BILL E. KUNKLE INTERDISCIPLINARY BEEF SYMPOSIUM: Impact of mineral and vitamin status on beef cattle immune function and health[1,2]

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ABSTRACT: The importance of optimal mineral and vitamin nutrition on improving immune function and health has been recognized in the preceding decades. In the southeast, beef cattle are raised predominantly on forages that may be limiting in nutrients for optimal health, especially trace minerals such as Cu, Zn, and Se. Clinical deficiencies of these nutrients produce classic symptoms that are common to several nutrient deficiencies (e.g., slow growth and unthrifty appearance); however, subclinical deficiencies are more widespread and more difficult to detect, yet may result in broader economic losses. Dietary mineral concentrations often considered adequate for maximum growth, reproductive performance, or optimal immune function have been found to be insufficient at times of physiological stress (weaning, transport, comingling, etc.), when feed intake is reduced. The impacts of these deficiencies on beef cattle health are not apparent until calves have been subjected to these stressors. Health problems that are exacerbated by mineral or vitamin deficiencies include bovine respiratory disease, footrot, retained placenta, metritis, and mastitis. Many micronutrients have antioxidant properties through being components of enzymes and proteins that benefit animal health. In dairy cattle, high levels of supplemental Zn are generally associated with reduced somatic cell counts and improved foot health, possibly reflecting the importance of Zn in maintaining effective epithelial barriers. Neutrophils isolated from ruminants deficient in Cu or Se have reduced ability to kill ingested bacteria in vitro. Supplemental vitamin E, in its role as an intracellular antioxidant has been shown to decrease morbidity in stressed calves. There is more understanding of the important biological role that these nutrients play in the functioning of the complex and multifaceted immune system. However, there is still much to be learned about determining the micronutrient status of herds (and hence when supplementation will be beneficial), requirements for different genetic and environmental conditions, understanding the bioavailability of these nutrients from feedstuffs and forages, quantifying the bioavailability of different supplemental sources of these nutrients, and identifying the impact of dietary antagonists on these nutrients.

Key words: beef cattle, health, immune response, minerals, vitamins

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INTRODUCTION

Enhancing immunity through optimizing nutrition has received increasing emphasis over the last 3 decades. Respiratory disease alone is responsible for 28% of deaths in beef calves before weaning (USDA, 2011), and 16% of feedlot cattle show signs of respiratory disease (USDA, 2013). Respiratory disease increases medication costs, reduces rates of gain, and negatively affects quality grades at harvest (Gardner et al., 1999), although segregating and feeding treat-

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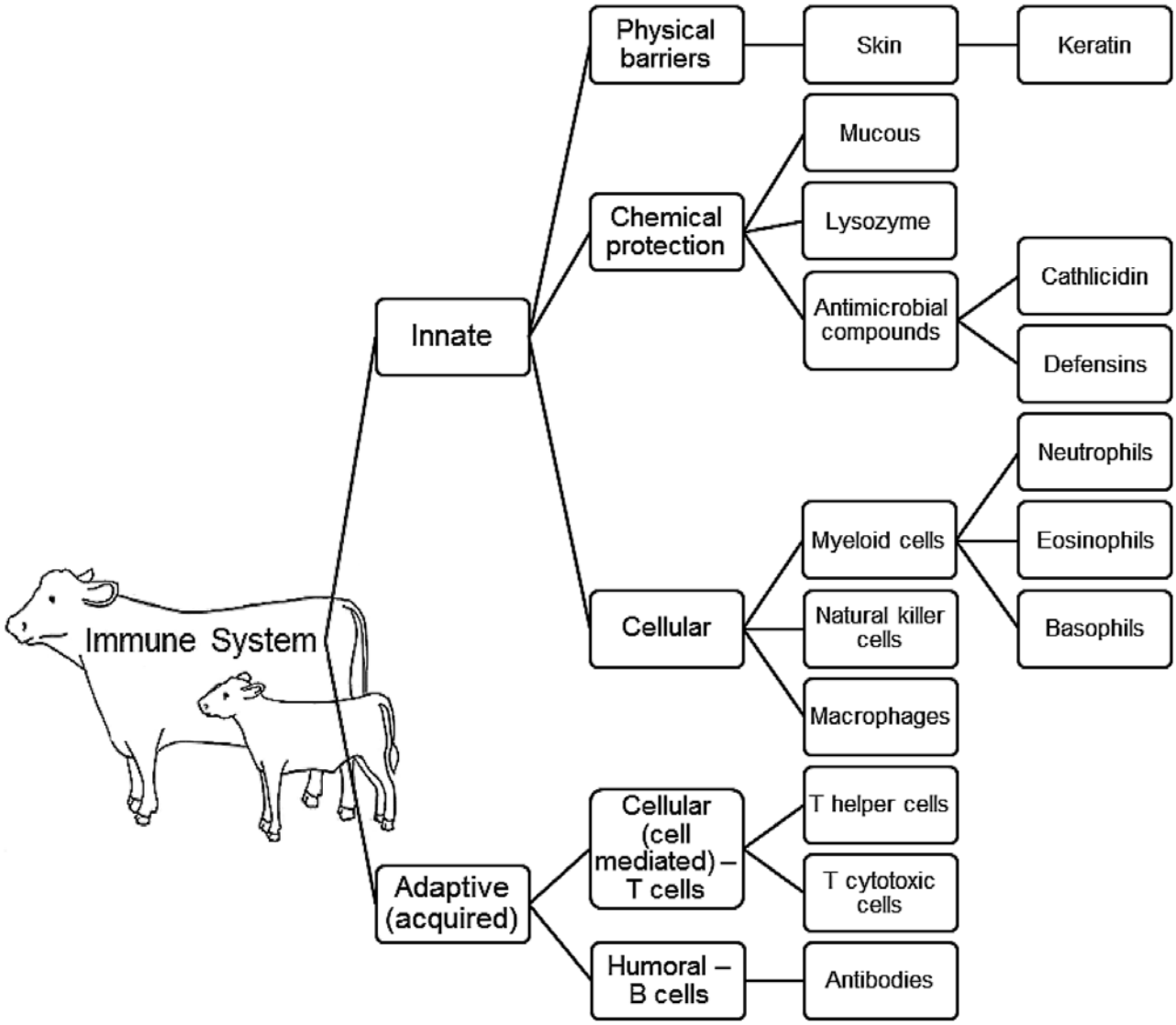

Figure 1. Overview of the immune system, as described by Abbas et al. (2015).

ed cattle a greater amount of time mitigated some of these negative consequences (Holland et al., 2010). Duff and Galyean (2007) reviewed factors both pre- and post-weaning that affect occurrence rates and outcomes of bovine respiratory disease (**BRD)** and included the status of micronutrients as factors contributing to BRD incidence.

Nutrition has long been recognized as important for maintaining health. Dietary energy, protein, mineral, and vitamin concentrations have profound effects on immune function (Beisel, 1996; Calder, 2013). Specifically, mineral and vitamin deficiencies or excesses alter various components of the immune system (Wintergerst et al., 2007; McClure, 2008). Dietary requirements for minerals and vitamins for optimizing immune function may be greater than those needed for maximal growth or reproductive performance. This is complicated by variability in the ability of cattle to retain and mobilize different micronutrients. The authors suspect that subclinical deficiencies are more widespread than clinical deficiencies and probably result in greater economic losses. Nutritional intervention cannot prevent all disease but may lessen the severity of morbidity, and incidences of mortality. Other reviews on the roles of micronutrients in immune function in ruminants include those by Galyean et al. (1999), Spears (2000), and Spears and Weiss (2014). This manuscript further reviews how optimizing micronutrient nutrition improves immune function and health.

OVERVIEW OF THE IMMUNE SYSTEM

The immune system (Fig. 1) is an extremely complex system (Abbas et al., 2015). For descriptive purposes, it can be divided into 2 branches, innate and adaptive (acquired) immunity. Both are important in mounting an

efficient immune response. Innate immunity is the first line of defense against foreign pathogens, it includes the physical barriers such as the skin, and chemicals such as mucous and lysozyme. Immune cells of the innate system initiate the inflammatory response and process and present foreign particles (antigens) to the adaptive immune system. The primary cell types of innate immunity are the myeloid cells (neutrophils, eosinophils and basophils) and macrophages. Laboratory methods of assessing innate immunity include determining differential cell numbers and measuring the chemotactic and phagocytic activity of neutrophils and macrophages.

Adaptive immunity is antigen-specific, has memory, and can be further subdivided into the cellular and humoral branches. The cellular immune system is mediated by T lymphocytes. These lymphocytes have matured in the thymus, and then reside in the lymph nodes and other lymphoid areas. Different subclasses of T lymphocytes provide the primary defense against viral infection (T cytotoxic cells), or produce cytokines (T helper cells) that enhance antibody responses, regulate the level of the immune response, or stimulate macrophages. Measures of the cellular immune response include in vitro assays of cell proliferation in response to a mitogen, such as phytohemmaglutinin (**PHA**) or concanavalin A, and measures of cytotoxic T lymphocyte response. An analysis of cell populations can be conducted through flow cytometry. Another assessment, an intradermal injection of PHA coupled with measurements of skin-fold thickness has been conducted in experiments with ruminants. This in vivo test elicits a reaction with many features of a delayed hypersensitivity response and is thought to correlate with the animal's ability to mount a cell mediated response (Tizard, 2000).

The humoral immune response is also called the antibody response. It is important for removal of bacteria, free virus particles, and soluble antigens from the body. Antibodies are proteins that are produced by B-lymphocytes and are specific for these foreign antigens. Laboratory measures of the humoral response include isotype-specific and (or) antigen-specific antibody production.

All of these branches are interrelated, and a failure in any of them will negatively impact other components of the system. Thus far, research with ruminants has mainly measured effects on immune cells that can be isolated from the blood. While these are important, they represent a small percentage of the immune cells in the body. In the future, more research will, hopefully, be done at mucosal and other immune sites in the body. Data generated in ruminants using transcriptomic and proteomic approaches are thus far limited, but this is an area of increasing research. Ultimately, rates of morbidity and mortality in production situations are what animal scientists strive to improve. Research indicates that the micronutrients (minerals and vitamins) are important in maintaining the integrity of this complex system.

Complexity is increased in ruminant nutrition because diet compositions vary in ingredients, and nutrient contents also vary within ingredients based on the growing conditions of the plant. Forages alone do not typically meet all the nutrient requirements of cattle during critical stages of production. Supplemental grain while providing important nutrients to meet these requirements can, if using co-products, also add trace mineral antagonists such as S to the diet. Davis et al. (2002) published some mineral content of forages and reported that hay samples analyzed in Arkansas were below NRC (2016) recommended levels in Se (62% of samples), Cu (52% of samples), and Zn (41% of samples), and that 34% of hay samples tested had antagonistic levels of S. In Tennessee, > 82% of the forage samples submitted were at least marginally deficient in Cu, > 73% were deficient in Zn, and > 81% had marginally antagonistic concentrations of S (Fisher et al., 2003).

In addition, this review will discuss some micronutrients (Ca, Mg, and S) where, under practical conditions, there is potential for a deficiency, acute or chronic, to affect health or physical wellbeing. For Mg and S, the effects on health are not due to direct influences on immune function. The role of Ca is complicated by its interaction with vitamin D, which could have effects on inflammation and immunocompetence.

ROLE OF MACROMINERALS

In ruminant nutrition, macrominerals are those required at > 0.1% of the diet, and include Ca, Cl, P, K, Na, Mg, and S. Whereas a clinical deficiency or excess of any of these would cause negative health consequences, the following discussion focuses on the most common concerns.

Calcium. Certainly, clinical deficiency of Ca has negative consequences on health. Chronic clinical deficiency of Ca manifests as rickets in young animals and osteomalacia in adults. Acute hypocalcemia results in parturient paresis (milk fever), a much researched and reviewed problem in mature dairy cows (Murray et al., 2008; Goff, 2014; Martin-Tereso and Martens, 2014) that is not a nutritional deficiency of Ca and is not as significant a problem in beef cows. In beef cattle, low concentrations of Ca in wheat forage have been indicated to play a role in reduced gut motility and, thus, possibly are related to incidence and severity of bloat in growing cattle grazing this forage (Horn et al., 2005).

Magnesium. Acute Mg deficiency in cool season annual forages is a practical problem (i.e., grass tetany) in beef cows and rarely in stocker cattle (wheat pasture

poisoning; Horn et al., 2005). If demand for Mg exceeds dietary supply, there is no mechanism for the animal to rapidly mobilize Mg from bone, so acute Mg deficiency leads to a tetany condition. Hypomagnesemia is exacerbated by high levels of K in feeds, such as lush forages, because K negatively affects Mg absorption (Fontenot et al., 1989; Martin-Tereso and Martens, 2014).

Sulfur. At the present time, mostly due to the use of co-product feedstuffs, excessive levels of S in cattle diets is a more common problem than deficiencies. High S is a risk factor for polioencephalomalacia, a disease affecting the central nervous system. Clinical signs are dullness, blindness (circling), muscle tremors, opisthotonos (star gazing), and death. This may be an effect of S on thiamin metabolism (thiamin deficiency will also cause this disease) or it may be a direct effect of H_2S on brain tissue.

Chronic S toxicity also results in negative interactions with other minerals. There is formation of thiomolybdates in the rumen that bind Cu making it unavailable to the animal. Pogge et al. (2014) found decreased Cu, Mn, and Zn retention in beef steers fed a high S diet (0.68%), which would result over time in deficiencies of these trace minerals. Irrespective of thiomolybdates, because S and Se have similar chemical properties, they may compete for intestinal sites for absorption or for incorporation into selenoenzymes in microbes, plants, and animals; a review of S in beef cattle diets is available (Drewnoski et al., 2014).

ROLE OF TRACE MINERALS

The trace minerals, or microminerals, are those required at dietary levels discussed in mg/kg or µg/kg DM, and include Cr, Co, Cu, I, Fe, Mn, Mo, Ni, Se, and Zn. They often have roles as components or activators of enzymes, many of which have antioxidant functions.

Zinc. In a retrospective study in 2,080 herds in France and Belgium (10,325 animals [3 to 5/herd]) Zn status was assessed based on plasma Zn, and inadequate Zn was associated with impaired locomotion in dairy herds and poor growth and diarrhea in calves (Enjalbert et al., 2006). Probably the most researched trace mineral, Zn plays a major role in disease resistance and immune responsiveness of humans (Prasad, 2000; Salgueiro et al., 2000) and laboratory animals (Gershwin et al., 1985). Research with laboratory animals indicates that Zn deficiency can impair thymus activity, lymphocyte function (particularly type 1 helper T cells important in the cell mediated immune response), natural killer cell function, antibody-dependent cell-mediated cytotoxicity, neutrophil function (decreased chemotaxis and oxidative burst; Rink and Gabriel, 2000), and cytokine production (reduced IL-2).

Zinc is a component of more than 200 enzymes and proteins, including proteins containing Zn fingers. These enzymes and proteins are necessary for protein synthesis, configuration of DNA and RNA, and carbohydrate metabolism. When activated, the specific immune system undergoes rapid cell proliferation and protein synthesis, which would require these Zn compounds. Zinc influences the activity of thymulin, a hormone that affects the development of lymphocytes in the thymus. Zinc is required to maintain enzymatic activity of inducible nitric oxide synthase and, therefore, nitric oxide production (Mocchegiani et al., 2000). Nitric oxide is important in macrophages for killing bacteria, fungi, and protozoa (Abbas et al., 2015). A Zn transporter, solute-linked carrier 39A8, also known as ZIP8, is potentially a link between regulation of nuclear transcription factor-kappa B (**NF-kB)** activity during innate immune activation and Zn metabolism (Liu et al., 2013). A transcription factor, NF-kB, is essential for cytokine synthesis.

Zinc deficiency may also weaken the first line of resistance to infection, the skin and other stratified epithelia. Zinc is required for the synthesis and maturation of keratin. Adequate Zn status has long been recognized as required for normal wound healing. In a Zn deficient animal, Zn supplementation increases the rate of epithelial tissue repair and maintains cellular integrity. Evidence for the importance of Zn in ruminants includes the effects of lethal trait A46. This is a rare genetic disorder that has been found in dairy cattle that results in reduced capacity of the intestine to absorb Zn. Calves homozygous for this trait become Zn deficient after birth and will die within 5 mo of age unless aggressively supplemented with Zn. These calves possess normal numbers of functional lymphocyte subpopulations at birth, but the activity of these lymphocytes is altered as the calves become Zn deficient (Perryman et al., 1989). Delayed wound healing is observed and infection is 1 of the more common causes of mortality in these calves (Machen et al., 1996).

Engle et al. (1997) reported that after 21 d, calves fed a basal diet containing 17 mg Zn/kg DM had a depressed response to an intradermal injection of PHA compared to calves fed the basal diet supplemented with 23 mg of Zn/kg DM. This depression in immune response occurred before any differences in plasma and liver Zn were detected. Using lambs fed a semi-purified diet (3.7 mg of Zn/kg DM), Droke and Spears (1993) reported that severely Zn-deficient lambs had reduced in vitro lymphocyte blastogenesis to PHA, but an increased response to pokeweed mitogen. Marginally Zn-deficient lambs (basal plus 5 mg Zn/kg DM as Zn oxide) did not differ from Zn-adequate lambs (basal plus 40 mg Zn/kg DM as Zn oxide) for any immune response measure.

Fraker and King (2001) proposed that as Zn becomes limiting, lymphopoiesis is downregulated while cells of the myeloid lineage (neutrophils, etc.) are pro-

tected to maintain the first line of immunity (the innate response). In early research, residual lymphocytes from Zn-deficient mice retained their functions and were possibly more potent than normal lymphocytes (Cook-Mills and Fraker, 1993). Thus, the severity and length of exposure to Zn deficiency affects the magnitude of impairment of immune function.

Research is ongoing about how the source of a trace mineral affects performance. Sources of trace minerals may have unique absorption and transport mechanisms. In steers challenged with infectious bovine rhinotracheitis virus, supplementation with Zn-methionine increased feed intake and lowered rectal temperatures compared with unsupplemented controls (Chirase et al., 1991). Calves supplemented with Zn-methionine tended to recover from disease more rapidly than calves supplemented with ZnO (Chirase et al., 1991; Chirase and Greene, 2001). In stressed calves, those supplemented with Zn-methionine and Mn-methionine before weaning and in the receiving ration had greater DM intake after arrival at the feedyard than unsupplemented controls. A group supplemented with isolevels of ZnO and MnO was intermediate and did not differ statistically from either group (Chirase et al., 1994).

The requirement for Zn in most beef cattle diets is 30 mg/kg DM (NRC, 2016). However, stressed calves are considered separately in the NRC publication and the recommended Zn concentration for these calves is 75 to 100 mg/kg DM. This recognizes that these calves typically have a reduction in feed intake, and that additional Zn may be required for optimal immune function. Galyean et al. (1995) observed a tendency for decreased morbidity in newly weaned calves supplemented with 70 mg Zn/kg DM (as either Zn sulfate or Zn methionine) vs. a basal diet (30 mg Zn/kg DM) or the basal diet supplemented with 35 mg of Zn/kg DM. George et al. (1997) found that supplementing 318 mg Zn/kg DM for 14 d and then reducing to 106 mg/kg DM (as Zn-methionine and in combination with higher levels of Cu, Mn, and Co) reduced the incidence of BRD compared with calves supplemented with 106 mg Zn/kg DM. However, Nunnery et al. (2007) found no differences in morbidity and decreased G:F in heifers supplemented with 75 mg Zn/kg DM vs. a non-supplemented control during a 35-d feedlot receiving period.

Incidence of footrot in finishing steers during a 112-d study was 20, 7, and 0% in control, Zn oxide-, and Zn methionine-supplemented steers, respectively (Greene et al., 1988). Brazle (1992) reported that Zn methionine decreased the incidence of foot rot by 55% in grazing calves (2.4 vs. 5.4%). In addition, calves supplemented with Zn methionine gained more weight during the grazing period. Moore et al. (1988) reported that hoof growth and wear were similar in dairy cows fed a control and supplemental Zn (as Zn-methionine) diet during a 1-yr study; however, they observed improved hoof scores for texture, heel cracks, and interdigital dermatitis in Zn methionine-supplemented cows. In a summary of 12 trials, lactating dairy cows supplemented with Zn (180 to 400 mg/d) as Zn-methionine had lower somatic cell counts (196 vs. 294 $\times$ 10^3 cells/mL; Kellogg et al., 2004). These changes in the incidence of footrot and the level of somatic cell counts may reflect the importance of Zn in maintaining effective epithelial barriers at these sites. Zinc is required for the incorporation of cysteine into keratin (Hsu and Anthony, 1971). The keratin lining of the teat canal protects the teat from bacterial invasion (Nickerson, 1985). Keratin is lost during the milking process and must be regenerated to maintain this protective barrier (Capuco et al., 1992).

Copper. Inadequate Cu status, as assessed based on plasma Cu concentrations, was associated with poor calf performance and health (Enjalbert et al., 2006). Copper deficiency results in decreased humoral, cell-mediated and non-specific immune function in many species (Stabel and Spears, 1990). Although the exact biochemical role has not been determined, Cu is required for a number of enzymes involved in energy or antioxidant metabolism and for electron transport proteins (Bonham et al., 2002). However, research in ruminants is complicated by the fact that Cu deficiency is often associated with high concentrations of the Cu antagonists, Mo, S, and (or) Fe. The effects of high levels of these minerals often cannot be differentiated from the effects of low Cu.

Neutrophils from Cu deficient lambs (Jones and Suttle, 1981) and calves (Boyne and Arthur, 1981; Torre et al., 1996) had reduced ability to kill ingested bacteria in vitro. These neutrophils had decreased activity of the Cu metalloenzyme, superoxide dismutase. Ceruloplasmin and superoxide dismutase, Cu-containing enzymes, have anti-inflammatory activity. Superoxide dismutase prevents oxidative tissue damage from superoxide radicals. Impaired microbicidal activity may also be a direct result of decreased concentrations of hydrogen peroxide radicals produced by superoxide dismutase-mediated reduction of superoxide radicals. Hydrogen peroxide radicals are utilized by the neutrophil myeloperoxidase system for the formation of powerful oxidizing agents, such as hypochlorous acid, and for generation of hydroxyl radicals, also potent oxidizers (Stabel and Spears, 1990). Although this has not always been observed, Arthington et al. (1995) found no difference in neutrophil bactericidal activity in heifers marginally deficient (55 d on a low Cu and high Mo diet) or adequate in Cu, based on liver Cu concentrations.

Saker et al. (1994) reported enhanced monocyte function in growing beef calves supplemented with

Cu-lysine as compared with controls fed no supplemental Cu (16 vs. 7 mg of Cu/kg DM). Monocytes from Cu-lysine supplemented calves had enhanced oxidative burst and phagocytic activities (Saker et al., 1994). A trend for decreased tumor necrosis factor production by monocytes from calves fed levels of Mo that are antagonistic to Cu (Gengelbach and Spears, 1998), and lower plasma tumor necrosis factor concentrations after an infectious bovine rhinotrachitis virus challenge in calves supplemented with Mo (Gengelbach et al., 1997) compared with Cu adequate calves have been observed.

Ward et al. (1993) reported that prolonged exposure to Mo (10 mg/kg DM) and S (0.2%) decreased in vivo cell mediated immune function in feeder cattle as measured by an intradermal injection of PHA. However, supplementation of Cu (5 mg/kg DM as Cu sulfate or Cu lysine) to steers with adequate Cu status did not improve animal performance or affect antibody production to ovalbumin, or impact in vivo cell mediated immune response (intradermal PHA). In another study, Cu supplementation (5 mg/kg DM for 133 d) increased antibody titers to ovalbumin (Ward and Spears, 1999). In addition, when transportation stress was applied, stressed calves supplemented with Cu had increased humoral response to pig red blood cells and increased delayed type hypersensitivity reaction to dinitrochlorobenzene; however, Cu depressed these responses in unstressed cattle (Ward and Spears, 1999). Supplemental Mo (5 mg/kg DM) did not affect any immune response measurement in calves, even though plasma Cu and erythrocyte superoxide dismutase were decreased (Ward and Spears, 1999). Antibody responses tended to be enhanced by Cu supplementation (either 10 or 20 mg supplemental Cu/kg DM to a control diet containing 7 mg/kg DM) in growing Angus steers; however, the response varied by the antigen administered (Dorton et al., 2003). Results with ruminants indicate little effect of Cu deficiency on specific immune function. While their specific immune function tests were not different (antibody production to pig red blood cells and in vitro lymphocyte blastogenesis), 33% of the calves fed the high Mo diet died or were removed from the study due to disease, versus no calves fed control, high iron, or supplemental Cu, indicating the importance of Cu to the entire immune system (Ward et al., 1997).

Copper deficiency altered the acute-phase protein response in cattle (Arthington et al., 1996, 2003). Copper is a component of ceruloplasmin, one of the acute phase proteins. After a bovine herpes virus-1 inoculation, plasma ceruloplasmin concentration increased in control (Cu adequate) calves, but did not change in calves Cu deficient due to antagonistic levels of dietary Mo. In contrast, fibrinogen, an acute phase protein that does not contain Cu, increased in Mo-supplemented but not in control calves (Arthington et al., 1996).

Studies investigating the effect of supplemental Cu in the receiving ration have generally found no benefits on health (Galyean et al., 1995; Beck et al., 2002). However, sheep that are Cu deficient have decreased resistance to bacterial infection (Woolliams et al., 1986). Muehlenbein et al. (2001) found no effect of supplemental Cu from 45-d before to 60-d after calving in 2-yr-old cows on passive transfer of immunoglobulin or calf health; control cows were Cu deficient based on liver Cu concentrations.

Selenium. Selenium deficiency, as assessed by red blood cell glutathione peroxidase activity, has been associated with retained placenta in cows. Both marginal and deficient Se status were associated with poor health due to infectious disease in calves (Enjalbert et al., 2006).

Selenium has been shown to affect health in many species. However, the nutritional requirements and mechanisms of action remain poorly defined. Selenium is a component of glutathione peroxidase, an important water-soluble antioxidant found in the cytosol of cells. Selenium deficient cattle have decreased neutrophil bactericidal activity (Boyne and Arthur, 1979 and 1981). Glutathione peroxidase may be needed indirectly along with glutathione reductase to provide NADPH for the respiratory burst. If the respiratory bursts were compromised, there would be reduced free radical generation and, thus, decreased killing capacity in Se-deficient neutrophils (Suttle and Jones, 1989). In general, Se status does not appear to impair the ability of bovine neutrophils to engulf microorganisms, but it does decrease their microbicidal activity after ingestion (Finch and Turner, 1996). On d 22 post-weaning in vitro macrophage phagocytosis was enhanced in calves supplemented pre-weaning with high Se-yeast but not Na selenite as compared to controls (Beck et al., 2005).

Reffett et al. (1988) observed that Se deficient calves had a reduced humoral immune response after a viral challenge. But in this study feed intake and rectal temperatures were not affected by Se status. In cattle, supplemental Se has enhanced antibody response to hen egg lysozyme inoculation (Swecker et al., 1989). Selenium-supplemented sheep had a greater antibody response to tetanus toxoid (Moksnes et al., 1988).

Selenium deficiency has been correlated with increased incidence of metritis in dairy cows (Harrison et al., 1984). Selenium supplementation reduced the severity and duration of acute coliform mastitis caused by *E. coli* (Erskine et al., 1989) but not *Staphylococcus aureus* (Erskine et al., 1990). The difference may be due to the nature of the pathogenesis

of staphylococcal infection versus *E. coli* infection. *E. coli* grows quickly, eliciting a large neutrophil influx into the mammary gland, which is enhanced by Se. *Staphylococcus aureus* grows more slowly and does not elicit an acute inflammatory response, and there was no benefit from Se. This highlights the complexity of the immune response and how different pathogens try to evade it. Rate of clinical mastitis was negatively correlated with plasma Se concentrations in 9 dairy herds in Ohio (Weiss et al., 1990).

Hall et al. (2013) fed calves alfalfa hay harvested from land that had been fertilized with various levels of sodium selenite; all of the Se-enriched forages (0.95 to 3.26 mg Se/kg DM) exceeded recommended Se concentrations (0.10 mg Se/kg DM; NRC, 1996). Weaned calves were fed a control alfalfa hay (0.07 mg Se/kg DM) or Se-enriched alfalfa hay for a 7-wk backgrounding phase, then calves were shipped to a commercial feedlot where a common diet was fed. Over the following 27 wk in the feedlot, fewer cattle that had been fed the Se-enriched alfalfa hay during backgrounding died from BRD (5 vs. 36%).

Chromium. Four of 8 studies with stressed beef calves have shown beneficial effects of supplemental organic Cr on morbidity and (or) growth (NRC, 1997). Lymphocytes from lactating cows fed supplemental Cr produced lower concentrations of IL-2, interferon-γ, and tumor necrosis factor-α after stimulation in vitro (Burton et al., 1996). This agrees with Myers et al. (1997) who found that pigs supplemented with Cr-picolinate had lower serum concentrations of tumor necrosis factor-α after an endotoxin challenge. These pigs exhibited fewer of the negative metabolic effects associated with endotoxin challenge, and these results support the hypothesis that Cr is immunomodulatory. Bernhard et al. (2012) observed a tendency for a reduction in clinical BRD in receiving cattle supplemented with 0.3 mg/kg Cr-propionate. They found a linear improvement in ADG of cattle from d 0 to 56 from the control diet with 0 mg/kg supplemental Cr, and 0.1, 0.2, and 0.3 mg/kg supplemental Cr.

Cobalt. Cobalt deficiency results in reduced lamb survival (Fisher and MacPherson, 1991) and increased the susceptibility to parasitic infection in lambs and cattle (Ferguson et al., 1989; MacPherson et al., 1987). A reduction in neutrophil function was apparent after 10 wk of receiving a low Co diet and before a depression in weight gain was observed after 40 wk for Co-deficient calves (Paterson and MacPherson, 1990). Minimal research has been conducted on the effects of varying Co concentrations in beef cattle diets; thus, precise requirements for optimal immune response are unknown. Interestingly, an increase in the dietary requirement for Co was the only change to the mineral requirements in the updated nutrient recommendations for beef cattle (NRC, 2016).

Combinations of trace minerals. Supplemental trace minerals from injection have reduced the incidence of BRD in highly-stressed, newly-received stocker cattle (Richeson and Kegley, 2011), with a concurrent improvement in ADG and G:F. However, in cattle that were never stressed, the use of an injectable trace mineral did not affect ADG from 28 d preweaning to harvest and no cattle were treated in either group for BRD (Kegley et al., 2011). There was no benefit to performance or health from an injectable trace mineral given to beef calves 28 d before weaning when calves had continual access to dietary trace mineral supplementation, were weaned and grazed on their ranch of origin, and were shipped to the feedlot and fed altogether. The use of an injectable solution of trace minerals (Cu, Zn, Mn, and Se) concurrently with vaccination enhanced the antibody response to bovine herpesvirus-1, but not bovine viral diarrhea virus (Arthington and Havenga, 2012). Similarly, Arthington et al. (2014) found that use of an injectable trace mineral solution (Cu, Zn, Mn, and Se) increased the antibody response to a novel antigen (porcine red blood cells) in heifers.

Offering cow-calf pairs access to free choice mineral that included supplemental Cu, Mn, Zn, and Co from organic complexes or sulfates (at twofold the levels of the organic complexes) resulted in fewer calves offered the organic complexes requiring treatment for BRD after weaning than calves from the sulfate-supplemented pairs, unsupplemented calves were intermediate (Grotelueschen et al., 2001). However, post-weaning morbidity results are potentially confounded for the unsupplemented calves because a portion of the calves on this treatment had been fed supplemental feed due to a lack of forage availability because of drought; this preweaning acclimation to feed probably reduced weaning stress and thus decreased their susceptibility to BRD.

Ahola et al. (2005) supplemented cows with Cu, Zn, and Mn from 80 d pre-calving through 120 d post-calving and followed the weaned calves to the feedlot, where they stayed on similar dietary treatments. A negative control received no supplemental Cu, Zn, and Mn; and 2 supplemental treatments were formulated to receive NRC (1996) recommended levels of supplemental Cu, Zn, and Mn as sulfates or a combination of sulfates and mineral proteinate sources. Researchers reported no differences in antibody response to vaccinations, in vivo cell mediated immune response, or morbidity rates [although overall morbidity rate was low (14.8%)].

Several experiments supplementing combinations of trace minerals in the diets of receiving cattle have been conducted. Dorton et al. (2006) supplemented Cu,

Zn, Mn, and Co from 2 sources (sulfates or amino acid complexes) for 30 d of on-farm backgrounding and a 28 d feedlot receiving period, and they found no differences in morbidity or mortality rates. Ryan et al. (2015) found no effects of source of trace mineral (Zn, Cu, and Mn from sulfates, organic amino acid complexes, or hydroxyl sources) on BW gain or morbidity during the receiving period; however, in a previous study Kegley et al. (2012) observed a greater final weight in receiving cattle supplemented with organic amino acid complexes versus sulfates. Sharman et al. (2008) compared trace minerals (Cu, Zn, and Mn) from sulfates and Co carbonate versus iso-amounts of Cu, Zn, Mn amino acid complexes and Co glucoheptonate and found no effect on growth performance or percentage morbidity.

ROLE OF VITAMINS

The majority of research on the influence of vitamins on immunocompetence has focused on their roles as antioxidants. Oxidants, including free radicals, are products of many metabolic activities and can damage animal tissues. Oxidants are produced at greater levels during detoxification of many chemicals and with exercise, stress, tissue injury, and infection (Nockels, 1996). Under these conditions, the ratio between antioxidants and these reactive oxygen metabolites may become unbalanced, and the structural and functional integrity of cells would be compromised. Peroxidation of fatty acids in cellular membranes reduces the fluidity of cell membranes. This decreased fluidity appears to decrease the ability of lymphocytes to respond to immune challenges (Bendich, 1993). Vitamin E and the carotenoids have been most often studied as to their role in immune function. With the possible exception of vitamin E, there has been minimal research conducted in cattle, particularly beef cattle, on the effect of supplemental vitamins on immune function.

Vitamin E. Vitamin E is the primary fat-soluble antioxidant in the body; it is concentrated in membranes both within and surrounding the cell. In laboratory animals, a vitamin E deficiency impairs macrophage and natural killer cell activity (Erickson et al., 2000). Supplementation with vitamin E generally potentiates their antibody responses (Finch and Turner, 1996). Although Horn et al. (2010) increased calf circulating α-tocopherol concentrations 24 h after birth by supplementing the dams with 1000 IU/d for 6 wk pre-partum through breeding season, they found no benefit in calf health or immune function between unsupplemented controls (who were still considered adequate based on serum tocopherol concentrations) and calves from supplemented dams. In dairy cattle, in most studies supplementation with vitamin E improved neutrophil killing activity (Smith et al., 2000). Supplementation of 740 mg vitamin E/d with or without supplemental Se throughout the dry period reduced the incidence and duration of clinical mastitis at calving (Smith et al., 1984).

Summarizing the results of 5 research trials (1,106 calves), Secrist et al. (1997) reported that supplementing the diets of newly-received cattle with vitamin E concentrations from 450 to 1,600 IU daily tended to reduce morbidity from 55 to 48%, and numerically improved ADG and feed efficiency, although results from individual studies varied. Gill et al. (2000) conducted a study with a large number of calves (502) and reported that 1,600 IU/d of supplemental vitamin E in the receiving period tended to reduce the number of sick pen d/calf by 15.6% (2.7 vs. 3.2 d/calf) and morbidity (37.5 vs. 43.3%). Rivera et al. (2002) observed an increased humoral immune response in calves supplemented with vitamin E. In contrast, Rivera et al. (2003) reported that receiving calves fed supplemental vitamin E (570 IU E/d for 5-d) were treated more often for respiratory disease than calves drenched or injected with vitamin E (2,850 IU) on feedlot arrival. In another trial, Rivera et al. (2003) observed an increased febrile response during an IBRV challenge in calves supplemented with the greatest concentration of vitamin E (1,140 IU/d). Carter et al. (2005) found decreased medical costs when supplemental vitamin E (2,000 IU/d from d 1 to 28 after feedlot arrival) was used. In summary, doses > 400 IU/d seem beneficial for decreasing BRD morbidity and possibly increasing ADG (Duff and Galyean, 2007). In contrast, Cusack et al. (2009) conducted a meta-analysis using 35 published experiments and concluded there was no benefit on morbidity by feeding or administering vitamin E as an injection above the NRC (1996) recommendation.

Carotenoids. Beta-carotene is a vitamin A precursor that is the most potent naturally occurring quencher of singlet oxygen. In laboratory animals, a vitamin A deficiency impairs natural killer cell number and activity and reduces the production of reactive oxidative molecules in neutrophils (Erickson et al., 2000). Beta-carotene generally has a stimulatory activity on bovine lymphocyte blastogenesis and enhances the killing ability of bovine blood neutrophils in the peripartum period (Chew, 1996). Dairy cows supplemented with 300 or 600 mg β-carotene 4 wk before calving had enhanced in vitro intracellular killing of bacteria by blood neutrophils, as well as a reduced incidence of retained placenta and metritis than control cows (Michal et al., 1994). A typical ruminant diet contains many different carotenoids that have not been studied as to their effect on immune function, including lutein and lycopene (Chew, 1993).

There are a limited number of controlled studies investigating effects of dietary vitamin A concentra-

tions for receiving cattle. Low vitamin A compromised antibody response to an inactivated bovine coronavirus vaccine given on d 112 to feedlot calves (Jee et al., 2013). Restricting vitamin A for 141 d did not affect antibody response to an ovalbumin vaccine (Gorocica-Buenfil et al., 2008).

Vitamin D. Vitamin D has an important role in modulating the inflammatory response in nonruminants (Barreda et al., 2014), being a regulator of gene expression, and low serum 25-hydroxyvitamin D_3 was associated with reduced killing capacity of macrophages (Liu et al., 2006). Cattle monocytes produced the active form of the vitamin (1,25-dihydroxyvitamin D_3) in response to bacterial challenge through toll-like receptor signaling (Nelson et al., 2010), and this locally-produced 1,25-dihydroxyvitamin D_3 upregulated genes involved in the innate immune system (Nelson et al., 2010; Merriman et al., 2015). Newly-published research (Nelson et al., in press) challenges assumptions that beef cattle are generally adequate in vitamin D because of exposure to sunlight and concentrations in forages; these researchers found that whereas all cows had adequate serum 25-hydroxyvitamin D_3, most newborn calves (spring-born) had low serum 25-hydroxyvitamin D_3. The effect on calf immune function has not been determined.

Biotin. Hoof health improved when cattle were supplemented with 10 to 20 mg of biotin/d (Spears and Weiss, 2014). In beef cattle, there was a reduction in the percentage of heifers with vertical fissures (sand cracks) when supplemented with biotin at 10 mg/d (Campbell et al., 2000).

SUMMARY AND CONCLUSIONS

Duff and Galyean (2007) summarized published research on the effect of supplementing trace minerals to receiving cattle and found, at best, the responses were mixed for Cu, Zn, and Se; and there had been minimal research for Mn. These mixed responses are derived from interactions between nutrients in typical ruminant diets, differences in bioavailability of micronutrients (both in the basal diet and from supplemental sources), unknown micronutrient status of test animals (hence variations in body stores), variations in pathogens, and genetic variation in cattle. More is not always better; Berrett et al. (2015) reported improved G:F in cattle fed no supplemental trace minerals throughout the feedlot phase. This negative control diet contained 58 mg Zn, 7 mg Cu, and 26 mg Mn/kg DM, and was compared with diets supplemented with an additional 30 mg Zn, 10 mg Cu, 20 mg Mn/kg DM, or with 100 mg Zn, 20 mg Cu, and 50 mg Mn/kg DM from varying sources. More basic research that increases the ability to quantify micronutrient status and that effect on response to supplementation is needed. More information is needed on the contribution of basal feeds to micronutrient status, as well as information on the bioavailability of supplemental micronutrients.

Parturition and weaning are stressful events during which cattle eat less; thus, mineral and vitamin levels in the diet need to be increased to accommodate this. Results are variable on whether there is an increased demand for these nutrients at this time. Once cattle get to the feedlot, it is potentially too late to influence immune status during the most stressful time. Therefore, mineral supplementation is needed at the home ranch to mitigate many of these effects. Thus, minerals and vitamins are an investment in an insurance policy to ensure optimal calf performance.

Finally, consider that in mice an avirulent virus has been shown to develop virulence, due to mutations in the viral genome, as a consequence of replicating in a Se-deficient host. These mutated viruses will infect Se-adequate mice (Beck and Matthews, 2000). The hypothesis is that the increased oxidative stress of the host, due to a lack of antioxidant protection, influences the change in virulence or a lack of interferon-γ mRNA production in the Se-deficient animals (Beck and Matthews, 2000). Thus, we are not just feeding the calf, we are altering how that calf interacts with all pathogens in its environment.

Zinc, Cu, Se, vitamin E, and carotenoids are essential for optimal immune function. These trace minerals and vitamins are (or are a part of) important antioxidant systems in the body. Basic research indicates that they have additional roles as enzyme components in other critical pathways. Results from research with ruminants have varied because of the complex interactions that occur between micronutrients in the diet, as well as during absorption and retention of the nutrient. In addition, various pathogens interact differently with the complex immune system. While nutrient requirements for some aspects of immunity may be greater than those required for growth, some aspects of immune function probably have a high priority for nutrients and would not be depressed until a severe deficiency existed.

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