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## Nutrition therapy and neonatal sepsis

### *Terapia nutricional e sepse neonatal*

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#### ABSTRACT

This article reviews the current understanding of enteral and parenteral nutrition therapy in preterm infants, with an emphasis on very low birth weight babies. The protective effects of nutrition therapy against neonatal sepsis and necrotizing enterocolitis are discussed. Different methods of feeding preterm infants are evaluated. Special attention is given to the problems of very low birth weight babies and the protective effects of nutrition to counteract complications, especially infection. The preferential use of breast milk for enteral nutrition, the management of protein and energy offers, the use of early and minimal enteral nutrition, the

early introduction of parenteral nutrition (within the first 24 hours of life) and the use of immunonutrients that are appropriately supported by a sufficient number of studies can provide good adjuvant therapy guidelines to prevent neonatal sepsis and necrotizing enterocolitis. However, we conclude that additional multicenter, randomized controlled studies are necessary to clarify the protective role of nutrition in preterm infants. Appropriate nutrition is not only effective in treating and preventing infective complications, but it also promotes neurodevelopment and prevents future harmful consequences.

**Keywords:** Nutrition; Sepsis; Infant, newborn

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#### INTRODUCTION

Although advancements within the field of neonatal intensive care have improved preterm newborn survival rates, neonatal sepsis continues to be one of the major causes of neonatal morbidity and mortality.<sup>(1-5)</sup> Sepsis is a problem among preterm infants because their immune systems are immature and their innate immunities are not fully developed. The specific therapeutic interventions utilized in these patients also increases the risk of sepsis.<sup>(6-8)</sup> In an attempt to cope with this condition, septic preterm newborns are in a hypermetabolic state, triggered and perpetuated by a combination of hormonal, neural and environmental stimuli. This results in a loss of cellular protein levels and a depletion of organ nutrients, resulting in organ dysfunction.<sup>(2,3,9)</sup>

The increased frequency of necrotizing enterocolitis (NEC), which is associated with a loss of function in the intestinal barrier and bacterial translocation, is usually related to sepsis, fasting and a lack of breast milk feeding.<sup>(9)</sup> Indeed, early feeding, both enteral and parenteral, is fundamental to minimizing the chances of a poor nutritional status. Early feeding also stimulates the development of the newborn's gastrointestinal tract. The nutritional needs of very low birth weight newborns deserve particular attention because appropriate nutrition supports their appropriate growth and neuropsychomotor development. Nutritional therapy may also help

to prevent future sequela. Early introduction of parenteral and/or enteral nutrition should be considered as a routine, with a focus on providing appropriate weight increases and recoveries during the time when an infant is hospitalized.<sup>(10,11)</sup>

This article aims to review the current literature on enteral and parenteral nutrition therapy for preterm newborn infants, especially for those infants with very low birth weight. The protective role of nutrition therapy against neonatal sepsis and necrotizing enterocolitis is emphasized.

## METHODS

We searched the BVS (*Biblioteca Virtual em Saúde*), MEDLINE (International Database for Medical Literature), LILACS (Latin-American and Caribbean Health Sciences Information Database), SciELO (Scientific Electronic Library online) and the Cochrane Library databases. In addition, articles referenced by selected publications and textbooks, as part of a literature review, were also used. We used the following keywords, in both Portuguese and English, in our searches: nutrition, sepsis and premature.

Full articles, in both Portuguese and English, that mentioned “neonatal sepsis” and “nutrition interface” in their abstract or title were selected. Articles were selected by reading the title and abstract, followed by a more detailed review. We excluded articles that did not mention preterm newborns and/or humans. We also excluded articles that were found, after a detailed analysis, to not be associated with neonatal sepsis and nutrition.

Table 1 presents the search strategies according to the databases and keywords used, as well as the number of references that were retrieved and selected.

## SEPSIS AND NUTRITION

Birth before the end of the third trimester of pregnancy exposes the newborn to a high risk of inadequate

nutrition. This risk is due to the low levels of available nutrients, the fast growth rate of infants, and an immature gastrointestinal tract.<sup>(12-15)</sup>

Clinical assessment and vigilance continue to be the most practical methods for the early diagnosis of neonatal sepsis. The clinical signs that are important for the diagnosis of infection are motor activity patterns, peripheral perfusion changes and respiratory distress.<sup>(6,16,17)</sup> Additional tests that should be performed are white blood cell counts, C-reactive protein (CRP) analysis and bacterial cultures.<sup>(18)</sup>

A preterm newborn should be considered as an immunosuppressed patient; therefore, one should assume that every infection is severe and may quickly progress from bacteremia to sepsis, septic shock with multi-organ failure, and disseminated intravascular coagulation.<sup>(17,18)</sup> The pathophysiological changes are mostly dependent on the host and the toxins released by the offending organism.<sup>(5,19)</sup> These toxins may trigger the release of acute inflammatory response mediators<sup>(20)</sup> and increase the amount of circulating pro-inflammatory and anti-inflammatory cytokines. The balance between the host and the pathogen defenses will determine the infant's outcome.<sup>(17)</sup> Early and appropriate antibiotic therapies, in conjunction with other supportive measures, are fundamental to infant survival rates in these cases.<sup>(2,21)</sup>

After the delivery, the preterm newborn is in a hypercatabolic state. This state is intensified by sepsis because the body attempts to provide amino acids for the synthesis of elements that are essential for the inflammatory response and the activation of the immune system. In addition, glucose is produced via hepatic gluconeogenesis and provides energy. Glucides and lipids are directed toward energy production, while amino acids released from muscles are transported to the liver for glucose production, thereby boosting gluconeogenesis.<sup>(8)</sup> Additionally, as lipid metabolism changes, lipolysis and increased plasma

**Table 1 – Distribution of articles retrieved from the MEDLINE, LILACS, SciELO and Cochrane databases**

Database	Keywords	Number of citations	Number of selected articles
MEDLINE/PUBMED	Sepsis + premature + nutrition Limits: human, newborn, English or Portuguese, full text and free access	40	7
LILACS	Nutrition + sepsis + premature Limits: human, newborn	5	None
SciELO	Nutrition + sepsis + premature	1	None
Cochrane Library	Nutrition + sepsis + premature Limits: full reviews	65	10
Total of selected articles			17

fatty acids levels should be emphasized.<sup>(9)</sup> Liver protein synthesis becomes equally directed toward the production of C-reactive protein and fibrinogen.<sup>(8)</sup> Catabolic processes and the use of amino acids for energy production lead to a negative nitrogen balance, which is poorly corrected for by the introduction of exogenous nitrogen.<sup>(10)</sup> This imbalance leads to progressive malnutrition and cellular nutrition changes.<sup>(18)</sup>

The intestines have a significant amount of gut-associated lymphoid tissue (GALT), and the development of immune and digestive function in a preterm newborn is dependent on digestion, absorption, osmolarity regulation and lymphoid components.<sup>(9)</sup> Especially in preterm newborns with sepsis, the intestinal barrier is immature, favoring bacterial translocation<sup>(19)</sup> by the following methods: 1) changes in the intestinal microbial content, 2) a reduced immune response and 3) an incompetent intestinal epithelial barrier. The loss of function of the intestinal barrier that is associated with bacterial translocation and the increased frequency of NEC are caused by sepsis, fasting and a lack of breast milk feeding,<sup>(9)</sup> which leads to increased morbidity and mortality rates.<sup>(22)</sup>

Nutrition in preterm newborns, especially in those with a very low birth weight,<sup>(11)</sup> is a challenge. Early life malnutrition may have permanent effects on the development of the central nervous system and body growth.<sup>(20,21,23)</sup>

Nutrition, both enteral and parenteral, has an important role in the prevention of neonatal sepsis by minimizing nutrient loss and stimulating the maturation of the gastrointestinal tract. The use of breast milk and early enteral nutrition are important for reducing the risk of infections.<sup>(4,10,17,24)</sup> In addition, early enteral nutrition allows for bacterial carbohydrate fermentation, with the resulting short chain fatty acids (mainly butyric) exerting trophic intestinal epithelial effects. Additionally, enteral nutrition improves glucose tolerance by generating gluconeogenesis precursors (pyruvates, lactates, alanine and glycerol), non-ester fatty acids and ketone bodies (beta-hydroxybutyrate and acetoacetates).<sup>(9)</sup>

## THE RELEVANCE OF HUMAN MILK

Breast milk plays a primordial role in nutrition and the intestinal maturation of critically ill preterm neonates. Neonatal intensive care units (NICUs) should promote breastfeeding, as it is the best metabolic support for the neonate.<sup>(9)</sup> The protective effects of breast milk are related to its nutritional characteristics and the multiple functions of its non-nutritive components. Exclusive and/or partial

feeding of volumes of at least 50 mL/kg/day of breast milk, compared to exclusive formula feeding, reduces the risk of infection and NEC.<sup>(25-32)</sup>

## NUTRIENT OR IMMUNE NUTRIENT OFFER

Parenteral energy provided during the acute phase should be sufficient to maintain basal metabolism. Glucose should be the preferred energy source. Offering 3 to 5 mg/kg/day is indicated for glucose oxidation rates of 5 to 6 mg/kg/min. Physicians should aim to maintain glucose concentrations within the physiologic range and avoid hyperglycemia.<sup>(8)</sup> Lipids should be offered in amounts up to 20 to 35% of the non-protein calories due to metabolic limitations and lipid clearance. However, there is no association between early lipid administration and the occurrence of sepsis or NEC, as shown in a meta-analysis by Simmer et al.<sup>(33)</sup> Regarding proteins, a minimum of 1 to 1.5 g/kg/day of amino acids is recommended for a 30 kcal/kg/day energy offer.<sup>(8)</sup> Rapid cell division tissues, such as the intestinal immune system, are rich in glutamine. In addition to the regulation of the intestine-regulated inflammatory response, this amino acid also has an important role in the maintenance of the intestinal mucosa and the mucosa barrier.<sup>(25,34)</sup> This means that glutamine is essential in preterm newborns and is insufficiently synthesized during stressful conditions.<sup>(8)</sup> However, different studies have failed to find significant clinical benefits of either oral or parenteral glutamine supplementation during sepsis or NEC.<sup>(35-38)</sup>

Reduced tissue nitric oxide synthesis may also be associated with NEC, and arginine is a substrate for this synthesis. Although some trials tried to clarify this relationship, there are no data supporting either oral or parenteral arginine supplementation. Additional multicenter, controlled randomized trials are required to assess this supplementation.<sup>(37)</sup>

In a recent meta-analysis, Pammi et al. found no evidence that oral supplementation with lactoferrin, a component of human colostrum and milk, would reduce the incidence of late sepsis or NEC in low birth weight preterm newborns.<sup>(39)</sup> A meta-analysis by Mohan et al. also found no evidence to recommend or contraindicate oral lactoferrin administration for the adjunctive therapy of neonatal sepsis or NEC.<sup>(40)</sup> A study by Berseth et al. showed that there was no change in the incidence of NEC in newborns receiving iron-fortified breast milk. However, the study emphasized that the fortified milk could reduce the need for blood transfusions in low birth weight newborns.<sup>(41)</sup>

Selenium is a trace element known to have a role in immunocompetence, and it is found in lower concentrations in premature infants. Its supplementation may be associated with benefits, such as the reduction of sepsis rates. A large trial conducted in a country with a low concentration of selenium indicates that there are benefits from parenteral supplementation; however, these findings cannot be extrapolated to other populations.<sup>(42)</sup>

Different studies have shown that enteral probiotics can help to prevent severe NEC, as well as other causes relating to premature death in children, suggesting that current practices should be revised. However, it is recognized that additional studies are necessary to assess the effectiveness of enteral probiotics in extremely low birth weight newborns. The formulation of enteral probiotics and their most effective dosages also needs further study.<sup>(22,43)</sup> In a meta-analysis, Deshpande et al. confirmed the beneficial effects of probiotics against fatal NEC and neonatal sepsis and recommended its routine use.<sup>(44)</sup>

Antioxidants are involved in several immune response phases, such as phagocytosis, cytokine production, cell-mediated responses and immunoglobulin production; these substances are therefore considered immunonutrients.<sup>(45)</sup> Vitamin A and Vitamin E are prominent within this group of substances, and maintaining the appropriate levels of these vitamins in plasma and tissue can contribute to an anti-infective response.<sup>(8)</sup> However, additional studies are required.

## ENTERAL AND PARENTERAL NUTRITION

The literature recommends minimal enteral nutrition (EN) as early as possible (because the intestine is functional). This serves to accelerate intestinal tract recovery and development, thereby favoring growth and reducing infections.<sup>(46,47)</sup> Even minimal EN, preferably with maternal breast milk, in association with parenteral nutrition, can help mitigate intestinal mucosa atrophy and prevent bacterial translocation. It can also decrease the duration of parenteral nutrition.<sup>(48-51)</sup>

Parenteral nutrition (PN) is indicated when normal metabolic and nutritional needs are not sufficiently provided by EN. PN is considered extremely important in a preterm newborn infant just after birth, within the first 24 hours of life, and is necessary in septic patients.<sup>(2,33,35,48)</sup> PN significantly impacts nutrition status and reduces neonatal mortality.<sup>(8)</sup>

The approach to premature infant feeding varies widely based on each NICU's experience. For low birth weight newborn infants, current nutrition routines are based on

early total PN (within the first 24 hours of life)<sup>(45)</sup> and careful EN introduction with slowly progressing volumes. With this approach, most premature infants are able to receive full enteral nutrition by the end of their second week of life. This more careful approach usually results in a reduced incidence of NEC and may delay NEC until the third week of life.<sup>(52)</sup> Conversely, the reviews by Morgan et al. failed to find evidence that a slower enteral feeding progression would reduce the risk of NEC in low birth weight newborn infants. They found no clear differences between slow and fast progressing approaches (30-35 mL/kg/day).<sup>(53,54)</sup>

There is evidence of a significant relationship between the age when preterm newborn infants achieve full EN and late sepsis. As shown in the studies by Flidel-Rimon et al., the earlier an infant achieves full EN (12.5 days has been identified as the boundary), the lower the risk of late sepsis<sup>(8)</sup>, although there is no change in the risk of NEC.<sup>(55)</sup> Additionally, Brotschi et al. showed that early achievement of full EN will reduce the incidence of catheter-related sepsis.<sup>(56)</sup> However, as highlighted by some investigations, currently, the benefits and risks of trophic nutrition and full EN are not well-established. Therefore, the results are still insufficient to provide clear clinical practice guidance.<sup>(53,54,57)</sup>

Additionally, it is important to stress the theory that adult degenerative diseases have a fetal origin. This has been thoroughly assessed within the past 15 years based on the concept that nutritional insults during fetal or neonatal life could cause future harmful consequences. Such harmful consequences include growth, development, metabolic and degenerative diseases that manifest during childhood, adolescence or adult life. This has led to the reformulation of nutritional targets for preterm newborns, i.e., in addition to promoting a body growth rate similar to intrauterine life, the limitations resulting from immaturity should also be seriously considered.<sup>(58-61)</sup>

There is much to learn about preterm newborn feeding. Indeed, feeding practices are not always based on scientific evidence, and scientific evidence is also frequently lacking. Consequently, the literature proposes approaches that are widely variable.<sup>(48,62)</sup> Notwithstanding the large variability in proposed approaches, nutrition management should be emphasized as a good clinical practice because it is known to favor healing and reduce the incidence of complications arising from infections in preterm newborns.<sup>(63)</sup>

## CLOSING REMARKS

The appropriate care of preterm newborn infants with sepsis continues to challenge contemporary medicine. The

goal is to feed preterm infants in an effort to promote appropriate growth, mimicking that of the intrauterine rate. This helps to ensure adequate neurological development and prevent future sequel. There is much to learn about preterm infant nutrition, especially in very low birth weight infants, and the outcomes of various nutritional therapy approaches. In many cases, feeding approaches are not clearly evidence based.

The nutrition principles described in this article, namely preferential use of maternal breast milk for EN, control of energy and protein offer, the early start of minimal enteral nutrition, the early start of parenteral nutrition within the first 24 hours of life and the use of sufficiently evidence-based immunonutrients, can provide good adjuvant guidelines for the prevention and treatment of sepsis and necrotizing enterocolitis.

Given the considerable controversy over nutrition practices in these patients, there is clearly a need for additional multicenter, controlled and randomized trials to clarify preterm newborn nutrition and its protective role in the prophylaxis of infections as well as in neurodevelopment and the prevention of future harmful consequences.

#### Authors' contributions

B. A. C. de Freitas and R. T. Leão drafted the manuscript and prepared the first version. Both authors,

in conjunction with A. P. Gomes and R. Siqueira-Batista, revised the final manuscript.

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#### RESUMO

O objetivo do presente artigo é revisar a literatura acerca dos conhecimentos atuais relativos à terapia nutricional – enteral e parenteral – para os recém-nascidos pré-termo, principalmente os de muito baixo peso, destacando seu efeito protetor na sepse neonatal e na enterocolite necrosante. As diferentes modalidades de alimentação do recém-nascido prematuro – especialmente para aqueles de muito baixo peso – e seu efeito protetor na diminuição de complicações (mormente as infecciosas) foram analisadas. A utilização preferencial do leite materno na nutrição enteral, o controle das ofertas energético-proteicas, o início precoce da nutrição enteral mínima, a introdução precoce da alimentação parenteral – nas primeiras 24 horas – e a utilização dos imunonutrientes que tenham estudos suficientes para fundamentar sua indicação podem se constituir em boas diretrizes adjuvantes na prevenção da sepse neonatal e da enterocolite necrosante. Sem embargo, percebe-se a necessidade de mais estudos – preferencialmente multicêntricos, controlados e randomizados – para esclarecer o papel protetor da nutrição no RNPT, não somente na prevenção de infecções, mas também para auxiliar o desenvolvimento neural e a prevenção de consequências deletérias futuras.

**Descritores:** Nutrição; Sepse; Recém-nascido

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