Current Concepts on the Role of Viruses in Respiratory Tract Disease of Cattle

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Introduction

Much effort has been devoted to understanding, preventing and controlling respiratory tract disease of cattle. The volume of scientific literature on this subject is enormous. Nevertheless, the incidence of bovine respiratory disease remains high and the economic impact of the disease is substantial (19,22,32,46,48). It has been estimated that 40% to 80% of all cattle diseases involve the respiratory system (32). Antibiotic therapy is extensively applied to control the disease, but although it may be lifesaving, the cost of treatment and loss in production by surviving animals may result in economic liability.

Bovine respiratory tract disease is not a single disease entity, but rather a complex of diseases involving the respiratory system (32). Respiratory tract disease in cattle usually occurs as enzootic pneumonia of calves, shipping fever of older calves and young adults and atypical interstitial pneumonia of adults (32). The latter syndrome is probably a hypersensitivity reaction and will not be discussed in this paper. Enzootic pneumonia and shipping fever are manifestations of infections of the respiratory tract but the pathogenesis is complex. Bovine respiratory disease has a complex multicomponent etiology but virus infection is a significant factor in precipitating the disease (19,22,46,48).

Viruses that have been associated with bovine respiratory tract disease include infectious bovine rhinotracheitis (IBR) virus, adenoviruses, reoviruses, parainfluenza-3 (PI^3) virus, bovine virus diarrhea (BVD) virus, DN599 herpesvirus, FTC2 herpesvirus, bovine respiratory syncytial (BRS) virus, bovine rhinovirus, influenza virus, and enteroviruses. Several reviews have been published on the etiology of bovine respiratory tract disease (32,36,46,48). The latter publications may be consulted for further information and a more comprehensive bibliography since it is not the intention of this review to be complete, but rather to discuss current concepts of "old" problems and to focus on "new" problems. An attempt has been made to emphasize etiology, diagnosis, and control of viral bovine respiratory tract disease.

Infectious Bovine Rhinotracheitis Virus

The involvement of IBR virus in respiratory tract disease is well known (22,36,83). This herpesvirus, unlike most other viruses associated with bovine respiratory tract disease, is capable of causing frank respiratory disease without assistance from any other factors. The disease is characterized by pyrexia, dyspnea, rhinitis, sinusitis, tracheitis, conjunctivitis, and occasionally, bronchopneumonia. In some affected cattle the muzzle may be hyperemic and crusted. Approximately 3% of affected cattle die which is usually due to bronchopneumonia. The virus is also responsible for other distinct clinical syndromes: encephalitis, abortion, vaginitis, conjunctivitis, and balanoposthitis.

Vaccines have been extensively used to control IBR, and, as a consequence, the disease incidence is low (22,48). However, ubiquitous use of modified live virus vaccines has not eliminated the virus. Virulent and perhaps vaccine strains of IBR virus often remain latent in cattle after primary infection (19,62). Periodic shedding of IBR virus by recovered animals has been demonstrated (19,48). Latent virus can be recovered from cattle after experimental corticosteroid stress (62) and probably also under natural stress conditions (19). Stress-induced recrudescence of mild clinical signs may also occur (19,62). Recrudescence of IBR could thus erroneously be interpreted as a primary infection and the actual inciting factor may not be recognized. In addition, isolation of IBR virus from an animal with respiratory disease could confuse diagnostic interpretation if the virus isolated is an activated latent non-virulent vaccine strain. Few laboratories can distinguish vaccine from "wild" strains of the virus since sophisticated procedures such as neutralization kinetics with 19S antibody are required (53). These problems would argue for the use of killed vaccines instead of modified live virus.

Laboratory diagnosis of IBR virus infection is done by virus isolation, serology, and by the direct fluorescent antibody test (76). Serologic examination is the most efficient means (46) but a four-fold rise in antibody titer from the acute to convalescent phase of the disease has to be demonstrated. The virus neutralization and complement fixation tests are most commonly used. Recent infections are more likely to be recognized by the latter test (14).

Available commercial IBR vaccines include modified live virus for parenteral administration, modified live virus for intranasal administration, and

killed virus for parenteral administration. Killed adjuvanted vaccine require at least two vaccinations but can be protective (23,36). Live vaccines are more effective and one vaccination usually provides life-long immunity (24). However, the duration of immunity in individual animals may be dependent on reinfections (83) or recrudescence and may be quite variable (24,36). Revaccination should perhaps be considered in valuable animals.

The relative merit of intranasal and parenteral live virus vaccines has been controversial (8,19,24,37,73,75). Superior local immunity within the respiratory tract (70,73,75), a faster onset of protection (73,75) and transient interferon-induced nonspecific protection (74) are claimed for the intranasal vaccine. No significant difference was found in some studies (8,37). However, there is agreement that intranasal vaccines are less likely to elicit abortion in pregnant cows than parenterally-administered live virus vaccines (25,75). Failure of vaccination by intranasal administration is possible if vaccine virus infection is prevented by interferon (or other interference mechanism) due to prior existence of viruses (or other microorganisms) (19). A potential exists for modified live virus to spread from vaccinates to contact animals with the concommitant risk of the virus reverting to virulence or recombining with "wild" strains (71). Transmission has been demonstrated with intranasally administered vaccine virus (37) but parenterally modified live virus does not spread readily (8).

Calfhood vaccination for IBR is recommended (24,48). Intranasally administered live virus vaccine or killed virus vaccines should be used in adults to reduce the risk of vaccine-induced abortions (25). Calves younger than 4 months should not be vaccinated (24,46) but if it cannot be avoided, intranasally administered live virus vaccine should be used to circumvent the immunosuppressive effect of colostral antibodies (73).

Bovine Virus Diarrhea (BVD)

Bovine virus diarrhea virus is a togavirus (69) and it is antigenically related to hog cholera virus (12). Disease caused by BVD virus is usually thought of as gastroenteritis with diarrhea and fever (22). Other signs which may accompany BVD virus infection include salivation, mouth erosions, nasal discharge, crusted muzzle, muzzle erosions, conjunctivitis, keratitis, dermatitis (interdigital, perineal, and pericornual), abortions, fetal anomalies, nervous signs (muscular tremors, incoordination), weak calves, and respiratory involvement (22). However, most instances of BVD infection result in subclinical infections since 60-80% of cattle have antibodies to the virus (22,33). Subclinical infections may render cattle unthrifty for a variable period of time (22,33).

Infection by BVD virus often appears clinically as respiratory disease (24,48) and some strains primarily involve the respiratory tract (82). It has been suggested the BVD virus may compromise an animal's immune response (33) which could result in secondary infection of the respiratory tract by opportunistic bacteria and viruses. Several instances of multiple viral infections involving BVD virus have been reported (33). In a recent study of 14 typical cases of shipping fever in a feedlot, *Pasteurella hemolytica* was isolated from respiratory tissues of 13 cases. *P. multocida* from 1 case, IBR virus from 7 cases, and BVD virus from 5 cases (49). In one instance both IBR and BVD were recovered (49).

Diagnosis can be achieved by virus isolation correlated with clinical signs and pathological and histopathological lesions. Since many subclinical infections occur, it is sometimes difficult to establish a causal role for the virus. Presumptive diagnosis can readily be made by serologic examination (60). However, it should be noted that the antibody response to BVD virus may be delayed for variable periods (up to several months) after infection in some animals (33). The virus neutralization and complement fixation tests are usually used (60). The latter test is more likely to indicate a recent infection (60). Evidence is accumulating that several serotypes of BVD exist (15,16,17). It is not known whether antigenic variation of BVD strains influence the accuracy of laboratory diagnostic procedures. It is possible that serologic testing using only one strain is unlikely to detect all infected animals (16,17).

Commercial vaccines are readily available. However, a disease resembling BVD has been associated with the vaccine (38,45), leading to the recommendation by some not to use live virus vaccines except where heavy losses due to BVD have occurred (22). It has been suggested that failure of the immune response in some animals may result in clnical BVD from vaccine virus (45). However, many of the cases of vaccinal BVD may be true BVD since vaccine is frequently administered to animals that could be incubating BVD (38).

Calfhood vaccination in 6- to 8-month-old calves is recommended (24). Calves under 6 months of age should not be vaccinated because of the immunosuppressive effect of colostral antibodies. However, some calves are infected *in utero* (33), and may have an active immunity at birth and would probably respond anamnestically to vaccination under 6 months of age.

Bovine Respiratory Syncytial (BRS) Virus

Bovine respiratory syncytial virus is a paramyxovirus and is antigenically related to human respiratory syncytial virus (13). The virus is very widespread since approximately 70% of cattle in the U.S.A. have antibodies to the virus (51,59,66). Recent information suggests that this virus may be one of the most important causes of respiratory infection in calves (31,56,66,77).

Experimental infection with this virus results in mild upper respiratory tract disease (43,65,66) but about 1% of infected calves develop severe pneumonia (65). However, in several herds with high incidence of

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bovine respiratory disease, a great majority of convalescent animals developed BRS antibody, indicating a casual relationship (31,56,59,66). In addition, BRS infections in conjunction with other virus infections have been reported (28,31). It has been suggested that, at least in some instances of respiratory syncytial virus infections, pathogenicity is due to an immune mediated mechanism since disease in subjects with antibodies (10,66), particularly colostral antibodies (10) has been reported.

Vaccines are not available in the U.S.A. but are used in Europe (77). Modified live virus vaccines are preferred since killed virus vaccines have been associated with allergic reactions (77). If BRS virus is indeed an important cause of bovine respiratory disease in the U.S.A., a mechanism to control the virus infection in cattle is urgently needed.

Diagnosis of BRS virus infection is rarely achieved by virus isolation. The virus is difficult to isolate and can usually only be recovered from infected calves for a few days prior to the onset of clinical signs (65). Serologic diagnosis can be made readily by virus neutralization, complement fixation or the indirect fluorescent antibody test (IFAT) (77). The IFAT is the method of choice because it is rapid, sensitive, and convenient (51). Unfortunately, very few diagnostic laboratories perform serologic tests for BRS virus.

Parainfluenza-3 (PI^3) Virus

Comprehensive reviews on PI^3 virus and its pathogenicity for cattle have been published (22,48,81). It is a paramyxovirus and is very widespread in cattle since approximately 85% of cattle have specific antibodies.

Experimental infection of calves usually results in very mild signs of upper respiratory tract disease. The pathogenicity of this virus has been questioned but PI^3 virus probably assists in causing shipping fever in cattle under certain environmental and managerial conditions. Variation in virulence between different strains has been reported (48) and at least one strain appears capable of eliciting pneumonia in calves (5).

Diagnosis of PI^3 infection can be made by virus isolation or by serologic means. The virus neutralization and hemagglutination inhibition tests are commonly used.

Commercial vaccines are readily available for PI^3 virus and should probably be administered annually (24). Modified live virus PI^3 vaccines do not appear to interrupt pregnancy but they should not be administered to calves with colostral antibody (24). Intranasally administered modified live virus may be more successfully used in calves under 4 months of age (73).

Adenoviruses

At least 10 serotypes of adenoviruses belonging to 1 of 2 antigenic and biological subgroups have been described (2,39). Adenovirus infections of cattle are common (34,39) and several serotypes, particularly types 1, 3, 4, and 5, have been incriminated as the cause of pneumonia or pneumoenteritis in calves (9,34,35,39). Viruses of subgroup 1 (serotypes 1, 2, and 3) are more likely to cause pneumonia, whereas subgroup 2 viruses (serotypes 4 through 10) are more often associated with pneumoenteritis (34). However, this distinction is not always true (34,35,39). Signs other than respiratory involvement and diarrhea that have been observed in adenovirus-infected calves include conjunctivitis, keratitis, rhinorrhea, and fever (34). Disease may occur in spite of colostral antibodies (34,35).

Diagnosis can be achieved by virus isolation from respiratory tissues, feces, intestine, and conjunctiva but subgroup 2 serotypes are difficult to isolate and may require several blind passages in cell cultures (2,34,39). Moreover, virus isolation from tissues of infected calves may be hampered by the presence of antibodies (34). Direct fluorescent antibody tests of tissues may be helpful to diagnose adenoviral infections (34). Serologic investigation can also establish the occurrence of adenovirus infections in cattle. The virus neutralization, immuno-diffusion, and complement fixation tests are commonly used. A group-specific complement fixation test can be used for subgroup 1 adenoviruses (2,34,39).

Commercial vaccines are not available in the U.S.A. but experimental killed vaccines appear promising (9). Although evidence exists that colostral antibodies may not be protective (34), the prophylactic use of hyperimmune serum appears to reduce the frequency of clinical disease (18).

DN599 Herpesvirus

Several antigenically related herpesviruses (Movar 33/63, DN599, V11, FTC-2, DDV-71, CK-54 BPX/11), but unrelated to IBR virus, have been isolated from cattle with respiratory disease or from healthy cattle (67). It has been suggested that these viruses should be named bovid herpesvirus 5 (BHV5) (67).

There is some disagreement about the pathogenicity of BHV5. Experimental infections in calves with different strains of the virus were reported as severe upper and lower respiratory tract disease (41), mild upper respiratory tract disease (68), or no disease at all (3). The virus has been isolated in widely separated geographic locations (52). Very little is known about the epizootiology and economic significance of BHV5 infections in cattle since a suitable test for serologic surveys has not been available until the indirect fluorescent antibody test (IFAT) was successfully adapted (50,52,61). A recent serologic survey using the IFAT indicated that the virus is not very widespread since only 2% of 351 randomly selected cows in Oklahoma had antibodies (50). Diagnosis can be made by virus isolation but the preferred method is by demonstrating a rise in antibody titer using the IFAT (50). Commercial vaccines are not available and it is premature to consider control methods because of the paucity of knowledge on this virus.

Bovine Rhinovirus

Rhinoviruses have been isolated from healthy calves (44,48) and from calves with acute respiratory disease (7,27,48,54,57,64) in Europe, Britain, Japan, and the U.S.A. Bovine rhinoviruses have been classified into at least two antigenic subgroups (29). Serologic evidence suggests that rhinovirus infections are widespread in cattle (7,20,44,64).

Experimental infection with rhinoviruses usually results in very mild (7) or no (20) respiratory tract disease. However, distinct respiratory tract disease has been reproduced with some strains of the virus (4,42). Consequently, some have questioned the pathogenicity of bovine rhinoviruses (6) but there is sufficient evidence to believe the strains may vary in their pathogenicity (40).

The virus is difficult to isolate in the laboratory since it is rather labile and requires special growth conditions (27,54,64). Serologic diagnosis using the virus neutralization test can also be done (7,20,44,64) but few laboratories test for rhinoviruses.

The economic significance of rhinovirus infections in the U.S.A. is not known since little work has been done on the incidence of bovine rhinoviruses. One serologic survey established that about 48% of Maryland cattle had neutralizing antibody to the virus (40).

Commercial vaccines are not available. It is premature to recommend control measures because of the lack of the knowledge on epizootiology, incidence, and economic impact of the virus. It is quite labile and its survival in the environment for any length of time is unlikely (6,64).

Bovine Reoviruses

Mammalian reoviruses have been classified into 3 antigenic types by virus neutralization. All 3 types as well as additional serotypes have been recovered from the respiratory tract and gastrointestinal tract of cattle (30,55). Several workers have reported an association between reoviruses and respiratory disease (1,30,79). Serologic evidence suggests that reovirus infections are very widespread in cattle in the U.S.A. (55) except for reovirus type 2 infections which are comparatively rare. Infections by types 1 and 3 appear to occur most frequently from November to April (55).

Experimental infections with various reoviruses in calves usually do not result in illness (48,55) but serologic evidence indicate that reoviruses could have a casual role in bovine respiratory disease (28,78,79). Reovirus vaccines are not available in the U.S.A. but have been included in multivalent vaccines in Britain and Europe (47,63,80).

Influenza Virus

Bovine infections by strains of influenza virus related to human strains have been reported in Hungary and Russia (21,48,72). The disease was described as an upper respiratory tract infection with fever and in some cases, pneumonia and death. Influenza virus infection of cattle in the U.S.A. has not been described yet.

Enteroviruses

Enteroviruses have been isolated from cattle with respiratory tract disease. However, the presence of these viruses in affected animals is probably coincidental (48).

Discussion

The cause of respiratory tract disease is complex. Undoubtedly such factors as passive immunity, stress, age, management, viruses, bacteria (including mycoplasmas and chlamydia) interact in varying degrees to produce respiratory tract disease (32,46,48). Experimental manipulation of any one of these factors is frequently insufficient to reproduce the severity of respiratory tract disease as it is often seen in the field (32,46).

Only a few organisms are frank respiratory tract pathogens, and many are considered autochthonous flora of the respiratory tract (32). However, disease ensues when the right combination of the complex multicomponent factors occurs (32). Stress appears to be an essential element in the development of respiratory tract disease (32,46,48,79) followed by viral infections which may then allow bacterial entry into respiratory tract tissues (32,46,48,79). Many viruses are capable of entry and replication in respiratory tract epithelial tissues whereas most bacteria are incapable of doing so without help (32). Therefore viruses seem to be the key to the problem of bovine respiratory tract disease since they may be the primary infectious element (46).

Several instances of multiple viral infections in cattle with respiratory tract disease have been reported (28,33,49,58). Perhaps viral pathogenicity for the respiratory tract is enhanced when certain multiple viral infections occur. The immune response of cattle may be compromised by BVD virus infections (33) which may predispose cattle to infections to bacteria and other viruses.

The control of bovine respiratory tract disease has two facets; control of stress and control of infectious agents (46). Stress factors contributing to bovine respiratory tract disease are not completely defined but much can be done to reduce stress by sound management. However, stress cannot be eliminated entirely since this would involve eliminating entrenched management and marketing methods and total control of the environment.

Controlling infectious agents requires an immunity to the initiators of infection — the viruses (46). The alternative, eliminating contact between cattle from different sources, would be prohibitively expensive. Vaccines will thus be required to control respiratory tract infections but available products are far from satisfactory.

The problem of immunosuppression by colostral antibodies can partially be overcome by using modified live intranasally administered vaccines (73) or by multiple vaccinations (46). Vaccination of feedlot animals should be done before transportation and assembly (46) during which animals are

stressed and may become infected with various viruses. Vaccination of stressed cattle incubating viral infections may just further stress these animals (18,32).

Vaccines can be improved by increasing their valency (46). If the solution of controlling respiratory tract disease is in vaccines, as many of the potential viral pathogens as possible must be included (46). Multivalent viral vaccines available in the U.S.A. contain IBR, BVD, and PI^3 viruses. European and British workers have also included adenoviruses, reoviruses, respiratory syncytial virus, and chlamydia in their vaccines (47,67,77,80).

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Practice Methods

Nutrition Consulting

How do you charge for nutritional consulting, especially if you are called to the farm for another reason, but it may have an underlying nutritional cause? The client may not question the cause, but you interject it and explain it and give recommendations. Maybe most or part of this time is used during examination and treatment of the case, plus time dispensing drugs and supplements. How much for feed sampling? I don't want to loan out the hay bale corer because it takes so long to get it back.

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Reply by Dallas Horton, D.V.M.
Colorado State University

In my opinion the best approach to charging for nutritional counseling is to do it by the hour and do your ration calculations at home in the evening or in your office and do not try to specifically compute a ration on the man's farm. First of all, it is highly unlikely that this can be accomplished in a short period of time. My experience is that it takes at least an hour with a calculator and an NRC requirement booklet which includes not only the requirements of the animals but the specific nutrient content of each feed. I would suggest making a minimal charge when first starting this service in your practice, and as you become more confident in ration formulations and your clientele become more confident in your ability, then you could continue to increase the fee to $30-$40 an hour for your office time for calculation.

A hay core is all right, but I believe representative samples can be taken by selecting a few bales at random, breaking the bale and taking several leafs of hay from different areas of the bale. Feed sampling charges will vary according to the laboratory but most charge $5 for each ingredient analyzed (i.e., a sample of hay sent in for a protein, calcium, phosphorus, and vitamin A or carotine would cost $20). Moisture is by far the most important factor to analyze a feed for, particularly when dealing with silages or high moisture grains. The reason for this is moisture is the largest variable in these feeds and the one that is most important with reference to cost per unit of dry feed. I hope this answers the question adequately.