Inflammation and Behavioral Changes in Cattle

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We have all heard this story from a producer: “I just got a load of them in last week, gave them all their shots and here we go again. Just look at them! Heads down, not moving around, not eating or drinking, they just look rough. We treated three head yesterday evening and all of them had a fever. Looks like another 10-15 today…typical pneumonia, again!”

While listening to this producer explaining his woes, you might find yourself nodding in agreement. As a mixed set of light weight, highly stressed, sale barn-origin animals that were recently shipped 1000 miles to their new home, the signs and timing are right for pneumonia to occur. We have conditioned ourselves to expect calves with these symptoms to have “typical pneumonia”.

Understanding “Sickness Behavior”

Cattle, like other mammals and humans, have developed a complex adaptive response to a variety of diseases or illnesses. This response is called “sickness behavior.” Sickness behavior is highly evolved in animals in order to combat viral, rickettsial, protozoal and bacterial infections and related toxins. When animals were in their wild state, this was absolutely necessary for their survival. Does the same response apply to today’s typical sick calf? You bet! Animals responding to severe local or systemic inflammation will have a fever, muscle weakness, lethargy, malaise (generally expressed by reluctance to move around or associate with herd mates), groom less, lie down more (saves energy and increases sleep) and will go off feed and drink less (Borderas, 2008). These behaviors offset more metabolically expensive behaviors such as grazing or walking to water and decrease energy loss while increasing heat production. We now know that many of these signs of sickness are caused by pro-inflammatory cytokines, primarily interleukin-1β (IL-1β), interleukin – 6 (IL-6), tumor necrosis factor alpha (TNFα) and gamma interferon (IFN-γ) acting in the brain (Dantzer, 2001, Kelley, 2003).

Cytokines are any number of substances secreted by virtually all nucleated cells in the body, particularly cells in the immune system, such as macrophages in the lung. During an infection like pneumonia, immune cells recognize a pathogen, or in the case of gram negative organisms, endotoxin produced by the pathogen and become activated. At both a local and systemic level, activated immune cells need to communicate with one another. Cytokines act to facilitate intercellular communication by regulating the animal’s responses to infection, further activation of the immune system, inflammation and injury.

Some cytokines can be anti-inflammatory while others particularly those that induce sickness behavior are pro-inflammatory (Dinarello, 2000). Anti-inflammatory cytokines work to keep the reactivity of pro-inflammatory cytokines in check, thus preventing extensive tissue damage. Anti-inflammatory cytokines are more associated with the Th2 or humoral side of the immune response while pro-inflammatory cytokines are more associated with Th1 or the cellular immunity side of the immune response (Elenkov, 2009). During trauma or infection, the circulating concentration of a pro-inflammatory cytokine like IL-6 can increase up to 1000X. Pro-inflammatory cytokines accelerate inflammation by causing the synthesis of cellular adhesion molecules and chemokines that attract and hold inflammatory cells (neutrophils early and monocytes, macrophages and lymphocytes, later in the process) locally at the site of infection. Along with nitric oxide and prostaglandins, pro-inflammatory cytokines released from activated immune cells create the classical signs of inflammation: redness, heat, swelling and pain. When circulating systemically, cytokines initiate the synthesis of acute phase proteins such as haptoglobin, fibrinogen, ceruloplasmin and amyloid A in the liver that are critical to pathogen inactivation, coagulation and immune cell recruitment. Pro-inflammatory cytokines have the ability to induce fever by activating blood monocytes, tissue macrophages and other white cells to release endogenous pyrogens into the circulation (Hart, 1988).

While necessary to overcome an infection or resolve an injury, this cascade of pro-inflammatory responses comes at a metabolic cost to the animal (Baracos, 1987). The immune system response requires vast amounts of energy for tissue repair, increased metabolism and for fever maintenance. Yet, fever alters eating and drinking behavior. Cattle with pneumonia spend less time eating and drinking (Sowell, 1999, Buhman, 2000) and have reduced feed efficiency (Jim, 1993). This phenomenon is occurring at the same time that the animal's response to a febrile condition is increasing protein and energy metabolism (Howard, 1972). This is especially critical in newly arrived cattle as they are already in a negative protein and energy balance due to transitional changes in the rumen following transportation and dietary changes.

On the one hand, cattle try to reduce heat losses during a time of fever by postural changes such as lying down and tucking up, piloerection of the hair and shifting blood flow from the skin to deeper organs, yet are increasing heat production through shivering and in the case of young calves, brown fat metabolism. A prolonged response to infection leads to muscle breakdown for gluconeogenesis to help fuel energy requirements and to release amino acids for the production of immunogloblulins, the proliferation of lymphocytes and the synthesis of collagen for tissue repairs (Hart, 1988). The net being that if an animal survives a disease event and initial metabolic losses, at harvest additional economic losses can still occur due to the effect of the inflammatory process associated with an earlier disease event on subsequent carcass traits, particularly fat deposition (Larson, 2005).

Understanding the chemical and metabolic creation of "sickness behavior" in cattle raises a fundamental question: "Is the problem described in the opening paragraph detailing clinical signs in newly arrived and processed calves specific for pneumonia?" The answer is no. Cattle dramatically change the way they behave following *any* infection or trauma. In their 2002 book, *Clinical Examination of Farm Animals* (Jackson and Cockcroft, 2002), the authors describe numerous common clinical conditions of cattle with clinical signs similar to those described in the above scenario. As a note to the reader, the authors of this book advise under the respiratory section, "Some of the signs may be encountered in diseases of other systems and regions." What we as health care providers look for are changes in an animal's behavior that indicate an animal is sick or becoming sick. We assume it is pneumonia because it generally is in highly stressed calves during the first 45-days after weaning or arrival at a feeding facility.

In a recent discussion with Dr. Tom Noffsinger, whose practice has incorporated lung auscultation as part of their respiratory case workups, they have found that 20-25% of weaned calves and 30-50% of yearling cattle in feedlots initially pulled for treatment for respiratory disease have no or minimal lung sounds attributable to pneumonia at their initial examination (Noffsinger, personal communication, 2009). So why do the cattle look sick? The cattle may be in the early stages of a viral illness or responding to inflammation in other tissues or organs. This may be further supported in part by findings at slaughter where significant percentages of cattle previously treated for bovine respiratory disease (BRD) had no residual lung lesions (Bryant, 1999, Gardner, 1999, Thompson, 2006). Findings such as those of Leite *et al.* (Leite, 2002) suggest the presence of inflammatory cytokines contribute to the growth and pathogenicity of *Mannheimia haemolytica* setting the stage for later pneumonic episodes.

Other "Sickness Behavior" Contributors

A basic contributor to why cattle may be showing "sickness behavior", yet not actually having pneumonia at this point in time is the unintended consequences of the management procedures used in the operation. A number of injectable products commonly used at processing are pro-inflammatory. These include, but are not limited to, clostridials, oil-based vaccines, certain other adjuvated products, vitamin/mineral products, antibiotics (particularly those containing glycerol formal or propylene glycol), bacterins and avermectins (Rasmussen, 1978, Stokka, 1994, Rae, 1994, Troxel, 2001, Eco Animal Health Bulletin, 2009).

While acting singularly, these products may not contribute to the amount of inflammation that could cause a cascade of the inflammatory response (Buhman, 2000). The use of multiple pro-inflammatory products coupled with the use of products potentially containing endotoxins such as Salmonella, Mannheimia, Pasteurella, E. coli, Histophilus, Morexella, Brucella, Campylobacter, Leptospira and Fusobacteria vaccines could induce "sickness behavior" as small amounts of endotoxins cause dramatic behavioral and immunological changes (Borderas, 2008, Carroll, 2009).

Other factors can be major contributors to "sickness behavior". Severe injection site reactions can make an animal more reluctant to move to the feeder or water when other animals are present. This is an avoidance mechanism due to the pain response at the injection site, particularly the neck region. Age at weaning may influence the inflammatory response as six-month-old beef calves respond more aggressively as evidenced by higher acute phase proteins than do eighty-day-old calves, thus making the older calf more susceptible to subsequent health issues (Carroll, 2009).

Stacking onto this elevated state of pro-inflammatory response are the effects of transportation and related injuries and pain-inducing management procedures such as castration and dehorning (Mitchell, 1988, Hoffman, 1998, Stanger, 2005, Rust, 2007). Recent evidence suggests that receiving diets may also contribute to a pro-inflammatory state as elevated acute phase proteins have been associated with increasing energy in rations and modulation by the use of omega 3 fatty acids (Alexander, 1998, Duff and Galyean, 2007, Ametaj, 2009).

We are continuously asking a great deal of newly arrived cattle. We routinely train cattle health care providers to let the cattle tell us when something is wrong with them. We do it by close observation of clinical signs the cattle may be presenting. We are rapidly discovering that cattle display "sickness behaviors" that may indicate that they are ill, but we cannot assume that it is BRD and be arbitrarily treating or revaccinating. Our management practices may actually be a contributor to their "ill-health".

If you have any questions about sickness behavior, inflammation or any changes in the health of your cattle, please contact your veterinarian or animal health care provider.

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