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Prevention of Necrotizing Enterocolitis Through Manipulation of the Intestinal Microbiota of the Premature Infant

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Abstract

In spite of four decades of research, necrotizing enterocolitis (NEC) remains the most common gastrointestinal complication in premature infants with high mortality and long-term morbidity. The composition of the intestinal microbiota of the premature infant differs dramatically from that of the healthy term infant and appears to be an important risk factor for NEC. Promising NEC prevention strategies that alter the intestinal microbiota include probiotics, prebiotics, synbiotics, lacteroferrin, and human milk feeding.

Keywords

human milk; probiotic; prebiotic; synbiotic; lactoferrin; necrotizing enterocolitis; premature infant

Introduction

Necrotizing enterocolitis (NEC) is a common and devastating disease of premature infants. It affects approximately 7% of infants weighing between 500 and 1,500 g with mortality rates as high as 30%[1]. The pathophysiology of NEC has been an area of active study for four decades. Current thinking suggests that NEC is not a single disease or infection but the final pathway of a variety of insults. Risk factors include prematurity of the innate and adaptive immune responses (e.g. a poorly regulated inflammatory responses and alterations in intestinal permeability, motility, apoptosis, and autophagy), enteral feeding, an altered intestinal microbiota and variation in intestinal perfusion[1-3]. The current clinical staging of NEC was initially proposed by Bell[4] and modified by Walsh[5] and has endured for three decades. The challenges of this classification include disagreements among experts as to the clinical relevance of stage 1 NEC (resulting in variation in inclusion of stage 1 NEC in

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reports of clinical trials and cohort studies), the lack of distinction between NEC and spontaneous ileal perforation without necrosis, and a lack of evidence regarding applicability to term infants with NEC. Treatment of NEC has changed little over the decades: bowel rest, broad-spectrum antibiotics, parenteral nutrition, with support of ventilation and blood pressure and either peritoneal drainage or resection of necrotic bowel in severe cases. There is significant short-term morbidity, including abnormal bowel function, prolonged parenteral nutrition requiring central line placement, and longer lengths of stay in hospital with significantly higher costs[6]. Long term morbidity includes poor growth, malabsorption and delays in neurodevelopment[7].

Two compelling observations shed light on the pathogenesis of NEC. First, the onset of NEC is generally at 2-6 weeks of life and tends to occur later in the most premature infants with the highest risk of NEC at 29-33 weeks corrected gestational age[8]. This observation supports the hypothesis that a certain level of "maturation" of the immune system is required for NEC pathogenesis. It is likely not coincidental that the Paneth cells of the small intestine become functional at about this time. These sentinels of the crypts of Lieberkuhn shape the composition of the intestinal microbiota and protect the intestinal stem cells from injury[9, 10]. Second, small but carefully performed studies demonstrate alterations in the intestinal microbiota prior to the onset of NEC. The term dysbiosis implies an alteration in the composition of the intestinal microbiota and/or microbiome related to disease. Independent investigators have demonstrated that an early predominance of Firmicutes (particularly Clostridiaceae) in the first weeks of life predisposes to NEC and that a sudden bloom of Proteobacteria (particularly Enterobacteriaceae) is common in the days just prior to the onset of NEC[11-14]. The latter observation is particularly compelling in light of the capacity of several Enterobacteriaceae to trigger an inflammatory response and then outcompete other commensal bacteria by selective consumption of the products of inflammation[15]. In this article, we will touch briefly on the causes of dysbiosis in the premature infant and review the efficacy of attempts to prevent NEC by dietary interventions designed to correct dysbiosis including probiotics, prebiotics, synbiotics, lactoferrin, and human milk.

Gut colonization and dysbiosis in premature infants

For many years, accepted dogma maintained that the *in utero* environment was sterile and that the intestinal tract of the fetus was not colonized with bacteria until the time of rupture of membranes. Recent studies suggest that the fetal membranes are not impermeable to bacteria and that many fetuses are exposed to microbes in the amniotic fluid before delivery[16-18]. The impact of this early exposure is unclear. While early colonizers of the infant gut are heavily influenced by mode of delivery[19], the "second wave" of colonists in term infants is mostly determined by feeding type with breast fed infants dominated by bifidobacteria and bacteroides and formula fed infants dominated by streptococci, staphylococci and lactobacilli[20]. The "second wave" of gut colonists in premature infants is less influenced by type of feeding and differs markedly from that of term infants with high numbers of Clostridiaceae and Enterobacteriacea and relatively low numbers of Bifidobacteriaceae and Bacteroidetes[21-25]. Perhaps the most important influence on the composition of the premature gut microbiota is degree of prematurity[26]. The use of acid suppressive medication delays intestinal transit time, alters the intestinal microbiota[27] and

increases the risk of NEC[28]. In addition, antibiotic administration leads to changes in the composition of the gut microbiota, suppressing growth of both commensal and pathogenic bacteria, and increases the risk of NEC[25, 29, 30]. In spite of (or perhaps in part related to) aggressive cleaning protocols, the NICU environment is an important source of pathogenic organisms and influences intestinal colonization of infants with prolonged hospitalizations[31]. Other potential influences on the intestinal microbiota of premature infants include duration of feeding tubes, kangaroo skin-to-skin care, periods of gut rest, administration of colostrum to the buccal mucosa[32] and genetic factors (e.g. common mutations in the FUT2 gene)[33, 34]. Among the many factors predisposing to dysbiosis in premature infants, those with clear associations with NEC include degree of prematurity[26], formula feeding[35], antibiotics[29, 36], and acid-blocking agents[28]. The concept of altering the intestinal microbiota or correcting dysbiosis to decrease risk of NEC is promising. We will review five overlapping strategies: probiotics, prebiotics, synbiotics, lactoferrin and human milk (Figure 1).

Probiotics

Probiotics are biological formulations or dietary supplements containing living microorganisms, most commonly one or more of the following genera: Bifidobacterium, Lactobacillus, Streptococcus, Escherichia, or *Saccharomyces*[37, 38]. Most currently available probiotics were selected because of their ease of production, stability, or food-preservative properties, rather than based on a specific mechanism of disease prevention. Mounting evidence suggests that in addition to influencing the composition and diversity of the intestinal microbiota, probiotic microbes influence the host innate and adaptive immune systems through a variety of mechanisms. Many of these mechanisms appear to be species, subspecies, or even strain specific. For example, three species of *Bifidobacterium* decrease incidence and severity of NEC in animal models[39-41] but appear to utilize different mechanisms: *B. longum* subsp *infantis* attenuates induction of IL6, IL8, TNFα and IL23 in the rat NEC model[39], decreases IL1β induced IL8 and IL6 expression in immature human gut xenografts[42], and has a competitive advantage over other gut microbes in the presence of human milk oligosaccharides[43]; *B. bifidum* improves barrier function[44], decreases apoptosis[45] and attenuates IL6 induction in the rat NEC model[40] and alters short chain fatty acid production *in vitro* in feces from premature infants[46]; and *B. breve* decreases inflammation in the rat NEC model[41] and alters butyrate production[46] and increases serum levels of TGFβ expression in premature infants[47]. Lactobacilli also show diversity of function with 3 species that decrease NEC in animal models[48-50] with different mechanisms: *L. acidophilus* secretes one or more molecules that inhibit induction of inflammation by platelet activating factor[51] and alters expression of hundreds of genes important in apoptosis, angiogenesis, and immune response[52]; *L. reuteri* decreases expression of IL6 and TNFα and increases ileal regulatory T cells in the rat NEC model[53] and increases intestinal motility[54]; *L. rhamnosus* (strain GG, ATCC 53103) decreases expression of TNFα and MIP2 through upregulation of the IL10 receptor[55] and decreases intestinal permeability[56] through both increased expression of tight junction proteins[57] and decreased apoptosis[58], while a different strain (HN001) decreases incidence and severity of NEC in both a mouse and a piglet model, through alterations in TLR9 signaling[49].

Multiple randomized placebo-controlled clinical trials (RCT) and cohort studies of probiotics in premature infants have been performed. A recent meta-analysis of 20 RCTs found probiotics to decrease the risk of NEC (OR 0.43, 95% CI 0.31-0.56) and death (OR 0.65, 95% CI 0.52-0.81) in this high risk population[37]. A meta-analysis of 12 cohort studies including more than 10,000 premature infants found similar rates of protection (RR for NEC 0.55, 95% CI 0.39-0.78 and RR for death 0.72, 95% CI 0.61-0.85)[59]. Tables 1[47, 60-91] and 2[92-101] summarize English language RCTs and cohort studies in premature infants that included NEC, sepsis, or death as a reported outcome. The recent publication of the much awaited PiPS trial[60] which showed no improvement in NEC, sepsis, or mortality in 1315 premature infants with gestational age 23-30 weeks randomized to receive either *B. breve* (strain BBG-001) or placebo underscores the importance of determining the best species and strain of probiotic for NEC prevention and that this choice may differ based on populations and genetics. Clinical trials comparing probiotic species or strains in premature infants are needed. Given the significant challenges, including the large required sample size and the high rates of cross-contamination, cluster-randomized trials may be of particular value[69].

Probiotics are not without risk, particularly in vulnerable populations such as premature infants. Oversight of production of probiotic products varies from country to country. In the U.S. most commercial probiotics are marketed as dietary supplements with no claims of prevention, treatment, or mitigation of disease. Several studies have demonstrated that most commercial products have limited reliability in terms of purity, composition and numbers of live organisms[102, 103]. Observations of cross-contamination among infants within a NICU suggest that results of RCTs may be blunted by colonization of the probiotic in the placebo infants[104, 105]. Even more concerning are rare reports of contamination of commercial probiotics with pathogenic microbes; a recent such case resulted in the death of a premature infant[106]. Sepsis cases resulting from translocation of ingested probiotics into the systemic circulation are rare but have been reported for many probiotic species[107-109].

Prebiotics

Prebiotics are non-digestible dietary products that selectively stimulate the growth or activity of beneficial commensal bacteria[110, 111]. The most commonly administered prebiotics include lactulose, inulin, polydextrose, short-chain (sc) and long-chain (lc) fructo-oligosaccharides and galacto-oligosaccharides, and combinations of the above. The potential complexity of the prebiotic approach to altering the gut microbiota is exemplified by the observations that different isomers of GOS are preferentially consumed by different species of *Bifidobacterium*[112] and that some gut pathogens (e.g. *E coli* EHEC and *C. perfringens*) are able to consume some isomers of GOS[113]. Studies in premature infants demonstrate that prebiotics increase fecal *Bifidobacteria*[114-116], decrease fecal pH[115, 117, 118], reduce stool viscosity[118], improve gastric motility[117, 119], decrease feeding intolerance[117, 119], alter production of protective short chain fatty acids[120], enhance immune response[121], and increase secretory IgA[119, 122, 123].

RCTs of prebiotics in premature infants that reported NEC, sepsis or death are summarized in Table 3[61, 124-127]. Most studies randomized infants and initiated therapy with the first feed or before the third day of life, and duration of therapy was typically until hospital discharge.

A meta-analysis including 7 trials in premature infants found that supplementation with prebiotics increased fecal *Bifidobacteria* and *Lactobacilli*, but did not improve the outcomes of NEC, sepsis or time to full enteral feeding[114]. Limited follow-up studies of premature infants treated with prebiotic supplements show no significant decrease in allergic or infectious diseases or vaccine response at 12 months of age[128, 129]. Two possible explanations for the limited efficacy of prebiotics in premature infants include 1) lack of specificity of commercial prebiotics (i.e. both commensal and potentially pathogenic bacteria are able to use some commercial prebiotics as a food source[113]) and 2) provision of a targeted prebiotic (food source for a limited number of species) without an inoculation of the associated probiotic commensals may be ineffective in cases of severe dysbiosis as seen in premature infants.

Synbiotics

A synbiotic is a product that contains both a probiotic microbe and a prebiotic substrate. This combination is particularly compelling as competition for food often determines the composition of the microbiota in a given anatomic niche. The challenge in administration of an effective synbiotic may be in the careful selection of both the prebiotic and the probiotic, with the ideal combination likely including a prebiotic that is consumable by specific commensal gut microbes and not by pathogens or pathobionts and a probiotic with desirable mechanisms of protection. RCTs of synbiotics in premature infants are summarized in Table 4[61, 130, 131]. Future studies of highly specific synbiotic combinations are needed. Human milk is discussed separately, but may represent the quintessential synbiotic given the presence of both prebiotic human milk oligosaccharides and live bacteria.

Lactoferrin

Lactoferrin is a complex molecule found in abundance in human milk with prebiotic[132], antimicrobial[133], and anti-inflammatory properties[134]. In addition lactoferrin may influence the intestinal microbiota by sequestering iron (the competition for iron in the intestinal lumen is fierce as evidenced by the complexity of bacterial products that facilitate iron recruitment[135]). Both bovine lactoferrin and recombinant human lactoferrin have been studied in RCTs in premature infants with and without a probiotic with mixed results (Table 5[136-140]). A recent meta-analysis reported that oral lactoferrin supplementation decreased late onset sepsis (number needed to treat for an additional beneficial (NNTB) 11), NEC (NNTB 20) and all-cause mortality (NNTB 20). Supplementation with both lactoferrin and a probiotic decreased late onset sepsis (NNTB 8) and NEC (NNTB 20) but not all-cause mortality. Oral lactoferrin with or without probiotics decreased fungal sepsis but did not decrease chronic lung disease or length of hospital stay[141]. Most reports supported administration of lactoferrin as safe in preterm infants[136, 138]. Some researchers have excluded infants with a family history of cow's milk allergy from trials of bovine lactoferrin[142].

Human milk

Human milk has been described as a tissue (similar to plasma) rather than simply a food source given its incredible complexity. Human milk contains secretory immunoglobulin A, lactoferrin, lysozyme, bile salt-stimulating lipase, growth factors, and human milk

oligosaccharides (HMOs), all of which provide protective benefits that could potentially contribute to a reduction of NEC. The decrease in NEC with provision of human milk seems to be dose related[35]. As we have already addressed lactoferrin and data on specific activity of most other human milk components are limited, we will focus on HMOs and human milk bacteria.

HMOs are abundant complex sugar molecules that are not digestable by the human intestinal tract due to the lack of glycosidases necessary to cleave the specific linkages that characterize these molecules. The obvious question is why a mother expends tremendous energy at great cost to herself, even in times of famine, to produce molecules that are not a food source for her infant. The partial answer to this compelling question is that HMOs are a potential food source for intestinal microbes (ie a prebiotic)[143]. Testing of a wide variety of gut microbes in culture media with HMOs as the only carbon source has revealed that HMOs are highly specific: only a relatively few species of bifidobacteria and bacteroides are able to consume HMOs[144-146]. Evaluation of bacterial genomes has confirmed that only these few species encode the complex array of glycosidases necessary to transport and digest HMOs[147, 148]. In other words, HMOs and the few bacteria that are able to consume them either represent a marvelously complex co-evolution of human lactation and a select group of commensal bacteria or incredibly clever design. The complexity of HMO production (with variability from woman to woman and within a given woman over time in the numbers and types of HMOs) allows a mother to shape the microbiota of her offspring[149].

Recent studies suggest that some HMO structures are more readily consumed by gut microbes than others[150, 151] and that some HMOs are absorbed from the gut into the bloodstream and can be detected in plasma[152] with a subset of these structures filtered by the kidneys and detectable in the urine[153]. In addition, mothers who deliver prematurely have a higher degree of variability in production of fucosylated HMOs than mothers who deliver at term[154]. This variation among the more than 100 HMOs characterized to date suggests that some HMOs may be more important in shaping the gut microbiota than others. As an example, about 20% of the North American population is homozygous for a common deletion in the FUT2 gene. These individuals are unable to produce a fucosyl transferase that is essential to creation of α1-2 fucosyl linkages in secreted glycans and have been historically referred to as non-secretors. Non-secretor individuals are at higher risk for some inflammatory diseases of the intestinal tract (e.g. Crohn's disease and celiac disease) and at lower risk for some intestinal infectious diseases (e.g. norovirus and rotavirus)[155-158]. Non-secretor mothers are unable to create specific fucosylated HMOs (e.g. 2'fucosyllactose) which appears to influence the intestinal microbiota of their infants[159].

In a rat model, a specific HMO, disialyllacto-N-tetraose (DSLNT) appears to be protective against NEC[160, 161]. One clinical study indicated that low concentrations of DSLNT in 4-day mother's milk were associated with increased risk of NEC in VLBW premature infants with HIV-infected mothers ($p < 0.05$)[162]. These observations suggest that the protective effect of HMOs against NEC may be highly structure-specific.

The questions of whether human milk contains live bacteria and the origin of these bacteria may have particular relevance to the intestinal microbiota of the premature infant.

Historically milk was thought to be sterile until contaminated by bacteria from the mother's skin and the baby's oral cavity. However recent studies of the milk microbiota suggest that some of the microbes present in human milk originate in the mother's gut with transfer likely occurring through the fecal-skin route or through the maternal lymphatic system with gut microbes being shuttled to the breast by dendritic cells or macrophages[163]. Much is yet to be discovered in this area, however studies of manipulation of the mother's intestinal microbiota to improve the health of her infant are promising, particularly in the prevention of allergies and atopic disease[164], necrotizing enterocolitis[165] and preterm labor[166].

Conclusion

The premature infant is particularly vulnerable to NEC and sepsis likely due to the combination of immature immune responses and dysbiosis. Manipulating the composition of the intestinal microbiota and expression of gut microbial genes is a promising strategy which impacts both of these factors. Among the interventions reviewed, human milk, probiotics, and lactoferrin are currently the most promising. Second generation probiotics, selected based on specific mechanisms of action and/or bacterial genomic sequence and produced at high standards of purity and viability are high priorities. Given that none of the current approaches completely eliminates NEC, further clinical trials and cohort studies of novel probiotics or probiotic combinations for mother and/or baby, combinations of lactoferrin and novel probiotics, and individualized supplementation of human milk with deficient components (e.g. specific HMO or sIgA molecules) in premature infants are indicated.

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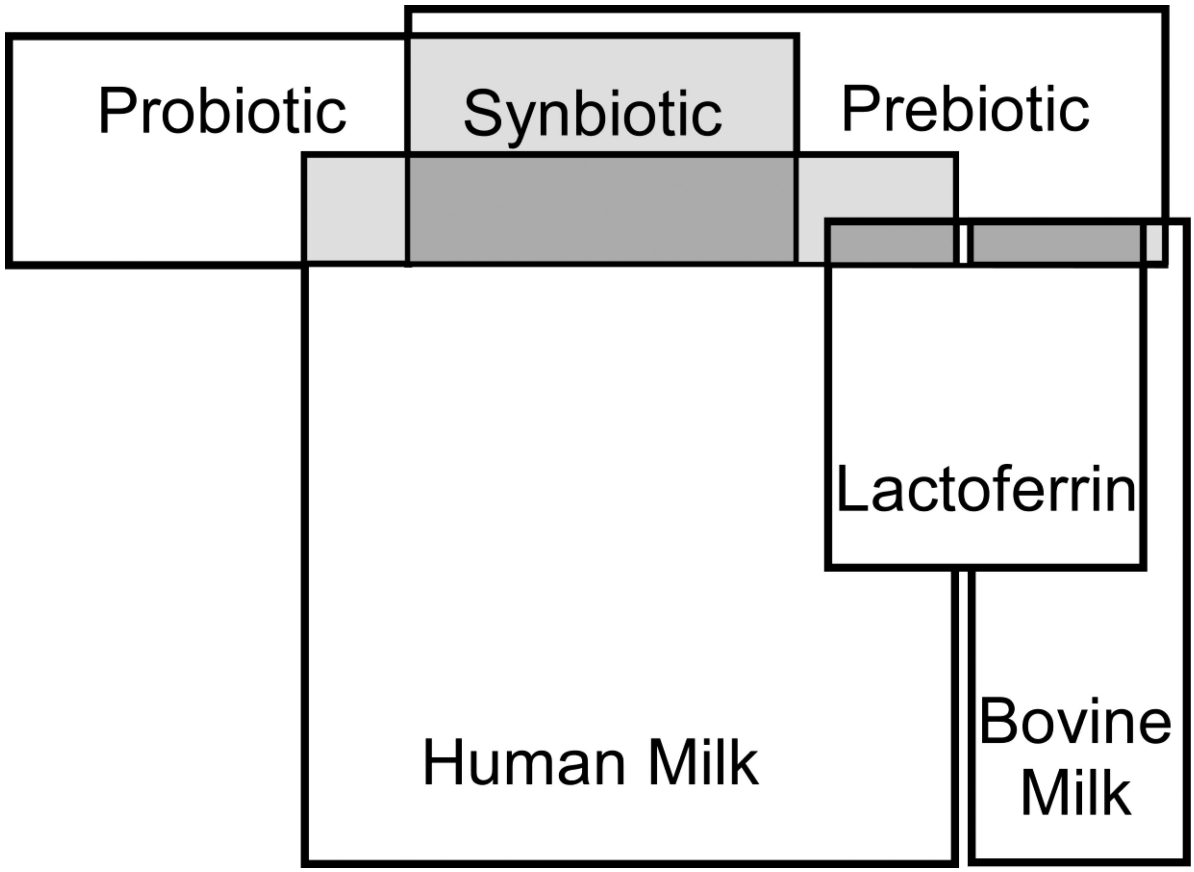

Figure 1.
Dietary and supplemental strategies for altering the intestinal microbiota of the premature infant. Shading represents areas of overlap.

Table 1

Summary of probiotic RCTs in premature infants

Author Year	Country	Probiotic Species (strain)	Brand (Company)	Population	Dose × duration	Number enrolled		NEC cases Stage 2, 3		Culture + sepsis cases		Deaths	
						Prob	Cont	Prob	Cont	Prob	Cont	Prob	Cont
Costeloe 2015[60]	UK	B breve (BBG 001)	NR (Yakult)	GA 23-30w	1.6e8-1.6e9/d until 36w	650	660	62	66	73	77	54	56
Dilli 2015[61]	Turkey	B lactis (NR)	Maflor (Mamse l)	BW < 1500g + GA < 32w	5e9/d × 8w	100	100	2	18	8	13	3	12
Saengtawes in 2015[62]	Thailand	L acidophilus + B bifida (NR)	Infloran (NR)	BW < 1500g + GA < 34w	2e9 BID × 6w	31	29	1	1	2	1	0	0
Tewari 2015[63]	India	Bacillus clausii (NR)	Enterogermina (Sanofi Aventis)	GA < 34w	8e8 TID × 3-5w	123	121	0	0	20	25	12	14
Hays 2015[64]	France	B lactis + B longum(NR)	NR	BW 700-1600g + GA 25-31w	1e9/d × 4-6w	48	52	5	3	8	10	1	1
		B lactis (NR)				50		2		9		1	
		B longum (NR)				49		1		8		3	
Van Niekirk 2015[65]	South Africa	B infantis (NR) + L rhamnosus (GG)	Pro-B2 (C Pharm)	BW < 1250g	7e8/d × 28d	91	93	0	4	15	10	5	7
Dutta 2015[66]	India	L acidophilus + L rhamnos	NR (Aristo)	GA 27-33 w	1e10 BID × 21d us + B longum + S boulardii (NR)	38	35	1	0	3	6	3	2
					1e10 BID × 14d	38		3		1		3	
					1e9 BID × 21d	38		2		6		2	
Patole 2014[67]	Australia	B breve (M-16V)	NR (Morinaga)	BW < 1500g + GA < 33w	3e9/d until 37w	79	80	0	1	17	12	0	0
Oncel 2014[68]	Turkey	L reuteri (DSM 17938)	NR (Biogaia AB)	BW < 1500g + GA < 32w	1e8/d until discharge	200	200	8	10	13	25	15	20
Totsu 2014[69]	Japan	B bifidum (OLB 6378)	NR (Meiji)	BW < 1500g	1.25e 9 BID until > 2kg	153	130	0	0	6	10	2	0
Jacobs 2013[70]	Australia + NZ	B infantis (BB-02) + S thermophiles (TH-415957) + B lactis (BB-1215954)	ABC Dophilus (Solgar)	BW < 1500g + GA < 32w	1e9/d until discharge	548	551	11	24	72	89	27	28
Serce 2013[71]	Turkey	Saccharomyces boulardii (NR)	Reflor (Biocodex)	BW < 1500g + GA < 32w	5e8/kg BID until discharge	104	104	7	7	72	89	27	28
Demirel 2013[72]	Turkey	Saccharomyces boulardii (NR)	Reflor (Biocodex)	BW < 1500g + GA < 32w	5e9/kg BID until discharge	135	136	6	7	20	21	5	5
Rojas 2012[73]	Colombia	L reuteri(DSM 17938)	NR (Biogaia AB)	BW < 2000g	1e8/d until discharge	372	378	9	15	24	17	22	28

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Author Year	Country	Probiotic Species (strain)	Brand (Company)	Population	Dose × duration	Number enrolled		NEC cases Stage 2, 3		Culture + sepsis cases		Deaths	
						Prob	Cont	Prob	Cont	Prob	Cont	Prob	Cont
Fernandez-Carrocera 2012[74]	Mexico	L acidophilus + L rhamnosus + L casei + L plantarum + B infantis + S thermophiles (NR)	107M96 y 106M96 (Italmex)	BW < 1500g	3e9/d (NR)	75	75	6	12	NR	NR	1	7
Al-Hosni 2012[75]	USA	B infantis (NR) + L rhamnosus (GG)	Align (Proctor and Gamble) + Culturelle (Amerifit)	BW 501-1000g	1e9/d until 34w	50	50	2	2	13	16	3	4
Sari 2011[76]	Turkey	L sporogenes (NR)	NR (DMG Italia)	BW < 1500g or GA <33w	3.5e8/d (NR)	110	111	6	10	NR	NR	3	4
Braga 2011[77]	Brazil	L casei + B breve (NR)	NR (Yakult)	BW 750-1499g	3.5e7-3.5e9/d × 28d	119	112	0	4	NR	NR	26	27
Romeo 2011[78]	Italy	L reuteri (ATCC 55730)	NR	BW < 2500g + GA < 37w	1e8/d until discharge	83	83	NR	NR	1	9	NR	NR
		L rhamnosus (ATCC 53103	NR		6e9/d until discharge	83		NR		2		NR	
Awad 2010[79]	Egypt	L rhamnosus (GG)	Lacteol Fort (Axcan)	GA 28-41w	6e9 BID until discharge	60	30	0	5	NR	NR	NR	NR
		Killed L rhamnosus (GG)				60		1		NR		NR	
Mihatsch 2010[80]	Germany	B lactis (BB12)	NR (Nestle)	BW < 1500g + GA < 30w	2e9/kg q 4h × 6w	91	89	2	4	28	29	2	1
Samanta 2009[81]	India	B longum + B infantis + B bifidum + L acidophilus (NR)	NR	BW < 1500g + GA < 32w	1e10 BID until discharge	91	95	5	15	13	28	4	14
Rouge 2009[82]	France	B longum (BB536) + L rhamnosus (GG)	NR (Morina + Valio)	BW < 1500g + GA < 32w	1e8 QID until discharge	45	49	2	1	15	13	2	4
Lin 2008[83]	Taiwan	L acidophilus (NCDO 1748) + B bifidum (NCDO 1453)	Infloran (Laboratorio Farmaceutico)	BW < 1500g + GA < 34w	1e9 BID until 6w	217	217	4	14	40	24	2	9
Stratiki 2007[84]	Greece	B lactis (NR)	Prenan (Nestle)	GA 27-37w	varied with feeding volume × 30d	41	36	0	3	0	3	NR	NR
Wang 2007[85]	Japan	B breve (M-16V)	NR (Morinaga)	GA 23-36w	1.6e8 BID until discharge	33	33	0*	0*	0	0	NR	NR
Manzoni 2006[86]	Italy	L rhamnosus (GG)	Dicoflor 60 (Dicofarm)	BW < 1500g	6e9/d until 6w	39	41	1	3	19	22	5	6
Fujii 2006[47]	Japan	B breve (M-16V)	NR (Morinaga)	GA 31w (SD 3w)	1e9 BID until discharge	11	8	0	0	1	1	NR	NR
Lin 2005[87]	Taiwan	L acidophilus + B infantis (NR)	Infloran (Swiss Serum and Vaccine Institute)	BW < 1500g	1e9 BID until discharge	180	187	2	10	22	36	7	20
Bin-Nun 2005[88]	Israel	B infantis + S thermophilus + B lactis (NR)	ABC Dophilus (Solgar)	BW < 1500g	1e9/d until 36w	72	72	1	10	NR	NR	3	8
Costalos 2003[89]	Greece	Saccharomyces boulardii (NR)	NR	GA 28-32w	1e9/d × 30d	51	36	5	6	3	3	NR	NR
Dani 2002[90]	Italy	L rhamnosus (GG)	Dicoflor (Dicofarm)	BW < 1500g + GA < 33w	6e9/d until discharge	295	290	4	8	14	12	0	2

Author Year	Country	Probiotic Species (strain)	Brand (Company)	Population	Dose × duration	Number enrolled		NEC cases Stage 2, 3		Culture + sepsis cases		Deaths	
						Prob	Cont	Prob	Cont	Prob	Cont	Prob	Cont
Reuman 1986[91]	USA	L acidophilus (NR)	NR	BW < 2000g	1e8 BID until discharge	15	15	NR	NR	NR	NR	1	3
				Total		4668	4298	161	263	548	601	244	310
				% of reported		100	100	3.59	6.26	13.18	15.48	5.75	7.62

NR: not reported, BW: birth weight, GA: gestational age, g: grams, w: weeks, d: days

1.6e8: 1.6×10^{8} organisms

* number of NEC cases obtained by personal communication with the author

Table 2

Summary of probiotic cohort studies in premature infants

Author Year	Country	Probiotic Species (strain)	Brand (Company)	Population	Dose × duration	Number enrolled		NEC cases Stage 2, 3		Culture + sepsis cases		Deaths	
						Prob	Cont	Prob	Cont	Prob	Cont	Prob	Cont
Dang 2015[92]	USA	L rhamnosus (GG) + B infantis (NR)	Culturelle (Amerifit) + Align (Proctor and Gamble)	BW < 1250g and/or GA < 28w	1e9/d until 34w	128	135	2	8	NR	NR	19	21
Repa 2015[93]	Austria	L acidophilus + B infantis(NR)	Infloran (Laboratoriofarmaceutico)	BW < 1500g	2e9 BID (NR)	230	233	16	24	60	78	16	30
Hartel 2014[94]	Germany	L acidophilus + B infantis(NR)	Infloran (Berna)	BW < 1500g + GA < 32w	1e9/d × 14d	3789	1562	116*	76*	428	195	292	160
Janvier 2014[95]	Canada	B bifidum + B breve + B infantis + B longum + L rhamnosus (NR + GG)	FloraBA BY (Renew Life)	GA < 32w	2e9/d until 34w	294	317	16	31	54	57	20	31
Bonsante 2013[96]	France	L rhamnosus (LCR35)	Lcr Restituo (Probionov)	GA 24-31w	2e8 BID until 36w	347	783	4	41	37	130	8	38
Li 2013[97]	USA	B bifidum + B infantis + S thermophilus	NR	BW < 1500g	NR	291	289	7	8	NR	NR	4	3
Hunter 2012[98]	USA	L reuteri (DSM 17938)	BioGaia (BioGaia)	BW < 1000g	5.5e7/d until 40w	79	232	2	35	19	72	NR	NR
Luoto 2010[99]	Finland	L rhamnosus (GG)	NR	BW < 1500g	6e9/d until discharge	418	1900	19	61	NR	NR	NR	NR
Yamashiro 2010[100]	Japan	B breve (M-16 V)	NR	BW < 1500g	1e9/d (NR)	338	226	0	6	70	65	39	38
Hoyos 1999[101]	Colombia	L acidophilus + B infantis	Infloran	All NICU admit	5e8/d (NR)	1237	1282	34	85	69	70	137	140
				Total		7151	6959	100	299	737	667	535	461
				% of reported		100	100	1.40	4.30	11.67	14.37	8.04	9.55

NR: not reported, BW: birth weight, GA: gestational age, g: grams, w: weeks, d: days

2e9: 2×10^9 organisms, Prob: probiotic, Cont: control

*Only surgical NEC reported

Table 3

Summary of prebiotic RCTs in premature infants

Author Year	Country	Prebiotic (composition)	Brand (Company)	Population	Dose × duration	Number enrolled		NEC cases Stage 2, 3		Culture + sepsis cases		Deaths	
						Preb	Cont	Preb	Cont	Preb	Cont	Preb	Cont
Dilli 2015[61]	Turkey	Inulin	Maflor (Mamsel)	BW < 1500g + GA < 32w	900mg/d until discharge	100	100*	12	18*	10	13*	2	12*
Armanian 2014[124]	Iran	scGOS:lcF OS(9:1)	NR (Nutricia MMP)	BW < 1500g + GA < 34w	varied with feeding volume	25	50	1	11	4	17	1	1
Riskin 2010[125]	Israel	1% lactulose	Laevo lac, (Fresenius Kabi)	GA 23-34w	1g/100 ml each feed until discharge	15	13	1	2	2	4	0	1
Modi 2010[126]	UK	scGOS:lcF OS (9:1)	NR (Danone)	GA < 33w	0.8g/10 ml(of formula feedings only)	73	81	2	1	9	10	2	1
Westerbeek 2010[127]	Netherlands	80% scGOS/lcF OS + 20% AOS	NR	BW < 1500g and/or GA < 32w	1.5g/kg/d × 28d	55	58	10	6	32	48	2	3
				total		268	302	26	38	57	92	7	18
				% of reported		100	100	9.70	12.58	21.27	30.46	2.61	5.96

NR: not reported, BW: birth weight, GA: gestational age, g: grams, w: weeks, d: days

scGOS: short-chain galacto-oligosaccharides, lcFOS: long-chain fructo-oligosaccharides, AOS: acidic oligosaccharides

*Same control group as reported in Table 1

Table 4

Summary of synbiotic RCTs in premature infants

Author Year	Country	Synbiotic	Brand (Company)	Population	Dose × duration	Number enrolled		NEC cases Stage 2, 3		Culture + sepsis cases		Deaths	
						Synb	Cont	Synb	Cont	Synb	Cont	Synb	Cont
Dilli 2015[61]	Turk	Inulin + B lactis	Maflor (Mamsel)	BW < 1500g + GA < 32w	inulin 900 mg + 5e9/d × 8w	100	100 *	4	18 *	8	13 *	3	12 *
Nandhini 2015[130]	India	Inulin + L acidophilus + LGG + L casei + L plantarum + L bulgaricus + B infantis + B breve + B longum	Prepro HS (Fourrts)	BW > 1000g + GA 28-34w	100 mg/d + 7×10^9 4×10^9 3×10^9 3×10^9 3×10^9 3×10^9 4×10^9 BID × 7d	108	110	0	3	4	4	10	9
Underwood 2009[131]	USA	Inulin + LGG	ProBio Plus (UAS)	BW 750-2000g + GA < 35w	5e8 BID × 28d or until discharge	30	29	1	1	6	5	0	0
		Inulin + L acidophilus + B longum + B bifidum + B infantis				31		1		2		0	
				total		269	239	6	22	20	22	13	21
				% of reported		100	100	2.23	9.20	7.43	9.20	4.83	8.79

LGG: L rhamnosus (GG), NR: not reported, BW: birth weight, GA: gestational age, g: grams, w: weeks, d: days

5e9: 5×10^9 organisms

* Same control group as reported in Table 1

Table 5

Summary of lactoferrin RCTs in premature infants

Author Year	Country	Lactoferrin	Brand (Company)	Population	Dose × duration	Number enrolled		NEC cases Stage 2, 3		Culture + sepsis cases		Deaths	
						Lact	Cont	Lact	Cont	Lact	Cont	Lact	Cont
Kaur 2015[136]	India	bLF	apolactoferrin (NR)	BW < 2000g	varied with BW × 28d	63	67	NR	NR	2	9	0	5
Ochoa 2015[137]	Peru	bLF	NR (Tatua)	BW < 2500g	200mg/kg/d devided 3 doses × 28d	95	95	NR	NR	4	4	7	3
Akin 2014[138]	Turk	bLF	LF100 (Dicofarm)	BW < 1500g + GA < 32w	200mg/d until discharge	22	25	0	5	4	8	0	1
Manzoni 2014[139]	Italy	bLF	LF100 (Dicofarm)	BW < 1500g	100mg/d × 30d BW > 1000g × 45d BW < 1000g	247	258	5	14	NR	NR	5	18
		bLF + LGG	Dicoflor 60 (Dicofarm)		100mg/d + 6e9/d	238		0		NR		9	
Sherman 2013 *[140]	USA	talactoferrin	NR	750-1500g	150 mg/kg BID	60	60	NR	NR	4	4	1	1
				total		725	505	5	19	14	25	22	28
				% of reported		100	100	0.99	6.71	5.83	10.12	3.03	5.54

NR: not reported, BW: birth weight, GA: gestational age, g: grams, w: weeks, d: days

bLF: bovine lactoferrin , LGG: L rhamnosus (GG)

*Abstract only