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Bovine Viral Diarrhea: Review

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Abstract: Bovine viral diarrhea (BVD) is a viral disease of cattle and other ruminants. This review paper is done with the objectives of reviewing the epidemiology and diagnostic methods of BVD disease and to provide information on the economic importance and strategies used for control and prevention of the disease. Bovine viral diarrhea is caused by the Bovine viral diarrhea virus (BVDV) which is a member of the genus pestivirus in the flaviviridae family. Cattle of all ages are susceptible to infection with BVDV, but the disease is most common in animals 6-24 months of age. The distribution of the virus is world-wide. The virus spreads mainly by contact between cattle. Vertical transmission also plays an important role in its epidemiology and pathogenesis. Persistently infected animals, which shed virus in secretions and excretions, are particularly important sources of infection. The clinical signs range from subclinical to the fulminating fatal condition called mucosal disease. Diagnosis of BVD is accomplished by clinical signs, virus isolation, serology, fluorescent antibody, or polymerase chain reaction (PCR) tests. Economically, BVDV adversely affects both health and productivity. Successful control and eventual eradication of BVDV requires a multidimensional approach, involving vaccination, bio-security and identification of BVDV reservoirs. In conclusion, since there is no treatment for BVDV infection there is a huge economic loss. Therefore, there should be improved diagnostic methods and prevention and control measures.

Key words: Bovine Viral Diarrhea · Cattle · Epidemiology · Prevention and Control

INTRODUCTION

Bovine viral diarrhea has been recognized as a disease syndrome since 1946 [1]; however, in this year veterinary workers at Cornell demonstrated that a virus was the cause of a transmissible bovine diarrhea and thereby named Bovine viral diarrhea virus [2].

Bovine viral diarrhea virus causes Bovine viral diarrhea and mucosal disease, which is similar to the viruses causing Border disease in sheep and swine fever in pigs. These three viruses are together classified as pestiviruses with in the flaviviridae [2].

Bovine viral diarrhea virus infection, disease, or both have been described in cattle, sheep, goats, pigs, bison, alpacas, llamas and white-tailed deer. However, in 2007, the Office of International Epizootics added bovine viral diarrhea to its list of reportable diseases, but the listing is as a reportable disease of cattle rather than as a reportable disease of multiple species [3]. In addition to this, the virus has been identified worldwide as a most serious cause of cattle disease, particularly reproductive diseases [2].

Bovine viral diarrhea virus uses multiple strategies to ensure survival and successful propagation in mammalian hosts and this includes suppression of the host's immune system, transmission by various direct and indirect routes and perhaps most importantly, induction of persistently infected (PI) hosts that shed and transmit BVDV much more efficiently than non-PI animals [3]. The virus spreads mainly by contact between cattle. Vertical transmission also plays an important role in its epidemiology and pathogenesis [4].

Infection with BVDV is common in cattle populations throughout the world. The virus can cause both acute disease, bovine viral diarrhea and a protracted form of illness, mucosal disease (MD), arising from persistent infection [5].

Although the naming of the virus and illness implies gastrointestinal disease in cattle, BVDV is a pathogen that affects multiple organ systems in many animal species [3]. The result in a variety of signs of illness like depression, anorexia, excessive salivation, recumbency, dehydration; reduced lactation, cessation of rumination and conjunctivitis [6].

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Disease in cattle resulting from infection with BVDV is responsible for economic losses throughout the world that are realized through decreased weight gains, loss of milk production, reproductive wastage and increased rate of morbidity and mortality [1]. Successful control and eventual eradication of BVDV requires a multidimensional approach, involving vaccination, bio-security and identification of BVDV reservoirs [3].

Therefore, the objectives of this seminar paper are:

- To review the epidemiology and diagnostic methods of bovine viral diarrhea disease and
- To provide information on the economic importance and strategies used for control and prevention of the disease.

Bovine Viral Diarrhea

Etiology: Bovine viral diarrhea virus is an enveloped, single-stranded RNA virus and is the prototypic member of the genus *Pestivirus* within the family Flaviviridae. Currently recognized species within the *Pestivirus* genus include BVDV1, BVDV2, border disease virus and classical swine fever virus (hog cholera virus). The virus is pleomorphic, spherical structures 50-60nm in diameter, with a bilaminar envelope of cellular origin surrounding a semi dense core of 20-25mm diameters. Virons mature within intracytoplasmic membranes and it is liberated by exocytosis of virus-containing membrane vesicles. Infectivity of pestiviruses is lost at elevated temperatures and by treatment with detergents and lipid solvents. The viruses can withstand a relatively broad pH range [7].

Strains of BVDV can exist as different biotypes, which are either cytopathic (CP) or noncytopathic (NCP) [8]. The classification of biotypes are independent of genotype, as there exist CP and NCP BVDV1 strains and CP and NCP BVDV2 strains. This distinction is important in the pathogenesis and understanding of mucosal disease. Cytopathic virus in tissue culture cause severe damage to the cell and complete destruction within 48-72 hours. The non-cytopathic virus causes no cell damage and is identified by staining with fluorescein-labeled BVDV antisera [2]. Cytopathic BVDV strains are relatively rare, with NCP isolates accounting for approximately 90% of BVDV isolates at a diagnostic laboratory [9]. The non cytopathic biotype is the source for CP strains, which arise by mutations and recombinations in the NCP strain. A third biotype of BVDV, the lymphocytopathic biotype, consists of a subpopulation of NCP strains that are capable of causing CP effect in lymphocytes cultured in vitro. Non cytopathic strains that are lymphocytopathic have been associated with severe clinical disease [10].

There is also genetic and antigenic variation between isolates of BVDV. Bovine viral diarrhea virus has been divided in to two groups based on genotypes BVDV type one and BVDV type two. Bovine viral diarrhea virus type two infections have been associated with a severe acute disease and a hemorrhagic syndrome characterized by thrombocytopenia and death. The significant genotypic and antigenic variations among BVDV isolates may be a factor in achieving complete control of BVDV infections through vaccination [1].

Epidemiology

Occurrence and Geographical Distribution: The bovine viral diarrhea-mucosal disease was diagnosed for the first time in the world in the USA in 1946 from a herd outbreak of acute fatal Rinderpest like syndrome with ulceration of the alimentary mucosa and diarrhea. Later, the disease was detected in different countries of the world. The disease confirmed in Egypt for the first time in 1975. Bovine viral diarrhea-mucosal disease is widely distributed in Africa, Europe, North America and the Middle East including Egypt [11]. Although prevalence was reported in European and some African countries, there is no research or published information available on the investigation of BVDV in Ethiopia [12].

Even though cattle are the primary hosts, the virus can infect most even-toed ungulates [13]. For example, sheep, goats, pigs, bison, alpacas, llamas and white-tailed deer can be infected [2].

Source of Infection and Mode of Transmission: Young cattle which are persistently infected with a non-cytopathic strain of the virus are the major source of infection in a herd [14]. Because the infection also occurs in sheep and goats, as well as swine, deer, bison and other wild ruminants, these species may also be sources of virus for initiation of infection in cattle herds [15].

Cattle persistently infected with BVDV shed large amounts of virus through their entire life and are the major source of BVDV transmission. Acutely infected cattle are also an important source of BVDV transmission, but the level of virus shed is considerably lower and the length shedding is limited. Recently, *camelid* species have been identified as being susceptible to BVDV and have emerged as a potential source of transmission to cattle [1].

Bovine viral diarrhea virus is transmitted easily from animal to animal and from herd to herd by indirect means through feed and fomites contaminated with urine, oral and nasal secretions, feces, or amniotic fluid from infected cattle [15]. The most efficient mode of transmission is direct contact with body fluids from PI cattle. Indirect transmission can occur through blood feeding insects or contaminated mechanical vectors such as common needles, nose tongs and animal care takers. Horizontal transmission has also occurred with frozen semen collected from BVDV infected bulls and inseminated into susceptible cows. Vertical transmission results with transplacental infection of the fetus in cows acutely or persistently infected with BVDV [1].

The rate of transmission of BVDV with in a herd varies depending on the source of the virus. Introduction of a PI animal into a herd can result in rapid dissemination of the virus among the majority of susceptible cattle in less than six months. Conversely, if acutely infected cattle are the source of the virus, the spread of BVDV may require an extended period [1].

Risk Factors

Animal Risk Factors: In general, young cattle are most susceptible to BVDV infection but adult cattle may develop sever disease if infected with the virulent genotypes of the virus. Cattle that are persistently infected with non cythopathic BVDV serve as a natural reservoir for virus. The calf is born infected with virus, remains infected for life and usually is immunotolerant to the resident non cythopathic virus [13]. Unvaccinated animals, improperly vaccinated animals, or animals whose immune status has waned are most susceptible to infection and the potential for clinical disease [14].

Pathogen Risk Factors: The bovine pestivirus is one of the most wide spread and important virus infections in cattle throughout the world. While only one serotype of BVDV is recognized, isolates of these viruses vary genomically, antigenically and biotypically. These pathogen characteristics are important in the pathogenesis of the various diseases associated with the virus, the immune response of the animals to different isolates of the virus and the laboratory diagnosis [14].

Environmental and Management Risk Factors: The bovine viral diarrhea virus is spread through many body fluids including saliva, respiratory secretions and feces. The virus does not persist in the environment but can survive long enough to be transmitted via infected equipment, needles and palpation sleeves [16].

The major management risk factors are the introduction of PI animals into a susceptible herds and the failure of a vaccination program or an inadequate vaccination program [14].

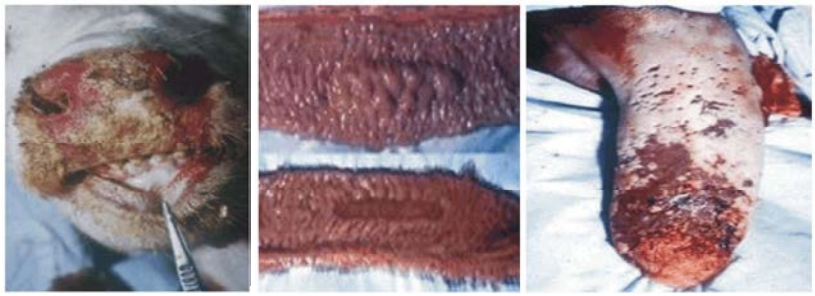
Pathogenesis: The pathogenesis and consequences of BVDV infection of cattle are dependent on the age and immune status of cattle at infection, as well as the biological properties of the infecting virus strain [6].

The virus is usually acquired by the oronasal route and initial replication occurs in the oronasal mucosa. In the subsequent viraemia, the virus spread throughout the body either free in the serum or in associated with leukocytes. Both B and T lymphocyte numbers decrease. As the virus has an immunosuppressive effect, infection may predispose calves to respiratory and enteric disease, fetal infections, which persist in the fetus until and after birth in persistently-infected cattle are also immunotolerant and may develop mucosal disease [17].

Clinical Findings: Disease induced by BVDV varies in severity, duration and organ system involved. Most BVDV infections are subclinical. Outbreaks of BVD are usually associated with high morbidity and low mortality. When present, clinical signs include inappetance, depression, fever and diarrhea [17]. Although a significant proportion of persistently-infected animals are clinically normal, some are born undersized and demonstrate retarded growth rate and poor viability [5]. Persistent infection occurs as a result of in utero exposure of the fetus to BVDV at less than 125 days of gestation. Only NCP strains of BVDV induce persistent infection [8].

Mucosal disease is usually sporadic in occurrence. It is induced when persistently infected cattle become super infected with cythopatic BVDV. Clinical signs for MD include depression, fever, profuse watery diarrhea, nasal discharge, salivation and lameness. Ulcerative lesions are present in the mouth and inter-digital clefts. Case fatality rate is 100%. Death from the mucosal disease usually occurs two to three weeks after infection with the cythopatic virus [2].

Generally, signs of BVD illness include recumbency, dehydration; reduce lactation, cessation of rumination, conjunctivitis, congestion, ulceration in the mucous membrane of the oral cavity and reproductive problems



A B C

Fig. 1: Ulcerated nose and mouth (A), above is a normal Peyer's Patch and below is a necrotic Patch(B) and ulcerated tongue(C) of a cow with mucosal disease [18]

(abortion, teratogenesis) in pregnant cows. Severely affected cattle have a high temperature (40°C to 41.5°C) and a leucopenia. A relatively more severe BVDV-associated disease in calves has been recently recognized, characterized by severe thrombocytopenia and hemorrhage of mucosal surfaces and internal organs (Hirsh and Zee, 1999). Laboratory-indicated changes that may occur with BVDV include leucopenia, neutropenia and thrombocytopenia. Animals with chronic mucosal disease may also have anemia [1].

Pathological Lesions: Cattle suffering from BVD and MD show lesions in the alimentary tract. The pathological changes in MD are much more severe than in BVD, the MD lesions are often found only in the upper alimentary tract. In both BVD and MD, pathological changes consist mainly of erosions and ulcers of varying severity [18].

In those few cattle that die off acute bovine viral diarrhea virus infection, gross lesions characteristically include erosive or ulcerative lesions extending from the mouth through the esophagus, fore stomachs, abomasums and intestine. In the intestine discoloration of mucosal folds due to hyperemia and hemorrhage may occur, giving a striped appearance to the luminal surface [15].

The post mortem findings are usually strongly suggestive of mucosal disease and vary depending on the acuteness and chronicity of the disease [1, 2]. In case of Acute Mucosal Disease, erosions and ulcerations may be found throughout the gastrointestinal tract. The mucosa over payer's patches may be hemorrhagic and necrotic. Extensive necrosis of lymphoid tissues, especially gut- associated lymphoid tissue, is seen on microscopic examination .While in Chronic case Lesions found at necropsy are less pronounced than, but similar to, those seen in acute mucosal disease [13]. The necrotic epithelium may not be eroded by alimentary movements but instead remain in situ as slightly elevated, yellow, friable plaque, especially on the tongue and the rumen [14].

Diagnosis: Bovine viral diarrhea is diagnosed tentatively from disease history, clinical signs and gross and microscopic lesions [12]. When present, oral lesions are especially suggestive of this disease [15]. The clinical diagnosis of MD is usually made on the basis of the presence of characteristic clinical and pathological findings [14].

Many diagnostic tests are available for BVDV detection and the choice of test depends on the clinical problem, the local availability of tests and financial considerations. The majority of diagnostic tests developed are used to identify PI animals. Isolation of BVDV in cell cultures using validated methodology is the gold standard for diagnosis of BVDV infection [19]. Thus, Diagnostic laboratory support is required when clinical signs and gross lesions are minimal. Because of the greater expense and time taken to report a result for this method, antigen detection or nucleic acid detection has largely replaced virus isolation for diagnosis of BVDV infection. The virus can be cultured and isolated from a variety of samples including serum, whole blood, semen, nasal swabs and various tissues. Buffy coat cells from whole blood are the preferred sample for ante-mortem diagnosis, whereas lymphoid organ-related tissues are preferred samples from necropsies Spleen and lesions from gastrointestinal tract are also suitable for laboratory examinations [20].

Laboratory diagnosis is based on virus isolation in cell culture, viral antigen detection in tissues, detection of viral RNA in tissues by the reverse transcription-polymerase chain reaction (RT-PCR) and serology. Immunofluorescence may be used to detect viral antigen in cell cultures and tissues. Paired acute and convalescent sera may be tested by a neutralization test, but interpretation of negative results must be made with an application of the immunologically tolerant state of some cattle [15].

Screening young calves for PI status is best accomplished by PCR (Polymerase chain reaction), ACE (Antigen capture enzyme-linked immunosorbent assay), or IHC (Immuno histochemical) on skin samples. The use of skin samples for testing young calves is advantageous in that sample collection is simple, samples can be taken from calves that have maternal antibodies and a single positive test usually indicates PI status. Because the occasional acutely infected animal might be PCR, IHC, or ACE positive [21]. valuable cattle should be retested after 30 days using virus isolation or RT-PCR assays on blood samples. Because of high sensitivity, RT-PCR assays using pooled samples have been developed to screen herds for PI animals [22].

Pooled samples of serum, whole blood, bulk tank milk and skin have been utilized in RT-PCR assays [21, 22]. Pooled sample testing by RT-PCR is rapid and cost-effective for screening populations of cattle for PI animals. However, failed attempts to replicate this work in multiple laboratories indicate the sensitivity of the assay to changes in sample handling or operator variability. Subsequent testing of individuals within the positive pools can be performed by IHC, ACE, virus isolation, or RT-PCR methods [3].

Differential Diagnosis: Similarities in clinical signs and lesions require differentiation of BVDV infection from Malignant Catarrhal Fever (MCF), Foot and Mouth Disease (FMD), Para poxvirus disease (Bovine popular Stomatitis), Herpes virus infections (Cervid herpesvirus1, bovine herpesvirus1, caprine herpesvirus1 and rangifer herpesvirus1), Salmonellosis, Enzootic Keratoconjunctivitis, Blue Tongue, Epizootic hemorrhagic disease and enteritis caused by gastrointestinal parasites [23]. Malignant catarrhal fever is usually a sporadic disease in more mature cattle. A corn poisoning can look similar on post-mortem, but biochemistry and histology of the kidney should distinguish it from mucosal disease. Other poisoning events may also be considered as differential diagnosis, but the characteristics oral erosions are generally absent. The main features of MD are mucosal erosions, diarrhea and death. Foot and Mouth Disease and Malignant Catarrhal Fever are the principal differential diagnoses [2].

Treatment: No specific treatment is available for animals showing clinical sings of BVDV infection. Owners should be informed that severely ill animals may have mucosal disease, which normally is fatal. The goals of therapy for cattle suspected of having acute BVDV infection are supportive care and prevention of secondary bacterial infection. Broad-spectrum antimicrobial agents, fluids, electrolytes and vitamins may be indicated [1].

Economic Importance: The bovine viral diarrhea virus causes acute clinical disease, but subclinical infections in dairy herds may be major causes of economic loss because of decreased milk production and more severe respiratory disease in calves. Following the development of improved diagnostic and research techniques, BVDV has now been shown to be associated with significant reproductive loss in cattle. The economic losses associated with the introduction of BVDV into a susceptible herd of pregnant cattle are due to abortion, congenital defects, still births, increased neonatal mortality, increase occurrence of other infectious disease, prenatal and post natal growth retardation, suboptimal reproduction performance due to infertility, death from MD and the early disposal of PI animals [14].

Prevention and Control: The economic importance of BVD is clear, especially in feed lots and dairy herds, but control is far from satisfactory. The major objective of control measures is to prevent the further occurrence of persistently infected cattle in the herd. This requires the identification and elimination of such animals and the avoidance of further introductions by quarantine; this is expensive, as it requires a serological survey of the herd and attempted virus isolation from sero-negative animals [15].

Development and implementation of herd health programs that limit exposure of pregnant cattle to BVDV are important for successful control. When developing a BVDV prevention and control program, three aspects should be considered these are: identification and elimination of PI animals, enhancing immunity through

vaccination and implementing bio-security measures to prevent BVDV exposure of susceptible cattle. Each of these three principles has been applied to BVDV control and greater success can be expected when used simultaneously in BVDV control programs [23].

Identification and Elimination of Persistently Infected Cattle: Eliminating pathogen reservoirs and limiting transmission from infected individuals to susceptible animals are the major principles for infectious disease control. Persistently infected cattle are the major reservoir of BVDV, although transiently infected animals can, to a lesser extent, also serve as a reservoir. Therefore, prevention or elimination of PIs is central to BVDV control [23]. Removal of PI animals should occur before their entry into breeding herds. This can be more easily achieved in beef cow-calf operations that follow a controlled breeding season. In this situation, all calves, replacement heifers, bulls and non pregnant cows without calves should be tested for PI status [24]. Because PI cows always produce PI calves, a negative test result of a calf indicates a negative PI status for the dam [25].

Dams of test-positive calves need to be tested for PI status. Most PI calves result from acute infection of their dam, so dams that test negative could re-enter the breeding herd. If pregnant cattle are present at the time of testing in herds with a controlled breeding season, they should be segregated and their calves be tested before return to the breeding herd. In herds without a controlled breeding season, young calves should be tested and removed as soon as possible to avoid transmission to the breeding herd [21].

Vaccination: Vaccines are an important component to BVDV prevention and their effectiveness has been to limit transmission and clinical disease rather than completely prevent infections with BVDV, as it has been demonstrated in experimental and field studies using either inactivated or modified-live BVDV vaccines [26].

Many vaccines or vaccine combinations are available for BVDV and the majority of these USDA (United States department of agriculture) licensed vaccines contain BVDV in combination with other bovine respiratory and reproductive pathogens. In the past, most BVDV vaccines contained only BVDV1 strains, but because of antigenic diversity, modified-live and inactivated vaccines containing both BVDV1 and BVDV2 strains are now widely available. There are advantages and disadvantages to use of BVDV modified-live viral vaccines and inactivated vaccines [9]. One disadvantage of inactivated BVDV vaccines is that two doses are required for the initial immunization and a major problem with programs using inactivated vaccines is the widespread lack of compliance among producers by failing to booster the primary series [27].

Protection from clinical disease is important for stocker/backgrounder and feedlot operations and cattle that arrive at a feedlot with antibody titers to BVDV tend to have protective immunity against bovine respiratory disease complex [25]. Preconditioning cattle by pre-weaning and vaccinating against BVDV and other respiratory pathogens before commingling and shipping reduces the incidence of bovine respiratory disease in feedlot cattle [28].

Vaccination against BVDV should protect against viraemia and prevent dissemination of virus throughout the host, including preventing infection of the reproductive tract and fetus. The focus for vaccine efficacy has shifted from protection against clinical disease to protection against fetal infection. Protection against fetal infections after BVDV vaccination varies, being influenced by use of inactivated or modified-live vaccine, the timing of challenge and the degree of homology between vaccine and challenge strains. Fetal protection is superior when animals are challenged with strains from the same genotype. Although protection is not 100%, the level of protection is superior to that observed when proper vaccination is not utilized as evidenced by higher rates of PI animals in unvaccinated cattle [3].

Bio-Security: After the elimination of PI animals, strict bio-security is essential to prevent reintroduction of the virus. All purchased cattle should be isolated and tested for PI status before entry into the herd. Isolation of new additions for three weeks before entry into the resident herd should prevent transmission of BVDV from acutely infected animals. Most lapses in herd bio-security involve purchasing PI cattle or purchasing pregnant cattle with unknown BVDV status of the fetus. Purchased pregnant cattle should be isolated and their offspring tested to ensure that they are free of BVDV. Semen should only be used from bulls that have been tested for BVDV infection. For purebred herds marketing valuable embryos and livestock, testing of embryo transplantation recipients for PI status is essential. Exposure of cattle to other

ruminants at exhibitions should be limited and animals should be quarantined for three weeks before reentry into the breeding herd [3].

Bulls that are purchased and brought on to the farm from outside sources pose a significant risk of infection to herds that are otherwise closed. It is possible that the disease may be transmitted from other ruminants, so maintaining separation between such animals and susceptible cattle is recommended [29]. Most bio-security principles instituted for BVDV control will benefit disease control of other pathogens. Further bio-security principles include elimination of fence-line contact with neighboring livestock and sanitation of equipment and people entering the farm [3].

CONCLUSION AND RECOMMENDATIONS

Bovine Viral Diarrhea is one of the most economically important OIE list diseases of cattle, which is caused by bovine viral diarrhea virus. Although prevalence was reported in European and some African countries, there is no research or published information available on the investigation of BVDV in Ethiopia. The virus affects the immune, respiratory, reproductive and enteric systems. Not only PI animals shed BVDV and serve as a source of infections for other animals, but also managmental factors can predispose animals to this disease. The agent can be transmitted from infected animals to non-infected animals in different ways such as vertically and horizontally. Clinically, the disease is difficult to diagnose because the clinical signs vary from subclinical to fatal mucosal disease and confuse with other diseases that produce diarrhea and mucosal lesions. Since there is no treatment for BVDV infection as a result it leads to a huge economic loss. Control and prevention measures are very important to avoid the occurrence of PI cattle in the herd. Therefore, based on the above conclusion the following recommendations are forwarded:

- The epidemiology of BVD in various geographic areas should be studied further.
- Even if it is not yet reported in Ethiopia it does not mean that the disease is absent in this country so that attention should be in place.
- Clinically, the disease should be considered with other diseases that produce diarrhea and mucosal lesions.

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