Functional Outcomes in Pediatric Severe Sepsis: Further Analysis of the Researching Severe Sepsis and Organ Dysfunction in Children: A Global Perspective Trial*

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Objectives: To evaluate risk factors for poor functional outcome in 28-day survivors after an episode of severe sepsis.

Design: Retrospective cohort study examining data from the Researching Severe Sepsis and Organ Dysfunction in Children: A Global Perspective trial (NCT00049764).

Setting: One hundred and four pediatric centers in 18 countries.

Subjects: Children with severe sepsis who required both vasoactive-inotropic infusions and mechanical ventilation and who survived to 28 days ($n = 384$).

Interventions: None.

Measurements and Main Results: Poor functional outcome was defined as a Pediatric Overall Performance Category score greater than or equal to 3 and an increase from baseline when measured 28 days after trial enrollment. Median Pediatric Overall Performance Category at enrollment was 1 (interquartile range, 1–2). Median Pediatric Overall Performance Category at 28 days was 2 (interquartile range, 1–4). Thirty-four percent of survivors had decline in their functional status at 28 days, and 18% were determined to have a "poor" functional outcome. Hispanic ethnicity was associated with poor functional outcome compared to the white referent group (risk ratio = 1.9; 95% CI: 1.0–3.0). Clinical factors associated with increased risk of poor outcome included CNS and intra-abdominal infection sources compared to the lung infection referent category (risk ratio = 3.3; 95% CI: 1.4–5.6 and 2.4; 95% CI: 1.0–4.5, respectively); a history of recent trauma (risk ratio = 3.9; 95% CI: 1.4–5.4); receipt of cardiopulmonary resuscitation prior to enrollment (risk ratio = 5.1; 95% CI: 2.9–5.7); and baseline Pediatric Risk of Mortality III score of 20–29 (risk ratio = 2.8; 95% CI: 1.2–5.2) and Pediatric Risk of Mortality III greater than or equal to 30 (risk ratio = 4.5; 95% CI: 1.6–8.0) compared to the referent group with Pediatric Risk of Mortality III scores of 0–9.

Conclusions: In this sample of 28-day survivors of pediatric severe sepsis diminished functional status was common. This analysis provides evidence that particular patient characteristics and aspects of an individual's clinical course are associated with poor functional outcome 28 days after onset of severe sepsis. These characteristics may provide opportunity for intervention in order to improve functional outcome in pediatric patients with severe sepsis. Decline in functional status 28 days after onset of severe sepsis is a frequent and potentially clinically meaningful event. Utilization of functional status as the primary outcome in future pediatric sepsis clinical trials should be considered. (*Pediatr Crit Care Med* 2013; 14:835–842)

Key Words: functional status; mechanical ventilation; multiple organ failure; outcome assessment; Pediatric Overall Performance Category; sepsis; septic shock; severe sepsis

Sepsis is an infection-initiated clinical syndrome that can progress to shock, multiple organ dysfunction syndrome, and death (1). In 1995, the age and sex-adjusted prevalence of severe sepsis in the United States was estimated at 0.6 per 1,000 in individuals aged 19 or less (2, 3). Case fatality among children with sepsis ranges from 7.8% to 20%, depending on age, the presence of chronic comorbid conditions, and the source of infection (3).

Even among survivors of sepsis, impairment in physical and mental function may be common. Gross cognitive and physical functioning has been measured in critically ill pediatric patients with two scoring tools. The Pediatric Cerebral Performance Category (PCPC) is a measure of a child's cognitive function. The Pediatric Overall Performance Category

*See also p. 893.

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(POPC) is a measure that combines the PCPC with an assessment of developmentally appropriate physical abilities to provide an "overall" measure of a child's cognitive and physical function (4–6). Each of these scores represents a composite measure on a scale of 1–6, with a score of 1 representing no impairment with full, typical function; a score of 2 representing mild dysfunction; a score of 3 denoting moderate impairment; a score of 4 indicating severe dysfunction; a score of 5 representing an individual in a persistent vegetative state, and a score of 6 equivalent to death/brain death. Although a rough measure of overall function, POPC scoring has been validated against and shown to be associated with measures obtained using the Bayley Psychomotor Developmental Index and the Vineland Adaptive Behavior Scales scores (6).

The RESOLVE (*Re*searching Severe *S*epsis and *O*rgan Dysfunction in Children: A G*l*obal Perspecti*ve*) trial (F1K-MC-EVBP, NCT00049764), evaluating the efficacy and safety of activated protein C (Xigris; Eli Lily and Company, Indianapolis, IN), was the largest international randomized trial of a pharmacologic therapy targeted at improving outcomes in severe pediatric sepsis (7). The investigators used a composite organ failure resolution score as their primary outcome. Paired POPC scores were collected as well.

It is the intent of this study to report the 28-day functional outcomes of a large cohort of pediatric subjects who survived an episode of severe sepsis and to examine the risk factors for "poor" functional outcome in them.

METHODS

Data Source

The RESOLVE trial was conducted from November 2002 through April 2005. Subjects were enrolled at 104 study sites in 18 countries and were eligible if they were between the ages of 38 weeks corrected gestation and 17 years. Inclusion criteria included a suspected or proven infection and systemic inflammation, as well as the presence of sepsis-induced cardiovascular dysfunction (despite adequate fluid resuscitation) and respiratory dysfunction within the 12 hours preceding enrollment. Subjects could meet criteria for study enrollment at any point in their hospitalization. Additionally, it was not a requirement for enrollment that severe sepsis was present at admission. Subjects were excluded if they were judged to have a high risk of intracranial bleeding or if they were expected to die of preexisting conditions and end-stage renal or end-stage liver failure before the end of the 28-day study. Subjects were randomized to an infusion of placebo (0.9% NaCl) or activated protein C for 96 hours. Clinical management was otherwise at the discretion of the primary physician and not per a study protocol (7).

Baseline (pre-illness) POPC score was evaluated by trained study personnel both at the time of enrollment via caregiver history for all 477 enrolled subjects and for 466 subjects (98% follow-up) 28 days later at the conclusion of the trial. These assessments were performed either by direct evaluation if the subject remained hospitalized or via caregiver history if discharged. The 82 subjects (17% of full cohort) who did not survive to 28 days were not considered in this study, leaving 384 subjects available for univariate analysis. Another 21 subjects were eliminated from the multivariate analysis due to missing data or characteristics perfectly predictive of the outcome of interest, thus providing 363 subjects for inclusion in the model (**Fig. 1**).

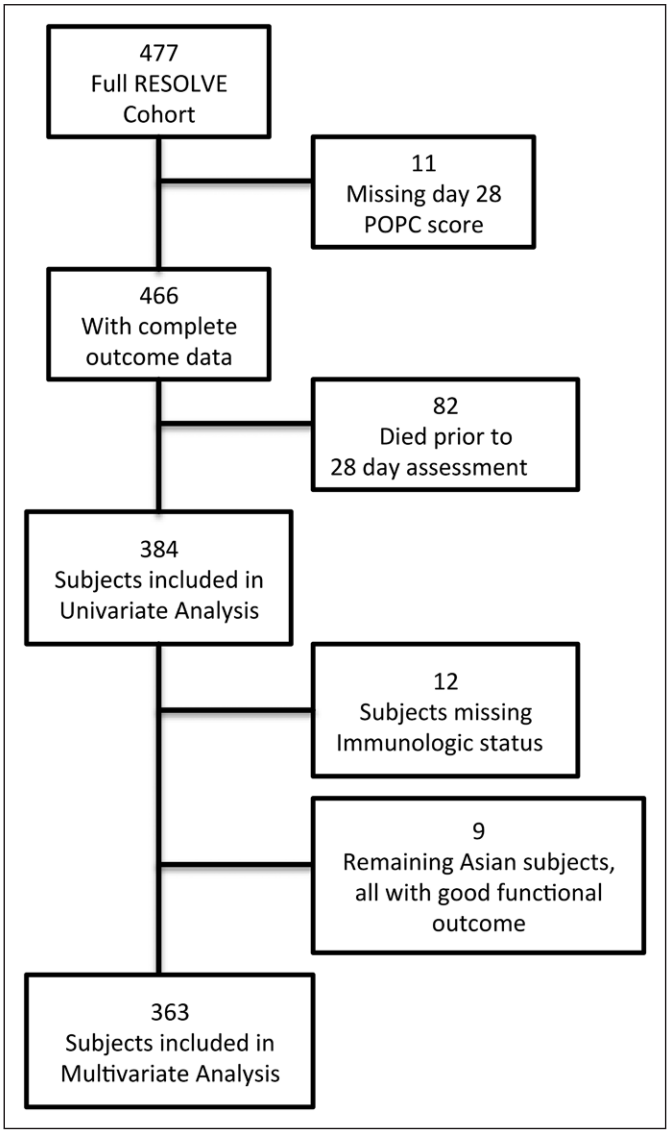

Figure 1. Diagram of Researching Severe Sepsis and Organ Dysfunction in Children: A Global Perspective (RESOLVE) subjects analyzed in univariate and multivariate analysis. POPC = Pediatric Overall Performance Category.

Statistical Methods

We dichotomized functional outcome for the purpose of analysis, with "poor" functional outcome defined as a 28-day POPC score from 3 to 5 and an increase in score of 1 or more. This definition takes into account the relatively short follow-up period as well as the fact that a certain proportion of subjects were moderately to severely impaired at baseline. Although a multitude of variables were available for analysis, we selected a limited range from the dataset for univariate analysis based on completeness of data, clinical relevance, and likely association with functional outcome assessed at 28 days from enrollment

in the trial. We assessed univariate differences in functional outcome using chi-square test and Fisher exact test.

In order to explore the multivariate relationships, we further limited the variables of interest based on the presence of an association represented by the statistical threshold of a *p*-value less than 0.25 in the univariate analysis. The multivariate analysis was performed using backward stepwise logistic regression with likelihood ratio tests. Variables were assessed for collinearity prior to inclusion in the stepwise analysis and no missing data were imputed. Demographic characteristics (gender, age, and ethnicity) were forced into the model, as were all levels of a categorical variable if any one level met inclusion criteria. All nine Asian subjects who had complete data for inclusion in the multivariate model had good functional outcomes, and thus these observations were dropped from this aspect of the analysis. Because of the frequency of the primary outcome, odds ratios obtained from logistic regression were corrected to provide more accurate estimates of relative risk (8, 9). Subject randomization status in the RESOLVE trial was excluded from the stepwise model, although frequency of exposure to activated protein C is provided in the results for descriptive purposes.

All statistical analyses were performed using STATA 10.1 SE (StataCorp, College Station, TX). In accordance with the Common Rule (10) and the policies of Seattle Children's Hospital Institutional Review Board, our research, using a de-identified dataset, was considered exempt human subjects research.

RESULTS

The majority of subjects (77%) had a POPC score of 1 prior to their illness, indicative of a child performing at a level considered typical for age (**Table 1**). Poor functional outcome, as defined in this study, was observed in 315 subjects (18%) who survived for 28 days (**Table 2**). The variables that did not meet our statistical threshold for inclusion in the multivariate model or were excluded due to perceived collinearity are presented in Table 2 but lack adjusted odds ratios and 95% CIs.

TABLE 1. Distribution of Pediatric Overall Performance Category Scores at Baseline and at 28 Days in Pediatric Survivors of Severe Sepsis (*n* = 384)

	Baseline POPC	28-D POPC
POPC Score with Description	Median (IQR) or *n* (%)	Median (IQR) or *n* (%)
Cohort median	1 (1–1)	2 (1–3)
1—Good overall performance	296 (77.1)	183 (47.7)
2—Mild overall disability	33 (8.6)	87 (22.7)
3—Moderate overall disability	25 (6.5)	46 (12.0)
4—Severe overall disability	30 (7.8)	63 (16.4)
5—Coma or vegetative state	0	5 (1.3)

POPC = Pediatric Overall Performance Category, IQR = interquartile range.

The POPC score remained unchanged for 249 subjects (65%) and was noted to deteriorate at least one point from pre-illness in 132 subjects (34%). In three subjects (0.7%), the POPC score improved one point over the 28 days of observation (**Fig. 2**). The majority of subjects (71%) with good functional outcomes were at home at the time of outcome assessment at 28 days. An additional 85 subjects (27%), with good functional outcomes, remained hospitalized at 28 days. In contrast, the majority of the subjects with poor functional outcomes (83%) remained hospitalized at 28 days (**Table 3**). Forty-nine subjects remained in the ICU at the 28-day outcome assessment, 19 (39%) with good functional outcomes and 30 (61%) with poor functional outcomes. A number of subjects continued to receive support for dysfunctional organ systems at the time of the 28-day assessment. Four subjects remained on renal replacement therapy, none were considered to have a good functional outcome. Eight subjects continued to receive vasoactive infusions at 28 days, three (38%) of whom were considered to have a good functional outcome. A total of 22 subjects were receiving mechanical ventilator support at 28 days, five (23%) were considered to have a good functional outcome. It is not clear how many of these subjects were receiving their ventilatory support via tracheostomy at the time of their 28-day evaluation. The changes observed differed somewhat between subjects felt to have impairments at baseline (POPC > 1) and those felt to have good overall function (POPC = 1). Of the 296 28-day survivors considered to have good overall function at baseline, 115 (39%) had deterioration in their functional status at the end of the observation period, whereas, of the 88 subjects with a baseline POPC score of 2 or more, 17 (19%) had a worsening.

In general, few differences were noted when comparing the proportion of subjects with a poor functional outcome among categories of gender and age. A somewhat lower proportion of infants less than 1 month old had a poor functional outcome compared with the 1- to 5-year-old referent group. However, there were only two subjects in this age category with a poor outcome. No substantial differences in outcome according to age were noted in the multivariate analysis (Table 2).

Hispanic subjects were more likely to have a poor functional outcome compared with the overall cohort, whereas Asian subjects were more likely to have a good functional outcome compared with the cohort as a whole. These differences persisted in the multivariate model. Hispanic ethnicity was associated with an 86% increased risk of poor functional outcome compared with the White referent group (risk ratio [RR] = 1.9; 95% CI: 1.0, 3.0). Most of the Asian subjects (91%) for whom a POPC score was available at 28 days had a good functional outcome. All of the Asian subjects ($n = 9$) for whom complete data were available for inclusion in the multivariate model had good functional outcomes.

Individuals with a history of malignancy ($n = 16$) as well as those considered immune compromised ($n = 34$) had increased frequency of "poor" functional outcome. However, because almost all of the subjects with a history of malignancy were considered immune compromised at the time of their

TABLE 2. Characteristics of 28-Day Survivors at the Time of Enrollment in Trial of Activated Protein C for Pediatric Severe Sepsis, Stratified by Functional Outcome

Cohort Characteristic	Total	Children With Good Functional Outcome *n* (%)	Children With Poor Functional Outcome *n* (%)	Relative Risk[a]	95% CI
Entire cohort	384	315 (82.0)	69 (18.0)		
Gender					
Male	204	165 (80.9)	39 (19.1)	Referent	
Female	180	150 (83.3)	30 (16.7)	0.67	0.38, 1.1
Age					
< 1 mo	24	22 (91.7)	2 (8.3)	0.44	0.06, 2.3
1 mo to < 1 yr	92	73 (79.4)	19 (20.7)	1.5	0.77, 2.6
1 to < 5 yr	125	104 (83.2)	21 (16.8)	Referent	
5 to < 12 yr	82	69 (84.2)	13 (15.9)	0.89	0.39, 1.8
12 to < 18 yr	61	47 (77.1)	14 (23.0)	1.5	0.72, 2.7
Ethnicity					
White	259	215 (83.0)	44 (17.0)	Referent	
Hispanic	71	52 (73.2)	19 (26.8)	1.9	1.0, 3.0
African descent	21	17 (81.0)	4 (19.1)	0.99	0.32, 2.5
Other (mixed racial)	22	21 (95.5)	1 (4.6)	0.28	0.03, 1.8
Asian (western and southeast)[b]	11	10 (90.9)	1 (9.1)	0	
Immune status					
Noncompromised	338	283 (83.7)	55 (16.3)	Referent	
Compromised	34	23 (67.7)	11 (32.4)	1.9	0.94, 3.3
Source of infection					
Lung	133	117 (88.0)	16 (12.0)	Referent	
Blood	131	105 (80.2)	26 (19.9)	1.8	0.89, 3.2
Intra-abdominal	33	23 (69.7)	10 (30.3)	2.4	0.98, 4.5
CNS	30	22 (73.3)	8 (26.7)	3.3	1.4, 5.6
Other[c]	57	48 (84.2)	9 (15.8)	1.1	0.43, 2.5
Recent trauma					
No	377	312 (82.8)	65 (17.2)	Referent	
Yes	7	3 (42.9)	4 (57.1)	3.9	1.4, 5.4
Cardiopulmonary resuscitation prior to enrollment					
No	378	313 (82.8)	64 (17.2)	Referent	
Yes	6	2 (33.3)	4 (66.7)	5.1	2.9, 5.7
Pediatric Risk of Mortality III					
0–9	75	68 (90.7)	7 (9.3)	Referent	
10–19	186	158 (85.0)	28 (15.1)	1.2	0.47, 2.8
20–29	103	76 (73.8)	27 (26.2)	2.8	1.2, 5.2
≥ 30	20	13 (65.0)	7 (35.0)	4.5	1.6, 8.0

(*Continued*)

TABLE 2. (*Continued*). Characteristics of 28-Day Survivors at the Time of Enrollment in Trial of Activated Protein C for Pediatric Severe Sepsis, Stratified by Functional Outcome

Cohort Characteristic	Total	Children With Good Functional Outcome *n* (%)	Children With Poor Functional Outcome *n* (%)	Relative Risk[a]	95% CI
Dysfunctional organ systems					
≤ 2	77	72 (93.5)	5 (6.5)		
3	108	86 (79.6)	22 (20.4)		
4	101	87 (86.1)	14 (13.9)		
≥ 5	98	70 (71.4)	28 (28.6)		
Chronic disease[d]					
None	227	187 (82.4)	40 (17.6)		
Cardiac	24	20 (83.3)	4 (16.7)		
Respiratory	24	22 (91.7)	2 (8.3)		
Malignancy	16	10 (62.5)	6 (37.5)		
Neurologic	45	38 (84.4)	7 (15.6)		
Diabetes	4	4 (100%)	0 (0%)		
Congenital anomaly	43	37 (86.1)	6 (14.0)		
Infection type					
No culture done or culture negative	124	108 (87.1)	16 (12.9)		
Viral	15	14 (93.3)	1 (6.7)		
Fungal	24	20 (83.3)	4 (16.7)		
Bacterial					
Pure gram positive	105	83 (79.1)	22 (21.0)		
Pure gram negative	77	60 (77.9)	17 (22.1)		
Mixed gram	39	30 (76.9)	9 (23.1)		
Acute respiratory distress syndrome at enrollment					
No	323	266 (82.4)	57 (17.7)		
Yes	37	27 (73.0)	10 (27.0)		
Recent surgery					
No	343	280 (81.6)	63 (18.4)		
Yes	41	35 (85.4)	6 (14.6)		
Randomized to receive activated protein C					
No	190	159 (83.7)	31 (16.3)		
Yes	194	156 (80.4)	38 (19.6)		
Baseline steroids					
No	234	193 (82.5)	41 (17.5)		
Yes	150	122 (81.3)	28 (18.7)		
Prior ICU admission					
No	379	312 (82.3)	67 (17.7)		
Yes	5	3 (60.0)	2 (40.0)		

[a]Odds ratio obtained from multivariate logistic regression model adjusted for frequent outcome.
[b]All nine Asian patients with nonmissing data had "good" functional outcome.
[c]Includes cardiac, gynecologic, pleural, urinary tract, vascular catheter, skin, head, ear, eye, nose, throat, and bone/joint.
[d]Does not represent mutually exclusive categories.

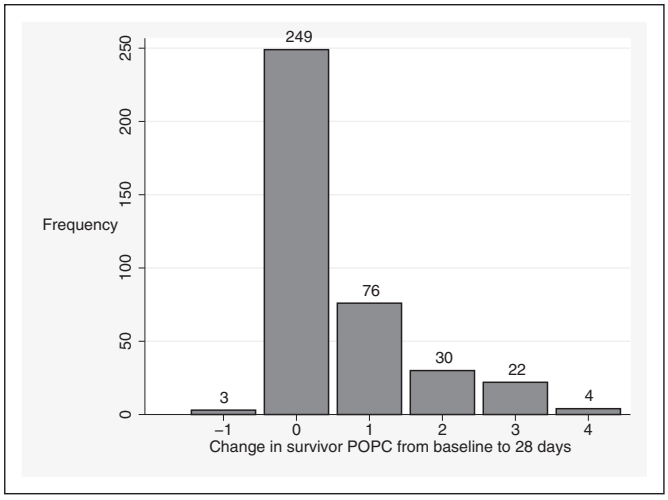

Figure 2. Change in Pediatric Overall Performance Category (POPC) scores in pediatric sepsis survivors ($n = 384$) from baseline to 28 d.

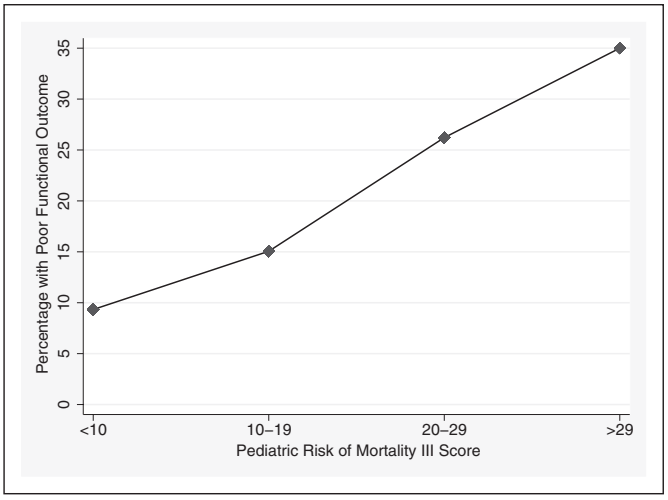

Figure 3. Frequency of poor functional outcome in survivors by Pediatric Risk of Mortality III score.

infection ($n = 14$), a history of malignancy was not included in the multivariate model. Immune compromised status was associated with an almost two-fold increased risk of "poor" functional outcome (RR = 1.9; 95% CI: 0.94, 3.3).

Children with intra-abdominal and CNS infections had an increased frequency of "poor" functional outcome (30.3% and 26.7%, respectively) compared with the children whose infections originated elsewhere in the body (multivariate RR = 2.4; 95% CI: 0.98, 4.5 and RR = 3.3; 95% CI: 1.4, 5.6, respectively). Subtle, but not statistically significant, differences in outcome at 28 days were observed based on the type of organism identified as causing the episode of sepsis. The relatively few subjects identified with viral infections ($n = 15$) more frequently had good functional outcomes.

The small number of individuals with a history of trauma ($n = 7$) within the 30 days prior to study enrollment were more likely to have a poor functional outcome than those without such a history (RR = 3.9; 95% CI: 1.4, 5.4). Those who received cardiopulmonary resuscitation ($n = 6$) prior to enrollment were five times more likely to have a poor functional outcome 28 days after the onset of sepsis (RR = 5.1; 95% CI: 2.9, 5.7).

A high degree of illness severity at the time the subject met clinical criteria for enrollment in the study, as measured by Pediatric Risk of Mortality (PRISM) III score, was associated with "poor" functional outcome. The relationship between frequency of poor functional outcome and PRISM III score demonstrated a positive association across categories of increasing PRISM III (**Fig. 3**). This relationship persisted in the multivariate model. Those survivors with a PRISM score from 20 to 29 had a 2.8-fold increased risk of poor function at 28 days compared with the referent group with PRISM scores from 0 to 9 (RR = 2.8; 95% CI: 1.2, 5.2). Individuals with a PRISM score greater than or equal to 30 had even greater risk compared with the referent group (RR = 4.5; 95% CI: 1.6, 8.0).

No substantial difference was noted in the functional outcomes of the subjects who received activated protein C compared with those who received placebo.

TABLE 3. Subject Location at the Time of 28-Day Functional Status Assessment

Location of Care	Subjects With Good Functional Outcome *n* (%) *n* = 315	Subjects With Poor Functional Outcome *n* (%) *n* = 69
Home		
No support	164 (52.1)	3 (4.4)
Unpaid support	46 (14.6)	4 (5.8)
Paid support	14 (4.4)	4 (5.8)
Rehabilitation center	0	1 (1.5)
Study hospital	74 (23.5)	55 (79.7)
Other hospital	11 (3.5)	2 (2.9)
Other	6 (1.9)	0

DISCUSSION

Major Findings

This study represents the first description of short-term functional outcomes in a cohort of pediatric survivors of severe sepsis. The definition used here for poor functional outcome is a conservative one. In order to be categorized as having a poor functional outcome, a subject with normal function (POPC = 1) prior to their illness would have to have moderate dysfunction (POPC = 3) at the 28-day evaluation. This represents a significant functional decline in a relatively short time period. In spite of this conservatism, poor functional outcome was observed in 18% of the cohort. A third of subjects (34%) had some degree of decline in functional status as represented by any increase in POPC from baseline to 28 days. Whether this decline in functional status persists over time in this cohort is

unknown as this study is unable to evaluate longer-term functional outcomes. In addition, the specific reasons for functional decline in this cohort are not clear and could be related to any number of processes including organ injury, deconditioning, persistent technology dependence, medications, limb loss, and many more. The reasoning for improvement in functional status over the course of the trial in a small number of subjects is not entirely clear. It is possible that what the subject or parent defined as their baseline functional status reflects the presence of a comorbid condition that improved by the 28-day assessment. An improved understanding of functional status outcomes and risk factors for functional decline in pediatric critical illness may allow providers to target and develop therapies to not only prevent mortality but also minimize morbidity.

Many of the findings presented here are consistent with those obtained in studies of other groups of hospitalized, critically ill children. The functional outcomes of general PICU populations have been evaluated using POPC as an assessment tool. Beyond the foundational work done by Fiser, the functional outcomes of pediatric patients after an ICU stay have been associated with baseline functional status as well as measures of illness severity at the time of ICU admission (4, 11–13). The association between organ dysfunction and alteration in functional status has been previously described, although at the time of discharge from the ICU rather than at a predetermined time point (14). In addition, although this study assessed an international cohort, the case fatality of 17% is within the ranges reported by Watson et al in their epidemiologic study of pediatric severe sepsis in the United States. Some of the risk factors for poor functional outcome identified here, including the presence of an immunologic or oncologic comorbidity and a CNS infection, are consistent with characteristics placing individuals at higher risk of mortality in that nationally representative sample (2).

The findings related to categories of ethnicity are difficult to interpret. Ethnic category was assigned by study personnel based on a combination of racial category and "geographic origin" and may or may not be consistent with how a subject or their family might categorize themselves. Exploratory review of the Hispanic and Asian subjects' risk factors for poor functional outcome did not reveal any convincing trends. Hispanic subjects did have somewhat more frequent intra-abdominal infections although in general this group had somewhat lower severity of illness scores.

Some of the findings presented here likely reflect the performance of the POPC score itself. The increased frequency of functional status decline in subjects with a POPC = 1 at baseline may represent the fact that the degree of dysfunction that results in an increase in score from 1 to 2 is likely different from that required to increase from 2 to 3 or 3 to 4. This finding is consistent with Fiser's original description and validation of the POPC score (4).

The clinical implications of the high frequency of impaired function in children treated in an ICU for severe sepsis may include a need for increased attention to the functional status of these patients throughout their clinical course. An improved understanding of specific risk factors for decline in functional status during a severe illness and ICU stay may help clinicians rationally alter the care provided in an effort to minimize functional decline. These interventions may include early provision of various therapeutic supports including physical and occupational services initiated early in the ICU course. These efforts have been studied in adult critical care settings and have demonstrated effectiveness (15).

Limitations

This study represents a secondary analysis of data obtained from 2002 to 2005. It is certainly possible that changes in therapy and practice over the last 10 years have altered the generalizability of these findings in the modern era. In addition, the reliability of our outcome depends on the accurate and precise application of the POPC scoring system. Although trained study personnel conducted the assessments, interrater reliability data are unavailable for the cohort presented here, limiting our ability to assess the possible impact of improper evaluations.

The initial, pre-illness assessment was obtained by parental history at the time of enrollment in the clinical trial. Parental assessment of the subject's pre-illness function may have been biased by recently acquired comorbidities and possible decline in function prior to onset of their episode of severe sepsis. If this were true, one would expect a decreased ability to detect a change in status in these subjects at 28 days, resulting in bias toward an underascertainment of functional decline.

The pathophysiologic processes present in this cohort of subjects were widely varying. It is possible that the risk factors for "poor" functional outcome identified here apply broadly to a general population of patients with severe sepsis and may not apply to specific subgroups of patients with a particular type of severe sepsis, for example, patients with meningococcemia and purpura fulminans.

Receipt of mechanical ventilation and a continuous infusion of a vasoactive or inotropic medication were both criteria for study enrollment. Although the duration that an individual subject required these therapies was dependent on severity of illness as well as local practice, the care that was necessary to provide these therapies to children could conceivably have had an impact on their functional status in the near term. For example, in order to safely and effectively provide mechanical ventilation to developmentally appropriate 2-year-old children, sedative medications and neuromuscular blockade are often used. Requiring this type of support for a prolonged period may lead to a decline in functional status if the patient is assessed in the days to weeks following discontinuation of that support. Differentiating the relative contributions of illness severity and the residual effects of critical care supportive therapies that may impact global function in the short term was not possible in this study.

In addition, the 28-day time point at which these subjects were assessed represents a relatively short time frame of follow-up. It is likely that some proportion of the subjects who experienced significant functional declines will improve over time. This study does not address long-term functional status.

TABLE 4. Trial Sample Sizes Required to Demonstrate Improvement in Different Outcomes

28-D Outcome	Pediatric Overall Performance Category Scoring	Baseline Frequency (%)	Treatment Effect (30% Improvement) (%)	Subjects Required[a]
All-cause mortality	28-d score = 6	17	11.9	1,568
At least moderate disability	≥ 3 and increase from baseline	32	22.4	714
At least mild disability	Any increase from baseline	46	32.2	420

[a]$\alpha = 0.05$ and $1 - \beta = 0.8$.

CONCLUSIONS

The primary outcome of poor functional outcome in 28-day survivors of pediatric severe sepsis was relatively frequent (18%). Specific subject characteristics and aspects of their clinical course were associated with poor functional outcome 28 days after the onset of severe sepsis. These characteristics may represent opportunities for intervention in order to improve functional outcomes in pediatric patients with severe sepsis.

A composite outcome of mortality or poor functional outcome was present in 151 of the 466 total subjects (32%) for whom 28-day data were available. Almost half of the total cohort, 214 subjects (46%), had a measurable decline in functional status at 28 days. Comparing 28-day mortality to the composite outcome and to any decline in functional status at 28 days shows that adequately powered randomized trials designed to detect a 30% improvement are more logistically feasible with both the composite functional outcome as well as any change in functional status (**Table 4**). Further consideration should be given to using functional outcome or a composite of mortality and functional outcome as the primary outcome in pediatric critical care trials going forward.

In addition, the findings presented here suggest directions for future study. As mentioned, the duration of follow-up in this particular cohort was relatively short. Increased observation time points spread over a longer duration would provide an improved sense of the severity and duration of morbidity experienced by survivors of pediatric severe sepsis. Longer duration of follow-up would also provide an indication of the proportion of patients that return to their baseline functional status and how much time is required to achieve this.

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