europe and the U.S. screened a total of 5,639 PICU patients with 413 meeting criteria for severe sepsis. Two patients declined consent for data collection (both from the United States), leaving 411 patients in the final cohort. Europe included 39 sites with 86 patients (21%), and the United States included 53 sites with 325 patients (79%). Sites in Europe were less likely to be free-standing children's hospitals than those in the United States (38% vs 51%; $p = 0.001$). In addition, there was a lower median number of PICU beds (11 [IQR, 8–15] vs 24 [IQR, 19–32]; $p < 0.001$) and annual PICU admissions (500 [IQR, 300–740] vs 1,300 [IQR, 850–1,800]; $p < 0.001$) in Europe versus U.S. sites. The European and U.S. sites participating in the SPROUT study and included in this analysis are listed in Supplemental Table 1 (Supplemental Digital Content 1, http://links.lww.com/PCC/A251).

The point prevalence of severe sepsis was 6.2% (95% CI, 5.0–7.6) in European sites and 7.7% (95% CI, 6.9–8.5) in U.S. sites ($p = 0.06$). Table 1 shows patient characteristics by region. European patients were younger (1 yr [IQR, 0.4–7 yr] vs 6 yr [IQR, 1–13 yr]; $p < 0.001$) and had higher PIM3 scores (5.0 [IQR, 2.3–9.8] vs 3.8 [IQR, 1.6–7.9]; $p = 0.02$) and higher proportions of MODS at sepsis recognition (73% vs 51%; $p < 0.001$). There was no correlation between age and PIM3 (Spearman ρ, 0.02; $p = 0.67$) and median PIM3 did not differ by age 1 year or less (4.4 [IQR, 1.7–9.2] and > 1 yr [3.9 (IQR, 1.7–8.5)]; $p = 0.40$). The majority of patients from both regions had one or more comorbid conditions prior to admission (Europe: 88% vs United States: 86%; $p = 0.60$). However, the types of comorbid conditions differed, with cardiovascular conditions predominating in Europe and respiratory, gastrointestinal, and neuromuscular conditions more common in the United States. More patients in Europe than the Unites States were admitted to PICUs from general hospital wards (37% vs 24%) rather than emergency departments (EDs) (8% vs 35%).

The most common site of infection was respiratory in both regions but more patients in Europe had bacteremia than in the United States (32% vs 19%; $p = 0.01$; Table 2). Gram-positive bacteria were more commonly identified in European patients, whereas viruses were more often identified in U.S. patients. European patients had a higher proportion of HAIs (35% vs 25%; $p = 0.004$).

Therapies used in the 48-hour window around the SPROUT study days are presented in Table 3. The majority of patients in both regions had respiratory failure and were being actively mechanically ventilated within the time window of data collection. However, invasive mechanical ventilation was more common in Europe compared with U.S. patients (85% vs 68%; $p = 0.002$) as were vasoactive infusions (71% vs 50%; $p < 0.001$). Dopamine was used more frequently in Europe (43% vs 25%; $p = 0.02$), but epinephrine, norepinephrine, vasopressin, phenylephrine, dobutamine, and milrinone were used similarly between the two regions (all $p > 0.05$). European patients were more likely to receive enteral

nutrition (64% vs 50%; $p = 0.03$), as well as blood products, synthetic colloid, and renal replacement therapies. Overall, central venous catheters were used slightly more often in European patients (91% vs 82%; $p = 0.05$), with peripherally inserted central catheters more common in the United States.

Unadjusted hospital and PICU mortality was higher in European compared with U.S. PICUs (30% vs 22% and 29% vs 22%, respectively) although these differences did not reach statistical significance (Table 4). European patients had fewer vaso-active-free days, ventilator-free days, and longer hospital LOS than U.S. patients. NPMODS and mild and moderate disability at hospital discharge were not different between regions, and although the composite outcome of death or moderate disability trended higher in European patients, this did not reach statistical significance. After adjusting for age, source of PICU admission, HAI, PIM3, and bacteremia, there were no significant differences between European and U.S. patients for hospital mortality (aOR, 1.25; 95% CI, 0.69–2.28; $p = 0.46$), NPMODS (aOR, 0.68; 95% CI, 0.39–1.19; $p = 0.18$), or death/moderate disability (aOR, 1.02; 95% CI, 0.59–1.75; $p = 0.95$). Similarly, after adjusting for covariates, there were no longer significant differences in vasoactive-free days (β, −0.17; 95% CI, −0.40 to 0.06; $p = 0.14$) or hospital LOS (β, 0.003; 95% CI, −0.21 to 0.22; $p = 0.98$) between regions. The supplementary analysis using age-matched patients further demonstrated no differences in outcomes between Europe and the United States (data not shown).

DISCUSSION

Using data from the recently completed SPROUT study, we compared pediatric patients treated for severe sepsis in European versus U.S. PICUs. European patients were more frequently admitted from hospital wards, were younger, had a higher severity of illness, had more HAIs, and received more intensive care therapies than patients in the United States. However, after adjusting for these factors, there were no significant differences in morbidity and mortality between regions. The lack of adjusted outcome differences raises concern that there may be a differential approach to care for hospitalized children with severe sepsis between regions, such that patients admitted to European PICUs are at a different phase of their septic illness than in the United States. Such differences in patient characteristics and care models need to be considered in the design of future international clinical trials in pediatric severe sepsis. In particular, it may be more appropriate to use consensus criteria to establish study eligibility irrespective of hospital location or PICU admission, especially if a study intervention is best delivered at initial sepsis recognition.

Our results concur with a recent study investigating severe sepsis in adult patients using the large voluntary Surviving Sepsis Campaign database. Paralleling our study, adult European ICUs possessed fewer beds but had more severely ill patients and admitted more patients from the hospital ward when compared with the U.S. ICUs. After accounting for differences in illness severity and source of ICU admission, raw differences in outcomes disappeared between European and U.S. adults with severe sepsis leading the authors to question the effect of regional differences in the approach to critical care, including ICU bed availability (10). In our study, we similarly found that European PICUs possessed fewer beds and admitted more severely ill patients who more often came from hospital wards rather than the

ED. In addition, outcomes did not differ significantly after adjustment for baseline differences in illness severity for children with severe sepsis treated in European and U.S. PICUs.

The difference in severity of illness for pediatric patients with severe sepsis at admission to European versus U.S. PICUs is a notable finding. Admission PIM3 and the proportion with MODS at severe sepsis recognition were significantly higher in the European cohort of patients. Although PIM3 uses systolic blood pressure unadjusted for age as part of the risk prediction, there was no indication that the higher PIM3 distribution in European patients was explained by the overall lower age. Further reflecting the higher severity of illness, European patients more commonly received intensive care therapies than their U.S. counterparts. For example, the European group used more vasoactive infusions and mechanical ventilation. Although such treatment differences between regions could reflect practice variability, it is likely that these therapeutic differences underlie the higher baseline severity of illness on entering European PICUs.

Similar to the previously published adult study from the Surviving Sepsis Campaign, the median number of PICU beds per site was lower in Europe and more patients were admitted with severe sepsis from the general ward than the ED when compared with sites in the United States. This suggests that children are less likely to be triaged to an intensive care setting at hospital admission in Europe, which, consequently, leads to a smaller number of patients with an overall higher severity of illness at PICU admission. This difference in the number of available PICU beds may be an important factor in our observed trend toward a mortality difference in the unadjusted analyses because our study design did not account for those patients with severe sepsis who recovered on the wards and were never admitted to the PICU. The complete lack of difference in outcomes between regions after adjusting for severity of illness and source of admission further suggests that outcome differences may be related to differing thresholds for PICU admission between regions. Unfortunately, the SPROUT study did not capture illness severity at hospital admission or hospital LOS prior to PICU admission in order to compare triage decisions prior to the PICU. Further investigation into the illness severity threshold triggering PICU admission in each region may help to identify an optimal balance of PICU to total hospital beds. Interestingly, the PICU to total hospital bed ratio may be more important than the absolute number of PICU beds alone. For example, adult ICU patients admitted to low ICU-to-hospital bed ratio institutions used significantly more intensive care therapies than those admitted to institutions with high ratios (18). Future studies should consider the characteristics of the population served and the ratio of ICU to total available hospital beds, perhaps even extending to regional availability of beds, to account for interhospital transfers rather than the number of intensive care beds alone.

Other differences noted between patients in Europe and the United States were patient age, site of infection, and causative organism. European patients tended to be younger, have more primary bloodstream infections, bacteremia with Gram-positive bacteria, and HAIs. The age difference reflects a bimodal age distribution in the United States compared with a more right-skewed distribution in Europe (Supplemental Fig. 1, Supplemental Digital Content 2, http://links.lww.com/PCC/A252; legend: Age by region. The distribution of age [yr] is

shown separately for PICU patients with severe sepsis in the United States and Europe. U.S. patients exhibited a bimodal age distribution, whereas European patients exhibited a right-skewed distribution.). This may reflect regional differences in patient flow in which newborns may be preferentially admitted to neonatal ICUs in the United States, whereas older adolescents are more likely to be treated in adult ICUs in Europe. It is possible that the higher rate of HAIs seen in Europe is a function of being admitted from the general hospital wards rather than from EDs as is generally the case in the United States. One prior study examining hospital-acquired bloodstream infections in Europe and the United States reported similar age- and sex-adjusted incidences per 100,000 person-years, but these estimates included only small numbers of children and were not representative of all of Europe or the United States (19). Our findings support the need for further comparative studies to better understand infection control practices in Europe and the United States.

A recent report outlining a roadmap to improve sepsis research noted that participation of additional clinical sites will be necessary to account for a declining case fatality rate and to better address patient heterogeneity in sepsis (8). For pediatrics, this will increasingly require international cooperation. Based on the findings of our study, we suggest that future international clinical trials should use physiologic and laboratory criteria for severe sepsis to establish study eligibility without the requirement for PICU admission. This approach would be most important for testing therapies that need to be administered near sepsis recognition, such as antibiotic timing, choice of fluid resuscitation, early blood transfusions, and initial vasoactive infusion selection. Many of these therapies are likely to begin and evolve outside of the PICU setting, particularly in regions with few available PICU beds. In addition, epidemiologic studies comparing incidence and outcomes across geographic regions need to account for the apparent differential threshold for PICU admission to better understand how patient care is transferred between units within different hospitals. Although we endorse this approach, the precise physiologic and laboratory criteria used to identify pediatric sepsis and the optimal approach to ensure early and complete recognition remain important challenges (8).

This study has several important limitations. First, given the cross-sectional nature of data collection limited to a brief window of time, it is likely that the use of therapies over the entire course of illness was underestimated. Second, although most organ dysfunction in pediatric sepsis occurs in the first 7 days, some cases of NPMODS may have been missed by only measuring organ dysfunction for seven instead of 28 days following sepsis recognition (16). Third, we were not able to compare illness severity at hospital admission, duration of hospital LOS prior to PICU admission, therapies received at PICU admission, or the quality of the initial resuscitation for septic shock. It is possible that some of the differences observed in use of intensive therapies may reflect regional differences in sepsis recognition and early management. Similarly, we cannot determine if practice variation in viral testing contributed to the higher proportion of viral sepsis noted in the United States. Fourth, as this was a secondary analysis of an existing dataset, power may have been insufficient to detect true differences in outcome. This limitation is reflected in the width of our 95% CIs, which suggests that the true OR for hospital mortality may be as high as 2.28 for European versus U.S. patients. In addition, this study was limited to PICU patients and thus does not account for mortality that occurred outside of this setting. A recent study from the United Kingdom

suggested that early deaths in pediatric sepsis may be important to consider (20). Finally, we have compared the care practices and outcomes for patients from one country (United States) with those of many countries throughout Europe. Other than the United Kingdom and Spain, each European country contributed data from only a few sites. Consequently, the generalizability of our findings to any single European country is limited. Similarly, there were not sufficient numbers of sites from other geographic regions in the SPROUT study to facilitate broader global comparisons. Still, the finding that patient characteristics and therapies differed between regions and accounted for much of the raw differences in outcomes supports the need to account for regional variability in multicenter international studies.

CONCLUSIONS

Despite European PICU patients with severe sepsis having a younger age, higher severity of illness, more HAIs, and more frequent need for intensive care therapies than those in the United States, there were no significant differences in adjusted estimates of morbidity and mortality between regions. Our findings suggest that the approach to care between regions, perhaps related to PICU bed availability, needs to be considered in the design of future international clinical trials in pediatric severe sepsis. Patients meeting consensus definitions rather than PICU admission may be a more appropriate criterion of study eligibility.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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TABLE 1

Patient Characteristics by Region

Variable	Europe	United States	*p*
Patients, *n*	86	325	
Age (yr)	1 (0.4–7)	6 (1–13)	< 0.001
Sex (male)	48 (56)	169 (52)	0.55
Race, *n* (%)			
White	64 (74)	168 (52)	< 0.001
Black	4 (5)	61 (19)	
Asian	10 (12)	10 (3)	
Other/unknown	8 (9)	88 (27)	
Source of PICU admission, *n* (%)			
Emergency department	7 (8)	113 (35)	< 0.001
Hospital ward	32 (37)	79 (24)	
Operating room	13 (15)	24 (7)	
Other hospital	31 (36)	92 (28)	
Other	3 (3)	17 (5)	
Previously healthy, *n* (%)	10 (12)	46 (14)	0.60
Comorbid conditions,[a] *n* (%)			
Respiratory	22 (26)	129 (40)	0.02
Gastrointestinal	16 (19)	111 (24)	0.006
Cardiovascular	33 (38)	82 (25)	0.02
Genetic	15 (17)	88 (27)	0.07
Hematologic/immunologic	19 (22)	76 (23)	0.89
Neuromuscular	10 (12)	76 (23)	0.02
Neoplastic	11 (13)	48 (15)	0.73
Prematurity	12 (14)	56 (17)	0.52
Metabolic	12 (14)	41 (13)	0.72
Renal	5 (6)	42 (13)	0.09
Solid organ/stem cell transplant	10 (12)	38 (12)	0.99
Pediatric Index of Mortality-3[b]	5.0 (2.3–9.8)	3.8 (1.6–7.9)	0.02
Pediatric Logistic Organ Dysfunction[c]	11 (2–20)	11 (2–12)	0.49
Multiple organ dysfunction syndrome at sepsis recognition[d]	63 (73)	166 (51)	< 0.001

[a]Categories do not add up to 100% because some patients had multiple comorbid conditions.

[b]Pediatric Index of Mortality-3 was measured at the time of PICU admission.

[c] Pediatric Logistic Organ Dysfunction score was calculated from data within a 48-hr time window around the study day (9:00 AM on the day before to 9:00 AM on the day after the study day).

[d] Multiple organ dysfunction syndrome based on criteria by Proulx et al [16].

Data presented as median (interquartile range) unless noted.

TABLE 2

Site and Type of Infection Identified by Region

Characteristic	Europe	United States	*p*
Primary site of infection			
Respiratory	32 (37)	136 (42)	0.002
Primary bloodstream	26 (30)	48 (15)	
Abdominal	11 (13)	17 (5)	
Central nervous system	2 (2)	12 (4)	
Genitourinary	2 (2)	15 (5)	
Skin	0	8 (2)	
Other	3 (3)	18 (6)	
Unknown	10 (12)	70 (22)	
Any bacteremia[a]	28 (32)	63 (19)	0.01
Microbiology[b]			
Gram-positive bacteria	31 (36)	77 (24)	0.03
Gram-negative bacteria	26 (30)	86 (26)	0.50
Fungus	12 (15)	43 (13)	0.72
Virus	9 (10)	79 (24)	0.005
No organism identified	25 (29)	124 (38)	0.13
Hospital-acquired infection[c]	41 (35)	80 (25)	0.004

[a]Patients with secondary bacteremia (e.g., pneumonia as primary site of infection with associated bacteremia).

[b]Categories do not add up to 100% as some infections were polymicrobial.

[c]New infections more than 48 hr after admission to the hospital.

Data presented as *n* (%).

TABLE 3

Regional Comparison of Therapies Used Within the 48-Hour Data Collection Window

Therapy	Europe	United States	*p*
Invasive mechanical ventilation	73 (85)	222 (68)	0.002
Vasoactive infusion[a]	61 (71)	161 (50)	< 0.001
Synthetic colloid	12 (14)	4 (1)	< 0.001
Albumin	25 (29)	66 (20)	0.11
Blood products[b]	44 (51)	118 (36)	0.01
Corticosteroids	31 (36)	152 (47)	0.09
Hydrocortisone[c]	19 (61)	81 (53)	0.44
Prednisone/methylprednisone[c]	9 (29)	53 (35)	0.68
Insulin[d]	9 (10)	41 (13)	0.71
Granulocyte/granulocyte-macrophage colony stimulating factor	2 (2)	13 (4)	0.75
IV immunoglobulin	6 (7)	17 (5)	0.60
Renal replacement therapy[e]	20 (23)	37 (11)	0.008
Plasma exchange	1 (< 1)	1 (< 1)	0.38
Extracorporeal membrane oxygenation	2 (2)	22 (7)	0.19
Nutrition, enteral	55 (64)	163 (50)	0.03
Nutrition, parenteral	40 (47)	140 (43)	0.63
Central venous catheter			
Tunneled or implantable	17 (20)	68 (21)	0.88
Nontunneled	60 (70)	119 (37)	< 0.001
Peripherally inserted central catheter	5 (6)	104 (32)	< 0.001

[a] Dopamine > 5 mg/kg/min, dobutamine > 5 mg/kg/min, or any dose of epinephrine, norepinephrine, vasopressin, phenylephrine, milrinone, levosimendan, or a vasodilator.

[b] Packed RBCs, platelets, fresh frozen plasma, cryoprecipitate, granulocytes, and WBCs.

[c] Denominator is the number of patients receiving any vasoactive infusion (n = 152 for United States; n = 31 for Europe).

[d] IV insulin by continuous infusion only.

[e] Hemodialysis, all continuous renal replacement modalities, and peritoneal dialysis.

Data presented as n (%).

TABLE 4

Unadjusted Patient Outcomes by Region

Outcome Measure	Europe	United States	*p*
Hospital mortality	26 (30)	73 (22)	0.16
PICU mortality	25 (29)	70 (22)	0.15
Hospital LOS, median (IQR)	31 (19–73)	24 (12–56)	0.007
PICU LOS, median (IQR)	18 (11–39)	15 (6–38)	0.08
Vasoactive-free days, median (IQR)	21 (2–26)	25 (15–28)	< 0.001
Ventilator-free days, median (IQR)	15 (0–22)	17 (0–26)	0.08
New or progressive multiple organ dysfunction syndrome[a]	33 (38)	128 (39)	0.90
At least mild disability[b]	17 (28)	67 (27)	0.87
At least moderate disability[c]	11 (18)	48 (19)	0.99
Death or moderate disability[d]	37 (43)	121 (37)	0.38

LOS = length of stay, IQR = interquartile range.

[a]New or progressive multiple organ dysfunction syndrome was considered starting the day after sepsis recognition.

[b]Any increase in Pediatric Overall Performance Category from baseline to hospital discharge in the 312 hospital survivors.

[c]Discharge Pediatric Overall Performance Category ≥ 3 and an increase of ≥ 1 from baseline in the 312 hospital survivors.

[d]Death or at least moderate disability at discharge.

Data presented as *n* (%) unless noted.