Available online at www.sciencedirect.com

Seminars in Perinatology

www.seminperinat.com

Impact of probiotics on necrotizing enterocolitis

Mark A. Underwood, MD, MAS

Division of Neonatology, UC Davis School of Medicine, Ticon 2, 2516 Stockton Blvd, Sacramento, CA 95817

ARTICLE INFO

Keywords:
Bifidobacterium
Lactobacillus
Human milk oligosaccharide
Probiotic
Prebiotic
Premature infant
Necrotizing enterocolitis

ABSTRACT

A large number of randomized placebo-controlled clinical trials and cohort studies have demonstrated a decrease in the incidence of necrotizing enterocolitis with administration of probiotic microbes. These studies have prompted many neonatologists to adopt routine prophylactic administration of probiotics while others await more definitive studies and/or probiotic products with demonstrated purity and stable numbers of live organisms. Cross-contamination and inadequate sample size limit the value of further traditional placebo-controlled randomized controlled trials. Key areas for future research include mechanisms of protection, optimum probiotic species or strains (or combinations thereof) and duration of treatment, interactions between diet and the administered probiotic, and the influence of genetic polymorphisms in the mother and infant on probiotic response. Next generation probiotics selected based on bacterial genetics rather than ease of production and large cluster-randomized clinical trials hold great promise for NEC prevention.

It has been more than 20 years since the first premature infants were enrolled in the first published cohort study of probiotic microbes for the prevention of necrotizing enterocolitis (NEC). In that landmark study, Dr. Angela Hoyos and her colleagues gave every baby admitted to the neonatal intensive care unit (NICU) in Hospital Simon Bolivar, Bogota, Colombia for a one year period, a probiotic formulation containing *Lactobacillus acidophilus* and *Bifidobacterium infantis* (Infloran, Swiss Serum and Vaccine Institute, Bern, Switzerland) at a dose of 2.5×10^8 of each organism once daily for the entire hospitalization. They then compared the incidence of NEC during the probiotic year and the previous year and found a dramatic decrease with administration of probiotics.[1]

Since that time, 35 randomized placebo-controlled clinical trials with NEC, death and/or sepsis as a reported outcome (the first 33 of these trials have recently been summarized[2] with two additional trials published subsequently[3,4]) and an additional 10 cohort studies comparing periods of time with universal treatment with probiotics to control periods[2,5] have been published in English language journals. Tables 1[6–12] and 2[1,5,13–17] present the data for the largest of these trials and cohort studies (those with at least 200 infants per arm). When all 35 randomized controlled trials are combined a total of 5559 premature infants received probiotics and 5513 premature infants received either a placebo or a blinded non-treatment. Among those studies reporting stage 2 or greater NEC as an outcome, unweighted percentages were 3.3% in infants receiving probiotics and 6.1% in control infants. Among those studies reporting culture positive sepsis the unweighted percentages were 12% and 14%, and among those studies reporting death 5.1% and 7.2% in the probiotic and control groups respectively. When the 11 cohort studies are combined, the unweighted percentages are strikingly similar to the randomized trials and are as follows: 7742 infants received probiotics (NEC 1.4%, sepsis 12%, and death 7.6%) and 7592 did not (NEC 4.4%, sepsis 14%, and death 9.2%). Multiple English language meta-analyses of the randomized controlled trials have been performed (the most recent are

Supported in part by a Grant from the NIH, United States: HD059127
E-mail address: munderwood@ucdavis.edu

http://dx.doi.org/10.1053/j.semperi.2016.09.017
0146-0005/

Table 1 – Probiotic RCTs with 200 or more premature infants in each arm.

Study	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
No benefit													
Costeloe et al.[a,6]	U.K.	*B. breve* (BBG 001)	NR (Yakult)	GA 23-30 wk	1.6e8-1.6e9/d until 36 wk	650	660	62	66	73	77	54	56
Oncel et al.[7]	Turkey	*L. reuteri* (DSM 17938)	NR (Biogaia AB)	BW ≤ 1500 g ± GA ≤ 32 wk	1e8/d until discharge	200	200	8	10	13	25	15	20
Rojas et al.[8]	Colombia	*L. reuteri* (DSM 17938)	NR (Biogaia AB)	BW < 2000 g	1e8/d until discharge	372	378	9	15	24	17	22	28
Dani et al.[9]	Italy	*L. rhamnosus* (GG)	Dicoflor (Dicofarm)	BW < 1500 g ± GA < 33 wk	6e9/d until discharge	295	290	4	8	14	12	0	2
Benefit													
Manzoni et al.[10]	Italy + NZ	*L. rhamnosus* (GG) + *Bovine lactoferrin*	NR	BW < 1500 g	6e9/d until day 30	238	258	0	14	NR	NR	9	26
Jacobs et al.[b,11]	Australia + NZ	*B. infantis* (BB-02) + *S. thermophiles* (TH-4 15957) + *B. lactis* (BB-12 15954)	ABC Dophilus (Solgar)	BW < 1500 g + GA < 32 wk	1e9/d until discharge	548	551	11	24	72	89	27	28
Lin et al.[12]	Taiwan	*L. acidophilus* (NCDO 1748) + *B. bifidum* (NCDO 1453)	Infloran (Laboratorio Farmaceutico)	BW < 1500 g + GA < 34 wk	1e9 BID until 6 wk	217	217	4	14	40	24	2	9

[a] Subgroup analysis showed a decrease in NEC among infants with colonization with the probiotic compared to those not colonized.
[b] Subgroup analysis showed a decrease in sepsis in infants ≥28 wk but not <28 wk.