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Etiopathogenesis and economic significance of bovine respiratory disease complex (BRDC)

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Abstract: BRDC is the most expensive disease of fattening cattle throughout the world. The reasons for this are high morbidity and mortality, weight loss, reduced food utilization, reduced quality of carcasses and extensive measures of prophylaxis and therapy. BRDC is caused by a substantial number of pathogens (viruses and bacteria), with predisposing risk factors from the ambient and host. Calves are at the highest risk of developing BRDC shortly after shipping. Lighter-weight calves appear to be at greater risk, although this has not been consistent. The complexity of BRDC makes it difficult to define the role of individual factors that predispose to or cause the disease. Stress factors may be ”necessary, but not sufficient“, but they require additional effects to cause the disease. Increasing the production of meat and milk worldwide would be sustainable by improving the prevention and control of BRDC.

Keywords: Bovine Respiratory Disease Complex (BRDC), predisposing factors, viruses, bacteria, beef cattle, economic loss

Introduction

Bovine respiratory disease complex (BRDC) is a major disease, classically occurring in indoor calves and feedlot young cattle, and is responsible for major

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economic losses in both beef and dairy production (Smith, 2000; van der Fels-Klerx *et al*., 2001). The etiopathogenesis of BRDC is multifactorial and complex, with equal involvement of infectious agents and environmental factors – environmental stressors (Nickell and White, 2010). The most studied infectious agents which participate in the etiopathogenesis of BRDC are the following viruses: bovine respiratory syncytial virus (BRSV), parainfluenza virus type 3 (PI3V), bovine herpes virus type 1 (BHV1) and bovine viral diarrhea virus (BVDV) (Bednarek *et al*., 2012). Viruses predispose to the appearance of bacterial infection by direct damage to respiratory clearance mechanisms and lung parenchyma, enabling the bacteria to settle from the upper respiratory tract, and to the occurrence of infection in damaged lungs (Pardon *et al*., 2011). The second mechanism is that it is a viral infection that can interfere with the immune system's ability to fight against bacterial infection (Martin and Bohac, 1986; Czuprynski *et al*., 2004). Agents that cause concurrent bacterial infections are: *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni*, *Arcanobacterium pyogenes, Streptococcus pneumonie, Staphylococcus aureus, Chlamydiales spp., Fusobacterium necrophorum, Corynebacterium bovis, Streptococcus spp.* and *Micrococcus spp.* (Taylor *et al*., 2010a). Mycoplasmal pathogens are: *Mycoplasma bovis*, *Mycoplasma bovirhinis*, *Mycoplasma dispar*, *Ureaplasma diversum* and even *Mycoplasma canis* (Szymańska *et al*., 2010). Among bacteria, *M. haemolytica* and *P. multocida* have been considered as the most common bacterial infectious agents in the BRDC etiology. One of the most frequently isolated mycoplasmal factors from BRDC cases is *Mycoplasma bovis* (Bednarek *et al*., 2012).

About 91 percent of calves diagnosed with BRDC were diagnosed within the first 27 days after arrival (Buhman *et al*., 2000). Morbidity risks of BRDC cases in feedlot cattle occur within the first 45 days after arrival to the feedlot. Morbidity was highest in weeks 1 to 3, and decreased through the end of the 12-week period (Edwards, 1996). Clinical signs most commonly observed include high fever (40–41.5 $^{\circ}$C), depression, decreased appetite, nasal and ocular discharge, coughing and varying degrees of dyspnea. The etiology of BRDC is almost always polymicrobial and associated with predisposing environmental or host risk factors.

The economic losses of the cattle breeding industry resulting from the emergence of BRDC are expressed through the rate of morbidity and mortality, the cost of prevention and drug treatment, reduced productivity and the value of carcasses of cattle. In the European Union, production losses (excluding livestock deaths) are about 576 million euros annually (Barrett, 2000). The annual loss of the US cattle breeding industry is estimated to be $ 1 billion, and the cost of prevention and treatment is $ 3 billion a year (Griffin, 2006, Snowder *et al*., 2007). The average cost of the individual treatment is estimated at $ 15.60. This cost increases to $ 92.30 when account is taken of indirect costs, such as reducing average daily increase and efficiency of nutrition, and reduced carcasses value

(Schneider *et al*., 2009). An estimated 1.9 million animals (Nicholas, 2011) are affected by BRDC each year in the UK cattle industry with costs estimated at around £60 million annually (NADIS, 2007).

Predisposing Factors

Numerous studies around the world have pointed to a significant impact of predisposing factors in the occurrence of the BRDC (Taylor *et al*., 2010a). Predisposing factors can be divided into environmental factors (weather and ambient temperature, humidity and dust), host factors (age, sex, race, genetics, immune status) and stressful management practices (transportation, changes in diet, high density of animals, handling and surgeries). All of the above predisposing factors pose a high risk of development of BRDC.

Environmental factors

Weather and ambient temperature

A number of authors have pointed out that stunning and extreme changes in weather conditions, rather than exclusively cold or bad weather, predispose cattle to BRDC. Data confirming this statement are presented by Ribble *et al*. (1995), indicating that BRDC mortality peaked at approximately the same time as the largest decrease in mean daily ambient temperature. Two other studies revealed opposite correlations between onset of BRDC and the maximum range in temperature within a 24-hour period. The first study showed that increased variation in ambient temperature corresponded with increased disease (MacVean *et al*., 1986), whereas in the second research increased temperature variation correlated with a decrease in BRDC (Alexander *et al*., 1989). Cusack *et al*. (2007) examined the correlation of a variety of temperature measurements (daily mean, minimum, and range) with morbidity and mortality, and found that minimum temperature had a higher correlation with BRDC morbidity. The researchers did not determine the relationship between climate variables and mortality.

Humidity

Investigations of relative humidity (MacVean *et al*., 1986), wind speed (Cusack *et al*., 2007) and precipitation (Alexander *et al*., 1989; Cusack *et al*., 2007) indicated that they did not significantly affect the emergence of BRDC.

Dust

MacVean *et al.* (1986) investigated the effect of dust in the feedlot on respiratory morbidity. They suggested that dust particles are associated with the occurrence of BRDC. Based on visual appraisal, the authors determined that cattle on feed 16 to 30 days had the closest correlation between disease and presence of dust, and regression analysis showed that a 15 day lag time from peak exposure to peak disease yielded the closest correlation.

Host factors

Age

Feedlot cattle are commonly categorized as "calves" or "yearlings", based upon weight and phenotype after the arrival at the fattening units. Yearling cattle have a lower incidence of morbidity and mortality (Radostits, 2001; Jensen R. and Mackey, 1979), although no data were provided to support the assertion. The youngest calf was 5 times more likely to be diagnosed with fever when compared to the oldest calf, wherein there was a difference of 100 d in age (Townsend *et al*., 1989). More research revealed that lighter-weight calves were at greater risk than heavier ones (Martin *et al*., 1989; Bateman *et al*., 1990; Taylor *et al*., 1999; Gummow *et al*., 2000; Sanderson *et al*., 2008).

Sex

Studies of the impact of sex on the emergence of BRDC gave contradictory results. In 2 trials analyzing disease from birth through feedlot determined higher risk for the BRDC in male calves than in female calves (Muggli-Cockett *et al*., 1992; Wittum and Perino, 1995). Two studies that examined only cattle after feedlot arrival also found that males were at a greater risk than females for developing respiratory disease (Alexander *et al*., 1989; Gallo and Berg, 1995). Contrary to the results of the above research, retrospective research of records of over 21 million feedlot cattle revealed a higher incidence of BRDC-associated mortality in females than in males from 1997 to 1999. For cattle, no difference was determined between genders from 1994 to 1996 (Loneragan *et al*., 2001).

Race (Genetics)

Differences in the susceptibility to the emergence of BRDC between different breeds of cattle were identified, although the heritability of the mentioned traits appears to be low (Muggli-Cockett *et al*., 1992; Snowder *et al*., 2005). Snowder *et al*. (2005) showed that heifers have lower antibody levels in colostrum, thus their calves would be susceptible at a younger age. More resistant cows would

provide longer lasting passive immunity, possibly interfering with development of acquired immunity. The highest incidence of BRDC among feedlot calves was found in Braunvieh calves, but the highest mortality rates (18%) were observed in the Simmental (Snowder *et al*., 2005, 2007).

Angus and Hereford races did not have higher incidences of postweaning BRDC when compared to other feedlot breeds such as Charolais, Gelbvie, Limousin, Red Poll, Simmentaler or Belgian Blue (Muggli-Cockett *et al*., 1992).

Immune status

Younger calves are more susceptible to potential pathogens, because they have less immunity and experience more stress in the transition to the feedlot and may respond less efficiently and fully to exposure to respiratory pathogens compared to older cattle (Urban-Chmiel and Grooms, 2012).

Stressful management practices

Transportation

Transportation is one of the most important predisposing non-infectious factors for BRDC, hence the widespread name "shipping fever". Many factors can lead to increased stress and risk of BRDC, including loading and unloading, time duration of transport (Dixit *et al*., 2001), food and water deprivation and weather conditions. A large number of studies have confirmed a positive association between distance transported and morbidity (Sanderson *et al*., 2008). It is important to identify shipping-related factors which are the most critical in increasing BRDC incidence (weather conditions, type of transportation and the distance or time of transit). For example, calves transported below 240 km had less morbidity than those transported 240 to 320 km. The incidence of BRDC risk increased by 10% for each 160 km of transport distance. Method of transport is another variable that has been determined as a potential contributor to BRDC occurrence. Dehydration is a frequent consequence of transportation and has been suggested as a mechanism by which transport impacts the disease. After arrival into a feedlot, calves may be dehydrated, with a lack of appetite and some of them show clinical signs of the early stage of BRDC (Urban-Chmiel and Grooms, 2012).

Changes in diet

Formulations of diets for newly received cattle have to provide nutrient concentrations for low-feed intake and optimal performance during arrival and acclimatization (Urban-Chmiel and Grooms, 2012). Correlation between nutrition of stockers, immunoglobulin production and respiratory disease

frequency was confirmed by Duff and Galyean (2007). Low energy and protein concentration in feed increases the suppression of immunological response and decreases the Average Daily Gain (ADG) in calves. Taylor *et al.* (2010b) determined that the concentration of energetic substances in feed during the first 4 weeks of feedlot should be 72%.

High density of animals

Good management practices (GMP), including low stocking density, good ventilation and hygiene, reduce stress. During shifting of pens, the youngest animals are put in a pen where the oldest (immune) animals have been (Valarcher and Hägglund, 2006).

Surgical procedures (castration, dehorning)

Castration upon arrival is considered a risk factor for BRDC. Delayed castration has repeatedly been found to reduce ADG (Zweiacher *et al*., 1979; Berry *et al.*, 2001; Fisher *et al.*, 2001), a result that was not influenced by analgesia during castration (Faulkner *et al.*, 1992). Previous facts indicate that castration is stressful. Castration of adult bulls increased plasma cortisol concentrations (Chase *et al.*, 1995). The immunosuppressive nature of rising levels of cortisol leads to adult bull's castration casting a higher risk of BRDC than non-castrated cattle or those castrated at a younger age.

Dehorning is recommended to be performed early in life (similar to castration because it is painful). Regardless of the negative effects that may result from castration and dehorning, the procedures should be performed to meet current industry standards, but the question remains how and when they should be performed.

Viral agents (infections)

The basis of the action of the BRDC virus is to create an environment that allows the formation of colonies and the replication of pathogenic bacteria that lead to pneumonia. Viruses may cause alteration in mucosal surfaces such that adhesion of bacteria to virus-infected cells is increased. Subsequent colonization more easily involves tissue parts where erosion of the mucosa is caused by the virus, but those parts where mucosa is intact (Rivera-Rivas *et al*., 2009). Viruses can cause modifications of innate and acquired immunity by altering the function of alveolar macrophages, suppression of lymphocyte proliferation, induced apoptosis, modified release of cytokine and other inflammatory mediators, inhibition of interferon production, a decrease in the number of leukocytes and weakening of humoral immunity by reducing the production of antibodies that fight bacterial infections (Srikumaran *et al*., 2007; Polak, 2008).

BRDC-induced viruses act synergistically with bacteria that are most often isolated in the diagnosed cases of this disease, creating more severe BRDC. An example of this synergy is when the primary viral infection results in increased release of cytokines i.e. IL-1, 8, which activate and increase the migration of neutrophils and the inflammatory process (Leite *et al*. 2002). This can result in the most acute form of BRDC, with greater adherence of bacteria, such as *M. haemolytica*, to bronchial epithelial cells, causing progressive inflammation characterized by fibrinous bronchopneumonia (Hodgson *et al*. 2005).

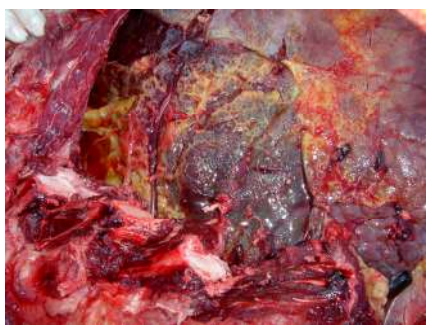

Figure 1. Bronchopneumonia fibrinosa (Pleuritis fibrinosa adhesiva) (Courtesy: Nikola Vaskovic, Veterinary Specialized Institute, Kraljevo, Serbia)

Experimentally, a syndrome resembling BRD can be induced by exposure to *M. haemolytica* following infection by BHV-1 (Jericho and Langford, 1978). Similar results were revealed with endo-bronchial instillation of BVDV, followed 5 d later by *M. haemolytica* (Potgieter *et al*., 1984). Specific viral agent is BVDV, because intrauterine infection in the first trimester can result in cattle that are persistently infected (PI). Cattle that were PI were usually chronically ill or dying in feedlots (Loneragan *et al*., 2005). Persistently infected cattle shed large amounts of the virus, increasing the risk of infection and consequently the risk for BRDC. Antigens to BRSV and PI3V were considered in over 50% of clinically diseased lungs in Mexico (Juarez Barranco *et al*., 2003), while BVDV was identified in naturally affected calves in a study of Fulton *et al*. (2000). Serological data has linked BRD outbreaks to BRSV (Durham *et al*., 1991; Hagglund *et al*., 2007), PI3V and BVDV (Fulton *et al*., 2000), as well as multiple concurrent viral infections (Richer *et al*., 1988; Martin and Bohac, 1986). Disease caused by BRSV usually occurs in cattle younger than 18 months and calves at the age of 10 days to several months (Quinting *et al*., 2007).

Lazić *et al*. (1995) confirmed that prevalence of BHV-1 in Serbia is more than 50%. Confirmation of the previously obtained results was published by Lazić *et al*. (2003), who conducted a preliminary serological testing of 10 cattle herds. Infection caused by the BHV-1 was present in 8 herds, with the

percentage of seropositive animals ranging from 37% to 98%. In Serbia, Nišavić *et al*. (2010) isolated the BHV-1 from bovine nasal and ocular swabs, lungs, trachea and tonsil samples, and identified it by the virus-neutralization test (VNT). Comparative analysis of DNA fragments of controlled laboratory BHV-1 strain TN 41 and isolated strains obtained by PCR with primers for viral thymidine kinase gene coding region confirmed that the isolated strain belongs to BHV-1. Šamanc *et al*. (2009) examined in parallel 92 samples of blood serum of unvaccinated calves and heifers from Serbian farms, for the presence of antibody (Ab) against BRSV, PI-3 and BHV-1 by indirect enzyme immunoassay (iELISA). They confirmed the presence of Ab against BHV-1 in 19 (20.65%) of the samples, Ab against the PI-3 virus in 77 samples (83.69%) and Ab against the BRSV in 40 samples (43.47%).

Bugarski *et al*. (2011) conducted serological examination on dairy farms and cattle feedlots in Vojvodina (Serbia) on BRSV infection and revealed that from a total of 223 examined serum samples from feedlots, 60.09% contained Ab against BRSV, and seroprevalence depending on the phase of fattening.

Brodersen (2010) and Raaperi *et al*. (2012) stated that the BRSV is a major cause of respiratory diseases and a major contributor to the onset of BRDC. Kurćubić *et al*. (2013) confirmed previous findings and determined the genome of the BRSV by Real-Time RT-PCR in all 20 examined samples of discharge from the nasal mucosa of the diseased beef cattle from two farms in Serbia.

The presence of BVDV infection in Serbia was unofficially confirmed earlier (Kurćubić, 1993; Petrović, 2002; Petrović *et al*., 2004; Petrović, 2006), but official registration of BVDV infection of cattle in Serbia and Montenegro was received from the OIE reference laboratory (Veterinary Laboratories Agency, Weybridge, UK – December 9, 2002). Direct sequencing of PCR products, alignment and phylogenetic analysis showed that the 0016 and Beograd isolates were of genetic subtype BVDV-1f (first report of a cp BVDV belonging to the 1f subgroup), whilst the 0017 isolate belonged to subtype 1b. Official registration was obtained after research by Petrović *et al*. (2004), who detected the ncp BVDV isolates 0016 and 0017 and the cp isolate Beograd by indirect immunostaining methods. Kurćubić (1993) conducted VNT on dairy farms where the percentage of BVDV seropositive animals varied between 30.55 and 52.24%, depending on the age category and herd management. On the second farm with 6 to 7 months old beef cattle, 55.81% of seropositive sera were detected. Kurćubić *et al*. (2010) tried to determine the presence of PI in cattle of various ages from different production purpose herds (fattening/milk), and BVDV Ag was not confirmed in either of the cases. The explanation for the lack of experimental proof of the presence of PI cattle can be found in the fact that the prevalence of PI cattle was extremely low (0.75–2%), and that not all animals whose age allowed testing were subjected to serum assays for the presence of BVDV Ag.

In Vojvodina (Serbia), 12,083 blood samples of cattle older than 6 months were examined, and the presence of specific Ab against BVDV was established in 4647 (38.46%) of the examined animals (Petrović, 2006).

Virus PI-3 often takes part in mixed infections with BHV-1 and BVDV, manifested with severe clinical signs and fatal outcome. Lazić *et al*. (2009) indicate that in Serbian literature there are only few data on PI-3V as the causative agent of BRDC, especially in beef cattle. Serological surveys of PI-3V infection are strongly recommended. His research presented the BRDC outbreak accompanied by PI-3V infection in a bull calf fattening unit of industrial type. The geometric mean value of Ab titre against PI-3V was 14.58 at the moment of disease, while 3 and 6 weeks after outbreak it was 45.25 and 54.44, respectively, and at the end of fattening it was 22.11.

Bacterial agents (infections)

The most common bacteria found in the lungs of cattle with BRDC are *Mannheimia haemolytica* and *Pasteurella multocida*. Sixteen different serotypes of biotype A and T of *Mannheimia haemolytica* were classified; with twelve different serotypes based on capsular serotypes for the A serotype (Fulton, 2009).

Today's researchers' opinions that the *P. multocida* is a primary pathogen in the lungs of cattle have been confirmed in five-year research of Kurćubić *et al*. (2000). They tested a total of 1435 nasal swabs originating from beef cattle with respiratory symptoms that indicate BRDC. The most commonly isolated were *Pasteurella multocida* and *Pasteurella haemolytica* (62.78 and 40.20%, respectively), *Corynebacterium pyogenes* (53.44%), *Staphylococcus albus* (24.87%) and *Streptococcus viridans* (14.07%). When the presence of *Mannheimia haemolytica* in diseased cattle is confirmed, the disease has a sever character and ends in quick death (Bednarek, 2010). Infection with *M. haemolytica* in affected animals leads to the extensive damage and inflammation of lung tissue. *M. haemolytica* produces many other potentially virulent factors, like leukotoxin (Lkt; Hinghlander, 2001). The leukotoxin izoform produced by *M. haemolytica* biotype A, serotype 1, has the most visible cytotoxic proprieties in relation to bovine leukocytes. Bovine leukocytes exposed to low doses of exotoxin show reduced phagocytic and killing activity against engulfed bacteria. A lot of reactive substances (free radicals, lizosomal enzymes, proteases) in relation to phagocytes (netrophils, monocytes) are realised from destroyed cells and then they stimulate different pathological lesions in affected bovine lung tissue, leading to acute lobar fibrionecrotising pneumonia, characteristic of acute BRDC. Lung lesions at slaughter are extremely common with an observed prevalence ranging between 29.7 and 77% (Thompson *et al*., 2006) in feedlot cattle. All the changes are consequences of Lkt action and the development of lung inflammatory cascade regulated additionally by some pro-inflamatory cytokines (Bednarek *et al*., 2009). The leukopenia resulted from the toxic influence of *M. haemolytica* A1 Lkt,

showing a species-specific depletion effect with respect to bovine leukocytes (Bednarek *et al*., 2008). Additionally, the concentrations of some acute phase proteins (CRP, Cp, Tf, Hp, SAA and also eicosanoids (PGE2, PGF2α, LTB4) had also significantly changed, because there were their higher values after leukotoxin administration (Bednarek *et al*., 2009, 2010).

Histophilus somni is a Gram-negative coccobacillus that causes respiratory, reproductive, cardiac and neuronal diseases in cattle. It was discovered that bovine neutrophils and macrophages produce extracellular traps in response to *M. haemolytica*, which suggests that extracellular traps may play a role in the host response to *H. somni* infection in cattle.

Mycoplasma bovis is one of the commonly isolated mycoplasmal agents from BRDC cases. Its adaptive ability to a host organism increases owing to different versions of the same vsp gene family which encode particular adhesive factors of the mycoplasma (variable surface proteins - Vsps), and possess the ability to immunomodulate host defence against infection (Razin *et al*., 1998). The stimulation of production of some acute phase proteins (haptoglobulin and serum amyloid A) is one of the most important components of acute phase response for cattle (Dudek, 2010).

Conclusion

The ultimate purpose is to improve the production of beef meat intended for human consumption. It is necessary to study in detail a large number of predisposing environmental factors and applications of obtained results for herd management adjustments, taking into account the principles of Good Animal Practice. Future research is needed to determine the best method to identify resistant animals.

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ETIOPATOGENEZA I EKONOMSKI ZNAČAJ KOMPLEKSA RESPIRATORNOG OBOLJENJA GOVEDA (BRDC)

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Rezime

BRDC je najskuplje oboljenje tovnih junadi širom sveta. Razlozi za to su visok morbiditet i mortalitet, gubitak telesne mase, smanjeno iskorišćenje hrane, smanjen kvalitet trupova i obimne mere profilakse i terapije. BRDC uzrokuje veći broj patogena (virusa i bakterija), uz predisponirajuće faktore rizika iz ambijenta i samog domaćina. Telad su najizloženija riziku od nastanka BRDC neposredno nakon transporta. Većem riziku su izložena telad manje težine, mada to nije jedinstveno mišljenje. Kompleksnost BRDC otežava definisanje uloge individualnih faktora koji predisponiraju ili uzrokuju oboljenje. Stresogeni faktori mogu biti „neophodni, ali ne dovoljni“, jer zahtevaju dodatne efekte koji izazivaju bolest. Rast proizvodnje mesa i mleka širom sveta može biti održiv unapređenjem prevencije i kontrole BRDC.

Ključne reči: Kompleks respiratornog oboljenja goveda (BRDC), predisponirajući faktori, virusi, bakterije, tovna junad, ekonomski gubici