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Routine Probiotics for Premature Infants: Let's be Careful!

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Recent technological advances have provided us with the knowledge that when one evaluates the number of genes or cells in the average human, only 10% are mammalian and the rest are microbial.(1,2) The recent development of non-culture-based-techniques to evaluate microbial DNA is providing new insights into the relationship that exists between microbes and their mammalian hosts, especially the microbes that reside in the gastrointestinal tract(2). Manipulation of the microbial environment of the gastrointestinal tract using probiotics has been considered a means to promote health and prevent disease. Probiotics, according to Food and Agriculture Organization/World Health Organization (FAO/WHO) definition, are: "Live microorganisms which when administered in adequate amounts confer a health benefit on the host." Probiotics are commonly found in certain fermented foods or supplements with specially added active live cultures, such as in yogurt and dietary supplements. Specific health effects attributed to probiotics that are currently being investigated include alleviation of diarrheal illness, constipation, urogenital infections, atopic diseases, and neonatal necrotizing enterocolitis (NEC).(3)

NEC is among the most common and devastating diseases encountered in neonates. It has also has been one of the most difficult to eradicate(4) and thus has become a priority for research.(5) The incidence of NEC and its accompanying morbidity and mortality has remained unchanged since the 1970s. Large multicenter neonatal network databases from the United States and Canada describe a mean prevalence of NEC of about 7% in infants with birth weight between 500–1500 grams.(6–9) The excessive inflammatory process initiated in the highly immunoreactive intestine in NEC extends systemically, affecting distant organs such as the brain, placing affected infants at much higher risk of neurodevelopmental delays.(10,11) Intestinal microbes play a significant role in the pathogenesis of NEC, (12)and preventative strategies based on manipulation of the microecology of the intestine thus appear reasonable.

Controversy about routine prophylactic probiotic administration for preterm infants has emerged over the past years with some of the claims in support of its use bordering on hyperbole. For example, based on a meta-analysis of several studies using several different probiotics bacteria that show varying results,(13) authors have stated "Do we, knowing what we now know, have the right to deny parents the option of giving a probiotic if that is what they would like?"(14,15) Furthermore, based on a meta-analysis result, it is being claimed that additional placebo controlled trials are unnecessary if a suitable probiotic product is available.(13) In reply to such a parental request, should the physician provide the infant

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with whatever probiotic product the parent wishes to provide to the infant? Is there a "suitable probiotic product" with adequate quality control that is FDA approved [as safe and effective for NEC] currently on the market? To this author's knowledge there is not such a product. Should physicians be advised to administer any probiotic dietary supplement to their patients when FDA is limited in its ability to effectively regulate dietary supplements? Indeed, adverse effects,(16) including increased mortality,(17) have been reported with this class of agents. At a minimum, if they are to be used, physicians need to be aware and convey to parents the potential risks associated with such products.

In neonatal intensive care, several meta analyses have been reported, one of the most recent generating not only enthusiasm but also concern.(13) Desphande et al evaluated 11 trials using 10 different probiotic preparations and concluded that they incurred such a benefit that no further studies were needed. In addition, an accompanying commentary suggested that the evidence is so strong that "most deaths or cases of NEC in eligible infants who are not given probiotics may, on balance of probability, be ascribed to that omission."(15) Some of these concerns will be summarized and additional evidence will indicate that we need to proceed with caution. Several caveats were raised, including the concern that 10 different probiotic preparations were used in the meta-analysis. (18) Some of the probiotic preparations appeared to be effective, but others were not. When slightly different preparations were used in a similar population in subsequent studies, some of the outcomes, such as effectiveness against sepsis and mortality, dramatically changed.(19,20) Previous studies have also shown that different probiotic microorganisms when used to prevent diarrheal illness are not equal (21). Clinical trials should evaluate carefully selected, precisely defined probiotic strains to address clinically important endpoints. The likelihood of publication bias also exists. In a recent systematic review of the effects of Bifidobacterium animalis that evaluated both published and unpublished data, the risks of NEC, sepsis, and antibiotic use were not reduced. (22)This raises the question - what product or combination of products should be used?

Issues beyond the combination of different probiotics in a meta analysis should also be considered. The validity of biostatistical methods used in the meta analysis has been brought into question. (23–25) The empirically weighted random effects methods used in this study(13) tend to understate sampling error, leading to systemic undercoverage of confidence intervals.(24,25) Furthermore, it needs to be emphasized as noted by Soll, that "meta-analyses and multiple small trials have led us astray before and should not be overinterpreted".(18)

Another issue that was only partially alluded to was that the causes of death in the studies included in the meta analysis were not clearly delineated in the original studies. Most of the significant differences in mortality were derived from one study,(19) with one combination of probiotics. When this study was repeated as a multicenter trial by the same investigators(20) using a slightly different probiotics preparation, there were no longer statistically significant differences in mortality. Only 2 deaths in the study group and 3 deaths in the control group could be attributed to NEC. Although there were 6 non-NEC deaths in the control group and 0 in the study group, the causes of these deaths were not stated and could have been due to a pathophysiology unrelated to the probiotics use. Furthermore in the second study, there was a difference in sepsis between the groups, with the control group having the lower incidence of sepsis. In the babies weighing < 750 grams, there were 12 babies in the probiotic group with sepsis and only one baby in the control group that developed sepsis,(20) a statistically significant difference.

The results of the existing studies also raise the question of whether routine use of probiotics would provide benefit in the majority of settings. In the meta analysis, there was a large

heterogeneity of outcomes among intensive care units, with some reporting NEC rates less than 3% in VLBW infants. One of the groups with significant differences in NEC had a baseline NEC rate of nearly 16.4%.(26) Another group had a NEC rate of 2.7% in the baseline group and there were no differences in NEC from that latter group of NICUs.(27) Furthermore, the mortality differences were not reported in the original report from this study,(27) despite this being the largest of the trials reported. Would it make sense to use routine prophylactic probiotics in NICUs with a very low NEC rate?

Of additional concern is that in many countries, including the US, regulatory agencies such as the FDA have limited ability to intervene with the use of probiotics in premature infants without a specific product marketed for such purpose, particularly given the that FDA does not regulate the practice of medicine. Because the scenario of numerous untested and unregulated products being used in premature babies is highly plausible if the recommendations of Tarnow-Mordi(28) are followed, the possibility of adverse effects being associated with the use of untested and uncontrolled products needs to be considered.

In summary, despite evidence that certain probiotics may be promising, rational science with a sound mechanistic basis appears to be lagging behind a more empiric approach. In other words, we still do not specifically know how probiotics work, even though the science of the intestinal microbiome is rapidly emerging. Understanding the mechanism would be useful in determining whether long term detrimental effects could occur. We presently have no studies of overall long term health effects of probiotics when administered to preterm infants. In fact early interventions such as Cesarean section versus vaginal delivery can have a significant effect on early intestinal colonization and may have long lasting effects on health. (29)The potential for another misadventure in neonatal intensive care is real, and the data that we would be doing harm by not using probiotics at this time are still lacking. Thus, despite encouraging results for specific probiotics, there is no conclusive evidence to recommend the routine use of probiotics in preterm infants. The available trials do not permit a decision to be made with respect to optimum strain, dosing, or protocol. There are probiotic products on the market that cannot be recommended because they have not been studied sufficiently and may be harmful. Because NEC also appears to be a highly heterogeneous and etiologically multifactorial disease, targeting the neonates at highest risk with the lowest potential for harm, rather than routinely prophylaxing all infants appears prudent. The perspective of the Committee on Nutrition of the European Society for Pediatric Gastroenterology and Nutrition is also in agreement with this more cautious approach. (30,31) Further studies, preferably single protocol multicenter trials, including rational approaches based on scientific evidence for choosing the agents and with close regulatory oversight are warranted.

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