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A Comprehensive Protocol for Safe and Effective Enteral Feeding in Critically Ill Pediatric Patients

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Abstract

Background: Nutritional support in the Pediatric Intensive Care Unit (PICU) is critical for promoting recovery and reducing complications in critically ill children. Although guidelines exist, variability in Enteral Nutrition (EN) practices underscores the need for standardized protocols tailored to the unique needs of PICU patients. This study aimed to develop a standardized enteral feeding protocol for PICU patients, informed by current evidence and expert consensus, to improve feeding tolerance and clinical outcomes.

Methods: A two-phase study was conducted. Phase 1 involved a systematic review of global guidelines and evidence-based practices for EN in PICUs to identify key variables in EN delivery. In Phase 2, a multidisciplinary panel of PICU experts, including nutritionists and pediatric intensivists, used a structured focus group approach to develop a consensus on feeding initiation, volume advancement, prokinetic use, and complication management.

Results: The resulting protocol recommends initiating EN within 24 hours for hemodynamically stable patients, with gradual, weight-based volume advancement tailored to patient tolerance. Prokinetic agents (metoclopramide, domperidone, and erythromycin) were incorporated to improve feeding tolerance; and guidelines for managing potential complications, such as refeeding syndrome, gastrointestinal issues, and electrolyte imbalances, were established.

Conclusion: This protocol provides a comprehensive, evidence-based framework for EN in PICUs, offering structured guidance to support the nutritional needs of critically ill pediatric patients. While rigorous development ensures relevance and adaptability, further clinical evaluation is necessary to assess its impact across diverse PICU settings.

Key Words: Critically ill children, Enteral nutrition, Feeding protocol, Nutrition support, Pediatric critical care, PICU, Prokinetics.

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1- INTRODUCTION

Undernutrition is a prevalent issue among critically ill children admitted to Pediatric Intensive Care Units (PICUs) and is closely linked to adverse clinical outcomes, underscoring the role of nutritional support as a critical therapeutic strategy (1). During the acute phase of critical illness, Enteral Nutrition (EN) is essential for delivering sufficient energy and nutrients to support cellular function and counteract catabolic processes. EN is widely preferred for critically ill children due to its benefits in maintaining gut integrity, enhancing immune function, and reducing bacterial translocation risk (2).

Evidence from large observational studies has suggested that early initiation of EN, with a goal of meeting at least 60% of energy and protein needs within the first week of PICU admission, may improve survival rates (3). However, numerous barriers exist in the effective delivery of EN in PICU settings. Global surveys of healthcare providers, including nurses, physicians, and dietitians, have identified challenges such as fasting for procedures, inadequate education on EN, competing clinical priorities, and delays in achieving small bowel access (4). Common issues include delays in EN initiation, slow escalation of feeding rates, frequent interruptions, and challenges in reaching caloric targets. Such interruptions often lead to insufficient caloric intake, which can negatively impact clinical outcomes, though many disruptions are preventable (5).

Meeting nutritional requirements in the PICU remains challenging due to illness severity, comorbidities, and procedural interruptions (6). Recent recommendations from the European Society for Pediatric and Neonatal Intensive Care (ESPNIC) provide targeted EN guidelines for specific patient populations; however, uncertainties remain regarding optimal feeding progression, especially in vulnerable groups (7).

Despite international guidelines advocating early EN initiation after ICU admission, practices and definitions of "early EN" vary significantly worldwide. Moreover, there is limited consensus on indications for trophic feeding and management strategies for comorbid conditions (8, 9). Although several feeding protocols exist in PICUs (10-12), their lack of standardization and the diversity of practices across institutions highlight the need for a unified approach.

This study addresses this gap by designing the first enteral nutrition protocol specifically for the PICU in Akbar Hospital in Mashhad, Iran. Developed through consensus among a multidisciplinary team of nutritionists, pediatricians, and ICU professionals, this protocol is tailored to address the unique challenges and healthcare context of our setting. By establishing clear guidelines on the initiation, progression, and management of common EN complications, this protocol aims to standardize care, potentially serving as a model for similar PICUs in Iran and the surrounding region.

2- MATERIALS AND METHODS

This study was conducted in two phases to develop a standardized EN protocol for PICUs. In the first phase, a systematic review of the existing literature identified evidence-based practices related to EN in PICU patients. In the second phase, a consensus process with a multidisciplinary panel of clinical experts was employed to design a tailored EN protocol for PICU settings.

a) Phase 1: Systematic Review of the Existing Guidelines to Identify Key Variables for Enteral Nutrition in PICU Patients

In Phase 1, a structured systematic review was conducted to examine current global guidelines and review articles on nutritional support—specifically EN—for critically ill pediatric patients in PICUs. The review aimed to identify key variables and evidence-based recommendations critical to EN practices for this patient population.

The search strategy employed Medical Subject Headings (MeSH) leading to terms such as "energy requirements," "enteral nutrition," "nutrition assessment," "nutritional deficiency," "nutrition monitoring," "diet therapy," "critical care," "critical illness," "intensive care enteral," "feeding algorithms," and "Pediatric Intensive Care Units." These terms helped retrieve guidelines, protocols, and systematic reviews from reputable sources, focusing on evidence-based EN practices that could be adapted for our PICU protocol.

A total of 187 results were identified using the specified key terms, out of which five were deemed directly relevant to our work after evaluation. Despite the significance of this issue, no specific algorithm has been accepted globally thus far. Our review findings indicate that implementing an algorithm will notably improve the adequacy of energy delivery and reduce the time required to meet energy and protein intake goals in critically ill children. However, more studies are essential to comprehensively assess the outcomes of different algorithm implementations in critically ill pediatric patients.

b) Phase 2: Expert Panel Discussion and Consensus Process Using a Focus Group

In Phase 2, a consensus process was conducted using a focus group approach to adapt and localize the findings from Phase 1. The expert panel consisted of clinical nutritionists and pediatric intensivists, all with substantial expertise in pediatric critical care. The focus group method was chosen to facilitate open discussion, encourage diverse viewpoints, and promote collaborative problem-solving on complex clinical issues.

Focus groups are structured sessions designed to gather detailed insights and facilitate in-depth discussion among participants. In this context, the focus group allowed panelists to openly share their perspectives on each of the parameters identified in Phase 1, contributing to a well-rounded consensus. As suggested in a prior study, fitting focus groups within qualitative research approaches in the field of medical education can lead to more valid findings (13).

During the first round, experts provided feedback on each of the EN parameters. Their responses were compiled and redistributed to the group for further review. Parameters that received unanimous agreement were accepted as final recommendations.

For parameters where differences in opinion remained, individual perspectives were presented for further deliberation. Through additional discussion rounds, the panelists reached a consensus, ensuring that the final protocol recommendations were both evidence-based and practically applicable in the PICU setting**.**

3- RESULTS

The EN algorithm developed in this study provides a structured approach to managing nutritional support for PICU patients. Key components include indications for EN, contraindications (absolute and relative), detailed protocols for initiating and advancing feeding, and criteria for discontinuing EN and transitioning to oral feeding. Our protocol offers practical and evidence-based guidance tailored to the unique needs of critically ill pediatric patients.

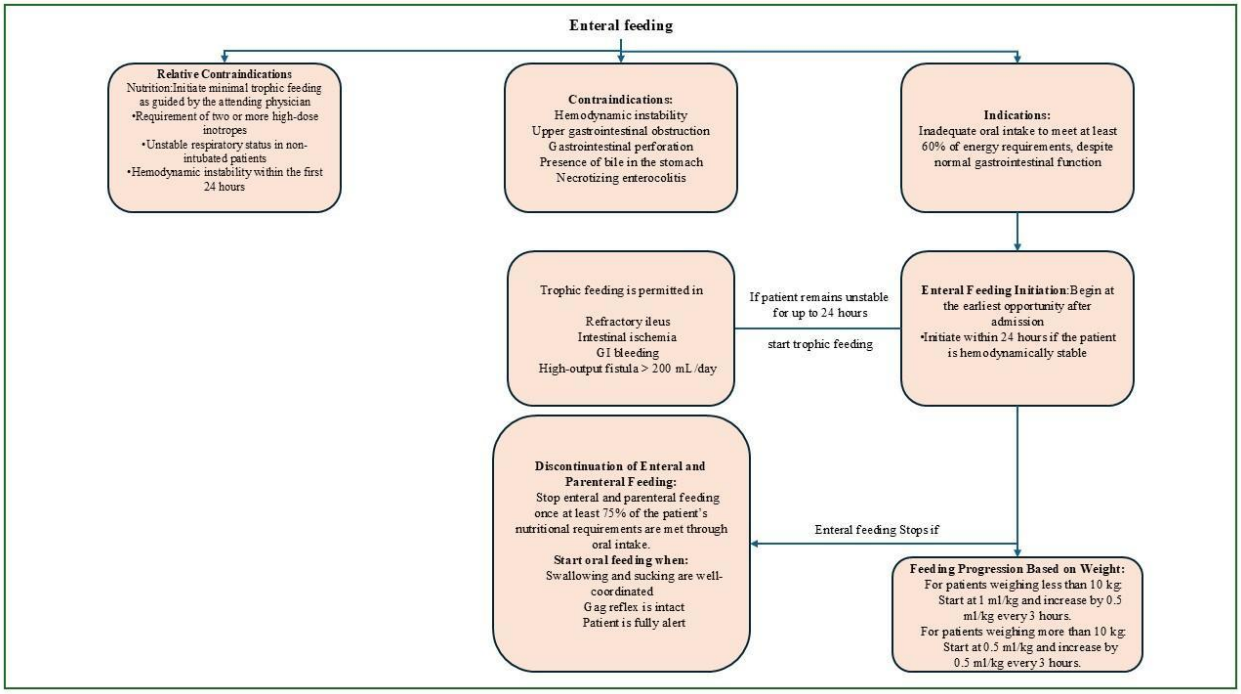

Fig. 1: Algorithm for enteral feeding in PICU

The developed algorithm in Figure 1, outlines a comprehensive protocol for enteral nutrition in PICU patients, covering key aspects such as indications, contraindications, initiation, progression, and discontinuation. Enteral feeding is indicated for patients unable to meet 60% of energy needs orally, with contraindications including hemodynamic instability, gastrointestinal obstruction, and necrotizing enterocolitis. However, in specific scenarios such as intestinal ischemia, gastrointestinal bleeding, or high-output fistula (where feeding is often avoided) trophic feeding is recommended to prevent intestinal villous atrophy and maintain gastrointestinal functi**on.** Feeding is initiated within 24 hours for stable patients, progressing based on weight: 1 ml/kg (increased by 0.5 ml/kg every 3 hours) for those <10 kg, and 0.5 ml/kg (increased similarly) for those >10 kg. Enteral and parenteral feeding discontinue is suggested once 75% of nutritional needs are met orally, transitioning to oral feeding when swallowing is coordinated, the gag reflex is intact, and the patient is fully alert. This stepwise approach ensures safe and effective nutritional support for critically ill pediatric patients.

The prokinetic agents listed in Table 1, including metoclopramide, domperidone, and erythromycin, are recommended in this protocol to promote gastrointestinal motility and enhance feeding tolerance in PICU patients. Their use is tailored to each patient's needs, considering their specific mechanisms of action, efficacy, and safety profiles, to address issues like delayed gastric emptying and high aspiration risk. The dosing protocol is designed to optimize therapeutic benefits while minimizing potential adverse effects.

Tables 2 and 3 outline the complications of enteral feeding and their management strategies, reflecting the protocol's holistic approach. Table 2 addresses metabolic complications, such as refeeding syndrome and electrolyte imbalances, with preventive measures like gradual caloric increases and electrolyte monitoring. Table 3 focuses on mechanical, gastrointestinal,

and aspirational complications, recommending interventions like prokinetics, fiber-enriched formulas, and proper positioning. Beyond the feeding protocol, our consensus group provided guidance to mitigate these complications, ensuring safer and more effective nutritional support for PICU patients.

Table-1: Prokinetics

Drug	Dose	Consideration
Metoclopramide	0.1–0.2 mg/kg, with a maximum dose of 10 mg, administered up to 4 times daily.	Due to the risk of complications such as dyskinesia, treatment duration should not exceed 12 weeks.
Domperidone	0.1–0.2 mg/kg, with a maximum dose of 10 mg, administered up to 4 times daily.	May prolonged QTc interval in ECG
Erythromycin	IV Dosage: a) 2.8 mg/kg infused over 20 minutes, with a maximum dose of 250 mg. Oral Dosage: b) 3 mg/kg per dose, administered up to 4 times daily. c) Maximum daily dose: 10 mg/kg or 250 mg	Antibiotic resistance Tachyphylaxis and the risk of tachycardia.

Table-2: Metabolic complications of enteral feeding and nutritional approach to them.

Complication	Possible reasons	Nutritional approach (after medical reasons check)
Dehydration	Increased fluid excretion Inadequate fluid intake	Sufficient supply of water and electrolytes
Hyperglycemia	Insulin inadequacy relative to carbohydrate intake High infusion rate Excessive energy intake	Adjusting the carbohydrate content of the formula. Slowing the infusion rate Modifying the received energy Regulating insulin based on carbohydrate intake
Hyponatremia	Increased water intake	Fluid restriction
Hypernatremia	Insufficient fluid intake.	Changing the formula type Increasing fluid intake
Hypokalemia	diarrhea / refeeding syndrome	Regulation of potassium excretion Correction of potassium intake
Hyperkalemia	There are no nutritional-related causes.	Pharmacological treatment
hypophosphatemia	Refeeding Syndrome/ DKA	Phosphorus administration Reducing energy intake.Management of DKA
Hyperphosphatemia	There are no nutritional-related causes.	Pharmacological treatment

Table-3: Mechanical, gastrointestinal, and aspirational complications of enteral feeding and their approaches

A sign of intolerance	Approach
High GRV volume:	This check is typically unnecessary unless specified in the following cases: • Upon doctor's advice • Before the second feeding round or if the remaining volume exceeds 10 ml/kg • If more than 50% of the given volume remains, stop the gavage, and resume feeding with the previous tolerated volume.
Vomiting/Distention	Stop feeding. Correct the patient's position (raise the head of the bed to an angle of 30 to 45 degrees) (Improving gravitational flow and reducing intra-abdominal pressure). Examine for intestinal obstruction (Abdominal examination, imaging, symptoms). Review the patient's medications. Side-effects of Medication, interactions, osmotic agents. Reduce the speed of gavage administration. Modify the formula's viscosity and density based on the doctor's diagnosis.
Diarrhea	Change the type of formula to one containing soluble fiber. Switch to a continuous gavage feeding method. Consider parenteral nutrition.
Constipation	Adequate fluid intake Formulas containing insoluble fiber Medications that stimulate bowel movements Laxatives and agents that increase stool volume
Aspiration	Administer gavage over 20 minutes using gravity. Raise the head of the patient's bed to a 30 to 45-degree angle. Change the type and concentration of the formula. Use the post-pyloric feeding method.

Tables 2 and 3 outline the complications of enteral feeding and their management strategies, reflecting the protocol's holistic approach. Table 2 addresses metabolic complications, such as refeeding syndrome and electrolyte imbalances, with preventive measures like gradual caloric increases and electrolyte monitoring. Table 3 focuses on mechanical, gastrointestinal, and aspirational complications, recommending interventions like prokinetics, fiber-enriched formulas, and proper positioning. Beyond the feeding protocol, our consensus group provided guidance to mitigate these complications, ensuring safer and more effective nutritional support for PICU patients.

4- DISCUSSION

In this study, we developed a standardized EN protocol for PICU patients using a multidisciplinary expert consensus approach. Our protocol, grounded in a systematic review conducted in Phase 1, highlights key factors essential for effective EN delivery in critically ill

children. Through this approach, our expert panel achieved consensus on crucial EN parameters, including the timing of initiation, energy targets, and strategies to manage feeding interruptions and complications. These findings underscore the importance of a unified protocol to enhance nutritional support and clinical outcomes in PICUs worldwide.

4-1. Initiation Timing and Volume of Enteral Feeding

The protocol recommends initiating enteral feeding within the first 24 hours of PICU admission for hemodynamically stable pediatric patients, aligning with existing guidelines that link early nutrition to improved clinical outcomes in critically ill patients. Early initiation of EN has demonstrated benefits, such as preserving gut integrity, supporting immune function, and promoting recovery. For instance, critical care guidelines advocate for early EN within 24-48 hours post-admission for critically ill adults, noting that timely EN helps maintain caloric intake and protein balance during the acute stress response (14). Similarly, the Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition recommend early EN within the first 24-48 hours for critically ill children to optimize recovery (15).

In this protocol, an expert panel defined "early feeding" as initiating enteral nutrition within the first 24 hours of PICU admission, while "delayed feeding" refers to initiation after the first 24 hours. While early feeding is widely encouraged, variations in its exact definition across studies pose challenges to direct outcome comparisons. For instance, some studies define early feeding as EN started within 6-24 hours, while others extend this window to 24-48 hours. A recent trial comparing EN initiation within 6-24 hours versus delayed feeding found no significant difference in the length of hospital stay; however, limitations in sample size and baseline patient differences may have influenced these findings (16). Additional evidence from a multicenter study in Spanish PICUs found that initiating EN within 24 hours was associated with higher energy intake, faster achievement of target energy levels, and reduced ventilation duration (17, 18). In adult patients, early EN has been linked to improved outcomes, including reduced mortality, increased ventilator-free days, and decreased hospital costs (3). Observational studies in pediatric populations further suggest that early EN initiation helps maintain mucosal integrity and prevent gastrointestinal dysfunction (19-21). Although early feeding is recommended, the optimal timing remains a subject of debate, highlighting the need for further research to refine and standardize definitions in clinical practice.

4-2. Feeding Volume and Advancement Strategies

Our protocol proposes a gradual, weight-based advancement of enteral feeds, tailored to the specific metabolic needs and gastrointestinal tolerance of critically ill pediatric patients. Various feeding protocols recommend differing volume advancement strategies, highlighting the lack of a universally accepted standard. For instance, some protocols recommend starting feeds at 1 ml/kg/hour and advancing by 3 ml/kg/hour every four hours for infants under 25 kg (22). Another approach advocates beginning with 25% of the target volume during the first four hours, then gradually increasing based on patient tolerance (23, 24). Other guidelines suggest starting at 1-2 ml/kg/hour with increments every four hours (14).

In contrast, our protocol specifically addresses the unique needs of PICU patients with a more conservative and tailored approach. For infants and children under 10 kg, feeds are initiated at 0.5–1 ml/kg, with increments of 0.5 ml/kg every three hours, while larger patients can

tolerate slightly more rapid advancements. This weight-sensitive, stepwise approach seeks to balance caloric intake with the risk of gastrointestinal complications, particularly in smaller, critically ill children. By closely aligning the feeding rate with patient-specific tolerance and metabolic needs, our protocol minimizes feeding intolerance and optimizes nutritional delivery in a manner that accounts for the nuanced requirements of PICU patients.

4-3. Use of Prokinetics

Our protocol includes the use of prokinetic agents—metoclopramide, domperidone, and erythromycin—to support gastrointestinal motility and minimize complications like reflux and aspiration in the PICU. Prokinetic agents stimulate gastrointestinal contractions, addressing challenges such as delayed gastric emptying, impaired motility, and a high risk of aspiration that may compromise feeding tolerance (25). In this context, prokinetics act as adjunctive therapies following dietary interventions, aimed at optimizing gastric emptying and alleviating symptoms of gastroparesis (26). However, their use in the PICU has been moderated due to potential side effects and limited data on efficacy in critically ill children (14).

Metoclopramide, a dopamine antagonist, is frequently used to enhance gastric motility, particularly for managing nausea and vomiting related to reflux. While effective, its use in pediatric patients is constrained by the risk of side effects such as extrapyramidal reactions and QT interval prolongation, requiring careful dose management and monitoring (27). **Domperidone** acts as a dopamine-2 receptor antagonist with peripheral prokinetic effects, avoiding central nervous system side effects because it has limited penetration across the blood-brain barrier. This safety profile makes it preferable for long-term use in pediatric populations, provided that doses remain within recommended ranges (28).

Erythromycin functions as a motilin receptor agonist, facilitating gastric contractions and promoting gastric emptying. It is particularly effective in patients with high gastric residual volumes, where it has shown benefits for early enteral nutrition, especially in mechanically ventilated patients (29, 30). Nevertheless, prolonged erythromycin use is limited by tachyphylaxis and potential side effects, including QT interval prolongation and, in rare cases, pyloric stenosis. Therefore, erythromycin is typically reserved for cases unresponsive to other agents, used with close clinical monitoring (31).

The selection of prokinetics in our protocol balances motility benefits with safety concerns, tailored to the heightened vulnerability of PICU patients. By employing agents with different mechanisms of action, clinicians can individualize prokinetic therapy based on patient-specific factors, thereby improving feeding tolerance while mitigating adverse effects (29).

4-4. Complications of Enteral Feeding and Nutritional Strategies for Management

While enteral feeding is essential for meeting the nutritional needs of critically ill pediatric patients, it also introduces potential risks. Our protocol addresses complications such as refeeding syndrome, dehydration, and hyperglycemia, with strategies for effective monitoring and management.

4-5. Refeeding Syndrome

Refeeding syndrome poses a significant risk when caloric intake is reintroduced or increased after a period of restricted intake, potentially causing electrolyte imbalances—particularly in potassium, magnesium, and phosphorus—and

conditions like thiamine deficiency and sodium retention. Malnourished children or those who have had restricted intake for more than seven days are at particularly high risks (32). Guidelines suggest that before initiating nutrition, clinicians should correct electrolyte imbalances (including hypophosphatemia, hypokalemia, and hypomagnesemia**)** to near-normal levels and administer thiamine supplementation at a dose of 100 mg per day. During the acute phase of critical illness, energy intake should not exceed Resting Energy Expenditure (REE), with a gradual increase in caloric intake to prevent complications arising from sudden metabolic shifts (33).

Our protocol includes close monitoring of electrolytes and blood glucose levels to mitigate these risks. For children with low levels of key electrolytes, initial correction and daily supplementation with multivitamins and thiamine are advised. These precautions support safe nutrition in critically ill children, particularly as the controlled progression of caloric intake and ongoing metabolic monitoring can reduce the incidence of refeeding syndrome in the PICU. This approach provides balanced nutritional support while addressing potential electrolyte and glucose complications.

4-6. Gastrointestinal Complications and Management Approaches

Enteral feeding in the PICU can lead to gastrointestinal complications, including high Gastric Residual Volumes (GRV), vomiting, diarrhea, constipation, and an increased risk of aspiration. Our protocol presents targeted strategies for managing these issues, aiming to improve feeding tolerance and reduce adverse outcomes.

Monitoring GRV is a common practice in ICUs to guide feeding adjustments and potentially minimize complications like aspiration or vomiting. However, evidence remains inconclusive on the clinical benefits of GRV monitoring for improving patient outcomes, and there is no consensus on the optimal monitoring frequency or threshold levels (34) .Current practices vary; some protocols recommend checking GRV every six to eight hours, but no clear impact on outcomes like mortality or length of stay has been confirmed (35).

Recent recommendations from the American Society for Parenteral and Enteral Nutrition (ASPEN) advise against routine GRV monitoring in ICU patients (36), whereas the European Society for Clinical Nutrition and Metabolism (ESPEN) suggests delaying enteral nutrition if GRV exceeds 500 mL within six hours in adult (37). The reliance on GRV remains prevalent in many ICUs, partly due to the lack of alternative bedside markers to assess feeding tolerance and gastrointestinal dysfunction. Studies indicate that GRV thresholds vary widely among units, reflecting the absence of standardized protocols. Additionally, clinicians often consider the color and consistency of GRV, with findings such as blood or fecal content signaling possible gastrointestinal pathology (38). While increasing GRV thresholds or omitting GRV monitoring has not been associated with higher rates of complications like aspiration pneumonia (39), GRV assessments may still be warranted in specific high-risk populations, such as those receiving high-dose sedatives or catecholamines (40, 41).

The ongoing debate over the utility of GRV highlights the need for further research into reliable biomarkers and functional measures of gastrointestinal dysfunction. Current evidence suggests that feeding intolerance should be assessed holistically, considering gastrointestinal symptoms and the ability to achieve adequate enteral intake rather than relying solely on GRV levels. These insights emphasize the importance of balancing

patient safety with efficient nutritional delivery in critically ill patients (40, 42).

Studies suggest that slower controlled feeding methods such as intermittent gravity feeding, as opposed to rapid bolus feeding, may reduce gastrointestinal symptoms like vomiting, regurgitation, constipation, and abdominal distension (34). Specific enteral formulas have also shown fewer incidences of regurgitation and constipation, underscoring the importance of formula selection to improve feeding tolerance (34). Clinical trials have demonstrated that thickened infant formulas containing a combination of pectin, locust bean gum, and either tapioca or cornstarch significantly decrease regurgitation within three days while maintaining a normal stool pattern in formula-fed infants. These formulations are both safe and effective in mitigating overt regurgitation and related discomfort (43-46). Additionally, a starch-thickened "comfort formula" supplemented with the probiotic Limosilactobacillus reuteri DSM 17938, prebiotic fibers (FOS/GOS), and reduced lactose content has been shown to improve the quality of life in infants. This formula reduced the daily frequency of regurgitation, decreased the number of days with colic, and shortened the total crying duration (47) A multi-center randomized controlled trial also evaluated formulas thickened with Locust Bean Gum (LBG), confirming their efficacy in reducing regurgitation while maintaining safety and tolerance (48).

Continuous feeding is generally recommended for infants with very low birth weights (<1250 g) or those with hemodynamic instability, as these groups are more susceptible to gastrointestinal stress (49).

Additionally, fiber-enriched formulas may help reduce the risk of motility disorders by promoting regularity and minimizing constipation in critically ill children (50, 51). Rapid or large-volume bolus feeds are associated with a higher incidence of gastrointestinal symptoms and aspiration risk, especially if administered with abrupt changes in feeding volume or temperature. To minimize temperature-related complications, feeding formulas should be administered at room temperature (20–25°C) to improve gastrointestinal tolerance. Extreme temperatures—either too cold or too hot—should be avoided as they can exacerbate motility disorders and increase discomfort for the patient (52). Patient positioning during feeding also plays a role; improper positioning may increase the risk of tube obstruction and aspiration (49, 53).

These strategies are designed to balance effective nutrition delivery with safety, ensuring that critically ill pediatric patients benefit from enteral feeding while minimizing the risk of gastrointestinal complications.

4-7. Strengths and Limitations

This protocol's main strength lies in its foundation on both systematic evidence and expert consensus, making it comprehensive, clinically relevant, and adaptable to various PICU settings. Its multidisciplinary development ensures a balanced approach to pediatric enteral feeding.

However, limitations include the lack of clinical validation, which may affect its applicability in diverse healthcare environments. Additionally, further feedback from real-world use could refine its effectiveness. Future studies should assess its impact on patient outcomes to guide improvements.

5- CONCLUSION

Our enteral feeding protocol for the PICU provides a structured approach for meeting the complex nutritional needs of critically ill pediatric patients. By offering detailed guidance on the timing of feeding initiation, incremental volume

adjustments, the judicious use of prokinetic agents, and strategies for managing feeding-related complications, the protocol aims to enhance feeding tolerance, optimize patient outcomes, and minimize the risks associated with enteral nutrition. Developed through a systematic review and consensus among experts, this protocol aligns with the best current practices and provides a versatile framework suitable for various clinical settings. Our recommendations address the specific physiological requirements of PICU patients, particularly their increased susceptibility to metabolic and gastrointestinal complications.

6- ETHICAL CONSIDERATIONS

This study was confirmed by Mashhad University of Medical Science Research committee (ID: 4001970). As this study involved a systematic review and expert consensus without direct patient participation, informed consent was not applicable.

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