

## Review Paper:

# A Practical Approach to the Nutritional Management of Mechanically Ventilated Children: A Review



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## ABSTRACT

**Context:** Malnutrition is associated with a longer duration of mechanical ventilation and an increased risk of healthcare-acquired infections in critically ill children who are mechanically ventilated.

**Objectives:** Therefore, nutritional therapy plays a critical role in the initiation and duration of mechanical ventilation and clinical outcomes in such patients.

**Data Sources:** This review was conducted by searching the Web of Science, Scopus, Embase, and Medline databases. A combination of related mesh terms and keywords was used to find the relevant articles. Finally, we screened search results through titles and abstracts and related articles were enrolled in the review process. We tried to address all aspects of nutritional management of mechanically ventilated critically ill children.

**Results:** Energy demand in mechanically ventilated children is a controversial issue and Indirect Calorimetry (IC) is the recommended method to measure resting energy expenditure; however, in the absence of IC, predictive equations may be used. A minimum protein intake of 1.5 g/kg/day and a balanced diet in other macronutrients ratio, including carbohydrates and lipids could be appropriate for mechanically ventilated children. However, the administration of major substrates should be based upon the patient's metabolism regarding the nature and phase of the illness. Moreover, individualized nutritional supplementation is among the treatment strategies in these children.

**Conclusions:** The optimum individualized nutrition support of mechanically ventilated children is considered a major therapeutic strategy and an essential aspect of their medical management. Further large population-based studies are required to provide appropriate feeding protocols for preventing nutritional inadequacy in such patients.

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## 1. Context

Critical illnesses and mechanical ventilation are associated with anorexia, inability to oral intake, catabolism state, altered gut absorption, and malnutrition (undernutrition/overnutrition) (1, 2). The aforementioned issues predispose patients to poor clinical outcomes (including delayed wound healing, the loss of lean body mass, nutrition deficits, and prolonged recovery), as well as increased morbidity and mortality rates (1, 2). Particularly, critically ill mechanically ventilated children are at higher risks for malnutrition, compared to adults. This is because of their higher relative energy requirements and lower energy reserves (3, 4).

Malnutrition involves up to 30%-45% of children admitted to the Pediatric Intensive Care Unit (PICU); it is associated with prolonged mechanical ventilation and increased risk of healthcare-acquired infections (5-8). The nutritional status of critically ill pediatric patients upon their PICU admission time is considered as a major predictor of the initiation and duration of stay on mechanical ventilation, in addition to its related complications (9). The optimal nutrition support of such patients, particularly adequate protein and energy intake is associated with improved clinical outcomes and decreased mortality and morbidity rates in mechanically ventilated children (7, 10).

As per previous studies, critically ill mechanically ventilated children are considered as a nutritionally high-risk group; thus, the nutrition support of such patients is an essential therapeutic strategy in the PICU (1, 11). However, consistent and convincing evidence on various features of the nutrition support of critically ill mechanically ventilated children is scarce (1, 10). Therefore, this study was performed to describe the main aspects of nutritional management in mechanically ventilated PICU patients.

## 2. Evidence Acquisition

The current review aimed to provide updates on the different aspects of the nutrition support of critically ill mechanically ventilated pediatric patients. Accordingly, we searched the relevant publications in the Web of Science, Cochrane, National Library of Medicine's PubMed, Embase, and Scopus databases using the combination of keywords and MeSH terms, including "nutrition", "nutritional support", "nutrition therapy", "nutritional status", "critical illness", "critically ill children", "mechanically ventilated children", and "Pediatric Acute Respiratory Distress Syndrome (PARDS)". Relevant publications of all

types were identified. We limited the search to English language articles published since January 1<sup>st</sup>, 2005.

All Search results were screened through abstracts and titles. Primarily, 1566 records were identified. Additionally, to ensure study identification, two researchers cross-checked the reference lists of the relevant search results. Secondly, 6 additional studies were retrieved. The duplicate records were also removed. For the quality assessment of the relevant search records, we used "the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials" and "the risk of bias in observational studies of exposures" tools (12, 13).

Finally, disagreements were resolved through discussion in a focus group panel, including 3 clinical nutritionists and 2 pediatricians who were PICU subspecialists. After eligibility screening and quality assessment, 79 articles and guidelines were included in the review process.

## 3. Results

### Stepwise nutrition support

Similar to all PICU patients, the nutritional management of mechanically ventilated children consisted of 3 main steps, including baseline nutritional assessment, intervention, and monitoring (14). A primary nutritional assessment and routine monitoring as well as a nutrition care program for all critically ill mechanically ventilated pediatric patients is of particular importance since they are a nutritionally high-risk group (1, 11, 14). Anthropometric assessments, including body weight, height/length, body mass index, and Mid-upper Arm Circumference (MAC) should be performed at the baseline and routinely with a preset schedule (15). Alterations in weight/MAC may be correlated with cumulative suboptimal protein and energy delivery during PICU stay (16). Further, the routine measurement of nitrogen balance should be performed in PICU patients to modify diet in negative nitrogen balance situations (15). Additionally, measuring prealbumin as a major indicator of visceral protein pool may be helpful for such patients. However, clinicians should interpret the prealbumin level per the patient's illness severity and inflammation status (15).

Finally, some further routine assessments, such as complete blood count, liver function test, lipid profile, blood glucose, C-reactive protein, phosphorus, magnesium, and calcium levels may be indicated according to the underlying disease and baseline nutritional status (14, 15). The key aspects of the nutritional management

**Table 1.** Key aspects of the nutritional management of mechanically ventilated critically ill children

Variables	Outcomes
Nutritional assessment	Anthropometric parameters
	Nitrogen balance
	Pre-albumin
	CRP
Possible potential laboratory abnormalities	MAC Body weights Height/lengths  Complete blood count Glucose Phosphorus Lipid profile AST ALT Direct bilirubin GGT
Energy requirement	Indirect calorimetry; if possible Achieving delivery of at least two-thirds of the prescribed daily energy requirement by the end of the first week
Macronutrients requirements	Protein intake of $\geq 1.5$ g/kg/d Lipid and Carbohydrate intake: Based upon metabolism in the dependence of phase and nature of the acute illness
Micronutrients requirements	Routinely in RDAs amounts Assessment of possible potential micronutrients deficiencies and treatment of documented deficiencies: Vitamin B1 (Thiamine) Vitamin B2 (Riboflavin) Vitamin B6(Pyridoxine) Vitamin A (Beta-carotene/Retinol)

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MAC: Mid-upper arm circumference; CRP: C-reactive protein; AST: Aspartate aminotransferase; ALT: Alanine amino transaminase; GGT:  $\gamma$ -glutamyl transpeptidase; PICU: Pediatric Intensive Care Unit; RDA: Recommended Dietary Allowance.

of mechanically ventilated PICU patients are presented in [Table 1](#).

**Mechanically ventilated children: nutrition support route**

Enteral nutrition (EN) is the preferred route of nutrition support for all critically ill children (including mechanically ventilated patients) with a functioning gastrointestinal tract (17). EN keeps regular bowel movements; therefore, it reduces bacterial translocation, decreases the production of toxic cytokines, prevents mucosal atrophy, and maintains the epithelial barrier integrity (18).

The prioritization of Early EN (EEN) is defined as initiating EN within 48-72 h of PICU admission. EEN may provide several beneficial effects, including better tolerance of EN, higher odds of adequate intake achievement, shorter hospital and PICU stay, and reduced morbidity and mortality rates (19-26). For example, a study explored 500 mechanically ventilated children; patients who received less than 1/3 of the calorie goal during the first 10 days of PICU admission presented a higher mortality rate (7). Therefore, EEN should be initiated imme-

diately after the hemodynamic stability in the absence of medical contraindication to EN (27). Delayed EN initiating is commonly detected in such patients, i.e. associated with inadequate nutrition support (28).

Furthermore, several factors can disrupt EN delivery in critically ill children. Feed intolerance, several situations of gastrointestinal tract dysfunctions, prolonged fasting periods before procedures, failure to reinstitute nutrient intake timely after procedures, mechanical issues with feeding tubes, and restricted fluid intake are the most frequent impediments to EN (29-31). These barriers to EN may decrease nutrient delivery and lead to poor clinical outcomes in mechanically ventilated pediatric patients. Therefore, minimizing the aforementioned barriers in the PICU is of particular importance.

If EN fails to meet nutritional requirements, supplemental/total Parenteral Nutrition (PN) should be used in mechanically ventilated PICU patients (17). Moreover, Van Puffelen et al. reported better outcomes of withholding PN in the first week of PICU admission, compared to initiating supplemental PN within the first 24 h, in their clinical trial (32). Therefore, it is recommend-

**Table 2.** Nutrition support route in mechanically ventilated children

Route	Recommendations
EN	<p>EN is the preferred mode of nutrient delivery unless it is contraindicated.</p> <p>A stepwise algorithmic approach is recommended.</p> <p>It is essential to select the best site and optimum method for EN delivery.</p> <p>Continuous vs. intermittent gastric feeding: data are insufficient to make recommendations.</p>
PN	<p>PN should be initiated if EN is contraindicated.</p> <p>Supplemental PN should be initiated if EN is insufficient.</p>

EN: Enteral Nutrition; PN: Parenteral Nutrition.

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ed that PN not be started within the first 24 h of PICU admission (15). Table 2 illustrates the nutrition support route-related recommendations.

### Energy, macronutrients, and micronutrients requirements

The accurate estimation of energy requirements is crucial to prevent the under/overfeeding of patients during critical illnesses. Accurately measured energy expenditure in adult and pediatric critically ill patients is of particular significance (17, 33, 34).

According to previous studies, underfeeding contributes to nutritional deprivation, leading to poor clinical outcomes. For example, undernutrition-induced endogenous protein breakdown may lead to the loss of lean body mass (including the respiratory, cardiac, & skeletal muscles) and immunosuppression; accordingly, it may predispose the patient to delayed ventilator support weaning, nosocomial infections acquisition, and delayed wound healing (27, 35). On the other hand, overfeeding provides some deleterious consequences, including electrolyte imbalance, increased carbon dioxide production, respiratory and cardiovascular systems overload, delayed ventilator support weaning, and increased duration of PICU stay (15, 36-38).

Metabolic state in mechanically ventilated critically ill children is unpredictable; some of them present with a hypermetabolic state and most of them demonstrate lower energy expenditure, compared to their healthy counterparts. This declined energy expenditure may be due to the sedation, non-functioning respiratory system, the transient absence of growth, and activity reduction. Therefore, energy requirement estimation would be difficult and complex (39, 40). Using predictive equations (i.e. World Health Organization/Schofield/Food Agriculture Organization/United Nations University equations) would be inaccurate and may under/overestimate the REE (17, 41). According to the literature, Indirect Calo-

rimetry (IC) is identified as the gold standard to provide an accurate bedside measurement of REE in critically ill children (41-43). Given the inaccuracy of estimating energy needs by predictive equations and negative outcomes of under and overfeeding, PICU nutritional guidelines emphasize accurate and personalized energy requirement measurement, using IC (17).

However, applying IC in most centers and PICUs is cumbersome, as IC is only available in 14% of PICUs (44). Therefore, in the absence of IC, various predictive equations can be employed to measure the REE in such patients (41).

Another study reported that REE in PICU patients can be measured using VCO<sub>2</sub> values alone ( $REE = \frac{1}{4} 5.5 * VCO_2 (L/min) * 1440$ ) (45). Ventilators can measure VCO<sub>2</sub> (based on the instantaneous flow); thus, clinicians can calculate the REE from ventilator-derived VCO<sub>2</sub> in mechanically ventilated children weighing  $\geq 15$  kg (46).

Following REE estimation, macronutrient administration, including carbohydrates, proteins, and lipids should be performed regarding the phase and nature of the patient's illness (15, 40).

The critical illness period is associated with an increased protein requirement due to the catabolic phase; this is developed to support the production of immune-related and acute-phase proteins, as well as tissue repair. For instance, protein requirements can be increased by 100% in severe sepsis, and by 25% even in mild stresses (47).

According to the studies performed in the mechanically ventilated adult population, protein intake is independently crucial for clinical outcomes improvement. Therefore, it should be considered as a separate nutritional goal by clinicians (1). Adequate protein delivery is associated with a shorter duration of mechanical ventilation, lower mortality rate, and higher 60-day survival,

even in subjects with inadequate energy intake (48). PICU patients are a high-risk group for depleting protein reserves which may lead to increased morbidity and mortality rates (7, 49). Especially, mechanical ventilation exacerbates protein catabolism and may contribute to negative nitrogen balance (50, 51). Thus, meeting the protein requirements of critically ill, children especially the mechanically ventilated ones is critical. On the other hand, excessive protein intake should be avoided, because it can lead to some adverse clinical outcomes, such as azotemia, metabolic acidosis, and neurologic dysfunction (52, 53). The ASPEN guideline recommended that a minimum of 1.5 gr/kg of body weight (kg/day) of protein should be considered in the nutritional management of all critically ill pediatric patients (15). Particularly, the protein requirement for mechanically ventilated infants and young pediatric patients with critical illnesses is estimated to be 2.5-3 g/kg/d (54, 55). Additionally, concurrent sufficient carbohydrate and lipid delivery increase protein synthesis and turnover (56, 57).

Marta Botran et al. demonstrated that the standard enteral diets provide insufficient amounts of protein for the majority of pediatric patients with critical illnesses. Moreover, using the enteral protein supplementations presents several desirable consequences, including improved biochemical parameters of protein metabolism, decreased protein hyper-catabolism, and improved recovery without producing any adverse effects in such patients (54). Similarly, this anabolic response was observed in critically ill children/infants who received high protein diets or protein supplementation in Keshen's (58) and Van Waardenburg's studies (59). These data emphasize the critical role of protein delivery in the successful nutritional management of PICU patients. However, there is inadequate evidence to support the routine administration of high amounts of protein in all categories of children with critical illnesses; an accurate assessment of protein status is required (60). Prealbumin and albumin plasma/serum concentrations are not reliable markers to assess the protein status. This is because they are affected by several factors, including trauma, renal or liver diseases, fluid status, inflammation, and infection (61). Thus, nitrogen balance measurement is more sensitive to the acute changes of protein status in pediatric patients who are critically ill (61). As protein requirements are provided, carbohydrates and lipids, as the sources of energy are required for protein synthesis and meeting total energy expenditure (62).

In children with ARDS, traditional feeds consist of 40%-50% carbohydrates and <30% lipids. However, some

studies evaluated different formulations with high lipid and low carbohydrate evaluated. As a result, it may be associated with decreased production of CO<sub>2</sub>, in comparison to higher carbohydrate formulations, contributing to lower mechanical ventilation and ICU stay days (63). However, Hasan M. et al. argued that a higher fat-to-carbohydrate ratio was not related to decreased mechanical ventilation duration and further ventilator-free days (64). According to the PICU guidelines, a balance of carbohydrates and lipid ratio, as well as providing enough energy is suggested for mechanically ventilated critically ill children (17). However, there is a lack of evidence in this field and further cohort and clinical trials are required.

Similar to all critically ill children, mechanically ventilated patients should receive the RDA amounts of micronutrients and routinely be assessed for potential deficiencies (17). Finally, children with critical illnesses are at a higher risk of vitamin deficiencies (including vitamin A(beta-carotene/retinol), vitamin B1(thiamine), vitamin B2(riboflavin), and vitamin B6(pyridoxine)) concerning their underlying disease, nutritional status upon the PICU admission time, and metabolic status (65, 66).

### Immunonutrition

Most pediatric patients with critical illnesses are at increased risk of compromised immunity. Immunosuppression is associated with an increased risk of infection acquisition and susceptibility to early hyper-inflammation status (67, 68). Thereby, immunonutrition support for improving immune system function and regulating inflammatory responses may be beneficial in such patients (69). These substances/supplementations include several antioxidants, glutamine, arginine, vitamin D (ergocalciferol/cholecalciferol), omega-3 fatty acids, metoclopramide, zinc, and selenium (62, 70-75).

Administering omega-3 fatty acids in critically ill children and particularly in PARDS may present several beneficial effects. Such advantages include up-regulating the production of pro-inflammatory eicosanoids, increasing the synthesis of anti-inflammatory lipid mediators (e.g., resolvins & protectins), and reducing the chemotaxis (76). Moreover, omega-3 fatty acids may lead to decreased pro-inflammatory cytokines, reactive oxygen species, and the expression of adhesion molecules (76). The aforementioned effects may contribute to a decrease in leukocyte binding as well as the activation and significant reduction of inflammatory markers (27, 76). The results of a meta-analysis by Dushianthan A et al. demonstrated that omega-3 fatty acids had no beneficial effects on clinical outcomes in ARDS adult

patients (77). However, Briassoulis G et al. concluded that omega-3 fatty acids and glutamine supplementation positively impacted the lipid profile of critically ill children (78). However, they detected no effects of the aforementioned supplementation on the ventilator dependency time and mortality rate (78). Evidence for routine omega-3 fatty acids supplementation in critically ill ventilated children is limited; therefore, further studies are needed to investigate the exact indications of supplementation in this group.

Arginine is a conditionally essential amino acid with several critical roles in various metabolic processes in human health and even diseases. Such health conditions include the detoxification of ammonia in the urea cycle, the synthesis of creatine and polyamines, the regulation of immune function, the production of Nitric Oxide (NO), and the release of anabolic hormones (79-81).

Previous studies reported low arginine plasma concentrations in adults and children with critical illnesses (82). In critical illness states, inflammation is related to higher cortisol levels and lower insulin concentrations which contribute to alternations in plasma arginine level (83). In critically ill children with sepsis and burns, and increased arginine breakdown as well as unchanged de novo synthesis of arginine were reported; subsequently, they resulted in negative arginine balance in such situations. Thus, the increased breakdown of arginine was associated with the higher synthesis of NO and increased oxidation (84, 85). However, there is insufficient data on the possible beneficial effects of arginine in critically ill children. Therefore, further clinical trials are required to provide strong recommendations. Similar to arginine, glutamine is a conditionally essential amino acid that becomes crucial in some critical conditions, such as sepsis, major trauma, or surgery (27, 86, 87).

Most critically ill patients, including the pediatric population, have low plasma glutamine concentrations, i.e. correlated with increased risk of multiple organ failure and mortality rate (88). Further studies are required concerning glutamine administration in mechanically ventilated critically ill children; however; this plasma glutamine depletion is the rationale for glutamine supplementation in PICU patients.

Vitamin D is considered as an immunonutrient that crucially influences the immune system cell functions, such as macrophages, lymphocytes, epithelial and T-helper 2 cells (89). Vitamin D deficiency is a major predisposing factor for muscle loss, cardiovascular diseases, immune dysfunction, impaired glucose metabo-

lism, and compromised pulmonary function (90-93). It is reported that 30%-70% of PICU patients suffer from vitamin D deficiency (94). Furthermore, vitamin D deficiency is associated with increased illness severity, vasopressor administration, and mechanical ventilation requirements in critically ill children (94). Moreover, vitamin D insufficiency/deficiency may lead to an increased risk of respiratory infections acquisition (95).

Vitamin D deficiency is related to decreased vitamin D receptor expression, contributing to impaired micro-organism clearance and uncontrolled inflammation; subsequently, such conditions may lead to lung damage and impaired oxygenation (96). In a study on critically ill children, low vitamin D levels were associated with increased sepsis rate; however, there was no statistically significant association between vitamin D concentrations and mortality rate, duration of PICU stay, and mechanical ventilation duration (97). Furthermore, Rippel C et al. documented that hypovitaminosis D was prevalent in PICU patients; it was associated with hypocalcemia and an increased necessity for calcium replacement particularly in the cardiac population (98). However, there was no association between vitamin D status and survival or PICU duration (98).

Finally, immunonutrition substances provide various potentially beneficial effects; however, some studies demonstrated that immunonutrition presents no beneficial effect on inflammatory and immune responses (99, 100). Thus, further clinical trials are required to find the exact indications, contraindications, and recommended dose of aforementioned supplementations in mechanically ventilated children with critical illnesses.

#### 4. Conclusion

Mechanically ventilated critically ill children constitute a nutritionally high-risk group. Therefore, a reasonable stepwise nutrition care program is necessary for this respect. Optimum and individualized nutrition support of these children is considered a major therapeutic strategy.

IC is strongly recommended to calculate their energy requirement; however, in the absence of IC, predictive equations should be used. Administering major substrates should be based on the patient's metabolism according to the phase of the illness. Immunonutrition substances present various potentially beneficial effects; however, further studies, especially randomized clinical trials are required to find the accurate indications of such supplementations.

## Ethical Considerations

### Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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### Authors' contributions

All authors equally contributed to preparing this article.

### Conflicts of interest

The authors declared no conflict of interest.

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