CHAPTER 14

BOVINE RESPIRATORY DISEASE COMPLEX (BRD)

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INTRODUCTION

Despite of advances in veterinary medicine and animal welfare, the economic impact of cattle diseases on the livestock industry still remains important. Bovine respiratory disease complex (BRD) is one of the most important disease prevalent in both dairy and beef production farms (Amat 2019). BRD defines the cases of pneumonia associated with inflammation, consolidation, lung abscesses, and fibrosis caused by one or more infectious agents (Guterbock 2014). This disease complex affects both the upper airways causing rhinitis, pharyngitis, tracheitis and bronchitis and the lower airways/lungs (Woolums et al. 2015; Taylor et al. 2010). Post-weaned calves are most affected by BRD. Respiratory system infections lead to a decrease in feed efficiency, a decrease in development/growth performance, a loss of workforce and productivity for the animal enterprise/producer, and even death in severe cases. It also negatively affects reproductive performance, milk yield, and carcass quality in the long term (McGuirk 2008). The economic effects of BRD increase with the severity of the disease and treatment practices (Amat 2019). It has been reported that the rate of antibiotic use, which has taken an important place in BRD control, is 91.9% (USDA 2010), and this may lead to an increase in drug-resistant bacterial strains (Woolums et al. 2018). In addition, inappropriate and intensive use of antibiotics creates serious public health problems due to antimicrobial drug residues in animals consumed as food (Klima et al. 2014; Woolums et al. 2018).

Etiology

The anatomical and physiological structure of the respiratory system of ruminants makes them more susceptible to BRD. In contrast to other species, the lung capacity of cattle is small compared to their bodies and their functional capacity is low. In addition, low respiratory rate, breathing by mouth, excess lung lobes, limited lung lysozyme and phagocytosis capacity reduced ventilation capacity in cold weather and being sensitive to environmental temperature cause respiratory system diseases to be more common (Cooper and Brodersen 2010). The immune status of the host, environmental risk factors, mismanagement practices, and infectious agents play vital role in the development of BRD (Amat 2019).

Predisposing Factors

The main host-related risk factors predisposing calves to BRD are immune status, age, body weight, and genetics (Taylor et al. 2010). It has been reported that BRD is the most important disease of calves older than 30 days (McGuirk 2008; Woolums et al. 2015) and especially 50.4% of the cases occur in the post-weaning period (USDA 2010). As the weaning age and body weight of calves increase, their susceptibility to BRD decreases (Sanderson et al. 2008). Transfer of calves to group pens, sudden climate changes, poorly ventilated and crowded housing are important environmental risk factors predisposing calves to BRD. Shipping adversely affects the immune system of the animal due to stress and malnutrition during transport and predisposes to the BRD. In addition, exposure of cattle to different pathogens after transport or hierarchical social stress in group pens is an important management risk factor (Taylor et al. 2010; Amat 2019).

Viral Pathogens

The most important role of viral pathogens in BRD is to increase the susceptibility to secondary bacterial infections by inhibiting the defense mechanisms of the lungs (Taylor et al. 2010; Grissett et al. 2015; Amat 2019). The most common viral agents associated with BRD are *bovine herpesvirus type-1* (BoHV-1), *parainfluenza virus-3* (PI-3), *bovine viral diarrhea virus* (BVDV), *bovine respiratory syncytial virus* (BRSV), and *bovine coronavirus* (BCV). Although the viral-bacterial synergism in BRD is well known, the clinical signs of viral infection are absent in most cases. Viral pathogens cause primary infection, which is usually accompanied by mild clinical signs of BRD (Panousis 2009; Panciera and Confer 2010).

Bacterial Pathogens

Bacterial pathogens are responsible for severe clinical findings, chronic disease, and deaths in the BRD. The most important bacterial pathogens associated with this disease complex are *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni*, *Mycoplasma bovis*, *Arcanobacterium* (*Trueperella*) *pyogenes*, and *Bibersteinia trehalosi*. Each of these bacteria has different virulence factors such as biofilm, capsule, adhesin, toxin, and enzyme that increase their ability to colonize the lower respiratory tract, escape from the immune system, antimicrobial resistance, tissue damage, and inflammatory response (Confer 2009; Panousis 2009; Panciera and Confer 2010). A small number of *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni* are naturally present in the nasal cavities of healthy cattle (Ackermann et al. 2010; Griffin et al. 2010). These microorganisms become opportunistic pathogens when host defense mechanisms are disrupted (Confer 2009; Ackermann et al. 2010; Gorden and Plummer 2010).

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***Mannheimia haemolytica* (*M. haemolytica*)**

M. haemolytica is a gram-negative, fermentative, non-motile, non-spore-forming, oxidase-positive, and facultative anaerobic coccobacillus from the Pasteurellaceae family. It usually produces weak hemolysis on sheep or cattle blood agar plates. The virulence factors of *M. haemolytica* make this bacterium the main bacterial agent of BRD, as it causes high mortality and loss of yield in young calves. Pneumonia caused by *M. haemolytica* is characterized by lesions that begin with acute cranioventral fibrinous pneumonia and progress to fibrinopurulent pleuropneumonia. The prevalence of *M. haemolytica* is estimated to be around 15% in suckling or young calves. Important virulence factors of *M. haemolytica* are capsular polysaccharides, lipopolysaccharide (LPS), protein adhesins, secreted enzymes, iron-binding proteins, and leukotoxin (LKT). Lipopolysaccharide and LKT are the two most important virulence factors responsible for most of the devastating lesions of *M. haemolytica* infection (Rice et al. 2007; Assie et al. 2009; Griffin et al. 2010).

***Pasteurella multocida* (*P. multocida*)**

Pasteurella multocida is a gram-negative, non-motile, aerobic coccobacillus belonging to the Pasteurellaceae family. It is found as a facultative pathogen in epithelial cells of the upper respiratory tract of healthy cattle. *P. multocida* isolates are classified into 5 serogroups (A-F) according to their capsular antigens and 16 serotypes (1-16) according to their somatic antigens. *P. multocida* A:3, the most commonly isolated serotype in BRD, is responsible for severe suppurative bronchopneumonia of calves. *P. multocida* is responsible for 40% of enzootic and shipping fever pneumonia cases. In *P. multocida* infections, typically cranioventral bronchopneumonia lesions are determined in the lungs. These lesions are characterized by acute fibrinosuppurative, subacute-chronic fibrinopurulent, fibrinous-fibrinopurulent, suppurative, and fibrino-necrotic pneumonia. The main virulence factors of *P. multocida* are various adhesins, lipopolysaccharide, and a thick polysaccharide capsule (Welsh et al. 2004; Dabo et al. 2007; Confer 2009).

***Histophilus somni* (*H. somni*)**

Histophilus somni (formerly *Haemophilus somnus*) is a gram-negative coccobacillus belonging to the Pasteurellaceae family. It is one of the main causes of BRD, especially in beef cattle. Like other bacteria, *H. somni* is found in the normal nasopharyngeal flora, but it colonizes mainly in the lower respiratory tract. In cattle, the infection can develop with *H. somni* directly or with the presence of other opportunistic viruses or bacteria. The tendency to disease is increased in overcrowded and poorly ventilated barns and poorly fed cattle. The bacterium alone causes fibropurulent bronchopneumonia. In mixed infections, it can cause thromboembolic meningoencephalitis, polyarthritis, abortion, abscessed laryngitis, fibrinous pericarditis, and sudden death associated with septicemia. *H. somni* virulence factors are lipooligosaccharide, immunoglobulin binding protein, outer membrane proteins, and exopolysaccharides. Histamine production also plays a role in the pathogenesis of *H. somni* (Confer 2009; Dabo et al. 2007; Rice et al. 2007).

***Mycoplasma bovis* (*M. bovis*)**

Caseonecrotic pneumonia of calves is defined as characteristic Mycoplasma infections. However, the causative agent in this disease is *M. bovis*, which is different from other *Mycoplasma* spp. and is more virulent (Haines et al. 2001; Shahriar et al. 2002). In various studies related to BRD, *Mycoplasma* spp. were isolated in combination with other bacteria in 70% of cases while in 20% cases, it has been isolated alone (Gagea et al. 2006). *M. bovis* infections in calves cause chronic pneumonia, lameness, and weight loss. Such cases usually do not respond to antibiotic therapy. *M. bovis* infections typically present multiple miliary caseous (cheese-like) abscesses with a cranioventral distribution, varying in diameter from a few millimeters to several centimeters. Histologically, caseousnecrotic foci are seen in the airways, alveoli, or interlobular spaces (Maunsell et al. 2011; Fulton and Confer 2012). Variable surface proteins form the virulence factors of *M. bovis*. Responsible for phenotypic changes among *M. bovis* strains, these surface proteins enable *M. bovis* to escape from the host immune response. It also functions as an adhesin by allowing *M. bovis* to colonize the bronchioles. Other virulence factors of *M. bovis* are biofilm formation and hydrogen peroxide (McAuliffe et al. 2006).

Pathogenesis

The respiratory tracts of healthy cattle have various mechanisms that prevent the colonization of harmful microorganisms. These mechanisms include retention of microorganisms and particles by mucus and cilia, physical removal, mucosal immune response, and maintenance of the saprophytic bacterial population (Ackermann et al. 2010). Viral agents affect the mucosal barrier, disrupting the clearance of respiratory tract pathogens, damaging the pulmonary parenchyma, and suppressing immune responses. It also facilitates the multiplication of opportunistic bacterial pathogens in the upper respiratory tract and their translocation to the lung, causing pneumonia. In a recent study on humans, it has been reported that viruses can weaken the host's resistance to bacterial pathogens by affecting the structure and composition of the nasal microbiota (Grissett et al. 2015; Korten et al. 2016).

Bacterial pathogens inhaled by the respiratory tract first colonize in the bronchoalveolar junction, overcoming the host defense system and causing inflammation in the region. It spreads through the airways or lung tissue adjacent components, causing suppurative bronchopneumonia (lobular bronchopneumonia), fibrinous pneumonia (lobar pneumonia, fibrinous bronchopneumonia), or caseonecrotic pneumonia (mycoplasmal pneumonia) (Caswell and Williams 2007). The type of bronchopneumonia is classified according to the rate and path of the spread of the infection in the lung, the type of exudation, the place of onset of bacterial colonization, the variety of bacterial virulence factors, and host resistance (Panciera and Confer 2010).

Clinical Findings

Symptoms of the respiratory system diseases in cattle, usually develop within 2 weeks after exposure to stress factors (weaning/transport). The clinical symptoms differ depending on whether the disease is acute or chronic. In the early period of

the disease; mild depression, serous ocular, and nasal discharge and an increase of body temperature up to 39.5-42 °C may be observed. In bacterial cases, the body temperature reaches 40.5-41 °C with signs of toxemia. While signs of toxemia are not observed in viral cases, an increase in body temperature (viremia period) and partial or complete loss of appetite is observed. In the later stages of the disease, unwillingness to move, loss of appetite, varying degrees of dyspnea, and harsh/persistent cough are observed. Nasal and ocular discharges are the mucopurulent-purulent character. Hardened sounds in the anteroventral lobes may be heard on lung auscultation. Clinical symptoms are variable in chronic BRD cases. Impaired hair coat and weight loss are observed in animals. The respiratory rates are above normal, and there is a slight or moderate intermittent fever. Bilateral mucopurulent nasal discharge and chronic productive dry cough are common. Abnormal lung sounds (ronchus and wheezing) can be heard in the entire lung area during auscultation examination of the lungs, but these sounds are most often heard in the ventral region of the lungs (Joshi et al. 2016; Kumar et al. 2018).

Diagnosis

Early diagnosis and accurate determination of etiological agents are significant for effective control of respiratory system diseases (Poulsen and McGuirk 2009; McGuirk and Peek 2014). Early diagnosis increases the effectiveness of treatment and eliminates most of the herd's problems. Delayed diagnosis in respiratory tract diseases may cause long-term antibiotic use, increased disease recurrence rate, lung abscess (chronic case), and otitis. As a result, affected and poorly treated calves may cause endemic herd problems when they enter collective calf shelters after weaning (Panousis 2009; Burgess et al. 2013; Buczinski et al. 2014).

Diagnosis of respiratory system diseases can be made by identifying the causative agent and laboratory analysis by evaluating clinical findings, osculopercussion, hematology, radiography, ultrasonography, nasal-pharyngeal swab, tracheal wash, and the tracheobronchial secretions collected by bronchoalveolar lavage procedures. In addition, more invasive procedures such as thoracocentesis and lung biopsies can be utilized (Burgess et al. 2013; Buczinski et al. 2014; Abutarbush et al. 2019).

Clinical Diagnosis

Diagnosis of respiratory tract diseases is usually made with clinical findings in field conditions. Instead of comprehensive and equipment-requiring scanning devices, different scoring systems have been developed recently by standardizing clinical examination findings and scoring each of the clinical parameters according to the degree of importance (Poulsen and McGuirk 2009; Ider and Maden 2021). For this purpose, the Wisconsin (WI) scoring system based on five clinical parameters, including rectal temperature, cough, nasal discharge, ocular discharge, and ear position, was started to be used by Poulsen and McGuirk (2009). According to this scoring system, calves with a total respiratory score of five or higher (if there are at least two abnormal parameters) are considered sick. It is stated that screening calves with the WI score system at least twice a week before weaning provides a significant advantage in the early diagnosis and control of respiratory system diseases (Poulsen and McGuirk 2009; McGuirk and Peek 2014; Ider and Maden 2021).

Hematological Analyzes

Blood gas analyzes are shown as an important analyses method that provides useful information in the evaluation of BRD severity and in making therapeutic decisions. Compensable respiratory acidosis develops in most calves with respiratory system disease. Ventilation, pulmonary diffusion, pulmonary hemodynamic disorders, and/or deterioration in ventilation-perfusion balance in the pathogenesis of BRD cause a decrease in blood pO_2 levels. It has been stated that the decrease in blood pO_2 level and the increase in pCO_2 level concurrently indicate obstructive changes and ventilation disorders in animals with signs of catarrhal and catarrhal-purulent bronchopneumonia. The decrease in blood pCO_2 levels in calves with pneumonia is associated with tachypnea and hyperventilation, frequently seen in respiratory system diseases (Nagy et al. 2006; Šoltésová et al. 2015; Ok et al. 2019; Ider and Maden 2021).

Leukocytosis and neutrophilia are observed in severe bacterial bronchopneumonia, while viral cases of pneumonia, leukopenia, and lymphopenia can be determined. In the biochemical analyzes of calves with BRD, it was determined that ALT, AST, CK, LDH, BUN, and creatinine levels were high, while albumin, glucose, magnesium, phosphorus, iron, and zinc concentrations were low (El-Bahr and El-Deeb 2013; Šoltésová et al. 2015; Ok et al. 2019; Ramadan et al. 2019).

Recently, some potential biomarkers, cytokines, acute-phase proteins (APP) and biochemical parameters involved in the pathogenesis of pneumonia have been investigated as diagnostic or prognostic markers in bronchoalveolar lavage (BAL) fluid and serum/plasma in BRD (Ider and Maden 2019). Haptoglobin (Hp), serum amyloid A (SAA), albumin, fibrinogen (Fb), and Lipopolysaccharide Binding Protein (LBP) are the most commonly used APPs in BRD. Most of cases (94%) in cattle with BRD have Hp levels above 0.15 mg/mL (Wolfger et al. 2015). When evaluated together with SAA, it has been reported to be more useful than hematological tests in the differential diagnosis of acute and chronic inflammation. In addition, it has also been reported that Hp increases significantly in viral and bacterial diseases and can be used to differentiate viral/bacterial diseases (Horadagoda et al. 1999). Lipopolysaccharide Binding Protein has been indicated as an earlier and more sensitive biomarker in respiratory tract diseases compared to other APPs (Nikunen et al. 2007; Ider and Maden 2019).

Analysis of Body Fluid Sample

Specific determination of the etiologic agent associated with pneumonia is made through nasal or pharyngeal swab, transtracheal fluid aspirate, BAL fluid, autopsy, or serology of lung tissue samples. Samples are taken from the lower respiratory tract, bypassing the nasopharynx in the transtracheal washing technique. However, this technique is difficult to apply in the field because it requires operative preparation of the ventral part of the neck. In addition, it is not suitable for routine examinations in the field because it is an invasive technique. The nasal swab technique is easy to apply and is a useful technique especially used to detect acute viral infections such as BHV-1. However, it is not a reliable technique because most of the microorganisms associated with the BRD complex are found in the normal upper respiratory tract flora (Caldow 2001). BAL fluid analysis is the best

technique used to accurately determine the etiologic agent (in the field or the clinic) in live calves (Panousis 2009).

Bronchoalveolar lavage (BAL) is the process of collecting fluid for examination from the lower respiratory tract, especially the alveolar cavity of the lung, as a result of giving fluid to the lung alveolo-bronchial system (Ok et al. 2019; Ider and Maden 2019). BAL is a relatively safe procedure that helps to diagnose respiratory diseases. Although it requires some training, it is a safe and efficient technique. It can be performed by using fiberoptic endoscopes or simple commercially available catheters (Caldow 2001). In addition to the isolation of the agent, this procedure is also used to evaluate antimicrobial drug therapy for lung diseases. Lung inflammation and damage cause changes in enzyme activity and cellular components in BAL fluid. Changes in BAL fluid are useful tools in determining pulmonary damage (Abutarbush et al. 2019; Ider and Maden 2019).

Diagnostic Imaging

Radiography and ultrasonography are diagnostic imaging devices used in the diagnosis of BRD. Although these are non-invasive methods for the antemortem diagnosis of pneumonia, the use of radiography for the diagnosis of BRD is impractical. Today, ultrasonography has taken its place because it is more practical in field conditions. Thoracic ultrasonography has a sensitivity of 79.4% (66.4-90.9) and a specificity of 93.9% (88.0-97.6) in the diagnosis of BRD (Buczinski et al. 2015). Thoracic ultrasound detects non-ventilated or consolidated lung lesions and diagnoses pneumonia in all its stages. Lung consolidation can be observed ultrasonographically only a few hours after infection. Thoracic ultrasonography allows consolidation of the lung as well as visualization of the pattern of pneumonia, abscesses, and extrapulmonary air/fluid. Ultrasonographic examination of both sides of the thorax may reveal an anechogenic or hyperechogenic area due to fluid in the pleural space in the ventral region of the thorax in cattle with pleuropneumonia (Siegrist and Geisbühler 2011; Buczinski et al. 2014; Ollivett and Buczinski 2016).

Treatment

Antimicrobial and adjunctive therapy (anti-inflammatory, bronchodilator, antitussive, expectorant/mucolytic, diuretics, immunomodulators, and vitamins) applications are included in the treatment of BRD. Antibiotic therapy is aimed at reducing and controlling bacterial proliferation by preventing the further release of bacterial virulence factors. For an effective treatment protocol, it is important to determine the causative agent of the disease, the time to start treatment, choose antibiotics that reach and maintain an effective therapeutic concentration and follow accurate dosage and duration protocol. Macrolides, tetracyclines, phenicols, fluoroquinolones, cephalosporins, and penicillins are widely used antimicrobial agents in the therapy of BRD. Among these antibiotics, macrolides (tilmicosin, spiramycin, erythromycin, tulathromycin, tylomycin, tildipirocin) can be used alone, as well as macrolides and florfenicol; macrolide and tetracycline (doxycycline or oxytetracycline); quinolones (enrofloxacin, marbofloxacin, danofloxacin), and cephalosporins (ceftiofur, cefquinome) or penicillin or ampicillin (sulbactam), amoxicillin-clavulanic acid combinations are also used (Güreli 2009; Tütüncü et al. 2017; Ok et al. 2019). Antimicrobial therapy in bacterial pneumonia can be successful if it is used for a sufficient time and most importantly at an early stage of the BRD complex. In the late stage of disease, antibiotics and other treatments may not be successful in the regeneration of normal lung parenchyma (Woolums et al. 2009). The efficacy of metaphylaxis in pneumonia is variable. In a study conducted in North America, it was shown that metaphylaxis reduces the rate of mortality and morbidity (Lekeux 2007; Wileman et al. 2009).

The second component of the BRD therapeutic strategy is anti-inflammatory agents (steroidal and non-steroidal). Anti-inflammatory therapy targets the control of local and systemic inflammatory processes. Steroidal anti-inflammatory drugs (SAIDs) are recommended to be used in a single dose because of their immunosuppressive effects. For this purpose, a single dose of dexamethasone (5-25 mg/animal) can be used. The use of non-steroidal anti-inflammatory (NSAIDs) drugs reduces fever, clinical signs, and lung pathology, and increases daily weight gain. The most commonly used NSAIDs in the treatment of BRD are flunixin meglumine, meloxicam, ketoprofen, carprofen, tolfenamic acid, and metamizole sodium (Lekeux 2007; Joshi et al. 2016; Tütüncü et al. 2017).

In calves with respiratory distress syndrome, nebulized bronchodilators such as salbutamol (0.025 mg/kg/6h), formoterol (15 µg totally/12 h), ipratropium bromide (2 µg/kg/12h) can be used to improve pulmonary functions in a short time (Ok et al. 2020). Parenteral form theophylline (1-10 mg/kg), clenbuterol (0.8 µg/kg) and atropine sulfate (2.2 mg/45 kg) can be used to relieve bronchospasm in BRD cases. Mucolytics are used because they facilitate mucociliary clearance. For this purpose, N-acetyl cysteine, bromhexine, and ambroxol are administered orally or intramuscularly for 5 days at a dosage of 0.25-0.4 mg/kg/day. If pulmonary edema is suspected in severe BRD cases, diuretics (furosemide 1 mg/kg) may be used (Joshi et al. 2016; Tütüncü et al. 2017).

Regardless of the cause, there is localized or generalized immunosuppression in respiratory system diseases. Immune modulator therapy provides rapid recovery and prevents relapses, especially in cases where viral pathogens are at the forefront. For this purpose, levamisole and inactivated *Parapoxvirus ovis* strain D1071 are commonly used in cattle. Levamisole (2.5 mg/kg) can be administered at 3 times intramuscularly or subcutaneously, and *Parapoxvirus ovis* (zylexis) can be administered in 3 doses, 2 days, and 1 week later as a single dose. For supportive purposes, vitamin A and C supplementation and limited fluid therapy can also be performed (Lekeux 2007; Tütüncü et al. 2017).

Prophylaxis

The protection practices related to the control of respiratory diseases in calves include the development of a strong immune system by providing sufficient amount of good colostrum, proper vaccination, healthy nutrition, biosecurity, and ensuring adequate ventilation. The importance of vaccinating pregnant cattle and colostrum management in the control of respiratory diseases is emphasized. Ensuring adequate passive transfer to calves and proper care of the umbilical cord are practices that reduce the rate of respiratory system diseases. Vaccination against the pathogens that cause BRD is a frequently used method of protection to control the disease. For this purpose, many vaccines have been produced commercially against BRD agents. In animals with good colostral immunity, firstly modified live vaccines are administered at the age of 3-4 months. The

combination of the vaccine with intranasally modified live PI-3 and infectious bovine rhinotracheitis (IBR) viruses in newborns, provides specific and nonspecific protection against respiratory diseases that can affect calves in the first week of life. Intranasal vaccination of one-week-old or older calves is beneficial in rapidly stimulating immunity by avoiding the undesirable effects of circulating maternal antibodies. An early vaccination program may be recommended for animals with insufficient colostral immunity (McGuirk 2008; Gorden and Plummer 2010).

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