PEER REVIEWED

Role of Bovine Viral Diarrhea Virus in the Bovine Respiratory Disease Complex

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Introduction

Bovine viral diarrhea virus (BVDV) is one of the most important infectious agents of cattle. The annual economic loss caused by BVDV is difficult to quantify but certainly is significant. The insidious nature of BVDV combined with the biology of the virus and complex disease pathogenesis has made control and prevention of this virus challenging.

BVDV has been associated with many clinical diseases.[1] There is little doubt that BVDV plays a role in bovine respiratory disease (BRD). The exact nature and the significance of this role is not understood and at times is controversial. This review will attempt to present past and current information on the role that BVDV plays in BRD.

The Agent

BVDV is a member of the genus *Pestivirus* within the family Flaviviridae.[2] Other members of the pestivirus genus include hog cholera virus of swine and border disease virus of sheep. Prototypes of other genera in the flaviviridae family include hepatitis C virus and yellow fever virus.

BVDV is a small enveloped virus which contains a single strand of positive sense RNA as its genomic material. The RNA is translated in the cytoplasm of host cells into a single polyprotein which is then processed into mature viral proteins. This results in the production of 4 structural and 6 or 7 nonstructural proteins.[3]

Cytopathic (CP) and noncytopathic (NCP) biotypes of BVDV are recognized based on their ability to cause cytopathology in cell culture.[4,5] Several types of mutational events within specific regions of the BVDV genome have been described which result in the production of the protein NS3 which is unique to CP-BVDV.[6,7]

The major neutralizing epitopes of BVDV are found in the glycoprotein E2.[8] Not surprisingly, analysis of this area has identified regions in which nucleotide and amino acid sequences vary significantly between different BVDV isolates.[9] These differences help to explain the wide antigenic diversity of BVDV.

Recently, BVDV isolates have been divided into two genotypes, identified as Type I and Type II BVDV.[10] This classification is based on significant nucleotide sequence differences in the 5' noncoding region of the viral genome. Correlated with this are different reactivity patterns to panels of monoclonal antibodies directed against the E2 protein, suggesting significant antigenic variation. In addition, type II BVDV has been associated with outbreaks of disease which are characterized by higher morbidity and mortality.[11]

Clinical Disease

Acute Infection: The outcome of acute infection is dependent on several factors, including the health and immune status of the host and the virus strain. In susceptible cattle, the majority of acute infections are subclinical. Mild disease, often referred to as bovine viral diarrhea (BVD), may be characterized by diarrhea, fever, anorexia, leukopenia and production loss (milk or body condition).[1] Peracute/acute forms of BVD have been described in the United Kingdom, Canada and the United States in which mortality rates were as high as 20%.[11-13] Mortality rates from BVDV outbreaks among veal calves in Quebec was 22% in 1993, a four fold increase from normal losses.[11] Type II BVDV has been associated with these outbreaks in the United States. Acute BVDV infection has also been reported to cause a hemorrhagic syndrome characterized by thrombocytopenia with resulting petechial and ecchymotic

hemorrhages, bloody diarrhea and epistaxis.[14] Only type II BVDV isolates have been identified in association with hemorrhagic syndrome.

Reproductive Outcomes: BVDV has been associated with a variety of events leading to reproductive wastage which may represent the largest economic loss associated with BVDV infection.[15] Infection of susceptible cows around the time of breeding can result in reduced conception rates by mechanisms that are not yet understood. Infection during early gestation can lead to early embryonic death manifested by reduced pregnancy rates or return to estrus. Transplacental infection can result in fetal death at any stage of gestation although this occurs most commonly during the first 4 months. Fetal infection before 125 days of gestation with NCP-BVDV may result in immunotolerance to the virus. Immunotolerance results in the birth of calves persistently infected (PI) with BVDV. Fetal infection has also been associated with a variety of congenital defects which are dependent on the time of virus exposure and the stage of organogenesis. Some of the more common defects include cerebellar hypoplasia, cataracts, and growth retardation. Transplacental infection late in gestation most often results in the birth of normal calves which are seropositive to BVDV. BVDV has been associated with both late term abortions and weak calf syndrome, although numerous other causes of these conditions have been identified.

Mucosal Disease: Classic mucosal disease is a rare, highly fatal manifestation of BVDV which is characterized by extensive mucosal ulceration of the entire gastrointestinal tract and severe lymphoid depletion. Mucosal disease occurs when cattle persistently infected with BVDV become superinfected with CP-BVDV.[16] The most common source of CP-BVDV is believed to be from specific mutations of the persistently infecting NCP-BVDV. External sources of CP-BVDV include live vaccines, acutely infected cattle and other cattle with mucosal disease. The outcome of superinfection with CP-BVDV is largely dependent on the antigenic homology between the two biotypes. Identical homology, as would be expected following a mutational event of the persistent NCP-BVDV, results in acute mucosal disease with death usually occurring in less than 1 week from onset of clinical signs. Chronic mucosal disease is believed to occur when the NCP and CP viral pairs are not completely homologous as might be expected following postvaccinal mucosal disease. Cattle with chronic mucosal disease exhibit weight loss, unthriftiness, persistent nasal and ocular discharge and intermittent to chronic diarrhea. Chronic erosive lesions of mucosal surfaces and mucocutaneous junctions are evident. These cattle may survive for as long as 18 months. Recently, delayed-onset mucosal disease has been described. This is thought to involve genetic recombination between the persistent NCP-BVDV and an externally-introduced, heterologous CP-BVDV such as of vaccine origin. In this case, mucosal disease may take up to 4 weeks to occur following exposure to the CP-BVDV. Persistently infected cattle exposed to heterologous CP-BVDV can also mount an immune response to the CP-BVDV and clear the virus with no significant clinical outcome.

Role in Bovine Respiratory Disease

Bovine respiratory disease is the most frequent cause of morbidity and mortality in North American feedlots and is the major cause of economic loss.[17] It is generally agreed that *Pasturella haemolytica* is the major contributor to pneumonic lesions.[18] Considerable research has focused on the mechanisms by which *P. haemolytica* colonizes the lungs. Many predisposing factors have been implicated in reducing the local clearance mechanisms of the lungs including stress from weaning, transportation, mixing of cattle, handling, and processing. Viruses, including parainfluenza-3, bovine respiratory syncytial virus, bovine herpes virus-1, coronavirus, and BVDV, have been implicated as predisposing causes of BRD.

BVDV has been implicated in bovine respiratory disease since it was first described by Olafson, MacCallum and Fox in 1946.[19] Although not conclusive, both circumstantial and experimental evidence suggest that BVDV is involved in BRD.[20]

Clinical: Circumstantial evidence that BVDV is involved in BRD comes from clinical pathological observation. As mentioned earlier, clinical descriptions of cattle undergoing acute BVDV infection often involve respiratory signs. In Sweden, severe respiratory disease outbreaks were described involving both BVDV and PI-3.[21] In the United States, BVDV has been reported as the most commonly isolated virus from pneumonic lungs [22] and in outbreaks of BRD.[23]

Experimental studies attempting to reproduce respiratory disease with BVDV alone have resulted in mild lesions. In studies by Potgeiter *et al.,* calves infected with BVDV alone had less severe clinical signs and pulmonary pathology when compared to calves infected with both BVDV and *P. haemolytica* [24,25] (Table 1). Synergistic effects between BVDV and *P. haemolytica* [24], BHV-1 [26] and BRSV [27,34] have been documented. Differences in pneumopathogenicity have been demonstrated for isolates of BVDV[25] (Table 1). These findings suggest an immunocompromising role for BVDV in bovine respiratory disease.

Table 1. Experimental production of respiratory tract disease in calves with BVDV and *P. haemolytica* (Adapted from: Potgeiter *et al.*, Am J Vet Res 1984;45;1582-1585 and Am J Vet Res 1985;46:151-153)

Treatment	Clinical Score[a]	Lung Pathology[b]
BVDV 72[c] (3)	1.0	2.0
BVDV 72 (2)	1.75	4.5
BVDV 2724[d] (2)	1.0	1.5
Ph[d] (2)	1.0	14.5
Ph (2)	1.0	15.0
Ph & BVDV 72 (5)	7.5	56.0
Ph & BVDV 72 (3)	7.	58.0
Ph & BVDV 2724 (2)	2.75	30.0

[a] 0=No signs, 10=Severe signs. (#) = Number tested
[b] Percent of lung affected.
[c] BVDV strain 72 — cytopathic biotype
[d] BVDV strain 2724 — noncytopathic biotype
[d] Ph = *Pasturella haemolytica*

Epidemiological: Epidemiological studies have both implicated and shown no evidence that BVDV is associated with outbreaks of respiratory disease. Interpretation of results is often difficult because of the multiple etiologies of the BRD complex and the variability of exposure to various pathogens prior to being studied.

It is obvious from a review of seroepidemiological studies that seroconversion to BVDV is variable during outbreaks of BRD (Table 2). However, the risk of developing BRD in association with BVDV seroconversion varies. In two studies by Martin *et al.* involving feedlot calves, seroconversion to BVDV was significantly associated with the development of BRD[28,29] (Table 3).

Table 2. Seroconversion rates to BVDV during respiratory disease outbreaks.

Study	Rate
Lehmkuhl & Gough, 1977[34]	10%
Martin & Bohac, 1986[29]	24%
Richer *et al.*, 1988[23]	57%
Martin *et al.*, 1989[28]	40%
Allen *et al.*, 1992[32]	51%
Caldow *et al.*, 1993[33]	12%

Similarly, young calves seronegative to BVDV were at higher risk for developing respiratory disease[31] while seroconversion to BVDV was associated with respiratory disease.[30] Protection from respiratory disease has been shown in calves entering a feedlot when seropositive to BVDV.[29] Highlighting the importance of colostral antibodies, a protective effect against respiratory disease has been shown in calves being born to BVDV seropositive dams.[31,52] In contrast, other studies have provided no evidence between seroconversion to BVDV and risk of developing BRD. Allen *et al.* reported a 51% rate of seroconversion to BVDV in both BRD cases and controls.[32] In young dairy calves entering a commercial calf rearing unit, BVDV was not identified as a risk factor for developing clinical respiratory disease.[33] It should be noted that in all of the above studies, other agents in addition to BVDV were identified as being associated with respiratory disease. This highlights the complex nature of BRD and the fact that it is a multifactorial disease.

Table 3. Association between initial titer and seroconversion to putative respiratory disease agents (Adapted from: Martin SW *et al., Can J Vet Res* 1989;53:355-362).

	Odds Ratio[a]	
Agent	Initial Titer	Seroconversion
Ph[b]	1.89	1.08
Ph-cytox[c]	0.71	1.97
PI3	0.42	1.54
BHV 1	1.25	1.57
BRSV	0.42	1.36
BVDV	**0.63**	**1.49**

[a] Risk of developing respiratory disease given either an initial titer or seroconversion to a specific agent.
[b] Ph = *Pasturella haemolytica*
[c] Ph-cytox = *P.haemolytica* cytotoxin

Immunosuppressive Role: Several field studies have reported that clinical disease caused by a particular organism appears to be more severe when concurrent BVDV infection is present. The compromising effect of BVDV is thought to be due to immunosuppressive effects of the virus. The most important role that BVDV may play in BRD is in suppressing local immune system function in the lungs, thus allowing pathogenic bacteria to become established.

Several reports have suggested synergistic effects between BVDV and other pathogenic organisms. In calves infected simultaneously with BVDV and BHV-1, the latter virus became systemically disseminated as compared to remaining localized in the respiratory tract in calves not infected with BVDV.[26] BVDV infection has also been associated with concurrent *Salmonella* [36], *E. coli* [37], bovine papular stomatitis[38] and rotavirus and coronavirus infections.[39]

In experimental studies involving BVDV and *Pasteurella haemolytica*, sequential infection with the two organisms produced more severe fibrinopurulent

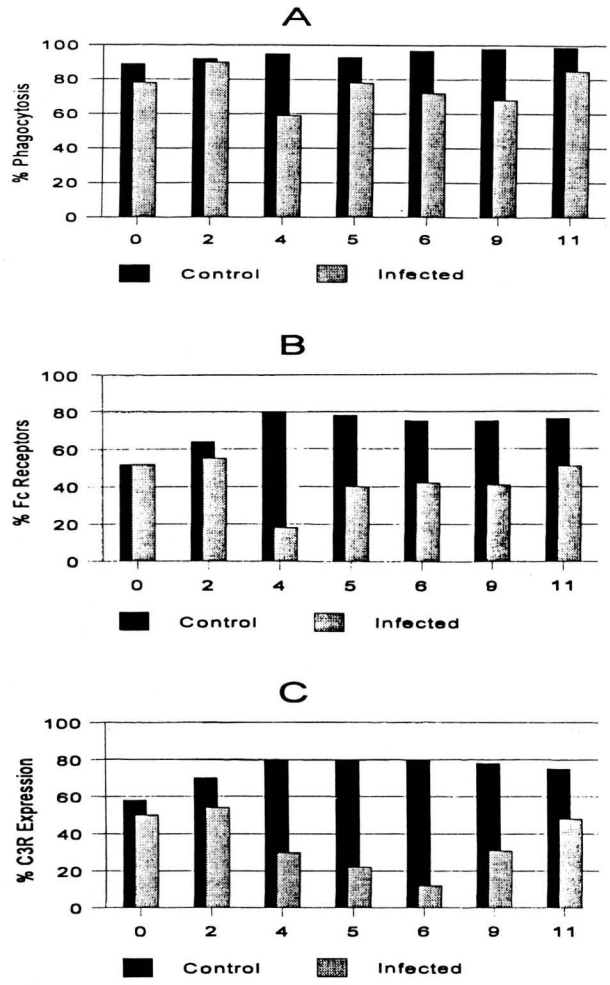
bronchpneumonia when compared to each organism by itself. [24] Interestingly, when calves were inoculated with BVDV only, bacteria could often be cultured from the lower respiratory tract and were assumed to be endogenous bacteria originating from the upper respiratory tract. In contrast, Lopez *et al.* showed no effect of BVDV on inhibiting pulmonary clearance of *P. haemolytica*.[35] In a small study, Pollreisz *et al.* provided evidence that BVDV and bovine respiratory syncytial virus (BRSV) can potentiate each other in dual virus infections of calves [53]. In this study, the severity of clinical signs and extent of lung injury was greater in calves infected simultaneously with BVDV and BRSV than that caused by either virus alone.

The mechanisms of immunosuppression may involve several aspects of the immune system. Lymphocytes and macrophages are specific targets of BVDV.[40] Systemically, acute infection with BVDV results in a transient leukopenia with lymphoid depletion often noted.[41] A decrease in CD4+ and CD8+ T-lymphocytes, B-lymphocytes and neutrophils has been reported.[48] *In vitro* studies have suggested different causes of immunosuppression. These include a decreased responsiveness of infected lymphocytes to mitogen stimulation[42], decrease in interferon production [43], reduction in monocyte interleukin-1[49], interleukin-2 [50] and tumor necrosis factor-alpha[44] production and a decrease in the chemotactic responses by monocytes.[45] Neutrophils from BVDV infected cattle have decreased activity in their myeloperoxidase, halide, and hydrogen peroxide systems which are bacteriocidal.[51] In addition, neutrophil-mediated, antibody-dependent, cell-mediated cytotoxicity can be impaired significantly.[46] BVDV mediated immunosuppression may be the indirect result of prostaglandin production from infected cells. This was suggested when indomethacin, a prostaglandin synthesis inhibitor, reversed the immunosuppressive effects of infected cell culture supernatant.[47]

Evidence also exists that infection with BVDV may have a direct effect on local pulmonary immune functions. BVD virus has been shown to replicate in bovine alveolar macrophages.[54] In bovine alveolar macrophages recovered from calves acutely infected with BVDV, the ability to phagocytize bacteria and the expression of complement receptors (C3R) and antibody Fc receptors (FcR) was significantly reduced when compared to control calves (Table 4) .[55] Similar findings were found in alveolar macrophages infected *in vitro*.[55] In addition, Olchowy *et al.* demonstrated that BVDV infected macrophages independently have an increased propensity to produce procoagulant which is part of the fibrin deposition cascade.[56] Increased fibrin deposition in the alveoli may provide an enhanced environment for secondary bacterial replication.

Regardless of the mechanism, host, agent, and environmental factors undoubtedly influence the degree of immunosuppression that occurs following acute infection with BVDV.

Table 4. Bovine alveolar macrophage function following infection with bovine viral diarrhea virus. Percent of alveolar macrophages A) able to phagocytize bacteria, B) expressing antibody Fc receptors (FcR), C) expressing complement receptors (C3R). Adapted from Welsh *et al.*[55]



Conclusions

The involvement of BVDV in respiratory disease is obviously complicated. However, enough evidence exists to include it as an integral part of the bovine respiratory disease complex. This warrants further study on its importance so that sound judgements can be made on developing and instituting control and prevention programs.

Current available technology for preventing BVDV infection should be implemented when possible, including vaccination, biosecurity and the elimination

of persistently infected cattle. Vaccination programs should be targeted to provide high levels of antibodies at times of maximum exposure.

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