The impacts of disease on nutritional requirements and performance of lactating cows

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ABSTRACT

Mastitis continues to plague the dairy industry. Management strategies have greatly reduced the incidence of contagious mastitis and in recent decades the microorganisms often isolated are environmental Enterobacteriacae, particularly *Escherichia coli* and *Streptococcus uberis*. The epidemiology of clinical mastitis indicates that the highest relative risk of infection is during either dry-off or colostrogenesis, but the infection remains quiescent until early lactation, when clinical disease manifests. The pro-inflammatory response is part of the coordinated response of the host with the primary goal to eliminate the invading pathogen. Therefore the host shifts from performance to survival. Many pro-inflammatory mediators, including, cytokines, chemokines, and eicosanoids, are at least partly involved in mediating both the local and systemic effects of mastitis. Reduced milk production, changes in milk composition, and decreased reproductive efficiency are all putative biological tradeoffs occurring during clinical mastitis. The pro-inflammatory mediators have both local and systemic effects influencing the performance and altering the nutritional status of cows during and following clinical mastitis. The systemic effects include reduced dry matter intake, hyperthermia, and changes in whole-body nutrient partitioning, which decreases substrate availability for milk synthesis; whereas the local effects include the nutrient requirements of the activated leukocyte pool, decreased synthetic capacity of mammary epithelium independent of substrate availability, and lastly the loss of milk components because of damage to the milk-blood barrier. This paper will discuss the nutritional costs of: immune protection, disease, and the recovery from disease; as well as discuss potential strategies to ameliorate these metabolic expenses.

INTRODUCTION

Clinical mastitis among peripartum dairy cows has severe economic impacts on the dairy industry. Recent estimates are that each case of clinical mastitis costs the producer $179 (Bar et al., 2009), and the cost could be even more, as Santos et al. (2004) reported an average loss of milk production of 671 kg of milk over that entire lactation among cows that developed clinical mastitis in early lactation. In addition to lost milk production, lost income is also due to discarded milk, increased cull rate, pharmacologic costs, and increased labor. Therefore, the cost of clinical disease is economically expensive, and the pro-inflammatory response to infection is responsible for much of the loss associated with clinical mastitis. The pro-inflammatory response is imperative in controlling the spread of an infection as well as the eliminating the invading pathogen. However, if the pro-inflammatory response is either excessive or unnecessary it can compromise the survival and/(or) productivity of cows. The pro-inflammatory mediators have pluripotent effects on tissues that control the whole-body response to the infection, and these responses contributes to costs of disease.

TRADEOFF BETWEEN PERFORMANCE AND SURVIVAL

Innate Immune System

The innate or non-specific immune system is the first line of defense against pathogens and is comprised of physical barriers, microbiostatic or microbicidal secretions, and effector immune cells. My discussion will focus solely on the nutritional costs associated with the innate immune system because it is known that the costs associated with the adaptive immune response are minimal when compared to the innate immune response. The low nutritional costs associated with the adaptive immune response are evident when animals are vaccinated; where most of decreased performance of animals is actually associated with the innate inflammatory response to the adjuvants or the modified live pathogen used in the vaccine.

The physical barriers of the immune system protect the internal environment from microbial laden external environment. The physical barriers of the immune system include: skin, closed teat end, mucous, pH, antimicrobial peptides, and normal microbiota. A disruption in any of these physical barriers greatly increases the relative risk for developing an infection and disease.

Once a pathogen evades the physical barriers, the innate immune system will initiate an immune response with the goal of localizing and eliminating the infection through the recruitment of effector leukocytes, such as neutrophils, and other antimicrobial compounds. The innate immune response is initiated through the recognition of conserved structures on pathogens called pathogen-associated molecular patterns (PAMP). When tissue resident cells of the immune system recognize these PAMP the cells secrete various pro-inflammatory mediators including: chemokines, cytokines, and eicosanoids. These various inflammatory mediators can act either locally or systemically and again the primary goal is the recruitment of effector leukocytes and antimicrobial compounds to the infection. Recruitment of neutrophils during a bacterial infection is imperative in controlling the growth and eliminating the bacteria (Burvenich et al., 2003). Neutrophils move to the infection site by following a chemokine concentration gradient and recognize the pathogens either by the PAMP or other immune factors called opsonins, which have recognized and coated the pathogen. In many cases, ligation of a neutrophil with a bacteria leads to phagocytosis and subsequent enzymatic or oxidative death of the pathogen. The inflammatory mediators synthesized by the tissue resident immune cells activate the phagocytic and killing capacities of neutrophils (Simms and D'Amico, 1997). Therefore, a competent innate immune system limits the access of pathogens to the internal environment and if a pathogen does invade the local immune cells recruit effector leukocytes, such as neutrophils, as well as other antimicrobial factors that help control the growth and eliminate the pathogen. In many situations, although animals are constantly exposed to microorganisms, a competent innate immune system keeps the host free of disease. The nutritional costs of maintaining a competent immune system has been an area of debate and remains an area not well understood (Klasing, 1998; Lochmiller and Deerenberg, 2000). I lean toward the hypothesis that the nutritional costs of maintaining a competent immune system is minimal relative to the expense of maintenance and/(or) performance of animals (Klasing, 1998). This is based on data that reports that immune tissues make up less than 5% of the total body mass (Klasing, 1998) and the amount of ATP used by leukocytes per mg protein is not

excessively great (Pithon-Curi et al., 2004). Interestingly though, data indicate that the energetic demands of the peripartum cow contribute to the suppressed neutrophil function observed during the peripartum period (Kimura et al., 1999). However, it is unknown whether the suppressed neutrophil function is a direct effect of reduced substrate availability or through an indirect mechanism. This is an area that warrants further research.

Disease

As discussed previously the economic costs of infectious disease are great (Santos et al., 2004; Bar et al., 2009). Infectious disease occurs when an infection is associated with specific symptoms such as: pain, swelling, achiness, and fever. An infection can be cleared without any clinical signs of disease if a relatively small number of microorganisms evade the physical barriers of the innate immune system. However, if a larger number of bacteria are present or the pathogens become systemic the production of the inflammatory mediators increases and causes clinical disease. Burvenich et al. (2003) reported that the concentration of environmental *E. coli* was the predominant determinant of the severity of clinical mastitis in peripartum cows. In addition, Ballou et al. (2011) reported that the intensity of the inflammatory response was related to the dose of *E. coli* during a systemic challenge. The inflammatory mediators that were imperative in recruiting and activating the influx of neutrophils and other antimicrobial compounds are also responsible for the clinical signs of infectious disease (Bannerman, 2009). In addition, to influencing leukocyte recruitment and activation, the inflammatory mediators have pluripotent effects on many tissues within the body that will influence the performance and health of dairy cows (Table 1).

Table 1. Effects of inflammatory mediators on net tissue metabolism

TISSUE	EFFECTS
Immune	Increase glycolysis
	Increase glutaminolysis
Neural	Supress appetite
	Increase thermogenesis
Adipose	Increase net lipolysis
	Decrease lipoprotein lipase
Skeletal Muscle	Increase protein degradation
	Decrease protein synthesis
	Increase glycogenolysis
Hepatic	Increase gluconeogenesis
	Increase glycogenolysis
	Increase acute phase protein synthesis

There are many inflammatory mediators secreted during clinical disease and much is still unknown regarding the precise influence of each mediator and to complicate the picture further,

many of the inflammatory mediators have redundancies, synergies, stimulatory, or inhibitory relationships with the other inflammatory mediators. This coordinated physiological response, known as infectious disease, is thought of as a biological tradeoff between performance and survival (Lochmiller and Deerenberg, 2000). During pathogen invasion, the primary goal is to eliminate the pathogen without compromising the survival of the host; therefore, the host diverts nutrients away from performance and toward the immune system (Table 1). The secretion of inflammatory mediators increases during clinical mastitis (Bannerman, 2009) and is likely involved in changes in behavior, reduced dry matter intake, alterations in nutrient partitioning, breakdown of milk-blood barrier, and decreased synthetic capacity of mammary epithelial cells (Oliver and Calvinho, 1995; Ballou, 2012). This whole body coordination by the inflammatory mediators favors immune protection over performance and we will see that we can partition the effects of the inflammatory response into local versus systemic responses.

LOCAL VERSUS SYSTEMIC RESPONSES

The mammary gland is an excellent model to partition the systemic and local effects of the inflammatory response because the 4 quarters of a cow's mammary gland are independent from one another. Therefore, the gland that is diseased reflects both the systemic and local effects of the inflammatory response; whereas the non-diseased gland(s) exhibit the systemic effects only. The systemic and local effects of the inflammatory response are shown in Table 2. Generally, the systemic response contributes to the acute inflammatory response; whereas local effects persist even after signs of systemic disease have ameliorated (Hoeben et al., 2000; Ballou, 2007).

Table 2. Systemic and local effects of the inflammatory response during mastitis

SYSTEMIC	LOCAL
Reduced dry matter intake and absorption of nutrients	Energetic and nutrient requirements of leukocytes
Hyperthermia	Paracellular leakage of milk components
Changes in systemic nutrient partitioning decreasing nutrient availability for mammary epithelial cells	Decreased synthetic capacity of mammary epithelial cells - independent of nutrient availability

Systemic

Dry matter intake is consistently reduced during clinical mastitis and contributes to the reduced milk production (Hogan et al., 1992; Ballou et al., 2007). An apparent paradox is observed, dry matter intake is reduced at the same time energetic and nutrient demands of the immune system are increased. A suppressed dry matter intake during inflammatory challenges is conserved across species, and even mild inflammatory challenges, such as vaccination, reduce dry matter intake. Kyriazakis et al. (1998) postulated two hypotheses to explain the benefits of anorexia during disease. One of the hypothesis states that that the reduced dry matter intake helps

promote a catabolic state, which in itself may be an effective immune response. The other hypothesis (not necessarily mutually exclusive from the first) was that the reduced dry matter intake allows the animal to be more selective in its diet; thereby reducing the risk for further infection. Regardless, of the host benefit, reduced dry matter intake is a significant contribution to the reduced performance and nutritional cost of disease.

The use of metabolizable energy (ME) for the febrile response further decreases the available ME for maintenance and product formation. If the cow does not mobilize more retained energy to meet the increased energy requirements associated with the febrile response, milk energy production will decrease. Data from lipopolysaccharide induced mastitis suggest that during the acute inflammatory response cows will compensate for the reduced ME by suppressing production rather than further compromising their energy balance (Waldron et al., 2006; Ballou, 2007). However, the compensation was predominantly a local response, and in the absence of the local inflammatory effects, the systemic inflammatory response would further compromise the energy balance of peripartum cows (Ballou, 2007). Quantitative estimates on the energetic costs of the inflammatory response have ranged from 10 to 23% increase per degree increase in Celcius (Banet, 1981; Marais et al., 2011) in rats and birds. Septic humans had approximately a 40% increase in net energy for maintenance requirements during the first week of disease (Plank and Hill, 2000). The increased energy maintenance requirements will be fueled partially with mobilized amino acids from skeletal muscle and the remainder from carbohydrates and lipids.

As evident in Table 1, generally the inflammatory mediators induce a catabolic state in both adipose tissue and skeletal muscle with a concomitant increase in hepatic protein synthesis and gluconeogenesis (Waldron et al., 2003; Ballou et al., 2008). As we'll discuss in a few paragraphs activated leukocytes require energy and nutrients and the animal's body will repartition nutrients toward immune tissues. Animals typically become insulin-resistant during disease, which may be a mechanism to ensure that glucose remains available for insulin-independent leukocytes (Chiolero et al., 1997). Most glucose metabolized by leukocytes is anaerobic (Pithon-Curi et al., 2004); therefore, at least part of the increased gluconeogenesis is from lactate (Waldron et al., 2003). In addition, carbon skeletons following deamination of amino acids from skeletal muscle also likely contribute to the gluconeogenic pool. In response to an intra-mammary lipopolysaccharide challenge, lactose secretion was decreased in both diseased and non-diseased quarters (Ballou, 2007). The suppressed lactose secretion was predominately a local effect; whereas systemic effects only contributed 34 and 8.5% of the total effect at the 1^{st} and 2^{nd} milking following the challenge, respectively. Quantitatively that was a 14.3 and 4.3% reduction in milk production due to systemic effects at the 1^{st} and 2^{nd} milking, respectively.

Studies on the ability of septicemic animals to use lipids as an energy source have not yielded definitive conclusions. Hypertriglyceridemia, hypoketonemia, and decreased lipoprotein lipase and carnitine palmitoyltransferase activities are often observed following lipopolysaccharide challenges (Takeyama et al., 1990). Therefore, there is strong evidence that whole body utilization of lipids does not contribute significantly to meeting the energy demands associated with disease. Wolfe et al. (1985) reported that 17% of the production of CO_2 of septicemic dogs could be accounted for by very low density lipoprotein fatty acid oxidation. The

hypertriglyceridemia during disease may have an energy-independent beneficial mechanism, as plasma lipoproteins were reported to detoxify lipopolysaccharide (Harris et al., 1990).

The increased hepatic protein synthesis is associated with a repartitioning of which proteins are being synthesized. During disease, hepatocytes increase the secretion of acute phase proteins, which play a role in host defense and repair, and decrease the synthesis of other proteins such as albumin. Much of the amino acids required for the synthesis of the acute phase proteins are supplied from the net efflux of amino acids from skeletal muscle. Inflammatory cytokines directly promote catabolism of amino acids from skeletal muscle (Humphrey and Klasing, 2005). Septic laboratory rodents had approximately a 40% increase in muscle protein degradation (Hobler et al., 1998). As discussed previously, not all the amino acids from skeletal muscle will be used for acute phase protein synthesis. Some of the amino acids will be deaminated and the carbon skeletons used as gluconeogenic substrates. Nitrogen excretion as urea is elevated in septicemic animals and was approximately 160% (Carlson et al., 1977) and 200% (Ballou et al., 2008) above baseline in septicemic humans and calves, respectively. The yield of milk proteins decreased in both diseased and non-diseased quarters following an intra-mammary lipopolysaccharide challenge (Ballou et al., 2009). At the first milking post-challenge, 86% of the decrease in milk protein yield was attributable to systemic effects; whereas at the 2nd milking only 35% was due to the systemic effects. The decreased milk protein yield, due to systemic effects only, were 19.4 and 13.9% at the 1st and 2nd milking following the challenge (Ballou et al., 2009). Therefore, during the acute response to lipopolysaccharide, decreased substrate availability, through repartitioning of nutrients, contributes to the decreased milk protein yield.

Local

The local production of inflammatory mediators increases vascular permeability, with the goal of increasing the recruitment of effector leukocytes and other antimicrobial compounds to the site of infection. This is known as breakdown of the blood-milk barrier, and is evident by the increase in milk bovine serum albumin concentrations, which in a healthy gland is low because this protein is not synthesized in the mammary gland. The increased vascular permeability decreases the secretion of milk components because synthesized milk components can also leak into blood, which is evident by increased excretion of urinary lactose during mastitis. The breakdown of the blood-milk barrier is rapid, but does not quantitatively contribute to the local reduction in milk production because the increased milk bovine serum albumin concentrations peaks prior to the maximal local suppression in both lipopolysaccharide and *E. coli* mastitis (Shuster et al., 1991; Vandeputte-Van Messom and Burvenich, 1993; Ballou, 2012).

As discussed previously, activated leukocytes, require energy and nutrients for oxidation and biosynthetic reactions, which are met through the repartitioning of nutrients away from growth. Quantitative estimates of leukocyte metabolism in cows are not known, but estimates can be inferred from glucose utilization by rodent neutrophils (Ballou, 2012). Briefly, glucose utilization by neutrophils has ranged from 460 to 1,000 nmol of glucose h^{-1} mg of $protein^{-1}$ (Newsholme et al., 1996; Pithon-Curi et al., 2004). Using somatic cell count data from mastitic cows it can be estimated that 19.9 to 43.2 g of glucose are required per day to fuel the activity of the milk somatic cells (Ballou, 2012). As noted by Ballou (2012), this is likely an overestimation

because the assumption was that the milk somatic cells were present and active in the mammary gland over the entire 24 h period. Regardless, the estimated amount of glucose required by the milk somatic cell counts is low when compared to the reduction of 275 g of glucose synthesized by the diseased mammary gland (Ballou, 2007). This data support the notion that the local increase and activity of milk somatic cell counts during mastitis is not a major sink for glucose.

In addition to glucose, activated leukocytes and cells near activated leukocytes have elevated utilization of antioxidants (Hogan et al., 1996; Batra et al., 2000). This response is due to the large quantity of reactive oxygen species produced by neutrophils during the oxidative burst, which is an important bactericidal mechanism. The redox status of an animal is the balance between the antioxidant potential and the amount of reactive oxygen species present. Therefore, the large production of reactive oxygen species during disease may deplete antioxidants and shift the redox balance in favor of an oxidative stressed state. Many nutrients are themselves antioxidants (α-tocopherol, ascorbic acid, and retinol) or components of antioxidant systems (selenium, copper, zinc, and manganese). It remains to be determined how much of each of these nutrients is used during mastitis and this information will be important in determining these nutrient recommendations during and the recovery from mastitis. This is an area that warrants further research, as a prolonged period of oxidative stress may contribute to chronic diseased states as reduced concentrations of antioxidants is associated with an impaired immune competence (Hogan et al., 1993).

Inflammation causes local damage to host tissues and the recruited population of neutrophils is responsible for much of the injury. As noted in the previous paragraph, neutrophils produce a large quantity of reactive oxygen species during the oxidative burst. Furthermore, neutrophils contain lysosomes that contain many degradative enzymes. Both the oxidative and enzymatic pathways are important in the antimicrobial activity of neutrophils. Capuco et al. (1986) reported that neutrophils damage mammary tissue. Phagocytizing neutrophils produced more damage than necrotic neutrophils, which were more lethal than resting neutrophils. These data support that mammary gland epithelial cells are damaged during clinical disease when neutrophils are recruited and actively phagocytizing invading microorganisms. Both the secretion of glucose and milk proteins decreased in the diseased quarter, independent of the systemic effects due repartitioning of whole body metabolism previously discussed (Ballou, 2007). It remains to be determined if the local production of inflammatory mediators acts directly at reducing milk component synthesis or if the effect is primarily driven by tissue damage. Infusing 100 μg of recombinant bovine tumor necrosis factor-α into a mammary gland decreased the synthesis of the major milk proteins, casein, α-lactalbumin, and β-lactoglobulin. The exact reason for the persistent local effects on milk secretion is not known, but damage to the mammary epithelial cells fits within the temporal model.

Mastitis is metabolically expensive and is partly mediated by inflammatory mediators at both the local and systemic levels. A better understanding of both the local and systemic effects of the inflammatory response during clinical mastitis will help develop management strategies that can limit the adverse effects of mastitis on the lactational performance and survivability of peripartum cows.

STRATEGIES TO ATTENUATE METABOLIC COSTS OF MASTITIS

Inflammatory mediators are important in the recruitment and activation of immune defenses against invading microorganisms, but they are also implicated in the reduced lactational performance and health of mastitic cows. Potential strategies to limit the adverse effects of mastitis obviously include reducing the incidence of disease through management strategies that limit the number of microorganisms and/(or) improve immune responses. However, additional approaches include attenuating the inflammatory response or enhancing the recovery of the secretory capacity of mammary epithelium. I will focus on the later 2 strategies below; for a more complete review see Ballou (2012).

Immunization against rough mutant strains of gram-negative bacteria has become common management practice during the dry period over the past 2 decades (González et al., 1989; Hogan et al., 1992). The J5 mutant of *Escherichia coli* has been used as a dry cow vaccine and cows develop adaptive immunity to the inflammatory lipopolysaccharide core antigen. Cows vaccinated against the J5 mutant had a 5-fold reduction in the likelihood of developing clinical mastitis (González et al., 1989). In addition, Hogan et al. (1992) reported that vaccinating dry cows with the J5 mutant did not reduce the number of gram-negative infections, but did reduce the number of clinical cases of mastitis from 66.7 to 20%.

Additional strategies to limit the interaction of lipopolysaccharide with host cells; thereby reducing the inflammatory response focused on the administration of either soluble CD14 protein (Lee et al., 2003) or polymyxin B (Ziv and Schultze, 1983). The ligation of lipopolysaccharide with a soluble binding protein increases the affinity for membrane-bound CD14 protein, and activation of the inflammatory response is initiated through this interaction. The soluble form of CD14 protein attenuates lipopolysaccharide induced production of tumor necrosis factor-α (Haziot et al., 1994). In the study by Lee et al. (2003), concurrent intramammary administration of soluble CD14 protein and 50 colony forming unit of a live *E. coli* improved neutrophil recruitment and the clearance of the *E. coli* when compared to cows challenged with *E. coli* only. The exact mechanism of the improved neutrophil response remains to be determined. Polymyxin B is a bactericidal antibiotic that also neutralizes lipopolysaccharide. Administration of polymyxin B delayed and attenuated the inflammatory response when cows were challenged intramammary with lipopolysaccharide (Ziv and Schultze, 1983).

Pharmacological strategies to reduce the production of inflammatory mediators produced through the cyclooxygenase and lipooxygenase pathways have been studied during mastitis. Nonsteroidal anti-inflammatory drugs had positive effects on limiting the clinical pathogenesis, but had limited or no effects on lactational performance (Burvenich and Peeters, 1982; Shpigel et al., 1994; Banting et al., 2008). In addition to pharmacological strategies, supplementing omega-3 fatty acids from fish oil decreased the production of cyclooxygenase derived inflammatory mediators (Mattos et al., 2004). However, supplementing 250 grams of fish oil during the prepartum period and 0.91% of the dry matter during the postpartum period did not influence either the clinical or lactational performance of multiparous cows when they were challenged with 100 µg of lipopolysaccharide intramammary at 7 days in milk (Ballou et al., 2009). However, the dose of fish oil supplemented by Ballou et al. (2009) was approximately 42 and 53% of the dose supplemented by Mattos et al. (2004). More research is need using rumen protected fish oil supplements and mastitis models with smaller doses of lipopolysaccharide and live pathogen challenges before definitive conclusions can be drawn on the role omega-3 fatty acids may play in limiting the inflammatory response.

The administration of recombinant bovine somatotropin (rBST) has galactopoietic actions on mammary epithelial cells; therefore, rBST may reduce the lactational effects of mastitis. Cows prophylactically treated with rBST had attenuated clinical disease and improved lactational performance when challenged with *Streptococcus uberis* (Hoeben et al., 1990) or *E. coli* (Vandeputte-Van Messom and Burvenich, 1993). However, the improvements in the pathogenesis of disease could not be differentiated between an enhanced immune competence or the galactopoietic actions or both of rBST because Vandeputte-Van Messom and Burvenich (1993) observed a more rapid recruitment of neutrophils when cows were treated with rBST. In addition to prophylactic treatment with rBST, Vandeputte-Van Messom and Burvenich (1993) also treated cows with rBST only after clinical signs of disease were observed. They observed only a small, 5% increase in the recovery of milk production from the diseased gland when cows were treated with rBST. In contrast, they reported that the normalization of milk composition from diseased quarters among cows that were classified as severe responders was more rapid when they were treated with rBST, which suggests that the integrity of the blood-milk barrier was restored more quickly. More research is needed on the role that treatment with rBST plays in reducing the pathogenesis and improving the recovery from mastitis.

IMPLICATIONS AND FUTURE RESEARCH

Mastitis continues to plague peripartum dairy cows and greatly decreases the profitability of the cow. The inflammatory response, although it is an essential innate immune response, is responsible for a lot of the decreased performance and survivability of the cow. The metabolic costs of maintaining a competent immune system are likely not excessively great when compared to maintenance and production; however, disease is metabolically and nutritionally expensive. The inflammatory response during mastitis has both systemic and local effects that contribute to the suppressed performance and health. A better understanding on the contributions of the systemic and local effects to the overall reduced performance and which inflammatory mediators are playing the major roles will aid in developing new prophylactic and therapeutic treatments. Future research should also address the nutritional demands of the cow during and following clinical mastitis as this likely influences the pathogenesis of the disease.

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