The Controversy Surrounding the Role of the Bovine Virus Diarrhea Virus (B.V.D.V.) in the Pathogenesis of Pneumonic Pasteurellosis in Cattle

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Introduction

This is a brief review and discussion of the evidence which has proposed for about the last 20 years that the bovine virus diarrhea virus (BVDV) has a role in the pathogenesis of pneumonic pasteurellosis of cattle which is one of the most common causes of acute undifferentiated bovine respiratory disease or the "shipping-fever complex." We propose to show that there is no substantive evidence to implicate the BVDV in the pathogenesis of acute respiratory disease in cattle.

Acute undifferentiated bovine respiratory disease (AUBRD) is the most frequent cause of illness and death in feedlot cattle in North America and is a major cause of economic loss (1). The clinical findings include a rapid onset of acute illness characterized by anorexia, toxemia, nasal discharge, coughing, a fever of 104°F (40°C), abnormal lung sounds and a beneficial response to treatment with antimicrobials. While a definitive etiological diagnosis is usually not made clinically, the rapid response to therapy indicates the presence of a bacterial bronchopneumonia. It is assumed that disease such as acute infectious bovine rhinotracheitis can be recognized clinically and differentiated from acute pneumonias. It is also accepted that accurate and reliable differentiation between the different causes of pneumonia can be difficult if not impossible based on clinical examination alone. However, it can also be argued that pneumonic pasteurellosis is the most common cause of acute undifferentiated respiratory disease in cattle in North America. There is general agreement that *Pasteurella hemolytica* (Biotype A, serotype I) is the ultimate cause of the lesions of pneumonic pasteurellosis (2). During active growth *Pasteurella hemolytica* is known to produce a soluble cytotoxin with specificity for ruminant leukocytes (3). This leukotoxin is believed to act as a virulence factor in the production of pneumonia by impairing pulmonary macrophage function and bacterial clearance or by the induction of damage to the lung through the release of proteolytic enzymes from lysed leukocytes (3). The terminal lesion is a fibrinous bronchopneumonia with varying degrees of fibrinous pleuritis.

Considerable research has centered on determining how *P. hemolytica*, which are part of the normal flora of the nasopharynx, get into the terminal bronchioles and alveoli. Under normal conditions the lung is relatively free of *P. hemolytica* due to an effective lung clearance mechanism. It has been postulated that the lung clearance mechanisms may be affected by viral infections of the respiratory tract or by devitalizing influences such as prolonged transportation leading to fatigue, temporary starvation, the stress of weaning, rapid fluctuations in ambient temperature, mixing cattle from different sources after arrival in the feedlot and the handling and processing procedures of commercial feedlots. It is suggested that a defective pulmonary clearance mechanism would allow the bacteria to be inhaled into the alveoli and not be effectively cleared (2).

Many viruses have been incriminated as so-called predisposing causes of acute undifferentiated bovine respiratory disease (4). Parainfluenza type 3 (PI-3) virus, infectious bovine rhinotracheitis (IRB), bovine respiratory syncytial virus (BRSV), and the bovine virus diarrhea virus (BVDV) have all been implicated (4,5,6). It is postulated that three viruses have a role in the pathogenesis of pneumonic pasteurellosis because they may be found in the lungs of cattle which have died with the disease and cattle affected with acute undifferentiated respiratory disease may seroconvert to one or more of the viruses (21,22,23,24,25,26). To obtain supporting evidence that these viruses may be initiators of acute undifferentiated respiratory disease the PI-3, IBR and the BVDV viruses have been used to experimentally reproduce respiratory disease by aerosol exposure of young cattle to the viruses followed by aerosol exposure with *P. hemolytica* several days later (2,7,8,9,10,11). Some elegant experimental

models of acute pneumonic pasteurellosis in cattle have been developed with the PI-3 and IBR viruses followed by exposure to *Pasteurella hemolytica* (2,7,8,9). Much less research has been done to determine if the BVDV can act synergistically with *Pasteurella hemolytica* to reproduce pneumonic pasteurellosis and the results are contradictory (11,27).

The experimental reproduction of acute undifferentiated bovine respiratory disease has been attempted using the BVDV as an aerosol exposure (27) or by direct inoculation into the lungs (11) followed by either aerosol exposure or endobronchial inoculation with *Pasteurella hemolytica.* In one experiment there was no significant effect of the BVDV on the mean clearance rate of *Pasteurella hemolytica* (27). In the other experiment in which both the virus and the bacteria were inoculated endobronchially severe fibrinopurulent bronchopneumonia and pleuritis involving 40-75% of the lung volume developed in 5 calves inoculated sequentially with the BVD virus and *Pasteurella hemolytica* (11). How can these differences be explained? It is possible that the strains of BVD may vary in their pneumopathogenicity. In one experiment a cytopathic strain of the BVDV was found to be more severe as a synergistic agent with *Pasteurella hemolytica* than the non-cytopathic strain, indicating that strains of the BVDV may vary in their pneumopathogenicity for calves (10). The BVDV is not considered to be a primary pneumopathogen (31).

A seroepidemiological survey has shown an association between antibody titers to infectious bovine rhinotracheitis, parainfluenza-3, bovine virus diarrhea and bovine respiratory syncytial viruses and the treatment for acute undifferentiated bovine respiratory disease in feedlot cattle (26). The results of the study suggested a possible role for I.B.R., PI-3, B.V.D. and B.R.S. viruses as associated causes of acute undifferentiated bovine respiratory disease. However, a seroepidemiological association does not necessarily provide supporting evidence for the role of the viruses as predisposing pathogens. Although a significant relationship between an increased titer to BVDV and the occurrence of AUBRD was demonstrated over all of the animals in the study, the authors point out that the exact relationship between seroconversion to BVDV and AUBRD could not be clarified. For example, the animals studied fell into five natural groups. Within these groups an increase in the rate of seroconversion was not associated with a similar increase in the AUBRD. In fact, within one group, animals exposed to BVDV appeared less likely to develop respiratory disease than those that were not exposed. In addition, animals in all five groups also experienced significant titer changes to IBR and PI-3 viruses. The combined effect of all three viruses upon the occurrence of respiratory disease was not examined, raising the concern that the apparent relationship between seroconversion to BVDV and AUBRD may have been due to the effect of another, concurrent viral infection. Finally, due to the design of this study it was not possible to determine which came first, seroconversion to BVDV or the cases of AUBRD. In other words, AUBRD may have led to changes in the BVDV titer rather than the other way around.

The BVDV is thought to be a predisposing cause of pneumonic pasteurellosis because the virus can impair the immune response of cattle. On an experimental basis the virus can alter neutrophil function (12), cause hyporesponsiveness of peripheral lymphocytes to various mitogens (13), affect the distribution of immunoglobulins between the cytoplasm and surface of lymphocytes (14), impair clearance of bacteria from the blood (15), allow the IBR virus to be more widely distributed in various tissues (16) and in tissue culture cells it can cause the release of substances which can suppress the proliferative response of bovine mononuclear cells to blastogenic substances(17). A modified live-virus vaccine strain of BVDV can experimentally have a detrimental effect on lymphocyte function (18). Both cattle persistently infected with the BVDV and healthy cattle mounting an immune response to a recent infection with the BVDV have impaired neutrophil function; the impairment in persistently infected animals is different than in healthy cattle (19).

The virus causing bovine viral diarrhea (BVD) and mucosal disease (MD) is distributed worldwide. The most frequent form of BVD infection in cattle is the subclinical or benign form which is characterized by a transient fever, a moderate leukopenia, slight inappetance, a mild diarrhea in some cases and the production of BVD virus-neutralizing antibodies, elimination of the virus and rapid recovery (20). It has been suggested that this benign form of the disease may cause sufficient immunosuppression which acts as a predisposing factor to allow the development of pneumonia caused by *Pasteurella hemolytica* (4).

Fatal mucosal disease occurs in young cattle from 6 to 24 months of age which were infected in utero with a non-cytopathogenic strain of the virus before 125 days of gestation, and were born with persistent viral infection and specific immunotolerance. These animals are usually clinically normal at birth but may develop fatal mucosal disease, perhaps following superinfection with a cytopathic strain of the virus between 6 and 24 months of age or even later. It is thought that persistently viremic animals are the principal carriers of the virus and provide the source of the virus to immunocompetent animals which develop the benign form of the infection known as bovine virus diarrhea.

The prevalence of persistently viremic animals in the cattle population is about 1% but prevalence rates of up to 10% of the progeny of heifers when they are first exposed to the BVDV in early pregnancy have been reported. Even higher values up to 27% have been reported in individual

herds (20).

There is no published information to indicate that persistently viremic cattle or those which are affected with the benign form of the disease are more susceptible than immunocompetent cattle (which have had no experience with the virus) to the experimental reproduction of respiratory disease using an aerosol exposure of *Past. hemolytica*. All of the published information indicates that the BVDV was inoculated directly into the lungs of the experimental animals along with or followed a few days later by *Past. hemolytica*.

The widespread availability of bovine vaccines which contain the PI-3, IBR, BRSV and BVD viruses in various combinations with or without bacterial antigens for the control and prevention of bovine respiratory disease has also contributed to the notion that viruses predispose to respiratory disease caused by *Pasteurella hemolytica*. However, there is no supporting evidence that the use of these vaccines will aid in the economical control of naturally-occurring cases of acute undifferentiated respiratory disease or pneumonic pasteurellosis (1).

Another major question with regard to the role of the BVDV in bovine respiratory disease is whether or not the use of modified live BVDV vaccines can cause immunosuppression and interfere with the development of protective immunity of cattle which are vaccinated with infectious bovine rhinotracheitis vaccine. One experiment has shown that vaccination of calves with a modified live BVDV vaccine did not interfere with the immunity induced by an IBR vaccine against the experimental model of pneumonic pasteurellosis calves in which an aerosol of the IBR virus is followed a few days later by an aerosol of *Pasteurella hemolytica* (5).

A modified live-virus vaccine strain of the BVD can experimentally have a detrimental effect on lymphocyte and neutrophil function (28). This suggests that stressed cattle should not be vaccinated with a modified-live virus BVD vaccine because impaired lymphocyte or neutrophil function could potentiate other viral or bacterial infection. This impairment may be potentiated by increased plasma cortisol caused by stress. In the Bruce County Project in Ontario in the early 1980's it was shown that there was a greater incidence of health problems in cattle which were vaccinated with vaccines containing the modified live BVD virus compared to those which did not receive the BVDV vaccines (30).

Stress has been associated with increased susceptibility to bacterial pneumonia in animals. The exact mechanisms whereby increased susceptibility occurs have not been fully investigated, but it has been suggested that stress may increase the release of adrenocorticotrophic hormones (ACTH) which in turn stimulates the synthesis and secretion of cortisone. Increased cortisone levels may then alter immune functions and increase susceptibility to bacterial pneumonia. Stressful conditions which contribute to increased cortisone levels in cattle include weaning, transportation, handling, castration and dehorning, parturition, forced exercise and marked fluctuations in ambient temperature. Calves experimentally stressed under field conditions were not susceptible to bacterial infection by aerosol challenge with *Pasteurella hemolytica* (29). However, when the stressed calves were challenged with an aerosol of IBR virus, they developed lesions consistent with infectious bovine rhinotracheitis but they were not susceptible to an aerosol infection with *Pasteurella hemolytica*.

A recent report indicated that in utero infection of dairy cows with the BVDV was significantly associated with an increase in the risk of death in their calves (23). More of these calves died of pneumonia than did calves from cows that were not suffering an in utero infection. *Pasteurella hemolytica* was the organism that was most frequently isolated from the pneumonic lungs. It was suggested that immunosuppression due to persistent infections with the BVDV, in combination with suboptimal management conditions, may have predisposed the calves to a bacterial infection. Even if subsequent investigations confirm this pathogenesis for respiratory disease, this cannot be taken as evidence that acute infection of immunocompetent cattle predisposes them to AUBRD.

The new concepts of the pathogenesis, diagnosis and control of the disease caused by the BVDV which have emerged within the last 10 years suggest that the published literature dealing with the use of BVDV vaccine for the control and prevention of bovine respiratory disease prior to 1980 may be irrelevant. A detailed review of the literature of these new concepts is available (20).

The necessary evidence required to show that exposure of immunocompetent animals to the BVDV increases the risk of AUBRD would require several consistent studies. These would have to show that the rate of AUBRD was greater in animals exposed to the BVDV than in those that were not. Alternately, the degree of serological response to BVDV would have to differ significantly between diseased and non-diseased animals. With respect to groups of animals, the rate of AUBRD within groups should increase with the frequency of seroconversion to the BVDV. In addition, reasonable evidence that the occurrence of AUBRD was not due to some other factor (e.g. another pathogen) that was also acting at the same time as the BVDV would also be required. Finally, it would have to be shown that exposure to the BVDV preceded the development of AUBRD. If these criteria are accepted, then one must conclude that the existing, published evidence is not sufficient to support the belief that the BVDV has a role in the pathogenesis of AUBRD.

References

1. Martin, SW. Vaccination: Is it effective in preventing respiratory disease or influencing weight gains in feedlot calves? Can Vet J 24:10-19, 1983. 2. Yates WDG: A review of infectious bovine rhinotracheitis, shipping fever pneumonia and viral bacterial synergism in respiratory disease in cattle. Can J Comp Med 46:225-263, 1982. 3. Shewen PF, Wilkie BN: Vaccination of calves with leukotoxic culture supernatant from *Pasteurella hemolytica* Can J Comp Res 52:30-36, 1988. 4. Potgieter LND: Current concepts on the role of viruses in respiratory tract disease of cattle. Bovine Pract 12:75-81, 1977. 5. Yates, WDG. Interaction between viruses and bacteria in bovine respiratory disease. Can Vet J 25:37-41, 1984. 6. Stott, EJ, Thomas, LH, Collins, AP, Crouch, S, Jebbett, J, Smith, GS, Luther, PD & Caswell, R. A survey of virus infections of the respiratory tract of cattle and their association with disease. J Hyg Camb 85:257-270, 1980. 7. Yates, WDG, Babiuk, LA & Jericho, KWF. Viral-bacterial pneumonia in calves: Duration of the interaction between bovine herpesvirus I and *Pasteurella hemolytica*. Can J Comp Med 47:257-264, 1983. 8. Yates, WDG, Jericho, KWF & Doige, CE. Effect of viral dose on experimental pneumonia caused by aerosol exposure of calves to bovine herpesvirus I and *Pasteurella hemolytica*. Can J Comp Med 47:57-63, 1983. 9. Yates, WDG, Jericho, KWF & Doige, CE. Effect of bacterial dose on pneumonia induced by aerosol exposure of calves to bovine herpesvirus-I and *Pasteurella haemolytica*. Am J Vet Res 44:238-243, 1983. 10. Potgieter LND, McCracken MD, Hopkins FM and Guy JS: Comparison of the pneumonopathogenicity of two strains of bovine viral diarrhea virus. Am J Vet Res, Vol. 46, No. 1, 151-153, 1985. 11. Potgieter LND, McCracken MD, Hopkins FM, Walker RD and Guy JS: Experimental production of bovine respiratory tract disease with bovine viral diarrhea virus. Am J Vet Res, Vol. 45, No. 8 1582-1585, 1984. 12. Roth JA, Kaeberle ML, Griffith RW: Effects of bovine viral diarrhea virus infection on bovine polymorphonuclear leukocyte function. Am J Vet Res 42:244-250, 1981. 13. Johnson, DW, Muscoplat, CC. Immunologic abnormalities in calves with chronic bovine viral diarrhea. Amer J Vet Res 34:1139-1141, 1973. 14. Muscoplat, CC, Johnson, DW, Teuscher, E. Surface immunoglobulin of circulating lymphocytes in chronic bovine diarrhea. Abnormalities in cell population and cell function. Amer J Vet Res 34:1101-1105, 1973. 15. Reggiardo C, Kaeberle ML: Detection of bacteremia in cattle inoculated with bovine viral diarrhea virus. Am J Vet Res 42:218-221, 1981. 16. Potgieter LND, McCracken MD, Hopkins FM, Walker RD: Effect of bovine viral diarrhea virus infection on the distribution of infectious bovine rhinotracheitis virus in calves. Am J Vet Res 45:687-690, 1984. 17. Markham, RJF & Ramnaraine, ML. Release of immunosuppressive substances from tissue culture cells infected with bovine viral diarrhea virus. Amer J Vet Res 46:876-883, 1985. 18. Roth, JA & Kaeberle, ML. Suppression of neutrophil and lymphocyte function induced by a vaccinal strain of bovine viral diarrhea virus with and without the administration of ACTH. Amer J Vet Res 44:2366-2372, 1983. 19. Roth, JA, Bolin, SR, & Frank, DE. Lymphocyte blastogenesis and neutrophil function in cattle persistently infected with bovine viral diarrhea virus. Amer J Vet Res 47:1139-1141, 1986. 20. Radostits, OM & Littlejohns, IR. New concepts in the pathogenesis, diagnosis and control of diseases caused by the bovine viral diarrhea virus. Can Vet J 29: 513-528, 1988. 21. Reggiardo C: Role of BVD virus in shipping fever of feedlot cattle. Case studies and diagnostic considerations. Proc Annu Meet Am Assoc Vet Lab Diagn 22:315-320, 1979. 22. Woods GT, Krone J, Mansfield ME et al: Bovine virus diarrhea associated with severe pneumotropism. VM SAC 48:418-422, 1973. 23. Barber, DML, Nettleton, PF & Herring, JA. Disease in a dairy herd associated with the introduction and spread of bovine virus diarrhea virus. Vet Rec 117:459-464, 1985. 24. Reed, DE, Mattson, JM, McCrow, L & Larson, MS. A diagnostic survey of bovine viral infections in the Northern Plains States. Proc Annu Meet Amer Assoc Vet Lab Diab 17:199-206, 1974. 25. Richer, L, Marois, P, & Lamontagne, L. Association of bovine viral diarrhea virus and multiple viral infections in bovine respiratory disease outbreaks. Can Vet J 29:713-717, 1988. 26. Martin, SW, & Bohac, JG. The association between serological titers in infectious bovine rhinotracheitis, bovine virus diarrhea virus, parainfluenza-3 virus, respiratory syncytial virus and treatment for respiratory disease in Ontario feedlot calves. Can Vet J Res 50:351-358, 1986. 27. Lopez A, Maxie MG, Savan M et al: The pulmonary clearance of *Pasteurella haemolytica* in calves infected with bovine virus diarrhea or *Mycoplasma bovis*. Can J Comp Med 46:302-306, 1982. 28. Edwards, S, Wood, L, Hewitt-Taylor, C, & Drew, TW. Evidence for an immunocompromising effect of bovine pestivirus of bovid herpesvirus I vaccination. Vet Res Communication 10:297-302, 1986. 29. Filion, LG, Willson, PJ, Bielefeldt-Ohmann, H, Babiuk, LA & Thomson, RG. The possible role of stress in the induction of pneumonia pasteurellosis. Can J Comp Med 48:268-274, 1984. 30. Martin, SW, Meek, AH, Davis, DG, Thomson, RG, Johnson, JA, Lopez, A, Stephens, L, Curtis, RA, Prescott, JF, Rosendal, S, Sauan, M, Zubaidy, AJ, Bolton, MR. Factors associated with mortality in feedlot cattle: The Bruce County Beef Cattle Project. Can J Comp Med 44:1-10, 1980. 31. Thomas LH, Stott EJ, Collins AP, et al: Evaluation of respiratory disease in calves. Comparison of disease response to different viruses. Res Vet Sci 23:157-164, 1977.