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Using probiotics to prevent necrotizing enterocolitis: Why have we not changed practice?

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Abstract Very low birth weight preterm infants are at risk to develop multiple health co-morbities; one of the most devastating of which is necrotizing enterocolitis (NEC). NEC is a life altering infection with increased morbidity and mortality. While the exact etiology of NEC remains unknown, several factors related to gut proliferation seems to be linked to this infection. A thorough review of the literature revealed that evidence does support the use of probiotics to prevent NEC. Although clinical research implies the use of probiotics, practice guidelines have yet to adopt this change. This article presents the evidence behind the justification for probiotics, and suggestions for future practice.

Anyone who works with premature infants is familiar with the morbidity and mortality associated with Necrotizing Enterocolitis (NEC). NEC is more frequently seen in very low birth weight infants (VLBW - born weighing less than 1500 g). Pietz et al., 2007, agrees, "the incidence of NEC among VLBW infants is 10.1%, and NEC carries a mortality rate of 54% among infants" (p. e167). Not only does NEC put infants at higher risk for complications and death, but it also extends their hospital stay and increases health care costs. Bisquera et al., 2002, state "the total additional hospital charges in our institution attributable to NEC alone are $7,200,000.00 [approximately 5,340,852.00] per year and $238,333.00 [approximately 176,790.00] per survivor (p. 426).

Numerous risk factors for the development of NEC have been identified. Lack of exposure to antenatal steroids, ethnic group, small for gestational age (SGA) infants, diagnosis of patent ductus arteriosis (PDA), placement of an umbilical arterial catheter (UAC), and placement of an umbilical venous catheter (UVC) are all thought to be risk factors (Bisquera et al., 2002, p. 423). Several theories about causes of NEC relate to a relationship between bacterial growth and the

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inflammatory response. Evidence supporting the notion that NEC is somehow mediated by intestinal microbes includes the common findings of bacteremia and endotoxinemia in affected neonates and frequent x-ray finding of pneumatosis intestinalis, which likely represents submucosal gas produced by bacterial fermentation (Morowitz et al., 2010, p. 788).

Lin et al. (2008), states, "the inflammatory cascade promotes the spread of bacteria or toxin, resulting in ischemia, necrosis, and, in some cases, perforation. In vitro evidence showed that pathogenic flora attach to the epithelial cells of preterm infants much more easily than to those of term infants, and studies indicated that commensal bacteria could inhibit or reduce inflammatory signaling in intestinal epithelial cells." (p. 694).

Minocha (2009), states, "about 60—80% of immune system components can be found in the gut. Low-level gut inflammation may have far-reaching effects, including but not limited to the brain" (p. 227). Full term, healthy infants, are exposed to bacteria in their environment, starting with the birth process and through daily activities. These bacteria help them develop their natural supply of normal flora. Colonization by commensal bacteria is required for the normal development and maturation of the newborn intestine, which is virtually sterile at birth. (Sari et al., 2011, p. 434) Infants who are living in an intensive care unit, are less likely to be exposed to the same beneficial bacteria that healthy, full term, breast fed neonates are exposed to. This difference in bacteria present in healthy full term, versus preterm infants is a contributing factor in development of NEC. Thompson and Bizzarro (2008) noted, "the predominant bacteria found in the GI tract of healthy, term, breast fed infants is Bifidobacteria. In contrast, species of Staphlococcus, Enterobacter, Enterococcus, and Clostridia are the predominant fecal bacterial species in premature neonates undergoing intensive care, with very little colonisation with bifidobacteria" (p. 1230).

Since flora present in a neonate's gut is implicated in the development of NEC, there is a potential that the use of probiotics bacteria could prevent this condition. Probiotics are defined as, "live microorganisms which when administered in adequate amounts confer a health benefit on the host" (Hickson, 2013, p.35). These microorganisms should be live, need to be given at a certain dose, and should be proven to benefit the recipient (Hickson, 2013, p.35). Lin et al., in 2008 performed a multicenter, randomized, controlled trial in 7 neonatal intensive care units (NICUs) in Taiwan that supported the use of probiotics to prevent NEC. In fact, "the incidence of death or stage $\geq$2 NEC was significantly lower in the probiotic-treated group in both unadjusted and adjusted analyses" (p. 696). The predicted number of patients needing treatment to save one child from developing NEC was 20 and the number to prevent a single death was 14 (Lin et al., 2008, p. 696). This study used the probiotic bacteria bifidobacterium bifidum and lactobacillus acidophilus. Dilli et al., 2013, studied treatment outcomes of infants with cyanotic heart defects who were treated with synbiotics. Synbiotics are substances that contain both prebiotics and probiotics. Probiotics have been previously defined and prebiotics contain ingredients that help supply normal flora bacteria with the nutrients they need to grow. Infants in the Dilli et al. study group were given Bifidobacterium lactis, a probiotic plus inulin, a prebiotic and together they are referred to as a synbiotic. "There were 5 cases of NEC (10%) in the placebo group and none in the symbiotic group and the incidence of death was lower in the symbiotic group (10% vs. 28%)" (p. e932).

In reviewing different studies, it is evident that studies that used bifidobacterium species seemed to have more favorable results, whereas studies that used other probiotics had varying results. For example, Sari et al. (2011), studied the use of Lactobacillus sporogenes for prevention of NEC in VLBW infants. "The incidence of NEC was not significantly lower in the probiotic group than the control group" (Sari et al., 2011, p. 438). Although their results did not support using Lactobacillus sporogenes in infants, other variables may have skewed their results. The study group had longer duration of umbilical venous catheters. As stated previously, the use of umbilical venous catheters are a risk factor for developing NEC.

In another study Lin et al. (2005), found that, "the incidence of death or NEC was significantly lower in the probiotic group when compared with the control group. There were 6 cases of severe NEC in the control group and none in the probiotic group" (p. 2). They used Infloran as their probiotic of choice. Infloran is a brand name, containing both *L acidophilus* and *B infantis*. Deshpande et al., in 2010 published an updated meta-analysis of the use of probiotics for the prevention of NEC in preterm infants. In the review of 14 trials, they found that, "The risk for NEC and death was significantly lower and analysis showed a 30% reduction in the incidence of NEC" (Deshpande et al., 2010, p. 921). The probiotics used were strains of Lactobacillus, Saccharomyces, and Bifidobacteria. Thompson and Bizzarro's article in 2008 discusses several