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The association of nutrition status expressed as body mass index z-score with outcomes in children with severe sepsis: a secondary analysis from the Sepsis Prevalence, Outcomes and Therapies (SPROUT) study

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Abstract

Objectives: The impact of nutrition status on outcomes in pediatric severe sepsis is unclear. We studied the association of nutrition status [expressed as body mass index (BMI) z-score] with outcomes in pediatric severe sepsis.

Design: Secondary analysis of the *S*epsis *P*revalence, *OU*tcomes and *T*herapies (SPROUT) study. Patient characteristics, intensive care unit (ICU) interventions, and outcomes were compared across nutrition status categories [expressed as age- and sex-adjusted BMI z-scores using World Health Organization standards]. Multivariable regression models were developed to determine adjusted differences in all-cause ICU mortality and ICU length of stay (LOS) by nutrition status.

Setting: 128 pediatric ICUs across 26 countries

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Conflicts of interest: The authors do not have any conflicts of interest related to this study.

Patients: Children <18 years with severe sepsis enrolled in the SPROUT study (n = 567)

Interventions: None

Measurements and Main Results: Nutrition status data were available for 417 patients. Severe undernutrition was seen in Europe (25%), Asia (20%) South Africa (17%) and South America (10%), with severe overnutrition seen in Australia/New Zealand (17%) and North America (14%). Severe undernutrition was independently associated with all-cause ICU mortality (adjusted OR = 3.0, 95% CI: 1.2 - 7.7; p = 0.02), while severe overnutrition in survivors was independently associated with longer ICU LOS (1.6 days, p =0.01).

Conclusions: There is considerable variation in nutrition status for children with severe sepsis treated across this selected network of pediatric ICUs from different geographic regions. Severe undernutrition was independently associated with higher all-cause ICU mortality in children with severe sepsis. Severe overnutrition was independently associated with greater ICU LOS in childhood survivors of severe sepsis.

Keywords

severe sepsis; septic shock; nutrition status; nutrition support; children; critical illness; outcomes

Introduction

Globally, severe sepsis and septic shock are leading causes of mortality and morbidity in children (1-3). The recent *S*epsis *P*revalence, *OU*tcomes and *T*herapies (*SPROUT*) study estimated the point prevalence of severe sepsis amongst an international network of pediatric intensive care unit (ICU) patients at 8% with ICU mortality of 24% and new moderate to severe disability in 17% of survivors (4). In addition to the primary etiology inciting severe sepsis, pre-existing nutrition status may impact the course of illness, ICU therapies and clinical outcomes in children with severe sepsis. Malnutrition (encompassing both undernutrition and overnutrition) is globally estimated to affect more than 248 million children under 5 years of age (5, 6). The overall prevalence of malnutrition in hospitalized children is approximately 40%, and as high as 65% in critically ill children (7-9). Undernutrition (with energy, fat and protein depletion) is associated with higher mortality, prolonged ICU dependency and an increase in hospital-acquired infections (HAI) in critically ill children (10-15). Similarly, overnutrition and obesity may be independent risk factors for poor outcomes in critically ill children (11, 12, 16). Notably, these studies have typically consisted of general pediatric ICU populations that have variably included subsets of children with severe sepsis.

Given the potential for nutrition status to directly impact outcomes from pediatric severe sepsis, we sought to understand the relationship between nutrition status and outcomes in children with severe sepsis. We conducted this study as an *a priori* planned analysis from data prospectively collected for the SPROUT study that exclusively enrolled children with severe sepsis. Our primary objective was to determine the associations of nutrition status with ICU mortality and ICU length of stay (LOS) in children with severe sepsis. Our secondary objective was to describe variations in nutrition status and nutrition support in critically ill children during treatment of severe sepsis across geographic regions.

Materials and Methods

The SPROUT study was a prospective point prevalence study that reported characteristics, therapies provided, and outcomes for 567 critically ill children with severe sepsis across 128 pediatric ICUs in 26 countries (4). The pediatric ICUs included were selectively targeted as centers capable of participating in future international clinical trials of pediatric severe sepsis. Participants were enrolled on five seasonally-distributed study days from June 2013 through June 2014. Site participation was voluntary and ethics approval was obtained at all sites using a waiver of informed consent, with the exception of three sites where written informed consent was required. Details of the SPROUT study and primary results have been previously published (4).

Study Design and Data Collection

Children less than 18 years of age hospitalized in participating pediatric ICUs in six geographically defined regions (North America; South America; Europe; South Africa; Asia; and Australia/New Zealand) were eligible for SPROUT study enrollment if they met criteria for severe sepsis within the 24-hour period preceding the study day (17). Infants less than 42 weeks corrected gestational age, and children who required cardiopulmonary bypass in the preceding five days were excluded from the study. Information on patient characteristics at ICU admission, and data on ICU therapies (including nutrition) within a 48-hour time period surrounding the study day (from 9:00 am prior to the study day through 9:00 am following the study day) were collected and recorded. Data elements for this analysis included weight (kg) and length (cm) measured per individual site practice and reported closest to 9:00 am on each study day, and mode of nutrition support (enteral nutrition - EN and/or parenteral nutrition - PN) provided during the 48 hour time period surrounding the study day. Pediatric Overall Performance Category (POPC) and Pediatric Cerebral Performance Category (PCPC) scales were used to characterize baseline functional status in all patients, as well as change from baseline functional status in survivors (18). In addition, patients were followed for seven consecutive days from the day of severe sepsis diagnosis to assess for new or progressive multiple organ dysfunction syndrome (NPMODS) (19). Severity of illness was expressed in terms of the Pediatric Index of Mortality-3 (PIM-3) calculated at PICU admission, and organ dysfunction was expressed as the Pediatric Logistic Organ Dysfunction (PELOD) score determined on the study day (20,21). For vasoactive-free days (VAFD) and ventilator-free days (VFD), one point was assigned for each day following sepsis recognition up to 28 days that patients were both alive and free from use of vasoactive medications and invasive mechanical ventilation, respectively (22).

Exposures and Classifications

Nutrition status was expressed as age- and sex-adjusted body mass index (BMI) z-scores which were calculated from the initial weight and height measurements obtained closest to the day of study enrollment using World Health Organization (WHO) Anthro software (version 3.2.2, 2011) for patients younger than 10 years and AnthroPlus software (version 1.0.4, 2007) for patients 10 years of age or older. Using calculated BMI z-scores, nutrition status was classified into seven mutually-exclusive categories ranging from undernutrition to overnutrition (Supplemental Digital Content 1 - eTable 1) to determine associations of

nutrition status with patient outcomes. We adapted this classification from the stratification scheme previously used to study the association of weight-for-age z-scores and risk adjusted mortality in critically ill children (23). The mode of nutrition support was defined as EN only, PN only, EN and PN, or none.

Outcomes

The primary outcome was all-cause ICU mortality. The secondary outcome was ICU LOS in survivors. Both ICU mortality and ICU LOS were censored at 90 days from study enrollment for patients still hospitalized at this time point. Additionally, we calculated hospital LOS and the relative change in functional status (change in POPC/PCPC in relation to baseline POPC/PCPC) in survivors. We also reported incidence of NPMODS, VAFD, and VFD.

Statistical Analysis

Standard descriptive statistics were used to compare patient characteristics, ICU therapies, and outcomes across nutrition status categories. Continuous variables with normal distribution are reported as means (± standard deviation, SD) and compared across categories using analysis of variance (ANOVA). Continuous variables that were not normally distributed are reported as medians (with interquartile ranges, IQR) and compared across categories using the Kruskal-Wallis test. Categorical variables are reported as proportions (with percentages) and compared across categories using chi-square or Fisher's exact tests, as appropriate. Due to the point-prevalence study design, we reported only descriptive analyses of modes of nutrition support as we did not have detailed data on nutrition prescription, initiation or duration of nutrition support in the enrolled patients to draw inferences between nutrition support and outcomes.

Multivariable logistic regression was used to determine the association of nutrition status with the binary outcome of all-cause ICU mortality. Based on clinical relevance, biologic plausibility, and previously reported associations, covariates identified as potential confounders of the association between nutrition status and all-cause ICU mortality were entered into the model using backwards selection at a threshold of $p \leq 0.1$ and retained at $p \leq 0.05$. Multicollinearity was examined using pairwise Spearman correlations and by regressing BMI z-scores onto other covariates to detect significant associations.

Multivariable generalized linear regression was used to determine the association of nutrition status with ICU LOS amongst survivors. Due to its non-parametric distribution, ICU LOS was log-transformed prior to analysis to satisfy model assumptions. Covariates were first selected based on clinical relevance with entry into the model at $p \leq 0.1$ in univariate analyses. Backwards selection was used to develop the final linear regression model, with covariates retained at the $p \leq 0.05$ level.

Based on the parent study cohort of 567 patients, a power analysis was performed to assess adequacy of sample size for the primary outcome of all-cause ICU mortality with an alpha of 0.025. For the multivariable logistic regression model to examine the primary outcome of ICU mortality, a sample size of 324 would achieve 80% power to detect a change corresponding to an odds ratio of 1.5 attributable to nutrition status (expressed as BMI z-

score), adjusted for additional covariates with an R^2 of 0.05. Statistical significance was defined as a p-value <0.05. SAS software Version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for all analyses.

Results

Of the 567 patients with severe sepsis enrolled in the SPROUT study, complete nutrition status data were available for 417 patients. There were no significant differences in patient characteristics, ICU therapies, and outcomes between patients with complete nutrition status data and the 150 patients excluded for lack of anthropometric measurements (146 missing length measurement, and 4 missing weight measurement; data not shown). The proportions of patients with undernutrition, normal nutrition and overnutrition were 30%, 33% and 37%, respectively. In patients with complete nutrition status data, ICU mortality was 25% (103 deaths) while the median ICU LOS in survivors (n = 314) was 14 days (IQR: 6 – 29 days).

Variations in nutrition status across geographic regions

The majority of patients were from North America (68%). The geographic distribution of patients by nutrition status is shown in Supplemental Digital Content 2 - eFigure 1. Not all nutrition status categories were represented in all geographic regions. Severe undernutrition was seen in Europe (25%), Asia (20%) and South Africa (17%), while severe overnutrition was seen in Australia/New Zealand (17%) and North America (14%). Nutrition status distribution by geographic region is presented in Supplemental Digital Content 3 – eTable 2.

Patient characteristics and ICU interventions by nutrition status

Overall, children with undernutrition were younger than those with overnutrition or normal nutrition status. Infants accounted for approximately 55% of patients in the severe and moderate undernutrition groups. Overnutrition was more prevalent in White patients (44%) and undernutrition was more prevalent in Asian patients (80%). Of all racial/ethnic groups, Black children had the lowest prevalence of normal nutrition status (10%). The remaining patient characteristics were comparable across nutrition status categories (Table 1).

Differences in ICU interventions across nutrition status categories are depicted in Table 2. The number of vasoactive infusions did not differ by nutrition status, though the majority of patients in each category were supported by one or more vasoactive infusions. There were no differences in diuretic administration or need for renal replacement therapies across nutrition status categories. Similarly, there were no differences in the use of common ICU devices (e.g. arterial catheter, central venous catheter, or urinary catheter) across nutrition status categories.

Nutrition status and ICU mortality

The highest proportions of ICU deaths occurred in patients with severe undernutrition (35%) and moderate undernutrition (35%). After adjusting for confounders, severe undernutrition (compared to normal nutrition status as the reference) was independently associated with all-cause ICU mortality (adjusted odds ratio = 3.0, 95% confidence interval 1.2 - 7.7; p = 0.02) (Table 3).

Nutrition status and secondary outcomes

Survivors with severe overnutrition (using normal nutrition status as the reference) had a significantly longer ICU LOS (by 1.6 days, β=0.45, e^ β=1.56, p = 0.01) after adjusting for confounders (Supplementary Digital Content 4 - eTable 3). There were no differences in hospital LOS across nutrition status categories in survivors. In addition, there were no differences in relative change in functional status (i.e., calculated delta scores for POPC and PCPC) across nutrition status in survivors. There were also no differences in NPMODS across nutrition status categories (Table 4). Additionally, there were no differences across nutrition status for VAFD (p = 0.59) or VFD (p = 0.37).

Nutrition support in children at the time of severe sepsis

Of the 567 patients with complete nutrition support data during the 48 hour time period surrounding the study day, 17% did not receive any nutrition support, 58% received EN either exclusively or in combination with PN, and 25% received PN only during this 48 hour time period. Supplementary Digital Content 5 - eTable 4 depicts select patient characteristics and ICU interventions related to nutrition support in children at the time of severe sepsis during this 48 hour time period. Compared to all modes of nutrition support at the time of severe sepsis, exclusive EN use predominated in South Africa (80%), Australia/New Zealand (60%), South America (61%) and Asia (58%), in contrast to Europe (45%), and North America (37%) (p < 0.001). More patients from North America did not receive any form of nutrition support (25%) compared to other regions (11%) (p = 0.006). EN use was negatively impacted by vasopressor infusion therapy at the time of severe sepsis (corresponding to this 48 hour time period surrounding the study day). While 55% of patients not treated with vasopressor infusion received EN, only 36% of patients receiving one or more vasopressor infusion(s) received EN (p < 0.001). Specifically, 41% of patients managed with epinephrine infusion received EN, while 63% of patients not managed with epinephrine infusion received EN (p < 0.001). EN use was associated with lower severity of illness (PIM-3), p < 0.001 (Supplementary Digital Content 5 - eTable 4).

Discussion

In this secondary analysis of the SPROUT data, we observed considerable variations in nutrition status and mode of nutrition support across geographic regions in critically ill children during the 48 hour time period at the time of severe sepsis. Severe undernutrition was independently associated with higher all-cause ICU mortality, while severe overnutrition was independently associated with greater ICU LOS in survivors. The findings of this investigation highlight the importance of nutrition status in critically ill children with severe sepsis with implications for clinical outcomes. However, given the SPROUT network of pediatric ICUs was selectively targeted to include centers capable of participating in future international clinical trials of pediatric severe sepsis, our findings are most appropriately generalizable to future research populations rather than viewed as global epidemiological estimations.

The relationship between abnormal nutrition status, infection and critical illness is notable for complex synergistic interactions (24-28). We observed a strikingly high prevalence of

abnormal nutrition status in 67% of patients, with approximately one-third (31%) being undernourished. Undernutrition is strongly influenced by reduced nutrient intake, increased metabolism from underlying infection, and co-morbidities (e.g. malabsorptive disorders, chronic lung disease, congenital heart disease), all of which can directly predispose to critical illness. In the present study, though 57% of patients had two or more co-morbidities, there was no appreciable association of the number of co-morbidities with nutrition status. It is possible that the type of co-morbidity may be a more important determinant than the number of co-morbidities, but we did not have sufficient numbers in each type to explore this association further. The metabolic alterations that occur during critical illness can result in further deterioration of pre-illness nutrition status and in turn increase predisposition to infection and sepsis. Additionally, both undernutrition and overnutrition may directly impair immune function, glucose homeostasis and the inflammatory response in severe sepsis further impairing recovery and survival (10, 24).

The increased risk of ICU mortality associated with severe undernutrition that we observed is consistent with results from previous studies of critically ill children, including specific sub-groups such as post-operative cardiac surgery and renal failure managed with renal replacement therapies (11, 12, 23, 29, 30). Our finding that severe undernutrition was as common in Europe as in Asia and South Africa in this cohort of patients with severe sepsis may represent the possibility that more severely undernourished children in Asia and South Africa die before the timely recognition of severe sepsis and the ability to seek appropriate medical care. Additionally, the parent SPROUT study recruited patients from selected pediatric ICUs that would be more likely to participate in future prospective clinical trials of pediatric severe sepsis, which may have biased the results.

In contrast, overnutrition was not associated with ICU mortality in our cohort, similar to other studies in critically ill children that appear to favor “an obesity paradox” (31, 32). Instead, we observed an association of severe overnutrition with greater ICU LOS in survivors, which is also consistent with prior studies of critically ill children (12, 33, 34). Obesity and overnutrition can predispose to neuromuscular deconditioning, pulmonary atelectasis with reduced chest wall compliance, cardiovascular dysfunction, acute kidney injury, and gastroesophageal reflux due to alterations in lower esophageal sphincter tone with prolonged need for ICU level interventions (35). The evidence for a protective effect of obesity is mixed with several studies suggesting that obesity may have a negative effect on outcomes in critically ill children (12, 16, 23).

We also observed considerable variations in mode of nutrition support in children with severe sepsis, similar to other published studies in the general pediatric ICU population (36, 37). A considerable proportion of patients (17%) did not receive any form of nutrition support during the period of data collection, which we speculate may have been due to ongoing resuscitation and electrolyte abnormalities requiring frequent titration of fluid therapy and electrolyte supplementation. Interestingly, mode of nutrition support (EN vs. PN) did not appear to be influenced by nutrition status (Table 2). Additionally, we observed that almost two-thirds (64%) of patients managed with one or more vasoactive infusions did not receive EN, despite evidence that suggests EN is safely tolerated in critically ill children supported with vasoactive infusions (38, 39). Unfortunately, we did not have data to

determine if withholding of EN was related to dose of vasoactive infusions. In contrast, 25% of patients in the present study received PN exclusively. We were also surprised by our observation that PN was used more often in North America and Europe compared to other regions, which might reflect the relative difficulties in prescribing and obtaining PN in other regions of the world. The findings from this investigation highlight that EN use was preferred in the majority of patients (almost 60%, either alone or in combination with PN) due to perceived benefits from a growing body of evidence that favors EN as the preferred mode of nutrition support in critically ill children. These observations are in line with previous studies that have clearly demonstrated the benefits of early EN in improving nutritional indices as well as nitrogen balance and energy stores in the acute phase of stress in critically ill children (14, 15).

Our study has several strengths and limitations. The parent SPROUT study collected prospective data using precise definitions of sepsis from a wide international network of pediatric ICUs with follow-up for 90 days to obtain meaningful clinical outcomes (4). We calculated BMI z-scores to enable meaningful comparisons of nutrition status across a variety of geographic regions; however, BMI reflects only one dimension of nutrition status in children. Given more adequate subgroup sample sizes, it is possible that moderate undernutrition and moderate overnutrition may have detected significant associations with mortality in opposing directions. Additionally, 68% of patients in this study were enrolled from ICUs in North America thus tempering the generalizability of the findings to other regions in the world. To account for the possibility of regional bias from North America, we performed a sensitivity analysis with only subjects from North America, and did not observe any differences in our key outcomes after adjusting for confounding variables i.e. severe undernutrition remained independently associated with all-cause ICU mortality, while severe overnutrition remained independently associated with greater ICU LOS (data not shown). As such, SPROUT was a point prevalence study conducted in key academic hospitals with pediatric ICUs in major cities across the world. Thus, patients may not be truly representative of their respective national make-up for indicators of health and nutrition status. This may limit external validity for global epidemiological estimates, but should not affect internal validity of our findings and highlights the importance of considering nutrition status in the design of future international trials for pediatric sepsis. Additionally, each site reported weight and length measurements according to local institutional standards of measurement, which may have resulted in systematic errors. Weight measurements can be influenced by dehydration or volume overload in critically ill children with severe sepsis, which could have led to erroneous BMI z-score estimates in relation to pre-illness states of health. Challenges to length measurements in critically ill children are well described, particularly in children with contractures and growth abnormalities (40). Although length measurements were missing in 26% of the parent study sample, patient characteristics, interventions and outcomes were similar between those included and those excluded from analysis. It is possibly that specific co-morbidities could have associations with both changes in nutrition status as well as mortality. However, the numbers in each nutrition status sub-group were too small to draw meaningful inferences regarding such associations. Details on timing of initiation and advancement of nutrition support in relation to time of ICU admission in this population were unavailable due to the point-prevalence survey

methodology of SPROUT, which limited our interpretation of nutrition support provided beyond reported results.

Conclusions

Substantial variations exist in nutrition status and nutrition support in children with severe sepsis treated within a selected network of PICUs across different geographic regions. Severe undernutrition was independently associated with higher all-cause ICU mortality in children with severe sepsis. In contrast, severe overnutrition was independently associated with longer ICU LOS in survivors of pediatric severe sepsis. Future studies of critically ill children with severe sepsis should identify children at risk for malnutrition. Consideration of nutrition status at the time of severe sepsis diagnosis in children can serve to identify those patients at risk for poor outcomes, prompting specific interventions for these high-risk patients to potentially decrease mortality and length of hospital stay.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1.

Patient characteristics by nutrition status in children with severe sepsis.

	← Undernutrition →			Normal	← Overnutrition →			
BMI z-scores	**Severe z ≤ −3**	**Moderate −3 < z ≤ −2**	**Mild −2 < z ≤ −1**	**Normal −1 < z < +1**	**Mild +1 ≤ z < +2**	**Moderate +2 ≤ z < +3**	**Severe z ≥ +3**	**p-value**
N = 417 (%)	**40 (10)**	**34 (8)**	**52(13)**	**138 (33)**	**74 (18)**	**31 (7)**	**48 (12)**	
Anthropometry *								
Weight (kg)	6 (4, 20)	6 (4, 15)	9 (6, 21)	18 (8, 31)	20 (11, 50)	30 (11, 66)	18 (10, 43)	<0.001
Length (cm)	80 (61, 137)	66 (57, 109)	79 (60, 125)	110 (73, 135)	104 (75, 153)	122 (74, 153)	90 (64, 128)	<0.001
BMI z-score	−4.3 (−5.2, −3.7)	−2.4 (−2.6, −2.2)	−1.3 (−1.5, −1.1)	0.0 (−0.5, 0.4)	1.4 (1.2, 1.7)	2.4 (2.2, 2.6)	4.3 (3.6, 5.2)	<0.001
Age, months *	10 (4, 87)	11 (3, 66)	24 (4, 81)	66 (12, 120)	66 (12, 156)	84 (21, 156)	36 (12, 111)	<0.001
≤ 12mos, n (%)	22 (55)	19 (56)	25 (48)	44 (32)	23 (31)	7 (23)	15 (31)	0.003
Male sex, n (%)	23 (58)	15 (44)	30 (58)	72 (52)	36 (49)	17 (55)	26 (54)	0.87
Race/ethnicity, n (%)								
Hispanic	8 (20)	6 (18)	8 (15)	33 (24)	17 (23)	3 (10)	12 (25)	0.03
White	15 (38)	12 (35)	17 (33)	49 (36)	38 (51)	17 (55)	18 (38)	
Black	4 (10)	6 (18)	10 (19)	14 (10)	10 (14)	5 (16)	8 (17)	
Asian	11 (28)	7 (21)	12 (23)	23 (17)	4 (5)	2 (7)	1 (2)	
Other	2 (5)	3 (9)	5 (10)	19 (14)	5 (7)	4 (13)	9 (19)	
Co-morbidities, n (%)								
None	8 (20)	4 (12)	7 (14)	37 (27)	15 (20)	7 (23)	10 (21)	0.41
1	12 (30)	8 (24)	13 (25)	25 (18)	20 (27)	6 (19)	6 (13)	
2 or more	20 (50)	22 (65)	32 (62)	76 (55)	39 (53)	18 (58)	32 (67)	
Admission source, n (%)								
Emergency room	16 (40)	10 (29)	12 (23)	49 (36)	26 (35)	13 (42)	10 (21)	0.22
Other	24 (60)	24 (71)	40 (77)	89 (64)	48 (65)	18 (58)	38 (79)	
Admission status, n (%)								
Medical	21 (53)	23 (68)	38 (73)	100 (73)	57 (77)	25 (81)	39 (81)	0.06

	← Undernutrition →			Normal	← Overnutrition →			
BMI z-scores	**Severe z ≤ −3**	**Moderate −3 < z ≤ −2**	**Mild −2 < z ≤ −1**	**Normal −1 < z < +1**	**Mild +1 ≤ z < +2**	**Moderate +2 ≤ z < +3**	**Severe z ≥ +3**	**p-value**
N = 417 (%)	**40 (10)**	**34 (8)**	**52(13)**	**138 (33)**	**74 (18)**	**31 (7)**	**48 (12)**	
Surgical	19 (47)	11 (32)	14 (27)	38 (27)	17 (23)	6 (19)	9 (19)	
Surgery < 4 weeks, n (%)	8 (20)	10 (29)	7 (14)	23 (17)	14 (19)	7 (23)	14 (29)	0.32
Admission POPC, n (%)								0.64
Good	16 (40)	16 (47)	27 (52)	79 (57)	42 (57)	13 (42)	21 (44)	
Mild/Moderate	17 (43)	12 (35)	18 (35)	36 (26)	20 (27)	13 (42)	16 (33)	
Severe/Coma	7 (17)	6 (18)	7 (13)	23 (17)	12 (16)	5 (16)	11 (23)	
Admission PCPC								0.42
Normal	18 (45)	16 (47)	30 (58)	85 (62)	46 (62)	17 (55)	21 (44)	
Mild/Moderate	16 (40)	13 (38)	16 (31)	32 (23)	17 (23)	11 (35)	17 (35)	
Severe/Coma	6 (15)	5 (15)	6 (11)	21 (15)	11 (15)	3 (10)	10 (21)	
Primary infection, n (%)								0.22
Bloodstream	11 (27)	4 (12)	9 (17)	24 (17)	13 (18)	8 (26)	8 (17)	
GI/GU	7 (18)	5 (15)	4 (8)	18 (13)	7 (10)	2 (7)	7 (15)	
Respiratory	18 (45)	19 (56)	26 (50)	50 (36)	27 (37)	12 (39)	23 (48)	
Other	4 (10)	6 (18)	13 (25)	46 (33)	27 (36)	9 (29)	10 (21)	
Bacterial infection, n (%)	15 (38)	10 (29)	17 (33)	30 (22)	24 (32)	9 (29)	15 (31)	0.44
Viral infection, n (%)	5 (13)	8 (24)	9 (17)	27 (20)	18 (24)	9 (29)	12 (25)	0.59
Fungal infection, n (%)	4 (10)	2 (6)	9 (17)	19 (14)	8 (11)	5 (16)	8 (17)	0.70
PIM-3 risk of mortality *	3 (2, 6)	4 (2, 9)	4.0 (2, 10)	5 (2, 11)	4 (2, 9)	4 (3, 6)	5 (2, 11)	0.49
PELOD score *	10 (2, 11)	11 (2, 12)	10 (2, 12)	11 (2, 12)	11 (2, 20)	12 (11, 13)	11 (2, 12)	0.06

* median (interquartile range)

BMI = body mass index; POPC = pediatric overall performance category; PCPC = pediatric cerebral performance category; GI = gastrointestinal; GU = genitourinary; PIM = Pediatric Index of Mortality; PELOD = Pediatric Logistic Organ Dysfunction

Percentages are calculated per nutrition status in columns (column sums to 100%)

Table 2.

ICU interventions by nutrition status in children with severe sepsis.

	← Undernutrition →			Normal	← Overnutrition →			
BMI z-scores	**Severe z ≤ −3**	**Moderate −3 < z ≤ −2**	**Mild −2 < z ≤ −1**	**Normal −1 < z < +1**	**Mild +1 ≤ z < +2**	**Moderate +2 ≤ z < +3**	**Severe z ≥ +3**	**p-value**
N = 417 (%)	**40 (10)**	**34 (8)**	**52(13)**	**138 (33)**	**74 (18)**	**31 (7)**	**48 (12)**	
Mechanical ventilation (%)	30 (75)	26 (77)	32 (62)	96 (70)	52 (70)	25 (81)	35 (73)	0.58
Steroids (%)	14 (35)	11 (32)	13 (25)	62 (45)	38 (51)	14 (45)	27 (56)	0.02
GI prophylaxis (%)	29 (73)	23 (68)	42 (81)	113 (82)	55 (74)	26 (84)	41 (85)	0.32
Nutrition support (%)								0.50
None	4 (10)	2 (6)	8 (15)	28 (20)	11 (15)	9 (29)	8 (17)	
EN only	21 (53)	17 (50)	26 (50)	55 (40)	32 (43)	12 (39)	19 (40)	
PN only	9 (23)	13 (38)	12 (23)	36 (26)	24 (32)	5 (16)	13 (27)	
EN and PN	6 (15)	2 (5.9)	6 (12)	19 (14)	7 (10)	5 (16)	8 (17)	
Vasoactive infusions (%)								0.82
None	14 (35)	14 (41)	27 (52)	66 (48)	33 (45)	16 (52)	20 (42)	
1	9 (23)	9 (27)	11 (21)	30 (22)	20 (27)	9 (29)	14 (29)	
2	11 (28)	6 (18)	7 (14)	22 (16)	8 (11)	5 (16)	9 (19)	
≥ 3	6 (15)	5 (15)	7 (14)	20 (15)	13 (18)	1 (3)	5 (10)	

ICU = intensive care unit; BMI = body mass index; GI = gastrointestinal; EN = enteral nutrition; PN = parenteral nutrition

Percentages are calculated per nutrition status in columns (column sums to 100%)

Table 3.

Multivariable logistic regression model of variables associated with ICU mortality in children with severe sepsis.

Variables	Adjusted odds ratio	95% confidence intervals		p
BMI z-score				
Severe undernutrition	**3.03**	**1.20**	**7.67**	**0.02**
Moderate undernutrition	1.80	0.67	4.84	0.25
Mild undernutrition	0.87	0.33	2.26	0.77
Normal nutrition (reference)	.	.	.	.
Mild overnutrition	1.23	0.54	2.79	0.62
Moderate overnutrition	0.45	0.12	1.63	0.22
Severe overnutrition	1.07	0.41	2.79	0.89
Region				
North America (reference)	.	.	.	.
South America	0.37	0.11	1.24	0.11
Europe	1.03	0.39	2.73	0.95
Asia	**2.96**	**1.31**	**6.70**	**0.01**
Africa	2.18	0.29	16.30	0.45
Australia & New Zealand	6.48	0.91	46.28	0.06
PIM-3 risk of mortality	**1.05**	**1.02**	**1.07**	**<0.001**
PELOD score	**1.04**	**1.01**	**1.07**	**0.023**
PCPC at admission				
Normal (reference)	.	.	.	.
Mild/moderate	**2.08**	**1.08**	**3.97**	**0.028**
Severe/coma	2.33	0.99	5.50	0.054
Mechanical ventilation	**2.80**	**1.37**	**5.73**	**0.005**
Antifungal	**2.63**	**1.47**	**4.71**	**0.001**
Insulin use	**3.26**	**1.46**	**7.26**	**0.004**
Volume expanders				
None (reference)	.	.	.	.
Colloid only	0.73	0.21	2.52	0.62

Variables	Adjusted odds ratio	95% confidence intervals		p
Blood products only	**2.81**	**1.42**	**5.56**	**0.003**
Both colloid and blood products	**3.20**	**1.49**	**6.89**	**0.003**

Covariates were backwards selected with an alpha of 0.10 to enter and 0.05 to stay in the model.

ICU = intensive care unit; BMI = body mass index; PIM = Pediatric Index of Mortality; PELOD = Pediatric Logistic Organ Dysfunction; PCPC = pediatric cerebral performance category

Table 4.

Secondary outcomes by nutrition status in children with severe sepsis.

	← Undernutrition →			Normal	← Overnutrition →			
BMI z-scores	**Severe z ≤ −3**	**Moderate −3 < z ≤ −2**	**Mild −2 < z ≤ −1**	**Normal −1 < z < +1**	**Mild +1 ≤ z < +2**	**Moderate +2 ≤ z < +3**	**Severe z ≥ +3**	**p-value**
N = 417 (%)	**40 (10)**	**34 (8)**	**52 (13)**	**138 (33)**	**74 (18)**	**31 (7)**	**48 (12)**	
ICU LOS in survivors, days* (n=314)	10 (6, 20)	21 (9, 42)	10 (5, 33)	13 (5, 26)	14 (5, 31)	16 (7, 24)	17 (11, 60)	0.14
Hospital LOS in survivors, days* (n=314)	25 (13, 44)	30 (18, 72)	23 (12, 44)	25 (13, 48)	23 (11, 49)	25 (17, 72)	30 (17, 89)	0.70
NPMODS (%)	17 (43)	17 (50)	14 (27)	63 (46)	28 (38)	15 (48)	21 (44)	0.27
Delta POPC Change Score*								
Good at admission	1.9 ± 2.3	2.6 ± 2.3	1.8 ± 2.1	1.8 ± 2.0	1.5 ± 1.9	1.4 ± 2.0	1.8 ± 1.9	0.24
Mild/Mod at admission	0.3 ± 0.9	0.6 ± 0.7	0.3 ± 0.7	0.4 ± 0.8	0.7 ± 0.9	0.3 ± 0.8	0.5 ± 0.7	0.52
Severe/Coma at admission	0.4 ± 0.2	-0.1 ± 0.2	0.1 ± 0.3	0.1 ± 0.2	0.1 ± 0.2	0.1 ± 0.2	0.1 ± 0.2	0.21
Delta PCPC Change Score*								
Normal at admission	1.4 ± 1.8	2.1 ± 1.9	1.3 ± 1.7	1.4 ± 1.7	1.2 ± 1.7	1.1 ± 1.6	1.3 ± 1.6	0.30
Mild/Mod at admission	0.3 ± 0.7	0.4 ± 0.7	0.4 ± 0.6	0.4 ± 0.5	0.4 ± 0.7	0.3 ± 0.5	0.4 ± 0.6	0.86
Severe/Coma at admission	0.2 ± 0.1	-0.1 ± 0.1	0.0 ± 0.2	0.1 ± 0.1	0.0 ± 0.1	0	0.0 ± 0.1	0.12

*mean, SD

BMI = body mass index; ICU = intensive care unit; LOS = length of stay; NPMODS = new or progressive multiple organ dysfunction syndrome; POPC = pediatric overall performance category; PCPC = pediatric cerebral performance category

Percentages are calculated per nutrition status in columns (column sums to 100%)