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Advances in Enteral Nutrition Strategies for Preterm Infants

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Abstract

With the continuous progress of medical care, the survival rate of preterm infants is increasing year by year, and adequate nutrition is crucial for the growth and development of preterm infants. Enteral nutrition (EN) is a nutritional support method that provides metabolically required nutrients and various other nutrients through the gastrointestinal tract, which is the best way to supply nutrition to preterm infants. A reasonable EN strategies can help improve the quality of survival, and long-term prognosis of preterm infants. This article summarizes and discusses the literature reports on EN for preterm infants at home and abroad in recent years, and reviews the research progress of EN strategies for preterm infants, personalized feeding programs, and related clinical problems affecting the establishment of EN, to provide reference for clinical work. EN for preterm infants requires the comprehensive use of a variety of research strategies and continuous exploration and innovation to provide better nutritional support for preterm infants and promote their healthy growth.

Keywords

Preterm Infant, Enteral Nutrition Strategies, Influence Factor, Low Birth Weight Infant, Minimal Enteral Feeding, Feeding Intolerance

1. Introduction

Preterm infants are newborns whose gestational age is less than 37 weeks. Due to the short intrauterine development time, preterm infants are immature in the structure and function of various physiological systems, and they are more susceptible to various diseases than full-term infants. In recent years, with the development of medical technology, the survival rate of preterm infants has increased

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year by year. To improve the survival quality of preterm infants, adequate nutritional supply is crucial. The goal of nutrition for preterm infants is to meet the growth rate of healthy fetuses of the same gestational age. Adequate nutritional supply provides preterm infants with the impetus to catch up with the growth, and early malnutrition will have a direct impact on the future growth of the body and the development of the nervous system, and at the same time, it will lead to the lack of immune defenses and increase the susceptibility to infectious diseases, and decrease the ability to repair the damaged tissues, which will increase the incidence of a variety of complications.

The way of supplying nutrition includes parenteral nutrition (PN) and enteral nutrition (EN), and EN is the main component. Preterm infants need a reasonable EN program after birth. At present, many guidelines and recommendations have been published at home and abroad on EN for preterm infants, but different medical institutions are not uniform in referring to the guidelines, and there are significant differences in the choice of EN programs by physicians in their clinical work, which leads to unsatisfactory growth and development and prognosis of preterm infants. The immaturity of the development of various systems in preterm infants means that the establishment of EN is a long and arduous process, and in particular, the problem of enteral feeding in very-low and ultra-low-birth-weight infants is more common in the NICU. Therefore, this article provides a review of recent studies on strategies related to enteral nutrition in preterm infants and the main problems affecting the successful establishment of EN, to provide a meaningful theoretical basis for clinical practice.

2. Enteral Nutrition Strategies for Preterm Infants

2.1. Minimal Enteral Feeding (MEF)

MEF is the beginning of EN for preterm infants within 24 h after birth. The feeding amount is 12 - 24 $ml \cdot kg^{-1} \cdot day^{-1}$ [1] and lasts for 2 - 4 d after birth [2]. The advantages of MEF include: 1) Promoting the maturation of the digestive system of preterm infants [3]. MEF stimulates the intestinal nervous system to release gastrointestinal hormones, promotes gastrointestinal dynamics, and prevents mucosal atrophy. 2) Reducing self-protein catabolism to promote restoration of birth weight (BW), and reducing extrauterine growth restriction (EUGR) [4]. 3) Promoting the establishment and balance of intestinal microbiota, reducing intestinal permeability, keeping intestinal barrier function intact, and reducing the risk of infection [5]. The onset of MEF in preterm infants is closely related to gestational age, BW, clinical conditions, etc. There is no uniform standard at home and abroad. The Guide to Canada didn't emphasize the duration of MEF [6]. The Chinese Medical Association (CMA) and Chinese Medical Doctor Association (CMDA) successively proposed the starting time of MEF in 2013 and 2024 [7] and suggested maintaining MEF for 2 - 4 days after birth. All domestic and international guidelines emphasize that the duration of MEF in extremely preterm infants and ELBWI needs to be weighed against the risk of feeding intolerance (FI),

necrotizing enterocolitis (NEC), parenteral nutrition (PN) time, cholestasis, and metabolic bone disease (MBD) [8].

2.2. Choice of EN Dairy Products for Preterm Infants

2.2.1. Human Milk and Donor Human Milk (DHM)

Human milk (HM) is rich in nutrients such as alpha-linolenic acid (C18:3n-3) [9], growth factors [10], microorganisms, antioxidant components, and immunoglobulins [11]. These ingredients can reduce postnatal oxidative stress injury in preterm infants, reduce the risk of infections, and help promote the developmental maturation of preterm infants. So it is the preferred choice of preterm infants for EN. Breastfeeding can reduce the occurrence of serious diseases such as NEC, bronchopulmonary dysplasia (BPD), and sepsis in preterm infants, and promote the early establishment of EN in preterm infants, which is beneficial for the long-term prognosis of preterm infants [12]. DHM is an option for preterm infants who can't receive sufficient parental HM. There is no clinical controlled trial to prove the difference between DHM and parental breastfeeding on the growth and development of preterm infants. A retrospective study found that the use of pasteurization may reduce the level of certain pituitary hormones, the content and physiological function of lactoferrin, secretory IgA, and other biologically active components of the donor breastmilk [13].

2.2.2. Formula Milk

Some preterm infants can not partially or completely obtain HM and DHM. Firstly, it is difficult to deliver HM and DHM to the NICU for a variety of reasons. Secondly, some mothers are unable to breastfeed due to illness, allergies, or lack of nutritional knowledge during lactation. Breastfeeding will lead to children with abdominal distension, diarrhea, bloody stools, poor growth intestinal infections, and so on. Thirdly, HM calories are relatively low, and breastfeeding alone cannot meet the high-calorie needs. In the above cases, formula milk can be used for EN. Formula milk is available in a wide range of brands, functions, and types. Currently, it is recommended to individualize the choice of formula milk and feeding method according to the disease, tolerance, and growth of different preterm infants.

2.2.3. Human Milk Fortifier (HMF)

CMDA recommends the implementation of a personalized fortification program to provide HMF for preterm infants to meet their individualized nutritional needs and support physical growth. Exclusive HM feeding not only doesn't meet the nutritional needs of some preterm infants, but it may also lead to the development of EUGR and MBD. HMF sources are HM, cow's milk, or other mammalian milk. Preterm infants tolerate human milk source fortification more readily and gain more weight [14]. The start timing of HMF in preterm infants is currently controversial. Adding HMF too early may increase the risk of FI and NEC, and too late may result in EUGR. CMA recommends that HMF be given to preterm infants with a BW of <2000 g when breastfeeding 50 to 100 $mL \cdot kg^{-1} \cdot day^{-1}$ in 2013.

In 2019, Chinese expert consensus recommends that preterm infants with a BW of <1800 g should be given HMF when breastfeeding amount up to 50 - 80 $ml \cdot kg^{-1} \cdot day^{-1}$, starting from half dose fortification, and reaching full dose fortification within 3 - 5 d for those who can tolerate it [15]. The Guide to Canada recommends the addition of HMF to preterm infants when breastfeeding up to 100 $ml \cdot kg^{-1} \cdot day^{-1}$. The European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) proposed to add HMF when the feeding volume of preterm infants reaches 40 - 100 $ml \cdot kg^{-1} \cdot day^{-1}$ [16]. Hilditch C reported that there was no significant difference in the effects of fortification on the development of NEC, sepsis, FI, and growth in preterm infants when the fortification was initiated at the amount of EN ≤40 $ml \cdot kg^{-1} \cdot day^{-1}$ versus delayed until 75 $ml \cdot kg^{-1} \cdot day^{-1}$ [17].

2.3. Feeding Methods

Preterm infants are usually fed by tube feeding and transoral feeding. Tube feeding includes transgastric tube feeding, transpyloric feeding, or gastrostomy feeding. Transgastrictube feeding is preferred for preterm infants ≤32 weeks of gestational age, either by push or gravity, with the option of intermittent or continuous feeding; for preterm infants 33 - 34 weeks of gestational age, it is recommended to try transoral feeding. The ESPGHAN recommends that preterm infants be started on a transoral feeding basis at a corrected age of 32 weeks of gestational age.

2.3.1. Tube Feeding

1) Transgastric tube feeding

It is commonly push-feeding or gravity-feeding, with the option of intermittent or continuous. Intermittent push feeding promotes the cyclic fluctuation of gastrointestinal hormones [18], but the rapid increase in push speed and intestinal luminal wall pressure will irritate the gastric mucosa, which is prone to predispose FI [19]. Gravity-feeding utilizes the gravity of the milk to flow into the stomach along the gastrostomy tube, so the drip rate of the feeding increases with the height of the suspension of the milk [20]. But there is a lack of uniform standards for the height of the suspension [21], and the studies only emphasize that gravity feeding is completed within 10 - 30 minutes. Previous studies have concluded that intermittent feeding reduces the time to reach full EN in preterm infants compared to continuous feeding and has no adverse effect on weight and head circumference gain and development of NEC in preterm infants [22]. However, a study by Vijay Kumar found that in both continuous infusion (CI), intermittent bolus by infusion (IBI), and intermittent bolus by gravity (IBG), there was no difference in the time to achieve total EN (180 $ml \cdot kg^{-1} \cdot day^{-1}$) in preterm infants with a gestational age of ≤32 weeks and a BW of ≤1250 g [23]. Li Shuai concluded that CI can enhance gastrointestinal peristalsis in preterm infants, which solves the problems of reduced gastric capacity and slow gastric emptying to significantly reduce the incidence of vomiting and abdominal distension, and at the same time, promote the elimination of fetal stools and reduce jaundice. The study also found that the

combination of non-nutritive sucking can significantly improve the nutritional status, accelerate the growth of the body, and promote the development of behavioral neurological in VLBWI. Funda Yavanoglu Atay *et al.* found that slow infusion feeding (SIF) is suitable for FI and FI high-risk infants [24]. They found SIF combined with non-nutritive sucking can significantly improve gastrointestinal dysfunction, promote the maturation of gastrointestinal function, improve nutritional status, and accelerate the growth of VLBW, thus promoting the development of behavioral nerves of VLBW.

2) Transpyloric feeding (TPF)

TPF is the placement of the feeding tube in the duodenum or jejunum for feeding ensuring that milk reaches the main site of nutrient absorption, which can reduce the incidence of FI and gastroesophageal reflux (GER) [25]. It is suitable for infants with upper GI malformations, gastrointestinal insufficiency, and preterm infants with a high risk of inhalation and severe GER. Previous studies have concluded that TPF not only has no significant advantage on feeding tolerance and growth in preterm infants but may also increase the risk of gastrointestinal disorders and death in preterm infants [26]. The Guide to Canada recommends that TPF should only be used as a last resort for EN in GER preterm infants. A study by Zhu-Xin Zhang *et al.* recommended TPN feeding as the first choice for GER and FI preterm infants when interventions such as continuous pumping and positional therapy were ineffective. A retrospective study found that TPF starting in the 1st week of life in preterm infants may reduce the risk of VLBWI death or BPD [27]. The systematic review study found that TPF in preterm infants after the 1st week of life reduces GER-induced bradycardia and apnea, and improves the oxygenation status of preterm infants with respiratory insufficiency. However, the multicenter cohort study found that the use of TPF in preterm infants with severe BPD was associated with an increased risk of prolonged hospitalization, tracheotomy, or death [28].

3) Gastrostomy/Percutaneous Extraction Gastrostomy (PEG)

Most preterm infants can be gradually converted to oral feeding after birth with swallowing training, and only a very small number of preterm infants need to be fed through a gastrostomy. PEG feeding has a high degree of compliance, a good quality of life, and reduces the incidence of reflux and aspiration pneumonia [29]. However, PEG can lead to complications including skin infections, granulation tissue formation, tube leakage, and tube occlusion [30]. In more severe cases, it can cause stoma failure, peritonitis, tubal displacement, adjacent intestinal injuries, hemorrhage, esophageal laceration, and gastrocolic fistulae. In 2013, CMA suggested that PEG should be used for congenital anomalies such as prolonged tube feedings, esophagogastric fistulae, esophageal atresia, esophageal injury, and growth retardation in preterm infants. The European Society of Pediatric Gastroenterology, Hepatology, and Nutrition recommends that PEG feeding be considered in preterm infants with an EN of more than 3 - 6 weeks [31]. The site of gastrostomy in preterm infants depends on the local level of medical technology

and the choice of institution [32], but the optimal site still needs to be determined by further research.

2.3.2. Transoral Feeding

Preterm infants, especially those less than 34 weeks of gestational age, lack coordinated sucking and swallowing movements [33]. Most of them undergo a period of tube feeding early in life, and then gradually transition to a transoral mode of feeding as they enter the stabilization period.

1) Frequency of feeding

The frequency of feeding in preterm infants needs to be individualized. Reactive feeding includes on-demand feeding, modified on-demand feeding, etc. [34]. The frequency of feeding depends on the preterm infant's hunger response. A meta-analysis included nine randomized controlled trials that found that reactive feeding resulted in slow weight gain in preterm infants but facilitated the transition from tube feeding to oral feeding [35]. Planned feeding includes timed and rationed feeding. The Guide to Canada recommends Q3H feeding for preterm infants with a BW >1250 g, and CMDA suggests Q2-3 H feeding for preterm infants. Compared with Q2H feeding, Q3H feeding can promote gastric emptying to reduce the risk of FI, decrease the duration of central venous catheterization and PN in preterm infants, and do not increase the adverse outcomes of preterm infants in terms of growth or respiratory outcomes [36]. The systematic evaluation and meta-analysis recommended Q2H feeding in preterm infants with a BW of <1000 g, Q3H feeding is preferred for 1000 - 1500 g preterm infants in stable condition [37].

2) Feeding rate

There is no uniform guideline on the rate of breastfeeding for preterm infants EN. It is recommended to individualize the breastfeeding strategy according to the feeding tolerance, and the feeding regimen varies among different medical centers. The Guide to Canada recommends 15 - 20 $ml \cdot kg^{-1} \cdot day^{-1}$ for preterm infants with BW <1000 g and the rate can be increased if they can tolerate feeding for 2 - 3 d. They also recommend 30 $ml \cdot kg^{-1} \cdot day^{-1}$ for preterm infants with BW ≥1000 g. ESPGHAN recommends that stable preterm infants who can tolerate EN be fed at a rate of 18 - 30 $ml \cdot kg^{-1} \cdot day^{-1}$. CMDA recommends that breastfed preterm infants be fed at a rate of 20 - 30 $ml \cdot kg^{-1} \cdot day^{-1}$, and infants with formula or early addition of cow's milk-derived HMF with HM feeds 50 - 80 $ml \cdot kg^{-1} \cdot day^{-1}$ be fed at a rate of ≤20 $ml \cdot kg^{-1} \cdot day^{-1}$ milk addition rate. It was previously thought that too rapid a rate of milk addition in preterm infants [38] (20 - 35 $ml \cdot kg^{-1} \cdot day^{-1}$) could lead to choking, reflux, or NEC [39], and conservative milk addition was usually used in clinical practice. However, Lin concluded that slow addition of milk (10 - 20 $ml \cdot kg^{-1} \cdot day^{-1}$) during the first 8 weeks of life may increase rates of hypotension, surgical rate of hemodynamically significant patent ductus arteriosus (hsPDA), late-onset sepsis, and gastrointestinal surgery, as well as unfavorable head circumference growth and an increased risk of microcephaly and neurodevelopmental disorders [40]. Dorling found that feeding preterm infants at 30

$ml \cdot kg^{-1} \cdot day^{-1}$ did not increase the risk of late-onset sepsis, NEC, and moderate and severe neurodevelopmental disorders at 24 months of age [41]. It suggests that a fast-feeding regimen may be appropriate for some preterm infants, but we still need to consider gestational age, BW, and tolerance to make a situation individualized scheme.

3. Common Causes Affecting the Achievement of Total Enteral Nutrition in Preterm Infants

3.1. Feeding Intolerance (FI)

Clinical manifestations such as abdominal distension, vomiting, gastric retention, diarrhea, and bloody stools after feeding in preterm infants are usually considered FI. The incidence of FI in preterm infants is reported to be 33.80% - 53.45% in China [42] which is slightly higher than that of 27% in foreign countries [43] and it is a common cause of interruption or delay of feeding program in preterm infants. FI may be related to immature intestinal development, dysbiosis of intestinal flora, allergy to cow's milk proteins, reduced release of gastrointestinal hormones, meconium adhesion or delayed elimination of meconium, infections, gastrointestinal tract deformities, and so on [44]-[46]. FI in preterm infants may be a preexisting manifestation of NEC. There is an increased risk of secondary NEC after FI, so early recognition of FI is most important. CMDA recommends daily assessment of preterm infants for GI signs and symptoms such as abdominal shape, the color of the abdominal wall, intestinal sounds, etc. It suggests monitoring of gastric retention if necessary to help early recognition of FI.

3.2. Neonatal Necrotizing Enterocolitis (NEC)

Preterm infants who are generally ill and have significant digestive symptoms should be alerted to the occurrence of NEC. Both suspected and confirmed phases can usually significantly prolong the time to full EN. NEC may begin with FI, then progress to intestinal ischemia within a short period, necrosis or even perforation, fulminant NEC, infectious shock, severe acidosis, and multi-organ dysfunction [47]. The mortality rate in NEC is 10% - 50% [48]. The etiology of NEC is unknown, we just know that it is related to factors such as immaturity of the digestive tract, impaired barrier function of the intestinal mucosa [49], and abnormal colonization of microorganisms [50]. It may also be related to feeding practices, which mainly affect the intestinal flora, the immunity of the digestive system, and inflammatory responses [51]. Early diagnosis is still a difficult clinical task. In addition to monitoring NEC by routine blood tests and abdominal plain film, some fecal markers such as fecal calprotectin (FC), lipid transport protein-2, and fecal volatile organic compounds (VOCs) have been discovered [52]. We also found some serum markers and urinary metabolites such as intestinal fatty acid binding protein (I-FABP), interleukin (IL)-27, IL-6, IL-8, plasma citrulline-p, ischemic modified albumin, D-dimer, prostaglandin E2. Near-infrared spectroscopy and high-frequency ultrasound have been more helpful for the early identification of

NECs in recent years [53] [54].

3.3. Gastroesophageal Reflux (GER)

GER is the reflux of gastric or duodenal contents into the esophagus as a result of systemic or localized causes that cause lower esophageal sphincter (LES) insufficiency, gastric motility disorders, delayed emptying, etc. [55]. Its occurrence is related to the low function of the LES anti-reflux barrier, weak esophageal clearance, anatomical abnormalities of the esophagus and stomach, and gastrointestinal hormone levels. Symptoms of GER are often manifested as vomiting, refusal of breast milk, lack of weight gain, bradycardia, and decreased oxygen saturation [56] [57]. All of those can cause apnea, aspiration pneumonia, choking, and BPD which can impede the EN program. Most temporary physiologic reflux resolves spontaneously with age, but pathologic reflux occurs in 22% of preterm infants. Prompt diagnosis and treatment of GER is especially important. Diagnosis can be made by contrast fluoroscopy, ultrasound, a combination of radionuclide scanning, pH monitoring, and combined pH multichannel intraluminal impedance (pH-MII) [58]. However, NEC and FI need to be excluded when considering GER.

3.4. Meconium Stickiness

Normal meconium passage is closely related to the function of the digestive system, especially in preterm infants. When delayed passage of meconium and meconium stickiness manifests as abdominal distention, no or little defecation [59]. They are prone to gastric retention, meconium ileus (MI) [60], and even perforation, increasing the risk of FI, EUGR, and infection [61]. And delay the time to full EN. Simple meconium ileus (SMI) is more common in Asians, which only shows delayed expulsion of meconium without other imaging features, making preoperative diagnosis difficult and negative surgical exploration rate higher. For MI, it is suggested to use saline or glycerol enemas to stimulate defecation, abdominal touch, non-nutritive sucking, postural therapy, warm compresses, anal dilation, and oral contrast media are used in NICUs to assist defecation. Iodinol enemas have both diagnostic and therapeutic significance and can be repeated if necessary. A recent single-center randomized controlled trial found that breast milk enemas were also effective in promoting meconium evacuation in preterm infants and shortening the time to achieve total enteral nutrition. Aggressive promotion of meconium evacuation in the early postnatal period can save most children from surgical exploration and lead to the quicker and more successful establishment of EN.

4. Summary & Future Direction

Several guidelines at home and abroad have developed management strategies for EN in preterm infants, but there are still many problems in the successful establishment of EN due to the differences in the management of individuals and healthcare institutions, and an individualized feeding regimen should be adopted

in clinical work after a comprehensive assessment of the condition of the preterm infant. Meanwhile, the smooth implementation of EN in preterm infants requires the participation of multiple parties, and a multidisciplinary teamwork model including pediatricians, dietitians, gastroenterologists, biologists, and rehabilitators should be incorporated into the clinical application. In addition, multicenter clinical studies can be conducted in the future to compare the effects of different EN regimens on the growth, development, and prognosis of preterm infants, to study in depth the physiological mechanisms of gastrointestinal development in preterm infants, and to explore new ways to promote gastrointestinal maturation, and then to determine the optimal feeding and nutritional formulas.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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