Prescribed Feeding Prepartum for Improved Health and Performance Postpartum

Matthew R. Waldron[1]
Nutrition Professionals, Inc.

Abstract

Dairy cows experience a reduced immune capacity around the time of calving. To date, no single factor has been reported to be responsible for this immune dysfunction. Experimental models of under-nutrition outside of the time around calving have generally failed to reproduce the typical periparturient problem. Among other factors, ketones, nonesterified fatty acids, and calcium metabolism may contribute to periparturient immunosuppression. In addition to these metabolites, many dietary nutrients are involved in immune protection. Some of these nutrients are involved in immune cell function, but many others serve to limit inflammatory damage. Inflammatory damage is often due to oxidative stress – the reaction of unstable oxidizing molecules with tissue lipids, proteins, and DNA. Many of the micronutrients that are important for immune function and health serve in this role of tissue protection as antioxidants. The exact quantity of these dietary micronutrients needed to maximize immune function and tissue protection is unknown, but likely varies depending on the cow and her environment. Vitamin E, selenium, other trace minerals, and some feed additives can directly affect immune function. Nutritional management to provide highly bioavailable nutritional profiles and to maximize metabolic health is our best strategy to maximize immune function. Best management practices to maximize hygiene and minimize stressors also are crucial to helping prevent infection.

Introduction

Metabolic management of the periparturient cow has been extensively studied and the research literature reviewed on multiple occasions since the early 1990's - the purpose of this paper is not to rehash the details of management for metabolic health. However, as will be discussed, failed metabolic adaptations do contribute to impaired immunity around the time of calving; thus, much like a human doctor tells us that sound basic nutrition, exercise, sufficient rest, and moderate psychologic stress are all important for our own immune protection, maintenance of a balanced nutritional profile, appropriate body condition, and minimum psychologic stress for the periparturient cow also are important. These basic underpinnings of health are therefore the most basic and most important parts of "prescriptive" feeding the transition dairy cow.

Periparturient Health

The dairy cow transitioning between physiologic states around the time of parturition undergoes numerous physiologic adaptations in order to successfully bring her fetus to term and initiate lactation. As part of these adaptations, feed intake decreases

[1]Contact at: W1840 Steiner Rd., Chilton, WI 53014, (920) 540-8900, FAX: (920) 849-2256, Email: mrwaldron@bugnet.net.

around the time of calving even though nutrient requirements of the fetus and placenta continue to increase prepartum and energy secretion in the form of milk increases dramatically postpartum (Grummer, 1993; Bell, 1995). This period of decreased feed intake coupled with stout energetic and nutrient demands creates a period of negative nutrient balance, such that energy, protein, and macromineral balances run deficits during the periparturient period (Goff and Horst, 1997). In addition to the adaptations of nutritional physiology that must occur to support periparturient metabolic health, the immune system of the cow also undergoes changes during this time-frame that decrease its effectiveness.

These changes in immune protection, often termed immunosuppression or immune dysfunction, affect the functional activity of multiple immune cell types around the time of calving (Mallard et al., 1998; Sordillo and Streicher, 2002). The reasons for these immunological changes is not entirely understood, although maternal-fetal recognition and hormonal changes associated with the initiation of parturition may play a role (Burton et al., 1995; Weber et al., 2001). Furthermore, the cotyledonary placenta of the bovine necessitates a sequestration of immune components into colostrum for passive transfer of immunity to the newborn calf. However, the mastectomized cow model (Kimura et al., 1999) has shown definitively that colostrogenesis is not wholly responsible for impaired immunity during the periparturient period. The question becomes, other than these physiological changes associated with parturition, how does nutrition tie-in to periparturient immune function? Does nutrition or downstream metabolism have the potential to impair immunity and do specific nutrients or feed additives directly affect the immune system?

Negative Energy Balance and Immune Dysfunction

Periparturient negative energy balance has been implicated in contributing to immunosuppression. Perhaps one of the most convincing experiments implicating the metabolic demand of lactation on impaired immunity utilized the mastectomized cow model (Kimura et al., 1999). In this experiment, the presence of the mammary gland (vs. mastectomized cows) and its attendant metabolic demands slowed recovery of neutrophil function postpartum, suggesting that fuel use, metabolite concentrations, or endocrine profiles associated with lactation exacerbated periparturient immunosuppression (Kimura et al., 1999). Furthermore, associative studies have linked lower prepartum dry matter intake with either reduced immune function (Hammon et al., 2006) or increased severity of inflammatory disease postpartum (Huzzey et al., 2007).

It stands to reason that if negative nutrient or energy balances around the time of calving were a significant cause of periparturient immunosuppression, it should be possible to recreate immune dysfunction in virtually any cattle class using experimental feed restriction models. Experimental induction of immunosuppression would help to prove causality of periparturient dysfunction but would also yield valuable help in our research of this problem - less expensive animal models could be used and greater experimental flexibility would be created without depending on the (unknown) exact day of an expected calving. However, research results using feed restriction models have been largely disappointing; few experiments have resulted in widespread immunological changes mimicking those seen around the time of natural parturition in dairy cows. Experimentally-induced negative energy

balance alone had little effect on the expression of adhesion molecules on the surface of bovine leukocytes (Perkins et al., 2001). Furthermore, experimental negative energy balance in midlactation cows did not affect the clinical symptoms associated with an intramammary endotoxin infusion (Perkins et al., 2002). Similarly, Moyes et al. (2009a) reported only minor differences in immunocompetence of post-peak cows subjected to nutrient restriction for 5 days prior to intramammary experimental mastitis. The disagreement between experimental models of nutrient restriction and periparturient dairy cows suggests that other variables during the periparturient period are more likely responsible for immunosuppression than just nutrient balance or transient changes in circulating metabolites.

Relating to metabolites, other work has investigated individual metabolic components associated with negative energy balance; specifically, ketones, and more recently, nonesterified fatty acids **(NEFA)** have been the most studied. Kremer et al. (1993) reported that experimental mastitis was more severe in ketotic than non-ketotic cows, and as reviewed by Suriyasathaporn et al. (2000), ketosis may increase the risk of mastitis in periparturient immunosuppressed cattle because many immune cell types are negatively affected by metabolite levels typical of a ketotic environment (i.e., low concentrations of glucose and high concentrations of ketone bodies and NEFA). Other studies have suggested that it is the NEFA, not the ketones per se, that are responsible for the negative postpartum immune influences. Ster et al. (2012) reported that in vitro concentration of NEFA equivalent to that reported in periparturient cows in vivo decreased peripheral blood mononuclear cell proliferation and also polymorphonuclear neutrophil **(PMN)** respiratory burst activity. This study lends support to that of Scalia et al. (2006), wherein in vitro incubation of PMN with NEFA resulted in decreased PMN function and viability. These laboratory experiments are consistent with field experiments suggesting that elevated concentrations of NEFA and (the ketone) beta-hydroxybutyrate **(BHBA)** around the time of calving are predictive for subsequent clinical mastitis (Moyes et al., 2009b) and the development of displaced abomasum, clinical ketosis, metritis, and retained placenta (Ospina et al., 2010). Galvão et al. (2010) reported that cows who developed metritis and subclinical endometritis had elevated levels of both plasma NEFA and BHBA, and PMN from these same cows had lower intracellular glycogen energy stores. From a practical standpoint, strategies that have been reported to help manage periparturient energy metabolites, such as maintaining moderate periparturient body condition scores (Lacetera et al., 2005) and not overfeeding during the prepartum period (Graugnard et al., 2012) appear beneficial to immune function around the time of calving.

Tipping the Scale - Body Condition Score

At the animal level, body condition score is related to the previously discussed metabolites associated with negative energy balance (i.e., NEFA and BHBA). Recent research suggests that immune function is related to body condition score; specifically, it may be that over-conditioned cows are at greater risk for inflammation and infection. It is still early in this area of research, but we are beginning to "connect the dots" to build the scientific story behind fat cows and immune imbalance. It is well documented that over-conditioned cows are at greater risk for metabolic disorders related to energy metabolism (Rukkwamsuk et al., 1999; Grummer, 1993). Specifically, these animals have greater lipid stores entering the period of negative energy balance and are therefore

more likely to have greater concentrations of NEFA and ketones in circulation, and greater triglyceride accumulation in the liver. Each of these factors has been associated with impaired immune function (NEFA – Scalia et al., 2006; Hammon et al., 2006; ketones – Suriyasathaporn et al., 2000; hepatic lipidosis – Andersen et al., 1996). In addition to the energetic related variables, over-conditioned cows are also more likely to experience higher levels of oxidative stress (Bernabucci et al., 2005; O'Boyle et al., 2006), are considered to be at greater inflammatory risk (O'Boyle et al., 2006), and have been reported to have impaired immune function (Lacetera et al., 2005). Greater oxidative stress may impair leukocyte function and also increase the potential inflammatory damage to productive tissue during an immune response. Insufficient data exists for in-depth discussion of the immune status of severely under-conditioned cattle, but one would expect immunosuppression similar to other examples of malnutrition below some threshold of animal well-being.

A Role for Calcium in Periparturient Immunity

Another aspect of periparturient metabolism that has the potential to impact immune competence is calcium metabolism. Significant quantities of calcium are required for milk synthesis and an inadequate adaptation to this calcium sink at the onset of lactation results in hypocalcemia (milk fever). Although it is important for milk synthesis, calcium is also important for intracellular metabolism and signaling in most cell types, including the leukocytes of the immune system. Returning to the previously discussed mastectomized cow study (Kimura et al., 1999), one of the key variables that was different between mastectomized and intact cows was plasma calcium concentration. This revelation rekindled interest in the potential role for calcium metabolism to be causal toward impaired immunity. Ducusin et al. (2003) reported that PMN from hypocalcemic cows had decreased phagocytic activity and that phagocytic capacity could be manipulated by adjusting extracellular concentrations. Similarly, Kimura et al. (2006) reported that calcium stores in mononuclear leukocytes are depleted prior to the development of hypocalcemia in the blood, and that this depletion of intracellular calcium potentially contributes to immunosuppression. Not only may clinical hypocalcemia be important, Martinez et al. (2012) reported that even subclinically hypocalcemic cows (SCH; serum Ca < 8.59 mg/dL in at least one sample from the first 3 days postpartum) may have impaired immune function. These authors reported that SCH cows had lower numbers of circulating PMN in blood and that these PMN had impaired phagocytic and killing capacities. As follows, these SCH cows also were at increased risk for development of fever, metritis, and puerperal metritis; the relative risk for developing metritis decreased by 22% for every 1 mg/dL increase in serum Ca (Martinez et al., 2012). Nutritional management of periparturient calcium metabolism may have implications for immune function, not just metabolic health.

The Role of Some Dietary Nutrients in Immunity

Completing the relationship between immune function and metabolism, it also has been reported that multiple dietary nutrients influence immunity. The role of dietary nutrients in supporting immune function has received significant research attention. Vitamins (e.g., vitamins C, D, and E) and trace minerals (e.g., zinc or selenium) are all familiar to us from advertisements touting the role of these nutrients in human health and disease.

Furthermore, at least basal levels, and in some cases supranutritional levels, of these nutrients have been shown be supportive for animal health in livestock production systems (Weiss, 1998; Spears, 2000; Spears and Weiss, 2008). Other nutrients, such as specific fatty acids, have been studied for their ability to influence immune function (Calder, 2006) and hold promise for future use in livestock species.

Although some micronutrients are directly involved in immune cell function, one of the most common ways that nutrients are involved in animal health is through their role as antioxidants. Antioxidants protect the animal from reactive or unstable compounds that set off chain reactions and cause tissue damage. These chain reactions are initiated by oxidized products of metabolism, such as superoxide anion, hydrogen peroxide, hydroxyl radical, hypochlorous acid, and peroxynitrite (Valko et al., 2007). These unstable compounds typically fall under the categories of reactive oxygen species **(ROS)** or reactive nitrogen species **(RNS)**. The ROS and RNS are normal products of healthy metabolism. That is, as energy is created through aerobic metabolism, some unpaired electrons attach to molecular oxygen and form superoxide anion (Valko et al., 2007). This unstable molecule can pass the single electron to other metabolic intermediates or induce instability in other compounds. This group of unstable compounds interacts with lipids, proteins, DNA, and other molecules within the body to induce instability and create tissue damage. The antioxidants that work to oppose these unstable molecules either directly quench these oxidants or sometimes repair tissue that has already suffered oxidative damage. Under basal conditions (in a micronutrient-supplemented animal), antioxidants generally reduce most of the oxidants, and little tissue damage occurs. However, any factor that tips the balance toward greater production of pro-oxidant molecules (e.g., diet imbalances, increased metabolic rate, toxins, or inflammation) or decreased presence of antioxidants (e.g., nutrient deficiencies or a greater oxidative stress load) result in greater oxidative stress on the tissues of the animal (Miller et al., 1993).

Oxidative Stress – A Common Denominator Between Active Metabolism and Inflammation

During inflammatory disease states, immune cells produce ROS and RNS (Sordillo and Aitken, 2009). The leukocytes then use these toxic compounds as part of their arsenal to kill invading pathogens. Indeed, these same molecules that can induce damage in mammalian tissue also can cause lethal damage to bacteria and other invading pathogens. Although very effective against pathogens, unfortunately these oxidants are not selective about which cells are destroyed, and often, significant collateral damage to mammalian tissue occurs. Then, the antioxidants enter. As previously discussed, antioxidants either present in circulation or residing in tissues help to preserve the integrity and functionality of the mammalian tissue. If antioxidant status is adequate and the inflammation is moderate, little significant or permanent tissue damage is done. However, severe inflammation or marginal antioxidant protection can lead to extensive tissue damage and permanently compromised tissue function (Zhao and Lacasse, 2008).

Antioxidants typically fall into two groups - either individual nutrients (or compounds) serve to directly quench oxidants, or enzymes containing a specific nutrient at their catalytic site serve to convert these toxic compounds to less harmful intermediates or inert end-products (Miller et al., 1993; Sordillo and Aitken, 2009). Several micronutrients

commonly supplemented to livestock serve directly as antioxidants. Tocopherols (vitamin E metabolites) and carotenoids (vitamin A precursors and metabolites) are commonly supplemented to dairy cows commercially, and compounds such as vitamin C, lipoic acid, and glutathione, while not routinely supplemented in commercial diets, are important molecules in oxidative scavenging within the animal. Other nutrients serve as antioxidants within the structure of an enzyme. Of these, selenium is perhaps the most well-studied and recognized as important by commercial nutritionists and veterinarians. Other micronutrients with important enzymatic antioxidant roles include zinc, copper, manganese, and iron. Although when incorporated into an enzyme, iron has some antioxidant activity, it is most commonly recognized to actually contribute to oxidative stress rather than alleviate it.

Vitamin E and Health

The metabolically active form of vitamin E, α-tocopherol, is a lypophyllic antioxidant that is responsible for scavenging and breaking free radical oxidative reactions at the cell membrane. This free radical scavenging prevents lipid peroxidation (damage) and is especially important for cells that that have a high degree of unsaturated fatty acids in the cell membrane. Not only do leukocytes (immune cells) have high levels of polyunsaturated fatty acids in their cell membrane, but their production of ROS to kill pathogens also makes them highly susceptible to lipid membrane damage. Weiss et al. (1990) reported that α-tocopherol concentrations are decreased in the blood of dairy cows during the periparturient period, suggesting that higher levels of vitamin E supplementation may be warranted. Smith et al. (1984) reported that prepartum dietary vitamin E supplementation resulted in a 37% decrease in clinical mastitis and decreased the duration of clinical signs of mastitis. Consistent with this finding, Hogan et al. (1992) reported that prepartum vitamin E injections increased plasma vitamin E concentrations and improved PMN intracellular killing capacity compared to cows supplemented with 1040 IU/day dietary vitamin E. These authors reported that 1040 IU/day of vitamin E was insufficient to improve indices of PMN function around the time of calving. In addition, Weiss et al. (1997) reported that 4000 IU/day for 14 days prepartum and 2000 IU/day postpartum of dietary vitamin E maintained plasma α-tocopherol levels around the time of calving. However, in contrast to the earlier study by Hogan et al. (1992), Weiss et al. (1997) reported that in addition to the 4000 IU/day prepartum treatment previously described, a treatment regime of 1000 IU/day prepartum and 500/day IU postpartum of dietary vitamin E also improved mammary clinical health compared to treatments that were below NRC recommended levels of vitamin E (100 IU/day vitamin E prepartum and postpartum). Whereas the research of Weiss et al. (1997) suggested 4000 IU/day of vitamin E prepartum might improve health, a subsequent study (Bouwstra et al., 2010) suggested that high levels of vitamin E could result in higher rates of mastitis in dairy cows. However, to date, these detrimental effects of vitamin E have not been replicated, and indeed, a recent extensive review of the research literature from the past 30 years reported that relatively high concentrations of plasma vitamin E and dietary vitamin E levels of 3000 IU/day are not associated with increased risk of mastitis or increased milk somatic cell counts **(SCC)** (Politis, 2012). Politis (2012) recommended that dry cows should be supplemented with 1000 to 3000 IU/day, lactating cows 500 to 1000 IU/day, and herds with poor mammary health should consider supplementation levels of 3000 IU/day of dietary vitamin E.

Selenium and Immune Function

Selenium **(Se)** is a trace mineral that is found in insufficient concentrations in many feedstuffs to meet animal requirements and thus must be supplemented in animal feeds in order to prevent nutritional deficiencies. Whereas vitamin E is a lypohyllic antioxidant and some selenoenzymes are membrane-bound, selenium performs much of its antioxidant function in the aqueous cellular environment. In its main antioxidant role, Se is genetically incorporated into the amino acid selenocysteine and sits at the catalytic site of free radical quenching enzymes, such as glutathione peroxidase and thioredoxin reductase, among others (Sordillo and Aitken, 2009). Although part of the immunological impact of Se is due to protection from oxidative stress, other direct mechanistic effects of Se on leukocyte signaling, trafficking, and killing have been reported (Sordillo, 2013). Several studies by one research group remain some of the most convincing regarding the role of Se in immune protection of the lactating dairy cow. In studying 32 dairy herds, Erskine et al. (1987) reported an inverse correlation between blood Se (and selenoenzymes) and herd somatic cell count SCC such that low SCC herds had high levels of Se-related variables and high SCC herds had low Se-related variables. These researchers then followed up these studies with several intramammary immune challenge studies in which lactating dairy cattle were fed diets deficient in Se (~0.04 ppm DM dietary Se) or supplemented with 2 mg Se/head/day. Whether challenged with live E. coli or S. aureus organisms, or administered E. coli lipopolysaccharide **(LPS)** to elucidate an immune response, Se supplementation, even at these modest levels of dietary supplementation, resulted in improved immune function and less severe experimental mastitis (Erskine et al., 1989, 1990; Grasso et al., 1990). As reviewed by Sordillo (2013), multiple subsequent studies have confirmed a role for Se in immune protection.

Effects of an Organic Trace Mineral Supplement Neutrophil Gene Expression

While at the University of Missouri, my lab group conducted an experiment (Revelo et al., 2014b) to investigate the effects of trace mineral supplementation from inorganic or organic sources on the global gene expression in PMN collected from dairy cows during the periparturient period. Twenty one pregnant Holstein cows entering second or greater lactation were randomly assigned to a basal diet with no added dietary Mn, Co, Cu, and Zn (basal, n = 7); supplemented with 200 mg Mn, 25 mg Co, 125 mg Cu, and 360 mg Zn from sulfate and carbonate sources (inorganic, n = 7); or supplied by amino acid complexes of Mn, Cu, and Zn, and cobalt glucoheptonate (organic, n = 7). The organic supplementation was accomplished using a combination of Avail-4® and COPRO® (Zinpro Corp., Eden Prairie, MN). Total supplementation for inorganic and organic cows was brought to 65, 15, 75, and 2.5 ppm of diet using the inorganic sources added to each gelcap for Mn, Cu, Zn, and Co, respectively. Oral treatments were administered by gelcap bolus between day 57.1 ± 1 prior to parturition until day 8 after parturition. For the results reported here, PMN were harvested from the blood of cows on day 6.4 ± 0.1 after parturition. After isolation of the cells in the lab, PMN were incubated with 0 or 50 μg/mL of Escherichia coli LPS for 120 minutes to activate the cells using a compound that would normally be present during an E. coli infection in the animal. Messenger RNA was purified from the PMN and expression of virtually all active genes within PMN was measured using high-throughput sequencing technology, a process termed RNA-Seq. The resulting digital count data were analyzed to determine

the effects of trace mineral supplementation source on the global gene expression profile of non-activated and LPS-activated PMN in the days after calving. To better appreciate the biological meaning of gene expression data, gene pathway and ontology enrichment analyses were conducted using differentially expressed genes. When compared with trace minerals from inorganic sources, organic trace mineral supplementation altered the expression of 230 and 47 genes in non-activated and LPS-activated PMN, respectively. Pathway analysis revealed that organic trace mineral supplementation (relative to inorganic) up-regulated genes that enriched the RIG-I-like receptor signaling, cytosolic DNA-sensing, and TOLL-like receptor **(TLR)** signaling pathways. The RIG-I-like receptor signaling and cytosolic DNA-sensing pathways were up-regulated in both, non-activated and LPS-activated PMN; whereas, the TLR signaling pathway was only enriched in non-activated PMN. These results suggest that the specific formulation of organic trace minerals used in this study (vs. inorganic) stimulate gene pathways involved in antigen recognition and the immune response, meaning that PMN can potentially be better equipped to identify and respond to the presence of different types of pathogens. Thus, an infection can potentially be more quickly identified, an immune response mounted, and the pathogen destroyed. This finding, that a specific dietary trace mineral formulation can affect the expression of hundreds of genes in a specific population of immune cells, is a very important finding. Further research utilizing a live pathogen challenge model to cows fed these same treatments could be useful in confirming the suggestions of these gene expression results. Of note, this research only involved the feeding of one particular formulation of the trace minerals Zn, Cu, Mn, and Co – these results should not be interpreted to mean that all trace mineral formulations would have the same effect. Different organic trace mineral formulations will have different bioavailability, and thus, may not produce the same results.

Effects of a Commercial Nutritional Supplement on Neutrophil Gene Expression

In another study from my former laboratory at the University of Missouri (Revelo et al., 2014a), we investigated the effects of a commercially available feed additive for its potential immune-modulating activity in the periparturient dairy cow. The objective of this study was to investigate the effects of OmniGen-AF® (OAF; Prince Agri Products, Quincy, IL) on the global gene expression profile of PMN. Cows received 56 g/day of either the supplement OAF (n = 5) or sham control (soybean hulls; n = 5) mixed into total-mixed rations from day 46 $\pm$ 1 before calving until day 31 after parturition. For the results reported in this paper, PMN were collected from the blood of the cows on day 7 postpartum and incubated with 0 or 50 µg/mL of E. coli LPS for 120 minutes to activate the cells using a compound that would normally be present during an E. coli infection in the animal. Messenger RNA was purified from the PMN and expression of virtually all active genes within PMN was measured using RNA-Seq. The resulting digital count data were analyzed to determine the effects of OAF supplementation on the global gene expression profile of non-activated and LPS-activated PMN in the days after calving. To better appreciate the biological meaning of gene expression data, gene pathway and ontology enrichment analysis were conducted using differentially expressed genes. Feeding OAF to periparturient dairy cows resulted in the differential regulation of 43 genes (7↑ and 36↓) in PMN upon activation with LPS. Functional annotation analysis indicated that the lysosome pathway was enriched by the genes with down-regulated expression due to

OAF supplementation. Lysosomes are involved in the inactivation, destruction, and recycling of endocytic and phagocytic particles, including pathogenic organisms (Eskelinen et al., 2003); thus, the biological relevance of a potential lower activity in the lysosome pathway in PMN collected from supplemented cows is difficult to infer. However, the periparturient dairy cow is subject to excessive inflammation during an immune response, and it is possible that a decrease in PMN lysosome inflammatory activity due to OAF could decrease the risk of tissue damage. Independent from LPS activation, OAF altered the expression of 53 transcripts (12↑ and 41↓, relative to non-supplemented controls). Pathway analysis revealed that genes with down-regulated expression enriched the oxidative phosphorylation pathway. Unlike other cells, leukocytes rely on glycolysis rather than on oxidative phosphorylation as their main source of energy under both low (hypoxic) and normal O2 conditions (Borregaard and Herlin, 1982). Therefore, one could speculate that lowering of oxidative phosphorylation activity may allow PMN to shunt oxygen toward the production of ROS for pathogen killing. Finally, OAF increased the expression of tumor necrosis factor receptor superfamily, member 17 by approximately 130%. Our laboratory previously reported that PMN from early lactation cows have reduced LPS-dependent expression of the cytokine tumor necrosis factor (Revelo and Waldron, 2012); thus, up-regulation of this receptor group by OAF may increase PMN responsiveness to inflammatory signals in periparturient cows. These results identify several potential molecular mechanisms by which OAF may influence the performance of PMN around the time of calving.

Conclusions

Cows experience immune dysfunction around the time of calving. To date, no single factor has been reported to be responsible for this immune dysfunction. Metabolites associated with negative energy balance, such as NEFA and ketones, have been reported to negatively impact immune function. Defective calcium metabolism may also contribute to periparturient immunosuppression. At this time, some of the best strategies for us to avoid losses due to infectious disease are to pay strict attention to the details of close-up and fresh cow management such that metabolic insults to the immune system are avoided. Further research elucidating endocrine, metabolic, and immune interactions around the time of calving are warranted. In addition to metabolites, many dietary nutrients are involved in immune protection and may play roles in immunosuppression. Some of these nutrients are involved in immune cell function, but many others serve to minimize damage to nearby healthy cells during the immune response by limiting inflammatory damage. Much of the potential damage caused during inflammation is due to oxidative stress – the reaction of unstable oxidizing molecules with tissue lipids, proteins, and DNA. Many of the micronutrients that are important for immune function and health serve in this role of tissue protection as antioxidants. Although many of these nutrients are known to be important for health, the quantity of these dietary micronutrients needed to maximize immune function and tissue protection is unknown. Recent studies continue to support the role of micronutrients and certain small inclusion feed additives in altering the mechanisms of immune protection. However, sound, peer-reviewed, controlled research should accompany the specific nutrient being considered to aid immune function – just as very small inclusion ingredients can

affect immune function, small differences in formulation of nutrient packages and feed additives might mean that one formulation is effective, while a similar formulation is not. Careful nutritional management to provide highly bioavailable nutritional profiles and to maximize metabolic health is currently our best strategy to maximize immune function. In addition to sound nutritional management, best management practices to maximize hygiene and minimize stressors are also crucial to helping prevent infection.

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