Beneficial Effects of Probiotic Administration in Extremely Low Birthweight Infants: A Review

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Abstract: The aim of this review was to evaluate the beneficial effects of probiotic supplementation on extremely low birthweight infants (birthweight <1000 g). Extremely low birthweight (ELBW) infants are the most vulnerable population in the neonatal intensive care unit (NICU). They are at the highest risk for necrotizing enterocolitis (NEC), sepsis, and inadequate nutrition due to their immature gastrointestinal (GI) function. Nutrition plays an important role in the future neurodevelopmental outcomes of these infants. Research methods for the review were conducted using PubMed and Cumulative Index to Nursing and Allied Health Literature (CINAHL). In total, eight research studies evaluated the effect of probiotic use in ELBW infants: three studies assessed GI colonization, five studies assessed enteral feeding and GI tolerance, one study assessed growth, five studies assessed NEC, five studies assessed sepsis, and two studies assessed length of hospital stay. This review found the use of probiotics improved GI tolerance, weight gain and length of hospital stay in ELBW infants, but was unable to make conclusions on the effect of probiotic use on incidences of NEC and sepsis. More research is needed in ELBW infants before making probiotic supplementation a standard of care in this population.

Keywords: *Bifidobacterium,* extremely low birth weight infant, *Lactobacillus*, low birth weight infant, probiotics, very low birth weight infant.

INTRODUCTION

Extremely low birthweight (ELBW) infants are the highest risk group in the neonatal intensive care unit (NICU). Preliminary data from 2014 found that 8% of infants in the United States were born low birth weight (LBW), defined as a birthweight <2500 g [1]. Of those infants, the mortality rates have been the highest in infants with a birthweight of 500 g or less and has been found to decrease as birthweight increases [2]. Therefore, these ELBW infants, defined as a birthweight <1000 g, are at the highest risk, especially for gastrointestinal (GI) issues [3]. In addition, ELBW infants are also in greatest need of optimal nutrition to ensure adequate catch-up growth.

The two most common causes of morbidity and mortality in preterm infants are sepsis and necrotizing enterocolitis (NEC). These two conditions are responsible for up to 30% of deaths in this population and have substantial impact on long-term neurodevelopment [4]. NEC is a disease of the GI tract that is characterized by ischemic necrosis of the intestinal mucosa with associated inflammation and invasion of the enteric gas forming organisms [5]. The mortality rate ranges from 15.9-42% of premature infants, and ELBW infants are at three times greater risk of developing NEC than very low birthweight infants (VLBW) [6]. Diagnosis of NEC is based on three stages. Stage 1 consists of nonspecific findings such as feeding intolerance or abdominal distention. Diagnosis of stage 2 requires radiographic findings of pneumatosis intestinalis, and stage 3 findings include perforated viscus with or without intestinal necrosis [5]. Although the causes of these disorders are multifaceted, it has been hypothesized that the immaturity of the gut and the lower diversity of beneficial bacteria can play a role in the immunoprotective functions of the GI tract [7]. Occurrence of NEC or sepsis often requires enteral feedings to be held, which can result in the inadequate provision of nutrition and impact growth. Ensuring sufficient nutrition is one of the leading priorities for preterm infants. Failure to meet nutritional needs can have a negative impact on growth, neurodevelopment and morbidity [8].

Probiotics are suggested as a possible treatment option for improved GI health in premature infants. Probiotics are live microorganisms that alter the microflora and provide a health benefit to the host when given in sufficient amounts [8-9]. Numerous studies have evaluated the effect of probiotics on VLBW infants. A Cochrane review found that probiotic

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use in preterm neonates significantly reduced the risk of stage 2 or greater NEC, but found no significant difference in rate of sepsis. This review did a subgroup comparison for ELBW infants. The authors of the review found no reduction in cases of severe stage 2 to 3 NEC, sepsis, or mortality, but were unable to come to any significant conclusions due to insufficient data regarding this population [10]. A systematic review of the benefits of probiotics on enteral nutrition in preterm infants found a significant decrease in the time it took to reach full enteral feeds in VLBW infants [11]. Although these reviews included studies with ELBW infants in their cohort, they did not look exclusively at the effect of probiotics on this population. This review aimed to evaluate the beneficial effects of probiotics in ELBW infants, as they are the highest risk patient group cared for in the neonatal intensive care unit (NICU).

PROBIOTIC USE IN PREMATURE INFANTS

Preterm infants' GI tracts have less diverse bacterial colonization due to their prematurity. Healthy, term, breastfed infants typically have high concentrations of the bacteria *Lactobacillus* and *Bifidobacterium* species in their gut [7,12-16]. These beneficial bacteria are often acquired during birth through the vaginal canal, but many ELBW infants are not exposed to this due to high rate of caesarean sections [7,17]. Preterm infants in the NICU are also at increased risk for colonization of the gut by pathogens from the hospital environment [7,18]. It has been hypothesized that the supplementation of probiotics can help to increase microbial diversity in the premature infant gut to make it more comparable to that of a healthy term infant [19]. Studies on premature infants have found that colonization of the GI tract with probiotics can competitively inhibit bacterial pathogens and decrease the likelihood of bacterial translocation and infection [20]. Probiotics have also been hypothesized to help maintain the gut mucosal barrier to bacteria, increase immune response, and control intestinal inflammation [8-9,21].

The goal for premature infants is to obtain a similar rate of growth and nutrient intake compared to a fetus of the same gestational age in utero [22-24]. It is often difficult for these premature infants to obtain adequate growth, since their intestinal function is less mature than their term counterparts [17]. Their immature gut can cause issues with feeding intolerance that delay the advancement of enteral feedings and makes it difficult to meet nutritional needs [23].

Inadequate nutrition in these high-risk infants can have adverse effects on long-term development, immune capability, resistance to infection, and ability to recover from chronic diseases of prematurity. Studies have shown that growth during hospitalization is positively associated with improved neuro-developmental outcomes in ELBW infants [25]. To optimize their growth, many of these infants require supplemental parenteral nutrition, which brings additional risks such as sepsis, thrombosis and cholestasis [26]. By decreasing the time it takes to reach full enteral feedings, total parenteral nutrition could be discontinued earlier and prevent these potential complications.

ELBW infants are at an increased risk for GI issues compared to their term counterparts. They are more likely to experience dysfunction of the epithelial barrier and dysmotility of the gut [27]. This can cause translocation of bacteria from the GI tract, which plays a role in the initiation of late-onset sepsis and NEC [17]. In addition to the increased risk of NEC and sepsis in ELBW infants, it is harder for them to meet their needs because in addition to increased metabolic demands, they have poor energy and protein stores [28].

To identify studies for this review, a literature search of PubMed and CINAHL was conducted on probiotic use in ELBW infants. Searches included combinations of the following medical subject heading terms and keywords: "extremely low birth weight infant," "very low birth weight infant," "low birth weight infant," "probiotics," "*Bifidobacterium,*" and "*Lactobacillus.*" For inclusion in this review, studies needed to include subjects who had a birthweight exclusively <1000 g or stratify results into infants <1000 g. Studies also needed to have probiotic supplementation as an intervention. From these criteria, eight research papers published between 2006 and 2014 were identified and included in this review.

Effect of Probiotic Supplements on GI Tract Colonization in ELBW Infants

Three authors studied probiotic use and effect on GI tract colonization (Table **1**). One study found the probiotic group had decreased stool fungal colonization compared to the control [21]. Similarly, another study evaluated the rate of GI fungal colonization. It found that the overall rate of GI colonization of fungal species and high-grade colonization were reduced, but it was not statistically significant in the stratification of infants

Table 1: Effect of Probiotic Use on Gastrointestinal Colonization in Extremely Low Birthweight Infants

Reference	Study type/ number of participants	Probiotic dosage/ frequency/ type of EN	Entry Criteria	Results
Manzoni 2006 [3]	Double-blinded, PRCT Infants <1000 g: pro = 12, C = 8	6 x10^9 CFU *L. rhamnosus GG* Given once per day starting the third DOL until 6 wk or DC BM	BW <1500 g, >3 DOL, stable oral feeding with human milk before randomization, no baseline fungal colonization, no antifungal prophylaxis	Incidence of GI colonization: pro=41.7% vs. 61.5% (p=0.27), incidence of low-grade colonization: pro=16.7% vs. C=30.8% (p=0.36), high-grade colonization: pro=25% vs. 30.8% (p=0.55), incidence of invasive fungal infection: pro=16.7% vs. C=15.4% (p=0.63).
Roy 2014 [21]	SC, double-blinded, placebo, PRCT Infants <1000 g: pro =11, C =11	1.5 x10^9 CFU *L. acidophilus*, *B. infantis*, *B. lactis* (increased to 3 x10^9 CFU once EN reaches 50-60 ml/kg/day) Given pro daily from the first 72 h for 6 wk or until DC BM	Stable feeding within 72 h of birth, <37 wk GA, BW <2500 g, adequate renal and liver function, postnatal age <2 wk, no baseline fungal colonization at enrollment, no antifungal prophylaxis	Stool fungal colonization: pro=3.06 ± 2.03x10^5 CFU vs. C=3 ± 1.3x10^5 CFU (p=0.02).
Rougé 2009 [26]	MC, double-blinded, PRCT Infants ≤1000 g (no numbers given)	10^8 cells per unit *L. rhamnosus GG* and *B. longum* Given 4 times daily beginning on the first day of enteral feeds until DC BM	<32 wk GA, BW <1500 g, postnatal age ≤2wk, absence of any disease other than those linked to prematurity, start of EN prior to inclusion	Lower incidence of pro strain colonization in infants ≤1000 g than those >1000 gm (p=0.02).

BM=breast milk, BW=birthweight, C=control, CFU= colony forming unit, DC=discharge, DOL=day of life, ELBW=extremely low birth weight, EN=enteral nutrition, GA=gestational age, GI=gastrointestinal, h=hour, MC=multicenter, PRCT=prospective randomized controlled trial, pro=probiotic, SC=single center, wk=weeks.

<1000 g. There was also no difference in invasive fungal infection between the two groups [3]. An additional study found that GI colonization of the probiotic strain provided was reduced with decreasing weight [26].

Effect of Probiotic Supplements on Enteral Feeding and GI Tolerance in ELBW Infants

Five studies evaluated the effect of probiotic supplementation on enteral feeding and GI tolerance (Table **2**). To evaluate the benefits on enteral nutrition, many studies looked at the time it took to reach full enteral feedings and average feeding volume. Two studies found the probiotic group reached full feeds sooner and had an increased rate of feeding advancement [9,21]. In contrast, other studies found no difference in the time it took to reach full enteral feedings, the feeding ratio or feeding volume [26,29]. An additional study found no difference in average feeding volume in infants <1000 g but did encounter an increase when stratified to infants with a birthweight between 751-1000 g [8].

One study evaluated the effect of probiotics on feeding intolerance. Feeding intolerance was defined as infants having gastric residuals greater than half of the provided feeding, abdominal distention, or bloody stools. The study found an improvement in feeding tolerance of the probiotic group compared to control [9].

Another trial investigated the role of probiotic use on gastric motility and intestinal blood flow. Pre and postprandial superior mesenteric artery blood flow velocity measurements were recorded in the second week of life after at least seven days of probiotic supplementation had been provided. Researchers found that the probiotic group had an increased postprandial time-averaged mean velocity, indicating improved intestinal motility. However, this did not decrease the time to full enteral feeding, as was expected [29].

Effect of Probiotic Supplements on Growth in ELBW Infants

One study evaluated the effect of probiotic use on weight gain and growth. It found that growth velocity was increased in the probiotic group compared to control in infants <1000 g. When stratified further by birthweight, there was also an increase in growth velocity and average weight gain per day in the probiotic group with a birthweight of 501-750 g. However, this improvement in growth was not statistically significant in the 751-1000 g group [8].

Table 2: Effect of Probiotic Use on Gastrointestinal Tolerance and Time to Full Enteral Feedings in Extremely Low Birthweight Infants

Reference	Study type/ number of participants	Probiotic dosage/ frequency/ type of EN	Entry Criteria	Results
Al-Hosini 2012 [8]	MC, double blinded, PRCT pro = 50, C= 51	$5x10^8$ CFU *L. rhamnosus GG* and *B. infantis* Given once daily with first EN and continued until DC or 34 wk PMA BM	BW = 501-1000 g, AGA, ≤14 DOL at time of feeding initiation	Average volume of feeding: In whole study of infants ≤1000 g: pro=59±33 ml/kg vs. C=71±36 ml/kg (p=0.11). 501-750 g: pro=50±38 ml/kg vs. C=48±35 ml/kg (p=0.9). 751-1000 g: pro= 67±27 ml/kg vs. C=84±30 ml/kg (p=0.03).
Oncel 2014 [9]	SC, double-blinded, PRCT Infants <1000 g: pro = 93, C= 103	10^8 CFU *L. reuteri* Given once daily starting with the first EN and continued until DC BM or mixed feedings	≤32 wk GA, BW<1500 g, survived to feed enterally	TFEF: pro=9.3±3.2 d vs. C=11±4.9 d (p=0.04), rates of FI: pro=31% vs. C=51% (p=0.016), ≥2 episodes of FI: pro=9% vs. C=12% (p=0.65).
Roy 2014 [21]	SC, double-blinded, placebo, PRCT Infants <1000 g: pro =11, C =11	1.5 $x10^9$ CFU *L. acidophilus*, *B. infantis*, *B. lactis* (increased to 3 $x10^9$ CFU once EN reaches 50-60 ml/kg/day) Given pro daily from the first 72 h for 6 wk or until DC BM	Stable feeding within 72 h of birth, <37 wk GA, BW <2500 g, adequate renal and liver function, postnatal age <2 wk, no baseline fungal colonization at enrollment, no antifungal prophylaxis	Rate of feeding advancement: pro=3.51±3.0 ml vs. C=2.27±2.0 ml (p=0.013), TFEF: pro=13.22±5.04 d vs. C=17.41± 8.07 d (p=0.014).
Rougé 2009 [26]	MC, double-blinded, PRCT Infants ≤1000 g (no numbers given)	10^8 cells per unit *L. rhamnosus GG* and *B. longum* Given 4 times daily beginning on the first day of enteral feeds until DC BM	<32 wk GA, BW <1500 g, postnatal age ≤2weeks, absence of any disease other than those linked to prematurity, start of EN prior to inclusion	TFEF: pro=34 d vs. C=32 d (p=0.12).
Havranek 2013 [29]	Double-blinded, placebo, PRCT pro = 15, C =16	$5x10^8$ CFU *L. rhamnosus GG* and *B. infantis* Given pro once daily with first EN and continued until DC or 34 wk PMA BM	BW = 501-1000 g, AGA, ≤14 DOL at time of feeding initiation	Mean percent change in TAMV from preprandial state to 60 min after EN feeding: pro=43% vs. C=5.2% (p=0.035), TFEF: pro=23.9±8.3 d vs. C=22.1±8.5 d (p=0.55), feed ratio: pro=26.2±19.4 ml/kg/d vs. C=27.7±18.5 ml/kg/d (p=0.82), feed volume: pro=3.63±2.2 ml vs. C=4.00±2.6 ml (p=0.67).

AGA=appropriate for gestational age, BM=breast milk, BW=birthweight, C=control, CFU=colony forming unit, DC=discharge, DOL=day of life, EN=enteral nutrition, ELBW=extremely low birth weight, FI=feeding intolerance, GA=gestational age, GI=gastrointestinal, h=hours, SC=single center, PMA=postmenstrual age, PRCT=prospective randomized controlled trial, pro=probiotic, TAMV=time-averaged mean velocity, TFEF=time to full enteral feedings, wk=weeks.

Effect of Probiotic Supplements on Necrotizing Enterocolitis in ELBW Infants

Five studies evaluated the effect of probiotics on NEC in ELBW infants (Table **3**). A retrospective study compared the incidence of NEC in infants before and after the introduction of prophylactic use of probiotics. They found a decreased rate of all stages of NEC and NEC stage 2 after the introduction of prophylactic probiotic use [30]. Another study found a decreased incidence of death or NEC ≥ stage 2 in infants weighing 500-750 g, but not for infants weighing 751-1000 g [31]. Other studies found no significant difference between probiotic and control in incidence of NEC [8-9,21], NEC ≥2 stage 2 [9,31], or death attributable to NEC [9].

Effect of Probiotic Supplements on Rates of Sepsis and Infection in ELBW Infants

Six studies investigated rates of sepsis and infection (Table **4**). One study found that sepsis occurred more frequently in the probiotic group, but there was no difference in Gram-positive or negative sepsis between the two groups [31]. Another study found a reduced rate of Candida infection and total fungal infection in

Table 3: Effect of Probiotic Use on Necrotizing Enterocolitis in Extremely Low Birthweight Infants

Reference	Study type/ number of participants	Probiotic dosage/ frequency/ type of EN	Entry Criteria	Results
Al-Hosini 2012 [8]	MC, double blinded, PRCT pro = 50, C= 51	5x10^8 CFU *L. rhamnosus GG* and *B. infantis* Given once daily with first EN and continued until DC or 34 wk PMA BM	BW = 501-1000 g, AGA, ≤14 DOL at time of feeding initiation	Incidence of NEC in pro=6% vs. C=8% (RR=0.77).
Oncel 2014 [9]	SC, double-blinded, PRCT Infants <1000 g: pro = 93, C= 103	10^8 CFU *L. reuteri* Given once daily starting with the first EN and continued until DC BM or mixed feedings	≤32 wk GA, BW<1500 g, survived to feed enterally	Incidence of death or NEC: pro=16.1% vs. to C=3.3% (p=0.14), NEC stage ≥2: pro=5.4% vs. C=8.7% (p=0.26), death attributable to NEC: pro=2.2% vs. C=2.9% (p=0.73), death attributable not to NEC: pro=9.7% vs. C=13.6% (p=0.39).
Roy 2014 [21]	SC, double-blinded, placebo, PRCT Infants <1000 g: pro =11, C =11	1.5 x10^9 CFU *L. acidophilus*, *B. infantis*, *B. lactis* (increased to 3 x10^9 CFU once EN reaches 50-60 ml/kg/day) Given pro daily from the first 72 h for 6 wk or until DC BM	Stable feeding within 72 h of birth, <37 wk GA, BW <2500 g, adequate renal and liver function, postnatal age <2 wk, no baseline fungal colonization at enrollment, no antifungal prophylaxis	NEC: pro=1 vs. C=1 (p>0.5).
Hunter 2014 [30]	Retrospective cohort study pro= 79, C = 232	~5.5 x10^7 CFU *L. reuteri* Given once daily starting beyond the first 1-2 wk of life (starting 2010, given within the first wk of life) and continued until DC BM or mixed feedings	BW ≤1000 g	NEC: years before routine pro prophylaxis=15.1% vs. years with routine pro prophylaxis=2.5% (p=0.0475).
Lin 2008 [31]	MC, blinded, placebo, PRCT Infants 500-750 g: pro=33, C=18; Infants 751-1000 g: pro=69, C=61	10^9 CFU *L. acidophilus*, 10^9 CFU *B. bifidium,* 125 mg/kg per dose twice daily Given twice daily starting with first feeding for 6 wk BM or mixed feedings	<34 wk GA, BW <1500 g, survived to feed enterally	Death without NEC: infants 500-750 g: pro=0% vs. C=16.66% (p=0.04), infants 751-1000 g: pro=0% vs. C=4.91% (p=0.11), death or NEC: 500-750 g: pro=3.03% vs. C=27.77% (p=0.02), 751-1000 g: pro=4.34% vs. C=13.11% (p=0.7), NEC stage ≥2: 500-750 g: pro=3.03% vs. C=11.11% (p=0.29), 751-1000 g: pro=4.34% vs. 8.19% (p=0.47).

BM=breast milk, BW=birthweight, C=control, CFU=colony forming units, DC=discharge, DOL=day of life, EN=enteral nutrition, ELBW=extremely low birthweight, MC=multicenter, NEC=necrotizing enterocolitis, PMA=postmenstrual age, PRCT=prospective randomized controlled trial, pro=probiotic, SC=single center, wk=weeks.

the probiotic group [21]. In contrast, one study found a decreased incidence of culture-proven sepsis in the group that was given probiotics [9]. Other studies found no difference in the incidence of sepsis [8,26], or culture-positive bacterial or fungal infection [30].

Effect of Probiotic Supplements on Length of Hospital Stay in ELBW Infants

Two studies evaluated the effect of probiotic use on length of hospital stay. Both studies found that infants' length of time in the hospital decreased when they were given probiotic supplements. The length of time in the hospital was decreased by more than five days in one study [21], and more than ten days in the other [9].

DISCUSSION

This review shows mixed results on the benefit of probiotic use on GI colonization and time to full enteral feedings. One study found that there was a decreased colonization of fungal species with the use of probiotics [21]. This suggests that the probiotics were able to compete with the harmful bacteria and reduce development of infection. This same study found an improvement in time to full enteral feedings, which is in

Table 4: Effect of Probiotic Use on Sepsis and Infection in Extremely Low Birthweight Infants

Reference	Study type/ number of participants	Probiotic dosage/ frequency/ type of EN	Entry Criteria	Results
Al-Hosini 2012 [8]	MC, double blinded, PRCT pro = 50, C= 51	$5x10^8$ CFU *L. rhamnosus GG* and *B. infantis* Given once daily with first EN and continued until DC or 34 wk PMA BM	BW = 501-1000 g, AGA, ≤14 DOL at time of feeding initiation	Bacterial or fungal sepsis: pro=26% vs. C=31% (RR=0.83), any bacterial sepsis: pro=22% vs. C=31% (RR=0.70).
Oncel 2014 [9]	SC, double-blinded, PRCT Infants <1000 g: pro = 93, C= 103	10^8 CFU *L. reuteri* Given once daily starting with the first EN and continued until DC BM or mixed feedings	≤32 wk GA, BW<1500 g, survived to feed enterally	Incidence of culture proven sepsis: pro=6.5% vs. 18.4% (p=0.01).
Roy 2014 [21]	SC, double-blinded, placebo, PRCT Infants <1000 g: pro =11, C =11	1.5 $x10^9$ CFU *L. acidophilus*, *B. infantis*, *B. lactis* (increased to 3 $x10^9$ CFU once EN reaches 50-60 ml/kg/day) Given pro daily from the first 72 h for 6 wk or until DC BM	Stable feeding within 72 h of birth, <37 wk GA, BW <2500 g, adequate renal and liver function, postnatal age <2 wk, no baseline fungal colonization at enrollment, no antifungal prophylaxis	Candida infection: pro=1 vs. C=3 (p=0.001), no fungal infection: pro=6 vs. C=2 (p=0.001).
Rougé 2014 [26]	MC, double-blinded, PRCT Infants ≤1000 g (no numbers given)	10^8 cells per unit *L. rhamnosus GG* and *B. longum* Given 4 times daily beginning on the first day of enteral feeds until DC BM	<32 wk GA, BW <1500 g, postnatal age ≤2weeks, absence of any disease other than those linked to prematurity, start of EN prior to inclusion	Nosocomial infection: pro=75% vs. C=64% (p=0.51).
Hunter 2014 [30]	Retrospective cohort study pro= 79, C = 232	~5.5 $x10^7$ CFU *L. reuteri* Given once daily starting beyond the first 1-2 wk of life (starting 2010, given within the first wk of life) and continued until DC BM or mixed feedings	BW ≤1000 g	Late onset gram-negative bacterial or fungal infection: years before routine pro prophylaxis=31% vs. years with routine pro prophylaxis=22.8% (p=0.1112)
Lin 2008 [31]	MC, blinded, placebo, PRCT Infants 500-750 g: pro=33, C=18; Infants 751-1000 g: pro=69, C=61	10^9 CFU *L. acidophilus*, 10^9 CFU *B. bifidium,* 125 mg/kg per dose twice daily Given twice daily starting with first feeding for 6 wk BM or mixed feedings	<34 wk GA, BW <1500 g, survived to feed enterally	Gram-positive sepsis: 500-750 g: pro=27.3% vs. C=5.6% (p=0.08), 751-1000 g: pro=11.6% vs. C=14.8% (p=0.59), gram-negative sepsis: 500-750 g: pro=9.1% vs. 0% (p=0.54), 751-1000 g: pro=13.0% vs. 6.6% (p=0.22).

AGA= appropriate for gestational age, BM=breast milk, BW=birthweight, C=control, CFU=colony forming units, DC=discharge, DOL=day of life, EN=enteral nutrition, ELBW=extremely low birthweight, GA=gestational age, h=hours, MC=multicenter, PMA=postmenstrual age, PRCT=prospective randomized controlled trial, pro=probiotic, SC=single center, wk=weeks.

agreement with numerous studies on VLBW infants [4,17,20,32-33]. An additional study found that probiotic supplementation improved GI tolerance and time to full enteral feeding, suggesting that probiotics may improve intestinal motility, feeding tolerance, and assist in reaching full enteral feedings sooner [9]. Comparably, another study found improved intestinal motility, but this did not correlate with an improvement in time to full enteral feedings [29]. In contrast, one study found GI colonization of beneficial bacteria was improved in infants <1500 g, but the effect was reduced as weight decreased. Consequently, these ELBW infants failed to have improvement in time to full enteral feedings. The authors noted that these results may also be related to the increased use of antibiotics and increased frequency of held feedings in these ELBW infants, making it more unlikely for colonization [26].

Multiple meta-analyses have found a significant reduction in NEC with use of probiotics in VLBW infants. Due to the low number of ELBW infants included in these meta-analyses, the researchers were unable to detect a significant difference in those using probiotics [10,34]. The risk of NEC was inversely associated with birthweight, indicating that ELBW infants were the highest risk group. This review found

mixed results on the effect of probiotic use on NEC in ELBW infants. Two studies did find a decrease in the incidence of NEC [30,31]. Another study found significance for only the infants with a birthweight between 500-750 g. Of note, this study failed to stratify based on birthweight during randomization, which makes the results more difficult to translate due to type II error [31].

This review found varied results on probiotics reducing the incidence of sepsis and infection. The meta-analyses on VLBW infants found a slight positive effect on incidence of sepsis but did not reach statistical significance [10,34]. There was one study in this review that found a decrease in culture-positive sepsis [9]. Three others found no difference [8,26,31], and the remaining study found an increased rate of sepsis in those receiving probiotics [9]. In addition, multiple case studies have found associations between probiotic use and sepsis in VLBW and ELBW infants [35-37]. This suggests that probiotics likely do not decrease the incidence of sepsis, but these few cases do not necessarily indicate that they are the cause.

It is difficult to determine the effect of probiotic use on growth in ELBW infants. There was only one study that reported results on growth and found positive effects [9]. This is in agreement with a previous study in VLBW infants [12]. There were also minimal studies that reported on length of hospital stay in this review. Two studies did find a decrease in length of hospital stay with the use of probiotics [9,21]. As expected, both of these studies found that infants reached full enteral feedings sooner.

This review suggests that probiotic supplementation may have a positive effect on the health and wellness of ELBW infants. Probiotics have been found to improve GI tolerance and motility, which is often an obstacle in providing adequate nutrition in ELBW infants. Interestingly, not all studies found an improvement in time to full enteral feedings, which would be expected with improvement GI function. This may be due to differing practices of facilities on how long enteral feedings are held for procedures or frequency of antibiotic use. Of those studies with reduced time to enteral feedings, there was also found to be improved weight gain, and decreased length of hospital stay. Due to the mixed results, it is difficult to make conclusions regarding the effect of probiotic use on NEC in ELBW infants. The risk of sepsis also needs to be considered in this immunocompromised population. Since there is convincing evidence of the benefit of probiotics on NEC in VLBW infants, it is reasonable to assume that there may be benefits for ELBW infants. More studies are needed on exclusively ELBW infants to weigh out the risks and benefits in this population.

In order to accurately interpret these results, there are strengths and limitations to this review that must be considered. One strength is that seven of the eight studies included were randomized controlled trials (RCT). All of these RCT were blinded and used a placebo for comparison. In addition, a majority of the studies followed a feeding protocol to ensure that feedings were started and advanced in the same manner to eliminate any inconsistency. A major weakness of this review is the variation in type, dosage, initiation and duration of probiotics use, as well as the use of single-strain versus multiple-strains supplement. Another important limitation is the lack of studies that included only ELBW infants. Only three of the eight studies evaluated included infants <1000 g. The other five studies stratified the study infants into the <1000 g category, creating small sample sizes of these infants. The studies that stratified their results into <1000 g did not evaluate all outcomes that were assessed in the full study.

The conclusions drawn here suggest several areas for future research. While it may be assumed that results in VLBW infants can be extrapolated to ELBW infants, they have unique barriers to overcome. ELBW infants begin with lower nutrient stores and are more likely to have medical conditions that are given priority over delivering adequate nutrition. Since they are the most vulnerable population and at highest risk of NEC, it would make finding prevention strategies in this group even more imperative. More research is needed to determine an appropriate probiotic strain to be sure it can be produced by a reputable source in a safe manner. Further studies should also measure long term outcomes in these infants to provide a full picture of the benefits.

CONCLUSION

Although there have been numerous research studies on the benefits of probiotic use in VLBW infants, data are insufficient in the ELBW population. This vulnerable group could benefit the most from normalizing gut microbiota, advancing enteral feedings more quickly, and the prevention of devastating diseases such as NEC. This review found that probiotics may provide a benefit on feeding tolerance

and GI motility. Even the slightest improvement in GI tolerance can promote positive nutritional outcomes and effect long-term development in ELBW infants. It is difficult to determine the effectiveness of probiotic use on growth and length of hospital stay due to the limited studies available on ELBW infants. Although there were some positive results in the use of probiotics, more research is needed in these ELBW infants before conclusions can be reached and it is made a standard of care in this population.

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