19

Bovine Respiratory Syndrome (BRD) Etiopathogenesis, Diagnosis and Control

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1. Introduction

1.1 Etiopathogenesis

Bovine respiratory disease (BRD) complex is a major disease, classically in the indoor calves and feedlot young cattle. The etiopathogenesis of BRD is multifactorial and complex. In this complex etiology an equivalent role plays both the infectious agents as well as the environmental factors which are called also as environmental stressors (inappropriate livestock management like mistakes in animal nutrition, transport, handling, veterinary interventions etc.) (tab. 1). The most significant pathogens which are involved in the etiopathogenesis of BRD, i.e. suitable species of viruses such as (bovine respiratory syncytial virus (BRSV), parainfluenza virus type 3 (PI3V), bovine herpes virus type 1 (BHV1), bovine viral diarrhea virus (BVDV), are usually associated with concurrent bacterial infections represented by: *Mannheimia haemolytica*, *Pasteurella multocida, Histophilus somni* and others (tab. 1) (Jared et al., 2010a, Kita et al., 1994, Klimentowski et al., 1995) and also mycoplasmal factors such as: *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 traditionally considered as the most common bacterial infectious factors in the BRD etiology (Fulton et al.; Reggiardo et al., 2005). On the other hand the one of the most often isolated mycoplasmal factors from BRD cases is *Mycoplasma bovis*. Its adaptative ability to a host organism increases owing to different versions of the same *vsp* gene family which encode particular adhesive factors of the mycoplasma, i.e. variable surface proteins (Vsps; Razin et al., 1998). The variability of *vsp* gene based on DNA transposition (Lysnyansky, 1996). Therefore the high Vsp variation determines the phenotypic variability of the antigen (Rosengarten et al., 1994) which further increases the virulence of the pathogen. *M. bovis* possess the ability to immunomodulate host defence against infection (Razin et al., 1998), for example inducing a synthesis of proinflammatory agents, i.e. TNF-α and nitric oxide (Jungi, et al., 1996) or stimulation of some acute phase protein production, such as haptoglobulin and serum amyloid A, which represent one of the most important components of acute phase response for cattle (Dudek, 2010). It is known that *M. bovis* acts as a stimulant on major subsets of T-lymphocytes (Vanden Bush, 2003). In contrast, some data show inhibitory properties of the pathogen which come down to its suppressive effect on lymphocytes (Vanden Bush & Rosenbusch, 2002; Thomas et al., 1990)

and some neutrophil functions (Thomas, et al. 1991). The inhibitory effect of *M. bovis* on the mononuclear cells is not connected with arginine depletion or cytotoxic activity (Thomas et al., 1990). Recently, *M. bovis* is considered as primary pathogen in BRD, not only acting in coinfection conditions. The significance of *M. bovis* in etiopathogenesis of the syndrome is also important with regard to synergistic effect with some infectious factors involved in BRD. For example, *M. bovis* exhibits the colonising synergism with *Mannheimia haemolytica* (Houghton & Gourlay, 1983), whereas coinfection with bovine viral diarrhea virus (BVDV) may increases a pathogenicity of concomitant infectious agents mainly considering suppression of host immune response (Potgieter, 1997; Haines et al., 2001). The disease course during infection with *M. bovis* is generally acute and relates to young cattle (Wikse, 1985). Clinical symptoms mainly limited to dysfunction of the respiratory tract of animals, including cases of fatal diseases, and their intensity decreases with the development of chronic phase of infection (Nicholas & Ayling, 2003). However, complicated infections with *M. bovis* have usually severe course and may take the form of necrosuppurative bronchopneumonia. Pathological changes of the disease are characterized by consolidation areas with nodular lesions containing necrosuppurative material surrounded with fibrous capsule, whereas in histology they are rich in foci infiltrated by degenerating leukocytic cells (Radaelli et al., 2008).

Stress factors	**Viruses**	**Bacteria**
Heat Cold Dust Dampness Injury Fatigue Dehydration Hunger Anaxiety Irritant gases Nutrional deficiencies Surgery	*Bovine respiratory syncytial virus (BRSV)* *Parainfluenza virus type 3* (PI3) *Bovine herpes virus type 1 (BHV))* *Bovine viral diarrhoea virus (BVDV)* *Adenoviruses* *Rhinovirus* *Enteroviruses* *Bovine respiratory coronavirus*	*Mannheimia haemolytica* *P. multocida* *Histophilus somni* *Arcanobacterium pyogenes* *Streptococcus pneumonie* *Staphylococcus aureus* *Chlamydiales spp.* *Fusobacterium necrophorum* *Corynebacterium bovis* *Streptococcus spp.* *Micrococcus spp.* Mycoplasmas *M. bovis* *M. bovirhinis* *M. dipsar* *M. alkalesscens* *M. canis* *M. bovigenitalium* *Ureaplasma spp.* *Ureaplasma diversum*

Table 1. The most important etiological causes of BRD

In the complex etiology of BRD also other mycoplasmas, such as *M. dispar*, *M. bovirhinis* or *U. diversum* can play an important role (Autio et al., 2007). These mycoplasma species were concurrently present in 50% of examined herds and bacterial agents of the syndrome, i.e. *P. multocida*, *Arcanobacterium pyogenes* or *M. haemolytica* coexisted with these cases.

Additionally, main viruses of bovine respiratory system were concomitant factors of the infections. However, the highest correlation between the prevalence and clinical respiratory signs of disease were observed for *U. diversum* when compared with *M. dispar* and *M. bovirhinis* (Autio et al., 2007).

In the chronic form of the respiratory syndrome should be also mention about chlamydia, particularly *Chlamydophila psittaci* and *Ch. pecorum* apart from that anaerobes bacteria such as *Clostridium* sp. are often engaged in the etiopathogenesis of the disease. Moreover, the different endogenous factors play also an important etiological role in the BRD etiology. First of all young cattle before one - year - old have an insufficient developed respiratory system for an efficient gas exchange and fully effective and constructive mucociliary clearance mechanisms. Calves have almost by a half lower of the lung surface for gas exchange and higher primary activity of pulmonary ventilation, which in connection with the increased of metabolic demand in these animals is the main cause of low supply of oxygen in the body. The low partial pressure of oxygen causes a significant weakening of the movement of cilia snapshot, phagocytic activity of pulmonary macrophages and a reduction in lung clearance of harmful microorganisms. When an affectivity of pulmonary clearance and local immune response of the lungs are reduced, a variety of infectious agents (viruses, bacteria, mycoplasmas) have better access to lower parts of the respiratory tract and they can initiate the development of pathological lesions (Lekeux et al., 1995).

While the different pathogens involved in etiology of BRD are presented in the heard throughout the years, the outbreak of the disease and an appearance of clinical symptoms are seasonal. Usually, there are two seasonal peaks of enzootic pneumonia occurred: the first was between October and December and the second from February to May (Andrews, 2004). The sigs of the disease depend on its clinic form i.e. chronic or acute. The chronic form of BRD generally shows no signs. The calves are bright, eats well but may have a slight mucoid or mucopurulent oculonasal discharge, the body temperature is normal or slightly raised at 38.5-39.5°C and dry, explosive cough usually is produced singly. During the acute case of the disease inappetance, pyrexia (40-42°C), dull sweaty coat, mucoid and mucopurulent oculo-nasal discharge, tachypnoea (respiratory rate- RR over 40 breaths per minute) are presented. Moreover, there is a tendency to a persistent coughing. The cough can be harsh, dry, hacking type but sometimes is moist. During the auscultation of the thorax under both inspiration or expiration there are loud, harsh sounds or whistling, wheezing or squeaking (Andrews, 2004).

At present, BRD is a great economic problem in cattle husbandry, especially in young and feedlot animals all over the world. It accounts for approximately 30% of the total cattle deaths worldwide and is associated with an annual economic losses of over one billion dollars in North America alone (Adamu, 2007). However, the most often outbreak of acute disease occurs when there are calves from different sources in herds. The congestion and inadequate ventilation are the predisposing factors for the development of BRD. Despite that the different pathogens cause of BRD its initial clinical symptoms are very similar i.e. bronchitis and bronchiolititis. In the first phase of the disease the mucus production in diseased calves increases and its stand over in respiratory tract. This is cause a main cause for handicap of defence mechanism in the course of the respiratory disease and the spread of bacterial infections in lungs, which resulted in the intensification of the primary viral infections. The studies recently conducted in Poland have been found the mixed viral

infections in field outbreaks of BRD (Kita et al., 1994). The highest specific antibody titres were detected particularly in relation to: BRSV, BHV-1, BVDV, PI-3 and Adeno-3.

During the necropsy the anatomicopathologic changes are observed in the ventral part of the lung lobes and involve, in the decreasing the apical, cardiac and cranial part of the caudal lobes. The area can involved 5 - 40% of the lung tissue. Histologically, the changes concerning intensive accumulations of lymphocytes in the peribronchiolar tissue are usually found, macroscopically it is seen as a mottling of the lesion's cut surface. In the acute pneumonia there are three types of pathological changes. Type 1- pulmonary tissue consolidation - is noted in the cranial lobes of lungs and the tissue is dark red, friable and there is no necrosis changes. The type 2 – in a form of the marked consolidation is very often observed in cranial lobes too with red/grey hepatisation, necrosis and suppuration. The extensive consolidation and suppuration are seen during *A. pyogenes* and *F. necrophorum* infections. The 3th type of pathological entity is characteristic for calves that suddenly developed respiratory diseases. In this case there is interstitial emphysema, pulmonary oedema and congestion with alveolar epithelia hyperplasia and hyaline membrane formation (Andrews, 2004).

Viruses are believed to predispose to bacterial infections in two distinct ways. The first, viral agent can cause direct damage to the respiratory clearance mechanism and translocation of bacteria from the upper respiratory tract. The second way, viral infection can interfere with the immune system's ability to respond to bacterial infections. The viruses can affect the leukocytes causing impairment of their function which result in increased susceptibility to infection of *Mannheimia haemolytica* (Jared et al., 2010a). The virus which seen to be the most often responsible for the appearance of BRD is BVD/MD. The virus may suppress the immune system in the affected animals. The infection of BVD/MD leads to inhibition the production of interferon, a decline in the number of leukocytes and the weakening of humoral immunity by reducing production of antibodies it causes bacterial infections (Polak, M., 2008).

The clinical cases which confirmed the presence of *Mannheimia haemolytica* have a sever character and finishing quick death (Bednarek, 2010). In sick animals are usually found high fever, mucopulurent or pulurent nasal discharge, lacrimation, incidence of painful cough with symptoms of severe shortness of breath, weakness and apathy. In some animals may have been presented watery diarrhea and ill animals not shown willingness to foraging. As a result of this pathogen infection in affected animals occur the extensive damage and inflammation of lung tissue. *M. haemolytica* produces many other potentially virulent factors, among them leukotoxin (Lkt; Hinghlander, 2001; Whitley et al., 1992). The leukotoxin izoform produced by *M. haemolytica* biotype A, serotype 1, has the most visible cytotoxic proprieties in relation to bovine leukocytes. It has been discovered that bovine leukocytes exposed to low doses of exotoxin show reduced phagocytic and killing activity engulfed bacteria. On the other hand, higher concentration of the agent causes complete destruction of the leukocytes leading to their swelling and bursting (Clinkenbeard et al., 1989; Bednarek et al., 2009). The Lkt binds specific leukocyte adhesion molecules, signal-inducing trans-membrane pore formation is generated, leading to efflux of K^+, influx of Ca^{2+}(Clinkenbeard et al., 1989). Many potentially profitable reactive substances (free radicals, lizosomal enzymes, proteases) in relation to phagocytes (netrophils, monocytes) are realised from the

destroy cells and then they stimulate different pathological lesions in host affected lung tissue. The process manifested with an acute lobar fibrionecrotising pneumonia. This histopathological picture is characteristic for acute BRD. All the changes are consequences of Lkt action and the development of lung inflammatory cascade regulated additionaly by some pro-inflamatory cytokines (Bednarek et al., 2009). The clinical cases in which the *M. haemolityca* is included have severe clinical courses. According to the literature the intravenous administration of *M. haemolytica* A1 leukotoxin to clinically healthy calves caused the occurrence of the leukopenia manifested with the significant decrease of total peripheral WBC count with lower values of polymorphonuclear leukocyte and MID cell percentages, the last is a total value of all blood peripheral monoctes, eosinophils and basophils. Moreover, there were significant changes regarding some lymphocyte subpopulations such as: $CD2^+$ (T lymphocytes), $CD4^+$ (T helper lymphocytes) and $CD8^+$ (supresor/cytotoxic lymphocytes). The leukopenia resulted from the toxic influence of *M. haemolytica* A1 Lkt, demonstrating a species-specyfic 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, $PGF_{2\alpha}$, LTB4) had also significantly changes, because there were their higher values after administration of leukotoxin (Bednarek et al., 2009, 2010).

2. Diagnosis

The initial viral or mycoplasmal diseases are usually mild and are clinically distinguishing. The syndrome can be form subclinical to acute; most are somewhere in between. The initial viral/mycoplasmal diseases causes a moderate fever, sometimes accompanied by constipation. This is followed by rhinitis with a serous-to-mucopulurent discharge and pneumonia with a harsh, hacking cough, tachypnea, dyspnea and diarrhea. The calves very often are depressed, listless and anorectic. The bacterial infection causes intensity these sigs, with higher fevers, more severe dyspnea and depression and sigs of toxaemia. Calves are particularly difficult to auscult and abnormal lungs sounds may be hard to detect. In cases with severe consolidation, the normal breath sounds are replaced by harsh, high-pitched, large airway noises in the anterior-ventral lung fields. When secondary infection with *Pasteurella multocida* occurs the temperature rise to 41 -41.5°C, the area of lung affected is much increased, and increased breath sounds due to congestion are followed by pleuritic friction rub. The acute course is 10 to 14 days. The differential diagnoses should include aspiration pneumonia from improper tubing or feeding practices and purely viral pneumonias such as those caused by IBR, BVD and bovine respiratory syncytial virus (Blood et al., 1983; Smith, 1990).

The laboratory diagnostics of BRD is directly connected with an isolation and identification of suitable species of viruses, bacteria or mycoplasmas presented in a sample tested. These methods are in the various cases the same or similar, but some are specific to a given agent. However, at present the routine diagnostics is divided into two parts. The first one mainly consist of serological methods and the second is nowadays dominated by the molecular biology (PCR and real time-PCR). In the intravital diagnostic process an usual material collected is the nasal swabs or lung lavages and sera samples. On the other hand, post-mortem there are collected tissue samples from lungs and parenchymatous organs (liver, kidneys, spleen). The random amplified polymorphic DNA polymerase chain reaction

(RAPD-PCR) found excellent correlation between lung and nasal isolates. The nasal passages of sick animals may provide clues as to what strain is present in the lung (Jared et al., 2010b).

In the diagnosis of mycoplasmal infection there are used both microbiological, serological and molecular biology methods. It is worth mentioning that mycoplasmas need specific media (Eaton's or Hayflik's medium) and suitable conditions to grow, i.e. 37°C and 5% of CO_2. Mycoplasma culture methods were also described by Autio et al. (Autio et al., 2007). A characteristic feature of mycoplasmas is their growth on solid media in the form of „fried eggs" (Miles, 1998). Some species of mycoplasmas such as *M. bovis* have the ability to create spot and film reactions and the latest increase their resistance to adverse environmental conditions during culture. In order to diversify the presence of mycoplasmas and bacteria in the material from culture microscope method by Diens's was applied. In this method, mycoplasmal colonies are visible due to their ability to absorb dye (Malinowski & Kłossowska, 2002). Polymerase Chain Reaction (PCR) and its modification - real-time PCR (rt-PCR) are the techniques for identifying mycoplasmas from biological material (Sachse et al. 2010; McAuliffe et al., 2005; Miles et al., 2004; Vasconcellos et al., 2000) but they have some limitations. Technique which is devoid of these limitations is denaturing gradient gel electrophoresis (DGGE) that allows differentiation of sixty seven mycoplasma species from one sample, including thirteen bovine pathogens in this *M. bovis*, *M. dispar*, *M. bovirhinis* and *M. canis* (McAuliffe et al., 2005). However, to detect the presence of anti-mycoplasma antibodies in sera samples there were applied ELISA tests (Ghadersohi, 2005; Bansal et al., 1995).

The diagnosis of bacterial infections involved in BRD is based on many species-specific methods, such as conventional bacterial cultivation (Autio et al. 2007, Angen et al., 1998), phenotyping characterization (Angen et al., 2002), indole reaction (Autio et al., 2007) or molecular biology techniques. From the latest a PCR method was applied for main bacterial agents of the syndrome, such as *P. multocida* (Miflin & Blackall 2001), *M. haemolytica* (Angen et al., 2009) or *H. somni* (Angen et al., 1998).

In order to identify viral infections in the respiratory syndrome there are used methods detecting the presence of both antigens and specific antibodies. An antigen of some virus species, such as BVDV, BHV1, PIV-3 or BRSV can also be identified using isolation test or Elisa methods (Uttenthal et al., 1996; Autio et al., 2007). From molecular biology techniques to identify the viruses species-specific PCR and rt-PCR methods were applied (Autio et al., 2007; Vilcek et al., 1994). However, the presence of specific anti-viral antibodies in sera samples is possible to detect using Elisa techniques (Anderson et al., 2011) and others.

3. Control

The control of Bovine respiratory disease (BRD) mainly based on therapeutic management because of its multifactorial etology past prophylactic measures, including different vaccination programmes with using both mono- and polyvalent inactivated or modified live vaccines are not sufficiently effective till now. Therefore, at present new advanced, mostly complex - adjunctive therapeutic strategies are widely recommended in order to minimise the economic impact of the respiratory syndrome. According to the generally accepted opinion preferred by Pierre Lekeux (2006), i.e. a very known international expert in this

discipline, the fully effective BRD system of treatment should be included three independent steps and the system could be called as "a three-pillar therapeutic strategy of BRD". The first is an elimination of infectious agents using an appropriate antibacterials, the second is modulation of the pulmonary inflammatory reaction and the third – correction of mechanical and secretolitic lung disorders.

However, directly before undertaking of the treatment due to the economic considerations and potencial reduction of therapeutic costs, the field cases of the syndrome should be classified into four grades: Grade 1, subclinical disease (therapy is usually not necessary); Grade 2, compensated clinical disease (at this stage, the inflammatory reaction generated tends to limit the impact of the disease on the animal, this clinical form of the disease needs mainly antibacterial therapy); Grade 3, noncompensated clinical disease (at this stage, the inflammatory reaction is excessive and must be controlled by additional use of anti-inflammatory drugs); Grade 4, irreversible clinical disease (which threatens the animal's survival, this BRD form is not treated because conceivable profitable effects not compensate costs, and affected animals most often die).

The first element of complex therapeutic strategy of BRD aimed quick pathogenic bacteria elimination, particularly these originated from *Pasteurellacae* family (*M. haemolytica, P. multocida, H. somni*) which as important infectious factors participate in the development of pulmonary lesions and dysfunction associated with the syndrome. These bacteria play a crucial role in the pathologic cascade: therefore, the antibiotic must be administered as soon as possible after the induction of the infection, which is most often clinically characterized by hyperthermia, reduced appetite, and nasal discharge. Antibiotic treatment must be initiated before irreversible damage (characterized by oral breathing, orthopnea, lactatemia, and cyanosis) occurs. Among antibiotics presently used most often are administered long acting antibacterials such as some tetracyklines (oxyteracykline), macrolides (florfenicol, tulathromycin, gamythromycin) and fluoroquinolones (enrofloxacin, marbofloxacin, danofloxacin) with a wider antibacterial spectrum included also mycoplasmas (*M. bovis, M. bovirhinis, Ureaplasma diversum*). Significant role of mycoplasma in BRD etiology is not now questioned, and it is especially important because their effective control is very difficult. It is generally known that the mycoplasmas are resistant to beta-lactames and cephalosporins because of the lack of cell wall. The same resistance can be observed to nalidixic acid, polymyxin, rifamycin, tylosin, lincomycin, tylmicosin, trimethoprim and to sulfonamides (Poumarat *et al*., 1996; Ayling *et al*., 2007). Therefore, in this case there are intensively searching new more effective generations of antibiotics against mycoplasma infection. The most important mycoplasmal etiological agent in BRD i.e. *M. bovis* as other mycoplasmas is sensitive to antibiotics, which inhibit the protein or nucleic acid synthesis. Recently, in cattle respiratory treatment there are recommended antibiotics which were only applied in swine medicine i.e. pleuromutilins (tiamulin, valnemulin). At present it is known too, that tiamulin has also excellent activity against cattle mycoplasmas like *M. bovis*. In addition an analog compound of tiamulin is valnemulin, which has proven to be affective in the control *M. bovis* infection under field conditions (Stipkovits *et al*., 2001; Tenk, 2005).

Recently, new antibiotic-treatment conceptions of BRD have been presented during the first European Buiatrics Forum in Marseille (2009). There were described three independent conceptions which in shortening forms are called as SISAAB, SILAAB and MILAAB. The

first of them means: Single Injection Shot Acting AntiBiotic among others things represented by new formulations of fluoroquinolones like Marbocyl S (marbofloxacin 100 mg/ml, administered at a single dose of 8 mg/kg b.w. *i.m.*), Baytril One or Enroxil Max (enrofloxacin 100 mg/ml, administered at a single dose of 7.5 mg/kg b.w. *s.c.*). Moreover, also long acting tetracyclines (Tetradur) could be administered here in a form of single intramuscular injections. The second conception is Single Injection Long Acting AntiBiotic represented by new generations of macrolides such as tultromycin (Draxxin) and gamytromycin (Zactran), and also the third one i.e. Multiple Injection Long Acting AntiBiotic which however is considered to be a little controversial conception due to take real risks of antibiotic-resistance increasing.

In the complex of advanced therapeutic strategy of BRD the second its component is the modulation of pulmonary inflammatory reaction. In this aspect, at present there are use anti-inflammatory medicines originated from both steroidal (SAIDs) and non-steroidal anti-inflammatory drugs (NSAIDs) (Lekeux, 2006). Steroids are powerful anti-inflammatory agents, but their effects on the animal's defensive machanisms reduce the value of their use in syndromes of infectious origin unless they have a short duration of action or are administered locally. Generally the drugs stabilise cellular and lysosomal membranes and thereby inhibit release of the chemical pro-inflammatory mediators and proteolytic enzymes. Other steroidal effects include inhibition of antibody synthesis; suppression of activity of fibroblasts; elevation of circulating neutrophil count and reduction in eosinophil count. Steroids also increase microvascular tone and decrease permeability thus reducing exudation and oedema formation. In BRD adjunctive therapy there were used different kinds of corticosteroids include betamethasone (2-10 mg/animal), dexamethasone (2-5 mg/animal), prednisolone (up to 20 mg/animal), cortisone (up to 500 mg/animal), hydrocortisone (up to 300 mg/animal), flumethasone (0.5 mg/animal) and trimcinolone (up to 5 mg/animal). The drugs because of their strong immunosupresive character were usually use only in a single administration throughout of the therapy.

In contrast to steroids, which reduce the yield of all products of arachidonic acid cascade, nonsteroidal anti-inflammatory drugs (NSAIDs) have a narrower anti-inflammatory spectrum, acting as inhibitors of cyclooxygenase. However, NSAIDs have a wider safety margin, which largely compensates for their narrower spectrum. NSAIDs act principally to inhibit the biosynthesis of prostaglandins. They also inhibit kallikrein activity and kinin formation and at the same time pharamacologically antagonise the tissue effects of kinins, prostaglandins and slow-reacting substance of anaphylaxis (SRS-A). NSAIDs are, with some exceptions, analgesic and antipyretic: effects not shown by steroids. Apart from that NSAIDs have also the ability to improve gas exchange what it has been shown in pneumonic calves in experimental conditions (Van de Weerdt *et al*, 1999). The benefits of NSAIDs therapy in bovine respiratory disease have also been demonstrated multiple in a field study (Bednarek *et al*, 2003; Bednarek *et al*, 2004; Lockwood *et al* 2003; Weingarten, 2009).

NSAIDs should be administered to animals at grade 3 of severity, which is mainly characterized by hyperthermia, anorexia, and dyspnea. NSAIDs act rapidly in the pneumonic lung, so the modulation of inflammation and the resulting improvement in the clinical status should follow quickly in the absence of irreversible damages (Lekeux, 2006). The drugs most commonly used in BRD therapy in Europe are flunixin meglumine (2.2

mg/k b.w. *i.v.*), carprofen (1.4 mg/kg b.w. *i.v., s.c.*), ketoprofen (3 mg/kg b.w. *i.v., i.m.*), meloxicam (0.5 mg/kg b.w. *s.c., i.v.*), tolfenamic acid (2 mg/kg b.w. *i.m.*), metamisole sodium (10 – 50 mg/kg b.w. i.m., i.v.).

In the most severe cases of BRD, a short-acting steroidal anti-inflammatory drug, bronchodilator, and diuretic could be added to the NSAID when pulmonary fulminating infalammation, bronchospasm, and edema are present, respectively. These additional supparative drugs i.e. bronchodilators and diuretics are included into the third component of the complex therapeutic strategy of BRD. Among bronchodilators mostly atropine sulfate (cholinolitics) and theophylline (methylxanthines) are administered. The first of them is classified as an anticholinergic drug (parasympatholytic). In general, atropine lowers the parasympathetic activity of all muscles and glands regulated by the parasympathetic nervous system. This occurs because atropine is a competitive antagonist of the muscarinic acetylcholine receptors (acetylcholine being the main neurotransmitter used by the parasympathetic nervous system). Therefore, it may cause bronchictasis and reduced secretions salivary, sweat, and mucus glands. As adjuncts in BRD therapy atropine sulfate 1% is recommended by Lekeux (2002) once a day for three consecutive days at a dose of 0.06 mg/kg b.w. s.c. Theophylline, also known as dimethylxanthine, as a methylxanthine drugs is rarely administered in cattle practice against bronchoconstriction in course of BRD mostly intramuscularly or slowly intravenously at a dose of 1-10 mg/kg b.w. However, it is recommended in veterinary medicine as bronchodilators in adjuntive therapy for respiratory diseases such as BRD, COPD in horses and feline asthma under a variety of brand names. Because of its numerous side-effects, the drug is now rarely administered for clinical use. As a member of the xanthine family, it bears structural and pharmacological similarity to caffeine.

On the other hand within the veterinary diuretics mostly in calves suffering from severe form of BRD caused with pulmonary edema is furosemide (1 mg/kg b.w. i.v.). Furosemide (INN) or frusemide (former BAN) is a loop diuretic used in the treatment of congestive heart failure and edema. It is most commonly marketed by Sanofi-Aventis under the brand name Lasix. It has also been used to prevent Thoroughbred and Standardbred race horses from bleeding through the nose during races.

It should be remember that very important is also to use expectorants (mucolitic drugs) like bromhexine hydrochloride (bromhexine HCl) in order to inflammatory mucose evacuation from the obturated respiratory airways. Bromhexine is a mucolytic agent used in the treatment of respiratory disorders associated with viscid or excessive mucus. In addition, bromhexine has antioxidant properties (Morton, 1999). Bromhexine supports the body's own natural mechanisms for clearing mucus from the respiratory tract. It is secretolytic: that is, it increases the production of serous mucus in the respiratory tract and makes the phlegm thinner and less sticky. This contributes to a secretomotoric effect: it helps the cilia - tiny hairs that line the respiratory tract - to transport the phlegm out of the lungs. For this reason at present it is generally recommended as a adjunct in the complex therapy of BRD. In clinical studies, bromhexine showed secretolytic and secretomotoric effects in the bronchial tract area which facilitates expectoration and eases cough. It is indicated as "secretolytic therapy in bronchopneumonia of calves associated with abnormal mucus secretion, impaired mucus transport and bromhexine has also antiinflammatory properties"

(Bednarek & Kondracki, 2002). Bromhexine also enhances mucus transport by reducing mucus viscosity and by activating the ciliated epithelium. Bromhexine is contained in various formulations (high and low strength syrups, tablets intended mainly for companies animals), however in cattle practice the most useful form is injectable preparation (Eres, Bisolvon, Bisolvomicin, Flegamina) recommended in affected calves at a dose of 0.5 mg/kg b.w. *i.m.* for 5 to 7 consecutive days. Bromhexine is a well established and well tolerated product in its indication.

Other expectorants have been used too in chronic cases of coughing in course of BRD (Andrews, 2004). These include a mixture of strychnine hydroxide, arsenic trioxide and ferric ammonium citrate given at a dose of about 5 ml orally twice daily, or diphenhydramine hydrochloride, ammonium chloride, sodium citrate and menthol at 5-10 ml orally two or three times daily. There is limited benefit form the antihistaminic action of diphenhydramine hydrochloride in cases of calf pneumonia. This resent indication has been accepted too but many clinicians consider that using antihistamines is a little effective in calf bronchopneumonia. This is probably because the main proinflammatory mediator of cattle is not histamine like and human and other mammals but 5-HT (5-hydroxytryptamine). The histamine that is released occurs very quickly following the antibody-antigen reaction so that antihistamines can only be of use in the early stages of the inflammatory response. Among of the drugs in USA recently for the large animal medicine (horses, cattle) are used tripelennamine hydrochloride at a dose of 1 mg/kg b.w. *i.m.* once a day (Divers, 2011). The dose may be repeated in 6 to 12 hours if necessary.

Presented above the basic principles and drugs used for the optimal therapeutic strategy of BRD especially within Grade 3 of the disease are very important to maintain the profitability of cattle breading. This strategy is a combination of an antibiotic acting against the relevant pathogens (eg. florfenicol) and an NSAID acting against the deleterious effects of inflammation (eg, flunixin) additionally supported by the correctors of mechanical and secretolitic lung disorders (Expectorants, bronchodilators). This strategy were confirmed by several experimental and field tests showing an improvement of clinical signs and a reduction of pulmonary dysfunction and lung consolidation in animals receiving such a combined therapy.

In the complex control measures of BRD should be added too about prevention using vaccination programmes. There are various vaccines available both live or attenuated consist of only one or a few bacterial or/and viral antigens. Dead vaccines are used to provide immunity against *P. multocida* and septicemic and pneumonic strains of *M. haemolytica* and *H. somni* (eg, Hiprabovis pneumos, Pastobov, Bovilis Bovipast). Killed or modified live polyvalent vaccines are used in many countries and also in Poland, and contain antigens such as BRSV, PI3 (Rispoval, Bovilis Bovipast), BVDV (Mucosiffa, Bovilis BVD) and BHV1. Recently the last presented antigen is widely utilized in the construction of so-called marker vaccines both live (eg, Rispoval-IBR marker vivum, Hiprabovis-IBR marker live) and inactivated (eg, Ibraxion, Rispoval-IBR-marker inactivatum, Bovilis IBR – marker inactivatum) applied in IBR eradication based on DIVA system i.e. **D**ifferentiating **I**nfected from **V**accinated **A**nimals. The vaccines are usually administered parenterally and usually require two injections to produce immunity. Recent developments have included combined live and dead viral components of the four main antigens which are injected intramuscularly (eg, Rispoval 3). When live vaccines are used, the integrity of the vaccine

must ensure absence of other potential contaminats, both viral and other pathogens. Subsequently, modified live intranasal vaccines have been available (eg. Rispoval RS+PI3 IntraNasal). Till now numerous studies have demonstrated that immunization calves via the intranasal route not only is most effective and it gives active immunity in very young animals despite maternal antibodies, it also generates a significant systemic response and interferon induction (Stokes, 2006). Given the relative ease of antigen delivery and the organization of the local lymphoid tissue (MALT), intranasal immunization offers attractive possibilities. However, to successfully achieve this there are a number of obstacles that have to be overcome. For example in the context of IBR vaccination, sometimes, although good immunity was conferred to animals by modified live vaccination, it was shown that some cattle became carriers after exposure to field strains of BHV.

In multifactorial etiology of BRD at present there is also valued the role of mycoplasmal infectious agents. Therefore, many scientific centers all over the world try to produce suitable vaccines mainly against the most important mycoplasma i.e. *M. bovis*. Till now in Europe the saponin inactivated vaccine has been produced in the UK (by The Mycoplsma Group, AHVLA in Webridge), but it has had only limited success experimentally. The inactivated vaccine containing saponin-killed cells was shown to be safe, highly immunogenic and protective against a strong experimental challenge with virulent *M. bovis* (Nicholas *et al*., 2002). Vaccinated calves showed few respiratory signs while all unvaccinated calves developed signs of pneumonia. Moreover, vaccination gave a statistically significant degree of protection against pyrexia, lung lesions and loss of body weight. The vaccine also reduced the spread of *M. bovis* to internal organs, including the joints. This vaccine is now under commercial development and AHVLA (Weybridge) has a licence to produce this as an autogenous vaccine in the UK. Therefore, practically no commercial vaccines currently exist for *M. bovis* in Europe. Various commercial vaccines, including autogenous preparations, are available in the USA; however there is no published evidence to support their effectiveness.

Recapitulating, the control of the Bovine respiratory syndrome is essential to maintain the profitability of most intensive bovine ventures, and veterinary practitioners have the opportunity to play an important role in this effort. Preventive and therapeutic measures must be adapted to the type of production operation, the specific features associated with the individual animal, the environment and the pathogens, the availability of drugs, and the state of the art in science.

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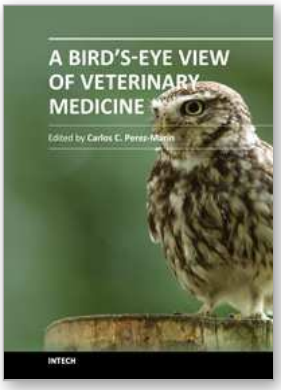

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Veterinary medicine is advancing at a very rapid pace, particularly given the breadth of the discipline. This book examines new developments covering a wide range of issues from health and welfare in livestock, pets, and wild animals to public health supervision and biomedical research. As well as containing reviews offering fresh insight into specific issues, this book includes a selection of scientific articles which help to chart the advance of this science. The book is divided into several sections. The opening chapters cover the veterinary profession and veterinary science in general, while later chapters look at specific aspects of applied veterinary medicine in pets and in livestock. Finally, research papers are grouped by specialisms with a view to exploring progress in areas such as organ transplantation, therapeutic use of natural substances, and the use of new diagnostic techniques for disease control. This book was produced during World Veterinary Year 2011, which marked the 250th anniversary of the veterinary profession. It provides a fittingly concise and enjoyable overview of the whole science of veterinary medicine.

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