of the patient's nutritional status and delivery of an appropriate energy source has been emphasized in these findings. This highlights the need for a proactive and aggressive attitude toward nutritional rehabilitation in any patient awaiting liver transplantation. The choice of the primary calcineurin inhibitor immunosuppression regimen, which favored tacrolimus over cyclosporine, has also been suggested in both adult recipients and large single-center pediatric reports.[10]

We are now at the stage in the treatment of patients with BA in whom major improvements in outcomes will not come from refinements in surgical issues or operative techniques but rather from the micromanagement of the patients before and after the initial Kasai procedure. Earlier diagnosis and timelier operative intervention may help. Antifibrotic, or anti-inflammatory therapies, might also be worthy of study post-Kasai procedure. Nutritional status and management should be considered essential and nonnegotiable in these patients. These efforts, in concert with the continuing expansion of donor options, should reduce the waiting list mortality rates.

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PROBIOTICS: PROTECTING THE INTESTINAL ECOSYSTEM?

Shortly after birth, the intestine of the human neonate becomes rapidly colonized with microbes thath communicate with the huge, highly active mucosal surface. The microbes derived from the environment are not always optimal, leading to the concept that supplementation with live microbes (probiotics) that normalize the intestinal microenvironment might confer health benefits. Two articles in this edition of *The Journal* provide additional evidence supporting a beneficial role for probiotics. Bin-Nun et al[1] demonstrate the efficacy of probiotics in preventing necrotizing enterocolitis (NEC) in premature infants. Rinne et al[2] develop the concept that providing probiotics to mothers before delivery and to their infants in conjunction with breast-feeding increases the production of immunoglobulins in the infants as the result of an increase of soluble CD14 (sCD14) in the mother's milk. The presence of increased concentrations of sCD14 (a pattern recognition receptor molecule not found on the intestinal surface) in human milk is known to prevent inflammatory conditions of the gut and has been shown to induce B-cell growth and differentiation.[3] This is especially intriguing because of previously reported studies that show that breast-feeding combined with providing probiotics to mothers and their infants is associated with less atopic disease.[4]

The mechanisms of probiotic action appear to be multifactorial. Probiotic bacteria can promote fermentation processes that metabolize varying quantities of lactic, acetic, and formic acids; synthesis of vitamins; and the production of antimicrobial bacteriocidins and fatty acids.[5] Probiotics can also affect innate intestinal host defenses, including strengthening intestinal tight junctions, increasing mucous secretion, enhancing motility, and producing metabolic products (amino acids such as arginine and glutamine and short-chain fatty acids) that secondarily function as protective nutrients. They contribute to microflora diversity, thus helping to establish a normal commensal flora that protect against potential microbial pathogens.

See related articles, p 186, and p 192.

Our understanding about the interaction between the intestine and its commensal microflora, the development of the intestinal innate immune system, and their relation to nutritional environment ("cross talk") is only

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beginning to evolve. The microflora of the adult human is found primarily in the colon and distal small intestine and consists of more than 10^{13} microorganisms (the "microbiota"), comprising nearly 500 species and nearly 2 million genes (the "microbiome").[6] This is mostly a mutually beneficial relationship, as evidenced by the important role commensal bacteria play in nutrition,[7] angiogenesis,[8] and mucosal immunity.[9,10] Lack of intestinal bacteria can have detrimental consequences. Mice raised in a germ-free environment have a blunting of normal villus capillary development, which can be ameliorated by providing the animals with a conventional mixed microflora or even only one species of a commensal bacterium.[8]

The intestinal epithelium partially relies on toll-like receptors (TLRs) and their signal transduction pathways to interface between the luminal microflora and inflammation. Studies of the interaction between resident microflora and TLRs are beginning to shed light on how the healthy intestinal surface defuses the threat of microbes and how bacteria or their components, which may serve as TLR ligands, are actually required to maintain the architectural integrity of the epithelium. The epithelium and resident immune cells do not simply tolerate commensal bacteria but appear to be dependent on them.[10] TLR-mediated ligation and signaling induced by lipopolysaccharides and lipoteichoic acid enhances the ability of the epithelial surface to withstand injury while also priming the surface for enhanced repair responses.[10] Therefore, either the disruption of TLR signaling or the removal of TLR ligands (derived from intestinal microflora) compromises the ability of the intestinal surface to protect and repair itself in the face of inflammatory or infectious insult. The interaction of the TLR ligand with the receptor is known to be enhanced by sCD14, which is present in substantial quantities in breast milk.[3]

Another mechanism for the action of commensal microflora providing protection for the intestinal tract resides in their ability to prevent ubiquitination of I-κB, a molecule that binds in the cytoplasm to nuclear factor-κB, a critical factor that stimulates production of inflammatory mediators when allowed to traverse to the nucleus and bind to DNA.[11] Ubiquitin-mediated degradation of I-κB allows the nuclear translocation and subsequent activity of nuclear factor-κB.

Might probiotics given during infancy also play a role in prevention of diseases that manifest later in childhood such as allergies, atopy, and perhaps even autoimmune disorders such as type 1 diabetes? The increasing prevalence of these diseases in certain geographic locations has prompted the hygiene hypothesis. The increased use of antibiotics, not only for the treatment and or prophylaxis of disease in infancy but also in agriculture, has been linked to the development of resistance in some human pathogens.[12] Could this be changing the microbial environment in our gastrointestinal tracts? There are differences in intestinal flora in the feces of allergic compared with nonallergic infants.[13] These alterations in gut microbial flora might explain both the inverse relationship between exposure to farm animals and the positive association with antibiotic use in early life. For example, studies have suggested that use of antibiotics during infancy predisposes to the development of asthma.[14] The findings of the study by Rinne et al[2] in this edition of *The Journal* relate to previous studies by this group that showed a reduction of atopic eczema with probiotic use in the newborn infant.[15] The current study demonstrates that an increase in colostral sCD14 correlates with an increase in the numbers of IgM-, IgA-, and IgG-secreting B-lymphocytes in infants who were breast fed and supplemented with probiotics before and after birth. This suggests a synergistic effect of human milk and probiotic bacteria on the development of humoral immune responses. Breast-feeding had a strong impact on the *Bifidobacteria* microbiota.

Neonatal exposures and atopy are fascinating areas of research that are no longer based merely on invoking a preponderance of T_H1 versus T_H2 responses. T-regulatory lymphocytes and dendritic cells along with a myriad of regulatory products from these cells are emerging as links between the intestinal microecology and the development of these pediatric conditions. Soluble CD14 is a target of interest because of its ability to respond to microbial products such as LPS and peptidoglycan and to link these signals through TLRs to the innate and eventually the adaptive immune system. The implication that probiotic supplementation and human milk promote the production of this immunomodulator deserves further investigation.

Preterm infants represent a special situation for probiotics. Preterm infants have immature intestines, incur delayed feeding, and are very often treated with broad-spectrum antibiotics shortly after birth. It is generally considered that diversity is an important factor in determining the stability of ecological systems to perturbation. The lack of microbial diversity in the bowel of preterm infants predisposes them to significant changes in patterns of colonization such as the acquisition of antibiotic-resistant strains or the loss of strains associated with antibiotic treatment. These factors make the preterm more susceptible to antibiotic-resistant infections, systemic inflammatory response syndrome, and NEC.

Bin-Nun et al,[1] in this edition of *The Journal*, report that preterm infants randomly assigned to receive a daily feeding supplement of a probiotic mixture had a relative risk reduction of 75% in the incidence of NEC, translating to a number needed to treat of 8. The study group had decreased severity of disease compared with the control group and no adverse effects such as bacteremia, diarrhea, or feeding intolerance. These findings add support to previous studies[16,17] for prevention of NEC with probiotics. It bears recalling that a large multicenter trial conducted in 12 Italian neonatal intensive care units on 565 patients did not elicit a statically significant beneficial effect.[18] Whether the differences in outcomes in these studies are associated with the use of different probiotic preparations, a different baseline incidence of NEC in the various neonatal intensive care units, or other factors remain speculative. The role of human milk versus formula feedings in these infants was not examined, which brings up an important point. Commentary[19,20] on the Lin et al[17] trial of prevention of NEC with probiotics favors