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Biologicals 31 (2003) 133–135
BIOLOGICALS
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# The persistence of bovine viral diarrhea virus

Kenny V. Brock*

*Department of Pathobiology, Auburn University, Auburn, AL 36849-5519, USA*

Received 15 January 2003; accepted 15 January 2003

**Abstract**

Bovine viral diarrhoea virus (BVDV) has a unique capacity to cause persistent infections of foetuses exposed within the first 150 days of gestation. Preventing foetal BVDV infection will aid in improved control. This unique ability gives BVDV a selective advantage allowing continual mutation and antigenic variation within cattle populations. Therefore, BVDV has become widespread and causes economic losses due to respiratory, reproductive and enteric disease. Vaccination (modified-live or killed) can provide some protection from acute disease and the development of persistently infected foetuses. However, vaccination programmes alone cannot control or eliminate BVDV. In naturally exposed and vaccinated herds, BVDV infections are not self-limiting and may persistent over time. This underscores the ability of the BVDV genome to remain fluid and adapt under selective pressures. Factors influencing persistence of BVDV infections in cattle populations include: non-lytic infections; evasion of host immune responses; foetal infections; acute infections; management practices; contaminated biologics; secondary hosts; defective replicated intermediates; antigenic variation; and replication in privileged anatomical sites.


The survival of viruses depends on their ability to change and reach homeostasis within host organisms or resist environmental degradation outside a host organism. For viruses that do not survive for long periods outside the host, persistent replication is necessary for continued survival. The interaction of host, pathogen, and environment requires that viruses become attenuated for their hosts providing an equilibrium between pathology/disease and virus replication. Viruses have several mechanisms for persistence in host populations; including, replication by non-lytic infection, the long-term maintenance of the genome in the host, and evading the host's immune response.

Several factors have influenced the persistence of BVDV in cattle. Non-lytic infections produced by non-cytopathic BVDV strains and the ability to evade the host immune response are the primary mechanisms of persistence. In addition, some man-made factors have provided opportunities for BVDV to persist in cattle populations. Others mechanisms unique to BVDV probably result from its adaptation to cattle as a primary host.

*Foetal immunotolerance and persistent infections*: The ability to induce foetal persistent infections is a unique aspect of BVDV pathogenesis. The host immune response is evaded by the establishment of immunotolerance to BVDV, which allows persistent infections to continue. Immunocompetance of the bovine foetus is established at approximately 125 to 150 days of gestation. An additional requirement of this mechanism is a non-lytic infection with BVDV which does not adversely affect foetal development and maturation. Therefore, transplacental infection in a susceptible pregnant animal at less than 150 days of gestation with a non-cytopathic BVDV may produce a persistent foetal infection [1]. This unique phenomenon is the primary mechanism whereby BVDV is maintained in cattle populations providing for direct and indirect transmission. Although persistently infected (PI) animals may represent approximately one percent of the cattle population [2], they shed virus and initiate further virus replication and genetic variation [3]. Therefore, control and prevention programmes must focus on prevention of persistent

* Corresponding author. Dr K. V. Brock, Auburn University, College of Veterinary Medicine, Department of Pathobiology, 264 Greene Hall, Auburn, AL 36849-5519, USA. Tel.: +1-334-844-2663; fax: +1-334-844-2652

*E-mail address:* brockkv@auburn.edu (K.V. Brock).

1045-1056/03/$30.00 
doi:10.1016/S1045-1056(03)00029-0

infections and identification and removal of PI animals [4]. Breaking the cycle of exposure of pregnant animals in the first 125 to 150 days of gestation is the key to preventing persistent infections.

*Acute infections*: The ability of BVDV to circulate in cattle populations is also influenced by acute infections. Although persistent infections represent a major source of virus spread, acutely infected animals may be the primary source of virus introduction into naive herds and may be responsible for continued circulation of BVDV within infected herds. Due to the constant movement and turn-over of animal groups, acute infections can be very important in the spread and maintenance of BVDV in cattle. In addition, acute infections produce reproductive and respiratory disease which results in major economic losses to the cattle industry.

*Management practices involving moving and mixing of cattle*: Management practices directly affect the maintenance of BVDV in cattle populations. Co-mingling of different groups of cattle is one risk factor associated with bovine respiratory disease. Acute BVDV infections may cause respiratory disease, in stressed animals. The practice of mixing and shipping cattle provides opportunities for BVDV to maintain itself in cattle populations by circulation of acute infections in susceptible cattle. Increasing the percentage of vaccinated animals and removing potential sources of BVDV such as PI animals would reduce the potential for acute infections. Management practices aimed at reducing stress associated with co-mingling are also desirable.

*Contamination of biologicals*: The use of materials of animal origin such as foetal bovine serum and cell cultures provides an additional manner for BVDV to persist by serendipity. Once the pathogenesis of persistent foetal infections was characterized, it became evident that foetal bovine serum was a major source of contamination and that the majority of manufactured foetal bovine serum lots and cell culture stocks were contaminated with BVDV. Most BVDV researchers use equine serum to circumvent this problem. However, the contamination of established cell lines due to the use of contaminated foetal bovine serum continues to be a problem. In addition, when materials of animal origin such as co-culture systems in in vitro fertilization are used, BVDV contamination becomes a quality assurance issue [5]. When contamination of laboratory systems or biologicals occurs, it is equivalent to infection of secondary hosts where virus can subsequently return to circulate in cattle populations following serial passage. During cell culture passage mutations may occur in the absence of immunological selection. This becomes another method whereby variation may provide antigenic or phenotypic changes that may affect pathogenesis of BVDV. Quality assurance of biologicals, used in cattle, will continue to be a vital component of BVDV control.

*Secondary hosts*: The ability of BVDV to replicate in numerous wild ruminant species such as camels, deer, elk, and bison has been well documented [6]. Currently, due to the prevalence of BVDV, it is difficult to measure or predict the importance of such secondary hosts in the maintenance of the virus in cattle populations. As the prevalence of BVDV is reduced by prevention and control methods, it is likely that the significance of infections in secondary hosts will be realized.

*Defective replicative intermediates*: The dual nature of cytopathic and non-cytopathic BVDV has been characterized. However, the significance of these two biotypes in animals remains unclear. Replicative intermediates provide a method of attenuation of cytolytic viruses by reducing cytopathology and allowing replication and persistence in the host. Defective replicative intermediates of cytopathic virus have been identified in cattle [7], however little is known concerning their importance in the biology of BVDV, especially non-cytopathic virus.

*Antigenic variation*: As an RNA virus, BVDV generates mutations that precipitate antigenic changes. Changes in the E2 glycoprotein are the primary sites of variation in neutralizing epitopes. Recently, the phylogenetic classification of BVDV isolates as type Ia, Ib, and II has emphasized the significance of genetic variation [8]. Infection of immunocompetent animals with BVDV stimulates cross-reactive antibody and provides protection from disease due to infection with diverse strains [9]. Due to the ease with which BVDV crosses the placenta, the foetus may remain susceptible to infection although the pregnant dam is protected by cross-reactive antibody [10]. Variations in BVDV have led to vaccine failures against foetal infection due to differences between vaccine virus and field virus. However, continued genetic and antigenic variation is responsible for the circulation of BVDV in susceptible cattle and the development of persistent foetal infections in susceptible pregnant animals. The move toward multivalent vaccines is in response to the recognition of the importance of genetic variation of BVDV.

*Replication in privileged sites*: Recently, Voges et al. reported a chronic BVDV infection in the testicles of a bull that was previously acutely infected with the virus [11]. The bull was not viraemic and possessed high levels of anti-BVDV antibody while shedding approximately $10^3$ $CCID_{50}$ of virus/ml of semen. Previously, Grooms et al. identified BVDV antigen present in ovaries of heifers 60 days post-infection [12]. Currently, studies are being conducted to determine the prevalence and potential of chronic persistent infections that may follow acute BVDV infections. The establishment of chronic infections would provide an additional mechanism for BVDV to persist in cattle populations.

Recognition of the pathogenic mechanism of immunotolerant foetal persistent infection*s was* an important step in the evolution of BVDV control and prevention.

The identification and removal of PI animals is an important component of current prevention and control methods. Due to the prevalence of PI animals and their shedding of BVDV they represent a high risk and are justifiable targets of control methods. However, it is clear that BVDV has many mechanisms at its disposal to ensure that it can persist and be maintained in cattle populations. When this is considered, the slow progress in preventing and controlling BVDV infections is understandable. In addition, this aspect will be an important consideration as increased emphasis is placed on the eradication' of BVDV from cattle.

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