

The Effectiveness of the Use of Probiotics in the Prevention of Necrotizing Enterocolitis

Luke D. Febrizio, Danae L. Hershberger, Caroline E. Price, and Miranda A. Sternsher

Cedarville University School of Nursing

Abstract

PICO Question

In very low birth weight infants (VLBW), does the use of prophylactic probiotics decrease the incidence of necrotizing enterocolitis?

Method

Databases searched include PubMed, Cochrane, Medline, ScienceDirect, UpToDate, and CINAHL databases, resulting in 10 relevant articles (four meta-analyses, two systematic reviews, three randomized controlled trials, and one cohort study).

Results

The research concluded that overall there is a decrease in the incidence of NEC when VLBW infants are given prophylactic probiotics.

Recommendations

In conclusion, probiotics have shown efficacy in preventing NEC, and pose no observable adverse effects to VLBW infants. The final recommendation would be to implement the use of probiotics for VLBW infants. The conclusions strongly suggest a change in practice, and hospital NICUs would greatly benefit from the use of probiotics.

Keywords: necrotizing enterocolitis, probiotics, preventative, prophylactic, very low birth weight, nursing

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Background

Statistics and Definitions

Necrotizing Enterocolitis (NEC) is a gastrointestinal disease affecting approximately 10% of all VLBW premature infants (Springer, 2014). In this disease process, mucosal integrity is lost, allowing the onset of infection in the bowel wall by colonizing bacteria such as *Escherichia coli*, *Klebsiella*, *Clostridium perfringens*, *Staphylococcal epidermis* and *Rotavirus* (Samanta, 2009). VLBW infants are categorized as those born weighing <1500 grams, and extremely low birth weight (ELBW) infants as those weighing <1000 grams. This EBP review will focus on only those in the VLBW category (1000-1499 g). Although it is possible for NEC to affect full term, appropriate for gestational age infants, the literature has shown that these are at far less risk for developing NEC than those born prematurely with very low birth weights. Mortality rates of 15% to 30% occur in VLBW infants who have developed NEC, depending on severity (Butte, 2014). Severity can be determined based on Modified Bell's Staging for NEC. See Appendix C, Table 3 for stage detailing.

Probiotics are defined as “microbial food supplements that beneficially affect the host by improving its intestinal microbial balance” (Gibson, 1995). These beneficial microbes typically include those of the *Lactobacillus* and *Bifidobacteria* genus, although others may be used. While breast milk is typically the first source of these probiotics, infants in the NICU undergo delayed colonization due to the heavy use of broad spectrum antibiotics, facilitating the development of NEC (Samanta, 2009).

PICO Question

In very low birth weight infants, does the use of prophylactic probiotics decrease the risk of developing necrotizing enterocolitis? P: very low birth weight infants; I: prophylactic probiotics; C: no use of probiotics; O: prevention of necrotizing enterocolitis.

Registered Nurse Interviews

After discussion with several registered nurses who routinely work in the NICU, a few common themes began to arise. In the care of VLBW infants, the use of breast milk is often encouraged. Nurses also take frequent abdominal girth measurements and check gastric residual before each feeding. These three practices aid in the prevention and early detection of NEC. There were no policies pertaining to the particular issue of NEC at the facilities in which the RNs were employed. When asked about the use of probiotics as a preventative measure for NEC, none of the nurses had any previous knowledge about this potential prophylactic treatment.

Search Methods

A literature search and review was conducted in October 2014. The search was intended to find peer-reviewed articles published in journals regarding the topic of probiotics and how their use is related to the prevention of NEC in infants. The online databases used for the search included CINAHL, Cochrane, Medline, PubMed, ScienceDirect, and UpToDate. The keywords used in all of the searches included “probiotics” and “necrotizing enterocolitis.” Other keyword variations used to narrow the search included “prophylactic,” “prevention,” “nursing,” “very low birth weight,” and “preterm.” Articles were included in the review of literature if they were specifically about probiotics being used prophylactically to prevent NEC in VLBW infants. Articles were excluded from the review if they were published before 2008, the full text was not available or not available in English, prebiotics were the main preventative measure, the study focused on ELBW infants, or if probiotics were not used prophylactically.

Results

Critique

Our review included four meta-analyses and two systematic reviews (Appendix A, Table 1A) and three individual RCTs and one cohort study (Appendix A, Table 1B). All of the studies were published within the last six years. The studies included in the review of literature had several basic similarities. Each study had the purpose of examining the relationship between the use of probiotics in the prevention of NEC in VLBW infants. Additionally, all of the studies classified the development of NEC as \geq stage 2 according to Modified Bell Staging (Appendix C, Table 3). This classification represents definite cases of NEC as opposed to suspected cases (Schanler, 2014). The consistency found in these studies coincides with the purpose of this review.

Synthesis

There were many overlapping findings between the studies reviewed. The decrease in the incidence of NEC when treated prophylactically with probiotics was determined by all studies included (AlFaleh & Anabrees, 2014; Bernardo et al., 2012; Braga et al., 2011; Deshpande et al., 2010; Guthmann et al., 2010; Li et al., 2013; Lin et al., 2008; Rohan & Wainwright, 2014; Samanta et al., 2009; Wang et al., 2011). Multiple other factors were observed as well, such as decreased hospitalization time (Bernardo, et al., 2012; Samanta et al., 2009) and decreased time to full enteral feeds (Bernardo, et al., 2012; Braga, et al., 2011; Samanta et al., 2009). Adverse effects of probiotics have not been observed thus far in their use (AlFaleh & Anabrees, 2014; Braga et al., 2011; Guthmann et al., 2010; Li et al., 2013). One concern with the use of probiotics is the potential cause of sepsis by probiotic administration¹; however, none of the studies included in this review found a significant link between probiotic administration and the

development of sepsis. Two articles (Guthmann et al., 2010; Rohan & Wainwright, 2014) made the observation that studies which administered a combination of multiple probiotics (as opposed to one strain) presented with better outcomes and lower percentages of the development of NEC. Samanta et al. (2009) noted that while the administration of probiotics lowered the incidence of NEC, it did not affect the severity of NEC developed. This emphasizes the use of probiotics as a preventative measure, not a treatment plan. For a summary of findings, implications, and recommendations of each study included, refer to Table 2 found in Appendix B.

Discussion

Study Model and Recommendations

The Iowa Model of Evidence-Based Practice to Promote Quality Care was used to guide this review to determine a topic of study and the relevance of the topic to nursing practice, as well as in the gathering and evaluation of the present literature (Titler et al., 2001). Due to the amount and level of evidence already present in the literature on this topic, more research is not necessary to establish the benefits of probiotic use in preventing NEC. As mentioned previously, probiotics have been shown to decrease length of hospital stay and time to full enteral feeds (Bernardo, et al., 2012; Samanta et al., 2009; Braga et al., 2011). This supports the use of probiotics in their cost-to-benefit ratio, as decreased hospitalization time will decrease cost of treatment. Additionally, probiotics are considered to be an easy-to-handle treatment that is also low cost (Bernardo et al., 2012), further validating their efficacy in hospital use.

Probiotic use should become a standard in practice among neonatal intensive care units in the care of VLBW infants. Until these changes can be made and policies established, probiotics should be an informed option for parents of VLBW infants in the care of their child; however, more research is needed to evaluate the efficacy of specific types, combinations, and dosages of

probiotics required to be most beneficial and practical. Furthermore, there is a lack of research pertaining to the beneficial use of probiotics in ELBW infants, warranting further research.

Limitations

This review focused on reducing the risk of NEC through prophylactic probiotic therapy, but it was found that each study mentioned several different types or combinations of probiotics. It was difficult to compare these strains and combinations because each study used a different combination or used a single strain for therapy. Furthermore, it could not be determined which probiotic was most effective, as none of the studies compared the efficacy of certain probiotics to others. Refer to Appendix D, Table 4 to see the specific types of probiotics, as well as the different combinations of probiotics that were used in each study.

Footnotes

¹Theoretically, because probiotic therapy is the intentional introduction of bacteria to the gastrointestinal system, overgrowth and potential sepsis could occur (Zupancic, 2009). One such case was reported by Land et al. (2005), who advocated for awareness of this complication but state that their “report should not discourage the appropriate use of [...] probiotic agents.”

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Appendix A

Table 1A

Meta-Analyses and Systematic Reviews Included

Author/Date/ Type	Purpose	Number of RCTs Included	Inclusion Criteria/Study Details	Exclusion criteria	LOE
AlFaleh & Anabrees, 2014, Systematic Review	To analyze whether prophylactic probiotics are more effective than no treatment in the prevention of severe NEC and/or sepsis in preterm infants.	24 RCTs	Weight: <1500 g Gestational Age: <37 weeks NEC Staging: ≥stage 2 Additional Criteria: Any trials that involved enteral administration of any live microbial supplement (probiotics), and measured at least one prespecified clinical outcome	Studies that included bias and were not applicable	1
Bernardo et al., 2012, Meta-Analysis	To demonstrate the advantages of probiotic use to prevent NEC and its consequences in preterm infants	11 RCTs	Weight: <1500 g Gestational Age: <34 weeks NEC Staging: ≥stage 2 Additional Information: Infants ≥34 weeks may have been included if they were <1500 g at birth	Studies that included patients with ≥34 weeks gestation and ≥1500 g at birth, and studies in which it they did not establish limits	1
Deshpande et al., 2010, Meta-Analysis	To update a previous systematic study by the same authors in order to see the effect of probiotic supplementation on NEC prevention	11 RCTs	Weight: <1500 g Gestational Age: <34 weeks NEC Staging: ≥stage 2 Additional Criteria: enteral administration of any probiotic started within the 10th day of life and carried out for at least 7 days	No specific exclusion criteria listed	1
Guthmann et al., 2010, Meta-Analysis	To provide an updated meta-analysis including 2 new RCT studies since previous publication	11 RCTs	Weight: <1500 g NEC Staging: ≥stage 2 Additional Information: RCTs included from previous analyses, including 2 newly published RCTs	Any trials that were not prospective or controlled	1
Rohan & Wainwright, 2014, Systematic Review	Investigate whether use of probiotic use in premature and VLBW infants reduces the incidence of NEC	7 RCTs	Weight: <1500 g NEC Staging: ≥stage 2	No specific exclusion criteria listed	1
Wang et al., 2011, Meta-Analysis	Updated synthesis of the effects of probiotics in the prevention of necrotizing enterocolitis in preterm, very low birth weight infants	20 RCTs	Weight: <1500 g Gestational Age: <34 weeks NEC Staging: ≥stage 2 Additional Criteria: probiotics administered within first 10 days of life for at least 7 days	Studies that did not have clinically relevant data	1

Table 1B

RCTs and Cohorts Included

Author/Date/Type	Purpose	Sample	Key Variables Measured	Treatment	LOE
Braga et al., 2011, RCT	To analyze the effectiveness of prophylactic combination probiotics in the prevention NEC	Total sample size: 231 preterm infants Treatment: 119 infants Control: 112 infants Inclusion criteria: locally born neonates who were admitted to the NICU and weighed between 750 and 1499 g at birth Exclusion criteria: major congenital malformations, previously diagnosed life-threatening chromosomal alterations, and/or congenital infections diagnosed at birth	- Incidence of NEC (Bell's stage \geq 2) - Sepsis - Death	The study group received 3 ml of human milk with added probiotics; the control group received the same volume of human milk minus the probiotics.	2
Li et al., 2013, Cohort	To analyze the effectiveness of prophylactic probiotics in the prevention NEC in VLBW infants in the NICU	Total sample size: 580 Control: 289 Treatment: 291 Inclusion criteria: VLBW infants who received at least 5 days of feeding or probiotics Exclusion criteria: early death, received inotropic support at birth for more than 3 days, or active gastrointestinal bleeding	- NEC (stage II or III) - Death attributable to NEC - Severity of NEC - NEC scare	A probiotic administration using a three-strain supplement was implemented.	4
Lin et al., 2008, RCT	To analyze the effectiveness of orally administrated prophylactic probiotics in the prevention of NEC in VLBW infants	Total sample size: 434 infants Control: 217 Treatment: 217 Inclusion criteria: VLBW infants, <34 weeks gestational age who survived to feed enterally Exclusion criteria: VLBW preterm infants with severe asphyxia, fetal chromosomal anomalies, cyanotic congenital heart disease, congenital intestinal atresia, gastroschisis or omphalocele, fed exclusively by formula, and who were fasted >3 weeks	- Death due to NEC - NEC (Bell's stage \geq 2; determination made by 2 independent attending physicians who were unaware of the group assignment of the infant)	Treatment group was administered probiotics, which were added to breast milk or mixed feeding (breast milk and formula) for 6 weeks.	2
Samanta et al., 2009, RCT	To analyze the effectiveness of probiotic in reducing food intolerance and reducing incidence and severity of NEC in pre-term VLBW infants	Total sample size: 186 infants Control: 95 Treatment: 91 Inclusion Criteria: Preterm (<32 w), VLBW, born between October 2007 and March 2008, who started feed enterally and survived beyond 48 hours of life Exclusion Criteria: babies with major congenital and GI anomalies and babies who expired due to other neonatal illnesses	- Days to reach full enteral feeding - Duration of hospital stay - Incidence of NEC (at least stage II) - Sepsis - Death rate	Probiotics were added to breast milk for the treatment group.	2

Note. Specific probiotics used in each study are listed in Appendix D, Table 4.

Appendix B

Table 2

Key Findings and Implications/Recommendations of the Included Studies

Author/Date	Findings and Implications
AlFaleh & Anabrees, 2014	<p>Findings: Enteral supplementation of probiotics prevents severe NEC and all-cause mortality in preterm infants.</p> <p>Implications: More studies are needed to investigate the most effective formulation and dose to be utilized. Parents of preterm infants should be informed of current evidence if further RCTs are to be conducted.</p>
Bernardo et al., 2012	<p>Findings: Patients that received probiotic supplementation had lower food reintroduction time, hospitalization time, and incidence of NEC when compared to those not receiving probiotics. There was no difference in mortality caused by NEC or the severity of the disease.</p> <p>Implications: The use of probiotics is effective as a prophylactic treatment for NEC and its complications.</p>
Braga et al., 2011	<p>Findings: More cases of NEC occurred in the control group than in the treatment group. The infants who received probiotics received enteral feeds sooner than the control group.</p> <p><i>Additional information:</i> The study was stopped halfway through (one year into a planned two year study) because the External Study Committee determined that the positive results for the use of probiotics was established.</p> <p>Implications: Probiotics may prevent the development of NEC.</p>
Deshpande et al., 2010	<p>Findings: Fewer of the neonates who received probiotic treatment developed definite NEC (stage 2 or higher) as compared to those in the control group. The probiotic group demonstrated a decreased rate in death from all causes.</p> <p>Implications: Because of this evidence, Deshpande states “withholding probiotics from high-risk neonates is now almost unethical.”</p>
Guthmann et al., 2010	<p>Findings: The incidence of NEC and mortality was reduced with the prophylactic use of probiotics. Trials that used multiple strains of probiotics tended to have further improved results.</p> <p>Implications: Probiotics can be used as an effective prophylactic treatment for NEC; however, local statistics on the incidence of NEC need to be considered.</p>
Li et al., 2013	<p>Findings: Probiotics were shown to be safe and effective in the prevention of NEC for VLBW infants. There were no cases of infection related to this treatment.</p> <p>Implications: More research needs to be done since this study was observational.</p>
Lin et al., 2008	<p>Findings: The incidence of death or NEC \geq stage 2 was significantly lower in the treatment group. No adverse effects were related to the probiotic treatment.</p> <p>Implications: Probiotics should be administered orally for six weeks reduce the incidence of NEC.</p>
Rohan & Wainwright, 2013	<p>Findings: In the seven RCTs studied, there was a lack of consistency in the types, combinations, and dosages of probiotics used. The five RCTs that used multiple probiotic types all showed a decrease in NEC development while the two RCTs that tested the use of one probiotic did not demonstrate a beneficial outcome.</p> <p>Implications: Although results are promising, more research is needed regarding specific types, dosages, and combinations of probiotics before it becomes a routine practice.</p>
Samanta et al., 2009	<p>Findings: Administration of probiotics reduced incidence of NEC, number of days to enteral feedings, hospital stay, incidence of death, and sepsis, but did not significantly impact the severity of NEC when developed.</p> <p>Implications: Enteral administration of prophylactic probiotics in neonatal intensive care setup could significantly reduce morbidity due to NEC in VLBW newborns.</p>
Wang et al., 2011	<p>Findings: Probiotic supplementation was shown to significantly reduce the risk for NEC and mortality in preterm VLBW infants. There was no significant difference in the risk for sepsis for those that used probiotics.</p> <p>Implications: Probiotic supplements should be included in regular, routine therapies for preterm infants. The optimum strain of probiotics and the long term effects need further study.</p>

Appendix C

Table 3

Modified Bell's Staging of Necrotizing Enterocolitis (Gordon et al., 2007)

Review of Bell's stages	Clinical findings	Radiographic findings	Gastrointestinal findings
Stage I	Apnea and bradycardia, temperature instability	Normal gas pattern or mild ileus	Gastric residuals, occult blood in stool, mild abdominal distention
Stage II A	Apnea and bradycardia, temperature instability	Ileus gas pattern with one or more dilated loops and focal pneumatosis	Grossly bloody stools, prominent abdominal distention, absent bowel sounds
Stage II B	Thrombocytopenia and mild metabolic acidosis	Widespread pneumatosis, ascites, portal-venous gas	Abdominal wall edema with palpable loops and tenderness
Stage III A	Mixed acidosis, oliguria, hypotension, coagulopathy	Prominent bowel loops, worsening ascites, no free air	Worsening wall edema, erythema and induration
Stage III B	Shock, deterioration in laboratory values and vital signs	Pneumoperitoneum	Perforated bowel

Note. This chart was taken from Gordon et al. (2007); however, they adapted the chart based on the article by Kliegman and Walsh (1987), where a more comprehensive staging chart is provided. Bell's Staging of NEC was first developed by Bell et al. in 1978, where there was no breakdown within stages, but simply stages I, II, and III.

Appendix D

Table 4

Probiotics Used in RCT and Cohort Studies Included

Author/Date	Probiotics Used in Experimental Group
Braga et al., 2011	<i>Lactobacillus casei</i> , <i>Bifidobacterium breve</i>
Li et al., 2013	<i>Streptococcus thermophilus</i> , <i>Bifidobacterium infantis</i> , <i>Bifidobacterium bifidum</i>
Lin et al., 2008	<i>Bifidobacterium bifidum</i> , <i>Lactobacillus acidophilus</i>
Samanta et al., 2009	<i>Bifidobacteria infantis</i> , <i>Bifidobacteria bifidum</i> , <i>Bifidobacteria longum</i> , <i>Lactobacillus acidophilus</i>

Note. Meta-Analyses and Systematic Reviews not included in the chart. See original studies for information on probiotics used in each individual study.