Rev. sci. tech. Off. int. Epiz., 1990, **9** (1), 223-230.

Bovine virus diarrhoea virus: speculation and observations on current concepts

J. BROWNLIE and M.C. CLARKE *

Summary: This final chapter highlights the advances and some of the unanswered questions concerning bovine virus diarrhoea virus (BVDV) presented in this Review *by specialists from around the world.*

Persistently viraemic cattle play an essential role in the dissemination of BVDV but it is suggested that acute infections with the virus are also important. The role of latency is considered but, as yet, there is no evidence that it plays a part in pathogenesis.

It is well established that BVDV, Border disease virus and hog cholera virus infect sheep and pigs. There is also some indication that pestiviruses may be involved in other infections of ruminants, such as syndrome X and hyena disease. They also infect other ruminants, such as deer, and human infections have been reported.

It is now known that the pathogenesis of mucosal disease is due to the combined action of the two BVDV biotypes. However, the cause of death remains an enigma. It is suggested that, due to the importance of this syndrome, it may be an appropriate time to reconsider the use of "mucosal disease virus" to replace the ungainly name "BVDV".

KEYWORDS: Acute infections - Bovine virus diarrhoea virus - Control - Death - Epidemiology - Latent infections - Monoclonal antibodies - Mucosal disease virus - Pestiviruses - Terminology.

Introduction

The search for truth and understanding is one of life's great tasks. This issue of the *Review* sets out the endeavour to examine bovine virus diarrhoea virus (BVDV) and its infections. Specialists from around the world have contributed to provide an account of our present knowledge. There can be little doubt that considerable progress has been made since the diseases investigated by Olafson *et al.* (18), Childs (6) and Ramsey and Chivers (21) were first recorded, but there still remains much to be unravelled. This chapter of the *Review* provides an opportunity to highlight the advances and to comment on some of the unanswered questions.

* Agricultural and Food Research Council, Institute for Animal Health, Compton Laboratory, Compton, Newbury, Berkshire RG16 0NN, United Kingdom.

Acute infections

In this *Review* some difference of emphasis has been placed on the role of transient acute infections in the epidemiology of BVDV. It seems generally agreed that the persistently infected animal is a potent source of virus as discussed, for example, by Meyling *et al.* (16). They suggest, however, that "it is possible that transmission" from acute infections "sometimes occurs". Littlejohns and Horner (15) write that acute infections "appear to be of little consequence as spreaders of infection" and Shimizu (23) states that "persistently infected cattle play a more significant role... than acutely infected cattle". Nevertheless, it has been shown that cattle will seroconvert in the absence of a persistently viraemic animal and at a time when some are pregnant (5). The hazards of venereal transfer following acute infections of bulls have been described by Bolin (3) and Meyling *et al.* (16) and there is increasing evidence presented by Baker (1) for the role of BVDV in respiratory disease. Both routes may be important in the dissemination of the agent (16). The potential risks from acute infections should not, therefore, be overlooked.

Latent infections

It is well known that some viruses can establish latent infections (e.g. herpes) and the observation recorded by Littlejohns and Horner may provide an indication that this can occur with BVDV. They reported that two calves seroconverted at a farm on which there appeared to be no virus activity. Although the dams had antibody, it is suggested that the most likely source of infection was maternal. Ssentongo *et al.* (24) recovered BVDV from the ovaries of cattle which were antibody positive and an ovaritis was observed after a period of 61 days in experimentally infected animals. It was suggested that this was due to an immune response against persisting antigen. Both Howard (13) and Edwards (9) point out that the antibody response to BVDV continues for some weeks after infection and this, together with observations mentioned above, implies that antigens are able to persist when neutralising antibody is present in the circulation. Thus, although viral antigen may persist, there is no satisfactory evidence that virus latency is established or that it plays any part in pathogenesis (4). The final proof may have to await the detection, by molecular probes, of viral sequences within the host genome.

BVDV infections in species other than cattle

Although many chapters of this *Review* have considered cattle disease, BVDV infections of other ruminants and pigs do occur and these are discussed by Nettleton (17) and Liess and Moennig (14). There are pestiviruses, other than BVDV, which will infect sheep (Border disease virus) and pigs (hog cholera virus) and their worldwide significance should not be underrated.

However, it would be remiss not to mention some other diseases in which a pestivirus is implicated, for example, syndrome X of sheep which first occurred during 1983 in several regions of France (17). The cause of syndrome X appeared to be multifactorial but the presence of antibodies to Border disease virus and BVDV suggested that a pestivirus was involved. A pestivirus was isolated from some cases.

Hyena disease of cattle has been reviewed by Espinasse *et al.* (10). This condition, a skeletal disorder, was also first reported in France and, since that time, has been

described in a number of other countries but not the United Kingdom. The cause is uncertain but, in some outbreaks, a BVDV aetiology has been considered.

A pestivirus infection of humans has also been suggested. Two medical syndromes, microencephaly and a diarrhoea which lack proven aetiologies, appear to have similar counterparts within the BVDV pathogenesis. Firstly, a congenital malformation of the central nervous system which results in microencephaly is observed after pestivirus infections of ruminants, and this pathology has been described in children. A group of mothers, with children suffering from microencephaly, were examined and shown to have low titres of neutralising antibody to ruminant pestiviruses (19). Secondly, in a study of children with diarrhoea, BVDV antigen was detected in their faeces (25). Furthermore, in a survey of 31 individuals, which included veterinarians in a group at high-risk from exposure to pestiviruses, some 87% had antibody to the A19 strain of BVDV (11). However, a human pestivirus has still to be identified (8) and, until that time, these results must be viewed with both interest and caution.

Aspects of epidemiology and control

From investigations of a number of outbreaks of mucosal disease, including our own unpublished observations, it is apparent that the possible effect from the introduction of just one animal into a herd, is not always considered by the farmer. The risks are frequently overlooked when a "sweeper bull" is employed in an otherwise closed herd. An additional risk may arise from chance exposure to an infected animal (e.g. "over the fence") and this should be considered when maintaining a closed herd. Whilst other ruminants or pigs may play a role in the epidemiology of BVDV (14, 17) there is, as yet, no conclusive evidence for the involvement of other mammals, insects or birds in the spread of this infection.

It is clearly an advantage, when there is a risk of infection, to ensure that cattle are immune to BVDV before service or insemination. For that reason, there would appear to be some attraction in the practice of retaining persistently viraemic animals within the herd to act as sentinel "vaccinators" (15). However, it must be said that this does not have universal acceptance. Some animals appear to be refractory to infection even when in close contact (16) and sometimes the virus spreads so slowly through a group of cattle that virus infection may extend into the period of early pregnancy before all animals have become immune (5). The safer alternative is the identification of virus carriers and their disposal (3, 16, 23). This would seem to be a preferred guideline for dairy herds and breeding units in many parts of the world. No doubt the veterinarian and farmer must consider the risks and costs involved in the two options.

The use of infected serum as a vaccine (15) is also an interesting idea but may not be permitted as a prophylactic in some countries.

The observation reported by Zhidkov and Khalenev (26) is novel. They note that cytopathogenic virus is frequently associated with acute disease. Usually this form of the virus is linked only with the fatal mucosal disease (4, 9) but, since the final outcome of this complex condition has an acute phase, it may be that differences of terminology are implicated. Both biotypes of virus are shed from an animal affected by mucosal disease and an acute disease may, therefore, develop in susceptible sero-negative cattle that are in-contact. Consequently both, or either, biotypes might be recovered from such a case. It is worth noting that although it is often difficult

to isolate BVDV from faeces (9) a number of isolations are reported by Rweyemamu *et al.* (22). Success may depend on the rapid examination of these specimens before inactivation of the virus occurs.

Methods of control described by Bolin (3) are based on herd management and vaccination but it may be of value to note the apparent success of prophylaxis with immunoglobulins, described by Zhidkov and Khalenev (26) and their application in an aerosol fog.

Accurate diagnosis of mucosal disease is paramount for those areas with foot and mouth disease (FMD) control programmes. Rweyemamu *et al.* (22) have considered this in the context of "FMD-like" diseases.

Cause of death

The cause of death from clinical mucosal disease has not been established. Undoubtedly an intercurrent or secondary infection may quicken the pace and interfere with diagnosis (9) but the fundamental pathogenesis has not been described. The clinical signs of mucosal disease are often of short duration, perhaps only a few days (4). The animal will have been anorexic and often diarrhoeic but neither sign would be sufficient to cause death. At autopsy, the gross pathology often appears confined to intestinal lesions but widespread damage to lymphoid cells has been described by Bielefeldt Ohmann (2). This may also seem insufficient to cause death. The feature of mucosal disease that has now been identified as pathognomonic is the presence of the cytopathogenic form of BVDV. As the name of this biotype implies, it causes a cytopathic effect in cell culture and is specifically associated with the erosions seen in Peyer's patch tissue which appear to develop within a few days of death (4). It is tempting to speculate that death is directly related to these lesions and the massive destruction of cells with, perhaps, the release of a toxic substance. The cause of death is of more than academic interest and may be due to some important and, as yet, unrecognised aspect of pathogenesis.

Recent advances

Monoclonal antibodies, developed to epitopes of BVDV and other pestiviruses, are making significant contributions to our understanding of these viruses and can be included amongst the most important of the recent advances. They are already in use for various aspects of diagnosis, ELISA and immune staining of samples of tissue (9) and have an important role in the differential diagnosis of hog cholera (14). It can be anticipated that monoclonal antibodies will enable advances to be made in epidemiology and an improved identification of strains (3).

These monoclonal antibodies have also enabled significant advances to be made in studies on the molecular biology of pestiviruses and the identification of the protective epitopes (8, 12). These findings together with data from gene sequences (8) will be essential for the next generation of diagnostics and vaccines. Studies on pathogenesis will also be aided by monoclonal antibodies (2) and nucleic acid probes, particularly those that distinguish biotypes and different isolates.

The origin of the cytopathogenic biotype, perhaps by mutation (4, 12), remains an enigma as does the cause of cytopathic effect. As indicated by Horzinek (12),

the examination of pairs of "homologous" isolates, cytopathogenic and non-cytopathogenic, is essential. It can be hoped that answers will be forthcoming when comparisons of gene sequences from these pairs are completed.

Dubovi (8) has referred to an insertion in the Osloss strain of BVDV. This insertion has been identified as ubiquitin but has no complementary sequence in the NADL strain of this virus. It is not clear what role, if any, these inserts have and whether or not they are present in other isolates.

Terminology

The terminology used in the numerous reports and articles about infections and experimental studies with BVDV has led to some confusion. This is particularly relevant in the retrospective analysis of earlier data (20). It now seems clear, for example, that chronic mucosal disease (1, 4) is a more appropriate name than chronic BVD, to describe those cases which appear to result from the superinfection of persistently viraemic animals with an antigenically "heterologous" strain of virus as defined by Brownlie (4). These cases are characterised by a protracted illness.

The designation of acute mucosal disease should be retained for those cases with a short time course that show the typical clinical signs and pathology and from which both biotypes can be isolated.

Acute BVDV should describe the transient post-natal infection of cattle. In most cases, this results in a mild or inapparent illness from which there is rapid recovery. Occasionally, acute infections can be complicated by other pathogens.

BVDV or MDV?

The name bovine virus diarrhoea virus, the topic of this issue of the *Review*, is rightly described by Horzinek (12) as "graceless and redundant" and is perhaps an inappropriate title for this agent. This view was also taken by Done *et al.* in 1980 (7) and is supported by Littlejohns (personal communication).

As we now know, BVDV is the cause of both acute disease and of mucosal disease. For some time, this was not realised and the terms "BVDV" and "mucosal disease virus" (MDV) were used separately to describe the virus originating from the two respective conditions. When the true relationship was revealed, the name "BVDV" was suggested *a priori* to describe the virus. However, the terrible and overwhelming aspect of cattle dying of mucosal disease dissuaded clinicians and diagnosticians from using the more enfeebled term BVDV. A compromise was sometimes found by calling it the bovine virus diarrhoea-mucosal disease virus. However, this was clumsy and even more "graceless". Of the two conditions, mucosal disease had the more outstanding and individual pathology and so, in 1956, the Department of Agriculture of the United States of America grouped the syndromes together as the "mucosal disease complex".

In the present issue, specialists from around the world have considered all aspects of this virus and its pathogenesis. There is little doubt that the great strides in understanding over recent years have come about from their analysis of the pathogenesis of mucosal disease and the molecular description of the viral biotypes. The fascinating pathway from foetal infection to immunotolerance, persistent

viraemia, superinfection by the cytopathogenic biotype and the final precipitation of fatal disease are all crucial steps in the development of mucosal disease. With this new realisation, it might now be an appropriate time to reconsider the use of the ''mucosal disease virus'' in place of BVDV. It avoids the use of ''diarrhoea'' and ''bovine'', both of which are misleading epithets for infections with this virus, and brings it more in line with the naming of other pestiviruses. It also has distinction and brevity, if not grace.

Conclusions

The preface by L. Blajan draws attention to the importance of cattle for food, clothing and transport. The international authorship of this *Review* shows that BVDV is on every continent in the world and represents one of the most important pathogens of ruminants. It will be evident to readers of this issue that considerable effort has been made to provide a distillation of the current research and concepts regarding the virus. Studies are continuing and are at an exciting stage of development; mankind is being well served.

ACKNOWLEDGMENTS

We are pleased to have the opportunity to thank the contributors to this issue for providing the compilers with an easy and enjoyable task. We would also like to thank the Office International des Epizooties for inviting us to assist in the preparation of this work and to acknowledge the excellent help and support from the OIE staff, in particular G.S. Dilmitis.

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VIRUS DE LA DIARRHÉE VIRALE BOVINE : RÉFLEXIONS ET OBSERVATIONS SUR LES NOTIONS ACTUELLES. – J. Brownlie et M.C. Clarke.

Résumé: *Ce chapitre final met l'accent sur les progrès dans la connaissance du virus de la diarrhée virale bovine et sur certaines des questions non élucidées, qui sont présentés dans cette* Revue *par des spécialistes du monde entier.*

Les bovins présentant une virémie persistante constituent un facteur essentiel de la propagation du virus de la diarrhée virale bovine, mais il convient aussi de ne pas négliger l'importance des infections aiguës par ce virus. Le rôle de l'infection latente est pris en compte, mais on n'a jusqu'ici aucune preuve qu'elle intervient dans la pathogenèse.

Il est reconnu que les virus de la diarrhée virale bovine, de la «border disease» (maladie de la frontière) et de la peste porcine classique peuvent infecter le mouton et le porc. Certains éléments permettent aussi de penser que les pestivirus peuvent intervenir dans d'autres maladies des ruminants, telles que le syndrome X et la maladie de la hyène. Les pestivirus peuvent également infecter d'autres ruminants, tels que le cerf, et plusieurs cas de maladies qu'ils ont provoqués chez l'homme ont été rapportés.

Si l'on sait actuellement que la pathogenèse de la maladie des muqueuses est due à l'action conjuguée de deux biotypes du virus de la diarrhée virale bovine, la cause de la mort reste une énigme. Cependant, en raison de

l'importance de ce syndrome, on devrait utiliser le terme «virus de la maladie des muqueuses» à la place de la lourde dénomination «virus de la diarrhée virale bovine».

MOTS-CLÉS : Anticorps monoclonaux - Epidémiologie - Infections aiguës - Infections latentes - Mort - Pestivirus - Prophylaxie - Terminologie - Virus de la diarrhée virale bovine - Virus de la maladie des muqueuses.

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VIRUS DE LA DIARREA VIRAL BOVINA: REFLEXIONES Y OBSERVACIONES ACERCA DE CONCEPTOS ACTUALES. – J. Brownlie y M.C. Clarke.

Resumen: *Los autores señalan los progresos recientes y algunas de las preguntas aún sin respuesta en relación con el virus de la diarrea viral bovina (BVDV), tal como son presentados en este número de la* Revista *por especialistas del mundo entero.*

Los terneros atacados por el virus de manera persistente desempeñan un papel central en la difusión de la enfermedad, pero se sugiere que las infecciones agudas también son importantes. En cuanto a la latencia, por el momento no hay datos que demuestren su participación en la patogénesis.

Se ha establecido que el BVDV, el virus de la enfermedad de la frontera (border disease) y el virus de la peste porcina clásica infectan ovinos y porcinos. Ciertos datos permitirían afirmar que los pestivirus pueden ser responsables de otras infecciones de los rumiantes, como el síndrome X y la enfermedad de la hiena. También otros rumiantes, como el gamo, pueden ser infectados, y ha habido casos de infecciones humanas.

Se sabe hoy que la patogénesis de la enfermedad mucosa se debe a la acción combinada de dos biotipos de BVDV, pero se desconocen las causas que provocan la muerte. Dada la importancia del síndrome, los autores sugieren la posibilidad de sustituir, llegado el caso, el término «virus de la diarrea viral bovina» por «virus de la enfermedad mucosa».

PALABRAS CLAVE: Anticuerpos monoclonales - Epidemiología - Infecciones agudas - Infecciones latentes - Muerte - Pestivirus - Profilaxis - Terminología - Virus de la diarrea viral bovina - Virus de la enfermedad mucosa.

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