

A SYSTEMATIC REVIEW ON THE EFFECTIVENESS AND SAFETY OF PROBIOTICS FOR THE PREVENTION OF NECROTIZING ENTEROCOLITIS

Bussières M., Larocque B., Hamel M., Rhainds M.

Unité d'évaluation des technologies et des modes d'intervention en santé (UETMIS), CHUQ, Canada

BACKGROUND

Necrotizing enterocolitis (NEC) is a serious complication observed mostly among preterm neonates. It occurs in about 1 to 8 % of infants admitted in neonatal intensive-care unit (NICU). Probiotics administration have been suggested to help prevent NEC.

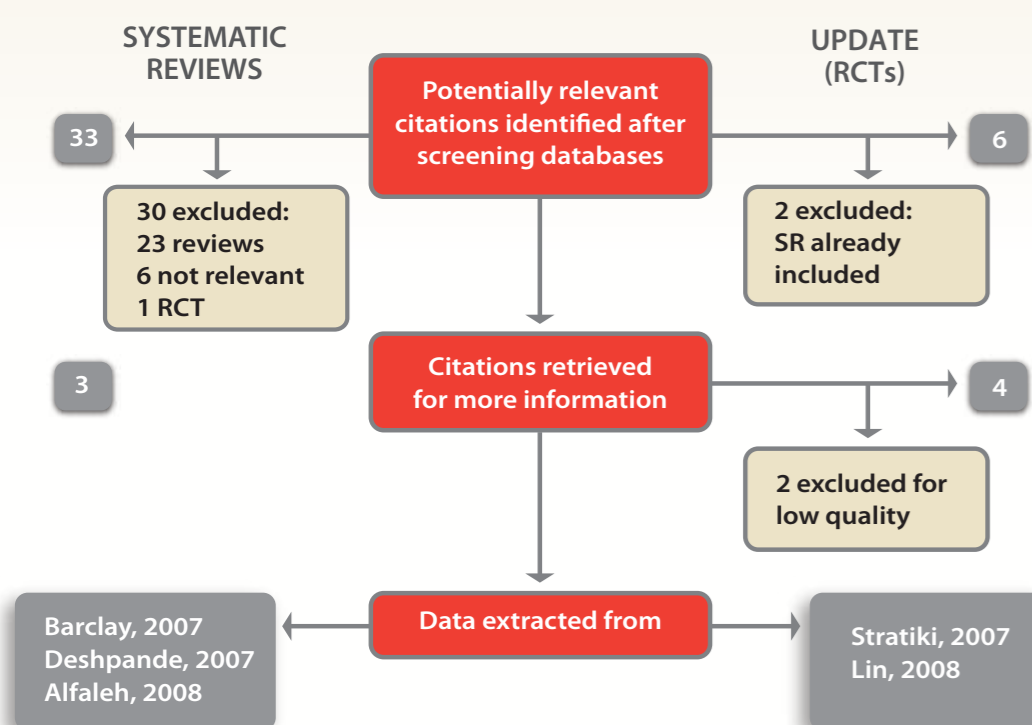
OBJECTIVE

To assess the effectiveness and safety of probiotics in the prevention of NEC.

METHODS

- Systematic reviews (SRs) and randomized controlled trials (RCTs) were searched in PubMed, Embase and Cochrane Central Register of Controlled Trials databases (January 1995 to September 2009). Prospective studies, case reports, and case series were also retrieved to evaluate safety
- Inclusion criteria:** Probiotics defined at the genus and species level, with a specified dose, and administered through the digestive tract
- Exclusion criteria:** *In vitro* or animal studies, publications in another language than French or English, studies that failed quality evaluation
- Article selection, quality assessment and data extraction were performed by two independent reviewers using standardized forms (UETMIS, 2007). Discrepancies were resolved by including a third reviewer to reach a consensus
- Synthesis review was shared with a group of medical experts in neonatology

Figure 1. Study selection process for effectiveness evaluation



RESULTS

Table 1. Characteristics of the neonates in the primary studies

Author, year Country/NICU (n)	Gestational age, mean (weeks) T/C	Birth weight, mean (g) T/C	Weight ≤ 1500 g (%)	CVC (days) T/C UVC (days) T/C	PROM (%) T/C	Cesarean section (%) T/C
†Dani, 2002 Italy/ (12)	30.8/30.7	1325/1345	NR	NR 7.1/7.8	NR	76.3/82.4
†Costalos, 2003 Greece/ (2)	31.1/31.8	1651/1644	NR	NR	19.6/16 6 ¹	49/38
†Bin-Nun, 2005 Israel/ (1)	29.2/29.3	1152/1111	100	NR	NR	78/78
†Lin, 2005 Taiwan/ (1)	28.5/28.2	1104/1071	100	0.7/0.7 0.8/0.8	29.4/23 0 ²	57.8/53.5
†Manzoni, 2006 Italy/ (1)	29.6/29.3	1212/1174	100	60/65 % ³ 90/92.5 % ⁴	NR	70/65
*Mohan, 2006 Germany/ (1)	NR ⁵	NR ⁵	NR	NR	NR	86.5/90.6
Stratiki, 2007 Greece/ (1)	31/30.5	1500/1500	NR	NR	NR	36.5/35
Lin, 2008 Taiwan/ (7)	NR ⁶	1029/1077	100	NR 4.4/4.1	21.2/29.8	69.6/63.3

NICU: neonatal intensive-care unit; T: treatment; C: control; CVC: central venous catheter; UVC: umbilical venous catheter;
 PROM: prolonged rupture of membranes; NR: not reported
¹ > 6 hours
² > 18 hours
³ % of neonates with CVC positioned
⁴ % of neonates with UVC in place at birth until the third day of life
⁵ Randomized on the basis of birth weight and gestational age
⁶ Gestational age not reported but age at enrollment was 4.5 and 4 days respectively
 * Included only in Deshpande (2007)
 † Included in the 3 SRs

Effectiveness :

- According to Barclay (2007), Deshpande (2007) and Alfaleh (2008), enteral administration of probiotics significantly decreased the incidence of severe stage ≥ 2 NEC
- Variations were observed among RCTs in patient demographics and for probiotic regimen including type, dose, duration as well as age of introduction (tables 1, 2). This heterogeneity prevents meta-analysis
- Available data did not allow the evaluation of the effectiveness of specific probiotic species
- Other risk factors like breast feeding and antibiotic policies in NICU may have not been controlled for
- There is insufficient data in infants less than 1000 g at birth to conclude on the effectiveness of probiotics for this population

Safety :

- Probiotic use was reported as safe and well tolerated in the RCTs. However, authors of SRs agreed that larger studies are required to adequately evaluate safety
- Incidence of proven sepsis was higher in probiotic group in 3 studies but doesn't seem due to the supplemented probiotic organisms
- 3 cases of bacteremia associated to LGG (Kunz, 2004 (2 cases); De Groot, 2005) were reported among neonates since 1970:
 - all patients had a CVC
 - 2 patients received LGG via a feeding tube (Kunz, 2004; De Groot, 2005)
 - 1 bacteremia was not confirmed by a molecular test (Kunz, 2004)

Table 2. Effect of probiotics on the incidence of necrotizing enterocolitis of stage ≥ 2 (NEC) and of proven sepsis before discharge

Author, year; n analyzed (T/C) Probiotics; CFU/day; duration	T (n)	C (n)	RR (95 % CI)
	NEC		
	Sepsis		
Dani, 2002; (295/290) LGG; 6x10 ⁹ ; first feed until discharge	4	8	0.49 (0.15 - 1.61)
Costalos, 2003; (51/36) S. boulardii; 100 mg/kg; first feed for 30 days	14	12	1.15 (0.54 - 2.44)
Bin-Nun, 2005; (71/72) L. bulgaricus + St. thermophilus + B. infantis; 3.5x10 ⁹ /strain; first feed to 36 weeks corrected age	5	6	0.59 (0.19 - 1.78) ¹
Lin, 2005; (180/187) L. acidophilus + B. infantis; 250 mg/kg; day 7 until discharge	3	3	0.71 (0.15 - 3.30)
Manzoni, 2006; (39/41) LGG; ½ packet; 3 rd day of life to 6 weeks or discharge	1	10	0.10 (0.01 - 0.77)
Mohan, 2006; (21/17) B. breve; Day 1-3: 1.6x10 ⁹ ; Day 4-21: 4.8x10 ⁹ ; NR	31	24	1.31 (0.86 - 2.00)
Stratiki, 2007; (41/34) B. lactis; 2x10 ⁷ ; within the first 2 days; NR	2	10	0.21 (0.05 - 0.94)
Lin, 2008; (217/217) L. acidophilus + B. bifidum; 10 ⁹ /strain; 6 weeks	22	36	0.63 (0.39 - 1.04)
	1	3	0.35 (0.04 - 3.23)
	19	22	0.91 (0.59 - 1.40)
	2	1	1.62 (0.16 - 16.37)
	NR	NR	--
	0	3	Not estimable
	0	3	Not estimable
	4	14	0.31 (0.09 - 0.99)²
	40	24	1.59 (0.91 - 2.86) ³

CFU: colony forming units; T: treatment; C: control; RR (95 % CI): relative risk (95 % confidence interval);
 LGG: L. rhamnosus or L. casei; S: Saccharomyces; St: Streptococcus; L: Lactobacillus; B: Bifidobacterium;
 NR: not reported
¹ NEC all stage
² Odd ratio adjusted for birth weight, umbilical venous catheter, intermittent mandatory ventilation, NICU stay, and center
³ Odd ratio adjusted for birth weight, surfactant use, pH, gestational age, and center

CONCLUSION

Among eight studies on NEC, six suggested a protective effect of the probiotics. However, study limitations on the effectiveness of probiotics to prevent NEC may not lead to a definite conclusion. Moreover, probiotic safety is of concern among vulnerable populations. Based on the available information and the medical expert consensus, probiotic use was not recommended in preterm infants in our hospital. Before introducing probiotics in clinical practice, further research is needed to clarify the probiotic type and dosing regimen.

References

- Alfaleh, K et al. (2008). Cochrane Database Syst Rev(1): CD005496.
- Barclay, AR et al. (2007). J Pediatr Gastroenterol Nutr 45(5): 569-76.
- Deshpande, G. et al. (2007). Lancet 369(9573): 1614-20.
- De Groot, MA et al. (2005). Pediatr Infect Dis J 24: 278-80.
- Kunz, AN et al. (2004). J Pediatr Gastroenterol 38 (4):457-8.
- Lin, HC et al. (2008). Pediatrics 122(4): 693-700.
- Stratiki, Z et al. (2007). Early Hum Dev 83(9): 575-9.
- UETMIS, 2007. Guide méthodologique. <http://www.chuq.qc.ca/fr/evaluation/uetmis/demarche/>

Corresponding author: martin.bussieres@chuq.qc.ca