Bovine Respiratory Disease Complex: An European Perspective

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Abstract

Respiratory disease is the principal cause of loss of young cattle worldwide. The syndrome arises from a number of factors, including those involving the animal, e.g., age, general condition and immune status; its environment, e.g., changes in food, temperature and humidity that lead to stress; and the presence of infectious agents, e.g., bacteria, viruses and mycoplasmas. The syndrome, in a method preferred by the author, can be classified into four grades; Grade 1, subclinical disease; Grade 2, compensated clinical disease (at this stage, the inflammatory reaction generated tends to limit the impact of the disease on the animal); Grade 3, noncompensated clinical disease (at this stage, the inflammatory reaction is excessive and must be controlled); and Grade 4, irreversible clinical disease (which threatens the animal's survival).

The increase in frequency and economic impact of bovine respiratory disease complex can be correlated with the escalating industrialization of cattle production. In intensive operations, commingling of animals from multiple sources, exposure to many organisms, stress and management practices are all factors that can lead to disease.

The predisposition of cattle, especially beef calves, to respiratory problems is related to their lack of functional pulmonary hardiness. Selection of breeds that demonstrate adequate pulmonary function and sufficient ventilatory reserve may help in the control of the bovine respiratory disease complex, but this approach is difficult to implement and slow to produce results.

Prophylactic measures, including vaccination programs and modifying management practices to reduce stress, also have a place in preventing the bovine respiratory disease complex. Unfortunately, these measures are not always easy to put into operation and cannot completely eradicate the problem. Therapeutic strategies to minimize the economic impact of the syndrome include use of appropriate antibacterial therapy, modulation of the pulmonary inflammatory reaction and correction of mechanical disorders.

In recent decades, the frequency and severity of bovine respiratory diseases have increased significantly and their epidemiology and clinical symptomatology have evolved as well. The reasons for these changes are many, but are directly related to three key factors: the conditions under which the animals are raised, the condition of the animals themselves and the pathogens involved.

First, the size of an operation, its specialization of the progressive industrialization of bovine production have contributed to the development of conditions that favor the outbreak of certain respiratory diseases. Individual animals infected with a single pathogen are rarely seen. The commingling of animals from multiple sources, exposure to many organisms, stress and management changes are all factors that can lead to disease despite comprehensive vaccination programs. Second, the ever-increasing selection of cattle for improved performance has led to a lack of adaptation in their oxygen transport chain, thus impairing their capacity for aerobic metabolism; aerobic metabolism has become a factor that potentially limits production, primarily because of effects at the weakest link in the chain, the respiratory system. Third, a number of factors have contributed to changes in clinical features of bovine respiratory disease; for example, changes in the type, pathogenicity and virulence of pathogens have occurred, certain vaccines have decreased the pathological impact of some (but not all) viruses involved in the bovine respiratory disease complex and new anti-infective agents have become available.

Currently, respiratory diseases are the principal cause of the loss of young cattle all over the world. A recent study in Belgium showed that more than 50% of the disease-related economic losses in beef cattle are due to respiratory problems.[1] In a 1991 U.S. survey of cattle and calf death loss, respiratory problems were responsible for 31% of the deaths, making these disorders the leading cause of mortality. The value of the 1.3 million cattle lost to the U.S. market as a result of respiratory problems was estimated to be $624 million (in U.S. dollars).[2] Thus, if veterinary practitioners are to have a positive effect on the profitability of bovine production, particular attention must be given to the management of these diseases.

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The Bovine Respiratory Disease Complex

The many forms of bovine respiratory disease can be arbitrarily classified into two categories. The first category includes any disease caused by a single factor; often a specific pathogen plays a crucial role. The epidemiology of these diseases is not very predictable because it depends on two factors, a pathogen and a susceptible animal, both of which are necessary for the clinical syndrome to be observed. Symptoms are relatively specific to the aetiological agent implicated.[3] These diseases are found primarily in small, relatively isolated units with intensive production. The frequency and economic impact of these diseases have tended to decrease because of a reduction in the number of these smaller operations and an increase in the efficacy of preventive measures.

The second category, often termed the bovine respiratory disease complex, includes diseases with multifactorial causes, such as a frail or stressed animal, a poor environment and a multitude of infectious agents. The epidemiology of these diseases is relatively predictable because they most often develop at specific times in the production scheme. These diseases usually arise as a consequence of stress placed on a susceptible animal rather than as a result of an encounter with a specific pathogen. Symptoms are not specific and most often assume the form of bronchopneumonia of variable intensity.[4] These diseases are encountered primarily in large units in which production has been both specialized and intensified. The frequency and economic impact of these diseases have tended to increase because of the escalating industrialization of cattle production and the relatively poor efficacy of preventive measures.

The various considerations discussed in this article focus mainly on this second category, namely, the bovine respiratory disease complex.

Risk Factors

The frequency and severity of the bovine respiratory disease complex depend on the influence of a number of risk factors, which relate to the patient, its environment and the implicated pathogens. Respiratory disease results from a number of complex interactions among these factors.

Risk factors relating to the animal include its maturity, functional respiratory hardiness (see below), general condition and degree of immunity. **Functional maturity of the bovine respiratory system is not achieved before 1 year of age,[5] therefore, regardless of immunological and management considerations, respiratory disease occurs more frequently and is more severe in young cattle than in mature cattle.**

The functional hardiness of the respiratory system refers to its capacity to ensure adequate gas exchange when the animal is stressed or has a disease normally found in a given type of production. Functional hardiness requires a significant ventilatory reserve, which may avert a disturbance in gas exchange that would otherwise result in the face of stresses encountered by beef cattle during the production process. This ventilatory reserve appears to be inadequate in cattle used in meat production, especially double muscled breeds; therefore, their susceptibility to severe respiratory diseases and their death losses are greater than those of dairy breeds of cattle.[6]

Risk factors relating to the environment involve stress generated by changes in food, temperature, humidity and ventilation and by mixing of animals from different sources. These stresses—which are particularly important at birth, at weaning and during the transport of young cattle—often trigger respiratory disease.[7] Because stress cannot be completely eliminated and respiratory disease will occur, effective treatment regimens are especially important.

Risk factors relating to pathogens are many and complex. These factors often combine to cause the bovine respiratory disease complex. Some (e.g., viruses and mycoplasmas) primarily play a role in upsetting the defence mechanisms of the animal, while others (e.g., bacteria and their toxins) play a crucial role in the development of pulmonary lesions.[8] The microorganisms most frequently implicated in this syndrome are as follows[4]:

- **Viruses**—Bovine herpesvirus type 1, bovine respiratory syncytial virus, bovine adenovirus, parainfluenza virus type 3 and bovine viral diarrhoea virus
- **Bacteria**—*Pasteurella haemolytica, P. multocida* and *Haemophilus somnus*
- **Mycoplasmas**—*Mycoplasma bovis, M. dispar* and *Ureaplasma*

While triggering of the respiratory disease results from interactions among various risk factors, the relative importance of those factors varies. Risk factors associated with the patient are crucial. For example, beef calves are immature and not very robust with regard to respiratory function; those that are in poor general condition and whose immune level is inadequate have a relatively high risk to develop the bovine respiratory disease complex, even in the presence of only modest risk factors relating to the environment and pathogens. In contrast, dairy cows are mature and very hardy with regard to respiratory function; those that are in good general condition and whose immune sys-

tem is functioning properly have a very low risk to develop the bovine respiratory disease complex, even in the face of significant risk factors relating to the environment and pathogens.

Pathophysiological Mechanisms

The bovine respiratory disease complex results from a disturbance in the equilibrium between the defensive measures of the animal and potential disease factors. This loss of equilibrium develops most often in an animal that is incapable of overcoming or adapting to a change in environment. Stress interferes with the clearance and defense mechanisms of the respiratory system and fosters the proliferation of microorganisms and production of their toxins.[9]

In a typical scenario of clinical progression of disease, *Pasteurella haemolytica* is a common part of the bovine respiratory disease complex. The upper respiratory tract of cattle is not a sterile environment, and *Pasteurella* colonies are normally found in the nasal cavities of healthy animals. When an animal is stressed (as a result of shipping, weaning or viral infection), the organism proliferates and gains access to the normally sterile environment of the lower respiratory tract. To counteract this invasion, neutrophils are mobilized in the lung in attempts to engulf and digest the bacteria. However, *P. haemolytica* produces a leukotoxin that can destroy these neutrophils; as they die, the cells release neutrophilic enzymes and other inflammatory mediators that cause severe damage to lung tissue. Thus, the host's immune response can cause more serious complications than the bacteria themselves.

Despite the great variety of combinations of pathogens that have been implicated as causes of this disease, the clinical entity of most manifested is bronchopneumonia. The clinical appearance of this syndrome depends directly on the relationships of the causal factors and, in a method preferred by the author, can be classified into four grades, according to the severity of the disease, the pathophysiological mechanisms implicated and the level of reversibility.

Grade 1 is subclinical disease. The animal succeeds in controlling the proliferation of the pathogens because of appropriate functioning of its physiological defenses. There is no significant inflammatory reaction, which means that obvious pulmonary dysfunction is absent or of modest intensity and clinical symptoms are not evident.

Grade 2 is compensated clinical disease. The attack on the respiratory system and the resulting inflammatory reaction generate various mechanisms that tend to limit the functional impact on the animal, in accordance with the negative feedback principle.[10] For example, hypoxaemia and hypercapnia stimulate the respiratory centers, resulting in an increase in alveolar ventilation. Colonization of the respiratory tract with microparticles stimulates mucociliary clearance. The tone of the respiratory muscles increase, which improves respiratory efficiency. Hypoxic vasoconstriction prevents blood from perfusing poorly ventilated pulmonary zones to correct inadequacies in the ventilation/perfusion ratio. The effect of all of these mechanisms is to correct the impairment in gas exchange. The inflammatory reaction and functional adaptations that the pathogen induces are beneficial at this grade and should not be systematically combatted as a matter of course.

Grade 3 is noncompensated clinical disease. The disequilibrium between the disease factors and the animal is so significant and the resulting inflammatory reaction is so violent that the reactions of the animal tend to aggravate the functional deficit, in accordance with the positive feedback principle.[11] For example, tissue hypoxaemia increases anaerobic metabolism and generates the development of metabolic acidosis, which consequently aggravates the respiratory acidosis due to the hypercapnia. Dysfunction of the respiratory centers and inadequate mucociliary clearance result. The movement of blood cells into the lungs can cause an excess quantity of mediators of inflammation, proteolytic enzymes and oxygen radicals. This negatively affects pulmonary smooth muscle, the membrane permeability and the integrity of pulmonary tissue, further aggravating the deficits in gas exchange. The result is that the animal suffers more from these dysfunctions and the lesions induced by the inflammatory reaction than from the pathogens themselves. This excessive inflammatory reaction and the inappropriate functional adaptations that it generates must be controlled completely to prevent an unfavorable outcome.

Grade 4 is irreversible clinical disease. The pulmonary lesions that are generated—either by pathogens, proteolytic enzymes or oxygen radicals released by the inflammatory cells, or by mechanical disorders induced by proinflammatory mediators—threaten the animal's performance level and even its survival.

Control of the Bovine Respiratory Disease Complex

An overall approach to the control of the bovine respiratory disease complex must address breed selection, prevention and therapy to be effective.

The enormous predisposition of cattle, especially beef calves, to respiratory diseases is directly related to their lack of functional pulmonary hardiness. Therefore, selection of cattle should focus on those breeds that demonstrate

adequate pulmonary function and sufficient ventilatory reserve to avoid the frequency and the severity of respiratory diseases.[12] Although these measures are necessary, they are difficult to implement and slow to produce results.

Both medical and hygienic prophylactic measures have an essential place in controlling the bovine respiratory disease complex. Measures such as vaccination before leaving farms, raising animals in small units and short transportation time all promote bovine immunity against various pathogens and reduce the negative impact of various types of stress.[13] Unfortunately, the prophylactic measures that have been recognized as effective and available are not always easy to put into operation in modern production schemes. Further, their application helps to reduce the frequency and severity of the bovine respiratory disease complex but does not eliminate it.

Therefore, therapeutic measures remain indispensable to reduce the economic impact of the bovine respiratory disease complex. To meet the criteria of efficacy, safety and minimization of residues, a therapeutic strategy must be applied early enough to prevent the development of irreversible lesions and must be adaptable to the clinical grade of the disease. Strategies can be classified into three groups: suppression of infectious agents, modulation of the pulmonary inflammatory reaction and correction of mechanical disorders.[14]

Suppression of Infectious Agents

Bacteria, particularly *P. haemolytica, P. multocida* and *H. somnus* are important factors in the development of dysfunctions and pulmonary lesions associated with the bovine respiratory disease complex. Even if a microorganism is not the primary cause of the syndrome, it almost always systematically reduces the animal's defense mechanisms and pulmonary clearance, which aids bacterial proliferation and the secretion of their toxins. For example, the fibrinonecrotic pneumonia associated with the bovine respiratory disease complex results from colonization of the lower respiratory tract by microorganisms. Endotoxin released from the bacteria crosses the alveolar wall where it activates several proinflammatory mediators. It is the progression of this inflammatory response with neutrophil influx that is ultimately responsible for the pulmonary injury.[15] Therefore early and sufficiently prolonged application of effective antibacterial agents is crucial to the control of the bovine respiratory disease complex.

Modulation of the Pulmonary Inflammatory Reaction

The pulmonary inflammatory reaction plays a beneficial role in controlling the aggressors. When it is too intense, however, certain mediators (e.g., certain arachidonic acid derivatives, autacoids, cytokines, neuropeptides and cytolytic products), released *in situ,* have a tendency to contribute to the establishment of dysfunctions and pulmonary lesions and therefore to the worsening of gas exchanges. In this situation, use of an antinfective agent must be accompanied by therapy sufficient to control the pathological inflammatory process.

Nonspecific mediator antagonists, such as nonsteroidal anti-inflammatory agents, (NSAIDs) and steroid anti-inflammatory agents are available to the practitioner. Steroids are powerful anti-inflammatory agents, but their side effects on the animal's defensive measures reduce the value of their use in syndromes of infectious origin unless they have a short duration of action or are administered locally. In contrast to steroids, which reduce the yield of all products of arachidonic acid, NSAIDs have a narrower anti-inflammatory spectrum in that they act as inhibitors of cyclooxygenase; however, NSAIDs have a wider safety margin, which largely compensates for their narrower spectrum. The benefits of NSAIDs therapy in bovine respiratory disease have been well documented.[16]

Specific antagonists of proinflammatory mediators have yet to be developed for veterinary application.

Correction of Mechanical Disorders

Inappropriate functioning of pulmonary smooth muscles, permeability of pulmonary capillaries and mucociliary clearance contribute to the impairment of pulmonary gas exchanges. Correcting these disorders,—through the administration of bronchodilators, vasodilators or stimulators of mucociliary clearance—reduces the work involved in respiration (and therefore the risk of fatigue of respiratory muscles) and improves pulmonary gas exchange. This type of action can contribute significantly to restoring the patient's homeostasis.

Conclusions

Because of the considerable importance of this syndrome, control of the bovine respiratory disease complex is essential to maintain the profitability of most intensive bovine ventures. Veterinary practitioners have an important role in this effort, as preventive and curative measures must be adapted to the type of production operation, the specific features associated with the individual animals, the environment and the pathogens, the availability of drugs, and the state of the art in science.

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Abstract

An ultrasonographic study of bovine cystic ovarian disease and its treatment

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This study assessed the value of ultrasonography in characterizing bovine cystic ovaries and monitoring their responses to different treatments. Thirteen cows were diagnosed by ultrasonography as having luteinised ovarian cysts and seven were diagnosed as having follicular ovarian cysts. Six of the former were treated with prostaglandin, four with a progesterone intravaginal device (PRID) and three with gonadotrophin-releasing hormone (Gn-RH); five of the latter were treated with Gn-RH and two with a PRID. All the animals were re-examined by ultrasound and blood was collected for the measurement of plasma progesterone concentration at intervals until oestrus. The treatment of the luteinized cysts with prostaglandin caused marked decreases in size and plasma progesterone concentration and altered their echotexture within two to four days; oestrus occurred within three to four days. In two of the cows treated with a PRID the cysts regressed within one to two weeks but the other two cows required supplementary treatment with prostaglandin; oestrus and ovulation were observed only after the cysts collapsed. Gn-RH stimulated oestrus and ovulation within three to four days but the cysts did not collapse until much later. The treatment of the follicular cysts with Gn-RH or a PRID caused fresh ovulation and the formation of a corpus luteum but had little immediate effect upon the cyst. The plasma progesterone concentrations in some of the cows with either follicular or luteal cysts were similar on the day of treatment and were therefore of little value in differentiating the types of cyst. However, plasma progesterone concentration was a useful adjunct to the ultrasound interpretation of the function of the cysts.