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PATHOGENESIS AND EPIDEMIOLOGY OF BOVINE VIRUS DIARRHOEA VIRUS INFECTION OF CATTLE

BROWNlie J, CLARKE MC, HOWARD CJ and POCKOCk DH

A F R C Institute for Animal Disease Research, Compton, Newbury, Berkshire, RG16 ONN, UK

meeting on Pestivirus, 8th April 1986, Liège

The first report of disease associated with bovine virus diarrhoea virus (BVDV) was of a highly infectious diarrhoea in cattle of all ages (Olafson et al 1946). The diarrhoea was transitory and, although most animals soon recovered, 4-8 % died of the condition, subsequently called mucosal disease (Ramsey and Chivers 1953). In the latter report, mucosal disease was invariably fatal and extensive ulceration of the mucosa of the gastro-intestinal tract occurred. The viruses isolated from both conditions were shown to be serologically similar in experimental infections and gave the same mild diarrhoea (Gillespie et al 1961, Pritchard 1963, Thomson and Savan 1963) but not fatal mucosal disease.

Clinical evidence accumulated from outbreaks of disease showed that abortions were a consistent finding (Olafson et al 1946, Dow et al 1956) and later the transplacental transfer of virus to the foetus was shown experimentally (Casaro et al 1971, Kahrs 1973). The outcome of foetal infection depended on the stage of gestation; in early pregnancy it could result in abortion or stillbirth, whereas later the foetus could make antibody and be born perfectly normal. Another sequel of early infection occurred when the virus became established before the foetus developed immunocompetence at around 120 days; in these cases the virus persisted into postnatal life (Thomson and Savan 1963, Malmquist 1968). Immuno tolerance to the virus was confirmed by the lack of specific antibody in either the developing foetus or the postnatal calf and it was only these animals, that were persistently viraemic, which subsequently developed mucosal disease (Liess et al 1974). However, the aetiology of mucosal disease remained unknown until it was reproduced experimentally (Brownlie et al 1984, Bolin et al 1985).

Clinical disease

The considerable variation and severity of the clinical diseases which follow infection with BVDV is matched by the complexity of their aetiology (Brownlie 1985). This has caused much confusion and a better understanding has had to await experimental and epidemiological studies. At present, the clinical diseases can be separated as follows:
Acute disease

Acute disease represents the infection of seronegative cattle with BVDV. In the original description, there were explosive outbreaks of diarrhoea but low mortality. This type of outbreak is now rarely seen in the UK and most acute infections are mild if not subclinical. Experimental infection of calves produces a similar mild disease, sometimes with a transient leucopenia, and some animals may show a rise in temperature. In both, natural and experimental infections antibodies are produced in two to three weeks and the animal appears immune to rechallenge.

In utero infection

The first isolates of BVDV were non-cytopathic but cytopathic strains were later detected (Underdahl et al 1957, Gillespie et al 1960) and it is now known that the virus can be distinguished in cell culture by this difference. Central to the development of the remaining clinical diseases is the in utero infection of the foetus with a non-cytopathic form of BVDV. This virus can cross the placenta and infect the foetus at any age. If infection is before 120 days of gestation then the virus may persist. The immune system is not functional before this time and the virus can become widely established in foetal tissue. Subsequently, although the immune system becomes competent, it recognises the virus as «self» and a state of immunotolerance develops. It is this tolerance, demonstrated by the lack of specific antibody, that allows the virus to persist into post-natal life. However, it is interesting to note that there is no evidence, from either field or experimental work, that a persistent viraemia occurs with cytopathic virus.

Another outcome of in utero infection is abortion (Kendrick 1971, Done et al 1980), mummified foetuses (figure 1), or stillbirths. These are not thought to be associated with BVDV infection at the time but retrospective inquiries, following a case of mucosal disease, will often reveal a series of previous abortions and births of dead calves. Some calves may be so weak at birth that they die within the first few days of life and the virus is a possible cause of the «weakly calf syndrome». Similarly, there may have been an infertility problem or increased return to service caused by early embryonic loss.

All offspring from a persistently infected dam are likely to be persistently viraemic and if the dam does not succumb to mucosal disease, families of viraemic animals can be produced.

Mucosal disease

Mucosal disease usually occurs in 6 to 24 month old cattle and is invariably fatal. The first clinical sign is usually anorexia. Close inspection may reveal erosions in the mouth and occasionally on the coronet of the foot. There can be excessive salivation and nasal discharge. The animal is disinclined to walk and becomes recumbent. There is often profuse diarrhoea and invariable death. Death can be so sudden that it may be the first clinical sign and poisoning is immediately suspected, but normally the animal dies three to 10 days after the onset of disease.

Fig. 1. — Mummified foetus aborted following in utero infection with non-cytopathic BVDV.
Post mortem examination of suspected cases of mucosal disease can reveal immediate and valuable evidence for a correct diagnosis. Erosions can be present at most sites within the gastrointestinal tract, but most characteristic are those on the epithelium of the small intestine, overlying Peyer’s patches (fig 2).

These erosions can vary in type from acutely congested and haemorrhagic to chronically flattened and catarrhal. In the large bowel, there may be congestion of the mucosa which gives a thickening to the mucosal folds and a striped appearance. The contents are often dark and watery and may be foul smelling.

**Pathogenesis**

The development of disease associated with BVDV depends on both the virulence of the virus and the susceptibility of the host. A substantial amount of work has been devoted to descriptions of clinical disease but there still remains much to understand about its pathogenesis. For instance, there can be episodes of clinical disease following acute infection which have not been adequately explained by experimental studies. A summary of the association of clinical disease with BVDV infection can be seen in table 1.

**Acute disease**

Most infections of animals with BVDV go unnoticed and are confirmed only on serological evidence. Animals that are seronegative have a transient viraemia and virus may be detected in their blood from about days 4-7 following infection. There is a specific antibody response which develops slowly, starting at about the second week and reaching a maximum around weeks 10-12. Once immune, the animal appears to have lifelong resistance to further disease caused by BVDV but may show evidence of subsequent infections by further serological response.

Likewise, acute experimental infection with BVDV has only reproduced a mild or subclinical disease. Some reports have shown that there may be a transient leucopenia at about the time of viraemia but the significance of this may only be observed when there is a complicating mixed infection. There are, however, reports from field outbreaks that acute BVDV infection can cause clinical disease with anorexia, a temporary loss of milk production and even diarrhoea. This has not been reproduced experimentally and thus the role for mixed infections of BVDV and another pathogen awaits clarification.

A consequence of vireamia during early pregnancy is the transmission of virus across the placenta to the developing foetus. This does not
Fig. 3. — Hypothesis for the aetiology of Mucosal disease.
occur in those animals with antibody and provides good evidence for protection against viraemic spread of BVDV in seropositive animals.

**Chronic disease**

There are reports of animals with BVDV infections showing protracted disease over several weeks with progressive wastage and often diarrhoea. This is the basis for the description of chronic disease, but the precise pathogenesis in virological and immunological terms has yet to be defined. It is not known whether these chronically affected animals are always persistently viraemic and have then been superinfected with another pathogen or even a further isolate of BVDV. Our own unpublished observations have shown that a «chronic» type of wasting disease can be reproduced by superinfecting a persistently viraemic animal with a «heterologous» cytopathic BVDV isolate. This preliminary observation has to be confirmed.

**Mucosal disease**

The experimental production of the fatal mucosal disease supports our hypothesis that both non-cytopathic and cytopathic BVDV are required for the pathogenesis of this disease (Brownlie et al 1984). The proposed mechanism for pathogenesis is that initial infection of the pregnant cow occurs with a non-cytopathic form of BVDV before 120 days of gestation and induces immunotolerance to the virus; this permits the virus to persist in the calf after it is born. Then, the animals that survive this period can later (usually 6-24 months)

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**Fig. 4.** — Serum neutralising antibody in 5 animals from birth to 3 years.

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be superinfected with a cytopathic form of the same virus. This virus grows unhindered by any immunity as a result of the tolerance and the animal invariably dies demonstrating diarrhoea and severe damage to the lining (the mucosa) of the gut. This is Mucosal disease (fig 3).

### Epidemiology

There is little doubt that BVDV is widespread in the national herd in Britain, as well as in other countries. The level of seroconversion indicates that over 70% of cattle have been infected by the age of 1 year and yet, the evidence of associated clinical disease is far less (Harkness et al 1978, Stott et al 1980). Once an animal has produced antibodies, it appears to be immune to BVDV-induced disease for its lifetime. There is little evidence for virus shedding in such animals and, under normal conditions, they appear to play no further part in maintaining the disease. However, there is an interesting report that BVDV can be reisolated from the ovaries of cattle many months after they have seroconverted, although there is no evidence of persistent viraemia (Ssentongo et al 1980).

The separation of BVDV into non-cytopathic and cytopathic forms and the realisation of their substantive roles in the aetiology of mucosal disease raises two important questions relevant to the epidemiology: maintenance of non-cytopathic BVDV and origin of cytopathic BVDV.

1. **Maintenance of non-cytopathic BVDV**

The natural spread of virus appears to be by direct contact between animals. There is a transient viraemia and virus is excreted in all secretions such as nasal, lacrimal and urinal, although it is notable that faeces are a poor source of virus for the detection of excretors even when there is severe damage to the gut. The period of excretion following acute infection is from about day 4 to day 10, but the virus may be recovered from nasal swabs up to about day 19 after infection. Virus has been reported to reside in the lungs and bronchial nodes up to 56 days post inoculation (Mills...
and Luginbuhl 1968). By this means, a closely confined group of cattle can maintain the virus until all have become immune. At this point, there would be no further susceptible hosts and as a result, the virus would no longer be excreted. Thus within a group of cattle, there is the likelihood of an initial spread of virus followed by immunity and the subsequent elimination of that virus. When the virus has been eliminated and if there is no new introduction of infected cattle, a herd can become virus-free and, within a generation, antibody negative. This may be how many of the closed herds contain cattle free of BVDV antibody. Unfortunately, it is these antibody-free closed herds that are highly susceptible to the introduction of virus. It is not uncommon for the infection to be introduced by recently purchased heifers or a new bull, with either a transient or a persistent viraemia, as both of these types of animal may be mixed with resident cattle in early pregnancy (Roeder and Drew 1984). This is the time when infection causes greatest damage to the developing fetus.

It is possible that BVDV may become latent in those cattle that have been infected and subsequently immune but, at present, there is limited evidence for this (Ssentongo et al 1980).

The chance of spread of BVDV is that much greater when the infected animal introduced to the herd is persistently viraemic. The presence of such an animal maintains a continual source of virus within the herd. These animals constantly excrete high levels of virus in all their secretions and may be the major reason for maintenance of infection within the national herd. They are not always recognisable on clinical examination but can represent about 0.5-1 % of the cattle population (Meyling 1984, Howard et al 1986b). The incidence of persistent infection may not appear great in the national herd but on the individual farm it can be far greater and cause considerable loss in 60 % loss of replacement cattle.

A longitudinal study of 9 calves at this Institute was conducted to examine the decline of maternal antibody and the subsequent active seroconversion to BVDV (Clarke, Brownlie, Howard and Stott, unpublished material). All calves received colostrum which contained antibodies to the virus. Four of the calves had been born on one of the Institute farms and five on another. By the time these calves were collected into a single heifer pool at about 6 months of age, the group of five calves had actively seroconverted (fig 4). However, the other four calves had not done so and remained seronegative for up to 2 years. In that

**HOMOLOGOUS**

\[ \text{BVDVnc} \]

mutation to \[ \text{BVDVc} \]

\[ \text{Mucosal Disease} \]

**HETEROLOGOUS**

\[ \text{BVDVnc} \]

\[ \text{Outside} \]

\[ \text{BVDVc} \]

\[ \text{Antibody Response} \]

**BVDVnc** = noncytopathic

**BVDVc** = cytopathic

Fig. 6. — The possible outcome following "homologous" and "heterologous" cytopathic BVDV superinfection of persistently viraemic animals.

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time, the heifer pool remained a closed group of 50 animals, including the 9 calves mentioned above, with only the introduction of a young bull. All 50 calves, including the bull, were bled and none were persistently viraemic. However, three of the original group of four animals seroconverted at about 2 years of age when one heifer (n° S477) was in early pregnancy (fig 5). This animal subsequently produced a persistently viraemic calf. The relevance of this study is to show that even within a closed group of animals and in the absence of a persistently viraemic animal, there is still the possibility of infection. The source of virus within this group is not known but several interesting possibilities arise:

1. The spread of BVDV within a group of cattle, particularly those at pasture, can take many months.

2. The virus has become latent following infection (Ssentongo et al 1980) and later recrudesced perhaps due to the stress of early pregnancy.

3. Some vector other than cattle has reintroduced the virus into the group.

2. Origin of cytopathic BVDV

The epidemiology of infection with the cytopathic virus only assumes importance if its crucial role in the pathogenesis of mucosal disease is accepted. This interpretation has required the integration of clinical observation with detailed virology. When fresh tissues from mucosal disease cases have been examined, there has been a consistent association of cytopathic virus with natural disease (Brownlie et al 1984, Clarke et al 1986, Barber et al 1985). Cytopathic virus can readily be cloned by plaque purification and appears to retain its cytopathic effect in cell culture. Once cloned, it has a clearly defined role in the initiation of experimental mucosal disease (Brownlie et al 1984, Bolin et al 1985).

The possible origin of cytopathic virus has already been considered (Brownlie et al 1986, Howard et al 1986a). The two options for its introduction into a group of animals are either from outside the herd or from within. In fact both are possible but its origin from within the herd seems more likely.

Most outbreaks of mucosal disease occur in closed herds. The original source of non-cytopathic virus can sometimes be traced back some 18 months to the introduction of a persistently infected animal (Roeder and Drew 1984). However, in all the outbreaks, we have investigated, there was no evidence of a second and more recent introduction (ie within 2-4 weeks or so) of an animal infected with cytopathic virus. Such an animal, by our definition, would soon develop mucosal disease and so be easily identified. The isolation of cytopathic virus from acute infection is uncommon.

However, a more serious criticism of the outside introduction would be that the superinfecting cytopathic virus requires antigenic homology to the persisting non-cytopathic virus in order to escape immune recognition. BVDV is not a virus of single antigenic form. Serological differences between isolates have been recorded (Hafez et al 1976) and Howard et al (1986a) showed variation between strains isolated from the outbreaks described by Clarke et al (1986). Thus the chance of introducing a superinfecting virus of the correct antigenic type may be limited. It does not represent a convincing explanation of the many outbreaks of mucosal disease seen in the UK.

A more likely means of origin of the cytopathic virus is from within the herd by viral mutation. Direct evidence for the mutation of cloned non-cytopathic virus to cytopathic, in the laboratory, has yet to be provided, but circumstantial evidence from field observations suggests that it may occur. Sera from field and experimental cases of mucosal disease possess no antibody to the infecting viruses — neither the non-cytopathic or cytopathic virus. However, there can be low levels of BVDV antibody in these sera when assayed against heterologous virus. Thus, the persistently infected animal, although immunotolerant to its own virus, may still be able to recognize certain epitopes on other BVDV strains. It would suggest that immunotolerance is narrowly defined and only the most closely related viruses, ie those produced by mutation, would fail to be detected by the immune system.

Both non-cytopathic and cytopathic virus have been isolated and cloned from 5 outbreaks of mucosal disease. Single gnotobiotic calves were infected with cloned virus to produce monospecific convalescent sera for serological typing (Howard et al 1986a). The similarity within the pairs of viruses, ie non-cytopathic and cytopathic, was most noticeable and indicated close antigenic homology.

Futhermore, Pocock et al (1986) have recently shown that within a pair of cytopathic and non-cytopathic viruses isolated from a single clinical case, there was considerable identity between the viral-induced proteins. This is not the case with heterologous viruses.

These results indicate that the immunotolerance is highly specific and that the immune system of persistently viraemic animals is able to respond to alternative serotypes. Different antigenicity of cytopathic viruses may also give rise to variable clinical responses. The two extremes are shown in figure 6, whereby homology between the infecting viruses leads to mucosal disease but
heterology gives an immune response. Between these two extremes may be clinical responses such as prolonged incubation of disease, or chronic diarrhoea or even «apparent» recovery from mucosal disease.

There are certain implications for control measures if cytopathic virus arises by mutation from within an infected herd. Once the initial non-cytopathic virus is present there will always be the possibility that cytopathic virus could arise and superinfect cattle to give mucosal disease. Isolation, in order to avoid exposure to outside sources of cytopathic virus, would therefore be of little value. The best policy would be to slaughter persistently viraemic animals to avoid any possibility of mucosal disease. Slaughter would also be the best policy to avoid in utero infections.

Abstract

An outline of the clinical diseases that arise following BVDV infection is given. Isolates of BVDV can be separated into two forms non-cytopathic and cytopathic depending on their effect on cell cultures. In utero infection of the foetus with non-cytopathic virus may result in a number of syndromes, such as abortions, stillbirths or weak calves. It may also result in the birth of calves with a persistent viraemia and these animals may later develop mucosal disease as a result of superinfection with a «homologous» cytopathic strain of BVDV. Acute infection of seronegative animals in usually mild and subclinical. A chronic disease also occurs and this can be protracted with progressive wastage and diarrhoea. This condition has not yet been well defined but it is suggested that it may be the result of superinfection of a viraemic animal with a «heterologous» cytopathic strain of virus. The maintenance of non-cytopathic virus within the cattle population can be either by the slow spread following acute infections of seronegative animals or, more importantly, by spread from persistently viraemic cattle. The cytopathic virus is usually found in association with cases of mucosal disease and may be maintained in the population only by continually arising, possibly by mutation, from the non-cytopathic virus. It is recommended that persistently viraemic animals are eliminated from the herd to avoid in utero infections and the possibility of subsequent mucosal disease.

References


