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Review of BRD pathogenesis: the old and the new

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Abstract

The pathogenesis of bovine respiratory disease (BRD) is determined by a complex interaction of environmental, infectious, and host factors. Environment trends could impact feedlot cattle by increasing their level of stress. The polymicrobial nature of BRD produces synergies between infectious agents that can alter pathogenesis. However, the nature of the host response to these environmental and infectious challenges largely determines the characteristics of the progression and outcome of BRD.

Keywords: bovine respiratory disease, pathogenesis, host response

The fundamental concept of the pathogenesis of BRD in newly arrived feedlot cattle is relatively well defined. Stress and adverse environmental conditions predispose the animal to infection with a virus or other agent that damages respiratory mucosa and alters host immunity, so that commensal bacteria become pathogens and produce fibrinopurulent bronchopneumonia. The purpose of this brief review is to highlight a few specific topics of current interest regarding the environment, infectious agents, and the host that are relevant to the pathogenesis of BRD.

Environment

Intensive management contributes to many of the stressors that predispose cattle to BRD (e.g. crowding, shipping, food and water access, and exposure to multiple pathogens). Feedlot capacity has progressively shifted toward larger feedlots (>31,999 head) compared with smaller feedlots (MacDonald and McBride, 2009). Concurrently, global consumption and demand for beef is projected to increase over the next 10 years (Westcott and Trostle, 2014). These trends suggest that there will be continued pressures for intensive management, which will possibly increase exposure of cattle to known and unforeseen management stressors in the future.

Extreme weather (e.g. very high temperatures, decreased or excessive rainfall, and severe storms) has increased during the past 10–30 years and is projected to continue to increase (Coumou and Rahmstorf, 2012). Extreme events could increase challenges to cattle due to heat stress, dust or mud, high or low humidity, changes in pest and disease distribution, and altered impacts on services that support the feedlot industry (e.g. cattle inventories, and feed and water quality and supply; Henry *et al.*, 2012).

Regulatory issues related to climate change, environmental quality, and antimicrobial use could also impact the feedlot environment. Livestock reportedly account for 18% of the total climate change-associated global anthropogenic greenhouse gas emissions and contribute substantially to air and water pollution, land degradation and water shortages, and loss of biodiversity (Steinfeld *et al.*, 2006). Antimicrobial use in animal production is considered to contribute to antimicrobial resistance of human pathogens (Anonymous, 2014). Regulations to reduce greenhouse gas emissions, or to reduce emergence of antimicrobial resistance, could have substantial impacts on the characteristics of the feedlot industry and the stressors encountered by feedlot cattle.

Agents

'Stressed' cattle are more susceptible to the influence of contagious or commensal agents associated with BRD. Common viral components of BRD (e.g. bovine herpesvirus-1 (BHV-1), bovine parainfluenza virus 3, bovine respiratory syncytial virus (BRSV), bovine viral diarrhea virus (BVDV), and possibly bovine coronavirus), typically contribute to pathogenesis by

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damaging respiratory mucosa and by modifying the host innate and adaptive immune responses (Hodgins *et al.*, 2002). Many virus infections are self-limiting and predominately serve to promote secondary bacterial infection, but others may cause severe disease due to differences in host susceptibility and the heterogeneity that exists between strains of some BRD-associated viruses.

Common BRD-associated bacteria (e.g. *Mannheimia haemolytica* (MH), *Pasteurella multocida* (PM), *Histophilus somni* (HS), and *Mycoplasma bovis* (MB)) are commensals that most likely exist in healthy cattle as biofilms (Panciera and Confer, 2010). Some combinations of BRD-associated bacteria occur together in commensal polymicrobial biofilms, most notably HS and PM (Elswaifi *et al.*, 2012). The cooperative community of the biofilm creates an environment in which the bacteria co-exist with the host and are protected against toxins, antimicrobials, and other adverse substances, or agents (McDougald *et al.*, 2012). Bacteria in biofilms often down-regulate virulence factor production, but alteration of the biofilm microenvironment (e.g. changes in nutrient concentrations, hypoxia, high or low temperatures, and other stressors), can trigger dispersal of large numbers of planktonic (free-living) forms, which quickly convert to a virulent phenotype (Landini *et al.*, 2010; McDougald *et al.*, 2012). Biofilm dispersal is one mechanism by which commensal BRD-associated bacteria could become pathogenic and colonize deeper portions of the lung. Colonization of the upper respiratory tract by HS is the most efficient when phosphorylcholine is expressed on its surface lipooligosaccharides (LOS) (Elswaifi *et al.*, 2012). However, when phase-variable loss of phosphorylcholine expression occurs, the bacteria disperse from the biofilm and invade systemically. A similar situation may occur with capsular expression by MH. The capsular characteristics of typically non-virulent MH serotype 2 from the nasal cavity of normal calves may reflect a colonizing phenotype more likely to exist in a commensal biofilm. In contrast, the capsular characteristics of more virulent MH serotype 1 isolated from pneumonic lungs may represent a planktonic form dispersed from the biofilm.

Once established in the lung, bacteria are responsible for inflammation and bronchopneumonia associated with severe BRD. Bacteria associated with BRD damage the host by virtue of a variety of virulence factors and the host response to these factors (Panciera and Confer, 2010). Notable among the virulence factors are leukotoxin and lipopolysaccharide of MH (Singh *et al.*, 2011), LOS and immunoglobulin-binding protein A of HS (Agnes *et al.*, 2013), and variable surface proteins of MB (Caswell *et al.*, 2010). Similar to BRD-associated viruses, there is considerable strain variation within these bacteria which is sometimes reflected in differences in disease severity.

The polymicrobial nature of BRD determines many events in the pathogenesis of pneumonia. Enhanced or altered pathogenesis can occur due to the synergistic effects of various combinations of BRD-associated agents to cause more severe disease than that caused by either agent alone. Some combinations of agents that result in enhanced disease include MH with MB, BHV-1 or BVDV (Leite *et al.*, 2004; Caswell *et al.*, 2010; Ridpath, 2010), HS and BRSV (Gershwin *et al.*, 2005), and MB and BHV-1 (Prysliak *et al.*, 2011). The various combinations of virulence factors can cause direct host injury, but these synergisms also alter host responses involved in pathogenesis (e.g. enhancement or inhibition of cytokine production, alteration of cell surface receptors, activation or inhibition of neutrophil and macrophage functions, and immunosuppression and interference with immune functions) (Srikumaran *et al.*, 2008; Caswell, 2014).

Host

There are inherent anatomical, physiological, and immunological features of the bovine that make it more prone to pneumonia, such as a large amount of respiratory dead space volume and poor collateral ventilation, pulmonary intravascular macrophages, and high numbers of circulating gamma–delta T cells (Ackermann *et al.*, 2010). Within the lung, antimicrobial peptides, cytokines, activities of epithelial and inflammatory cells, and other innate or acquired immune responses are the resources available to prevent BRD (Ackermann *et al.*, 2010). However, these responses can fail or create adverse effects in response to a multitude of environmental and infectious pulmonary challenges (Caswell, 2014).

Innate responses are often considered an important source of damage to the lung during the pathogenesis of BRD. Most commonly incriminated is an excessive and poorly regulated pro-inflammatory response to BRD agents that can cause extensive cell and tissue injury. However, in some cases it may be the lack of an anti-inflammatory balance in the host response that enhances disease. In a mouse model of viral–bacterial synergism, viral involvement caused fatal disease even when the bacterial infection was controlled by the immune system (Jamieson *et al.*, 2013). Fatality and severe disease in this study was proposed to be due to an impaired ability to tolerate and manage tissue damage partially due to down-regulation of genes involved in tissue protection and repair. In bovine bronchial epithelial cells co-infected with BHV-1 and MH, a gene involved in wound healing, fibrosis, and apoptotic functions of inflammatory cells (CYR61), was up-regulated less than pro-inflammatory genes by the co-infection compared with either agent alone (N'jai *et al.*, 2013). The inhibition of pro-inflammatory NF-kappa B signaling and stimulation of secretion of anti-inflammatory substances by macrolide antibiotics is considered to be one reason for their effectiveness in treatment of BRD (Fischer *et al.*, 2014). The complex interactions between the pro- and anti-inflammatory components of the host response are critical aspects of BRD pathogenesis. The optimal situation is to strike a balance between a pro-inflammatory host response that eliminates the agents of BRD, without causing excessive tissue injury that could overwhelm anti-inflammatory responses that are necessary for healing and repair of the damaged lung.

Multi-institutional and United States Department of Agriculture Agricultural Research Service projects using large numbers of cattle are underway to determine the genetics of resistance to BRD, the results of which could have major implications for improving host responses to BRD in the future.

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Observational phenotypes (e.g. breed, treatment rates, lung lesions, and production parameters) are generally associated with low heritability for resistance to BRD (Snowder *et al.*, 2005). However, more specific criteria based on host response or accurate estimates of disease incidence could be more powerful indicators of resistance. Loci on bovine chromosomes 2, 20, and 26 were linked with BRD, and these loci also had associations with incidence of other infectious diseases (Casas and Snowder, 2008; Neibergs *et al.*, 2011). Immune responses to vaccination with viral and bacterial agents of BRD had moderately high heritability (Leach *et al.*, 2013). These and other studies suggest that targeting animals with the best immunity could provide inherited resistance to BRD as well as other infectious diseases. Selection for other traits such as heat tolerance, and good temperament may also improve the ability of the host to respond to BRD challenges (Burdick *et al.*, 2011).

Although the basic features of BRD pathogenesis are relatively well defined, the multiple factors involved create combinations and complex interactions between the environment, infectious agents, and the host which will continue to provide challenges to our understanding and management of BRD.

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