Nutrition and Immunity for Pre-weaned Dairy Calves

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Abstract

Dairy calves are extremely susceptible to gastro-intestinal disease during the pre-weaned period. The risk for enteric disease decreases as the calf ages; therefore, it is important to break the pre-weaned period up into at least 2 distinct phases that likely need to be managed differently, early life (1st and maybe the 2nd week of life) and the remaining time the calf is fed fluid. When a calf is born, they have never been exposed to any microorganisms and some aspects of their immune system are not fully developed. Since the calf *in utero* received its nutrients from the cow through placental transfer, the calf has never had any enteric nutrition. After birth, the calf is now in a microbial world and expected to receive all its nutrients orally from its mother's milk. The gastro-intestinal tract of the calf is naïve and develops rapidly during the first few days to weeks. The cells that make up the gastro-intestinal tract are the first line of defense of the immune system; therefore, until the cells are more adult-like, the calf is at an increased risk for developing gastro-intestinal diseases. Future research needs to focus on how much, the frequency of feeding, and composition of fluid fed affect the calf during this period. Currently, the primary strategies to improve the resistance to gastro-intestinal diseases during this period are focused on decreasing the interaction of potential pathogens with the cells of the calf's gastro-intestinal tract. The uses of prebiotics, probiotics, hyper-immunized egg protein, and spray-dried plasma proteins have all been shown to decrease the incidence of gastro-intestinal diseases and improve the growth of pre-weaned calves. The plane of nutrition that calves are fed during the entire pre-weaned period was reported to improve future lactational performance and emerging data suggest that it may improve the resistance to some diseases. Further, the effect may persist past the pre-weaned period. More research is needed in this area. Nutrition can influence disease resistance of calves in many ways, both directly by supplying specific nutrients and indirectly by influencing the exposure to microorganisms.

Introduction

It is well documented that dairy calves are extremely susceptible to gastro-intestinal diseases and mortality during the first few weeks of life (Roy, 1990). Recent reports from the USDA's National Animal Health and Monitoring System (NAHMS, 1993; 1996; 2007) report that the national mortality rate of heifer calves from 48 hr of life to weaning is approximately 7.8 to 10.8%. Producer perceived records indicate that scours account for 56.5 to 60.5% of all pre-weaned deaths. Approximately 25% of all pre-weaned calves are therapeutically treated for scours, and the major causes of death from scours are either dehydration or the pathogen gains access to the body and causes septicemia.

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The high incidence of disease indicates that there is a lot of room for improving gastro-intestinal disease resistance among pre-weaned calves. How much and the composition of fluid fed to pre-weaned calves and the use of additives, such as different prebiotics, probiotics, and proteins from either hyper-immunized eggs or spray-dried plasma, all may improve the health of pre-weaned calves.

First Weeks of Life

Dairy calves, like all mammalian species, are not exposed to microorganisms prior to birth. Furthermore, they are receiving all their nutrients from placental transfer from their mother and their gastro-intestinal tract has never seen food while they are *in utero*. Therefore, immediately after birth, they are no longer in a sterile environment and are required to get all their nutrition from milk. Many components of the immune system are functional at birth; however, some aspects of the adaptive immune system develop as the calf ages. Colostrum has a lot of antibodies, and during the first few days of life, the calf is able to absorb those antibodies into their body, which helps protect them from enteric and systemic disease. Colostrum also has a lot of other bioactive molecules that may influence gastrointestinal physiology and ultimately improve health, and the effects of these bioactive molecules effects on gastro-intestinal integrity and health warrant further investigation. Calves that do not receive colostrum are at an increased risk of developing scours and 74 times more likely to die in the first 21 days of life (Wells et al., 1996).

Colostrum is only part of the equation; many calves that receive adequate colostrum still develop gastro-intestinal disease. Data indicate that most scours occur during the first 3 weeks of life (Roy, 1990). Interestingly, by the time the calf is 3 weeks old, about 50% of the antibodies it received from the colostrum are gone and not much has really changed regarding the calves cellular or humoral immune system (Kampen et al., 2006). So why are calves not as likely to develop gastro-intestinal disease, despite having reduced passive derived immunoglobulins? Remember, when calves are born, they have never had food in their gastro-intestinal tract, so the cells that make up the gastro-intestinal tract need to adapt to extra-uterine life and enteric nutrition. Guilloteau et al. (2009) reported that many changes occur in the first few days to week regarding the structure of the cells that line the gastro-intestinal tract. Specifically, they reported fetal-type cells are replaced with more adult-like cells within 5 to 7 days after birth. The cells that make up the gastro-intestinal tract are very important and form the first line or the physical barriers of the immune system. Therefore, my lab hypothesizes that the physical barriers of the gastro-intestinal tract are impaired during the first week(s) of life, which increases the risk of developing scours. More research is needed to understand how we can manage the calf during that first week(s) after calving, while she is adapting to the *ex utero* environment. More research is needed on how nutrition, how much and frequency of feeding of fluid, of the calf during the first week of life influences the gastro-intestinal integrity and resistance to gastro-intestinal diseases.

The interest in the plane of nutrition that calves are fed during the pre-weaned period has increased primarily because data indicate that calves fed a greater plane of nutrition have decreased age at first calving and they may have improved future lactation performance (Soberon et al., 2012; Soberon and Van Amburgh, 2013). Most data on how plane of nutrition influences the health of calves during the first few weeks of life are limited to small, controlled experiments with fecal scores as the primary outcome variable (Nonnecke et al., 2003; Ballou, 2012). Many studies observed that the calves fed the greater plane of nutrition had more loose feces (Nonecke et al., 2003; Bartlett et al., 2006; Hengst et al., 2012; Osorio et al., 2012; Ballou et al., unpublished), while others showed no differences in fecal scores (Ballou, 2012; Obeidat et al., 2013). It is important to note that no study has reported greater fecal scores among calves fed a lower plane of nutrition when compared to calves fed a greater plane of nutrition. It has been suggested that the greater fecal scores were not due to a higher incidence of infection or disease, but may be associated with the additional nutrients consumed. It is unknown whether the digestibilities of nutrients of calves fed varying planes of nutrition are different during the first week of life; however, decreased nutrient digestibilities would likely not be independent of enteric health because increased supply of nutrients to the lower gastro-intestinal tract could provide a more favorable environment for pathogenic microorganisms to thrive. In agreement, Quigley et al. (2006) reported that feeding a greater plane of nutrition to high-risk Holstein bull calves, purchased from a sale barn, and raised on bedding contaminated with coronavirus, increased the number of days calves had scours by 53% and also increased the number of days calves received antibiotics, 3.1 versus 1.9 days. In contrast, a more recent study reported that calves fed a greater plane of nutrition had improved hydration and fecal scores improved faster when they were challenged with *Cryptosporidium parvum* at 3 days of age (Ollivett et al., 2012). Larger data sets with naturally occurring disease incidence and more experimentally controlled relevant disease challenges are needed before definitive conclusions on the role that plane of nutrition plays on enteric health of calves during the first few weeks of life. An additional comment from my experiences is that many dairy producers and calf raisers, if they feed a greater plane of nutrition, will start them off at a lower plane of nutrition and increase the plane of nutrition after 1 or 2 weeks.

In addition to plane of nutrition, many of the current strategies to improve the health of pre-weaned calves are focused on preventing the interaction of potentially pathogenic microorganisms with the gastro-intestinal tract of the calf and the use of prebiotics, probiotics, or proteins from hyper-immunized egg or spray-dried plasma have shown some merit. Prebiotics are dietary components that are not digested by the calf, but are used by bacteria in the gasto-intestinal tract to improve their growth. At first glance, this may seem bad; why would be want to improve the growth of bacteria in the gastro-intestinal tract? The gastro-intestinal tract is not sterile. Soon after birth, a wide range of bacterial species colonizes the gastro-intestinal tract of calves. Most of these bacterial species do not pose any immediate threat to the survival of the calf, and in the past they were called "good bacteria", and of which, many of the common probiotic species are routinely classified as, including: *lactobaccilus* species, *bifidobacteria*, *Enterocooccus faecium*, and *Bacillus* species. There are many plausible mechanisms explaining how both prebiotics and probiotics would reduce the interaction of more pathogenic microorganisms with the gastro-intestinal tract of the calf. Many of the probiotic species had a direct bactericidal activity (Midolo et al., 1995) or compete with the more pathogenic microorganisms for limited resources. In addition, probiotics are themselves bacteria, and they may "prime" the immune system of the calf by staying alert, as even the immune system recognizes the "good" bacteria as foreign (Blum et al., 2002; Lomax and Calder, 2009). The common, commercially-available prebiotics available are the fructooligosaccharides **(FOS)**, mannanoligosaccharides **(MOS)**, lactulose, and inulin.

Data on the influence of prebiotics and probiotics alone on the health of dairy calves are equivocal. There are data that show improvements in reducing scouring and improving growth (Abe et al., 1995; Heinrichs et al., 2003), whereas equally as many studies show no benefits to including either prebiotics or probiotics in milk (Morrill et al., 1995; Hill et al., 2008). The lack of a clear effect in calves is likely due to many environmental factors. Research does, however, support that many prebiotics and probiotics are generally safe and do not have any adverse effects on calf health or performance. In fact, most regulatory agencies around the world classify most prebiotics and probiotics as Generally Regarded As Safe (GRAS). I currently look at adding prebiotics and probiotics as an insurance policy; you do not know when you will need them, but when you do, it is good to have them. Lastly, it is important to note that not all probiotic species, and further, not all strains of a specific species, ie: not all *Lactobaccilus acidophilus* strains, behave similarly. Therefore, I would recommend only using probiotic species and strains that have been reported, through 3rd party research, to improve health and performance of calves.

Another strategy to reduce the interaction of pathogenic microorganisms is to feed egg protein from laying hens that were vaccinated against the very microorganisms that cause gastro-intestinal diseases in calves. The laying hens will produce immunoglobulins **(IgY)** and concentrate those proteins in their eggs, which can recognize the pathogen, bind to it, and prevent its interaction with a calf's gastro-intestinal tract. Inclusion of such whole dried egg decreased the morbidity due to various bacteria (Hennig-Pauka et al., 2003) and viruses (Kuroki et al., 1993; Ikemori et al., 1997). In addition to the use of hyper-immunized egg protein, spray-dried plasma proteins can improve gastro-intestinal health of calves. Spray-dried plasma is exactly what it sounds like; plasma is spray dried to preserve the functional characteristics of the diverse group of proteins in plasma. The use of spray-dried plasma has been used for many years in the swine industry to improve the performance and health during the post-weaned period. The addition of spray-dried plasma proteins in milk replacer reduced enteric disease in calves (Hunt et al., 2002; Quigley et al., 2002; Quigley and Wolfe, 2003).

In 2010, my lab evaluated the effects of supplementing a blend of prebiotics, probiotics, and hyper-immunized egg proteins to Holstein calves during the first 3 weeks of life (Ballou, 2011). Calves given the prophylactic treatment (n = 45) were administered directly into the milk 5 x 10^9 colony forming units per day (from a combination of *Lactobacillus acidophilus, Bacillus subtilis, Bifidobacterium thermophilum, Enterococcus faecium,* and *Bifidobacterium longum*), 2g/day of a blend of MOS, FOS, and charcoal, and 3.2 g/day of dried egg protein from laying hens vaccinated against K99+ *Escherichia coli* antigen, *Salmonella typhimurium*, *Salmonella Dublin*, coronavirus, and rotavirus. Control calves (n = 44) were not given any prebiotics, probiotics, or dried egg protein. All calves were fed 2 Liters (0.52 gal) of a 20% protein/20% fat non-medicated milk replacer twice daily. Prior to each feeding, fecal scores were determined by 2 independent trained observers according to Larson et al. (1977): 1 = firm, well-formed; 2 = soft, pudding-like; 3 = runny, pancake batter; and 4 = liquid splatters, pulpy orange juice. The prophylactic calves refused less milk ($P < 0.01$) during the first 4 days of life (57 vs 149 g of milk powder). There were no differences in starter intake or average daily gain due to treatments. However, calves that received the prophylactic treatment had decreased incidence of scours ($P < 0.01$) during the first 21 days of life (25.0 versus 51.1%). Scours were classified as a calf having consecutive fecal scores $\geq$ 3. The intensity of disease in this study was low and only 1 out of 90 calves died during the experiment. These data support that a combination of prebiotics, probiotics, and hyper-immunized egg protein improve gastro-intestinal health and could be an alternative to metaphylactic antibiotic use. Future research should determine the efficacy of prophylactic treatment in calves that are at a higher risk of developing severe gastro-intestinal disease and subsequently death.

After Two Weeks of Life

The risk of gastro-intestinal diseases dramatically declines after the first few weeks of life. There is emerging evidence that nutrition and environment of calves during the pre-weaned period has persistent effects on the health and physiology of an animal later in life (Ballou, 2012; Frei et al., 2012; Soberon et al., 2012; Ballou et al., unpublished). How much, the frequency of feeding, and the composition of fluid fed to calves during the pre-weaned period influences the health of calves. The majority of dairy calves in the US are fed restricted quantities of fluid to encourage them to consume calf starter earlier, so they can be weaned at a younger age. This management strategy was widely adopted because it was seen as more economical because a pound of powder was much more expensive than a pound of calf starter. Although it is more expensive to raise a calf during the pre-weaned period when fed higher planes of fluid nutrition, in most situations, the total cost to raise the calf to a first calf heifer is less expensive than when they are fed restricted quantities of fluid in early life. Further, this restricted fluid feeding strategy was widely adopted without any understanding of the potential long-term impacts on performance and health of the animal. Over the past decade, there was resurgence in the interest of feeding dairy calves higher planes of fluid nutrition (Raeth-Knight et al., 2009; Ballou, 2012). These higher planes of nutrition programs are often called "Accelerated", "Intensive", or "Full Potential".

A recent meta-analysis performed by Soberson and Van Amburgh (2013) suggested that higher planes of fluid nutrition positively impacted the lactation performance. Over the past 5 years, my laboratory has conducted research to understand the how plane of nutrition during the pre-weaned period influences leukocyte responses and resistance to infectious disease during the pre- and immediate post-weaned periods (Ballou, 2012; Obeidat et al., 2012; Ballou et al., unpublished). The results indicate that plane of nutrition influences leukocyte responses of calves (Ballou, 2012; Obeidat et al., 2013; Ballou et al., unpublished). In two studies, we reported that when calves were fed a lower plane of nutrition, their neutrophils were more active during the pre-weaned period, as evident by increased surface concentrations of the adhesion molecule L-selectin (Figure 1) and a greater neutrophil oxidative burst (Obeidat et al., 2013; Ballou et al., unpublished). After weaning, the elevated neutrophil responses were no longer apparent in either of those studies. The exact mechanisms for the more active neutrophils among the low plane of nutrition calves are not known but could be due to increased microbial exposure because of increased non-nutritive suckling or reduced stress among the calves fed the low plane of nutrition. If the neutrophils are more active because of increased microbial exposure, calves fed a lower plane of nutrition could be at an increased risk for disease during the pre-weaned period. Ongoing research in my laboratory is trying to understand the behavior and potential microbial exposure when calves are fed varying planes of nutrition and its influence on immunological development. In addition, plane of nutrition during the pre-weaned period may have effects on leukocyte responses that persist beyond the pre-weaned period (Ballou, 2012; Ballou et al., unpublished).

Jersey bull calves that were fed a greater plane of fluid nutrition had improved neutrophil and whole blood *E. coli* killing capacities after they were weaned when compared to Jersey calves fed a more conventional, low plane of nutrition (Figure 2; Ballou, 2012). These effects were only observed among the Jersey calves in this study and not the Holstein calves.

In a follow-up study, Jersey calves that were previously fed a greater plane of milk replacer had a more rapid up-regulation of many leukocyte responses, including neutrophil oxidative burst and the secretion of the pro-inflammatory cytokine tumor necrosis factor-α, after they were challenged with an oral bolus of 1.5 x 10^7 colony-forming units of a *Salmonella typhimurium* (data not shown; Ballou et al., unpublished). The increased activation of innate leukocyte responses among the calves previously fed the greater plane of nutrition tended (P=0.098; Figure 3) to prevent the increase in plasma haptoglobin, and those calves also had greater concentrations of plasma zinc (data not shown). The calves fed the greater plane of nutrition also had improved intake of calf starter beginning 3 days after the challenge (P = 0.039; Figure 4). These data indicate that the Jersey calves previously fed a greater plane of nutrition had improved disease resistance to an oral *Salmonella typhimurium* challenge approximately a month after weaning. Our 2 studies indicate that at least among Jersey calves, feeding a greater plane of nutrition during the pre-weaned period may influence the health of calves during the immediate post-weaned period. More data are needed to understand how plane of fluid nutrition influences the resistance to diseases that are common during the life cycle of dairy cattle, including: gastro-intestinal, respiratory disease, metritis, and mastitis. Further, more data are needed in Holstein calves to see if the responses observed in Jersey calves would be true in Holstein.

Implications

Dairy calves in the first few weeks of life are extremely susceptible to disease, which may be related to the naïve gastro-intestinal tract of calves. Currently, the uses of prebiotics, probiotics, and proteins from hyper-immunized egg or spray-dried plasma have all been shown to reduce the incidence of gastro-intestinal disease. If you have a high early mortality, it is recommended that you look into using a research-backed product with prebiotics, probiotics, or proteins from hyper-immunized egg or spray-dried plasma. Increasing the plane of nutrition in the first week or 2 appears to increase fecal scores, and more data are needed to determine if these calves are at an increased risk for enteric disease. Early data are suggesting that plane of nutrition during the entire pre-weaned period may influence leukocyte responses and disease resistance of calves that extend beyond the pre-weaned period. More data are needed before definitive conclusions can be drawn, but current data among Jersey calves do appear promising.

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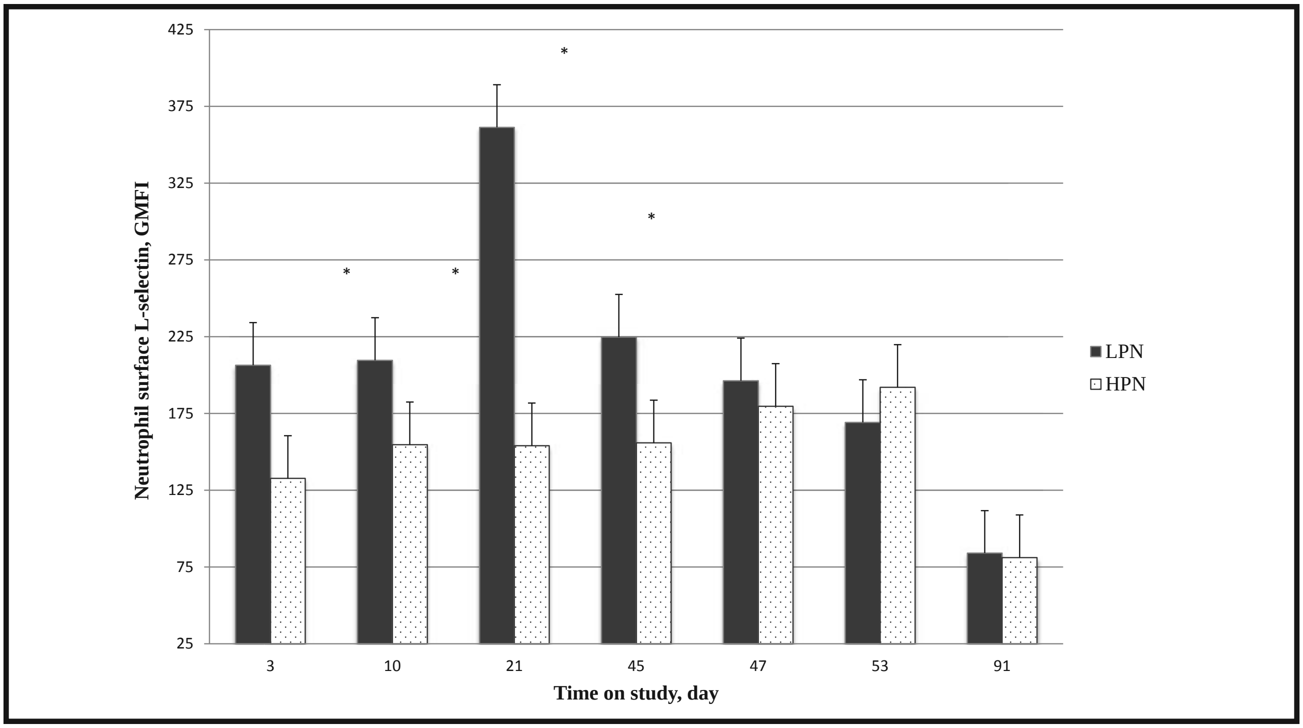

Figure 1: Feeding a lower plane of nutrition (LPN) during the pre-weaned period versus a higher plane of nutrition (HPN) increased L-selectin concentrations ($P < 0.05$) on the surface of neutrophils. An asterix denotes treatment differences ($P < 0.05$) sliced by time. Data reported as least square ± standard error of mean (Obeidat et al., 2013).

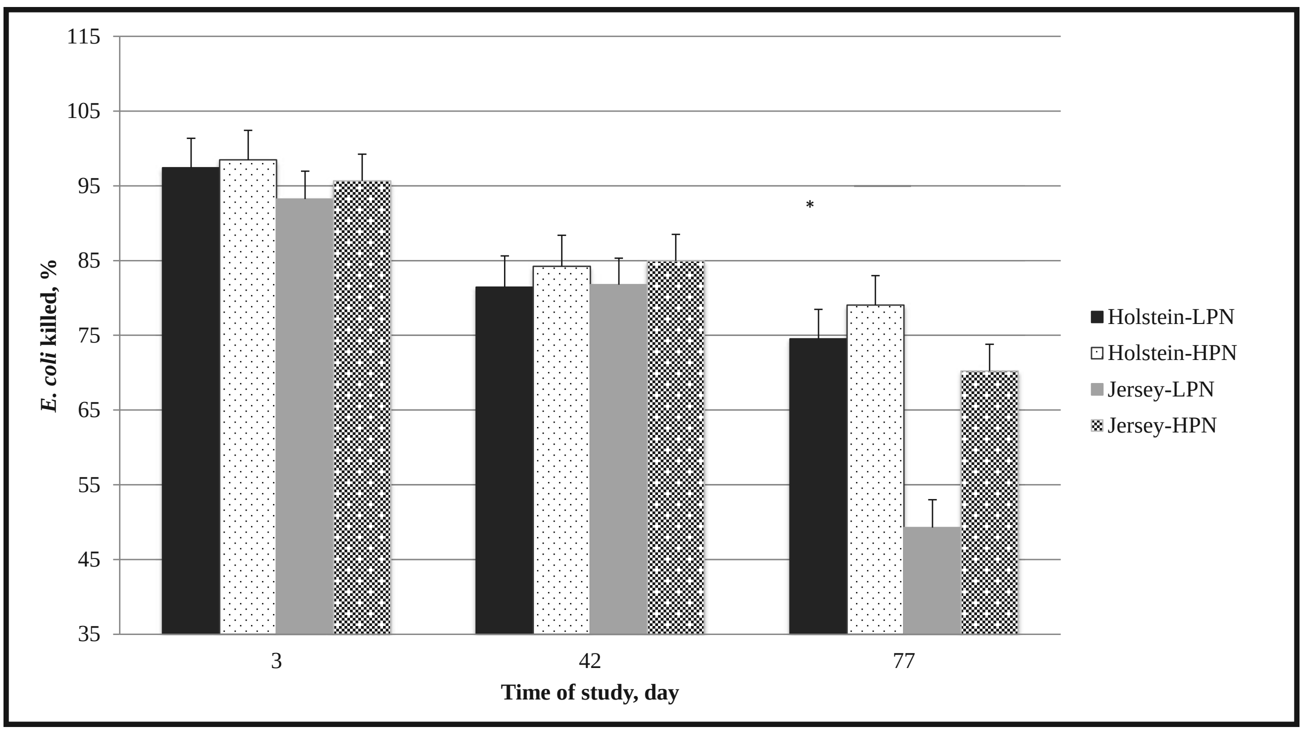

Figure 2: Feeding a higher plane of nutrition (HPN) versus a lower plane of nutrition (LPN) during the pre-weaned period improved the ability of whole blood from Jersey calves to kill a live *E. coli* during the immediate post-weaned period. An asterix indicates a sliced breed x plane of nutrition contrast at day 77 ($P < 0.04$). Data reported as least squares means ± standard error of mean (Ballou, 2012).

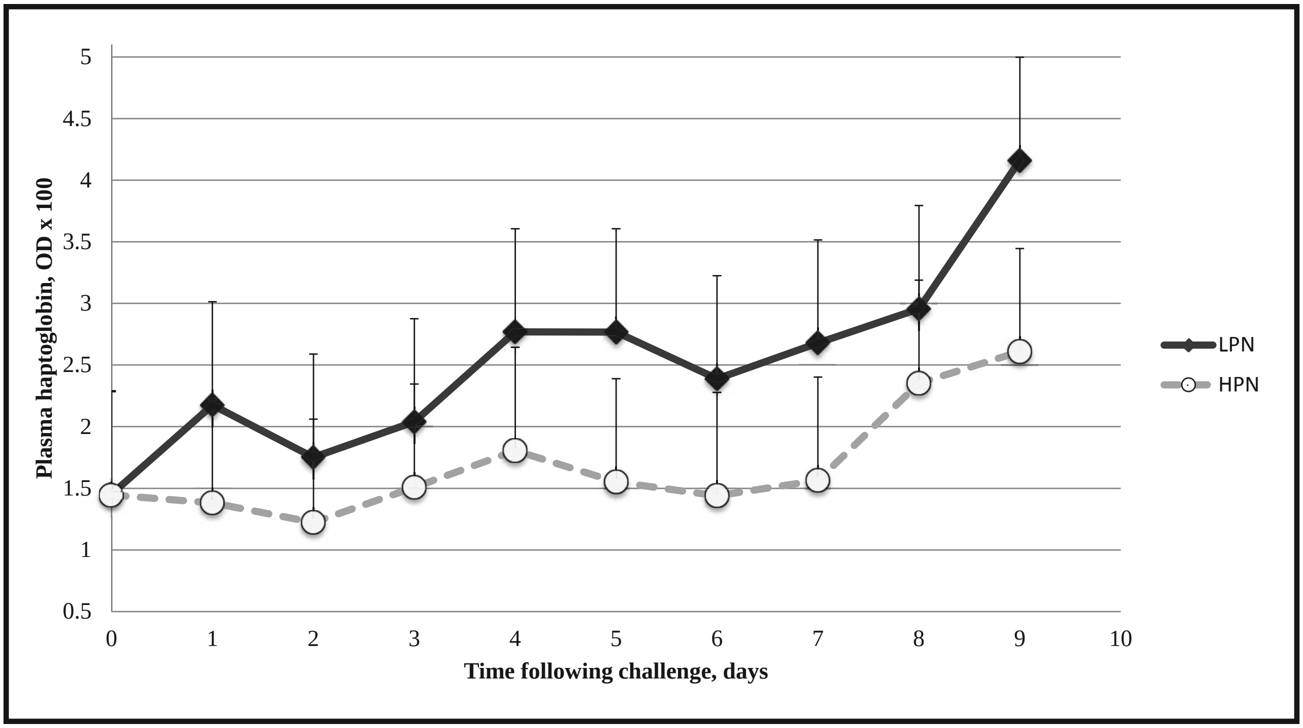

Figure 3. Feeding a higher plane of nutrition (HPN) versus a lower plane of nutrition (LPN) during the pre-weaned period tended ($P = 0.098$) to reduce plasma haptoglobin concentrations following an oral *Salmonella typhimurium* challenge approximately 1 month after weaning. Data reported as least squares means $\pm$ standard error of means. (Ballou et al., unpublished).

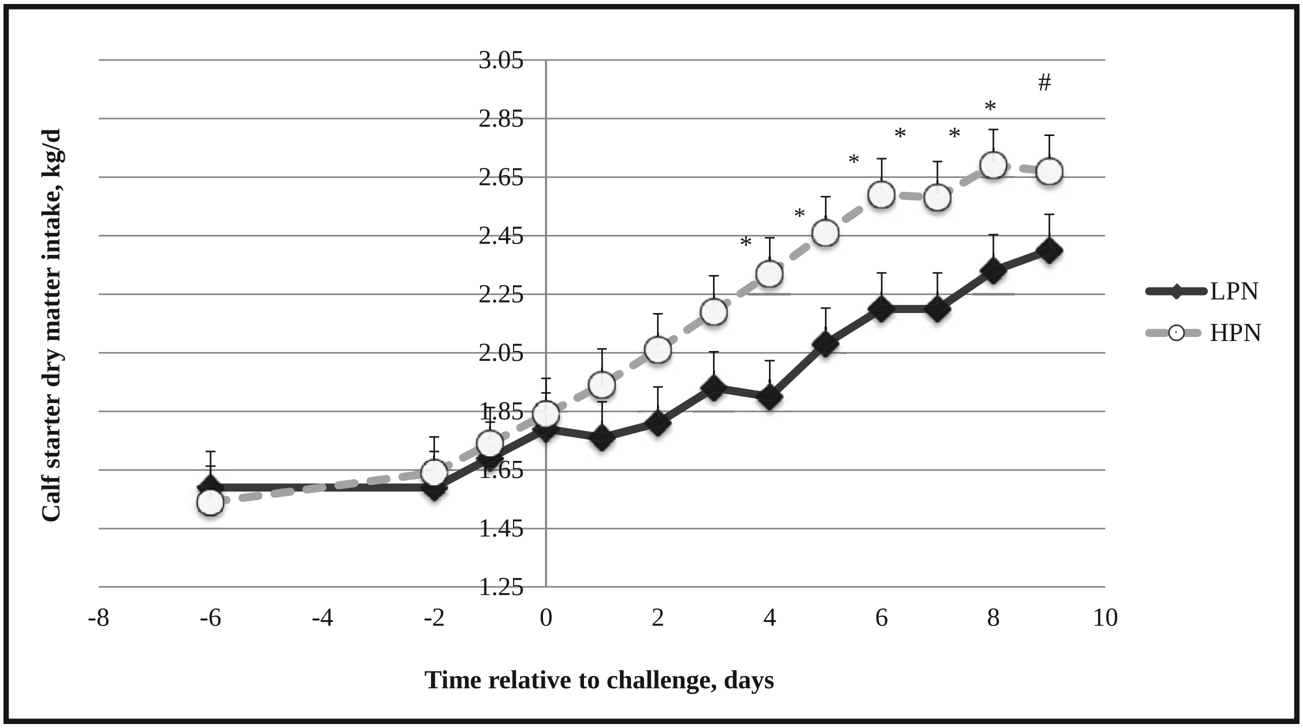

Figure 4. Feeding a higher plane of nutrition (HPN) versus a lower plane of nutrition (LPN) during the pre-weaned period improved (P = 0.039) calf starter intake following an oral *Salmonella typhimurium* challenge approximately 1 month after weaning. An asterix denotes treatment differences ($P < 0.05$) and a pound sign indicates a tendency ($P<0.10$) sliced by time. Data reported as least square means ± standard error of means (Ballou et al., unpublished).