



COMPLICATIONS AND RISKS ASSOCIATED WITH PROLONGED PARENTERAL NUTRITION IN PEDIATRIC AND NEONATAL ICU PATIENTS: A SYSTEMATIC REVIEW



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ABSTRACT

Objective: The general objective of the present study is to analyze the scientific evidence on the complications and risks associated with prolonged parenteral nutrition in pediatric and neonatal patients in intensive care units (ICU), in order to ensure greater knowledge about this therapeutic practice and its clinical implications. **Methodology:** Searches were carried out through searches in the PubMed Central (PMC) databases. Three descriptors were used in combination with the Boolean term "AND": Parenteral Nutrition, Neonatal Intensive Care Unit and Risk Factors. A total of 101 articles were found, which were subsequently submitted to the selection criteria. After applying the inclusion and exclusion criteria, 20 studies were selected, of which 10 articles were used for detailed analysis. **Results:** Parenteral nutrition (PN) is essential in the care of preterm infants and critically ill pediatric patients. However, it is associated with several potential complications, including hepatobiliary, infectious, mechanical, and metabolic problems like hyperglycemia and hypertriglyceridemia. The administration of PN requires careful planning and strict safety policies to minimize risks and maximize clinical benefits. Prolonged PN can lead to serious complications such as catheter-associated bloodstream infections, cholestasis, and liver dysfunction. **Conclusion:** Prolonged PN in pediatric and neonatal patients in ICUs is associated with significant risks that require close surveillance and preventive interventions. Continuous monitoring of glucose, triglycerides, and liver function levels, as well as rigorous infection control practices, is crucial to ensure the safety and efficacy of PN. Further studies are needed to identify management strategies that can reduce these complications and improve clinical outcomes.

Keywords: Parenteral Nutrition. Neonatal Intensive Care Unit. Risk Factors. Complications. Catheter-Associated Infections.

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INTRODUCTION

Parenteral nutrition (PN) represents a significant advance in the administration of essential nutrients to patients unable to feed orally or enterally. Introduced by Dudrick and colleagues, PN has been widely used in both pediatrics and adults, offering crucial nutritional support in situations where traditional nutrition is not feasible. (LAFUENTE CABRERO et al., 2023) Parenteral nutrition (PN) is an essential practice in the care of premature newborns, especially during the first postnatal days, filling the period until complete enteral feeding is established (VERNON-ROBERTS et al., 2022).

Parenteral nutrition (PN) in term and late preterm infants and critically ill late preterm infants involves administering nutrients directly into the bloodstream, replacing or supplementing oral or enteral feeding. The study discussed compares early and late onset of PN, suggesting that late PN may be associated with short-term clinical and economic benefits, such as reduced mortality, hospital-acquired infections, and length of hospital stay and mechanical ventilation (HUANG et al., 2024). However, these conclusions are based on low-quality evidence, due to methodological limitations and the small sample size of the single study analyzed, which requires caution in interpreting the results (CORSO et al., 2022).

The research underlines the need for more robust studies, with larger sample sizes and a more detailed analysis of factors such as blood glucose levels, to establish safer and more effective practices in the nutritional management of these frail patients (ALHALIMI et al., 2022). However, PN is a complex and expensive therapy, associated with several potential complications, including hepatobiliary, infectious, mechanical problems, as well as metabolic disorders such as hyperglycemia and hypertriglyceridemia (BERLANA, 2022). The administration of PN requires careful planning and strict safety policies to minimize risks and maximize clinical benefits (ALSHAHIRANI et al., 2023).

PN is indicated in situations where enteral or oral nutrition is not possible, insufficient, or contraindicated. It is especially relevant in cases of intestinal failure, high-output fistulas, severe intestinal obstructions, and when the gastrointestinal tract is inaccessible (GATTI et al., 2022). Patients who are malnourished or at risk of severe malnutrition also benefit from PN, particularly when the enteral route is inadequate (WIECHERS et al., 2021).

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nutritional support in situations where traditional nutrition is not feasible (OLALOYE; SWATSKI; KONNIKOVA, 2020).

Therefore, the aim of this systematic review is to critically review the existing literature on parenteral nutrition in newborns, highlighting the available evidence regarding its benefits and potential risks. This review is justified by the need to establish sound evidence-based practices for the administration of parenteral nutrition, especially in vulnerable populations such as newborns, thus ensuring a safe, effective, and cost-effective therapeutic approach. Considering the methodological limitations of the available studies, this review will seek to identify knowledge gaps and propose directions for future research.

METHODOLOGY

This is a systematic review that seeks to understand the complications and risks associated with prolonged parenteral nutrition in pediatric and neonatal patients in intensive care units (ICU), with the aim of ensuring greater knowledge about this therapeutic practice and its clinical implications. For the development of this research, a guiding question was elaborated through the PVO (population, variable and objective) strategy: "What are the complications and risks associated with prolonged parenteral nutrition in pediatric and neonatal patients?"

The searches were carried out through searches in the PubMed Central (PMC) databases. Three descriptors were used in combination with the Boolean term "AND": Parenteral Nutrition, Neonatal Intensive Care Unit and Risk Factors. The search strategy used in the PMC database was: Parenteral Nutrition AND Neonatal Intensive Care Unit AND Risk Factors, Parenteral Nutrition AND Catheter-Related Infections, and Parenteral Nutrition AND Risk Factors. From this search, 101 articles were found, which were subsequently submitted to the selection criteria.

The inclusion criteria were: articles in English, Portuguese and Spanish; published in the period from 2019 to 2023; and that addressed the themes proposed for this research. In addition, review, observational, and experimental studies were included, which were made available in full. The exclusion criteria were: duplicate articles, available in abstract form, which did not directly address the proposal studied, and which did not meet the other inclusion criteria.

After associating the descriptors used in the database, a total of 101 articles were found. After applying the inclusion and exclusion criteria, 20 studies were selected to compose the collection, of which 10 articles were used for detailed analysis.

RESULT

TABLE 1 - Table created by the author

Author	Summary of Contributions
ALSHAHRIANI et al., 2023	Clinical impacts and risk factors for central line-associated bloodstream infection. Study shows the need for rigorous care and constant monitoring.
BERLANA, 2022	It provided an overview of parenteral nutrition, highlighting complications such as hepatobiliary and infectious problems, and the importance of careful planning.
COLOMBA et al., 2020	He reviewed Candida thrombophlebitis in children, addressing the prevention of liver complications through continuous monitoring and attention to the administration of antibiotics.
CORSO et al., 2022	It examined infectious risks related to the permanence time of the umbilical venous catheter in newborns and their mechanical and thrombotic complications.
GATTI et al., 2022	He investigated metabolic bone disease in children with intestinal failure and long-term parenteral nutrition, highlighting the importance of adequate nutrition for growth.
HUANG et al., 2024	It analyzed risk factors for bloodstream infections in intensive care units, highlighting the need for rigorous safety practices.
KOPANOOU TALIAKA et al., 2023	She studied risk factors, diagnosis and treatment of fungal liver abscesses in neonates, with emphasis on prevention through the use of antifungals and probiotics.
ODIE; YOUNG; MCGUIRE, 2021	They evaluated the slow advancement of enteral feeding volumes to prevent necrotizing enterocolitis in very low birth weight infants, suggesting long-term benefits.
WATTAL et al., 2020	They investigated mortality and morbidity in neonatal sepsis caused by multidrug-resistant organisms, highlighting the need for rigorous interventions to minimize complications.
WIECHERS et al., 2021	They optimized early neonatal nutrition in premature infants, highlighting the importance of adequate nutrition in the first weeks of life for cognitive development.

DISCUSSION

Parenteral nutrition plays an essential role in all phases of the treatment of intestinal failure. During the early phase of short bowel syndrome, parenteral nutrition is critical for Parenteral nutrition (PN) is an essential practice in the care of preterm infants, especially during the first few postnatal days, filling the period until full enteral feeding is established. (GATTI et al., 2022) However, PN is a complex and expensive therapy, associated with several potential complications, including hepatobiliary, infectious, mechanical problems, as well as metabolic disorders such as hyperglycemia and hypertriglyceridemia. The administration of PN requires careful planning and strict safety policies to minimize risks and maximize clinical benefits. (BERLANA, 2022) PN is indicated in situations where enteral or oral nutrition is not possible, insufficient, or contraindicated. It is especially relevant in cases of intestinal failure, high-output fistulas, severe intestinal obstructions, and when the gastrointestinal tract is inaccessible. Patients who are malnourished or at risk for severe malnutrition also benefit from PN, particularly when the enteral route is inadequate. (BERLANA, 2022)



Parenteral nutrition in pediatrics involves the intravenous administration of a solution that contains glucose, lipids, amino acids, electrolytes, and trace elements such as minerals and vitamins. This treatment is essential in several cases, such as in neonates weighing less than 1500 grams, as their low body mass requires intensive nutritional supplementation. In addition, parenteral nutrition is indicated in situations of intestinal hypomotility, where the movement of the gastrointestinal tract is insufficient to absorb nutrients properly, and in cases of low gastric capacity, where the stomach's ability to process food is limited. (WIECHERS et al., 2021)

Children who experience breathing difficulties or frequent apneas also benefit from parenteral nutrition, as these conditions can impair normal eating. In preoperative preparations, parenteral nutrition is vital to regain body weight properly before surgery, usually between 7 to 15 days before the procedure. In the postoperative period, especially in cases of prolonged fasting of more than 5 to 6 days, fistulas, ileus, or infections, parenteral nutrition becomes essential to ensure that the patient receives the necessary nutrients for recovery. (WIECHERS et al., 2021)

In addition, children with burns, multiple injuries, severe malnutrition, or gastrointestinal diseases such as short bowel syndrome, pancreatitis, and severe inflammatory bowel disease require this type of nutrition due to their debilitating conditions. Parenteral nutrition is crucial in cases of chronic or persistent severe diarrhea, where the digestive tract's ability to absorb nutrients is significantly compromised. This form of nutrition is also necessary when enteral nutrition is insufficient, such as in patients with renal or hepatic insufficiency, states of unconsciousness that contraindicate enteral or oral feeding, and congenital malformations of the gastrointestinal tract, such as omphalocele, gastroschisis, and fistulas, which prevent normal food intake or absorption. (WIECHERS et al., 2021)

Parenteral nutrition plays an essential role in all phases of the treatment of intestinal failure. During the initial phase of short bowel syndrome, parenteral nutrition is critical to patient survival. In cases of reversible bowel failure, parenteral nutrition provides support until the bowel adaptation process allows for complete enteral nutrition. In the most severe forms of intestinal failure, parenteral nutrition can be a lifelong strategy. (OLALOYE; SWATSKI; KONNIKOVA, 2020)

Feeding premature babies is challenging due to their high nutritional needs, which are higher than those of full-term babies. The physiological growth rate is four times higher during this period, which makes PN an integral component of neonatal care. Studies indicate that parenteral nutrition improves short-term growth and reduces the time it takes to

regain birth weight. Although PN has demonstrated short-term growth improvements, its long-term benefits for metabolism and neurological development are still uncertain. However, evidence suggests that a higher intake of nutrients in the first few weeks postpartum may improve cognitive outcomes. (GATTI et al., 2022)

Prolonged parenteral nutrition in neonates, particularly preterm infants, poses significant risks due to the immaturity of the immune system and underdeveloped physical barriers. Administration of nutrients directly into the bloodstream through umbilical venous catheters (UCV) may predispose to invasive infections and the development of fungal liver abscesses. The peculiar anatomy of umbilical vessels increases the risk of necrosis of liver tissue when hypertonic solutions, such as parenteral nutrition and lipids, are infused through a misplaced CVU. To prevent complications such as liver necrosis and abscesses, continuous monitoring is crucial, as well as attention to the administration of broad-spectrum antibiotics, which can unbalance the gut microbiota and facilitate colonization by pathogens. Therefore, rigorous evaluation of patients' conditions is essential to ensure the safety and efficacy of parenteral nutrition in these cases. (KOPANOOU TALIKA et al., 2023)

Total parenteral nutrition (TPN) is given to critically ill newborns who are unable to feed orally. It uses central venous catheters (CVCs) to deliver essential nutrients directly into the bloodstream. These catheters include the Umbilical Venous Catheter (UVC) and the Peripherally Inserted Central Catheter (PICC). UVC is inserted within the first few hours of life and must be removed within a short period due to the risk of infection. On the other hand, the PICC can be placed at any time during the neonatal intensive care unit (NICU) stay, and is often used when the UVC is removed or fails. Correct catheter tip placement is crucial for the efficacy and safety of TPN, and this is ensured through ultrasounds or x-rays. However, prolonged use of catheters increases the risk of infections and mechanical complications. (DERMITZAKI et al., 2024)

The Guidelines recommend limiting the use of UVCs to 7-10 days to reduce these risks, with some more stringent suggestions indicating replacing the UVC with a PICC within 4 days if extended central access is required. In addition to infectious complications, catheters can present risks such as malposition, venous thrombosis, and other mechanical complications. Preventive strategies highlight the importance of planned and early removal of UVCs, when the initial clinical indications are no longer necessary, suggesting replacement by PICCs to minimize the risks of infections. Studies and narrative reviews also discuss the use of scorecards and questionnaires to help clinicians decide on catheter permanence or replacement, based on individual risk factors such as birth weight, gestational age, and enteral feeding tolerance. (DERMITZAKI et al., 2024)

Refeeding Syndrome (RS) is a potentially life-threatening metabolic complication that occurs during the initiation of nutritional support. In pediatrics, close monitoring of serum electrolytes, especially phosphorus, potassium, and magnesium, is essential. Thiamine and vita replacement administration of PN may be continuous or cyclic. In hospital settings, continuous 24-hour infusion is common as it reduces manipulation and limits glucose and fluid overload. The composition of NP mixtures should be customized to meet the individual needs of patients. This includes the proper ratio of carbohydrates, proteins, and lipids, as well as micronutrients such as electrolytes, vitamins, and trace elements. (BERLANA, 2022)

Mix stability is a critical aspect, influenced by factors such as temperature, pH, and light exposure. The mixtures must be protected from light to prevent photodegradation of nutrients. Photoprotection is essential in pediatric PN due to the toxic degradation of light-sensitive nutrients such as lipids and vitamins, which can result in adverse effects. This recommendation also extends to PN for adults, given that the same components are susceptible to photo-oxidation. (BERLANA, 2022) The composition of NP mixtures should be carefully adjusted to avoid precipitate formation. Nutrient compatibility is critical, especially in all-in-one blends, which can be more susceptible to instability. Paediatric guidelines strongly recommend the use of in-line filters during the administration of PN, especially in neonates, to reduce the risk of particle and precipitate infusion. (BERLANA, 2022) Still on the composition of PN, there are recommendations to limit the osmolarity of peripheral PN for pediatric patients to <900 mOsm/L to minimize the risk of phlebitis. Attention should also be paid to glycemic concentrations; hyperglycemia is a common metabolic complication of PN, resulting from excessive glucose administration. In pediatric patients, it is essential to regularly monitor glucose levels and adjust insulin administration as necessary to avoid hyperglycemic events. Tight glycemic control is crucial to reduce mortality and morbidity. (BERLANA, 2022)

Lipid overload can lead to hypertriglyceridemia and hepatic dysfunction. In pediatrics, intravenous lipid emulsions (IVFE) should be administered at appropriate doses, and triglyceride levels should be monitored to avoid metabolic complications. Parenteral nutrition-associated liver disease (PNALD) can occur due to overfeeding and long-term use of intravenous lipid emulsions (IVFE). (ODDIE; YOUNG; MCGUIRE, 2021) In children, PNALD can manifest as steatosis, cholestasis, and gallbladder sludge/stone formation. Prevention includes modification of the PN formula to prevent overfeeding, use of appropriate lipid emulsions, and early reintroduction of enteral feeding to stimulate bile flow. (BERLANA, 2022) (ODDIE; YOUNG; MCGUIRE, 2021)

Since 2018, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines recommend that parenteral nutrition (PN) for preterm infants include the administration of amino acids from the first postnatal day, starting with at least 1.5 g/kg/d and increasing to 2.5–3.5 g/kg/d from the second day. Intravenous lipid emulsions, which provide low-volume energy, should be started soon after birth without exceeding 4 g/kg/d. Glucose should be started at 4–8 mg/kg/min, avoiding overfeeding. It is recommended to start PN immediately after birth of preterm infants, with regular glucose monitoring to avoid overload. In addition, the fortification of breast milk must be personalized to meet the nutritional needs of these babies. (GATTI et al., 2022)

Vongbhavit's study highlighted that delaying the start of enteral nutrition after surgery increased the risk of cholestasis, defined as conjugated bilirubin ≥ 2 mg/dL. Infants without PNAC had an earlier initiation of enteral nutrition (10 days for initiation and 25 days for complete feeding) compared with those with PNAC (20 days for initiation and 46 days for complete feeding), showing a correlation between early onset of EN and reduced duration of TPN and risk of cholestasis. (COLOMBA et al., 2020)

Refeeding Syndrome (RS) is a potentially life-threatening metabolic complication that occurs during the initiation of nutritional support. In pediatrics, close monitoring of serum electrolytes, especially phosphorus, potassium, and magnesium, is essential. Thiamine and B vitamin replacement should be considered before starting PN in patients at risk for SR. (BERLANA, 2022)

In pediatrics, total parenteral nutrition (TPN) through a central line significantly increases the risk of central line-associated bloodstream infection (CLABSI). This risk is elevated due to prolonged catheter use and potential compromises in children's immune systems, especially in severe conditions. Studies show that children receiving TPN have a higher incidence of CLABSI compared to those not receiving this nutrition, highlighting the need for rigorous care and constant monitoring. (BERLANA, 2022) (ALSHAHRANI et al., 2023)

The use of TPN in pediatrics, especially in resistant infections, requires close monitoring to minimize complications. Central venous catheters increase the risk of infections (CRBSI), worrying pediatricians about the possibility of sepsis and death. Aseptic insertion and maintenance protocols, antimicrobial-impregnated VADs, and appropriate fixation techniques are essential to minimize risks, as well as correct catheter maintenance to prevent thrombosis and obstructions. (BERLANA, 2022) (ALSHAHRANI et al., 2023)

In pediatric patients, renal function, liver tests, blood glucose, and serum electrolyte and triglyceride levels should be checked daily until stabilization, and then weekly. Close

surveillance is crucial to detect and prevent complications associated with PN. Safety protocols should be established for all PN processes, from prescription to final administration. Additions of high electrolyte loads to the NP mixture should be avoided to maintain the stability of the solution. (BERLANA, 2022)

Use of Total Parenteral Nutrition (TPN): In the Taiwan study, which analyzed 376 episodes of gram-negative bacteremia (GNB), it was highlighted that the use of total parenteral nutrition (TPN) was significantly higher in patients with multidrug-resistant GNB (MDR) compared to the non-MDR GNB cohort. The use of TPN was reported in 80% of MDR GNB cases compared to 67.6% in the non-MDR GNB cohort. (WATTAL et al., 2020)

In the study conducted in Taiwan, 376 episodes of gram-negative bacteremia (GNB) in pediatric patients were analyzed. Of these, 80% of multidrug-resistant GNB (MDR) cases received total parenteral nutrition (TPN), while only 67.6% of non-MDR GNB cases required TPN. This data suggests a high dependence on TPN in patients with severe and resistant bacterial infections. (ODDIE; YOUNG; MCGUIRE, 2021)

Pediatric patients with MDR GNB had a higher incidence of neurological sequelae (22.9% vs. 13.4%), kidney disease (12.9% vs. 1.3%), previous episodes of bacteremia (35.7% vs. 23.5%), and central venous catheter use (87.1% vs. 73.2%) compared to the non-MDR GNB cohort. The high incidence of TPN use in patients with MDR GNB suggests the need for close monitoring and interventions to minimize complications associated with long-term parenteral nutrition use in pediatric patients. (WATTAL et al., 2020) B-complex mines should be considered before starting PN in patients at risk of MR. (BERLANA, 2022)

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triglyceride levels should be checked daily until stabilization, and then weekly. Close surveillance is crucial to detect and prevent complications associated with PN. Safety protocols should be established for all PN processes, from prescription to final administration. Additions of high electrolyte loads to the NP mixture should be avoided to maintain the stability of the solution. (BERLANA, 2022)

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Pediatric patients with GNB MDR who received TPN had a number of complications and associated conditions. Neurological Sequelae: The incidence of neurological sequelae was significantly higher in patients with MDR GNB (22.9%) compared to the non-MDR GNB cohort (13.4%). Renal disease: 12.9% of patients with MDR GNB had kidney disease, while only 1.3% of the non-MDR GNB cohort had such complications. History of Bacteremia: 35.7% of patients with MDR GNB had previous episodes of bacteremia, in contrast to 23.5% in the non-MDR cohort. Central Venous Catheter Use: The need for central venous catheter use was significantly higher in patients with MDR GNB (87.1%) compared to 73.2% in the non-MDR GNB cohort. (ODDIE; YOUNG; MCGUIRE, 2021)

In addition, parenteral nutrition is a critical element in the treatment of very low birth weight (VLBW) neonates in neonatal intensive care units (NICUs). However, its prolonged use is recognized as a risk factor for bacterial and fungal infections, including late-onset sepsis, due to the lipid emulsion that facilitates the proliferation of *Candida* and biofilm formation in catheters. Contamination during the preparation of the solution can also trigger

outbreaks of *Candida*. To prevent candidiasis, prophylactic administration of antifungals such as fluconazole is common, showing efficacy since the 1990s in reducing *Candida* colonization and systemic candidiasis. However, there are variations in dosages and concerns about resistant strains. Alternatives such as micafungin and non-absorbable antifungal agents such as nystatin and miconazole gel are used, although they carry their own risks. In addition, probiotics show potential in reducing necrotizing enterocolitis (NEC), late-onset sepsis, and mortality, competing with *Candida* for colonization sites. Continuous monitoring and careful evaluation of practices is essential to ensure the safety and effectiveness of treatment. (SOKOU et al., 2024)

TPN can lead to electrolyte imbalances and hyperglycemia, necessitating adjustments in insulin administration and frequent monitoring of glucose levels. Parenteral nutrition-associated liver disease (PNALD) can occur due to overfeeding and long-term use of intravenous lipid emulsions (IVFE). (ODDIE; YOUNG; MCGUIRE, 2021)

Transitioning from PN to enteral nutrition (EN) is crucial to minimize the risks associated with prolonged PN, such as cholestasis and thrombosis. It is recommended to start EN in the first few days after birth, preferably with supplemented milk or donated human milk (DHM). Studies indicate that rapid advances in enteral feeding volume do not increase the risk of necrotizing enterocolitis (NEC) or death, and can achieve growth rates similar to intrauterine trajectories. (WIECHERS et al., 2021)

CONCLUSION

Parenteral nutrition (PN) has been shown to be essential in the nutritional management of pediatric patients, particularly in premature newborns and critically ill children. This systematic review highlights the importance of PN in improving short-term clinical outcomes, such as weight growth and reduced length of hospital stay, especially in the first days of life. However, the implementation of PN is associated with several challenges and complications, including infections, hepatobiliary problems, and metabolic disorders, which require continuous monitoring and rigorous management strategies.

Evidence suggests that early initiation of enteral nutrition can reduce PN dependence and minimize risks such as cholestasis and infections associated with long-term use of central venous catheters. The research points to the urgent need for additional robust studies, with larger sample sizes and improved methodologies, to establish safer and more effective guidelines in the administration of PN in pediatrics. Thus, the integration of evidence-based practices and the personalization of nutritional therapy are crucial to optimize the care and outcomes of pediatric patients who rely on PN.



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