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Gastrointestinal Maturation and Feeding

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The intestine serves not only as a digestive absorptive organ, it is also one of the largest immune organs of the body, has a huge endocrine and exocrine role, and also encompasses neural tissue equivalent to that of the entire spinal cord. The microbial microenvironment also plays a critical role in development. This brief overview of developmental aspects of these intestinal functions will be related to clinical problems in the neonatal period and subsequent health.
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As the premature infant matures, several aspects of gastrointestinal development become important issues in terms of the capability of the GI tract to function as an organ of digestion and absorption. However, the intestine serves not only as a digestive absorptive organ, it is also one of the largest immune organs of the body, it plays a major endocrine and exocrine role, and also encompasses neural tissue equivalent to that of the entire spinal cord. The microbial microenvironment also plays a critical role for not only the developing intestine, but for future health. Here, some of these developmental issues will be presented along with how they relate to clinical issues in premature, late preterm, and term infants.

As the GI tract develops, tremendous growth occurs with a doubling of intestinal length in the last trimester of pregnancy; but the surface area increase is even more dramatic, largely because of the villus and microvillus growth during this period of development. Despite this, digestive absorptive capabilities seem not to be a critical problem in the late preterm infant. In terms of protein intake, even though gastric acid secretion remains low[1]and the protease cascade is limited because of enterokinase activation of pancreatic proteases,[2] these babies seem to tolerate whole protein formulas. Studies evaluating hydrolyzed proteins have been shown to have only minimal effects in terms of tolerance and hospital stay.[3] Lipid digestion is theoretically limited by low bile acid secretion and a lack of ileal reabsorption (low enterohepatic circulation).[4] Despite this limitation, meta-analysis of studies comparing medium chain triglyceride feeding to long chain triglycerides do not show clear benefits in terms of weight gain.[5] In regards to carbohydrate digestion and absorption, small intestinal lactase activity is low relative to the other disaccharidases.[2] Despite this limitation, these infants appear to adapt rapidly to lactose feedings[6] and also possess intestinal microflora that have the capability to ferment lactose into 2 and 3 carbon fragments that are absorbed in the distal intestine and utilized for energy production (lactose salvage pathway).[7]

Various aspects of intestinal motor function immaturity result in feeding intolerance in premature infants. Suck swallow coordination are usually not developed until approximately 34 weeks gestation. Motility and gastric emptying can be delayed and some infants take considerably longer to feed normally. This is certainly a factor keeping many infants hospitalized or causing rehospitalization, especially when pediatricians equate the capabilities of the late preterm to the term infant. Intestinal dysmotility is limited largely to infant less than 34 weeks gestation, but may extend to later gestational ages.[8] Esophageal tone is considerably lower in infants less than 30 weeks gestation,[9] but this appears to be not that critical of a problem in terms of tolerance to enteral feeds. The ability to breathe, suck, and swallow in a coordinated manner is dependent on degree of maturity of the infant[10] (Fig. 1), and delays of this maturational process often prolongs hospitalization. Observation of babies in the NICU suggests an association between apneic and bradycardic episodes and GE reflux. The use of H-2 blockers, motility agents (eg, cisapride), and antireflux medications for prevention of apnea related to GE reflux has varied highly over the past several years, with some units using such agents in a majority of infants at risk for apnea. However, several studies have evaluated this relationship and found no cause–effect relationship; therefore, the likelihood of treating premature infants with acid blockers and other agents such as metaclopramide

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Summary Points

1. Most digestive-absorptive processes are well developed in late preterm infants. There should be very few limitations in terms of digestion and absorption of lactose, long chain lipid, or protein.
2. Suck–swallow incoordination and motility remain immature in many late preterm infants and may result in feeding difficulty and prolonged hospitalization.
3. The dynamic role of the intestine during early development along with the interactions with the microbial environment in early nutrition, immunity, and endocrine and exocrine function should not be underestimated in terms of not only health of the neonate, but subsequent health beyond the neonatal period.

Knowledge Gaps

1. Suck–swallow immaturity leads to the necessity to use feeding tubes and frequently delays discharge. Are there interventions that might accelerate our ability to feed these infants?
2. Immaturities of gastric emptying and intestinal motility frequently lead to feeding intolerance. Are there better techniques for breastfeeding these infants, and/or formulas with a composition (preferably a non-pharmacologic approach) that can be used to overcome these immaturities?
3. The intestinal microbial environment plays a critical role in overall nutrition, maturation of the intestine, and the innate and adaptive immune systems. This likely plays an important role not only during neonatal life (eg, necrotizing enterocolitis), but early alterations in the microflora may be critical for subsequent health. It likely plays a role in allergies, asthma, and autoimmune diseases such as Type 1 diabetes. We need a better understanding of how the intestinal microbiota interact with the host immune system during all stages of neonatal life (very preterm, late preterm, or term).

Needed Research

Practical techniques to improve suck–swallow coordination.

A better understanding of basic mechanisms of development pertaining to gastric emptying, and intestinal motility.

Development of practical techniques for more efficient breast feeding, readily tolerated infant formulas designed for late preterm infants.

A better understanding of basic mechanisms of action of intestinal microbial-host interactions and perturbations (antibiotics, nutrients, other environmental agents) that can interfere (program positively or negatively) for future disease.

Practical interventions for promoting positive microbial–intestinal interactions (probiotics, prebiotics, microbial components).

or cisapride are likely to be of minimal if any benefit in the prevention or treatment of apnea.[11,12] Of interest is the recent suggestion that GE reflux in low birth weight infants may play a role in the development of adenocarcinoma of the esophagus when these children reach late adulthood.[13]

Necrotizing enterocolitis is one of the most important diseases seen in the NICU. It is most commonly (80-90% of cases) seen in very low birth weight infants, but can also be seen in term and late preterm infants. The more premature the infant, the later NEC appears to occur after birth. Furthermore, compared with preterms, NEC in term and late preterm infants has a greater association with other predisposing factors such as low APGAR scores, chorioamnionitis, exchange transfusions, prolonged rupture of membranes, congenital heart disease, and neural tube defects.[14]

The development of the intestinal innate and adaptive immune systems of human infants remains largely unexplored. Several aspects of the innate immune system are beginning to emerge as critical in not only short term diseases during the immediate neonatal period, but also appear to play a role during later life. The intestinal barrier is critical in terms of preventing bacterial translocation and initiating the inflammatory response, which might not only affect the well-being of the intestine but distal organs such as the lung and central nervous systems as well.[15,16] Diseases that emerge in later life, such as type 1 diabetes, inflammatory bowel disease, allergy, atopy, asthma, and even autism, may have part of their origins during the neonatal period due to intestinal barrier dysfunction[15] (Fig. 2).

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").[17] This is mostly a mutually beneficial relationship, as evidenced by the important role commensal bacteria play in nutrition,[18] angiogenesis,[18,19] and mucosal immunity.[19] Reduction of normal commensal bacteria in the context of infection or after antibiotic treatment may interfere with availability of critical nutrients and impair stimulation of gastrointestinal mucosal development and the innate and adaptive immune responses.