Cow/Calf and Feedlot Split Sessions

Moderator - Gary Rupp

Immunology of Bovine Pestivirus Infection

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The bovine pestiviruses (here referred to as bovine viral diarrhea viruses-BVDV) cause three types of disease: bovine viral diarrhea (BVD), mucosal disease (MD) or fetal disease (FD). In each case, the immune system of the host responds in a characteristic fashion (Nettleton and Entrican, 1995).

Infection of normal, healthy cattle (with no previous exposure to BVDV) with BVDV results in mild pyrexia, mild diarrhea and some ocular/nasal inflammation (Nettleton and Entrican, 1995). Occasionally, BVDV infection of young calves may cause neutropenia and thrombocytopenia with pyrexia (Pellerin *et al.*, 1994). In any case, clinical illness is usually mild. Most cattle develop antibodies to all of the BVDV glycoproteins (reviewed in Potgieter, 1995). Antibodies to gp53, the major envelope glycoprotein, will neutralize the virus (Donis *et al.*, 1988; Wailand *et al.*, 1992). There is some serologically-defined variation of gp53 epitopes among field isolates of BVDV (Xue *et al.*, 1990). Other BVDV glycoproteins, gp25 and gp48, are antigenic but the antibodies are not effective at neutralization (Bolin, 1988; Bolanger, 1991; Xue *et al.*, 1990). However, gp25 and gp48 may be very important antigens for cellular immunity (Kwang *et al.*, 1992; Rumenapetal, 1991). There is evidence that $CD4^+$, class II-restricted, cytotoxic T-lymphocytes are important for protective immunity (Howard et al., 1992). Both gp25 and gp48 antigens are highly conserved among BVDV isolates (Kang *et al.*, 1992). These observations suggest that cellular immunity to gp25 and gp48 may protect against several different strains and/or isolates.

There is considerable cross-neutralization of pestiviruses by monoclonal or polyclonal antibodies (Bolin *et al.*, 1988; Castrucci *et al.*, 1975; Wensvoort *et al.*, 1985). There is also quite a bit of antigemic diversity among BVDV isolates (Xue *et al.*, 1990). Heterotypical neutralizing antibodies are generated after infection or immunization with either attenuated or inactivated vaccines (Bolin and Ridpath, 1989; Bolin and Ridpath, 1990). However, inactivated vaccines are often not protective against heterologous virus challenge (Bolin *et al.*, 1991; Martin *et al.*, 1994). The p80/125 protein is nonstructural and may be immunodominant (Bolin and Ridpath, 1989; Collett, 1992). High concentrations of non-neutralizing antibodies are generated to p80/125 after infection. The four domains of the p80/125 protein are highly conserved among all pestiviruses (Deregt *et al.*, 1990; Kamstrap *et al.*, 1991; Paton *et al.*, 1991). These epitopes are antigenic, but they are not immunogenic.

Most primary infections of cattle are mild (Ames, 1986). However, BVDV infection can cause a transient immunosuppression (Edwards *et al.*, 1986; Potgieter *et al.*, 1984 a and b; Potgeiter *et al.*, 1985). This immunosuppression may increase the severity of disease caused by other pathogens or give an opportunity to secondary

pathogens.

The most significant losses from BVDV infections are due to infection of susceptible pregnant females (Nettleman and Entrican, 1995; Van Oirschot, 1983). The virus rapidly crosses the placenta within 5 to 7 days of initial infection of the respiratory tract (Nettleman and Entrican, 1995). The dam's immune system will usually clear the infection from maternal tissues. But, the fetus is susceptible and several sequelae may develop (reviewed in Nettleman and Entrican, 1995). The bovine fetus is more resistant to BVDV infection than the lamb fetus. Up to 70% of bovine fetuses may survive even when infected before 100 days gestation. Fetal death results in resorption if death occurs rapidly and abortion of a small fetus if death occurs more slowly. The surviving fetuses will usually be persistently infected and will remain infected for life. These animals shed virus and are immunotolerant (antibody negative). Rough hair coats and muscle tremors have been observed.

Calves infected approximately 95 to 160 days after conception are capable of mounting an immune response. However, BVDV infection of developing nervous tissue and the subsequent fetal immune/inflammatory response cause severe tissue damage. Cerebellar hypoplasia, cerebral cavitation and retinal lesions are the most frequent central nervous system lesions observed. These calves may occasionally be persistently infected but are usually virus free and antibody positive. When the fetus is infected after 150 days, the immune system will eliminate the virus. These calves may be small and born prematurely. They are usually virus-free and antibody positive.

Persistent infection is probably the key factor that allows BVDV to be a major pathogen of cattle. Calves infected before 100 days of gestation may die (around 30% fetal loss). However, many of them become immunotolerant (Steck, 1980; Bolin, 1988). These animals never clear the virus and thus are infected for life. Virtually all tissues are infected. Immunotolerant, persistently infected (IPI) animals shed virus at concentrations up to one million pfu/ml in blood, saliva and nasal secretions. These secretions are the major reservoir of virus for infection of other animals (Gunn, 1993).

The tolerance in IPI calves is specific. It is specific for BVDV only and only for the epitopes of the isolate from the IPI animal (Bolin, 1988). These IPI cattle will respond to heterologous BVDV epitopes. Leukocytes of IPI cattle are infected with BVDV. This infection affects antigen processing, antigen presentation, antigen recognition, cellular proliferation, cellular maturation, cellular differentiation and cytokine synthesis (Nettleton and Entrican, 1995). It is likely that many IPI animals are not immunocompetent (McClurkin *et al.*, 1992). As such, these animals are often unthrifty. But, it is interesting that many IPI cattle are healthy and are sometimes very productive (Bolin *et al.*, 1985).

Mucosal disease (MD) results when IPI cattle are exposed to a second BVDV. Almost all strains of BVDV isolated from IPI cattle are non-cytopathic (reviewed in Deregt and Loewen, 1995). In fact, almost all wild-type, field isolates of BVDV are non-cytopathic. Usually, MD occurs after exposure of an IPI animal with cytopathic BVDV. Cattle with MD have a profuse, fetid, hemorrhagic diarrhea with profound depression. Most of these animals will die. At necropsy, numerous deep mucosal erosions are observed.

More complete understanding of the pathogenesis of fetal BVDV infection and FD will require more information about the ontogeny of the thymus and the initiation of negative selection. Further, control of BVD/MD complex disease will require immunity measured by protection of the fetus and not just a reduction of clinical symptoms in the primary host. Attenuated vaccines produce antibodies to many BVDV-specific antigens. Presumably, cellular responses to these antigens also occur. It is not known what balance or combination of antibodies and cells is required for protection, especially to prevent infection of the fetus. Inoculation of cattle with attenuated, live virus vaccines generates a long-lasting immunity that probably protects against most wild-type strains of BVDV. However, these attenuated strains are usually the cytopathic phenotype and can induce mucosal disease, fetal disease or immunosuppression. Recombinant vaccines may be useful eventually, but the required antigenic composition is not yet clear. Inactivated vaccines are safe and do induce antibodies to gp53 that will neutralize BVDV. These neutralizing antibodies recognize heterotypic epitopes. However, experimental evidence suggests that immunity may only last 4 to 6 months and heterotypic protection is inadequate.

The most significant advances in technology and science for control of BVDV will include development of systems to drive antigen presentation towards initiation of cellular and humoral responses to key epitopes of BVDV. The use of advanced diagnostics (detecting antibodies to p80/125) may differentiate vaccinated vs. naturally infected animals. Eventual control of BVDV will develop as we gain the ability to effectively manipulate antigen processing-presentation and immune response initiation.

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Abstract

Preferential sites for arterial blood sampling in cattle

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The aim of this study was to compare the feasibility and reliability of different methods for obtaining samples of arterial blood from calves and adult dairy cows. The intermediate branch of the caudal auricular artery was easy to use in animals of all ages. The common carotid artery was also suitable, but only in standing animals. In recumbent animals, the brachial artery and the common palmar digital artery were suitable in calves up to six months old, and the saphenous artery was suitable in both young and adult cattle. The facial, axillary and median caudal arteries were either difficult to use or unreliable.