**Using a mathematical model to analyze the role of probiotics and inflammation in necrotizing enterocolitis.**
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**OBJECTIVES:**

Necrotizing enterocolitis (NEC) is a severe disease of the gastrointestinal (GI) tract primarily observed in pre-term babies. Although not entirely understood, NEC is thought to be related to the physiological immaturity of the GI tract and the altered levels of normal flora in the intestines. Understanding the contributing factors of NEC can help suggest treatment strategies for re-establishing the integrity of the epithelial wall and preventing the propagation of inflammation. Several studies have shown a reduced incidence and severity of NEC in neonates treated with probiotics. The objective of this study is to use a mathematical model to predict the conditions under which probiotics may be successful in promoting the health of infants susceptible to NEC. The model is simulated in the presence and absence of probiotic treatment, and the effects of breast-feeding are considered.

**METHODS:**

A system of ordinary differential equations is used to track pathogenic and probiotic bacteria in the intestinal lumen and in the blood/tissue regions. The degree of “leakiness,” or permeability, of the intestinal epithelial layer is also treated as a variable. A healthy state corresponds to a low, baseline level of leakiness with no bacteria in the blood. The two lumen bacteria species are assumed to leak into the blood/tissue region if they exceed a given threshold. Once in the blood/tissue, bacteria invoke an immune response. Injury to the epithelial wall occurs as a consequence of inflammation, and thus leakiness increases with macrophage activation. Probiotics are assumed to compete with pathogenic bacteria in the lumen and decrease intestinal leakiness.

**RESULTS:**

The model predicts that in the presence of probiotics, health is restored in many cases that would have otherwise exhibited sustained inflammation. Although probiotics are typically viewed as helpful, if the growth rate of probiotics increases substantially, leakiness and bacteria levels in blood both increase, and the health state is compromised. A sensitive interplay between the strength of the immune response and the positive and negative effects of probiotics is observed.

**DISCUSSION:**

The effects of breast milk are evaluated by this model by including probiotics and reducing the growth rate of pathogenic bacteria in the lumen. The model predicts the re-establishment of the healthy state under these conditions, which is consistent with experiments that have shown NEC to be six times more likely in formula-fed babies than in breast-fed babies. The model also predicts that the timing of probiotic administration can affect whether or not health is restored. Finally, the model concludes that probiotics may be harmful to the patient under very specific conditions, as observed by Dani et al. 2002. To summarize, the mathematical model is able to predict outcomes consistent with experiment and can be used to suggest conditions under which probiotics may be a successful treatment for infants suffering from NEC.