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**Original article**

**Impact of early enteral nutrition therapy on morbimortality reduction in a Pediatric Intensive Care Unit: A systematic review<sup>☆</sup>**

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A B S T R A C T

**Objective:** To assess the impact of early introduction of enteral nutrition therapy on morbidity and mortality reduction in a pediatric intensive care unit.

**Methods:** A search was performed in the literature of the last 10 years in English, with the target population of individuals aged 1 month to 18 years admitted to pediatric intensive care units in the PubMed, Lilacs and Embase databases using the keywords: Critical Care, Nutritional Support and Nutrition Disorders or Malnutrition.

**Results:** Despite advances in the quality of clinical care, the prevalence of malnutrition in hospitalized children remains unchanged in the last 20 years (15-30%) and has implications for the time of admission, course of illness and morbidity. Malnutrition is common and is often poorly recognized and therefore, untreated. Nutritional therapy is an essential part in the treatment of severely ill pediatric patients who have hypercatabolic protein state, which can be minimized with an effective nutritional treatment plan. In this study, we reviewed publications which have shown that there is still a paucity of randomized and controlled studies with good statistical treatment in relation to enteral nutritional therapy with outcomes related to morbidity and mortality. The current guidelines for nutritional therapy in these patients are largely based on expert opinion and data extrapolated from adult studies and studies in healthy children.

<sup>☆</sup> Study conducted at Instituto da Criança do Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo, SP, Brazil.

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*Conclusion:* The scientific evidence on the use of enteral nutrition therapy in improving the development of critically ill pediatric patients is still scarce and further studies are needed focusing on it, and better guidelines must be formulated.

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## O impacto da introdução precoce de terapia nutricional enteral na redução da morbimortalidade na Terapia Intensiva Pediátrica: uma revisão sistemática

### R E S U M O

*Objetivo:* Avaliar o impacto da introdução precoce de terapia nutricional enteral na redução da morbimortalidade em unidades de terapia intensiva pediátrica.

*Métodos:* Pesquisa bibliográfica nas bases de dados PubMed, Lilacs e Embase dos últimos 10 anos, em língua inglesa e população-alvo de indivíduos de 1 mês de idade a 18 anos, internados em unidades de terapia intensiva pediátrica, usando as palavras-chave: Critical Care, Nutritional Support e Nutrition Disorders or Malnutrition.

*Resultados:* Apesar dos avanços na qualidade dos cuidados clínicos, a prevalência de desnutrição em crianças hospitalizadas permanece imutável nos últimos 20 anos (15-30%) e tem implicações no tempo de internação, curso da doença e morbidade. A desnutrição é comum e é com frequência pouco reconhecida e então, não tratada. A terapia nutricional é parte essencial no tratamento dos pacientes pediátricos gravemente doentes que apresentam estado de hipercatabolismo proteico, que pode ser minimizado com um plano terapêutico nutricional efetivo. Neste estudo, foram revisadas publicações que mostraram que ainda há uma escassez de pesquisas controladas e randomizadas com bom tratamento estatístico em relação à terapia nutricional enteral com desfecho relacionado à morbimortalidade. As diretrizes atuais para terapia nutricional desses pacientes são amplamente baseadas na opinião de *experts* e em dados extrapolados de estudos em adultos, bem como de estudos realizados em crianças saudáveis.

*Conclusão:* A evidência científica na utilização de terapia nutricional enteral na melhora da evolução dos pacientes pediátricos gravemente doentes ainda é escassa e são necessários novos estudos focados nisso, além de diretrizes mais bem-formuladas.

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## Introduction

Malnutrition is a continuous process that begins with inadequate nutrient intake followed by functional and metabolic changes that lead to loss of body composition, resulting in growth and muscle strength impairment, as well as increasing the risk of aspiration pneumonia with a negative impact on brain growth and development, which may increase the length of hospital stay and hospital costs.<sup>1-7</sup> It should be emphasized that malnutrition is a disease with adverse consequences on body composition and function and not just a change in the body appearance and shape.<sup>5</sup>

Approximately 15-55% of patients admitted to any hospital have malnutrition, especially those critically-ill admitted at pediatric intensive care units (ICUs), with a mortality rate of 9-38%. A part of them arrive at the hospital in an already malnourished state; however, most of them develop malnutrition during hospitalization due to hypercatabolism caused by sepsis, shock and inflammation, which rapidly leads to decreased lean body mass, impaired function of vital organs

and destruction of immune processes, consuming as much as 30-50% more energy from the individual.<sup>3,5,7-14</sup>

Nutrition is an important part of the treatment of critically-ill children. The onset of early nutritional therapy and an appropriate therapeutic plan can reverse hypercatabolism. Adequate nutritional support focused on the patient's nutritional risk, especially when he or she cannot be fed orally, aims to improve resistance to infections, promote wound healing and reduce morbidity and mortality of critically-ill malnourished patients, preventing loss of muscle protein, as that survival of critically-ill patients is inversely proportional to the loss of lean mass.<sup>4,6-8,14-16</sup>

Enteral nutrition is always the first option when there is no gastrointestinal involvement, as it inhibits the intestinal mucosa atrophy, reducing the incidence of bacterial translocation, in addition to being less expensive. However, if this is not a possibility, parenteral nutrition should be used as a source of macro and micronutrient uptake or as supplement to the enteral nutrition.<sup>4,10</sup>

In order to treat these patients, it is desirable to design an appropriate treatment plan, considering the indication

of nutritional therapy, side effects and available feeding techniques. One should take into consideration the patient's clinical history, physical and laboratory assessment (especially micronutrient levels such as zinc, calcium and magnesium), use of drugs and alcohol, gastrointestinal function, including dentition, swallowing and absorption.<sup>3,14</sup>

The follow-up of this treatment plan should emphasize aspects of the consequences of malnutrition, such as decreased lean body mass, fatigue and depression, food intake and vital functions.<sup>3,14</sup> The results of this plan and its follow-up should be communicated to all professionals involved, including those who treat the patient in future consultations after discharge or those who will treat the patient after hospital transference.<sup>4</sup>

## Methods

A research was performed by two independent reviewers, in the PubMed, Embase and Lilacs databases, using the following key words: Critical Care, Nutritional Support and Nutrition Disorders or Malnutrition. The filters were articles published in the last 10 years, in the English language and the target population aged from 1 month of to 18 years. Letters, editorials and commentary articles were excluded. A total of 261 articles were found.

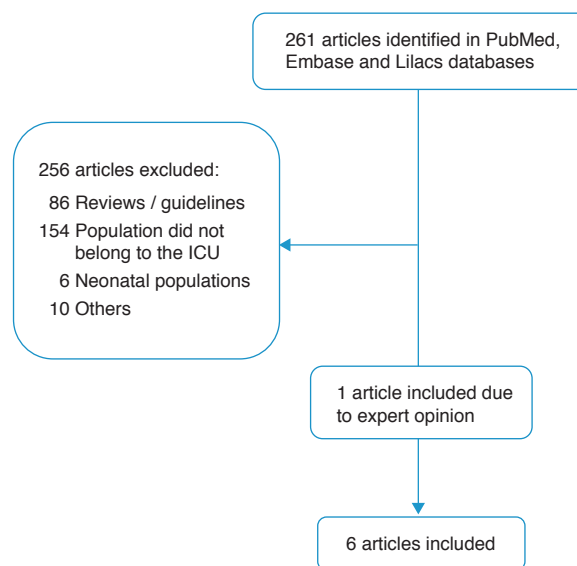
At a later phase, the two reviewers independently selected the articles based on titles and abstracts, excluding those that were reviews and of which populations were not related to the theme and thus, five articles were included. At another moment, the two reviewers met with a third researcher (expert), who suggested the inclusion of another article that was considered relevant to the study.

Article selection was directed to meet the questions structured in the PICO methodology (Population, Intervention, Comparison and Outcome). The population consisted of critically-ill pediatric patients admitted to tertiary intensive care units, excluding the neonatal period; the intervention included morbimortality, evaluating the nutritional therapeutic plan defined during hospitalization in the ICU; the comparison was made with other studies in which there was no therapeutic plan for enteral nutritional therapy for critically-ill patients; and finally, the outcome sought to minimize morbimortality with enteral nutritional therapy. The degree of recommendation and level of evidence used in this study results are based on the model proposed by the BMA<sup>17</sup> (2008).

## Results

Article selection was performed as shown in Figure 1. Of the six selected articles, two were carried out in Burn Units and four in General Pediatric ICUs. The data are shown in Table 1.

Gottschlich et al.<sup>18</sup> studied 77 children admitted to a Burn Unit with a mean of  $52.5 \pm 2.3$  of burned body surface area (BSA), mean age  $9.3 \pm 0.5$  years, who were randomized to receive enteral nutrition within 24 hours or after 48 hours of hospitalization. The groups were homogenous in terms of percentage of burned BSA, age, sex, presence of inhalation



**Fig. 1 – Flowchart of article selection.**

injury, need for mechanical ventilation and weight at admission and there was no statistically significant difference regarding mortality (11% vs. 8%,  $p = 0.9999$ ) between them. Regarding morbidity, nutritional assessment was performed, which showed no significant weight loss in both groups and no patient had gastric aspiration.

Khorasani et al.<sup>19</sup> studied 688 children with a mean burned BSA  $> 20\%$  who were randomized to receive early-onset enteral nutrition in the first 3-6 hours post-injury or after 48 hours. The groups were homogenous according to age, weight, percentage of burned BSA, cause of burn, time of debridement start, antibiotic therapy and number of grafts. In the group of early-onset enteral feeding, lower mortality (8.5% vs. 12%) was observed, as well as shorter hospital stay ( $12.6 \pm 1.3 \times 16.4 \pm 3.7$  days) and less weight loss in relation to admission (3% x 9%) ( $p < 0.05$  for all variables).

Briassoulis et al.<sup>20</sup> randomized 25 patients to receive intervention (I) formula, which consisted of enteral nutrition supplemented with glutamine, arginine, antioxidants, omega 3 fatty acids, and another 25 patients to receive the control (C) formula, which consisted of enteral nutrition for critically-ill children modified for age. The groups were similar regarding demographic and clinical characteristics, as well as nutritional indices on the first day. There was no difference in mortality (12% Group I vs. 4% Group C,  $p > 0.05$ ) and length of hospital stay ( $13 \times 11.5$  days,  $p > 0.05$ ).

Van Waadendurg et al.<sup>21</sup> randomized 10 children with acute respiratory failure requiring mechanical ventilation to receive a standard formula and other 10 children to receive formula enriched with calories and protein. The duration of mechanical ventilation and length of ICU stay did not change significantly between groups ( $5.5 \pm 0.7 \times 7.1 \pm 2.2$  days and  $9.0 \pm 2.7$  vs.  $6.7 \pm 0.7$  days, respectively,  $p > 0.05$ ). The intake of calories and protein was higher in the intervention group ( $112 \times 82$  kcal/kg/day and  $2.8 \times 1.5$  g/kg/day;  $p < 0.01$ ), as well as nitrogen balance ( $297 \times 123$  mg/kg/day,  $p < 0.05$ ).

**Table 1 – Research data.**

Author	Year	Population	Intervention	Study design	Results	Level of evidence	Degree of recommendation
Gottschlich et al. <sup>19</sup>	2002	72 children > 3 years old admitted in a Pediatric Intensive Care Unit in the first 24 hours after the burn, with > 25% burned body surface area (BSA)	After admission, patients were randomized to receive enteral feeding within the first 24 hours of hospitalization or conventional treatment with enteral feeding after 48 hours of hospital admission	Prospective cohort study randomized to evaluate the effects of hormonal, nutritional and clinical as well as the adverse effects of early enteral nutrition in pediatric patients with more than 25% of burned body surface area. 36 patients were randomized in each group	There was no difference in nitrogen balance in both groups, but the group receiving diet after 48 hours showed caloric deficit in the first and second weeks post-injury ( $p < 0.0001$ and $p = 0.022$ , respectively). There was no difference in the level of inflammation, infection, diarrhea, time of hospitalization and mortality	1B	A
Briassoulis et al. <sup>20</sup>	2005	50 patients admitted to a pediatric ICU aged 7 months to 18 years, on mechanical ventilation for at least 5 days and enteral feeding started within the first 12 hours of admission	During the first 12 hours, patients were randomized to receive the intervention formula (I) which consisted of enteral nutrition supplemented with glutamine, arginine, antioxidants, omega 3 fatty acids or the conventional formula (C) consisting of enteral nutrition for critically-ill children modified to age	Controlled, double-blind, randomized clinical trial to evaluate nitrogen balance, nutritional and clinical indices, and antioxidant catalysts in two groups of pediatric patients receiving immunologically enhanced diet and conventional early-onset enteral nutrition. 25 patients received the intervention formula (I) and 25 patients received the control (C) formula	The intake of protein, calories and nitrogen was equal between groups. Nutritional indices and antioxidant catalysts improved during nutritional support. All patients had negative nitrogen balance (NB) during the first 24 hours of admission; 24 hours after admission, NB became positive in 40% of patients in group C and in group I it was positive on day 5 in 64% of patients. These differences are significant for both groups, although the mean of NB became positive on day 5 in group I ( $p < 0.001$ ), the mean remained negative in group C ( $p < 0.001$ ). There was no difference in mortality and length of stay	1B	B

(Continues)

Table 1 – Research data. (Continuation)

Author	Year	Population	Intervention	Study design	Results	Level of evidence	Degree of recommendation
Waardendurg et al. <sup>15</sup>	2009	20 infants between 4 weeks and 12 months of age with acute respiratory failure secondary to RSV Bronchiolitis + need for mechanical ventilation	Infants were randomized within 24 hours of admission to receive standard formula or formula enriched with calories and protein for 5 days	Double-blind controlled study comparing the nutritional effects between formula enriched with calories and protein (2.6 g prot. and 100 kcal/100 mL and standard infant formula (1.4 g prot., and 67 kcal/100 mL). 10 patients were randomized in each group	There was no difference in duration of mechanical ventilation and length of ICU stay. The intake of calories and protein was higher in the intervention group (112 × 82 kcal/kg/day and 2.8 × 1.5 g/kg/day - p < 0.01) as well as nitrogen balance (297 × 123 mg/kg/day - p < 0.05)	1B	A
Khorasani et al. <sup>21</sup>	2010	688 children aged 1 month to 12 years old with more than 10% of burned body surface area without concomitant chronic diseases, admitted in a Pediatric Burn Unit	The children were randomized on the day of admission to receive conventional intravenous resuscitation and introduction of enteral nutrition after 48 hours or enteral resuscitation and early-onset enteral nutrition through a nasogastric tube within 3 to 6 hours after injury	Prospective cohort study randomized to evaluate the efficacy and safety of early enteral nutrition in pediatric burn victims. 366 patients were randomized to receive early-onset enteral feeding and 322 patients to receive enteral nutrition within 48 hours of admission	The mortality in the group receiving early enteral diet was lower (8.5% vs. 12%, p < 0.05), length of hospital stay was shorter (12.6 ± 1.3 vs. 16.4 ± 3.7 days, p < 0.05) and there was less weight loss at the discharge when compared to the admission (3%. 9%, p < 0.05)	1B	A
Zamberlan et al. <sup>7</sup>	2011	90 patients admitted to a tertiary pediatric ICU, aged 1-18 years, with a hospital stay longer than 7 days in the period of 1 year	Description of the restrictions, monitoring and complications associated with Nutritional Therapy in tertiary pediatric ICU	Descriptive, prospective study. Anthropometric measurements were performed (weight, height / estimated length or height, arm circumference and triceps skinfold thickness. Calculation of daily macronutrient and micronutrient intake	After 1 week of hospitalization, the mean amount of calories offered was 82 kcal/kg/day (± 47 kcal/kg/day) and protein intake was 2.7 g/kg/day (± 1.9 g/kg/day). Parenteral nutrition was used in 10% of patients. There was a significant difference in z-score of arm circumference for age (p < 0.001) and mean triceps skinfold thickness (p < 0.001) between the first day and the seventh day of hospitalization	2C	B

(Continues)

**Table 1 – Research data. (Continuation)**

Author	Year	Population	Intervention	Study design	Results	Level of evidence	Degree of recommendation
Metha et al. <sup>14</sup>	2010	117 patients from newborns to 36 years admitted during the 4 weeks of the study in a tertiary intensive care unit with a minimum stay of 24 hours	After admission, data were collected from patients who had received at least 24 hours EN on: time of start of the diet, route of administration, EN intolerance and any interruption of the administration of EN	Prospective cohort observational study to identify risk factors associated with preventable EN interruption in critically-ill patients admitted to a multidisciplinary tertiary ICU	68% of patients received EN for at least 24 hours during hospitalization. Among these patients, 75% started EN until the third day of hospitalization. EN was interrupted in 30% of patients with a mean of 3.7 times per patient. Avoidable interruptions were more frequent in patients < 1 year (p < 0.006). Patients with longer hospital stay and greater delay starting EN showed more interruptions (p < 0.01). Patients with preventable interruptions were 3x more likely to use PN and needed significantly more time to reach their caloric goals	2B	B

EN, enteral nutrition.



Zamberlam et al.<sup>10</sup> demonstrated that 80% of patients received enteral nutrition (complete polymeric diet according to the age, when the administration route was gastric and oligomeric diet when the administration route was post-pyloric) and 35% received oral feeding. After a week of hospitalization, the mean amount of calories offered was 82 kcal/kg/day ( $\pm$  47 kcal/kg/day) and the amount of protein offered was 2.7 g/kg/day ( $\pm$  1.9 g/kg/day). Parenteral nutrition was used in 10% of patients. There was a significant difference in z-score of arm circumference for age ( $p < 0.001$ ) and mean triceps skinfold thickness ( $p < 0.001$ ) between the first day and the seventh day of hospitalization.

Metha et al.<sup>22</sup> demonstrated that 68% of the patients received enteral nutrition (EN) for at least 24 hours during hospitalization. Among these patients, 75% started EN until the third day of hospitalization. EN was interrupted in 24 patients (30%) with a mean of 3.7 times per patient (1483 hours without receiving EN). The interruption was considered avoidable in 58% of the episodes in 15 patients. Avoidable interruptions were more frequent in patients younger than 1 year ( $p < 0.006$ ). Patients with longer hospital stays and greater delay starting EN showed more interruptions ( $p < 0.01$ ). Patients with avoidable interruptions were three times more likely to use parenteral nutrition and needed significantly more time to reach their caloric goals.

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## Discussion

Despite advances in the quality of clinical care, the prevalence of malnutrition in hospitalized children has remained unchanged over the past 20 years and has implications for the time of hospitalization, course of disease and morbidity. Malnutrition is common among those children, and is often poorly recognized and therefore, goes untreated. The reported prevalence of malnutrition in pediatric hospitals is around 15-30% of patients. Children admitted to the ICU are at risk of change in the nutritional status and anthropometric measures over time.<sup>1,22</sup> The energy deficit accumulated in the first days of hospitalization in critically-ill patients may have an important role in clinical outcomes and length of ICU stay.<sup>23</sup>

Nutritional therapy is an essential part in the treatment of critically-ill pediatric patients and inadequate nutrition therapy is associated with increased morbidity and mortality. This is particularly true in patients with prolonged ICU length of stay. The majority of patients with a defined therapeutic plan can achieve the established calorie-protein and micronutrient goals within the first 5 days of hospitalization with early-onset enteral nutritional therapy (within 72 hours).

Critically-ill patients may have reduced energy demand for several reasons, such as the use of sedation and analgesic agents that decrease the basal metabolic rate, the energy required for activity is minimal, especially if the patient is on mechanical ventilation and patients during severe metabolic stress are in a catabolic state and are not growing.<sup>7,24,25</sup> However, most critically-ill children show a protein hypercatabolic state, with high consumption of endogenous reserves, which can be minimized with an effective therapeutic plan.

Enteral nutritional therapy is supported as it reduces intestinal mucosa atrophy and decrease intestinal permeability, with consequent reduction in the incidence of bacterial translocation and septic complications, as well as being of lower cost and more physiological.<sup>11</sup> There are three major obstacles to providing nutritional supply to critically-ill pediatric patients: fluid restriction, gastrointestinal intolerance and diet interruptions caused by procedures or after the performance of tests.<sup>7</sup>

In the study by Mehta et al.<sup>22</sup> carried out in a tertiary pediatric ICU to identify risk factors associated with avoidable interruptions of enteral nutrition, it was shown that despite the early onset of diet infusion, it was interrupted numerous times, some in avoidable situations, which led to a three-fold increase in the use of parenteral nutrition and significant delay in achieving the caloric goals. The study had no statistical power to detect results such as infectious complications, long-term morbidity and mortality.<sup>22</sup>

In patients with gastrointestinal intolerance, trophic feeding may be instituted, which is also called minimal enteral nutrition, that is, to supply small volumes of diet (10-15 mL/kg/day) with no intention of providing adequate calories for growth, but enough to exert trophic effects on the intestinal mucosa improving milk tolerance, reducing sepsis and length of hospital stay.<sup>26,27</sup>

In this study, literature articles published in the past 10 years were systematically reviewed, totaling six original articles, showing that studies in children are still less than expected when compared with the number of publications in adults. There is a paucity of randomized controlled studies performed in children, mainly regarding enteral nutritional therapy with morbimortality-related outcomes. Current guidelines for nutrition therapy in critically-ill pediatric patients are largely based on the opinion of experts and data extrapolated from studies carried out in adults, as well as studies in healthy children.<sup>7</sup>

According to a literature review carried out on adults by Zaloga et al.,<sup>28</sup> the majority of prospective controlled studies support the idea that early-onset enteral nutritional therapy improves clinical outcomes in critically-ill patients. Using an evidence-based approach, the recommendation for the use of early enteral nutrition in these patients is a grade A recommendation.<sup>17</sup>

Evidence-based studies for enteral nutritional therapy in pediatrics that were reviewed in this study mention the level of evidence 1B, which are randomized controlled trials with narrow confidence interval, the level of evidence 2B, which are cohort studies including randomized clinical trials of lower quality, and 2C, which is the observation of therapeutic results. This result shows that further randomized studies with best scientific treatment in pediatric patients are lacking.<sup>17</sup>

However, the selected studies may suggest a higher degree of recommendation for early-onset enteral nutrition therapy in reducing morbidity and mortality, helping to construct guidelines, flowcharts and standards for pediatric intensive care with secondary and mainly tertiary care level.

Thus, studies that prioritize results from established therapeutic plans, such as the studies by Mehta et al.,<sup>29</sup> Briassoulis et al.<sup>24</sup> and Taylor et al.<sup>30</sup> or that identify

well-defined effects regarding the progression of nutritional assessment, such as that by Zamberlam et al.<sup>10</sup> can improve the content of guidelines and flowcharts. After establishing a treatment plan, it is very important to follow strict guidelines provided to the entire multidisciplinary team of intensive care, so there is no inadvertent interruption and worsening in morbimortality (Mehta et al.<sup>22</sup>).

## Conclusion

The scientific evidence for the use of enteral nutritional therapy in improving the evolution of critically-ill pediatric patients is still scarce. Further studies with better design and statistical analysis are needed, according to the evaluation of the systematic review. In addition, guidelines for prioritizing pre-established therapeutic plans may be better formulated.

## Conflicts of interest

The authors declare no conflicts of interest.

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