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Human and bovine respiratory syncytial virus: immunopathologic mechanisms

John C. Baker¹

SUMMARY. *Human respiratory syncytial virus (HRSV) is the major respiratory tract pathogen of infants and young children. Bovine respiratory syncytial virus (BRSV) is recognised as an important cause of respiratory tract disease in calves. Both of these viruses and their respective diseases share many similarities. Immunopathologic mechanisms have been proposed to be involved in the pathogenesis of respiratory syncytial virus (RSV) infections. This review examines the current understanding of the role of immunopathologic mechanisms in RSV infections. The role of vaccines in inducing hypersensitivity is also examined. Additionally, non-immunopathogenic mechanisms involved in RSV infections are discussed.*

INTRODUCTION

Bovine respiratory syncytial virus (BRSV) as an important cause of respiratory tract disease in nursing beef calves, feedlot calves and dairy calves (4, 6, 7, 9, 10, 15, 20, 34, 41, 45, 66, 86). In a recent study in Minnesota, BRSV was the viral agent most commonly associated with enzootic pneumonia of dairy calves (9). Beef calves, entering Ontario feedlots, had a higher seroconversion rate to BRSV (71.3%) than to other respiratory viruses (infectious bovine rhinotracheitis virus, bovine viral diarrhoea virus and parainfluenza virus type 3) (67).

The epidemiology, clinical signs and pathologic findings associated with BRSV infections have been described (4, 7). Morbidity is high and case fatality is variable, ranging up to 20% and disease is characterised by pyrexia, anorexia, increased respiratory rate and dyspnoea. Gross lesions include severe diffuse interstitial pneumonia with subpleural and interstitial emphysema, and pulmonary oedema. Histopathologic lesions include syncytial cell formation in bronchiolar epithelium and lung parenchyma, intracytoplasmic inclusion bodies, proliferation and/or degeneration of bronchiolar epithelium, alveolar epithelialisation, alveolar oedema and hyaline membrane formation.

BRSV has emerged as a major viral component of the bovine respiratory disease complex for a number of reasons. There is a high prevalence of seropositive animals in the cattle population indicating that exposure to BRSV is common (5). The incidence of infections caused by this virus is high and there is a strong correlation between BRSV infection and the occurrence of respiratory disease (9, 67, 87). Also, BRSV has a predilection for the lower respiratory tract and in sheep, BRSV has been demonstrated to act synergistically with bacteria in causing pneumonia (2, 86, 95).

Respiratory syncytial virus (RSV) is also an important cause of respiratory disease in humans. Human respiratory syncytial virus (HRSV) is the principal respiratory tract pathogen of infants, and during infancy and early childhood few individuals escape infection with this virus (13, 22, 28, 37, 38, 55, 69). Severe lower respiratory

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tract disease occurs most frequently in infants experiencing their first HRSV infection between 1 and 6 months of age and is characterised by bronchiolar epithelial necrosis, bronchiolar occlusion, parenchymal inflammation and necrosis, and alveolar exudation (13).

Similarities between BRSV and HRSV are striking and include: 1) both viruses are pneumoviruses within the paramyxovirus family and are antigenically related (76), 2) respiratory syncytial virus infections are common in infants and calves causing severe disease in these age groups (39, 45), whereas infection in adults results in less severe disease (6, 43), 3) maternally derived passive immunity does not prevent infection in either infants or calves (6, 9, 10, 39, 65, 80), 4) repeated infection with RSV occurs in both humans and cattle, but after the initial infection, subsequent infections cause less severe disease (6, 7, 39, 40, 42, 46, 65, 80, 86), and 5) the lesions caused by BRSV and HRSV are similar, with both viruses causing lymphocytic bronchiolitis and bronchiolar epithelial necrosis, bronchiolar occlusion, parenchymal inflammation and alveolar exudation (1, 7, 86, 89, 109). It has been proposed that immunopathologic mechanisms may be involved in the pathogenesis of RSV infections (7, 15, 34, 70, 86). This review examines the current understanding of the role of immunopathologic mechanisms which may be involved in BRSV infections. As HRSV and BRSV share many epidemiologic clinical and pathologic features, both viruses will be discussed.

SERUM ANTIBODY INTERACTING WITH VIRUS (TYPE 3 HYPERSENSITIVITY)

Human Respiratory Syncytial Virus

The role of maternally-derived antibody in protection of the infant from HRSV has been controversial. During the first six months of life, the infant has maternally-derived serum antibody to HRSV (86). As there was a high incidence of HRSV infections observed in infants with passively-acquired antibody and the most severe consequences of infection occur in this same age group, it was initially concluded that passively-derived antibody did not provide resistance to infection nor did it prevent severe disease (22). Based on the above assumptions it was hypothesised that serum antibodies may participate in an immunopathologic reaction with HRSV antigens in the lung and contribute to the severity of disease through a mechanism similar to an Arthus reaction (type 3 hypersensitivity) (70). However, this hypothesis has not been supported by subsequent research. No positive correlation was found between high levels of pre-existing serum antibody and the severity of disease (18, 64, 77). In addition, HRSV infection can cause severe disease in infants lacking detectable antibody (68, 77). Maternal antibody may provide some protection as there is a relative sparing from bronchiolitis and pneumonia in infants less than 3 weeks old, who have the highest levels of maternally derived antibodies, and symptoms are mainly confined to the upper respiratory tract (44, 75, 77). Additionally, following infection, this age group sheds less virus than older children (77). Even in older children the presence of maternal antibodies appears to reduce the quantity and duration of shedding of HRSV (53). Severity of HRSV pneumonia is related to low pre-existing neutralising antibody titers (39, 64).

There is no evidence for immune complex formation in HRSV infections; however, it is possible formation occurs in the respiratory tract and not in serum, making identification difficult (32). Complement has not been demonstrated to play a role in the pathogenesis of HRSV infections. Circulating haemolytic complement and C3 remain unchanged in HRSV bronchiolitis (3) and C3 has not been demonstrated by immunofluorescence techniques in lungs of infants dying of HRSV bronchiolitis (21).

In addition, studies conducted in laboratory animals have also failed to demonstrate a pathogenic role for serum antibody. Passive immunisation of mice and cotton rats to HRSV failed to enhance the severity of the lung lesions (92, 103). In summary, the available evidence fails to support a type 3 hypersensitivity reaction, but to the contrary, suggests that actively acquired or passively derived antibody conveys a degree of protection against infection and disease. However, the correlation between titres of maternal antibody in the infant and protection are not perfect and disease may still occur in the presence of moderate levels of antibody (86).

Bovine Respiratory Syncytial Virus

Even though BRSV has not been studied in the same detail as HRSV, it appears that the role of passively-acquired antibodies in disease is similar. Observations on the naturally occurring respiratory tract disease associated with BRSV and the results from experimental infections indicate that passively derived antibody does not prevent infections (6, 9, 10, 23, 60, 65, 80, 83). There has been no evidence presented that maternally-derived antibody enhances the severity of disease associated with BRSV infections in calves. Recent evidence from an epidemiology study of BRSV infections in calves suggests a protective role for maternal antibody, as it was demonstrated that although maternal antibody did not prevent disease, both the incidence and severity of disease was inversely related to the level of BRSV-specific maternal antibody (61). Recently, the disease response has been studied in colostrum-fed and colostrum-deprived calves in an experimental BRSV infection model (12). Based on clinical parameters, blood gas measurement, quantitation of lung lesions and immunoperoxidase staining for BRSV antigen, a protective role for passively-derived maternal antibody was demonstrated. Bovine respiratory syncytial virus antigen and antibody have been detected concurrently in the lungs of calves undergoing BRSV infection; however, immune complexes have not been detected (59). Contrary to finding with HRSV, complement component C3 has been detected in areas of lung where BRSV antigen is also present (59). Although RSV-infected cells are capable of activating complement (29, 54, 84), the possibility of immune complexes contributing to this process cannot be excluded in that attempts to identify immune complexes may have failed because of factors such as lack of sensitivity of tests employed, masking of antigenic determinants or breakdown of antigenic sites in phagocytes (59). In conclusion, no definitive evidence for involvement of type 3 hypersensitivity in the pathogenesis of BRSV infections has been demonstrated.

PRIOR SENSITISING INFECTION (TYPE 1 HYPERSENSITIVITY)

Human respiratory syncytial virus

It has been hypothesised that the pathogenesis of the most severe form of HRSV associated disease, bronchiolitis, is the result of an IgE-mediated type 1 hypersensitivity reaction (36). This hypothesis states that the first exposure to HRSV in infancy results in a sensitising infection and subsequent disease occurs following a second infection when the virus induces a IgE-mediated reaction in the sensitised infant. Analysis of epidemiologic studies of HRSV infections in children fails to support the requirement of a sensitising infection (16). In fact, subsequent infections decrease in severity. However, the severe form of HRSV infection, bronchiolitis, appears to be mediated, at least in part, by the production of HRSV-specific IgE antibody. IgE bound to HRSV-infected nasopharyngeal cells has been detected and HRSV-specific IgE antibody has been found in nasal secretions (106, 108). Virus-specific IgE and histamine titres in nasopharyngeal secretions are

greater in individuals with wheezing at time of infection than individuals with HRSV infection without wheezing (106, 108). The quantity of virus-specific IgE and histamine in nasopharyngeal secretions at the time of HRSV infection correlates with the severity of infection (19, 108). Also, the level of HRSV-specific IgE response after primary infection is useful in predicting future episodes of wheezing (91). Recently, a defect in suppressor cell numbers and function was reported in infants with HRSV-bronchiolitis, which may explain the overproduction of IgE and exaggerated lymphocyte proliferation response (discussed later) in these patients (107). Possibly, the severe form of HRSV infection occurs only in those individuals with a hereditary tendency to overproduce IgE. Further support for this theory is demonstrated by the fact that a similar defect in histamine-induced suppressor cell function has been demonstrated in people with asthma and other atopic disorders (11).

Bovine respiratory syncytial virus

The pathogenesis of BRSV infections in cattle may involve a type I hypersensitivity reaction (4, 15, 34). This hypothesis has evolved from observations made on the clinical and pathologic features of BRSV infections, and on the basis of response to treatment with corticosteroids and antihistamines (4, 7, 10, 15, 34). A clinical observation presented to support this hypothesis is that two recognisable clinical stages of disease are sometimes observed following BRSV infections. The early stage of disease is characterised by pyrexia and mild signs of respiratory disease, whereas the second stage follows initial improvement or recovery from the first stage, and is characterised by the onset of extreme respiratory distress. The time interval between the two stages is variable and ranges from several days to several weeks. It has been suggested that the first stage of disease represents a sensitising infection and the second stage represents an IgE-mediated hypersensitivity reaction, or that a persistent infection is established which then culminates with a hypersensitivity reaction. Epizootologic evidence does not support a role for a prior sensitising infection in the pathogenesis of BRSV disease (99). During the seasonal occurrence of BRSV, only calves not present during previous epizootics are affected with respiratory tract disease. Additionally, there is little experimental evidence to either support or refute this hypothesis.

Interestingly, this biphasic disease pattern is not a consistent finding in BRSV epizootics. Possibly the biphasic disease corresponds to a more severe form of disease such as bronchiolitis in infants, but this has not been studied. As BRSV acts synergistically with bacteria in the production of pneumonia (2, 86, 95), possibly the second stage of the disease may be a manifestation of the onset of secondary bacterial pneumonia rather than a hypersensitivity reaction. Other factors, such as environmental stressors and nutrition may be important. As suggested for HRSV infections, genetic factors may also be important in controlling the immune response following infection. In a recent study, calves were initially infected with BRSV and rechallenged 10 days later using the same infection protocol (24). Rechallenge did not cause a more severe disease. In fact, the calves appeared to be resistant to disease at the time of the second exposure. Treatment of BRSV infections with corticosteroids and antihistamines during the second phase of disease is reported to be beneficial (15, 34). This finding has been used to support the involvement of a type I hypersensitivity reaction, but these field observations and have not been further substantiated by controlled trials. Also, merely because the disease is responsive to corticosteroid and antihistamine therapy, does not necessarily mean that the disease is IgE-mediated.

The lesions in BRSV infections are similar to those described in adult cattle with atypical interstitial pneumonia (AIP) (25). Atypical interstitial pneumonia in cattle

also occurs in association with several hypersensitivity diseases, including extrinsic allergic alveolitis, milk allergy and systemic anaphylaxis (17). The lesions in these hypersensitivity diseases and in BRSV infections are similar, and therefore it has been suggested that this supports the role of hypersensitivity in the pathogenesis of BRSV infections. However, it is important to note that AIP has multiple causes.

In addition to those previously mentioned, others include parasitic diseases, several plant poisonings, exposure to irritant gases and fumes, and a forage-related disease known as acute bovine pulmonary emphysema or fog fever (17). Thus, it appears that there are several pathogenetic mechanisms which result in lesions of AIP in addition to type 1 hypersensitivity. Viral infection of the respiratory tract may cause these lesions through yet another mechanism. For example, parainfluenza virus type 3 causes respiratory tract lesions similar to those induced by BRSV, although generally these are less extensive (52). Parainfluenza virus type 3 has been well studied in cattle, but it is not thought to cause disease through a hypersensitivity mechanism. Based on the current evidence it cannot be concluded that a type 1 hypersensitivity reaction is involved in the pathogenesis of BRSV.

Limited investigations have been done on the role of BRSV-specific IgE in BRSV infections. One study, in which calves had been previously immunised to BRSV, there was a positive correlation between clinical signs and BRSV-specific IgE in lung lavage fluid (85). Also, there was a direct correlation between signs and histamine levels in nasopharyngeal exudate in immunised and non-immunised calves experimentally infected with BRSV, which may indirectly implicate a role for IgE in BRSV infections.

CELL-MEDIATED OR DELAYED-TYPE HYPERSENSITIVITY (TYPE 4 HYPERSENSITIVITY)

Human respiratory syncytial virus

The role of cell-mediated immunity in the pathogenesis of HRSV infection was first suggested based on a marked increase in lymphocyte transformation response to HRSV antigens in infants receiving an inactivated HRSV vaccine (57). When these infants subsequently became infected with HRSV, severe disease resulted.

Additionally, infants with HRSV-bronchiolitis had a greater systemic cell-mediated immune response, as measured by lymphocyte transformation, than infants who had pneumonia or upper respiratory disease associated with HRSV infection (8, 105). Furthermore, infants that develop a greater lymphocyte transformation response are more likely to develop subsequent episodes of wheezing than those with only a lesser lymphocyte transformation response (105).

This finding suggests that an altered cell-mediated immune response might affect peripheral airway reactivity. The reason for this exaggerated lymphocyte transformation response in some infants is unknown, but several possibilities have been proposed including prior sensitisation, prenatal exposure, transplacental transfer of reactivity or an imbalance in immunoregulatory mechanisms modulating T-cell response (86). As previously mentioned, a defect in suppressor cell numbers and function may explain the exaggerated lymphocyte proliferation response in infants with bronchiolitis associated with HRSV infections. However, other research efforts have failed to demonstrate a relationship between lymphocyte transformation response to HRSV with either patient age or severity of infection (26, 82). At this time the role of a delayed-type hypersensitivity in HRSV infection is not known.

Bovine respiratory syncytial virus

Limited research has been conducted on the cell mediated immune response to BRSV infection. A cell mediated immune response was elicited in calves following intranasal inoculation of BRSV as detected by a leucocyte migration-inhibition test and delayed hypersensitivity skin response test (33). Following experimental infection, 4 of 6 gnotobiotic calves and 6 of 21 conventional calves developed a cell-mediated immune response as detected by a significant lymphocyte transformation response (93). A virus-specific lymphocyte transformation response was detected in calves vaccinated with a glutaraldehyde-fixed whole cell BRSV vaccine (93). Subsequent challenge with live virus did not result in an increase severity of respiratory tract disease, unlike the response which occurred when formalin-inactivated HRSV vaccine was administered to children. Currently there is no evidence to support a role for delayed-type hypersensitivity in the pathogenesis of BRSV infections in cattle.

VACCINATION AND HYPERSENSITIVITY

Human respiratory syncytial virus

In the 1960's a formalin-inactivated HRSV vaccine was evaluated in infants and young children and was found to stimulate moderately high levels of serum antibody, but it failed to induce resistance to infection and disease (35, 55, 56). The disease contracted by the vaccinates was not different from the severe naturally occurring disease except that it occurred in children who were older than the usual age group that develops this form of HRSV-induced disease (70). Several theories have been proposed to explain this phenomenon of disease enhancement by the vaccine and include: 1) serum antibody in the absence of nasal antibody was immunopathogenic, 2) altered reactivity to killed virus, and, 3) delayed hypersensitivity induced by the vaccine (3, 55, 56). Recent research has provided a great deal of insight into the mechanism of enhancement of disease response by formalin-inactivated vaccines. The fusion glycoprotein of HRSV induces two types of functional antibodies, neutralising and fusion inhibiting antibody (101, 102). By re-examination of the sera from the infants and children inoculated 20 years ago with the formalin-inactivated vaccine, it was demonstrated that an antibody response to the fusion protein occurred but was deficient in neutralising activity and the sera was also deficient in fusion-inhibiting activity (73, 74). It appears that the formalin-inactivated vaccine stimulated an unbalanced immune response in which a large portion of the induced antibodies were directed against non-protective antigen rather than epitopes that induce functional antibodies such as neutralising and fusion-inhibiting antibodies (74).

These findings are further supported by similar findings obtained in cotton rats after vaccination with a formalin-inactivated HRSV vaccine (79). Failure to induce functional antibodies may have decreased the protective efficacy of the vaccine and could have contributed to potentiation of disease in vaccinates following subsequent HRSV infection (74). Thus, the mechanism of vaccine enhancement of disease response on subsequent infection may be a different mechanism than that involved in the naturally occurring disease.

Bovine respiratory syncytial virus

A similar experience as described for formalin-inactivated HRSV vaccines has not been documented in cattle. A formalin-inactivated BRSV vaccine induced moderate levels of serum antibody when administered to calves, but did not cause exacerbation of the mild respiratory tract disease following challenge infection (71). Administration of an inactivated vaccine consisting of glutaraldehyde-fixed

bovine nasal mucosa cells persistently infected with BRSV was not associated with an increase in the severity of respiratory disease following challenge with live virus, but in contrast was associated with an increase in resistance to BRSV infection (93). Subsequent field trials with this inactivated BRSV vaccine failed to demonstrate adverse effects from vaccination (27, 104).

A modified live virus vaccine for BRSV manufactured under the trade name Rispoval® (Smith Kline - RIT, Rixensart, Belgium) has been available in Europe since 1978. Extensive field trials demonstrated efficacy of this vaccine with no adverse effects reported, with the exception of one report of post-vaccinal reaction which was attributed to contamination of some lots of vaccine with bovine viral diarrhoea virus (48, 49, 94, 97, 98, 100, 110).

In the United Kingdom, field trials of a quadrivalent vaccine which contained inactivated BRSV was not associated with adverse effects following vaccination (50, 88). Currently in the United States there are three BRSV vaccines federally licensed. Two of these are modified-live virus vaccines produced by Norden Laboratories and Diamond Scientific, and late in 1988 a killed BRSV vaccine was released by Fort Dodge Laboratories. The BRSV vaccine produced by Norden Laboratories has been most extensively reported on and has been found to be efficacious in field trials with no reports of local or systemic post-vaccinal reactions (8, 14, 63, 72, 90). Thus, a review of the published literature on BRSV vaccines failed to identify adverse reactions associated with use of these vaccine except in the situations when the vaccines had been contaminated with bovine viral diarrhoea virus.

NON-IMMUNOPATHOGENIC MECHANISMS

This review has only discussed immunopathogenic mechanisms in RSV infections. Any hypothesis that attempts to explain the pathogenesis of severe RSV in early life in infants or calves must take into consideration the intrinsic pathogenic potential of the virus itself (22). Thus, if immunologic factors are important in the pathogenesis of RSV infections, these must act to enhance the basic pathogenic effects of the virus. Respiratory viruses, including RSV, may produce disease as a direct consequence of viral replication in epithelial cells of the respiratory tract, resulting in necrosis and lysis of cells with release of breakdown products which can act as mediators of inflammation.

Other mechanisms which may explain the age distribution of severe infection with HRSV include immunologic immaturity of the infant causing impairment of the immune response and anatomic-mechanical considerations based on the fact that airway diameter in the infant lung is markedly less than that of the adult, and thus, more easily obstructed (46). Bovine respiratory syncytial virus infections may disrupt immunologic and non-immunologic defense mechanisms of the respiratory tracts as indicated by the finding that secondary bacterial pneumonia is a common complication (7, 9, 31, 47, 51, 62, 78, 86, 96). Experimentally, BRSV and *Pasteurella haemolytica* have synergistic effects in producing respiratory disease in lambs (2, 95). Following BRSV infection in lambs, decreased numbers of Fc receptors on alveolar macrophages were detected (95). The effects of BRSV infection of macrophages may be important in the establishment of secondary bacterial pneumonia. Additionally, scanning electron microscopic studies in calves 8 to 10 days following infection with BRSV have demonstrated disruption of ciliated respiratory epithelium (30), which may impair the clearance of bacteria from the lung.

In a recent study of naturally occurring, severe BRSV-associated disease it was observed that although the infections appeared to be acute, bronchiolar lesions and serologic response suggested a longer duration of infection (58, 59). Viral

antigen and cytologic features of BRSV infection were only detected in the cranioventral portion of the lung whereas the caudodorsal aspect of the lung had extensive lesions consisting of emphysema and edema. Immune complexes were not detected in the lungs, but the complement component C3 was observed in the virus-infected portions of the lungs. Evidence of mast cell activation and degranulation was demonstrated throughout the lungs. Based on these findings, the following model of BRSV pathogenesis was proposed (58, 59). Bovine respiratory syncytial virus infection is established in epithelial cells in the airways and alveoli in the cranioventral portion of the lung resulting in destructive changes, followed by inflammation and repair. Infected cells express new surface antigens and these cells have the ability to activate complement with the possibility that this process is enhanced by BRSV-specific IgM or IgG1 (the IgG1 may be actively produced or of maternal origin). It is proposed that the activated complement reaches the caudodorsal parts of the lungs through the vasculature where it has spasmogenic properties on smooth muscle and causes the release of preformed mast cell mediators and stimulates the production of other mediators. The combined effect of complement and mast cell mediators may result in severe edema and emphysema observed diffusely throughout the lungs. Additionally, this hypothesis helps to explain the biphasic disease (previously described) sometimes associated with BRSV infection.

SUMMARY AND CONCLUSIONS

The hypothesis that passively or actively acquired antibody is involved in the pathogenesis of RSV infections is not well supported in either infants or calves. Based on current understanding, it appears that passively derived antibody does not afford complete protection but may reduce the incidence and modulate the severity of RSV infections. While it has been suggested that specific RSV antibody may have a role in activation of complement by forming immune complexes, this has yet to be demonstrated.

Evidence suggests that HRSV-specific IgE has a role in HRSV infection in infants, particularly those affected with the most severe form of the disease, bronchiolitis. In those infants affected with bronchiolitis a defect in suppressor cell numbers and function has been demonstrated which may explain the over production of IgE and exaggerated lymphocyte proliferation response in these individuals. Thus, genetic factors may play a role in the immune response to HRSV infection and those individuals with a defect in suppressor cell function are predisposed to the more severe form of the disease. The role of IgE in the pathogenesis of BRSV infection is in need of further study and there has been no investigation into the possibility of a defect in suppressor cell function.

Although a role for cell-mediated immunity in the pathogenesis of RSV infections has been suggested, findings have been inconclusive and evidence to support this mechanisms is incomplete. Study of the cell-mediated immune response and possible role in pathogenesis is in need of better definition in both infants and calves.

Recent research has begun to elucidate the mechanism involved in disease enhancement following vaccination of children with a formalin-inactivated HRSV vaccine. It appears that this vaccine stimulated an unbalanced immune response in which a large portion of the induced antibodies were directed against non-protective antigens rather than epitopes that induced the formation of functional antibodies, such as neutralising and fusion inhibiting antibodies. These findings suggest that the mechanism involved in vaccine enhancement of the disease response may be unrelated to those mechanisms involved in the naturally occurring disease. Similar findings have not been observed in association with the

use of either inactivated or live-virus vaccines in cattle. In cattle, BRSV vaccines, which have not been contaminated with adventitial agents, have not been associated with adverse reactions. In addition to immunopathologic mechanisms, other mechanisms may play important roles in the pathogenesis of RSV infections. The contribution of direct effects of RSV infection of cells of the respiratory tract with subsequent release of inflammatory mediators and the disruption of immunologic and non-immunologic respiratory defense mechanisms should also be considered in a discussion of pathologic mechanisms.

The quantity of research on the pathogenesis of HRSV has far exceeded that on BRSV. Because of the similarity of these two viruses and their associated diseases in infants and cattle, this article has drawn heavily upon the research conducted on HRSV in discussing immunopathologic mechanisms in BRSV infections. Although the viruses are similar, it does not necessarily follow that their mechanism of disease production are the same. Many of the studies and observations made in regards to HRSV are in need of confirmation with BRSV, and some degree of caution should be employed in extrapolating findings between these two viruses. Further study of the pathogenesis of BRSV infections in cattle is indicated because of both the economic importance of respiratory disease to the livestock industry and on the basis that calves represent the only well characterised, naturally occurring animal model and can potentially be used to study and define the pathogenic mechanisms of RSV infections.

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