Bovine Respiratory Syncytial Virus and Acute Respiratory Distress Syndrome in Cattle

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Introduction

Many studies have been done on respiratory syncytial virus (RSV) infections, some in cattle and sheep but most of them in man and small experimental animals. Nonetheless the pathogenetic mechanisms at work in RSV-caused diseases are not well understood at the present time in any species. While there are important host species differences in the immune response to any given infectious agent, there are always similarities as well. Because of the paucity of research on the basic immunology of bovine RSV infections, we are obliged to draw on human RSV research in developing hypotheses from which plans can be made for further studies with BRSV. Attention is drawn to some of the studies on natural and experimental RSV infections in several host species. Also mentioned are other recent research findings relevant to our understanding of how RSV infection may be the common denominator in at least 2 important respiratory disease syndromes in cattle. Much of the speculation herein about those diseases is hypothetical, but it is based on considerable experience with the disease, its treatment response, virus isolation and serology.

This information is presented here to encourage continued and more enlightened clinical observation and history-taking, which will permit still more accurate speculation on the various pathogenetic mechanisms involved in producing RSV-associated acute respiratory distress syndrome (ARDS).

The differences between human and bovine origin strains of RSV appear to be minor - probably no greater than with PI-3 strains from the respective species. Herein distinction is seldom made between bovine RSV (BRSV) and human RSV (HRSV), and any described experimental infections in those two host species were done using species-homologous strains.

There are excellent recent reviews (8,12,13,50) on the etiology and pathology of atypical interstitial pneumonia and, as it has long been referred to in human literature, acute respiratory distress syndrome (ARDS), and the terminology surrounding these and related respiratory conditions in cattle. Breeze et al. (8) suggested ARDS as an acceptable term for any sudden onset respiratory condition in cattle that is accompanied by dyspnea and results from any combination of 1) congestion and edema, 2) hyaline membranes, 3) alveolar epithelial hyperplasia and 4) interstitial emphysema. Dungworth (13) called ARDS a "convenient clinical term used to lump together a variety of circumstances leading to acute pulmonary injury". Of course the term should be used by itself only so long as the etiology remains obscure. As soon as the cause is known, it becomes "ARDS due to . . . . .". Herein ARDS due (at least in part) to RSV infection will be designated as ARDS-RSV. Previously the disease has been called such names as adenomatosis or calf emphysema.

Clinical Disease, Treatment and Diagnosis

The clinical disease and its treatment, as it is seen in recently weaned beef calves in Nebraska and surrounding states has been described in several publications (4,5,25). Briefly, calves show decreased feed and water consumption, usually a non-productive cough and some head hanging, although they brighten up remarkably well when the observer walks among them. Other early signs include mild nasal, oral and sometimes ocular discharge. Many of the calves, even those that appear entirely normal, will have increased temperatures ranging from 40° C to 42.5° C. Along with increased temperature there is nearly always an increased respiration rate. Subcutaneous edema is first seen as a slight puffiness around the eyes, and as it becomes more severe it shows as swelling in the mandibular area and throatlatch. In some calves the disease soon becomes less severe, but in others it rapidly progresses to dyspnea, accompanied by foamy saliva around the mouth and a failure to eat or drink (even though they still exhibit a desire to drink) and accompanying dehydration and loss of fill. The onset and progression of signs in acute cases is very rapid. Frequently the signs will not be noticed until the first death has occurred.

The severity of disease varies considerably from group to group, and within groups. But all or nearly all calves within a group will be affected, even though fever may be the only discernible abnormality. Death rate also varies greatly, with the highest mortality usually occurring in well-bred animals on a high plane of nutrition. Certain feeds like corn silage have been associated by some with an increased incidence or

severity of disease. There appear to be susceptibility differences according to breed, and within breeds according to bloodline. As most beef calves are weaned in late summer or nearly fall, it would be expected that the highest incidence would be in late fall to early winter, but beyond that, the severe outbreaks of disease seem to be associated with a rapid change from moderate to cold weather, expecially a sudden temperature change of greater than 25° C as often occurs when a cold front moves in after a warm fall day.

Disease severity varies considerably from year to year in calves of the same breeding on one ranch but, as a general rule, herds that have severe problems one year have severe disease in subsequent years if there is no early treatment. The disease may occur in unweaned calves, especially those that are being creep fed. Perhaps it is because of a lack of cold stress, but most outbreaks in non-weaned calves are easier to control. On the other hand calves weaned under 7 weeks of age seem to get the disease before the time of severe temperature drops, and they sometimes have a high mortality rate (17, 38).

Earlier work in this country and Canada (15, 38, 42, 54, 55, 58) had given evidence of association between RSV infection and moderate to severe respiratory disease in calves, but experimental infections with the virus had produced only mild disease. In most respects the ARDS in weaning calves that we see in Northern Plains States resembles very closely the ARDS reported some years earlier by European investigators (28, 65). Those investigators satisfied themselves that RSV was the important pathogen involved in much of ARDS of young cattle. British investigators have recently associated RSV with a severe respiratory disease in 3-month-old calves that started to get sick the day of weaning (51). Numerous other reports, starting with the very first reported isolation of BRSV, in Switzerland in 1970 (46), give indication of the widespread incidence of RSV.

Most treatment regimens for ARDS-RSV consist of the administration of antihistamines, corticosteroids and antibacterials during the acute phase, and providing for sustained antibacterial activity for several additional days (5). Aspirin is used in lieu of corticosteroids in some treatment regimens, including that of the USDA Meat Animal Research Center at Clay Center, Nebraska (36). Change of feed or a 48 hour fast has become an important part of treatment for many clinicians, and that alone may be enough to turn around an outbreak caught in the very early stages (4, 36). Monensin, effective in preventing acute bovine pulmonary emphysema in adult cattle, does not prevent ARDS in weaning calves (4, 22). Experimental vaccination shows promise as a means of decreasing losses (5), and the experience in Europe with vaccines has been favorable.

Diagnosis is best accomplished by use of fluorescent antibody (FA) tests on slides prepared from nasal swabs or wash samples, or preferably on frozen lung sections or lung wash cells from calves that die in the acute stages (30, 63, 64). Virus isolation takes much longer and is not very reliable, particularly when the sample is collected after the first few days of disease (17, 64). Serology, when available, also takes too long unless the laboratory is set up for FA tests. Because the acute disease appears about the same time that the titer rises sharply, a single sample or two samples taken only 3 or 4 days apart may suffice.

Pathogenesis Studies - RSV in Various Host Species

RSV is recognized as the most important respiratory pathogen in infants and children. Being an important cause of both pneumonia and acute bronchiolitis (a hypersensitivity-type reaction). As mentioned earlier much effort has been expended in trying to gain understanding of the pathogenesis of the human diseases and from that an understanding of how best to control them. Excellent reviews are available summarizing much of that work through 1980 (20, 40), and only a relatively few studies will be cited here, along with some pertinent studies in cattle and other species.

While RSV infection in human beings recurs many times in life - sometimes annually in urban dwellers - one study (23) showed that severe disease is normally associated with only the first and second infection. Those same authors concluded that vaccination might be used to prevent severe disease, but could not be expected to prevent infection. Another study, done in rats, showed that RSV is probably a serious pathogen of immune suppressed hosts of any age or infection history (31).

As it becomes evident that there was probably some immunopathology involved in pathogenesis of the human diseases, several theories were advanced to explain the mechanisms of injury. Among the postulated injury mechanisms were 1) serum antibody interacting in tissues with virus antigen, 2) prior "sensitizing" infection resulting in production of reaginic antibody which causes severe disease with a subsequent infection, and 3) participation of one of several kinds of cell-mediated immunity (CMI) in production of disease (20, 40). Other recently advanced hypotheses attribute the severe disease in children not to immunopathology *per se,* but to either immunologic or anatomic immaturity (20). Antibody-dependent cell cytotoxicity (ADCC) is one of the CMI responses that has obtained considerable attention recently. (Being antibody-dependent, although cell effected, ADCC would not be classified as a CMI response by some definitions.) Kaul *et al.* (33) were able to detect ADCC early in infections in children, and they found enhanced responses in repeat infections, leading them to believe that ADCC might play an important role in recovery from RSV infection. Meguro *et al.* (41) found that ADCC antibody rose and fell more rapidly than neutralizing antibody in natural RSV infection in children.

Sun *et al.* (61) found that pneumonia in RSV-infected cotton rats was accompanied by appearance of leukocytes that had characteristics of activated cells and cytotoxic cells. The cytotoxic activity peaked at 5 days post-infection, and

was not virus-specific. The localness and early appearance of the CMI responses that they saw led them to believe that they were an early line of defense for the control of RSV replication. Welliver *et al.* (66) reported evidence of significant increases in indices of CMI activity early in the course of natural RSV infections in children, but only in the cases with the acute bronchiolitis, the hypersensitivity form of the disease. They postulated that the intensity of early cell proliferation in the disease correlated with the overall severity of the disease.

Alveolar macrophage cells have also been implicated as playing a role in determining the severity of RSV infection in human beings. The work of Bellanti *et al.* (3) suggested that the effects of RSV infection on alveolar macrophages might be apparent not only during the acute infection but for years thereafter. There may be interference with their clearance and scavenger and other functions, including a postulated immunoregulatory function for IgE production. A recent study of both natural and experimental RSV infection in the lungs of cattle (63) indicated that there was RSV infection of alveolar macrophages as well as cells of the bronchiolar and alveolar epithelium. The primary histopathology finding was acute bronchiolitis and alveolitis.

Results of studies of interferon were inconclusive in RSV infections, but it appears that the virus probably induces less interferon and itself is less sensitive to inhibition by interferon than are other myxoviruses and paramyxoviruses (21). Unusually early production of anti-RSV antibodies has been demonstrated in disease in both human beings and cattle (17, 18, 64) suggesting possible priming by an earlier infection. Exacerbation of disease accompanying high levels of antibody production was seen after vaccination with killed RSV antigen in children (34). Mohanty *et al.* (43) were not successful in an attempt to demonstrate a similar result in cattle.

Lamprecht *et al.* (37) found that preexisting maternal antibody in children decreased the severity of RSV pneumonia but had no effect on bronchiolitis. A study by Glezen *et al.* (19) also obtained results that suggested a protective role for specific maternal antibody (or an accompanying immune factor), when they found a positive correlation between the level of maternal antibody and the age of infants at the time they first acquired RSV infection. Again, other factors may have been responsible. Suffin *et al.* (59) found that 3-day-old ferrets could be protected from RSV challenge if their mothers were given a gestational infection. The immunity was acquired post partum, via immunizing products of lactation from either natural or foster mothers. Passive administration of high titer adult ferret anti-RSV antiserum did not confer immunity. They also reported that whole maternal milk had 5.5 times higher RSV neutralizing titer than maternal serum despite a higher immunoglobulin concentration in the serum (60). Another source of maternal protection was also indicated in work showing that cell mediated immunity to RSV is passed to infants via lymphocytes in the cord blood (Sieber, O.F.; cited in 20).

Apart from any protection provided by nursing, age appears to be an important factor in severity of infection in cattle (17) and in human beings and several other species susceptible to natural or experimental RSV infection (20). In cattle as in human beings it appears that susceptibility increases for a time after birth, plateaus for a time and then decreases fairly rapidly. In cattle much more work needs to be done, but it appears that colostrum-deprived calves raised on milk replacer reach maximum susceptibility somewhere between 2 and 4 months of age (17). Nursing probably delays peak susceptibility by several months, at least to severe disease although perhaps not to infection. The decline in susceptibility may have nothing to do with age *per se,* but may reflect virus exposure sufficient to have gained protection. There have been reports of severe RSV disease with considerable mortality in adult cattle (36, 46).

A number of studies would suggest that RSV, apart from its potential as a primary infecting agent, may be important in combination infections in cattle with other viral or bacterial agents. Eis (14) demonstrated by scanning electron microscopy that the cilia of the respiratory epithelium were almost completely destroyed in susceptible calves 8 to 10 days after experimental RSV infection, thus opening the way for possible secondary infection with any agents present in the upper respiratory tract. Removal of dust, other foreign material, fluid, excess hyaline and the debris from dead epithelial cells otherwise would be prevented. It is not surprising that many RSV-positive lungs from field cases of respiratory disease also yield *Pasteurella spp.* Yet from many such lungs no bacteria are isolated, especially if they come from peracute cases (17, 30). Al-Darraji *et al* (1) showed that in sheep RSV and *Pasteurella hemolytica* combined produced more severe pneumonic lesions than did either agent alone. *Eikenella corrodens,* another gram negative bacterium isolated from two cases of RSV-positive ARDS (17), might be a much more frequent co-infecting agent than given credit for because it is quite difficult to isolate. *Hemophilus somnus* is more frequently isolated although perhaps also missed more often than not (see section IV). Certain mycoplasmas are frequently present in the lungs of RSV infected cattle when the effort is made to look for them in lungs from newly dead animals (17).

At least in verbal communications European researchers have mentioned both PI-3 and BVD as frequent co-infecting viruses in bovine ARDS-RSV. We occasionally have isolated those viruses and IBR virus, but most of the cattle we have observed with RSV associated disease earlier had been vaccinated with modified live PI-3, IBR and BVD viruses (17). Mahrt (39) demonstrated 100% seroconversion to RSV in several groups of ARDS affected calves at the U.S. Meat Animal Research Center. Along with that he found a high but not 100% seroconversion rate with 2 adenovirus serotypes and expected seroconversions to IBR, PI-3 and BVD, with which the calves had been vaccinated.

Studies with RSV in vitro have also provided some clues

as to possible mechanisms for long lasting lung damage after infection. Parry *et al.* (47) demonstrated persistent virus infection with HRSV in cell cultures from several mammalian species. They also saw striking changes in the surface properties of the infected cells, with formation of long filaments off the cell membranes concomitant with insertion of viral antigens. The presence of virus antigen at the cell surface was enhanced at lower than normal body temperature, and diminished at a temperature elevated from normal. Identical appearing filaments were seen in our laboratory when a bovine turbinate cell line was infected with BRSV and the cells were incubated at 33° C (17).

Other Relevant Research and Some Speculation

The research reports referred to in this section did not deal directly with RSV infections, but they have relevance to formulating hypotheses on the pathogenesis of ARDS-RSV.

Some studies relating to the pathogenetic mechanisms of gram-negative bacteria and mycoplasmas are appropriate because, as noted, those organisms frequently are present in ARDS-RSV lungs. Pulmonary edema accompanying gram negative sepsis in human beings was shown to be due to an increase in permeability of pulmonary microvasculature (2). In another study increased permeability and lung edema were demonstrated in experimental *Pseudomonas sp.* sepsis in sheep (9). A report from Texas (26) describes acute disease in stocker cattle attributed to *Hemophilus somnus* infection which sounds very similar to ARDS-RSV, except that they report little or no coughing. The people working with RSV probably need to try harder to isolate fastidious bacteria; conversely, bacteriologists need to rule out the presence of hard-to-isolate viruses.

Another report appropriate to our thinking about the possible role of endotoxin in ARDS-RSV is one on the presence of bacterial endotoxins in feedstuffs (44). Still another is the discovery that the lipoglycan in a species of mycoplasma has endotoxin-like properties (56). *Eikenella corrodens,* mentioned earlier as a secondary infecting agent in two ARDS-RSV cases, is reported to have a second toxin additional to endotoxin. In addition to the role endotoxin may play in causing lung edema, it also can cause activation of complement via the alternate pathway. Resulting complement split products then cause mast cell degranulation and immunopathology in the presence of IgE (67).

Microbiologists have discouraged the use of corticosteroids in treating bovine respiratory disease, because of the impairment of anti-microbial defenses. The reaction on the part of practitioners perhaps has been too strong. The important element is good judgment, including proper diagnosis and use of optimum effective dose for a limited period. Non steroidal anti-inflammatory drugs such as aspirin are also effective in many cases and have the advantage of not inhibiting bodily defenses (except perhaps interferon). For background reading on the importance of administering corticosteroids at the time of treatment of gram-negative bacterial infections, or to offset endothelium damage, edema or other changes that accompany RSV infection, a readily available article by Bowen (6) is recommended. For in-depth but clinically oriented further reading the article by Jones (32) is excellent.

Mycoplasmas may contribute to the severity of ARDS-RSV in ways other than that mentioned earlier. Cuffing pneumonia, seen in calves 2 to 3 months of age and older, and significantly associated with mycoplasma infection, results in formation of a cellular sheath that narrows the bronchiolar lumen and compresses surrounding alveoli (50). The small airways in immaturity are thought to be one reason for the greater severity of RSV infection in children (20), and certainly could be a factor in calves. Further narrowing obviously would compound the problem. Mycoplasmas also may contribute to the severity of the disease by affecting ciliated epithelium of the airways (62) and by production of interferon (13), as discussed in the next paragraph.

It was mentioned earlier that other viruses are suspected of contributing to the severity of ARDS-RSV. It may be that the increased severity of the disease seen in the fall is partly due to an increase in the number of different viruses present. Maternal protection to other common respiratory viruses has waned, and the crowding of calves into pens results in increased rates of infection with many viruses. Most of the calves are inoculated with one or more modified live virus vaccines at the same time they are crowded together.

The observation has been made (4) that intranasal IBR - PI-3 vaccine is very effective in helping to treat an outbreak in unweaned calves but that vaccine administered in the face of a late fall or winter outbreak may exacerbate the disease. We can speculate that the amount of histamine (and other mediators) released may make the difference. In summer outbreaks in unweaned calves, there probably is not much background histamine release at the time the vaccine is administered. Interferon is produced in response to the vaccination, and some histamine is released in response to presence of the interferon (29). The interferon helps control the RSV infection, which is probably mild because of the presence of maternal antibody, and the calf tolerates the released histamine. In later (post-weaning) infections, perhaps there is greater histamine release, either as part of an IgE-mediated hypersensitivity reaction to RSV infected cells (48), or possibly due to feed allergy especially associated with feeding of protein supplements (57). There may be positive feedback once histamine reaches a certain threshold level (27), and the result is a cascading increase in histamine release. The additional interferon associated with either natural infection or intranasal vaccination with a potent inducing virus may provide the histamine necessary to reach that threshold.

Other observations about the role of diet are worth mentioning at this point. That a fast or a change in ration early in the course of ARDS-RSV has a beneficial effect

certainly indicates that there are dietary factors to be considered. Silage feeding is by no means an absolute requirement for development of the disease, yet the association between severe outbreaks and silage feeding is hard to ignore. Something to keep in mind is a reported connection between hyperferremia and silage feeding. Øverås (45) demonstrated such an association in sheep, and in the report cited unpublished work of others that has shown a similar association in cattle. The ability of mammals to limit the availability of iron for bacterial growth is an important part of serum bacteriostasis (35). Bullen and Rogers (7), for example, showed that the bacteriostatic effect of rabbit serum for *Pasteurella septica* and for *Escherichia coli* is lost with the addition of iron. Hibbs (24) was unsuccessful in a search of ARDS-RSV lung tissues for the presence of *Micropolysporum faeni* antigen, which is associated with silage feeding and with hypersensitivity pneumonitis (67). Although the search for *M. faeni* antigen in lung tissues was negative it could contribute even if it were confined to the upper respiratory tract. It is one of a rapidly growing list of substances recognized as being able to activate complement non-specifically (in the absence of antiserum) and induce the release of histamine, SRS and other mediators of the inflammatory response (10).

Another observation mentioned earlier, concerning cold weather, is also empirical but has gained much support over the years. There is little doubt but that some of the really dramatic herd outbreaks occur at the time of a sudden change to cold weather. It is known that cold induces hypoxia, and hypoxia in turn causes vasoconstriction along with increased pulmonary arterial pressure (53, 68), and this finding is probably related to the role that cold plays in ARDS-RSV.

In human beings dry, cold air is thought to trigger bronchial hyperreactivity in asthmatics (16), and in cell cultures persistently infected with human RSV, a marked increase in viral antigen was found at the cell surface when the temperature was decreased from normal body temperature (47). One or more of these factors - or still others - must contribute to the development of bovine ARDS-RSV.

A final variable to introduce into the equation is genetics. Earlier it was pointed out that there apparently are breed differences in susceptibility to the acute disease, although all cattle seem to be susceptible to infection with RSV. Hypoxic vasoconstriction may be a factor here again, as there appear to be considerable strain differences in how cattle react to both acute and chronic hypoxia (53). Studies in mouse cells indicate that the rate of production of RSV could well be another way that genetic makeup would influence the severity of disease (52). If IgE is in fact involved in production of the disease, there doubtless are genetic differences in that parameter in cattle, as there are in human beings (49). There also are anatomic differences between lungs in various breeds of cattle, and they may be very important as well.

Conclusions

ARDS-RSV is a disease thought to result from the interaction of a virus with several other etiologic factors, which may differ from outbreak to outbreak. Some of those factors apparently work together additively, others perhaps synergistically or even in antagonism. When disease is produced it is usually on a herd basis, perhaps because of such things as: 1) calves of a highly susceptible age are grouped together just as they reach that age, 2) loss of suspected "sparing" activity associated with milk of the dam, 3) concurrent exposure to other microbial agents, 4) simultaneous exposure to other exogenous influences such as cold or dietary antigens, and 5) frequently a similar genetic makeup. The explosive nature of the disease and the rapid production of antibodies strongly suggests that the virus is carried as a persistent infection for some time before the acute disease develops, and that the pathology is immune mediated. Adding credence to that supposition is the observation that many groups of calves that later break with ARDS appear to go through an earlier milk, smoldering type infection from which the virus can be isolated but which is fairly easily controlled with antibacterial medication alone.

Many of the predisposing or complicating factors of ARDS-RSV would appear to have one thing in common - the potential for causing pulmonary edema. At this point we can only guess which is the important contributing event(s), 1) the pathologic consequences of the lung edema alone, 2) the carrying of serum RSV antibodies into a persistently infected lung, or both.

Treatment of the acute disease usually is successful if it is caught very early and includes both antibacterial and anti-inflammatory drugs, but it is intensive and expensive. In the early stages of the disease a change of feed or fast alone may head off an outbreak.

Prevention of ARDS with vaccines appears to be feasible, but even in vaccinated calves the virus may continue to cause infection of ciliated respiratory epithelium, thus predisposing to bacterial infection.

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