**Respiratory Diseases of Cattle**

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Bovine respiratory disease (BRD) continues to plague the cattle feeding industry and dairy calf industry despite more than 5 decades of intensive research efforts.\(^1\)\(^2\) It has a complex etiology including various physical stressors, environmental factors, host factors, and infectious diseases, both viral and bacterial. Pathologists nearly always see these animals postmortem, and death is typically caused by a bacterial infection. It is important to realize that this bacterial infection may be primary or secondary. The critical factor in pathogenesis of the bacterial infection is compromise of the pulmonary defenses to allow bacterial colonization of the bronchoalveolar junction, the most vulnerable site. This colonization is by bacteria that are mostly normal inhabitants of the upper respiratory tract and are usually rapidly cleared from the lower respiratory tract. The ensuing inflammatory response is responsible for the majority of the pulmonary damage.\(^3\)

The most important bacterial pathogens involved in the BRD complex are *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somnus*, *Mycoplasma bovis*, and *Bibersteinia trehalosi*. The important viral diseases in BRD are Infectious Bovine Rhinotracheitis (IBR), Bovine Respiratory Syncytial Virus (BRSV), Parainfluenza-3 (PI-3), Bovine Viral Diarrhea (BVD), and Bovine Respiratory Coronavirus (BRC).\(^3\) The viral-bacterial synergism in BRD is well-known and oft-discussed. However, many cases or outbreaks of BRD have no evidence of viral infection. Viral infections are efficient inhibitors of the pulmonary defenses, which allow bacterial colonization of the lungs, but this role is equally effectively performed by various physical and/or environmental stressors.\(^4\)

Unfortunately for the pathologist, there is considerable overlap in the lesions caused by the various agents of BRD. Some lesions are characteristic (the lesions of *Mycoplasma bovis* or BRSV, for example) but there are nearly always exceptions. Therefore, close cooperation among the pathologist, bacteriologist, virologist, and referring veterinarian are required for accurate diagnosis and effective management of the syndrome in the affected herds. As more sensitive and broader spectrum molecular techniques become available and are put into use, it will again fall on the pathologist and clinical veterinarian to determine the significance of positive results, which, for example, may detect very few copies of a genome in the sample.\(^5\)

**Bacterial Diseases of BRD**

*Mannheimia haemolytica* is generally considered to be the most significant pathogen in acute BRD in feedlot cattle.\(^6\) The major virulence factor for this organism is its ruminant-specific leukotoxin. It is an RTX type of bacterial exotoxin. Its receptor is the CD18 portion of the integrins and unique sequences in the ruminant CD18 molecules account for its specificity. In high concentrations, leukotoxin causes rapid lysis of ruminant WBC and platelets by forming pores in the cell membrane. In lower concentrations, it promotes apoptosis of the WBC. It is also antigenic and is being employed in many of the current vaccines. Additional virulence factors include lipopolysaccharide, capsular polysaccharide, and iron binding proteins.\(^4\)\(^5\)
The classical lesion associated with *M. haemolytica* is a fibrinous pleuropneumonia. This lesion can also be called lobar pneumonia or bronchopneumonia with fibrinous pleuritis. At necropsy the lungs have severe consolidation of from 30 to 90% of the cranioventral portions. The pleural surface, roughly corresponding to the consolidated areas but sometimes diffusely, is covered by white to tan to yellow, friable fibrin. The opposing parietal pleural is usually similarly affected and fibrinous adhesion are common. The cut surface reveals the classical lesion of *M. haemolytica*, the black-cherry red to pale, irregular foci that are surrounded by a distinct, narrow white zone of suppuration. These foci may be confined to a portion of a single lobule or cross several lobules. They have the classical appearance of an infarct, but proof of infarction as the cause of these lesions has proved elusive. With chronicity these foci can form sequestra, which are ideal nidi for secondary bacterial infections. Additionally, there is thickening of the pleura and expansion of the interlobular septa. The septal expansion can be clear (edema) to white (fibrin clots and/or WBC infiltrates). Fibrinous to supplicative exudates can be expressed from the bronchi.3 However, the mottled appearance with bronchocentric, white infiltrates is not commonly seen. These lesions are highly suggestive of *M. haemolytica* as being the etiology, but other bacterial pathogens can cause indistinguishable lesions.

With chronicity affected lungs have variable cranioventral scarring. Sequestra may be evident and these will eventually resolve with scarring or abscessation. Bronchiectasis is sometimes seen. Fibrous pleural adhesions are common. Heat stress will often cause an acute death due to severe emphysema. Emphysema can also be seen with reinfection (reinfection syndrome) and can mimic the classical lesions of BRSV. This residual pulmonary damage adversely affects performance in the feedlot and is a major cause of economic loss due to BRD.8

The histological lesions correspond well with the gross lesions. The infarct-like lesions have widespread alveolar wall necrosis in the centers. The alveoli are flooded with serum, fibrin, and variable hemorrhage. These are demarcated from adjacent viable tissues by a zone of intense neutrophil infiltration. These neutrophils have been affected by leukotoxin and exhibit the classical streaming oat cell (a.k.a. streaming mononuclear cell) appearance that is highly suggestive of mannheimiosis.3

*Pasteurella multocida* is the most important bacterial pathogen in enzootic pneumonia of dairy calves, the summer pneumonia of beef calves, and is an important contributor to BRD of feeder cattle.9 Encapsulation is required for virulence but otherwise, virulence factors are poorly understood.

The lesions most commonly seen with *P. multocida* are those of a typical bronchopneumonia. Cranioventral consolidation of the lungs is consistently present. The cut surface has a mottled appearance with red to gray parenchyma and white zones (cellular infiltration) surrounding bronchi and bronchioles, i.e. a bronchocentric distribution. Thick, white pus/mucopus can be expressed from the bronchi and bronchioles. Pleuritis in not usually present nor is there profound expansion of the pleura and interlobular septa. This pattern is fairly consistent in enzootic pneumonia.3 In feeder cattle, *P. multocida* is the only organism isolated somewhat commonly from lungs that have lesions indistinguishable from *M. haemolytica*.4

Histological lesions are again consistent with the gross lesions. An intense, bronchocentric, supplicative inflammatory infiltrate is present. Bronchioles and bronchi are filled with supplicative exudates. The lesions tend to be limited by interlobular septa. Suppurative infiltrates in the alveoli tend to decrease with intensity with distance from the bronchioles.3
**Histophilus somni** is an important component of BRD of feeder cattle. In some areas of the USA, for example the Northwest, it may be the most important bacterial pathogen. Several virulence factors have been described. Some allow antigenic variation and immune escape, such as phosphocholine modification and phase variation of its lipooligosaccharide. It expresses the Fc-binding protein, IbpA, and a transferrin-binding protein. The truncated lipopolysaccharide of *H. somni* can induce apoptosis in endothelial cells and induce platelet aggregation. It also has the ability to survive in macrophages by as yet unknown mechanisms.3,4

*Histophilus somni* has the ability to produce a variety of disease manifestations including thromboembolic meningoencephalitis, fibrinous pericarditis and myocarditis, polyarthritis, and abortion. The respiratory form is thought by some to precede the other manifestations. The respiratory form causes a bronchopneumonia with a fibrinous pleuritis. This can be extremely difficult to distinguish from the pleuropneumonia of *M. haemolytica*.3

*Bibersteinia trehalosi* may be increasing in significance as a pathogen of BRD. The pathogenic factors are poorly understood. Some strains produce a leukotoxin very similar to that of *M. haemolytica*, whereas other strains do not. It is not currently know whether or not LKT is required for pathogenicity. Other outer membrane proteins and fibrin-binding proteins have been identified, but their significance for pathogenicity is unknown.3

Lesions of *B. trehalosi* are indistinguishable from *M. haemolytica.*3

*Mycoplasma bovis* is increasing in significance as a pathogen in chronic BRD of feeder calves. In dairy calves it has more significance as an agent of otitis media, but pneumonia and arthritis may accompany it. M. bovis has a large family of immunodominant variable surface lipoproteins, which undergo high frequency phase and size variation resulting in antigenic variability, immune evasion, and persistent infection. Persistent infection along with a high degree of antibiotic resistance makes the disease particularly devastating. The organisms also produce phospholipases and reactive oxygen species and can form biofilms, which may contribute to virulence. Co-infection with the other bacterial pathogens of BRD is very common. Its importance as a primary or secondary pathogen has been debated, but the evidence suggests that both occur.10,11

The lesions of *M. bovis* are characteristic. The typical pneumonia has a cranioventral distribution of numerous, often densely packed, caseous to inspissated abscesses, which vary from a few millimeters to several centimeters in diameter. Interlobular septa can have linear necrotic lesions. These are usually accompanied by extensive fibrosis. Histologically, the caseonecrotic foci develop in airways, in alveoli, or in interlobular septa. Macrophages and fewer neutrophils, viable and degenerate, are present at the periphery, and there is often a capsule of fibrous tissue containing lymphocytes and macrophages.3,11

**Viral Diseases of BRD**

**Infectious bovine rhinotracheitis (IBR, bovine herpesvirus 1)** is arguably the most important viral component of the BRD complex in feeder cattle. Acute infection causes mucoid to mucopurrulent oculonasal discharge, anorexia, and fever. Lesions associated with the acute disease include numerous small clusters of gray ulcers, mostly on the nasal septum. Keratoconjunctivitis is usually also present. This can progress to a severe mucopurrulent to fibrinopurrulent rhinitis and fibrinous tracheitis. The virus readily establishes latency in the trigeminal ganglion in respiratory infections, and reactivates during times of stress, translocates to the respiratory and conjunctival tissues, and is shed. This likely accounts for the high rates of infection that can be seen shortly after arrival of cattle in the feedlots.12
In general, the disease typically remains mild unless there is secondary bacterial infection. Viral-bacterial synergism between IBR and the various bacterial pathogens described above is well-known. IBR has immunosuppressive properties that play a role in this synergism. These properties include CD8 and CD4 lymphocyte suppression, interferon signaling, and inhibition of MHC class 1 antigen presentation. Additionally, airway epithelial necrosis and alterations in mucus composition and viscosity likely impair mucociliary clearance.12

**Bovine respiratory syncytial virus (BRSV)** has more potential than the other respiratory viruses for causing primary lethal disease. This was especially true in the initial epidemic seen in the mid-80s, but it is still occasionally seen in isolated, naïve herds. As the disease has become more endemic, its importance has shifted towards viral-bacterial synergism in BRD. Bronchial epithelial cell necrosis and inhibition of pulmonary alveolar macrophage function are the major factors promoting this synergy.13

The uncomplicated lesions of BRSV in susceptible cattle consist of moderate cranioventral, red consolidation of the lungs with a lobular pattern. The affected lobules are usually confluent but occasionally are scattered. In fatal cases there is usually emphysema of the caudodorsal lungs fields. The emphysematous lesions are associated with high pulmonary levels of BRSV-specific IgE, leading to the theory that this is a hypersensitivity reaction. Histologically, the pulmonary lesions are of bronchial epithelial necrosis with variable formation of syncytial cells. Bronchointerstitial pneumonia is also present with increased alveolar macrophages, with multinucleate cell formation. Alveolar septal damage may be manifested by hyaline membranes and later type 2 pneumocyte proliferation.13

**Bovine Parainfluenza-3 (PI-3)** has been dubbed in a recent review as “a forgotten virus” of the BRD complex. This is most likely because of its high rate of seroprevalence in feeder cattle coupled with its rarity of isolation from disease outbreaks. How important a contributor to the BRD complex that PI-3 is at the current time is uncertain.14

The gross lesions of PI-3 include a possible rhinitis with mucopurulent exudate in nasal passage. The gross pneumonic lesions produced by experimental inoculation of PI-3 consist of atelectasis and consolidation in the cranioventral aspects of the lungs. These appear initially as swollen and later depressed, red-purple, firm areas that may exude mucopurulent exudate from airways on cut surface. There may be interlobular edema. These lesions are similar to those of BRSV, but emphysema is typically absent. Histologically, experimental infection causes bronchial/bronchioloar epithelial cell necrosis with inflammatory cellular exudation into the lumens. Early in the infection, eosinophilic intracytoplasmic inclusion bodies are present. Syncytial cells may be present, but this is strain-dependent. The repair phase has bronchial, bronchiolar, and alveolar epithelial cell hyperplasia. Bronchiolitis obliterans may occur.14 Reports in the literature of the lesions of pure PI-3 infections from field cases is lacking. From the pathology of experimental infections, one can infer that PI-3 may promote bacterial infection of the lower respiratory tract through epithelial necrosis and interference with the mucociliary apparatus. The effects on immunity or alveolar macrophage function are subjects deserving of additional study.

**Bovine viral diarrhea virus (BVD)** infection is generally included in the list of important BRD pathogens, even though the primary effects of viral infection on the respiratory tract are usually minimal. Its true impact on BRD is not known, despite it being an intensely studied pathogen. Marked strain variability and syndrome variability complicate our abilities to make generalities about the virus. There is no doubt that BVD infection is immunosuppressive and through this mechanism likely enhances severity and/or susceptibility to other BRD pathogens. Calves infected in utero with non-cytopathic strains from 40-125 days of gestation become persistently infected and may shed large numbers of viruses over long periods of time and serve as sources of infection in cattle grouped together in feedlots. Persistently
infected animals are much more likely to develop fatal BRD than their uninfected counterparts. BVD infection inhibits lymphocytic functions and cause necrosis/apoptosis of lymphocytes, inhibits phagocytic and chemotactic functions of leukocytes, and inhibits interferon and cytokine responses. Studies have also shown definite synergy of BVD infection with nearly all the significant viral and bacterial pathogens of BRD.\textsuperscript{15,16}

Experimental infection with certain strains causes mild lower respiratory epithelial damage and decreased BALT. Otherwise, there are no specific gross or histological lesions in the lungs associated with BVD infection.\textsuperscript{15,16}

**Bovine respiratory coronavirus (BRCV)** infection has been associated with several severe BRD outbreaks. Evan’s postulates have been fulfilled for the viral disease, but Koch’s postulates have not.\textsuperscript{17} As a result, no suitable model for study of the disease has been developed and no lesions can be ascribed to the virus. We have shown that the virus is shed in a biphasic manner from the upper and lower respiratory tract of experimentally infected calves, but no significant respiratory signs or lesions were produced.

### OTHER RESPIRATORY DISEASES OF FEEDER CATTLE

**Atypical interstitial pneumonia (AIP)** tends to occur in late summer to early fall in heavy feeder cattle. The lesions are identical to acute bovine pulmonary edema and emphysema (formerly also called atypical interstitial pneumonia) caused by the ingestion of high tryptophan, which is metabolized to the toxic 3-methyl indole, 4-ipomeanol from moldy sweet potatoes, and perilla ketones. There is a sex predisposition for heifers and incidence is increased in those being fed melengestrol acetate to inhibit estrus, but feeding it is not required for development of the syndrome. Some studies have given evidence supporting 3-methyl indole or BRSV involvement in the syndrome, but other studies have shown development of the syndrome in the absence of either, so the cause is currently undetermined.\textsuperscript{18}

The gross lesions of AIP are severe pulmonary emphysema with severe gas-distension of interlobular septa with formation of bullae. The emphysema usually extends into the mediastinum and subpleural tissues. It frequently extends to the subcutis over the withers and back. Despite the hyperinflated and emphysematous appearance of the lungs, they are extraordinarily heavy. This is due to the extensive pulmonary edema, which can be appreciated by the wet appearance of the lobules and extensive foam in the airways. The histological lesions consist of extensive alveolar edema with hyaline membrane formation and striking type 2 epithelial cell hyperplasia. Interlobular lymphatics are distended with air with frequent escape of air into surrounding tissues.\textsuperscript{18}

**Honkers** is an acute upper respiratory syndrome of heavy feeder cattle. The lesion is severe tracheal edema, which partially occludes the tracheal lumen and creates the high pitched respiratory sounds that are responsible for its name. The etiology is unknown.

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