

Neonatal Nutrition & Immune System

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The intestine, which has the largest interface between the external environment and the internal milieu, harbors a highly complex system that allows for assimilation of certain molecules and exclusion of others. The first line of defense is the innate immune system, which works in association with the adaptive immune system. We are just beginning to understand the intricacies of these systems and how they relate to health and disease. Evidence is accumulating that the defense mechanisms in the newborn that normally maintain a healthy balance in the intestine (both immune and nonimmune) may be inadequate or at least not functioning at levels observed in adults. Infants, particularly undernourished infants, may be at an increased risk for luminal proliferation of and mucosal invasion by microbial pathogens and intact dietary antigens.

Several factors lead to a hostile GI environment that predisposes the preterm infant to disease¹. These include the introduction of feeding tubes into the stomach or more distal intestine, the routine use of broad-spectrum antibiotics that select for resistant pathogens that thrive in the unusual microbial environment of the neonatal intensive care unit, intrinsic immaturities of the infant GI tract, and the lack of adequate nutrition.

We will review several aspects of host defenses in the newborn including external factors such as feeding, the type of feeding, the intestinal microbial environment, physical and chemical factors in the intestine and the immune system with an emphasis on the innate immunity of the intestinal mucosa. Human milk protects the intestine from infectious pathogens and intact dietary antigens. Numerous components of human milk are believed to be protective, including immunoglobulins, lactoferrin, lysozyme, glycoconjugates, oligosaccharides, and various types of white blood cells². Antibodies in human milk reflect the antigenic repertoire of the mother's intestine and respiratory tract³. If the mother and infant are colonized by the same bacteria, the mother can produce specific antibodies that can protect the infant through her milk⁴.

Although a commonly held belief is that the intestinal tract of the fetus is sterile, recent studies suggest that many preterm infants are exposed to microbes found in the amniotic fluid, even without a history of rupture of membranes or culture-positive chorioamnionitis⁵. One of the first comprehensive nonculture-based studies of intestinal microbes in 14 healthy term infants, using a ribosomal DNA microarray-based approach, showed that the composition and temporal patterns of the microbial communities varied widely

from baby to baby, suggesting a broader definition of «healthy colonization» than previously recognized⁶. Studies of microbial ecology in premature infants using non culture based techniques, remain few, but this is an area of active investigation. One study used high throughput 16S based techniques to analyze intestinal microbial ecology in premature neonates in 23 neonates born at 23 to 32 weeks gestational age⁷. Surprisingly, microbial DNA was detected in meconium, suggesting an intrauterine origin. Differences in diversity were detected in infants whose mothers intended to breast feed, babies born to mothers with chorioamnionitis, and in babies born at <30 weeks gestation. A 16S ribosomal RNA sequence analysis detected Citrobacter-like sequences only in cases with NEC (3 of 4) and an increased frequency of Enterococcus-like sequences in cases and Klebsiella in control subjects.

Intestinal motility can be a critical factor in clearing antigens presented to the intestinal mucosal barrier from the gut lumen. In postnatal life, motility patterns change with development and may not reach a mature pattern (comparable to that of the term infant) until 34 to 35 weeks postgestation⁸.

The preterm neonate increases gastric acid secretion over the first several weeks after birth⁹. Normal gastric acid and pancreaticobiliary secretions decrease the load of viable microorganisms as well as intact dietary protein antigens that reach the small intestine. Pancreatic insufficiency in the preterm infant can last through the first year of life. Low gastric acid and pancreaticobiliary secretions coupled with histamine blocker prophylaxis can affect the intestine adversely by allowing a greater bacterial or antigenic load, thus predisposing the infant to sepsis and necrotizing enterocolitis¹⁰.

Other aspects of the intestinal physiochemical environment also play a protective role. Intestinal mucus plays a significant role in intestinal defense¹¹. Mucin from the small intestine of newborn rats contains more protein than mucin from adult rat intestine. Carbohydrate composition also changes; the newborn mucin has less fucose and N-acetyl-cysteine than adult mucin¹². Developmental aspects of mucin in the human small intestine remain poorly understood. Follicular dendritic cells are important nonphagocytic antigen-presenting cells. They are present in lymphoid follicles and are essential in presenting antigen to CD 4+ T cells as well as B cells and play a role in signaling to undifferentiated T cells and thereby play a central role in the maintenance of local immunologic homeostasis.

Numerous innate humoral factors are secreted onto

mucosal surfaces by exocrine glands, and they can carry out their protective functions in the absence of specific antibodies. They protect the mucosa against pathogens and other insults before the immune system has had time to mount specific responses.

The role of cytokines produced by the intestinal epithelial cell (IEC) is just beginning to be elucidated. Although one of the most obvious functions of the IEC is to maintain a functional barrier to intestinal luminal contents, the cytokine-related inflammatory response drastically alters this barrier function. Glutamine, the most abundant amino acid in the human body, plays a central role in inter-organ carbon and nitrogen flux. Traditionally, glutamine has not been used as a nutritional supplement and is considered as a «non-essential amino acid» because it can be synthesized in the body. Glutamine stores may become depleted, particularly in the course of a catabolic insult such as injury, infection or chronic glucocorticoid treatment. A number of roles have been ascribed to glutamine as an immunonutrient. Glutamine and nucleotides appear to act synergistically in intestinal epithelial proliferation and differentiation. The antioxidant glutathione is also formed from glutamine.

Preterm neonates who subsequently develop NEC have been found to have lower plasma glutamine and arginine concentrations¹³. Two large multicenter trials have evaluated the safety and efficacy of glutamine supplementation. A trial of parenteral supplementation showed no effects¹⁴ where as the enteral trial showed indices consistent with better feeding tolerance¹⁵. Secondary outcomes from the enteral trial also suggested decreased intraventricular hemorrhage and periventricular leukomalacia with glutamine supplementation¹⁵.

Arginine is an essential amino acid in the fetus and neonate, and is a conditionally essential nutrient for adults. Adequate concentration of arginine may be necessary not only for tissue growth but also for normal physiological function. It had been shown that premature infants who subsequently developed NEC had a significant lower plasma concentration of arginine than did infants who did not develop NEC^{16,17}. Reduced arginine concentrations may be due to an increased metabolic demand for arginine or limited endogenous synthesis. In the face of inflammation or injury, NO is a mediator critical for the regulation of blood flow in the intestine.

Dietary fatty acids such as linoleic acid (LA; 18:2n-6) and α -linolenic acid (ALA; 18:3n-3) of the n-6 and n-3 series of PUFA, respectively, are considered «essential» because they must be derived from the diet.

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Once ingested, the essential fatty acids are converted to longer-chain, more highly unsaturated fatty acids, including arachidonic acid (AA) from LA; and eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA) from ALA. Modulation of immune and inflammatory responses has been reported with increased intakes of PUFA of the n-3 series. PUFA supplementation of neonatal formula has been studied extensively for the outcomes of central nervous system development and visual acuity with mixed results, but appears to be safe and has been added to numerous formulas for both term and preterm infants.

Lactoferrin (LF), an iron-binding protein, is the most abundant whey protein in human milk. As implied by its name, LF was first isolated from milk. Subsequently it was found to be present in most exocrine fluids such as saliva, bile, pancreatic fluid, and tears. Plasma also contains LF. A recent study showed decreased late onset sepsis in premature infants treated with bovine lactoferrin¹⁸.

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Satellite Symposium



Pre- and Early Post-Natal Nutrition: New Evidence on Neonates Healthy Growth & Protection

17:45 - 19:15

Sunday, October 24th, 2010

3rd Congress of the European Academy of Paediatric Societies (EAPS)

Hall B (Auditorium 15)
Copenhagen, Denmark



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17:45 - 19:15

Sunday, October 24th, 2010

Chairperson:

Prof. Hans van Goudoever, Netherlands
Emma Children's Hospital / AMC Amsterdam

Co-chairperson:

Prof. Ferdinand Haschke, Switzerland
Nestlé Nutrition Institute

Speakers:

Enteral Feeding for Premature Babies.
Prof. Hans van Goudoever, Netherlands

Neonatal Nutrition & Immune System.
Dr. Joseph Neu, USA

Food Allergy and Very Early Allergy Prevention in Neonates.
Dr. Anne Des Roches, Canada



Enteral Feeding for Premature Babies Prof. Hans van Goudoever

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In Europe every year 500.000 infants are born preterm. Since the widespread availability of recent important neonatal innovations (surfactant, prenatal corticosteroids) an increasing number of infants are surviving at decreasing gestational age^(1,2). These infants are born around the time at which for the healthy fetus in utero a period of rapid brain growth commences. The obligatory nutrients to achieve this rapid growth are continuously supplied to the fetus through the umbilicus. The premature newborn however is, during admission to the neonatal ICU, faced with assaults like sepsis and necrotizing enterocolitis. These assaults are likely to increase energy expenditure at a time when intake is usually low due to physician's concerns of fluid overload or intolerance, and therefore the majority of preterm infants slip into poor nutritional status during admission. Hulst et al. showed that 44% of the preterm infants drop more than 1 SD in weight-for-age (WFA) scores⁽³⁾ during NICU admission. The percentage of infants that are >2 SDS below the mean WFA increases from 14% to 55% during this period. Six months after discharge 15% of children are >2 SDS below the mean WFA. This indicates that a large proportion of premature neonates who experience growth failure during their admission undergo catch-up growth after an initial period of malnutrition. Catch-up growth has been associated with an increased risk of insulin resistance and obesity in later life⁽⁴⁾. Lack of substrate availability during early life endangers body- and organ growth in general and brain growth in particular. Nutrition and growth are known to have a major impact on later physical health and mental ability of prematurely born children. This is illustrated in a retrospective study by Stephens et al. on the effect of protein and energy intake on neurodevelopmental outcome in ELBW infants. They found that after adjusting for confounding variables, a 10 kcal/kg per day increase in energy intake during the first week of life was associated with a 4.6-point increase in MDI at 18 months corrected age. Even more striking, an increase of 1 gr/kg per day of protein was associated with a 8.2 point increase in MDI⁽⁵⁾.

Both the amount of macro-nutrients and the type of feeding infants receive is known to influence outcome. Human milk has shown to have a beneficial effect on serum cholesterol and to reduce diastolic blood pressure in later life. Singhal et al. showed that adolescents who were born preterm and were randomized to receive human milk during early life had a 3.2 mmHg lower diastolic blood pressure than their formula fed peers⁽⁶⁾. This effect size, if persisting into adulthood, corresponds to a more than 20% risk reduction to suffer from stroke. However, the exact amount and composition of nutrients that the premature neonate requires in order to completely meet his genetic growth and academic potential remain unknown. Present nutritional recommendations are based upon the composition of human milk and the estimated composition of tissue that is acquired during fetal growth (factorial approach). The factorial approach estimations are derived from analysis of carcasses of deceased fetuses. However, both methods have several drawbacks. Human milk is intended for the healthy term infant who has a very different physiology and physical activity level from the sick preterm infant. The fetuses studied by the factorial method might have been growth restricted. New approaches to gain more insight in the needs of premature neonates have to be sought. Although human fetal studies are complicated by maternal and placental metabolism and there are various ethical issues involved, they are likely to provide us with valuable information. For example, van den Akker et al. found that fetuses at around 30 weeks of gestation had higher albumin synthesis rates than fetuses close to term⁽⁷⁾. This indicates that the fetal liver is capable of synthesizing large amounts of albumin. It can therefore be hypothesized that the hypoalbuminemia we often see in premature neonates is not so much a consequence of prematurity but rather a lack of substrate availability. But also results obtained from these studies can not be extrapolated completely to the premature newborn as the fetus has, although the same post conceptional age, a very different physiology due to the different environment. During fetal life there is no use of the lungs, gut activity is different and there is hardly any bacterial colonisation, which is likely to influence metabolism and energy expenditure. In a series of series, we have shown that e.g. gut metabolism has a major impact on nutrient requirements⁽⁸⁾.

Nutritional management of preterm neonates has gone through major changes during the last few decades but as long as premature neonates are still becoming growth restricted during admission to our NICU's and long-term outcome is not comparable to the healthy infant born at term, we have not reached our goals yet. Optimal amino acid/energy intakes are not yet defined. Nutritional deficits mostly occur in the first few days/weeks of life, when parenteral and enteral nutrition is slowly started. There is no empirical evidence for this gradual increase in parenteral amino acid and energy supply; this practice is probably based on concerns of intolerance or fluid overload. As mentioned earlier, the unborn fetus is continuously supplied with high amounts of amino acids and glucose. After preterm birth restoration of this supply should be of primary concern to the neonatologist, and achieving a high protein intake as soon as possible should be the major goal⁽⁹⁾. The thereby accomplished prevention of growth faltering in early life will make the discussion about "harmful catch-up growth" futile.

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Food Allergy and Very Early Allergy Prevention in Neonates Dr. Anne Des Roches

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Food allergy
In the last decades, the prevalence of food allergy has increased. Food allergy is a hypersensitivity reaction, mostly IgE-mediated, that occurs in reaction to various food proteins. It is estimated that the prevalence of food allergy peaks at 6-8 % at one year of age and then falls progressively until late childhood. Milk allergy will affect nearly 2% and peanut allergy 1% of the pediatric population. Many infants with food allergy have their first reaction on the first known exposure. It is the case for 80% of peanut allergic children. It implies that young children are previously and insidiously exposed to antigen. The long-term impact of food allergy is also not negligible: at least 80% of peanut allergic children, 25% of egg allergic children and 15% of milk allergic children will not lose their allergy. The persistence of their allergy, especially milk allergy, is associated with a clear impact on quality of life for these children and their families.

Manifestation of food allergy

Classical symptoms of food allergy are urticaria, angioedema, bronchospasm, vomiting, diarrhea, hypotension and shock. However, in neonates, the allergic reaction is more subtle. Many breastfeeding mothers, but not all of them, excrete food proteins in their milk. Cow milk proteins are found in the breast milk of approximately 50-95% of breastfeeding mothers, egg proteins in 60-75%, wheat protein in 70% and peanut protein in 50%. The quantity of food proteins found in human milk is very low, ranging from nanogram to microgram per ml. However, even with such a small quantity, it is enough for some neonates to sensitize themselves to these proteins and for some, to cause allergic reaction after ingestion via breast milk. In general, food allergic reactions in breastfed infants are less severe, which could be explained by the low level of food proteins ingested through breast milk. Symptoms most often seen in breastfed infants and neonates are vomiting, diarrhea, crying, atopic dermatitis. We already described the case of a 6 weeks-old breastfed baby who presented allergic reaction to peanut protein via breast milk exposition. Few food allergic reactions are reported in premature babies. However, we reported three cases of

necrotizing enterocolitis in pretermatures probably secondary to milk allergy. These premature infants were fed with breast milk enriched with fortifier.

Diagnosis in neonates

The diagnosis of food allergy is made based on the history of reactions to food exposure and the presence of IgE specific to the food proteins. The gold standard is the oral food challenge. However, in neonates and infants, the diagnosis of food allergy could be difficult to confirm. As specific IgE can go undetected before the age of 9 to 12 months, even with non-doubtful allergic reaction, an eviction-reintroduction diet with the suspected allergen could be used to diagnose food allergy.

Prevention

Preventive diet during pregnancy and breastfeeding is still a matter of debate. The lack of valid studies on that topic does not allow to conclude on the value of preventive diet. Even if the official authorities in allergy do not recommend preventive diet during pregnancy and breastfeeding, they do not disapprove it. Recent studies show that peanut consumption during pregnancy increases the risk of developing peanut allergy in babies coming from at risk families. Also, peanut consumption at home seems to correlate with a higher incidence of peanut allergy. Skin exposition seems to be another important way of sensitization. Recommendation on peanut avoidance during pregnancy, breastfeeding and exposition at home will probably be revisited in the next years. Milk avoidance during the first year of life has been associated with a significant decrease of milk allergy. Even if this was considered of minor interest in the past, the impact of this preventive measure is not without interest now as 15% of milk allergy persists and is associated with a clear impact on quality of life. In that way, use of hypoallergenic formula for premature infants and hypoallergenic formula in neonates should be privileged in those coming from atopic families and so, at greater risk to develop milk allergy.