Infectious Bovine Rhinotracheitis

S. van Drunen Littel - van den Hurk

Take Home Message

Bovine herpesvirus-1 (BHV-1), the causative agent of infectious bovine rhinotracheitis (IBR), is a major feedlot pathogen, which can cause substantial economic losses to the cattle industry. Since IBR is common and highly contagious, control through vaccination is essential. Modified-live viral vaccines, although unsafe under certain conditions, are the most effective for prevention of IBR in the feedlot. New generation 'marker' BHV-1 vaccines are under development, which promise to be at least as effective, safer and usable in cattle destined for export.

Introduction

Infectious bovine rhinotracheitis (IBR) is caused by bovine herpesvirus-1 (BHV-1) and is recognized as one of the major cattle diseases of economic importance. Because BHV-1 can infect a number of tissues in the body, there are five distinct disease syndromes. In addition to causing respiratory disease, BHV-1 can cause conjunctivitis (red eye), infectious pustular vulvovaginitis or balanoposthitis (IPV; genital disease in both females and males), abortions, and encephalitis (brain infections) ([1], [2]). In newborn calves, the virus can cause generalized systemic infections. BHV-1 has also been suggested to be the major viral pathogen involved in the development of the complex respiratory disease syndrome called 'shipping fever' ([3]). Consequently, the respiratory disease form, alone or in combination with other pathogens, causes heavy economic losses among feedlot cattle due to reduced weight gain, cost of treatment and death loss. Factors influencing the type and severity of the clinical syndromes caused by BHV-1 include the strain of virus, its evolutionary history, dose and route of exposure, the immunological status of the host and environmental influences like management practices.

Subsequent to primary BHV-1 infection, the virus establishes latent infection in nerve tissue, meaning that the animal is then infected for life. It can be reactivated by factors like stress, inclement weather, transport, treatment with steroids or

calving, and re-excreted (**4**). Although carrier animals generally do not develop fever or clinical disease following virus reactivation, they may shed large amounts of infectious virus in nasal and other secretions. Thus, reactivation of latent virus is thought to be responsible for the survival of the virus in cattle populations (**5**).

Epidemiology

In feedlots, IBR is commonly observed and may be associated with eye infections (conjunctivitis), abortions or secondary bacterial infections. Although all ages and breeds of cattle are susceptible to IBR, the disease is most common in calves over six months of age, at which time the immunity received through the dam's colostrum declines and the exposure to the virus increases. Outbreaks usually occur in fall and winter when large numbers of susceptible animals are mixed together and confined in feedlots.

BHV-1 is highly contagious, specifically under circumstances whereby susceptible calves are in close contact. Consequently, the virus may spread very efficiently under conditions of crowding and mixing in the feedlots. Additional factors contributing to the high incidence of IBR infections in feedlots include high stress levels due to weaning and transport, as well as the simultaneous exposure to multiple pathogens upon arrival. Transmission occurs through nasal secretions, saliva and aerosol droplets containing the virus. Outbreaks of disease occur through introduction of infected animals into a feedlot or herd or by reactivation of latent virus already present in feedlot calves, which then spreads to newly arrived, susceptible animals. An outbreak of IBR usually lasts for two to four weeks.

Clinical Signs

The respiratory form (IBR) is by far the most significant and economically important manifestation of BHV-1 infection, specifically in feedlots. Acute IBR is characterized by a combination of clinical signs like rapid breathing, inappetence, temperatures of 40-42°C (104-108°F), coughing, nasal discharge, foamy salivation, open-mouth breathing, tearing, severe inflammation of the nasal passages (red nose) and tissue surrounding the eyes (conjunctivitis), and loss of weight and condition (**Photo 1**). The course of an uncomplicated IBR infection lasts 7 to 10 days. However, IBR may have several sequelae. The infection in calves 4-6 months of age has resulted occasionally in meningitis, with signs indicating central nervous system involvement, and cows may abort,

Photo 1: Nasal discharge typical of IBR.

particularly if exposure occurs between 5.5 and 7.5 months of gestation. Frequently, IBR is followed by secondary bacterial infections, like *Pasteurella haemolytica*, which results in severe pneumonia and, sometimes, death.

Although infrequent, IBR can occur in young calves and cause either severe respiratory disease or fatal systemic disease and rapid death. Neonatal IBR infections probably occur due to lack of maternal immunity and are complicated by a number of management factors (nutrition, stress, other diseases).

In unvaccinated, susceptible populations, IBR commonly affects 20 to 30% or more of exposed animals. Although the mortality rate due to uncomplicated IBR is low, averaging from 1 to 2%, secondary bacterial infections may lead to severe pneumonia and death. Whereas reduced weight gain is the major economic loss among beef calves, losses in dairy animals are usually due to reduced milk yield, abortion and disease in newborn calves. Mortality is mostly the result of secondary bacterial infections in both beef and dairy cattle.

Diagnosis and Treatment

With experience, a diagnosis of uncomplicated IBR can usually be made based on the clinical signs, pattern of onset and lesions. However, this diagnosis should be confirmed by laboratory tests. BHV-1 can be easily isolated from swabs from all lesions, since the virus grows well in bovine cells in culture. Since maximal virus replication and shedding occurs between three and six days after infection, swabs for virus isolation should be taken early in the course of the disease. The swabs should be kept cool and shipped as quickly as possible to the diagnostic laboratory. A number of diagnostic tests are available. Among them is the specific and sensitive method known as the polymerase chain reaction (PCR). With this method it is possible to detect very small quantities of virus in nasal secretions or tissue. Because of its high sensitivity, this technique may specifically find important application as a detection method of BHV-1 in bovine semen. One of the most relevant diagnostic tools for the detection of BHV-1 infected herds is still serology using virus neutralization (VN) tests or enzyme-linked immunosorbent assays (ELISAs). Preferably,

two blood samples should be taken, one at the onset of disease and the other three weeks later. A four-fold increase in BHV-1 specific serum antibody titre should be considered diagnostic of an active BHV-1 infection.

Since there are no antiviral agents commercially available, treatment of IBR is symptomatic. During an outbreak of IBR, sick animals should be identified and isolated. Depending on the severity of the disease, infected calves may be treated with a broad-spectrum antibiotic to reduce the risk of secondary bacterial infections (**6**). During an outbreak it is not advisable to introduce susceptible cattle. Animals of unknown vaccination status should be vaccinated immediately upon arrival and housed separately from the rest of the animals.

Prevention and Control

Go To Update

Prevention and control of IBR is mainly dependent on development of immunity to BHV-1, which occurs following natural exposure or vaccination. Since BHV-1 is a ubiquitous, highly contagious virus, vaccination is recommended as soon as passive immunity in calves has disappeared, usually around four to six months of age. Currently available vaccines for IBR include modified-live-virus (MLV) vaccines and inactivated or killed-virus (KV) vaccines.

Several MLV vaccines are available for intranasal or intramuscular immunization as single or combination products. Live viral vaccines offer several advantages, namely the induction of a rapid immune response, relatively long duration of immunity and the induction of local mucosal immunity. Protection from BHV-1 has been observed within 40-96 hours after intranasal (**7**) or intramuscular (**8**) vaccination with MLV vaccines. In order to induce maximal protection, vaccination at least three weeks before exposure to BHV-1 is recommended. If this is not possible, the next best time to vaccinate is on feedlot entry. The first IBR vaccines developed were MLV vaccines for intramuscular use, which are easy to administer. However, some intramuscular MLV vaccines can cause abortions, so these vaccines should not be used in or around pregnant cattle. More recently developed MLV vaccines are meant to be administered intranasally and usually are less virulent, which makes them safe for use in pregnant cattle. Administration of intranasal vaccine may be difficult because head restraint is required. In addition, care must be taken that the full dose of vaccine reaches the nasal passages, which may be time consuming. The duration of the immune responses induced by BHV-1 MLV vaccines has not been adequately studied, so most pharmaceutical companies

recommend annual re-vaccination. In the feedlot, revaccination at reimplanting (60-70 days post-arrival) may be necessary if outbreaks of IBR have occurred at this time post-arrival. Since MLV vaccines replicate, they can induce persistent infections, like the wild-type virus.

Because of the disadvantages of using MLV vaccines under certain conditions, killed or inactivated virus vaccines may need to be used in certain circumstances. Killed BHV-1 vaccines should be administered twice with a three to four week interval. Annual and maybe more frequent revaccination is necessary. The main advantage of using inactivated vaccine is the safety including the absence of virus shedding, risk of abortions or establishment of persistent infection. However, the immunity to killed BHV-1 vaccines is generally of shorter duration and there is controversy regarding their effectiveness in the feedlot.

The timing of vaccination is at least as important as the choice of vaccine. Since maximum protection does not generally occur until approximately three weeks after vaccination, calves should be vaccinated two to three weeks before weaning at which time they start to be at risk of infection. A single vaccination will reduce the severity of disease, but not provide complete protection. It is recommended to re-vaccinate upon arrival in the feedlot and again 60-70 days post-arrival if disease is observed at that time in the feeding period. In cow/calf herds and dairy herds, replacement heifers should be vaccinated at five to six months of age and again at least two weeks before breeding (**9**).

Future BHV-1 Vaccines

Go To Update

The use of improved molecular biological and immunological technology has led to a much better understanding of the pathogenesis of BHV-1. By identifying factors associated with virulence and protective components of BHV-1, it is now possible to design and develop more efficacious and safer vaccines. A BHV-1 subunit vaccine, containing the major protective component of BHV-1 in an effective adjuvant, has been shown to be more efficacious than current MLV or KV vaccines (**10**). This vaccine induces strong immune responses, which mediate protection from BHV-1. Subunit vaccines have all the safety features of killed BHV-1 vaccines, but at the same time, are more efficacious due to a defined antigen load, the absence of potentially suppressive components and no need for chemical inactivation. This vaccine is currently at the stage of commercial development.

A novel approach to the generation of modified-live vaccines is based on the knowledge of virulence genes of BHV-1, some of which are not essential for the virus to grow, and thus can be deleted or modified. Several experimental vaccines have been developed using this approach (**11**). Gene-deleted BHV-1 vaccines are at least as effective as the current MLV vaccines, but safer.

Another novel and potentially very powerful approach for evoking an immune response in animals is based on immunization with noninfectious DNA. By injecting DNA, responsible for production of protective antigens, directly into animals, these antigens are produced in the animal's cells. The animal develops an immune response against these proteins and is protected from infection (**12**). Although in a very early stage of development, this approach is very promising. By using DNA immunization, it may be possible to immunize at an early age, use one dose of a multi-component vaccine and expect to see life-long immunity in cattle.

These types of BHV-1 vaccines not only provide protection from infection, but they can also be identified in vaccinated animals as a 'marked' vaccine. Animals immunized with subunit, DNA or gene-deleted marker vaccines can be differentiated from carrier animals with a companion diagnostic assay. This is important for export of cattle to countries that only permit import of seronegative animals. In addition, should eradication of BHV-1 become a priority, each of these recombinant vaccines could be used to achieve this goal.

Conclusion

IBR, which may predispose cattle to potentially fatal bacterial pneumonia, is a major cause of economic losses to the beef cattle industry. Vaccination has been the most important strategy to prevent and control IBR infections in cattle. For vaccination to be optimally effective, the timing is critical such that the animals are sufficiently protected upon entry into a high-risk situation. Therefore, animals should be vaccinated at least three weeks prior to feedlot entry, as well as immediately afterwards, because two doses of any of the currently available vaccines are needed for complete protection. Revaccination at reimplanting may be necessary if outbreaks of IBR have occurred post-arrival in the feedlot. Once highly effective novel 'marker' vaccines become commercially available, these vaccines should be used, specifically for bulls to be sent to artificial insemination units and cattle destined for export.

References

1. Wyler, R., Engels, M. and Schwyzer, M. 1989. Infectious bovine rhinotracheitis/vulvovaginitis (BHV-1). In: Herpesvirus Diseases of cattle, horses and pigs. Developments in Veterinary Virology. G. Wittmann (ed.). Kluwer Academic Publications, Boston, USA.

2. Gibbs, E.P. and Rweyemamu, M.M. 1977. Bovine herpesviruses, part 1. Vet. Bull. 47: 317-343.

3. Yates, W.D.G. 1982. A review of infectious bovine rhinotracheitis, shipping fever pneumonia and viral-bacterial synergism in respiratory disease of cattle. Can. J. Comp. Med. 46: 225-263.

4. Sheffy, B.E. and Davies, D.H. 1972. Reactivation of bovine herpesvirus after corticosteroid treatment. Proc. Soc. Exp. Biol. Med. 140: 974-976.

5. Pastoret, P.P., Babiuk, L.A., Misra, V. and Griebel, P. 1980. Reactivation of temperature-sensitive and non-temperature-sensitive infectious bovine rhinotracheitis with dexamethasone. Infect. Immun. 29: 483-488.

6. Kahrs, R.F. 1977. Infectious bovine rhinotracheitis: A review and update. J.A.V.M.A. 171: 2055-2064.

7. Todd, J.D., Volence, F.J. and Paton, I.M. 1972. Interferon in nasal secretions and sera of calves after intranasal administration of avirulent infectious bovine rhinotracheitis virus: Association of interferon in nasal secretions with early resistance to challenge with virulent virus. Infect. Immun. 5: 699-706.

8. Sutton, M.L. 1980. Rapid onset of immunity in cattle after intramuscular injection of a modified-live virus IBR vaccine. Vet. Med. 75: 1447-1456.

9. Hjerpe, C.A. 1990. Bovine vaccines and herd vaccination programs. Vet. Clin. N. Am. Food Anim. Pract. 6: 188-194.

10. Van Drunen Littel-van den Hurk, S., Tikoo, S.K., van den Hurk, J.V., Babiuk, L.A. and Van Donkersgoed, J. 1996. Protective immunity in cattle following vaccination with conventional and marker bovine herpesvirus-1 (BHV1) vaccines. Vaccine. In press.

11. Van Drunen Littel-van den Hurk, S., Tikoo, S.K., Liang, X. and Babiuk, L.A. 1993. Bovine herpesvirus-1 vaccines. Immunology and Cell Biology 71: 405-420.

12. Cox, G.J.M., Zamb., T.J. and Babiuk, L.A. 1993. Bovine herpesvirus-1: Immune responses in mice and cattle injected with plasmid DNA. J. Virol. 67: 5664-5667.