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PRODUCTION AND MANAGEMENT: *Invited Review*

# INVITED REVIEW: Nutritional regulation of gut function in dairy calves: From colostrum to weaning

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## ABSTRACT

**Purpose:** Published literature regarding calf nutrition was reviewed to create an information base for the implementation of proper nutritional management to maximize health and productivity.

**Sources:** The main source of data and information for this review was peer-reviewed literature.

**Synthesis:** Feeding a sufficient volume of colostrum during the first hours of life is crucial to calf health and survival; however, less is known about transition milk feeding and the potential benefits of the myriad of bioactive compounds it contains. After feeding colostrum and transition milk, calves are susceptible to diarrhea when moved onto high amounts of milk, and antibiotic use is often necessary to decrease disease. Feeding an elevated plane of milk nutrition results in increased ADG and, in some studies, increased future milk production. Thus, this nutritional strategy is recommended; however, weaning calves from high volumes of milk represents massive changes in the structure and microbiology of the gastrointestinal tract.

**Conclusions and Applications:** Colostrum and transition milk contain an abundance of bioactive molecules that can positively affect gut development and microbiota. There is significant potential for the use of novel feeding strategies and microbial-based products as alternatives to antibiotics. Calves fed an elevated plane of nutrition in the first month of life have greater productivity and growth. However, weaning should take place later in life. Moreover, applying a proper step-down feeding protocol is recommended, as it allows calves to intake and digest sufficient solid feed for growth and minimize distress at weaning.

**Key words:** colostrum, gut health, plane of nutrition, weaning, dairy calf

## INTRODUCTION

Raising healthy and productive calves is crucial for the long-term success of the dairy industry. The preweaning and weaning periods are considered the most challenging times in dairy production and are associated with the highest morbidity and mortality rates among the herd. The most recent survey conducted by the USDA—between 2014 and 2015—reported that preweaning mortality and morbidity rates for calves have decreased to 5 and 33.8%, respectively, from 7.8 and 38.5% in the previous 2007 USDA study (NAHMS, 2007; Urie et al., 2018). Although these numbers have decreased, digestive diseases and disorders remain the most common reported cause of morbidity and mortality, accounting for approximately 56% of all sick calves and 32% of all deaths (Urie et al., 2018). This high prevalence of digestive disorders, as well as its association with morbidity and mortality, can be costly to producers and also causes concern from an animal welfare standpoint. Digestive diseases and disorders can often be mitigated through the use of sound nutritional and management programs, and developing knowledge and strategies to promote gut health in young calves is fundamental to ensuring a profitable dairy industry.

Early life nutritional programming is based on the observation that nutritional and environmental changes, or lack thereof, can reset the developmental path during a critical period of life, when tissues still have plasticity and are in a higher proliferating state and differentiating phase (de Moura et al., 2008; Gomes et al., 2011). Research has demonstrated that nutritional programming can occur via epigenetics and can take place as early as late gestation (Moisa et al., 2016). A wide range of data has shown that increasing the volume of colostrum fed during the first hours of life (Faber et al., 2005) and milk nutrient intake during the preweaning period result in increased milk yield during the first lactation compared with restricted-fed calves (Bar-Peled et al., 1997; Terre et al., 2009; Moalem et al., 2010; Soberon et al., 2012), likely through epigenetic events that are associated with enhanced nutrient intake. Moreover, a lack of proper nutrition can depress immune function and increase the likelihood of infection and disease (Nonnecke et al., 2003). It is clear that nutri-

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tion plays a key role in the regulation of gut development, as well as calf health, growth, and productivity. Therefore, for this review, we focused on the effect of common nutritional strategies on gut health and function during 3 distinctly different periods of the young calf's life. Specifically, we focused on colostrum and transition milk feeding during the first week of life, plane of milk nutrition and gut health challenges during the first month of life, and weaning strategies and their effects on gut function.

## FIRST WEEK OF LIFE

### Colostrum Feeding

Because there is no transfer of immunoglobulins from the dam to the calf in utero, one of the most critical management factors in reducing calf morbidity and mortality is feeding a sufficient amount (~10% of BW, 3–4 L) of colostrum that contains >50 g of IgG/L (Weaver et al., 2000), a total bacteria count <100,000 cfu/mL, and a total coliform count <10,000 cfu/mL (McGuirk and Collins, 2004) shortly after birth to ensure that the newborn calf absorbs adequate IgG. Passive transfer is defined as the transfer of IgG from colostrum to the neonate; serum concentrations >10 mg of IgG per milliliter of blood at 1 to 7 d of age signifies successful passive transfer (Tyler et al., 1996; BAMN, 2001). A recent large-scale study evaluated the rate of failure of passive transfer (FPT) and determined that among the 1,623 Holstein heifer calves included in the study, 12.1% were considered to have FPT (Shivley et al., 2018). This percentage has decreased from a study conducted by Beam et al. (2009), which reported 19.1% of heifer calves had FPT, as well as from 1991 to 1992, in which over 40% of calves had FPT (USDA, 1993). It appears that this number may be decreasing over time; however, it is important to note that the most recent large-scale studies (Beam et al., 2009; Shivley et al., 2018) were conducted either as a convenience study, due to less farms participating in the study than anticipated (Shivley et al., 2018), or included only healthy heifer calves (Beam et al., 2009), whereas the USDA (1993) did not distinguish between healthy and unhealthy calves before blood collection. Therefore, although the most current rate of FPT is reported as 12.1%, it is likely that the true rate of FPT on North American dairy farms could be greater.

As mentioned previously, one of the most critical factors in ensuring passive transfer is the timely feeding of colostrum. Immediately following birth, the calf gut is considered “open,” as enterocytes possess the ability to nonselectively absorb large molecules, such as IgG, by pinocytosis from the intestinal lumen into blood circulation. At approximately 24 h after birth (Stott et al., 1979a), “gut closure” occurs, which is defined as “the cessation of absorption of macromolecules from the gut into blood in neonates” (Lecce and Morgan, 1962). Shivley et al. (2018) found that serum IgG concentrations decreased by 0.32 mg/mL every hour following birth after colostrum

feeding, and it is widely accepted that the absorption of IgG decreases in a linear trend as calves age (Stott et al., 1979a; Bush and Staley, 1980; Matte et al., 1982). However, Fischer et al. (2018c) recently demonstrated a nonlinear trend in the absorption of IgG, with calves fed immediately after birth (0 h) having greater serum IgG concentrations compared with calves fed at 6 and 12 h after birth, which did not differ. In addition, the apparent efficiency of absorption of IgG, which is the amount of IgG absorbed from colostrum into the blood circulation on a percentage basis, was greater in 0-h calves (51.8%) compared with 6-h (35.6%) and 12-h (35.1%) calves. These results suggest that there may be a critical time point between 1 and 6 h of life when the closure of the small intestine progresses to a finite degree (Fischer et al., 2018c). Although it is known that IgG crosses the small intestine through a pinocytotic mechanism (Smeaton and Simpson-Morgan, 1985; Louis and Lin, 2009), little is known about the factors that influence the closure of the gut and its subsequent impermeability to IgG. Interestingly, recent research has shown that IgG absorption is negatively associated with colostrum total bacteria count (Godden et al., 2012; Cummins et al., 2017), and a study conducted in the 1980s showed that when infused directly into the intestine, the number of bacteria per gram of intestinal tissue was negatively correlated with immunoglobulin uptake (James et al., 1981). It is speculated that this relationship may be due to physical binding of bacteria to colostral antibodies, pathogenic bacteria accelerating the replacement of cells permeable to IgG or damaging these cells, or nonspecific pinocytosis of viable bacteria preventing the absorption of IgG (Corley et al., 1977; Staley and Bush, 1985; Godden et al., 2012; Cummins et al., 2017). However, no specific mechanism for these correlations has been demonstrated, and therefore, the mechanism by which calves absorbed the same quantity of IgG at 6 and 12 h of life still needs to be elucidated.

Although it is well-known that feeding colostrum stimulates the activation of passive immunity, Malmuthuge et al. (2015) demonstrated that feeding colostrum also accelerates the bacterial colonization of the calf's small intestine. It was found that calves receiving fresh colostrum after birth had a total bacteria density of  $10^{10}$  16S rRNA gene/g of sample when euthanized at 12 h of life, whereas calves that do not receive colostrum only achieved  $10^8$  16S rRNA gene/g of sample (Malmuthuge et al., 2015). The initiation of a balanced gut microbial community in early life is a key factor influencing calf health and performance. More specifically, a high prevalence of *Bifidobacterium* and *Lactobacillus* in the feces of exclusively breast-fed infants has been shown to provide protection against infection (Yoshioka et al., 1983; Harmsen et al., 2000), and calves with a high prevalence of *Faecalibacterium* in the feces during the first week of life had a lower incidence of diarrhea within the first 4 wk of life, as well as increased BW gain (Oikonomou et al., 2013). Therefore, it is clear that early-life feeding strategies that positively influence ben-

eficial gut bacterial species may have an effect on overall calf health. In the aforementioned study (Fischer et al., 2018c), it was demonstrated that the timing of colostrum feeding can affect gut bacterial populations, with calves not fed colostrum until 12 h after birth tending to have a lower prevalence of *Bifidobacterium* spp. and *Lactobacillus* spp. associated with the colon mucosa compared with calves fed immediately after birth, whereas no differences were observed between calves fed colostrum at 6 h and calves fed at birth and 12 h. As Malmuthuge et al. (2015) recently demonstrated, this result suggests that bacterial colonization occurs at a slower rate in the absence of colostrum. Interestingly, Fischer et al. (2018c) also demonstrated that calves fed colostrum at 6 and 12 h had a lower prevalence of total *Escherichia coli* associated with ileum mucosa compared with calves fed immediately after birth. *Escherichia coli* has previously been reported as the dominant bacterial group present in the feces of 1- to 7-d-old calves (Mayer et al., 2012) and can benefit the host by creating an anoxic environment necessary for beneficial obligate anaerobes, such as *Bifidobacterium*, to become established (Madigan et al., 2015). However, a study (Ma et al., 2019) conducted using the same calves as Fischer et al. (2018c) found that calves fed at 12 h had an increased relative abundance of *Enterococcus* and *Streptococcus*—numerous species of which are regarded as opportunistic pathogens—compared with calves fed earlier. The authors suggested that this finding may be associated with reduced IgG transfer in calves fed at 12 h, which may increase the probability of pathogen invasion of the intestinal barrier (Stott et al., 1979b). These studies offer insight into the establishment of the calf gut microbiome and its potential modulation of the host immune system; however, how the presence and colonization of these specific bacterial groups may affect future productivity and health needs to be explored further.

The utility of colostrum as a substrate for microbial species has recently been demonstrated by Fischer et al. (2018b). In particular, it was shown that calves fed heat-treated colostrum containing a greater concentration of free sialylated oligosaccharides (OS) had a greater prevalence of *Bifidobacterium* (Malmuthuge et al., 2015) in the small intestine at 6 h of life, compared with calves fed fresh colostrum, which contained a lower concentration of OS. The concentration of free OS in bovine milk has previously been increased through heat treatment (Neeser et al., 1991), likely from their cleavage from glycoconjugate structures, which is hypothesized to have occurred in the study conducted by Fischer et al. (2018b). Further, the correlation between increased concentrations of OS and a high proportion of *Bifidobacterium* suggests that bovine colostrum OS may mediate the early establishment of beneficial bacteria in the neonatal calf gut. To date, over 50 bovine colostrum and milk OS have been detected (Aldredge et al., 2013; Albrecht et al., 2014), with 3'sialyllactose being the most abundant and more than double the concentration of other primary colostrum OS, name-

ly 6'sialyllactose, 6'sialyllactosamine, and disialyllactose (Fischer et al., 2018a). In addition to promoting the colonization of beneficial bacteria, colostrum OS are hypothesized to enhance the absorption of IgG (Gill et al., 1999), inhibit gastrointestinal tract (GIT) pathogens (Martin et al., 2002), support intestinal barrier function (Chichlowski et al., 2012), and indirectly modulate positive immune responses (Ganguli et al., 2013). It has been demonstrated that bovine OS can be extracted during whey processing, which may offer affordable production for potential use as a beneficial additive to colostrum or milk during early life to promote gut health (Barile et al., 2009).

The beneficial compounds in colostrum do not stop at IgG and OS; other nutritive and immune components include several types of Ig (IgA, IgM), growth factors, hormones, cytokines, enzymes, polyamines and nucleotides, antimicrobial components, and white blood cells. These components contribute to the calf's ability to fight infection (Hammon and Blum, 2002; Langel et al., 2015) and promote growth and development. Insulin is one of the many bioactive factors present in colostrum that is shown to have a positive effect on the development of the neonatal GIT. Insulin has been demonstrated to increase small intestinal mass (Shulman, 1990) and may support post-natal growth indirectly through the sequestration of macronutrients in peripheral tissues, such as fat and muscle (Schaff et al., 2016). Similar to insulin, insulin-like growth factor 1 in colostrum can stimulate intestinal epithelial cell proliferation (Baumrucker et al., 1994), whereas other compounds, such as lactoferrin, lysozyme, and lactoperoxidase, may help to maintain a healthy GIT (Pakkanen and Aalto, 1997). In addition to containing bioactive molecules, the consumption of colostrum also stimulates endogenous production of beneficial hormones that assist in the maturation of the GIT. For instance, Inabu et al. (2018) demonstrated that plasma glucagon-like peptide-1 and -2 concentrations increase after colostrum feeding and that glucagon-like peptide-1 concentration was lower for calves not fed colostrum until 12 h of life compared with calves fed immediately after birth. As glucagon-like peptide-1 and -2 play a key role in glucose homeostasis (Fukumori et al., 2012) and stimulating gastrointestinal growth (Taylor-Edwards et al., 2011), respectively, it is clear that the feeding of colostrum has beneficial effects on gut development and furthers our understanding on the role of gut-derived peptides and their potential implications for the improvement of calf health and performance (Inabu et al., 2018).

### Transition Milk Feeding

After calves are fed colostrum, most producers transition calves directly onto whole milk or milk replacer (MR; Figure 1). Unfortunately, this is a stark contrast to what calves would naturally consume from their dam (Figure 1). Transition milk (TM) is defined as milkings 2 to 6 after calving, and like colostrum, it contains greater



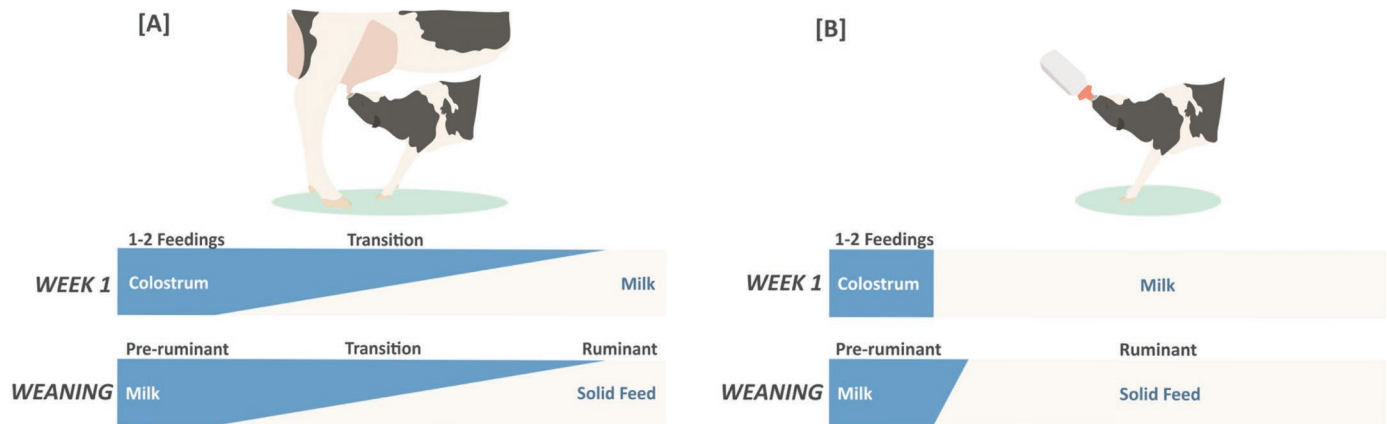
concentrations of certain bioactive compounds compared with mature milk (Blum and Hammon, 2000). For instance, milkings 2 and 3 contain a greater concentration of the primary acidic OS, 3'sialyllactose and 6'sialyllactose (Fischer et al., 2018a), as well as elevated levels of nucleotides, insulin-like growth factor 1, and insulin, among many others (Blum and Hammon, 2000; McGrath et al., 2016). Although these compounds likely have a beneficial effect on the immature neonatal gut, TM continues to be discarded on farm, mainly due to difficulties managing the feeding of TM to calves and it being undesirable for human consumption. Recently, research has demonstrated that calves fed TM following the colostrum meal have lower odds of being assigned a worse eye/ear score (Conneeley et al., 2014), which is associated with a lower incidence of disease and infection, and have increased intestinal villi height and greater small intestinal surface area (Pyo et al., 2018) compared with calves fed whole milk. It appears that the calf may be missing out on an opportunity for increased maturation and development of the gut when they are not fed TM; however, research regarding the specific TM compounds responsible for these beneficial effects is lacking. The nutrient compositions of true colostrum, TM, and whole milk are very different from the standpoint of nutritional and bioactive compounds (Blum and Hammon, 2000), and this leaves an interesting and potentially useful gap in our knowledge worth investigating.

## FIRST MONTH OF LIFE

### Gut Health Challenges

Most calves develop digestive disorders at approximately 2 wk of age (Urie et al., 2018). During this time, calves undergo a multitude of stressful situations, such as separation from the dam, vaccinations, and varying housing and

feeding protocols. While calves are exposed to the dam at birth, moved to a calf pen, and exposed to other calves and farm personnel, their vulnerability to infectious agents is very high—especially given that their immune system remains naïve. The most common infectious agents reported in diarrheic preweaning calves are viruses: bovine coronavirus and group A bovine rotavirus; bacteria: *Salmonella* spp. and *E. coli* K99+; or protozoa: *Cryptosporidium parvum* (de la Fuente et al., 1999; Cho et al., 2010). As these infectious agents can be detrimental to calf health, proper calf management protocols, such as housing on noncontaminated ground, proper colostrum management and nutrition strategies (Vasseur et al., 2010), as well as maintaining a low population density and stress conditions (Costa et al., 2016), should be followed to reduce the incidence of infection. Unfortunately, even if hygienic and proper housing and nutrition protocols are followed, calves often still become sick, and subsequent treatment is required. A study conducted in the United States and Canada demonstrated that 23% of preweaning dairy calves are treated with antibiotics for diarrhea (Windeyer et al., 2014). Moreover, antibiotics are not only used for the treatment of disease, but often as a preventative measure, with 54% of cow-calf operations administering antibiotics to prevent illness (Walker et al., 2012) and 57.5% of dairy farms feeding medicated MR (USDA-APHIS, 2007). Unfortunately, antibiotic exposure has been linked to gut microbial imbalance, known as dysbiosis, in preweaned calves (Oultram et al., 2015; Van Vleck Pereira et al., 2016; Malmuthuge and Guan, 2017) and can lead to a high number of antimicrobial-resistant bacterial phenotypes (Maynou et al., 2016). With this knowledge, the dairy research community and industry have turned to other strategies to prevent digestive disorders and support calf digestion and health and have begun investigating several



**Figure 1.** (A) A calf suckling from the dam, as would occur in nature or in a beef cow-calf pair. During wk 1, the calf would consume colostrum from the dam during the first 1 to 2 milkings, followed by transition milk in milkings 2 to 6 and mature milk by milkings 7 to 8. In nature, weaning would occur at approximately 8 mo of life and would take place over 2 to 4 mo. (B) A calf suckling a bottle, as occurs in commercial dairy production. On commercial dairy farms, calves are typically fed 1 or 2 meals of colostrum, followed by an abrupt transition to whole milk or milk replacer. Calves are typically weaned at 5 to 6 wk of age to encourage early starter intake and rumen development. Weaning on commercial dairy farms is often abrupt and takes place over 1 to 2 wk. Color version available online.

microbial-based products. The 2 most commonly used microbial additives are lactic acid bacteria and *Saccharomyces* yeast, as well as their fermentation products. Although their modes of action have not been elucidated, numerous studies report their ability to reduce diarrhea incidence in calves. A meta-analysis conducted in 2012 based on 15 studies (Signorini et al., 2012) reported a lower relative risk of diarrhea in calves supplemented with lactic acid bacteria (mainly *Lactobacillus* spp. and *Bifidobacterium* spp.) compared with control animals. More recently, Aluongo et al. (2017) reported a reduction in diarrhea incidence and an improvement in fecal score in 8 studies out of 11 when calves were supplemented with *Saccharomyces cerevisiae* spp. To achieve the best results while using microbial-based products on farm, it is important to consider the concentration, time period, interaction with the feed (colostrum, milk, and starter), initial health status of the animal, and the specificity of the microbial-based product. It is clear that microbial-based products may be a promising solution to prevent and treat diarrhea and minimize the high rate of antibiotic treatment for milk-fed calves experiencing diarrhea (Villot et al., 2019).

### Plane of Nutrition

After colostrum and TM are fed to calves, they are transitioned to feeding programs that use either whole milk or MR. These programs aim to encourage starter intake (conventional) or to allow calves to consume milk as they would directly from the dam (elevated). Elevated milk feeding programs allow dairy calves to be fed ad libitum or often at 20% of their birth BW, which is greater than 8 L/d at a typical solids concentration of 12 to 13% or 1.2 kg of MR per day (MacPherson et al., 2016). In contrast, conventional feeding programs usually limit milk consumption to around 10% of birth BW, which is roughly 4 to 5 L/d at a typical solids concentration of 12 to 13% (Khan et al., 2007a,b; Silper et al., 2014). It is thought that by decreasing milk intake, starter intake will increase, thus leading to enhanced rumen development (Tamate et al., 1962). Moreover, due to the lower volume of milk fed, there is typically a reduced feeding cost associated with using a conventional plane of milk/MR nutrition. However, lower rates of BW gain (0.3 to 0.5 kg/d) are often observed (Jasper and Weary, 2002) compared with elevated feeding programs (approximately 0.75 kg/d averaged over several trials; Soberon and Van Amburgh, 2013)—especially in the first month of life when starter intake is limited.

Whether on a conventional or elevated plane of milk/MR nutrition, calves are often provided with milk twice daily on commercial dairy operations, which is a drastic contrast to how calves consume milk when fed ad libitum or naturally from their dam. There is concern that feeding more milk, especially when calves are only fed twice a day, may lead to abomasal ulcers and a decrease in insulin sensitivity in milk-fed calves (Berends et al., 2015); however, it was demonstrated that insulin sensitivity was

not altered in calves fed elevated planes of milk at different meal sizes and frequencies (4 L/meal 2 times or 2 L/meal 4 times of 150 g of MR powder per L; MacPherson et al., 2019). Previous studies have shown that veal calves fed large amounts of MR develop insulin sensitivity (Hugi et al., 1998; Blum and Hammon, 1999), but this decrease in sensitivity appears to be a natural progression as calves age (Gerrits, 2019). A study by Bach et al. (2013) also investigated the effect of plane of nutrition (high vs. low) on insulin response to high plasma glucose and found that all calves were able to control glycemia. However, results from Bach et al. (2013) also showed that calves fed a high plane of nutrition needed significantly greater insulin to control their high plasma glucose levels compared with calves fed a lower plane of nutrition. In contrast, recent studies by MacPherson et al. (2016, 2019) demonstrated that feeding an elevated plane of nutrition in 2 or 4 meals per day had minimal effect on glucose metabolism and insulin sensitivity, which may be associated with the calf's ability to slow down the delivery of large meals from the abomasum to the intestine. The major difference between these studies was that calves in the studies by MacPherson et al. (2016, 2019) were fed elevated planes of nutrition from the first week of life, which may be a critical developmental window for the calf to adapt to the higher level of milk. Moreover, there may have been differences in the MR composition between these 2 studies, such as the percentage of skim milk powder or whey protein, that may have had an effect on abomasal clotting (Constable et al., 2005) and thereby affected abomasal emptying and insulin sensitivity (Stahel et al., 2016). Due to the conflicting results among studies, it is clear that further research is needed regarding calf insulin response to large meal sizes and the possible mechanisms involved.

Another area of milk feeding that is gathering attention is the alteration of macronutrient composition to improve growth and nutrient digestibility, as well as gut health and function. Previous studies have demonstrated that when fat content is increased in MR, calves have an increase in fat deposition, and that there are limiting effects of both metabolizable energy and protein at differing levels of MR intake (Tikofsky et al., 2001; Hill et al., 2008). However, considering the bioactive nature of lipid molecules found in whole milk (e.g., sphingomyelin and phytanic acid; Keenan and Huang, 1972; Chalfant et al., 2004; Zandbergen and Plutzky, 2007), as well as the increased fat intake from the liquid diet resulting in decreased mortality in preweaned calves (Urie et al., 2018), there may be additional mechanisms at play in regard to fat inclusion. This is an area of debate that is difficult to investigate considering the overlapping roles of metabolites in the body. Nonetheless, it offers an interesting area for future research focus.

The source of fat in MR is also worthy of further investigation considering the differences in proportion of fatty acids used in MR. For example, tallow is an animal fat, often substituted in MR for milk fat, that contains great-

er amounts of long-chain saturated palmitic (C16:0) and stearic acids (C18:0), as well as monounsaturated oleic acid (C18:1), or coconut oil that contains palmitic, stearic, and oleic acid, but additionally contains greater medium-chain fatty acids, such as decanoic (C10:0), lauric (C12:0), and myristic acids (C14:0; Jenkins et al., 1985; Hill et al., 2007). Jenkins et al. (1985) demonstrated feeding a high PUFA source (i.e., corn oil containing C18:2n-6) resulted in poorer growth, nutrient digestibility, and increased diarrhea compared with calves fed MR containing medium- to long-chain saturated and long-chain monounsaturated fatty acids. This result was recently corroborated by McDonnell et al. (2019), who reported decreased starter DMI and weight gain when MR was supplemented with n-3 fatty acids [i.e., eicosapentaenoic (C20:5n-3) and docosahexaenoic acids (C22:6n-3)]. In comparison, bovine milk fat contains medium- to long-chain SFA (C8:0 through C18:0) and long-chain monounsaturated fatty acids (C16:1 and C18:1) found in animal and plant fat sources. A major difference is the presence of the short-chain fatty acid butyric acid (C4:0; Glass et al., 1967), which is known to have many positive effects on promoting GIT development (reviewed by Gorka et al., 2018). Considering the unknowns surrounding the optimal inclusion of amount and type of fat in MR, there are still many opportunities to improve our ability to effectively provide fat in the liquid diet of preweaning calves.

## WEANING TRANSITION

### *Weaning Strategies*

Under natural conditions, the gradual weaning process occurs over several weeks, when milk supply from the dam declines and solid feed intake increases—a process that occurs at approximately 10 mo of age (Reinhardt and Reinhardt, 1981). This is in contrast to what occurs on commercial dairy farms, with more than 75% of US dairy farms weaning calves between 6 and 8 wk of age and implementing an early and abrupt weaning protocol (NAHMS, 2011). In the past decade, researchers have focused on alternative milk feeding procedures in an attempt to improve calf performance and optimize the weaning transition. In early weaning programs, in which weaning occurs at approximately 4 to 6 wk of life, calves have limited access to milk or MR (10% of birth BW) to limit feed costs, encourage early intake of starter feed, and facilitate rumen development (Kertz and Lofton, 2013). Calves consuming high quantities of milk experience a challenge at weaning because of low solid feed intake before weaning (Jasper and Weary, 2002), which can lead to reduced digestibility of DM and OM, as well as NDF, CP, and GE after weaning (Terré et al., 2007). This suggests that the digestive tract of calves fed a high plane of milk nutrition may not be accustomed to the digestion of solid feed following weaning (Terré et al., 2007). Fiber (ADF and NDF) digestibility

is commonly decreased during the preweaning and weaning period by feeding greater amounts of milk (Hill et al., 2016; Dennis et al., 2018). This impairment may last up to wk 16 (Hill et al., 2016) and could potentially affect growth performance because calves are generally fed diets greater in fiber after weaning or soon thereafter. A previous study showed that delaying age of weaning increased total weight gain in calves fed an elevated plane of nutrition before weaning and decreased the transient reduction of weight gain at weaning (Meale et al., 2015). Eckert et al. (2015) reported that calves fed an elevated plane of MR during the preweaning stage had greater starter feed intake and weight gain during the weaning period when weaning was extended from 6 to 8 wk of age. Furthermore, late-weaned calves were better able to cope with weaning compared with early-weaned calves, as they had greater solid feed intake during weaning transition.

In addition to weaning later in life, a weaning protocol termed the “step-down” method was developed to minimize the challenges of weaning from high amounts of milk or MR. In the first paper to report on the step-down protocol (Khan et al., 2007a,b), calves either received elevated amounts of milk at 20% of BW until d 23, followed by 10% of BW from d 23 to 44, or were fed milk conventionally at 10% of BW until d 44. After d 44, all calves were weaned gradually through diluting milk with water at an increasing rate of 10% per day until all calves received 100% water on d 50. The results demonstrated that intake of solid feed and weight gain increased during weaning in calves fed elevated amounts of milk and weaned through the step-down method compared with those fed milk conventionally. More recent studies (Schäff et al., 2016, 2018) have also used the “step-down” method by feeding MR (125 g of MR powder per L) ad libitum for 5 wk, followed by reduction in MR proportionally day by day to 6 L of MR at wk 7 compared with calves fed only 6 L until weaning to investigate growth, metabolic adaptation, health, and rumen and small intestinal growth. The benefits reported in this study were greater perirenal fat and muscle mass and increased anabolic metabolism (as indicated by increased insulin-like growth factor 1 concentration in blood) for step-down calves compared with those who had restricted amounts of milk. Overall, this study reported that using a step-down protocol when feeding greater amounts of milk early in life encourages solid feed intake, which has a positive effect on GIT development and growth, as well as calf health. However, this study was only conducted during the preweaning and weaning phase, and therefore, the long-lasting effect of using the step-down weaning method is unknown. When feeding with automation, the step-down protocol can be less abrupt, as milk can be gradually decreased on a daily basis without an increase in farm labor costs. Welboren et al. (2019) reported that a weaning transition consisting of a gradual linear decline, specifically by linearly reduc-



ing MR (150 g of MR powder per L) allowance by 2.5% daily from 6 L/d at d 36 to 2 L/d until d 63, results in increased performance compared with a step-down protocol consisting of MR supply reduced to 6 L/d on d 36, 4 L/d on d 49, and 2 L/d on d 57 to 63. Sweeney et al. (2010) showed that the ideal step-down period for calves fed an elevated plane of nutrition was 10 d, as it encouraged dry feed intake and maintained growth during the weaning period. The authors also reported that a longer (22-d period) weaning transition is not always best. When calves were weaned over a 22-d period, this allowed for increased solid feed intake and greater BW gains after weaning, yet the period that calves were fed a greater amount of milk was substantially shorter than that in calves weaned abruptly, over a 4-d period or over a 10-d period. Therefore, these calves did not achieve substantial weight gain during the preweaning phase, which is the main benefit to feeding an elevated plane of milk/MR nutrition.

Another weaning strategy that could possibly be implemented to mitigate the negative effect observed when feeding a greater amount of milk is to use a combination of a step-down weaning process and weaning calves based on the amount of solid feed consumed. In a study conducted by Benetton et al. (2019), calves were stepped-down at 30 d by 25% of previous daily milk provided, followed by another 25% decrease when the following calf starter intake goals were reached: 225, 675, and 1,300 g/d. In this combination system, calves consumed less milk and more calf starter than calves that were weaned using only the step-down system; however, at the end of the trial there were no BW differences between the groups. Moreover, out of the 16 calves enrolled in the combination treatment, 6 calves failed to reach all 3 calf starter intake goals by wk 9. The authors investigated this result and found that by extending the final weaning week from wk 9 to 12, 12 out of 43 calves still were not meeting the 3 calf starter intake goals between wk 9 and 12, whereas the others were fully weaned by wk 9. The calves that took longer to reach the goals had lower final BW because more milk was consumed, at the cost of less calf starter intake. This indicates that each calf experiences the transition onto solid feed differently, and with the help of automation it is possible to allow calves to be weaned on an individual basis. More research is required to determine the interaction between age of weaning and different step-down protocols, especially around the postweaning period, to develop sound protocols that avoid declines in growth during weaning. There is also the need to know how these protocols will affect the calf long-term, specifically greater than 4 mo of age, as research regarding this effect in postweaned, prepubertal calves is lacking.

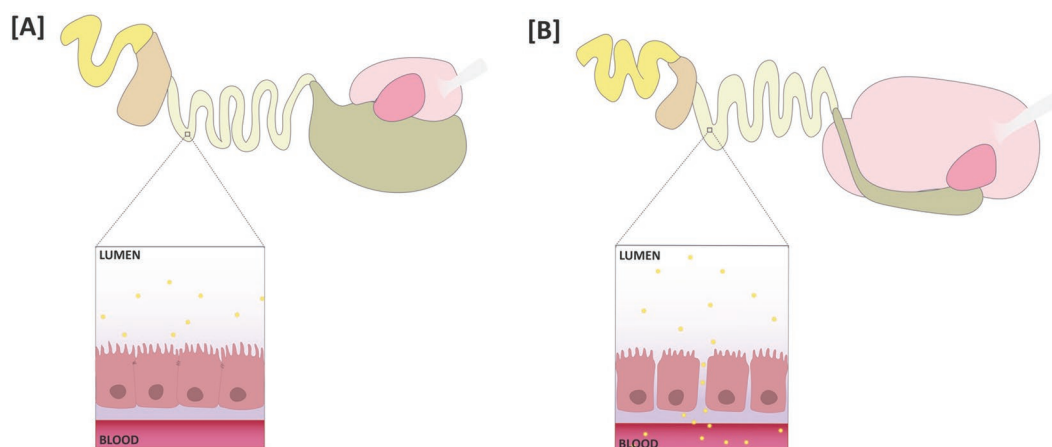
### **Gut Function During Weaning**

During the weaning process, the GIT undergoes significant changes, with the total volume of the rumen increasing from 30 to 70% of the entire forestomach (Warner et

al., 1956), enhanced expression of metabolic genes (Connor et al., 2013), and altered microbial populations (Meale et al., 2017). The physical growth of rumen tissue accommodates absorption of the end products of ruminal fermentation to meet the demands for growth (Figure 2; Baldwin et al., 2004). The maturation of both the rumen tissue transcriptome and microbiome are the result of exposure to substrates in the form of starter. Interestingly, changes in the expression of genes regulating growth during rumen development appear to be correlated with changes in the rumen microbial population. A recent study revealed that the expression of genes belonging to the first-line defense mechanisms, gut barrier functions (i.e., toll-like receptor,  $\beta$ -defensin, peptidoglycan recognition protein 1, claudin 4, and occludin), and bacterial diversity changed in response to the introduction of solid feed during the weaning process (Malmuthuge et al., 2013). Also, current findings from next generation DNA sequencing techniques show that the rumen microbiota of 2-mo-old, preruminant calves share 20 genera with 6-mo-old and 2-yr-old mature ruminants, accounting for 95 and 96% of the community for each group, respectively (Jami et al., 2013). Li et al. (2012) showed that species belonging to the *Bacteroidetes* phylum decreased and bacteria belonging to the *Firmicutes* and *Proteobacteria* phyla increased during the weaning process. Interestingly, the lower gut microbiota also undergoes transformations during weaning, with the microbial diversity increasing in the fecal microbiota (Li et al., 2012). However, research regarding the functional changes that occur to initiate the differences in the microbial populations of the lower gut during weaning are lacking.

High-starch diets are commonly fed to calves to facilitate rumen development (Baldwin et al., 2004), which increases ruminal fermentation, leading to short-chain fatty acid accumulation and a decrease in ruminal pH (Aschenbach et al., 2011). During weaning and shortly thereafter solid feed intake increases substantially to accommodate the calf's energy supply, making the calf more susceptible to decreased ruminal pH (Suarez et al., 2006; Laarman and Oba, 2011; Laarman et al., 2012; Kim et al., 2016). It has been reported that it can take up to 5 wk after weaning for the ruminal environment of calves fed high amounts of MR solution (15% of BW/d) before weaning to be in a state that would not be considered subacute ruminal acidosis (Van Niekerk et al., 2017). When mature ruminants are fed high-grain diets, it causes ruminal acidosis, and if acidosis is severe, it can lead to excessive amounts of starch reaching the hindgut (Li et al., 2012), which may induce hindgut acidosis as well. Ruminal and hindgut acidosis are unfavorable because they can trigger a systemic inflammatory response due to lipopolysaccharide being translocated into the peripheral circulation (Khafipour et al., 2009). Calves that are fed high amounts of milk before weaning (>8 L/d or >1.2 kg of MR powder/d) and reach consumption of greater than 1.5 kg/d of calf starter ex-





**Figure 2.** (A) The gastrointestinal tract (GIT) of a preruminant animal (approximately 4 wk of age). At this time the primary source of nutrition is milk, and the abomasum is the dominant compartment of the forestomach. The rumen remains undeveloped because of low starter intake. (B) The GIT of an animal after weaning. The rumen becomes more developed through increased starter intake. During this time high amounts of starch from starter often cause ruminal acidosis and bypass the rumen to damage the lower gut. This can cause a “leaky” lower gut, in which the tight junctions between enterocytes become disjointed and permeable to potentially harmful molecules, allowing them to enter systemic circulation. Color version available online.

hibit increased levels of fecal starch after weaning (Eckert et al., 2015; Van Niekerk et al., 2018), which indicates that starch reaching the hindgut could possibly lead to excessive hindgut fermentation. Steele et al. (2017) demonstrated that calves abruptly weaned at d 48 with a 0-d step-down period had greater amounts of fecal starch compared with calves that were gradually weaned over a 12-d period starting at d 36 until d 48, with fecal starch exceeding 5%, which is similar to the values reported in a functional ruminant (Fredin et al., 2014). It is clear that these high levels of fecal starch are due to the lack of GIT and microbial adaptation needed to digest high amounts of starch in calf starter (Steele et al., 2017). In this study, calves were fed steam-flaked corn (processed grain), which leads to an increased risk of ruminal acidosis (Krause and Oetzel, 2006), whereas whole grain, such as whole corn, can shift the site of fermentation from the rumen to the lower gut (Gressley et al., 2011). The lower gut is a monolayer structure, whereas the rumen is a multilayered structure (Graham and Simmons, 2005; Steele et al., 2016), possibly making the lower gut more susceptible to environmental changes (pH) that can be caused by excessive fermentation. Van Niekerk et al. (2018) reported that feeding a high amount of milk (10 L/d or 1.5 kg of MR powder/d) combined with texturized calf starter containing whole corn can decrease fecal pH 2 wk after weaning compared with calves fed calf starter containing flaked corn, which can be an indication of hindgut acidosis. Recently, it was reported that digesta acidity plays a bigger role in the activation of inflammatory signaling pathways (toll-like receptor 4) in the rumen (Kim et al., 2019) and mucosa damage in the colon (Tao et al., 2014) compared with lipopolysaccharides. However, limited literature is available regarding the influences of preweaning feeding regimens and weaning on the intestinal function of dairy calves. This paucity of information

ultimately highlights the amount of future research still needed to fill this gap in our understanding.

## APPLICATIONS

Differing nutritional management strategies for dairy calves, in particular colostrum feeding, plane of nutrition, and weaning strategy, can result in great differences in growth performance, health, and gastrointestinal development. Strategies to optimize gastrointestinal health and development of calves, such as the timely feeding of colostrum after birth and feeding transition milk to calves, are encouraged to combat the high prevalence of mortality and morbidity related to abnormal GIT function. Moreover, maximizing nutrient intake before weaning has the potential to affect long-term cow health and future milk production. The long-term effects of particular feeding regimens during the first week and first month of life, as well as the weaning period, are currently unknown, which represents a significant knowledge gap in calf nutrition. Research examining the effects of nutrition schemes from the first hours, weeks, and months of life is required to properly understand the influence that gastrointestinal function has on the health and performance of calves.

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