

VACCINATION AND MEDICATION AGAINST BOVINE RESPIRATORY DISEASE COMPLEX (BRDC)

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Review paper

Abstract: BRDC causes pneumonia of cattle, due to which high morbidity and mortality, decreasing food intake and daily growth, and quality of carcasses is significantly reduced. Preventive application of cattle vaccination and treatment of diseased animals with therapeutic agents, with the aforementioned losses, leads to the fact that BRDC is the most expensive cattle disease worldwide. Given the complex etiology (the influence of more viral and bacterial agents), it is characteristic that if viral agents cause disease, the morbidity level is high and the mortality rate is lower. Cattle affected by bacterial infections have a sporadic morbidity and a higher mortality rate. There are a number of predisposing factors originating from the environment or hosts that have a negative impact on the health status of cattle. So, there are a number of challenges that must be solved in the future, with the aim of developing new technologies that would contribute to increasing animal resistance, eliminating risk factors and reducing exposure to pathogens.

Key words: Bovine respiratory disease complex (BRDC), viruses, bacteria, vaccination, medication

Introduction

Bovine respiratory disease complex (BRDC) continues to be one of the most expensive syndromes in fattening and dairy cattle throughout the world. BRDC leads to huge economic losses due to high morbidity and mortality, weight loss, reduced food utilization, reduced quality of carcasses and extensive measures of prophylaxis and therapy (*Edwards, 2010*). In the European Union, production losses (excluding livestock deaths) are about 576 million euros annually (*Barrett, 2000*). The losses on the cattle industry in the US are calculated on US \$1 billion, while prevention and treatment costs amounted to over 3 billion US dollars

annually (Griffin, 2006; Snowden et al., 2007). The losses in beef production in the US in 2010 (1,055,000 cattle) were estimated at \$643 million (NASS, 2011). 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).

The major viral and bacterial pathogens that they presume are the causes of BRDC have been identified with largely clarified etio-pathogenesis. Numerous predisposing factors bear a high risk of development of BRDC, including environmental (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), as described by Taylor et al. (2010). The most common viruses that causes BRDC are 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). Bacterial infections causes by *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni*, *Arcanobacterium pyogenes*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Chlamydiales spp.*, *Fusobacterium necrophorum*, *Corynebacterium bovis*, *Streptococcus spp.* and *Micrococcus spp.* (Taylor et al., 2010). A larger number of preventative tools (vaccines) and effective medicines (anti-microbial and anti-inflammatory products) have been developed with the potential to enable BRDC control. BRDC is complex, multi-factorial and despite the contemporary tools continues to endanger cattle health, welfare and farm profitability (Caldow, 2011).

Vaccination

One of the main ways to combat the emergence of BRDC is the vaccination of cattle against the most common viral and bacterial agents (Urban-Chmiel and Grooms, 2012). In the US, are currently available different combinations of vaccines against the viral agents BHV1, BVD, PI3, BRSV and the bacterial pathogens *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somnus*. BVDV is unique because intrauterine infection can result in persistently infection (PI) of cattle. Cattle that were PI are with the symptoms of chronic illness or dying in feedlots (Loneragan et al., 2005). In Serbia, determination of the presence of PI in cattle of various ages from a herd with a different purpose (fattening/milk) explored by Kurćubić et al. (2010). BVDV Ag was not confirmed in either of the cases, probably that the prevalence of PI cattle was extremely low (0.75-2%), and not examined sera of all animals from the farms on presence of BVDV Ag, whose age allowed this examine. Due to the specificity of viral agents, the attenuated live and killed vaccines can be found on the market. Depending on the type of vaccine, the development of immunity requires a period of one to three weeks, and it may be necessary to apply multiple doses of vaccines

(“booster” immunization) to achieve the protective level of the immune response. The time that the initial vaccination will be carried out is variable. If the time of the transport of the cattle to the feedlot is longer than 12 hours, it is recommended that the animals rested a certain time before they are vaccinated. The safest preventive approach is if the calves are vaccinated before they are transported to the feedlots, especially if the vaccination is part of a pre-conditioning program (management strategies which allow creating an immune response at a time when the stress and the presence of infectious agents are minimal). *Richeson et al. (2008)* compared the results of the use of a polyvalent vaccine prepared from modified live viruses (MLV), which was administered upon arrival at the site or postponed after 14 days. They revealed improvement in daily body weight gain at day 0 to 14 and day 0 to 42 in the postponed procedure.

A very illustrative and interesting review of the study of bovine respiratory illness for 26 years (1983-2009) was announced by *Fulton (2009)*. The list of vaccines and therapeutic agents in the *Veterinary Pharmaceuticals and Biologicals (1982/1983)* showed several MLV vaccines containing BHV1, BVDV with no genotype noted, and PI3V for parenteral use. Data for intranasal use were very small for MLV BHV1 vaccines. Only two vaccines from killed viruses (KV) were available: one KV vaccine with BHV1, PI3V and BVDV, and a second KV vaccine with BHV1 and PI3V. In that time, no licensed vaccines against BRSV. During 2009 (26 years later) in the *Compendium of Veterinary Products, 11th edition (2008)*, lists a much larger number of vaccines. The contemporary vaccines listed in above mentioned *Compendium* reflect the innovation in the identification and the addition of selected strains of viruses. Such representatives are MLV vaccines for injection or intranasal use for BHV1, BVDV1a and BVDV2a, PI3V, and BRSV as well as KV vaccines for these same viruses for injection. Certain vaccine strains from 1983 are now described much more precisely, such as the BVDV1a and BVDV2a identified in many current vaccines, which was simply listed as BVDV in 1983. Although many changes have occurred in the period of 26 years and progress has been made in the research and formulation of vaccines, most vaccine strains of BHV1, BVDV, PI3V are isolates from 35 to over 50 years ago.

In Serbia, the immunogenicity of two (mono and polyvalent) experimentally prepared inactivated vaccines containing BVDV reference and field strains evaluated by *Kurćubić et al. (2011a)*. They formed 3 experimental groups: Group I - 10 calves vaccinated twice (days 1 and 28) s/c with 2 mL of inactivated polyvalent vaccine per animal; Group II - 10 calves vaccinated in same manner with inactivated monovalent vaccine; Control group (C) consisted of 9 unvaccinated calves. Blood serums are taken from experimental animals on days 0, 14, 28, 42 and 56 post vaccinations, and examined by VNT. The immune response developed more rapidly and values of geometric mean titer (GMT) for BVDV neutralizing Ab were strongly higher in blood sera of calves from Group II. Second

part of the study (Kurćubić et al., 2011b) included evaluation of the immune response to same BVDV vaccine by the iELISA method. The occurrence of a specific Ab against BVDV was first detected on day 42 post immunization in both experimental groups of beef calves and remained steady until day 56. The statistically very significant differences observed between the experimental animals of groups I and II on days 42 and 56 after vaccination suggest considerably higher immunogenicity of the monovalent vaccine.

Bednarek et al. (2012) described the market situation when it comes to different types of vaccines against the infective agents which cause of BRDC. Inactivated vaccines for immunization of cattle against *P. multocida* and septicemic and pneumonic strains of *M. haemolytica* and *H. somni* are available under various commercial names: Hiprabovis pneumos, Pastobov, Bovilis Bovipast. Inactivated or modified live polyvalent vaccines that are used in a number of countries contain antigens such as BRSV, PI3 (Rispoval, Bovilis Bovipast), BVDV (Mucosiffa, Bovilis BVD) and BHV1. Recent research is an antigen of the IBR virus used in the formulation of marker vaccines, whether live vaccines (Rispoval-IBR marker vivum, Hiprabovis-IBR marker live) or inactivated (eg, Ibraxion, Rispoval-IBR-marker inactivatum, Bovilis IBR - marker inactivatum) applied in IBR eradication. The most common is the parenteral vaccine application, but it usually has to be twice as stimulating a quality protective response. Recent vaccine produced (Rispoval 3) have combined live and dead viral components of the four main antigens and is administered intramuscularly. They are also available MLV are administered intranasally (Rispoval RS+PI3 IntraNasal). More research has revealed that the intranasal immunization of calves gives active immunity in very young animals despite the presence of maternal antibodies and generates a significant systemic response and interferon induction (Stokes, 2006).

In Serbia, according to the *National Veterinary Medicines Register* (2017), there are no registered and available vaccinations of domestic producers for the immunization of healthy cattle and calves against respiratory diseases, although they were available in the previous period (Kurćubić et al., 2014). The six available registered import vaccines are: Bovilis® IBR marker inac (Intervet International B.V., ATCvet QI02AA03), which contains inactivated BHV1, modified (gE-) strain GK/D; BOVILIS BVD (Intervet International B.V., ATCvet QI01AA01), vaccine which contains inactivated BVDV, strain C 86; BIOBOS RESPI 4 (BIOVETA, A.S., Czech Republic, ATCvet QI02AL**), which contains inactivated BRSV (strain BIO-24), inactivated PI3V (strain BIO-23), inactivated BVDV (strain BIO-25) and inactivated *Mannheimia (Pasteurella) haemolytica* (strain DSM 5283) serovar 1A; RISPOVAL 3-BRSV-PI3-BVD (ZOETIS BELGIUM S.A., Belgium, ATCvet QI02AH**), vaccine which contains modified live PI3V, strain RLB103, live BRSV, strain 375 and inactivated BVDV type 1, strains 5960 (cp) i 6309 (ncp); RISPOVAL IBR-MARKER VIVUM (ZOETIS

BELGIUM S.A., Belgium, ATCvet QI02AD01), vaccine which contains live BHV1, modified (gE-) strain Difivac; RISPOVAL RS+PI3 INTRANASAL (ZOETIS BELGIUM S.A., Belgium, ATCvet QI02AD07), vaccine which contains live modified PI3V, strain RLB103 and live modified BRSV, strain 375.

Therapeutic agents

The rapid destruction of the pathogenic bacteria of the BRDC, especially the *Pasteurellaceae* family, is the first step in the treatment of this complex syndrome, and prevents the formation of more serious lesions on the lungs. The use of antibiotics must be at an earlier stage after an infection (usually accompanied by fever, loss of appetite and nasal discharge), and certainly before irreversible changes (oral breathing, orthopnea, cyanosis). The most commonly used are antibiotics that have prolonged action and the spread of the antibacterial spectrum: tetracyclines (oxytetracycline), macrolides (florfenicol, tulathromycin, gamythromycin) and fluoroquinolones (enrofloxacin, marbofloxacin, danofloxacin). At the first European Buiatrics Forum in Marseille (2009), three new concepts of antibiotic application in the treatment of cattle affected by BRDC were presented. Single Injection Shot Acting AntiBiotic (SISAAB) primarily represents new formulations of fluoroquinolones (Marbocyl S - marbofloxacin), Baytril One or Enroxil Max (enrofloxacin). In this concept, tetracyclines (Tetradur) with long acting can be used here like single intramuscular injections. Single Injection Long Acting AntiBiotic (SILAAB) implies application of new generations of macrolides: tulathromycin (Draxxin) and gamythromycin (Zactran). Multiple Injection Long Acting AntiBiotic (MILAAB) is a risky concept due to increased potential for resistance to antibiotics.

Mannheimia haemolytica (formerly *Pasteurella haemolytica*) and *Pasteurella multocida* bacterins were available, but they were probably replaced by more modern products in the meantime. The most commonly used antibiotics for BRDC therapy in the period 1982-1983 (Fulton, 2009) were erythromycin, penicillin-dihydrostreptomycin, tylosin injectable and oral oxytetracycline and injectable sulfamethazine, while today they are almost forgotten. In the *Compendium of Veterinary Products, 11th edition (2008)* is displayed almost completely new list of drugs available in 2009. Modern antibiotics that are used today include the principal marketed injectable: ceftiofur, oxytetracycline, enrofloxacin, florfenicol, danofloxacin, tilmicosin and tulathromycin. Also listed in the 2008 *Compendium* are injectable tylosin, erythromycin and penicillin. A new drug available in 2009 is the non-steroidal anti-inflammatory product flunixin meglumine. They are also used oral medications such as sulfas, tetracyclines and tylosin.

Kurćubić *et al.* (2013) revealed that the most common bacteria in fattening cattle sick of BRDC were *P. multocida*, *Aeromonas viridans* and *Corynebacterium*

bovis, pointing to their greater importance in BRDC in Serbian beef cattle in regard to *Mannheimia haemolytica*, predominantly represented worldwide. Sensitivity testing showed that the most efficient antibiotics against *P. multocida* were enrofloxacin and florfenicol (100% of tested *P. multocida* isolates sensitive on both antibiotics). Jezdimirović *et al.* (2011) tested the clinical efficacy of tulathromycin (TU) and florfenicol (FL) in the treatment of bronchopneumonia (BP) caused by *Pasteurella multocida* isolated from diseased six months old Holstein calves. TU proved to be a drug of first choice in the treatment of BP.

In the study researcher found that the percent of morbidity was decreased about two-fold in the case of tulathromycin injection and the percent of occurrence of mortality was reduced to 3.6% and 13.5% for tulathromycin and tilmicosin respectively (Nickell *et al.*, 2008). Administration of florfenicol (40mg/kg) in calves after transportation, especially in “high-risk” groups, significantly reduced (more than 35%) BRDC incidences during the first 3 week of feeding (Booker *et al.*, 2007).

Anti-inflammatory agents of steroidal and non-steroidal origin are used to control the inflammatory reaction in the lungs of cattle (Lekeux, 2006). In BRDC supportive therapies were applied different kinds of corticosteroids: betamethasone, dexamethasone, prednisolone, cortisone, hydrocortisone, flumethasone and trimcinolone. Because of their strong immunosuppressive character were usually use only in a single administration. Nonsteroidal anti-inflammatory drugs are, with some exceptions, analgesic and antipyretic. The drugs most commonly used in BRD therapy in Europe are flunixin meglumine, carprofen, ketoprofen, meloxicam, tolfenamic acid and metamisole.

Conclusions

BRDC is still the most serious health problem in cattle breeding, especially in fattening animals. In order to reduce the economic losses to an acceptable level, it is necessary to reduce stress (caused by various predisposing factors), improve the quality of vaccines and design the most optimal programs for vaccination and application of therapeutic agents (metaphylaxis strategy), as well as to better understand the impact of genetics on resistance against BRDC.

Vakcinacija i terapija protiv kompleksa respiratornog oboljenja goveda (BRDC)

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Rezime

BRDC uzrokuje upalu pluća goveda, usled čega je visok morbiditet i mortalitet, i dolazi do smanjenog unosa hrane i dnevnog prirasta, kao i kvaliteta govedih trupova. Preventivna primena vakcinacije goveda i lečenje terapeutskim agensima obolelih goveda, uz prethodno navedene gubitke, dovode do činjenice da je BRDC najskuplje oboljenje goveda širom sveta. Obzirom na kompleksnu etiologiju (uticaj većeg broja virusnih i bakterijskih uzročnika), karakteristično je da ukoliko virusni uzročnici izazivaju oboljenje, nivo morbiditeta je visok a stopa mortaliteta niža. Goveda zahvaćena bakterijskim infekcijama imaju sporadičan morbiditet i višu stopu mortaliteta. Postoji niz predisponirajućih faktora poreklom iz okoline ili domaćina koji imaju negativan uticaj na zdravstveni status goveda. Dakle, postoji niz izazova koji u budućnosti moraju biti rešeni, sa ciljem da se razviju nove tehnologije koje bi doprinele povećanju otpornosti životinja, otklanjanju faktora rizika i smanjenju izloženosti patogenima.

Ključne reči: kompleks respiratornog oboljenja goveda (BRDC), virusi, bakterije, vakcinacija, lečenje

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