General Session II

Infectious Disease Update

Dr. John A. Smith, *Presiding*

General Session II is intended to give the practitioner the most recent information available on some common and important bovine infectious diseases. Presentations are made by a group of speakers who are leading authorities in their assigned topics. General Session II is co-sponsored by AABP and the American College of Veterinary Internal Medicine.

Bovine Viral Diarrhea: The Unraveling of a Complex of Clinical Presentations.

Ruben O. Donis, *D.V.M., Ph.D.*
St. Jude's Children's Hospital
Dept. of Virology
P.O. Box 318
Memphis, TN 38107

Introduction

Bovine viral diarrhea virus is the most important viral pathogen of the bovine fetus. After birth it is responsible for two clinically dissimilar conditions: BVD and mucosal disease. It also causes significant losses as a result of its interaction with other pathogens, enhancing their morbidity in dual infections. Currently available prophylactic vaccines may be inadequate because they are not totally safe or afford incomplete protection. Our understanding of the pathogenesis of BVD virus infections in cattle is in a very dynamic state at the present time, as a result of work carried out by several groups (1-5). In contrast, progress in areas such as the molecular events of virus replication, the antigenic structure of the virus and the specificity of the immune response of the host has been slower.

In vitro Studies

Biotypes: There are two biotypes of BVD virus in nature: cytopathic and noncytopathic. Infection of bovine cell cultures with the cytopathic biotype leads to the complete destruction of the cell monolayer. No detectable cytopathic changes are observed in cells after infection with noncytopathic BVD virus.

We have detected a biochemical difference in the polypeptides induced in cells infected by cytopathic and noncytopathic BVD virus: noncytopathic BVD viruses lack the 80 k polypeptide. Thus, there are phenotypic differences that correlate with the biotypic differences (6-8).

We have developed a panel of nonoclonal antibodies to BVD virus which we used for the antigenic analysis of many field strains of both biotypes (9). In summary, the results of these studies suggest that there is extensive antigenic diversity among the field isolates of BVD virus. In addition, we concluded that there are no antigenic markers of the biotype, *i.e.* it is not possible to distinguish cytopathic from noncytopathic viruses on the basis of antigenicity.

Virus-Animal Host Interactions: Clinical and virological aspects

A variety of clinical and pathological conditions follow BVD virus infections in cattle. The major determinant of the outcome of these infections is the state of the host, therefore they will be considered in three separate groups:

1) Postnatal infection of normal, nonpregnant, susceptible, immunocompetent cattle.
2) Infection of pregnant susceptible animals with infection of the fetus, and birth of tolerant persistently infected animals.
3) Persistently infected cattle families
4) Superinfection of persistently infected animals.

The secondary determinant of the outcome of infection is the biotype of the virus (cytopathic or noncytopathic) that infects these animals, its relevance will be discussed within the context of the previously mentioned groups.

1) Postnatal infection of normal, nonpregnant, susceptible, immunocompetent cattle.

For the purposes of the following discussion, these animals will be defined as born cattle of any age that have never been previously exposed to BVD virus either spon-

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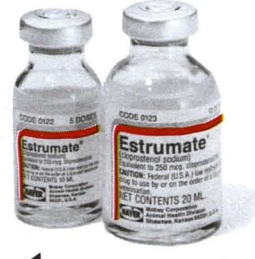

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taneously or through vaccination. The infection of pregnant cows is a special case and will be considered separately in the next section. Animals born to persistently infected dams and those exposed to the virus during their fetal developmental stages are excluded from this discussion and will be considered under the heading "Persistently infected animals."

BVD virus infection of normal immunocompetent animals results in a subclinical or mild disease, the animals recover quickly and mount an immune response that makes them immune to reinfection for a long period of time, if not for life.

This is the type of response that has been obtained after the experimental inoculation of normal immunocompetent seronegative animals with *either* cytopathic or noncytopathic isolates of BVD virus. This is also the most common outcome of infections in the field. The high prevalence of seropositive animals (approximately 60-80%) with no history of disease supports this contention.

Occasionally, in *field outbreaks,* severe respiratory disease and diarrhea are observed, in addition to the signs described above. These are likely the result of superimposed stressing environmental factors and *concurrent infections* with other potentially pathogenic organisms. It has been found that bacteremia is a common finding in animals undergoing BVD infections in the field, suggesting that perhaps neutrophils and macrophages have a reduced capacity to phagocytose bacteria in these animals. Experimental endobronchial inoculation of calves with BVD or *Pasteurella haemolytica* alone resulted in mild interstitial pneumonia with 2-7% of the lung affected or fibrinopurulent bronchopneumonia affecting 15% of the lungs, respectively. In both cases the clinical signs were benign. In contrast, if *P. haemolytica* was administered to calves 5 days after BVD inoculation the combined effects of both resulted in a severe clinical disease and extensive fibrinopurulent bronchopneumonia and pleuritis with 40-75% of the lung being affected. Although the routes of infection were unnatural, these results suggest a *synergism between pathogens* that would otherwise cause mild disease.

A viremia occurs from 3 to 10 days after BVD virus infection and during this period virus can be readily isolated from blood, mucosal surfaces and secretions *in vivo,* and almost any tissue in *post mortem* samples. (This is important for diagnostic purposes). Subsequently, the animals eliminate the virus, probably through humoral and cellular immune responses. The humoral immune response can be detected by serum neutralization assays approximately 2 weeks after infection and peaks at 6-8 weeks. *Antibody titers* remain for life, probably as a result of re-exposures that boost antibody production. These animals are in all likeli-hood immune to infection with BVD virus.

Several discussions of BVD virus infections in cattle stress its *"immunosuppressive"* effects. These data should not be overinterpreted. The current concept is that BVD virus infection of normal immunocompetent cattle alters certain specific and nonspecific defense functions and can increase the pathogenic potential of other organisms, but it is very seldom a fatal infection. In one carefully controlled study, it was found that the immune response to *Brucella abortus* as well as *in vitro* estimators of immunological function were within normal range in animals experimentally infected with both biotypes of BVD virus.

2) Infection of pregnant, susceptible cows and birth of tolerant persistently infected animals.

Infection of normal cows that had never been exposed to BVD virus and are not persistently infected with BVD virus results in a subclinical or mild disease, the characteristics of which have been described above in #1. In addition, the conceptus is also infected since the virus can readily cross the fetal membranes.

The possible outcomes of fetal infection depend on gestational age and the biotype of BVD virus involved.

The effects of BVD virus infection in the *pre-implantation and early embryo* are less well studied but there is some indication that it may result in embryonic death (11).

Inoculation of cows with *noncytopathic* BVD virus between *42 and 114 days of gestation* results in a variable proportion of abortions, stillbirths, the birth of weak calves with neurological signs and the delivery of *healthy-looking calves.* Some of these calves that are healthy-looking at birth develop normally, others are unthrifty and die at an early age or remain as *"poor doers"* in the herd for the rest of their lives. The most important feature of these calves is their immunological and virological status: they are *tolerant to the BVD virus* that infected them and are *persistently infected* with it. This persistent infection remains so for life. Immunological tolerance is specific for the antigenic type of the BVD virus that persists in their body, and results from the presence of the virus during the stages of development and maturation of the immune system. It is during this period that lymphocytes learn to discriminate between SELF and NON-SELF. In these early stages, one of the first phases involves the deletion or suppression of all lymphocytes that recognize SELF determinants to avoid autoimmune attack when the effector mechanisms become operative. Under normal conditions, all molecules present in the developing fetus are part of the SELF. The ability of noncytopathic BVD virus to infect the fetus at this early developmental stages without causing abortion allows the virus to persist being regarded as SELF. The virus is consequently recognized as self and no immune response will ever be developed against it, and no active antibody production specific for BVD virus takes place in these calves. These persistently infected calves may, however, acquire antibodies to BVD virus from their dams via colostrum. This represents one of only two possible situations in which antibodies to BVD can be present in the circulation of persistently infected animals. The second situation will be discussed below.

Calves *born persistently infected* may be smaller than their herdmates. As a result of intrauterine infection with BVD virus some fetuses show varying degrees of *intrauterine growth retardation* manifested as a generalized stunting, with reduced body weight and crown to rump length. Most

of these are born smaller than their herdmates and remain so. The reduced growth rate is permanent in some cases and some animals reach maturity without reaching the normal size expected from their genetic makeup and the nutritional supply.

Cows infected with *noncytopathic* BVD virus between approximately *120 and 160 days of gestation* deliver calves that may be normal (very small proportion of cases) or may have a variety of congenital defects. The defects recognized up to date include: hypomyelinogenesis, arthrogryposis, alopecia, ocular defects, cerebellar dysplasia, porencephaly and hydrenencephaly. The lesions do not always correlate with the severity of the clinical signs. In most cases, some neurological deficits subside, the calves improve their overall neurological function and survive with sequelae of varying severity. The vast majority of these calves are *immunocompetent,* that is, they mount an immune response to the virus *in utero* and are born *with antibodies* to BVD virus. The *in vitro* immune response eliminated the virus and these calves are *free of BVD virus* and immune to reinfection. It is important to bear in mind that not all calves with neurological signs necessarily belong to this category. As stated in the previous section some calves born persistently infected also show cerebellar signs. Obviously there is a continuum of situations. Summarizing: all calves that show cerebellar signs at birth are possible carriers of BVD virus and should be tested if they are to be kept in the herd.

Cows infected with BVD virus of either biotype *from 160 days of gestation to term* give birth to calves with no abnormalities except that they are born *with antibodies* to the virus. Infection of these fetuses at a stage in which they are already immunocompetent elicits an immune response that clears the virus. These calves are immune to reinfection.

Having discussed the possible outcomes of infections of pregnant cows with *noncytopathic* virus, it is important to stress that the effects of infection of this same type of animal with *cytopathic biotypes* of BVD virus are apparently remarkably different. *Cytopathic BVD* virus biotypes have the same ability to cross the placenta and infect the fetus. The results of fetal infection are however different. *No calves persistently infected with cytopathic BVD virus have been reported to date.* Cytopathic BVD virus infection of cows between *40 days of gestation and term* seems to result in *abortion* or the birth of calves that are *normal* and have antibodies to the virus at birth. It is unclear if these cytopathic viruses can cause congenital defects. The cause of this difference is not known.

3) Persistently infected cows give birth to calves also persistently infected.

Persistently infected animals may not thrive well and die at an early age or may be smaller and runted and as a result are usually culled from the herd. Some persistently infected animals may, however, be healthy-looking and remain in the herd as breeding stock. *The offspring of persistently infected cows are always persistently infected.* This is not surprising since these fetuses are exposed to the virus throughout and they probably are infected as soon as they become susceptible. These cases are of interest since they suggest that early embrionic death in cows infected during the first 3-5 weeks of gestation is not the result of the direct effect of the virus on the fetus. The inflammatory response of the genital tract to the viral infection seems to be embryotoxic, since the presence of the virus in the uterus does not affect conception in persistently infected cows.

In addition to being persistently infected, these calves will lack antibodies to BVD after receiving colostrum from their dams, a fact that could be used for diagnostic purposes.

4) Superinfection of persistently infected animals

The term superinfection is used here to refer to infection of persistently infected animals with a cytopathic biotype of BVD virus. When persistently infected animals are exposed in the field or under experimental conditions to a cytopathic biotype of BVD virus, these animals may succumb with a fatal disease known as *mucosal disease.* The disease has the characteristics of the one that Ramsey and Chivers described in Iowa in 1953. They named this entity mucosal disease and this name should be used whenever referring to the fatal form of BVD infections in which there is severe damage to the mucosae. The term BVD or BVD infection should be used to describe BVD virus infections in normal cattle; the more benign disease. Some authors have in the past described mucosal disease as "chronic BVD." This terminology may lead to confusion since no chronic infection has been described following the primary infection. Animals infected *in utero* are more appropriately described as persistently infected. Field cases of mucosal disease submitted to diagnostic laboratories for viral isolation have in many instances yielded BVD virus of both cytopathic and noncytopathic biotypes from the same animal. The biotype of the persisting virus is always noncytopathic. The isolation of the 2 biotypes from an animal has so far been seen almost exclusively in animals with mucosal disease. Experimentally, cattle persistently infected with BVD virus, but not normal animals, succumb with mucosal disease only if superinfected with certain isolates of cytopathic BVD virus.

Not every combination of persisting-superinfecting viruses will produce disease. There is experimental evidence indicating that the inoculation of persistently infected cattle with certain strains of cytopathic BVD will not lead to mucosal disease. These animals remain healthy and respond immunologically to the superinfecting virus with the production of neutralizing antibody specific for this virus, yet no neutralizing antibody response is mounted against the persisting virus. *This represents another situation in which persistently infected animals may have neutralizing antibody in their circulation.* The first was passively transferred antibody from the dam. Both are exeptions to the general rule that persistently infected animals lack neutralizing antibodies. It seems that the critical factor in the induction of mucosal disease is the nature of the pair persisting-superinfecting virus. This assertion is supported by experimental work in which cattle persistently infected with the same noncyto-

pathic virus did develop disease after challenge with one isolate of cytopathic BVD virus but not after challenge with another, suggesting that the nature of the persisting virus was not the only factor in mucosal disease development. Conversely, if cattle persistently infected with different noncytopathic BVD viruses are superinfected with a single cytopathic virus only one group persistently infected with one of the viruses developed disease, while the other group remained healthy. These findings suggested that the nature of the superinfecting cytopathic virus is not the only determinant of disease development.

Antigenic analysis of pairs of cytopathic and noncytopathic viruses isolated from single animals with mucosal disease carried out with monclonal antibodies revealed that in most instances both virus are antigenically very similar. This finding suggests that cytopathic virus arises as a mutant of cytopathic virus or that only a cytopathic virus that is antigenically similar to the persisting noncytopathic virus is capable of inducing mucosal disease.

Epidemiology: Virus Reservoirs

Infection of normal cattle with BVD virus results in the great majority of cases in a subclinical disease. This fact is supported by the overall high rates of seropositive animals (≈60%) in herds where no clinical disease was observed. Normal cattle mount an immune response to BVD virus that eliminates it and are subsequently immune to reinfection. Seropositive animals are free of BVD virus (there are exceptions to this general rule). Seronegative animals are susceptible to BVD virus infection. A small proportion (2-3%) of these seronegative animals are persistently infected with BVD virus. The only pathway leading to persistent infection is fetal infection. There are two possible modes of fetal infection: one is the infection with BVD virus of normal seronegative pregnant cows and the other is the infection of the fetus carried by a persistently infected cow. Normal cows can therefore yield one persistently infected calf in their lifetime (they will be immune during the next gestation) whereas persistently infected cows can produce several persistently infected offspring. The potential exists for the *perpetuation of persistently infected maternal families.*

The ability of BVD virus to persist in tolerant animals gives it an extraordinary capacity to remain in cattle populations in the face of a population of immune hosts. Herds in which persistently infected cattle are present have the largest rates of seropositive cattle. In these herds cattle are continuously exposed to virus shed by persistently infected animals and they become seropositive, usually with high neutralizing antibody titers. Other viral infections would be eliminated from the herd and would not be reintroduced until the proportion of susceptible animals is high, due to the "herd immunity" effect. BVD virus overcomes the efficacy of herd immunity by its ability to induce tolerance after fetal infection and persistence for life and for generations. Having defined the persistently infected animal as the reservoir for the virus, it follows that all control measures should be directed at the detection and elimination of these animals and the prevention of fetal infection.

Spread of BVD within the herd:

Persistently infected or acutely infected animals shed infectious virus in high concentration in all secretions and excretions. Direct contact is obviously an important means of transmission. Indirect contact via contaminated feed, water, instruments and equipment are also important. Special attention should be given to all those operations involving interruption of the continuity of the skin, especially when performed with the *same instrument on several animals* without previous disinfection: castration, supernumerary teats, ear tagging, foot trimming, dehorning, and last but not least, parenteral injections with hypodermic needles.

Introduction of BVD from outside the herd:

Before considering the particular possible cases it should be pointed out that although introduction of persistently infected animals seems *a priori* potentially much more damaging for the herd than other means of introduction, BVD virus introduced by any other means into a herd with susceptible pregnant cattle in early gestation will result in the production of such persistently infected animals anyway. Therefore, any introduction of BVD virus is potentially very harmful and undesirable.

Replacement animals are a source of infection for a herd. They can harbor BVD virus in different fashions:

1) *Persistent infection.* These animals will shed virus for life and produce persistently infected offspring.
2) *Acute transient infection.* These animals will shed virus for a brief period.
3) *Trojan cows.* These are pregnant cows that underwent infection during early gestation and subsequently seroconverted and are immune to reinfection but they carry a persistently infected fetus which will start shedding virus as soon as it is born. Beware of this tricky situation!! The cow may be apparently safe but the fetus is a time bomb.

Contaminated semen is also a possible means of dissemination of infection. Normal bulls undergoing an inapparent BVD infection virus will shed virus into the semen for several days contaminating a few ejaculates. Even after dilution this semen can infect inseminated susceptible cows which usually fail to conceive in this cycle. Persistently infected bulls are probably rare in AI centers since they usually have poor conformation and low semen quality. Their inadvertent presence in these facilities could be devastating since these animals produce contaminated semen. A systematic screening of these animals would be warranted.

Embryo transfer techniques are also potentially a means of introducing the disease if ova from persistently infected donors are transferred or if persistently infected recipients are used.

Modified live virus vaccines contaminated with noncytopathic BVD virus. They are especially dangerous when they are intended to be used during pregnancy or are not contraindicated in this period to protect cattle against viral

diseases other than BVD such as respiratory syncytial virus, rotavirus, bovine herpesvirus, etc. Numerous episodes of contamination of vaccines with BVD virus have been described and many more may have gone undetected. The source of BVD virus can usually be traced to the use of fetal calf serum in any of the manufacturing steps of the vaccine. The majority of the commercial lots of fetal calf serum are contaminated with BVD virus, a reflection of the high prevalence of fetal infections. Fetal calf serum is normally collected at slaughter plants and pooled. Most cell lines used in the cultivation of bovine viruses for vaccines are of bovine origin and they are commonly grown in medium supplemented with fetal calf serum. Stringent controls to certify the absence of BVD virus in the starting materials for vaccine production is mandatory.

A special case is presented by modified *BVD live virus vaccines.* Their fetopathogenicity has been demonstrated in some instances and their potential to induce persistent infection of the fetus suspected but not proven. The most disturbing possibility is their *contamination with wild-type noncytopathic virus.* It would be impossible with current technology to rule out by *in vitro* testing the presence of a small proportion of wild-type noncytopathic BVD virus in a lot of modified live BVD virus vaccine. The only means of proving the safety of a live virus vaccine is to administer it to pregnant susceptible cows in early gestation and to subsequently evaluate the fetus and the cow virologically and serologically. All lots of commercial live virus vaccines should be tested in this fashion to insure their safety for the fetus.

Economic impact of infections. Losses due to BVD virus infections can be divided into two major categories: infection of nonpregnant cattle and fetal infection. Infection of open cattle of any age probably represents a small fraction of all losses, but can be important in specific management operations such as feedlots. These losses are derived from the synergistic effect of dual infection between BVD virus and bacterial and viral pathogens.

Fetal infection results in abortions, congenital defects and the birth of persistently infected animals with reduced performance and early mortality due to superinfection and development of mucosal disease. In a study of fetal infections by Done et al. the authors concluded that an average of 6% of all bovine fetuses are at risk of being infected with BVD virus and developing a persistent infection. These figures were calculated on the assumption that about 25% of the pregnant animals (mostly heifers) were seronegative and one in four of them carried a fetus between 40-120 days of gestation.

The Field Picture or *the Tip of the Iceberg.* The most common situations that lead to a diagnosis of BVD virus in herds are:

1) Cases of mucosal disease. 6-18 month old animals with persistent diarrhea, nonresponsive to antibiotic treatment, poor condition, progressive weight loss. Usually one or two animals involved. Oral lesions may or not be present.
2) Newborn animals with neurological signs and/or other congenital defects.
3) Cases of unthrifty animals.
4) High SN titers in a large number of animals when serology is carried out for a variety of reasons: poor reproductive performance, abortions, febrile illnesses, etc.

1. In *mucosal disease cases* the diagnosis is easily confirmed by the isolation of virus from the buffy coat and/or swabs taken from any mucosal surface. Serum samples are negative for BVD SN.

If this is suspected to be an acute infection of a normal immunocompetent animal with BVD virus a second sampling after 2 weeks will resolve the question: A sample taken two weeks later from immunocompetent animals recovered from primary BVD virus infection should be negative for virus and the animal should have an antibody titer to BVD virus.

Occasionally, calves less than 6 months of age present with mucosal disase. These calves are usually born to persistently infected cows and as a result do not receive antibodies to BVD in colostrum which makes them susceptible to superinfection at any time after birth.

2. Calves born with cerebellar dysplasis, ocular defects, and a variety of other *congenital defects* were probably infected *in utero* with BVD virus. Most of these animals are negative in virus isolation and are not likely to be virus shedders, but some of them are. Submission of a blood sample for virus isolation will help decide on whether to recommend the client keeping the animal. The SN titers are usually difficult to interpret because of colostral antibody.

3. Unthrifty calves *"poor doers"*, some of which may die in the first few weeks of life while others may only be marginally subnormal, are sometimes the first clue leading to the detection of BVD. When serum and blood are submitted to the laboratory for SN and virus isolation, these animals are viremic and do not have antibodies to BVD (except for residual maternal colostral antibody). These animals are most likely persistently infected with BVD. If there is any question as to whether they are just normal animals transiently infected with BVD virus, a second convalescent sample will help establishing a definitive diagnosis as was discussed above. A very rewarding approach to detect persistently infected animals in herds where there is a confirmed persistently infected animal (or a calf with BVD-related congenital defects), has been to test all calves born around that period of time by SN. We suggest testing all calves three months younger and three months older than the index case. In a second phase all seronegative animals are blood tested for the presence of BVD virus by virus isolation.

4. When *high antibody titers* (in our laboratory >512) are detected in several animals in a herd, this is suggestive of recent infection or continued antigenic stimulation (reinfections) that boost the antibody titers. In most cases the source of virus for this continued boosting of the antibody titers is a viremic persistently infected animal that sheds virus. Since

these animals are almost always seronegative an SN screen of the herd will highlight them. The usual picture is that of a few seronegative animals in a herd with a majority of seropositive animals with high titers. Whenever a persistently infected animal is detected in a herd, in addition to testing animals of the same age, it is also advisable to test the dam of that particular animal. In some cases dams also happen to be persistently infected.

PROPHYLAXIS: Today and tomorrow.

BVD virus is so ubiquitous in the current farming environment that attempting to keep a BVD-free, closed herd and avoid the use of vaccines is utopic and economically dangerous. Current modified live virus vaccines are the most effective immunogen available. However, for those herds that have not used BVD caccines in the past we recommend initiating the vaccination program using killed vaccine due to its greater safety margin. Once all cattle have been immunized with the killed vaccine it would be safer to introduce modified live virus in the herd.

In the short term we should hope for the highest possible standards in the safety testing of modified live BVD virus vaccines, and in the immunogenicity of killed vaccines. In the long term we hope that genetic engineering technology will provide a completely safe, effective and economical vaccine making BVD a disease of the past (1).

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Questions & Answers:

Question: What about the cytopathic — non cytopathic vaccine?

Answer: There is a killed BVD vaccine that has a mixture of cytopathic and non cytopathic virus. I do not know what strains it is made out of but it could be a good vaccine if there is a mix of antigenically different viruses. If they are identical then the vaccine would not be very good.

Question: What about killed vaccines?

Answer: A safe and effective killed vaccine may become available with improved adjunct.

Question: There has been a lot of promotion of killed vaccines. I have used 5000 doses a year of modified live virus vaccine in Central Virginia with no problems and I feel they have helped a lot. Yet these have been maligned in advertisements. These make the veterinarian who uses them to be unethical. What do you think?

Answer: I agree with your assumption.

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