A Systematic Approach to Improving Transition Success

Michael A. Ballou, Ph.D.

Associate Dean for Research, Associate Professor, & Interim Chair
Texas Tech University
College of Agricultural Sciences and Natural Resources
Department of Animal and Food Sciences
Department of Veterinary Sciences

Contact: Goddard Building, Suite 108, MS 42123, Lubbock, TX 79409
PHONE (806) 834-6513, FAX (806) 742-2836, Email: michael.ballou@ttu.edu

2018 Pacific Northwest Animal Nutrition Conference Proceedings

EXECUTIVE SUMMARY

There are many factors that increase the risk for infectious diseases during the transition period. If a cow is able to adapt to all the physiological, environmental, and social changes that occur during the transition period she will be more productive during that lactation and more likely to reach the next one. Therefore, we must take a systematic approach to understand what influences immunity, so that we can increase the odds that cows will successfully navigate this important period, ultimately increasing production efficiency of the dairy.

First, we need to understand what aspects of the immune system are compromised that lead to the increased susceptibility to infectious diseases. There are many components and layers that make up a cow's immune system, including: physical barriers, antimicrobial secretions, and many cellular responses. The immune system is complicated and the competency of the system is a function of many interactions. Infections with environmental microorganisms are common around calving, primarily resulting from holes in the physical barriers of those tissues that are associated with milking and calving. Disease likely will not ensue if other aspects of the immune system can control the growth and ultimately eliminate the microorganism from that tissue. Unfortunately, other immune defenses are compromised or what I consider dysfunctional, which increases the risk the infection will develop into disease.

Cows are exposed to many potential stressors around calving, some physiological (i.e. associated with metabolic demands of lactation) and others social. If cows are overwhelmed by the number and/(or) severity of the stressor(s), various leukocyte responses may become compromised. Stressed animals were shown to have altered leukocyte responses. Cows stress about change and situations that create competition among cows can also create winners and losers, which can increase the risk for disease among some animals. Parturition and subsequent lactation are abrupt; therefore, management strategies need to try and make that change less dramatic and limit additional stressors that may interfere with the ability of the cow to adapt.

Additionally, metabolic demands of leukocytes may not be prioritized or sufficiently met around calving. Neutrophil functions of sub-clinically hypocalemic cows were reduced during early lactation. There also is evidence that elevated NEFA and BHBA concentrations have a negative

impact on immunity. Therefore, management strategies that can improve both calcium and energy homeostasis will improve the success rate of cows during the transition period.

Keywords: Health, Nutrition, Transition Cow

INTRODUCTION

The immune system is made up of many components including: various physical barriers, antimicrobial secretions, and cellular responses. A breakdown in any aspect of the immune system in the presence of a pathogen may increase the likelihood of infectious disease. It is well established that dairy cattle are highly susceptible to infectious diseases affecting many tissues during the transition period, and stress is often considered in the etiology. The word stress is commonly used, but the term itself can take on many different meanings and therefore the use is often vague or an over-generalization. As we alluded to in the previous sentence, stress is commonly referred to in the etiology of infectious disease in cows; therefore, stress is considered negative in the context of dairy cattle health. In contrast, stress is a natural, physiological response that is important in promoting a response to a threat or adaptation to a change (e.g. the transition period). Therefore, the paradox is that stress is likely both crucial for the adaptation to lactation to occur, but potentially damaging to the transition dairy cow.

This presentation will consider what are potential sources of stress for transition cows and will further describe how these potential stressor(s) influence immune defenses and risk for infectious diseases. To address this topic we will first describe the basic framework of the immune system and will briefly describe how the immune system of many transition cows differs from that of either a non-lactating or mid to late lactating cows. Then, we will attempt to define stress, describe possible stressors a transition cow may encounter, and investigate the potential role that various stressors alone or in combination influence immune defenses and risk for infectious diseases.

PERIPARURIENT COW IMMUNE SYSTEM

The principle role of the immune system is to recognize self from non-self, and in doing so protect the cow's organs against infectious, non-self microorganisms such as bacteria, virus, parasites, and fungi. The immune system is exactly that, a system, which is made up of many components. Understanding how any single measurement of the immune system influences the risk for disease is complicated because a break down in any component of the immune system may either increase the risk for disease or have no affect at all under the specific circumstances. The immune system has various layers ranging from the physical barriers to very specialized leukocyte functions. The physical barriers are often compromised (e.g. an open teat end and microbial contamination of the uterus), which contributes to the susceptibility to mastitis and uterine diseases in early lactation. However, if other components of immune system are functioning properly a mild infection is eliminated without any clinical signs of disease. An example of this was observed when Shuster et al. (1996) challenged cows intra-mammary in either early lactation, 6 to 10 DIM, or in mid lactation with the same strain and dose of *E. coli* and observed that the cows in early lactation had greater replication of the *E. coli* and developed more severe mastitis. Therefore, it is important to understand what other aspects of the immune system are compromised during the transition period that increases the risk for infectious disease.

Ballou (2012) described the immune system of many transition cows as dysfunctional. The compromised physical barriers when coupled with suppressed ability to control the growth of microorganisms in tissues increase the risk of clinical and sub-clinical diseases. Suppressed lymphocyte and neutrophil functions during the transition period are well documented in many studies from different lab groups (Guidry et al., 1976; Mallard et al., 1998; Burvenich et al., 2003). Additionally, other aspects of the innate immune system beyond lymphocyte and neutrophil functions appear to be suppressed during the transition period. Shuster et al. (1996) reported a reduced ability to control the growth of the *E. coli* in the mammary gland when the cows were challenged in early lactation, and this occurred before the recruitment of neutrophils. Additionally, Ballou et al. (2009) reported that whole blood bactericidal capacities against both an environmental *E. coli* and a pathogenic *Salmonella typhimurium* were reduced the day after calving and returned to prepartum levels by 21 DIM. In contrast, one aspect of the immune system that does not appear to be suppressed during the transition period is the inflammatory response. Lehtolainen et al. (2003) reported that cows in early lactation had greater local and systemic signs of inflammation after they were challenged with a large dose, 100 µg, of lipopolysaccharide intra-mammary. In agreement, Sordillo et al. (1995) reported greater *ex vivo* secretion of tumor necrosis factor-α when stimulated with lipopolysaccharide. These studies are important pieces of evidence for an increased propensity to produce inflammation in early lactation because both of these models did not use live microorganism challenges, but instead challenged with a fixed dose of an agonist that activates the inflammatory responses. Therefore, the immune system of a transition cow is dysfunctional because some responses are suppressed, whereas the inflammatory response appears elevated. This immunological phenotype is in contrast to a generalized immunosuppression (Ballou, 2012). This distinction is important when evaluating the role that transition period stress plays in the increased risk for disease.

ROLE OF STRESS IN PERIPARTURIENT DISEASE

Stress has for a long time been implicated in the etiology of many infectious diseases both in humans and dairy cattle, but how much does stress during the transition period actually play in the elevated risk for disease? Is the importance of stress in transition cows exaggerated? In order to establish a causal link between stress and impaired health during the transition period, there are a series of assumptions or steps that must be met, including: (1) the cow is stressed, (2) the classical stress response is elicited, (3) the duration or magnitude is sufficient to alter various immune functions, and (4) that increases the risk of getting an infectious disease, either clinical or sub-clinical. Further, alternative pathways from the first to the last step need to be considered. We will use this framework to investigate the role that stress may play in increasing the risk for infectious disease during the periparturient period.

Therefore, the first step is to understand what stresses a cow. In order to address this question we need to define stress, which is not as straightforward as one might expect. Stress is referred to in many contexts and the meaning is often subjective. Hans Selye was the first to coin the term stress in 1936 and he defined it as, "the non-specific response of the body to any demand for change”. Selye performed experiments in laboratory animals and observed consistent pathological changes in animals, lymphoid atrophy, stomach ulcers, and enlargement of the adrenal glands, in response to various psychological and physiological challenges. We will accept his original definition to evaluate what are potential stressors that a cow is exposed to during the transition period. The commonly used term, transition period, already appears to validate the first assumption that cows are exposed to stress during this time. Any transition involves change, so the next question is, what changes are taking place during this period?

Cows are not that different from humans in what causes stress. Have you ever wondered why cows are creatures of habit? It is the same reason that humans are creatures of habit or that humans are most comfortable when they are in a routine. It basically boils down to control. Change or uncertainty causes a loss of control, whether you are a human or a dairy cow. Common laboratory models of stress involve taking control away from the subject. An example would be put a loud alarm in a room housing animals that goes off randomly throughout the day. The alarm must be set to go off randomly so the subjects cannot adapt to the alarm. By setting the alarm to go off at random, the animals have no sense of control. In contrast, if the alarm goes off at a regular interval, the subjects regain control of the situation and therefore will adapt. Other common laboratory stress models include physical restrain, social re-organization, or inability to move away from a painful stimulus. If we apply the principle that a significant change can cause a loss of control and the stress response is the physiological response to help the animal regain control, then we must understand what changes are potentially stressful to transition dairy cows. Generally, the changes that occur during the transition period are primarily either psychological or physiological.

Let’s first consider the psychological or social stressors that a dairy cow may encounter during the transition period. Many potential pen moves occur throughout the transition period. Cook and Nordlund (2004) described these pen moves and how after every pen change there is the potential for social re-organizing that persists for 3 to 7 days. von Keyserlingk et al. (2008) reported increased competition at the feed bunk, decreased lying bouts, and reduced allogrooming events the day after a single lactating cow was introduced into a stable population of 11 lactating cows. The same group also observed a 9% decrease in DMI on the day that a dry cow was moved to a new pen when compared to baseline values (Schirmann et al., 2011). Further, they reported that the new cows displaced other cows at the feed bunk twice as much as they did before they were moved. The displacement behaviors are noteworthy because they indicate competition or aggressive/submissive actions. Dominant lactating cows when moved to a new pen did not change their behavior or drop milk production; however, intermediate and subordinate cows produced 3.8 and 5.5% less milk, respectively during the 2nd week after pen moves (Hasegawa et al., 1997). In contrast, Chebel et al. (2016) reported that highly dominant cows with multiple interactions at the feed bunk throughout the day were more likely to have uterine disease and be culled from the herd.

Most dairy cows are raised in confinement and the temptation to maximize facility space can result in overstocking. We’ll define overstocking as the number of cows per pen exceeds available resources (i.e. access to feed and/(or) a comfortable place to rest), which creates unnecessary competition. When management creates competition among cows, there are winners, but there are also losers. This will likely increase the risk that the subordinate or overly dominant cows will be stressed and/or have other negative health and productive outcomes.

In addition to the psychological stressors, there are many physical changes taking place in the cow during the transition period that can elicit a stress response. Nutrient and energy demands increase during lactation. Additionally, energetic demands approximately double during lactation and most early lactation cows will be in some degree of negative energy balance. Antioxidants are also used at a greater rate and can cause depletion of antioxidant stores (Weiss et al., 1997). Similarly, increased calcium output in colostrum and milk can cause a rapid drop in ionized calcium in blood, until allosteric mechanisms activate osteoclasts to mobilize calcium from bone. There is evidence that these metabolic changes during the transition period have both direct and indirect effects on leukocyte responses (Lacetera et al., 2004; Moyes et al., 2009; Zarrin et al., 2014).

It is evident from the previous discussions that dairy cows during the transition period are exposed to many changes, both psychologically and physically that are potentially stressful. However, just because something is potentially stressful or even that behaviors of cows change does not necessarily mean that cows are stressed and further that immune function is altered and disease risk increased. Silva et al. (2016) reported an increased frequency of adverse behaviors when stocking density increased; however, they did not observe any differences in leukocyte function or incidence of periparturient disease. The author's suggested that although increasing stocking density may have been a mild stressor in this population, the overall good management of this herd did not make this stressor overwhelm the ability of the cows to cope with additional stressors associated with the periparturient period.

There is good evidence that cows are exposed to many changes that are potential stressors during the transition period. Additionally, activation of the stress response occurs around parturition; however, the impacts on immunity are not completely clear. Increased risk for disease persists past the period of elevated plasma cortisol in cows as well as leukocytes may be less responsive to glucocorticoids around calving because the glucocorticoid receptor is down regulated in those cells. Therefore, future research will need to delineate between stress and alternative routes that result in increased disease risk.

ALTERNATIVE ROUTES OF INCREASED PERIPARTURIENT DISEASE SUSCEPTIBILITY

Immune responses can be metabolically expensive and requirements may be limiting for optimal function during the periparturient period. Evidence from Martinez et al. (2013) indicated that cows classified as subclinical hypocalcemic (total serum calcium less than 8.59 mg/dL) had less reactive neutrophil oxidative burst when compared to normocalcemic cows. Further, they reported increased incidences of metritis and extended days to confirmed pregnancy in the subclinical hypocalcemic cows. These data indicate that even among subclinical hypocalcemic cows, leukocyte function may be impaired and increase the risk for periparturient disease. Interestingly, in our lab if we collect blood using an anticoagulant that chelates calcium, we are unable to activate neutrophils in whole blood.

There is also evidence that elevated NEFA and BHBA concentrations have a negative impact on immunity. Lacetera et al. (2004) reported that inclusion of NEFA in cell culture media as low as 0.25 mM reduced IgM secretion. Further, they reported attenuated mitogen induced interferon-γ secretion when the cell culture media included as low as 0.125 mM NEFA. Moyes et al. (2009) induced negative energy into post-peak cows by partially restricting feed intake. The feed restriction increased plasma NEFA and BHBA to levels common among periparturient cows. The cows were challenged intramammary with an environmental *Streptococcus uberis* and pathophysiological response determined. The cows in negative energy balance had reduced neutrophil phagocytosis immediately before the mastitis challenge and had elevated acute phase protein concentrations after the challenge. This indicated that the cows in NEB had greater inflammatory response to the mastitis challenge. More recently, Zarrin et al. (2014) infused cows with BHBA to induce hyperketonemia and infused control cows with normal saline. All cows were challenged intramammary with lipopolysaccharide in order to evaluate the intensity of the acute phase response. The hyperketonemia cows had elevated acute phase protein secretion and reduced the influx of somatic cells into the mammary gland after the lipopolysaccharide challenge. The reduced influx of somatic cells into the mammary gland after an infection would increase the risk for development of mastitis and as well as the severity of mastitis.

Lastly, increased metabolic activity and leukocyte derived oxidant production during early lactation can accelerate the use of antioxidants, and if it exceeds the supply of antioxidants can result in some degree of oxidative stress. The implications of this oxidative stress can have negative impacts on the immune responses of cows and ultimately disease resistance. This will be covered in more detail by Dr. Weiss, so I'll limit my discussion of the antioxidant systems.

IMPLICATIONS

The immune dysfunction of periparturient dairy cows is complex, and appears to involve many layers of the immune system. Increased exposure of microorganisms occurs from both calving and milking; however, a competent immune system should be able to eliminate most infections without any clinical disease. Many psychological and physiological stressors appear to be involved in increasing the risk for infectious disease; however, it appears to be somewhat of a cumulative effect. Some stress is unavoidable, but the goal should be to limit additional stressors that may ultimately impair the ability of a cow to cope with the change from non-lactating to lactating. In addition to stress, changes in nutrient supply or use may impair leukocyte function and ultimately increase the risk for infectious disease. Therefore, there is not a single source of immune dysfunction during the periparurient period. Management must look at each production system separately and take a systematic approach to improving transition success.

LITERATURE CITED

Ballou, M.A. 2011. Case Study: Effects of a blend of prebiotics, probiotics, and hyperimmune dried egg protein on the performance, health, and innate immune responses of Holstein calves. Prof. Anim. Sci. 27:262-268.

Ballou, M.A. 2012. Growth and Development Symposium: Inflammation: Role in the etiology and pathophysiology of clinical mastitis in dairy cows. J. Anim. Sci. 90:1466-1478.

Ballou, M.A. 2009. Supplemental fish oil does not alter immune competence or the pathophysiological response to an intramammary infusion of endotoxin in peri-partum multiparous Holstein cows. J. Dairy Res. 76:165-172.

Burvenich, C., V. Van Merris, J. Mehrzad, A. Diez-Fraile, and L. Duchateau. 2003. Severity of E. coli mastitis is mainly determined by cow factors. Vet Res. 34:521-564.

Chebel, R.C., P.R.B Silva, M.I. Endres, M.A. Ballou, and K.L. Luchterhand. 2016. Social Stressors and their effects on immunity and health of periparturient dairy cows. J. Dairy Sci. 99:3217-3228.

Cook, N.B., and K.V. Nordlund. 2004. Behavioral needs of the transition cow and considerations for special needs facility design. Vet Clin. North Am. Food Anim. Pract. 20:495-520.

Guidry, A.J., M.J. Paape, and R.E. Pearson. 1976. Effects of parturition and lactation on blood and milk cell concentrations, corticosteroids, and neutrophil phagocytosis in the cow. Am. J. Vet Res. 37:1195-2000.

von Keyserlingk, M.A., D. Olenick, and D.M. Weary. 2008. Acute behavioral effects of regrouping dairy cows. J. Dairy Sci. 91:2007-0532.

Lacetera, N., D. Scalia, O. Franci, U. Bernabucci, B. Ronchi, and A. Nardone. 2004. Short communication: effects of nonesterified fatty acids on lymphocyte function in dairy heifers. J. Dairy Sci. 87:1012-1040.

Lehtolainen, T., S. Suominen, T. Kutila, and S. Pyörälä. 2003. Effect of intramammary escherichia coli endotoxin in early- vs. late-lactating dairy cows. J. Dairy Sci. 86:2327-2333.

Mallard, B.A., J.C. Dekkers, M.J. Ireland, K.E. Leslie, S. Sharif, C.L. Vankampen, L. Wagter, and B.N. Wilkie. 1998. Alteration in immune responsiveness during the prepartum period and its ramification on dairy cow and calf health. J. Dairy Sci. 81:585-595.

Martinez, N., L.D. Sinedino, R.S. Bisinotto, E.S. Ribeiro, G.C. Gomes, F.S. Lima, L.F. Greco, C.A. Risco, K.N. Galvão, D. Taylor-Rodriquez, J.P. Driver, W.W. Thatcher, and J.E. Santos. 2013. Effect of induced subclinical hypocalcemia on physiological responses and neutrophil function in dairy cows. J. Dairy Sci. 97:874-887.

Moyes, K.M., J.K. Drackley, J.L. Salak-Johnson, D.E. Morin, J.C. Hope, and J.J. Loor. 2009. Dietary-induced negative energy balance has minimal effects on innate immunity during a streptococcus uberis mastitis challenge in dairy cows during midlactation. J. Dairy Sci. 92:4301-4316.

Schirmann, K., N. Chapinal, D.M. Weary, W. Heuwieser, and M.A. von Keyserlingk. 2011. Short-term effects of regrouping on behavior of prepartum dairy cows. J. Dairy Sci. 94:2312-2319.

Shuster, D.E., E.K. Lee, and M.E. Kehrli Jr. 1996. Bacterial growth, inflammatory cytokine production, and neutrophil recruitment during coliform mastitis in cows within ten days after calving, compared with cows at midlactation. Am. J. Vet Res. 57:1569-1575.

Silva, P.R., K.M. Lobeck-Luchterhand, R.L. Cerri, D.M. Haines, M.A. Ballou, M.I. Endres, and R.C. Chebel. 2016. Effects of prepartum stocking density on innate and adaptive leukocyte responses and serum and hair cortisol concentrations. Vet Immunol. Immunopathol. 169:39-46.

Sordillo, L.M., G.M. Pighetti, and M.R. Davis. 1995. Enhanced production of bovine tumor necrosis factor-alpha during the periparturient period. Vet Immunol. Immunopathol. 49:263-270.

Weiss, W.P., J.S. Hogan, D.A. Todhunter, and K.L. Smith. 1997. Effect of vitamin E supplementation in diets with a low concentration of selenium on mammary gland health of dairy cows. J. Dairy Sci. 80:1728-1737.

Zarrin, M., O. Wellnitz, H.A. van Dorland, R.M. Bruckmaier. 2014. Induced hyperketonemia affects the mammary immune response during lipopolysaccharide challenge in dairy cows. J. Dairy Sci. 97:330-339.