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The Epidemiology of Hospital Death Following Pediatric Severe Sepsis: When, Why, and How Children with Sepsis Die

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Abstract

Objective—The epidemiology of in-hospital death after pediatric sepsis has not been well characterized. We investigated the timing, cause, mode, and attribution of death in children with severe sepsis, hypothesizing that refractory shock leading to early death is rare in the current era.

Design—Retrospective observational study.

Setting—Emergency departments and intensive care units at two academic children's hospitals.

Patients—Seventy-nine patients <18 years-old treated for severe sepsis/septic shock in 2012–2013 who died prior to hospital discharge.

Measurements and Main Results—Time to death from sepsis recognition, cause and mode of death, and attribution of death to sepsis were determined from medical records. Organ dysfunction was assessed via daily PELOD-2 scores for seven days preceding death with an increase ≥5 defined as worsening organ dysfunction. The median time to death was 8 (IQR 1–12) days with 25%, 35%, and 49% of cumulative deaths within 1, 3, and 7 days of sepsis recognition,

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respectively. The most common cause of death was refractory shock (34%), then MODS after shock recovery (27%), neurologic injury (19%), single-organ respiratory failure (9%), and non-septic comorbidity (6%). Early deaths (< 3 days) were mostly due to refractory shock in young, previously healthy patients while MODS predominated after three days. Mode of death was withdrawal in 72%, unsuccessful CPR in 22%, and irreversible loss of neurologic function in 6%. Ninety percent of deaths were attributable to acute or chronic manifestations of sepsis. Only 23% had a rise in PELOD-2 that indicated worsening organ dysfunction.

Conclusions—Refractory shock remains a common cause of death in pediatric sepsis, especially for early deaths. Later deaths were mostly attributable to MODS, neurologic, and respiratory failure after life-sustaining therapies were limited. A pattern of persistent, rather than worsening, organ dysfunction preceded most deaths.

Keywords

sepsis; critically ill children; mortality; epidemiology

INTRODUCTION

Severe sepsis is a leading cause of death for critically ill children treated in a pediatric intensive care unit (PICU) (1). Across the United States, 7,000 children die from sepsis every year, and infections account for over half of all pediatric deaths worldwide (2, 3). While studies support three common pathways to death in adult sepsis—refractory shock, multiple organ dysfunction syndrome (MODS), and respiratory failure (4)—the epidemiology of death following childhood sepsis remains poorly described.

Understanding the epidemiology of death in sepsis is necessary to set appropriate clinical and research priorities, as patients who die early may have distinct risk factors, pathophysiology, and response to therapy than those who die further out from sepsis onset. Later deaths may also be increasingly attributed to an underlying comorbidity rather than to sepsis itself, which, if true, would challenge “all-cause mortality” as an outcome in pediatric sepsis trials (5, 6). However, few studies have reported on the timing, cause, mode, or attribution of death in pediatric sepsis and interventional studies commonly exclude patients who die early (before time allows for therapy) (7). Moreover, while “chronic critical illness” is an increasingly recognized syndrome in adult ICUs in which persistent, rather than worsening, organ dysfunction is the most common pre-morbid pattern (8), MODS following an acute septic episode in children has generally been studied as a progressive rather than chronic condition (9–11). Consequently, there are scant data as to when, why, and how septic children die.

We sought to characterize the timing, cause, mode, and attribution of death in children with severe sepsis and septic shock. We hypothesized that refractory shock leading to early death would be rare in the current era of systematic sepsis screening and early guideline-directed therapy, while persistent, rather than worsening, MODS and respiratory failure leading to withdrawal of support later in the illness course would be the most frequent pathway to death.

METHODS

Population

We conducted a retrospective analysis of all patients treated for severe sepsis (including septic shock) in the emergency department (ED) and/or PICU at the Children's Hospital of Philadelphia and Nationwide Children's Hospital who died between January 2012 and December 2013. Patients were included if they were <18 years-old, met criteria for severe sepsis as defined by the International Pediatric Sepsis Consensus Conference (12), were treated in either the ED and/or PICU, and died prior to hospital discharge. Septic shock was defined as the subset of patients with cardiovascular dysfunction. To ensure that all eligible deaths were captured, at CHOP we determined vital status for all patients identified with severe sepsis on a prospective daily screening log, and, at NCH (where prospective daily screening was not in place for the entire study period) we queried the medical record for all inpatient deaths. Patients admitted to a separate neonatal or cardiac intensive care unit and those with advanced directives limiting resuscitative therapies at the time of sepsis recognition were excluded. To determine eligibility, medical records and autopsy reports were reviewed by at least two independent investigators at each site. All discrepancies were adjudicated by a third investigator. The Institutional Review Boards at the Children's Hospital of Philadelphia and Nationwide Children's Hospital approved this study under a waiver of informed consent.

Data Collection

A detailed review of the medical record was completed for all severe sepsis and septic shock non-survivors, following published guidelines for chart reviews (13). Data were recorded onto a standardized case report form developed by collaborative input from all authors. A data dictionary defining each variable was developed prior to chart abstraction. Data were collected about demographics, comorbid conditions, source of infection, microbiology, organ dysfunction, use of mechanical ventilation, vasoactive infusions, renal replacement therapies, extracorporeal membrane oxygenation (ECMO), and location of death. Definitions for source of infection were adapted from published criteria (14). Organ dysfunction was defined using consensus criteria for pediatric sepsis, and MODS was defined as 2 concurrent organ system dysfunctions (12). Severity of illness at PICU admission was determined by Pediatric Risk of Mortality (PRISM)-3 scores (15). Patients who died in the ED were excluded from PRISM score determination. We also examined the pattern of sequential organ dysfunction in the seven days preceding death using the daily Pediatric Logistic Organ Dysfunction (PELOD)-2 (16) and inotrope/vasopressor scores (17). PELOD-2 is a continuous scale ranging from 0 to 33 that quantifies neurologic, respiratory, cardiovascular, renal, and hematologic dysfunction with higher values indicating more severe organ dysfunction. The vasopressor/inotrope score quantifies the amount of vasoactive support accounting for differences in dosing equivalents between different medications.

Outcomes

Timing of death was calculated as the number of calendar days from hospital admission, PICU admission, and sepsis recognition to death with one day assigned to those who died on

the day of hospital presentation. For patients with community-acquired sepsis who met criteria for severe sepsis or septic shock on arrival, day of sepsis recognition was defined as the day of hospital presentation. Cause of death was determined using all available data in the medical record, including clinician notes, death certificates, and autopsy reports. The *cause* of death was categorized as 1) refractory shock (including cardiac arrest), 2) single-organ respiratory failure, 3) MODS after shock recovery, 4) neurologic injury (including intracranial hypertension and hypoxic-ischemic injury), 5) other cause related to sepsis, or 6) non-sepsis comorbid condition (see Supplemental Table 1 for additional details). The *mode* of death was categorized as 1) cardiopulmonary arrest unresponsive to resuscitative attempts (unsuccessful CPR), 2) withdrawal or withholding of life-sustaining therapies, or 3) irreversible cessation of neurologic function. Given that disentangling the contribution of sepsis from underlying comorbidities toward death is challenging, we applied a pre-specified logic to determine the *attribution* of death. Only patients with full recovery from all sepsis-associated organ dysfunction prior to death were considered to have died of a comorbid condition (e.g., cancer) unrelated to sepsis. For all other patients, the attribution of death to severe sepsis was categorized as either 1) death without recovery from the primary infectious episode (i.e., no improvement in sepsis-associated organ dysfunction) or 2) death in the setting of chronic critical illness after at least some initial improvement in sepsis-associated organ dysfunction. Two investigators independently determined the timing, cause, mode, and attribution of death at each site, with all disagreements resolved by adjudication with involvement of a third investigator.

Statistical Analysis

Statistical analysis was performed using STATA (Version 12.1, College Station, TX). Descriptive data are presented as means $\pm$ standard deviation (SD) for normally-distributed variables, medians with interquartile ranges (IQR) for non-parametric continuous variables, and frequencies with percentages for categorical variables. Wilcoxon rank sum and Fisher's exact tests were used to compare continuous and categorical variables, respectively. For patients who died more than one day after sepsis recognition, we determined the change in PELOD-2 score from day -7 (or first available if death occurred earlier than seven days) to day -1 preceding death using paired Student's t-test. We defined worsening organ dysfunction as an increase of ≥ 5 in PELOD-2 score because a) the risk of mortality for PELOD-2 score ≤ 5 is below 1% and b) an increase of 5 or more in PELOD-2 is associated with a clinically meaningful increase in the probability of mortality over the majority of the score range (16). Therefore, an increase in PELOD-2 of ≥ 5 indicates a clinically-meaningful worsening of organ dysfunction linked to an increase risk of death. To further assess for worsening organ dysfunction, we compared changes in inotrope/vasopressor score using paired Student's t-test and the proportion of hospitalized patients treated with invasive mechanical ventilation, renal replacement therapy, and ECMO using Fisher's exact tests. For the subset of patients who died more than seven days after sepsis recognition, which is the time period over which end-of-life decisions are likely to be made, we examined longitudinal changes in mean daily PELOD-2 scores using analysis of variance (ANOVA). Finally, since patients who die early may be expected to have a more fulminant course of organ dysfunction than patients who die later, we compared the trajectory of mean daily

PELOD-2 scores between those who died ≤ 3 and >3 days after sepsis recognition using repeated measures ANOVA. Statistical significance was defined at $p < 0.05$.

RESULTS

Over the two-year study period, 79 patients treated for severe sepsis or septic shock in the ED and/or PICU died prior to hospital discharge and were included in this analysis. Patient characteristics by time from sepsis recognition to death are shown in Table 1. The time to death from hospital admission, PICU admission, and severe sepsis recognition was a median of 11 (IQR 2–41), 9 (IQR 3–25) and 8 (IQR 1–12) days, respectively. Twenty (25%) cumulative deaths occurred within one day of severe sepsis recognition, 28 (35%) within three days, and 39 (49%) within seven days (Figure 1). Patients who died ≤ 3 days from sepsis recognition were slightly younger, more likely to develop community-acquired sepsis with sepsis recognition in an ED, and more likely to be previously healthy than patients who died at later times while patients who died after seven days were most likely to have complicated infections, defined as any fungal or bacterial/viral co-infection (Table 1). Notably, 75% of deaths amongst previously healthy patients occurred ≤ 3 days from sepsis recognition.

The cause of death was determined from the medical chart in 59 (75%), signed death certificate in 5 (6%), and autopsy report in 15 (19%) cases. Most deaths (77%) occurred in the PICU, with a smaller number on the general ward (13%), ED (9%) and operating theater (1%). The most common cause of death was refractory shock (34%), followed by MODS after shock recovery (27%), neurologic injury (19%), single-organ respiratory failure (9%), and non-sepsis comorbid condition (6%). Four (5%) patients died from other causes related to sepsis (intestinal infarction, acute kidney injury, hemothorax from fungal pulmonary vascular disease, and acute exacerbation of chronic respiratory and neurologic disease). The cause of death varied significantly at different time points following sepsis recognition ($p < 0.001$, Table 2), with 61% of early deaths ≤ 3 days from sepsis recognition due to refractory shock compared to only 20% in patients who died after three days. Cause of death did not differ by site ($p = 0.32$).

The most common mode of death was withdrawal or withholding of life-sustaining therapies (57 patients [72%]). Seventeen patients (22%) died following unsuccessful CPR and five (6%) died after irreversible cessation of neurologic function. Mode of death varied significantly at different time points following sepsis recognition ($p < 0.001$, Table 2) but not by site ($p = 0.68$). Forty-three percent of deaths ≤ 3 days from sepsis recognition occurred after unsuccessful CPR and 54% followed withdrawal/withholding of life-sustaining therapies. For very early deaths ≤ 1 day from sepsis recognition, 60% died after unsuccessful CPR. In contrast, 82% of patients who died >3 days had withdrawal/withholding of life-sustaining therapy as the mode of death ($p = 0.002$ compared to deaths ≤ 3 days). Patients who died following withdrawal/withholding of life-sustaining therapies were less likely to be previously healthy, more likely to have sepsis diagnosed in an inpatient setting, and trended toward younger age and lower illness severity compared to other modes of death (Supplemental Table 2).

Fifty-two (66%) deaths were directly attributable to the acute sepsis event and an additional 19 (24%) were attributable to chronic critical illness that followed initial recovery from the septic insult without return to prior baseline state of health. In only eight (10%) cases was the cause of death attributable to a pre-existing comorbid medical condition after full recovery from the septic event. Ninety-three percent and 87% of deaths within three and seven days, respectively, were directly attributable to sepsis compared to only 45% beyond seven days ($p<0.001$). Attributiveness of death to sepsis did not differ by site ($p=0.31$).

The majority of patients had MODS at death (84% overall), irrespective of timing (93% for death ≤ 3 days and 78% for death >3 days, $p=0.12$). Table 3 shows the proportion with organ dysfunction on the day of death (but preceding time of cardiopulmonary arrest or withdrawal of life-sustaining therapies).

For the 59 patients who died more than one day after sepsis recognition, PELOD-2 scores increased by a mean of 2.2 ± 4.8 ($p=0.001$). However, only 14 (23%) patients met criteria for worsening organ dysfunction (PELOD-2 increase ≥ 5) compared to 45 (77%) with either persistent (PELOD change 0–4, $n=33$) or improving (PELOD change <0 , $n=12$) organ dysfunction. The mean inotrope/vasopressor score decreased by 6 ± 22 , but this change did not reach significance ($p=0.06$), and the proportion of hospitalized patients treated with invasive mechanical ventilation, renal replacement therapy, and ECMO also did not change significantly over time (Figure 2). For the subset of 40 patients who died more than seven days from sepsis recognition, for whom mode of death was most commonly withdrawal or withholding of life-sustaining therapies, PELOD-2 scores did not change significantly in the week preceding death ($p=0.22$; Figure 3). Finally, while patients who died within three days of sepsis recognition exhibited a slightly more rapid increase in PELOD in the three days preceding day of death compared to patients who died after day 3, this difference was not significant ($p=0.19$; Figure 4).

DISCUSSION

Contrary to our hypothesis, refractory shock leading to early death within one to three days of sepsis recognition was not rare in pediatric severe sepsis. Although 51% of deaths occurred more than seven days after sepsis recognition, usually when life-sustaining therapies were withdrawn/withheld, one-third of deaths occurred within three days. Refractory shock was the most common cause of death overall, though this cause was concentrated in early deaths while MODS, respiratory failure, and neurologic injury predominated after three days. The majority of deaths were attributed to sepsis, either to the primary infection or to an ensuing state of chronic critical illness after some clinical improvement. Finally, patients more commonly exhibited a pattern of persistent, rather than worsening, organ dysfunction prior to death.

Given the therapeutic arsenal available to reverse shock and broad implementation of pediatric septic shock guidelines (18, 19), we were surprised to find a high proportion of early deaths, with one-quarter of deaths within one day and nearly half within seven days of severe sepsis recognition. Two decades ago, Proulx et al. published that, amongst all PICU patients, 51% of deaths occurred within one day of MODS onset and 88% occurred within

seven days (20). More recently, Burns et al. found that only 25% of PICU deaths occurred within 1.5 days and 57% within seven days of admission (21). Our data, therefore, support that timing of death following pediatric sepsis mirrors contemporary trends in overall PICU mortality with a drift away from—though not elimination of—early deaths.

The persistence of early deaths in pediatric sepsis is particularly relevant for clinical trials, which are unlikely to enroll patients who die early because they are not alive long enough to complete informed consent and randomization procedures (22). To address these concerns, Cvetkovic et al. studied consecutive referrals to regional PICUs in the United Kingdom and found that 55% of pediatric deaths with suspected severe sepsis died within 24 hours of PICU referral, mostly from unsuccessful resuscitation from MODS and cardiac arrest (7). The higher rate of very early deaths in the study by Cvetkovic compared to our study may reflect their inclusion of deaths that occurred at referring hospitals and a high rate of fulminant meningococemia. In addition, the United Kingdom cohort included a four-fold higher proportion of previously healthy patients than our study (86% versus 20%), and previously healthy children were more likely to die in the first three days than patients with chronic comorbidities in both studies. Still, our data are generally consistent with the findings of Cvetkovic et al. that early deaths remain common in pediatric sepsis, raising concern that a significant number of children at high-risk for death could be excluded from clinical trials. In addition, since early deaths appear more likely in previously healthy children, interventions that might prove most beneficial when competing comorbid effects on mortality are absent may inadvertently exclude a sizable proportion of their intended population. Future efforts to include patients at-risk for early deaths into clinical trials are necessary, including enrollment of patients prior to PICU admission and proper use of waiver from informed consent (23, 24).

In adult sepsis, the most common causes of death are MODS, refractory shock, and respiratory failure (4). In pediatrics, a prior large study of severe infection in Africa reported refractory shock, respiratory failure, and intracranial hypertension as the three most common terminal clinical events (25). We found refractory shock to be the most common cause of death, followed by MODS, neurologic injury, and respiratory failure. Thus, consistent patterns of death emerge in both pediatric and adult sepsis and in developed and resource-limited areas.

Despite variability in the immediate cause of death, the use of “all-cause” mortality is commonplace in sepsis research (26). “All-cause” mortality provides a more straightforward and objective endpoint than differentiating between sepsis and one of potentially many comorbid conditions. However, the degree to which an intervention may improve mortality after sepsis is highly dependent on whether death is attributable to sepsis or to a comorbid condition (5, 6), especially when the majority of patients die following withdrawal or withholding of life-sustaining therapies, as in this and prior studies (21). If a comorbid condition is the primary impetus to forgo further care or contributes heavily to a sense of futility, then any benefit from a sepsis-directed therapy or prognostic insight from a sepsis-specific risk factor is likely to be minimized. We found that the majority of deaths in our study were attributable to sepsis, with two-thirds of deaths overall directly due to the acute sepsis event itself. However, after seven days, most deaths were not directly attributable to

the acute sepsis event and few patients were previously healthy suggesting that mortality estimates can be increasingly contaminated by deaths unrelated to sepsis over time. The extent to which deaths attributable to a post-sepsis chronic critical illness in the setting of comorbid conditions may be impacted by a sepsis-directed therapy is not clear. Thus, although the episode of sepsis played an important role in most deaths, we caution that use of “all-cause” mortality as an outcome measure, especially when measured at 28-days or later, will comprise a wide scope of deaths with regards to cause and timing, including some deaths that a given intervention may never have been expected to prevent.

The majority of patients in this study died following withdrawal/withholding of life-sustaining therapies, particularly for deaths >3 days from sepsis recognition. In a prior study of all PICU deaths, Burns et al. similarly reported that 70% of patients died following withdrawal or withholding of life-sustaining therapies (21). Moreover, in both our study and that of Burns et al., patients who died after one week were unlikely to be previously healthy. While we were not able to discern the underlying reasons to withdraw/withhold life-sustaining therapies, the lower rate of previously healthy patients for this mode of death suggests that the additional burden of comorbid conditions contributed to these decisions.

Although organ dysfunction may be expected to deteriorate in the days preceding death in sepsis, our data using PELOD-2 scores did not support a progressive worsening of organ dysfunction in three-quarters of pediatric patients with sepsis, including both those patients who die early (< 3 days) and in those who die later after a period of end-of-life decision-making. Moreover, the decrease in inotrope/vasopressor score and relatively stable use of invasive mechanical ventilation, renal replacement therapy, and ECMO in the week prior to death further supports a pattern of persistent, rather than worsening, organ dysfunction. Our findings are consistent with a previous study of mortality in adult sepsis in which the change in Sequential Organ Failure Assessment (SOFA) scores indicated a persistent, albeit high-level, organ dysfunction in the five days preceding death (4). However, as pointed out by Vincent et al., such findings may reflect the ability to support even severe organ dysfunction in the ICU as well as the limitations of organ dysfunction scores to capture the full breadth of physiological changes. Nonetheless, as in adult sepsis, our findings suggest that clinicians should not necessarily be reassured when organ dysfunction appears to have stabilized and that many pediatric patients with severe sepsis experience a state of “chronic critical illness” prior to death (27).

Several limitations of our study should be noted. First, because our data reflect the practices of only two sites, both of which are academic children’s hospitals and located in the United States, it is not clear how generalizable our findings are to other settings. In addition, because our data were limited to in-hospital deaths, we cannot determine if our findings are representative of the epidemiology of post-discharge mortality. Second, determining the cause and attributiveness of death is challenging, particularly when only one in five patients had available autopsy results (28). Although two investigators independently reviewed all cases at each site, some misclassification is possible. Third, we lacked information about end-of-life decision-making, including the factors that led family and caregivers to limit life-sustaining therapies, nor were we able to differentiate between absence of organ dysfunction versus withdrawal/withholding as the indication to not use invasive mechanical ventilation,

renal replacement therapy, or ECMO prior to death. Fourth, although PELOD-2 has been validated as a predictor of mortality, the score is relatively insensitive to changes in the intensity of organ support and fails to include any measure of hepatic dysfunction. Finally, because we did not anticipate such a high proportion of early deaths within 1–3 days of sepsis recognition, we had not planned a detailed investigation as to specific patient-level risk factors for early versus late death. Our findings, along with those of Cvetkovic et al. (7), clearly identify a future need to identify risk factors for and pathophysiology leading to early death in pediatric sepsis.

CONCLUSIONS

In this two-center study of the epidemiology of death after pediatric severe sepsis, we found that one-third of deaths occurred within three days and nearly half within seven days of sepsis recognition. Surprisingly, even in the current era of early-goal directed and guideline-directed resuscitation, early deaths from refractory shock remain common. Later deaths were mostly attributable to MODS, respiratory failure, or neurologic injury and usually occurred in the context of persistent, rather than worsening, organ dysfunction with eventual withdrawal or withholding of life-sustaining therapies. Future research priorities in pediatric sepsis should include determining risk factors for early death and consider that life-saving interventions may need to be differentially targeted based on timing and cause of death.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Days from Sepsis Recognition to Death

Frequency histogram of days from sepsis recognition to death. Inset shows timing of death within first 30 days following sepsis recognition with each bin equal to one day.

Figure 2. Proportion Treated on Days Preceding Death

The proportion of patients who died more >1 day after sepsis recognition who were hospitalized and treated with invasive mechanical ventilation, renal replacement therapies, and extracorporeal membrane oxygenation in the seven days preceding death. There was no significant change in proportion treated over time with invasive mechanical ventilation ($p=0.40$), renal replacement therapies ($p=0.62$), or extracorporeal membrane oxygenation ($p=0.59$).

Figure 3. Mean PELOD-2 by Day Preceding Death for Patients Who Died After Seven Days from Sepsis Recognition

Mean individual PELOD-2 scores increased by a mean of 1.5 ± 4.3 in the week preceding death for the 40 patients who died >7 days following sepsis recognition (ANOVA, $p=0.22$). Error bars represent standard deviation.

Figure 4. Mean PELOD-2 Trajectory by Timing of Death

Mean PELOD-2 scores in the three days preceding death for patients who died ≤ 3 and >3 days after sepsis recognition. PELOD-2 scores did not change significantly in either group (ANOVA, $p=0.45$ for death ≤ 3 days and $p=0.31$ for death >3 days), and there was no difference in the change in daily PELOD-2 scores over time between groups (repeated measures ANOVA, $p=0.19$). Error bars represent standard deviation.

Table 1

Patient characteristics for All and By Timing of Death

Characteristic	All Patients	Days Between Sepsis Recognition and Death				P-value
		0-1	2-3	4-7	>7	
N	79	20	8	11	40	
Age, years (median [IQR])	5 (1-10)	4 (0.3-10)	0.3 (0.2-2)	9 (5-10)	5 (2-11)	0.01
Sex, male	43 (54)	11 (55)	6 (75)	5 (45)	21 (53)	0.66
Race						0.98
White	49 (62)	13 (65)	4 (50)	8 (73)	24 (60)	
Black	18 (23)	4 (20)	3 (38)	2 (18)	9 (23)	
Asian	1 (1)	0	0	0	1 (3)	
Unknown	11 (14)	3 (15)	1 (13)	1 (9)	6 (15)	
Location of sepsis recognition						<0.001
ED	24 (30)	14 (70)	4 (50)	2 (18)	4 (10)	
PICU	29 (37)	5 (25)	3 (38)	2 (18)	19 (48)	
Hospital ward	15 (19)	0	1 (13)	4 (36)	10 (25)	
Referring hospital	11 (14)	1 (5)	0	3 (27)	7 (18)	
Previously healthy	16 (20)	10 (50)	2 (25)	3 (27)	1 (3)	<0.001
Cancer/HLH/BMT	25 (32)	0	2 (25)	2 (18)	21 (53)	<0.001
PRISM-III ¹ (median [IQR])	15 (11-24)	25 (11-37)	10 (13-33)	21 (16-29)	14 (10-21)	0.04
Primary site of infection						0.50
Blood	13 (16)	2 (10)	1 (13)	3 (27)	7 (18)	
Urinary tract	3 (4)	1 (5)	0	1 (9)	1 (3)	
Respiratory	34 (43)	7 (35)	5 (63)	2 (19)	20 (50)	
Abdominal	10 (13)	3 (15)	1 (13)	3 (27)	3 (8)	
Central nervous system	4 (5)	1 (5)	1 (13)	0	2 (5)	
Musculoskeletal/wound	1 (1)	1 (5)	0	0	0	
Unknown	14 (18)	5 (25)	0	2 (18)	7 (18)	
Sepsis pathogen ²						0.56 ⁴
Bacterial	36 (46)	9 (45)	6 (75)	4 (36)	17 (43)	
Viral	25 (32)	4 (20)	3 (38)	3 (27)	11 (28)	

Characteristic	All Patients	Days Between Sepsis Recognition and Death				P-value
		0-1	2-3	4-7	>7	
Fungal	7 (9)	0	1 (13)	1 (9)	9 (23)	
Unknown	20 (25)	7 (35)	0	3 (27)	10 (25)	
Complicated infection ³	13 (21)	0	1 (13)	1 (11)	11 (33)	0.046
Renal replacement therapy	7 (9)	0	1 (13)	1 (9)	5 (13)	0.34
ECMO	8 (10)	0	1 (13)	2 (18)	5 (13)	0.20
Veno-venous	5 (63)	0	1 (100)	1 (50)	1 (20)	
Veno-arterial	3 (28)	0	0	1 (50)	4 (80)	

Data presented as n (%), unless indicated

IQR, interquartile range; ED, emergency department; PICU, pediatric intensive care unit; HLH, hemophagocytic lymphohistiocytosis; BMT, bone marrow transplantation; PRISM, pediatric risk of mortality; ECMO, extracorporeal membrane oxygenation

¹Data available for 69 patients due to lack of scoring for deaths prior to PICU admission

²Due to patients with multiple pathogens, data do not add up to 100%

³Complicated infection is defined as any fungal infection or bacterial/viral co-infection; denominator excludes the 20 patients with unknown pathogen.

⁴For statistical analysis, patients with multiple pathogens were classified independently

Cause of death by timing of death

Table 2

Cause of Death ¹	Days Since Sepsis Recognition				Total, n (%)
	Days 0-1	Days 2-3	Days 4-7	>7 days	
Refractory shock	14	3	5	5	27 (34)
MODS	1	1	2	17	21 (27)
Neurologic injury	2	4	3	6	15 (19)
Respiratory failure	3	0	1	3	7 (9)
Other due to sepsis	0	0	0	4	4 (5)
Not due to sepsis	0	0	0	5	5 (6)
Mode of Death ¹	Days 0-1	Days 2-3	Days 4-7	>7 days	Total, n (%)
Withdrawal or withholding of life-sustaining therapies	7	8	6	36	57 (72)
Unsuccessful CPR	12	0	2	3	17 (22)
Irreversible Cessation of Neurologic Function	1	0	3	1	5 (6)

MODS, multiple organ dysfunction syndrome; CPR, cardiopulmonary resuscitation

¹Variation by days since sepsis recognition, p<0.001

Table 3

Organ dysfunction on the day of death

Organ Dysfunction	N (%)
Cardiovascular	57 (72)
Respiratory	75 (95)
Renal	30 (38)
Hepatic	34 (44)
Hematologic	31 (40)
Neurologic [/]	40 (58)

[/] Only 69 patients were able to be evaluated for neurologic dysfunction on the day of death