Gut Health Challenges: How Do We Feed to Improve Intestinal Integrity and Growth In Calves?

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Introduction

During the preweaning and weaning periods for calves, there is heightened susceptibility to disease and gastrointestinal dysfunction, specifically in the small intestine before maturation of the rumen (Steele et al., 2016). Morbidity and mortality related to diarrhea and other digestive issues continue to be an issue in young calves (Urie et al., 2018). Diarrhea in young calves reduces dry matter intake, body weight gain, and feed efficiency (Morrison et al., 2019). Understanding feeding practices that promote improved health and productivity of dairy replacement animals is critical for future success in the herd.

While nutritional focus in mature cattle is centered on the rumen, shifting focus to the small intestine in the preweaning period is essential and necessary to optimize gastrointestinal growth potential, while also minimizing the risk of enteric challenge. Gut growth is regulated by several factors, including metabolic and trophic hormones, and chemical and physical properties of the diet (Baldwin et al., 2004). The interaction of the gut mucosa, microbiota, and feed is complicated (Niewold, 2015). As we further develop our understanding of the gastrointestinal tract's (GIT) impact on calf health and growth, we can promote feeding strategies to optimize development and integrity of the GIT as well as minimize enteric challenges.

Incidence Rate and Outcome of Diarrhea in Calves

Incidence rate of morbidity and mortality continue to affect a large proportion of calves in the United States and around the globe. Survey information of morbidity and mortality rates of heifers collected in the United States in 2014 was 33.9% and 5.0%, respectively (Urie et al. 2018). Of the cases recorded, 56.0% of morbidity and 32.0% of mortality cases in heifer calves were attributed to digestive signs (Urie et al., 2018). The highest rate of abnormal feces is commonly seen within the first 3 wk of life (Bartels et al., 2010) with the greatest risk of treatment for diarrhea around 10 d of age (Waltner-Towes et al., 1986; Windeyer et al., 2014).

Calves may be predisposed to developing diarrhea in the first 21 d of life if they have increased intestinal permeability at birth (Araujo et al., 2015). Additionally, calves that are given a delayed colostrum feeding have greater paracellular permeability, which could indicate slower tight junction closure that could allow pathogenic bacteria to further disrupt intestinal permeability and could result in diarrhea (Araujo et al., 2015). Several studies in calves have indicated higher intestinal permeability in the second week of life

(Araujo et al., 2015; Morrison et al., 2017) which correspond to increased fecal scores and could indicate damage to the villi in the small intestine (Hall, 1999).

Animals that undergo either clinical or subclinical infections will eat and grow less and overall have reduced efficiency (Johnson, 1998). A dataset created from four experiments of transported calves classified them as either healthy or diarrheic in the first 21 d after arrival (Morrison et al., 2019). A retrospective analysis of health status was conducted to determine intake and growth of the calves which were managed similarly. In total data from 313 calves were used in the analysis with 96 calves classified as diarrheic [fecal score >2 (scale 1-4) for ≥3 d in the first 21 d after arrival]. Intake of milk replacer, water, starter, and electrolytes were all recorded. Body weight and growth were also measured.

The cumulative number of days with elevated fecal scores were 1.88 vs. 6.84 ± 1.19 d for healthy and diarrheic calves, respectively. Initial total protein concentrations were not different between classifications. Intake of milk replacer for calves classified as diarrheic was lower and those calves were more likely to refuse part of the offered milk replacer amount. Intake of electrolytes was greater for calves classified as diarrheic. Cumulative starter intake was 40% lower in calves that were classified as diarrheic (0.9 kg) compared with calves that were healthy (1.5 kg) in the first 21 d after arrival. While starter intake does not make up a large portion of intake in this early preweaning period, the impact of diarrhea was evident. Although not measured in this study and the timeframe was fairly short, lower starter intake resulting from a diarrheic event could delay rumen development if this pattern of reduced starter intake continued. Finally, calves that were diarrheic had a 27% reduction in average daily gain (491 vs. 669 g/d), lower stature growth, and were less efficient (0.56 vs. 0.77 kg/kg; Morrison et al., 2019).

Longevity and productivity of the cow have been associated with events in the calf period. Specifically, calves treated with antibiotics have decreased lifetime milk production (Soberon et al., 2012) and the number of days in the first 4 mo of life that a calf is sick negatively impacts first-lactation 305-d metabolizable energy and actual milk, protein, and fat production (Heinrichs and Heinrichs, 2011). Further work is needed to continue to minimize the effect of digestive illness to improve production and welfare, and reduce increased costs associated with this issue.

Interaction between the Calf Gastrointestinal Tract, Feed, and Microbiota

The GIT of the animal, feed, and microbiota interact to form a dynamically complex ecosystem that when in balance work to support the health and growth of the animal (Niewold, 2015). The GIT is a barrier that is able to selectively discriminate the contents of the lumen to allow selective absorption of nutrients, while also providing a protective barrier to harmful antigens and pathogens (Groschwitz and Hogan, 2009). A mixture of different epithelial cells in the GIT form a physical and biochemical barrier to separate the luminal contents and microorganisms from the host mucosa and immune system to maintain coexistence (Peterson and Artis, 2014).

Intestinal Structure and Cells

The small intestine is composed of absorptive epithelial cells (enterocytes), nerve cells, goblet cells, immune cells, and enteroendocrine cells (Peterson and Artis, 2014; Niewold, 2015). Mature enterocytes work through active and passive transport and brush border enzyme activity to absorb nutrients (McOrist and Corona-Barrera, 2015). The enteric nervous system is important for motility, secretion, blood flow, and the immune system (Hansen, 2003).

A physical barrier is formed with the production of mucus from goblet cells, antimicrobial peptides, and immunoglobulin A (IgA; Hooper and Macpherson, 2010) which are important sites for both innate and adaptive immunity (Turner, 2009). The mucus layer is a first line of defense against bacterial translocation to the mucosa while continuing to allow nutrients to be transported across the mucosa (Atuma et al., 2001; Kim and Ho, 2010). Antimicrobial peptides have different actions but many target the cell wall or membrane, while others enzymatically attack cell structures (Gallo and Hooper, 2012; Hooper and Macpherson, 2010). Intestinal epithelial cells secrete IgA antibodies that help regulate commensal bacteria by limiting bacterial association with the intestinal epithelial surface (Hooper and Macpherson, 2010; Peterson and Artis, 2014).

Enteroendocrine cells represent approximately 1% of epithelial cells in the intestine and link central and enteric neuroendocrine systems through hormone regulators of digestive function (Peterson and Artis, 2014). Biological functions regulated by gut peptides include food intake, gastric emptying, motility, barrier function, and glucose metabolism. Therefore, gut peptides secreted from enteroendocrine cells play an important part in absorption of nutrients but also maintenance of barrier function (Cani et al., 2013).

Intestinal Permeability

Permeability of the GIT is location dependent (Penner et al., 2014) and changes with age (Wood et al., 2015). Transcellular permeability is responsible for the transport of solutes, including amino acids, electrolytes, short-chain fatty acids, and sugars, through selective transporters (Groschwitz and Hogan, 2009). Paracellular permeability is the transport of molecules through the space between the epithelial cells via the apical-lateral membrane junction and the lateral membrane (Van Itallie and Anderson, 2006). Expression of junctional proteins are dependent on location within the intestine, location on the microvilli, and location between epithelial cell membranes (Groschwitz and Hogan, 2009). In ruminants, permeability of passive ions is greatest in the jejunum and least for the rumen and omasum (Penner et al., 2014). Furthermore, small pore permeability increased after the rumen and omasum until the jejunum and then decreased in the ileum (Penner et al., 2014). Small intestinal permeability can be measured non-invasively by dosing two different sized non-digestible probe molecules (Hall, 1999; Menzies et al., 1979; Uil et al., 1997). The larger molecules indicate paracellular permeability while the smaller molecules indicate transcellular permeability (Bjarnason et al., 1995).

Inflammatory Response

The mucosal immune system works to tolerate contents and microorganisms in the lumen and is activated when foreign antigens translocate the GIT barrier (Niewold, 2015). The recruitment of circulating inflammatory cells occurs with increased production and secretion of pro-inflammatory cytokines in response to foreign antigens (Al-Sadi et al., 2009). Pro- and anti-inflammatory cytokines regulate intestinal barrier function differently (Al-Sadi et al., 2009). An increase in pro-inflammatory cytokines increases the disruption of the tight junction barrier and overall increases GIT permeability (Al-Sadi et al., 2009; Ma and Anderson, 2006; Nusrat et al., 2000; Bruewer et al., 2006; Shen and Turner, 2006). Alternatively, anti-inflammatory cytokines counteract some inflammation to help maintain tight junction functionality (Madsen et al., 1997; Forsyth et al., 2007).

Trophic Hormones and Peptides

Cells within the GIT secrete a number of hormones and peptides that signal maintenance, growth, and repair of epithelial tissue (Drucker et al., 1994; Burrin et al., 2003). One of particular interest and research in recent years is glucagon-like peptide 2 (GLP-2) which has a role in influencing trophic and regenerative actions in the intestinal epithelium (Burrin et al., 2000). Upon ingestion of nutrients, specifically carbohydrates and lipids, GLP-2 is secreted from the intestinal L-cells along the jejunum, ileum, and colon (Estall and Drucker, 2006; Larsson et al., 1975; Eissele et al., 1992). Specifically, GLP-2 has been shown to increase crypt cell proliferation and reduce apoptotic cell numbers which increases small intestinal mass (Tsai et al., 1997; Drucker et al., 1997). Furthermore, reductions in intestinal inflammation and increases in nutrient absorption in response to GLP-2 have been observed (Furness et al., 2013; Sigalet et al., 2007; Brubaker et al., 1997; Shirazi-Beechey et al., 2011).

Overall, factors that regulate gut growth include metabolic and trophic hormones, and chemical and physical properties of the diet (Baldwin et al., 2004). There are large energetic and nutrient costs associated with maintenance of the GIT in animals that are growing which greatly influences whole body metabolism (Baldwin et al., 2004). However, the actual energetic and nutrient cost is complicated by the influence of changes in tissue mass in response to plane of nutrition, chemical composition of the diet, and physiological status of the animal (Baldwin et al., 2004).

Intestinal Dysfunction

There are several instances that can lead to intestinal dysfunction, including pathogenic and nutritional insults that negatively affect intake, growth, and efficiency. Dysfunction of the GIT can be classified into three categories: 1) mucosal barrier disruption, 2) altered motility, and 3) atrophy of the mucosa (Martindale et al., 2013). All of these effects have been associated with enteric disease attributed with pathogenic bacteria resulting in diarrhea (Connor et al., 2013, 2017; Walker et al., 2015) and weaning (Malmuthuge et al., 2013; Eckert et al., 2015; Wood et al., 2015).

As the intestinal barrier becomes dysfunctional, an increased risk of foreign antigens and harmful bacteria accessing the underlying mucosa can lead to increased inflammation in the intestine (Cameron and Perdue, 2005). Under these conditions, the adaptive immune system is activated which reallocates resources previously utilized for growth to the production of immune cells and antibodies (Iseri and Klasing, 2013). Reduced appetence and catabolism of muscle resulting in a reduction in growth is a consequence of increased inflammation, which further increases susceptibility to intestinal pathogens (Niewold, 2015). Actions of enteric pathogens, including viruses, bacteria and protozoa, vary and affect different locations in the GIT. Damage caused by enteric pathogens can include intestinal villus and colonic crypt atrophy, secretion of enterotoxins, necrosis, and disruption of epithelial tight junction (Cho and Yoon, 2014; Foster and Smith, 2009). Damage caused in the GIT can cause prolonged malnutrition and result in decreased growth rates (Cho and Yoon, 2014).

Nutrient induced secretion of GLP-2 and the associated effects in pig models has been suggested as an important element in intestinal adaptation during neonatal phases by improving mucosal cell proliferation, barrier function, and the inflammatory response (Burrin et al., 2003; Cameron and Perdue, 2005; Sigalet et al., 2007; Ipharraguerre et al., 2013). Since GLP-2 secretion is responsive to nutrient intake, circulating GLP-2 is reduced when milk ingestion drops below 0.875% of calf body weight on a DM basis (Castro et al., 2016). Understanding and promoting GLP-2 and other trophic hormones could be important targets for improvements in intestinal integrity in situations that reduce feed intake like incidences of diarrhea or weaning (Connor et al., 2016). Additional information on nutrient and ingredient influence of motility could also aid in preventing and recovering from intestinal dysfunction in calves.

Lower feed intake can lead to reduced growth and development of the intestinal mucosa (Buchman et al., 1995; Groos et al., 1996). In a piglet model, varying levels of intake were fed to evaluate the amount of intake required to normalize intestinal growth (Burrin et al., 2000). In this study, the authors observed that the proximal segments of the small intestine were most sensitive and that 40% of total nutrient intake was needed to increase wet weight and protein content, while the ileum requires 60% of enteral intake however, 80% of total intake was required to normalize wet weight and protein content in both sections (Burrin et al., 2000).

Feeding and Diet Considerations

While colostrum has critical importance in terms of nutrients and bioactive factors (Blum and Baumrucker, 2008; Nissen et al., 2017) and weaning strategies impact on GIT development and function, the focus for this will center on feeding strategies and diet considerations in the preweaning period. Obviously, the transition into the ruminant phase and ruminal development continues to be a priority in terms of long-term animal success within the herd but areas of opportunity for improvement in intestinal dysfunction contributing to morbidity and mortality in the preweaning period are important.

Feeding Rate and Intake

Enhanced feeding rates of 20% of body weight, which are close to ad libitum intake, have been linked to increased body weight and growth, organ development and growth, metabolic and endocrine changes, improved feeding behavior, and immune and health (Hammon et al., 2020). Increased GIT growth rate and protein accretion of calves with enhanced feeding have been observed when calves are fed whole milk or milk replacer in comparison to calves fed 4 to 6 L/d (Geiger et al., 2016; Schäff et al., 2016; Korst et al., 2017). If you consider a 50 kg calf that is fed 20% of its body weight as milk or milk replacer, the calf would be offered 10 L per day. In contrast, the same calf only fed 4 or 6 L/d would be only 40 to 60% of the enhanced feeding rate. In neonatal piglets, 40 to 60% of normal intake reduces small intestinal mass and protein content, while 80% of intake was needed to normalize this (Burrin et al., 2000). Decreased circulating GLP-2 concentrations at similar reduced intake has been observed when intake drops below 0.875% of body weight as DM indicating lower trophic actions in the gut (Castro et al., 2016).

These changes in intestinal growth would be in line with observed increases in organ growth, including the small intestine, in response to increased feeding levels in calves (Geiger et al., 2016; Koch et al., 2019). Furthermore, increased surface area and absorptive capacity in the small intestine results from increased feeding rates (Geiger et al., 2016; Koch et al., 2019). Intestinal growth was likely mediated by changes in the local IGF system (Ontsouka et al., 2016). Concerns over delayed rumen development because of delayed starter consumption (Khan et al., 2011) are common with higher levels of milk or milk replacer intake but comparable rumen development and transition can be achieved when an appropriate weaning timeline is used (Schäff et al., 2018).

Greater nutrient supply has been suggested to improve intestinal maturation by supporting a proper adaptive immune response and stabilizing microbiota within the GIT to minimize risk of enteric challenges preweaning (Hammon et al., 2020). Adequate nutrient supply may be required to mature the GIT immune system and to be able to defend against invasive enteric pathogens (Khan et al., 2011; Hammon et al., 2018). Increased feeding rate, and therefore energy intake with higher fat and protein, can result in faster improvement of fecal scores as a result of an infection with *Cryptosporidium parvum* (Ollivett et al., 2012). This may be a result of enhanced activation of the intestinal immune system (Hammon et al., 2018) and a better ability to resist infection (Ballou et al., 2015).

In addition to decreased milk allowance in the preweaning period, reductions in milk and starter intake during an enteric challenge, like diarrhea, may contribute to intestinal atrophy commonly observed with many enteric pathogen infections. There has not been a lot of work specifically looking at level of intake after an enteric disease challenge and how this might help with recovery of GIT size and integrity. It is commonly suggested to not completely withdraw milk or milk replacer feeding when calves have diarrhea and to allow them to consume at least part of their nutrients through that source to aid in recovery (Garthwaite et al., 1994; Quigley et al., 2006; McGuirk, 2011).

Prolonged time without enteral intake of nutrients would likely result in protracted recovery of GIT function and health, but more work in this area is needed.

Dietary Characteristics

Specific dietary factors can impact GIT permeability and tight junction expression (Steele et al., 2016). Milk replacers often have higher content of lactose (42 to 45% DM vs. 35% DM) and lower content of fat compared with whole milk (Wilms et al., 2019). Differences in fat and lactose content change the energy density of milk replacers and influence the osmolality. Whole milk has an osmolality close to 300 mOsm/kg (McGuirk, 2003). While milk replacers have a range from slightly hypertonic (>300 mOsm/kg) to very hypertonic (>450 mOsm/kg; McGuirk, 2003; Wilms et al., 2019). Changes in osmolality in milk replacers can lead to disturbances of the GIT. A study evaluated GIT permeability in response to varying levels of osmolality (439 to 611 mOsm/kg) and replacement of lactose with monosaccharides (dextrose and galactose) in milk replacers observed that as osmolality increased GIT permeability increased (Wilms et al., 2019). Interestingly, osmolality and source of sugar did not impact growth, fecal DM, or fecal pH (Wilms et al., 2019).

Summary and Perspectives

Morbidity and mortality rates related to diarrhea and other digestive issues continue to be an issue in replacement programs. The GIT is a dynamic and complex system that changes throughout the preweaning period. Promoting development of the structural and metabolic actions of the GIT can improve calf growth while also minimizing intestinal challenges. Intestinal dysfunction, including pathogenic and nutritional insults can negatively affect intake, growth, and efficiency. By continuing to expand our understanding of normal development of the GIT, including the small intestine, we can either work to prevent intestinal dysfunction from occurring or target strategies for recovery after intestinal dysfunction has occurred.

Reduced intake of nutrients, either in normal feeding practices or illness, can lead to reduced GIT growth and permeability. Under these circumstances, actions of metabolic hormones like GLP-2 are reduced, which increases susceptibility to pathogenic microbiota. Other insults to intestinal permeability can include changes in osmolality. Further work with more specific types of ingredients or additives could also be useful in promoting GIT development and integrity.

If we can maximize intestinal integrity and balance so that intake is maximized in the preweaning period, the nutrients consumed by the calf can go toward GIT growth and not be used for increased maintenance costs of an infection. Furthermore, this will result in increased growth of the calf, optimal feed efficiency, rumen development, reduced medication costs, labor, and productive potential.

Take Away Messages

1. Enteric challenges resulting in morbidity and mortality of calves results in reduced efficiency.
2. The gastrointestinal tract is a complex system, but our understanding of its importance to calf development and health is expanding.
3. Feeding rate and nutrient provision positively impacts the growth and integrity of the gastrointestinal tract which can minimize risk of enteric disease.
4. Dietary characteristics of feeds could manipulate permeability.

References

Al-Sadi, R., M. Boivin, and T. Ma. 2009. Mechanism of cytokine modulation of epithelial tight junction barrier. Frontiers Biosci. 14:2765.

Araujo, G., C. Yunta, M. Terré, A. Mereu, I. Ipharraguerre, and A. Bach. 2015. Intestinal permeability and incidence of diarrhea in newborn calves. J. Dairy Sci. 98:7309-7317.

Atuma, C., V. Strugala, A. Allen, and L. Holm. 2001. The adherent gastrointestinal mucus gel layer: thickness and physical state in vivo. Am. J. Physiol.-Gastrointest. Liver Physiol. 280:G922-G929.

Baldwin, R. L. VI, K. R. McLeod, J. L. Klotz, and R. N. Heitmann. 2004. Rumen development, intestinal growth and hepatic metabolism in the pre- and postweaning ruminant. J. Dairy Sci. 87:E55-E65.

Ballou, M. A., D. L. Hanson, C. J. Cobb, B. S. Obeidat, M. D. Sellers, A. R. Pepper-Yowell, J. A. Carroll, T. J. Earleywine, and S. D. Lawhon. 2015. Plane of nutrition influences the performance, innate leukocyte responses, and resistance to an oral *Salmonella enterica* serotype Typhimurium challenge in Jersey calves. J. Dairy Sci. 98:1972–1982.

Bartels, C. J. M., M. Holzhauer, R. Jorritsma, W. A. J. M. Swart, and T. J. G. M. Lam. 2010. Prevalence, prediction and risk factors of enteropathogens in normal and non-normal faeces of young Dutch dairy calves. Prev. Vet. Med. 93:162-169.

Bjarnason, I., A. Macpherson, and D. Hollander. 1995. Intestinal permeability: An overview. J. Gastroenterol. 108:1566-1581.

Blum, J. W. and C. R. Baumrucker. 2008. Insulin-like growth factors (IGFs), IGF binding proteins, and other endocrine factors in milk: role in the newborn. Adv. Exp. Med. Bio. 606:397-422.

Brubaker, P. L., A. Izzo, M. Hill, and D. J. Drucker. 1997. Intestinal function in mice with small bowel growth induced by glucagon-like peptide-2. Am. J. Physiol.-Endocrinol. Metab. 272:E1050-E1058.

Bruewer, M., S. Samarin, and A. Nusrat. 2006. Inflammatory bowel disease and the apical junctional complex. Ann. N.Y. Acad. Sci. 1072:242-252.

Buchman, A. L., A. A. Moukarzel, S. Bhuta, M. Belle, M. E. Ament, C. D. Eckhert, D. Hollander, J. Gornbeln, J. D. Kopple, and S. R. Vijayaroghavan. 1995. Parenteral nutrition is associated with intestinal morphologic and functional changes in humans. J. Parent. Enteral Nutr. 19:453-460.

Burrin, D. G., B. Stoll, R. Jiang, X. Chang, B. Hartmann, J. J. Holst, G. H. Greeley, and P. J. Reeds. 2000. Minimal enteral nutrient requirements for intestinal growth in neonatal piglets: how much is enough? Am. J. Clin. Nutr. 71:1603-1610.

Burrin, D. G., B. Stoll, and X. Guan. 2003. Glucagon-like peptide-2 function in domestic animals. Domest. Anim. Endocrin. 24:103-122.

Cameron, H. L., and M. H. Perdue. 2005. Stress impairs murine intestinal barrier function: Improvement by glucagon-like peptide-2. J. Pharmacol. Exp. Therap. 314:214-220.

Cani, P. D., A. Everard, and T. Duparc. 2013. Gut microbiota, enteroendocrine functions and metabolism. Curr. Opinions Pharmacol. 13:935-940.

Castro, J. J., S. Y. Morrison, A. Hosseinni, J. J. Loor, J. K. Drackley, and I. R. Ipharraguerre. 2016. Secretion of glucagon-like peptide-2 responds to nutrient intake but not glucose provision in milk-fed calves. J. Dairy Sci. 99:5793-5807.

Cho, Y.-i., and K.-J. Yoon. 2014. An overview of calf diarrhea - infectious etiology, diagnosis, and intervention. J. Vet. Sci. 15:1-17.

Connor, E. E., S. Kahl, T. H. Elsasser, R. L. Baldwin VI, R. Fayer, M. Santin-Duran, G. L. Sample, and C. M. Evock-Clover. 2013. Glucagon-like peptide-2 therapy reduces negative effects of diarrhea on calf gut. J. Dairy Sci. 96:1793-1802.

Connor, E. E., C. M. Evock-Clover, E. H. Wall, R. L. Baldwin Vi, M. Santin-Duran, T. H. Elsasser, and D. M. Bravo. 2016. Glucagon-like peptide-2 and its beneficial effects on gut function and health in production animals. Dom. Anim. Endocrinol. 56(Supp):S56-S65.

Connor, E. E., E. H. Wall, D. M. Bravo, C. M. Evock-Clover, T. H. Elsasser, R. L. V. Baldwin, M. Santín, B. T. Vinyard, S. Kahl, and M. P. Walker. 2017. Reducing gut effects from Cryptosporidium parvum infection in dairy calves through prophylactic glucagon-like peptide-2 therapy or feeding of an artificial sweetener. J. Dairy Sci. 100:3004-3018.

Drucker, D. J., T. Jin, S. L. Asa, T. A. Young, and P. L. Brubaker. 1994. Activation of proglucagon gene transcription by protein kinase-A in a novel mouse enteroendocrine cell line. Mol. Endocrinol. 8:1646-1655.

Drucker, D. J., Q. Shi, A. Crivic, M. Sumner-Smith, W. Tavares, M. Hill, L. DeForest, S. Cooper, and P. L. Brubaker. 1997. Regulation of the biological activity of glucagon-like peptide-2 in vivo by dipeptidyl peptidase IV. Nat. Biotechnol. 15:673-677.

Eckert, E., H. E. Brown, K. E. Leslie, T. J. DeVries, and M. A. Steele. 2015. Weaning age affects growth, feed intake, gastrointestinal development, and behavior in Holstein calves fed an elevated plane of nutrition during the preweaning stage. J. Dairy Sci. 98:6315-6326.

Eissele, R., R. Goke, S. Willemer, H. P. Harthus, H. Vermeer, R. Arnold, and B. Goke.1992. Glucagon-like peptide-1 cells in the gastroninetestinal tract and pancreas of the rat, pig and man. Eur. J. Clin. Invest. 22:283-291.

Estall, J. L., and D. J. Drucker. 2006. Glucagon-like peptide-2. Annu. Rev. Nutr. 26:391-411.

Forsyth, C., A. Banan, A. Farhadi, J. Z. Fields, Y. Tang, M. Shaikh, L. J. Zhang, P. A. Engen, and A. Keshavarzian. 2007. Regulation of oxidant-induced intestinal permeability by metalloprotease-dependent epidermal growth factor receptor signaling. J. Pharmacol. Exp. Ther. 321:84-97.

Foster, D. M. and G. W. Smith. 2009. Pathophysiology of diarrhea in calves. Vet. Clinics N. Amer.: Food Anim. Pract. 25:13-36.

Furness, J. B., L. R. Rivera, H. J. Cho, D. M. Bravo, and B. Callaghan. 2013. The gut as a sensory organ. Nat. Rev. Gastroenterol. Hepatol. 10:729-740.

Garthwaite, B. D., J. K. Drackley, G. C. McCoy, and E. H. Jaster. 1994. Whole milk and oral rehydration solution for calves with diarrhea of spontaneous origin. J. Dairy Sci. 77:835–843.

Gallo, R. L., and L. V. Hooper. 2012. Epithelial antimicrobial defence of the skin and intestine. Nat. Rev. Immun. 12:503-516.

Geiger, A. J., C. L. M. Parsons, R. E. James, and R. M. Akers. 2016. Growth, intake, and health of Holstein heifer calves fed an enhanced preweaning diet with or without postweaning exogenous estrogen. J. Dairy Sci. 99:3995–4004.

Groos, S., G. Hünefeld, and L. Luciano. 1996. Parenteral versus enteral nutrition: morphological changes in human adult intestinal mucosa. J. Submicrosc. Cytol. Pathol. 28:61-74.

Groschwitz, K. R., and S. P. Hogan. 2009. Intestinal barrier function: molecular regulation and disease pathogenesis. J. Allergy Clin. Immunol. 124:3-20.

Hall, E. J. 1999. Clinical laboratory evaluation of small intestinal function. Vet. Clin. N. Am.: Sm. Ani. Pract. 29: 441-469.

Hammon, H. M., D. Frieten, C. Gerbert, C. Koch, G. Dusel, R. Weikard, and C. Kühn. 2018. Different milk diets have substantial effects on the jejunal mucosal immune system f pre-weaning calves, as demonstrated by whole transcriptome sequencing. Sci. Reports. 8:1693.

Hammon, H. M., W. Liermann, D. Freiten, and C. Koch. 2020. Review: Importance of colostrum supply and milk feeding intensity and systemic development in calves. Anim. 14:s133-s143.

Hansen, M. B. 2003. The enteric nervous system II: gastrointestinal functions. Basic Clin. Pharmacol. 92:249-257.

Heinrichs, A. J., and B. S. Heinrichs. 2011. A prospective study of calf factors affecting first-lactation and lifetime milk production and age of cows when removed from the herd. J. Dairy Sci. 94:336-341.

Hooper, L. V., and A. J. Macpherson. 2010. Immune adaptations that maintain homeostasis with the intestinal microbiota. Nat. Rev. Immunol. 10:159-169.

Ipharraguerre, I. R., G. Ted, D. Menoyo, N. de Diego Cabero, J. J. Holst, M. Nofrarías, A. Mereu, and D. G. Burrin. 2013. Bile acids induce glucagon-like peptide-2 secretion with limited effects on intestinal adaptation in early weaned pigs. J. Nutr. 143:1899-1905.

Iseri, V. J., and K. C. Klasing. 2013. Dynamics of the systemic components of the chicken (*Gallus gallus domesticcus*) immune system following activation by *Escherichia coli*; implications for the costs of immunity. Dev. Comp. Immunol. 40:248-257.

Johnson, R. W. 1998. Immune and endocrine regulation of food intake in sick animals. Domest. Anim. Endocrinol. 15:309–319.

Khan, M. A., D. M. Weary, and M. A. Von Keyserlingk. 2011. Invited review: transitioning from milk to solid feed in dairy heifers. J. Dairy Sci. 99:885-902.

Kim, Y. S., and S. B. Ho. 2010. Intestinal goblet cells and mucins in health and disease: recent insights and progress. Curr. Gastroenterol. Reports 12:319-330.

Koch, C., C. Gerbert, D. Frieten, G. Dusel, K. Eder, R. Zitnan, and H. M. Hammon. 2019. Effects of ad libitum milk replacer feeding and butyrate supplementation on the epithelial growth and development of the gastrointestinal tract in Holstein calves. J. Dairy Sci. 102:8513–8526.

Korst, M., C. Koch, J. Kesser, U. Müller, F. J. Romberg, J. Rehage, K. Eder, and H. Sauerwein. 2017. Different milk feeding intensities during the first 4 weeks of rearing in dairy calves: part 1: effects on performance and production from birth over the first lactation. J. Dairy Sci. 100:3096–3108.

Larsson, L. I., J. Holst, R. Hakanson, and F. Sundler. 1975. Distribution and properties of glucagon immunoreactivity in the digestive tract of various mammals: An immunohistochemical and innunochemical study. Histochem. 44:281-290.

Ma, T., and J. M. Anderson. 2006. Tight Junctions and the intestinal barrier. In: Johnson, R., editor. Textbook of Gastrointestinal Physiology. Burlington, MA: Elsevier Academic Press. Pages 1559-1594.

Malmuthuge, N., M. Li, L. A. Goonewardene, M. Oba, and L. L. Guan. 2013. Effect of calf starter feeding on gut microbial diversity and expression of genes involved in host immune responses and tight junctions in dairy calves during weaning transition. J. Dairy Sci. 96:3189-3200.

Madsen, K., S. A. Lewis, M. M. Tavernini, J. Hibbard, and R. N. Fedorak. 1997. Interleukin 10 prevents cytokine-induced disruption of T84 monolayer barrier integrity and limits chloride secretion. J. Gastroenterol. 113:151-159.

Martindale, R. G., T. M. Enomoto, and M. McCarthy. 2013. Chapter 28 - Nutritional and Metabolic Therapy A2 - Hemmings, Hugh C. Pages 487-502 in Pharmacology and Physiology for Anesthesia. T. D. Egan, ed. W.B. Saunders, Philadelphia.

McGuirk, S. M. 2003. Solving calf morbidity and mortality problems. Am. Assoc. Bovine Pract., Columbus, OH.

McGuirk, S. M. 2011. Management of dairy calves from birth to weaning. Pages 175–193 in Dairy Production Medicine. C. A. Risco and P. M. Retamal, ed. John Wiley & Sons Inc. West Sussex, UK.

McOrist, S., and E. Corona-Barrera. 2015. Intestinal diseases in pigs. Pages 51-69 in Intestinal Health–Key to Maximise Growth Performance in Livestock. T. Niewold, ed. Wageningen Acadmeic Publishers, Wageningen, the Netherlands.

Menzies, I., R. Pounder, S. Heyer, M. Laker, J. Bull, P. Wheeler, and B. Creamer. 1979. Abnormal intestinal permeability to sugars in villous atrophy. Lancet 314:1107-1109.

Morrison, S. Y., J. J. Pastor, J. C. Quintela, J. J. Holst, B. Hartmann, J. K. Drackley, I. R. Ipharraguerre. 2017. Short Communication: Promotion of GLP-2 secretion in dairy calves with a bioactive extract from Olea europaea. J. Dairy Sci. 100:1940-1945.

Morrison, S. Y., P. A. LaPierre, K. N. Brost, and J. K Drackley. 2019. Intake and growth in transported Holstein calves classified as diarrheic or health within the first 21 days after arrival in a retrospective observational study. J. Dairy Sci. 102:10997-11008.

Niewold, T. 2015. General introduction- the gastrointestinal tract, the immune system and the maintenance of health. Pages 15-20 in Intestinal Health–Key to Maximise Growth Performance in Livestock. T. Niewold, ed. Wageningen Acadmeic Publishers, Wageningen, The Netherlands.

Nissen, A., P. H. Andersen, E. Bendixen, K. L. Ingvartsen, and C. M. Rontved. 2017. Colostrum and milk protein rankings and ratios of importance to neonatal calf health using a proteomics approach. J. Dairy Sci. 100:2711-2728.

Nusrat, A., J. R. Turner, and J. L. Madara. 2000. Molecular physiology and pathophysiology of tight junctions. IV. Regulation of tight junctions by extracellular stimuli: nutrients, cytokines, and immune cells. Am. J. Physiol. Gastrointest. Liver Physiol. 279:G851-G857.

Ollivett, T. L., D. V. Nydam, T. C. Linden, D. D. Bowman, and M. E. Van Amburgh 2012. Effect of nutritional plane on health and performance in dairy calves after experimental infection with *Cryptosporidium parvum*. J. Am. Vet. Med. Assoc. 241:1514–1520.

Ontsouka, E. C., C. Albrecht, and R. M. Bruckmaier. 2016. Invited review: Growth-promoting effects of colostrum in calves based on interaction with intestinal cell surface receptors and receptor-like transporters. J. Dairy Sci. 99:4111–4123.

Penner, G. B., J. R. Aschenbach, K. Wood, M. E. Walpole, R. Kanafany-Guzman, S. Hendrick, and J. Campbell. 2014. Characterising barrier function among regions of the gastrointestinal tract in Holstein steers. Anim. Prod. Sci. 54:1282-1287.

Peterson, L. W., and D. Artis. 2014. Intestinal epithelial cells: regulators of barrier function and immune homeostasis. Nat. Rev. Immunol. 14:141-153.

Quigley, J. D., T. A. Wolfe, and T. H. Elsasser. 2006. Effects of additional milk replacer feeding on calf health, growth, and selected blood metabolites in calves. J. Dairy Sci. 89:207–216.

Schäff, C. T., J. Gruse, J. Maciej, M. Mielenz, E. Wirthgen, A. Hoeflich, M. Schmicke, R. Pfuhl, P. Jawor, T. Stefaniak, and H. M. Hammon. 2016. Effects of feeding milk replacer ad libitum or in restricted amounts for the first five weeks of life on the growth, metabolic adaptation, and immune status of newborn calves. PLoS ONE 11:e0168974.

Schäff, C. T., J. Gruse, J. Maciej, R. Pfuhl, R. Zitnan, M. Rajsky and H. M. Hammon. 2018. Effects of feeding unlimited amounts of milk replacer for the first 5 weeks of age on rumen and small intestinal growth and development in dairy calves. J. Dairy Sci. 101:783–793.

Shen, L., and J. R. Turner. 2006. Role of epithelial cells in initiation and propagation of intestinal inflammation. Eliminating the static: tight junction dynamics exposed. Am. J. Physiol. Gastrointest. Liver Physiol. 290:G577-G582.

Shirazi-Beechey, S., A. Moran, D. Batchelor, K. Daly, and M. Al-Rammahi. 2011. Glucose sensing and signaling; regulation of intestinal glucose transport. Proc. Nutr. Soc. 70:185-193.

Sigalet, D. L., L. E. Wallace, J. J. Holst, G. R. Martin, T. Kaji, H. Tanaka, and K. A. Sharkey. 2007. Enteric neural pathways mediate the anti-inflammatory actions of glucagon-like peptide 2. Am. J. Physiol. Gastrointest. Liver Physiol. 293:G211-G221.

Soberon, F., E. Raffrenato, R. W. Everett, and M. E. Van Amburgh. 2012. Preweaning milk replacer intake and effects on long-term productivity of dairy calves. J. Dairy Sci. 95:783-793.

Steele, M. A., G. B. Penner, F. Chaucheyras-Durand, and L. L. Guan. 2016. Development and physiology of the rumen and the lower gut: Targets for improving gut health. J. Dairy Sci. 99:4955-4966.

Tsai, C. H., M. Hill, S. L. Asa, P. L. Brubaker, D. J. Drucker. 1997. Intestinal growth-promoting properties of glucagon-like peptide-2 in mice. Am. J. Physiol. 273:E77-84.

Turner, J. R. 2009. Intestinal mucosal barrier function in health and disease. Nat. Rev. Immunol. 9:799-809.

Uil, J. J., R. M. Van Elburg, F. M. Van Overbeek, C. J. J. Mulder, G. P. Vanberge-Henegouwen, and H. S. Heymans. 1996. Clinical implications of the sugar absorption test: Intestinal permeability test to assess mucosal barrier function. Scand. J. Gastroenterol. Supp. 233:70-78.

Urie, N. J., J. E. Lombard, C. B. Shivley, C. A. Kopral, A. E. Adams, T. J. Earleywine, J. D. Olson, and F. B. Garry. 2018. Preweaned heifer management on US dairy operations: Part V. Factors associated with morbidity and mortality in preweaned dairy heifer calves. 101:9229-9244.

Van Itallie, C. M., and J. M. Anderson. 2006. Claudines and epithelial paracellular transport. Annu. Rev. Physiol. 68:403-429.

Walker, M. P., C. M. Evock-Clover, T. H. Elsasser, and E. E. Connor. 2015. Short communication: Glucagon-like peptide-2 and coccidiosis alter tight junction gene expression in the gastrointestinal tract of dairy calves. J. Dairy Sci. 98:3432-3437.

Waltner-Toews, D., S. Martin, and A. Meek. 1986. Dairy calf management, morbidity and mortality in Ontario Holstein herds. II. Age and seasonal patterns. Prev. Vet. Med. 4:125-135.

Wilms, J., H. Berends, and J. Martín-Tereso. 2019. Hypertonic milk replacers increase gastrointestinal permeability in healthy dairy calves. J. Dairy Sci. 102:1237-1246.

Windeyer, M. C., K. E. Leslie, S. M. Godden, D. C. Hodgins, K. D. Lissemore, and S. J. LeBlanc. 2014. Factors associated with morbidity, mortality, and growth of dairy heifer calves up to 3 months of age. Prev. Vet. Med. 113:231-240.

Wood, K. M., S. I. Palmer, M. A. Steele, J. A. Metcalf, and G. B. Penner. 2015. The influence of age and weaning on permeability of the gastrointestinal tract in Holstein bull calves. J. Dairy Sci. 98:7226-7237.