

Assessment of Nutritional Support and its Correlation with Outcome of Critically Ill Children

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Abstract

Background: Malnutrition is a major challenge in caring for critically ill children. Therefore we aimed to assess the nutritional status in critically ill pediatrics.

Methods: This is a prospective observational study carried out on 180 children admitted into Pediatric Intensive Care Unit (PICU) of Menoufia University Hospital. Clinical examination performed including anthropometric measurement, screening for malnutrition risk using Pediatric Yorkhill Malnutrition Score (PYMS) and determination of disease severity by Pediatric Risk of Mortality score (PRISM). Nutritional feeding initiated 48 hours after admission and outcome parameters like mortality, duration of PICU stay and need for mechanical ventilation assessed in the patients groups.

Results: The mean age was 24.64 ± 3.78 months. Malnutrition on admission was prevalent in 31.1% (defined as Boy mass index (BMI) $< -2SD$ Z score (in >2 years) or weight (WT) /Length (L) $< -2SD$ Z score (in <2 years)). Malnutrition risk (defined by PYMS score ≥ 2) found in 80%. Need for mechanical ventilation, prolonged length of hospital stay and mortality were higher in patients with malnutrition risk (PYMS score ≥ 2) who fail to reach target caloric requirements (based on Schofield equation Wt/Ht) than in patients with malnutrition risk (PYMS score ≥ 2) who reached target caloric requirements.

Conclusion: Sufficient nutritional support is important in management of critically ill children to avoid negative impact on outcome.

Keywords: Children; Critically; Malnutrition; Nutrition; Outcome.

Abbreviations: BMI: Body mass index; GRV: Gastric Residual Volume; PICU: Pediatric Intensive Care Unit; PRISM: Pediatric Risk of Mortality score (PRISM); PYMS: Pediatric Yorkhill Malnutrition Score.

Introduction

Malnutrition and underfeeding are major obstacles in caring for critically ill children. Where malnutrition was significantly associated with high drawbacks, costs, and death [1]. Knowing of under nutrition in admitted children in hospitals has elevated in the last two decades [2]. The malnutrition prevalence in critically ill pediatrics is estimated to range from 6 to 51% [3].

Critical illness stress places significant metabolic demands on patient. Failure to accurately estimate and meet these demands can result in nutritional deterioration during illness [4].

In addition, the nutritional status on admission does not always related to actual nutritional risk that is the risk of successive disease related nutritional worsening [5]. Only some researches have assessed the undernutrition development in a pediatric population during hospital stays. These researches denote that nutritional status worsen in 5% to 27% of pediatrics after the hospital admission [6-7].

So it is an important to know the inpatient pediatrics at nutritional risk so that proper time and accurate nutrition interference and treatment policies may be fulfilled and nutrition worsening prevented to enhance outcomes of the health [8].

Pediatric Yorkhill Malnutrition Score (PYMS) is a five step Quick and easy to use score generated in Glasgow during 2008, responding to the national standards that recognized the significance of malnutrition screening for knowing children who are at malnutrition risk in order to assist with nutritional referral the five steps are: Measurement of BMI, History of new loss of weight, history of reduced intake for the past week, determination if the child nutritional status will be affected by the next status for the next week and calculation of total score [9].

There are many controversies in the support of the nutrition of the critically ill pediatrics, the supplementation of enteral feeding (EN) with parenteral nutrition (PN), and early versus late PN. There are a lot of doubts regarding EN supplementation with PN, understood as adding PN to children who receive inadequate or hypo caloric EN (trophic enteral input < 60% of the basal caloric input), and the accessible guide is not conclusive [10]. Also, the accurate time to add supplementary PN to a hypo caloric EN is still controversial [11]. So this research was done to assess the nutritional status in critically ill pediatrics and to evaluate the effect of applying proper nutritional support in PICU based on children's clinical status and on their outcome.

Materials and Methods

Study Design

This prospective observational research was carried out on 180 critically ill pediatrics were admitted into Pediatric Intensive Care Unit (PICU) of Menoufia university hospital from April 2018 to February 2019.

Study Population

Children were included who met the following criteria 1) age >1 month and <18 years and 2) length of PICU stay is more than 48 hours. Patients were classified into three groups regarding to the nutritional support route. The route of nutritional support was chosen according to the medical diseases, the stability of hemodynamics, and patients' tolerance to nutrition: Group (1): It included 60 children with functioning gastrointestinal tract (GIT) who had no contraindications to enteral feeding and were supplied by enteral nutrition (EN). Group 2: included 60 children with insufficient enteral feeding (average caloric delivery of EN is less than 30% of target and not more than 60% of target on day 7 of admission) and were supplied by supplementary parenteral nutrition with enteral nutrition to reach target calorie requirements with maintenance of enteral feeding. Group 3: included 60 children who had absolute contraindications to enteral feeding and were supplied by total parenteral nutrition (TPN).

Data Collection

The patients' demographic and clinical characteristics were listed on admission PICU sheet; these encompassed age, sex, history of complex chronic condition and diagnosis. Nutritional screening by Pediatric Yorkhill Malnutrition Score (PYMS) was done to detect children who are at nutritional risk and require nutritional supply (PYMS score ≥ 2 indicate malnutrition risk). Assessment of severity of disease by calculation of Pediatric risk of mortality score (PRISM) score within 24 hour of admission to PICU. Nutritional evaluation through: nutritional history, clinical examination, laboratory and anthropometry. The anthropometric measurements of these children were recorded upon admission; Weight was measured to the nearest 0.1 kg, and height was measured while lying head down in a neutral position with the legs extended at the knee and ankle using a non-stretch measuring tape. In children whose condition precluded the use of conventional measurement techniques (eg, those patients who are mechanically ventilated, on vasoactive drugs or with spasms) the four-point length measurement method is used by serial measurements from the vertex to the medial end of the clavicle, the lateral side of the shoulder to the anterior superior iliac spine, the anterior superior iliac spine to the lateral side of the knee joint, and the lateral side of the knee joint to the sole of the foot are then combined together to obtain the patient's height.

Malnutrition at admission is defined as body mass index (BMI) for age; BMI $< -2SD$ WHO Z-score growth charts (at >2 years) or weight-for-height WT/L $< -2SD$ WHO Z-score growth charts (in less than two years). Nutritional support was initiated 48 hours after PICU admission. Patients' target caloric requirements were calculated using the Schofield equation for weight and height without the stress factor.

Monitoring

For advancement of feeding supply aiming to reach target requirements on 7-10 day of admission, for development of electrolytes complications, sepsis occurrence or need for mechanical ventilation and for complications related to nutritional therapy as feeding intolerance (manifested by increased gastric residual volume (GRV), vomiting and abdominal distention).

Ethical Approval

All procedures done during the research were in agreement with the ethical standards of the Institutional Research Committee of Menoufia University. All children' parents gave their informed consent to participate in the study.

Statistical Analysis

Results were tabulated, and analyzed statistically by an IBM- compatible personal computer with the SPSS statistical package version 23. Two kinds of statistical analysis were performed: a) Description type e.g. Expressed in: number (no), percentage (%), mean (\bar{x}) and standard deviation (SD). b) Analysis kind for example; the Mann-Whitney test was used to compare quantitative parameters between two sets of non-normally distributed data, the ANOVA test was used to compare quantitative parameters between more than two sets of normally distributed data, and the Kruskal-Wallis test was used to compare quantitative parameters between more than two sets of normally distributed data. The chi-square test (χ^2) was used to examine the association between qualitative parameters. A P value < 0.05 was considered statistically significant.

Results

The baseline clinical and nutritional characteristics of studied groups on admission

Totally, 180 critically ill children admitted to the PICU included in this study categorized into 3 groups with mean age of admis-

sion was 24.64 month. The most common cause of admission was respiratory (40 %). Malnutrition on admission was prevalent in 31.1% of cases (defined as BMI<-2SD Z score (in > 2 years) or WT/L<-2SD Z score (in < 2 years). And malnutrition risk (defined by PYMS score ≥ 2) found in 80 % of cases which was higher in complementary PN group (p-value 0.013) (Table 1).

Variables	Enteral N group(no=60) No (%)	Complementary PN group (no=60) No (%)	Parenteral N group (no=60) No (%)	Total(no=180) No (%)	Test of significance	p-value
Age (month): Mean \pm SD	24.13 \pm 3.24	23.79 \pm 1.9	24.36 \pm 5.7	24.64 \pm 3.78	f= 1.81	0.833
sex: Male Female	36(60.0) 24 (40.0)	28 (46.7) 32 (53.3)	34 (56.7) 26 (43.3)	98 (54.4) 82 (45.6)	$\chi^2 = 1.16$	0.559
Complex chronic condition (CCC)**	30 (50.0)	42 (70.0)	22 (36.7)	94 (52.2)	6.77	0.034
Diagnosis: Chest	26 (42.3)	26 (42.3)	20 (33.3)	72 (40.0)	0.83	0.659
CNS	10 (16.7)	14 (23.3)	12 (20.0)	36 (20.0)	0.42	0.812
Renal	10 (16.7)	4 (6.7)	4 (6.7)	18 (10.0)	2.22	0.329
Cardiac	6 (10.0)	6 (10.0)	0	12 (6.7)	3.42	0.181
GIT	2 (3.3)	2 (3.3)	6 (10.0)	10 (5.6)	1.69	0.429
Sepsis	4 (6.7)	4 (6.7)	0	8 (4.4)	2.09	0.351
Surgical	0	0	8 (13.3)	8 (4.4)	3.37	0.15
Endocrine	2 (3.3)	2 (3.3)	0	4 (2.2)	1.02	0.600
Toxicology	0	0	4 (6.7)	4(2.2)	4.09	0.129
Hepatic	0	0	2 (3.3)	2 (1.1)	2.02	0.364
Nutritional	0	2 (3.3)	0	2 (1.1)	2.02	0.364
Oncology	0	0	2 (3.3)	2 (1.1)	2.02	0.364
Post Arrest	0	0	2 (3.3)	2 (1.1)	2.02	0.364
Weight for age: < -2 >+2 Normal	20 (33.3) 2 (3.3) 38 (63.3)	26 (43.3) 0 34 (56.7)	20 (33.3) 0 40 (66.7)	66 (36.7) 2 (1.1) 112 (62.2)	280	0.593
Nutritional assessment -Malnutrition (WHO z score) -PYMS score No malnutrition risk (0-1) malnutrition Risk (≥ 2)	16 (26.7) 22 (36.7) 38 (63.3)	24 (40.0) 10 (16.7) 50 (83.4)	16 (26.7) 4 (6.7) 56 (93.4)	56 (31.1) 36 (20.0) 144 (80.0)	2.09 $\chi^2=8.75$	0.719 0.013

PRISM score: Mean± SD	7.07±4.71	7.63±7.48	6.27±8.03	6.99±6.84		
< 10	40 (66.7)	42 (70)	46 (76.7)	128 (71.1)	K=0.30	0.743
≥ 10	20 (33.3)	18 (30)	14 (23.3)	52 (28.9)	χ ² =0.76	0.685

Table 1: Clinical and Nutritional characteristics of studied groups on admission (n=90).

**Complex chronic condition (CCC): refers to any medical condition that can be reasonably expected to last at least 12 months and to involve either several different organ systems.

SD = standard deviation, χ² = chi-square test, K= Kruskal-Wallis test, F=ANOVA test

Clinical and Nutritional Characteristics among Studied Groups After One Week

Nutritional support started after 48 hours in the three groups, after one week PYMS score was repeated with no increase in malnutrition risk indicating that no further nutritional deterioration occurred. Target caloric requirements were reached in 36.7% of cases which can explain why weight and malnutrition rate did not change after one week (Table 2).

Variables	Enteral(no=60) No (%)	Complementary PN (no=60) No (%)	Parenteral N (no=60) No (%)	Total (no=180) No (%)	χ ²	p-value
Weight for age: < -2 >+2 Normal	20 (33.3) 2 (3.3) 38 (63.3)	26 (43.3) 0 34 (56.7)	20 (33.3) 0 40 (66.7)	66 (36.7) 2 (1.1) 112 (62.2)	280	0.593
Nutritional assessment -Malnutrition (WHO z score) -PYMS score No malnutrition risk (0-1) malnutrition Risk (≥ 2)	16 (26.7) 22 (36.7) 38 (63.3)	24 (40.0) 10 (16.7) 50 (83.4)	16 (26.7) 4 (6.7) 56 (93.4)	56 (31.1) 36 (20.0) 144 (80.0)	2.09 χ ² =8.75	0.013*
Caloric need Reached Not reached	20 (33.3) 40 (66.7)	10 (16.7) 50 (83.3)	36 (60.0) 24 (40.0)	66 (36.7) 114 (63.3)	12.3 4	0.002*
Metabolic complication **	8 (13.3)	0	0	8 (4.4)	8.37	0.015*
Mechanical ventilation: Yes No	10 (16.7) 50 (83.3)	14 (23.3) 46 (76.7)	0 60(100.0)	24 (13.3) 156 (86.7)	7.50	0.024*
Sepsis: septic not septic	10 (83.3) 50 (83.3)	8 (13.3) 52 (86.7)	6 (10.0) 54 (90.0)	24 (13.3) 156 (86.7)	0.58	0.749
Mortality	0	4 (6.7)	6 (10.0)	10 (5.6)	11.3 3	0.079

Table 2: Clinical and Nutritional characteristics among studied groups after one week.

* Significant ** metabolic complication: include 3 cases with hypocalcaemia and hypokalemia, one case with hypernatremia

Clinical and Nutritional Outcomes among Studied Groups on Discharge

Upon discharge; evaluation of clinical outcomes in the patients over the study period showed that mechanical ventilation was required for 31.1% of all admitted cases. The mean duration of PICU length of stay was (19.90 ±17.59 day). Complementary parenteral nutrition group had significantly prolonged duration of mechanical ventilation and PICU length of stay than the two other groups (p-value 0.018 and 0.001 respectively). The overall mortality rate was 28.9% without significant relation with route of nutritional support (Table 3).

As regard adequacy of nutritional support; only 73.3% of children in enteral feeding group and 83.3% of complementary parenteral nutrition achieve target calories on PICU discharge in contrast to total parenteral nutrition group as all children reach target calories on PICU discharge. (Table 3).

On discharge, decreased weight (compared to patient weight on admission) was more prevalent in EN group while increased weight (compared to patient weight on admission) was common in complementary PN group and PN group without affection of overall malnutrition rate upon discharge as no further deterioration of nutritional state occurred during PICU stay (Table 3).

Variables	Enteral N group (no=60) No (%)	Complementary PN group (no=60) No (%)	Parenteral N group (no=60) No (%)	Total (no=180) No (%)	Test of significance	p-value
Need for MV Duration of MV (days): Mean± SD	12 6.00±7.97	24 24.07±25.78	20 6.58±3.73	56 (31.1) 13.43±18.74	$\chi^2=2.90$ K=4.55	0.018*
PICU stay /day: Mean± SD	13.37±7.37	29.13±25.58	17.20±10.07	19.90±17.59	$\chi^2=7.51$	0.001*
Adequacy of calories from nutrition therapy	44 (73.3)	50 (83.3)	60 (100.0)	154 (85.6)	$\chi^2=8.81$	0.012*
Wt. on discharge**: Decreased Increased The same	16 (26.7) 4 (6.7) 40 (66.7)	2 (3.3) 20 (33.3) 38 (63.3)	0 14 (23.3) 46 (76.7)	18 (10.0) 38 (21.1) 124 (68.9)	18.24	0.001*
Malnutrition (WHO z score)	16 (26.7)	24 (40.0)	16 (26.7)	56 (31.1)	2.09	0.719
Mortality:	16 (26.7)	22 (36.7)	14 (23.3)	52 (28.9)	$\chi^2=1.41$	0.495

Table 3: Clinical and Nutritional outcomes among studied groups on discharge

*Significant, **Wt. on discharge: compared to admission weight, MV: Mechanical ventilation

Comparison between Outcome Parameters among the Studied Groups

Regarding comparison between outcome parameters and route of nutritional support shown in (Table 4).

Variables		Outcome of EN		Mann-Whitney test	p-value	Outcome of complementary PN		Mann-Whitney test	p-value	Outcome of PN		Mann-Whitney test	p-value
		Survived (no=44) Mean±SD	Died (n=16) Mean±SD			Survived (no=38) Mean±SD	Died (n=22) Mean±SD			Survived (no=46) Mean±SD	Died (n=14) Mean±SD		
PYMS classifications: No risk (<2) Risk (≥ 2)		No (%)	No (%)	χ^2	0.012	No (%)	No (%)	χ^2	0.397	No (%)	No (%)	χ^2	0.419
		22 (50.0) 22 (50.0)	0 16 (100.0)			6.32	8 (21.1) 30(78.9)			2 (9.1) 20 (90.9)	0.72		
Mechanical Ventilation Need	Yes No	0 44 (100.0)	16 (100.0)	30.00	<0.001	6 (15.8) 32(84.2)	8 (36.4) 14 (63.6)	1.65	0.199	6 (13.0) 40 (87.0)	12 (85.7) 2 (14.3)	13.0	<0.001**
Sepsis:	Present Absent	2 (4.5) 42 (95.5)	8 (50.0) 8 (50.0)	8.73	0.003	2 (5.3) 36 (94.7)	6 (27.3) 16 (72.7)	2.92	0.087	4 (8.7) 42 (91.3)	2 (14.3) 12 (85.7)	0.19	0.666
Metabolic complication:	Present Absent	2 (4.5) 42 (95.5)	6 (37.5) 10 (62.5)	5.51	0.019	0 38 (100.0)	0 22 (100.0)	NA	NA	0 46 (100.0)	0 14 (100.0)	NA	NA
Chronic diseases:	Present Absent	22 (50.0) 22 (50.0)	8 (50.0) 8 (50.0)	NA	NA	26 (68.4) 12 (31.6)	16 (72.7) 6 (27.3)	0.06	0.804	18 (39.1) 28 (60.9)	4 (28.6) 10 (71.7)	0.09	0.763
PRISM score:		5.82±4.19	10.50±4.57	2.64	0.013	5.53±4.62	11.27±10.03	2.15	0.040	4.48±6.16	12.14±10.96	2.38	0.024*

Table 4: Comparison between outcome parameters among the studied groups

Relationship between Adequacy of Nutritional Support in Malnutrition Risk Patients and Outcome Parameters

Effect of adequacy of nutritional support on outcome rather than nutritional support route, we found that there were significant increase in using of mechanical ventilation and hospital stay length in malnutrition risk patients who not reached target calories than reached cases (P value, 0.001 and 0.009 respectively). Also, there was highly significant increase in prevalence of metabolic complication and in mortality among malnutrition risk who didn't achieve target calories than target calories reached cases (P value < 0.001) and there wasn't significant difference regarding sepsis. Otherwise; all children with no malnutrition risk achieve target calories except one child needed mechanical ventilation and other one case died, these are summarized in (Table 5).

Outcome parameters	Target calories reach in malnutrition risk(n=144)		Test of significance	P-value
	Reached (n=112) No (%)	Not reached (n=32) No (%)		
Mechanical Ventilation	32 (28.6)	24 (75.0)	$\chi^2=11.29$	0.001*
Sepsis	20 (17.6)	4 (12.5)	$\chi^2=0.26$	0.612
Metabolic complication	0 (0.0%)	8 (25.0)	$\chi^2=14.82$	<0.001**
Length of hospital stay(days):	10.88±10.20	24.78±19.99	U=2.67	0.009*
Mortality	22 (19.6)	28 (87.5)	$\chi^2=25.28$	<0.001**

Table 5: Relationship between adequacy of nutritional support in malnutrition risk patients and outcome parameters.

*Significant ** highly significant

Discussion

Malnutrition is a major problem for unfavorable results in critically ill children. The prevalence of malnutrition among seriously ill children is ranging from 6 to 51% [3]. Also critically ill children are liable to more nutritional worsening during their disease course due to illness or barriers to nutrient delivery in the intensive care unit [12].

So, nutritional assessment of these patients is therefore of great significance [12]. In our study malnutrition on admission was prevalent in 31.1% of cases which was in agreement with Pollack et al [13] who found rate of malnutrition is ranging from 32% to 37%.

All included children in our study were screened for malnutrition risk by PYMS score, PYMS score is an important malnutrition screening tool for children as proved by Gerasimidis et al [14] and Lestari et al [15] who showed that malnutrition risk by PYMS score was 86.4% with 95.7% sensitivity than other pediatric malnutrition scores. Malnutrition risk was found in 80 % of the studied cases.

Notably, mean PRISM score among studied cases was 6.99 ± 6.84 with no significant difference between the studied groups indicating that severity of illness was the same in the three groups on admission (PRISM calculated in 24 hr of PICU admission) before initiating nutritional supply and this was proven by the absence of a significant difference in mortality between the groups despite the different methods of nutritional support.

Complex chronic condition (CCC) was prevalent in 52.2 % of all admitted cases which was in agreement with Edwards et al [16] in which 53 % of PICU admissions had a CCC, also Typpo et al [17] found that 52% of admitted children to 28 pediatric intensive care units had a chronic disease.

In our results, 73.3% of children in enteral nutrition group and 83.3% in complementary parenteral nutrition group achieve target calories on PICU discharge (calculated based on Schofield equation) compared to 100% of patients in parenteral nutrition group. Similarly, Nicholas et al [18] noted that enteral feeding was associated with a significantly higher rate of failure to achieve target intake versus TPN.

Restriction of fluid, intolerance for feeding, and EN interruption are among the causes responsible for energy deprivation in the PICU [19]. These were also the main causes for failure to achieve target in EN group in our study.

Failure to deliver nutrients may result in significant low weight for age at discharge from the PICU [20]. Decreased weight on discharge compared to admission weight was observed in 10% of our patients and was more prevalent in EN group which was the least group in achieving target calories

The mean duration of PICU length of stay in our study was long (19.90 ± 17.59 day) with significantly longer duration in complementary PN group (29.13 ± 25.58 day) this can be explained as more than half of patients 52% had CCC with higher prevalence in complementary PN group which was 70 %. Similarly, Edwards et al [16] demonstrated that children with CCC had significant risk for prolonged LOS and mortality in the pediatric intensive care unit exceeds that predicted by commonly used disease severity models. Similarly in Bagri et al (3) malnutrition was accompanied with an increased risk of acquiring infections and longer length of stay, and the malnutrition prevalence in the research was 51.2% with an overall mortality rate of 38.8%. More children with severe malnutrition had prolonged periods in the intensive care unit (>7 days).

In our current study, mechanical ventilation was required for 31.1% of all admitted cases with no significant difference between the studied groups. This came in line with previous studies that reported frequency of utilizing mechanical ventilation varies from 24-60% of all Pediatric Intensive Care Units (PICUs)[21].

The underweight is associated with a higher need for mechanical ventilation than normal [22]; this can explain that mechanical ventilation was needed in 75% of patients with malnutrition risk who did not reach target requirements (p-value= 0.001).

The average duration of mechanical ventilation was significantly longer in complementary parenteral nutrition group (p-value= 0.018) which can be explained as 70% of studied group admitted with chronic condition and 40 % of them were malnourished on admission.

This was also reported in Grippa et al [23] as duration of mechanical ventilation was significantly related with malnutrition as Patients with malnutrition have a longer duration of mechanical ventilation. Similarly in Bagri et al (3) malnutrition was associated with duration of mechanical ventilation (>7 days).

In the current study, the mortality rate was 28.9% which came in line with Daynia et al [24] and Grippa et al [23] with mortality rate 27.1% and 27.8% respectively. Reported mortality rates in developing countries range between 9.8 and 35%, and these patients often arrive late due to many complications leading to death in spite of the best available treatment [25]. Our finding found that 87.5% of patients with malnutrition risk who failed to reach target calories died in comparison to death of 19.6% of patients with malnutrition risk who achieved target calories (p-value< 0.001).

An association between suboptimal macronutrients intake and outcome was demonstrated also in Mehta et al [26] study where children taking less than a third of the prescribed energy on average during the first 10 days after admission to the PICU had significantly higher odds of death compared with the rest and were significant even after adjusting for disease severity scores, feeding days, and PICU location.

In Bechard et al [12] study odds of 60-day mortality were higher in underweight mechanically ventilated children on PICU after adjusting for severity of illness. Also Prince et al [27] observe weight-for-age at admission as an independent risk factor for mortality. This explain our results that all died cases in enteral and parenteral nutrition groups and 91% of cases in complementary parenteral nutrition group were malnourished and/or had high malnutrition risk on PICU admission.

Sepsis in our study had no relation to the route of nutrition support; this finding was agreed with Nicholas et al [18] as there was no evidence to confirm an advantage of EN over TPN in terms of septic morbidity.

The optimum route of nutritional support depends on patient condition and tolerance to help the patient overcome the stress of critical illness. Sufficient nutritional support whether enteral, complementary parenteral or parenteral is important in the management of critically ill children as failure in achievement of goal requirements has negative impact on their outcome.

Authors' Contributions

NS: Took part in database design, data collection, and writing, reporting of search and corresponding author.

AE: Designed the study, compiled the results, and obtained ethics permission.

DE: Assisted with the study design, interpretation of analysis.

HE: Database design, data collection, writing, statistical analysis and presentation of results.

ZO: Took part in database design, data collection, reviewed the manuscript.

MG: Assisted with the study design, interpretation of analysis.

Disclosure

The authors declare no financial or other conflicts of interest related to this work.

Ethical Approval

All procedures performed in the study were in accordance with the ethical standards of the institutional research committee.

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Conflict of Interest

None

Informed Consent

Informed consent was obtained from all individual participants included in the study or their legally authorized representatives.

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