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## Outcomes Associated with Timing of Neurologic Dysfunction Onset Relative to Pediatric Sepsis Recognition

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### Abstract

**Objective:** To compare outcomes associated with timing – early versus late – of any neurologic dysfunction during pediatric sepsis

**Design:** Secondary analysis of a cross-sectional point prevalence study

**Setting:** 128 PICUs in 26 countries

**Patients:** <18 years with severe sepsis on five separate days (2013-2014)

**Interventions:** None

**Measurements and Main Results:** Patients were categorized as having either no neurologic dysfunction or neurologic dysfunction (i.e., present at or after sepsis recognition), which was defined as Glasgow Coma Scale score <5 and/or fixed dilated pupils. Our primary outcome was death or new moderate disability (i.e., pediatric overall [or cerebral] performance category score 3 and change 1 from baseline) at hospital discharge and 87/567 (15%) severe sepsis

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**Article Tweet:** Neurologic dysfunction during pediatric sepsis in the #PedsICU is associated with worse outcomes. Later neurologic dysfunction may confer worse outcomes.

patients had neurologic dysfunction within seven days of sepsis recognition (61 at sepsis recognition and 26 after sepsis recognition). Primary site of infection varied based on presence of neurologic dysfunction. Death or new moderate disability occurred in 161/480 (34%) without neurologic dysfunction, 45/61 (74%) with neurologic dysfunction at sepsis recognition, and 21/26 (81%) with neurologic dysfunction after sepsis recognition ( $p < 0.001$  across all groups). On multivariable analysis, in comparison with those without neurologic dysfunction, neurologic dysfunction whether at sepsis recognition or after were associated with increased odds of death or new moderate disability (adjusted odds ratio 4.9 [95%CI 2.3-10.1] and 10.7 [95%CI 3.8-30.5], respectively). We failed to identify a difference between these adjusted odds ratios of death or new moderate disability that would indicate a differential risk of outcome based on timing of neurologic dysfunction ( $p = 0.20$ ).

**Conclusions:** In this severe sepsis international cohort, the presence of neurologic dysfunction during sepsis is associated with worse outcomes at hospital discharge. The impact of early versus late onset of neurologic dysfunction in sepsis on outcome remains unknown and further work is needed to better understand timing of neurologic dysfunction onset in pediatric sepsis.

### Keywords

severe sepsis; children; neurologic dysfunction; outcomes; epidemiology; pediatric

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### Introduction

Sepsis remains an important cause of mortality and morbidity in critically ill children (1–5), with increasing number and severity of organ dysfunctions being a major risk factor for adverse outcomes (6,7). In particular, neurologic dysfunction at any time during sepsis occurs in up to 20% of children who die (8), with a five-fold increase in mortality among those who develop neurologic dysfunction at any point during sepsis (1,9). Survivors who have neurologic dysfunction during sepsis also have higher odds for experiencing a decline in health-related quality of life (HRQL) after discharge (2). Together, these data suggest that neurologic dysfunction has a significant impact on adverse outcomes in pediatric sepsis. However, there are limited data on whether the timing of neurologic dysfunction during pediatric sepsis is important.

We sought to determine the association between timing of neurologic dysfunction during pediatric sepsis with mortality and morbidity outcomes at hospital discharge. It has been previously shown that later onset of any organ dysfunction is associated with worse outcomes (1,8,9), which we hypothesize is due to differences in the pathophysiology of organ dysfunction before and after initiation of sepsis treatment. Thus, we hypothesized that neurologic dysfunction developing *after* sepsis recognition (i.e., on or after day 2 of sepsis), in comparison with development at the time of diagnosis, is associated with greater odds of death during hospitalization or, in survivors, new moderate disability at hospital discharge. An improved understanding of these relationships should inform future studies of explanatory risk factors and treatment of neurologic dysfunction during pediatric sepsis.

## Methods

We performed a secondary analysis of patients with and without neurologic dysfunction during sepsis from the previously reported Sepsis Prevalence, Outcomes and Therapies (SPROUT) study data set (1). The SPROUT study was a prospective, cross-sectional point prevalence sepsis study performed in 128 pediatric intensive care units (PICUs) across 26 countries (1). Patients were enrolled on five separate days from June 2013 to June 2014. Ethics approval was obtained at all study sites (IRB #12-009784, Children's Hospital of Philadelphia, main study site) (1). Waiver of consent was obtained at all sites for screening. Waiver of consent for data collection was approved at all but three sites where informed consent was required.

### Study population

On each study day, all patients <18 years of age in a participating PICU were screened for eligibility at 9:00am local time. Severe sepsis was defined using the 2005 International Pediatric Sepsis Consensus criteria. Patients were classified as having severe sepsis if they had 1) two or more systemic inflammatory response syndrome criteria, 2) confirmed or suspected infection, and 3) cardiovascular dysfunction, acute respiratory distress syndrome, or at least two other organ dysfunctions (10). The cohort with septic shock, defined by the presence of cardiovascular dysfunction, is included within the term severe sepsis. Patients were only included if they met criteria for severe sepsis within the 24 hours prior to the study day. Exclusion criteria were gestational age <42 weeks corrected or surgery requiring cardiopulmonary bypass within 5 days leading up to study enrollment. Additional SPROUT methodology details have been previously published (1).

### Data collection

Demographic, clinical, and infectious data were collected from the medical record. Day of sepsis recognition was determined as the first calendar day on which the patient met criteria for severe sepsis. Infectious data collected included primary site of infection and microbiological isolates (11). Illness severity was described using the Pediatric Index of Mortality-3 (PIM3) Risk of Mortality at PICU admission (12). For this analysis, we calculated the PIM3 Risk of Mortality without the neurologic component of the score for all analyses. Pediatric Overall Performance Category (POPC) and Pediatric Cerebral Performance Category (PCPC) scores measured prior to septic illness were obtained as indicator of baseline functional status (13).

During the SPROUT study, organ dysfunctions were measured daily for 7 days from sepsis recognition based on criteria first published by Wilkinson et al and later modified by Proulx et al (1,14,15). Specifically, neurologic dysfunction was defined as Glasgow Coma Scale (GCS) <5 and/or fixed dilated pupils on the day of interest (1,15). Study investigators were instructed to assess the GCS in patients when not pharmacologically sedated and to not record abnormal pupillary responses secondary to drugs, toxins, or eye injury. Patients that met this definition on day of sepsis recognition (day 1) were classified as having neurologic dysfunction *at sepsis recognition*. If the neurologic dysfunction definition was not met on day 1 but was met on any of days 2-7 of sepsis, patients were classified as

having neurologic dysfunction *after sepsis recognition*. Patients who did not meet criteria for neurologic dysfunction on days 1-7 were categorized as having no neurologic dysfunction.

The primary outcome was death or new moderate disability, defined as a composite of mortality or new moderate disability in survivors. Patients were followed until hospital discharge (or up to 90 days after the study day if still hospitalized) to determine all-cause mortality. For patients who survived, POPC and PCPC scores were calculated at the time of hospital discharge to characterize the development of a new disability in comparison to baseline POPC and PCPC scores. We defined new moderate disability as both a POPC or PCPC score  $\geq 3$  at hospital discharge **and**  $\geq 1$  increase from baseline in order to identify new functional decline even in those with moderate to severe baseline impairment (4). Although the initial SPROUT study analysis defined new disability only using the POPC score (1), we used a change in either POPC or PCPC to indicate new disability to more reliably include subtle cognitive deficits that might not be captured using the global POPC score alone (13). Secondary outcomes included hospital mortality, new moderate disability, new mild disability (defined as any increase in POPC or PCPC from baseline to discharge **and** did not meet definition for new moderate disability), PICU length of stay (LOS), and hospital LOS. Ventilator- and vasoactive-free days were determined from the day of sepsis recognition through day 28 or day of death (whichever came first) (1,16). Survivors who did not experience an increase in POPC and PCPC score were considered to have no new disability.

### Statistical Analysis

Data were analyzed using STATA (Version 16.1, Statacorp, College Station, Texas). Categorical data, expressed as frequencies, were analyzed with Fisher's exact test. Continuous data, expressed as median with interquartile range (IQR), were analyzed using the Mann-Whitney *U* or Kruskal-Wallis tests. We used logistic regression to create a bivariable model with neurologic dysfunction as the independent variable (modeled categorically as no neurologic dysfunction [reference], neurologic dysfunction at sepsis recognition, and neurologic dysfunction after sepsis recognition) and the primary outcome of death or new moderate disability as the dependent variable. Multivariable logistic regression was used to test for potential confounding effects of covariates on the association of neurological dysfunction with death or a new moderate disability. To assess for confounding, covariates that were significantly different between patients with no neurologic dysfunction, neurologic dysfunction at sepsis recognition, and neurologic dysfunction after sepsis recognition were added to the bivariable model. Covariates that changed the base model odds ratio (OR) by 5% or greater were included in the final multivariable model as confounders (17). A Wald Test was used to test if there was a difference between the adjusted odds ratio based on timing of neurologic dysfunction. A base p-value  $<0.05$  was used to indicate statistical significance with Bonferroni's methods used to account for multiple comparisons.

## Results

### Comparison by Presence versus Absence of Neurologic Dysfunction

Of the 6,925 patients screened during the five SPROUT study days, 569 met consensus criteria for severe sepsis. Data for analysis was available for 567 patients (2 patients did not provide consent). From these 567 patients, 87 patients (15%) had neurologic dysfunction at any time during sepsis. Demographic and clinical characteristics for patients with and without neurological dysfunction during sepsis are shown in eTable 1. Patients with neurological dysfunction at any time during sepsis had higher PIM3 risk of mortality score compared to patients who never had neurologic dysfunction ( $p<0.001$ ). Patients with neurologic dysfunction during sepsis had a higher number of non-neurologic organ dysfunctions on day 1 of sepsis but this was not statistically different from patients without neurologic dysfunction during sepsis after correction for multiple comparisons. Additionally, patients with neurologic dysfunction during sepsis had fewer ventilator- and vasoactive-free days compared to those who never had neurologic dysfunction ( $p<0.001$ , eTable 1). Seventy-six percent of patients experienced death or new moderate disability when neurologic dysfunction was present during sepsis compared to 34% in patients without neurologic dysfunction during sepsis (mean difference 42% [95%CI 31-51%],  $p<0.001$ ; eTable 1).

### Comparison by Presence and Timing of Neurologic Dysfunction

Among the 87 patients with neurologic dysfunction during sepsis, 61 patients (70%) had neurologic dysfunction at sepsis recognition (day 1) and 26 (30%) developed neurologic dysfunction after sepsis recognition (days 2-7; eFigure 1). Clinical and infectious characteristics for those with no neurologic dysfunction, neurologic dysfunction at sepsis recognition, and neurologic dysfunction after sepsis recognition are shown in Table 1. Across these three groups, there were no differences in age, sex, number of comorbidities, or type of isolates identified (all  $p>0.05$ ). PIM3 Risk of Mortality was significantly different between the three groups, with higher scores in patients with neurologic dysfunction at or after sepsis recognition compared to patients without neurologic dysfunction ( $p<0.001$ ). More non-neurologic organ dysfunctions were present in patients with neurologic dysfunction at or after sepsis recognition compared to patients without neurologic dysfunction ( $p=0.002$ ). Primary site of infection was different between the three groups ( $p<0.001$ ). In those without neurologic dysfunction during sepsis, respiratory and other site infections were most common, followed by bloodstream infections and then central nervous system (CNS) infections. However, for those with neurologic dysfunction at sepsis recognition, there were more CNS infections than bloodstream infections and for those with neurologic dysfunction after sepsis recognition bloodstream infections predominated above all sites of infections. Detailed microbiological isolate information is presented in eTable 2.

The distribution of baseline POPC scores was significantly different between the three groups ( $p=0.03$ ), with a greater proportion of patients with neurologic dysfunction at and after sepsis recognition having POPC scores 3-5 compared to patients without neurologic dysfunction during sepsis (Figure 1). However, the distribution of baseline POPC scores did not differ between those with neurologic dysfunction at versus after sepsis recognition.

## Outcomes

Death or new moderate disability occurred in 161/480 (34%) patients without neurologic dysfunction during sepsis compared to 45/61 (74%) patients with neurologic dysfunction at sepsis recognition and 21/26 (81%) patients with neurologic dysfunction after sepsis recognition ( $p < 0.001$  across all three groups, Table 2). When further stratifying by day of neurologic dysfunction onset, we failed to identify a difference in the proportion of patients who experienced death or new moderate disability by timing of neurologic dysfunction (Figure 2).

In assessing secondary outcomes, in comparison with patients without neurologic dysfunction, the presence of neurologic dysfunction whether at or after sepsis recognition were associated with death and new moderate disability (Table 2). We failed to find an association between presence of neurologic dysfunction and PICU and hospital LOS (all  $p > 0.05$ ). Neurologic dysfunction at and after sepsis recognition was associated with longer ventilator and vasoactive durations (lower ventilator- and vasoactive-free days) compared to those without neurologic dysfunction, although we failed to identify association in these outcomes and timing of neurologic dysfunction (Table 2). When mild dysfunction was also considered, the distribution of adverse outcomes remained different between those with neurologic dysfunction at or after sepsis recognition compared to patients without neurologic dysfunction ( $p < 0.001$ , Figure 3). However, this difference was due to higher proportions of patients with either death or new moderate disability among those with neurologic dysfunction compared to patients without neurologic dysfunction, while mild disability was less common.

After controlling for baseline POPC score, PIM3 Risk of Mortality, number of non-neurologic organ dysfunctions at sepsis recognition, number of co-morbidities, and primary site of infection, neurologic dysfunction at sepsis recognition (aOR 4.9, 95%CI 2.3-10.1) and neurologic dysfunction after sepsis recognition (aOR 10.7, 95%CI 3.8-30.5) were associated with increased odds of death or new moderate disability compared to patients without neurologic dysfunction (Table 3). We failed to identify a difference in odds of death or new moderate disability based on timing of neurologic dysfunction ( $p = 0.20$ ).

## Discussion

In this secondary analysis of the SPROUT study, we found neurologic dysfunction at or after sepsis recognition – as compared with no neurologic dysfunction – was associated with greater odds of death or, in survivors, new moderate disability at hospital discharge. Our study expands on prior literature of neurologic dysfunction in sepsis to compare the differential impact of timing of neurologic dysfunction during sepsis on the risk of death or new moderate disability among survivors. Although we failed to identify a difference between the adjusted odds ratios for death or new moderate disability between patients with neurologic dysfunction at versus after sepsis recognition, the higher point estimate and upper limit of the 95% confidence interval for the group with neurologic dysfunction after sepsis recognition suggests that larger studies might identify a differential risk for poor outcomes based on the timing of neurologic dysfunction during pediatric sepsis.

The timing and evolution of organ dysfunction during sepsis has been shown to be related to outcomes in pediatric and adult sepsis cohorts (9,18). Both new and worsening organ dysfunction have been associated with higher mortality in sepsis (9,18–22). Given the significant impact neurologic dysfunction has on mortality and morbidity outcomes in septic patients and the potential to impact patient outcomes (1–5,9), differentiating between early and late onset of neurologic dysfunction is imperative. There are several proposed mechanisms for the development of neurologic dysfunction in sepsis including neuroinflammation, metabolic derangements, neurotransmitter dysregulation, mitochondrial and endothelial dysfunction, and cerebral blood flow alterations (23,24). Similarly, dysregulation of immunological, microvascular, mitochondrial, and metabolic pathways has been linked to ongoing organ dysfunction and mortality in sepsis (25–30). Further studies about the pathophysiological mechanisms underlying early versus late onset of neurological dysfunction in sepsis will help guide therapies to manage initial neurologic dysfunction and prevent the development of new neurologic dysfunction in sepsis.

It is notable that neurologic dysfunction was recognized in only 15% of patients in this study using the Proulx criteria (GCS <5 and/or fixed dilated pupils). Acknowledging that this definition of neurologic dysfunction is conservative, we suspect that the prevalence of true neurologic dysfunction during sepsis was underestimated in this study. Studies in critically ill adults suggest neurologic dysfunction in sepsis occurs in up to 70% of patients with more inclusive definitions that consider clinical findings, delirium, and/or neuroimaging or electroencephalogram findings. Yet, the lack of a standardized definition accounts for the varying prevalence of neurologic dysfunction seen in these adult studies (31–33). There are limited pediatric studies describing sepsis-associated neurologic dysfunction and thus the true prevalence of this complication is not well described. Several studies have shown that GCS is limited by poor interrater reliability and scoring inaccuracies in critically ill children and those with developmental disabilities (34,35). While the accuracy of GCS in classifying neurologic dysfunction specifically in pediatric sepsis has not been evaluated to date, GCS is universally included in the definition of neurologic dysfunction in these patients (10,36–38). An improved definition for neurologic dysfunction in pediatric sepsis is needed to improve epidemiological understanding of this disease entity and guide further prospective and observational studies. We anticipate that a neurologic dysfunction definition in sepsis for future prospective studies will involve input from multiple modalities to reflect clinician concerns for neurologic dysfunction. However, further studies are needed to validate any proposed definition for these future studies.

With reduction in mortality rates from pediatric sepsis, a shift to understanding risk factors for adverse outcomes is emerging as a significant public health concern. The Life After Pediatric Sepsis (LAPSE) study showed that one-third of pediatric sepsis survivors have a reduction in HRQL that persists for one year following hospital discharge (5). This study found that patients who experienced an acute, clinically diagnosed neurologic event or new pathology (e.g., seizure, new hypoxic ischemic injury) had a five-fold increased risk for death or persistent deficit in HRQL at 3 months following discharge (2). Although this study used a clinical diagnosis for neurologic events and not a specific neurologic dysfunction definition, the LAPSE results are consistent with our finding that neurologic dysfunction at or after sepsis recognition is a risk factor for both mortality and

morbidity. In addition, a single-center study found that children with clinically diagnosed sepsis-associated encephalopathy had delayed development, lower intelligence, and decline in school function (39). Neither of these studies discussed the association of timing of the neurologic dysfunction onset with outcomes, further highlighting the gaps in our understanding of the difference between early and late onset of neurologic dysfunction as it pertains to long-term patient outcomes.

Our study has several strengths, including the multicenter and international study population, detailed data on timing of neurologic dysfunction onset despite the point prevalence study design, and data on new disability in survivors based on functional outcomes. This study also has several limitations. First, a small number of patients were categorized as having neurologic dysfunction during sepsis due to the restrictive yet accepted definition for neurologic dysfunction. The resulting small sample size limited statistical power and increased the risk of a type II error to fail to reject the null hypothesis of no difference in death or new moderate disability between patients with neurological dysfunction at versus after sepsis recognition. In addition, data were not available regarding neuroimaging or electroencephalogram results, neurological examinations, or the presence of delirium, thus we were unable to further characterize the full spectrum of neurologic dysfunction in this analysis. Such detailed neurological evaluation data and the relationship to the patients' clinical status would be best obtained in a prospective study aimed directly at evaluating the timing of neurologic dysfunction during sepsis. Although sites were asked to categorize neurologic dysfunction when the patient was not sedated, we were not able to ascertain if sedation use contributed to misclassification bias for the timing of neurologic dysfunction. This study only evaluated outcomes at the time of hospital discharge, further studies are needed to evaluate long-term morbidity outcomes following discharge based on the presence and timing of neurologic dysfunction in pediatric sepsis (40–42). Finally, although we were able to adjust for several potential confounding variables, the secondary nature of the analysis and limited sample size mean that our findings are best construed as exploratory rather than an effort to measure causal inference.

## Conclusion

Neurologic dysfunction during sepsis is a significant risk factor for death or new moderate disability irrespective of timing of neurologic dysfunction development relative to sepsis recognition. Although the odds of death or new moderate disability were not significantly different for children with neurologic dysfunction at versus after sepsis recognition, the higher point estimate and upper end of the 95% confidence interval for later onset of neurologic dysfunction support need for consideration of the association of timing of neurologic dysfunction with morbidity and mortality. Understanding risk factors for and the pathophysiology of neurologic dysfunction in pediatric sepsis could help to target mitigation efforts and identify treatment strategies for neurologic dysfunction to improve outcomes from pediatric sepsis.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.



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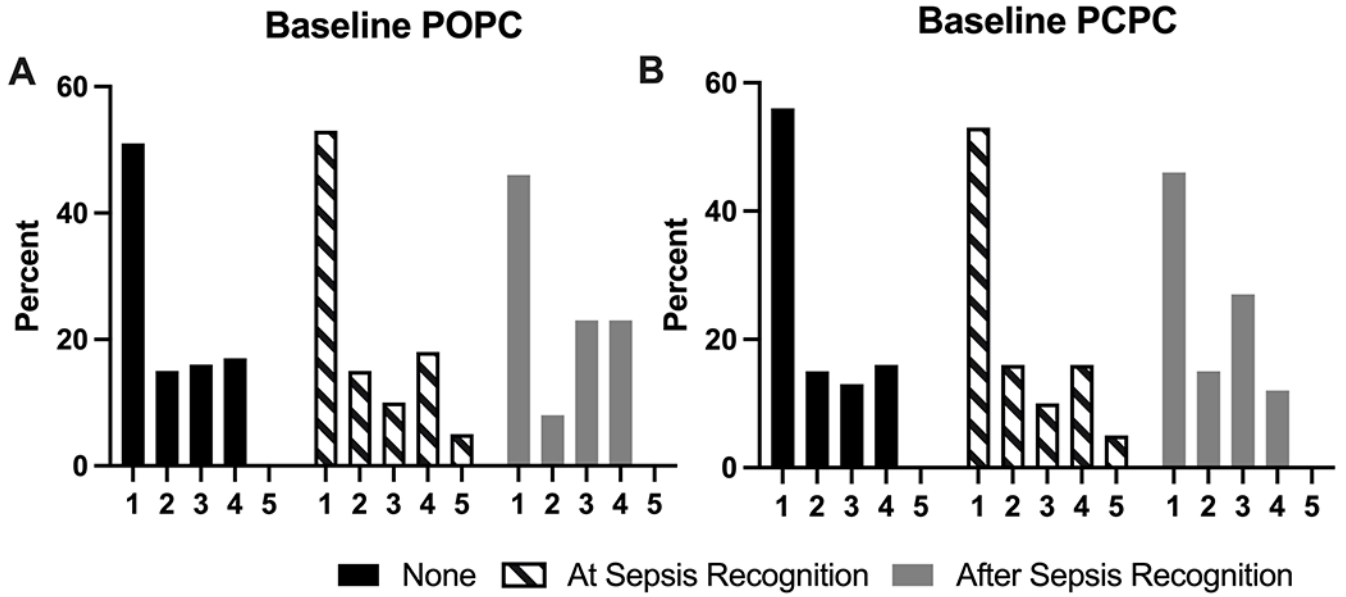
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**Report in Context:**

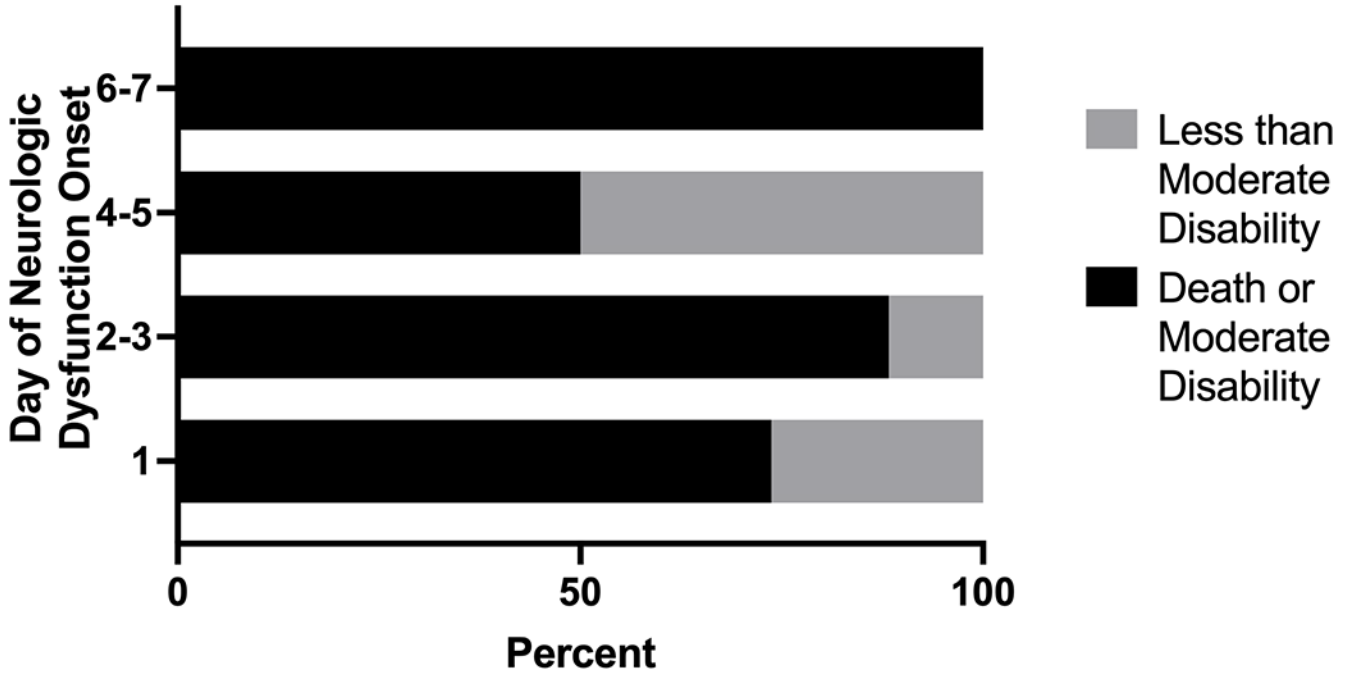
- Neurologic dysfunction during sepsis is associated with higher mortality and worse morbidity in survivors.
- The impact of early versus late onset of neurologic dysfunction in sepsis on outcomes is unknown.
- Understanding the association of timing of neurologic dysfunction onset to outcomes is imperative for future studies evaluating risk factors for and treatment of neurologic dysfunction in sepsis.

**At the Bedside:**

- Fifteen percent of children with sepsis develop neurologic dysfunction, with the majority of these children experiencing neurologic dysfunction at the time of sepsis recognition.
- Adjusting for confounders, our analysis showed that neurologic dysfunction at and after sepsis recognition is associated with higher odds of death or, in those who survive, development of a new moderate disability.
- We failed to identify an association between timing of neurologic dysfunction onset and outcome, which may be because of study design. Hence, additional work is needed to better understand timing of neurologic dysfunction onset in pediatric sepsis.

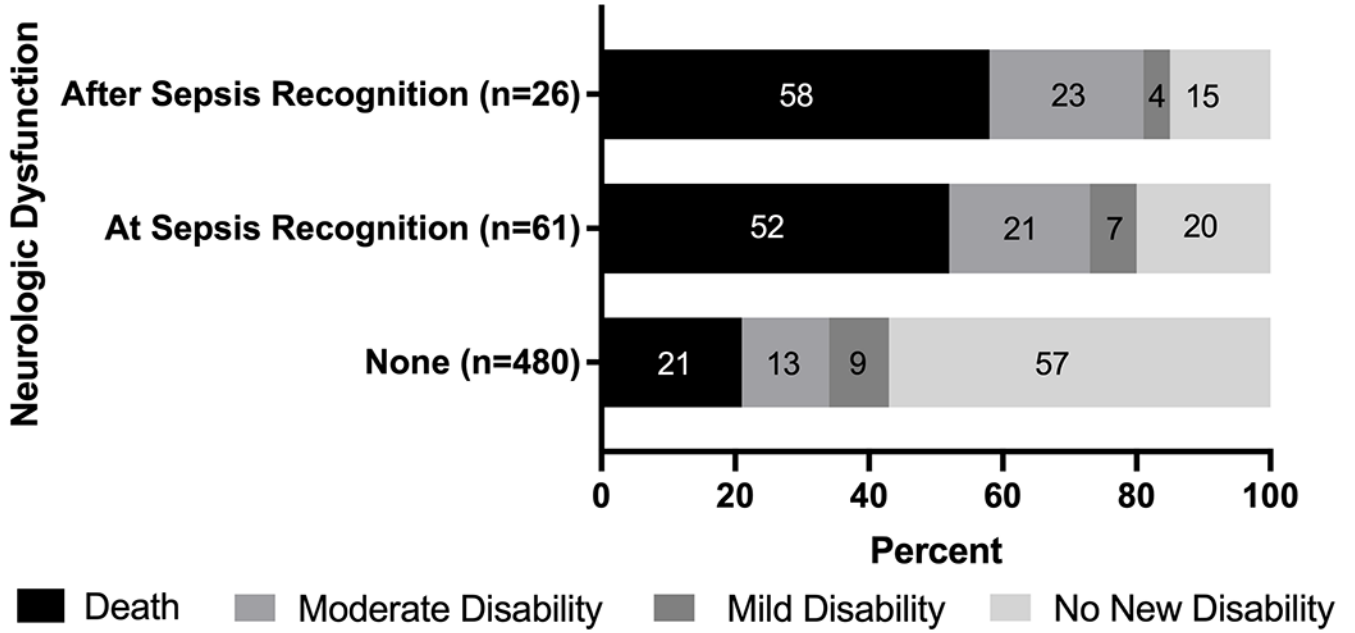


**Figure 1. Baseline Pediatric Overall Performance Category (POPC) and Pediatric Cerebral Performance Category (PCPC) Scores by presence and timing of neurologic dysfunction.** The distribution of POPC scores was different between the three groups ( $p=0.03$ , Fisher's exact test), but there was no difference in the distribution when comparing neurologic dysfunction by timing of onset ( $p=0.38$ , Fisher's exact test). The difference in PCPC score distribution was not different between the three groups ( $p=0.05$ , Fischer's exact test).



**Figure 2. Proportion of patients who experienced death or moderate disability based on day of neurologic dysfunction recognition.**

Graphical representation of outcomes based on timing of neurologic dysfunction onset in the first seven days of severe sepsis. Neurologic dysfunction at sepsis recognition is represented as day 1 of neurologic dysfunction onset (n=61). Neurologic dysfunction after sepsis recognition was stratified into three groups based on onset after sepsis recognition: days 2-3 (n=17), days 4-5 (n=6) and days 6-7 (n=3). The proportion of patients who died or had moderate disability was not different based on the specific day of sepsis recognition (p=0.22, Fisher’s exact test).



**Figure 3. Proportion of outcomes following pediatric sepsis based on presence and timing of neurologic dysfunction.**

All outcomes were determined at hospital discharge. Moderate disability was defined as POPC or PCPC score 3 and 1 increase from baseline and mild disability was any increase in POPC or PCPC score from baseline that does not meet criteria for moderate disability. Survivors without an increase in POPC or PCPC score were labeled as no new disability. The bars are labeled with the percentage of patients within each group that experienced the outcome. The total size for each group is displayed. The proportion of patients with each of these outcomes was different between the three groups ( $p < 0.001$ , Fisher’s exact test) but was no different based on the timing of neurologic dysfunction during sepsis ( $p = 0.96$ , Fisher’s exact test).



**Table 1.**

Clinical and Infectious Characteristics

	Neurologic Dysfunction		Neurologic Dysfunction Present		P value <sup>bc</sup> (Comparison between patients with Neurologic Dysfunction only)
	Absent (n=480)	At Sepsis Recognition (n=61)	After Sepsis Recognition (n=26)	P value <sup>ab</sup> (All groups)	
Age, years (median [IQR])	3 [0.7-10]	7 [0.9-12]	4 [0.5-14]	0.18	0.47
Male (n, %)	257 (54)	29 (48)	16 (62)	0.49	0.25
<b>Comorbid Conditions (n, %)</b>					
Respiratory	150 (31)	12 (20)	10 (36)	0.11	0.10
Gastrointestinal	124 (26)	10 (16)	7 (27)	0.27	0.38
Cardiovascular	121 (25)	10 (16)	5 (19)	0.28	0.76
Genetic	103 (22)	8 (13)	4 (15)	0.28	0.75
Hematologic/Immunologic	100 (21)	9 (15)	5 (19)	0.56	0.75
Neuromuscular	80 (17)	12 (20)	5 (19)	0.76	1.00
Neoplastic	70 (15)	8 (13)	2 (8)	0.72	0.72
Prematurity	73 (15)	2 (3)	1 (4)	0.008	1.00
Metabolic	52 (11)	8 (13)	2 (8)	0.80	0.72
Renal	45 (9)	7 (12)	3 (12)	0.72	1.00
Solid organ/Stem cell transplant	47 (10)	4 (7)	3 (12)	0.67	0.42
<b>Number of comorbidities (n, %)</b>					
None	100 (21)	21 (34)	7 (27)	0.09	0.61
1	118 (25)	17 (28)	6 (23)		
2 or more	262 (55)	23 (38)	13 (50)		
<b>Admission Type (n, %)</b>				<0.001	0.09
Medical	389 (81)	47 (77)	24 (92)		
Surgical	80 (17)	5 (8)	2 (8)		
Trauma	11 (2)	9 (15)	0 (0)		
<b>Non-Neurologic PIM3 Risk of Mortality (% , median [IQR])</b>	3.7 [1.6-7.2]	8.7 [3.9-20.2]	6.2 [4.3-11.1]	<0.001	0.09
<b>Non-Neurologic Organ Dysfunction, Day 1 (n, %)</b>					
None	92 (19)	3 (5)	5 (19)	0.002	0.11

	Neurologic Dysfunction Present		P value <sup>ab</sup> (All groups)	P value <sup>bc</sup> (Comparison between patients with Neurologic Dysfunction only)
	Neurologic Dysfunction Absent (n=480)	After Sepsis Recognition (n=26)		
1	151 (32)	10 (39)		
2	185 (39)	5 (19)		
More than 3	52 (11)	6 (23)	<0.001	0.11
<b>Primary Site of Infection (n, %)</b>				
Respiratory	199 (41)	8 (31)		
Bloodstream	89 (19)	10 (38)		
Central Nervous System	14 (3)	2 (8)		
Other	178 (37)	6 (23)		
<b>Bacterial Isolate (n, %)</b>	231 (48)	13 (50)	0.38	0.64
<b>Viral Isolate (n, %)</b>	93 (19)	8 (31)	0.17	0.79
<b>Fungal Isolate (n, %)</b>	60 (13)	6 (23)	0.17	0.08

IQR = interquartile range, PIM = Pediatric Index of Mortality;

<sup>a</sup> = Fisher's exact test or Kruskal-Wallis test across groups;

<sup>b</sup> = multiple comparisons p-value threshold for significance <0.0024;

<sup>c</sup> = Fisher's exact test or Mann-Whitney U test between groups

**Table 2.**

Outcomes

	Neurologic Dysfunction Absent (n=480)	Neurologic Dysfunction Present (n=26)		P value <sup>a,b</sup> (All groups)	P value <sup>c</sup> (Comparison between patients with Neurologic Dysfunction only)
		At Sepsis Recognition (n=61)	After Sepsis Recognition (n=26)		
Death or Moderate Disability <sup>d</sup> (n, %)	161 (34)	45 (74)	21 (81)	<0.001	0.59
Hospital Mortality (n, %)	98 (20)	32 (53)	15 (58)	<0.001	0.82
At Least Moderate Disability <sup>d</sup> (n, %)	63 (16)	13 (45)	6 (55)	<0.001	0.73
At Least Mild Disability <sup>e</sup> (n, %)	107 (28)	17 (59)	7 (64)	0.49	0.57
PICU LOS, days (median [IQR])	15 [8-35]	15 [5-32]	18 [8-46]	0.83	0.59
Hospital LOS, days (median [IQR])	27 [14-57]	18 [9-48]	28 [10-54]	0.11	0.59
Ventilator-free days (median [IQR])	19 [1-26]	0 [0-18]	0 [0-7]	<0.001	0.32
Vasoactive-free days (median [IQR])	24 [17-28]	18 [0-25]	13 [0-23]	<0.001	0.29
Ventilator days <sup>f</sup> (median [IQR])	7 [0-16]	11 [3-28]	24 [7-28]	0.001	0.65
Vasoactive days <sup>f</sup> (median [IQR])	2 [0-7]	4 [0-8]	6 [1-13]	0.09	0.51

PICU = pediatric intensive care unit; LOS = length of stay; IQR = interquartile range

<sup>a</sup> = Fisher's exact test or Kruskal-Wallis test across groups;

<sup>b</sup> = multiple comparisons, p-value threshold for significance <0.005;

<sup>c</sup> = Fisher's exact test or Mann-Whitney U test between groups

<sup>d</sup> = POPC/PCPC scores 3 and change 1 in survivors;

<sup>e</sup> = POPC/PCPC change 1 in survivors;

<sup>f</sup> = survivors only

**Table 3.** Multivariable Analysis Showing Association Between Neurologic Dysfunction and Confounders to Primary Outcome (Mortality or New Moderate Disability at Hospital Discharge)

Variable	aOR	95% CI	P value
<b>Neurologic Dysfunction</b>			
None	Reference		
At Sepsis Recognition	4.9	2.3-10.1	<0.001
After Sepsis Recognition	10.7	3.8-30.5	<0.001
<b>POPC score, baseline</b>			
1	Reference		
2	1.3	0.8-2.4	0.32
3	0.8	0.4-1.4	0.39
4	0.2	0.1-0.4	<0.001
5	0.3	0.0-4.5	0.42
Non-Neurologic PIM3 Risk of Mortality	1.1	1.0-1.1	<0.001
<b>Number of non-neurologic organ dysfunctions, Day 1</b>			
None	Reference		
1	2.5	1.3-4.8	0.004
2	2.8	1.5-5.2	0.001
More than 3	3.7	1.6-8.2	0.002
<b>Number of co-morbidities</b>			
None	Reference		
1	1.2	0.7-2.2	0.53
More than 2	2.7	1.5-5.1	0.001
<b>Primary Site of Infection</b>			
Respiratory	Reference		
Bloodstream	1.2	0.7-2.0	0.59
Central Nervous System	2.0	0.7-5.5	0.18
Other	1.1	0.7-1.7	0.67

POPC = Pediatric Overall Performance Category, PIM = Pediatric Index of Mortality