
**Background**

At the time of birth, the preterm infant’s gastrointestinal system is anatomically and physiologically immature. As the infant develops, tight junctions between the cells of the intestinal mucosa close, reducing the risk of invasion by pathogens in the environment.

Intestinal permeability can be accurately measured by the ratio of lactulose to mannitol in infants’ urine. Mannitol is a small molecule that easily passes through the intestinal epithelial cells by intracellular diffusion. A lactulose molecule is too large to diffuse through the epithelial cells. However, lactulose can pass between the intestinal cells if the junctions between the cells are open. Therefore, the lactulose to mannitol ratio (L/M ratio) is a direct measure of intestinal permeability, indicating the degree of closure of the junctions between intestinal epithelial cells.

The purpose of this study was to examine the relationship between feeding type – human milk and infant formula – on intestinal permeability in preterm infants over the first month of life.

Sixty-two preterm infants less than or equal to 32 weeks gestation were included. The median gestational age at birth was 29.2 weeks (range 24-32 weeks).

Infants were evaluated on postnatal days 7, 14, and 30 for degree of intestinal permeability. On each of these days, a lactulose/mannitol solution was administered by nasogastric tube and the infant’s urine was collected and analyzed for lactulose/mannitol ratio.

The authors collected detailed information on infant feeding, particularly the amounts of human milk and/or preterm infant formula the infants received. Human milk was fortified with standard human milk fortifier once feed volumes reached 120-150 mL/kg/day.

Infants were divided into four groups by the amount of human milk they received over the study period:

- Majority of human milk feeds: received >75% of enteral feeding as mother’s milk
- Partial human milk feeds: received 25-75% of enteral feeding as mother’s milk
- Minimal human milk feeds: received <25% of enteral feeding as mother’s milk
- No human milk feeds: received formula only

**Results**

Composite data show infants who received any mother’s milk demonstrated significantly lower L/M ratios, indicating reduced intestinal permeability and, therefore, better tight junction closure when compared to infants receiving no human milk (p = 0.006).

Infants who received >75% of feeding as mother’s milk demonstrated a 3.8-fold lower composite median L/M ratio (and decreased intestinal permeability) when compared to infants receiving <25% or no mother’s milk.
Conversely, exclusively formula-fed infants demonstrated a 2.8-fold higher composite median lactulose/ mannitol ratio when compared with those who received any mother's milk, indicating significantly greater intestinal permeability and risk for infection.

Conclusions

The authors conclude: "Preterm infant intestinal permeability was significantly decreased for those receiving human milk versus formula in a dose-related manner in the first postnatal month" (p.11).

The data suggest a possible relationship between increased gut permeability with formula feeding of preterm infants and a potential increased risk of NEC.

Commentary

This research contributes valuable insights into the question of how human milk protects preterm infants from gastrointestinal disturbances and disease: human milk feedings facilitate the maturation of tight junctions in a dose-response manner over the first month of life. This study also demonstrates the detrimental effect of formula feeding on the immature gastrointestinal system: formula feedings are associated with delayed closing of tight junctions, also in a dose response manner.

The gastrointestinal tract has a dual purpose of absorbing nutrients and protecting the organism from invasion of environmental pathogens. This protection begins in the lumen of the GI tract with functional barriers like mucus and commensal (or protective) bacteria and continues into deeper layers of the mucosa with cells specific to immune response and regulation of inflammation.

The human gastrointestinal tract is comprised of several layers of functional substances overlying the intestinal epithelial absorptive cells, commonly referred to as enterocytes. At the apical end of the enterocyte, several layers of coatings protect the epithelial cells from harmful microbes. The glycocalyx is a thick, mucin-rich glycoprotein matrix lining the entire gastrointestinal system. Together with the mucus layer, it forms a sticky gel-like barrier that lubricates and protects the intestine. Embedded within the mucus layer are antimicrobial inhibitors that help regulate gut colonization. Lastly, a biofilm of symbiotic bacteria develops at the interface with the intestinal lumen. All three layers work in concert to protect the infant from pathogenic bacteria.

Gut permeability is one of multiple developmental limitations of the preterm infant’s immature gastrointestinal system, all of which can contribute to an increased risk of feeding intolerance as well as short and long-term morbidities. Other aspects of the preterm gastrointestinal system related to immaturity include a need for rapid cellular growth and turnover, decreased peristalsis, decreased gastric acid, decreased proteolytic enzymatic activity, altered intestinal mucus, and an immature inflammatory response.
According to Wagner et al., amniotic fluid and human milk are sources of multiple growth factors important to the continuum of fetal-infant gut development and maturation. Like amniotic fluid, human milk promotes gut maturation by supplying epidermal growth factor as well as other trophic factors. After birth, human milk assumes the role of exogenous source of bioactive substances stimulating cell growth and repair through the synergistic actions of cytokines, insulin-like growth factors, transforming growth factors δ and β, insulin, erythropoietin and vasoactive endothelial growth factor. Wagner et al. hypothesize trophic factors in human milk also enhance the development and function of the intestinal mucus barrier. By promoting growth of enterocytes, tight junctions and the mucus barrier, human milk contributes to the overall functioning and integrity of the infant gastrointestinal system.

Human milk provides other benefits related to immaturity of the neonatal gastrointestinal tract. Human milk increases peristalsis, thereby decreasing the build up of toxins and pathogens in the intestinal lumen. Additionally, milk lipases breakdown triglycerides by into anti-microbial free fatty acids promoting an acidic gastric environment essential for nutrient degradation. These are just a few of the numerous protective functions of human milk in the preterm gastrointestinal tract.

As this study by Taylor et al. demonstrates, the absence of human milk and the presence of preterm infant formula can impair the system’s ability to mature. The next article and commentary delve deeper into the relationship between infant feedings and clinical outcomes.